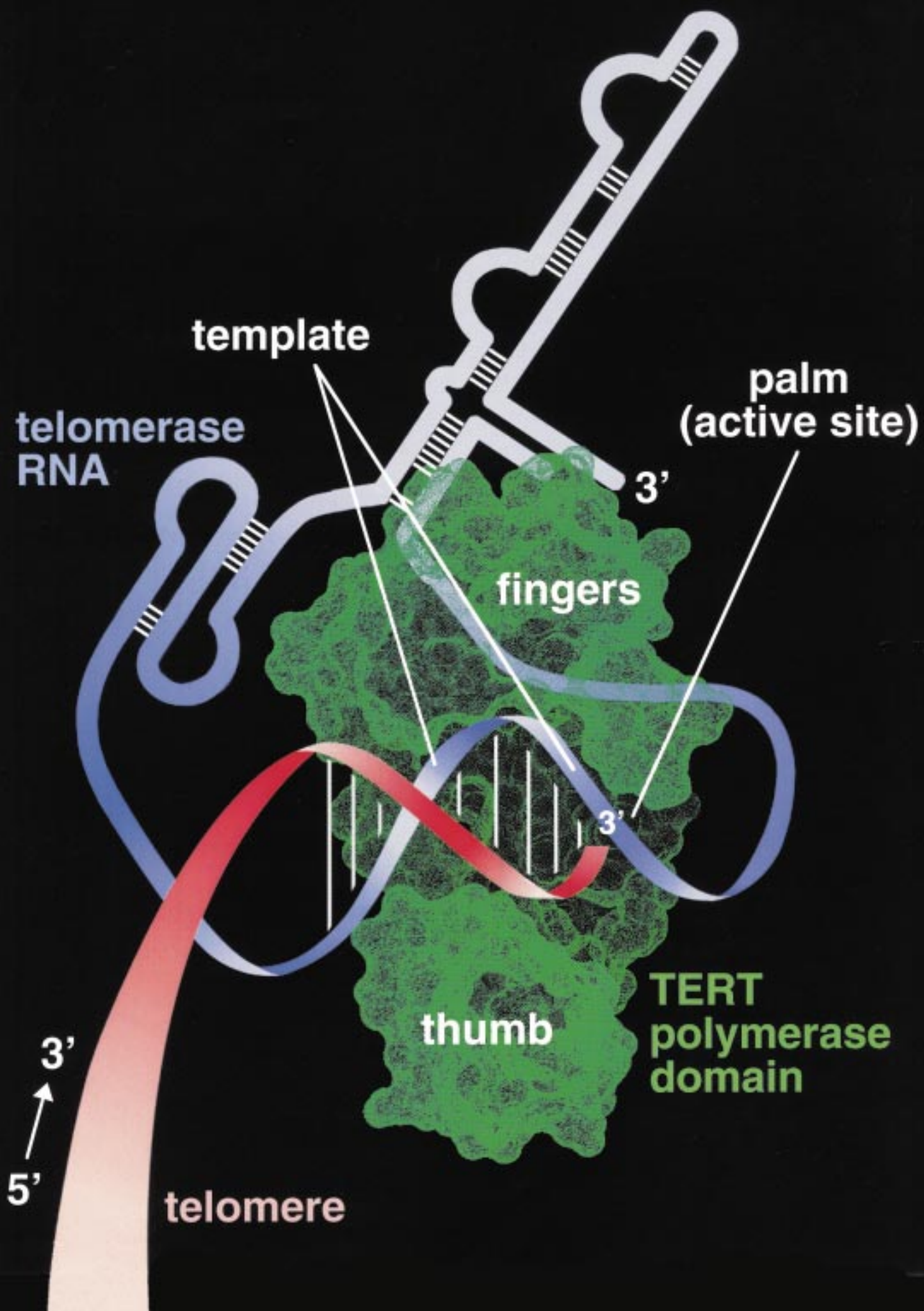




Life at the End of the Chromosome: Telomeres and Telomerase**

Thomas R. Cech*

Telomerase is the enzyme that replicates the ends of linear chromosomes, such as those found in human cells. Its absence has been implicated in cellular aging, and its reactivation promotes tumorigenesis. Telomerase is an unusual enzyme in that it contains an essential RNA subunit as well as protein components. Although the RNA component was described a decade ago, the first catalytic protein subunit of telomerase was discovered only recently through studies of a

ciliated protozoan, *Euplotes aediculatus*. Computer searching and biochemical experiments then led to the identification of the genes for the corresponding telomerase subunits in yeast and humans. These proteins comprise a new branch of the polymerase family called TERT (telomerase reverse transcriptase), distantly related to the enzyme responsible for copying the RNA of HIV (human immunodeficiency virus) and other retroviruses. The pathway by which TERT is assembled with

the RNA subunit to form telomerase and the mechanism of chromosome end-replication are topics of current research. In addition, the identification of TERT provides a new focus for the development of inhibitors with promise as antitumor agents.

Keywords: enzymes • ribonucleoprotein • RNA • telomerase • telomere • tumor therapy

1. Introduction

Chemists typically begin to take notice of a biological system after the molecules involved have been identified and their biochemical function at least partially revealed. Such initial characterization provides a starting point to probe the chemical mechanism of the reaction, dissect structure–function relationships, and synthesize or identify antagonists or agonists of the process. In the case of the chromosome-end-replicating enzyme telomerase, the key biomolecular components have been identified only in the past two years. Since then, striking support has been provided for causal relationships, on the one hand between telomerase shut-off and cellular senescence, and on the other hand between telomerase reactivation and oncogenic transformation of human cells. These events now provide ample incentive for chemists to become informed about this fascinating enzyme.

Before discussing telomerase, it is useful to define its substrate, the chromosome telomere (*telos*, end; *mere*, part).

Early observations of Hermann Muller, who studied fruit fly chromosomes, and of Barbara McClintock, who studied maize chromosomes, indicated that the natural ends of chromosomes are “sealed” and thereby protected from the fusion reactions characteristic of ends produced by chromosome breakage.^[1] Only decades later was the molecular nature of this “cap” on the ends of the chromosome ascertained. The DNA at the chromosome ends does not consist of a complex protein-coding sequence, but instead a simple sequence such as TTGGGG in the ciliate *Tetrahymena*^[2] or TTAGGG in humans is repeated dozens or even thousands of times at each chromosome end. This DNA sequence binds specific proteins, which cap the chromosome end either directly^[3] or by inducing a particular DNA structure.^[4]

While the bulk of telomeric DNA is double-helical, the GT-rich sequence paired with its CA-rich complement, the 3'-end of the DNA protrudes as a single-stranded extension in all eukaryotes studied (Figure 1). Complete replication of the overhanging end of such a chromosome cannot be accomplished by conventional DNA polymerases for the simple reason that an overhang has no template strand to guide its synthesis.^[5] Even if the chromosome were blunt-ended, there would be a problem with complete replication of its ends.^[6]

In almost all eukaryotes this chromosome end-replication problem is solved by telomerase, discovered by Carol Greider and Elizabeth Blackburn in 1985.^[7] Telomerase is an unusual enzyme in that it is an RNA–protein complex (ribonucleoprotein, RNP). A portion of the RNA subunit provides the

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[**] This review is an expanded version of a talk given by the author at the 37th IUPAC Congress in Berlin, August 15, 1999.

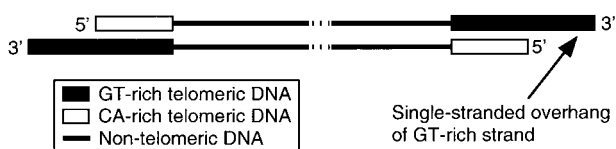


Figure 1. Telomeric DNA at the ends of eukaryotic chromosomes. Solid boxes, multiple repeats of a short sequence, typically GT-rich (TTAGGG in humans, TTTTGGGG in *Euplotes*). Open boxes, the complementary sequence, typically CA-rich (CCCTAA in humans, CCCCCAAA in *Euplotes*).

nucleic acid template that the DNA cannot provide for itself^[8, 9] (Figure 2). The catalytic protein subunit (TERT)^[4] catalyzes the polymerization of dNTPs onto the chromosome end (Figure 3), as described in detail in Section 4.

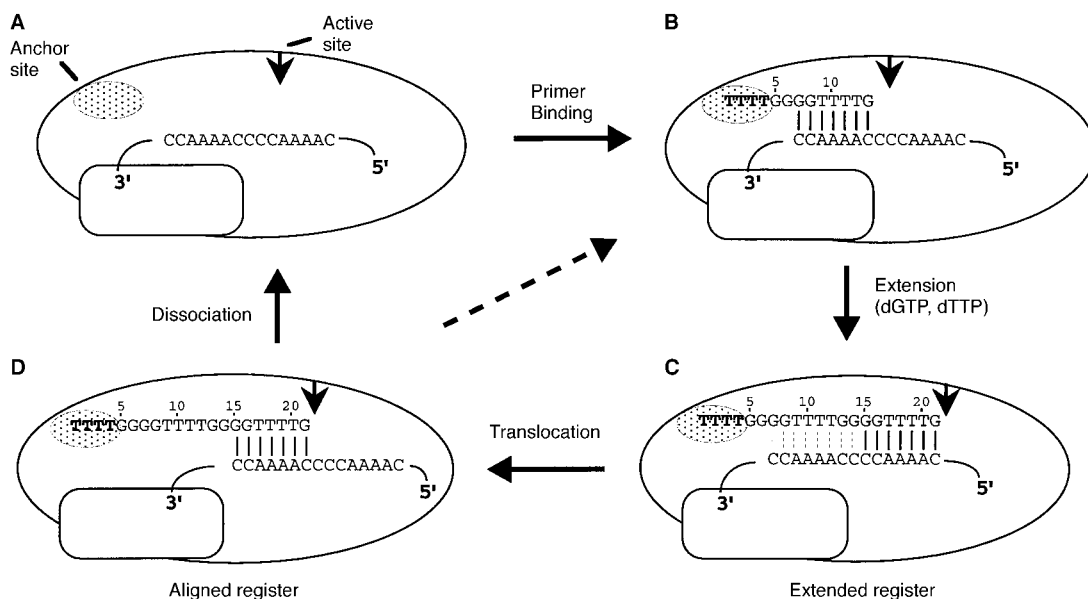


Figure 2. Telomeric DNA is synthesized by telomerase, a ribonucleoprotein enzyme. A) Empty telomerase enzyme, showing the nucleotide sequence of the RNA template region (*Euplotes* sequence). Oval represents the catalytic protein subunit (TERT); rounded rectangle represents a species-specific accessory subunit. B) DNA primer (3'-end of chromosome) binds to telomerase by base-pairing to the RNA template and by interaction with the anchor site.^[61] C) Reverse transcriptase activity of TERT extends the DNA until the end of the template is reached. Enzyme maintains a more-or-less constant amount of primer-template base-pairing during elongation, preventing formation of a long duplex that would inhibit dissociation.^[62] D) Following translocation, the DNA primer is in position to be extended again (dashed arrow), or it can dissociate. (Reproduced from ref. [62].)

[*] TERT = telomerase reverse transcriptase. This article follows the convention that the name of the gene is italicized (*TERT*, or *hTERT* for the human gene), while the protein is not italicized.

2. Newly Discovered Functions for Telomeres and Telomerase in Humans

2.1. Extending Cellular Lifespan

Normal human cells, when established in tissue culture, undergo only a limited number of cell divisions. They cease growing at a point called the Hayflick limit,^[10a] which occurs after about 50 population doublings in the case of connective tissue cells called fibroblasts. In this state of senescence, the cells express a different set of genes and cannot be stimulated to grow by plating at lower cell density or by adding fresh medium. Although they can be forced to proliferate by infection with certain viruses or by transformation with an oncogene, such forced cell divisions lead to a state of massive cell death called crisis.

Telomere length has been proposed to be the “meterstick” that measures the number of divisions a cell is allowed before it reaches the Hayflick limit (see ref. [10b]). Because telomer-



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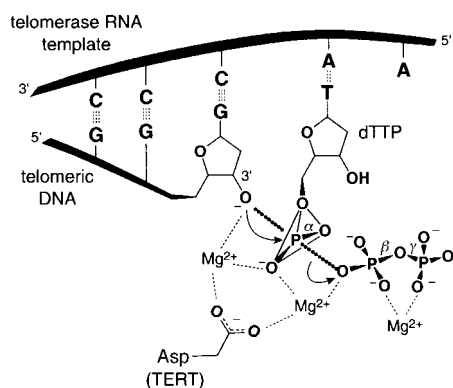


Figure 3. Possible chemical mechanism of catalysis of telomeric DNA extension by telomerase, based on a model of transcriptase by Joyce and Steitz.^[63] Three active-site aspartic acid side chains (only one of which is shown here) coordinate two divalent metal ions that are in turn coordinated to the nucleophile (3'-oxygen of G), the α -phosphate of the incoming nucleotide, and the leaving group oxygen atom. Metal ion ligand coordination is indicated by dashed lines. In this hypothetical transition state diagram, the dotted lines indicate bands half-formed or half-broken.

ase is turned off in most somatic cells (not in germ-line cells) about the time of birth, the chromosome telomeres cannot be fully replicated. Thus, they shrink from their original size of about 15 kbp (bp = base pairs) at a rate of about 100 bp per cell division.^[11]

It has been hypothesized that when the telomeres reach a critically short length (or when the shortest telomere in the cell reaches a critically short length), the cell enters the state of senescence. The exact signaling pathway connecting telomere length with cell cycle arrest is not known, but it may involve the release of telomere-bound proteins as their DNA binding sites are eroded away.

The correlation between the lifespan of cells in culture and telomere length did not necessarily imply any causal relationship. The discovery of hTERT (see Section 4), the catalytic subunit of human telomerase, enabled a direct test of the hypothesis. The other components required for telomerase activity are still present in telomerase-negative normal human cells, so reintroduction of hTERT is sufficient to restore telomerase activity and extend chromosomal telomeres.^[12, 13] Transfection of the *hTERT* gene^[*] (under control of a heterologous transcriptional promoter) also allowed two types of normal human cells—fibroblasts and retinal epithelial cells—to continue growing far beyond the Hayflick limit.^[12] (These cells may in fact be immortal, but given that reviews must be written in a mortal time frame, we will settle for the description “greatly extended lifespan.”) Transfection with *hTERT* did not represent merely a new way to transform human cells, as the *hTERT*-transfected cells retained a normal karyotype and were unable to grow in soft agar, a hallmark of transformed cells.

This remarkable life-extending effect is not totally generalizable, in the following sense. Other cell types (mammary epithelial cells and keratinocytes) require inactivation of the Rb/p16 growth control pathway in addition to gain of hTERT

function to achieve extended lifespan.^[14] (Rb is named for the retinoblastoma caused by loss or mutation of both copies of this tumor suppressor gene; p16 is another tumor suppressor acting in the same pathway as Rb.) Furthermore, some normal human cells have detectable telomerase activity in vitro but nevertheless still undergo senescence.^[15]

Some have considered that the ability to extend cellular lifetime might be a key to extending human lifespan. An emphatic disclaimer is therefore in order: the relationship between the lifetime of primary cultures of human cells in vitro and the longevity of the organism is at best obscure.^[16] Furthermore, as discussed in the next section, inactivation of telomerase is likely a tumor suppressor mechanism; although normal cells transfected with *hTERT* have shown no signs of transformation,^[12] we now have reason to believe that they may be one step closer to transformation. This in no way detracts from the potential of using these extended-lifespan normal cells as improved subjects for cell biology research, or as “bioreactors” to produce pharmaceutically important proteins on an ongoing basis.

2.2. Telomerase Required for Carcinogenesis in Humans

This section will read very much like the previous one. What was for a long time an intriguing correlation—in this case, between reactivation of telomerase and human tumors—now appears to be a cause-and-effect relationship.

About 85–90 % of diverse human tumors show telomerase activity, while adjacent healthy tissue is typically telomerase-negative. Thus, telomerase, which is generally not present in somatic cells, is reactivated in tumors. The telomerase component that is missing in normal cells is the hTERT protein;^[17, 18] the RNA subunit of telomerase is not only present in telomerase-negative cells, but it is efficiently recruited into an active telomerase complex upon introduction of hTERT.

Very recently, Weinberg and colleagues succeeded in solving a long-standing problem in human cancer biology: the oncogenic transformation of human cells with defined genetic components. Such transformation is easily accomplished with rodent cells by expression of two cooperating oncogenes. However, introduction of the same genes was known to be insufficient for stable transformation of human cells in culture. The missing component turned out to be hTERT.^[19] Thus, one pathway to transformation of human cells is shown to require three steps: activation of proliferation (accomplished by expression of a mutant form of the *ras* oncogene), inactivation of tumor suppressors p53 and the Rb protein (accomplished by expression of the SV40 T oncoprotein) and activation of telomerase (by expression of hTERT).^[**] Telomerase is therefore much more than a “marker” for neoplastic growth, it is a promising target for chemotherapeutic intervention in diverse cancers.

[*] Transfection refers to introduction of a gene into mammalian cells in a form that allows the gene to be expressed. Transformation refers to the oncogenic state characterized by unregulated growth.

[**] More accurately, the experiments^[19] show that some function of hTERT is required. We assume that this function is activation of telomerase activity, but a catalytically inactive mutant of hTERT needs to be tested to further support this hypothesis.

3. RNA Component of Telomerase

3.1. Biosynthesis

The RNA components identified first were those of the ciliated protozoa. These are transcribed by RNA polymerase III, which leaves a short run of U residues at the 3'-end of the transcript.^[8, 20] There was a switch in RNA polymerase usage during evolution, because the yeast RNA subunit (TLC1) is transcribed by pol II.^[21] As a result, the yeast RNA is 5'-capped and (initially) 3'-polyadenylated. The human RNA is also thought to be a pol II transcript and its mature form also has a 5'-trimethylguanosine cap.^[22] The 3'-half of the human RNA subunit constitutes a small nucleolar RNA (snoRNA) domain,^[23] previously found only in RNAs that mediate the conversion of certain uracils to pseudouracils in stable RNAs. This snoRNA domain is required for proper 3'-end formation of the human RNA.^[23]

3.2. RNA Structure

If the RNA subunit of telomerase were highly conserved in sequence and/or structure, one would argue that it was an attractive target for small-molecule inhibitors. However, the RNA subunit varies widely among species. Even among ciliated protozoa, very few conserved nucleotides can be ascertained, although the overall “frying-pan” like secondary structure is conserved (Figure 4).^[20, 24] The human RNA subunit is much larger, 450 nt (nt = nucleotides).^[25] However, when the snoRNA domain^[23] is subtracted, the remaining template-containing domain of the RNA consists of 210 nt, not too different in size from its ciliate counterparts (ca. 160–190 nt). It will therefore be of interest to see whether the secondary structure of this 5'-domain bears any resemblance to that of the ciliate RNAs.

3.3. RNA Function

The most obvious function of the RNA subunit is to template the addition of telomeric DNA repeat sequences onto chromosome ends. All known telomerase RNAs contain about 1.5 repeats of a sequence complementary to the telomeric DNA repeat sequence of that organism. That this RNA sequence in fact acts as the template was first proven in *Tetrahymena*^[9] and

yeast,^[26] where mutation of the template sequence led to incorporation of the predicted variant sequence at chromosome ends. Mutations in the RNA do not always simply change the sequence of the DNA product, but can cause infidelity of polymerization and other problems.^[27] Presumably the RNA template interacts with the active site of TERT much more intimately than the template RNAs that are copied by retroviral RTs.

Another function of the RNA subunit, at least in *S. cerevisiae*, is to provide a binding site for Sm proteins.^[22] These seven proteins, previously known to be associated only with small nuclear (sn) RNAs involved in RNA processing, promote the trimethylation of the 5'-cap of snRNAs and may mediate their intracellular transport. It seems likely that other regions of telomerase RNAs will be involved in bringing yet other proteins into the telomerase complex (see Section 4.4 below), but no RNA binding site for any of these proteins has yet been specified.

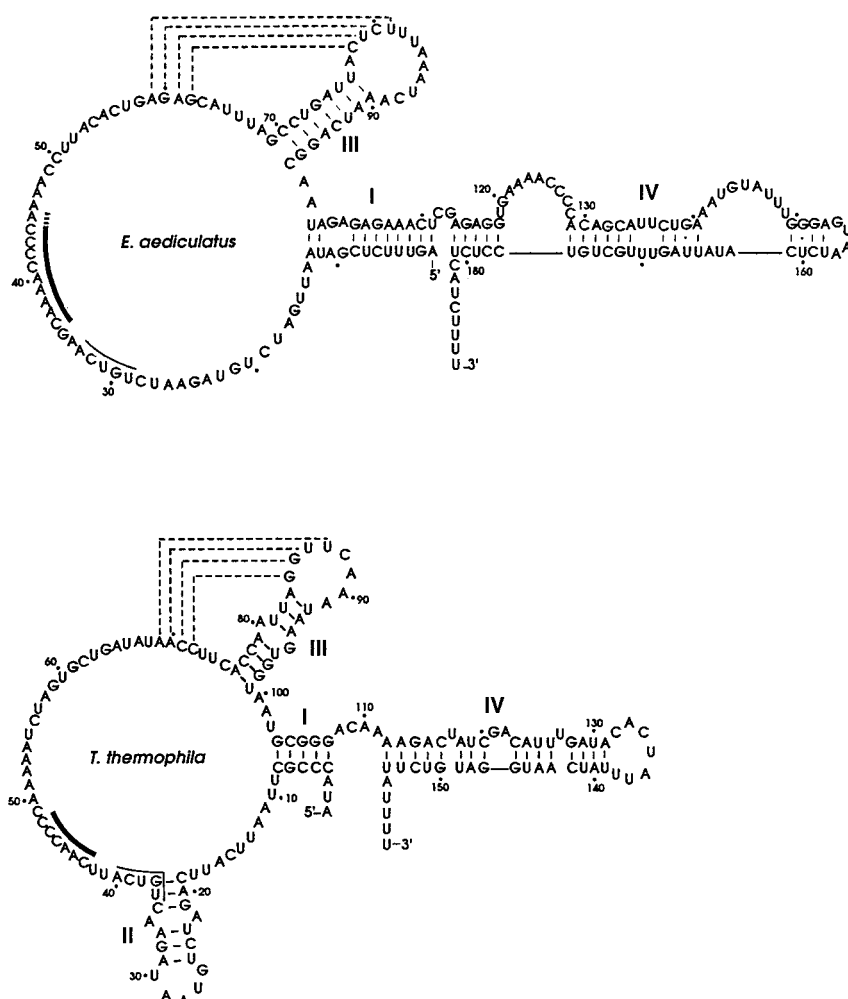


Figure 4. The secondary structure but not the nucleotide sequence of telomerase RNA is conserved among evolutionarily diverse ciliated protozoa. Dashed lines, pairing of the loop of helix III with a nearby sequence forming a pseudoknot. Bold lines highlight the template sequences. Adjacent thin lines mark a sequence conserved among ciliates. *E. aediculatus* from Lingner et al.,^[20] *T. thermophila* from Romero and Blackburn.^[24] (Reproduced from ref. [64].)

4. TERT and Other Protein Components

4.1. Discovery of TERT

The telomerase component that allowed both the extension of lifespan of normal human cells and the first oncogenic transformation of human cells with defined genetic components was hTERT, human telomerase reverse transcriptase. Despite intensive effort, this key human component escaped identification for many years. It was finally identified by a path that involved biochemical purification of the corresponding *Euplotes aediculatus* protein, identification and genetic analysis of its yeast homologue, and computer searching of the EST (expressed sequence tag) database for the human homologue.

Why *Euplotes*? This unicellular eukaryote carries germline, diploid micronuclei and a somatic, polyploid macronucleus within the same cell.^[28] Each macronucleus has about 50000000 DNA molecules, each containing a single gene flanked by canonical telomeres (TTTGGGG repeats ending with a 3'-overhang of two additional repeats). Thus, there are about 1000000 times more telomeres per cell in *Euplotes* than in human, and a concomitant increase in telomerase.

An affinity purification method was devised by Joachim Lingner in my laboratory to isolate *Euplotes* telomerase from a nuclear extract^[29] (Figure 5). The enzyme remained fully active during purification, as judged by the ratio of enzymatic

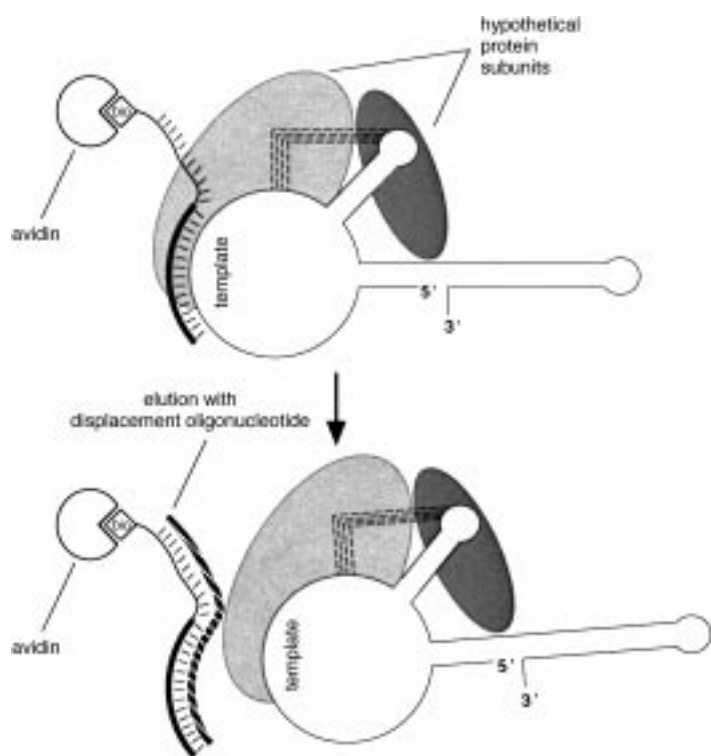


Figure 5. Active *Euplotes* telomerase was affinity-purified. Top: When a *Euplotes* extract is mixed with agarose containing a bound oligonucleotide, the telomerase is adsorbed by hybridization. Other components in the extract can then be washed away. Bottom: Telomerase is released from the column by adding a displacement oligonucleotide, which can form a more stable hybrid with the oligonucleotide on the column. (Reproduced from ref. [29].)

activity to the telomerase RNA content of the preparation. Two polypeptides copurified with the RNA in the active complex, one 123 kDa (p123) and one 43 kDa (p43), in amounts consistent with a 1:1:1 complex of the two proteins and the RNA.^[29]

Electrospray mass spectroscopy in collaboration with Matthias Mann and Andrej Shevchenko (EMBL, Heidelberg) then revealed enough peptide sequences to enable cloning and sequencing of genes for both p123 and p43.^[30] It was the larger of these two proteins that proved particularly interesting, because it contained reverse transcriptase motifs (short blocks of amino acid sequence characteristic of this family of proteins).^[31] Because telomerase uses an RNA template to synthesize telomeric DNA, it is by definition some sort of a reverse transcriptase. The finding of RT motifs went beyond this to say that the *Euplotes* telomerase protein was related in terms of protein structure and presumably in terms of its evolutionary origin to other known RTs, such as those encoded by retrotransposons and retroviruses.^[30]

This biochemical line of research then converged on a genetic approach that was ongoing, completely independently, in the laboratory of Victoria Lundblad (Baylor College of Medicine, Houston). Lundblad had set up a genetic screen to identify genes that, when mutated, gave the telomere-shortening effect expected for a telomerase mutant. Her laboratory found four such genes, which she named *EST1*, *EST2*, *EST3*, and *EST4*^[32] (*EST* = ever shorter telomeres; *EST1* had been previously described by Lundblad and Szostak,^[33] and *EST4* is also known as *CDC13*^[34]). The best sequence match to *Euplotes* p123 in protein databases turned out to be Lundblad's Est2p.^[30]

The yeast homologue was an important finding for several reasons. First, it was attractive to think that there would be a single catalytic subunit conserved among all telomerases; if so, the completely sequenced yeast genome would need to have a copy, and it did. Second, a definitive demonstration that this RT-containing protein was indeed essential for telomerase activity was much more easily carried out in yeast, where facile genetic tools are available, than in *Euplotes*. Indeed, a collaborative effort between our laboratory and the Lundblad laboratory in 1996 provided the evidence that Est2p was a reverse transcriptase and was essential for telomerase activity, both in an enzymatic assay *in vitro* and for telomere maintenance *in vivo*.^[30]

The *Euplotes* p123 sequence also revealed a portion of the corresponding human sequence in the Expressed Sequence Tag database (Washington University, St. Louis). A single amino acid deletion prevented the yeast Est2p from revealing the same human sequence, but once it was identified, pairwise sequence comparisons clearly showed that it was related as well. Also by this time, Toru Nakamura in my laboratory had identified and sequenced the *Schizosaccharomyces pombe* (fission yeast) *TERT*, and this sequence also retrieved the human expressed sequence tag from the database.^[17] Following this, and in collaboration with scientists from Geron Corporation we cloned and sequenced human open reading frame.^[17] The same gene, now called *hTERT*, was independently cloned and sequenced by several other laboratories,^[18, 35–37] all starting from the *Euplotes* p123 sequence.

Like the other TERTs, hTERT is a relatively large protein, with an overall net basic charge and reverse transcriptase motifs in its C-terminal half (Figure 6A). Subsequently, the

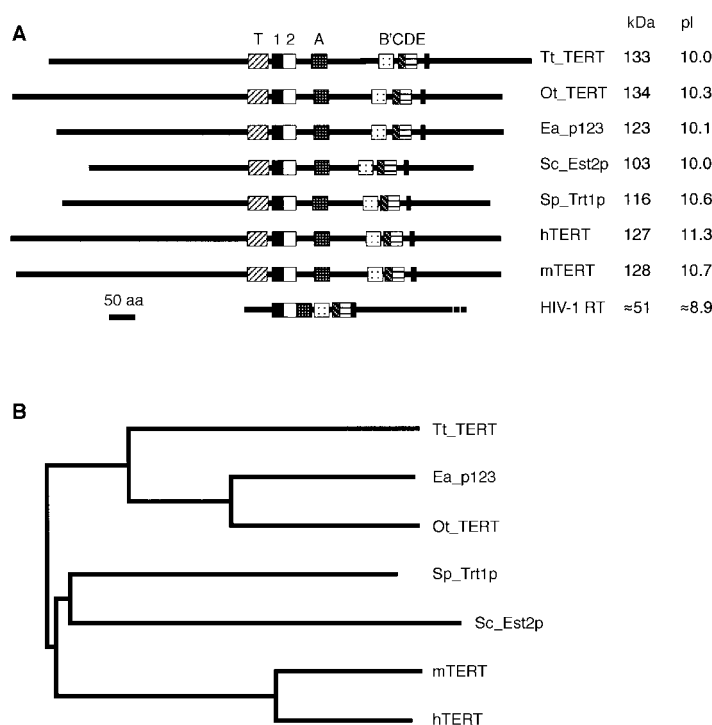


Figure 6. Relationship of the TERT family members to each other and to the HIV retroviral RT. A) Protein sequences are represented by lines. Cross-hatched box, the telomerase-specific motif T.^[17] Other boxes, reverse transcriptase motifs 1, 2 and A-E.^[31] HIV-1 RT, RNase H domain is omitted. B) Phylogenetic tree of TERTs calculated from sequence comparison of the motifs indicated in part A. Tt = *Tetrahymena thermophila*; Ot = *Oxytricha trifallax*; Ea = *Euplotes aediculatus*; Sc = *Saccharomyces cerevisiae* (baker's yeast); Sp = *Schizosaccharomyces pombe* (fission yeast); mTERT = mouse TERT. (Reproduced from [38].)

Tetrahymena,^[38, 39] *Oxytricha*,^[38] and mouse^[40] TERTs were added to the collection (Figure 6A) and, very recently, that of the plant *Arabidopsis*.^[41]

Expression of the *hTERT* gene was absent or barely detectable in telomerase-negative normal human cells, but easily detected in telomerase-positive immortalized human cells. This contrasted with the ubiquitous expression of the telomerase RNA component in all cells tested, and led to the idea that the presence of hTERT might be the “switch” that determined whether human cells had telomerase activity or not. This idea was subsequently verified when it was found that ectopic expression of hTERT in telomerase-negative cells was sufficient to provide chromosomal telomere lengthening in living cells as well as telomerase enzymatic activity in cell extracts.^[37, 42]

4.2. A New Subclass of Polymerases

Amino acid sequence comparisons show that the TERTs represent a discrete class of reverse transcriptases, more related to each other than to other RTs.^[30, 43] Features that

distinguish these proteins from other RTs include the following:

- 1) There are some distinctive variations within the RT motifs. For example, in motif C the sequence around the two catalytic aspartic acids (D) is LxDD(F/Y)L in the TERTs compared to a consensus of (F/Y)xDDxx in other RTs, where x is a less conserved amino acid and (F/Y) means that either Phe or Tyr is found in that position.
- 2) A distinctive amino acid sequence called the T (Telomerase-specific) motif precedes RT motif 1.

Compared to the other RTs, the TERTs are most closely related to the RTs of certain bacterial and mitochondrial elements and non-LTR (long terminal repeat) retrotransposons. (Retrotransposons are DNA elements that move within and between genomes through an RNA intermediate, and therefore need a reverse transcriptase to regenerate a DNA copy to integrate into a chromosome. Some retrotransposons have a long sequence repeated at their termini that resembles the LTRs involved in retroviral replication; the non-LTR retrotransposons do not.) The TERTs are more distantly related to the RTs of LTR retrotransposons and viruses, and to the RNA-dependent RNA polymerases of viruses such as poliovirus.

Transposition of non-LTR retrotransposons and Group II introns occurs by target-primed reverse transcription, in which the RT extends a 3'-OH at a DNA break; the DNA break can be created either by an endonuclease or by catalytic activity intrinsic to the intron RNA. Similarly, telomerase extends the 3'-OH of the chromosomal DNA terminus. Another similarity is that certain Group II intron and mitochondrial RTs, like telomerase, are found in stable complexes with their RNA templates. Therefore, the close relationship of TERTs to the non-LTR RTs obtained by sequence comparison is supported by functional criteria as well.^[43]

The phylogenetic tree of the TERTs is qualitatively similar to the tree of the organisms from which the telomerases were obtained: the two mammalian TERTs are the most closely related, the two yeast species group together, and the three ciliated protozoa form a third branch, with the two hypotrichs (*Euplotes* and *Oxytricha*) more closely related to each other than to the holotrich *Tetrahymena* (Figure 6B). Thus, the phylogenetic tree is unremarkable—it is just what one would expect for any gene that is ancient. We conclude that TERT is probably as old as the eukaryotic kingdom (see refs. [43, 44] for additional discussion).

4.3. Functions of TERT

Synthesis of telomeric DNA is the most obvious function of TERT, and as far as we know, the lengthening of chromosome telomeres it provides may be sufficient to explain the dramatic results described earlier: the extension of lifespan of normal human cells provided by ectopic expression of hTERT, and providing the “missing link” for stable transformation of human cells in culture. However, TERTs are large proteins, much larger than some of the retroviral RTs, suggesting the possibility of functions beyond their role as polymerases.

The telomerase-specific T motif of human TERT has been mutated and found to contribute to telomerase catalytic activity *in vitro*.^[42] The N-terminal half of Est2p (the yeast TERT) has been analyzed by making a large library of randomly mutated versions and recovering those that were able to rescue senescing *est2⁻* yeast.^[45] Four essential regions of the N-terminus were mapped, two of which are implicated in binding the RNA subunit and one of which may bring an unidentified subunit into the complex.^[45] Also in yeast, Est3p is associated with the telomerase RNA in an Est2p-dependent manner,^[46] which may implicate Est2p as contributing a binding site for Est3p. The specific contributions of the T motif and the rest of the N-terminal domain of TERT are only beginning to be evaluated. Thus, it is quite possible that the introduction or reactivation of TERT in human cells has consequences beyond the obvious one of lengthening telomeres.

4.4. Other Telomerase Protein Components

(Because these have been reviewed recently,^[47] they will be only briefly discussed here.) Aside from TERT, the other proteins found associated with telomerase appear to be species-specific. An exception is *Tetrahymena* p80,^[48] which is highly homologous to one domain of a much larger (230–240 kDa) human telomerase-associated protein now called TEP1.^[49, 50] Evidence of the importance of these proteins for telomerase activity *in vivo* or *in vitro* has not yet been reported.

Two non-TERT telomerase-associated proteins that have been shown to be essential for telomerase activity *in vivo* in yeast are Est1p and Est3p.^[32, 33] Est1p is a single-stranded telomeric DNA-binding protein, so it is plausible that its function is to help telomerase locate telomeres in the cell.^[51] This would also explain why it is dispensable for *in vitro* telomerase enzyme assays, where the telomeric DNA substrate is presented as a protein-free oligonucleotide and is readily available to the telomerase. A function for Est3p has not been proposed.

5. Opportunities for Chemical Intervention

Now that the importance of telomerase for oncogenic transformation and for lifespan extension of human cells has been established, medicinal and pharmaceutical chemists are focussing on how they might be able to intervene in telomerase pathways. Inhibitors of telomerase are promising candidates for antitumor drugs targeted against a wide variety of cancers. Activators of telomerase, on the other hand, should be able to extend the lifespan of normal human cells in culture and might find useful medical applications in certain age-related diseases.

The most obvious anti-telomerase target is the hTERT–RNA core of the enzyme. The protein component of this complex is related to other reverse transcriptases, as described above, so nucleoside analogues comprise one obvious class of inhibitors. However, differences in key active site amino acids

imply that TERTs will have structures distinct from other RTs (see Section 4.2); thus, it is not surprising that AZT (azido-thymidine) and other HIV RT inhibitors are only weak inhibitors of telomerase.^[52] Therefore, inhibitors must be developed specifically against hTERT. The RNA template moiety of telomerase can be targeted by oligonucleotides containing stable 2'-*O*-methylribose moieties or by peptide nucleic acids (PNAs).^[53]

Activation of telomerase in normal human cells cannot be achieved by compounds directed at hTERT, since hTERT is not expressed in these cells.^[17, 18] Chemical approaches to this problem may include the development of compounds that act at the level of induction of transcription of the *hTERT* gene, whose promoter is activated by the transcription factor c-Myc^[54] and presumably by other proteins not yet described. Alternative mRNA splicing provides another pathway to down-regulation of telomerase in some cells, so compounds capable of redirecting the RNA splicing machinery could potentially be useful. Finally, introduction of the *hTERT* gene by gene therapy is another conceivable pathway to telomerase activation in humans, as transfection has already proven to be successful in activating telomerase in cultured cells as described in Section 2.1.

Returning to the subject of inhibition of telomerase, the recognition that it has a complex pathway of maturation and assembly^[21–23] (Figure 7) suggests other possible points of

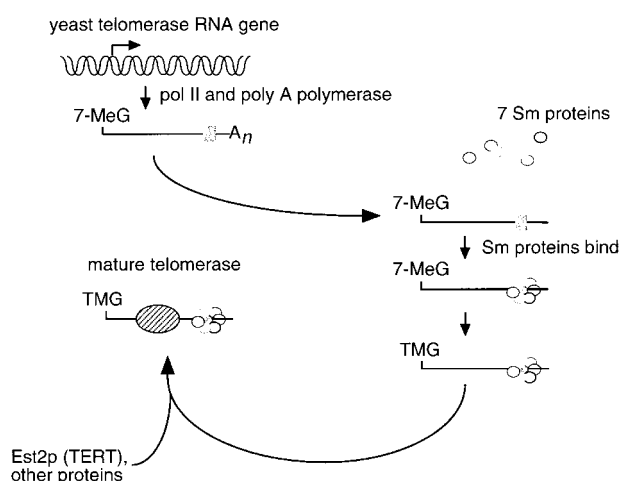


Figure 7. Telomerase is matured and assembled by a complex multi-step pathway. The model for the yeast pathway shown here incorporates data from Chapon et al.^[21] and Seto et al.^[22] 7-MeG = 7-methylguanosine; TMG = 2,2,7-trimethylguanosine.

intervention. In addition, Holt et al.^[55] have found that the molecular chaperones p23 and hsp90 (a heat shock protein) are necessary for the assembly of telomerase components into an active enzymatic complex *in vitro* and appear to stay associated with the assembled complex in cell extracts. Geldanamycin (a benzoquinone), which inhibits functions of hsp90 by binding to its ATP site, blocks assembly of active telomerase *in vitro* and in cultured human cells.^[55] A caveat regarding targeting of telomerase maturation, assembly, or chaperone components for pharmaceutical application is that such components are likely to be shared with other biochem-

ical pathways. Unless some telomerase-specific feature can be identified, inhibition of these cellular processes would presumably be toxic.

Finally, one could consider targeting the telomere (chromosome end) itself, because it is the substrate on which telomerase acts. The very ends of chromosomes have both single-stranded DNA and protein components. In many organisms including human, the single-stranded DNA contains G-rich repeats which can fold into intramolecular (or intermolecular) quadruple helix structures; each G is Hoogsteen–hydrogen-bonded to another G in a square-planar arrangement called a G-quartet.^[56] This structure hides the 3' end of the DNA from telomerase and thereby inhibits telomerase extension.^[57] Hurley and co-workers^[58] are developing compounds that stabilize the G-quartet form of telomeric DNA and could thereby prevent telomerase from acting. Protein components of telomeres also act as negative regulators of telomerase (see ref. [47]). Stabilizing their interaction with the DNA or inhibiting components that normally displace these proteins provides another possible route to inhibition of telomerase.

One possible challenge to successful implementation of an anti-telomerase therapeutic is suggested by the observation that a minority of human tumors use an alternative non-telomerase mechanism for maintaining telomere length.^[59] This ALT (alternative lengthening of telomeres) pathway may involve extension of a telomere using another telomere as a template, facilitated by DNA recombination proteins that catalyze DNA strand invasion. Application of a telomerase inhibitor might provide a selective growth advantage for the rare cells that utilized ALT and therefore did not require telomerase. Thus, one might next be faced with developing inhibitors of the ALT pathway. On the other hand, there are always pathways for resistance to any pharmaceutical, so this potential problem should not diminish interest in development of effective anti-telomerase compounds.

6. Summary and Outlook

Telomerase is an unusual enzyme, an RNA–protein complex, that extends the repeated DNA sequences at chromosome ends and thereby enables them to be fully replicated. The last few years have witnessed major breakthroughs in our understanding of this enzyme. The catalytic protein subunit of telomerase has been identified in diverse organisms, including human, and found to represent a new branch of the reverse transcriptase family. On the biomedical front, the long-suspected roles of telomerase deactivation in cellular senescence and of telomerase activation in tumorigenesis have received decisive experimental support.

Thus, chemists now have much more incentive to develop compounds that modulate telomerase activity, and they have clearly defined molecular components to target. A most attractive target is the hTERT catalytic subunit of telomerase. In addition, one can consider developing compounds to modulate *hTERT* gene expression, to interfere with the assembly of the protein–RNA complex, and to prevent access of telomerase to its telomeric DNA substrate. Recently,

dominant-negative versions of hTERT have been found to kill tumor cells by apoptosis (programmed cell death).^[60] These findings provide great reason for enthusiasm that anti-telomerase pharmaceuticals will indeed have antitumor potential.

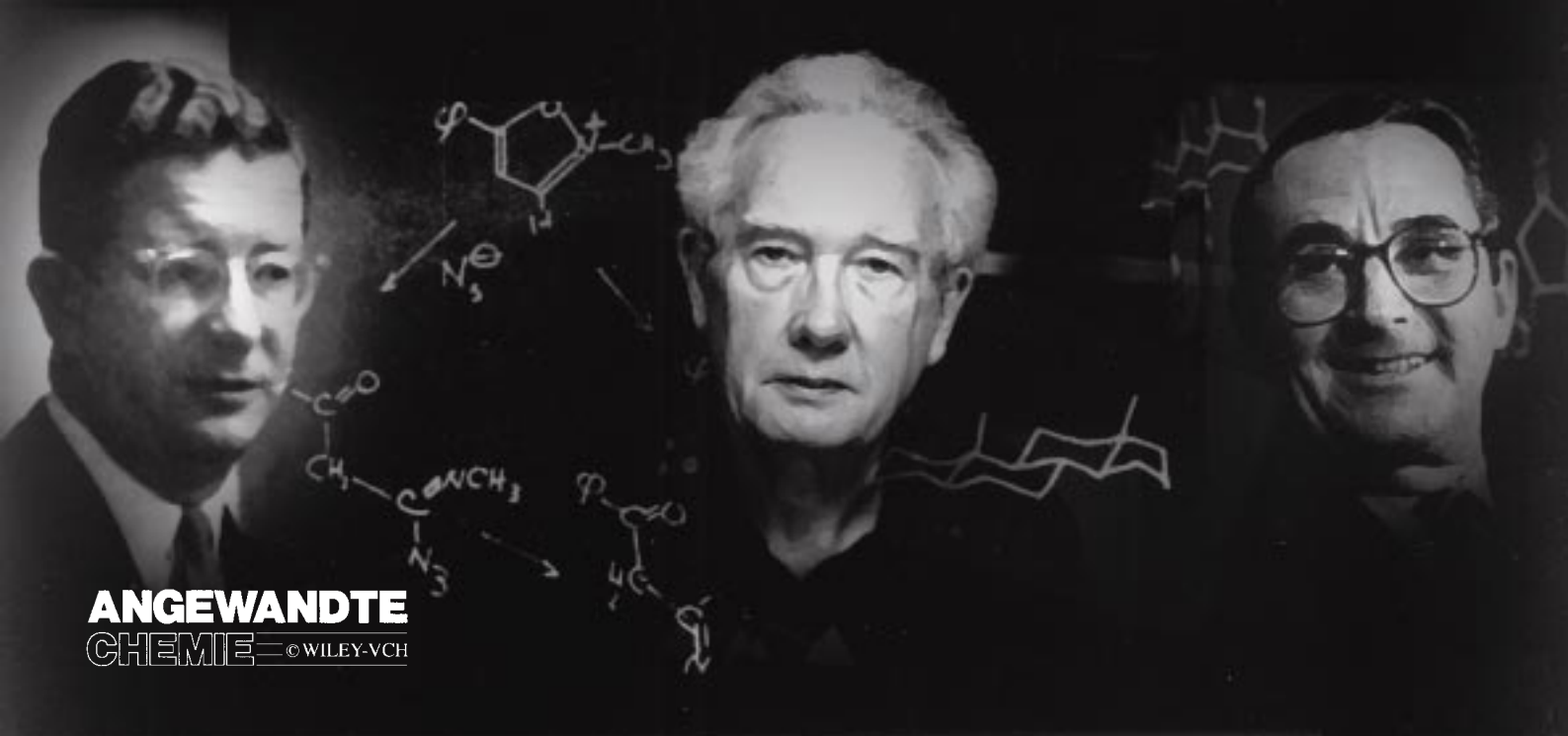
I thank Toru Nakamura, Anita Seto, Scott Silverman, Tracy Bryan, Phil Hammond, and Joachim Lingner for figures, and them and other members of the Cech lab for their contributions to the research described here.

Received: September 30, 1999 [A363]

- [1] J. G. Gall in *Telomeres* (Eds.: E. H. Blackburn, C. W. Greider), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, **1995**, pp. 1–10.
- [2] E. H. Blackburn, J. G. Gall, *J. Mol. Biol.* **1978**, *120*, 33–53.
- [3] M. P. Horvath, V. L. Schweiker, J. M. Bevilacqua, J. A. Ruggles, S. C. Schultz, *Cell* **1998**, *95*, 963–974.
- [4] J. D. Griffith, L. Comeau, S. Rosenfield, R. M. Stansel, A. Bianchi, H. Moss, T. de Lange, *Cell* **1999**, *97*, 503–514.
- [5] J. Lingner, J. P. Cooper, T. R. Cech, *Science* **1995**, *269*, 1533–1534.
- [6] a) M. Olovnikov, *J. Theor. Biol.* **1973**, *41*, 181–190; b) J. D. Watson, *Nature (London) New Biol.* **1972**, *239*, 197–201.
- [7] C. W. Greider, E. H. Blackburn, *Cell* **1985**, *43*, 405–413.
- [8] C. W. Greider, E. H. Blackburn, *Nature* **1989**, *337*, 331–337.
- [9] G. L. Yu, J. D. Bradley, L. D. Attardi, E. H. Blackburn, *Nature* **1990**, *344*, 126–132.
- [10] a) L. Hayflick, *Exp. Cell. Res.* **1965**, *37*, 614–636; b) T. de Lange, *Science* **1998**, *279*, 334–335.
- [11] C. B. Harley, A. B. Futcher, C. W. Greider, *Nature* **1990**, *345*, 458–460.
- [12] a) A. G. Bodnar, M. Ouellette, M. Frolkis, S. E. Holt, C. P. Chiu, G. B. Morin, C. B. Harley, J. W. Shay, S. Lichtsteiner, W. E. Wright, *Science* **1998**, *279*, 349–352; b) H. Vaziri, S. Benchimol, *Curr. Biol.* **1998**, *8*, 279–282.
- [13] C. M. Counter, M. Meyerson, E. N. Eaton, L. W. Ellisen, S. D. Caddle, D. A. Haber, R. A. Weinberg, *Oncogene* **1998**, *16*, 1217–1222.
- [14] T. Kiyono, S. A. Foster, J. I. Koop, J. K. McDougall, D. A. Galloway, A. J. Klingelutz, *Nature* **1998**, *396*, 84–88.
- [15] C. D. Belair, T. R. Yeager, P. M. Lopez, C. A. Reznikoff, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 13677–13682.
- [16] V. J. Cristofalo, R. G. Allen, R. J. Pignolo, B. G. Martin, J. C. Beck, *Proc. Natl. Acad. Sci. USA* **1995**, *95*, 10614–10619.
- [17] T. M. Nakamura, G. B. Morin, K. B. Chapman, S. L. Weinrich, W. H. Andrews, J. Lingner, C. B. Harley, T. R. Cech, *Science* **1997**, *277*, 955–959.
- [18] M. Meyerson, C. M. Counter, E. N. Eaton, L. W. Ellisen, P. Steiner, S. D. Caddle, L. Ziaugra, R. L. Beijersbergen, M. J. Davidoff, Q. Liu, S. Bacchetti, D. A. Haber, R. A. Weinberg, *Cell* **1997**, *90*, 785–795.
- [19] W. C. Hahn, C. M. Counter, A. S. Lundberg, R. L. Beijersbergen, M. W. Brooks, R. A. Weinberg, *Nature* **1999**, *400*, 464–468.
- [20] J. Lingner, L. L. Hendrick, T. R. Cech, *Genes Dev.* **1994**, *8*, 1984–1998.
- [21] C. Chapon, T. R. Cech, A. J. Zaug, *RNA* **1997**, *3*, 1337–1351.
- [22] A. G. Seto, A. J. Zaug, S. G. Sobel, S. L. Wolin, T. R. Cech, *Nature* **1999**, *401*, 177–180.
- [23] J. R. Mitchell, J. Cheng, K. Collins, *Mol. Cell. Biol.* **1999**, *19*, 567–576.
- [24] a) D. P. Romero, E. H. Blackburn, *Cell* **1991**, *67*, 343–353; b) M. McCormick-Graham, D. P. Romero, *Mol. Cell. Biol.* **1996**, *16*, 1871–1879.
- [25] A. J. Zaug, J. Lingner, T. R. Cech, *Nucleic Acids Res.* **1996**, *24*, 532–533.
- [26] M. S. Singer, D. E. Gottschling, *Science* **1994**, *266*, 404–409.
- [27] D. Gilley, E. H. Blackburn, *Mol. Cell. Biol.* **1996**, *16*, 66–75.
- [28] D. M. Prescott, *Microbiol. Rev.* **1994**, *58*, 233–267.
- [29] J. Lingner, T. R. Cech, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 10712–10717.
- [30] J. Lingner, T. R. Hughes, A. Shevchenko, M. Mann, V. Lundblad, T. R. Cech, *Science* **1997**, *276*, 561–567.
- [31] Y. Xiong, T. H. Eickbush, *EMBO J.* **1990**, *9*, 3353–3362.
- [32] T. S. Lendvay, D. K. Morris, J. Sah, B. Balasubramanian, V. Lundblad, *Genetics* **1996**, *144*, 1399–1412.

- [33] V. Lundblad, J. W. Szostak, *Cell* **1989**, 57, 633–643.
- [34] B. Garvik, M. Carson, L. Hartwell, *Mol. Cell. Biol.* **1995**, 15, 6128–6138.
- [35] L. Harrington, W. Zhou, T. McPhail, R. Oulton, D. S. Yeung, V. Mar, M. B. Bass, M. O. Robinson, *Genes Dev.* **1997**, 11, 3109–3115.
- [36] A. Kilian, D. D. Bowtell, H. E. Abud, G. R. Hime, D. J. Venter, P. K. Keese, E. L. Duncan, R. E. Reddel, R. A. Jefferson, *Hum. Mol. Genet.* **1997**, 6, 2011–2019.
- [37] J. Nakayama, H. Tahara, E. Tahara, M. Saito, K. Ito, H. Nakamura, T. Nakanishi, E. Tahara, T. Ide, F. Ishikawa, *Nat. Genet.* **1998**, 18, 65–68.
- [38] T. M. Bryan, J. M. Sperger, K. B. Chapman, T. R. Cech, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 8479–8484.
- [39] K. Collins, L. Gandhi, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 8485–8490.
- [40] R. A. Greenberg, R. C. Allsopp, L. Chin, G. B. Morin, R. A. DePinho, *Oncogene* **1998**, 16, 1723–1730.
- [41] K. Oguchi, H. Liu, K. Tamura, H. Takahashi, *FEBS Lett.* **1999**, 457, 465–469.
- [42] S. L. Weinrich, R. Pruzan, L. Ma, M. Ouellette, V. M. Tesmer, S. E. Holt, A. G. Bodnar, S. Lichtsteiner, N. W. Kim, J. B. Trager, R. D. Taylor, R. Carlos, W. H. Andrews, W. E. Wright, J. W. Shay, C. B. Harley, G. B. Morin, *Nat. Genet.* **1997**, 17, 498–502.
- [43] T. M. Nakamura, T. R. Cech, *Cell* **1998**, 92, 587–590.
- [44] T. H. Eickbush, *Science* **1997**, 277, 911–912.
- [45] K. Friedman, T. R. Cech, *Genes Dev.* **1999**, 13, 2863–2874.
- [46] C. I. Nugent, V. Lundblad, *Genes Dev.* **1998**, 12, 1073–1085.
- [47] T. M. Bryan, T. R. Cech, *Curr. Opin. Cell Biol.* **1999**, 11, 318–324.
- [48] K. Collins, R. Kobayashi, C. W. Greider, *Cell* **1995**, 81, 677–686.
- [49] L. Harrington, T. McPhail, V. Mar, W. Zhou, R. Oulton, M. B. Bass, I. Arruda, M. O. Robinson, *Science* **1997**, 275, 973–977.
- [50] J. Nakayama, M. Saito, H. Nakamura, A. Matsuura, F. Ishikawa, *Cell* **1997**, 88, 875–884.
- [51] V. Virta-Pearlman, D. K. Morris, V. Lundblad, *Genes Dev.* **1996**, 10, 3094–3104.
- [52] a) C. Strahl, E. H. Blackburn, *Nucleic Acids Res.* **1994**, 22, 893–900; b) C. Strahl, E. H. Blackburn, *Mol. Cell. Biol.* **1996**, 16, 53–65.
- [53] A. E. Pitts, D. R. Corey, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 11549–11554.
- [54] a) J. Wang, L. Y. Xie, S. Allan, D. Beach, G. J. Hannon, *Genes Dev.* **1998**, 12, 1769–1774; b) K.-J. Wu, C. Grandori, M. Amacker, N. Simon-Vermot, A. Polack, J. Lingner, R. Dalla-Favera, *Nat. Genet.* **1999**, 21, 220–224.
- [55] S. E. Holt, D. L. Aisner, J. Baur, V. M. Tesmer, M. Dy, M. Ouellette, J. B. Trager, G. B. Morin, D. O. Toft, J. W. Shay, W. E. Wright, M. A. White, *Genes Dev.* **1999**, 13, 817–826.
- [56] a) J. R. Williamson, M. K. Raghuraman, T. R. Cech, *Cell* **1989**, 59, 871–880; b) W. I. Sundquist, A. Klug, *Nature* **1989**, 342, 825–829; c) Y. Wang, D. J. Patel, *Structure* **1993**, 1, 263–282.
- [57] A. M. Zahler, J. R. Williamson, T. R. Cech, D. M. Prescott, *Nature* **1991**, 350, 718–720.
- [58] a) D. Sun, B. Thompson, B. E. Cathers, M. Salazar, S. M. Kerwin, J. O. Trent, T. C. Jenkins, S. Neidle, L. H. Hurley, *J. Med. Chem.* **1997**, 40, 2113–2116; b) H. Han, C. L. Cliff, L. H. Hurley, *Biochemistry* **1999**, 38, 6981–6986.
- [59] T. M. Bryan, A. Englezou, L. Dalla-Pozza, M. A. Dunham, R. R. Reddel, *Nat. Med.* **1997**, 3, 1271–1274.
- [60] a) X. Zhang, V. Mar, W. Zhou, L. Harrington, M. O. Robinson, *Genes Dev.* **1999**, 13, 2388–2399; b) W. C. Hahn, S. A. Stewart, M. W. Brooks, S. G. York, E. N. Eaton, A. Kurachi, R. L. Beijersbergen, J. H. M. Knoll, M. Meyerson, R. A. Weinberg, *Nat. Genet.* **1999**, 5, 1164–1170.
- [61] K. Collins, C. W. Greider, *Genes Dev.* **1993**, 7, 1364–1376.
- [62] P. W. Hammond, T. R. Cech, *Biochemistry* **1998**, 37, 5162–5172.
- [63] C. M. Joyce, T. A. Steitz, *Annu. Rev. Biochem.* **1994**, 63, 777–822.
- [64] T. R. Cech, J. Lingner, *Ciba Found. Symp.* **1997**, 211, 20–34.

The Art and Science of Total Synthesis



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The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century**

K. C. Nicolaou,* Dionisios Vourloumis, Nicolas Winssinger, and Phil S. Baran

Dedicated to Professor E. J. Corey for his outstanding contributions to organic synthesis

At the dawn of the twenty-first century, the state of the art and science of total synthesis is as healthy and vigorous as ever. The birth of this exhilarating, multifaceted, and boundless science is marked by Wöhler's synthesis of urea in 1828. This milestone event—as trivial as it may seem by today's standards—contributed to a “demystification of nature” and illuminated the entrance to a path which subsequently led to great heights and countless rich dividends for humankind. Being both a precise science and a fine art, this discipline has been driven by the constant flow of beautiful molecular architectures from nature and serves as the engine that drives the more general field of organic synthesis forward. Organic synthesis is considered, to a large extent, to be responsible for some

of the most exciting and important discoveries of the twentieth century in chemistry, biology, and medicine, and continues to fuel the drug discovery and development process with myriad processes and compounds for new biomedical breakthroughs and applications. In this review, we will chronicle the past, evaluate the present, and project to the future of the art and science of total synthesis. The gradual sharpening of this tool is demonstrated by considering its history along the lines of pre-World War II, the Woodward and Corey eras, and the 1990s, and by accounting major accomplishments along the way. Today, natural product total synthesis is associated with prudent and tasteful selection of challenging and preferably biologically important target molecules; the dis-

covery and invention of new synthetic strategies and technologies; and explorations in chemical biology through molecular design and mechanistic studies. Future strides in the field are likely to be aided by advances in the isolation and characterization of novel molecular targets from nature, the availability of new reagents and synthetic methods, and information and automation technologies. Such advances are destined to bring the power of organic synthesis closer to, or even beyond, the boundaries defined by nature, which, at present, and despite our many advantages, still look so far away.

Keywords: drug research • natural products • synthetic methods • total synthesis

1. Prologue

“Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

In our days, the chemistry of natural products attracts a very lively interest. New substances, more or less complicated,

more or less useful, are constantly discovered and investigated. For the determination of the structure, the architecture of the molecule, we have today very powerful tools, often borrowed from Physical Chemistry. The organic chemists of the year 1900 would have been greatly amazed if they had heard of the methods now at hand. However, one cannot say that the work is easier; the steadily improving methods make it possible to attack more and more difficult problems and the ability of Nature to build up complicated substances has, as it seems, no limits.

In the course of the investigation of a complicated substance, the investigator is sooner or later confronted by the problem of synthesis, of the preparation of the substance by chemical methods. He can have various motives. Perhaps he wants to check the correctness of the structure he has found. Perhaps he wants to improve our knowledge of the reactions and the chemical properties of the molecule. If the

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[**] A list of abbreviations can be found at the end of the article.

substance is of practical importance, he may hope that the synthetic compound will be less expensive or more easily accessible than the natural product. It can also be desirable to modify some details in the molecular structure. An antibiotic substance of medical importance is often first isolated from a microorganism, perhaps a mould or a germ. There ought to exist a number of related compounds with similar effects; they may be more or less potent, some may perhaps have undesirable secondary effects. It is by no means, or even probable, that the compound produced by the microorganism—most likely as a weapon in the struggle for existence—is the very best from the medicinal point of view. If it is possible to synthesize the compound, it will also be possible to modify the details of the structure and to find the most effective remedies.

The synthesis of a complicated molecule is, however, a very difficult task; every group, every atom must be placed in its proper position and this should be taken in its most literal sense. It is sometimes said that organic synthesis is at the same time an exact science and a fine art. Here nature is the uncontested master, but I dare say that the prize-winner of this year, Professor Woodward, is a good second.”^[1]

With these elegant words Professor A. Fredga, a member of the Nobel Prize Committee for Chemistry of the Royal Swedish Academy of Sciences, proceeded to introduce R. B. Woodward at the Nobel ceremonies in 1965, the year in which Woodward received the prize for the art of organic synthesis. Twenty-five years later Professor S. Gronowitz, then a member of the Nobel Prize Committee for Chemistry, concluded



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Dionisios Vourloumis, born in 1966 in Athens, Greece, received his B.Sc. degree from the University of Athens and his Ph.D. from West Virginia University under the direction of Professor P. A. Magriotis, in 1994, working on the synthesis of novel enediyne antibiotics. He joined Professor K. C. Nicolaou's group in 1996, and was involved in the total synthesis of epothilones A and B, eleutherobin, sarcodictyins A and B, and analogues thereof. He joined Glaxo Wellcome in early 1999 and is currently working with the Combichem Technology Team in Research Triangle Park, North Carolina.

Nicolas Winssinger was born in Belgium in 1970. He received his B.Sc. degree in chemistry from Tufts University after conducting research in the laboratory of Professor M. D'Alarcao. Before joining The Scripps Research Institute as a graduate student in chemistry in 1995, he worked for two years under the direction of Dr. M. P. Pavia at Sphinx Pharmaceuticals in the area of molecular diversity focusing on combinatorial chemistry. At Scripps, he joined the laboratory of Professor K. C. Nicolaou, where he has been working on methodologies for solid-phase chemistry and combinatorial synthesis. His research interests include natural products synthesis, molecular diversity, molecular evolution, and their application to chemical biology.

Phil S. Baran was born in Denville, New Jersey in 1977. He received his B.Sc. degree in chemistry from New York University while conducting research under the guidance of Professors D. I. Schuster and S. R. Wilson, exploring new realms in fullerene science. Upon entering The Scripps Research Institute in 1997 as a graduate student in chemistry, he joined the laboratory of Professor K. C. Nicolaou where he embarked on the total synthesis of the CP molecules. His primary research interest involves natural product synthesis as an enabling endeavor for the discovery of new fundamental processes and concepts in chemistry and their application to chemical biology.

his introduction of E. J. Corey, the 1990 Nobel prize winner, with the following words:

“...Corey has thus been awarded with the Prize for three intimately connected contributions, which form a whole. Through retrosynthetic analysis and introduction of new synthetic reactions, he has succeeded in preparing biologically important natural products, previously thought impossible to achieve. Corey’s contributions have turned the art of synthesis into a science...”^[2]

This description and praise for total synthesis resonates today with equal validity and appeal; most likely, it will be valid for some time to come. Indeed, unlike many one-time discoveries or inventions, the endeavor of total synthesis^[3–6] is in a constant state of effervescence and flux. It has been on the move and center stage throughout the twentieth century and continues to provide fertile ground for new discoveries and inventions. Its central role and importance within chemistry will undoubtedly ensure its present preeminence into the future. The practice of total synthesis demands the following virtues from, and cultivates the best in, those who practice it: ingenuity, artistic taste, experimental skill, persistence, and character. In turn, the practitioner is often rewarded with discoveries and inventions that impact, in major ways, not only other areas of chemistry, but most significantly material science, biology, and medicine. The harvest of chemical synthesis touches upon our everyday lives in myriad ways: medicines, high-tech materials for computers, communication and transportation equipment, nutritional products, vitamins, cosmetics, plastics, clothing, and tools for biology and physics.^[7]

But why is it that total synthesis has such a lasting value as a discipline within chemistry? There must be several reasons for this phenomenon. To be sure, its dual nature as a precise science and a fine art provides excitement and rewards of rare heights. Most significantly, the discipline is continually being challenged by new structural types isolated from nature’s seemingly unlimited library of molecular architectures. Happily, the practice of total synthesis is being enriched constantly by new tools such as new reagents and catalysts as well as analytical instrumentation for the rapid purification and characterization of compounds.

Thus, the original goal of total synthesis during the first part of the twentieth century to confirm the structure of a natural product has been replaced slowly but surely with objectives related more to the exploration and discovery of new chemistry along the pathway to the target molecule. More recently, issues of biology have become extremely important components of programs in total synthesis. It is now clear that as we enter the twenty-first century both exploration and discovery of new chemistry and chemical biology will be facilitated by developments in total synthesis.

In this article, and following a short historical perspective of total synthesis in the nineteenth century, we will attempt to review the art and science of total synthesis during the twentieth century. This period can be divided into the pre-World War II Era, the Woodward Era, the Corey Era, and the 1990s. There are clearly overlaps in the last three eras and many more practitioners deserve credit for contributing to the evolution of the science during these periods than are

mentioned. The labeling of these eras is arbitrary—not withstanding the tremendous impact Woodward and Corey had in shaping the discipline of total synthesis during their time. As in any review of this kind, omissions are inevitable and we apologize profusely, and in advance, to those whose brilliant works were omitted as a result of space limitations.

2. Total Synthesis in the Nineteenth Century

The birth of total synthesis occurred in the nineteenth century. The first conscious total synthesis of a natural product was that of urea (Figure 1) in 1828 by Wöhler.^[8] Significantly, this event also marks the beginning of organic synthesis and

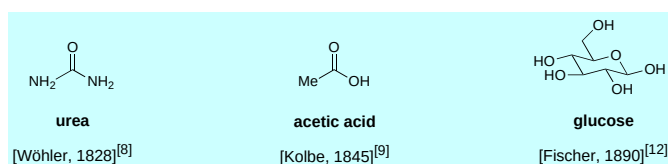


Figure 1. Selected nineteenth century landmark total syntheses of natural products.

the first instance in which an inorganic substance (NH_4CNO : ammonium cyanate) was converted into an organic substance. The synthesis of acetic acid from elemental carbon by Kolbe in 1845^[9] is the second major achievement in the history of total synthesis. It is historically significant that, in his 1845 publication, Kolbe used the word “synthesis” for the first time to describe the process of assembling a chemical compound from other substances. The total syntheses of alizarin (1869) by Graebe and Liebermann^[10] and indigo (1878) by Baeyer^[11] spurred the legendary German dye industry and represent landmark accomplishments in the field. But perhaps, after urea, the most spectacular total synthesis of the nineteenth century was that of (+)-glucose (Figure 1) by E. Fischer.^[12] This total synthesis is remarkable not only for the complexity of the target, which included, for the first time, stereochemical elements, but also for the considerable stereochemical control that accompanied it. With its oxygen-containing monocyclic structure (pyranose) and five stereogenic centers (four controllable), glucose represented the state-of-the-art in terms of target molecules at the end of the nineteenth century. E. Fischer became the second winner of the Nobel Prize for chemistry (1902), after J. H. van’t Hoff (1901).^[13]

3. Total Synthesis in the Twentieth Century

The twentieth century has been an age of enormous scientific advancement and technological progress. To be sure, we now stand at the highest point of human accomplishment in science and technology, and the twenty-first century promises to be even more revealing and rewarding. Advances

in medicine, computer science, communication, and transportation have dramatically changed the way we live and the way we interact with the world around us. An enormous amount of wealth has been created and opportunities for new enterprises abound. It is clear that at the heart of this technological revolution has been science, and one cannot deny that basic research has provided the foundation for this to occur.

Chemistry has played a central and decisive role in shaping the twentieth century. Oil, for example, has reached its potential only after chemistry allowed its analysis, fractionation, and transformation into myriad of useful products such as kerosene and other fuels. Synthetic organic chemistry is perhaps the most expressive branch of the science of chemistry in view of its creative power and unlimited scope. To appreciate its impact on modern humanity one only has to look around and recognize that this science is a pillar behind pharmaceuticals, high-tech materials, polymers, fertilizers, pesticides, cosmetics, and clothing.^[7] The engine that drives forward and sharpens our ability to create such molecules through chemical synthesis (from which we can pick and choose the most appropriate for each application) is total synthesis. In its quest to construct the most complex and challenging of nature's products, this endeavor—perhaps more than any other—becomes the prime driving force for the advancement of the art and science of organic synthesis. Thus, its value as a research discipline extends beyond providing a test for the state-of-the-art. It offers the opportunity to discover and invent new science in chemistry and related disciplines, as well as to train, in a most rigorous way, young practitioners whose expertise may feed many peripheral areas of science and technology.^[6]

3.1. The Pre-World War II Era

The syntheses of the nineteenth century were relatively simple and, with a few exceptions, were directed towards benzenoid compounds. The starting materials for these target molecules were other benzenoid compounds, chosen for their resemblance to the targeted substance and the ease by which the synthetic chemist could connect them by simple functionalization chemistry. The twentieth century was destined to bring dramatic advances in the field of total synthesis. The pre-World War II Era began with impressive strides and with increasing molecular complexity and sophistication in strategy design. Some of the most notable examples of total synthesis of this era are α -terpineol (Perkin, 1904),^[14] camphor (Komppa, 1903; Perkin, 1904),^[15] tropinone (Robinson, 1917; Willstätter, 1901),^[16–17] haemin (H. Fischer, 1929),^[18] pyridoxine hydrochloride (Folkers, 1939),^[19–20] and equilenin (Bachmann, 1939)^[21] (Figure 2). Particularly impressive were Robinson's one-step synthesis of tropinone (1917)^[16] from succindialdehyde, methylamine, and acetone dicarboxylic acid and H. Fischer's synthesis of haemin^[18] (1929). These total syntheses are among those which will be highlighted below. Both men went on to win a Nobel Prize for Chemistry (Fischer, 1929; Robinson, 1947).^[13]

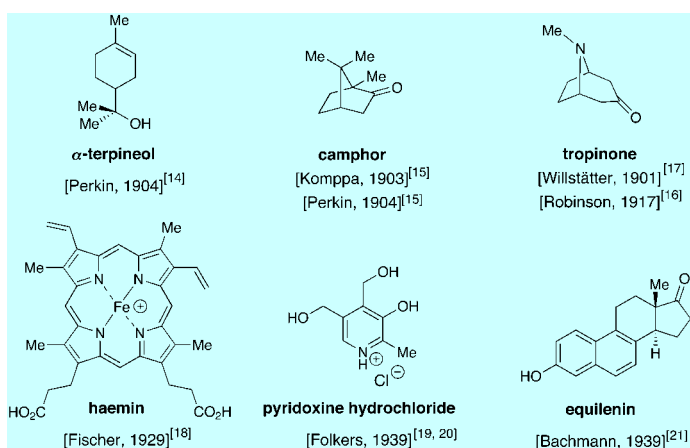


Figure 2. Selected landmark total syntheses of natural products from 1901 to 1939.

3.2. The Woodward Era

In 1937 and at the age of 20 R. B. Woodward became an assistant professor in the Department of Chemistry at Harvard University where he remained for the rest of his life. Since that time, total synthesis and organic chemistry would never be the same. A quantum leap forward was about to be taken, and total synthesis would be elevated to a powerful science and a fine art. Woodward's climactic contributions to total synthesis included the conquest of some of the most fearsome molecular architectures of the time. One after another, diverse structures of unprecedented complexity succumbed to synthesis in the face of his ingenuity and resourcefulness. The following structures (some are shown in Figure 3) are amongst his most spectacular synthetic achievements: quinine (1944),^[22] patulin (1950),^[23] cholesterol and cortisone (1951),^[24] lanosterol (1954),^[25] lysergic acid (1954),^[26] strychnine (1954),^[27] reserpine (1958),^[28] chlorophyll *a* (1960),^[29] colchicine (1965),^[286] cephalosporin C (1966),^[30] prostaglandin $F_{2\alpha}$ (1973),^[31] vitamin B₁₂ (with A. Eschenmoser) (1973),^[32] and erythromycin A (1981).^[33] Some of these accomplishments will be briefly presented in Section 3.5.

Woodward brought his towering intellect to bear on these daunting problems of the 1940s, 1950s, and 1960s with distinctive style and unprecedented glamour. His spectacular successes were often accompanied by appropriate media coverage and his lectures and seminars remained legendary for their intellectual content, precise delivery, and mesmerizing style, not to mention their colorful nature and length! What distinguished him from his predecessors was not just his powerful intellect, but the mechanistic rationale and stereochemical control he brought to the field. If Robinson introduced the curved arrow to organic chemistry (on paper), Woodward elevated it to the sharp tool that it became for teaching and mechanistic understanding, and used it to explain his science and predict the outcome of chemical reactions. He was not only a General but, most importantly, a generalist and could generalize observations into useful theories. He was master not only of the art of total synthesis, but also of structure determination, an endeavor he cherished

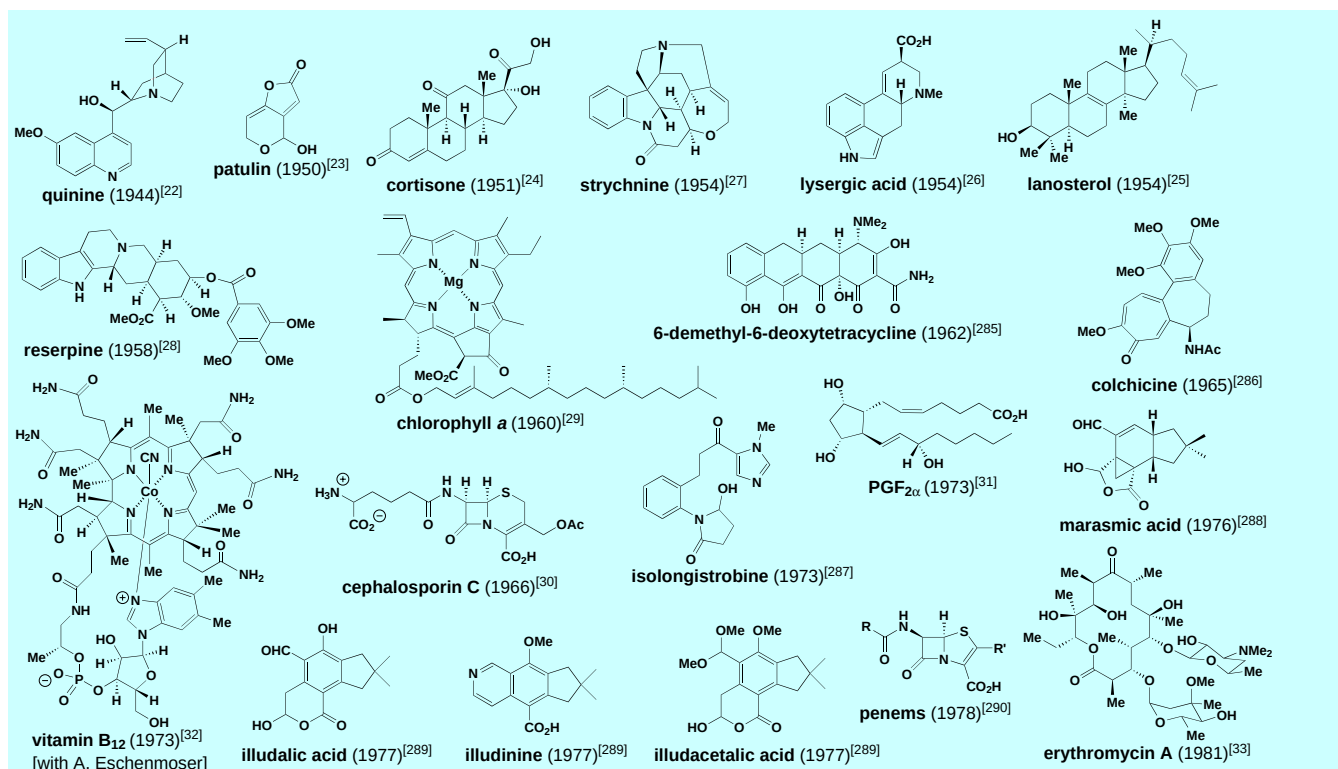


Figure 3. Selected syntheses by the Woodward Group (1944–1981).

throughout his career. He clearly influenced the careers of not only his students, but also of his peers and colleagues, for example, J. Wilkinson (sandwich structure of ferrocene), K. Block (steroid biosynthesis), R. Hoffmann (Woodward and Hoffmann rules), all of whom won the Nobel Prize for chemistry.^[13]

His brilliant use of rings to install and control stereochemical centers and to unravel functionality by rupturing them is an unmistakable feature of his syntheses. This theme appears in his first total synthesis, that of quinine,^[22] and appears over and over again as in the total synthesis of reserpine,^[28] vitamin B₁₂,^[3, 32] and, remarkably, in his last synthesis, that of erythromycin.^[33] Woodward's mark was that of an artist, treating each target individually with total mastery as he moved from one structural type to another. He exercised an amazing intuition in devising strategies toward his targets, magically connecting them to suitable starting materials through elegant, almost balletlike, maneuvers.

However, the avalanche of new natural products appearing on the scene as a consequence of the advent and development of new analytical techniques demanded a new and more systematic approach to strategy design. A new school of thought was appearing on the horizon which promised to take the field of total synthesis, and that of organic synthesis in general, to its next level of sophistication.

3.3. The Corey Era

In 1959 and at the age of 31 E. J. Corey arrived at Harvard as a full professor of chemistry from the University of Illinois,

Urbana-Champaign. His dynamism and brilliance were to make him the natural recipient of the total synthesis baton from R. B. Woodward, even though the two men overlapped for two decades at Harvard. Corey's pursuit of total synthesis was marked by two distinctive elements, retrosynthetic analysis and the development of new synthetic methods as an integral part of the endeavor, even though Woodward (consciously or unconsciously) must have been engaged in such practices. It was Corey's 1961 synthesis of longifolene^[34] that marked the official introduction of the principles of retrosynthetic analysis.^[4] He practiced and spread this concept throughout the world of total synthesis, which became a much more rational and systematic endeavor. Students could now be taught the "logic" of chemical synthesis^[4] by learning how to analyze complex target molecules and devise possible synthetic strategies for their construction. New synthetic methods are often incorporated into the synthetic schemes towards the target and the exercise of the total synthesis becomes an opportunity for the invention and discovery of new chemistry. Combining his systematic and brilliant approaches to total synthesis with the new tools of organic synthesis and analytical chemistry, Corey synthesized hundreds of natural and designed products within the thirty year period stretching between 1960 and 1990 (Figure 4)—the year of his Nobel Prize.

Corey brought a highly organized and systematic approach to the field of total synthesis by identifying unsolved and important structural types and pursuing them until they fell. The benefits and spin-offs from his endeavors were even more impressive: the theory of retrosynthetic analysis, new synthetic methods, asymmetric synthesis, mechanistic proposals, and important contributions to biology and medicine. Some of

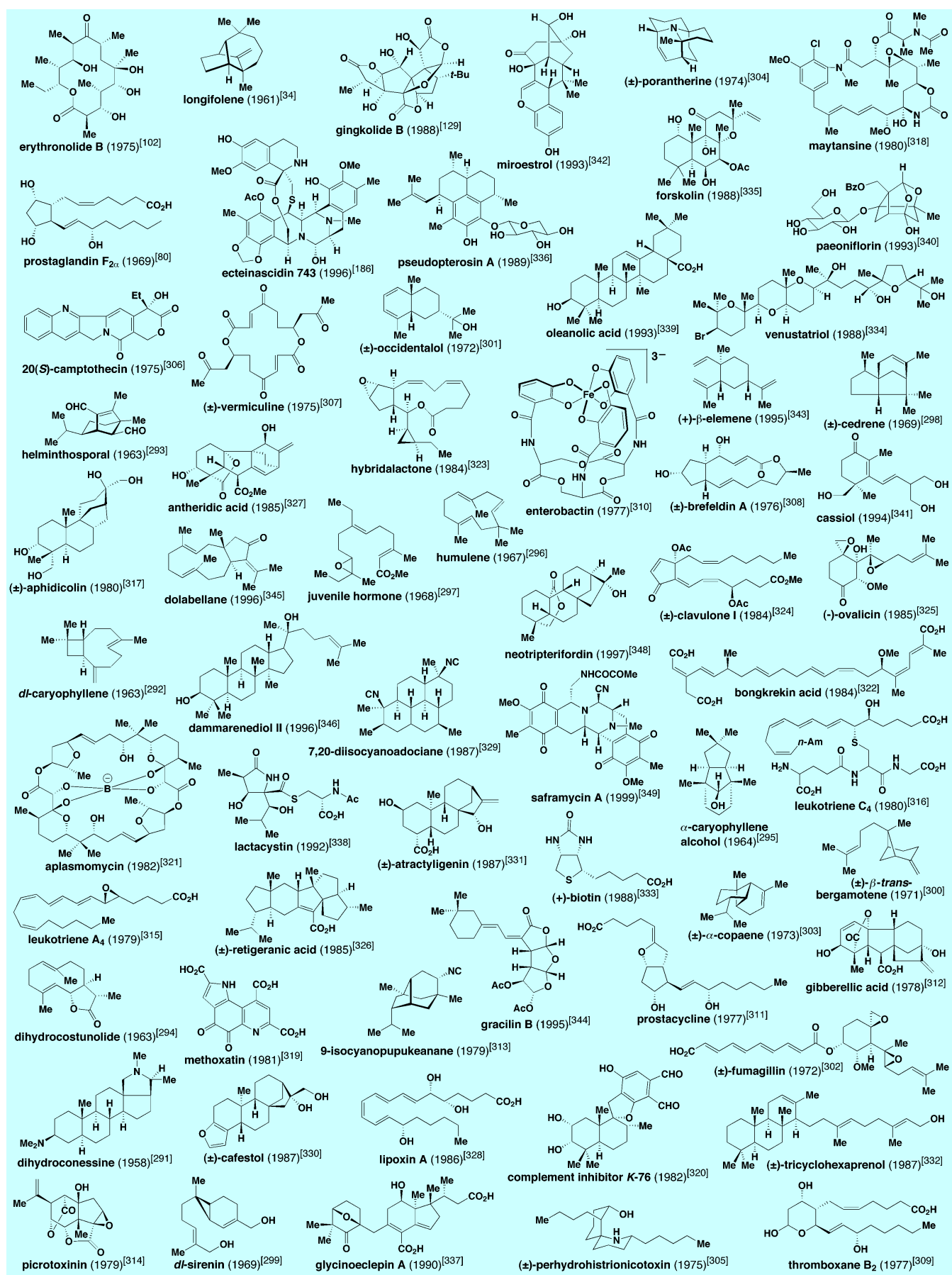


Figure 4. Selected syntheses by the Corey Group (1961–1999).

his most notable accomplishments in the field are highlighted in Section 3.5.

The period of 1950–1990 was an era during which total synthesis underwent explosive growth as evidenced by inspection of the primary chemical literature. In addition to the Woodward and Corey schools, a number of other groups contributed notably to this rich period for total synthesis^[3–5] and some continue to do so today. Indeed, throughout the second half of the twentieth century a number of great synthetic chemists made significant contributions to the field, as natural products became opportunities to initiate and focus major research programs and served as ports of entry for adventures and rewarding voyages.

Among these great chemists are G. Stork, A. Eschenmoser, and Sir D. H. R. Barton, whose sweeping contributions began with the Woodward era and spanned over half a century. The Stork–Eschenmoser hypothesis^[35] for the stereospecific course of biomimetic–cation cyclizations, such as the conversion of squalene into steroidal structures, stimulated much synthetic work (for example, the total synthesis of progesterone by W. S. Johnson, 1971).^[36] Stork's elegant total syntheses (for example, steroids, prostaglandins, tetracyclins)^[37–39] decorate beautifully the chemical literature and his useful methodologies (for example, enamine chemistry, anionic ring closures, radical chemistry, tethering devices)^[40–43] have found important and widespread use in many laboratories and industrial settings.

Similarly, Eschenmoser's beautiful total syntheses (for example, colchicine, corrins, vitamin B₁₂, designed nucleic acids)^[44–47] are often accompanied by profound mechanistic insights and synthetic designs of such admirable clarity and deep thought. His exquisite total synthesis of vitamin B₁₂ (with Woodward), in particular, is an extraordinary achievement and will always remain a classic^[3] in the annals of organic synthesis. The work of D. H. R. Barton,^[48] starting with his contributions to conformational analysis and biogenetic theory and continuing with brilliant contributions both in total synthesis and synthetic methodology, was instrumental in shaping the art and science of natural products synthesis as we know it today. Among his most significant contributions are the Barton reaction, which involves the photocleavage of nitrite esters^[49] and its application to the synthesis of aldosterone-21-acetate,^[50] and his deoxygenation reactions and related radical chemistry,^[51] which has found numerous applications in organic and natural product synthesis.

It seemed for a moment, in 1990, that the efforts of the synthetic chemists had conquered most of the known structural types of secondary metabolites: prostaglandins, steroids, β -lactams, macrolides, polyene macrolides, polyethers, alkaloids, porphyrinoids, endiandric acids, palitoxin carboxylic acid, and ginkgolide; all fell as a result of the awesome power of total synthesis. Tempted by the lure of other unexplored and promising fields, some researchers even thought that total synthesis was dead, and declared it so. They were wrong. To the astute eye, a number of challenging and beautiful architectures remained standing, daring the synthetic chemists of the time and inviting them to a feast of discovery and invention. Furthermore, several new structures were soon to be discovered from nature that offered

unprecedented challenges and opportunities. To be sure, the final decade of the twentieth century proved to be a most exciting and rewarding period in the history of total synthesis.

3.4. The 1990s Era

The climactic productivity of the 1980s in total synthesis boded well for the future of the science, and the seeds were already sown for continued breakthroughs and a new explosion of the field. Entirely new types of structures were on the minds of synthetic chemists, challenging and presenting them with new opportunities. These luring architectures included the enediynes such as calicheamicin and dynemicin, the polyether neurotoxins exemplified by brevetoxins A and B, the immunosuppressants cyclosporin, FK506, rapamycin, and sanglifehrin A, taxol and other tubulin binding agents, such as the epothilones eleutherobin and the sarcodictyins, ecteinascidin, the manzamines, the glycopeptide antibiotics such as vancomycin, the CP molecules, and everninomicin 13,384-1 (see Section 3.5).

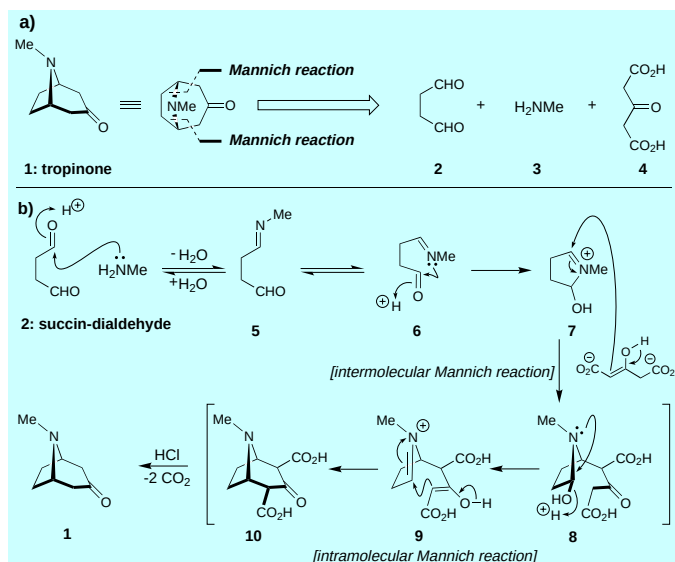
Most significantly, total synthesis assumed a more serious role in biology and medicine. The more aggressive incorporation of this new dimension to the enterprise was aided and encouraged by combinatorial chemistry and the new challenges posed by discoveries in genomics. Thus, new fields of investigation in chemical biology were established by synthetic chemists taking advantage of the novel molecular architectures and biological action of certain natural products. Besides culminating in the total synthesis of the targeted natural products, some of these new programs expanded into the development of new synthetic methods as in the past, but also into the areas of chemical biology, solid phase chemistry, and combinatorial synthesis. Synthetic chemists were moving deeper into biology, particularly as they recognized the timeliness of using their powerful tools to probe biological phenomena and make contributions to chemical and functional genomics. Biologists, in turn, realized the tremendous benefits that chemical synthesis could bring to their science and adopted it, primarily through interdisciplinary collaborations with synthetic chemists. A new philosophy for total synthesis as an important component of chemical biology began to take hold, and natural products continued to be in the center of it all. In the next section we briefly discuss a number of selected total syntheses of the twentieth century.

3.5. Selected Examples of Total Syntheses

The chemical literature of the twentieth century is adorned with beautiful total syntheses of natural products.^[3–5] We have chosen to highlight a few here as illustrative examples of structural types and synthetic strategies.

Tropinone (1917)

Perhaps the first example of a strikingly beautiful total synthesis is that of the alkaloid ($\pm$)-tropinone (**1** in Scheme 1) reported as early as 1917 by Sir R. Robinson.^[5, 16] In this elegant synthesis—called biomimetic because of its resem-



Scheme 1. a) Strategic bond disconnections and retrosynthetic analysis of (±)-tropinone and b) total synthesis (Robinson, 1917).^[16]

blance to the way nature synthesizes tropinone—Robinson utilized a tandem sequence in which one molecule of succindialdehyde, methylamine, and either acetone dicarboxylic acid (or dicarboxylate) react together to afford the natural substance in a simple one-pot procedure. Two consecutive Mannich reactions are involved in this synthesis, the first one in an inter- and the second one in an intramolecular fashion. In a way, the total synthesis of (±)-tropinone by Robinson was quite ahead of its time both in terms of elegance and logic. With this synthesis Robinson introduced aesthetics into total synthesis, and art became part of the endeavor. It was left, however, to R. B. Woodward to elevate it to the artistic status that it achieved in the 1950s and to E. J. Corey to make it into the precise science that it became in the following decades.

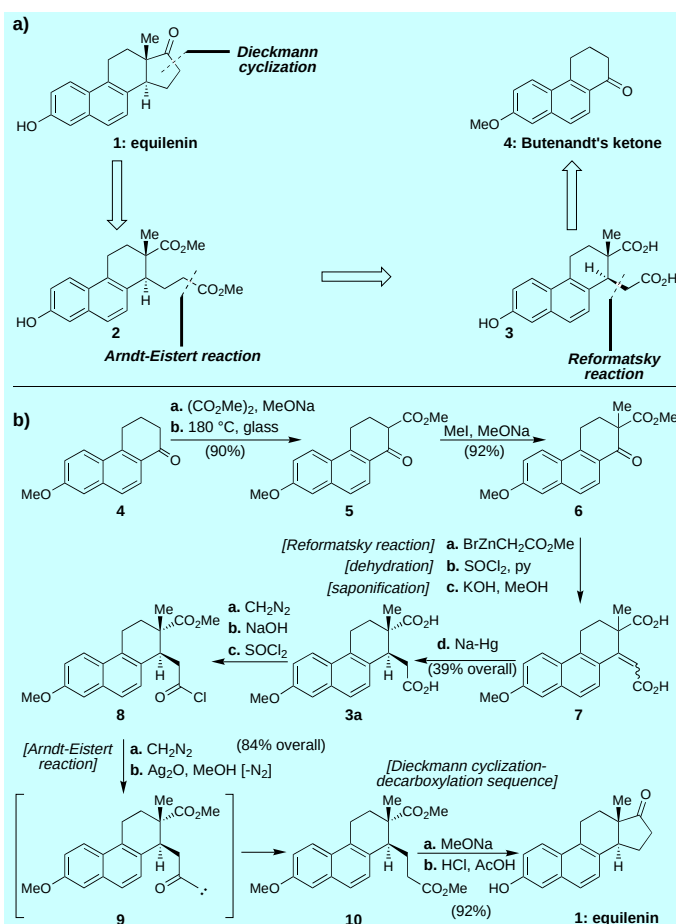
Haemin (1929)

Haemin (**1** in Scheme 2), the red pigment of blood and the carrier of oxygen within the human body, belongs to the porphyrin class of compounds. Both its structure and total synthesis were established by H. Fischer.^[5, 18] This combined program of structural determination through chemical synthesis is exemplary of the early days of total synthesis. Such practices were particularly useful for structural elucidation in the absence of today's physical methods such as NMR spectroscopy, mass spectrometry, and X-ray crystallography. In the case of haemin, the molecule was degraded into smaller fragments, which chemical synthesis confirmed to be substituted pyrroles. The assembly of the pieces by exploiting the greater nucleophilicity of pyrrole's 2-position, relative to that of the 3-position, led to haemin's framework into which the iron cation was implanted in the final step. Among the most remarkable features of Fischer's total synthesis of haemin are the fusion of the two dipyrrole components in succinic acid at 180–190 °C to form the cyclic porphyrin skeleton in a single step by two C–C bond-forming reactions, and the unusual way in which the carbonyl groups were reduced to hydroxyl groups

prior to elimination of the latter functionalities. In contrast to the rather brutal reagents and conditions used in this porphyrin's synthesis, the tools of the “trade” when Woodward faced chlorophyll *a*, approximately thirty years later, were much sharper and selective.

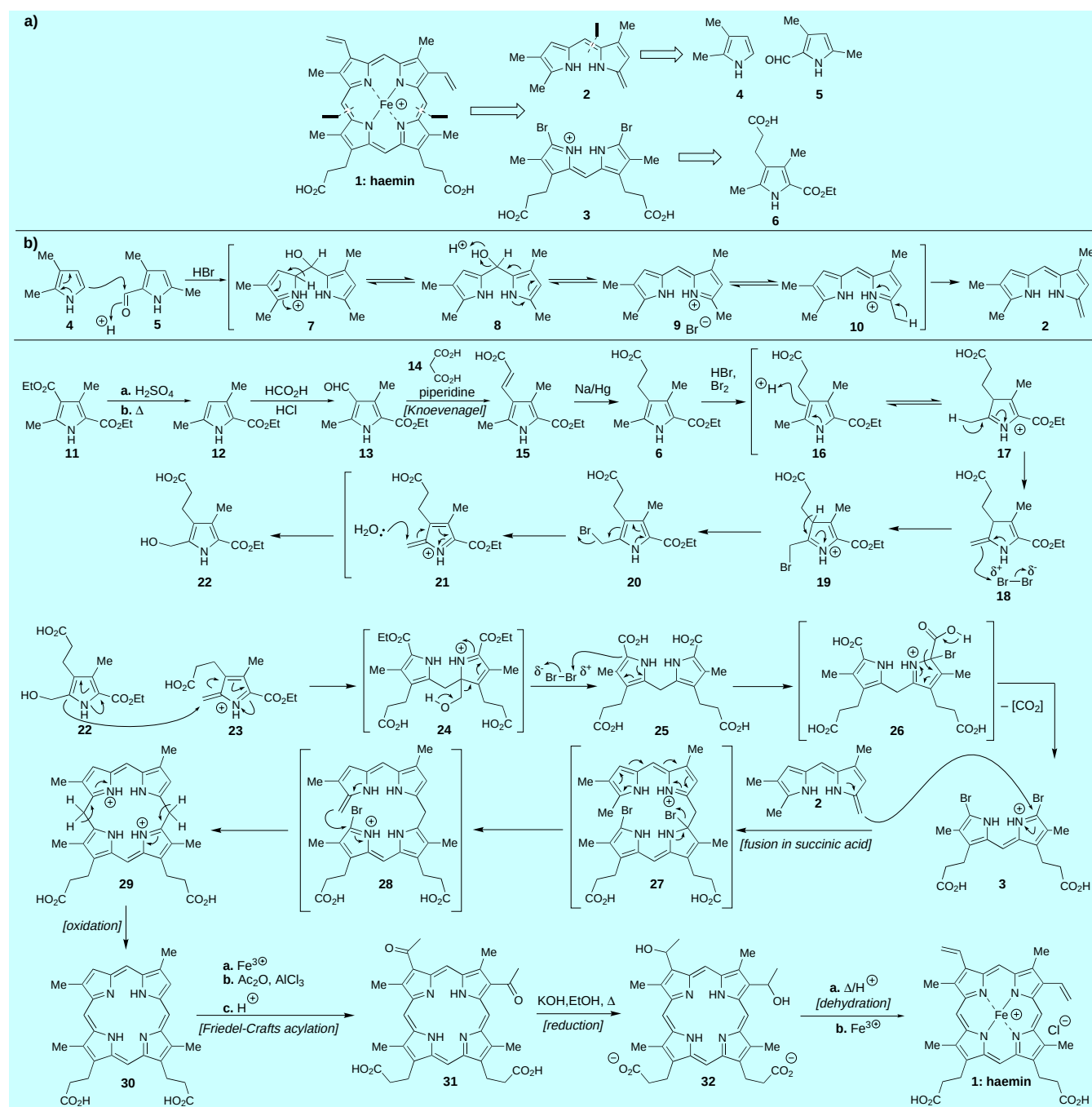
Equilenin (1939)

The first sex hormone to be constructed in the laboratory by total synthesis was equilenin (**1** in Scheme 3). The total synthesis of this first steroidal structure was accomplished in



Scheme 3. a) Strategic bond disconnections and retrosynthetic analysis of equilenin and b) total synthesis (Bachmann et al., 1939).^[21]

1939 by Bachmann and his group at the University of Michigan.^[21, 52] This synthesis featured relatively simple chemistry as characteristically pointed out by the authors: “The reactions which were used are fairly obvious ones...”^[21] Specifically, the sequence involves enolate-type chemistry, a Reformatsky reaction, a sodium amalgam reduction, an Arndt–Eistert homologation, and a Dieckmann cyclization–decarboxylation process to fuse the required cyclopentanone ring onto the pre-existing tricyclic system of the starting material. As the last pre-World War II synthesis of note, this example was destined to mark the end of an era; A new epoch was about to begin in the 1940s with R. B. Woodward and his school of chemistry at the helm.



Scheme 2. a) Strategic bond disconnections and retrosynthetic analysis of haemin and b) total synthesis (Fisher, 1929).^[18]

Before we close this era of total synthesis and enter into a new one, the following considerations might be instructive in attempting to understand the way of thinking of the pre-World War II chemists as opposed to those who followed them. The rather straightforward synthesis of equilenin is representative of the total syntheses of pre-World War II era—with the exception of Robinson's unique tropinone synthesis. In contemplating a strategy towards equilenin, Bachmann must have considered several possible starting materials before recognizing the resemblance of his target molecule to Butenand's ketone (4 in Scheme 3). After all, three of equilenin's rings are present in 4 and all he needed to do was fuse the extra ring and introduce a methyl group onto the

cyclohexane system in order to accomplish his goal. The issue of stereochemistry of the two stereocenters was probably left open to chance in contrast to the rational approaches towards such matters of the later periods. Connecting the chosen starting material 4 with the target molecule 1 was apparently obvious to Bachmann, who explicitly stated the known nature of the reactions he used to accomplish the synthesis.

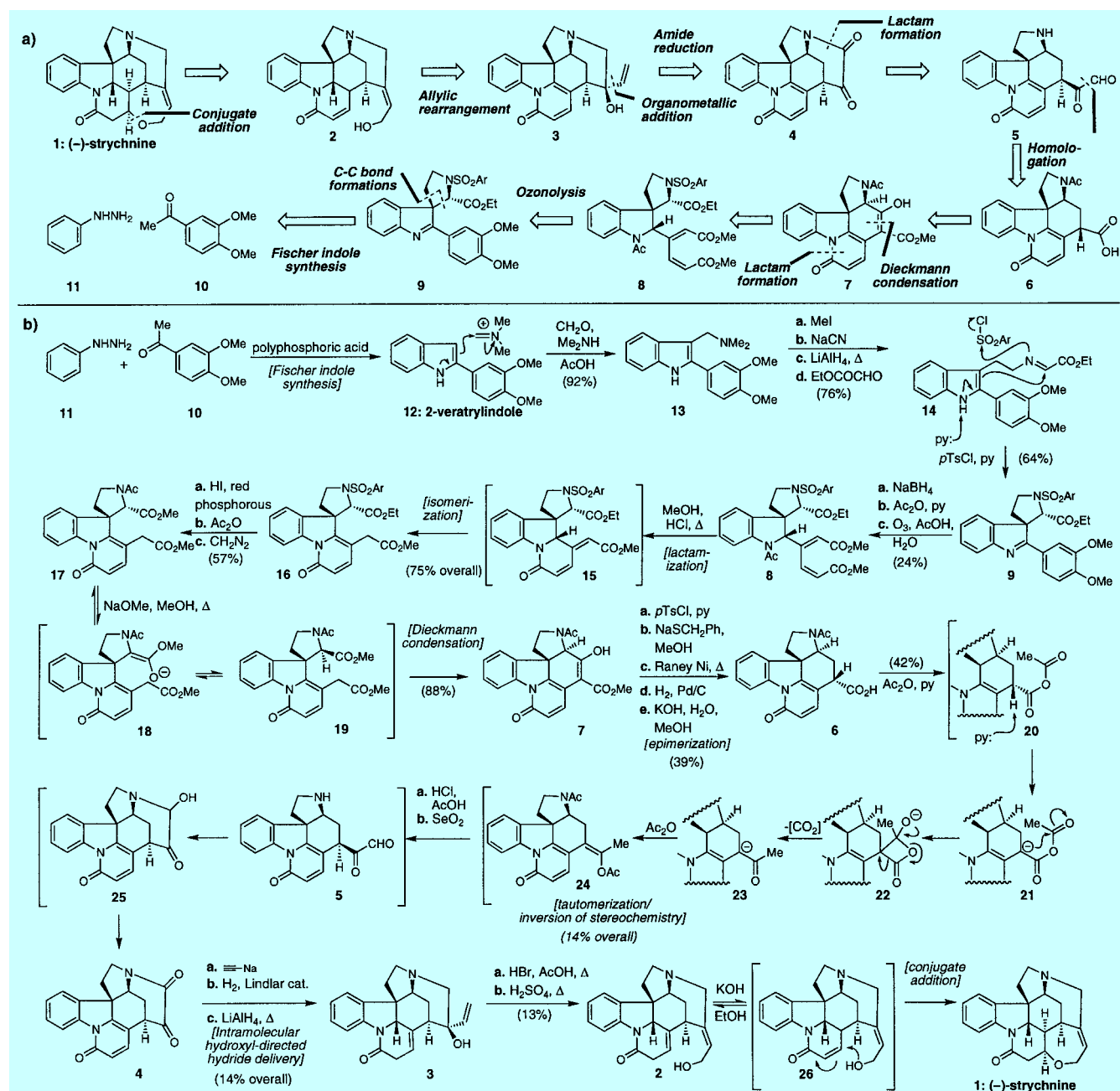
Since the motivations for total synthesis were strongly tied to the proof of structure, one needed a high degree of confidence that the proposed transformations did indeed lead to the proposed structure. Furthermore, the limited arsenal of chemical transformations did not entice much creative deviation from the most straightforward course. This high degree of

confidence that synthetic chemists had in their designed strategies was soon to decrease as the complexity of newly discovered natural products increased, thus catalyzing the development of novel strategies and new chemistry in subsequent years. In addition, advances in theoretical and mechanistic organic chemistry as well as new synthetic tools were to allow much longer sequences to be planned with a heightened measure of confidence and considerable flexibility for redesign along the way.

Strychnine (1954)

As the most notorious poison^[53] of the *Strychnos* plant species, strychnine (**1** in Scheme 4) occupied the minds of

structural chemists for a rather long time. Its gross structure was revealed in 1946^[54] and was subsequently confirmed by X-ray crystallographic analysis.^[55] In 1952, Sir Robert Robinson commented that strychnine: “For its molecular size it is the most complex substance known.”^[56] This estimation had not, apparently, escaped R. B. Woodward’s attention who had already been fully engaged in strychnine’s total synthesis. In 1948 Woodward put forth the idea that oxidative cleavage of electron-rich aromatic rings might be relevant in the biogenesis of the *strychnos* alkaloids.^[57] This provocative idea was implemented in his 1954^[27] synthesis of strychnine, which established Woodward as the undisputed master of the art at the time. The total synthesis of (–)-strychnine by Woodward (Scheme 4) ushered in a golden era of total synthesis and



Scheme 4. a) Strategic bond disconnections and retrosynthetic analysis of (–)-strychnine and b) total synthesis (Woodward et al., 1954).^[27]

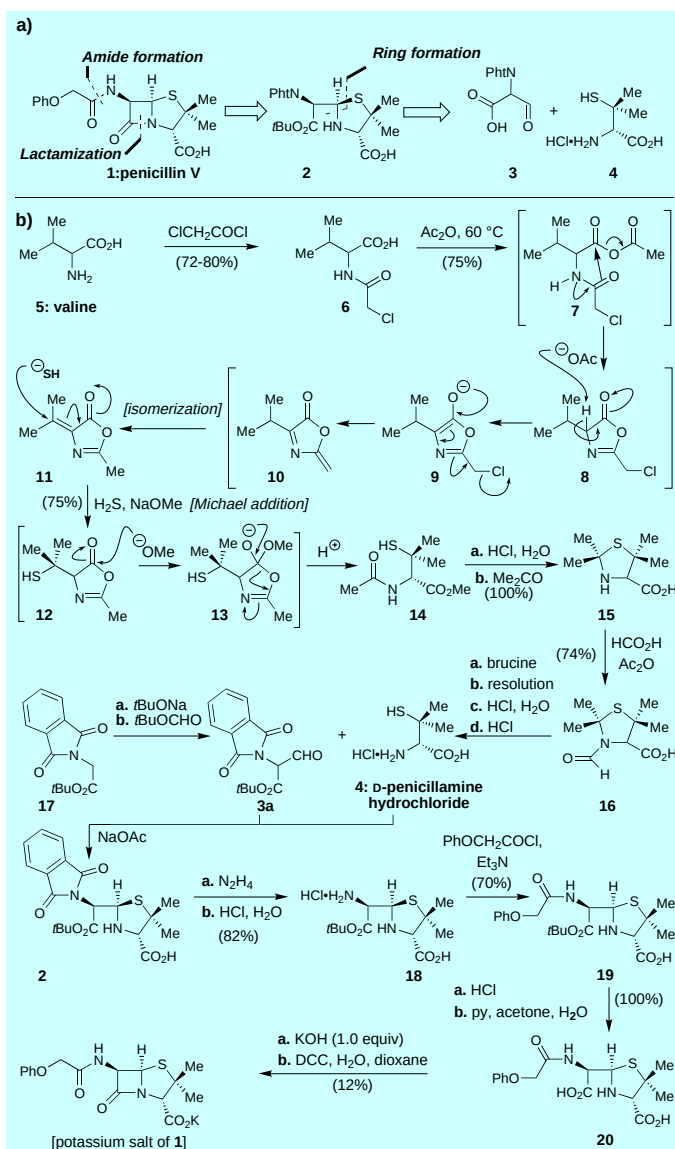
installed unprecedented confidence in, and respect for, the science of organic synthesis. Although several of its steps were beautifully designed and executed, perhaps the most striking feature is its reliance on only the simplest of reagents to carry out what seemed to be rather complex chemical transformations. With its challenging molecular structure, the molecule of strychnine continued to occupy the minds of several subsequent practitioners of the art and several other total syntheses have since appeared in the literature.^[58, 59]

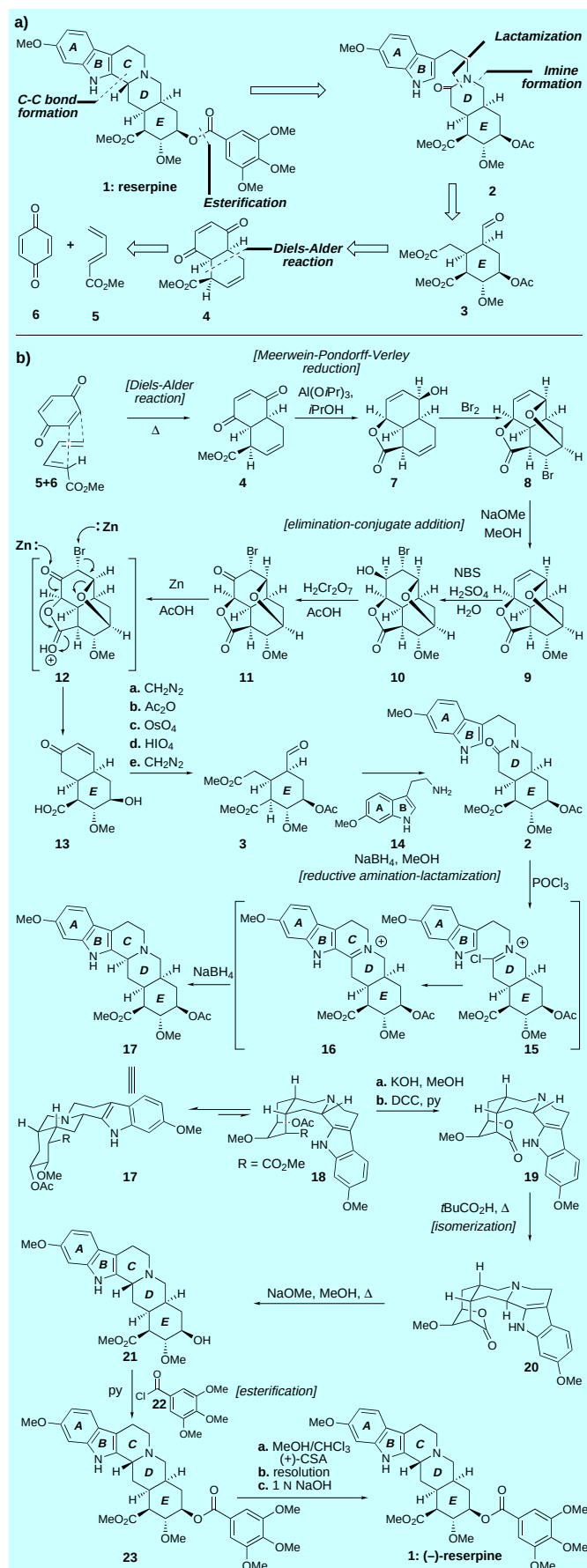
Penicillin (1957)

Few discoveries of the twentieth century can claim higher notoriety than that of penicillin (**1** in Scheme 5). Discovered in 1928 by Alexander Fleming^[60] in the secretion of the mold *Penicillium notatum*, penicillin was later shown to possess remarkable antibacterial properties by Chain and Florey.^[61] Following a massive development effort known as the Anglo–American penicillin project^[62, 63] the substance was

introduced as a drug during World War II and saved countless lives. Its molecular structure containing the unique and strained β -lactam ring was under the cloud of some controversy until Dorothy Crowfoot-Hodgkin confirmed it by X-ray crystallographic analysis.^[64]

Not surprisingly, penicillin immediately became a highly priced synthetic target attracting the attention of major players in total synthesis of the time. Finally, it was Sheehan and Henery-Logan^[65] at the Massachusetts Institute of Technology who delivered synthetic penicillin V by total synthesis of the “enchanted” molecule, as Sheehan later called it.^[66] Their synthesis, reported in 1957 and summarized in Scheme 5, was accompanied by the development of the phthalimide and *tert*-butyl ester protecting groups and the introduction of an aliphatic carbodiimide as a condensing agent to form amide bonds and—in the event—penicillin’s fragile β -lactam ring. With this milestone, another class of natural products was now open to chemical manipulation and a new chapter in total synthesis had begun.





Scheme 6. a) Strategic bond disconnections and retrosynthetic analysis of reserpine and b) total synthesis (Woodward et al., 1958).^[28]

cleverly coaxing his polycycle into an unfavorable conformation (through intramolecular tethering), which forced an isomerization to give the desired stereochemistry.

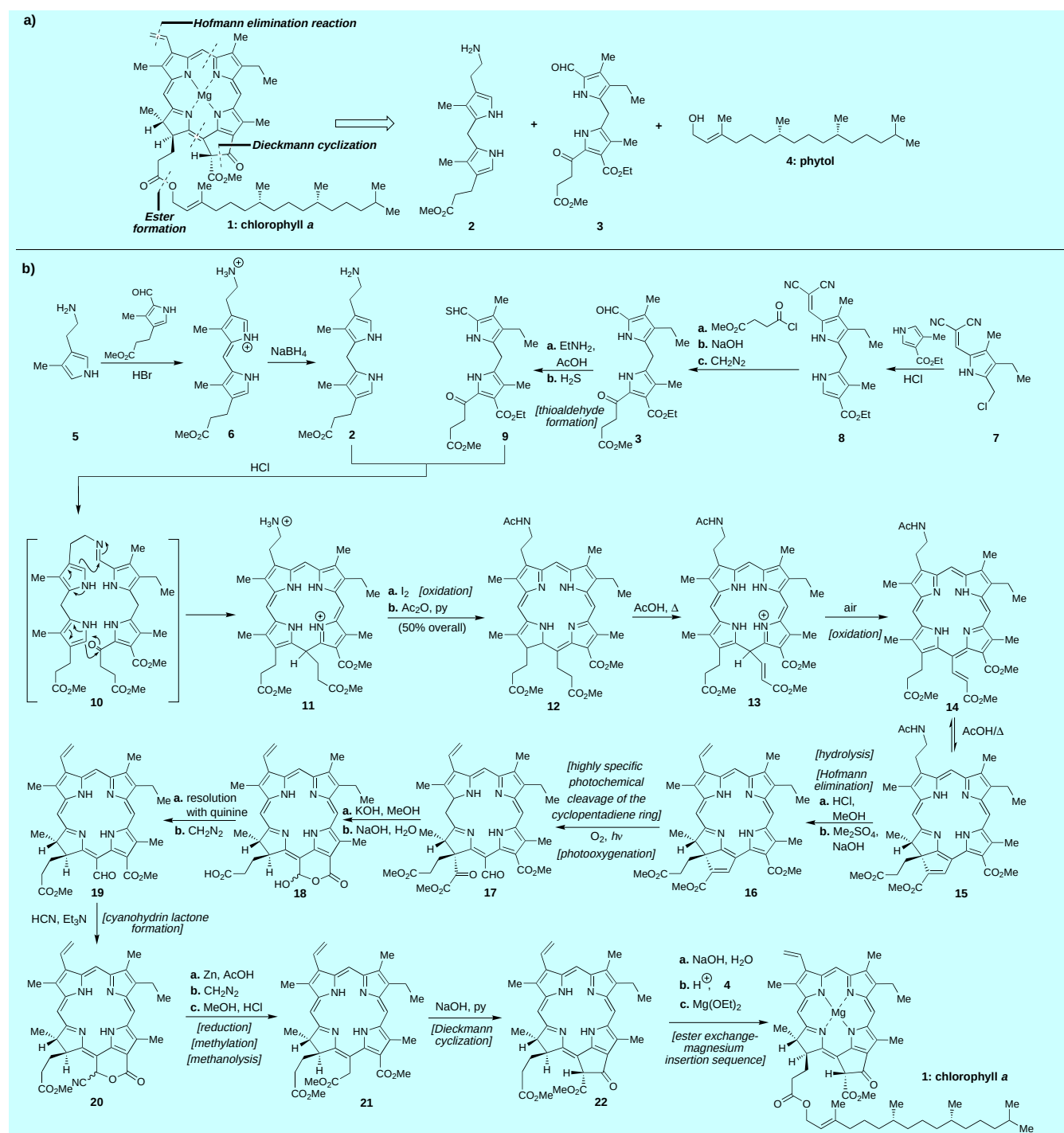
These maneuvers clearly constituted unprecedented sophistication and rational thinking in chemical synthesis design. While this rational thinking was to be further advanced and formalized by Corey's concepts on retrosynthetic analysis, the stereocontrol strategies of this era were to dominate synthetic planning for some time before being complemented and, to a large degree, eclipsed by acyclic stereoselection and asymmetric synthesis advances which emerged towards the end of the century.

Chlorophyll *a* (1960)

Chlorophyll *a* (1 in Scheme 7), the green pigment of plants and the essential molecule of photosynthesis, is distinguished from its cousin molecule haemin by the presence of two extra hydrogen atoms (and, therefore, two chiral centers) in one of its pyrrole rings, the presence of the phytol side chain, and the encapsulation of a magnesium cation rather than an iron cation. Its total synthesis by R. B. Woodward et al. in 1960^[29] represents a beautiful example of bold planning and exquisite execution. This synthesis includes improvements over Fischer's routes to porphyrin building blocks and, most importantly, a number of clever maneuvers for the installment of the three stereocenters and the extra five-membered ring residing on the periphery of the chlorin system of chlorophyll *a*. The chemical synthesis of chlorophyll *a* is a significant advance over Fischer's total synthesis of haemin,^[18] and must have given Woodward the confidence, and prepared the ground, for his daring venture towards vitamin B₁₂ in which he was to be joined by A. Eschenmoser (see p. 61).

Longifolene (1961)

The publication of the total synthesis of longifolene (1 in Scheme 8) in 1961 by Corey et al.^[34] is of historical significance in that in it Corey laid out the foundation of his systematic approach to retrosynthetic analysis. Our thinking about synthetic design has been profoundly affected and shaped by the principles of retrosynthetic analysis ever since, and the theory is sure to survive for a long time to come. Corey's longifolene synthesis^[34] exemplifies the identification and mental disconnection of strategic bonds for the purposes of simplifying the target structure. The process of retrosynthetic analysis unravels a retrosynthetic tree with possible pathways and intermediates from which the synthetic chemist can choose the most likely to succeed and/or most elegant strategies. The total synthesis of longifolene itself, shown in Scheme 8, involves a Wittig reaction, an osmium tetroxide-mediated dihydroxylation of a double bond, a ring expansion, and an intramolecular Michael-type alkylation to construct the longifolene skeleton. This synthesis remains a landmark in the evolution of the art and science of total synthesis.

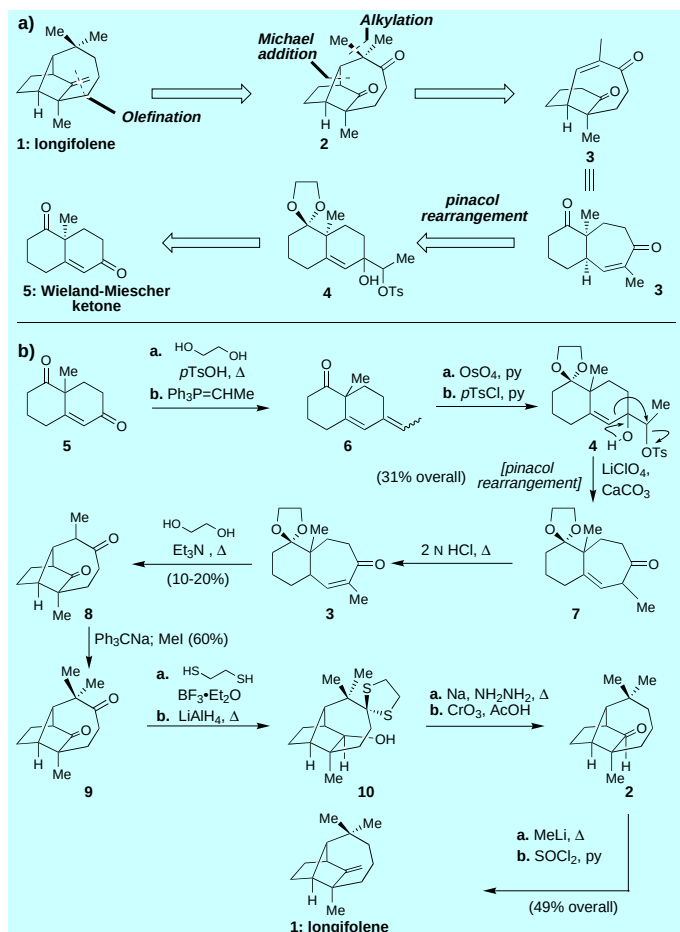


Scheme 7. a) Strategic bond disconnections and retrosynthetic analysis of chlorophyll *a* and b) total synthesis (Woodward et al., 1960).^[29] The locking of **2** and **9** together through formation of a schiff base forces the cyclization to proceed with the desired regioselectivity.

Lycopodine (1968)

Lycopodine (**1** in Scheme 9), first isolated in 1881, is the most widely distributed alkaloid from the genus *lycopodium*.^[71] In addition to the great challenge of synthesizing this novel polycyclic framework in a stereocontrolled manner, one must effectively address the challenge posed by the C13 quaternary center, which is common to all four rings. Gilbert Stork was one of the first to successfully complete the total synthesis of lycopodine.^[72] This masterfully executed synthesis

features a unique “aza-annulation” strategy which utilizes the Stork enamine methodology^[73] (a generally useful strategy to generate and trap enolates regioselectively) to construct quinolone systems, a stereospecific cationic cyclization to establish the C13 quaternary center, and a series of functional group manipulations to elaborate the resulting aromatic ring into ring D. Several syntheses of lycopodine have since appeared,^[74] each featuring a unique strategy complementary to Stork’s beautiful synthesis.

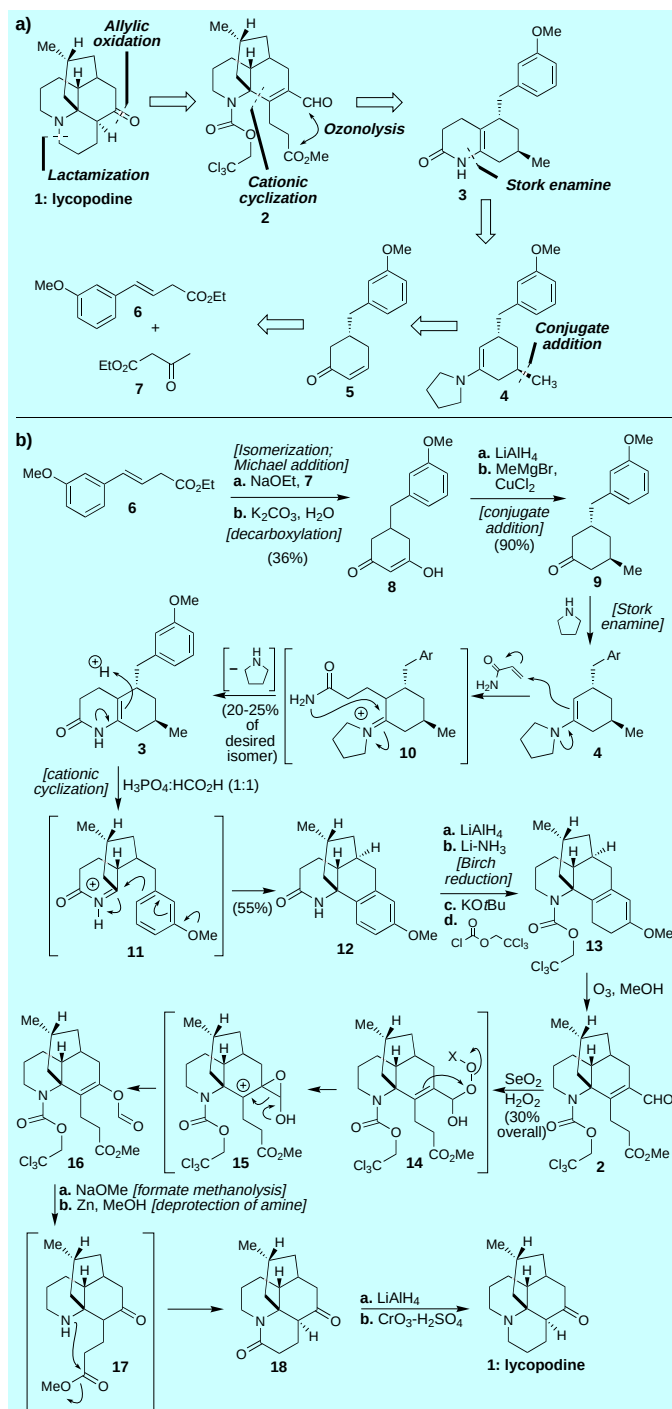


Scheme 8. a) Strategic bond disconnections and retrosynthetic analysis of longifolene and b) total synthesis (Corey et al., 1961).^[34]

Cephalosporin C (1966)

Cephalosporin C (**1** in Scheme 10) was isolated from *Cephalosporium acremonium* in the mid-1950s^[75] and was structurally elucidated by X-ray crystallographic analysis in 1961.^[76] Reminiscent of the penicillins, the cephalosporins represent the second subclass of β -lactams, several of which became legendary antibiotics in the latter part of the twentieth century. Having missed the opportunity to deliver penicillin, the Woodward group became at once interested in the synthesis of cephalosporin C and, by 1965, they completed the first total synthesis of the molecule.^[30]

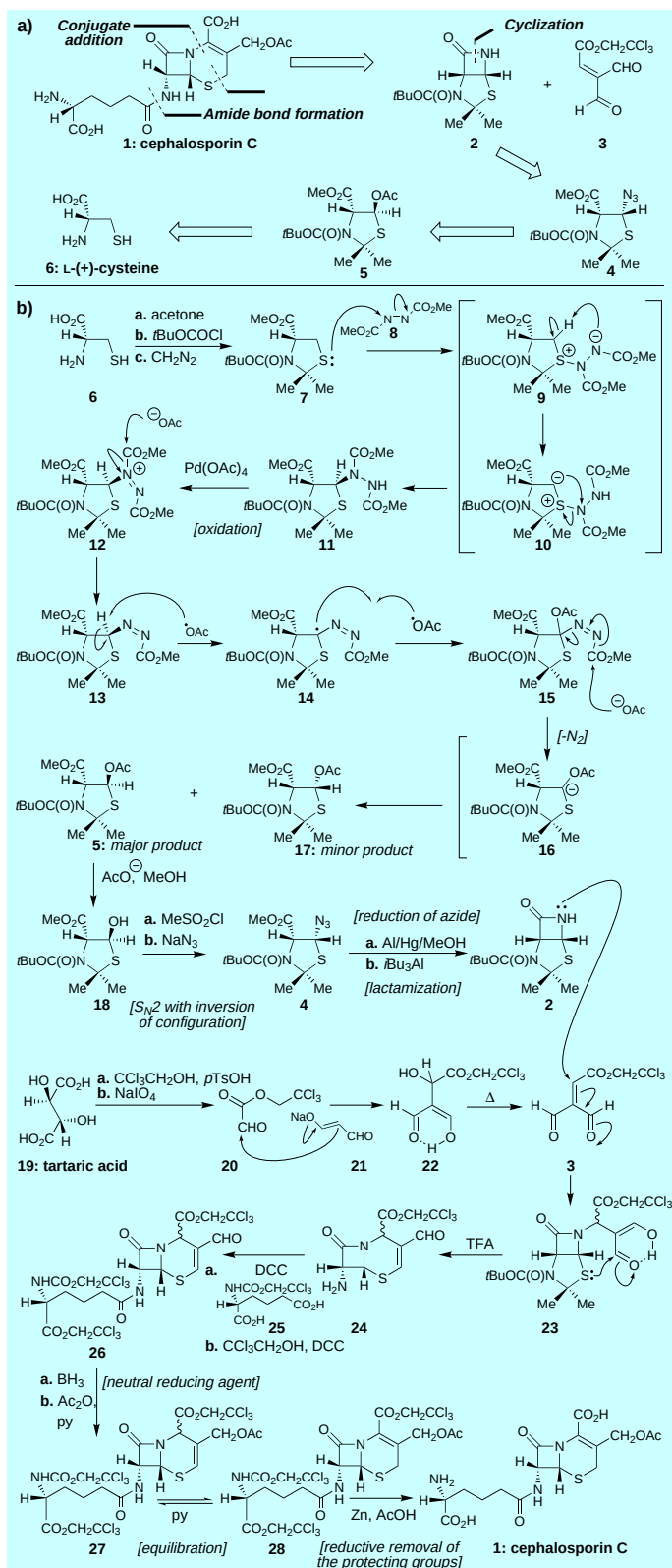
This total synthesis of cephalosporin C was the sole topic of Woodward's 1965 Nobel lecture in Stockholm. Indeed, in a move that broke tradition, R. B. Woodward described on that occasion for the first time, and in a breathtaking fashion, the elegant synthesis of cephalosporin C. Highlights of this synthesis, which is summarized in Scheme 10, include the development of the azodicarboxylate-mediated functionalization of the methylene group adjacent to the sulfur atom of L-cysteine, the aluminum-mediated closure of the aminoester to the β -lactam functionality, the brilliant formation of cephalosporin's sulfur-containing ring, and the use of the β,β,β -trichloroethoxy moiety to protect the hydroxyl group. This total synthesis stands as a milestone accomplishment in the field of natural product synthesis.



Scheme 9. a) Strategic bond disconnections and retrosynthetic analysis of (±)-lycospodine and b) total synthesis (G. Stork et al., 1968).^[72]

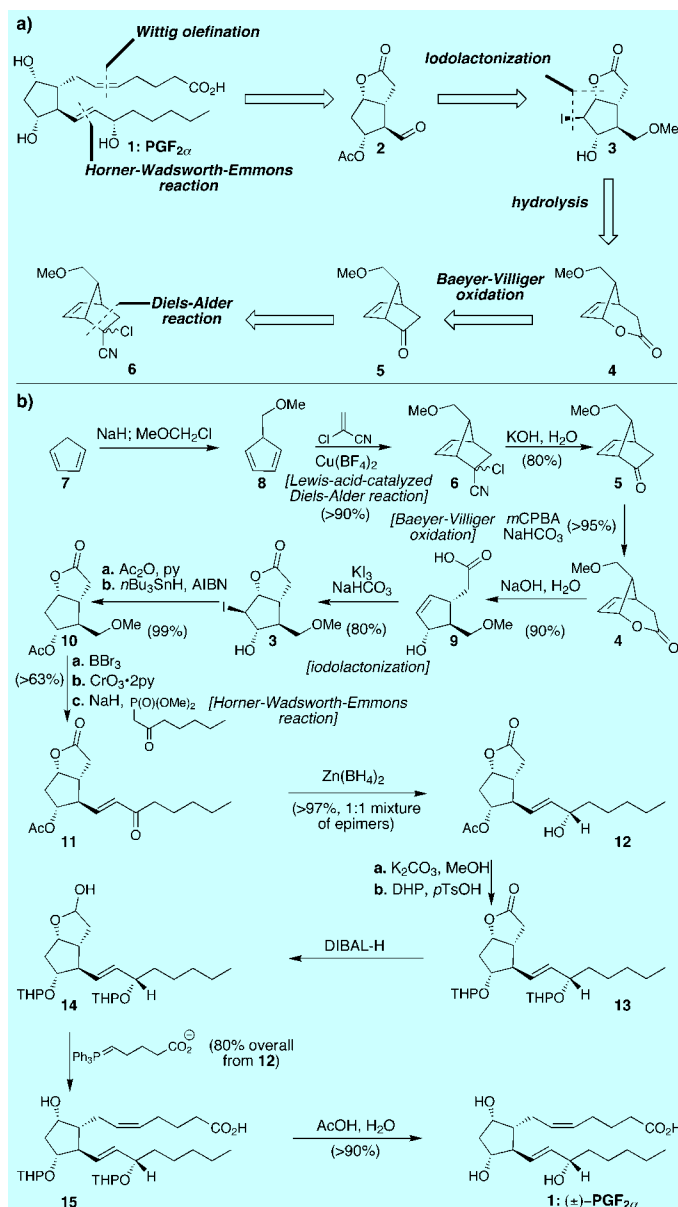
Prostaglandins $F_{2\alpha}$ and E_2 (1969)

The prostaglandins were discovered by von Euler in the 1930s^[77] and their structures became known in the mid-1960s primarily as a result of the pioneering work of Bergström and his group.^[78] With their potent and important biological activities and their potential applications in medicine,^[79] these scarce substances elicited intense efforts directed at their chemical synthesis. By 1969 Corey had devised and completed his first total synthesis of prostaglandins $F_{2\alpha}$ (**1** in Scheme 11) and E_2 .^[80] These syntheses amplified brilliantly Corey's



Scheme 10. a) Strategic bond disconnections and retrosynthetic analysis of cephalosporin C and b) total synthesis (Woodward et al., 1966).^[30]

retrosynthetic analysis concepts and demonstrated the utilization of the bicycloheptane system derived from a Diels–Alder reaction as a versatile key intermediate for the synthesis of several of the prostaglandins. A large body of



Scheme 11. a) Strategic bond disconnections and retrosynthetic analysis of (±)-PGF_{2α} and b) the total synthesis (Corey et al., 1969).^[80]

synthetic work^[81–83] followed the initial Corey synthesis and myriad prostaglandin analogues have since been synthesized, aiding both biology and medicine tremendously.

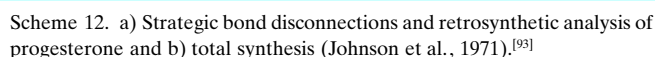
Corey's original strategy evolved alongside the impressive developments in the field of asymmetric catalysis, many of which he instigated, which culminated by the 1990s, in a refined, highly efficient and stereocontrolled synthesis of the prostaglandins.^[84] Thus, in its original version, the Corey synthesis of prostaglandins F_{2α} and E₂ was nonstereoselective and delivered the racemate and as a mixture of C15 epimers. Then, in 1975, came a major advance in the use of a chiral auxiliary to control the stereochemical outcome of the crucial Diels–Alder reaction to form the bicyclo[2.2.1]heptane system in its optically active form.^[85] The theme of chiral auxiliaries to control stereochemistry played a major role in the development of organic and natural products synthesis in the latter part of the century. In addition to the contributions

Finally came the era of catalyst design and here again the prostaglandins played a major role in providing both a driving force and a test. In a series of papers, Corey disclosed a set of chiral aluminum- and boron-based^[90, 91] catalysts for the Diels–Alder reaction (and several other reactions) that facilitated the synthesis of an enantiomerically enriched intermediate along the route to prostaglandins. And, finally, the problem of stereoselectivity at C15 was solved by the introduction of the oxazaborolidine catalyst (CBS) by Corey in 1987.^[92] These catalysts not only refined the industrial process for the production of prostaglandins, but also found uses in many other instances both in small scale laboratory operations and manufacturing processes of drug candidates and pharmaceuticals. For a more in-depth analysis of the Corey syntheses of prostaglandins F_{2α} and E₂ and other advances on asymmetric catalysis, the reader is referred to ref. [4] and other appropriate literature sources.

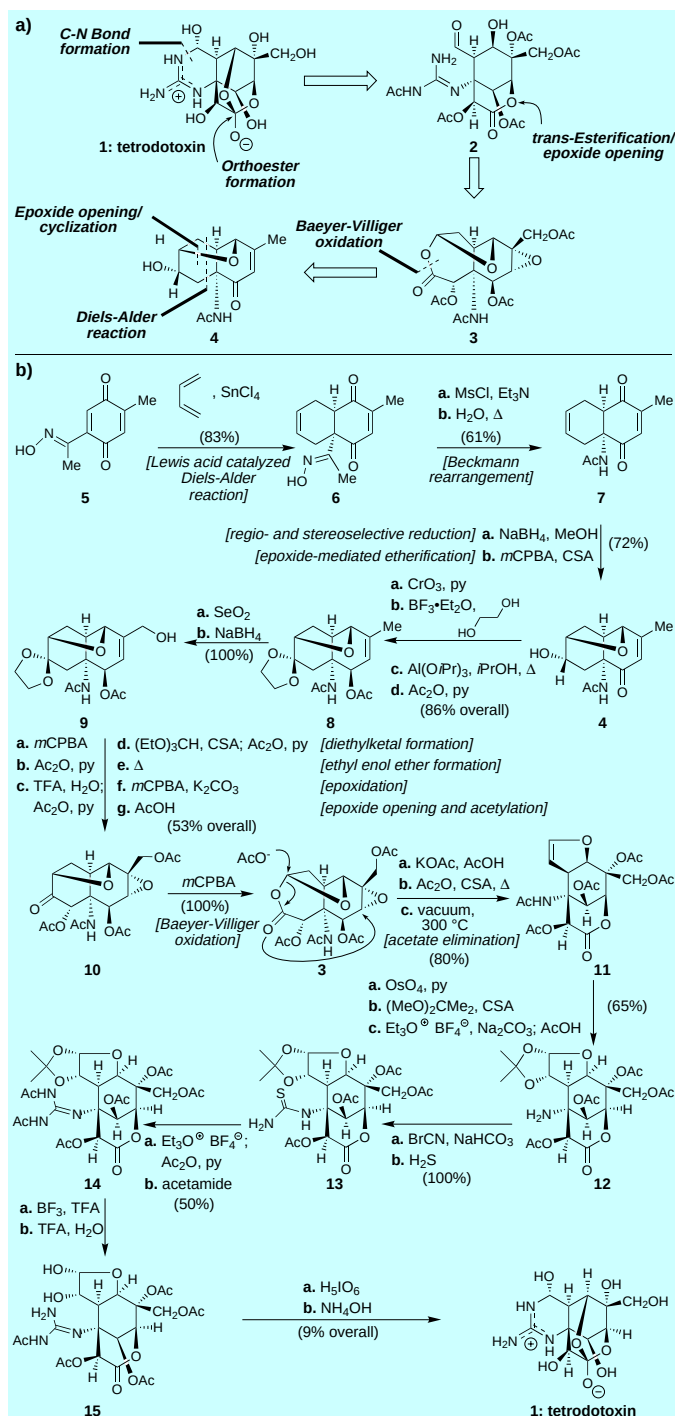
Progesterone (**1** in Scheme 12), a hormone that prepares the lining of the uterus for implantation of an ovum, is a member of the steroid class of compounds that is found ubiquitously in nature. Its linearly fused polycyclic carbon framework is characteristic of numerous natural products of steroidal or triterpenoid structures. A daring approach to progesterone's skeleton by W. S. Johnson^[93] was inspired by the elucidated enzyme-catalyzed conversion^[94] of squalene oxide into lanosterol or to the closely related plant triterpenoid dammaradienol. This biomimetic strategy was also encouraged by the Stork–Eschenmoser hypothesis, which was proposed in 1955^[35] to rationalize the stereochemical outcome of the biosynthetic transformation of squalene oxide to steroid. According to this postulate it was predicted that polyunsaturated molecules with *trans* C=C bonds, such as squalene oxide, should cyclize in a stereospecific manner, to furnish polycyclic systems with *trans,anti,trans* stereochemistry at the ring fusion.

This brilliant proposition was confirmed by W. S. Johnson and his group through the biomimetic total synthesis of progesterone (Scheme 12). A tertiary alcohol serves as the initiator of the polyolefinic ring-closing cascade, in this instance, but other groups have also been successfully employed in this regard (for example, acetal, epoxide). The methylacetylenic group performed well as a terminator of the cascade in the original work. A number of new terminating systems have since been successfully employed (for example, allyl or propargyl silanes, vinyl fluoride). The work of W. S. Johnson was complemented by that of van Tamelen^[95] and others^[3, 4] who also explored such biomimetic cascades.

Tetrodotoxin (**1** in Scheme 13) is the poisonous compound of the Japanese puffer fish and its structure was elucidated by



Woodward in 1965.^[96] By 1972 Kishi and his group had published the total synthesis^[97] of this highly unusual and challenging structure. This outstanding achievement from Japan was received at the time with great enthusiasm and remains to this day as a classic in total synthesis. The target molecule was reached through a series of maneuvers which included a Diels–Alder reaction of a quinone with butadiene, a Beckman rearrangement to install the first nitrogen atom, stereoselective reductions, strategic oxidations, unusual functional group manipulations, and, finally, construction of the guanidinium system. As a highly condensed and polyfunc-



Scheme 13. a) Strategic bond disconnections and retrosynthetic analysis of tetrodotoxin and b) total synthesis (Kishi et al., 1972).^[97]

tional molecule, tetrodotoxin was certainly a great conquest and elevated the status of both the art and the practitioner, and at the same time was quite prophetic of things to come.

Vitamin B₁₂ (1973)

The total synthesis of vitamin B₁₂ (**1** in Scheme 14), accomplished in 1973 by a collaboration between the groups of Woodward and Eschenmoser,^[3, 32] stands as a monumental achievement in the annals of synthetic organic chemistry.

Rarely before has a synthetic project yielded so much knowledge, including: novel bond-forming reactions and strategies, ingenious solutions to formidable synthetic problems, biogenetic considerations and hypotheses, and the seeds of the principles of orbital symmetry conservation known as the Woodward and Hoffmann rules.^[98] The structure of vitamin B₁₂ was revealed in 1956 through the elegant X-ray crystallographic work of Dorothy Crowfoot-Hodgkin.^[99] The escalation of molecular complexity from haemin to chlorophyll *a* to vitamin B₁₂ is interesting not only from a structural point of view, but also in that the total synthesis of each molecule reflects the limits of the power of the art and science of organic synthesis at the time of the accomplishment.

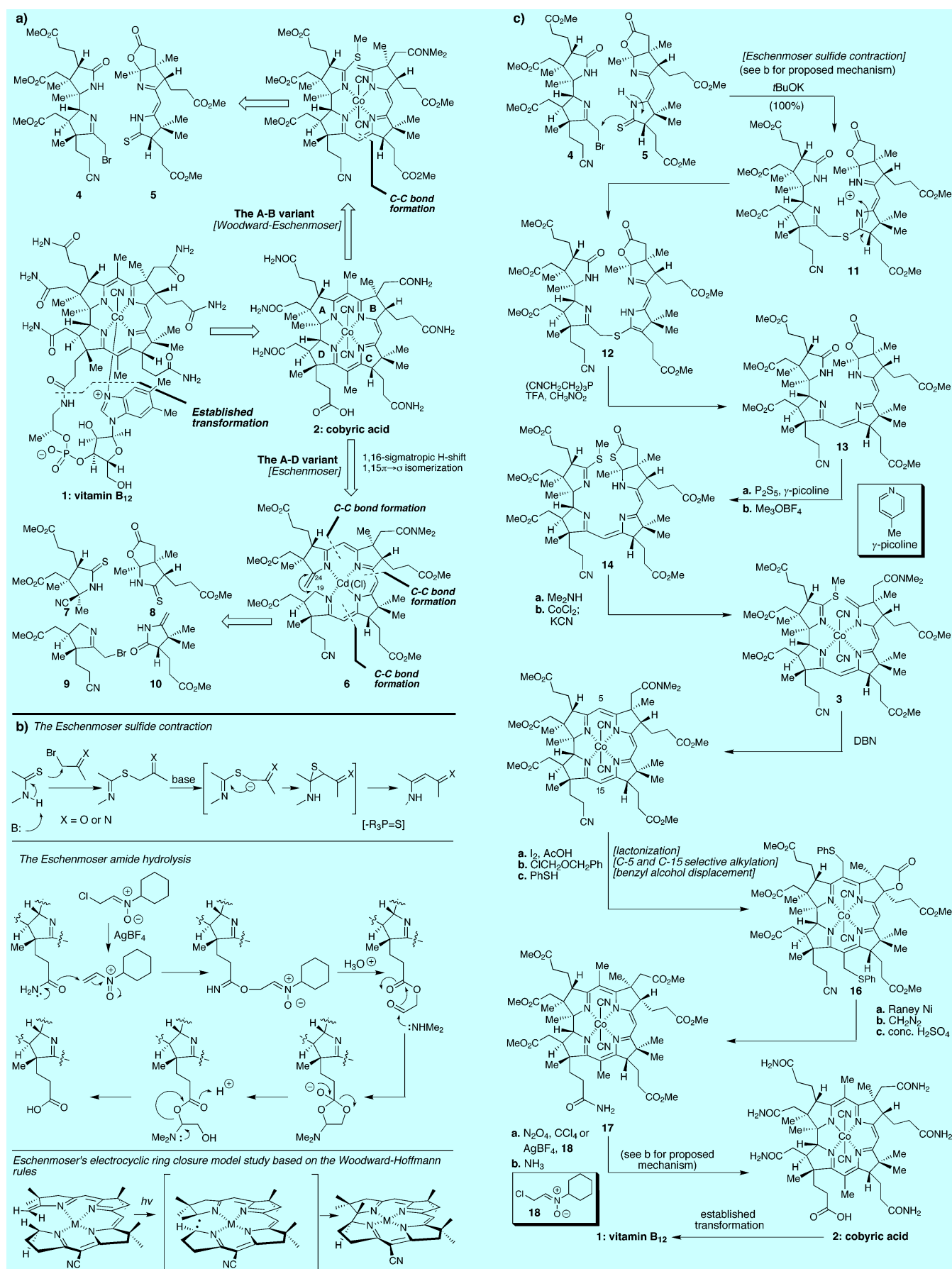
One of the most notable of the many elegant maneuvers of the Woodward–Eschenmoser synthesis of vitamin B₁₂ is the photoinduced ring closure of the corrin ring from a pre-organized linear system wrapped around a metal template, which was an exclusive achievement of the Eschenmoser group. The convergent approach defined cobyrinic acid (**2** in Scheme 14) as a landmark key intermediate, which had previously been converted into vitamin B₁₂ by Bernhauser et al.^[100] The synthesis of vitamin B₁₂ defined the frontier of research in organic natural product synthesis at that time. For an in depth discussion of this mammoth accomplishment, the reader is referred to ref. [4].

Erythronolide B (1978)

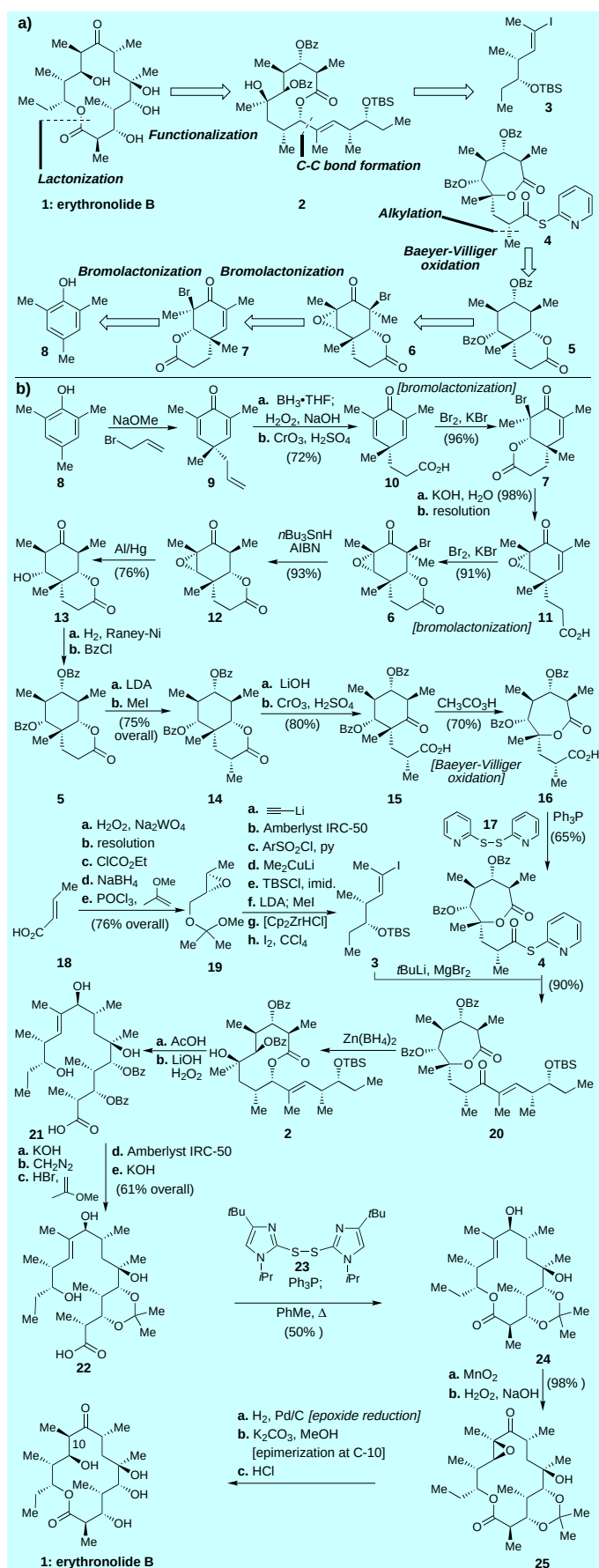
The macrolide antibiotics, of which erythromycin is perhaps the most celebrated, stood for a long time as seemingly unapproachable by chemical synthesis. The origin of the initial barriers and difficulties was encapsulated in the following statement made by Woodward in 1956, “Erythromycin, with all our advantages, looks at present hopelessly complex, particularly in view of its plethora of asymmetric centers.”^[101] In addition to the daunting stereochemical problems of erythromycin and its relatives, also pending was the issue of forming the macrocyclic ring. These challenges gave impetus to the development of new synthetic technologies and strategies to address the stereocontrol and macrocyclization problems.

The brilliant total synthesis of erythronolide B^[102] (**1** in Scheme 15), the aglycon of erythromycin B, by Corey et al. published in 1979, symbolizes the fall of this class of natural products in the face of the newly acquired power of organic synthesis. Additionally, it provides further illustration of the classical strategy for the setting of stereocenters on cyclic templates. The synthesis began with a symmetrical cyclohexane ring through a short sequence of reactions in which two bromolactonizations played important roles. A crucial Baeyer–Villiger reaction then completed the oxygenated stereocenter at C6 and rendered the cyclic system cleavable to an open chain for further elaboration.

As was the case in many of Corey’s syntheses, the total synthesis of erythronolide B was preceded by the invention of a new method, namely the double activation procedure for the formation of macrocyclic lactones employing 2-pyridinethiol esters.^[103] This landmark invention allowed the synthesis of



Scheme 14. a) Strategic bond disconnections and retrosynthetic analysis of (–)-vitamin B₁₂, b) key synthetic methodologies developed in the course of the total synthesis, c) and final synthetic steps in the Woodward-Eschenmoser total synthesis of vitamin B₁₂ (Woodward–Eschenmoser, 1973).^[32]



Scheme 15. a) Strategic bond disconnections and retrosynthetic analysis of erythronolide B and b) total synthesis (Corey et al., 1978).^[102]

several macrolides including erythronolide B and, most significantly, catalyzed the development of several improvements and other new methods for addressing the macrocyclization problem.^[104] Soon to follow Corey's synthesis of erythronolide B was Woodward's total synthesis of erythromycin A.^[33]

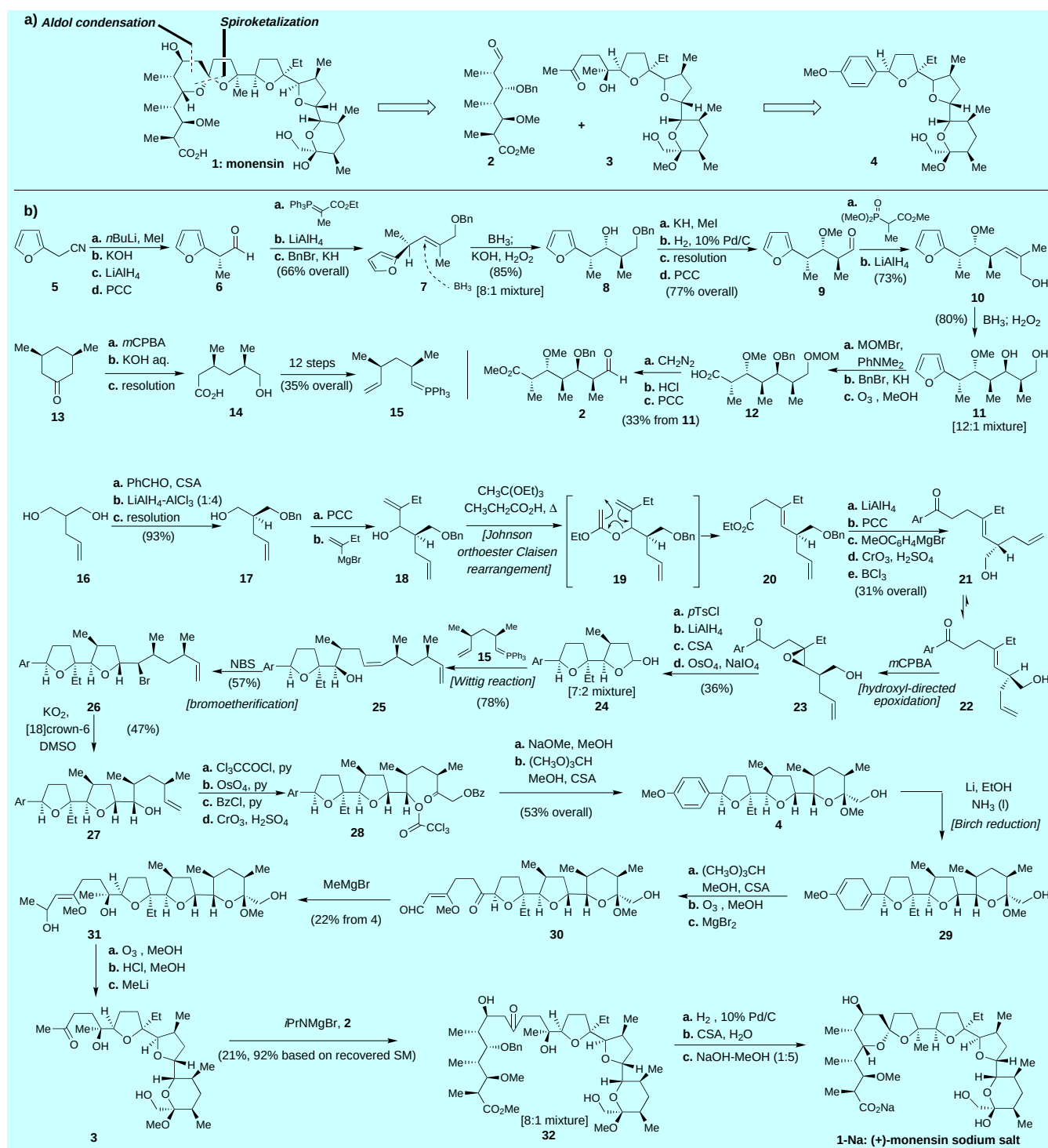
Monensin (1979, 1980)

Monensin^[105] (**1** in Scheme 16), isolated from a strain of *Streptomyces cinamonensis*, is perhaps the most prominent member of the polyether class of antibiotics. Also known as ionophores, these naturally occurring substances have the ability to complex and transport metals across membranes, thus exerting potent antibacterial action.^[106, 107] These structures are characterized by varying numbers of tetrahydropyran, tetrahydrofuran, and/or spiroketals. Kishi's total synthesis of monensin,^[108] which followed his synthesis of the simpler ionophore lasalocid,^[109] represents a milestone achievement in organic synthesis (Scheme 16). This accomplishment demonstrates the importance of convergency in the total synthesis of complex molecules and is one of the first examples of stereoselective total synthesis through acyclic stereocontrol, and elegantly marked the application of the Cram rules within the context of natural-product synthesis. By unraveling the spiroketal moiety of the molecule Kishi was able to adopt an aldol-based strategy to couple monensin's two segments. A series of daring reactions (for example, hydroborations, epoxidations) on acyclic systems with pre-existing stereocenters allowed the construction of the two heavily substituted fragments of the molecule which were then successfully coupled and allowed to fold into the desired spiroketal upon deprotection. Kishi's beautiful synthesis of monensin also provided a demonstration of the importance of 1,3-allylic strain in acyclic conformational preferences, which in turn can be exploited for the purposes of stereocontrolled reactions (for example, epoxidation).

A second total synthesis of monensin was accomplished in 1980 by W. C. Still and his group (Scheme 17).^[110] Just as elegant as Kishi's synthesis, the Still total synthesis of monensin demonstrates a masterful application of chelation-controlled additions to the carbonyl function. A judicious choice of optically active starting materials as well as a highly convergent strategy that utilized the same aldol–spiroketalization sequence as in Kishi's synthesis allowed rapid access to monensin's rather complex structure.

Endiandric Acids (1982)

The endiandric acids (Scheme 18) are a fascinating group of natural products discovered in the early 1980s in the Australian plant *Endiandra introsa* (Lauraceae) by Black et al.^[111] Their intriguing structures and racemic nature gave rise to the so called “Black hypothesis” for their plant origin, which involved a series of non-enzymatic electrocyclizations from acyclic polyunsaturated precursors (see Scheme 18). Intrigued by these novel structures and Black's hypothesis for their “biogenetic” origin, we directed our attention towards their total synthesis. Two approaches were followed, a

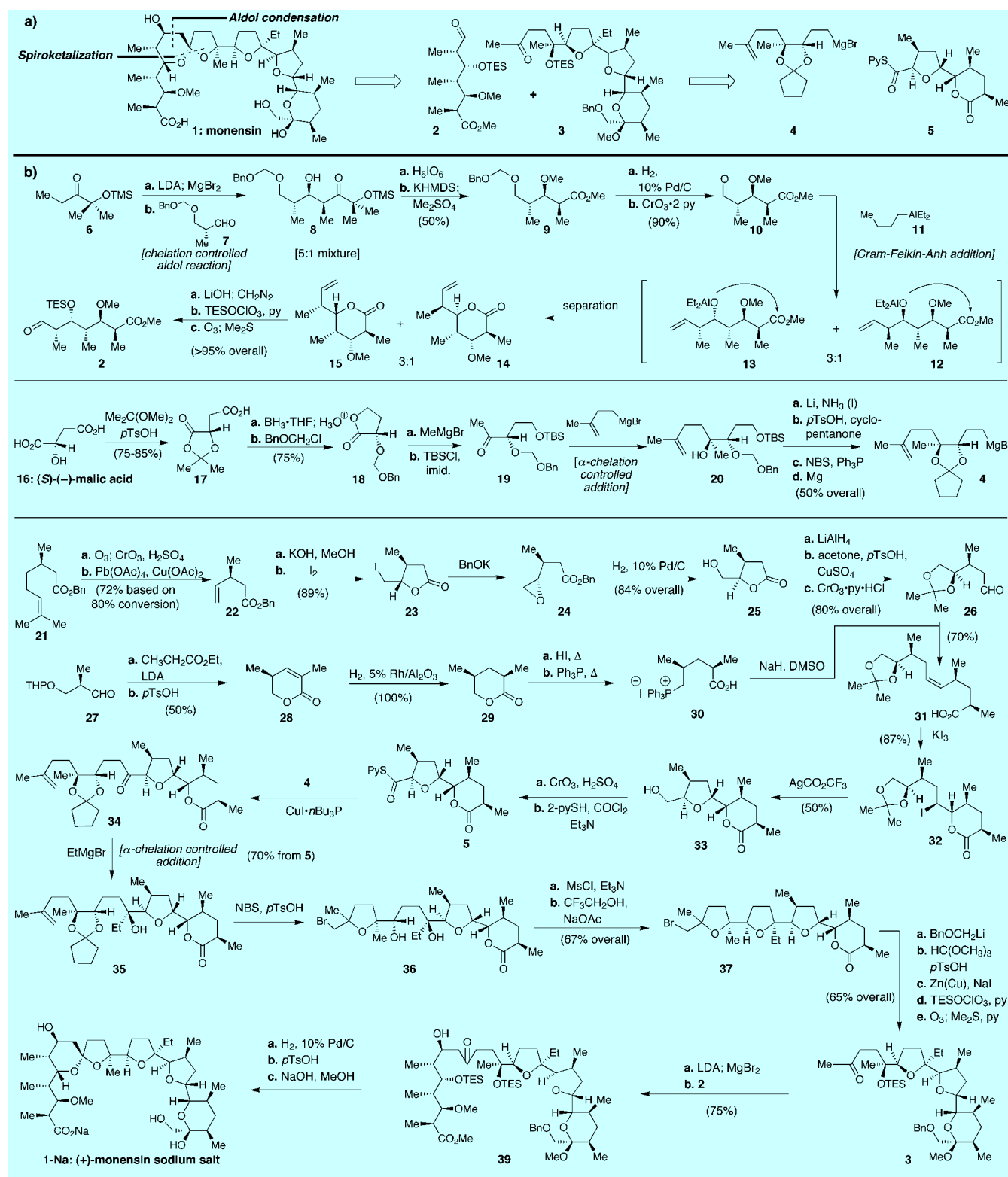

 Scheme 16. a) Strategic bond disconnections and retrosynthetic analysis of monensin and b) total synthesis (Kishi et al., 1979).^[108]

stepwise (Scheme 19b) and a direct one-step strategy (Scheme 19c). Both strategies involve an 8- π -electron electrocyclicization, a 6- π -electron electrocyclicization, and a Diels–Alder-type [4+2] cycloaddition reaction to assemble the polycyclic skeletons of endiandric acids. The total synthesis^[112] of these architecturally interesting structures demonstrated a number of important principles of organic chemistry and verified Black’s hypothesis for their natural origin. In particular, the “one-pot” construction of these target mole-

cules from acyclic precursors from the endiandric acid cascade is remarkable, particularly if one considers the stereospecific formation of no less than four rings and eight stereogenic centers in each final product.

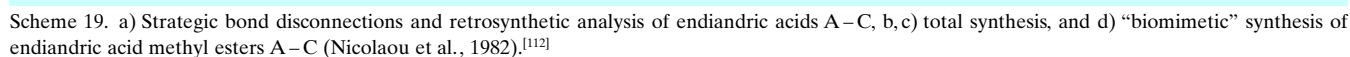
Efrotomycin (1985)

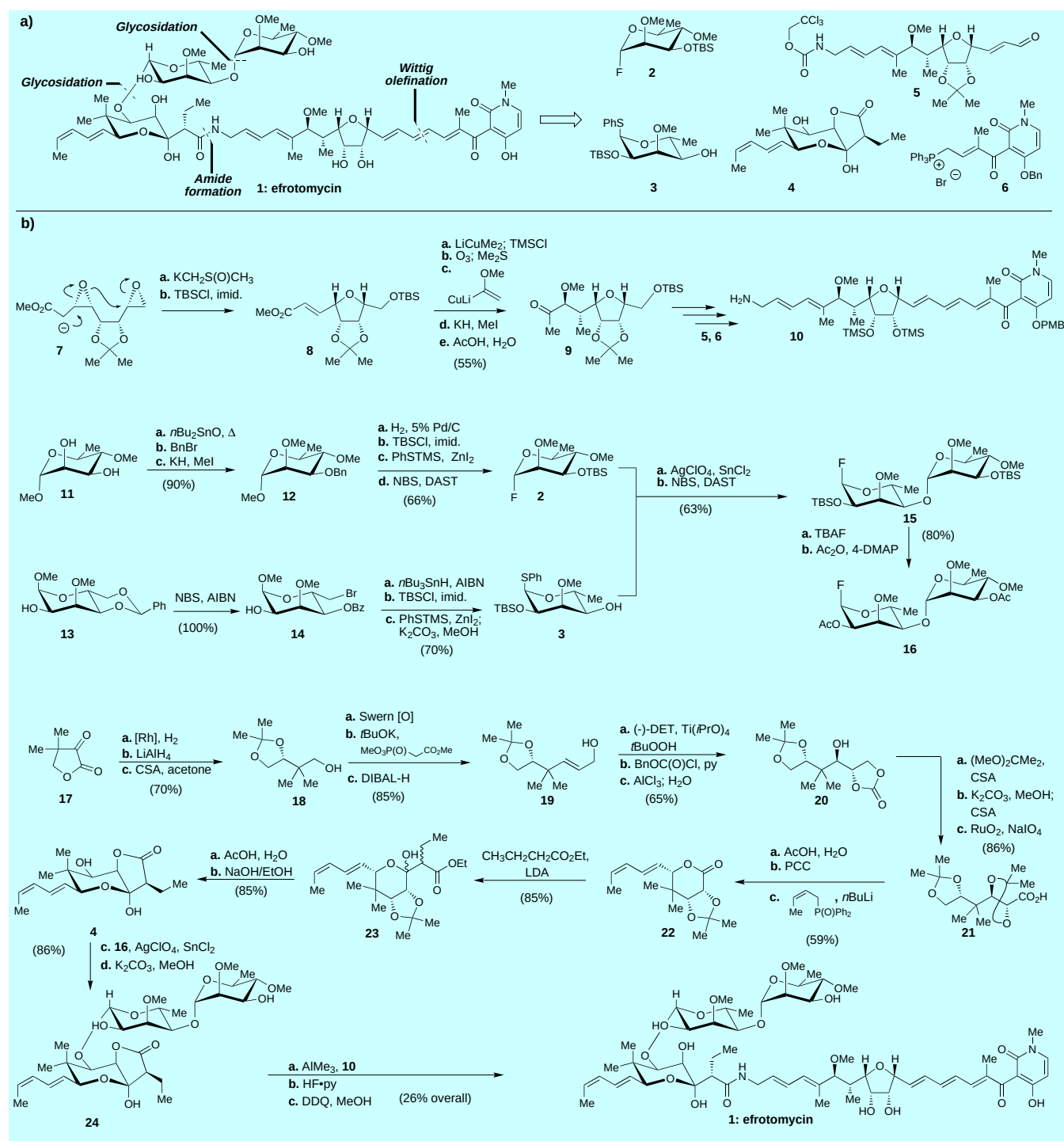
Efrotomycin (**1** in Scheme 20; see p. 67), the most complex member of the elfamycin class of antibiotics^[113] that includes

Scheme 17. a) Strategic bond disconnections and retrosynthetic analysis of monensin and b) total synthesis (Still et al., 1980).^[110]

aurodox, was isolated from *Nocardia lactamdurans*.^[114] Its molecular structure, which contains nineteen stereocenters and seven geometrical elements of stereochemistry, presented considerable challenge to the synthetic chemists of the 1980s, particularly in regard to the oligosaccharide domain and the all-*cis*-tetrasubstituted tetrahydrofuran system. The total syn-

thesis of efrotomycin, accomplished in 1985 in our laboratories,^[115] addressed both problems by devising new methodologies for the stereoselective construction of glycosides and tetrahydrofurans. Scheme 20 summarizes this total synthesis in which the two-stage activation procedure for the synthesis of oligosaccharides utilizing thioglycosides and glycosyl



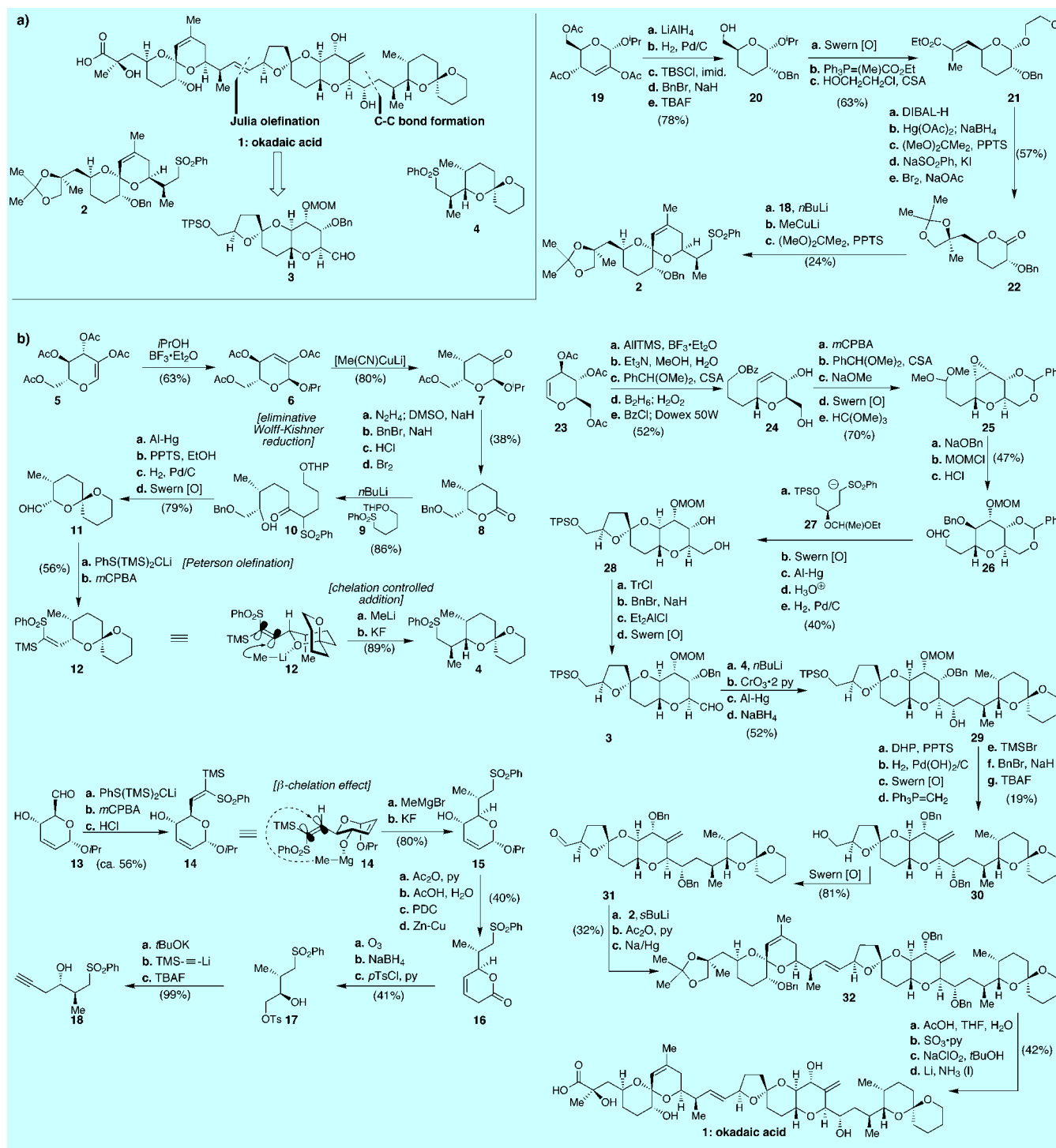
Scheme 20. a) Strategic bond disconnections and retrosynthetic analysis of efrotomycin and b) total synthesis (Nicolaou et al., 1985).^[115]

fluorides^[116] as well as the base-induced zip-type diepoxide opening were highlighted as powerful methods for organic synthesis. Numerous applications and extensions of these synthetic technologies have since followed.^[117]

Okadaic acid (1986)

Okadaic acid^[118] (1 in Scheme 21) is a marine toxin isolated from *Halichondria Okadae*. Besides its shellfish toxicity,

okadaic acid exhibits potent inhibition of certain phosphatases and is a strong tumor promotor. With its three spiroketal moieties and seventeen stereogenic centers, the molecule's polycyclic structure presented a serious challenge to synthetic chemistry. The first total synthesis of okadaic acid was achieved in 1984 by the Isobe group in Japan^[119] and was followed by those of Forsyth^[120] and Ley.^[121] The Isobe synthesis of okadaic acid, summarized in Scheme 21, highlights the use of sulfonyl-stabilized carbanions in synthesis, the

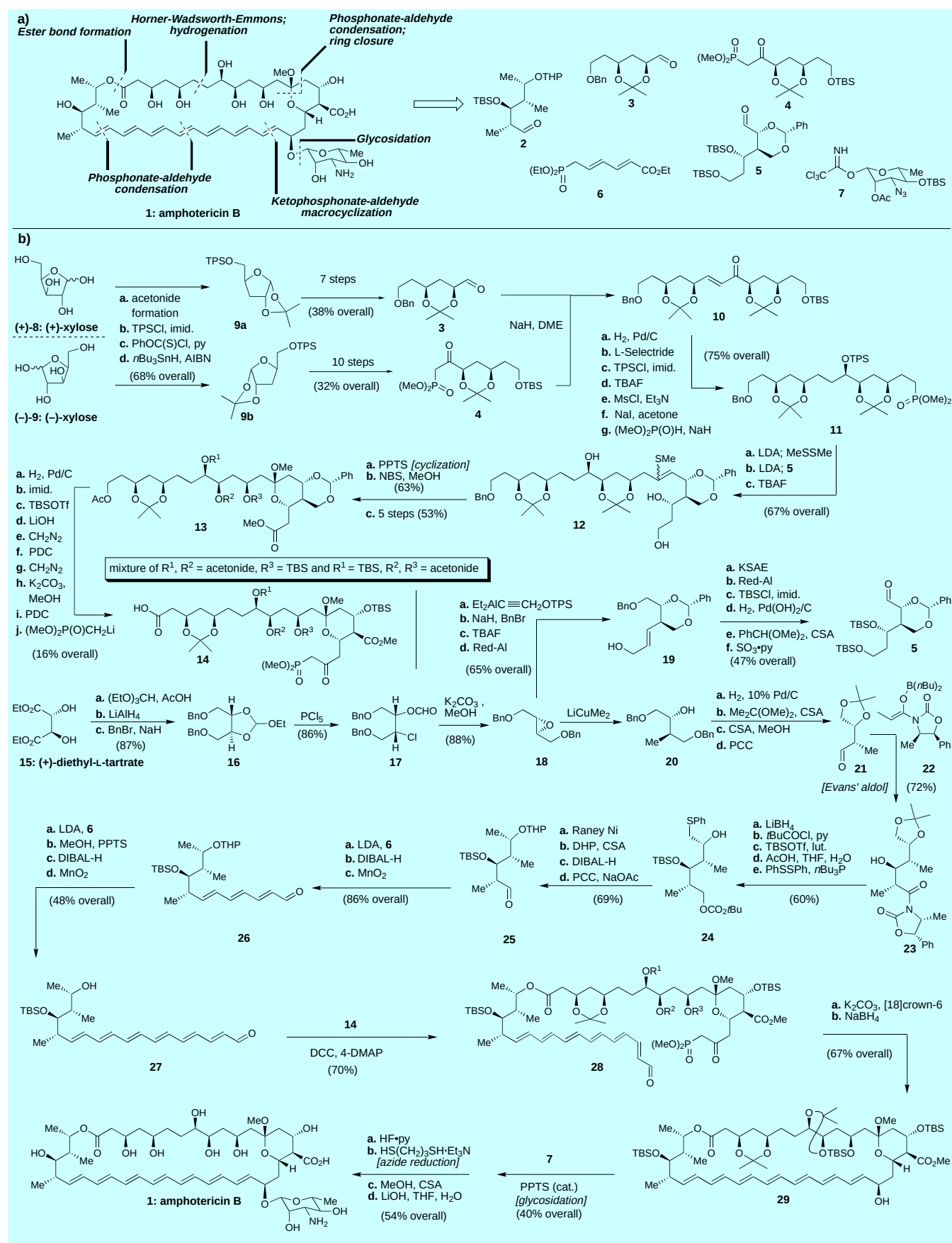

 Scheme 21. a) Strategic bond disconnections and retrosynthetic analysis of okadaic acid and b) total synthesis (Isobe et al., 1986).^[119]

control of stereochemistry through chelation, and the power of the anomeric effect to exert stereocontrol in spiroketal formation.

Amphotericin B (1987)

The polyene macrolide family of natural products is a subgroup of the macrolide class, which poses formidable challenges to synthetic organic chemistry. Among them,

amphotericin B^[122] (**1** in Scheme 22), isolated from *Streptomyces nodosus*, occupies a high position as a consequence of its complexity and medical importance as a widely used antifungal agent. Its total synthesis^[123] in 1987 by our group represented the first breakthrough within this class of complex molecules. This total synthesis featured the recognition of subtle symmetry elements within the target molecule that allowed the utilization of the same starting material to construct two, seemingly unrelated, intermediates and the

Scheme 22. a) Strategic bond disconnections and retrosynthetic analysis of amphotericin B and b) total synthesis (Nicolaou et al., 1987).^[123]

employment of the then newly discovered Sharpless asymmetric epoxidation reaction^[124] to stereoselectively construct the 1,3-diol systems.

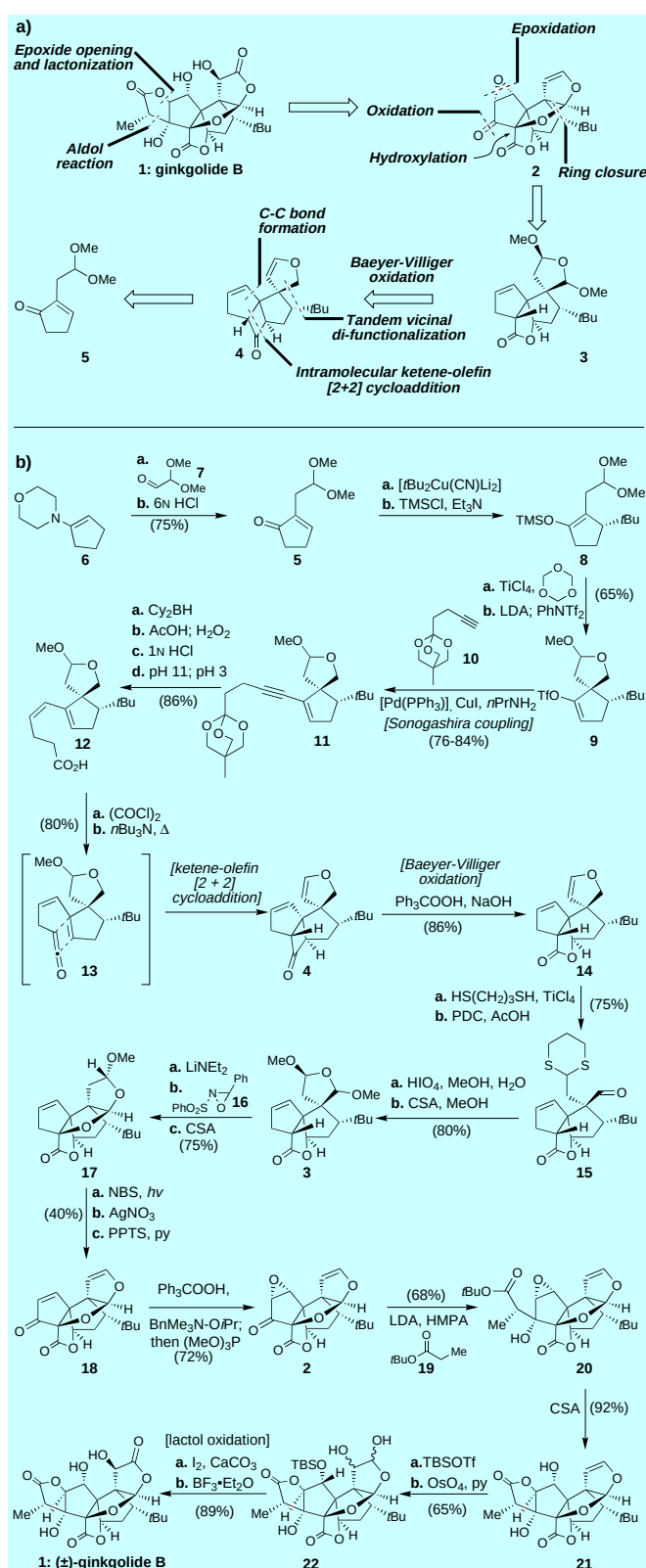
The Horner-Wadsworth-Emmons process^[125] emerged as the most valuable reaction of the synthesis, having been utilized five times to construct carbon-carbon double bonds. Particularly striking was the application of an intramolecular ketophosphonate-aldehyde condensation to construct the 38-membered ring of amphotericin B. A further, notable feature within this total synthesis is the strategy through which the carbohydrate moiety was installed stereoselectively on a derivative of amphoteronolide B to construct the challenging β -1,2-*cis*-glycoside bond of the target molecule. Important in this field is also Masamune's elegant synthesis of 19-dehydroamphoteronolide B.^[126]

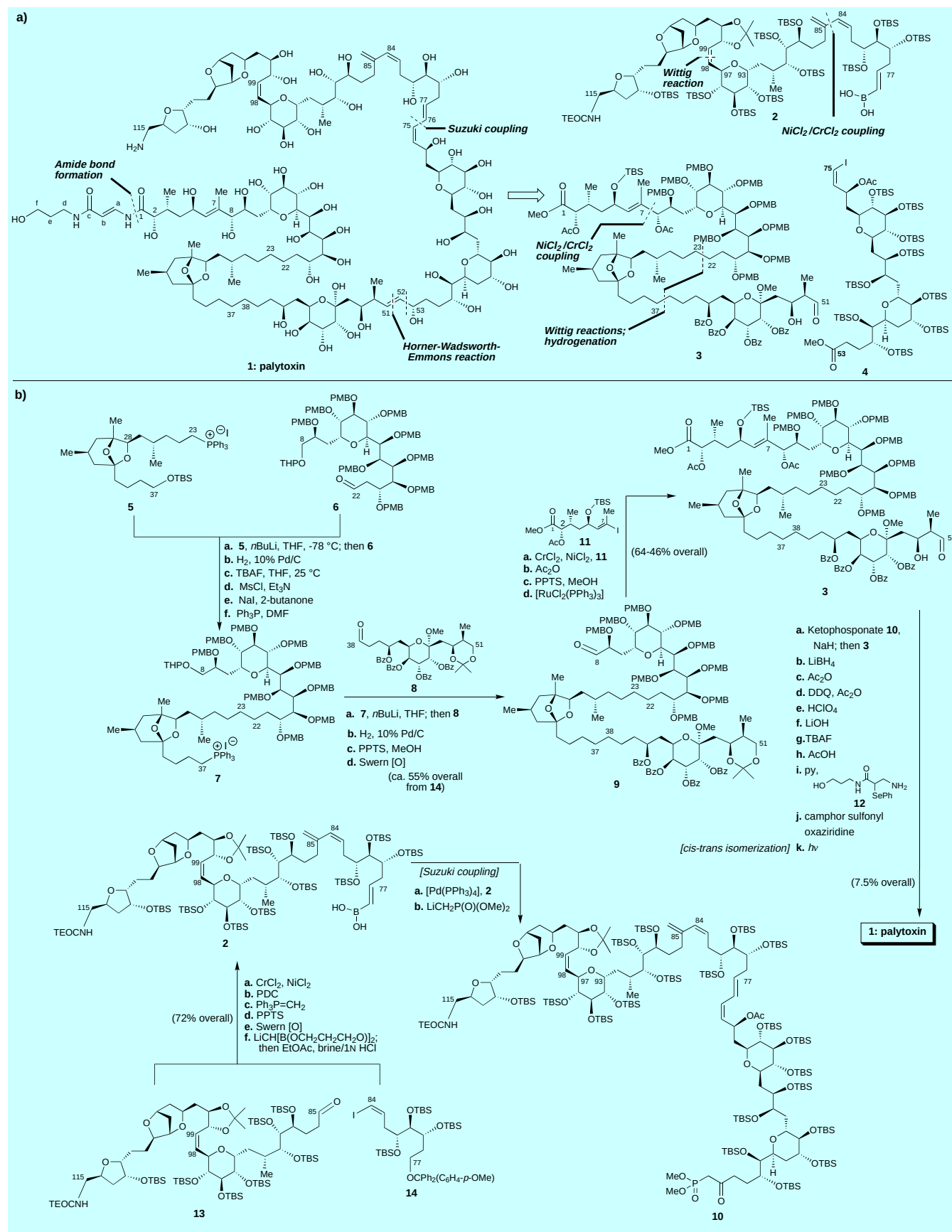
Ginkgolide B (1988)

Ginkgolide B (**1** in Scheme 23) is a highly functionalized natural substance isolated from the *Ginkgo biloba* tree, widely known for its medicinal properties.^[127] The structural elucidation of ginkgolide B in 1967 was a major accomplishment of the Nakanishi group.^[128] Its total synthesis by the Corey group in 1988^[129] stands as a landmark achievement in organic synthesis. Despite its relatively small size, ginkgolide B proved to be stubborn in its defiance to chemical synthesis, primarily because of its highly unusual bond connectivity. Among its most striking structural features are the *tert*-butyl group which occurs rather rarely in nature, the eleven stereogenic centers of which two are quaternary, and its six five-membered rings. The Corey synthesis of ginkgolide B abounds with brilliant strategies and tactics, but most impressive is, perhaps, the intramolecular [2+2] ketene cycloaddition reaction, which contributed substantially to the construction of the required carbon framework by delivering two of the most challenging rings.

Palitoxin (1989, 1994)

Isolated from soft corals of the *Palythoa* genus, palitoxin (**1** in Scheme 24) is endowed with toxic properties exceeded only by a few other substances known to man.^[130] Both its structural elucidation and total synthesis posed formidable challenges to chemists. While the gross structural elucidation of palitoxin was reported independently by the groups of Hirata^[131] and Moore^[132] in 1981, its total synthesis had to await several more years of intense efforts. Finally, after heroic efforts from Kishi and his group the synthesis of palitoxin carboxylic acid was published in 1989^[133] and that of palitoxin itself in 1994^[134] (see Scheme 24). The synthesis of palitoxin holds a special place in the history of total synthesis in that palitoxin is the largest secondary metabolite to be synthesized in the laboratory, both in terms of molecular weight and number of stereocenters. Most importantly, this mammoth endeavor led to the discovery and development of a number of useful synthetic reactions. Amongst them are the improvement of the $\text{NiCl}_2/\text{CrCl}_2$ -mediated coupling reaction

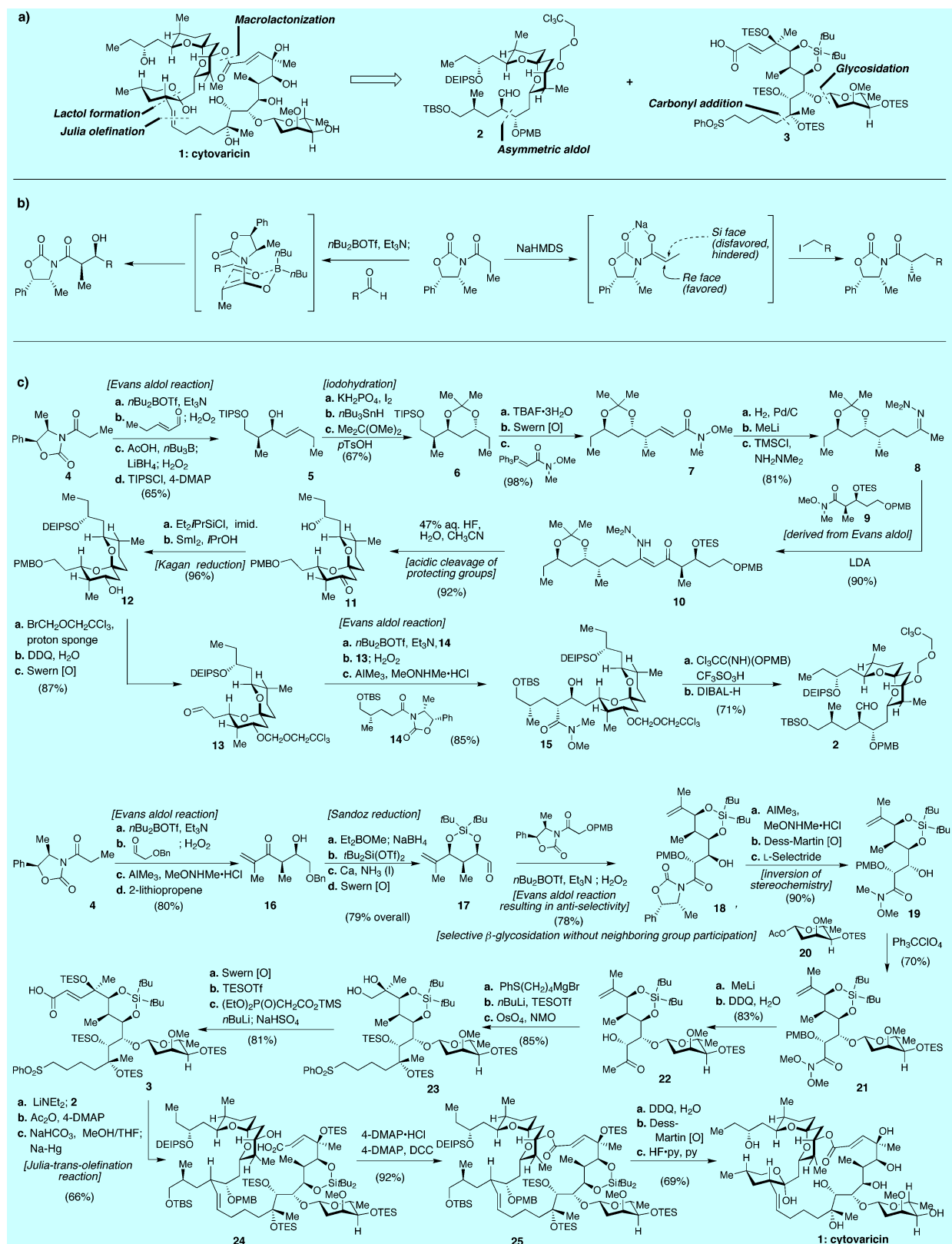


Scheme 24. a) Strategic bond disconnections and retrosynthetic analysis of palytoxin and b) highlights of the total synthesis (Kishi et al. 1989, 1994).^[133, 134]

Cytovaricin (1990)

Cytovaricin (**1** in Scheme 25) is a 22-membered macrolide, isolated from *Streptomyces diastatochromogenes* in 1981,^[135]

which is endowed with impressive antineoplastic activity and complex molecular architecture. Possessing seventeen stereogenic centers on its main framework, a spiroketal, and a glycoside moiety with four additional stereocenters, cyto-



Scheme 25. a) Strategic bond disconnections and retrosynthetic analysis of cytovaricin, b) key asymmetric alkylation and aldol reactions, and c) outline of the total synthesis (Evans et al., 1990).^[137]

icin presented a considerable challenge to synthetic chemistry in the 1980s. Its structural elucidation by X-ray crystallographic analysis in 1983^[136] opened an opportunity for Evans et al. to apply their elegant alkylation and aldol methodology for acyclic stereoselection to the solution of the cytovaricin problem. Indeed, by 1990 the group reported a beautiful total synthesis^[137] that clearly demonstrated the new concepts of stereochemical control by acyclic stereoselection as opposed to the classical methods applied previously to solve such problems. It is instructive to compare this synthesis to the cyclic-template strategy used by Corey,^[102] Woodward,^[33] and Stork^[138] to achieve stereochemical control in their syntheses of the erythromycin macrolide framework. This impressive use of acyclic stereocontrol through the use of the Evans chiral oxazolidone certainly propelled the area of polyketide synthesis, a class of compounds that are rather readily accessible synthetically by today's standards.

Calicheamicin γ_1^I (1992)

The arrival of calicheamicin γ_1^I ^[139] (**1** in Scheme 26) and its relatives, collectively known as the enediyne anticancer antibiotics,^[140] on the scene in the 1980s presented an entirely new challenge to synthetic organic chemistry. Isolated from *Micromonospora echinospora* ssp *calichensis*, this fascinating natural product provided a unique opportunity for discovery and invention in the areas of chemistry, biology, and medicine. Its novel molecular structure is responsible for its powerful biological properties, which include strong binding to duplex DNA, double-strand cleavage of the genetic material by formation of a benzenoid diradical, and—as a consequence—potent antitumor and antibiotic activity.

The structure of calicheamicin γ_1^I is comprised of a carbohydrate domain and an enediyne core carrying a trisulfide moiety that acts as a triggering device for the cascade of events which leads, via a Bergman cycloaromatization,^[141] to the diradical species and DNA rupture. The oligosaccharide domain of calicheamicin γ_1^I is endowed with high affinity for certain DNA sequences, and acts as the delivery system of the molecule to its biological target. The highly strained 10-membered enediyne system, the novel oligosaccharide fragment, and the trisulfide unit are but some of the unusual and challenging features of calicheamicin γ_1^I . Even more challenging, of course, was the chartering of the proper sequence for assembling all these functionalities into the final structure. Two groups rose to the challenge, ours (1992)^[142] and that of S. J. Danishefsky (1994).^[143]

Notable features of our total synthesis of calicheamicin γ_1^I (Scheme 26) are the installment of the sulfur atom in the carbohydrate domain through a stereospecific [3,3]-sigmatropic rearrangement and the [3+2] olefin–nitrile oxide cycloaddition reaction employed in the construction of the enediyne core. That a molecule of such complexity could be assembled in the laboratory in less than five years after its structural elucidation in 1987 is an accurate reflection of the high level of the state-of-the-art in the early 1990s. Just as impressive is Danishefsky's synthesis of calicheamicin, which can be found in the original literature.^[143]

Strychnine (1993)

Although (–)-strychnine had succumbed to the ingenuity of Woodward in 1954 (see Scheme 4) it can still be considered a target of choice to demonstrate the application of new reactions and novel strategies by virtue of its abundant stereochemical features densely packed in a heptacyclic framework. Almost 40 years after Woodward's seminal synthesis, Overman's synthesis of strychnine^[58] (Scheme 27; see p. 76) stands as a testimony to the evolution of organic synthesis. Indeed, powerful palladium-mediated reactions were used to expedite the assembly of the crucial intermediate **13** (Scheme 27) in a stereospecific fashion, thereby setting the stage for the key tandem aza-Cope rearrangement and Mannich reaction. This tandem reaction proved to be particularly efficient and well-suited to afford an advanced tricyclic system with concomitant formation of the quaternary center stereospecifically, under mild conditions, and in nearly quantitative yield. The sophisticated sequence of reactions which ultimately led to Overman's (–)-strychnine synthesis deserves special mention for its elegance.

Rapamycin (1993)

Rapamycin (**1** in Scheme 28; see p. 77) is an important molecule within the field of immunosuppression that was first isolated in 1975^[144] from *Streptomyces hygroscopicus*, a bacterial strain found in soil collected in Rapa Nui (Easter Island), and structurally elucidated in 1978.^[145] Its potent immunosuppressive properties are reminiscent of those of cyclosporin and FK506, whose biological and medical importance, particularly in the field of organ transplants, became evident in the 1980s.^[146] Although the structures of rapamycin and FK506 possess striking similarities, the former is considerably more complex and attracted serious attention from the synthetic chemists in the late 1980s and early 1990s. By 1995 there were four total syntheses of rapamycin,^[147–150] the first being reported from this group in 1993 (Scheme 28).^[147] This asymmetric synthesis of rapamycin is an example of high convergency and acyclic stereoselection, and is perhaps known best for the way in which the macrocyclic ring was formed. A palladium-catalyzed reaction based on Stille's chemistry allowed a “stitching cyclization” process to proceed, to furnish the required conjugated triene system concurrently as it formed the 29-membered ring of the target molecule.^[151]

Taxol (1994)

Taxol (**1** in Scheme 29; see p. 78), one of the most celebrated natural products, was isolated from the Pacific yew tree and its structure was reported in 1971.^[152] Its arduous journey to the clinic took more than 20 years, being approved by the Food and Drug Administration (FDA) in 1992 for the treatment of ovarian cancer.^[153] Synthetic chemists were challenged for more than two decades as taxol's complex molecular architecture resisted multiple strategies toward its construction in the laboratory. Finally, in 1994, two essentially simultaneous reports^[154, 155] described two distinctly different

total syntheses of taxol. These first two syntheses, by our group^[154] and that of Holton,^[155] were followed by those of Danishefsky,^[156] Wender,^[157] Mukaiyama,^[158] and Kuwajima.^[159] All these syntheses, which are characterized by novel strategies and brave tactics, contributed enormously to the advancement of total synthesis and enabled investigations in biology and medicine.

Amongst the most notable features of our total synthesis of taxol (Scheme 29) are the boron-mediated Diels–Alder reaction to construct the highly functionalized C ring, the application of the Shapiro and McMurry coupling reactions, and the selective manner in which the oxygen functionalities were installed onto the 8-membered ring of the molecule. Because of the great drama associated with cancer, this and the other syntheses of taxol received headliner publicity. The art and science of total synthesis was once again brought to the attention of the general public.

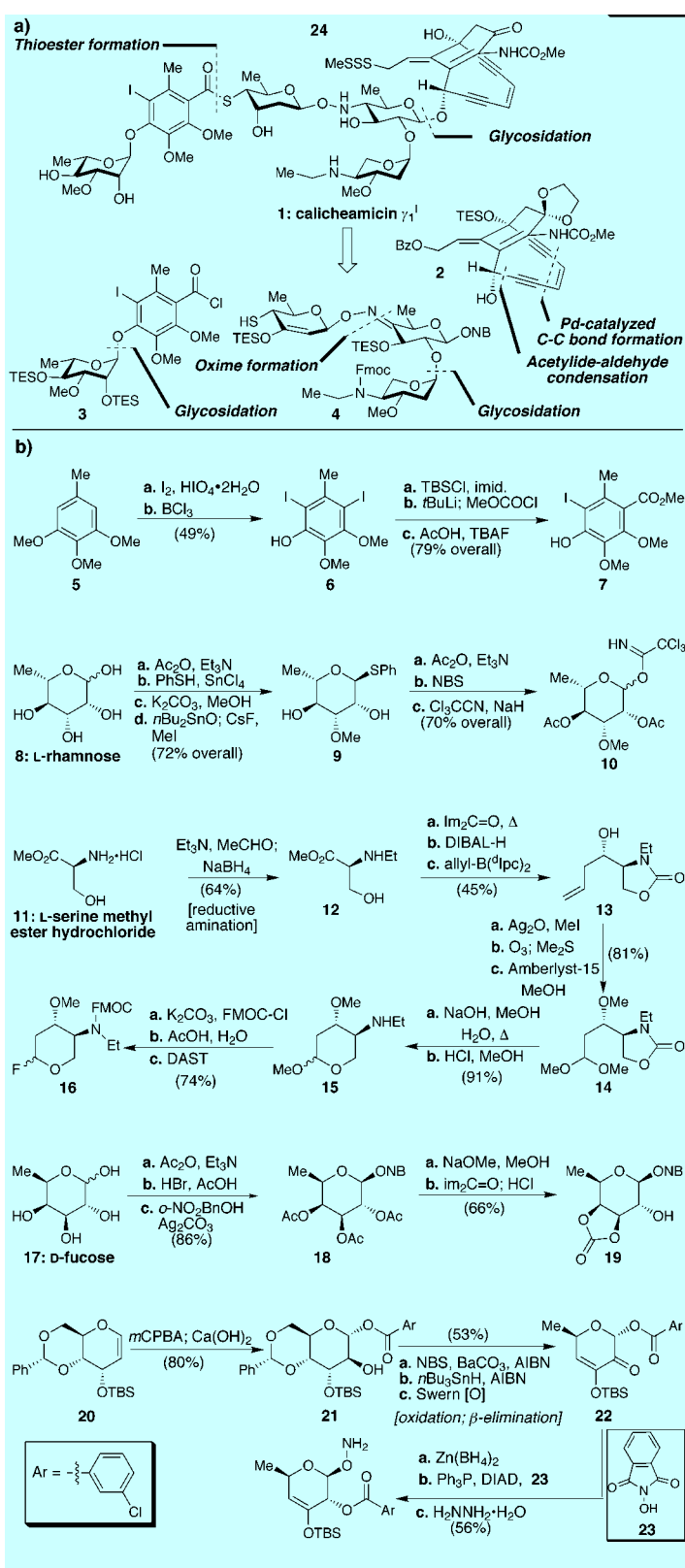
Zaragozic Acid (1994)

A new natural product with unprecedented molecular architecture often gives impetus to synthetic endeavors directed at its total synthesis. Such was the case with zaragozic acid A (**1** in Scheme 30; see p. 79) whose structure was released essentially simultaneously in 1992 by groups from Merck^[160] and Glaxo^[161] (the latter naming the compound squalastatin S1).^[162] Isolated from a species of fungi, zaragozic acid A exhibits impressive *in vitro* and *in vivo* inhibition of cholesterol biosynthesis by binding to squalene synthase.^[163] Zaragozic acid A, like its many relatives, possesses an unusual tricarboxylic acid core, whose highly oxygenated nature added to its novelty and complexity as a synthetic target. The distinguishing features of our synthesis^[164] of zaragozic acid A (Scheme 30) include the utilization of the Sharpless asymmetric dihydroxylation reaction^[165] to install the first two oxygen-bearing stereocenters onto a complex prochiral diene system and a multi-step, acid-catalyzed rearrangement to secure the zaragozic acid skeleton.

The synthesis of zaragozic acid was also accomplished and reported at approximately the same time as ours by the groups of Carreira (zaragozic acid C)^[166] and Evans (zaragozic acid C).^[167] In addition, Heathcock et al.^[168] reported another total synthesis of zaragozic acid A in 1996.

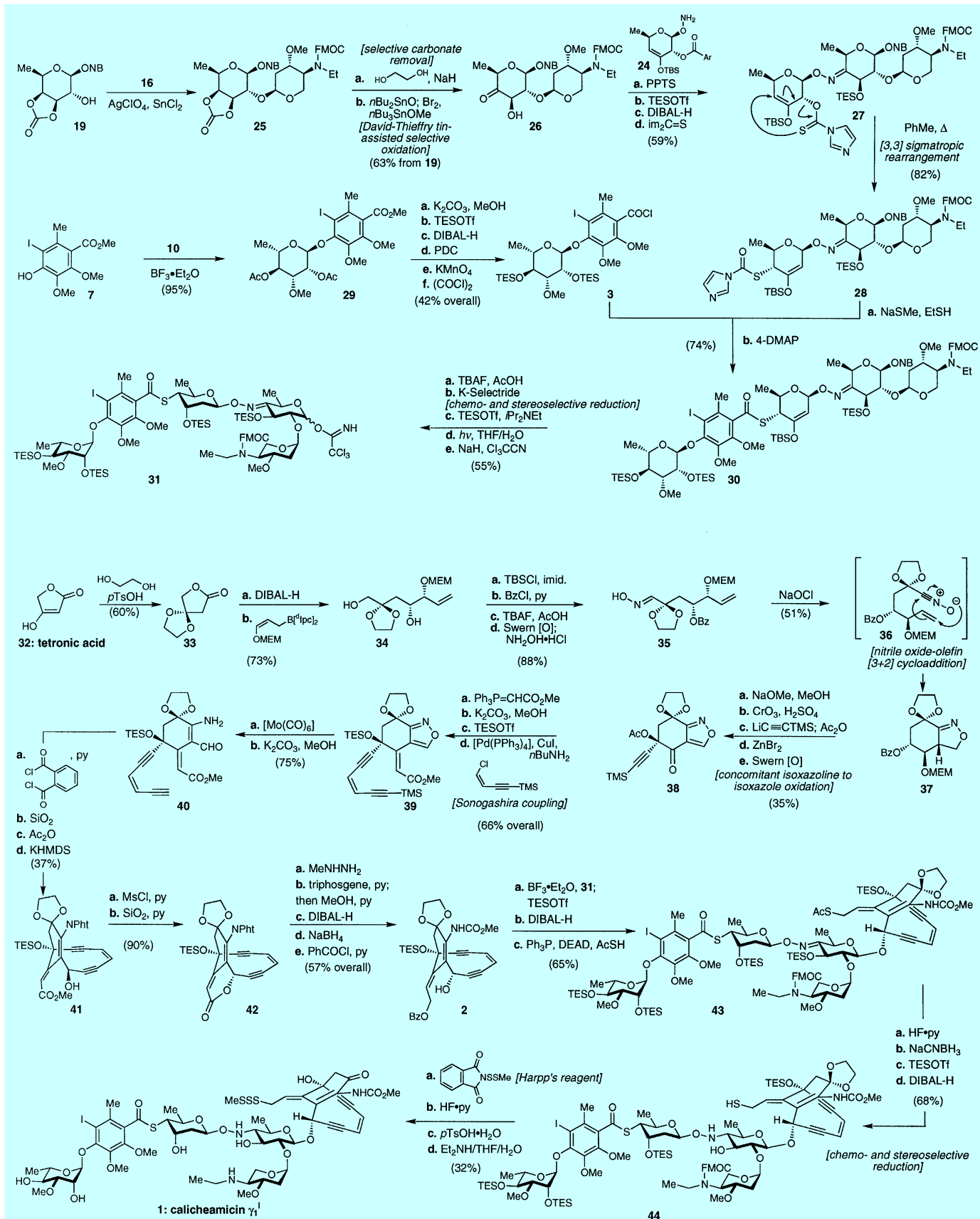
Swinholide A (1994)

Swinholide A (**1** in Scheme 31; see p. 80), a marine natural product with antifungal and antineoplastic activity, was originally isolated from the Red Sea sponge *Theonella swinhoei*.^[169a] Its structure was fully established in the late 1980s by X-ray crystallographic analysis.^[169b] The structure of swinholide A has *C*₂ symmetry and is distinguished by two conjugated diene systems, two trisubstituted tetrahydropyran systems and two disubstituted dihydropyran systems, a 44-membered diolide ring, and thirty stereogenic centers. Its challenging molecular architecture coupled with its scarcity



Scheme 26. a) Strategic bond disconnections and retrosynthetic analysis of calicheamicin γ_1 and b) total synthesis (Nicolaou et al., 1992).^[142]

and biological action prompted several groups to undertake synthetic studies towards its total synthesis. Two laboratories, that of I. Paterson at Cambridge^[170] and ours^[171] have succeeded in the task.



Scheme 26. (Continued)

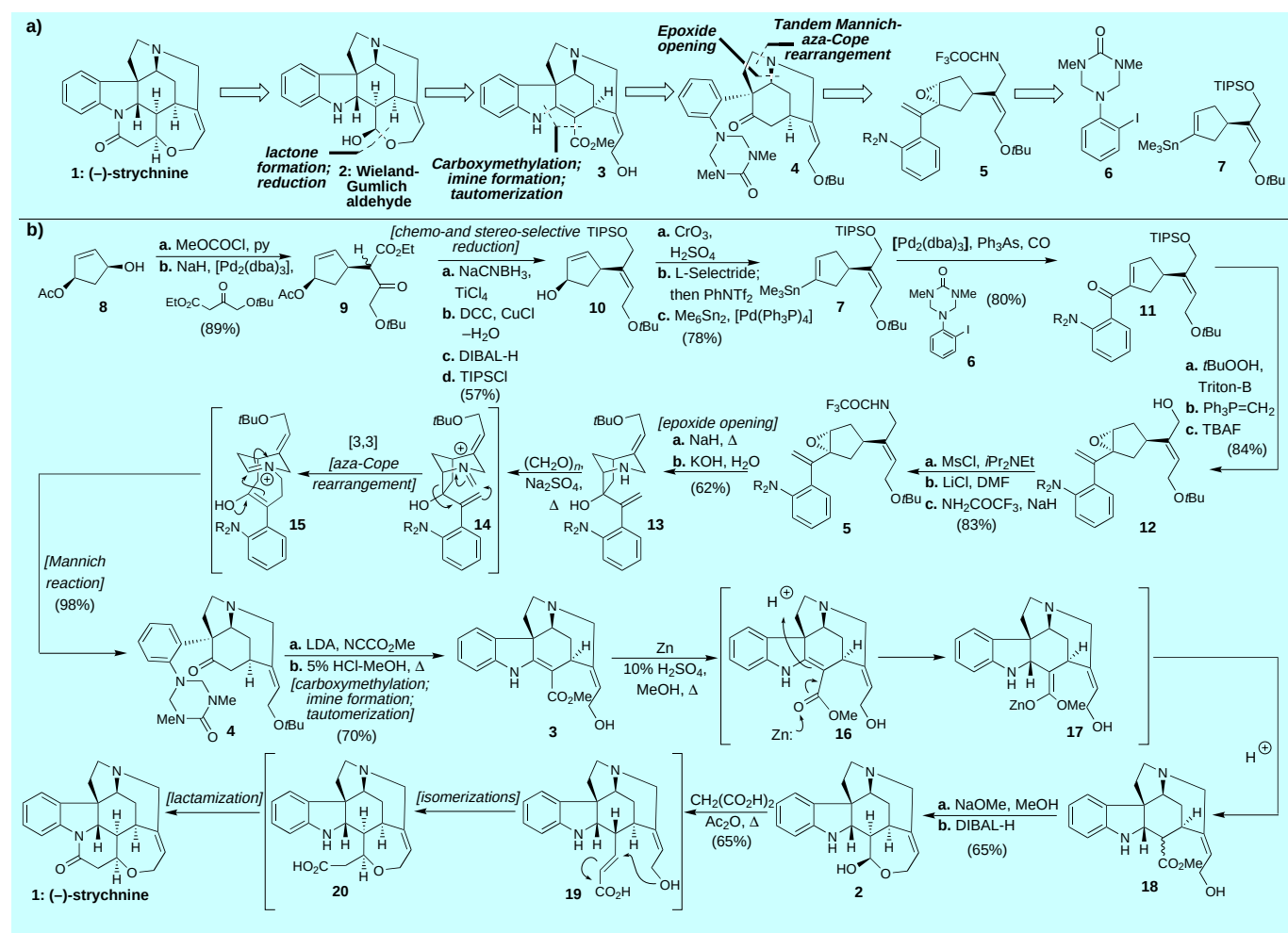
Paterson's total synthesis,^[170] shown in Scheme 31 (see p. 80), came first and was accompanied by the development and application of a number of various types of asymmetric boron-mediated aldol reactions to form key C–C bonds. Indeed, this new aldol methodology^[172] was utilized to install three contiguous chiral centers in two steps with high diastereoselectivity (**9**→**12** in Scheme 31), and represents a most welcomed progress in acyclic stereocontrol. Our total synthesis of swinholid A^[171] (Scheme 32; see p. 81) featured two relatively new, at the time, methods for C–C bond construction in complex-molecule synthesis, namely the Ghosez cyclization^[173] to form α,β -unsaturated β -lactones from orthoester sulfones and epoxides, and the dithiane-stabilized anion opening of cyclic sulfates.^[174] The macro-lactonization was performed by the Yamaguchi reagent^[175] in both strategies. Both total syntheses are highly convergent and demonstrated the power of the art in acyclic stereo-selection and large-ring construction and stand as important achievements in the field of macrolide synthesis.

Brevetoxin B (1995)

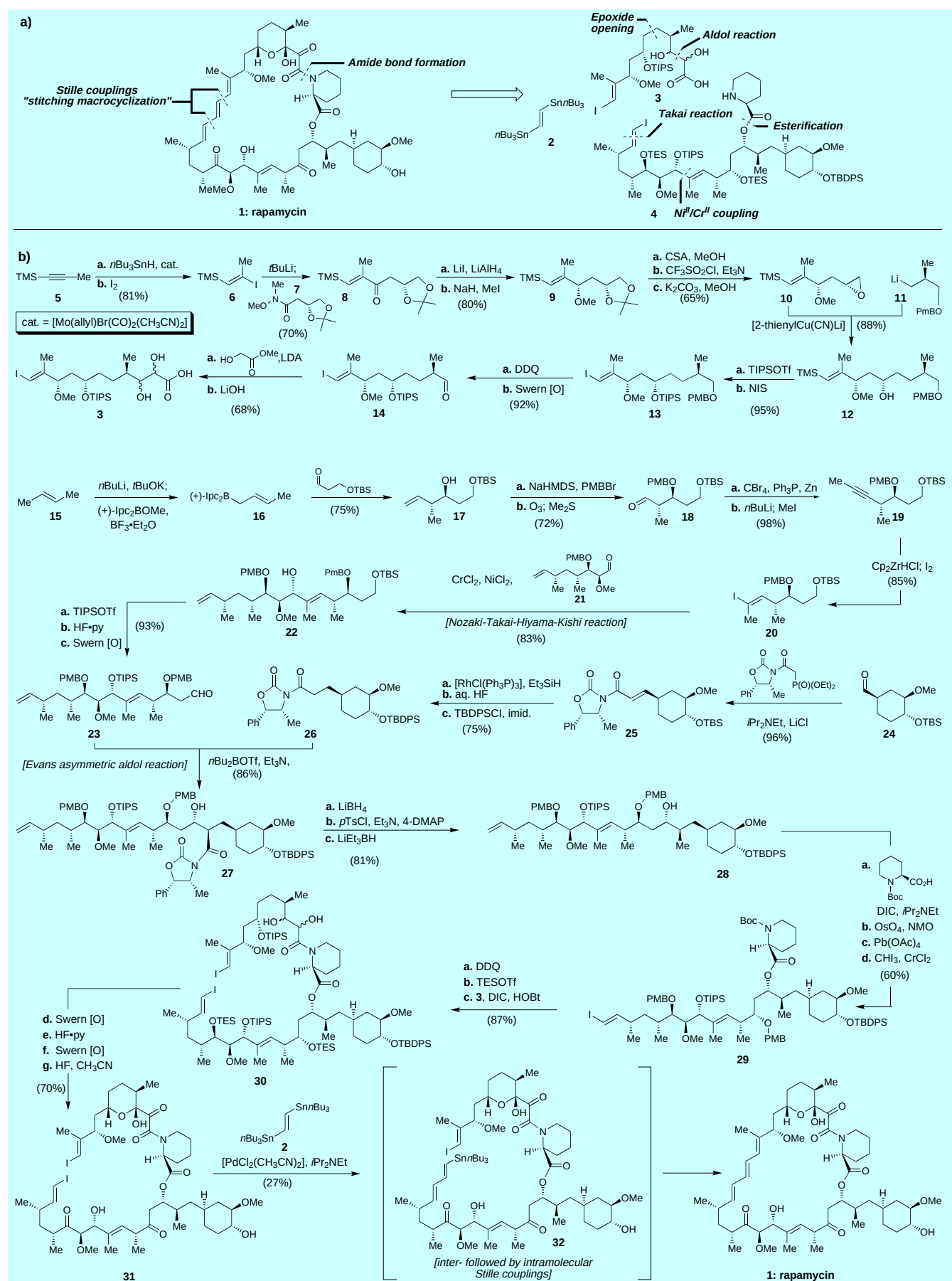
Brevetoxin B (**1** in Scheme 33; see p. 82), an active principle of the poisonous waters associated with the “red tide” phenomena,^[176] was the first structure of its kind to be

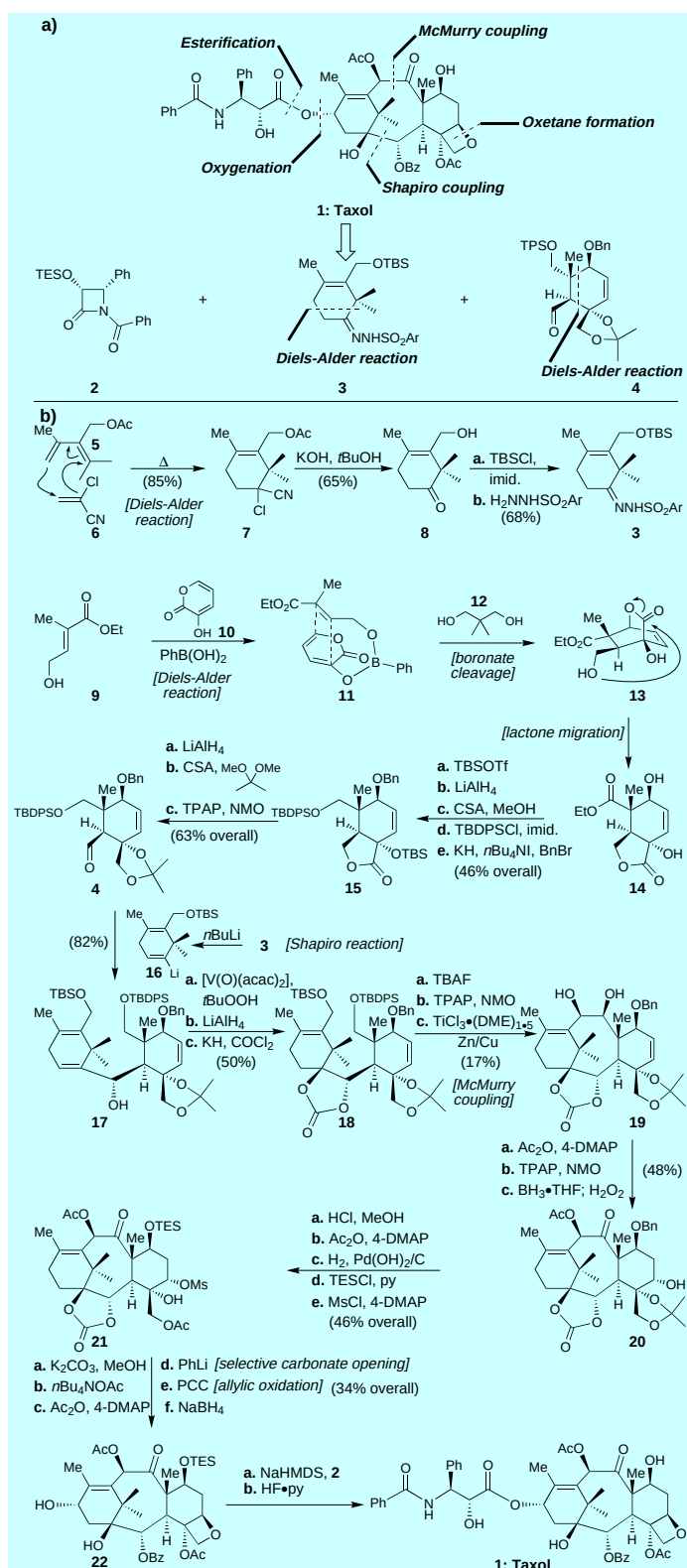
elucidated (1981).^[177] The beauty of brevetoxin's molecular architecture, which accommodates eleven rings and twenty-three stereogenic centers, attracted immediate attention from the synthetic community. This neurotoxin, whose mechanism of action involves the opening of sodium channels, shows remarkable regularity in its structure. Thus, all rings are *trans*-fused and each contains an oxygen atom. All ring oxygens are separated by a C–C bond and each is flanked by two *syn*-arranged hydrogen or methyl substituents—except for the first which carries a carbonyl to its “left” and the last which is flanked by two *anti*-oriented hydrogens. With its imposing structure, brevetoxin B presented a formidable and daunting problem to synthetic organic chemistry. Not only did new methods need to be developed for the construction of the various cyclic ether moieties residing within its structure, but, most importantly, the “right strategy” had to be devised for the global assembly of the molecule.

After several abortive attempts, brevetoxin B was finally conquered, and the total synthesis was reported in 1995 from these laboratories (Scheme 33).^[178] Along with the accomplishment of the total synthesis, this twelve-year odyssey^[179] yielded a plethora of new synthetic technologies for the construction of cyclic ethers of various sizes. Prominent among them are (see Scheme 33b): a) the regio- and stereo-selective routes to tetrahydrofuran, tetrahydropyran, and



Scheme 27. a) Strategic bond disconnections and retrosynthetic analysis of (-)-strychnine and b) total synthesis (Overman et al., 1993).^[58]

Scheme 28. a) Strategic bond disconnections and retrosynthetic analysis of rapamycin and b) highlights of the total synthesis (Nicolaou et al., 1993).^[147]



Scheme 29. a) Strategic bond disconnections and retrosynthetic analysis of taxol and b) total synthesis (Nicolaou et al., 1994).^[154]

oxepane systems employing specifically designed hydroxy epoxides; b) the silver-promoted hydroxy dithioketal cyclization to didehydrooxocanes; c) the remarkable radical-mediated bridging of bis(thionolactones) to bicyclic systems; d) the photoinduced coupling of dithionesters to oxepanes; e) the

silicon-induced hydroxy ketone cyclization to oxepanes; f) nucleophilic additions to thiolactones as an entry to medium and large ring ethers; g) thermal cycloadditions of dimethyl acetylene dicarboxylate with cyclic enol ethers as an entry to medium size oxocyclic systems; and h) the novel and unprecedented chemistry of dithiatopazine. For a more detailed analysis of this total synthesis, the reader should consult ref. [3].

Dynemicin A (1995)

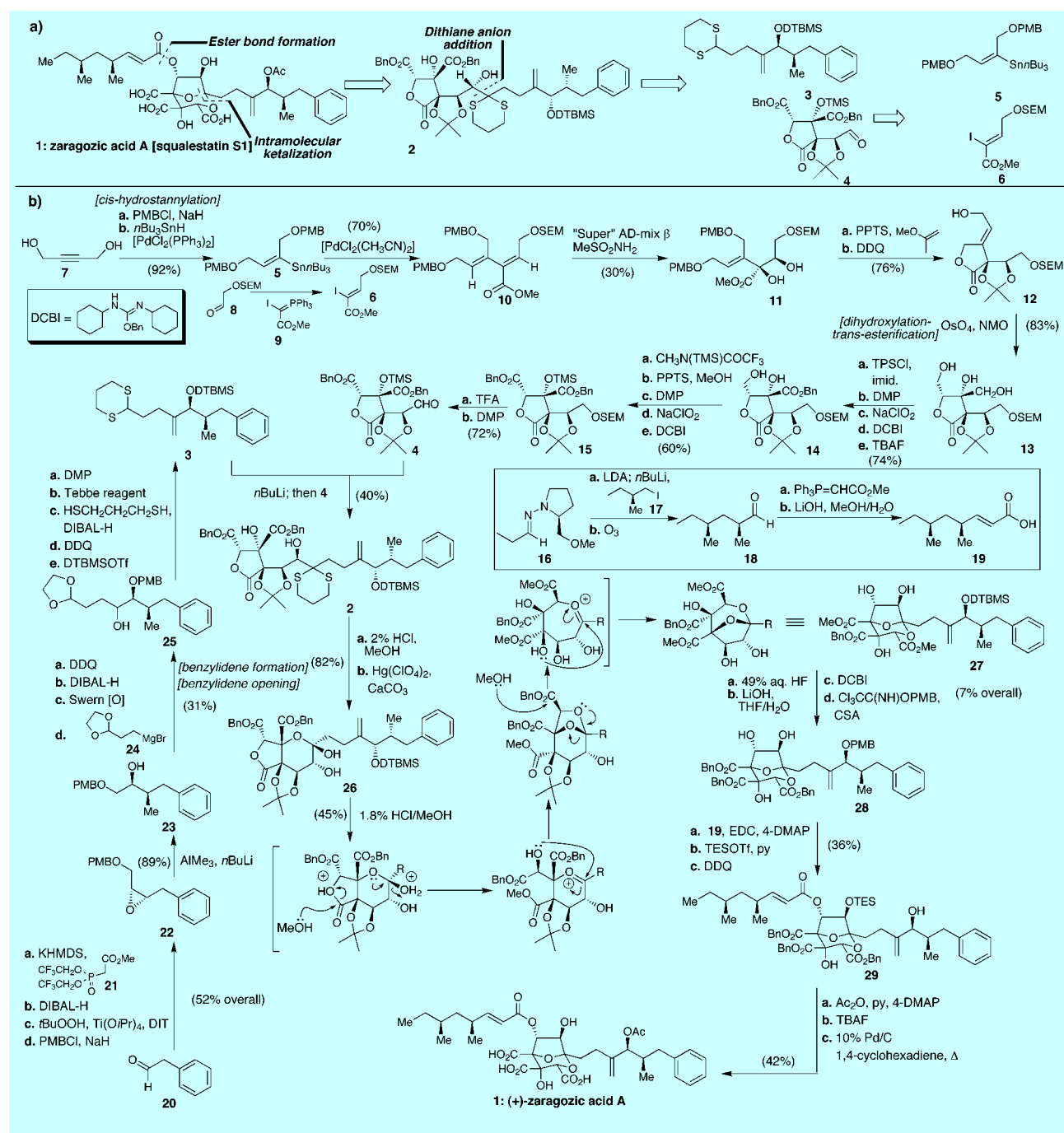
Dynemicin A^[180] (1 in Scheme 35; see page 84), a dark blue substance with strong antitumor properties and a member of the enediyne class of antitumor antibiotics that includes calicheamicin γ_1^1 (Scheme 26), possesses a striking molecular architecture.^[140, 181] Isolated from *Micromonospora chersina*, dynemicin includes in its structure a highly strained 10-membered enediyne ring, and a juxtaposition of epoxide, imine, and anthraquinone functionalities. The lure provided by this fascinating DNA-cleaving molecule resulted in intense synthetic studies directed towards its total synthesis. In 1993 Schreiber et al. first reported the total synthesis of di- and trimethoxy derivatives of dynemicin methyl ester (1 in Scheme 34; see p. 84).^[182] This synthesis relies on the powerful intramolecular Diels–Alder reaction to construct the complex enediyne region of the molecule and a series of selective follow-up reactions to reach the methylated dynemicin targets.

Myers et al. reported the first total synthesis of dynemicin itself in 1995.^[183] Their synthesis, summarized in Scheme 35, highlights a stereoselective introduction of the ene–diyne bridge, the use of a quinone imine as the dienophile in a regio- and stereoselective Diels–Alder reaction, and a number of other novel steps to complete the total synthesis. The second total synthesis of dynemicin was reported from the Danishefsky laboratory^[184] (Scheme 36; see p. 85) and features a double Stille-type coupling in its assembly of the enediyne grouping. All three syntheses project admirable elegance and sophistication.

Ecteinasidin 743 (1996)

A marine-derived natural substance, ecteinasidin (1 in Scheme 37) possesses an unusual molecular architecture and extremely potent antitumor properties. Isolated from the tunicate *Ecteinasidia turbinata*, ecteinasidin 743 is comprised of eight rings, including a 10-membered heterocycle, and seven stereogenic centers.^[185] Prompted by its attractive molecular architecture, impressive biological action, and low natural abundance, Corey et al. embarked on its total synthesis, and in 1996 they published the first total synthesis^[186] of ecteinasidin 743 based on a brilliant strategy (Scheme 37; see p. 86).

The plan was inspired, at least in part, by the proposed biosynthesis of the natural product. Of the many powerful transformations in Corey's total synthesis of ecteinasidin 743, at least three stand out as defining attributes; an intramolecular Mannich bisannulation sequence was instrumental in establishing the bridging aromatic core to the



Scheme 30. a) Strategic bond disconnections and retrosynthetic analysis of zaragozic acid A and b) total synthesis (Nicolaou et al., 1994).^[164]

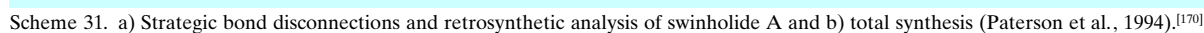
piperazine ring, which allowed the formation of the desired aminal functionality, while two asymmetric Pictet–Spengler reactions played key roles in forming the isoquinoline rings. The centerpiece of the synthesis is, however, the generation and biomimetic quinone methide capture by the sulfur atom to construct the 10-membered lactone bridge. The masterful use of substrate topology to predict reactivity, inflict asymmetry, and achieve selectivity is amply demonstrated throughout Corey’s synthesis.

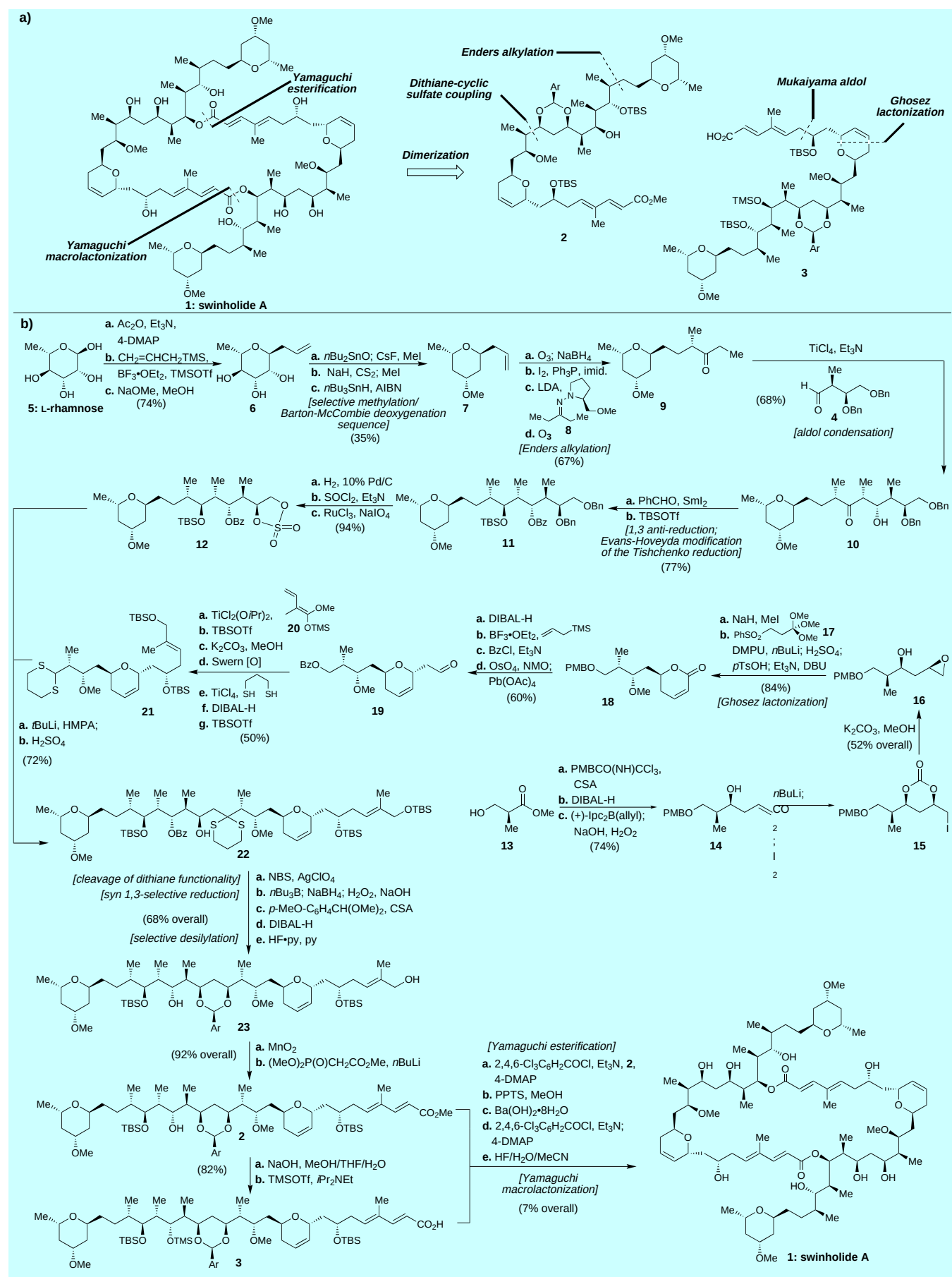
Finally, the success in recognizing subtle retrosynthetic clues left by nature and applying them in the context of a chemical synthesis elevates this total synthesis to a unique

level of brilliance. This impressive accomplishment also speaks for the efficiency that total synthesis has reached and the complex natural product analogues which can be synthesized in large quantities.^[187]

Epothilone A (1997)

Appearing in the mid-1990s, epothilones A (**1** in Scheme 38; see p. 87) and B^[188] stimulated intense research activities in several laboratories.^[189] The impetus for their total synthesis came not so much from their modestly complex macrolide structures but more so from their potent tubulin-





Scheme 32. a) Strategic bond disconnections and retrosynthetic analysis of swinholid A and b) total synthesis (Nicolaou et al., 1995).^[171]

binding properties and their potential to overshadow taxol as superior anticancer agents. The first total synthesis of epothilone A came from the Danishefsky laboratories in 1996^[190] and was followed shortly thereafter by syntheses from our laboratories^[191] and from those of Schinzer.^[192] Danishefsky's first total synthesis of epothilone A (Scheme 38) featured a Suzuki coupling reaction to form a crucial C–C bond and an intramolecular enolate–aldehyde condensation to form the 16-membered macrocyclic lactone. This method as well as others allowed the Danishefsky group to synthesize several additional natural and designed members of the epothilone family, including epothilone B,^[193] for extensive biological investigations.

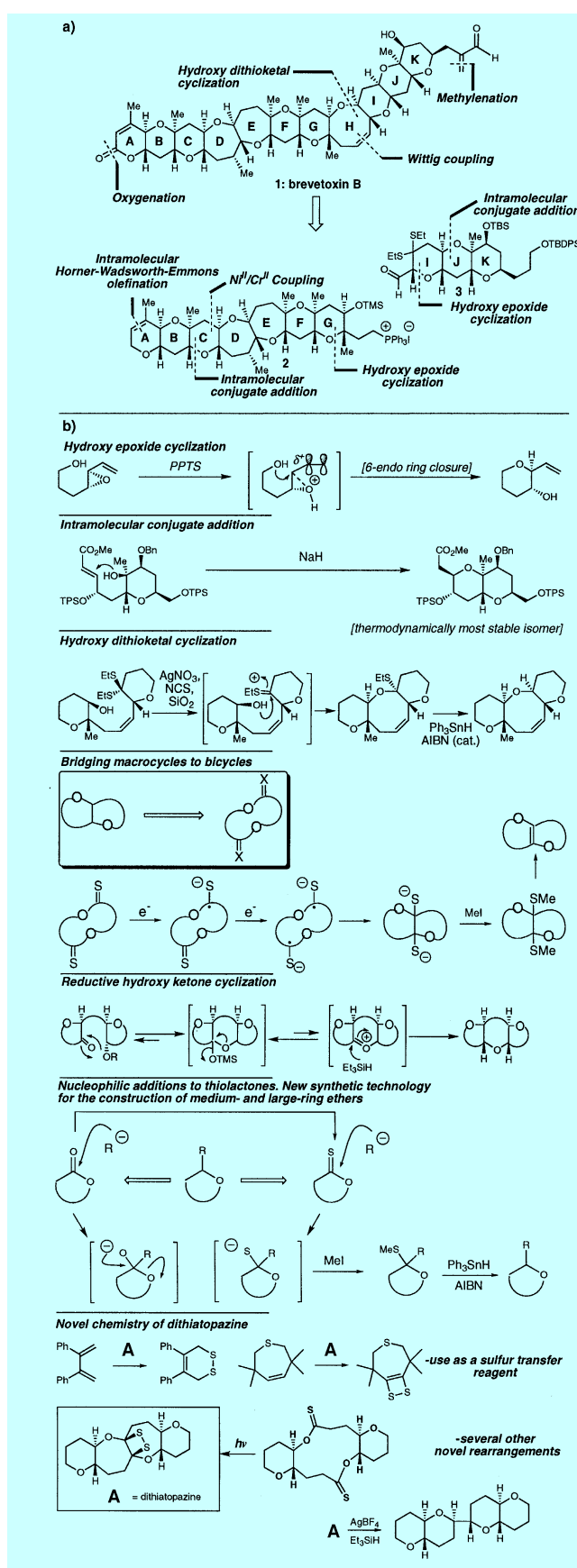
Chemical biology was also on our minds in devising a solution and a solid-phase total synthesis^[194] of epothilone A (**1**). As shown in Scheme 39 (see p. 87) this new solid-phase paradigm of complex molecule total synthesis relied on a novel olefin metathesis strategy.^[195] Of special note is the cyclorelease mechanism of this approach by which the 16-membered epothilone ring was constructed with simultaneous cleavage from the resin. Most importantly, this solid-phase strategy allowed the application of Radiofrequency Encoded Chemistry (REC; IRORI technology)^[196] to the construction of combinatorial epothilone libraries^[197] for chemical biology studies. The power of chemical synthesis of the 1990s in delivering large numbers of complex structures for biological screening was clearly demonstrated by this example of total synthesis, marking, perhaps, a new turn for the science.

Eleutherobin (1997)

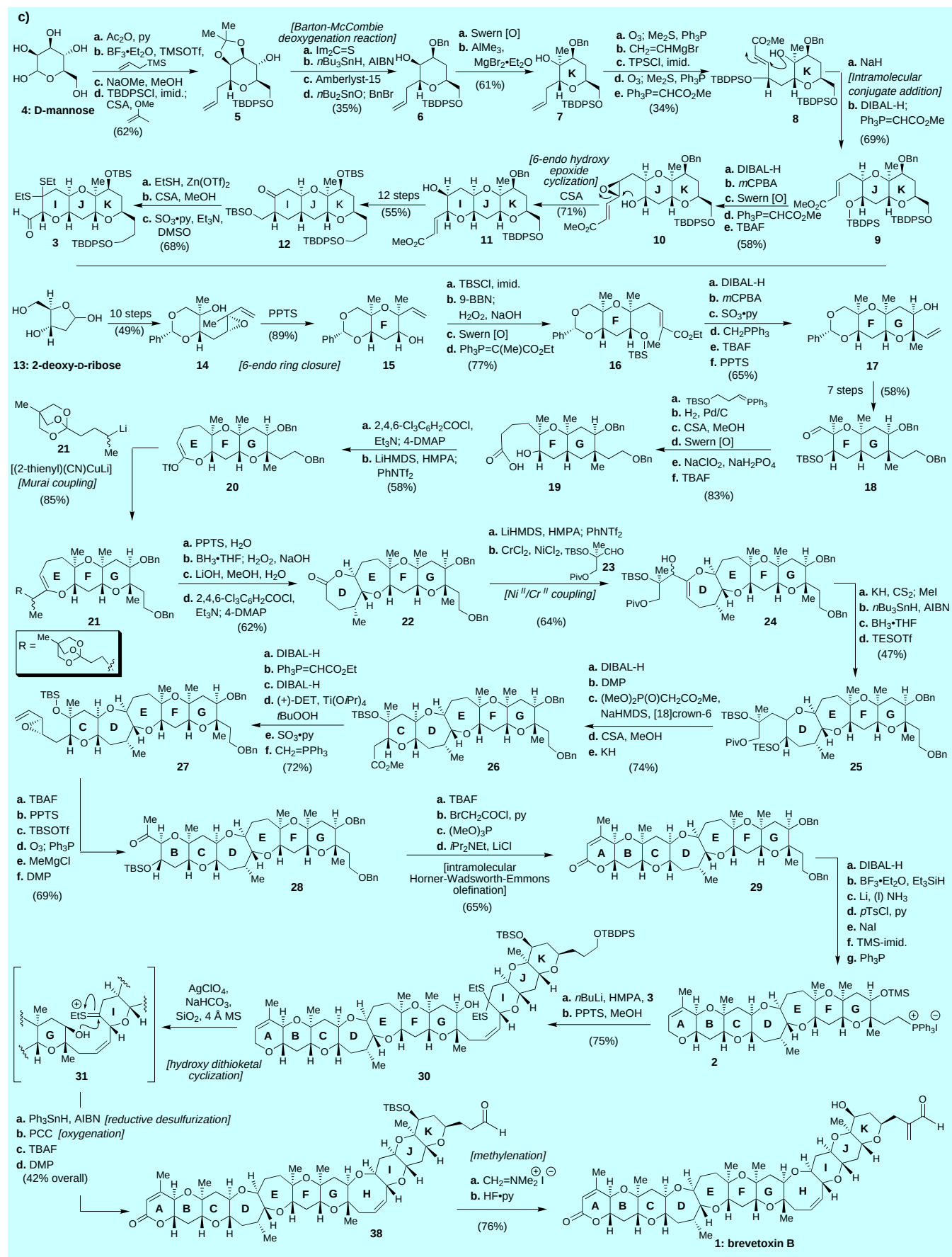
A marine natural product of some note, eleutherobin (**1** in Scheme 40; see p. 88) includes in its structure a number of unique features. Isolated from an *Eleutherobia* species of soft corals and reported in 1995,^[198] this scarce natural product elicited immediate attention from the synthetic community as a result of its novel molecular architecture and tubulin binding properties. Among the challenges posed by the molecule of eleutherobin are its oxygen-bridged 10-membered ring and its glycoside bond. Solutions to these problems were found in our 1997 total synthesis^[199] as well as in Danishefsky's total synthesis,^[200] which followed shortly thereafter. Scheme 40 summarizes our strategy to eleutherobin from (+)-carvone. Highlights include the intramolecular acetylide–aldehyde condensation to give the desired 10-membered ring and the spontaneous intramolecular collapse of an in situ generated hydroxycyclodecenone to form eleutherobin's bicyclic framework. This total synthesis exemplified the power of chemical synthesis in delivering scarce natural substances for biological investigations.

Sarcodictyin A (1997)

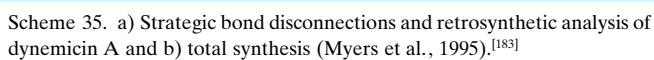
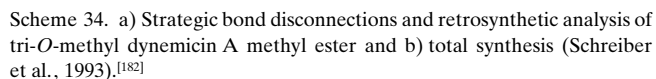
Sarcodictyins A and B (**1** and **2** in Scheme 41; see p. 88) are two marine natural products discovered in 1987 in the Mediterranean stoloniferan coral *Sarcodictyon roseum*.^[201]

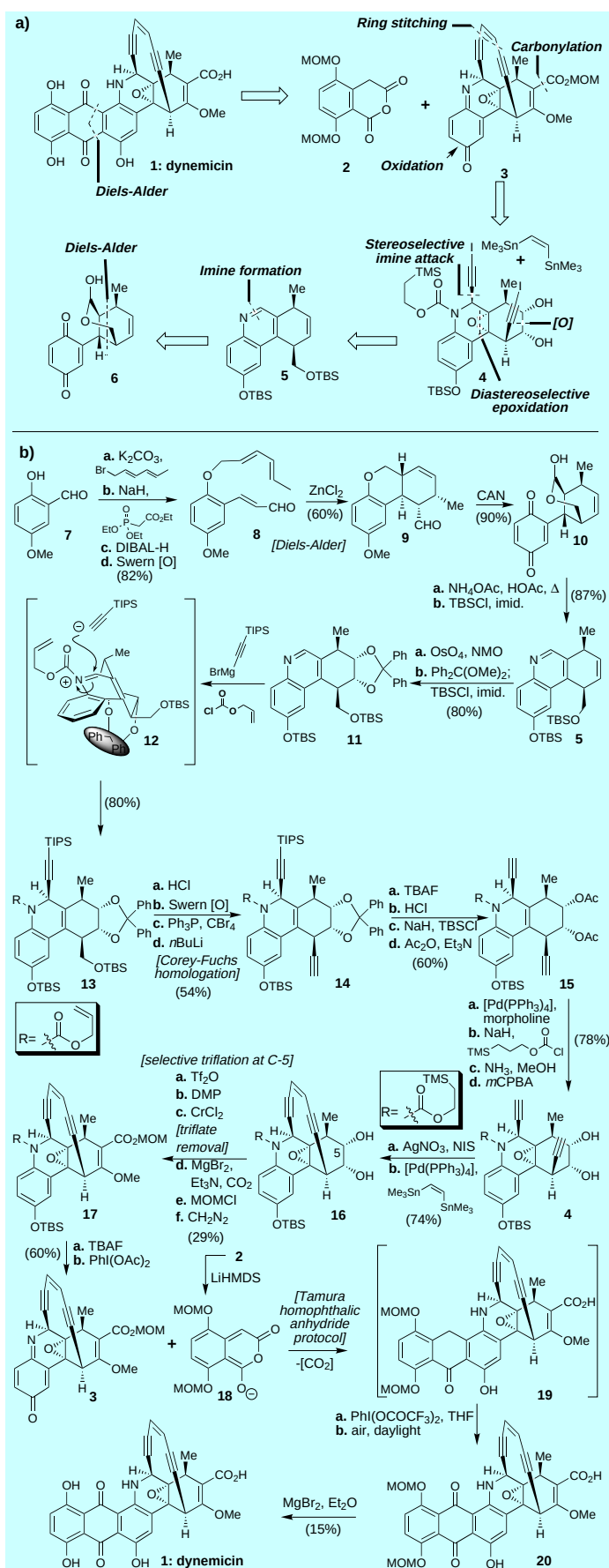


Scheme 33. a) Strategic bond disconnections and retrosynthetic analysis of brevetoxin B, b) key synthetic methodologies developed for the formation of polycyclic ethers and fundamental discoveries, and c) total synthesis of brevetoxin B (Nicolaou et al., 1995).^[178]



Scheme 33. (Continued)





Scheme 36. a) Strategic bond disconnections and retrosynthetic analysis of dynemicin A and b) total synthesis (Danishefsky et al., 1996).^[184]

Their potent antitumor properties are due, at least in part, to their tubulin-binding properties, resembling both eleutherobin and taxol in this regard.^[202, 203] While the structural similarities of the sarcodictyins to eleutherobin are apparent, the correspondence of these molecules to taxol is not so obvious.^[203] Nevertheless, the excitement generated from their taxol-like properties, coupled with their scarcity, led to the launching of programs directed toward their total synthesis.

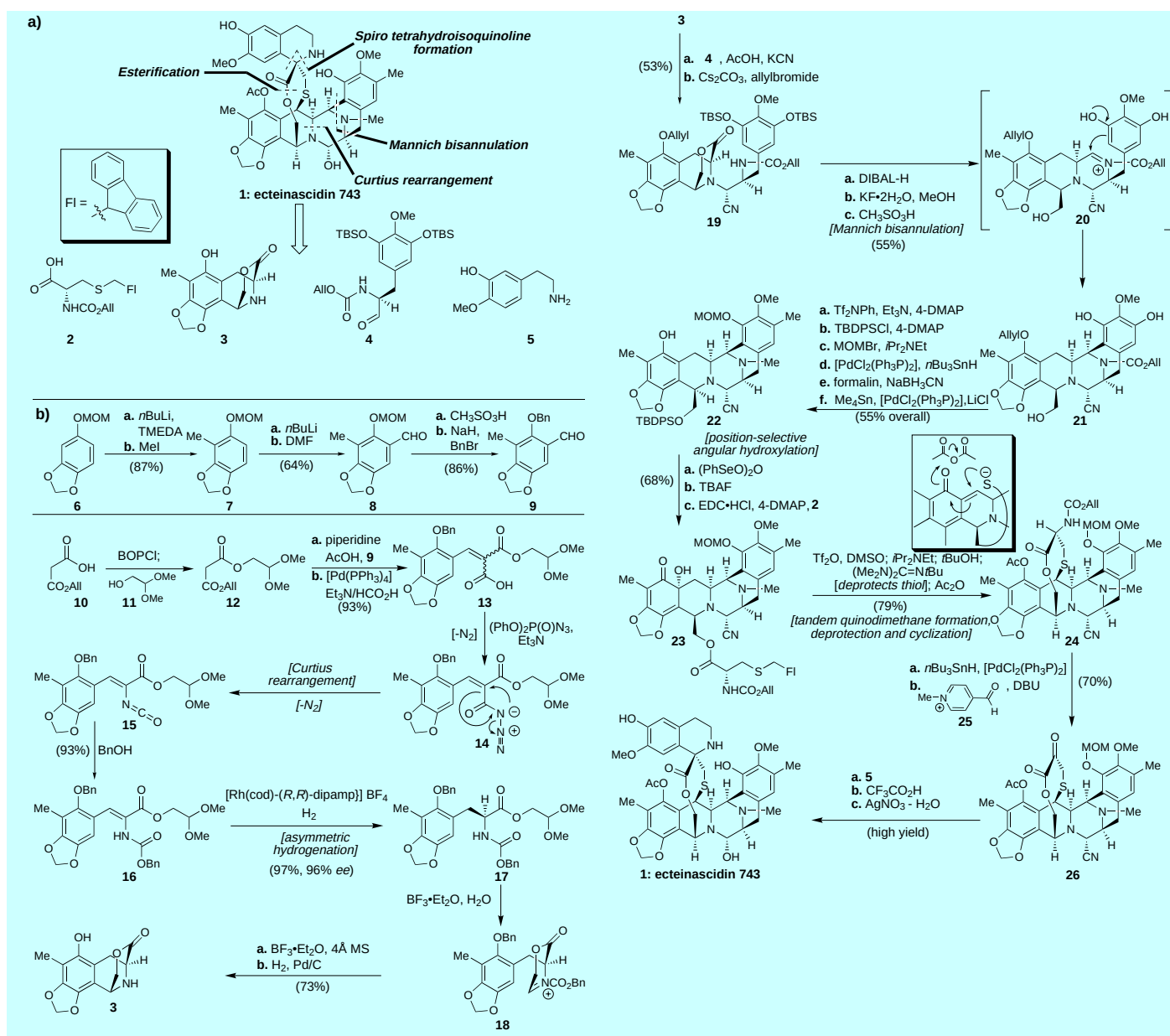
It is noteworthy that the impetus for the chemical synthesis of these molecules in the 1990s was provided not only from their structural novelty, but also from the desire to apply organic synthesis as an enabling technology for chemical biology. Thus, the total synthesis of sarcodictyins A and B, accomplished in these laboratories in 1997,^[204] went further than delivering the natural substances. It was applied, particularly in its solid-phase version (Scheme 41; see p. 88), to the construction of combinatorial libraries for the purposes of biological screening.^[203, 205] That complex natural products such as the sarcodictyins could be synthesized, at least partially, on a solid phase is testament to the power and potential of the recent advances in solid-phase chemistry. Even more telling is the ability of synthetic chemistry at the turn of the century to deliver combinatorial libraries of complex natural or designed products such as those synthesized in this program and in the one described above for the epothilones.

Resiniferatoxin (1997)

A structural relative of phorbol ester,^[206] resiniferatoxin (**1** in Scheme 43; see p. 92)^[207] was isolated from the *E. resinifera* cactus species and exhibits—unlike phorbol but like capsaicin^[208]—binding affinity to the vanilloid receptor present in sensory neurons. Besides its potential in biology and medicine, resiniferatoxin offers opportunities to the synthetic chemist, among which is the application of new methods of synthesis to the construction of the molecule. The structure of resiniferatoxin contains an ABC ring skeleton with two *trans* fusions. The C-ring carries five contiguous stereocenters, three of which bear hydroxyl groups which are engaged in a benzyl orthoester system. Following their success with phorbol ester^[209] the Wender group at Stanford reported the total synthesis of resiniferatoxin in 1997.^[210] This synthesis (Scheme 43) brilliantly blends classical synthetic methods with modern methodological advances in a strategy that stands as a hallmark to the progression of natural product synthesis. Highlights include an intramolecular [3+2] dipolar cycloaddition reaction between an oxidopyryllium ion and a terminal olefin to construct the BC framework, and a transition metal-induced ring closure of an eneyne to form the cyclopentane system (ring A).

Brevetoxin A (1998)

Within the polluted “red tide” waters often resides a more powerful neurotoxin, and that is brevetoxin A (**1** in Scheme 42; see p. 90). Isolated from the dinoflagellate species *Ptychodiscus brevis* Davis (*Gymnodium breve* Davis), breve-

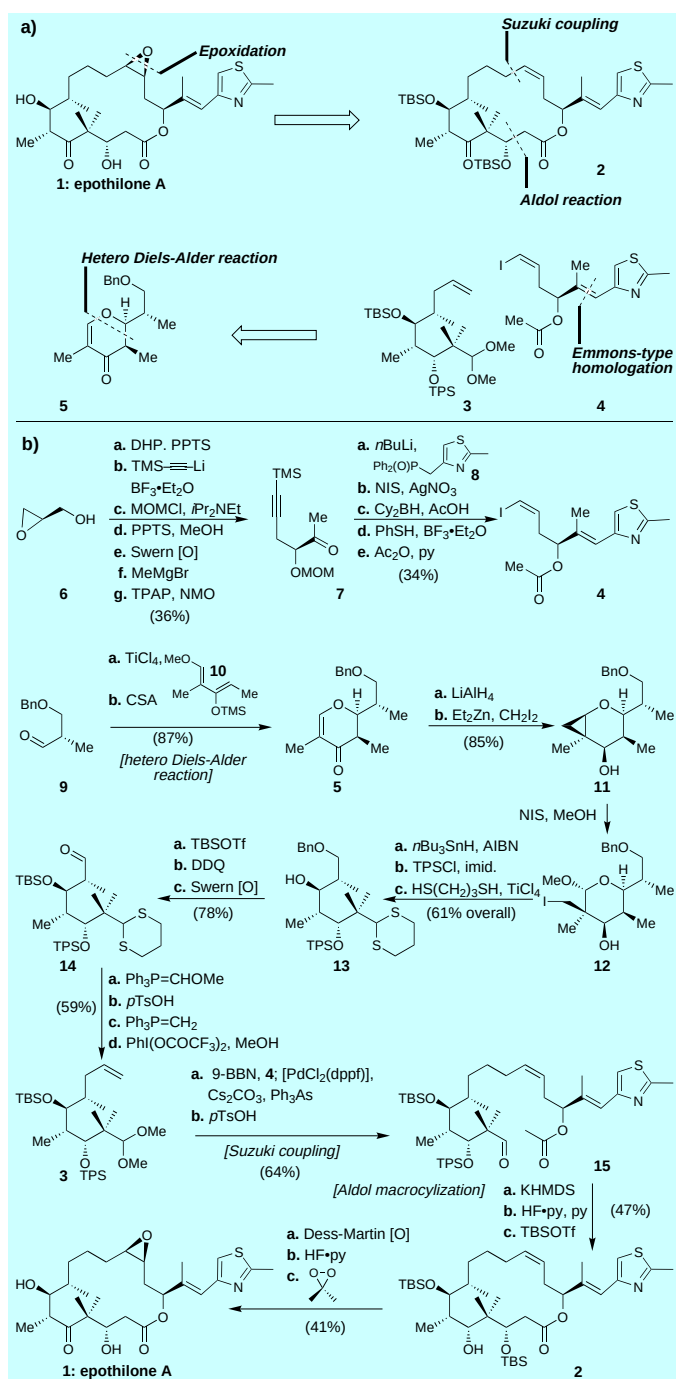

 Scheme 37. a) Strategic bond disconnections and retrosynthetic analysis of ecteinascidin 743 and b) total synthesis (Corey et al., 1996).^[186]

toxin A was structurally elucidated in 1986.^[211] With its ten fused ring structure and its twenty-two stereocenters, brevetoxin A rivals brevetoxin B in complexity, but as a synthetic target it arguably exceeds the latter in difficulty and challenge because of the presence of the 9-membered ring. Indeed, with rings ranging in size from 5- to 9-membered, all sizes in between included, brevetoxin A can be considered as the ultimate challenge to the synthetic chemist as far as medium-sized ring construction is concerned. After a ten-year campaign, our group reported the total synthesis of brevetoxin A (Scheme 42) in 1998.^[212] As in the case of brevetoxin B, this program was rich in new synthetic technologies and strategies, which emerged as broadly useful spin-offs (Scheme 42c). Amongst the most important synthetic technologies developed during this program was the palladium-catalyzed coupling of cyclic ketene acetal phosphates gen-

erated from lactones with appropriate appendages to afford cyclic enol ether diene systems^[213] suitable for a cycloaddition reaction with singlet oxygen (**24** → **26** in Scheme 42). This method provided the crucial turning point in solving the problems associated with the 7-, 8-, and 9-membered rings of the target and opened the gates for the final and victorious drive to brevetoxin A.

Manzamine A (1998)

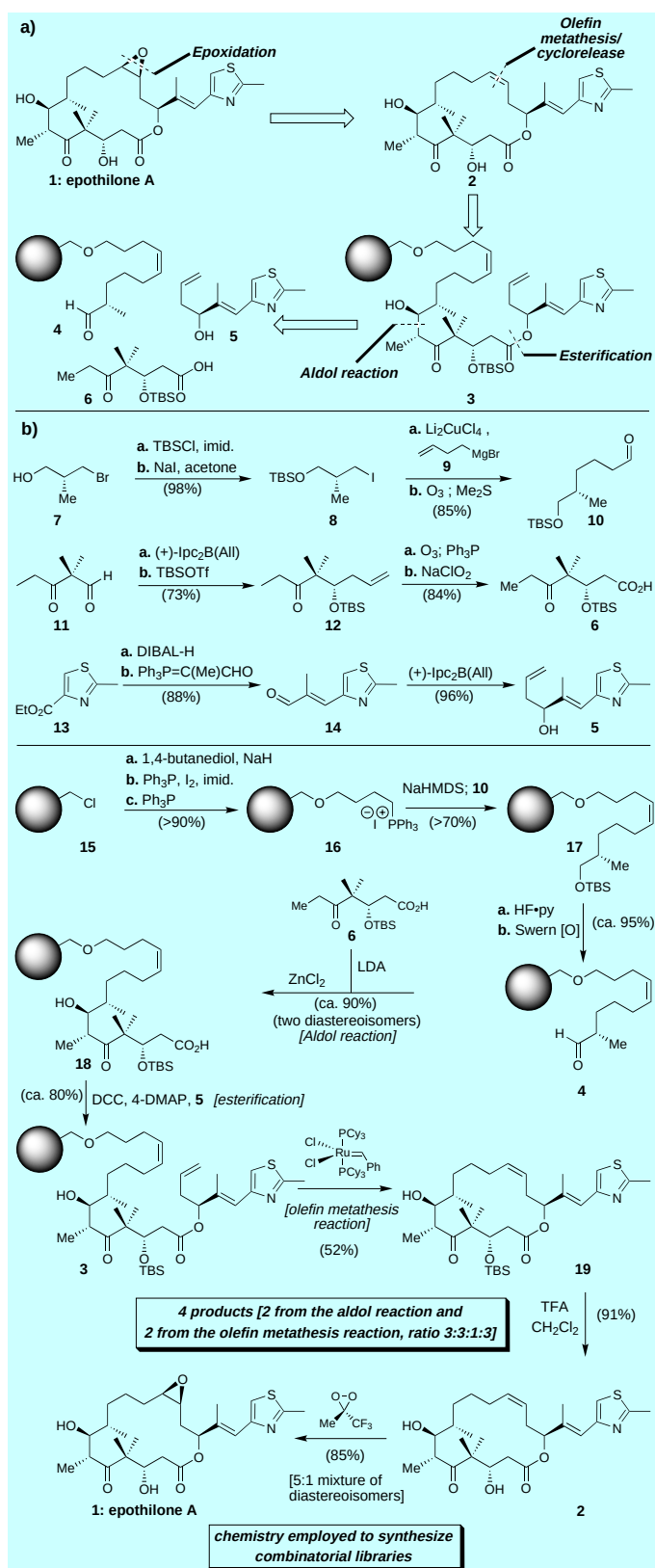
Manzamine A (**1** in Scheme 44; see p. 93) is a sponge-derived substance (genera *Haliclona* and *Pellina*) with potent antitumor properties. Disclosed in 1986,^[214] the structure of manzamine A, and those of its subsequently reported relatives,^[215] attracted a great deal of attention from synthetic chemists. The interest in the manzamines as synthetic targets



Scheme 38. a) Strategic bond disconnections and retrosynthetic analysis of epothilone A and b) total synthesis (Danishefsky et al., 1996).^[190]

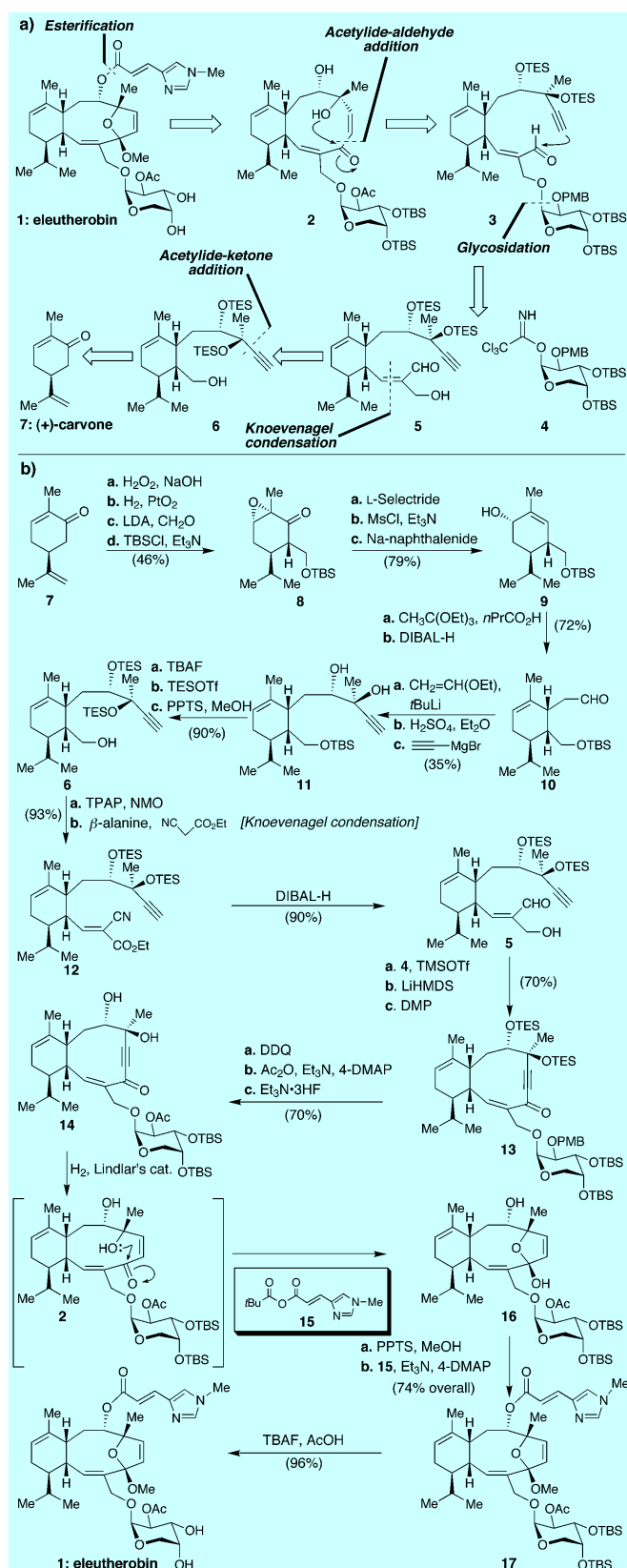
was heightened by a hypothesis put forward by Baldwin et al. in 1992 for their biosynthesis.^[216] By early 1999 two total syntheses^[217, 218] of manzamine A and evidence^[219] supporting the biosynthetic hypothesis had been reported.

Baldwin's intriguing hypothesis for the biosynthesis of the manzamine alkaloids postulates four simple starting materials and an intramolecular Diels–Alder reaction as the key process to assemble the polycyclic framework (see Scheme 45). The first total synthesis of manzamine A appeared from the Winkler group in 1998,^[217] proceeded through ircinal (**2** in Scheme 44), itself a natural product, and involved



Scheme 39. a) Strategic bond disconnections and retrosynthetic analysis of epothilone A and b) total synthesis (Nicolaou et al., 1997).^[194, 197]

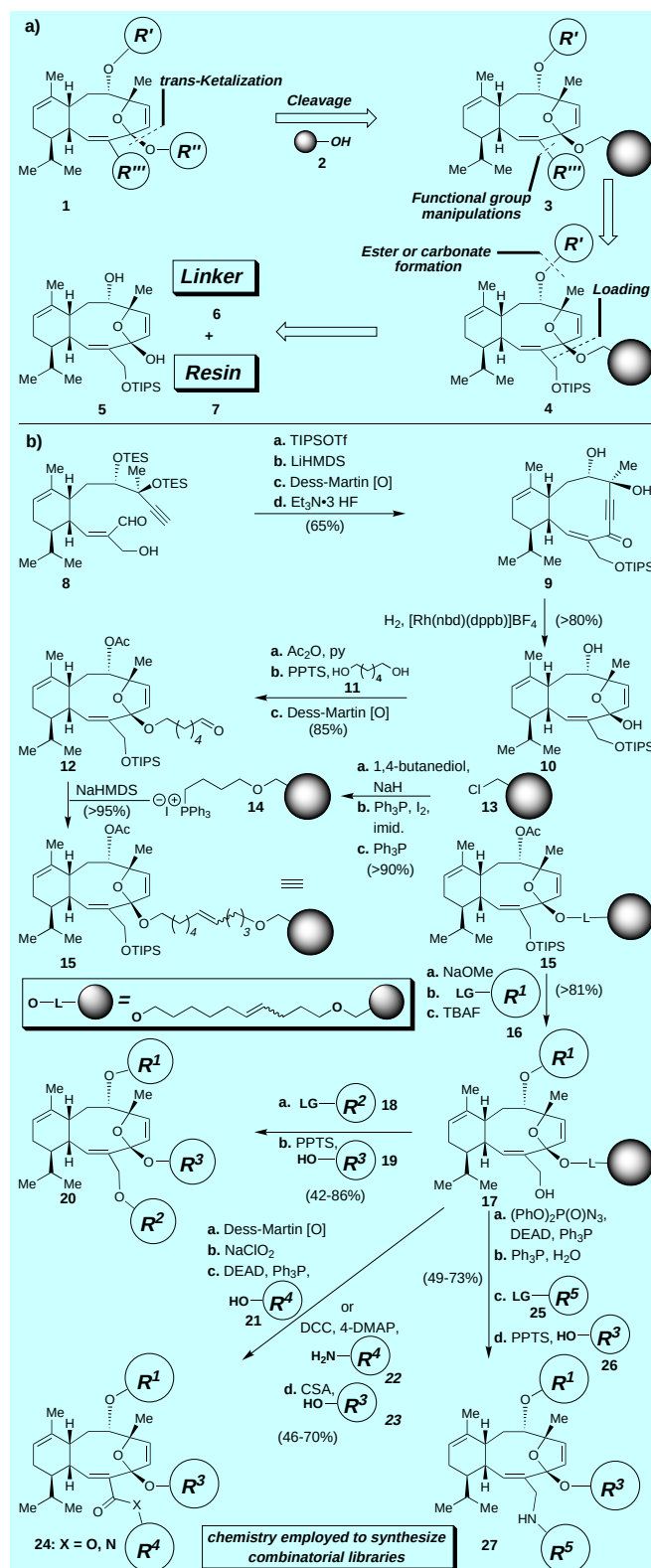
a photoinduced [2+2] cycloaddition reaction, a Mannich closure, and an intramolecular N-alkylation to assemble the polycyclic skeleton. In early 1999 the Baldwin group provid-



Scheme 40. a) Strategic bond disconnections and retrosynthetic analysis of eleutherobin and b) total synthesis (Nicolaou et al., 1997).^[199]

ed^[219] evidence for their hypothesis through synthetic studies culminating in the synthesis, albeit in low yield, of keramaphidin B (Scheme 45; see p. 93). The synthesis reported by

Martin et al. in 1999 (Scheme 46; see p. 94)^[218] on the other hand involved an intramolecular Diels–Alder reaction and two olefin metathesis ring closures to construct the pentacyclic framework of the target molecule. All three approaches



are elegant in their conception and brilliant in their execution, demonstrating once again the ability of organic synthesis to swiftly respond to new challenges posed by novel structures from nature.

Vancomycin (1999)

Vancomycin (**1** in Scheme 47 and 48; see p. 95), a representative of the glycopeptide class of antibiotics,^[220] was isolated in the 1950s and used for over four decades as a weapon of last resort to combat bacterial disease. Isolated^[221] from the actinomycete *Amycolatopsis orientalis*, vancomycin finally yielded to structural elucidation in 1982.^[222] Within a few years, it became the subject of synthetic investigations, primarily as a consequence of its novel molecular architecture, important biological action and medical applications, and intriguing mechanism of action. As a synthetic target, vancomycin offered a unique opportunity to synthetic chemists to develop new synthetic technologies and strategies. Among the most intriguing structural features of the molecule were its two 16-membered bisaryl ether macrocycles and its 12-membered bisaryl ring system, each of which is associated with an atropisomerism problem. The attachment of the two carbohydrate moieties onto the heptapeptide aglycon system added to the challenge presented by this target molecule.

By 1998 two groups, that of D. A. Evans^[223] and ours,^[224] had reported independent total syntheses of the vancomycin aglycon and by early 1999 the first total synthesis^[225, 226] of vancomycin itself appeared in the literature followed by another report of the aglycon synthesis by the Boger group.^[227] Emanating from these laboratories, the total synthesis of vancomycin is summarized in Scheme 48 (see p. 96). During the vancomycin campaign, a number of new methods and strategies were designed and developed, among which, perhaps, the triazene-driven biaryl ether synthesis^[228] is the most prominent. The strategy employed modern asymmetric reactions for the construction of the required amino acid building blocks, which were then assembled into appropriate peptides and cyclized to form the desired framework. While the two biaryl ether macrocycles were formed by the triazene-driven cyclization, the bisaryl ring framework was assembled by a sequential Suzuki coupling and a macrolactamization reaction. Finally, the sugar units were sequentially attached onto an appropriately protected aglycon derivative, which afforded a protected vancomycin system in a stereoselective manner from which free vancomycin was obtained.

The Evans synthesis of vancomycin's aglycon, shown in Scheme 47,^[223] featured the stereocontrolled construction of the amino acid building blocks and assembly to the heptapeptide backbone through a vanadium-mediated C–C bond forming reaction to construct the 12-membered biaryl ring system and two nucleophilic aromatic substitutions activated by *o*-nitro groups to form the two bisaryl ether macrocycles. The synthesis of vancomycin's aglycon^[227] by Boger et al. (Scheme 50; see p. 100) is distinguished by extensive studies to determine the activation energy required to atropisomerize each macrocycle, thereby allowing selective atropisomerization of the AB ring system in the presence of the COD framework. These total syntheses added yet another distin-

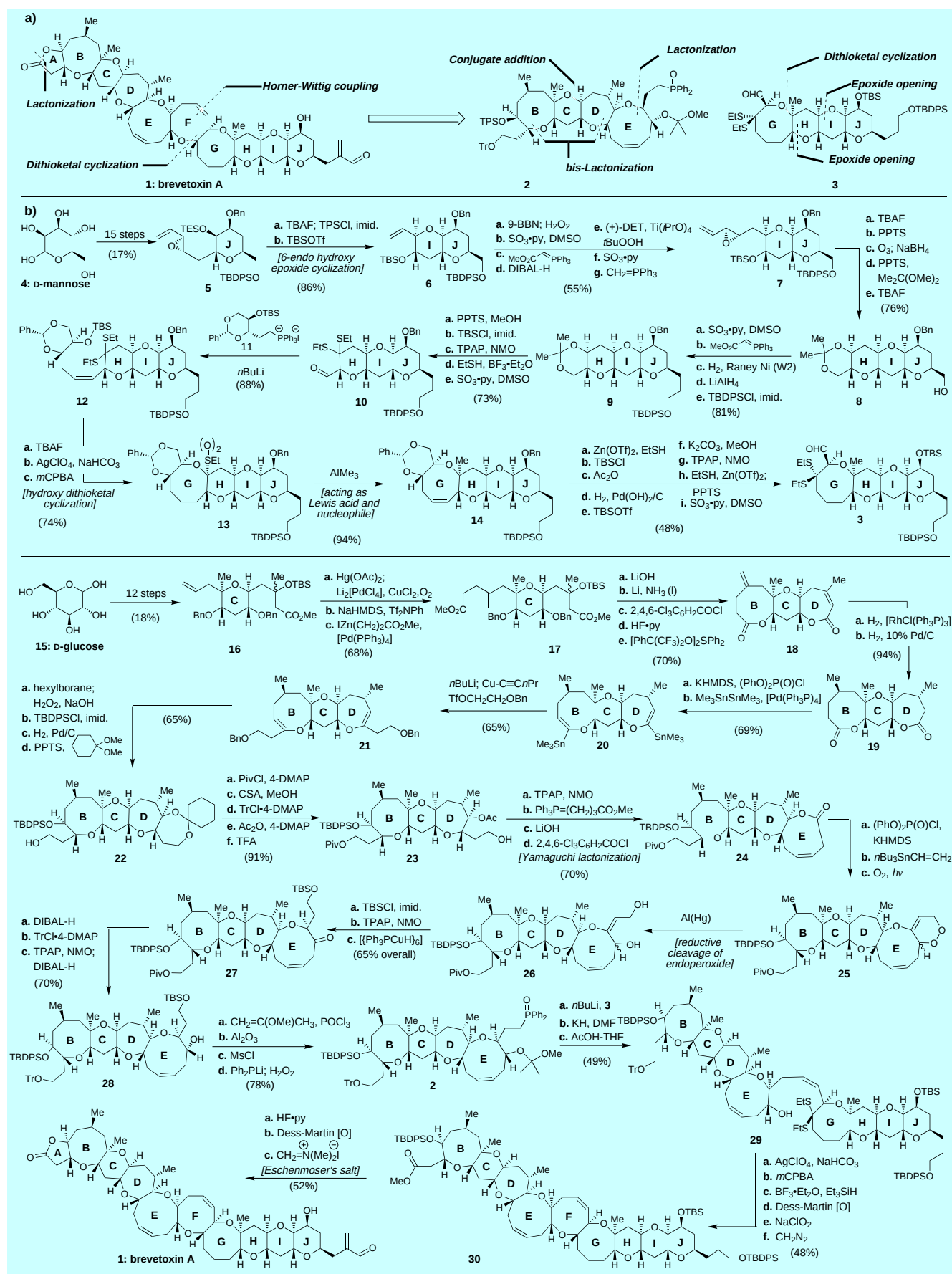
guished chapter to the annals of total synthesis and placed the glycopeptide antibiotics on the list of conquests of synthetic organic chemistry.

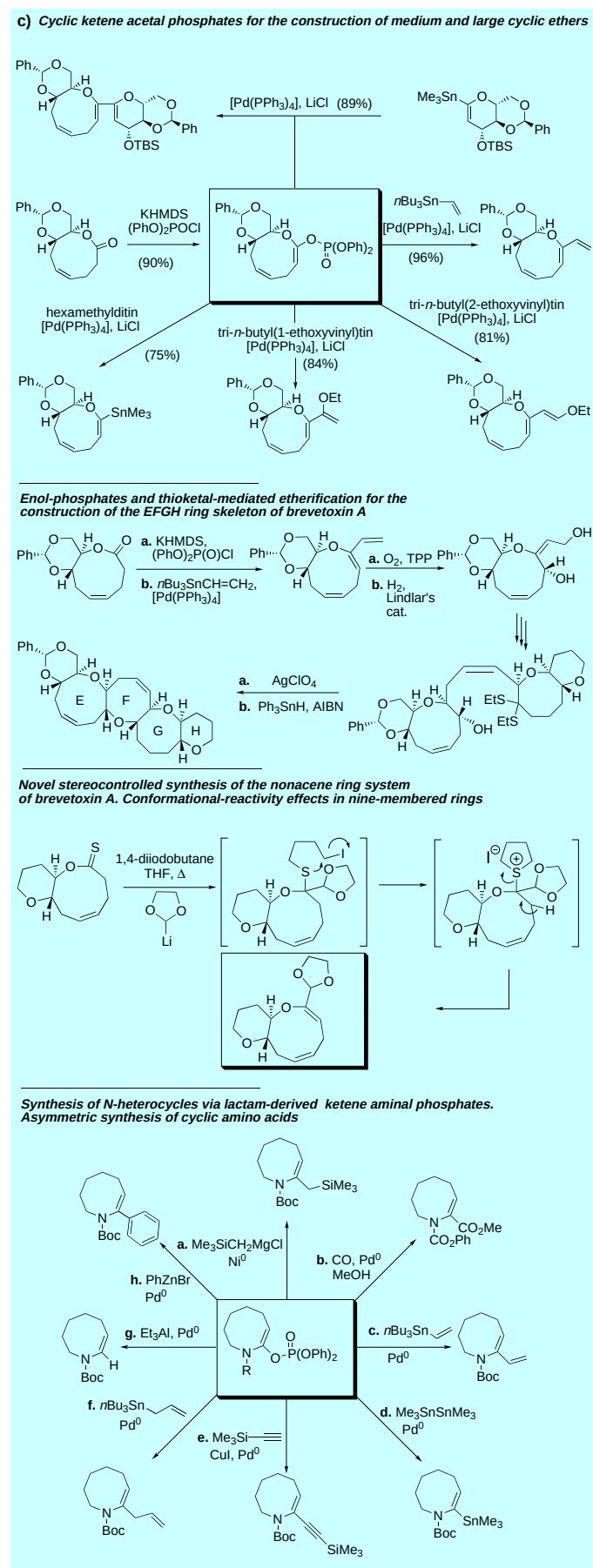
CP Molecules (1999)

CP-263,114 and CP-225,917 (**1** and **2**, respectively, in Scheme 49; see p. 98), isolated from an unidentified fungus by Pfizer scientists in 1997,^[229] inhibit squalene synthase and ras farnesyl transferase, and as such, represent important new leads for cholesterol-lowering and anticancer drugs. Nature molded within these structures an exotic display of delicate and rare functionalities that beckoned to synthetic chemists worldwide. The total synthesis of these compounds was finally accomplished in 1999 in our laboratories after a relentless campaign through a daunting synthetic labyrinth plagued with manifold and unexpected obstacles.^[230] This total synthesis is retrosynthetically blueprinted in Scheme 49 a. A critical disassembly maneuver called upon an intramolecular Diels–Alder reaction to simplify the bicyclic structure **6** of the CP molecules to the open-chain precursor **7**. Although this retrosynthetic analysis serves as a conceptual overview of the synthesis, it should be noted that it is actually the culmination of several unsuccessful retrosyntheses by which the conversion of ketone **6** into the CP molecules was planned.

Commencing with dimethyl malonate (**8**), the synthesis of the CP molecules proceeded smoothly through several intermediates and finally yielded the desired acyclic precursor **7** stereoselectively (Scheme 49 b). When compound **7** was treated with Me₂AlCl in dichloromethane at –20 °C, complete conversion to **6** through a Lewis acid catalyzed intramolecular Diels–Alder reaction was observed within two minutes. The formidable task of stereoselectively installing the remote stereocenter at C7 was addressed by utilizing dithiane chemistry (**6** → **15**). The reason for such a high level of diastereoselectivity (ca. 11:1) could possibly be a consequence of a shielding effect of the CP skeleton. Indeed, the surprisingly close proximity of this side chain to the rest of the molecule was quite apparent throughout the synthesis. The stage was now set for the installation of the fused maleic anhydride moiety. The synthesis of this delicate moiety was in itself a great challenge due to unique environment surrounding ketone **15**. The development of novel chemistry to construct the anhydride was a result of persistence in the face of several failed strategies.^[231] Thus, ketone **15** was smoothly converted to the enol triflate followed by palladium-catalyzed carboxymethylation and exchange of the dithiane for a dimethoxy ketal leading to the unsaturated ester **16**.

After reduction with DIBAL-H, a Sharpless hydroxyl-directed epoxidation of the allylic alcohol led to epoxide **17** selectively (ca. 10:1). Introduction of this electrophilic species allowed for the placement of an additional carbon atom with the correct oxidation state for the ensuing cascade sequence. This carbon atom, in the form of a cyanide, was added to epoxide **17** using Et₂AlCN and proceeded with complete regio- and stereospecificity (see **17b**). It was after considerable experimentation that we discovered that it was possible to convert diol **18** in one synthetic operation. Thus, selective mesylation of diol **18**, followed by treatment with base and





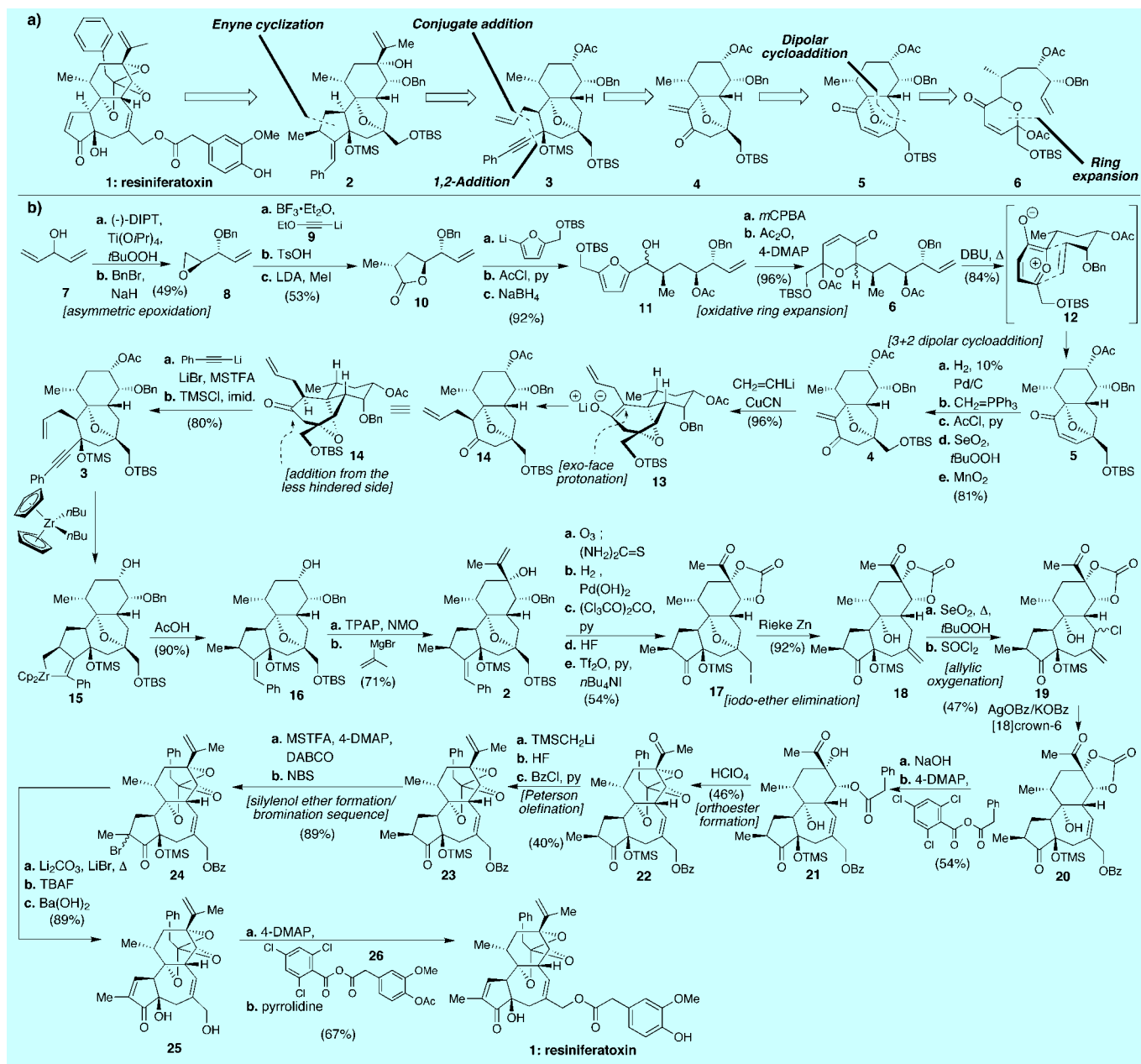
Scheme 42. (Continued)

finally acidic workup afforded the maleic anhydride **5**. The course of this dizzying domino sequence undoubtedly involves formation of the unprecedented carbocyclic imino butenolide **21** (a proven intermediate and new chemical entity isolated for the first time) whereupon facile tautomerization to the electron rich and easily oxidizable 2-amino-furan **22** occurs.

Stepwise oxidation of the furan **22** followed by nitrogen extrusion leads to anhydride **5**. The remarkable efficiency with which this reaction takes place (56% overall yield, seven transformations in one operation) is a testament to the utility of tandem reactions in organic synthesis. After some brief protecting group manipulations, the stage was set for the application of another cascade reaction. It was found that treatment of **23** with Dess-Martin-periodinane in refluxing benzene led to the desired γ -hydroxy lactonol in 63% yield. This tandem reaction was based on the simple ring-chain tautomerization of hydroxy ketones and permitted the crucial oxidation to take place.^[232]

The next key step involved the one-carbon elongation of intermediate **4** by the classic Arndt–Eistert reaction. Because of the extreme steric hindrance of the carboxylic acid derived from **4**, a new method specifically tailored for the preparation of hindered α -diazoketones was developed.^[233] This new synthetic technology was based on the expected extreme reactivity of the acyl mesylate species. In the event, acyl mesylate **25** successfully activated the hindered carboxylic acid for attack by diazomethane thus leading to the requisite α -diazoketone for the ensuing Wolff rearrangement. The final stage in the synthesis required conversion of indole **27** into the CP molecules. Although the conversion of **2** into **1** was known, the counterintuitive conversion of the seemingly robust **1** into its hydrated counterpart **2** appeared unlikely. We reasoned that LiOH might be useful for effecting this conversion by virtue of its unique solubility and reactivity. Not only did this LiOH-mediated cascade reaction succeed in hydrolyzing the indole amide of **27** to the corresponding carboxylic acid, it was also able to induce ring opening of the stable pyran motif to provide **2** directly. The conversion of **2** into **1** using acid catalysis proceeded smoothly, thus completing the total synthesis of the CP molecules.

In summary, the first total syntheses of these (racemic) compounds was accompanied by a plethora of fundamental discoveries, cascade reactions, and new synthetic technologies among which the following are, perhaps, most notable (see Scheme 49 c, d): 1) the design and execution of a cascade reaction involving no less than seven steps traversing through previously unknown chemical entities to construct the fused maleic anhydride moiety;^[231] 2) the enlistment of another tandem sequence predicated on the ring-chain tautomerization of hydroxy ketones to sculpt the γ -hydroxy lactone moiety onto the bicyclic skeleton;^[232] 3) development of a mild and effective method for the construction of extremely hindered diazoketones using acyl mesylates (Scheme 49 d, top);^[233] 4) a new paradigm for the two-step construction of strikingly complex natural-productlike heterocycles from commercially available chemicals (Scheme 49 d, middle);^[234] 5) a new method for the



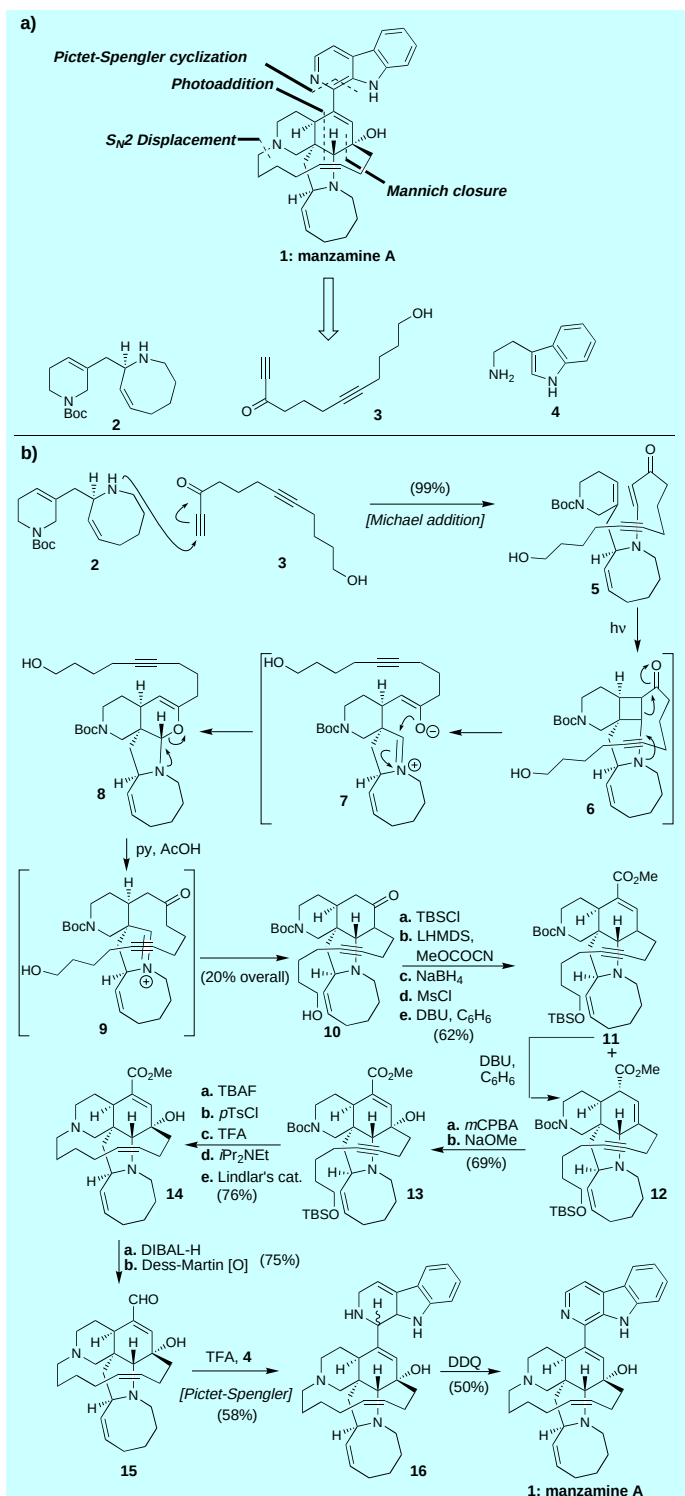
Scheme 43. a) Strategic bond disconnections and retrosynthetic analysis of resiniferatoxin and b) total synthesis (Wender et al., 1997).^[210]

one-carbon homologation of hindered aldehydes (Scheme 49d, bottom);^[235] and 6) the daring and counter-intuitive conversion of the structurally robust CP molecule **1** into its hydrated CP derivative **2** passing through a multiply-charged intermediate in yet another cascade sequence.^[230] The total synthesis of the CP molecules stands as an instructive example of how total synthesis can act as a driving force for the discovery and development of new concepts and methods in chemistry.

Aspidophytine (1999)

For over 25 years aspidophytine (**1** in Scheme 51; see p. 101) has remained an unanswered challenge for organic synthesis. Best known for its use as an antickroach/insecticidal

powder—at least since the Aztec era in parts of Mexico and Central America^[236]—its complex structure was not elucidated until 1973 by the groups of M. P. Cava, P. Yates, and D. E. Zacharias.^[237] The first total (enantioselective) synthesis of this molecule was finally completed in 1999 by E. J. Corey and co-workers and featured a rapid assembly of the aspidophytine core via a novel cascade sequence.^[238] The hallmark of the synthesis is the tandem sequence uniting dialdehyde **3** and indole **2** in a one flask tandem operation. Also notable is the conversion of acid **9** into lactone **11** by attack of the iminium species **10**. It is impressive that all four stereocenters (three quaternary) of **1** are derived from one chiral center secured early in the synthesis using the CBS reduction (see p. 58). Aside from developing a breathtaking new domino sequence to assemble the aspidophytine skeleton, this work raises the

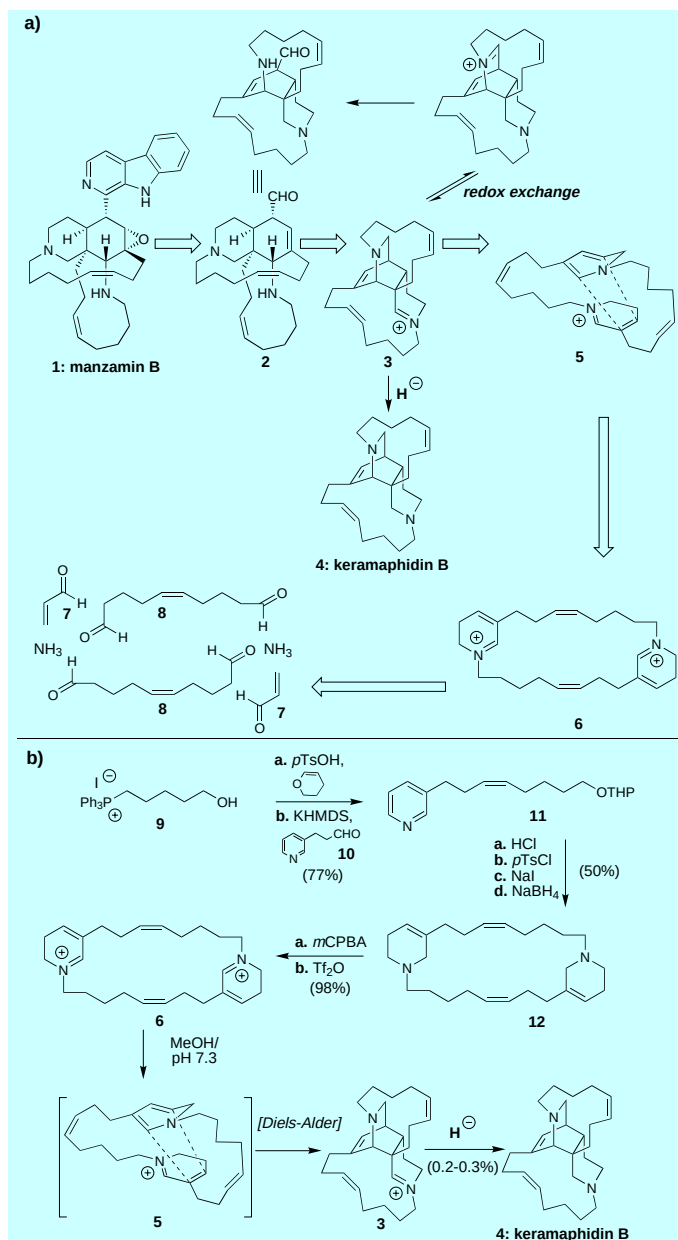


Scheme 44. a) Strategic bond disconnections and retrosynthetic analysis of manzamine A and b) total synthesis (Winkler et al., 1998).^[217]

standards for the concise synthesis of extremely complex alkaloids from simple starting materials.

Sanglifehrin A (1999)

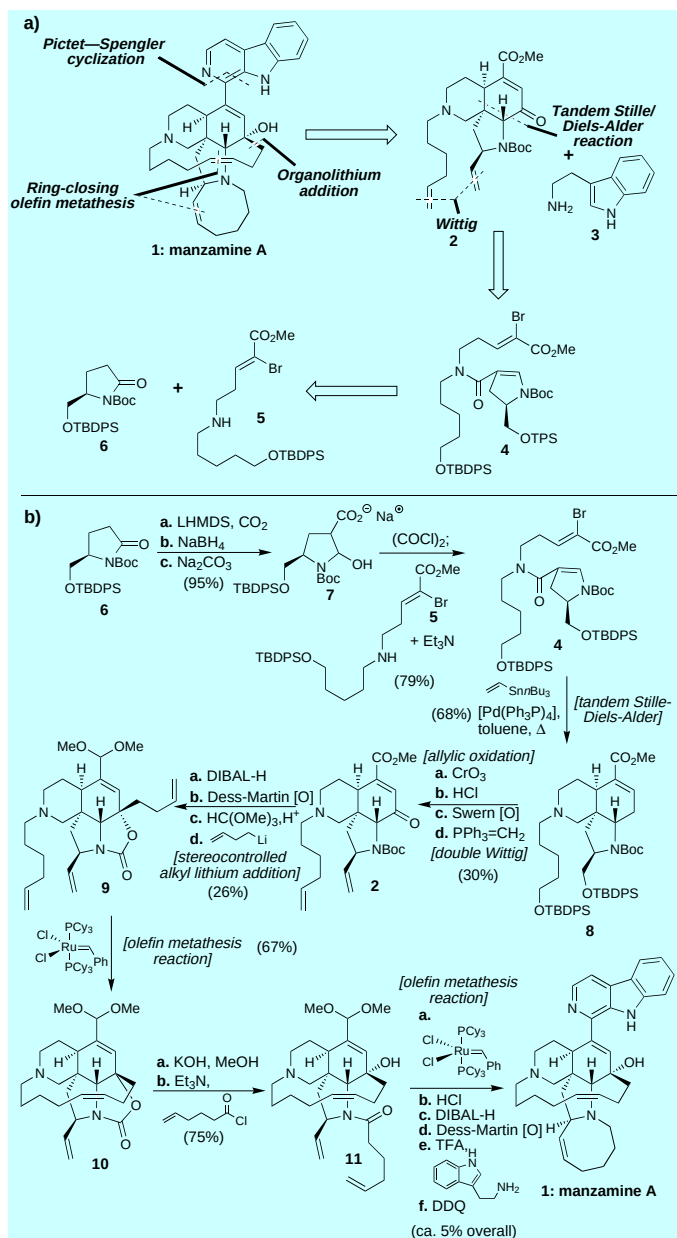
Sanglifehrin A (Scheme 53; see p. 104) was originally isolated by a team of Novartis scientists from an actinomycete



Scheme 45. a) Strategic bond disconnections and retrosynthetic analysis of manzamine B and b) biomimetic total synthesis of keramaphidin B (Baldwin et al., 1998).^[219]

strain found in a soil sample collected in Malawi.^[239] This molecule was found to display a very strong affinity for cyclophilin A (20-fold higher than cyclosporin A) and significant immunosuppressive activity (10-fold lower than cyclosporin A). Its mode of action seems to differ from other cyclophilin binders such as cyclosporin A and thus it raises a high interest for the understanding of immunosuppression mechanisms.

Sanglifehrin's chimeric structure is formed by a unique [5,5]-spiroactam fragment, linked to a 22-membered macrolactone ring that contains two unusual amino acid residues (piperazic acid and *meta*-tyrosine) as well as L-valine. Its unprecedented molecular features as well as its novel biological properties made sanglifehrin A a prime target for total synthesis. The first total synthesis of sanglifehrin A was



Scheme 46. a) Strategic bond disconnections and retrosynthetic analysis of manzamine A and b) total synthesis (Martin et al., 1999).^[218]

achieved in our laboratories in 1999.^[240] As indicated in Scheme 53, the two main domains of the molecule were assembled by an intermolecular Stille coupling. The construction of the sensitive iodomacrocyclic fragment was performed by an esterification, two peptide couplings, and eventually a regioselective intramolecular Stille coupling. The synthesis of the spiro lactam moiety involved the use of Paterson aldol reactions to establish the first five stereocenters, while the spiro lactam fragment was formed by intramolecular cyclization of a suitable 9-hydroxy-5-ketoamide precursor. The developed chemistry demonstrated once again the power of the Stille coupling reaction in the synthesis of complex molecules and opened the way for the construction of possible libraries for biological screening purposes.

Everninomicin 13,384-1 (1999)

Everninomicin 13,384-1 (Ziracin; **1** in Scheme 52; see p. 102),^[241] a member of the orthosomicin class of antibiotics^[242] and currently in clinical trials, is a promising new weapon against drug-resistant bacteria including methicillin-resistant Staphylococci and vancomycin-resistant Streptococci and Enterococci.^[243] Isolated from *Micromonospora carbonacea* var *africana* (found in a soil sample collected from the banks of the Nyiro River in Kenya), everninomicin 13,384-1 possesses a novel oligosaccharide structure containing two sensitive orthoester moieties, a 1,1'-disaccharide bridge, a nitrosugar, several β -mannoside bonds, and terminates with two highly substituted aromatic esters.^[244]

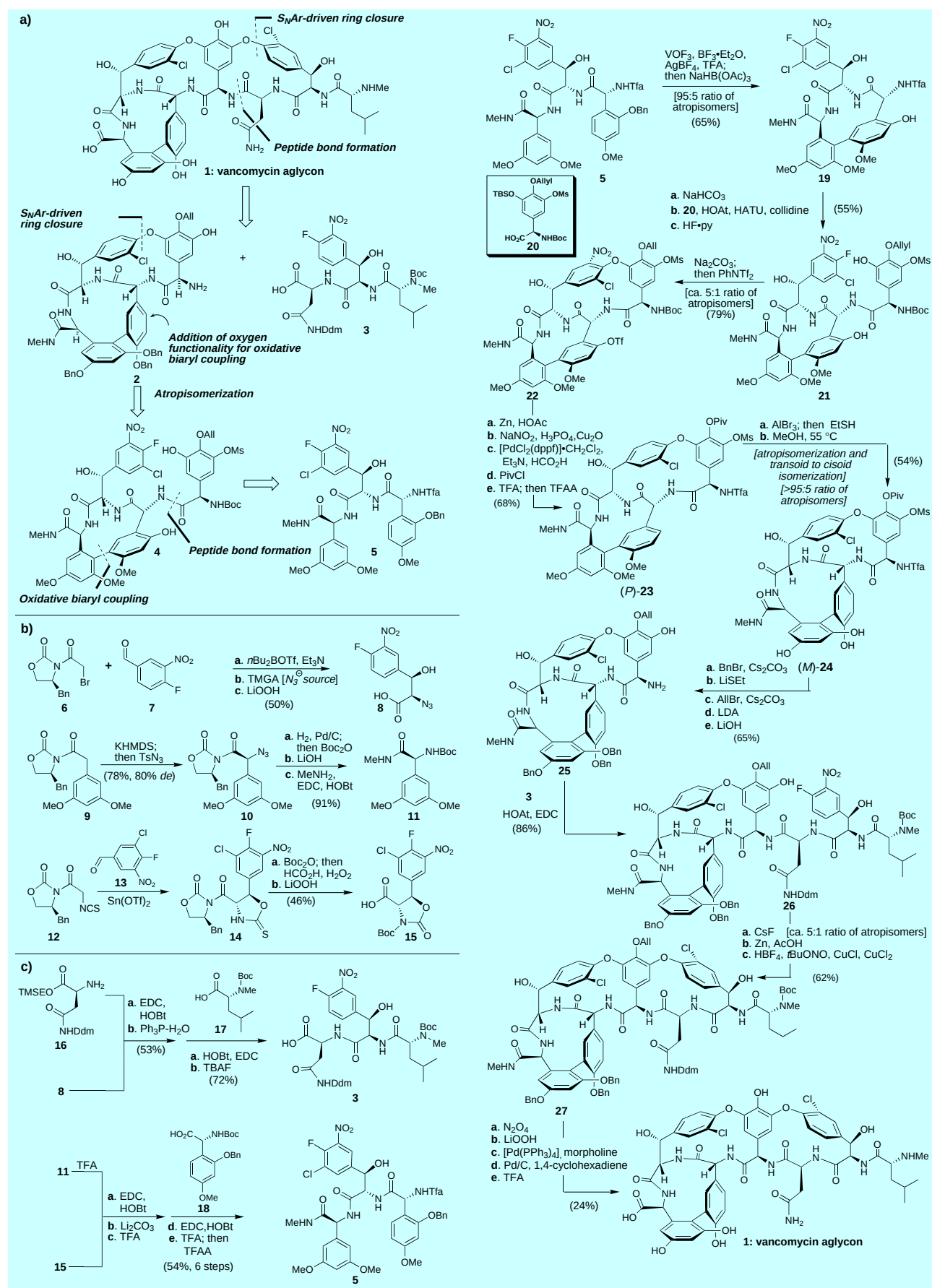
As a consequence of its unusual connectivity and polyfunctional and sensitive nature, everninomicin 13,384-1 constituted a formidable challenge to organic synthesis. After several generations of glycosylation and protecting group strategies had been explored and new synthetic methodologies were developed, the total synthesis of everninomicin 13,384-1 was finally completed in our laboratories in 1999.^[245] Highlights of this synthesis include: 1) the tin acetal-based stereocontrolled formation of the 1,1'-disaccharide linkage;^[246] 2) the 1,2-migration of selenophenyl groups leading to selective orthoester formation based upon a modification of Sinaÿ's method;^[247] and 3) the stereocontrolled formation of eight unique glycoside bonds using a variety of techniques including sulfur-, selenium-, and ester-based neighboring group participation.

Additional examples of natural products synthesized in the twentieth century are given in Figures 5–8 (see pp. 105–108),^[350–458] but even this listing does not do justice to the science of those whose brilliant contributions are not mentioned here as a result of the limited space available and unintentional oversight. For a more complete picture, the reader should consult the primary literature.

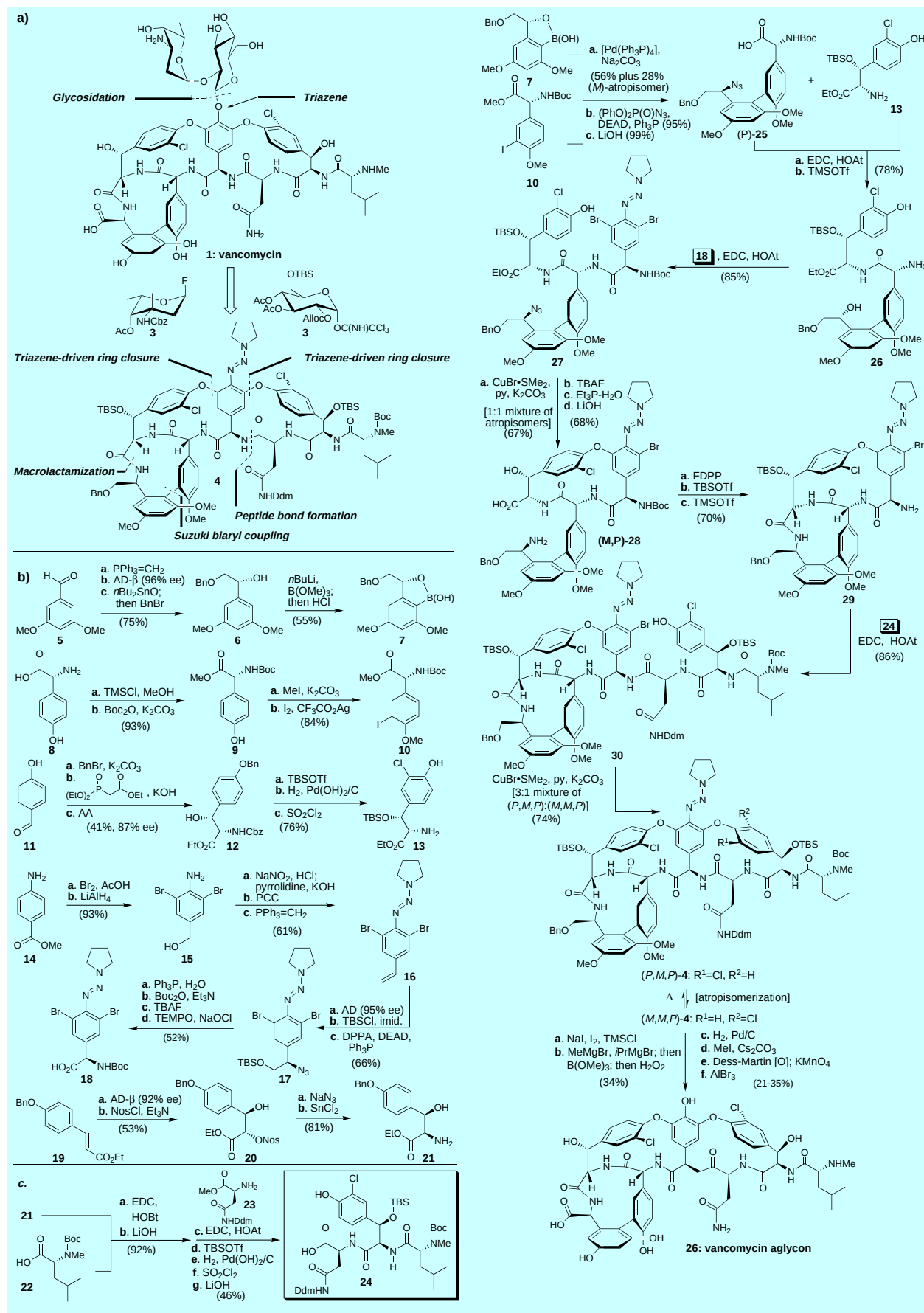
4. What Have We Learned from a Century of Organic and Natural Product Synthesis?

During the twentieth century, we have come, through the electronic theory and understanding of the nature of the chemical bond and mechanistic insights, to adopt the arrow to designate bond making and bond breaking. During this revolutionary period for organic synthesis, we have also come to understand and use conformational analysis, and to use pericyclic reactions, anions and cations, as well as carbenes and radicals in controlled ways to form and break chemical bonds. The Woodward and Hoffmann rules brought understanding and generalization to pericyclic reactions such as the Diels–Alder reaction, the photoinduced [2+2] cycloadditions, and the various 1,3-dipolar cycloaddition reactions.

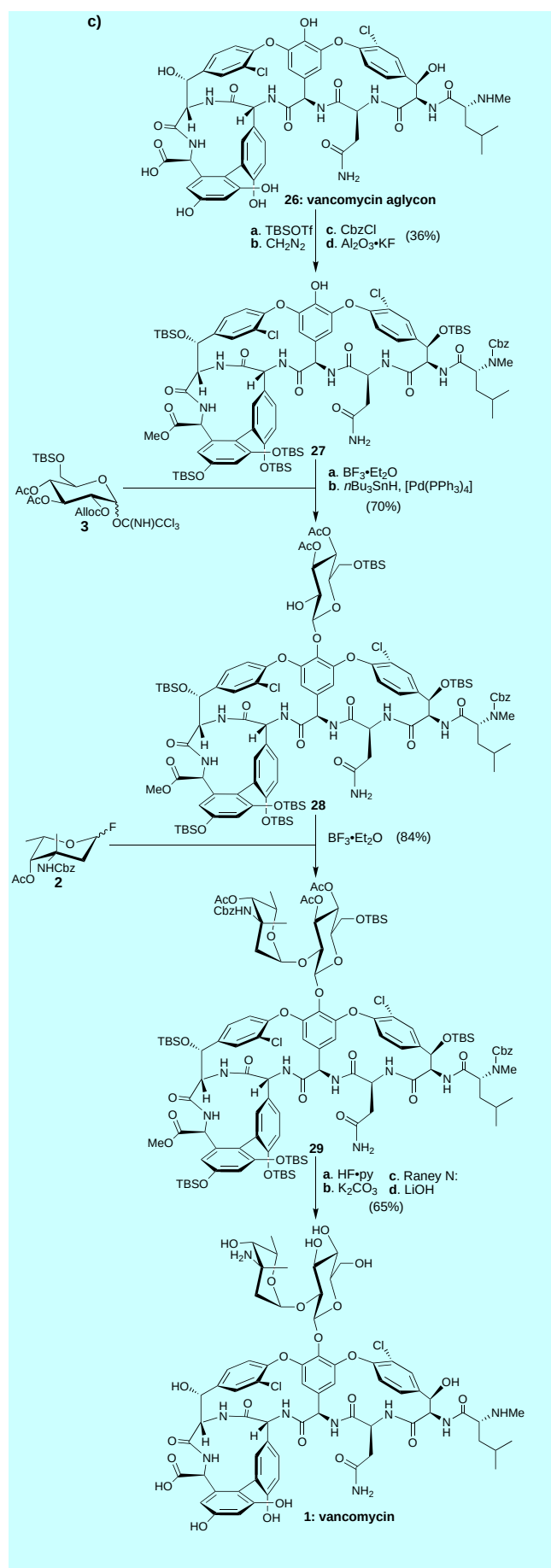
We have discovered new continents of chemistry and an amazing number of synthetic reactions based on heteroatoms and organometallic reagents and catalysts. Among the former are the chemistries of nitrogen, phosphorous, boron, sulfur, and silicon. Organometallic chemistry came a long way from the sodium and Grignard reagents to cuprates and titanium



Scheme 47. a) Strategic bond disconnections and retrosynthetic analysis of vancomycin aglycon, b) key methodology for unnatural amino acid synthesis, and c) total synthesis (Evans et al., 1998).^[223]



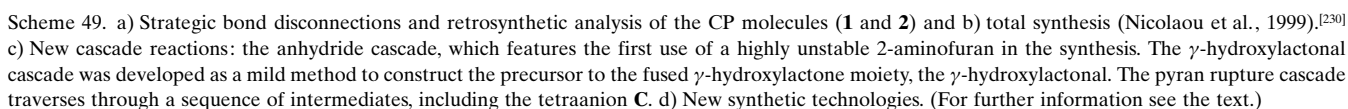
Scheme 48. a) Strategic bond disconnections and retrosynthetic analysis of vancomycin aglycon, b) key methodology for unnatural amino acid synthesis, and c) total synthesis of vancomycin (**1**) (Nicolaou et al., 1999).^[224–226]

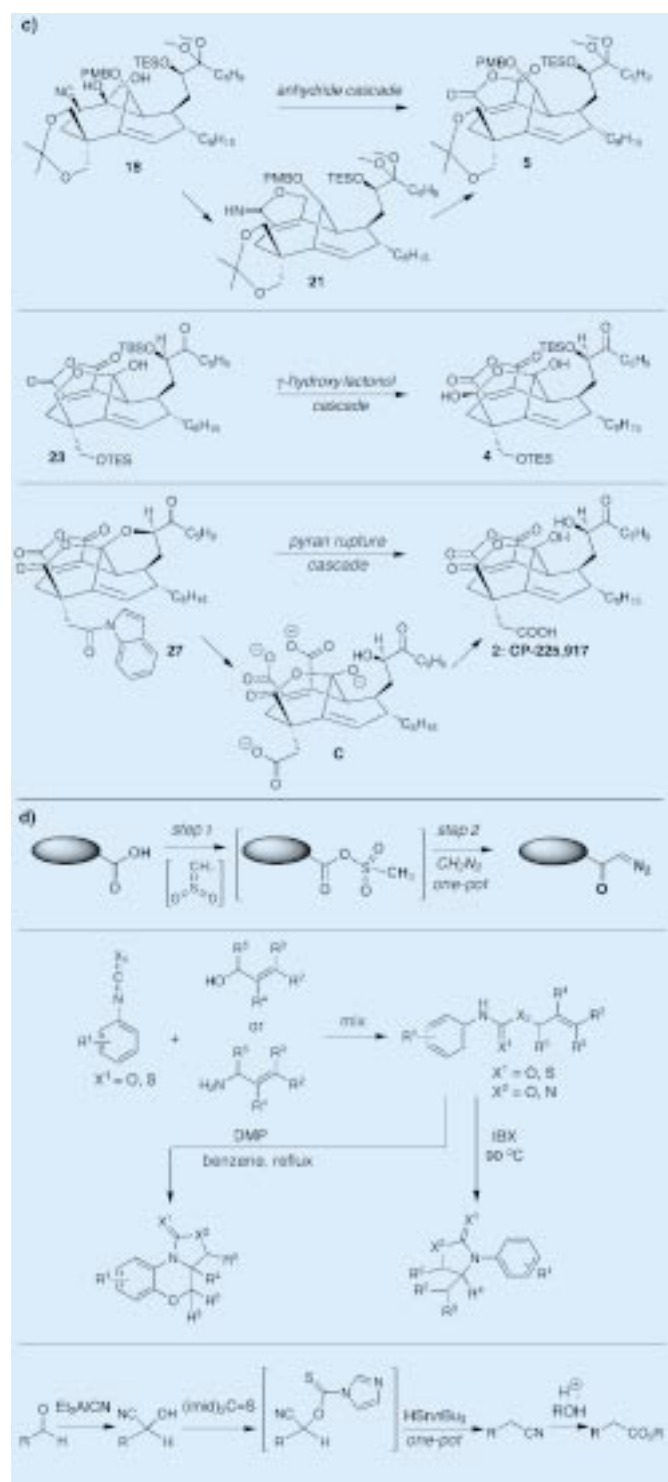


reagents. Of particular importance are the recent advances made in catalysis using transition metals both for the formation of carbon–carbon bonds and for asymmetric synthesis. The retrosynthetic analysis principles introduced by Corey revolutionized strategy design in total synthesis, while the many metal-catalyzed processes discovered during the second half of the century facilitated the construction of complex molecules in impressive ways. Most prominent among these catalytic processes are the various palladium-catalyzed reactions for carbon–carbon bond formation^[248] and the olefin metathesis reaction^[249] made synthetically useful by the Grubbs^[250] (ruthenium) and Schrock^[251] (molybdenum) catalysts. During this period, we have also witnessed the introduction of enzymes^[252] as important tools for organic synthesis and of catalytic antibodies^[253] as promising and useful reagents for synthetic and mechanistic studies, and the application of genetic engineering to total synthesis.^[254]

In terms of stereochemical control, a journey through the twentieth century reveals the dramatic progress from stereochemically random reactions to stereocontrolled processes, first carried out in a reliable manner on cyclic templates and later on acyclic systems. Acyclic stereoselection, both via internal chiral auxiliaries and external catalysts, brought us not only to diastereoselective processes, but also to asymmetric synthesis. Particularly impressive have been the advances in asymmetric catalysis by which many building blocks and final targets can nowadays be synthesized at will. Classical optical resolution methods that characterized the early total syntheses are being replaced by stereoselective processes delivering only the desired enantiomer in high enantiomeric excesses. Such processes include the Hajos–Wiechert cycloaldol/dehydration reaction catalyzed by optically active amino acids,^[255] the Knowles asymmetric hydrogenation process for the industrial production of L-DOPA employing soluble rhodium catalysts carrying chiral phosphane ligands,^[256] the Takasago process for the production of L-menthol via an asymmetric catalytic amino–enamine isomerization employing a rhodium–BINAP catalyst,^[257] the Noyori asymmetric catalytic hydrogenation of ketones ((*S*)- or (*R*)-[$\text{RuBr}_2(\text{binap})$]) catalyst,^[258] the Katsuki–Sharpless asymmetric catalytic epoxidation ((*L*)-(+)- or (*D*)-(–)-diethyl tartrate/ $\text{Ti}(\text{O}i\text{Pr})_4$ catalyst),^[259] the Sharpless dihydroxylation reaction (OsO_4 catalyst),^[165] the Corey oxazaborolidine-catalyzed reduction of ketones,^[92] and the Shibasaki carbon–carbon bond forming reactions employing bimetallic catalysts.^[260]

Cascade reactions in which several transformations are carried out in one reaction vessel in tandem have assumed increasing importance in total synthesis.^[261] Such cascades can be defined as one-pot sequences involving fleeting intermediates, each of which leads to the formation of the next until a stable product is formed, or pathways marked with distinct intermediates that can be isolated if so desired, but which are allowed to proceed to the next stage until the desired product is obtained. By expanding the definition of cascade reactions one can include the various one-pot reactions in which a number of reagents and/or components are added sequentially to form a final product without isolation of intermediate





Scheme 49. (Continued)

compounds or work-ups. Examples of cascade reactions include the Robinson synthesis of tropinone,^[16] the biomimetic synthesis of steroids,^[262] the endriandric acid synthesis,^[112] the Ugi three-component reaction,^[263] the Vollhardt synthesis of estrone,^[358b] the synthesis of the CP molecules and the many radical-based^[264] and palladium-catalyzed^[265] tandem sequences for the formation of polycyclic carbon frameworks.

5. The Impact of Total Synthesis

In tracing the evolution of organic synthesis and total synthesis to its present state, it is instructive to also consider its impact on other scientific disciplines and on society. Simply stated, this impact has been enormous and it boils down to profoundly shaping our world by providing the myriad synthetic materials we have around us today. To be sure, total synthesis has been aided by its own appeal and advances, but also by developments in analytical and purification techniques and spectroscopic methods.

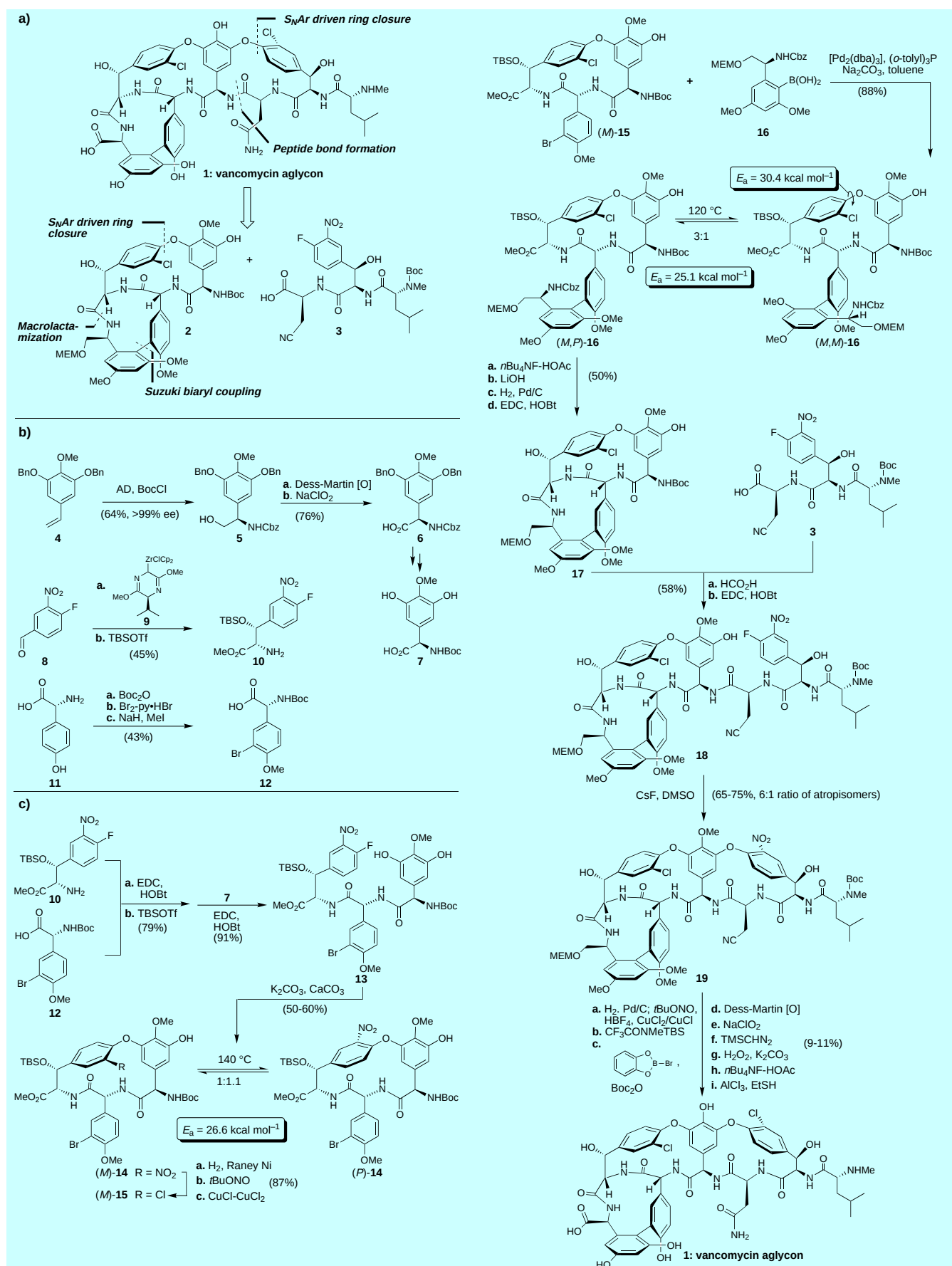
5.1. Driving and Testing the State-of-the-Art in Organic Synthesis

As the flagship of organic synthesis, total synthesis often guides and demands new synthetic methods and strategies. It also becomes the testing ground where new technologies and strategic concepts are tested and judged for their applicability, efficiency, and practicality. In a way, total synthesis provides the tough and real challenges to new synthetic methods, often before they are passed over to those who use them extensively in their daily research and/or for their manufacturing needs. Indeed, the total synthesis of complex natural products is frequently given as the reason for the need to develop a new synthetic method to achieve a goal unattainable by existing methods. Furthermore, newly appearing synthetic methods become convincingly useful once they have been successfully applied to total synthesis. Examples here include the Diels–Alder reaction,^[266] the Wittig reaction,^[267] the hydroboration reaction,^[268] the Corey dithiane reaction,^[269] the Sharpless asymmetric epoxidation reaction,^[259] the various palladium-catalyzed coupling reactions,^[270] the olefin metathesis reaction,^[271] and last but not least, the multitude of protecting groups available to the synthetic chemists.^[272]

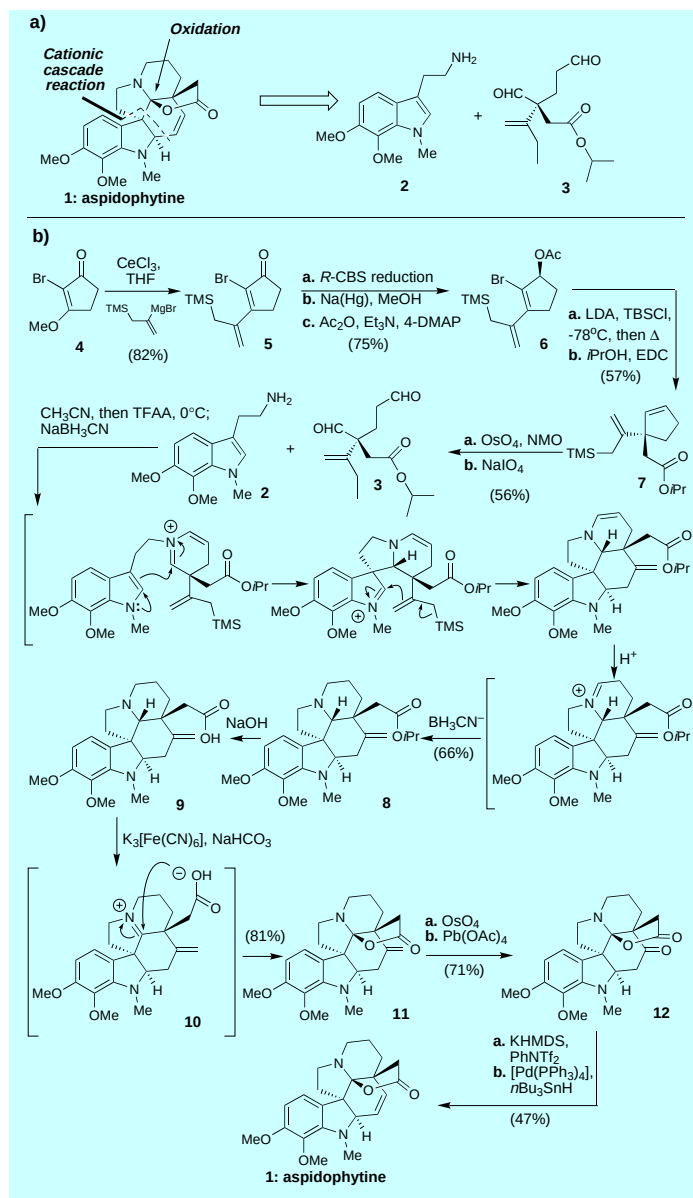
It is important to note that total synthesis not only drives organic synthesis forward in terms of synthetic technologies and strategies, but also frequently leads to fundamental theories and concepts. Thus, it was within the realm of the total synthesis of natural products that the theories of conformational analysis^[273] (Barton and Hassel), the Woodward and Hoffmann rules,^[98] and the Corey principles of retrosynthetic analysis^[3, 4, 34] crystallized.

Today our desire and ability to make contributions to biology and medicine is driven to a large extent by total synthesis, which can deliver not only scarce natural products but also combinatorial libraries of related substances for biological evaluation purposes.

Total synthesis not only dictates and demands the invention and development of new synthetic strategies, but it also provides opportunities for the discovery of such methods and techniques. Such discoveries are made either through rational pursuit or simply by serendipity. Indeed, some of the most dramatic and influential discoveries of our century are fruits of serendipity. A remark made by Pasteur: “Serendipity, however, appears to be most generous to those positioned to



Scheme 50. a) Strategic bond disconnections and retrosynthetic analysis of vancomycin aglycon, b) key methodology for unnatural amino acid synthesis, and c) total synthesis (Boger et al., 1999).^[227]



Scheme 51. a) Strategic bond disconnections and retrosynthetic analysis of aspidophytine and b) total synthesis (Corey et al., 1999).^[238]

detect and exploit the accidental,” is worthy of remembering. Serendipity will, no doubt, continue to be part of our science.

5.2. Drug Discovery and Development

While it is wonderful that total synthesis has made such great leaps from the beginning of the twentieth century, its greatest impact has been on the drug discovery and development process.^[274] Indeed, the evolution of the drug discovery and development process parallels closely that of total synthesis. The two disciplines must be considered in unison, for they are very synergistic and complementary. Academic research focuses on organic and natural product synthesis, which provides highly relevant basic knowledge and offers superb education and training to young men and women

wishing to pursue the science of drug discovery and development process.

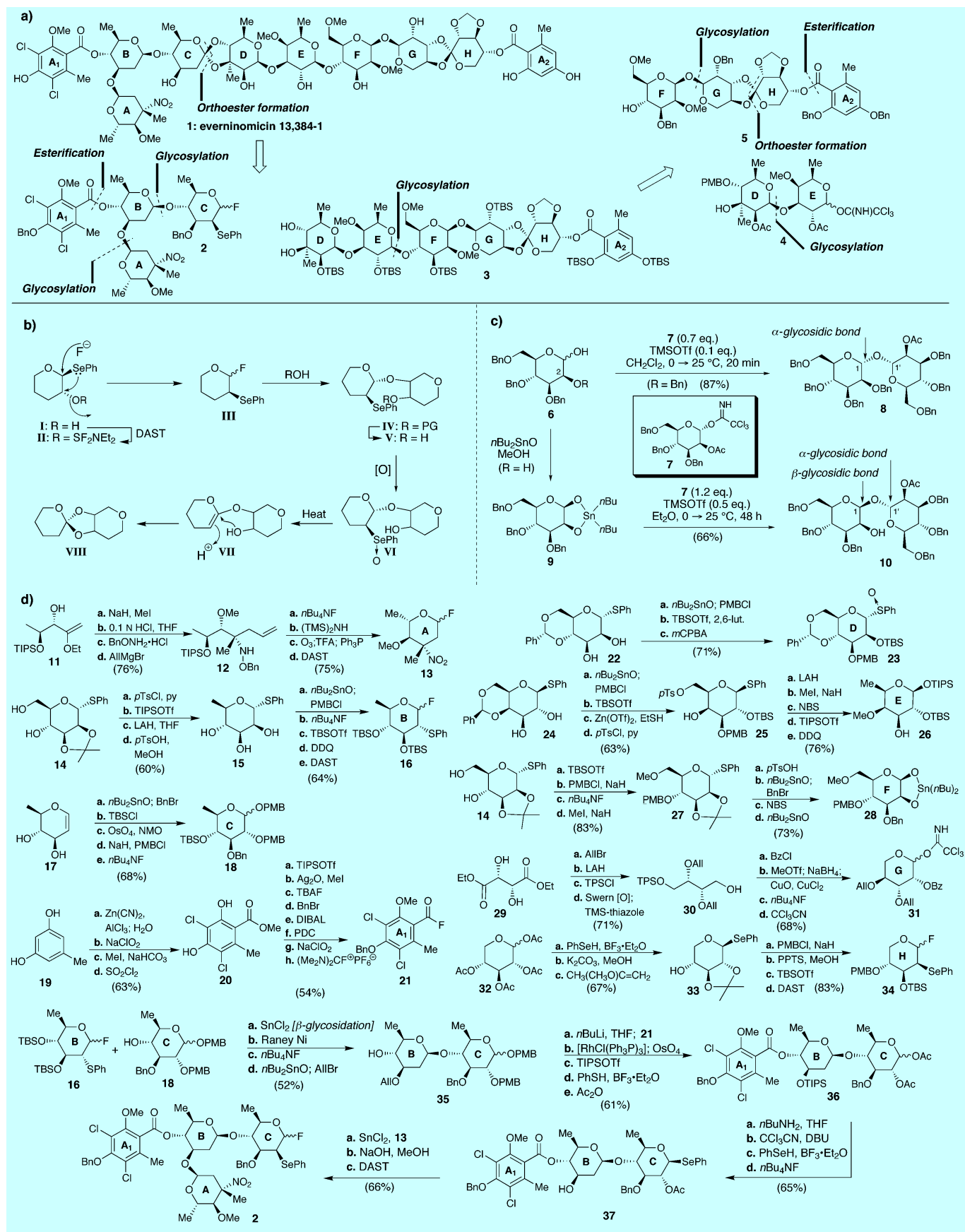
The pharmaceutical industry applies the knowledge gained to discovering and manufacturing new drugs for the benefit of society. That medicinal and combinatorial chemists have so many tools at their disposal today in their quests for huge numbers of novel and diverse small molecules is primarily the result of the contributions of total synthesis and of organic synthesis as a whole. A reminder of the importance of chemical synthesis as one of the two main arms of the drug discovery process—the other being identification of appropriate biological targets—will help appreciate total synthesis within a larger perspective. Just as advances in molecular biology facilitate drug discovery today by allowing the elucidation of the human genome and proteome, so does progress in total synthesis, which enables the construction of the molecules needed to bind and modulate the function of disease-associated biological targets.

The challenging and rewarding features of total synthesis invite competition, which, like in any other human endeavor, is both inevitable and healthy. Fortunately, and unlike many other sciences, the creative nature of organic and natural product synthesis allows equal opportunity for brilliant contributions to all practitioners, whether they are the first to finish or the last. And there are many things to discover and invent in this science; only our imagination is the limit.

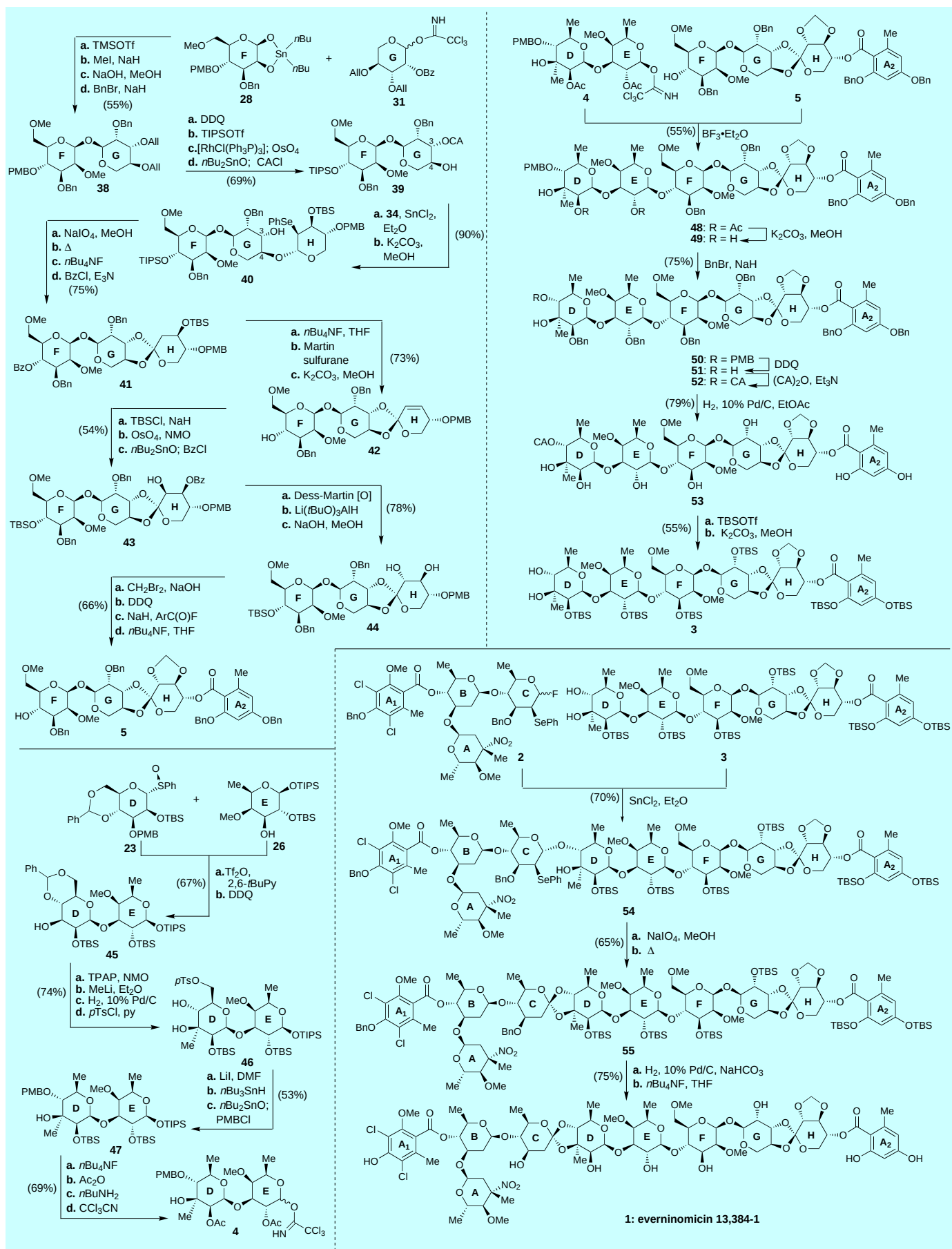
6. Future Perspectives

The science and art of organic synthesis attracts many who practice invention, discovery, and development of new synthetic reactions and reagents for wider use. Such new processes and engineered reactions are of paramount importance to research chemists and manufacturers of chemical products including pharmaceuticals. Other synthetic chemists adopt total synthesis as their main endeavor, with the aim of designing and executing elegant strategies toward complex targets. In judging such accomplishments, one has to give credit not only to the beauty and efficiency of the strategies and tactics, but also to the value of the exercise in providing access to the target molecule and its analogues for, usually but not always, biological studies. Yet, there are others who attempt to combine target-oriented synthesis with the discovery and development of new synthetic technologies. And finally, there are those who aim to incorporate biology into their total synthesis programs as well as methodology development, thus elevating natural products to opportunities for creative science in total synthesis, synthetic methodology, and chemical biology.

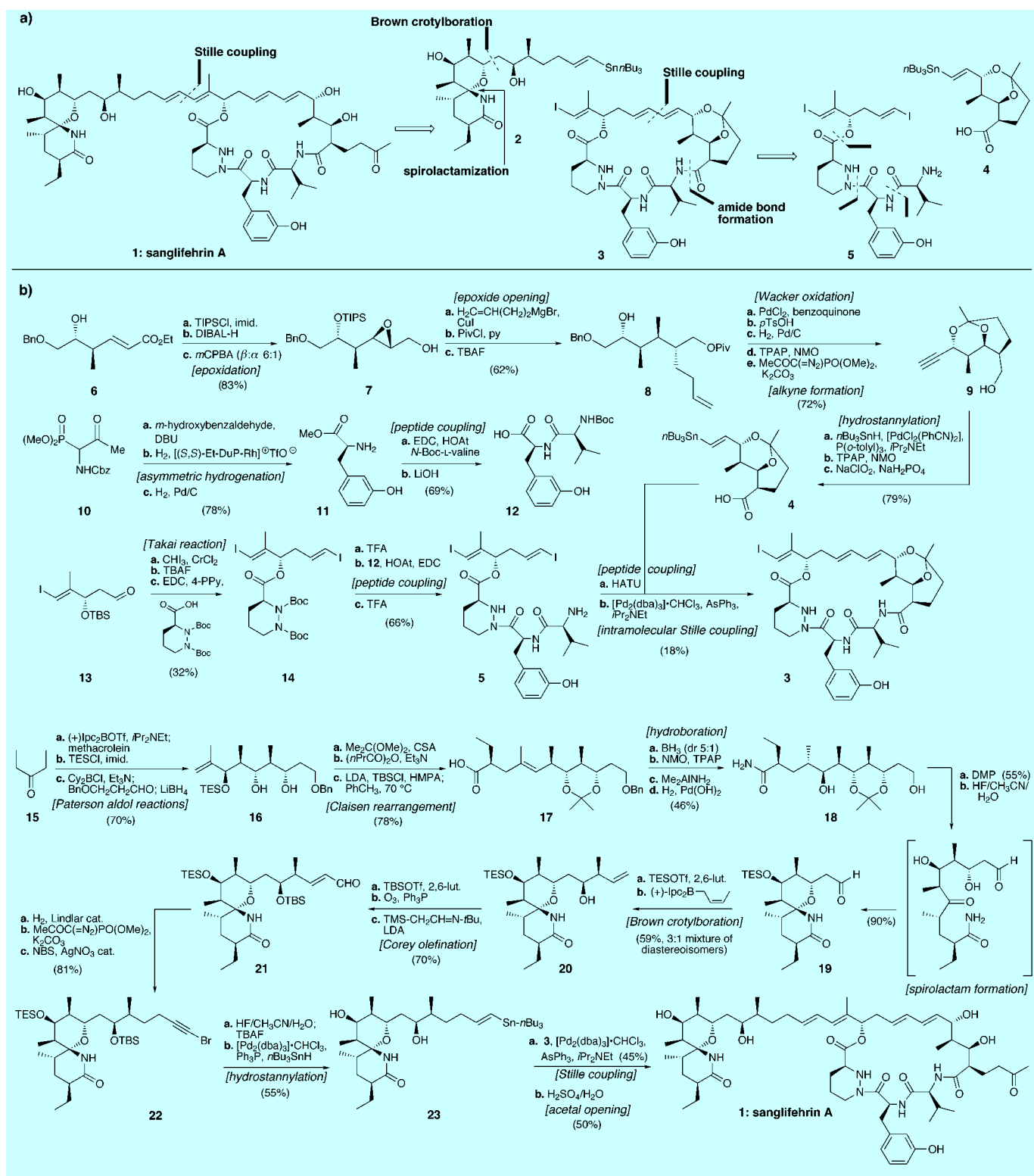
All sub-disciplines of organic natural product synthesis are to be equally respected as important to the advancement of knowledge and the benefit of humankind. Furthermore, one can choose which of these dimensions he or she will adopt in their research programs, for all three have their place in science. Indeed, the beauty of total synthesis lies in the challenge and opportunities that it provides to make creative and useful contributions to many other disciplines. It is, therefore, up to the practitioner to imagine new directions and



Scheme 52. a) Strategic bond disconnections and retrosynthetic analysis of everninomicin 13,384-1 and b, c) important synthetic methods; b) orthoester formation by 1,2-migration of the phenylselenanyl group followed by glycosylation (**I** → **II** → **III** → **IV**), and ring closure after syn-elimination (**V** → **VI** → **VII** → **VIII**); c) stereoselective construction of 1,1'-disaccharides; d) synthesis of the building blocks and completion of the total synthesis of everninomicin 13,384-1 (Nicolaou et al., 1999).^[245]



Scheme 52. (Continued)


 Scheme 53. a) Strategic bond disconnections and retrosynthetic analysis of sanglifehrin A and b) total synthesis (Nicolaou et al., 1999).^[240]

to constantly raise the bar to higher and higher expectations for the art and science of organic and natural products synthesis.

Throughout its history the art and science of total synthesis has demonstrated its nature as an aesthetically appealing endeavor and as a scientifically important discipline. As a science and an art, it has attracted some of the most creative

minds of the twentieth century and its impact on society is paramount, if not fully appreciated by the general public. As we close the chapter of the twentieth century and move into the twenty-first century many may be wondering of the fate of total synthesis. The best guides we have are history and the present state-of-the-art. They both speak volumes of the vigor

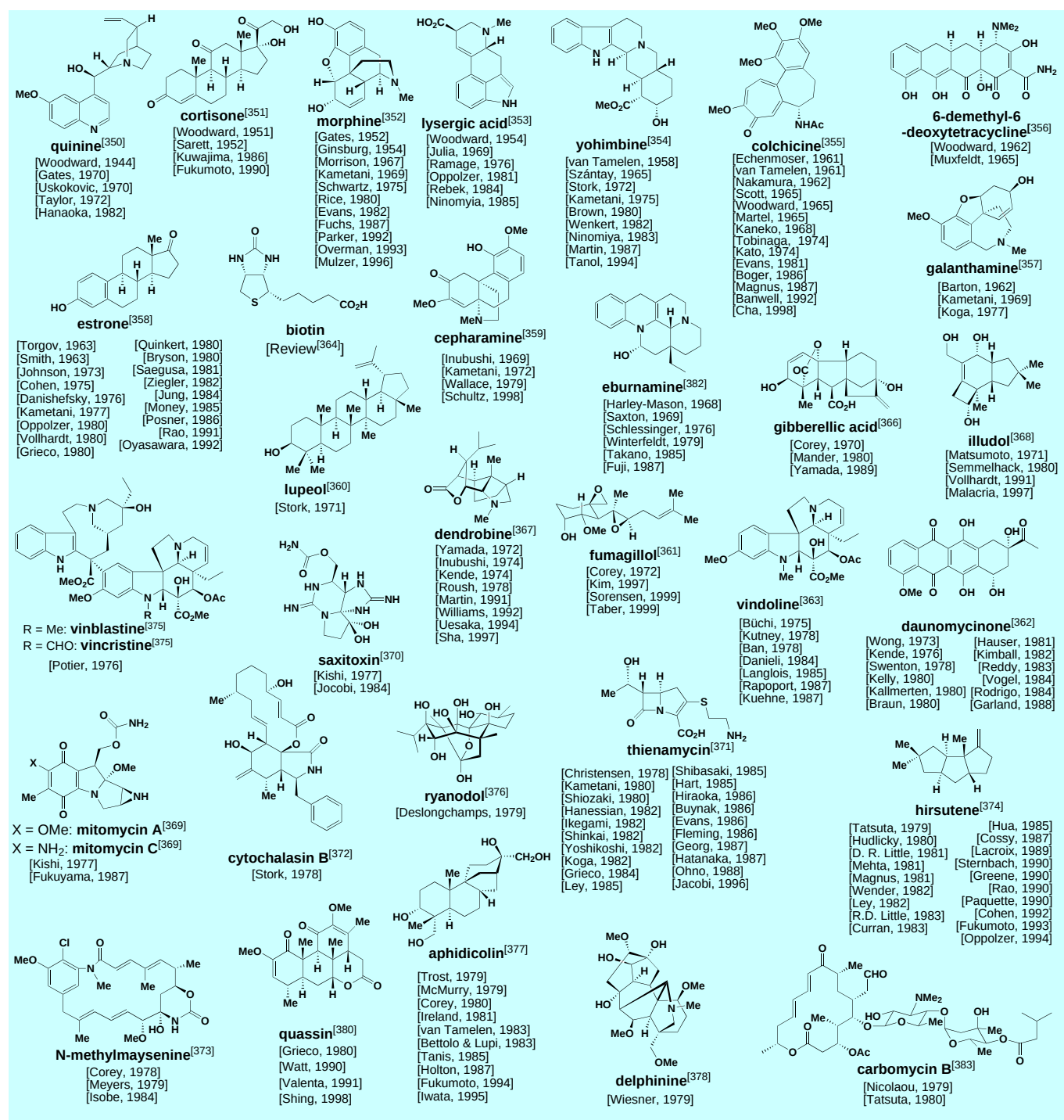


Figure 5. Selected natural product syntheses from the twentieth century.

of this art and science, and of its potential for further advances and contributions. For one, nature has not yet finished revealing its secrets to us, and many more novel, and presently unimaginable, structures are destined to dazzle our eyes, boggle our minds, and challenge our creativity. Furthermore, the state of the art is comparatively only in its early stages of development in light of nature's seemingly magical and powerful biosynthetic schemes. To be sure, the competitive nature of the pharmaceutical and biotechnology industries and their drive to discover and produce new cures for disease

will demand new and sharper tools for organic synthesis. Fueled by these and other industries, the discipline of total synthesis will be there to attract talented individuals as practitioners and to deliver the new tools needed for yet higher efficiencies and selectivities.

Targeting more complex structures will demand more effective reactions in terms of accomplishing bond constructions and functional-group transformations. The overall efficiency has to be pushed higher and so does selectivity. Cascade reactions and other novel strategies will have to be

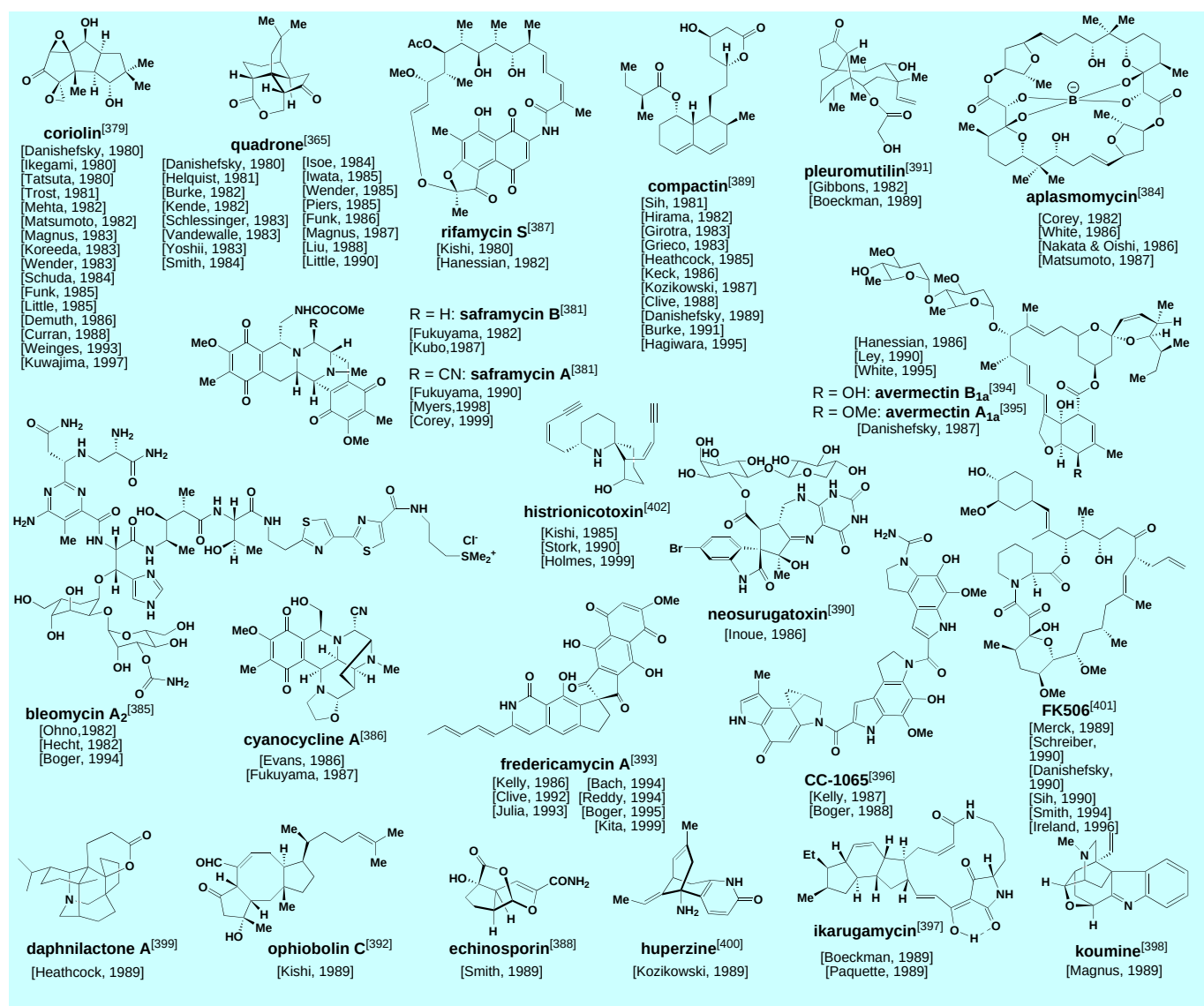


Figure 6. Selected natural product syntheses from the twentieth century.

devised for delivering complex and diverse structures in single operations in order to achieve such goals. New catalysts have to be invented to bring about otherwise difficult or impossible operations. There is little doubt that we can count on mother nature to provide us with the targets and the opportunities to invent and develop such methods in the future.

Solid-phase chemistry^[275] is now gathering momentum in natural product synthesis. Traditionally used for the synthesis of peptides^[276] and oligonucleotides,^[277] this approach is now being applied to construct small organic molecules in large numbers, particularly for the purposes of drug discovery,^[278] catalyst development,^[279] and material science.^[280] Again, new techniques, strategies, and tactics are needed to elevate this endeavor to a higher level of sophistication, applicability, and scope. As we have mentioned above, total synthesis is taking a leading role in spearheading developments in new technologies for solid-phase and combinatorial chemistry. With the strong foundation provided by such advances, automation of synthetic and combinatorial chemistry should also be possible

and forthcoming. Indeed, automation technologies are already entering the realm of chemical synthesis laboratories.^[281] Finally, a goal of paramount importance for the ensuing century will undoubtedly involve the development of synthetic strategies for the rapid construction of complex natural products that rival or even surpass the efficiency of nature.

In addition to natural products and their analogues, synthetic chemists are also beginning to target complex and exotic natural productlike structures for the purpose of biological screening.^[282] Such endeavors are clearly related to total synthesis and are both inspired and facilitated by advances in the latter field. Particularly enabling are those contributions that include both new synthetic technologies and novel molecular architectures. Examples of such endeavors include those from the Schreiber group,^[283a] Sharpless group,^[283b] and our own^[283c] (Figure 9; see p. 108).

In closing, in surveying the art and science of total synthesis of the twentieth century, one is left with awe at its accomplish-

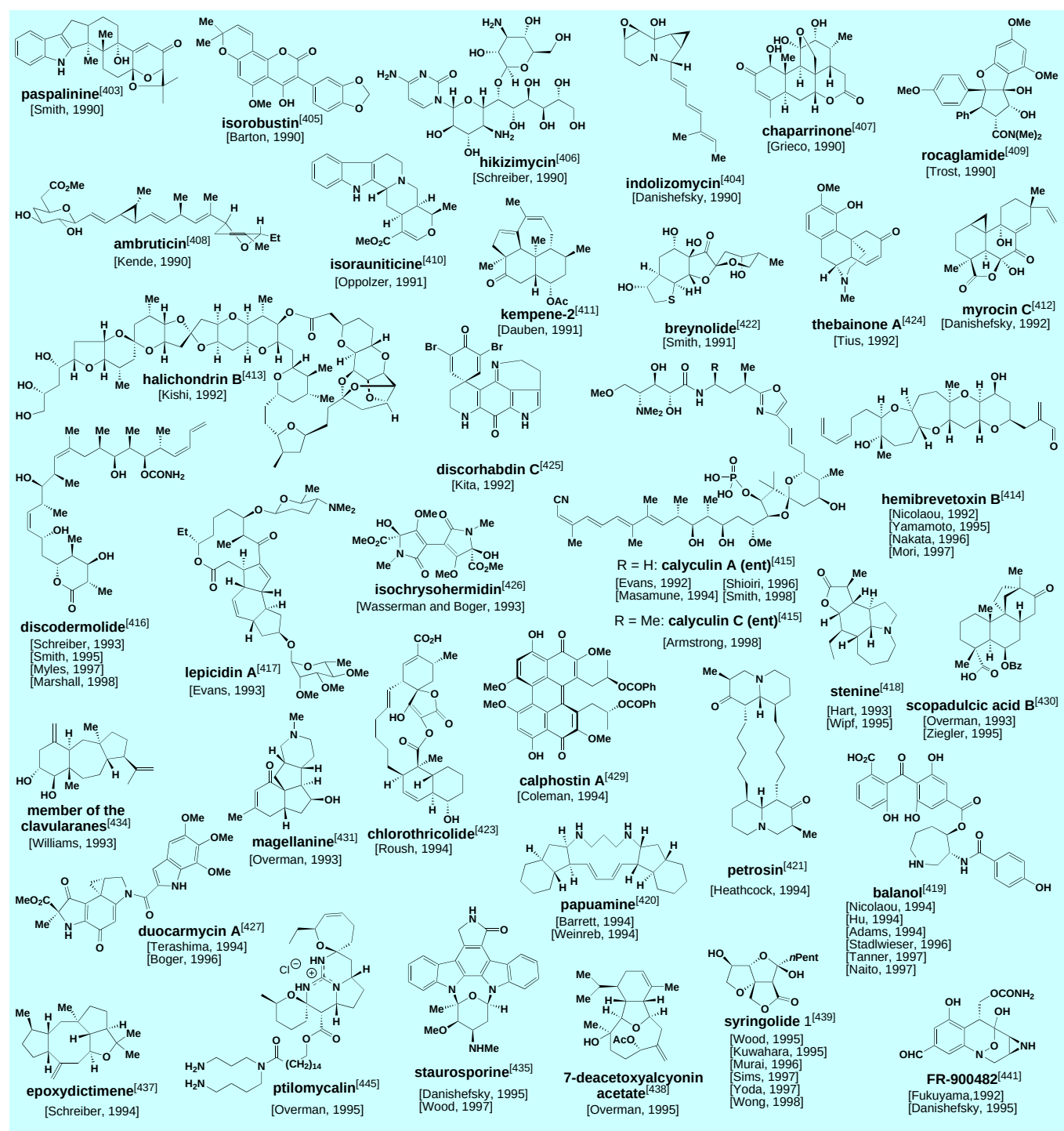


Figure 7. Selected natural product syntheses from the twentieth century.

ments and power. As a practitioner of the art, one is filled with overwhelming pride to be part of such attractive and vigorous endeavors and apprehensive in being responsible for conveying its true meaning and value to society.^[284] But, most importantly, the surveyor must be overly excited and optimistic about the future of the discipline and in transferring this enthusiasm to the next generation of chemists. It would, indeed, be of considerable interest to compare the present state-of-the-art with that at the end of the twenty-first century.

Abbreviations

AA	asymmetric aminohydroxylation
Ac	acetyl
acac	acetylacetyl
AD	asymmetric dihydroxylation
AIBN	2,2'-azobisisobutyronitrile
All	allyl
Alloc	allyloxycarbonyl
9-BBN	9-borabicyclo[3.3.1]nonane

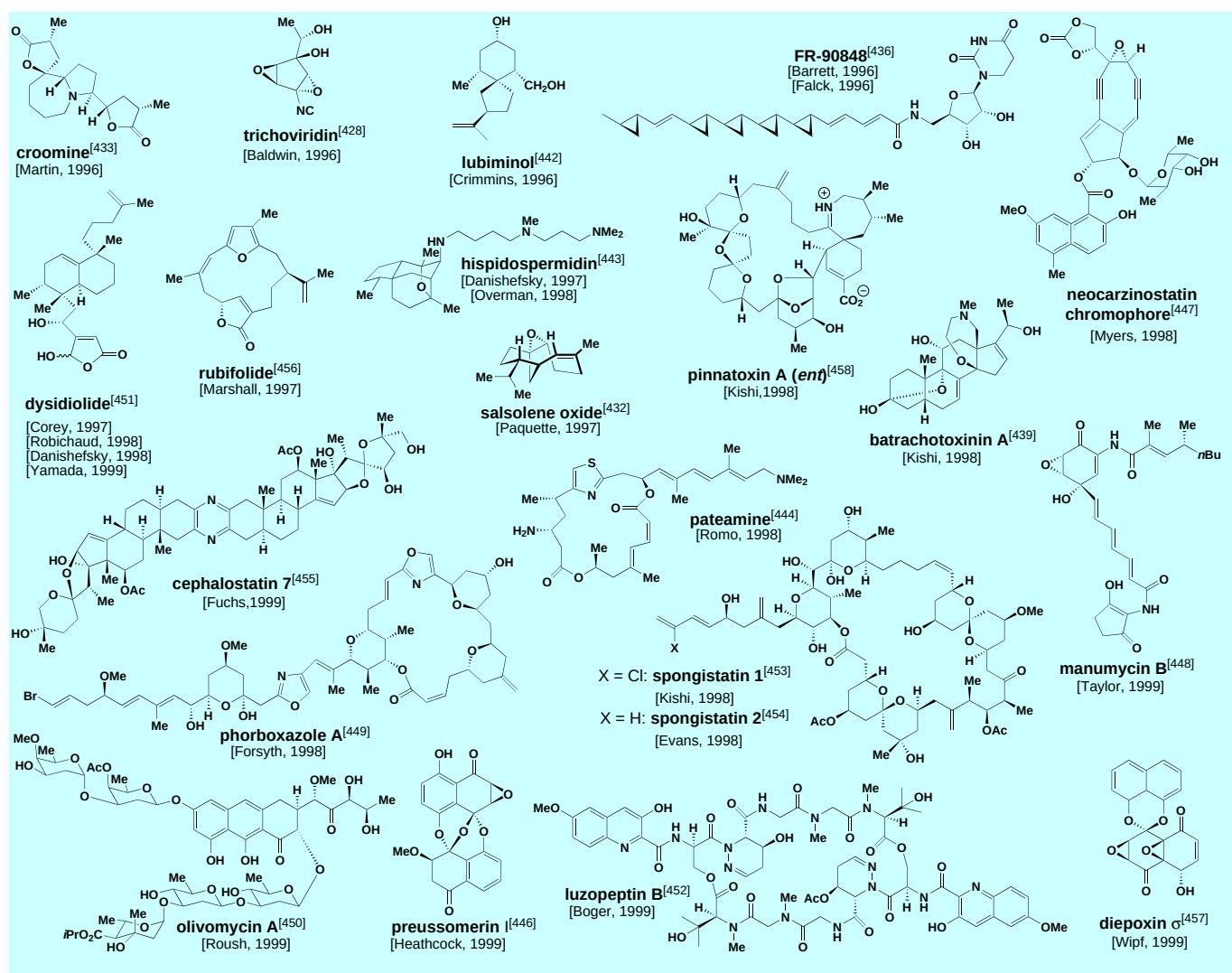
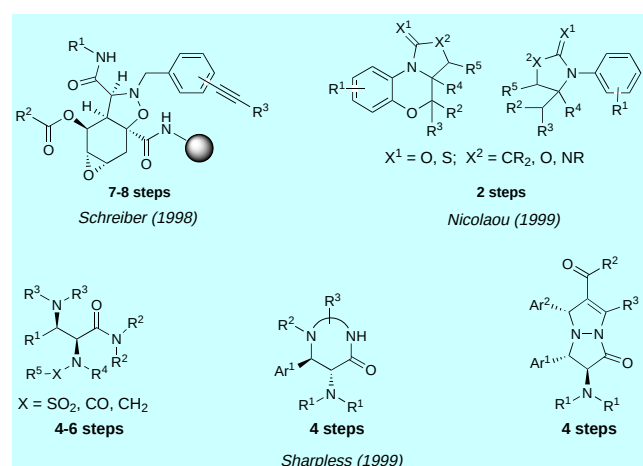


Figure 8. Selected natural product syntheses from the twentieth century.


 Figure 9. Novel, natural productlike, molecular architectures recently synthesized for biological screening purposes (number of steps from commercially available materials).^[283]

BINAP 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl
Bn benzyl
Boc *tert*-butoxycarbonyl

BOP benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluoride
Bz benzoyl
CA chloroacetyl
CAN cerium ammonium nitrate
Cbz benzyloxycarbonyl
Cod cyclooctadiene
Cp cyclopentadienyl
CSA 10-camphorsulfonic acid
Cy cyclohexyl
DABCO 1,4-diazabicyclo[2.2.2]octane
DAST (diethylamino)sulfur trifluoride
dba *trans,trans*-dibenzylideneacetone
DBN 1,5-diazabicyclo[5.4.0]non-5-ene
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCB 3,4-dichlorobenzyl
DCC *N,N'*-dicyclohexylcarbodiimide
Ddm 4,4'-dimethoxydiphenylmethyl
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD diethyl azodicarboxylate
DEIPS diethylisopropylsilyl
DET diethyl tritrate

DHP	3,4-dihydro-2 <i>H</i> -pyran
DIAD	diisopropylazodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIC	5-(3,3-dimethyl-1-triazenyl)-1 <i>H</i> -imidazole-4-carboximide
DIPT	diisopropyl tartrate
DMA	<i>N,N</i> -dimethylacetamide
4-DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin-periodinane
DMPU	<i>N,N</i> -dimethylpropyleneurea
DMSO	dimethylsulfoxide
Dopa	3-(3,4-dihydroxyphenyl)alanine
DPPA	diphenyl phosphoryl azide
dppb	1,4-bis(diphenylphosphinyl)butane
dppf	1,1'-bis(diphenylphosphanyl)ferrocene
DTBMS	di- <i>tert</i> -butylmethylsilyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
FDPP	pentafluorophenyl diphenylphosphinate
Fmoc	9-fluorenylmethoxycarbonyl
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
IBX	<i>o</i> -iodoxybenzoic acid
imid.	imidazole
Ipc	isopinocampheyl
KSAE	Katsuki–Sharpless asymmetric epoxidation
LDA	lithium diisopropylamide
lut.	2,6-lutidine
<i>m</i> CPBA	3-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
MSTFA	<i>N</i> -methyl- <i>N</i> -(trimethylsilyl) trifluoroacetamide
nbd	norbornadiene (bicyclo[2.2.1]hepta-2,5-diene)
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMO	4-methylmorpholine- <i>N</i> -oxide
Nos	4-nitrobenzolsulfonyl
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protecting group
Pht	phthalimidyl
Piv	pivaloyl
PMB	<i>p</i> -methoxybenzyl
PPTS	pyridinium 4-toluenesulfonate
<i>p</i> Ts	4-toluenesulfonyl
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl

TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TEOC	trimethylsilyl ethyl carbonyl
TES	triethylsilyl
Tfa	trifluoroacetyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMGA	tetramethylguanidinium azide
TMS	trimethylsilyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate
TPS	triphenylsilyl
Tr	trityl

It is with enormous pride and pleasure that we wish to thank our collaborators whose names appear in the references and whose contributions made the described work possible and enjoyable. We gratefully acknowledge the National Institutes of Health (USA), Merck & Co., DuPont, Schering Plough, Pfizer, Hoffmann-La Roche, Glaxo Wellcome, Rhone-Poulenc Rorer, Amgen, Novartis, Abbott Laboratories, Bristol Myers Squibb, Boehringer Ingelheim, Astra-Zeneca, CaPCURE, the George E. Hewitt Foundation, and the Skaggs Institute for Chemical Biology for supporting our research programs.

Received: June 10, 1999 [A 349]

- [1] *Nobel Lectures: Chemistry 1963–1970*, Elsevier, New York, **1972**, pp. 96–123.
- [2] *Nobel Lectures: Chemistry 1981–1990*, World Scientific, New Jersey, **1992**, pp. 677–708.
- [3] K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, **1996**.
- [4] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**.
- [5] I. Fleming, *Selected Organic Syntheses*, Wiley, New York, **1973**.
- [6] K. C. Nicolaou, E. J. Sorensen, N. Winssinger, *J. Chem. Educ.* **1998**, 75, 1225–1258.
- [7] R. Breslow, *Chemistry: Today and Tomorrow*, American Chemical Society, Washington, D.C. **1996**.
- [8] F. Wöhler, *Ann. Phys. Chem.* **1828**, 12, 253.
- [9] H. Kolbe, *Ann. Chem. Pharm.* **1845**, 54, 145.
- [10] a) C. Graebe, C. Liebermann, *Ber. Dtsch. Chem. Ges.* **1869**, 2, 332; b) first commercial synthesis: C. Graebe, C. Liebermann, H. Caro, *Ber. Dtsch. Chem. Ges.* **1870**, 3, 359; W. H. Perkin, *J. Chem. Soc.* **1970**, 133–134.
- [11] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1878**, 11, 1296–1297; first commercial production: K. Heumann, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 3431.
- [12] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 799–805.
- [13] See brochure of Nobel Committees for Physics and Chemistry, The Royal Swedish Academy of Sciences, *List of Nobel Prize Laureates 1901–1994*, Almqvist & Wiksell Tryckeri, Uppsala, Sweden, **1995**.
- [14] W. H. Perkin, *J. Chem. Soc.* **1904**, 85, 654–671.
- [15] See S. F. Thomas in *The Total Synthesis of Natural Products*, Vol. 2 (Ed.: J. Apsimon), Wiley, New York, **1973**, pp. 149–154.
- [16] R. Robinson, *J. Chem. Soc.* **1917**, 111, 762–768.
- [17] R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1901**, 34, 129–130; R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1901**, 34, and 3163–3165; R. Willstätter, *Ber. Dtsch. Chem. Ges.* **1906**, 29, 936–947. For an account in English, see H. L. Holmes in *The Alkaloids*, Vol. 1 (Eds.: R. H. F. Manske, H. L. Holmes), Academic Press, New York, **1950**, pp. 288–292.
- [18] H. Fischer, K. Zeile, *Justus Liebigs Ann. Chem.* **1929**, 468, 98.

- [19] S. A. Harris, K. Folkers, *J. Am. Chem. Soc.* **1939**, *61*, 1242–1244; S. A. Harris, K. Folkers, *J. Am. Chem. Soc.* **1939**, *61*, 1245–1247.
- [20] S. A. Harris, K. Folkers, *J. Am. Chem. Soc.* **1939**, *61*, 3307–3310.
- [21] W. E. Bachmann, W. Cole, A. L. Wilds, *J. Am. Chem. Soc.* **1939**, *61*, 974–975.
- [22] R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1944**, *66*, 849–850.
- [23] R. B. Woodward, G. Singh, *J. Am. Chem. Soc.* **1950**, *72*, 1428.
- [24] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, W. M. McLamore, *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251.
- [25] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. H. Ives, R. B. Kelly, *J. Am. Chem. Soc.* **1954**, *76*, 2852–2853.
- [26] E. C. Kornfield, E. J. Fornefeld, G. B. Kline, M. H. Mann, R. G. Jones, R. B. Woodward, *J. Am. Chem. Soc.* **1954**, *76*, 5256–5257.
- [27] a) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751; b) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *Tetrahedron* **1963**, *19*, 247–288.
- [28] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc.* **1956**, *78*, 2023–2055; R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc.* **1956**, *78*, 2657; R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *Tetrahedron* **1958**, *2*, 1–57.
- [29] a) R. B. Woodward, *Pure Appl. Chem.* **1961**, *2*, 383–404; b) R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, G. L. Closs, H. Dutler, J. Hannah, F. P. Hauck, S. Itô, A. Langermann, E. Le Goff, W. Leimgruber, W. Lwowski, J. Sauer, Z. Valenta, H. Volz, *J. Am. Chem. Soc.* **1960**, *82*, 3800–3802.
- [30] a) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, H. Vorbruggen, *J. Am. Chem. Soc.* **1966**, *88*, 852–853; b) R. B. Woodward, *Science* **1966**, *153*, 487–493.
- [31] R. B. Woodward, J. Gosteli, I. Ernest, R. J. Friary, G. Nestler, H. Raman, R. Sitrin, C. Suter, J. K. Whitesell, *J. Am. Chem. Soc.* **1973**, *95*, 6853–6855.
- [32] a) R. B. Woodward, *Pure Appl. Chem.* **1968**, *17*, 519–547; b) R. B. Woodward, *Pure Appl. Chem.* **1971**, *25*, 283–304; c) R. B. Woodward, *Pure Appl. Chem.* **1973**, *33*, 145–177; d) A. Eschenmoser, C. E. Wintner, *Science* **1977**, *196*, 1410–1420; e) R. B. Woodward in *Vitamin B₁₂, Proceed. 3rd European Symposium on Vitamin B₁₂ and Intrinsic Factor* (Eds.: B. Zagalak, W. Friedrich), de Gruyter, Berlin, **1979**, p. 37; f) A. Eschenmoser, *Pure Appl. Chem.* **1963**, *7*, 297–316; g) A. Eschenmoser, *Pure Appl. Chem.* **1971**, *15*, 69 (Special Lectures XXIII IUPAC Int. Congress, Boston); h) A. Eschenmoser, *Naturwissenschaften* **1974**, *61*, 513–525.
- [33] R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213; R. B. Woodward, B. W. Au-Yeung, P. Balaram, L. J. Browne, D. E. Ward, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3213–3215; R. B. Woodward, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3215–3217.
- [34] E. J. Corey, M. Ohno, P. A. Vatakencherry, R. B. Mitra, *J. Am. Chem. Soc.* **1961**, *83*, 1251–1253. See also E. J. Corey, M. Ohno, R. B. Mitra, P. A. Vatakencherry, *J. Org. Chem.* **1963**, *28*, 478–485.
- [35] a) G. Stork, A. W. Burgstahler, *J. Am. Chem. Soc.* **1955**, *77*, 5068–5077; b) A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890–1904; c) P. A. Stadler, A. Eschenmoser, H. Schinz, G. Stork, *Helv. Chim. Acta* **1957**, *40*, 2191–2198.
- [36] a) W. S. Johnson, M. B. Gravestock, B. E. McCarry, *J. Am. Chem. Soc.* **1971**, *93*, 4332–4334; b) M. B. Gravestock, W. S. Johnson, B. E. McCarry, R. J. Parry, B. E. Ratcliffe, *J. Am. Chem. Soc.* **1978**, *100*, 4274–4282.
- [37] a) G. Stork, F. West, H. Y. Lee, R. C. A. Isaacs, S. Manabe, *J. Am. Chem. Soc.* **1996**, *118*, 10660–10661; b) G. Stork, P. J. Franklin, *Aust. J. Chem.* **1992**, *45*, 275–284; c) G. Stork, N. A. Saccomano, *Tetrahedron Lett.* **1987**, *28*, 2087–2090; d) G. Stork, G. Clark, T. Weller, *Tetrahedron Lett.* **1984**, *25*, 5367–5370; e) G. Stork, J. D. Winkler, C. S. Shiner, *J. Am. Chem. Soc.* **1982**, *104*, 3767–3768; f) G. Stork, G. Clark, C. S. Shiner, *J. Am. Chem. Soc.* **1981**, *103*, 4948–4949; g) G. Stork, E. W. Logusch, *J. Am. Chem. Soc.* **1980**, *102*, 1219–1220; h) G. Stork, *Inf. Chim.* **1979**, *192–193*, 137–140; i) G. Stork, J. E. McMurphy, *J. Am. Chem. Soc.* **1967**, *89*, 5464–5465; j) G. Stork, D. Sherman, *J. Am. Chem. Soc.* **1982**, *104*, 3758–3759.
- [38] a) G. Stork, S. Raucher, *J. Am. Chem. Soc.* **1976**, *98*, 1583–1584; b) G. Stork, T. Takahashi, I. Kawamoto, T. Suzuki, *J. Am. Chem. Soc.* **1978**, *100*, 8272.
- [39] a) G. Stork, J. J. La Clair, P. Spargo, R. P. Nargund, N. Totah, *J. Am. Chem. Soc.* **1996**, *118*, 5304–5305; b) G. Stork, Y. K. Yee, *Can. J. Chem.* **1984**, *62*, 2627–2628; c) G. Stork, A. A. Hagedorn III, *J. Am. Chem. Soc.* **1978**, *100*, 3609–3611.
- [40] P. W. Hickmott, *Tetrahedron* **1982**, *28*, 1975–2050; see also ref. [73].
- [41] a) G. Stork, J. D. Winkler, N. A. Saccomano, *Tetrahedron Lett.* **1983**, *24*, 465–468; b) G. Stork, C. S. Shiner, J. D. Winkler, *J. Am. Chem. Soc.* **1982**, *104*, 310–312; c) G. Stork, A. R. Schoofs, *J. Am. Chem. Soc.* **1979**, *101*, 5081–5082; d) G. Stork, P. G. Williard, *J. Am. Chem. Soc.* **1977**, *99*, 7067–7068; e) G. Stork, A. Y. W. Leong, A. M. Touzin, *J. Org. Chem.* **1976**, *41*, 3491–3493; f) G. Stork, *Pure Appl. Chem.* **1975**, *43*, 553–562; g) G. Stork, J. C. Depezay, J. D'Angelo, *Tetrahedron Lett.* **1975**, 389–392; h) G. Stork, J. D'Angelo, *J. Am. Chem. Soc.* **1974**, *96*, 7114–7116; i) G. Stork, L. D. Cama, D. R. Coulson, *J. Am. Chem. Soc.* **1974**, *96*, 5268–5270; j) G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **1974**, *96*, 5272–5274; k) G. Stork, M. E. Jung, *J. Am. Chem. Soc.* **1974**, *96*, 3682–3684; l) G. Stork, B. Ganem, *J. Am. Chem. Soc.* **1973**, *95*, 6152–6153; m) G. Stork, J. O. Gilbert; R. K. Beckman, Jr., K. A. Parker, *J. Am. Chem. Soc.* **1973**, *95*, 2014–2016; n) G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **1971**, *93*, 5286–5287; o) G. Stork, S. Danishefsky, M. Ohashi, *J. Am. Chem. Soc.* **1967**, *89*, 5459–5460.
- [42] a) G. Stork, R. Mah, *Tetrahedron Lett.* **1989**, *30*, 3609–3612; b) G. Stork, M. E. Reynolds, *J. Am. Chem. Soc.* **1988**, *110*, 6911–6913; c) G. Stork, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 149–154; d) G. Stork, R. Mook, Jr., *Tetrahedron Lett.* **1986**, *27*, 4529–4532; e) G. Stork, R. Mook, Jr., *J. Am. Chem. Soc.* **1987**, *109*, 2829–2831; f) G. Stork, N. H. Baine, *Tetrahedron Lett.* **1985**, *26*, 5927–5930; g) G. Stork, M. J. Sofia, *J. Am. Chem. Soc.* **1986**, *108*, 6826–6828; h) G. Stork, M. Kahn, *J. Am. Chem. Soc.* **1985**, *107*, 500–501; i) G. Stork, P. M. Sher, *J. Am. Chem. Soc.* **1983**, *105*, 6765–6766; j) G. Stork, R. Mook, Jr., *J. Am. Chem. Soc.* **1983**, *105*, 3720–3722; k) G. Stork, R. Mook, Jr., S. A. Biller, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1983**, *105*, 3741–3742; l) G. Stork, N. H. Baine, *J. Am. Chem. Soc.* **1982**, *104*, 2321–2323.
- [43] a) G. Stork, J. J. La Clair, *J. Am. Chem. Soc.* **1996**, *118*, 247–248; b) G. Stork, T. Y. Chan, *J. Am. Chem. Soc.* **1995**, *117*, 6595–6596; c) G. Stork, T. Y. Chan, G. A. Breault, *J. Am. Chem. Soc.* **1992**, *114*, 7578–7579; d) G. Stork, G. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 1087–1088; e) G. Stork, H. S. Suh, G. Kim, *J. Am. Chem. Soc.* **1991**, *113*, 7054–7056.
- [44] A. Eschenmoser, C. E. Wintner, *Science* **1977**, *196*, 1410–1420.
- [45] A. Eschenmoser, *Quart. Rev. Chem. Soc.* **1970**, *24*, 366–415.
- [46] a) see ref. [32f–h]; b) A. Eschenmoser, *Angew. Chem.* **1988**, *100*, 5–40; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 5–40.
- [47] a) A. Eschenmoser, *Science* **1999**, *284*, 2118–2124; b) M. Beier, F. Reck, T. Wagner, R. Krishnamurthy, A. Eschenmoser, *Science* **1999**, *283*, 699–703.
- [48] *Reason and Imagination* (Ed.: D. H. R. Barton), World Scientific, New Jersey, **1996**.
- [49] a) D. H. R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet, *J. Am. Chem. Soc.* **1960**, *82*, 2640–2641; b) D. H. R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet, *J. Am. Chem. Soc.* **1961**, *83*, 4076–4083; c) D. H. R. Barton, *Pure Appl. Chem.* **1968**, *16*, 1–15; d) D. H. R. Barton, *Aldrichim. Acta* **1990**, *23*, 3–10.
- [50] a) D. H. R. Barton, J. M. Beaton, *J. Am. Chem. Soc.* **1960**, *82*, 2641; b) D. H. R. Barton, J. M. Beaton, *J. Am. Chem. Soc.* **1961**, *83*, 4083–4089.
- [51] a) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585; b) D. H. R. Barton, W. B. Motherwell, *Pure Appl. Chem.* **1981**, *53*, 15–31; c) W. Hartwig, *Tetrahedron* **1983**, *39*, 2609–2645; d) D. H. R. Barton, S. Z. Zard, *Pure Appl. Chem.* **1986**, *58*, 675–684.
- [52] A. A. Akhrem, Y. A. Titov, *Total Steroid Synthesis*, Plenum, New York, **1970**.
- [53] a) P. J. Pelletier, J. B. Caventou, *Ann. Chim. Phys.* **1818**, *8*, 323; b) P. J. Pelletier, J. B. Caventou, *Ann. Chim. Phys.* **1819**, *10*, 142.

- [54] a) L. H. Briggs, H. T. Openshaw, R. Robinson, *J. Chem. Soc.* **1946**, 903; b) R. Robinson, *Experientia* **1946**, 2, 28; c) For a comprehensive survey, see G. F. Smith, *Alkaloids* **1965**, 591.
- [55] a) C. Bokhoven, J. C. Schoone, J. M. Bijvoet, *Proc. K. Ned. Akad. Wet.* **1948**, 51, 990; b) C. Bokhoven, J. C. Schoone, J. M. Bijvoet, *Proc. K. Ned. Akad. Wet.* **1949**, 52, 120; c) C. Bokhoven, J. C. Schoone, J. M. Bijvoet, *Acta Crystallogr.* **1951**, 4, 275–280; d) J. H. Robertson, C. A. Beevers, *Nature* **1950**, 165, 690–691; e) J. H. Robertson, C. A. Beevers, *Acta Crystallogr.* **1951**, 4, 270–275; f) A. F. Peerdeman, *Acta Crystallogr.* **1956**, 9, 824.
- [56] R. Robinson, *Prog. Org. Chem.* **1952**, 1, 2.
- [57] R. B. Woodward, *Nature* **1948**, 162, 155–156.
- [58] a) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1993**, 115, 9293–9294; b) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1995**, 117, 5776–5788.
- [59] a) P. Magnus, M. Giles, R. Bonnert, G. Johnson, L. McQuire, M. Deluca, A. Merritt, C. S. Kim, N. Vicker, *J. Am. Chem. Soc.* **1993**, 115, 8116–8129; b) P. Magnus, M. Giles, R. Bonnert, C. S. Kim, L. McQuire, A. Merritt, N. Vicker, *J. Am. Chem. Soc.* **1992**, 114, 4403–4405; c) M. E. Kuehne, F. Xu, *J. Org. Chem.* **1993**, 58, 7490–7497; d) V. H. Rawal, S. Iwasa, M. T. Crimmins, *Org. Chem.* **1994**, 7, 262–265; e) D. Sole, J. Bonjoch, S. Garcia-Rubio, E. Peidro, J. Bosch, *Angew. Chem.* **1999**, 111, 408–410; *Angew. Chem. Int. Ed.* **1999**, 38, 395–397.
- [60] A. Fleming, *Brit. J. Exp. Path.* **1929**, 10, 226.
- [61] E. Chain, H. W. Florey, A. D. Gardner, N. G. Heatley, M. A. Jennings, J. Orr-Ewing, A. G. Sanders, *Lancet* **1940**, 239, 226.
- [62] a) For a detailed account of the British–American penicillin project, see *The Chemistry of Penicillin* (Eds.: H. T. Clarke, J. R. Johnson, R. Robinson), Princeton University Press, Princeton, NJ, **1949**; b) For a review, see: A. H. Cook, *Quart. Rev. (London)* **1948**, 2, 203.
- [63] During the course of the prodigious wartime effort to synthesize penicillin, a Merck group succeeded in synthesizing minute quantities of penicillin G: a) K. Folkers in *Perspectives in Organic Chemistry* (Ed.: A. Todd), Interscience, New York, **1956**, p. 409; b) V. duVigneaud, F. H. Carpenter, R. W. Holley, A. H. Livermore, J. R. Rachele, *Science* **1946**, 104, 431–433; c) V. duVigneaud, J. L. Wood, M. E. Wright in *The Chemistry of Penicillin* (Eds.: H. T. Clarke, J. R. Johnson, R. Robinson), Princeton University Press, Princeton, NJ, **1949**, pp. 893–894.
- [64] D. Crowfoot, C. W. Bunn, B. W. Rogers-Low, A. Turner-Jones in *The Chemistry of Penicillin* (Eds.: H. T. Clarke, J. R. Johnson, R. Robinson), Princeton University Press, Princeton, NJ, **1949**, p. 310.
- [65] a) J. C. Sheehan, K. R. Henery-Logan, *J. Am. Chem. Soc.* **1957**, 79, 1262–1263; b) J. C. Sheehan, K. R. Henery-Logan, *J. Am. Chem. Soc.* **1959**, 81, 3089–3094.
- [66] J. C. Sheehan, *The Enchanted Ring: The Untold Story of Penicillin*, The MIT Press, Cambridge, MA, **1982**.
- [67] J. M. Müller, E. Schlittler, H. J. Bein, *Experientia* **1952**, 8, 338.
- [68] A. Scriabine in *Pharmacology of Antihypertensive Drugs* (Ed.: A. Scriabine), Raven, New York, **1980**, p. 119.
- [69] a) C. F. Huebner, H. B. MacPhillamy, E. Schlittler, A. F. St. André, *Experientia* **1955**, 11, 303; b) E. Wenkert, L. H. Liu, *Experientia* **1955**, 11, 302–303; c) C. F. Huebner, E. Wenkert, *J. Am. Chem. Soc.* **1955**, 77, 4180; d) P. A. Diassi, F. L. Weisenborn, C. M. Dylion, O. Winterseiner, *J. Am. Chem. Soc.* **1955**, 77, 4687–4689; e) E. E. van Tamelen, P. D. Hance, *J. Am. Chem. Soc.* **1955**, 77, 4692–4693.
- [70] For other total syntheses of reserpine, see a) B. A. Pearlman, *J. Am. Chem. Soc.* **1979**, 101, 6398–6404, 6404–6408; b) P. A. Wender, J. M. Schaus, A. W. White, *J. Am. Chem. Soc.* **1980**, 102, 6157–6159; P. A. Wender, J. M. Schaus, A. W. White, *Heterocycles* **1987**, 25, 263–270; c) S. F. Martin, H. Rüeger, S. A. Williamson, S. Grzejszczak, *J. Am. Chem. Soc.* **1987**, 109, 6124–6134; d) G. Stork, *Pure Appl. Chem.* **1989**, 61, 439–442.
- [71] K. Wiesner, *Fortschr. Chem. Org. Naturst.* **1962**, 20, 271–297.
- [72] a) G. Stork, R. A. Kretschmer, R. H. Schlessinger, *J. Am. Chem. Soc.* **1968**, 90, 1647–1648; b) G. Stork, *Pure Appl. Chem.* **1968**, 17, 383–401.
- [73] a) G. Stork, R. Terrell, J. Szmuszkowicz, *J. Am. Chem. Soc.* **1954**, 76, 2029; b) G. Stork, H. Landesman, *J. Am. Chem. Soc.* **1956**, 78, 5128–5129; c) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkowicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, 85, 207–222.
- [74] a) W. A. Ayer, W. R. Bowman, T. C. Joseph, P. Smith, *J. Am. Chem. Soc.* **1968**, 90, 1648–1650; b) S. Kim, Y. Bando, Z. Horii, *Tetrahedron Lett.* **1978**, 2293–2294; c) C. H. Heathcock, E. F. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1978**, 100, 8036–8037; d) C. H. Heathcock, E. F. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1982**, 104, 1054–1068; e) D. Schumann, H. J. Mueller, A. Naumann, *Liebigs Ann. Chem.* **1982**, 9, 1700–1705; f) E. Wenkert, C. A. Broka, *J. Chem. Soc. Chem. Commun.* **1984**, 714–717; g) G. A. Kraus, Y.-S. Hon, *Heterocycles* **1987**, 25, 377–386; h) P. A. Grieco, Y. Dai, *J. Am. Chem. Soc.* **1998**, 120, 5128–5129.
- [75] a) G. G. F. Newton, E. P. Abraham, *Nature* **1955**, 175, 548; b) G. G. F. Newton, E. P. Abraham, *Biochem. J.* **1956**, 62, 651–658.
- [76] a) E. P. Abraham, G. G. F. Newton, *Biochem. J.* **1961**, 79, 377–393; b) D. C. Hodgkin, E. N. Maslen, *Biochem. J.* **1961**, 79, 393–402.
- [77] For an informative discussion and a compilation of leading references, see J. S. Bindra, R. Bindra, *Prostaglandin Synthesis*, Academic Press, New York, **1977**, p. 7.
- [78] a) S. Bergström, J. Sjövall, *Acta Chem. Scand.* **1957**, 11, 1086; b) S. Bergström, J. Sjövall, *Acta Chem. Scand.* **1960**, 14, 1693–1700; c) S. Bergström, J. Sjövall, *Acta Chem. Scand.* **1960**, 14, 1701–1705; d) S. Bergström, R. Ryhase, B. Samuelsson, J. Sjövall, *Acta Chem. Scand.* **1962**, 16, 501–502; e) S. Bergström, R. Ryhase, B. Samuelsson, J. Sjövall, *J. Biol. Chem.* **1963**, 238, 3555–3564.
- [79] P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, 93, 1533–1564.
- [80] a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **1969**, 91, 5675–5677; b) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, N. M. Weinshenker, *J. Am. Chem. Soc.* **1970**, 92, 397–398; c) E. J. Corey, R. Noyori, T. K. Schaaf, *J. Am. Chem. Soc.* **1970**, 92, 2586–2587; d) E. J. Corey, *Ann. N. Y. Acad. Sci.* **1971**, 180, 24–37.
- [81] a) J. S. Bindra, R. Bindra, *Prostaglandin Synthesis*, Academic Press, New York, **1977**; b) A. Mitra, *The Synthesis of Prostaglandins*, Wiley-Interscience, New York, **1977**.
- [82] *New Synthetic Routes to Prostaglandins and Thromboxanes* (Eds.: S. M. Roberts, F. Scheinmann), Academic Press, San Diego, **1982**.
- [83] a) M. P. L. Caton, *Tetrahedron* **1979**, 35, 2705–2742; b) K. C. Nicolaou, G. P. Gasic, W. E. Barnette, *Angew. Chem.* **1978**, 90, 356–379; *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 293–312; c) R. F. Newton, S. M. Roberts, *Tetrahedron* **1980**, 36, 2163–2196; d) R. Noyori, M. Suzuki, *Angew. Chem.* **1984**, 96, 854–882; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 847–876.
- [84] For the evolution of Corey's synthesis of prostaglandins, see refs. [3, 4].
- [85] E. J. Corey, D. H. Lee, *J. Am. Chem. Soc.* **1975**, 97, 6908–6909.
- [86] A. I. Myers, *J. Heterocycl. Chem.* **1998**, 35, 991–1002.
- [87] a) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, 103, 3099–3111; b) D. A. Evans, J. M. Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre, J. Bartroli, *Pure Appl. Chem.* **1981**, 53, 1109–1127; c) D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, 13, 1–115; d) D. A. Evans, *Aldrichim. Acta* **1982**, 15, 23–32.
- [88] W. Oppolzer, *Pure Appl. Chem.* **1990**, 62, 1241–1250.
- [89] a) H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1988**, 110, 1535–1538; b) P. K. Jadhav, K. S. Bhat, T. Perumal, H. C. Brown, *J. Org. Chem.* **1986**, 51, 432–439.
- [90] a) E. J. Corey, R. Imwinkelried, S. Pikul, Y. B. Xiang, *J. Am. Chem. Soc.* **1989**, 111, 5493–5495; b) E. J. Corey, N. Imai, S. Pikul, *Tetrahedron Lett.* **1991**, 32, 7517–7520.
- [91] a) E. J. Corey, T. P. Loh, *J. Am. Chem. Soc.* **1991**, 113, 8966–8967; b) E. J. Corey, T. P. Loh, T. D. Roper, M. D. Azimioara, M. C. Noe, *J. Am. Chem. Soc.* **1992**, 114, 8290–8292.
- [92] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, 109, 5551–5553; b) E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, 109, 7925–7926; c) E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, 53, 2861–2863; d) E. J. Corey, R. K. Bakshi, *Tetrahedron Lett.* **1990**, 31, 611–614.
- [93] a) W. S. Johnson, *Acc. Chem. Res.* **1968**, 1, 1–8; b) W. S. Johnson, *Angew. Chem.* **1976**, 88, 33–41; *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 9–16; c) W. S. Johnson, *Bioorg. Chem.* **1976**, 5, 51–98.
- [94] a) R. B. Clayton, *Quart. Rev. (London)* **1968**, 19, 168; b) R. B. Woodward, K. Bloch, *J. Am. Chem. Soc.* **1953**, 75, 2023–2024; c) E. E. van Tamelen, J. D. Willet, R. B. Clayton, K. E. Lord, *J. Am.*

- Chem. Soc.* **1966**, 88, 4752–4754; d) E. E. van Tamelen, *J. Am. Chem. Soc.* **1982**, 104, 6480–6481; e) E. J. Corey, W. E. Russey, P. R. Ortiz de Montellano, *J. Am. Chem. Soc.* **1966**, 88, 4750–4751; f) E. J. Corey, S. C. Virgil, *J. Am. Chem. Soc.* **1991**, 113, 4025–4026; g) E. J. Corey, S. C. Virgil, S. Sars, *J. Am. Chem. Soc.* **1991**, 113, 8171–8172; h) E. J. Corey, S. C. Virgil, D. R. Liu, S. Sarshar, *J. Am. Chem. Soc.* **1992**, 114, 1524–1525.
- [95] a) E. E. van Tamelen, *Acc. Chem. Res.* **1975**, 8, 152–158; b) E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler Chauvin, R. J. Anderson, R. S. Achini, *J. Am. Chem. Soc.* **1970**, 92, 7202–7204; c) E. E. van Tamelen, J. W. Murphy, *J. Am. Chem. Soc.* **1970**, 92, 7206–7207; d) E. E. van Tamelen, R. J. Anderson, *J. Am. Chem. Soc.* **1972**, 94, 8225–8228; e) E. E. van Tamelen, R. A. Holton, R. E. Hopla, W. E. Konz, *J. Am. Chem. Soc.* **1972**, 94, 8228–8229; f) E. E. van Tamelen, M. P. Seiler, W. Wierenga, *J. Am. Chem. Soc.* **1972**, 94, 8229–8231.
- [96] T. Goto, Y. Kishi, S. Takahashi, Y. Hirata, *Tetrahedron*, **1965**, 21, 2059, and references therein.
- [97] Total synthesis: a) Y. Kishi, F. Nakatsubo, M. Aratani, T. Goto, S. Inoue, H. Kakoi, S. Sugiura, *Tetrahedron Lett.* **1970**, 5127–5128; b) Y. Kishi, F. Nakatsubo, M. Aratani, T. Goto, S. Inoue, H. Kakoi, *Tetrahedron Lett.* **1970**, 5129–5132; c) Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, 94, 9217–9219; d) Y. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, S. Inoue, H. Tatino, S. Sugiura, H. Kakoi, *J. Am. Chem. Soc.* **1972**, 94, 9219–9221.
- [98] a) R. B. Woodward, *Spec. Publ. Chem. Soc.* **1967**, 21, 217; b) R. B. Woodward, R. Hoffmann, *Angew. Chem.* **1969**, 81, 797–869; *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 781–853; c) R. B. Woodward, R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York, **1970**, p. 178.
- [99] a) D. Crowfoot-Hodgkin, A. W. Johnson, A. R. Todd, *Spec. Publ. Chem. Soc.* **1955**, 3, 109; b) D. Crowfoot-Hodgkin, J. Kamper, M. MacKay, J. Pickworth, K. C. Trueblood, J. G. White, *Nature* **1956**, 178, 64–66; c) D. Crowfoot-Hodgkin, J. Kamper, J. Lindsey, M. MacKay, J. Pickworth, J. H. Robertson, C. B. Shoemaker, J. G. White, R. J. Prosen, K. N. Trueblood, *Proc. Roy. Soc. London Ser. A* **1957**, 242, 228; d) R. Bonnett, *Chem. Rev.* **1963**, 63, 573–605.
- [100] W. Friedrich, G. Gross, K. Bernhauser, P. Zeller, *Helv. Chim. Acta*, **1960**, 43, 704–712.
- [101] R. B. Woodward in *Perspectives in Organic Chemistry* (Ed.: A. Todd), Interscience, New York, **1956**, p. 160.
- [102] a) E. J. Corey, E. J. Trybulski, L. S. Melvin, Jr., K. C. Nicolaou, J. A. Secrist, R. Lett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. F. Haslanger, S. Kim, S. Yoo, *J. Am. Chem. Soc.* **1978**, 100, 4618–4620; b) E. J. Corey, S. Kim, S. Yoo, K. C. Nicolaou, L. S. Melvin, Jr., D. J. Brunelle, J. R. Falck, E. J. Trybulski, R. Lett, P. W. Sheldrake, *J. Am. Chem. Soc.* **1978**, 100, 4620–4622.
- [103] E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* **1974**, 96, 5614–5616.
- [104] a) E. J. Corey, K. C. Nicolaou, L. S. Melvin, Jr., *J. Am. Chem. Soc.* **1975**, 97, 653–654; E. J. Corey, K. C. Nicolaou, L. S. Melvin, Jr., *J. Am. Chem. Soc.* **1975**, 97, 654–655; b) K. C. Nicolaou, *Tetrahedron* **1977**, 33, 683–710; c) S. Masamune, G. S. Bates, J. W. Corcoran, *Angew. Chem.* **1977**, 89, 602–624; *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 585–607; d) I. Paterson, M. M. Mansuri, *Tetrahedron* **1985**, 41, 3569–3624.
- [105] A. Agtarap, J. W. Chamberlin, M. Pinkerton, L. Steinrauf, *J. Am. Chem. Soc.* **1967**, 89, 5737–5739.
- [106] a) M. Dobler, *Ionophores and Their Structures*, Wiley, New York, **1981**; b) J. W. Westley, *Adv. Appl. Microbiol.* **1977**, 22, 177; c) B. C. Pressman, *Ann. Rev. Biochem.* **1976**, 45, 501; d) J. W. Westley, *Ann. Rev. Med. Chem.* **1975**, 10, 246.
- [107] *Polyether Antibiotics: Naturally Occurring Acid Ionophores, Vol. 1–2* (Ed.: J. W. Westley), Marcel Dekker, New York, **1982**.
- [108] a) G. Schmid, T. Fukuyama, K. Akasaka, Y. Kishi, *J. Am. Chem. Soc.* **1979**, 101, 259–260; b) T. Fukuyama, C.-L. Wang, Y. Kishi, *J. Am. Chem. Soc.* **1979**, 101, 260–262; c) T. Fukuyama, K. Akasaka, D. S. Karanewsky, C.-L. Wang, G. Schmid, Y. Kishi, *J. Am. Chem. Soc.* **1979**, 101, 262–263.
- [109] T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, Y. Kishi, *J. Am. Chem. Soc.* **1978**, 100, 2933–2935.
- [110] a) D. B. Collum, J. H. McDonald III, W. C. Still, *J. Am. Chem. Soc.* **1980**, 102, 2117–2118; b) D. B. Collum, J. H. McDonald III, W. C. Still, *J. Am. Chem. Soc.* **1980**, 102, 2118–2120; c) D. B. Collum, J. H. McDonald III, W. C. Still, *J. Am. Chem. Soc.* **1980**, 102, 2120–2121.
- [111] a) W. M. Bandaranayake, J. E. Banfield, D. S. C. Black, G. D. Fallon, B. M. Gatehouse, *J. Chem. Soc. Chem. Commun.* **1980**, 162–163; b) W. M. Bandaranayake, J. E. Banfield, D. S. C. Black, *J. Chem. Soc. Chem. Commun.* **1980**, 902–903; c) W. M. Bandaranayake, J. E. Banfield, D. S. C. Black, G. D. Fallon, B. M. Gatehouse, *Aust. J. Chem.* **1981**, 34, 1655–1667; d) W. M. Bandaranayake, J. E. Banfield, D. S. C. Black, *Aust. J. Chem.* **1982**, 35, 557–565; e) W. M. Bandaranayake, J. E. Banfield, D. S. C. Black, G. D. Fallon, B. M. Gatehouse, *Aust. J. Chem.* **1982**, 35, 567–579; f) J. E. Banfield, D. S. C. Black, S. R. Johns, R. I. Willing, *Aust. J. Chem.* **1982**, 35, 2247–2256.
- [112] a) K. C. Nicolaou, N. A. Petasis, R. E. Zipkin, J. Uenishi, *J. Am. Chem. Soc.* **1982**, 104, 5555–5557; b) K. C. Nicolaou, N. A. Petasis, J. Uenishi, R. E. Zipkin, *J. Am. Chem. Soc.* **1982**, 104, 5557–5558; c) K. C. Nicolaou, R. E. Zipkin, N. A. Petasis, *J. Am. Chem. Soc.* **1982**, 104, 5558–5560; d) K. C. Nicolaou, N. A. Petasis, R. E. Zipkin, *J. Am. Chem. Soc.* **1982**, 104, 5560–5562; e) K. C. Nicolaou, N. A. Petasis in *Strategies and Tactics in Organic Synthesis, Vol. 1* (Ed.: T. Lindberg), Academic Press, San Diego, **1984**, p. 155–173.
- [113] K. C. Nicolaou, *Chem. Brit.* **1985**, 813–817.
- [114] R. S. Dewey, B. H. Arison, J. Hannah, D. H. Shih, G. Albers-Schonberg, *J. Antibiot.* **1985**, 38, 1691–1698.
- [115] a) R. E. Dolle, K. C. Nicolaou, *J. Chem. Soc. Chem. Commun.* **1985**, 1016–1018; b) R. E. Dolle, K. C. Nicolaou, *J. Am. Chem. Soc.* **1985**, 107, 1691–1694; c) R. E. Dolle, K. C. Nicolaou, *J. Am. Chem. Soc.* **1985**, 107, 1695–1698.
- [116] K. C. Nicolaou, R. E. Dolle, D. P. Papahatjis, J. L. Randall, *J. Am. Chem. Soc.* **1984**, 106, 4189–4192.
- [117] K. C. Nicolaou, *Chemtracts: Org. Chem.* **1991**, 4, 181–198.
- [118] a) K. Tachibana, P. J. Scheuer, Y. Tsukitani, H. Kikutsi, D. V. Engen, J. Clardy, Y. Gopichand, F. Schmitz, *J. Am. Chem. Soc.* **1981**, 103, 2469–2471; b) M. Murata, M. Shimatani, H. Sugitani, Y. Oshima, T. Yasumoto, *Bull. Jpn. Soc. Sci. Fish.* **1982**, 48, 549. For biological activity, see a) R. Boe, B. T. Gjertsen, O. K. Vintermyr, G. Houge, M. Lanotte, S. O. Diskeland, *Exp. Cell Res.* **1991**, 195, 237–246; b) A. Takai, G. Mieskes, *Biochem. J.* **1991**, 275, 233–239.
- [119] a) M. Isobe, Y. Ichikawa, H. Masaki, T. Goto, *Tetrahedron Lett.* **1984**, 25, 3607–3610; b) Y. Ichikawa, M. Isobe, T. Goto, *Tetrahedron Lett.* **1984**, 25, 5049–5052; c) M. Isobe, Y. Ichikawa, T. Goto, *Tetrahedron Lett.* **1985**, 26, 5199–5202; d) M. Isobe, Y. Ichikawa, D.-I. Bai, T. Goto, *Tetrahedron Lett.* **1985**, 26, 5203–5206; e) M. Isobe, Y. Ichikawa, T. Goto, *Tetrahedron Lett.* **1985**, 26, 963–966; f) M. Isobe, Y. Ichikawa, D.-I. Bai, H. Masaki, T. Goto, *Tetrahedron* **1987**, 43, 4767–4776.
- [120] a) C. J. Forsyth, S. F. Sabes, R. A. Urbanek, *J. Am. Chem. Soc.* **1997**, 119, 8381–8382; b) S. F. Sabes, R. A. Urbanek, C. J. Forsyth, *J. Am. Chem. Soc.* **1998**, 120, 2534–2542.
- [121] S. V. Ley, A. C. Humphries, H. Eick, R. Bownham, A. R. Ross, R. J. Boyce, J. B. J. Pavey, J. Pietruszka, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3907–3912.
- [122] a) J. Vandeputte, J. L. Wachtel, E. T. Stiller, *Antibiot. Annu.* **1956**, 587; b) W. Mechinski, C. P. Shaffner, P. Ganis, G. Avitabile, *Tetrahedron Lett.* **1970**, 3873–3876; c) P. Ganis, G. Avitabile, W. Mechinski, C. P. Shaffner, *J. Am. Chem. Soc.* **1971**, 93, 4560–4564.
- [123] a) K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis, T. K. Chakraborty, *J. Am. Chem. Soc.* **1987**, 109, 2205–2208; b) K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, *J. Am. Chem. Soc.* **1987**, 109, 2208–2210; c) K. C. Nicolaou, T. K. Chakraborty, R. A. Daines, N. S. Simpkins, *J. Chem. Soc. Chem. Commun.* **1986**, 413–416; d) K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, Y. Ogawa, *J. Am. Chem. Soc.* **1987**, 109, 2821–2822; e) K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, 110, 4672–4685; f) K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, Y. Ogawa, *J. Am. Chem. Soc.* **1988**, 110, 4685–4696; g) K. C. Nicolaou, R. A. Daines, Y. Ogawa, T. K. Chakraborty, *J. Am. Chem. Soc.* **1988**, 110, 4696–4705.
- [124] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, 102, 5974–5976.
- [125] For a recent review, see K. C. Nicolaou, M. W. Härter, J. L. Gunzner, A. Nadin, *Liebigs Ann.* **1997**, 1283–1301.

- [126] R. M. Kennedy, A. Abiko, T. Takemasa, M. Okumoto, S. Masamune, *Tetrahedron Lett.* **1998**, 451–454.
- [127] a) S. Furukawa, *Sci. Pap. Inst. Phys. Chem. Res.* **1932**, 19, 27; b) S. Furukawa, *Sci. Pap. Inst. Phys. Chem. Res.* **1933**, 21, 273; c) S. Furukawa, *Sci. Pap. Inst. Phys. Chem. Res.* **1934**, 24, 304; d) B. Max, *Trends Pharmacol. Sci.* **1987**, 8, 290; e) R. T. Major, *Science* **1967**, 157, 1270–1272; f) H. Lutz, *J. Am. Forests* **1931**, 37, 475; g) H. J. Prideux-Brune, *R. Hort. Soc.* **1947**, 72, 446; h) J. N. Wilford in *The New York Times: Medical Science*, **1988**, March 1, L, p. C3.
- [128] a) K. Nakanishi, *Pure Appl. Chem.* **1967**, 14, 89–113; See also b) N. Sakabe, S. Takada, K. Okabe, *J. Chem. Soc. Chem. Commun.* **1967**, 259–261; c) K. Okabe, K. Yamada, S. Yamamura, S. Takada, *J. Chem. Soc. C* **1967**, 2201–2206.
- [129] a) E. J. Corey, M. C. Kang, M. C. Desai, A. K. Ghosh, I. N. Houpis, *J. Am. Chem. Soc.* **1988**, 110, 649–651; see also b) M. C. Desai, A. K. Ghosh, M. C. Kang, I. N. Houpis in *Strategies and Tactics in Organic Synthesis*, Vol. 3 (Ed.: T. Lindenberg), Academic Press, New York, **1991**, p. 89. See also ref. [3]. Another synthesis of ginkgolide B recently appeared: M. T. Crimmins, J. M. Pace, P. G. Nantermet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson, A. S. Wagman, *J. Am. Chem. Soc.* **1999**, 121, 10249–10250.
- [130] For reviews of palytoxin, see a) R. E. Moore, *Prog. Chem. Org. Nat. Prod.* **1985**, 48, 81–202; b) Y. Hirata, D. Uemura, Y. Ohizumi, *Handbook of Natural Toxins*, Vol. 3 (Ed.: A. T. Tu), Marcel Dekker, New York, **1988**, p. 241.
- [131] D. Uemura, K. Ueda, Y. Hirata, H. Naoki, T. Iwashita, *Tetrahedron Lett.* **1981**, 22, 2781–2784.
- [132] R. E. Moore, G. Bartolini, *J. Am. Chem. Soc.* **1981**, 103, 2491–2494.
- [133] a) R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. McWhorter, Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J.-i. Uenishi, J. B. White, M. Yonaga, *J. Am. Chem. Soc.* **1989**, 111, 7525–7530; b) R. W. Armstrong, J.-M. Beau, S. H. Cheon, W. J. Christ, H. Fujioka, W.-H. Ham, L. D. Hawkins, H. Jin, S. H. Kang, Y. Kishi, M. J. Martinelli, W. W. McWhorter, Jr., M. Mizuno, M. Nakata, A. E. Stutz, F. X. Talamas, M. Taniguchi, J. A. Tino, K. Ueda, J.-i. Uenishi, J. B. White, M. Yonaga, *J. Am. Chem. Soc.* **1989**, 111, 7530–7533. See also ref. [3].
- [134] E. M. Suh, Y. Kishi, *J. Am. Chem. Soc.* **1994**, 116, 11205–11206. See also ref. [3].
- [135] T. Kihara, H. Kusakabe, G. Nakamura, T. Sakurai, K. Isono, *J. Antibiot.* **1981**, 34, 1073–1074.
- [136] T. Sakurai, T. Kihara, K. Isono, *Acta Crystallogr. Sect. C* **1983**, 39, 295–297; T. Kihara, K. Isono, *J. Antibiot.* **1983**, 36, 1236–1241.
- [137] D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, T. J. Stout, *J. Am. Chem. Soc.* **1990**, 112, 7001–7031. See also ref. [3].
- [138] a) G. Stork, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1987**, 109, 1564–1565; G. Stork, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1987**, 109, 1565–1566; b) G. Stork, S. D. Rychnovsky, *Pure Appl. Chem.* **1986**, 58, 767–772.
- [139] a) M. D. Lee, T. S. Dunne, M. M. Siegel, C. C. Chang, G. O. Morton, D. B. Borders, *J. Am. Chem. Soc.* **1987**, 109, 3464–3466; b) M. D. Lee, T. S. Dunne, C. C. Chang, G. A. Ellestad, M. M. Siegel, G. O. Morton, G. O. McGahren, D. B. Borders, *J. Am. Chem. Soc.* **1987**, 109, 3466–3468; c) M. D. Lee, T. S. Dunne, C. C. Chang, M. M. Siegel, G. O. Morton, G. A. Ellestad, W. J. McGahren, D. B. Borders, *J. Am. Chem. Soc.* **1992**, 114, 985–997.
- [140] Reviews: a) K. C. Nicolaou, W.-M. Dai, *Angew. Chem.* **1991**, 103, 1453–1481; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1387–1416; b) K. C. Nicolaou, A. L. Smith, E. W. Yue, *Proc. Natl. Acad. Sci. USA* **1993**, 90, 5881–5888.
- [141] a) R. G. Bergman, *Acc. Chem. Res.* **1973**, 6, 25–31; b) R. R. Jones, R. G. Bergman, *J. Am. Chem. Soc.* **1972**, 94, 660–661; c) T. P. Lockhart, P. B. Gomita, R. G. Bergman, *J. Am. Chem. Soc.* **1981**, 103, 4091–4096.
- [142] a) K. C. Nicolaou, C. W. Hummel, E. N. Pitsinos, M. Nakada, A. L. Smith, K. Shibayama, H. Saimoto, *J. Am. Chem. Soc.* **1992**, 114, 10082–10084; b) R. D. Groneberg, T. Miyazaki, N. A. Stylianides, T. J. Schulze, W. Stahl, E. P. Schreiner, T. Suzuki, Y. Iwabuchi, A. L. Smith, K. C. Nicolaou, *J. Am. Chem. Soc.* **1993**, 115, 7593–7611; c) A. L. Smith, E. N. Pitsinos, C.-K. Hwang, Y. Mizuno, H. Saimoto, G. R. Scarlato, T. Suzuki, K. C. Nicolaou, *J. Am. Chem. Soc.* **1993**, 115, 7612–7624; d) K. C. Nicolaou, C. W. Hummel, M. Nakada, K. Shibayama, E. N. Pitsinos, H. Saimoto, Y. Mizuno, K.-U. Baldenius, A. L. Smith, *J. Am. Chem. Soc.* **1993**, 115, 7625–7635; e) K. C. Nicolaou, *Angew. Chem.* **1993**, 105, 1462–1471; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1377–1385.
- [143] S. A. Hitchcock, S. H. Boyer, M. Y. Chu-Moyer, S. H. Olson, S. J. Danishefsky, *Angew. Chem.* **1994**, 106, 928–932; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 858–862.
- [144] a) C. Vézina, A. Kudelski, S. N. Sehgal, *J. Antibiot.* **1975**, 28, 721–726; b) S. N. Sehgal, H. Baker, C. Vézina, *J. Antibiot.* **1975**, 28, 727–732.
- [145] a) D. C. N. Swindells, P. S. White, J. A. Findlay, *Can. J. Chem.* **1978**, 56, 2491–2492; b) J. A. Findlay, L. Radics, *Can. J. Chem.* **1980**, 58, 579–590.
- [146] M. K. Rosen; S. L. Schreiber, *Angew. Chem.* **1992**, 104, 413–429; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 384–400; b) S. L. Schreiber, *Science* **1991**, 251, 283–287; c) S. L. Schreiber, J. Liu, M. W. Albers, R. Karmacharya, E. Koh, P. K. Martin, M. K. Rosen, R. F. Standaert, T. J. Wandless, *Transplant. Proc.* **1991**, 23, 2839–2844.
- [147] a) K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, 115, 4419–4420; b) A. D. Piscopio, N. Minowa, T. K. Chakraborty, K. Koide, P. Bertinato, K. C. Nicolaou, *J. Chem. Soc. Chem. Commun.* **1993**, 617–618; c) K. C. Nicolaou, P. Bertinato, A. D. Piscopio, T. K. Chakraborty, N. Minowa, *J. Chem. Soc. Chem. Commun.* **1993**, 619–622; d) K. C. Nicolaou, A. D. Piscopio, P. Bertinato, T. K. Chakraborty, N. Minowa, K. Koide, *Chem. Eur. J.* **1995**, 1, 318–323. See also ref. [3].
- [148] D. Romo, S. D. Meyer, D. D. Johnson, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, 115, 7906–7909.
- [149] C. M. Hayward, D. Yohannes, S. J. Danishefsky, *J. Am. Chem. Soc.* **1993**, 115, 9345–9346.
- [150] A. B. Smith III, S. M. Condon, J. A. McCauley, J. L. Leazer, Jr., J. W. Leahy, R. E. Maleczka, Jr., *J. Org. Chem.* **1995**, 117, 5407–5408.
- [151] M. A. Duncaton, G. Pattenden, *J. Chem. Soc. Perkins Trans. 1*, **1999**, 1235–1246.
- [152] M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, 93, 2325–2327.
- [153] K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* **1994**, 106, 38–69; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 15–44; K. C. Nicolaou, R. K. Guy, P. Potier, *Sci. Am.* **1996**, 272(6), 84–88.
- [154] a) K. C. Nicolaou, Z. Yang, J.-J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, E. J. Sorensen, *Nature* **1994**, 367, 630–634; b) K. C. Nicolaou, P. G. Nantermet, H. Ueno, R. K. Guy, E. A. Couladouros, E. J. Sorensen, *J. Am. Chem. Soc.* **1995**, 117, 624–633; c) K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorensen, C. F. Claiborne, R. K. Guy, C.-K. Hwang, M. Nakada, P. G. Nantermet, *J. Am. Chem. Soc.* **1995**, 117, 634–644; d) K. C. Nicolaou, Z. Yang, J.-J. Liu, P. G. Nantermet, C. F. Claiborne, J. Renaud, R. K. Guy, K. Shibayama, *J. Am. Chem. Soc.* **1995**, 117, 645–652; e) K. C. Nicolaou, H. Ueno, J.-J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan, R. Chadha, *J. Am. Chem. Soc.* **1995**, 117, 653–659; f) K. C. Nicolaou, R. K. Guy, *Angew. Chem.* **1995**, 107, 2047–2059; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2079–2090. See also ref. [3].
- [155] a) R. A. Holton, C. Somoza, K. B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc.* **1994**, 116, 1597–1598; b) R. A. Holton, K. B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc.* **1994**, 116, 1599–1600.
- [156] J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young, S. J. Danishefsky, *Angew. Chem.* **1995**, 34, 1886–1888; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1723–1726.
- [157] a) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, J. B. Houze, N. E. Krauss, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, M. G. Natchus, A. J. Shuker, J. C. Sutton, R. E. Taylor, *J. Am. Chem. Soc.* **1997**, 119, 2757–2758; b) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, C. Graenicher, J. B. Houze, J. Jaenichen, D. Lee, D. G. Marquess, P. L.

- McGrane, W. Meng, T. P. Mucciari, M. Muehlebach, M. G. Natchus, H. Paulsen, D. B. Rawlins, J. Satkofsky, A. J. Shuker, J. C. Sutton, R. E. Taylor, K. Tomooka, *J. Am. Chem. Soc.* **1997**, *119*, 2755–2756; c) P. A. Wender, D. G. Marquess, L. P. McGrane, R. E. Taylor, *Chemtracts: Org. Chem.* **1994**, *7*, 160–171.
- [158] I. Shiina, K. Saitoh, I. Frechard-Ortuno, T. Mukaiyama, *Chem. Lett.* **1998**, 3–4; T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y.-I. Tani, M. Hasegawa, K. Yamada, K. Saitoh, *Chem. Eur. J.* **1999**, *5*, 121–161.
- [159] K. Morihira, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama, I. Kuwajima, *J. Am. Chem. Soc.* **1998**, *120*, 12980–12981.
- [160] J. D. Bergström, M. M. Kurtz, D. J. Rew, A. M. Amend, J. D. Karkas, R. G. Bostedor, V. S. Bansal, C. Dufresne, F. L. VanMiddlesworth, O. D. Hensens, J. M. Liesch, D. L. Zink, K. E. Wilson, J. Onishi, J. A. Milligan, G. Bills, L. Kaplan, M. Nallin Omstead, R. G. Jenkins, L. Huang, M. S. Meinz, L. Quinn, R. W. Burg, Y. L. Kong, S. Mochales, M. Mojena, I. Martin, F. Pelaez, M. T. Diez, A. W. Alberts, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 80–84.
- [161] a) M. J. Dawson, J. E. Farthing, P. S. Marshall, R. F. Middleton, M. J. O'Neill, A. Shuttleworth, C. Stylli, R. M. Tait, P. M. Taylor, H. G. Wildman, A. D. Buss, D. Langley, M. V. Hayes, *J. Antibiot.* **1992**, *45*, 639–648; b) P. J. Sidebottom, R. M. Highcock, S. J. Lane, P. A. Procopiou, N. S. Watson, *J. Antibiot.* **1992**, *45*, 648–658.
- [162] A. Nadin, K. C. Nicolaou, *Angew. Chem.* **1996**, *108*, 1732–1766; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1623–1656.
- [163] A. Baxter, B. J. Fitzgerald, J. L. Hutson, A. D. McCarthy, J. M. Motteram, B. C. Ross, M. Sapra, M. A. Snowden, N. S. Watson, R. J. Williams, C. Wright, *J. Biol. Chem.* **1992**, *267*, 11705–11708.
- [164] a) K. C. Nicolaou, E. W. Yue, Y. Naniwa, F. DeRiccardis, A. Nadin, J. E. Leresche, S. La Greca, Z. Yang, *Angew. Chem.* **1994**, *106*, 2306–2309; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2184–2187; b) K. C. Nicolaou, A. Nadin, J. E. Leresche, S. La Greca, T. Tsuru, E. W. Yue, Z. Yang, *Angew. Chem.* **1994**, *106*, 2309–2312; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2187–2190; c) K. C. Nicolaou, A. Nadin, J. E. Leresche, E. W. Yue, S. La Greca, *Angew. Chem.* **1994**, *106*, 2312–2313; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2190–2191; d) K. C. Nicolaou, E. W. Yue, S. La Greca, A. Nadin, Z. Yang, J. E. Leresche, T. Tsuru, Y. Naniwa, F. De Riccardis, *Chem. Eur. J.* **1995**, *1*, 467. See also ref. [3].
- [165] a) For excellent reviews of the Sharpless asymmetric dihydroxylation (AD) reaction, see a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; b) D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159–1170, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059–1070.
- [166] a) E. M. Carreira, J. Du Bois, *J. Am. Chem. Soc.* **1994**, *116*, 10825–10827; b) E. M. Carreira, J. Du Bois, *J. Am. Chem. Soc.* **1995**, *117*, 8106–8125.
- [167] D. A. Evans, J. C. Barrow, J. L. Leighton, A. J. Robichaud, M. J. Seffkow, *J. Am. Chem. Soc.* **1994**, *116*, 12111–12112.
- [168] D. Stoermer, S. Caron, C. H. Heathcock, *J. Org. Chem.* **1996**, *61*, 9115–9125; b) S. Caron, D. Stoermer, A. K. Mapp, C. H. Heathcock, *J. Org. Chem.* **1996**, *61*, 9126–9134.
- [169] a) S. Carmely, Y. Kashman, *Tetrahedron Lett.* **1985**, *26*, 511–514; b) M. Kobayashi, J. Tanaka, T. Katori, M. Matsuura, I. Kitagawa, *Tetrahedron Lett.* **1989**, *30*, 2963–2966; c) M. Kobayashi, J. Tanaka, T. Katori, M. Matsuura, M. Yamashita, I. Kitagawa, *Chem. Pharm. Bull.* **1990**, *38*, 2409–2418; d) I. Kitagawa, M. Kobayashi, T. Katori, M. Yamashita, M. Doi, T. Ishida, J. Tanaka, *J. Am. Chem. Soc.* **1990**, *112*, 3710–3712; e) M. Doi, T. Ishida, M. Kobayashi, I. Kitagawa, *J. Org. Chem.* **1991**, *56*, 3629–3632.
- [170] a) I. Paterson, J. G. Cumming, R. A. Ward, S. Lambole, *Tetrahedron* **1995**, *34*, 9393–9412; b) I. Paterson, J. S. Smith, R. A. Ward, *Tetrahedron* **1995**, *34*, 9413–9436; c) I. Paterson, R. A. Ward, J. D. Smith, J. G. Cumming, K.-S. Yeung, *Tetrahedron* **1995**, *34*, 9437–9466; d) I. Paterson, K.-S. Yeung, R. A. Ward, J. D. Smith, J. G. Cummings, S. Lambole, *Tetrahedron* **1995**, *34*, 9467–9486.
- [171] A. P. Patron, P. Richter, M. J. Tomaszewski, R. A. Miller, K. C. Nicolaou, *J. Chem. Soc. Chem. Commun.* **1994**, 1147–1150; P. K. Richter, M. J. Tomaszewski, R. Miller, A. P. Patron, K. C. Nicolaou, *J. Chem. Soc. Chem. Commun.* **1994**, 1151–1152; K. C. Nicolaou, K. Ajito, A. P. Patron, H. Khatuya, P. K. Richter, P. Bertinato, *J. Am. Chem. Soc.* **1996**, *118*, 3059–3060; K. C. Nicolaou, A. P. Patron, K. Ajito, P. K. Richter, H. Khatuya, P. Bertinato, R. A. Miller, M. J. Tomaszewski, *Chem. Eur. J.* **1996**, *2*, 847–868.
- [172] a) C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1–200; b) I. Paterson, M. A. Lister, C. K. McClure, *Tetrahedron Lett.* **1986**, *27*, 4787–4190; c) I. Paterson, A. N. Hulme, *J. Org. Chem.* **1995**, *60*, 3288–3300; d) I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, R. D. Norcross, *Tetrahedron* **1990**, *46*, 4663–4684.
- [173] J. Carretero, L. Ghose, *Tetrahedron Lett.* **1988**, *29*, 2059–2063.
- [174] a) Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539; b) B. Kim, K. B. Sharpless, *Tetrahedron Lett.* **1989**, *30*, 655–658; c) B. Lohray, Y. Gao, K. B. Sharpless, *Tetrahedron Lett.* **1989**, *30*, 2623–2626.
- [175] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
- [176] a) *International Symposium on Red Tides* (Eds.: T. Okaichi, D. M. Anderson, T. Nemoto), Elsevier, New York, **1989**; b) “Marine Toxins: Origin, Structure and Molecular Pharmacology”: V. L. Trainer, R. A. Edwards, A. M. Szmant, A. M. Stuart, T. J. Mende, D. G. Baden, *ACS Symp. Ser.* **1990**, *418*; c) D. M. Anderson, A. W. White, *Oceanus* **1992**, *35*, 55; d) D. M. Anderson, *Sci. Am.* **1994**, *271*(8), 62–68, and references therein; e) V. L. Trainer, D. G. Baden, W. A. Catterall, *J. Biol. Chem.* **1994**, *269*, 19904–19909.
- [177] Y.-Y. Lin, M. Risk, S. M. Ray, D. Van Engen, J. Clardy, J. C. James, K. Nakanishi, *J. Am. Chem. Soc.* **1981**, *103*, 6773–6775.
- [178] a) K. C. Nicolaou, E. A. Theodorakis, F. P. J. T. Rutjes, J. Tiebes, M. Sato, E. Untersteller, X.-Y. Xiao, *J. Am. Chem. Soc.* **1995**, *117*, 1171–1172; b) K. C. Nicolaou, F. P. J. T. Rutjes, E. A. Theodorakis, J. Tiebes, M. Sato, E. Untersteller, *J. Am. Chem. Soc.* **1995**, *117*, 1173–1174; K. C. Nicolaou, C.-K. Hwang, M. E. Duggan, D. A. Nugiel, Y. Abe, K. Bal Reddy, S. A. DeFrees, D. R. Reddy, R. A. Awartani, S. R. Conley, F. P. J. T. Rutjes, E. A. Theodorakis, *J. Am. Chem. Soc.* **1995**, *117*, 10227–10238; K. C. Nicolaou, E. A. Theodorakis, F. P. J. T. Rutjes, M. Sato, J. Tiebes, X.-Y. Xiao, C.-K. Hwang, M. E. Duggan, Z. Yang, E. A. Couladouros, F. Sato, J. Shin, H.-M. He, T. Bleckman, *J. Am. Chem. Soc.* **1995**, *117*, 10239–10251; K. C. Nicolaou, F. P. J. T. Rutjes, E. A. Theodorakis, J. Tiebes, M. Sato, E. Untersteller, *J. Am. Chem. Soc.* **1995**, *117*, 10252–10263.
- [179] K. C. Nicolaou, *Angew. Chem.* **1996**, *108*, 644–664; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 588–607. See also ref. [3].
- [180] M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1990**, *112*, 3715–3716.
- [181] H. Kamei, Y. Nishiyama, A. Takahashi, Y. Obi, T. Oki, *J. Antibiot.* **1991**, *44*, 1306–1311.
- [182] J. Taunton, J. L. Wood, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 10378–10379.
- [183] A. G. Myers, M. E. Fraley, M. J. Tom, S. B. Cohen, D. J. Madar, *Chem. Biol.* **1995**, *2*, 33–43.
- [184] M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou, S. J. Danishefsky, *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525.
- [185] a) K. L. Rinehart, T. G. Holt, N. L. Fregeau, P. A. Keifer, G. R. Wilson, T. J. Perun, Jr., R. Sakai, A. G. Thompson, A. G. Stroh, L. S. Shield, D. S. Seigler, L. H. Li, D. G. Martin, C. J. P. Grimmelikhuijzen, G. Gade, *J. Nat. Prod.* **1990**, *53*, 771–792; b) K. L. Rinehart, R. Sakai, T. G. Holt, N. L. Fregeau, T. J. Perun, Jr., D. S. Seigler, G. R. Wilson, L. S. Shield, *Pure Appl. Chem.* **1990**, *62*, 1277–1280; c) K. L. Rinehart, T. G. Holt, N. L. Gregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li, D. G. Martin, *J. Org. Chem.* **1990**, *55*, 4512–4515; d) A. E. Wright, D. A. Forleo, G. P. Gunawardana, S. P. Gunasekera, F. E. Koehn, O. J. McConnell, *J. Org. Chem.* **1990**, *55*, 4508–4512; e) R. Sakai, K. L. Rinehart, Y. Guan, H.-J. Wang, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 11456–11460.
- [186] E. J. Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.
- [187] E. J. Martinez, T. Owa, S. L. Schreiber, E. J. Corey, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 3496–3501.
- [188] G. Hofle, N. Bedorf, H. Steinmetz, D. Schomberg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671–1673; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567–1569.
- [189] Review: K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120–2153; *Angew. Chem. Int. Ed.* **1998**, *37*, 2014–2045.

- [190] A. Balog, D. Meng, T. Kamenecha, P. Bertinato, D.-S. Su, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2976–2978; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801–2803.
- [191] Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170–172; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166–168.
- [192] D. Schinzer, A. Limberg, A. Bauer, O. M. Bohm, M. Cordes, *Angew. Chem.* **1997**, *109*, 543–544; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523–524.
- [193] D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T. C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, *109*, 775–777; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 757–759.
- [194] K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268–272.
- [195] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.* **1996**, *108*, 2554–2556; *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2399–2401.
- [196] K. C. Nicolaou, X.-Y. Xiao, Z. Parandoosh, A. Senyei, M. P. Nova, *Angew. Chem.* **1995**, *107*, 2476–2479; *Angew. Chem. Int. Ed. Engl.* **1995**, *33*, 2289–2291.
- [197] K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, N. P. King, M. R. V. Finlay, P. Giannakakou, P. Verdier-Pinard, E. Hamel, *Angew. Chem.* **1997**, *109*, 2181–2187; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2097–2103.
- [198] a) W.-H. Fenical, P. R. Jensen, T. Lindel, USA 5473057, **1995** [*Chem. Abstr.* **1996**: 34898]; b) T. Lindel, P. R. Hensen, W.-H. Fenical, B. H. Long, A. M. Casazza, J. Carboni, C. R. Fairchild, *J. Am. Chem. Soc.* **1997**, *119*, 8744–8745.
- [199] K. C. Nicolaou, F. van Delft, T. Ohshima, D. Vourloumis, J. Xu, S. Hosokawa, J. A. Pfefferkorn, S. Kim, T. Li, *Angew. Chem.* **1997**, *109*, 2631–2634; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2520–2524; K. C. Nicolaou, T. Ohshima, S. Hosokawa, F. van Delft, D. Vourloumis, J. Xu, J. A. Pfefferkorn, S. Kim, *J. Am. Chem. Soc.* **1998**, *120*, 8674–8680.
- [200] X.-T. Chen, B. Zhou, S. K. Bhattacharya, C. E. Gutteridge, T. R. R. Pettus, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 835–838; *Angew. Chem. Int. Ed.* **1998**, *37*, 789–892.
- [201] M. D'Ambrosio, A. Guerriero, F. Pietra, *Helv. Chim. Acta* **1987**, *70*, 2019–2027; **1988**, *71*, 964–976.
- [202] M. Ciomei, C. Albanese, W. Pastori, M. Grandi, F. Pietra, M. D'Ambrosio, A. Guerriero, C. Battistini, *Proc. Am. Assoc. Cancer Res.* **1997**, *38*, 5.
- [203] For a review on sarcodictyins and eleutherobins, see K. C. Nicolaou, J. A. Pfefferkorn, *Chem. Pharm. Bull.* **1999**, *47*, 1199–1213.
- [204] a) K. C. Nicolaou, J.-Y. Xu, S. Kim, T. Ohshima, S. Hosokawa, J. A. Pfefferkorn, *J. Am. Chem. Soc.* **1997**, *119*, 11353–11354; b) K. C. Nicolaou, J.-Y. Xu, S. Kim, J. A. Pfefferkorn, T. Ohshima, D. Vourloumis, S. Hosokawa, *J. Am. Chem. Soc.* **1998**, *120*, 8661–8662.
- [205] a) K. C. Nicolaou, N. Winssinger, D. Vourloumis, T. Ohshima, S. Kim, J. Pfefferkorn, J.-Y. Xu, T. Li, *J. Am. Chem. Soc.* **1998**, *120*, 10814–10826; b) K. C. Nicolaou, S. Kim, J. A. Pfefferkorn, J.-Y. Xu, T. Ohshima, S. Hosokawa, D. Vourloumis, T. Li, *Angew. Chem.* **1998**, *110*, 1483–1486; *Angew. Chem. Int. Ed.* **1998**, *37*, 1418–1421.
- [206] M. Hergenbahn, W. Adolf, E. Hecker, *Tetrahedron Lett.* **1975**, *19*, 1595–1598.
- [207] R. J. Schmidt, F. Evans, *J. Phytochem.* **1976**, *15*, 1778–1779.
- [208] M. J. Caterina, M. A. Schumache, M. Tominaga, T. A. Rosen, J. D. Levine, D. Julius, *Nature* **1997**, *389*, 816–824. See also M. A. Rouhi, *Chem. Eng. News* **1998**, *76*(4), 31–34.
- [209] P. A. Wender, K. D. Rice, M. E. Schnute, *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898; P. A. Wender, R. M. Keenan, H. Y. Lee, *J. Am. Chem. Soc.* **1987**, *109*, 4390–4392.
- [210] P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe, Y. Ueno, *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977.
- [211] Y. Shimizu, H.-N. Chou, H. Bando, G. VanDuyne, J. C. Clardy, *J. Am. Chem. Soc.* **1986**, *108*, 514–515; J. Pawlak, M. S. Tempesta, M. G. Zagorski, M. S. Lee, K. Nakanishi, T. Iwashita, M. L. Gross, K. B. Tomer, *J. Am. Chem. Soc.* **1987**, *109*, 1144–1150.
- [212] K. C. Nicolaou, Z. Yang, G.-Q. Shi, J. L. Gunzner, K. A. Agrios, P. Gartner, *Nature* **1998**, *392*, 264–269; K. C. Nicolaou, M. E. Bunnage, D. G. McGarry, S. Shi, P. K. Somers, P. A. Wallace, X.-J. Chu, K. A. Agrios, J. L. Gunzner, Z. Yang, *Chem. Eur. J.* **1999**, *5*, 599–617; K. C. Nicolaou, P. A. Wallace, S. Shi, M. A. Ouellette, M. E. Bunnage, J. L. Gunzner, K. A. Agrios, G.-Q. Shi, P. Gartner, Z. Yang, *Chem. Eur. J.* **1999**, *5*, 618–627; K. C. Nicolaou, G.-Q. Shi, J. L. Gunzner, P. Gartner, P. A. Wallace, M. A. Ouellette, S. Shi, M. E. Bunnage, K. A. Agrios, C. A. Veale, C.-K. Hwang, J. Hutchinson, C. V. C. Prasad, W. W. Ogilvie, Z. Yang, *Chem. Eur. J.* **1999**, *5*, 628–645; K. C. Nicolaou, J. L. Gunzner, G.-Q. Shi, K. A. Agrios, P. Gartner, Z. Yang, *Chem. Eur. J.* **1999**, *5*, 646–658.
- [213] K. C. Nicolaou, G.-Q. Shi, J. L. Gunzner, P. Gartner, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 5467–5468.
- [214] R. Sakai, T. Higa, C. W. Jefford, G. Bernardinelli, *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405.
- [215] Reviews: a) M. Tsuda, J. Kobayashi, *Heterocycles* **1997**, *46*, 765–794; b) N. Matzanke, R. Gregg, S. Weinreb, *Org. Prep. Proc. Intl.* **1998**, *30*, 1–51; c) E. Magnier, Y. Langlois, *Tetrahedron* **1998**, *54*, 6201–6258.
- [216] J. E. Baldwin, R. C. Whitehead, *Tetrahedron Lett.* **1992**, *33*, 2059–2062.
- [217] J. D. Winkler, J. M. Axten, A. Ali, M. C. Hillier, *J. Am. Chem. Soc.* **1998**, *120*, 6425–6426.
- [218] S. F. Martin, J. M. Humphrey, A. Ali, M. C. Hillier, *J. Am. Chem. Soc.* **1999**, *121*, 866–867.
- [219] J. E. Baldwin, T. E. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, D. C. Whitehead, R. J. Boughtflower, I. M. Mutton, R. J. Upton, *Angew. Chem.* **1998**, *110*, 2806–2808; *Angew. Chem. Int. Ed.* **1998**, *37*, 2661–2663.
- [220] K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem.* **1999**, *111*, 2230–2287; *Angew. Chem. Int. Ed.* **1999**, *38*, 2096–2152.
- [221] M. H. McCormich, W. M. Stark, G. E. Pittenger, J. M. McGuire, *Antibiot. Annu.* **1955–1956**, 606–611.
- [222] C. M. Harris, T. M. Harris, *J. Am. Chem. Soc.* **1982**, *104*, 4293–4295.
- [223] D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. K. Katz, *Angew. Chem.* **1998**, *110*, 2864–2868; *Angew. Chem. Int. Ed.* **1998**, *37*, 2700–2704; D. A. Evans, C. J. Dinsmore, P. S. Watson, M. R. Wood, T. I. Richardson, B. W. Trotter, J. L. Katz, *Angew. Chem.* **1998**, *110*, 2868–2872; *Angew. Chem. Int. Ed.* **1998**, *37*, 2704–2708.
- [224] K. C. Nicolaou, S. Natarajan, H. Li, N. F. Jain, R. Hughes, M. E. Solomon, J. M. Ramanjulu, C. N. C. Boddy, M. Takayanagi, *Angew. Chem.* **1998**, *110*, 2872–2878; *Angew. Chem. Int. Ed.* **1998**, *37*, 2708–2714; K. C. Nicolaou, N. F. Jain, S. Natarajan, R. Hughes, M. E. Solomon, H. Li, J. M. Ramanjulu, M. Takayanagi, A. E. Koumbis, T. Bando, *Angew. Chem.* **1998**, *110*, 2879–2881; *Angew. Chem. Int. Ed.* **1998**, *37*, 2714–2717; K. C. Nicolaou, M. Takayanagi, N. F. Jain, S. Natarajan, A. E. Koumbis, T. Bando, J. M. Ramanjulu, *Angew. Chem.* **1998**, *110*, 2881–2883; *Angew. Chem. Int. Ed.* **1998**, *37*, 2717–2719.
- [225] K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes, T. Bando, *Angew. Chem.* **1998**, *111*, 253–255; *Angew. Chem. Int. Ed.* **1999**, *38*, 240–244.
- [226] K. C. Nicolaou, H. Li, C. N. C. Boddy, J. M. Ramanjulu, T. Y. Yue, S. Natarajan, X.-J. Chu, S. Bräse, R. Rübsam, *Chem. Eur. J.* **1999**, *5*, 2584–2601; K. C. Nicolaou, C. N. C. Boddy, H. Li, A. E. Koumbis, R. Hughes, S. Natarajan, N. F. Jain, J. M. Ramanjulu, S. Bräse, *Chem. Eur. J.* **1999**, *5*, 2602–2621; K. C. Nicolaou, A. E. Koumbis, M. Takayanagi, S. Natarajan, N. F. Jain, T. Bando, H. Li, R. Hughes, *Chem. Eur. J.* **1999**, *5*, 2622–2647; K. C. Nicolaou, H. J. Mitchell, N. F. Jain, R. Hughes, N. Winssinger, S. Natarajan, A. E. Koumbis, *Chem. Eur. J.* **1999**, *5*, 2648–2667.
- [227] D. L. Boger, S. Miyazaki, S. H. Kim, J. H. Wu, O. Loiseleur, S. L. Castle, *J. Am. Chem. Soc.* **1999**, *121*, 3226–3227.
- [228] K. C. Nicolaou, C. N. C. Boddy, S. Natarajan, T.-Y. Yue, H. Li, S. Bräse, J. M. Ramanjulu, *J. Am. Chem. Soc.* **1997**, *119*, 3421–3422.
- [229] T. T. Dabrah, T. Kaneko, W. Massefski, Jr., E. B. Whipple, *J. Am. Chem. Soc.* **1997**, *119*, 1594–1598; T. T. Dabrah, H. J. Harwood, Jr., L. H. Huang, N. D. Jankovich, T. Kaneko, J.-C. Li, S. Lindsey, P. M.

- Moshier, T. A. Subashi, M. Therrien, P. C. Watts, *J. Antibiot.* **1997**, *50*, 1–7.
- [230] K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, H.-S. Choi, W. H. Yoon, Y. He, K. C. Fong, *Angew. Chem.* **1999**, *111*, 1774–1781; *Angew. Chem. Int. Ed.* **1999**, *38*, 1669–1675; K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, K. C. Fong, Y. He, W. H. Yoon, H.-S. Choi, *Angew. Chem.* **1999**, *111*, 1781–1784; *Angew. Chem. Int. Ed.* **1999**, *38*, 1676–1678.
- [231] K. C. Nicolaou, P. S. Baran, R. Jautelat, Y. He, K. C. Fong, H.-S. Choi, W. H. Yoon, Y.-L. Zhong, *Angew. Chem.* **1999**, *111*, 532–535; *Angew. Chem. Int. Ed.* **1999**, *38*, 549–552.
- [232] K. C. Nicolaou, Y. He, K. C. Fong, W. H. Yoon, H. S. Choi, Y. L. Zhong, P. S. Baran, *Org. Lett.* **1999**, *1*, 63–66.
- [233] K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, H.-S. Choi, K. C. Fong, Y. He, W. H. Yoon, *Org. Lett.* **1999**, *1*, 883–886.
- [234] a) K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* in press; b) K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* in press.
- [235] K. C. Nicolaou, **1999**, unpublished results.
- [236] a) E. F. Rogers, H. R. Snyder, R. F. Fischer, *J. Am. Chem. Soc.* **1952**, *74*, 1987–1989; b) H. R. Snyder, R. F. Fischer, J. F. Walker, H. E. Els, G. A. Nussberger, *J. Am. Chem. Soc.* **1954**, *76*, 2819–2825, 4601–4605; c) H. R. Snyder, H. F. Strohmayer, R. A. Mooney, *J. Am. Chem. Soc.* **1958**, *80*, 3708–3710.
- [237] P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Behforouz, M. V. Lakshmikantham, W. Zeigler, *J. Am. Chem. Soc.* **1973**, *95*, 7842–7850.
- [238] F. He, Y. Bo, J. D. Altom, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 6771–6772.
- [239] a) J.-J. Sanglier, V. Quesniaux, T. Fehr, H. Hofmann, M. Mahne, K. Memmert, W. Schuler, G. Zenke, L. Gschwind, C. Mauer, W. Schilling, *J. Antibiot.* **1999**, *52*, 466–473; b) T. Fehr, J. Kallen, L. Oberer, J.-J. Sanglier, W. Schilling, *J. Antibiotics* **1999**, *52*, 474–479; c) D. E. Zacharias, *Acta Crystallogr. Sect. B* **1970**, *25*, 1455–1464.
- [240] K. C. Nicolaou, J. Xu, F. Murphy, S. Barluenga, O. Baudoin, H. Wei, D. L. F. Gray, T. Ohshima, *Angew. Chem.* **1999**, *111*, 2599–2604; *Angew. Chem. Int. Ed.* **1999**, *38*, 2447–2451.
- [241] A. K. Ganguly, B. Pramanik, T. C. Chan, O. Sarre, Y.-T. Liu, J. Morton, V. M. Girijavallabhan, *Heterocycles* **1989**, *28*, 83–88.
- [242] D. E. Wright, *Tetrahedron* **1979**, *35*, 1207–1237.
- [243] a) J. A. Maertens, *Curr. Opin. Anti-Infect. Invest. Drugs* **1999**, *1*, 49–56; b) J. A. Maertens, *Idrugs* **1999**, *2*, 446–453.
- [244] a) A. K. Ganguly, J. L. McCormick, T. M. Chan, A. K. Saksena, P. R. Das, *Tetrahedron Lett.* **1997**, *38*, 7989–7991; b) T. M. Chan, R. M. Osterman, J. B. Morton, A. K. Ganguly, *Magn. Res. Chem.* **1997**, *35*, 529–532.
- [245] K. C. Nicolaou, H. J. Mitchell, H. Suzuki, R. M. Rodríguez, O. Baudoin, K. C. Fylaktakidou, *Angew. Chem.* **1999**, *111*, 3523–3528; *Angew. Chem. Int. Ed.* **1999**, *38*, 3334–3339; K. C. Nicolaou, R. M. Rodríguez, K. C. Fylaktakidou, H. Suzuki, H. J. Mitchell, *Angew. Chem.* **1999**, *111*, 3529–3534; *Angew. Chem. Int. Ed.* **1999**, *38*, 3340–3345; K. C. Nicolaou, H. J. Mitchell, R. M. Rodríguez, K. C. Fylaktakidou, H. Suzuki, *Angew. Chem.* **1999**, *111*, 3535–3540; *Angew. Chem. Int. Ed.* **1999**, *38*, 3345–3350.
- [246] K. C. Nicolaou, F. L. van Delft, S. C. Conley, H. J. Mitchell, J. Jin, M. Rodríguez, *J. Am. Chem. Soc.* **1997**, *119*, 9057–9058.
- [247] a) G. Jaurand, J.-M. Beau, P. Sinaï, *J. Chem. Soc. Chem. Commun.* **1982**, 701–703; b) M. Trumtel, P. Tavecchia, A. Veyrières, P. Sinaï, *Carbohydr. Res.* **1990**, *202*, 257–275.
- [248] R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, London, **1985**.
- [249] S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371–388. See also ref. [271]. For some early pioneering studies on this reaction, see T. J. Katz, S. J. Lee, N. Acton, *Tetrahedron Lett.* **1976**, 4247–4250; T. J. Katz, N. Acton, *Tetrahedron Lett.* **1976**, 4251–4254; T. J. Katz, J. McGinnis, C. Altus, *J. Am. Chem. Soc.* **1976**, *98*, 606–608; T. J. Katz, *Organomet. Chem.* **1977**, *16*, 283–317.
- [250] a) S. T. Nguyen, L. K. Johnson, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975; b) S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859; c) W. A. Herrmann, W. C. Schattenmann, O. Nuyken, S. C. Glander, *Angew. Chem.* **1996**, *108*, 1169–1170; *Angew. Chem. Int. Ed. Engl.* **1996**, *36*, 1087–1088; d) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
- [251] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O. Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.
- [252] C.-H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, **1994**.
- [253] a) K. Ehud, R. A. Lerner, *Isr. J. Chem.* **1996**, *36*, 113–116; b) P. G. Schultz, R. A. Lerner, *Science* **1995**, *269*, 1835–1842; c) P. G. Schultz, R. A. Lerner, *Acc. Chem. Res.* **1993**, *26*, 391–395.
- [254] a) D. E. Kane, C. T. Walsh, C. Khosla, *Science* **1998**, *282*, 63–68; b) C. Khosla, *Chem. Rev.* **1997**, *97*, 2577–2590; c) L. Katz, *Chem. Rev.* **1997**, *97*, 2557–2575; d) P. F. Leadlay, *Curr. Opin. Chem. Biol.* **1997**, *1*, 162–168; e) I. A. Scott, *Tetrahedron* **1994**, *50*, 13315–13333; f) C. A. Roessner, I. A. Scott, *Annu. Rev. Microbiol.* **1996**, *50*, 467–490; g) I. A. Scott, *J. Nat. Prod.* **1994**, *57*, 557–573.
- [255] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621; b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497; c) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1973**, *38*, 3239–3243; d) G. Sauer, U. Eder, G. Haffer, G. Neef, R. Wiechert, *Angew. Chem.* **1975**, *87*, 413; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 417.
- [256] a) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J. Am. Chem. Soc.* **1975**, *97*, 2567–2568; b) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106–112; c) W. S. Knowles, *J. Chem. Educ.* **1986**, *63*, 222–225.
- [257] a) H. B. Kagan, *Bull. Soc. Chim. Fr.* **1988**, 846–853; b) J. W. Scott, *Top. Stereochem.* **1989**, *19*, 209–226; c) J. Crosby, *Tetrahedron* **1991**, *47*, 4789–4846; d) S. Akutagawa in *Organic Synthesis in Japan, Past, Present, and Future* (Ed.: R. Noyori), Tokyo Kagaku Dozin, Co., Tokyo, **1992**, p. 75.
- [258] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
- [259] For original publication, see ref. [124]. For excellent reviews of the Sharpless asymmetric epoxidation reaction, see a) B. E. Rossiter in *Asymmetric Synthesis*, Vol. 5 (Ed.: J. D. Morrison), Academic Press, New York, **1985**, pp. 193–246; b) M. G. Finn, K. B. Sharpless in *Asymmetric Synthesis*, Vol. 5 (Ed.: J. D. Morrison), Academic Press, New York, **1985**, pp. 247–308; c) R. A. Johnson, K. B. Sharpless in *Comprehensive Organic Synthesis*, Vol. 7 (Eds: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, p. 389–436; d) R. A. Johnson, K. B. Sharpless in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**, p. 103; e) A. Pfenniger, *Synthesis* **1986**, 89–116; f) T. Katsuki, V. S. Martin, *Org. React.* **1996**, *48*, 1–299.
- [260] M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1237–1256.
- [261] a) K. Neuschuetz, J. Velker, R. Neier, *Synthesis* **1998**, *3*, 227–255; b) H. Waldmann, *Organic Synthesis Highlights II*, VCH, Weinheim, **1995**, pp. 193–202; c) S. T. Dennison, D. C. Harrowven, *J. Chem. Educ.* **1996**, *73*, 697–701; d) L. F. Tietze, *Chem. Ind.* **1995**, *12*, 453–457; e) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195–206; f) R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103–13159; g) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; h) J. D. Winkler, *Chem. Rev.* **1996**, *96*, 167–176; i) T. L. Ho, *Tandem Organic Reactions*, Wiley, New York, **1992**.
- [262] See refs. [93, 94] and a) E. E. van Tamelen, *Acc. Chem. Res.* **1975**, *8*, 152–158; b) E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler Chauvin, R. J. Anderson, R. S. Achini, *J. Am. Chem. Soc.* **1970**, *92*, 7202–7204; c) E. E. van Tamelen, J. W. Murphy, *J. Am. Chem. Soc.* **1970**, *92*, 7206–7207; d) E. E. van Tamelen, R. J. Anderson, *J. Am. Chem. Soc.* **1972**, *94*, 8225–8228; e) E. E. van Tamelen, R. A. Holton, R. E. Hopla, W. E. Konz, *J. Am. Chem. Soc.* **1972**, *94*, 8228–8229; f) E. E. van Tamelen, M. P. Seiler, W. Wierenga, *J. Am. Chem. Soc.* **1972**, *94*, 8229–8231; g) K. B. Sharpless, *J. Am. Chem. Soc.* **1970**, *92*, 6999–7001; h) P. A. Bartlett in *Asymmetric Synthesis*, Vol. 3 (Ed.: J. D. Morrison), Academic Press, New York, **1984**, p. 341; i) W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jaques, J. K. Crandall, *J. Am. Chem. Soc.* **1964**, *86*, 1959–1966; j) W. S. Johnson, J. K. Crandall, *J. Org. Chem.* **1965**, *30*, 1785–1790.
- [263] I. Ugi, *Angew. Chem.* **1982**, *94*, 826–835; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810–819.
- [264] D. P. Curran, *ACS Symp. Ser.* **1998**, *685*, 62–71.

- [265] B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; see also, A. de Meijerie, S. Bräse, *J. Organomet. Chem.* **1999**, *576*, 88–100.
- [266] a) O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98–122; b) *Nobel Lectures: Chemistry 1942–1962*, Elsevier, New York, **1964**, pp. 259–303; c) W. Oppolzer in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. A. Fleming, L. A. Paquette), Pergamon, New York, **1991**, p. 315–400.
- [267] a) G. Wittig, G. Geissler, *Justus Liebigs Ann. Chem.* **1953**, *580*, 44–53; b) K. C. Nicolaou, M. W. Härtner, J. L. Gunzner, A. Nadin, *Liebigs Ann. Chem.* **1997**, 1283–1301; c) *Nobel Lectures: Chemistry 1971–1980*, World Scientific, River Edge, NJ, **1993**, pp. 368–376.
- [268] H. C. Brown, B. C. S. Rao, *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695; b) H. C. Brown, *Hydroboration*, W. A. Benjamin, New York, **1962**; c) *Nobel Lectures: Chemistry 1971–1980*, World Scientific, Teaneck, NJ, **1993**, pp. 333–364.
- [269] a) E. J. Corey, D. Seebach, *J. Org. Chem.* **1966**, *31*, 4097–4099; b) D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 231–237.
- [270] *Palladium Reagents and Catalysts* (Ed.: J. Tsuji), Wiley, New York, **1996**.
- [271] a) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446–452; b) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2145; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2037–2056; c) “Alkene Metathesis in Organic Synthesis” in *Topics in Organometallic Chemistry, Vol. 1* (Ed.: A. Fürstner), Springer, New York, **1998**; See also R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450.
- [272] T. W. Greene, P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Wiley, New York, **1999**.
- [273] D. H. R. Barton, *Experientia* **1950**, *6*, 316–320.
- [274] R. A. Hirschmann, *Angew. Chem.* **1991**, *103*, 1305–1330; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1278–1301.
- [275] J. S. Fruechtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19–46; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17–42.
- [276] B. Merrifield in *Peptides* (Ed.: B. Gutte), Academic Press, San Diego, **1995**, pp. 93–169.
- [277] *Combinatorial Chemistry* (Eds.: S. R. Wilson, A. W. Czarnik), Wiley, New York, **1997**.
- [278] a) *Combinatorial Chemistry and Molecular Diversity Drug Discovery* (Eds.: E. M. Gordon, J. F. Kerwin, Jr.), Wiley, New York, **1998**, p. 516; b) R. E. Dolle, *Mol. Diversity* **1998**, *3*, 199–233; b) R. E. Dolle, K. H. Nelson, Jr., *J. Comb. Chem.* **1999**, *1*, 235–282.
- [279] a) K. D. Shimizu, M. L. Snapper, A. H. Hoveyda, *Chem. Eur. J.* **1998**, *4*, 1885–1889; b) A. H. Hoveyda, *Chem. Biol.* **1998**, *5*, R187–R191; c) M. B. Francis, T. F. Jamison, E. N. Jacobsen, *Curr. Opin. Chem. Biol.* **1998**, *2*, 422–428.
- [280] P. G. Schultz, X.-D. Xiang, *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 153–158.
- [281] IRORI (San Diego, CA) and Argonaut (San Francisco, CA) are two examples of companies specializing in the design and manufacturing of automated systems for chemical synthesis (K.C.N. is an advisor to IRORI).
- [282] W. Wells, *Chem. Biol.* **1999**, *6*, R209–R211.
- [283] a) D. S. Tan, M. A. Foley, M. D. Shair, S. L. Schreiber, *J. Am. Chem. Soc.* **1998**, *120*, 8565–8566; b) K. B. Sharpless, personal communication; see ref. [234].
- [284] *Chemical Research—2000 and Beyond: Challenges and Visions* (Ed.: P. Barkan), Oxford University Press, New York, **1998**, p. 218.
- [285] a) H. H. Rennhard, C. R. Stephens, R. B. Woodward, *J. Am. Chem. Soc.* **1962**, *84*, 3222–3224; b) R. B. Woodward, *Pure Appl. Chem.* **1963**, *6*, 561–573; c) J. J. Krost, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, R. B. Woodward, *J. Am. Chem. Soc.* **1968**, *90*, 439–457.
- [286] R. B. Woodward, *The Harvey Lectures, Vol. 31*, Academic Press, New York, **1965**.
- [287] a) M. A. Wuonola, R. B. Woodward, *J. Am. Chem. Soc.* **1973**, *95*, 284–285; b) M. A. Wuonola, R. B. Woodward, *J. Am. Chem. Soc.* **1973**, *95*, 5098–5099; c) M. A. Wuonola, R. B. Woodward, *Tetrahedron* **1976**, *32*, 1085–1095.
- [288] a) W. J. Greenlee, R. B. Woodward, *J. Am. Chem. Soc.* **1976**, *98*, 6075–6076; b) W. J. Greenlee, R. B. Woodward, *Tetrahedron* **1980**, *36*, 3361–3366; c) W. J. Greenlee, R. B. Woodward, *Tetrahedron* **1980**, *36*, 3367–3375.
- [289] R. B. Woodward, T. R. Hoye, *J. Am. Chem. Soc.* **1977**, *99*, 8007–8014.
- [290] a) I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, H. R. Pfaendler, R. B. Woodward, *J. Am. Chem. Soc.* **1978**, *100*, 8214–8222; b) M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernest, R. B. Woodward, *J. Am. Chem. Soc.* **1979**, *101*, 6296–6301; c) I. Ernest, J. Gosteli, R. B. Woodward, *J. Am. Chem. Soc.* **1979**, *101*, 6301–6305; d) H. R. Pfaendler, J. Gosteli, R. B. Woodward, *J. Am. Chem. Soc.* **1979**, *101*, 6306–6310; e) H. R. Pfaendler, J. Gosteli, R. B. Woodward, *J. Am. Chem. Soc.* **1980**, *102*, 2039–2043; f) M. Lang, K. Prasad, J. Gosteli, R. B. Woodward, *Helv. Chim. Acta* **1980**, *63*, 1093–1097.
- [291] a) E. J. Corey, A. G. Hortmann, W. R. Hertler, *J. Am. Chem. Soc.* **1958**, *80*, 2903–2905; b) E. J. Corey, A. G. Hortmann, W. R. Hertler, *J. Am. Chem. Soc.* **1959**, *81*, 5209–5212.
- [292] a) E. J. Corey, R. B. Mitra, H. Uda, *J. Am. Chem. Soc.* **1963**, *85*, 362–366; b) E. J. Corey, R. B. Mitra, H. Uda, *J. Am. Chem. Soc.* **1964**, *86*, 485–492.
- [293] a) E. J. Corey, S. Nozoe, *J. Am. Chem. Soc.* **1963**, *85*, 3527–3529; b) E. J. Corey, S. Nozoe, *J. Am. Chem. Soc.* **1965**, *87*, 5728–5733.
- [294] a) E. J. Corey, A. G. Hortmann, *J. Am. Chem. Soc.* **1963**, *85*, 4033–4034; b) E. J. Corey, A. G. Hortmann, *J. Am. Chem. Soc.* **1965**, *87*, 5736–5741.
- [295] a) E. J. Corey, S. Nozoe, *J. Am. Chem. Soc.* **1964**, *86*, 1652; b) E. J. Corey, S. Nozoe, *J. Am. Chem. Soc.* **1965**, *87*, 5733–5735.
- [296] a) E. J. Corey, E. Hamanaka, *J. Am. Chem. Soc.* **1967**, *89*, 2758–2759; b) E. J. Corey, S. Daigneault, B. R. Dixon, *Tetrahedron Lett.* **1993**, *34*, 3675–3678.
- [297] a) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, B. W. Erickson, *J. Am. Chem. Soc.* **1968**, *90*, 5618–5620; b) E. J. Corey, H. Yamamoto, *J. Am. Chem. Soc.* **1970**, *92*, 6636–6637; c) E. J. Corey, H. Yamamoto, *J. Am. Chem. Soc.* **1970**, *92*, 6637–6638.
- [298] a) E. J. Corey, N. N. Girotra, C. T. Mathew, *J. Am. Chem. Soc.* **1969**, *91*, 1557–1559; b) E. J. Corey, R. D. Balanson, *Tetrahedron Lett.* **1973**, *34*, 3153–3156.
- [299] E. J. Corey, K. Achiwa, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1969**, *91*, 4318–4320.
- [300] a) E. J. Corey, D. E. Cane, L. Libit, *J. Am. Chem. Soc.* **1971**, *93*, 7016–7021; b) E. J. Corey, M. C. Desai, *Tetrahedron Lett.* **1985**, *26*, 3535–3538.
- [301] D. S. Watt, E. J. Corey, *Tetrahedron Lett.* **1972**, 4651–4654.
- [302] E. J. Corey, B. B. Snider, *J. Am. Chem. Soc.* **1972**, *94*, 2549–2550.
- [303] E. J. Corey, D. S. Watt, *J. Am. Chem. Soc.* **1973**, *95*, 2303–2311.
- [304] E. J. Corey, R. D. Balanson, *J. Am. Chem. Soc.* **1974**, *96*, 6516–6517.
- [305] a) E. J. Corey, J. F. Arnett, G. N. Widiger, *J. Am. Chem. Soc.* **1975**, *97*, 430–431; b) E. J. Corey, M. Petrzilka, Y. Ueda, *Tetrahedron Lett.* **1975**, 4343–4346; c) E. J. Corey, M. Petrzilka, Y. Ueda, *Helv. Chim. Acta* **1977**, *60*, 2294–2302.
- [306] E. J. Corey, D. N. Crouse, J. E. Anderson, *J. Org. Chem.* **1975**, *40*, 2140–2141.
- [307] E. J. Corey, K. C. Nicolaou, T. Toru, *J. Am. Chem. Soc.* **1975**, *97*, 2287–2288.
- [308] a) E. J. Corey, R. H. Wollenberg, *Tetrahedron Lett.* **1976**, 4705–4708; b) E. J. Corey, P. Carpino, *Tetrahedron Lett.* **1990**, *31*, 7555–7558.
- [309] a) E. J. Corey, M. Shibasaki, J. Knolle, T. Sugahara, *Tetrahedron Lett.* **1977**, 785–788; b) E. J. Corey, M. Shibasaki, J. Knolle, *Tetrahedron Lett.* **1977**, 1625–1626.
- [310] E. J. Corey, S. Bhattacharyya, *Tetrahedron Lett.* **1977**, 3919–3922.
- [311] E. J. Corey, G. E. Keck, I. Székely, *J. Am. Chem. Soc.* **1977**, *99*, 2006–2009.
- [312] a) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, G. E. Keck, B. Gopalan, S. D. Larsen, P. Siret, J. L. Gras, *J. Am. Chem. Soc.* **1978**, *100*, 8034–8036; b) E. J. Corey, J. Gorzynski Smith, *J. Am. Chem. Soc.* **1979**, *101*, 1038–1039.
- [313] E. J. Corey, M. Behforouz, M. Ishiguro, *J. Am. Chem. Soc.* **1979**, *101*, 1608–1609.
- [314] E. J. Corey, H. L. Pearce, *J. Am. Chem. Soc.* **1979**, *101*, 5841–5843.
- [315] a) E. J. Corey, Y. Arai, C. Mioskowski, *J. Am. Chem. Soc.* **1979**, *101*, 6748–6749; b) E. J. Corey, S.-I. Hashimoto, A. E. Barton, *J. Am. Chem. Soc.* **1981**, *103*, 721–722; c) E. J. Corey, J. O. Albright, *J. Org. Chem.* **1983**, *48*, 2114–2115; d) E. J. Corey, W.-G. Su, M. M.

- Mehrotra, *Tetrahedron Lett.* **1984**, 25, 5123–5126; e) E. J. Corey, *J. Am. Chem. Soc.* **1979**, 101, 6748–6749.
- [316] E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, S. Hammarstroem, *J. Am. Chem. Soc.* **1980**, 102, 1436–1439.
- [317] E. J. Corey, M. A. Tius, J. Das, *J. Am. Chem. Soc.* **1980**, 102, 1742–1744.
- [318] E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho, D. H. Hua, *J. Am. Chem. Soc.* **1980**, 102, 6613–6615.
- [319] E. J. Corey, A. Tramontano, *J. Am. Chem. Soc.* **1981**, 103, 5599–5600.
- [320] E. J. Corey, J. Das, *J. Am. Chem. Soc.* **1982**, 104, 5551–5553.
- [321] a) E. J. Corey, D. H. Hua, B. C. Pan, S. P. Seitz, *J. Am. Chem. Soc.* **1982**, 104, 6818–6820; b) E. J. Corey, B. C. Pan, D. H. Hua, D. R. Deardorff, *J. Am. Chem. Soc.* **1982**, 104, 6816–6818.
- [322] E. J. Corey, A. Tramontano, *J. Am. Chem. Soc.* **1984**, 106, 462–465.
- [323] E. J. Corey, D. Biswanath, *J. Am. Chem. Soc.* **1984**, 106, 2735–2736.
- [324] E. J. Corey, M. M. Mehrotra, *J. Am. Chem. Soc.* **1984**, 106, 3384–3384.
- [325] a) E. J. Corey, J. P. Dittami, *J. Am. Chem. Soc.* **1985**, 107, 256–257; b) E. J. Corey, A. Guzman-Perez, M. C. Noe, *J. Am. Chem. Soc.* **1994**, 116, 12109–12110.
- [326] E. J. Corey, M. C. Desai, T. A. Engler, *J. Am. Chem. Soc.* **1985**, 107, 4339–4341.
- [327] a) E. J. Corey, A. G. Myers, N. Takahashi, H. Yamane, H. Schraudolf, *J. Am. Chem. Soc.* **1987**, 109, 5574–5575; b) E. J. Corey, A. G. Myers, N. Takahashi, H. Yamane, H. Schraudolf, *Tetrahedron Lett.* **1986**, 27, 5083–5084; c) E. J. Corey, H. Kigoshi, *Tetrahedron Lett.* **1991**, 32, 5025–5028.
- [328] a) E. J. Corey, M. M. Mehrotra, *Tetrahedron Lett.* **1986**, 27, 5173–5176; b) E. J. Corey, W. Su, M. B. Cleaver, *Tetrahedron Lett.* **1989**, 30, 4181–4184.
- [329] E. J. Corey, P. A. Magriotis, *J. Am. Chem. Soc.* **1987**, 109, 287–289.
- [330] E. J. Corey, G. Wess, Y. B. Xiang, A. K. Singh, *J. Am. Chem. Soc.* **1987**, 109, 4717–4721.
- [331] a) A. K. Singh, R. K. Bakshi, E. J. Corey, *J. Am. Chem. Soc.* **1987**, 109, 6187–6189; b) E. J. Corey, A. Guzman-Perez, S. E. Lazerwith, *J. Am. Chem. Soc.* **1997**, 119, 11769–11776.
- [332] E. J. Corey, R. M. Burk, *Tetrahedron Lett.* **1987**, 28, 6413–6416.
- [333] E. J. Corey, M. M. Mehrotra, *Tetrahedron Lett.* **1988**, 29, 57–60.
- [334] E. J. Corey, D. C. Ha, *Tetrahedron Lett.* **1988**, 29, 3171–3174.
- [335] a) E. J. Corey, P. da Silva Jardine, J. C. Rohloff, *J. Am. Chem. Soc.* **1988**, 110, 3672–3673; b) E. J. Corey, P. da Silva Jardine, T. Mohri, *Tetrahedron Lett.* **1988**, 29, 6409–6412; c) E. J. Corey, P. da Silva -Jardine, *Tetrahedron Lett.* **1989**, 30, 7297–7300.
- [336] a) E. J. Corey, P. Carpino, *J. Am. Chem. Soc.* **1989**, 111, 5472–5474; b) E. J. Corey, P. Carpino, *Tetrahedron Lett.* **1990**, 31, 3857–3858.
- [337] E. J. Corey, I. N. Houpis, *J. Am. Chem. Soc.* **1990**, 112, 8997–8998.
- [338] a) E. J. Corey, G. A. Reichard, *J. Am. Chem. Soc.* **1992**, 114, 10677–10678; b) E. J. Corey, S. Choi, *Tetrahedron Lett.* **1993**, 34, 6969–6972; c) E. J. Corey, W. Li, G. A. Reichard, *J. Am. Chem. Soc.* **1998**, 120, 2330–2336; e) E. J. Corey, W. Li, T. Nagamitsu, *Angew. Chem.* **1998**, 110, 1784–1787; *Angew. Chem. Int. Ed.* **1998**, 37, 1676–1679.
- [339] E. J. Corey, J. Lee, *J. Am. Chem. Soc.* **1993**, 115, 8873–8874.
- [340] E. J. Corey, Y. J. Wu, *J. Am. Chem. Soc.* **1993**, 115, 8871–8872.
- [341] E. J. Corey, A. Guzman-Perez, T.-P. Loh, *J. Am. Chem. Soc.* **1994**, 116, 3611–3612.
- [342] a) T. G. Gant, M. C. Noe, E. J. Corey, *Tetrahedron Lett.* **1995**, 36, 8745–8748; b) E. J. Corey, L. I. Wu, *J. Am. Chem. Soc.* **1993**, 115, 9327–9328.
- [343] E. J. Corey, B. E. Roberts, B. R. Dixon, R. Brian, *J. Am. Chem. Soc.* **1995**, 117, 193–196.
- [344] E. J. Corey, M. A. Letavic, *J. Am. Chem. Soc.* **1995**, 117, 9616–9617.
- [345] E. J. Corey, R. S. Kania, *J. Am. Chem. Soc.* **1996**, 118, 1229–1230.
- [346] E. J. Corey, S. Lin, *J. Am. Chem. Soc.* **1996**, 118, 8765–8766.
- [347] E. J. Corey, G. Luo, L. S. Lin, *Angew. Chem.* **1998**, 110, 1147–1149; *Angew. Chem. Int. Ed.* **1998**, 37, 1126–1128.
- [348] E. J. Corey, K. Lui, *J. Am. Chem. Soc.* **1997**, 119, 9929–9930.
- [349] E. J. Martinez, E. J. Corey, *Org. Lett.* **1999**, 1, in press.
- [350] Quinine: a) R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1944**, 66, 849; R. B. Woodward, W. E. Doering, *J. Am. Chem. Soc.* **1945**, 67, 860–874; b) M. Gates, B. Sugavanam, S. L. Schreiber, *J. Am. Chem. Soc.* **1970**, 92, 205–207; c) J. Gutzwiller, M. Uskokovic, *J. Am. Chem. Soc.* **1970**, 92, 204–205; d) E. C. Taylor, S. F. Martin, *J. Am. Chem. Soc.* **1972**, 94, 6218–6220; e) T. Imanishi, M. Inoue, Y. Wada, M. Hanaoka, *Chem. Pharm. Bull.* **1982**, 30, 1925–1928.
- [351] Cortisone: a) R. B. Woodward, F. Sondheimer, D. Taub, *J. Am. Chem. Soc.* **1951**, 73, 405–407; b) L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns, J. M. Constantin, *J. Am. Chem. Soc.* **1952**, 74, 4974–4976; c) Y. Horiguchi, E. Nakamura, I. Kuwajima, *J. Org. Chem.* **1986**, 51, 4323–4325; d) H. Nemoto, N. Matsuhashi, M. Imaizumi, M. Nagai, K. Fukumoto, *J. Org. Chem.* **1990**, 55, 5625–5631.
- [352] Morphine: a) M. Gates, G. Tschudi, *J. Am. Chem. Soc.* **1952**, 72, 1109–1110; M. Gates, G. Tschudi, *J. Am. Chem. Soc.* **1956**, 78, 1380–1393; b) D. Elad, D. Ginsburg, *J. Am. Chem. Soc.* **1954**, 76, 312–313; c) G. C. Morrison, R. O. Waite, J. Shavel, Jr., *Tetrahedron Lett.* **1967**, 4055–4056; d) T. Kametani, M. Ihara, K. Fukumoto, H. Yagi, *J. Chem. Soc. C* **1969**, 2030–2033; e) M. A. Schwartz, I. S. Mami, *J. Am. Chem. Soc.* **1975**, 97, 1239–1240; f) K. C. Rice, *J. Org. Chem.* **1980**, 45, 3135–3137; g) D. A. Evans, C. H. Mitch, *Tetrahedron Lett.* **1982**, 23, 285–288; h) J. E. Toth, P. L. Fuchs, *J. Org. Chem.* **1987**, 52, 473–475; i) K. A. Parker, D. Fokas, *J. Am. Chem. Soc.* **1992**, 114, 9688–9689; j) C. Y. Hong, N. Kado, L. E. Overman, *J. Am. Chem. Soc.* **1993**, 115, 11028–11029; k) J. Mulzer, G. Duerner, D. Trauner, *Angew. Chem.* **1996**, 108, 3046–3048; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2830–2832.
- [353] Lysergic acid: a) ref. [26]; b) M. Julia, F. Le Goffic, J. Igolen, M. Baillarge, *Tetrahedron Lett.* **1969**, 1569–1571; c) V. W. Armstrong, S. Coulton, R. Ramage, *Tetrahedron Lett.* **1976**, 4311–4314; d) W. Oppolzer, E. Francotte, K. Baettig, *Helv. Chim. Acta.* **1981**, 64, 478–481; e) J. Rebek, Jr., D. F. Tai, Y. K. Shue, *J. Am. Chem. Soc.* **1984**, 106, 1813–1819; f) I. Ninomyia, C. Hashimoto, T. Kiguchi, T. Naito, *J. Chem. Soc. Perkin Trans. 1* **1985**, 941–948.
- [354] Yohimbine: a) E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm, P. E. Aldrich, *J. Am. Chem. Soc.* **1958**, 80, 5006–5007; b) L. Toke, K. Honty, C. Szántay, *Chem. Ber.* **1969**, 102, 3248–3259; c) G. Stork, R. N. Guthikonda, *J. Am. Chem. Soc.* **1972**, 94, 5109–5110; d) T. Kametani, M. Kajiwar, T. Takahashi, K. Fukumoto, *Heterocycles* **1975**, 3, 179–182; e) R. T. Brown, S. B. Pratt, *J. Chem. Soc. Chem. Commun.* **1980**, 165–167; f) E. Wenkert, J. S. Pyrek, S. Uesato, Y. D. Vankar, *J. Am. Chem. Soc.* **1982**, 104, 2244–2246; g) O. Miyata, Y. Hirata, T. Naito, I. Ninomiya, *J. Chem. Soc. Chem. Commun.* **1983**, 1231–1232; h) S. F. Martin, H. Rueger, S. A. Williamson, S. Grzejszczak, *J. Am. Chem. Soc.* **1987**, 109, 6124–6134; i) J. Aube, S. Ghosh, M. Tanol, *J. Am. Chem. Soc.* **1994**, 116, 9009–9018.
- [355] Colchicine: a) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, A. Eschenmoser, *Helv. Chim. Acta.* **1961**, 44, 540–597; b) E. E. van Tamelen, T. A. Spencer, D. S. Allen, R. L. Orvis, *Tetrahedron* **1961**, 14, 8–34; c) T. Nakamura, Y. Murase, R. Hayashi, Y. Endo, *Chem. Pharm. Bull.* **1962**, 10, 281; d) A. I. Scott, F. McCapra, R. L. Buchanan, A. C. Day, D. W. Young, *Tetrahedron* **1965**, 21, 3605–3631; e) R. B. Woodward, *The Harvey Lectures Series* 59, Academic Press, New York, **1965**, p. 31; f) J. Martel, E. Toromanoff, C. Huynh, *J. Org. Chem.* **1965**, 30, 1752–1759; g) S. Kaneko, M. Matsui, *Agr. Biol. Chem.* **1968**, 32, 995–1001; h) E. Kotani, F. Miyazaki, S. Tobinaga, *J. Chem. Soc. Chem. Commun.* **1974**, 300–301; i) M. Kato, F. Kido, M. D. Wu, A. Yoshikoshi, *Bull. Chem. Soc. Jpn.* **1974**, 47, 1516–1521; j) D. A. Evans, S. P. Tanis, D. J. Hart, *J. Am. Chem. Soc.* **1981**, 103, 5813–5821; k) D. L. Boger, C. E. Brotherton, *J. Am. Chem. Soc.* **1986**, 108, 6713–6719; l) P. Magnus, L. M. Principe, M. J. Slater, *J. Org. Chem.* **1987**, 52, 1483–1486; m) M. G. Banwell, J. N. Lambert, M. F. Mackay, R. J. Greenwood, *J. Chem. Soc. Chem. Commun.* **1992**, 974–975; n) J. C. Lee, S.-J. Jin, J. K. Cha, *J. Org. Chem.* **1998**, 63, 2804–2805.
- [356] 6-Demethyl-6-deoxytetracycline: a) ref. [285a,b]; b) H. Muxfeldt, W. Rogalski, *J. Am. Chem. Soc.* **1965**, 87, 933–934. For a recent construction of the tetracycline framework, see [39a].
- [357] Galanthamine: a) D. H. R. Barton, G. W. Kirby, *J. Chem. Soc. Chem. Commun.* **1962**, 806–807; b) T. Kametani, K. Yamaki, H. Yagi, K. Fukumoto, *J. Chem. Soc. D* **1969**, 425–426; c) K. Shimizu, K. Tomioka, S. Yamada, K. Koga, *Heterocycles* **1977**, 8, 277–282.

- [358] Estrone: a) S. N. Ananchenko, I. V. Torgov, *Tetrahedron Lett.* **1963**, 1553–1558; b) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, H. Smith, *J. Chem. Soc. Chem. Commun.* **1963**, 5072–5094; c) P. A. Bartlett, W. S. Johnson, *J. Am. Chem. Soc.* **1973**, 95, 7501–7502; P. A. Bartlett, J. I. Brauman, W. S. Johnson, R. A. Volkmann, *J. Am. Chem. Soc.* **1973**, 95, 7502–7503; d) N. Cohen, B. L. Banner, W. F. Eichel, D. R. Parrish, G. Saucy, J.-M. Cassal, W. Meier, A. Furst, *J. Org. Chem.* **1975**, 40, 681–685; e) S. J. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1976**, 98, 4975–4983; f) T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, K. Fukumoto, *J. Am. Chem. Soc.* **1976**, 98, 3378–3379. See also T. Kametani, H. Nemoto, H. Ishikawa, K. Shiroyama, H. Matsumoto, K. Fukumoto, *J. Am. Chem. Soc.* **1977**, 99, 3461–3466; H. Nemoto, M. Nagai, M. Moizumi, K. Kohzaki, K. Fukumoto, T. Kametani, *Tetrahedron Lett.* **1988**, 29, 4959–4962; g) W. Oppolzer, *Helv. Chim. Acta* **1980**, 63, 1703; W. Oppolzer, *Synthesis* **1978**, 793–802; h) R. L. Funk, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1977**, 99, 5483–5484; R. L. Funk, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1979**, 101, 215–217; R. L. Funk, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1980**, 102, 5253–5261; i) P. A. Grieco, T. Takigawa, W. J. Schillinger, *J. Org. Chem.* **1980**, 45, 2247–2251; j) G. Quinkert, W. D. Weber, U. Schwartz, G. Duerner, *Angew. Chem.* **1980**, 92, 1060–1062; *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 1027–1029; G. Quinkert, U. Schwartz, H. Stark, W. D. Dietrich, H. Baier, F. Adam, G. Duerner, *Angew. Chem.* **1980**, 92, 1062–1063; *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 1029–1030; k) T. A. Bryson, C. J. Reichel, *Tetrahedron Lett.* **1980**, 21, 2381–2384; l) Y. Ito, M. Nakatsuka, T. Saegusa, *J. Am. Chem. Soc.* **1981**, 103, 476–477; m) F. E. Ziegler, T.-F. Wang, *Tetrahedron Lett.* **1981**, 22, 1179–1182; n) M. E. Jung, K. M. Halweg, *Tetrahedron Lett.* **1984**, 25, 2121–2124; o) J. H. Hutchinson, T. Money, *Tetrahedron Lett.* **1985**, 26, 1819–1822; p) G. H. Posner, C. Switzer, *J. Am. Chem. Soc.* **1986**, 108, 1239–1244; q) G. S. R. S. Rao, L. U. Devi, U. J. Sheriff, *J. Chem. Soc. Perkin Trans. 1* **1991**, 964–965; r) S. Takano, M. Moriya, K. Ogasawara, *Tetrahedron Lett.* **1992**, 33, 1909–1910.
- [359] Cephamine: a) Y. Inubushi, T. Ibuka, M. Kitano, *Tetrahedron Lett.* **1969**, 1611–14; b) T. Kametani, T. Kobari, K. Fukumoto, *J. Chem. Soc. Chem. Commun.* **1972**, 288–289; c) M. Schwartz, R. Wallace, *Tetrahedron Lett.* **1979**, 3257–3260; d) A. G. Schultz, A. Wang, *J. Am. Chem. Soc.* **1998**, 120, 8259–8260.
- [360] Lupeol: G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, J. Labovitz, *J. Am. Chem. Soc.* **1971**, 93, 4945–4947.
- [361] Fumagillol: a) E. J. Corey, B. B. Snider, *J. Am. Chem. Soc.* **1972**, 94, 2549–2550; b) D. Kim, S. K. Ahn, H. Bae, W. J. Choi, H. S. Kim, *Tetrahedron Lett.* **1997**, 38, 4437–4440; c) D. Vosburg, S. Weiler, E. J. Sorensen, *Angew. Chem.* **1999**, 1024–1027; *Angew. Chem. Int. Ed.* **1999**, 38, 971–974; d) D. F. Taber, T. E. Christos, A. L. Rheingold, I. A. Guzei, *J. Am. Chem. Soc.* **1999**, 121, 5589–5590.
- [362] Daunomycinone: a) C. M. Wong, R. Schwenk, D. Propien, T.-L. Ho, *Can. J. Chem.* **1973**, 51, 466–467; b) A. S. Kende, Y.-G. Tsay, J. E. Mills, *J. Am. Chem. Soc.* **1976**, 98, 1967–1969; c) K. Krohn, K. Tolkiehn, *Chem. Ber.* **1979**, 112, 3453–3471; c) J. S. Swenton, P. W. Reynolds, *J. Am. Chem. Soc.* **1978**, 100, 6188–6195; d) T. R. Kelly, J. Vaya, L. Ananthasubramania, *J. Am. Chem. Soc.* **1980**, 102, 5983–5984; e) K. A. Parker, J. Kallmerten, *J. Am. Chem. Soc.* **1980**, 102, 5881–5886; f) M. Braun, *Tetrahedron Lett.* **1980**, 21, 3871–3874; M. Braun, *Tetrahedron* **1984**, 40, 4585–4591; g) F. M. Hauser, S. Prasanna, *J. Am. Chem. Soc.* **1981**, 103, 6378–6386; h) D. S. Kimball, K. S. Kim, D. K. Mohanty, E. Vanotti, F. Johnson, *Tetrahedron Lett.* **1982**, 23, 3871–3874; i) A. V. R. Rao, K. B. Reddy, A. R. Mehendale, *J. Chem. Soc. Chem. Commun.* **1983**, 564–566; j) J. Tamariz, P. Vogel, *Tetrahedron* **1984**, 40, 4549–4560; k) B. A. Keay, R. Rodrigo, *Tetrahedron* **1984**, 40, 4597–4607; l) D. W. Hansen, Jr., R. Pappo, R. B. Garland, *J. Org. Chem.* **1988**, 53, 4244–4253.
- [363] Vindoline: a) M. Ando, G. Büchi, T. Ohnuma, *J. Am. Chem. Soc.* **1975**, 97, 6880–6881; b) J. P. Kutney, U. Bunzli-Trepp, K. K. Chan, J. P. De Souza, Y. Fujise, T. Honda, J. Katsube, F. K. Klein, A. Leutwiler, S. Morehead, M. Rohr, B. R. Worth, *J. Am. Chem. Soc.* **1978**, 100, 4220–4224; c) Y. Ban, Y. Sekine, T. Oishi, *Tetrahedron Lett.* **1978**, 151–154; d) B. Danielli, G. Lesma, G. Palmisano, R. Riva, *J. Chem. Soc. Chem. Commun.* **1984**, 909–911; e) R. Z. Andriamialisoa, N. Langlois, Y. Langlois, *J. Org. Chem.* **1985**, 50, 961–967; f) P. L. Feldman, H. Rapoport, *J. Am. Chem. Soc.* **1987**, 109, 1603–1604; g) M. E. Kuehne, D. E. Podhorez, T. Mulamba, W. G. Bornmann, *J. Org. Chem.* **1987**, 52, 347–353.
- [364] Biotin: For an authoritative review of the total syntheses of biotin (over 40 syntheses have been reported), see P. J. De Clercq, *Chem. Rev.* **1997**, 97, 1755–1792.
- [365] Quadrone: a) S. J. Danishefsky, K. Vaughan, R. C. Gadwood, K. Tsuzuki, *J. Am. Chem. Soc.* **1980**, 102, 4262–4263; b) W. K. Bornack, S. S. Bhagwat, J. Ponton, P. Helquist, *J. Am. Chem. Soc.* **1981**, 103, 4647–4648; c) S. D. Burke, C. W. Murtiashaw, J. O. Saunders, M. S. Dike, *J. Am. Chem. Soc.* **1982**, 104, 872–874; d) A. S. Kende, B. Roth, P. J. Sanfilippo, T. J. Blacklock, *J. Am. Chem. Soc.* **1982**, 114, 5808–5810; e) R. H. Schlessinger, J. L. Wood, A. J. Poss, R. A. Nugent, W. H. Parsons, *J. Org. Chem.* **1983**, 48, 1146–1147; f) J. M. Dewanckele, F. Zutterman, M. Vandewalle, *Tetrahedron* **1983**, 39, 3235–3244; g) K. Takeda, Y. Shimono, E. Yoshii, *J. Am. Chem. Soc.* **1983**, 105, 563–568; h) A. B. Smith III, J. P. Konopelski, *J. Org. Chem.* **1984**, 49, 4094–5; i) K. Kon, K. Ito, S. Isoe, *Tetrahedron Lett.* **1984**, 25, 3739–3742; j) C. Iwata, M. Yamashita, S. Aoki, K. Suzuki, I. Takahashi, H. Arakawa, T. Imanishi, T. Tanaka, *Chem. Pharm. Bull.* **1985**, 33, 436–439; T. Imanishi, M. Matsui, M. Yamashita, C. Iwata, *J. Chem. Soc. Chem. Commun.* **1987**, 1802–1804; k) P. A. Wender, D. J. Wolanin, *J. Org. Chem.* **1985**, 50, 4418–4420; l) E. Piers, N. Moss, *Tetrahedron Lett.* **1985**, 26, 2735–2738; m) R. L. Funk, M. M. Abelman, *J. Org. Chem.* **1986**, 51, 3247–3248; n) P. Magnus, L. M. Principe, M. J. Slater, *J. Org. Chem.* **1987**, 52, 1483–1486; o) H. J. Liu, M. Llinas-Brunet, *Can. J. Chem.* **1988**, 66, 528–530; p) C. G. Sowell, R. L. Wolin, R. D. Little, *Tetrahedron Lett.* **1990**, 31, 485–488.
- [366] Gibberellic acid: a) E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, J. L. Gras, *J. Am. Chem. Soc.* **1978**, 100, 8031–8034 and ref. [312a]; b) J. M. Hook, L. N. Mander, R. Ulreich, *J. Am. Chem. Soc.* **1980**, 102, 6628–6629; c) H. Nagaoka, M. Shimano, Y. Yamada, *Tetrahedron Lett.* **1989**, 30, 971–974.
- [367] Dendrobine: a) K. Yamada, M. Suzuki, Y. Hayakawa, K. Aoki, H. Nakamura, H. Nagase, Y. Hirata, *J. Am. Chem. Soc.* **1972**, 94, 8278–8280; b) Y. Inubushi, T. Kikuchi, T. Ibuka, K. Tanaka, I. Saji, K. Tokane, *J. Chem. Soc. Chem. Commun.* **1972**, 1252–1253; c) A. S. Kende, T. J. Bentley, R. A. Mader, D. Ridge, *J. Am. Chem. Soc.* **1974**, 96, 4332–4334; d) W. R. Roush, *J. Am. Chem. Soc.* **1978**, 100, 3599–3601; e) S. F. Martin, L. Wei, *J. Org. Chem.* **1991**, 56, 642–650; f) C. H. Lee, M. Westling, T. Livinghouse, A. C. Williams, *J. Am. Chem. Soc.* **1992**, 114, 4089–4095; g) N. Uesaka, F. Saitoh, M. Mori, M. Shibasaki, K. Okamura, T. Date, *J. Org. Chem.* **1994**, 59, 5633–5642; h) C.-K. Sha, R.-T. Chiu, C.-F. Yang, N.-T. Yao, W.-H. Tseng, F.-L. Liao, S.-L. Wang, *J. Am. Chem. Soc.* **1997**, 119, 4130–4135.
- [368] Illudol: a) T. Matsumoto, K. Miyano, S. Kagawa, S. Yu, J. I. Ogawa, A. Ichihara, *Tetrahedron Lett.* **1971**, 3521–3524; b) M. F. Semmelhack, S. Tomoda, K. M. Hurst, *J. Am. Chem. Soc.* **1980**, 102, 7567–7568; c) E. P. Johnson, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1990**, 112, 381–382; d) M. R. Elliott, A.-L. Dhimane, M. Malacria, *J. Am. Chem. Soc.* **1997**, 119, 3427–3428.
- [369] Mitomycins A and C: a) T. Fukuyama, F. Nakatsubo, A. J. Cocuzza, Y. Kishi, *Tetrahedron Lett.* **1977**, 18, 4295–4298; b) T. Fukuyama, L. Yang, *J. Am. Chem. Soc.* **1989**, 111, 8303–8304.
- [370] Saxitoxin: a) H. Tanino, T. Nakata, T. Kaneko, Y. Kishi, *J. Am. Chem. Soc.* **1977**, 99, 2818–2819; b) P. A. Jacobi, M. J. Martinelli, S. Polanc, *J. Am. Chem. Soc.* **1984**, 106, 5594–5598.
- [371] Thienamycin: a) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, B. G. Christensen, *J. Am. Chem. Soc.* **1978**, 100, 313–315; b) T. Kametani, S.-P. Huang, S. Yokohama, Y. Suzuki, M. Ihara, *J. Am. Chem. Soc.* **1980**, 102, 2060–2065; c) M. Shiozaki, T. Hiraoka, *Tetrahedron Lett.* **1980**, 21, 4473–4476; d) S. Hanessian, D. Desilets, G. Rancourt, R. Fortin, *Can. J. Chem.* **1982**, 60, 2292–2294; e) M. Shibasaki, A. Nishida, S. Ikegami, *Tetrahedron Lett.* **1982**, 23, 2875–2878; f) I. Shinkai, T. Liu, R. A. Reamer, M. Slettinger, *Tetrahedron Lett.* **1982**, 23, 4899–4902; g) M. Miyashita, N. Chida, A. Yoshikoshi, *J. Chem. Soc. Chem. Commun.* **1982**, 1354–1356; h) N. Ikota, O. Yoshino, K. Koga, *Chem. Pharm. Bull.* **1982**, 30, 1929–1931; i) P. A. Grieco, D. L. Flynn, R. E. Zelle, *J. Am. Chem. Soc.* **1984**, 106, 6414–6417; j) S. T. Hodgson, D. M. Hollinshead, S. V. Ley, *Tetrahedron* **1985**, 41, 5871–5878; k) T. Iimori, M. Shibasaki, *Tetrahedron Lett.*

- 1985**, 26, 1523–1526; l) D. J. Hart, D.-C. Ha, *Tetrahedron Lett.* **1985**, 26, 5493–5496; m) H. Maruyama, T. Hiraoka, *J. Org. Chem.* **1986**, 51, 399–402; n) J. D. Buynak, J. Mathew, M. N. Rao, *J. Chem. Soc. Chem. Commun.* **1986**, 941–942; o) D. A. Evans, E. B. Sjogren, *Tetrahedron Lett.* **1986**, 27, 4961–4964; p) I. Fleming, J. D. Kilburn, *J. Chem. Soc. Chem. Commun.* **1986**, 1198–1199; q) G. I. Georg, J. Kant, H. S. Gill, *J. Am. Chem. Soc.* **1987**, 109, 1129–1135; r) M. Hatanaka, H. Nitta, *Tetrahedron Lett.* **1987**, 28, 69–72; s) H. Kaga, S. Kobayashi, M. Ohno, *Tetrahedron Lett.* **1988**, 29, 1057–1060; t) P. A. Jacobi, S. Murphree, F. Rupprecht, W. Zheng, *J. Org. Chem.* **1996**, 61, 2413–2427.
- [372] Cytochalasin B: a) G. Stork, Y. Nakahara, Y. Nakahara, W. J. Greenlee, *J. Am. Chem. Soc.* **1978**, 100, 7775–7777; b) for an elegant synthesis of cytochalasin G, see H. Dyke, R. Sauter, P. Steel, E. J. Thomas, *J. Chem. Soc. Chem. Commun.* **1986**, 1447–1449.
- [373] *N*-Methylmaysenine: a) E. J. Corey, L. O. Weigel, D. Floyd, M. G. Bock, *J. Am. Chem. Soc.* **1978**, 100, 2916–2918. See also E. J. Corey, L. O. Weigel, A. R. Chamberlin, B. Lipshutz, *J. Am. Chem. Soc.* **1980**, 104, 1439–1441; b) A. I. Meyers, D. M. Roland, D. L. Comins, R. Henning, M. P. Fleming, K. Shimizu, *J. Am. Chem. Soc.* **1979**, 101, 4732–4734; c) M. Kitamura, M. Isobe, Y. Ichikawa, T. Goto, *J. Org. Chem.* **1984**, 49, 3517–3527.
- [374] Hirsutene: a) K. Tatsuta, K. Akimoto, M. Kinoshita, *J. Am. Chem. Soc.* **1979**, 101, 6116–6118; b) T. Hudlicky, T. M. Kutchan, S. R. Wilson, *D. T. Mao, J. Am. Chem. Soc.* **1980**, 102, 6351–6353; c) D. R. Little, G. W. Muller, *J. Am. Chem. Soc.* **1981**, 103, 2744–2749; d) G. Mehta, A. V. Reddy, *J. Chem. Soc. Chem. Commun.* **1981**, 756–757; e) P. Magnus, D. A. Quagliato, *Organometallics* **1982**, 1, 1243–1244; P. Magnus, D. A. Quagliato, *J. Org. Chem.* **1985**, 50, 1621–1626; f) P. A. Wender, J. J. Howbert, *Tetrahedron Lett.* **1982**, 23, 3983–3986; g) S. V. Ley, P. J. Murray, *J. Chem. Soc. Chem. Commun.* **1982**, 1252–1253; h) R. D. Little, R. G. Higby, K. D. Moeller, *J. Org. Chem.* **1983**, 48, 3139–3140; i) D. P. Curran, D. M. Rakiewicz, *J. Am. Chem. Soc.* **1983**, 107, 1448–1449; j) H. D. Hua, G. Sinai-Zingde, S. Venkataraman, *J. Am. Chem. Soc.* **1985**, 107, 4088–4090; k) J. Cossy, D. Belotti, J. P. Pete, *Tetrahedron Lett.* **1987**, 28, 4547–4550; l) G. Mehta, A. N. Murthy, D. S. Reddy, A. V. Reddy, *J. Am. Chem. Soc.* **1986**, 108, 3443–3452; m) M. Franck-Neumann, M. Miesch, E. Lacroix, *Tetrahedron Lett.* **1989**, 30, 3529–3532; n) D. D. Sternbach, C. L. Ensinger, *J. Org. Chem.* **1990**, 55, 2725–2736; o) J. Castro, H. Sorensen, A. Riera, C. Morin, A. Moyano, M. A. Pericas, A. E. Greene, *J. Am. Chem. Soc.* **1990**, 112, 9388–9389; p) T. K. Sarkar, S. K. Ghosh, P. S. V. S. Rao, V. R. Mamdapur, *Tetrahedron Lett.* **1990**, 31, 3465–3466; q) K. J. Moriarty, C. C. Shen, L. A. Paquette, *Synlett* **1990**, 263–264; r) K. Ramig, M. A. Kuzemko, K. McNamara, T. Cohen, *J. Org. Chem.* **1992**, 57, 1968–1969; s) M. Toyota, Y. Nishikawa, K. Motoki, N. Yoshida, K. Fukumoto, *Tetrahedron Lett.* **1993**, 34, 6099–6102; t) W. Oppolzer, C. Robyr, *Tetrahedron* **1994**, 50, 415–424.
- [375] Vinblastine, Vincristine: N. Langlois, F. Guéritte, Y. Langlois, P. Potier, *J. Am. Chem. Soc.* **1976**, 98, 7017–7024; P. Mangeney, R. Z. Andriamialisoa, N. Langlois, Y. Langlois, P. Potier, *J. Am. Chem. Soc.* **1979**, 101, 2243–2245.
- [376] Ryanodol: A. Belanger, D. J. F. Berney, H.-J. Borschberg, R. Brousseau, A. Doutheau, R. Durand, H. Katayama, R. Lapalme, D. M. Leturc, C.-C. Liao, F. N. MacLachlan, J.-P. Maffrand, F. Marazza, R. Martino, C. Moreau, L. Saint-Laurent, R. Saintonge, P. Soucy, L. Ruest, P. Deslongchamps, *Can. J. Chem.* **1979**, 57, 3348–3354. See also P. Deslongchamps, A. Belanger, D. J. F. Berney, H. J. Borschberg, R. Brousseau, A. Doutheau, R. Durand, H. Katayama, R. Lapalme, D. M. Leturc, C.-C. Liao, F. N. MacLachlan, J.-P. Maffrand, F. Marazza, R. Martino, C. Moreau, L. Ruest, L. Saint-Laurent, R. Saintonge, P. Soucy, *Can. J. Chem.* **1990**, 68, 115–127; P. Deslongchamps, A. Belanger, D. J. F. Berney, H. J. Borschberg, R. Brousseau, A. Doutheau, R. Durand, H. Katayama, R. Lapalme, D. M. Leturc, C.-C. Liao, F. N. MacLachlan, J.-P. Maffrand, F. Marazza, R. Martino, C. Moreau, L. Ruest, L. Saint-Laurent, R. Saintonge, P. Soucy, *Can. J. Chem.* **1990**, 68, 127–153; P. Deslongchamps, A. Belanger, D. J. F. Berney, H. J. Borschberg, R. Brousseau, A. Doutheau, R. Durand, H. Katayama, R. Lapalme, D. M. Leturc, C.-C. Liao, F. N. MacLachlan, J.-P. Maffrand, F. Marazza, R. Martino, C. Moreau, L. Ruest, L. Saint-Laurent, R. Saintonge, P. Soucy, *Can. J. Chem.* **1990**, 68, 153–186; P. Deslongchamps, A. Belanger, D. J. F. Berney, H. J. Borschberg, R. Brousseau, A. Doutheau, R. Durand, H. Katayama, R. Lapalme, D. M. Leturc, C.-C. Liao, F. N. MacLachlan, J.-P. Maffrand, F. Marazza, R. Martino, C. Moreau, L. Ruest, L. Saint-Laurent, R. Saintonge, P. Soucy, *Can. J. Chem.* **1990**, 68, 186–192.
- [377] Aphidicolin: a) B. M. Trost, Y. Nishimura, K. Yamamoto, *J. Am. Chem. Soc.* **1979**, 101, 1328–1330; b) J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser, M. A. Johnson, *J. Am. Chem. Soc.* **1979**, 101, 1330–1332; c) E. J. Corey, M. A. Tius, J. Das, *J. Am. Chem. Soc.* **1980**, 102, 1742–1744; d) R. E. Ireland, J. D. Godfrey, S. Thaisrivongs, *J. Am. Chem. Soc.* **1981**, 103, 2446–2448; e) E. E. van Tameelen, S. R. Zawacky, R. K. Russell, J. G. Carlson, *J. Am. Chem. Soc.* **1983**, 105, 142–143; f) R. M. Bettolo, P. Tagliatesta, A. Lupi, D. Bravetti, *Helv. Chim. Acta* **1983**, 66, 1922–1928; g) S. P. Tanis, Y. H. Chuang, D. B. Head, *Tetrahedron Lett.* **1985**, 26, 6147–6150; h) R. A. Holton, R. M. Kennedy, H. B. Kim, M. E. Krafft, *J. Am. Chem. Soc.* **1987**, 109, 1597–1600; i) M. Toyota, Y. Nishikawa, K. Fukumoto, *Tetrahedron Lett.* **1994**, 35, 6495–6498; See also M. Toyota, Y. Nishikawa, K. Fukumoto, *Tetrahedron Lett.* **1995**, 36, 5379–5382; j) T. Tanaka, O. Okuda, K. Murakami, H. Yoshino, H. Mikamiyama, A. Kanda, S.-W. Kim, C. Iwata, *Chem. Pharm. Bull.* **1995**, 43, 1407–1411.
- [378] Delphinine: K. Wiesner, *Pure Appl. Chem.* **1979**, 51, 689–703.
- [379] Coriolin: a) S. J. Danishefsky, R. Zamboni, M. Kahn, S. J. Etheredge, *J. Am. Chem. Soc.* **1980**, 102, 2097–2098; b) M. Shibasaki, K. Iseki, S. Ikegami, *Tetrahedron Lett.* **1980**, 21, 3587–3590; c) K. Tatsuta, K. Akimoto, M. Kinoshita, *J. Antibiot.* **1980**, 33, 100–2; d) B. M. Trost, D. P. Curran, *J. Am. Chem. Soc.* **1981**, 103, 7380–7381; e) G. Mehta, A. V. Reddy, A. N. Murthy, D. S. Reddy, *J. Chem. Soc. Chem. Commun.* **1982**, 540–541; f) T. Ito, N. Tomiyoshi, K. Nakamura, S. Azuma, M. Izawa, F. Maruyama, M. Yanagiya, H. Shirahama, T. Matsumoto, *Tetrahedron Lett.* **1982**, 23, 1721–1724; g) C. Exon, P. Magnus, *J. Am. Chem. Soc.* **1983**, 105, 2477–2478; h) M. Koreeda, S. G. Mislankar, *J. Am. Chem. Soc.* **1983**, 105, 7203–7205; i) P. A. Wender, J. J. Howbert, *Tetrahedron Lett.* **1983**, 24, 5325–5328; P. A. Wender, C. R. D. Correia, *J. Am. Chem. Soc.* **1987**, 109, 2523–2525; j) P. F. Schuda, M. R. Heimann, *Tetrahedron* **1984**, 40, 2365–2380; k) R. L. Funk, G. L. Bolton, J. U. Daggett, M. M. Hansen, L. H. M. Horcher, *Tetrahedron* **1985**, 41, 3479–3495; l) L. Van Hijfte, R. D. Little, *J. Org. Chem.* **1985**, 50, 3940–3942; m) M. Demuth, P. Ritterskamp, E. Weigt, K. Schaffner, *J. Am. Chem. Soc.* **1986**, 108, 4149–4154; n) T. L. Fevig, R. L. Elliott, D. P. Curran, *J. Am. Chem. Soc.* **1988**, 110, 5064–5067; o) K. Weinges, R. Braun, U. Huber-Patz, H. Irngartinger, *Liebigs Ann. Chem.* **1993**, 1133–1140; p) K. Domon, K. Masuya, K. Tanino, I. Kuwajima, *Tetrahedron Lett.* **1997**, 38, 465–468.
- [380] Quassin: a) P. A. Grieco, S. Ferriño, G. Vidari, *J. Am. Chem. Soc.* **1980**, 102, 7587–7588; b) M. Kim, K. Kawada, R. S. Gross, D. S. Watt, *J. Org. Chem.* **1990**, 55, 504–511; c) H. Stojanac, Z. Valenta, *Can. J. Chem.* **1991**, 69, 853–855; d) T. K. M. Shing, Q. Jiang, T. C. W. Mak, *J. Org. Chem.* **1998**, 63, 2056–2057.
- [381] Saframycin B: a) T. Fukuyama, R. A. Sachleben, *J. Am. Chem. Soc.* **1982**, 104, 4957–4958; b) A. Kubo, N. Saito, R. Yamauchi, S. Sakai, *Chem. Pharm. Bull.* **1987**, 35, 2158–2161; c) See also the syntheses of saframycin A: T. Fukuyama, L. Yang, K. L. Ajeck, R. A. Sachleben, *J. Am. Chem. Soc.* **1990**, 112, 3712–3713; A. G. Myers, D. Kung, *Book of Abstracts, 216th National Meeting of the American Chemical Society*, Washington, D.C., **1998**, ORGN0501; E. J. Martinez, E. J. Corey, *Org. Lett.* **1999**, 1, 75–77.
- [382] Eburnamine: a) L. Castedo, J. Harley-Mason, T.-J. Leeney, *J. Chem. Soc. Chem. Commun.* **1968**, 19, 1186; b) K. H. Gibson, J. E. Saxton, *J. Chem. Soc. D* **1969**, 799; c) J. L. Herrmann, G. R. Kieczkowski, S. E. Normandin, R. H. Schlessinger, *Tetrahedron Lett.* **1976**, 17, 801–804; d) E. Boelsing, F. Klatte, U. Rosentreter, E. Winterfeldt, *Chem. Ber.* **1979**, 112, 1902–1912; e) M. Node, H. Nagasawa, K. Fuji, *J. Am. Chem. Soc.* **1987**, 109, 7901–7903.
- [383] Carbomycin: a) K. C. Nicolaou, M. R. Pavia, S. P. Seitz, *Tetrahedron Lett.* **1979**, 20, 2327–2330; K. C. Nicolaou, S. P. Seitz, M. R. Pavia, N. A. Petasis, *J. Org. Chem.* **1979**, 44, 4011–4013; K. C. Nicolaou, S. P. Seitz, M. R. Pavia, *J. Am. Chem. Soc.* **1981**, 103, 1222–1224;

- K. C. Nicolaou, M. R. Pavia, S. P. Seitz, *J. Am. Chem. Soc.* **1981**, *103*, 1224–1226; b) K. Tatsuta, Y. Amemiya, S. Maniwa, M. Kinoshita, *Tetrahedron Lett.* **1980**, *21*, 2837–2840.
- [384] Aplasmomycin: a) E. J. Corey, B. C. Pan, D. H. Hua, D. R. Dear-dorff, *J. Am. Chem. Soc.* **1982**, *104*, 6816–6818; E. J. Corey, D. H. Hua, B. C. Pan, S. P. Seitz, *J. Am. Chem. Soc.* **1982**, *104*, 6818–6820; b) J. D. White, T. R. Vedananda, M. C. Kang, S. C. Choudhry, *J. Am. Chem. Soc.* **1986**, *108*, 8105–8107; c) T. Nakata, K. Saito, T. Oishi, *Tetrahedron Lett.* **1986**, *27*, 6345–6348; d) F. Matsuda, N. Tomiyosi, M. Yanagiya, T. Matsumoto, *Chem. Lett.* **1987**, 2097–2100.
- [385] Bleomycin: a) T. Takita, Y. Umezawa, S. Saito, H. Morishima, H. Naganawa, H. Umezawa, T. Tsushiyama, T. Miyake, S. Kageyama, S. Umezawa, Y. Muraoka, M. Suzuki, M. Otsuka, M. Narita, S. Kobayashi, M. Ohno, *Tetrahedron Lett.* **1982**, *23*, 521–524, and references therein; b) Y. Aoyagi, K. Katano, H. Suguna, J. Primeau, L.-H. Chang, S. M. Hecht, *J. Am. Chem. Soc.* **1982**, *104*, 5537–5538; c) For a review of the chemistry and biology of bleomycin, see D. L. Boger, H. Cai, *Angew. Chem.* **1999**, *111*, 470–498; *Angew. Chem. Int. Ed.* **1999**, *38*, 448–476; D. L. Boger, S. L. Colletti, T. Honda, R. F. Menezes, *J. Am. Chem. Soc.* **1994**, *116*, 5607–5618; D. L. Boger, T. Honda, Q. Dang, *J. Am. Chem. Soc.* **1994**, *116*, 5619–5630; D. L. Boger, T. Honda, R. F. Menezes, S. L. Colletti, *J. Am. Chem. Soc.* **1994**, *116*, 5631–5646; D. L. Boger, T. Honda, *J. Am. Chem. Soc.* **1994**, *116*, 5647–5656.
- [386] Cyanocycline: a) D. A. Evans, C. R. Illig, J. C. Saddler, *J. Am. Chem. Soc.* **1986**, *108*, 2478–2479; b) T. Fukuyama, L. Li, A. A. Laird, R. K. Frank, *J. Am. Chem. Soc.* **1987**, *109*, 15873–15879.
- [387] Rifamycin: a) H. Nagaoka, W. Rutsch, G. Schmid, H. Lio, M. R. Johnson, Y. Kishi, *J. Am. Chem. Soc.* **1980**, *102*, 7962–7965; H. Lio, H. Nagaoka, Y. Kishi, *J. Am. Chem. Soc.* **1980**, *102*, 7965–7967; b) S. Hanessian, J. R. Pougny, I. K. Boessenkool, *J. Am. Chem. Soc.* **1982**, *104*, 6164–6166.
- [388] Echinospirin: A. B. Smith III, G. A. Sulikowski, K. Fujimoto, *J. Am. Chem. Soc.* **1989**, *111*, 8039–8041.
- [389] Compactin: a) N. Y. Wang, C. T. Hsu, C. J. Sih, *J. Am. Chem. Soc.* **1981**, *103*, 6538–6539; b) M. Hirama, M. Uei, *J. Am. Chem. Soc.* **1982**, *104*, 4251–4253; c) N. N. Girotra, N. L. Wendler, *Tetrahedron Lett.* **1982**, *23*, 5501–5504; d) P. A. Grieco, R. E. Zelle, R. Lis, J. Finn, *J. Am. Chem. Soc.* **1983**, *105*, 1403–1404; e) T. Rosen, C. H. Heathcock, *J. Am. Chem. Soc.* **1985**, *107*, 3731–3733; f) G. E. Keck, D. F. Kachensky, *J. Org. Chem.* **1986**, *51*, 2487–2493; g) A. P. Kozikowski, C. S. Li, *J. Org. Chem.* **1987**, *52*, 3541–3552; h) D. L. J. Clive, K. S. K. Murthy, A. G. H. Wee, J. S. Prasad, G. V. J. Da Silva, M. Majewski, P. C. Anderson, R. D. Haugen, L. D. Heerze, *J. Am. Chem. Soc.* **1988**, *110*, 6914–6916; i) S. J. Danishefsky, B. Simoneau, *J. Am. Chem. Soc.* **1989**, *111*, 2599–2604; j) S. D. Burke, D. N. Deaton, *Tetrahedron Lett.* **1991**, *32*, 4651–4654; k) H. Hagiwara, T. Nakano, M. Konno, H. Uda, *J. Chem. Soc. Perkin Trans. 1* **1995**, 777–783.
- [390] Neosurugatoxin: S. Inoue, K. Okada, H. Tanino, H. Kakoi, *Tetrahedron Lett.* **1986**, *27*, 5225–5228.
- [391] Pleuromutilin: a) E. G. Gibbons, *J. Am. Chem. Soc.* **1982**, *104*, 1767–1769; b) R. K. Boeckman, Jr., D. M. Springer, T. R. Alessi, *J. Am. Chem. Soc.* **1989**, *111*, 8284–8286.
- [392] Ophiobolin C: M. Rowley, M. Tsukamoto, Y. Kishi, *J. Am. Chem. Soc.* **1989**, *111*, 2735–2736.
- [393] Fredericamycin: a) T. R. Kelly, S. H. Bell, N. Ohashi, R. J. Armstrong-Chong, *J. Am. Chem. Soc.* **1988**, *110*, 6471–6480; b) D. L. J. Clive, Y. Tao, A. Khodabocus, Y. J. Wu, A. G. Angoh, S. M. Bennett, C. N. Boddy, L. Bordeleau, D. Kellner, G. Kleiner, D. S. Middleton, C. J. Nichols, S. R. Richardson, P. G. Uernon, *J. Chem. Soc. Chem. Commun.* **1992**, 1489–1490; c) L. Saint-Jalmes, C. Lila, J. Z. Xu, L. Moreau, B. Pfeiffer, G. Eck, L. Pelsez, C. Rolando, M. Julia, *Bull. Soc. Chem. Fr.* **1993**, *130*, 447–449; d) J. A. Wendt, P. J. Gauvreau, R. D. Bach, *J. Am. Chem. Soc.* **1994**, *116*, 9921–9926; e) A. V. R. Rao, A. K. Singh, B. V. Rao, K. M. Reddy, *Heterocycles* **1994**, *37*, 1893–1912; f) D. L. Boger, O. Hueter, K. Mbiya, M. Zhang, *J. Am. Chem. Soc.* **1995**, *117*, 11839–11849; g) Y. Kita, K. Higuchi, Y. Yoshida, K. Lio, S. Kitagaki, S. Akai, H. Fujioka, *Angew. Chem.* **1999**, *111*, 683–686; *Angew. Chem. Int. Ed.* **1999**, *38*, 683–686.
- [394] Avermectin B_{1a}: a) J. D. White, G. L. Bolton, A. P. Dantanarayana, C. M. J. Fox, R. N. Hiner, R. W. Jackson, K. Sakuma, U. S. Warrior, *J. Am. Chem. Soc.* **1995**, *117*, 1908–1939; b) M. J. Ford, J. G. Knight, S. V. Ley, S. Vile, *Synlett* **1990**, 331–332; D. Diez-Martin, P. Grice, H. C. Kolb, S. V. Ley, A. Madin, *Synlett* **1990**, 326–328; A. Armstrong, S. V. Ley, A. Madin, S. Mukherjee, *Synlett* **1990**, 328–330; A. Armstrong, S. V. Ley, *Synlett* **1990**, 323–325; c) S. Hanessian, A. Ugolini, D. Dube, P. J. Hodges, C. Andre, *J. Am. Chem. Soc.* **1986**, *108*, 2776–2778; S. Hanessian, A. Ugolini, P. J. Hodges, P. Beaulieu, D. Dube, C. Andre, *Pure Appl. Chem.* **1987**, *59*, 299–316.
- [395] Avermectin A_{1a}: S. J. Danishefsky, D. M. Armistead, F. E. Wincott, H. G. Selnick, R. Hungate, *J. Am. Chem. Soc.* **1987**, *109*, 8117–8119; S. J. Danishefsky, H. G. Selnick, D. M. Armistead, F. E. Wincott, *J. Am. Chem. Soc.* **1987**, *109*, 8119–8120.
- [396] CC-1065: a) R. C. Kelly, I. Bebbard, N. Wicnienski, P. A. Aristoff, P. O. Johnson, D. G. Martin, *J. Am. Chem. Soc.* **1987**, *109*, 6837–6838; b) D. L. Boger, R. S. Coleman, *J. Am. Chem. Soc.* **1988**, *110*, 1321–1323.
- [397] Ikarugamycin: a) R. K. Boeckman, Jr., C. H. Weidner, R. B. Perni, J. J. Napier, *J. Am. Chem. Soc.* **1989**, *111*, 8036–8037; b) L. A. Paquette, D. Macdonald, L. G. Anderson, J. Wright, *J. Am. Chem. Soc.* **1989**, *111*, 8037–8039.
- [398] Koumine: P. Magnus, B. Mugrage, M. De Luca, G. A. Cain, *J. Am. Chem. Soc.* **1989**, *111*, 786–789.
- [399] Daphnilactone A: R. B. Ruggeri, K. F. McClure, C. H. Heathcock, *J. Am. Chem. Soc.* **1989**, *111*, 1530–1531.
- [400] Huperzine: Y. Xia, A. P. Kozikowski, *J. Am. Chem. Soc.* **1989**, *111*, 4116–4117.
- [401] FK506: a) T. K. Jones, S. G. Mills, R. A. Reamer, D. Askin, R. Desmond, R. P. Volante, I. Shinkai, *J. Am. Chem. Soc.* **1989**, *111*, 1157–1159; b) M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 5583–5601; c) A. B. Jones, A. Villalobos, R. G. Linde, S. J. Danishefsky, *J. Org. Chem.* **1990**, *55*, 2786–2797; d) R. L. Sih, C. J. Sih, *Tetrahedron Lett.* **1990**, *31*, 3287–3290; e) A. B. Smith III, K. Chen, D. J. Robinson, L. M. Laakso, K. J. Hale, *Tetrahedron Lett.* **1994**, *35*, 4271–4274; f) R. E. Ireland, J. L. Gleason, L. D. Gegnas, T. K. Highsmith, *J. Org. Chem.* **1996**, *61*, 6856–6872.
- [402] Histronicotoxin: a) S. C. Carey, M. Aratani, Y. Kishi, *Tetrahedron Lett.* **1985**, *26*, 5887–5890; b) G. Stork, K. Zhao, *J. Am. Chem. Soc.* **1990**, *112*, 5875–5876; c) G. M. Williams, S. D. Roughley, J. E. Davies, A. B. Holmes, J. P. Adams, *J. Am. Chem. Soc.* **1999**, *121*, 4900–4901.
- [403] Paspalinine: A. B. Smith III, T. Sunazuka, T. L. Leenay, J. Kingery-Wood, *J. Am. Chem. Soc.* **1990**, *112*, 8197–8198.
- [404] Indolizomycin: a) G. Kim, M. Y. Chu-Moyer, S. J. Danishefsky, *J. Am. Chem. Soc.* **1990**, *112*, 2003–2004; G. Kim, M. Y. Chu-Moyer, S. J. Danishefsky, *J. Am. Chem. Soc.* **1993**, *115*, 30–39.
- [405] Isorobustins: D. H. R. Barton, D. M. X. Donnelly, J.-P. Finet, P. J. Guiry, *Tetrahedron Lett.* **1990**, *31*, 7449–7452.
- [406] Hikizimycin: N. Ikemoto, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 9657–9658.
- [407] Chaparrinone: R. S. Gross, P. A. Grieco, J. L. Collins, *J. Am. Chem. Soc.* **1990**, *112*, 9436–9437.
- [408] Ambruticin: A. S. Kende, Y. Fujii, J. S. Mendoza, *J. Am. Chem. Soc.* **1990**, *112*, 9645–9646.
- [409] Rocaglamide: B. M. Trost, P. D. Greenspan, B. V. Yang, M. G. Saulnier, *J. Am. Chem. Soc.* **1990**, *112*, 9022–9024.
- [410] Isoraunicic: W. Oppolzer, H. Bienaymé, A. Genevois-Borella, *J. Am. Chem. Soc.* **1991**, *113*, 9660–9662.
- [411] Kempene-2: W. G. Dauben, I. Farkas, D. P. Bridon, C.-P. Chuang, K. E. Henegar, *J. Am. Chem. Soc.* **1991**, *113*, 5883–5884.
- [412] Myrocin C: M. Y. Chu-Moyer, S. J. Danishefsky, *J. Am. Chem. Soc.* **1992**, *114*, 8333–8334.
- [413] Halichondrin B: T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, M. C. Matelich, P. M. Scola, D. M. Spero, S. K. Yoon, *J. Am. Chem. Soc.* **1992**, *114*, 3162–3164.
- [414] Hemibrevetoxin B: a) K. C. Nicolaou, K. R. Reddy, G. Skokotas, F. Sato, X.-Y. Xiao, *J. Am. Chem. Soc.* **1992**, *114*, 7935–7936; b) I. Kadota, J.-Y. Park, N. Koumura, G. Pollaud, Y. Matsukawa, Y. Yamamoto, *Tetrahedron Lett.* **1995**, *36*, 5777–5780; c) M. Morimoto, H. Matsukura, T. Nakata, *Tetrahedron Lett.* **1996**, *37*, 6365–6358; d) Y. Mori, K. Yaegashi, H. Furukawa, *J. Am. Chem. Soc.* **1997**, *119*, 4557–4558.

- [415] Calyculin A: a) D. A. Evans, J. R. Gage, J. L. Leighton, *J. Org. Chem.* **1992**, 57, 1964–1965; D. A. Evans, J. R. Gage, J. L. Leighton, *J. Am. Chem. Soc.* **1992**, 114, 9434–9453; b) N. Tanimoto, S. W. Gerritz, A. Sawabe, T. Noda, S. A. Filla, S. Masamune, *Angew. Chem.* **1994**, 106, 674–676; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 673–675; c) F. Yokokawa, Y. Hamada, T. Shioiri, *Chem. Commun.* **1996**, 871–872; d) A. B. Smith III, G. K. Friestad, J.-W. J. Duan, J. Barbosa, K. G. Hull, M. Iwashima, Y. Qiu, G. P. Spoors, E. Bertounesque, B. A. Salvatore, *J. Org. Chem.* **1998**, 63, 7596–7597; calyculin C: e) A. K. Ogawa, R. W. Armstrong, *J. Am. Chem. Soc.* **1998**, 120, 12435–12442.
- [416] Discodermolide: a) J. B. Nerenberg, D. T. Hung, P. K. Somers, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, 115, 12621–12622; b) A. B. Smith III, Y. Qiu, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **1995**, 117, 12011–12012; c) S. S. Harried, G. Yang, M. A. Strawn, D. C. Myles, *J. Org. Chem.* **1997**, 62, 6098–6099; d) J. A. Marshall, B. A. Johns, *J. Org. Chem.* **1998**, 63, 7885–7886.
- [417] Lepicidin A: D. A. Evans, W. C. Black, *J. Am. Chem. Soc.* **1993**, 115, 4497–4513.
- [418] Stenine: a) C.-Y. Chen, D. J. Hart, *J. Org. Chem.* **1993**, 58, 3840–3849; b) P. Wipf, Y. Kim, D. M. Goldstein, *J. Am. Chem. Soc.* **1995**, 117, 11106–11112.
- [419] Balanol: a) K. C. Nicolaou, M. E. Bunnage, K. Koide, *J. Am. Chem. Soc.* **1994**, 116, 8402–8403; b) J. W. Lampe, P. F. Hughes, C. K. Biggers, S. H. Smith, H. Hu, *J. Org. Chem.* **1994**, 59, 5147–5148; c) C. P. Adams, S. M. Fairway, C. J. Hardy, D. E. Hibbs, M. B. Hursthouse, A. D. Morley, B. W. Sharp, N. Vicker, I. Warner, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2355–2362; d) P. Barbier, J. Stadlwieser, *Chimia* **1996**, 50, 530–532; e) D. Tanner, I. Tedenborg, A. Almario, I. Paterson, I. Csoregh, N. M. Kelly, P. G. Andersson, T. Hoegberg, *Tetrahedron* **1997**, 53, 4857–4868; f) H. Miyabe, M. Torieda, T. Kiguchi, T. Naito, *Synlett* **1997**, 580–682.
- [420] Papuamine: a) A. G. M. Barrett, M. L. Boys, T. L. Boehm, *J. Chem. Soc. Chem. Comm.* **1994**, 1881–1882; b) R. M. Borzilleri, S. M. Weinreb, M. Parvez, *J. Am. Chem. Soc.* **1995**, 117, 10905–10913.
- [421] Petrosin: R. W. Scott, J. R. Epperson, C. H. Heathcock, *J. Am. Chem. Soc.* **1994**, 116, 8853–8854.
- [422] Breynolide: A. B. Smith III, J. R. Empfield, R. A. Rivero, H. A. Vaccaro, *J. Am. Chem. Soc.* **1991**, 113, 4037–4038.
- [423] Chlorothricolide: W. R. Roush, R. J. Sciotti, *J. Am. Chem. Soc.* **1994**, 116, 6457–6458. See also W. R. Roush, R. J. Sciotti, *J. Am. Chem. Soc.* **1998**, 120, 7411–7419.
- [424] Thebainone A: M. A. Tius, M. A. Kerr, *J. Am. Chem. Soc.* **1992**, 114, 5959–5966.
- [425] Discorhabdin C: Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka, T. Yakura, *J. Am. Chem. Soc.* **1992**, 114, 2175–2180.
- [426] Isochrysohermidin: H. H. Wasserman, R. W. DeSimone, D. L. Boger, C. M. Baldino, *J. Am. Chem. Soc.* **1993**, 115, 8457–8458.
- [427] Duocarmycin: a) Y. Fukuda, Y. Itoh, K. Nakatani, S. Terashima, *Tetrahedron* **1994**, 50, 2793–2808; Y. Fukuda, K. Nakatani, S. Terashima, *Tetrahedron* **1994**, 50, 2809–2820; b) D. L. Boger, J. A. McKie, T. Nishi, T. Ogiku, *J. Am. Chem. Soc.* **1996**, 118, 2301–2302.
- [428] Trichoviridin: J. E. Baldwin, R. M. Adlington, I. A. O'Neil, A. T. Russell, M. L. Smith, *Chem. Commun.* **1996**, 41–42.
- [429] Calphostin A: R. S. Coleman, E. B. Grant, *J. Am. Chem. Soc.* **1994**, 116, 8795–8796.
- [430] Scopalulic acid: a) L. E. Overman, D. J. Ricca, V. D. Tran, *J. Am. Chem. Soc.* **1993**, 115, 2042–2043; See also L. E. Overman, D. J. Ricca, V. D. Tran, *J. Am. Chem. Soc.* **1997**, 119, 12031–12040; b) F. E. Ziegler, O. B. Wallace, *J. Org. Chem.* **1995**, 60, 3626–3636.
- [431] Magellanine: G. C. Hirst, T. O. Johnson, Jr., L. E. Overman, *J. Am. Chem. Soc.* **1993**, 115, 2992–2993.
- [432] Salsolene oxide: L. A. Paquette, L.-Q. Sun, T. J. N. Watson, D. Friedrich, B. T. Freeman, *J. Am. Chem. Soc.* **1997**, 119, 2767–2768.
- [433] Croomine: S. F. Martin, K. J. Barr, *J. Am. Chem. Soc.* **1996**, 118, 3299–3300.
- [434] The family of the clavularanes: D. R. Williams, P. J. Coleman, S. S. Henry, *J. Am. Chem. Soc.* **1993**, 115, 11654–11655.
- [435] Staurosporine: a) J. T. Link, S. Raghavan, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, 117, 552–553; b) J. L. Wood, B. M. Stoltz, S. N. Goodman, K. Onwueme, *J. Am. Chem. Soc.* **1997**, 119, 9652–9661.
- [436] FR-90848: a) A. G. M. Barrett, K. Kasdorf, *J. Am. Chem. Soc.* **1996**, 118, 11030–11037; b) J. R. Falck, B. Mekonnen, J. Yu, J.-Y. Lai, *J. Am. Chem. Soc.* **1996**, 118, 6096–6097.
- [437] Epoxydictimene: T. F. Jamison, S. Shambayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1994**, 116, 5505–5506; T. F. Jamison, S. Shambayati, W. E. Crowe, S. L. Schreiber, *J. Am. Chem. Soc.* **1997**, 119, 4353–4363.
- [438] 7-Deacetoxyalcyonin acetate: D. W. C. MacMillan, L. E. Overman, *J. Am. Chem. Soc.* **1995**, 117, 10391–10392.
- [439] Syringolide 1: a) J. L. Wood, S. Jeong, A. Salcedo, J. Jenkins, *J. Org. Chem.* **1995**, 60, 286–287; b) S. Kuwahara, M. Moriguchi, K. Miyagawa, M. Konno, O. Kodama, *Tetrahedron* **1995**, 51, 8809–8014; c) J. Ishihara, T. Sugimoto, A. Murai, *Synlett* **1996**, 4, 335–336; d) C.-M. Zeng, S. L. Midland, N. T. Keen, J. J. Sims, *J. Org. Chem.* **1997**, 62, 4780–4784; e) H. Yoda, M. Kawauchi, K. Takabe, K. Hosoyam, *Heterocycles* **1997**, 45, 1895–1898; f) P. Yu, Q.-G. Wang, T. C. W. Mak, H. N. C. Wong, *Tetrahedron* **1998**, 54, 1783–1788.
- [440] Batrachotoxinin: M. Kurosu, L. R. Marcin, T. J. Grinstead, Y. Kishi, *J. Am. Chem. Soc.* **1998**, 120, 6627–8662.
- [441] FR-900482: a) T. Fukuyama, L. Xu, S. Goto, *J. Am. Chem. Soc.* **1992**, 114, 383–385; b) J. M. Schkeryantz, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, 117, 4722–4723.
- [442] Lubiminol: M. T. Crimmins, Z. Wang, L. A. McKerlie, *Tetrahedron Lett.* **1996**, 37, 8703–8706; M. T. Crimmins, Z. Wang, L. A. McKerlie, *J. Am. Chem. Soc.* **1998**, 120, 1747–1756.
- [443] Hispidospermidin: a) A. J. Frontier, S. Raghavan, S. J. Danishefsky, *J. Am. Chem. Soc.* **1997**, 119, 6686–6687; b) L. E. Overman, A. L. Tomasi, *J. Am. Chem. Soc.* **1998**, 120, 4039–4040.
- [444] Pateamine: R. M. Rzaa, H. A. Shea, D. Romo, *J. Am. Chem. Soc.* **1998**, 120, 591–592.
- [445] Ptilomycalin: L. E. Overman, M. H. Rabinowitz, P. A. Renhowe, *J. Am. Chem. Soc.* **1995**, 117, 2657–2658.
- [446] Preussomerin I: S. Chi, C. H. Heathcock, *Org. Lett.* **1999**, 1, 3–6.
- [447] Neocarzinostatin chromophore: A. G. Myers, J. Liang, M. Hammond, P. M. Harrington, Y. Wu, E. Y. Kuo, *J. Am. Chem. Soc.* **1998**, 120, 5319–5320.
- [448] Manumycin B: J. J. C. Grové, X. Wei, R. J. K. Taylor, *Chem. Commun.* **1999**, 421–422.
- [449] Phorboxazole A: C. J. Forsyth, F. Ahmed, R. D. Cink, C. S. Lee, *J. Am. Chem. Soc.* **1998**, 120, 5597–5598.
- [450] Olivomycin A: W. R. Roush, R. A. Hartz, D. J. Gustin, *J. Am. Chem. Soc.* **1999**, 121, 1990–1991.
- [451] Dysidiolide: a) E. J. Corey, B. E. Roberts, *J. Am. Chem. Soc.* **1997**, 119, 12425–12431; b) J. Boukouvalas, Y.-X. Cheng, J. Robichaud, *J. Org. Chem.* **1998**, 63, 228–229; c) S. R. Magnuson, L. Sepp-Lorenzino, N. Rosen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1998**, 120, 1615–1616; d) Y. Kajiwar, H. Miyaoka, Y. Yamada, *41st Symp. Chem. Nat. Prod.* **1999**, 25–30.
- [452] Luzopeptin B: D. L. Boger, M. W. Ledebor, M. Kume, *J. Am. Chem. Soc.* **1999**, 121, 1098–1099.
- [453] Spongistatin 1: J. Guo, K. J. Duffy, K. L. Stevens, P. I. Dalko, R. M. Roth, M. M. Hayward, Y. Kishi, *Angew. Chem.* **1998**, 110, 198–202; *Angew. Chem. Int. Ed.* **1998**, 37, 187–192; M. M. Hayward, R. M. Roth, K. J. Duffy, P. I. Dalko, K. L. Stevens, J. Guo, *Angew. Chem.* **1998**, 110, 202–206; *Angew. Chem. Int. Ed.* **1998**, 37, 192–196.
- [454] Spongistatin 2: D. A. Evans, P. J. Coleman, L. C. Dias, *Angew. Chem.* **1997**, 109, 2951–2954; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2738–2741; D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, *Angew. Chem.* **1997**, 109, 2954–2957; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2741–2744; D. A. Evans, B. W. Trotter, B. Côté, P. J. Coleman, L. C. Dias, A. N. Tyler, *Angew. Chem.* **1997**, 109, 2957–2961; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2744–2747.
- [455] Cephalostatin 7: J. U. Jeong, C. Guo, P. L. Fuchs, *J. Am. Chem. Soc.* **1999**, 121, 2071–2084.
- [456] Rubifolide: J. A. Marshall, C. A. Sehon, *J. Org. Chem.* **1997**, 62, 4313–4320.
- [457] Diepoxin: P. Wipf, J.-K. Jung, *J. Org. Chem.* **1999**, 64, 1092–1093.
- [458] Pinnatoin: J. A. McCauley, K. Nagasawa, P. A. Lander, S. G. Mischke, M. A. Semones, Y. Kishi, *J. Am. Chem. Soc.* **1998**, 120, 7647–7648.

Ferrocene: Ironclad History or Rashomon Tale?*

Pierre Laszlo and Roald Hoffmann*

A critical stance is essential to science. Proving other people wrong is a favorite private and public satisfaction—there is nothing some scientists like better. But, excess zeal discounted, doubt serves as a powerful impulse to the advancement of knowledge. We document it here with the discovery of the structure of ferrocene, a story which also plays up the virtue of the spoken word.^[1] We base it on various published (and most fragmentary, if not mutually inconsistent!) accounts, supplemented with some very helpful correspondence from colleagues.

Two groups independently reported at the very end of 1951 preparation of a compound $C_{10}H_{10}Fe$ from cyclopentadiene. Kealy and Pauson published their contribution in the December 15, 1951 edition of *Nature*, while Miller, Tebboth, and Tremaine's account of their independent (and apparently earlier) preparation of the identical compound, with the same "traditional" formulation (what would today be called a di- σ -complex), appeared a little later in the *Journal of the Chemical Society*.^[2]

Let's turn to the reception of those two papers in the Chemistry Department at Harvard University. As soon as it arrived in the library, during the first couple of weeks in January 1952, R. B. Woodward apparently saw the Kealy and Pauson piece. And he had a hunch that the structure was wrong. He set a graduate student, Myron Rosenblum, preparing not only ferrocene, but also analogues from other transition metals and cyclopentadiene. For this Rosenblum needed ruthenium trichloride. He went to Geoffrey Wilkinson, who had recently taken up an Assistant professorship at Harvard, to ask for a sample of ruthenium. Wilkinson "rather brusquely wanted to know" what Rosenblum needed it for.^[3] Wilkinson writes:^[4]

"...Mike Rosenblum came into my laboratory asking if I had got any ruthenium. I can't remember what I said, except that I think it was along the lines of 'let me tell you what you want it for.'"

Clearly, Wilkinson had already also seen the Kealy and Pauson paper and had decided to study this problematic structure of ferrocene.^[4]

Wilkinson continues:

"However, the upshot was that Woodward and I had lunch at the Harvard Faculty Club on Monday^[5] and sorted things out. The possibility that the C_5H_5 ring in the iron compound could possibly undergo Friedel–Crafts or other aromatic reactions simply had not dawned on me, but other than the structure, this seemed to be Bob's main interest, whereas mine was to go on to other transition metals."

One can only bemoan the fact that Woodward left no account of the discovery, and apply all the reservations the science historian has painfully had to learn of the construction of history (yes, even by the very participants) after the fact. Myron Rosenblum offers a somewhat different perspective on the directions taken by the protagonists:^[3]

"Woodward certainly had an interest in extending the metallocene series vertically along the periodic table and possibly horizontally as well, since I set up four reactions simultaneously on January 31st. These involved the reactions of $NiCl_2$, $CoCl_2$, $CrCl_3$, and $RuCl_3$ with cyclopentadienylmagnesium bromide. From my research notebook I see that I had actually made two attempts to prepare anhydrous $RuCl_3$ on January 16th, five days prior to my first preparation of ferrocene itself. But in any event, Woodward and Wilkinson had apparently reached a private agreement which apparently left this initiative (extending the ferrocene family) to Geoff."

Woodward's contribution to the ferrocene story (and dare one identify this as the main contribution, too?) was the divination of the sandwich structure, and a beautiful piece of insight about its aromaticity. Of the latter Rosenblum writes:^[3]

"On a Thursday evening, March 13th (1952), as we were taking our seats before that evening's seminar, we were chatting about some of the chemistry of this new substance, when [RBW] suggested simply, almost matter-of-factly, that I might want to try a Friedel–Crafts reaction on this new substance....I put off doing the reaction until Monday, March 17th...the product was a beautiful red crystalline material with an enormous carbonyl stretching absorption in the infrared."

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[**] Akira Kurosawa's classic film "Rashomon" depicts a violent event (a rape and murder in a forest) as seen by four participants. In his autobiography (A. Kurosawa, *Something Like an Autobiography*, Vintage Books–Random House, New York, 1983, p. 183). Kurosawa writes of the difficulty his co-workers had understanding the complex plot. He told them: "This film is like a strange picture scroll that is unrolled and displayed by the ego...you can't understand the script at all, but that is because the human heart itself is impossible to understand."

The correct ferrocene structure and its aromaticity were most rapidly published in the form of a communication in *Journal of the American Chemical Society*;^[6] the coauthors were aside from Wilkinson and Woodward, Rosenblum and Mark C. Whiting (a postdoctoral associate in the Woodward group, who joined the research effort).

Meanwhile, during the spring of 1952, E. O. Fischer was independently studying the structure of ferrocene in his laboratory at the Technische Hochschule in Munich (with W. Pfab). Basing his conclusions on evidence from X-ray crystallography, and on very reasonable bonding notions, he also concluded that the molecule was best formulated as an iron(II) atom in-between two cyclopentadienide rings as ligands. Fischer and his co-workers immediately synthesized the ferrocenium cation, and started exploring cognate molecules such as the corresponding cobaltocene.^[7]

The structures proposed by Wilkinson, Woodward, Rosenblum, Whiting, Fischer, and Pfab were truly revolutionary. Contemporary chemists were shocked; here is a recent account by one of the greatest of structural chemists, J. D. Dunitz:^[8]

"One afternoon, I opened the Library copy of JACS [in Cambridge, England] and came across R. B. Woodward's proposal that the molecule consists of two parallel cyclopentadienyl rings with the iron atom sandwiched between them. I was skeptical. Nothing like this had ever been seen before. On my way out of the Library I met Leslie [Orgel] and asked if he had seen this astonishing proposal. He was as skeptical as I was. When we found that the compound was relatively easy to prepare in crystalline form, I decided to determine its crystal structure and so demonstrate the incorrectness [our emphasis] of the proposed molecular structure. Within a few weeks, it became clear to us that Woodward's proposal was correct after all. There was no doubt about it."

Leslie Orgel went on to devise a MO description of this novel structure, which he published together with Dunitz's structure determination. The title of their paper contained the "sandwich" descriptor.^[9–11] Which stuck.^[12]

Thus the ferrocene story unfolded: a conjectured structure was intuitively doubted, refuted, and replaced with what we now know as the true structure. But the true structure was deemed so unusual that it itself led to an attempt at refutation. Which failed, and thereby became an outstanding piece of corroborative evidence.

Our story is hardly complete! There is something to be learned (will it be done before the traces vanish?) of the complicated interactions that the experimentalists whose names we have mentioned above had with the theoreticians around them.^[13] And the sandwich structure was apparently suggested by William von E. Doering to Peter Pauson in September 1951, before the synthesis was published!^[14]

Also from the outset it was clear that this incredible breakthrough, opening up a whole new field within organometallic chemistry, was worthy of recognition. It led to the award of the Nobel Prize to both Wilkinson and Fischer. Woodward was inexplicably left out; he complained, of course to no avail. Access to the deliberations of the Nobel Committee still decades in the future, Thomas Zydowsky has nevertheless uncovered the fascinating correspondence that ensued, one that will also reveal Woodward's perspective on the initial discovery. But for that story you will have to wait.^[15]

We are grateful to many who have shared their memories and writings with us, most importantly Myron Rosenblum, Peter Pauson, Tom Zydowsky, Mark Whiting, Jack Dunitz, and F. Albert Cotton.

- [1] We expand here upon a segment from a recent paper aimed at sociologists, "The Say of Things": R. Hoffmann, P. Laszlo, *Soc. Res.* **1998**, 65, 653–693.
- [2] T. J. Kealy, P. L. Pauson, *Nature* **1951**, 168, 1039–1040; S. A. Miller, J. A. Tebbboth, J. F. Tremaine, *J. Chem. Soc.* **1952**, 632–635. For a description of the chemistry and chronology of these two papers, see G. B. Kauffman, *J. Chem. Educ.* **1983**, 60, 185–186.
- [3] Letters from Professor Myron Rosenblum, Brandeis University, to Roald Hoffmann of September 9, 1998, and March 29, 1999.
- [4] G. Wilkinson, *J. Organomet. Chem.* **1975**, 100, 273–278; Wilkinson dates the visit by Rosenblum to Saturday, January 31st. However, from the evidence in Rosenblum's notebook, the visit predates January 16, 1952. January 30th, 1952 was a Wednesday.
- [5] The evidence of the Rosenblum notebooks would seem to indicate January 19 and 21 for those dates.
- [6] G. Wilkinson, M. Rosenblum, M. C. Whiting, R. B. Woodward, *J. Am. Chem. Soc.* **1952**, 74, 2125–2126.
- [7] E. O. Fischer, W. Pfab, *Z. Naturforsch. B* **1952**, 7, 377–379.
- [8] J. D. Dunitz, *Origins Life and Evolution of the Biosphere* **1997**, 27, 421–427. See also "Forty Years of Ferrocene": J. D. Dunitz in *Organic Chemistry: Its Language and Its State of the Art* (Ed.: M. V. Kisakurek), Verlag Helvetica Chimica Acta, Basel, **1993**, pp. 9–23.
- [9] L. E. Orgel, J. D. Dunitz, *Nature* **1953**, 171, 121–122.
- [10] A third group independently determined the structure of ferrocene: P. F. Eiland, R. Pepinsky, *J. Am. Chem. Soc.* **1952**, 74, 4971.
- [11] Peter Pauson, private communication, recalls that he had crystals of ferrocene in the fall of 1951. He was trying to decide whether to ask Jack Dunitz, or the senior organic crystallographer of the time, J. Monteath Robertson (real or adopted Scotsmen all). Pauson decided on Robertson. Who, according to Pauson, took the crystals to...Cornell, where he asked Lynn Hoard if someone could look at them. The crystals were assigned to a beginning graduate student, who failed to solve the structure.
- [12] The felicitous coining of the name "ferrocene" is due to Mark Whiting and occurs in the second Harvard paper, R. B. Woodward, M. Rosenblum, M. C. Whiting, *J. Am. Chem. Soc.* **1952**, 74, 3458. Apparently "ferrozene" was an early favorite (e-mail from M. C. Whiting to Roald Hoffmann, May 4, 1999).
- [13] Wilkinson, for instance recounts that William Moffitt, a great young theoretician of the time, told him that the binding of benzene to a transition metal was "not on" (ref. [4], footnote on p. 278).
- [14] See footnote 41 of P. L. Pauson, *Q. Rev.* **1955**, 391–414.
- [15] T. M. Zydowsky [tmzinc@aol.com], *Chemical Intelligencer*, in press.

Thermochemical Data of Organic Ions Obtained from Investigations in the More or Less “Diluted” Gas Phase

Dietmar Kuck*

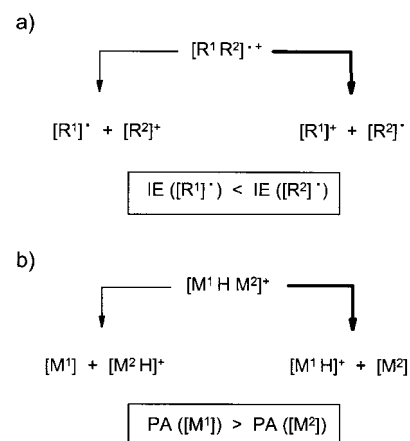
In memory of Bob Squires

The knowledge of quantitative thermochemical data for elementary steps of organic reactions falls short of the diversity of synthetic methods in organic chemistry. Whereas a qualitative assessment of relative stabilities, acidities, and basicities of starting materials and products supports our understanding of many reactions, it is only from heats of formation, enthalpies of deprotonation and protonation, electron affinities, and other thermochemical properties of the reactants and the reactive intermediates that we may achieve quantitative models of chemical reactions and a detailed understanding of chemical processes. Likewise, kinetic parameters for chemical conversions such as activation enthalpies are of central importance in this respect. In view of the multitude of solvents, catalysts, and reaction auxiliaries that affect chemical reactions, efforts to attain a systematic order in this world are often misjudged because, even today, a new recipe can be developed much faster than can a comprehensive quantitative understanding of a chemical reaction. Nevertheless there is progress that may also support the (often neglected) pretention of chemistry to be both a discipline of science *and* culture.

This contribution highlights recent progress in the field of gas-phase chemistry, which has been achieved by measurements concerning the reactivity of organic ions in the “dense” (namely, more or less “diluted”) gas phase, that is, in the range of approximately 1–1500 mbar. It will demonstrate by discussing a highly impressive investigation in detail, and also some independent work, the ways in which we can bridge the gap between the chemistry of organic ions in the condensed phase that is the domain of synthetic chemists, on the one hand, and the chemistry of isolated, unsolvated ions in vacuo, on the other.

Soon after the first applications of mass spectrometry as a technique for analyzing volatile organic compounds it was

discovered that the intrinsic properties of molecules, radicals, and ions in the diluted gas phase determine the unimolecular decomposition and thus the analytical information of these gaseous ions. For example, the Stevenson–Audier rule^[1] states that the fragmentation of a radical cation $[R^1R^2]^{\cdot+}$ yields the cationic fragment whose corresponding neutral species, that is, the radical $[R^1]^{\cdot}$ or $[R^2]^{\cdot}$, or molecule $[M^1]$ or $[M^2]$, has the lower ionization energy (IE) (Scheme 1 a).^[2] Cooks et al.^[3] later developed a method to determine proton



Scheme 1. Schematic representation of the principles a) of the Stevenson–Audier rule and b) of the kinetic method.

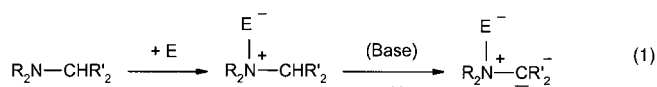
affinities (PA), by making use of the dissociation of a protonated adduct of two different molecules (a protonated “heterodimer”) $[M^1HM^2]^+$, to give the proton affinity of a molecule (M^1 or M^2) if that of the other molecule (M^2 or M^1 , respectively) is known (Scheme 1 b).^[4]

The large variety of methods that allow us to study isolated ions in the high vacuum of mass spectrometers, namely in the “diluted gas phase” at 10^{-9} – 10^{-5} mbar, has enabled large compilations of thermodynamic data on gaseous ions, molecules, and radicals to become available.^[5] This world of data is growing steadily and is not limited to organic compounds, but will include inorganic, element-organic, and biochemical species to increasing extents.^[6]

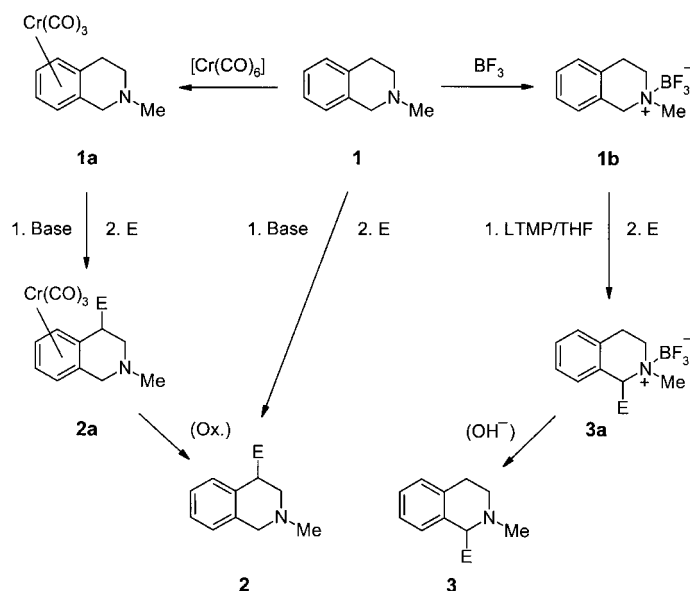
Quantitative data on Brønsted- and Lewis-acid catalyzed reactions are of particular importance.^[7] Thus, complexation

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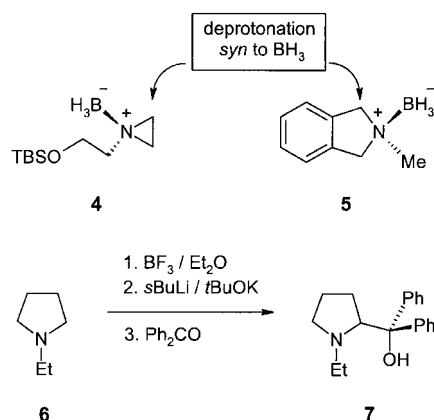
of carbonyl compounds by Lewis acids is well known to increase the electrophilicity of carbonyl groups, the acidity of adjacent C α –H bonds, and the dienophilicity of the reactant. In contrast, activation of C α –H bonds attached to saturated functional groups by Lewis acids is often much more difficult. Thus, useful synthetic methods for α -alkylations and α -acylations of tertiary amines have become available only recently.^[8] These methods make use of the coordination of Lewis acids E to the nitrogen atom to increase the C α –H acidity of the substrate [Eq. (1)].



Some impressive and most recent examples are collected in Schemes 2 and 3. Whereas deprotonation of *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**1**) and its Cr(CO)₃ complex **1a** with *n*-butyllithium occurs at C4 in the absence of Lewis acids,^[9, 10] the formation of **1b** by complexation of **1** with boron trifluoride gives rise to deprotonation at C1.^[11, 12] Instead of



Scheme 2. Regioselective deprotonation of free and complexed **1**. LTMP = lithium 2,2,6,6-tetramethylpiperide.

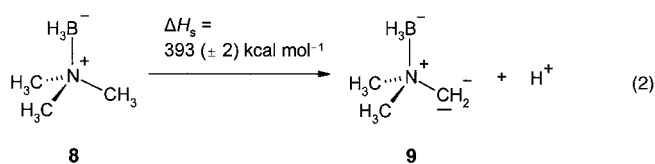


Scheme 3. Deprotection/alkylation of borane-complexed tertiary amines. TBS = *tert*-butyldimethylsilyl.

the complexes **2a** and the free bases **2**, the complexes **3a** are formed with high regioselectivity and they can be isolated readily and converted into the corresponding 1-alkylisoquinolines **3**. Recently, alkylation of Tröger's bases at the benzylic positions was considerably improved by using this method.^[13] Borane has also been used in place of boron trifluoride.^[11, 14–17] With this Lewis acid the 1-alkylation of **1** also takes place in very good yield, in analogy to the sequence **1** → **1b** → **3a** → **3**.^[15]

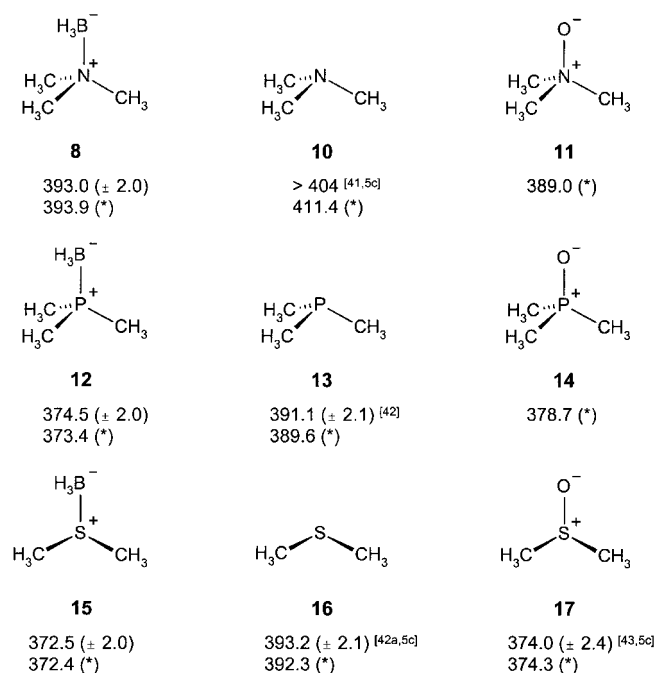
Another recent work demonstrates that this methodology can be successfully applied to the α -alkylation of *N*-alkylaziridines,^[18] and it has been revealed that the incoming substituent preferentially attacks the complex **4** at the *syn* position relative to the BH₃ ligand (Scheme 3). This stereoselectivity was confirmed in the case of the *N*-methylisoindole–borane complex **5**. Moreover, use of *sec*-butyllithium/(–)-sparteine as an enantioselective deprotonation reagent led to remarkably high *ee* values for the alkylated complex.^[17] With even stronger bases, such as those of the Lochmann–Schlosser type (for example, *s*BuLi/KOtBu),^[19] alicyclic amines such as *N*-ethylpyrrolidine (**6**) can be deprotonated and added to carbonyl compounds (Scheme 3).^[20] Thus, in summary, deprotonation/alkylation of borane-complexed tertiary amines offers a considerable extension to the chemistry of dipole-stabilized carbanions that have been known for more than twenty years.^[21–24]

What can be gained now and added to this novel chemistry in solution from investigations in the diluted gas phase? The gas-phase C–H acidities of the volatile complexes of trimethylamine, trimethylphosphane, and dimethyl sulfide with BH₃ were studied in 1997 by Squires et al.^[25] by employing flowing-afterglow mass spectrometry (FA-MS) or, more precisely, selected ion flow tube mass spectrometry (SIFT-MS).^[26, 27] In this impressive work the authors demonstrated, for the first time and on a quantitative scale, the tremendous increase of the C–H acidity of aliphatic amines, phosphanes, and sulfides (**10**, **13**, and **16**, see Scheme 4) that is induced by the BH₃ ligand. In Equation (2) the prototypical dissociation



of the trimethylamine–borane complex **8** as a gaseous Brønsted acid is shown. The thermodynamic activation in this case, and in the corresponding adducts of BH₃ with trimethylphosphane (**12**) and dimethyl sulfide (**15**), were found to be as large as 18–21 kcal mol^{–1}; thus, the equilibrium constant of the dissociation of the C α –H bond increases by 10¹³ < ΔK_s < 10¹⁵, which is very similar to the acidifying effect from the oxygen atom in the related amine oxides, phosphane oxides, and sulfoxides (**11**, **14**, and **17**, respectively; Scheme 4).

A schematic diagram of contemporary^[28] flowing-afterglow mass spectrometers based on the “selected ion flow tube” (SIFT) methodology is given in Figure 1. Ions generated in a flowing-afterglow ion source are selected according to their mass by a quadrupole mass filter (Q0) and introduced into a



Scheme 4. Brønsted acidities H_a (in kcal mol⁻¹) of the gaseous borane adducts **10**, **13**, and **16**, as compared to those of the free Lewis bases and the corresponding oxides. Unless quoted explicitly, the experimental and calculated (*) data were taken from Squires et al.^[25]

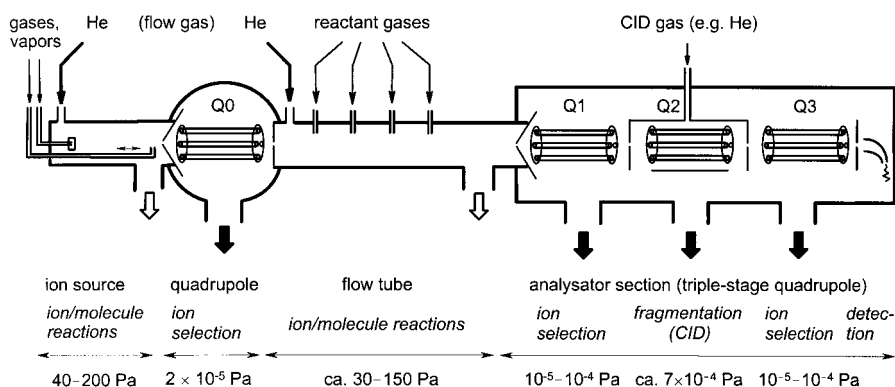


Figure 1. Schematic representation of a flowing-afterglow mass spectrometer. Selection of the reactant ions in the quadrupole mass filter (Q0) is followed by analysis of the product ions in a triple-stage quadrupole mass spectrometer (Q1/Q2/Q3).

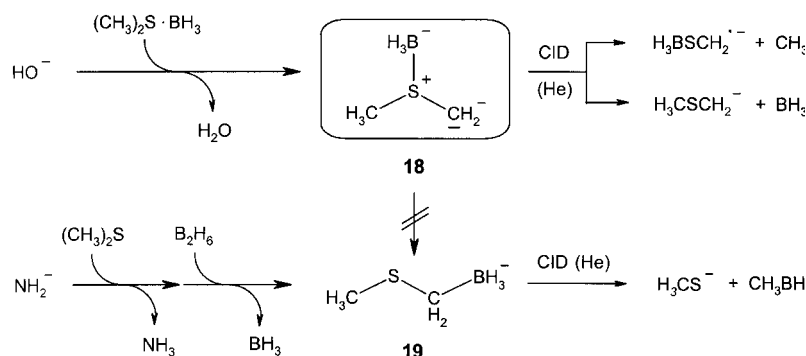
reaction tube approximately 1 m in length, where they are allowed to migrate downstream in a flow of helium gas at a pressure of 0.3–1.4 mbar (ca. 30–140 Pa). Owing to the relatively high pressure in the flow tube these “reagent ions” are quickly cooled to the temperature of the carrier gas (“thermalized”) by collisions with the helium atoms; therefore, they undergo ion/molecule reactions under thermal equilibrium with the volatile compounds injected into the gas stream through an inlet port. The product ions generated in this way can be subjected to characteristic ion/molecule reactions, such as proton transfer and H/D exchange reactions, by adding further gases “downstream” of the flow tube. At the end of the flow tube the carrier gas and other

volatile neutrals are pumped off and the product ions are identified and characterized by means of a triple-stage quadrupole mass spectrometer (TSQ-MS); their relative abundances reflect the chemical equilibrium attained within the flow tube and, owing to the well-defined concentrations and flow parameters, they also yield kinetic information. To identify the product ions after being mass-selected in the first quadrupole filter (Q1), they are decomposed in a structure-specific manner in the zone of the second quadrupole (Q2) by collisions with inert gases, as eventually determined by mass analysis of the fragment ions in the third quadrupole (Q3).

Squires et al. generated mass-selected OH⁻ ions and treated them with the volatile complexes **8**, **12**, and **15** in the flow tube. Organic anions generated by deprotonation [for example, **9** from **8**, Eq. (2)] were analyzed according to their mass and structure by collision-induced dissociation (CID) at the end of the flow tube after leaking into the triple-stage quadrupole mass spectrometer. The addition of reagent gases of known acidity into the flow tube allowed the authors to accurately determine the basicity of the anions generated within the flow tube by using the “bracketing” approach. The addition of suitable deuterated reagent gases, such as D₂O, revealed the number of exchangeable (“acidic”) protons. Similar to the anions generated initially, the product anions of the subsequent reactions were mass-analyzed and structurally characterized by CID in the TSQ analyzer.

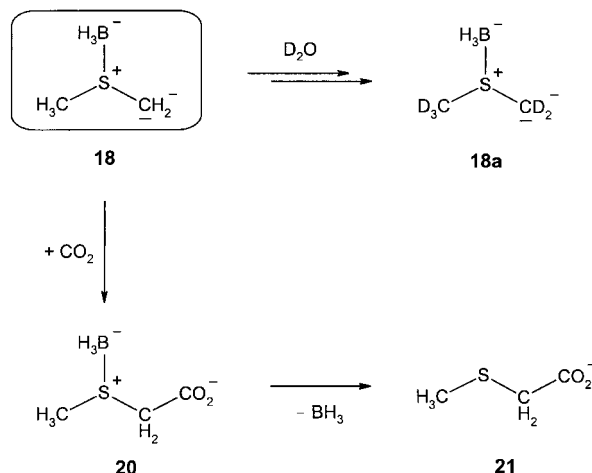
In this way, Squires et al. found that the anion **9** formed from the trimethylamine–borane complex incorporates up to eight deuterium atoms. A detailed study on anion **18** generated from the dimethyl sulfide–borane complex **15** demonstrates the stringency of the method.

Mass-selected OH⁻ ions deprotonated the complex **15** in the flow tube to give C₂H₈BS⁻ ions having the ylide structure **18**, and the collision-induced decomposition of **18** in the triple-stage quadrupole analyzer was found to be characteristically different from that of the isomeric ions **19**, which were generated by an independent reaction sequence involving NH₂⁻, Me₂S, and B₂H₆ (Scheme 5). According to ab initio calculations the isomerization **18** → **19** is exothermic but kinetically suppressed by a high activation barrier (29 kcal mol⁻¹).^[25b]



Scheme 5. Generation of isomeric anions C₂H₈BS⁻ by ion/molecule reactions and characterization by collision-induced dissociation (CID) in the SIFT mass spectrometer (see Figure 1).

The most convincing proof^[25] for the ylide structure of **18** was provided by repeated ion/molecule reactions with D₂O in the flow tube, through which up to five deuterons were incorporated into the anion (**18a**, Scheme 6). In line with the

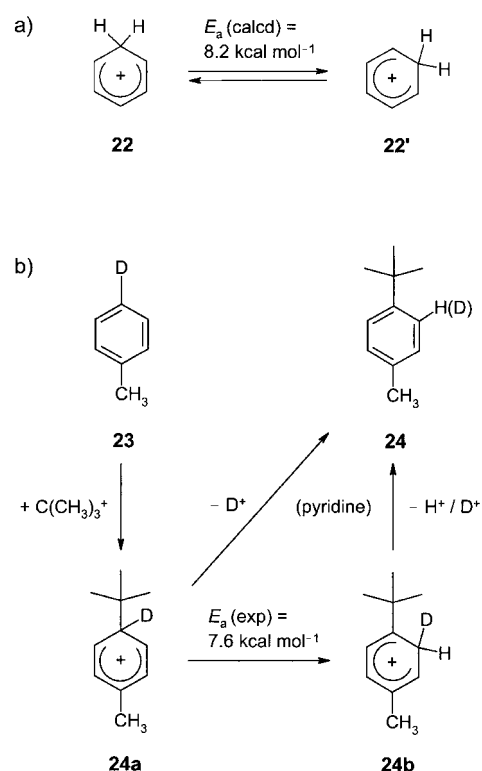


Scheme 6. Characteristic ion/molecule reactions of **18**.

carbanionic structure of **18**, these ions formed covalent adducts with Lewis acids; for example reaction with CO₂ gave the corresponding carboxylate **20** from which the borane fragment could be “evaporated” as a result of the exothermicity of the reaction. This completes the borane-assisted functionalization of **16** in the gas phase to give anion **21**, for example, in analogy to the synthetical sequence (see Scheme 3).

Other methods have also taken advantage of the thermalization of organic ions in the “dense” gas phase to contribute to the wealth of thermodynamic and kinetic data of important organic elementary reactions in recent years. Besides the flowing afterglow techniques, the γ -radiolysis methodology developed by Cacace^[29] has been applied by his group^[30] to study the chemistry of ions in gas mixtures at pressures of 100–1500 mbar (10⁴–1.5 × 10⁵ Pa) and at variable temperature. Carbocations generated under these conditions react by ion/molecule reactions and the ionic products are neutralized subsequently (for example, by deprotonation) to give mixtures of compounds whose composition and structures, respectively, allow one to not only draw mechanistic conclusions but also to derive activation parameters.

A topic that has been of fundamental interest in physical organic chemistry for half a century addresses the problem of bonding of a proton in a complex with benzene (**22**) and other aromatic nuclei and of its mobility within these resulting complexes (Scheme 7).^[31–33] To this end, several studies were performed during recent years in the “dense” gas phase, such as by gas-phase radiolysis^[34] and by flowing-afterglow (SIFT) techniques.^[35] Thus, the kinetics of deprotonation of radiolytically generated 4-*tert*-butyltoluenium ions **24a** and **24b** yielded the Arrhenius activation energy of the “proton ring walk” in protonated alkylbenzenes (alkylbenzenium ions) (Scheme 7b).^[34] This first experimental determination of these gas-phase elementary processes led to a value ($E_a = 7.6 \pm 0.2$ kcal mol^{−1}) that is in excellent agreement with the

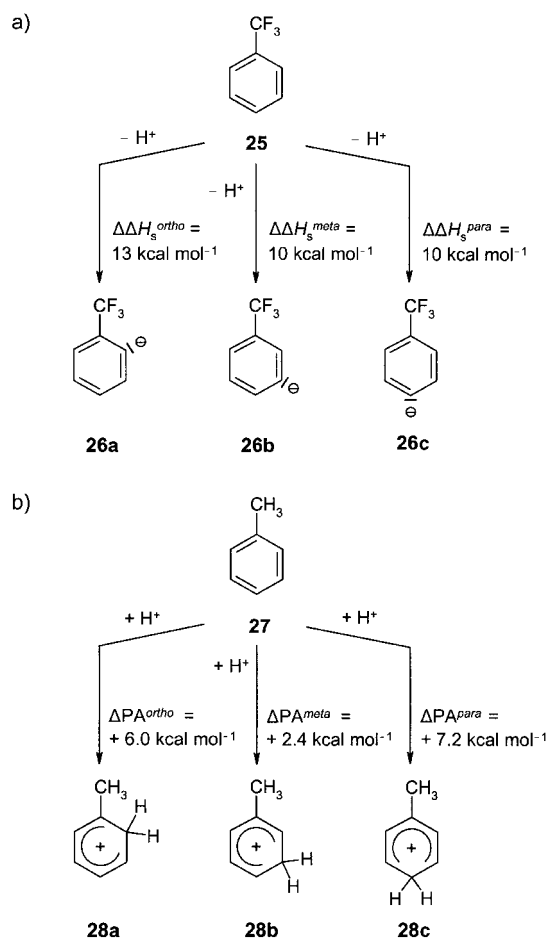


Scheme 7. Proton ring walk a) in benzenium ions and b) in 4-*tert*-butyltoluenium ions **24a** and **24b** generated by ion/molecule reactions in isobutane (ca. 10⁵ Pa, 47–120 °C).

results of the most recent ab initio calculations ($E_a = 7.9$,^[32a] 8.2,^[32b] and 7.8 kcal mol^{−1})^[32c] and also with the activation energy measured by Olah et al.^[36] in 1970 for the proton ring walk in the superacidic liquid phase ($E_a = 10 \pm 1$ kcal mol^{−1}, $\Delta G^\ddagger = 8.0 \pm 1$ kcal mol^{−1}).^[36c] It represents a landmark in the long research on this ubiquitous isomerization process of arenium ions.

Besides the dense gas phase, the “diluted” gas phase continues to represent an important medium for the determination of intrinsic thermodynamic and kinetic data, as demonstrated, for example, by recent investigations on the deprotonation of multiply CF₃-substituted benzenes under the conditions of Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry.^[37] Although FT-ICR mass spectrometers are usually operated under high vacuum, modern instruments offer routine procedures to efficiently cool the ions generated by exothermic ion/molecule reactions. In this case, thermalization is effected by allowing the ions to interact with short-term gas pulses. In a joint effort to compare the deprotonation behavior of trifluoromethylbenzenes towards strong bases in solution^[38] and in the gas phase, the groups of Schlosser, Dmowski, and Nibbering^[39] found considerable differences between the kinetic and the thermodynamic acidity in solution. The gas-phase studies, however, revealed a notably consistent additivity of the substituent effects. For example, a CF₃ group in the *ortho* position decreases the enthalpy of deprotonation of a C^{arom}–H bond by 13 kcal mol^{−1} and thus the thermodynamic acidity increases almost by a factor of 10¹⁰, whereas a CF₃ group in either a *meta* or *para* position to the same C–H bond enhances the acidity by

10 kcal mol⁻¹, that is, by more than a factor of 10⁶ (Scheme 8). Additivity of these “local acidities” of trifluoromethylbenzenes in the gas phase are strongly reminiscent of the long-known



Scheme 8. a) Increase of the local Brønsted acidities ($\Delta\Delta H_{\text{s}}$) of trifluoromethylbenzene (**25**) relative to benzene; b) increase of the local proton affinities (ΔPA) of toluene **27** relative to benzene. Note that ΔH_{s} (Brønsted acid) $\equiv \text{PA}([\text{Brønsted acid}] - \text{H}^+)$.

additivity of the local proton affinities of methylbenzenes in the gas phase (Scheme 8b).^[31, 40] The most recent systematic ab initio calculations on the additivity of substituent effects on the proton affinities of various arenes are in full agreement with these experimental findings.^[44]

- [1] a) D. P. Stevenson, *Discuss. Faraday Soc.* **1951**, 10, 35–45; b) H. E. Audier, *Org. Mass Spectrom.* **1969**, 2, 283–298.
- [2] For a comprehensive discussion and thermochemical applications, see F. W. McLafferty, F. Tureček, *Interpretation of Mass Spectra*, 4th ed., University Science Books, Mill Valley, **1993**, pp. 141–144.
- [3] a) S. A. McLuckey, D. Cameron, R. G. Cooks, *J. Am. Chem. Soc.* **1981**, 103, 1313–1317; b) R. G. Cooks, J. S. Patrick, T. Koitiah, S. A. McLuckey, *Mass Spectrom. Rev.* **1994**, 13, 287–339; c) R. G. Cooks, P. S. H. Wong, *Acc. Chem. Res.* **1998**, 31, 379–386; d) P. B. Armentrout, *J. Mass Spectrom.* **1999**, 34, 74–78; e) L. Drahos, K. Vékey, *J. Mass Spectrom.* **1999**, 34, 79–84; f) R. G. Cooks, J. T. Koskinen, P. D. Thomas, *J. Mass Spectrom.* **1999**, 34, 85–92.
- [4] For further methods for determining thermodynamic data of gaseous ions, see a) J. E. Bartmess, *Mass Spectrom. Rev.* **1989**, 8, 297–343; b) J. Szulejko, T. B. McMahon, *J. Am. Chem. Soc.* **1993**, 115, 7839–7848;

- c) I. A. Koppel, F. Anvia, R. W. Taft, *J. Phys. Org. Chem.* **1994**, 7, 717–724; d) G. Bouchoux, J. Y. Salpin, D. Leblanc, *Int. J. Mass Spectrom. Ion Processes* **1996**, 153, 37–48; e) P. G. Wenthold, W. C. Lineberger, *Acc. Chem. Res.* **1999**, 32, 597–604; f) A good review on the methods is given in ref. [5d].
- [5] For some compilations in chronological order, see a) J. L. Franklin, J. G. Dillard, H. M. Rosenstock, J. T. Herron, K. Draxl, F. H. Field, *Ionization Potentials, Appearance Potentials, and Heats of Formation of Gaseous Positive Ions*, U.S. Department of Commerce, NSRDS-NBS 26, Washington, **1969**; b) S. G. Lias, J. F. Liebman, R. D. Levin, *J. Phys. Chem. Ref. Data* **1984**, 13, 695–808; c) S. G. Lias, J. E. Bartmess, J. F. Liebman, J. L. Holmes, R. D. Levin, W. G. Mallard, *J. Phys. Chem. Ref. Data* **1988**, 17, Suppl. 1; d) E. P. L. Hunter, S. G. Lias, *J. Phys. Chem. Ref. Data* **1998**, 27, 413–656; e) “NIST Chemistry Webbook”: NIST Standard Reference Database, Vol. 69 (Eds.: W. G. Mallard, P. J. Linstrom), National Institute of Standards and Technology, Gaithersburg, MD, **1998** (<http://webbook.nist.gov>).
- [6] a) R. A. Jockusch, P. D. Schnier, W. D. Price, E. F. Strittmatter, P. A. Demirev, E. R. Williams, *Anal. Chem.* **1997**, 69, 1119–1126; b) W. D. Price, R. A. Jockusch, E. R. Williams, *J. Am. Chem. Soc.* **1997**, 119, 11988–11989; c) P. D. Schnier, W. D. Price, E. F. Strittmatter, E. R. Williams, *J. Am. Soc. Mass Spectrom.* **1997**, 8, 771–780; d) W. D. Price, P. D. Schnier, E. R. Williams, *J. Phys. Chem. B* **1997**, 101, 664–673.
- [7] See for example a) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, Plenum, New York, **1993**; b) R. Brückner, *Reaktionsmechanismen: Organische Reaktionen, Stereochemie, moderne Synthesemethoden*, Spektrum Akademischer Verlag, Heidelberg, **1996**.
- [8] Review: S. V. Kessar, P. Singh, *Chem. Rev.* **1997**, 97, 721–737.
- [9] a) Y. Ito, M. Nakatsuka, T. Saegusa, *J. Am. Chem. Soc.* **1982**, 104, 7609–7622; b) J. Blagg, S. J. Coote, S. G. Davies, *J. Chem. Soc. Perkin Trans. 1* **1987**, 689–694.
- [10] a) J. Blagg, S. J. Coote, S. G. Davies, B. E. Mobbs, *J. Chem. Soc. Perkin Trans. 1* **1986**, 2257–2261; b) J. Blagg, S. G. Davies, B. E. Mobbs, *J. Chem. Soc. Chem. Commun.* **1985**, 619–620.
- [11] S. V. Kessar, P. Singh, R. Vohra, N. P. Kaur, K. N. Singh, *J. Chem. Soc. Chem. Commun.* **1991**, 568–570.
- [12] For the 1-lithiation of *N*-pivaloyl-1,2,3,4-tetrahydroisoquinoline, see a) D. Seebach, I. Huber, *Chimia* **1985**, 39, 233–234; b) D. Seebach, J. Hansen, P. Seiler, J. M. Gromek, *J. Organomet. Chem.* **1985**, 285, 1–13; c) D. Seebach, M. A. Syfrig, *Angew. Chem.* **1984**, 96, 235–236; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 248–249.
- [13] M. Harmata, K. W. Carter, D. E. Jones, M. Kahraman, *Tetrahedron Lett.* **1996**, 37, 6267–6270.
- [14] M. R. Ebden, N. S. Simpkins, D. N. A. Fox, *Tetrahedron Lett.* **1995**, 36, 8697–8700.
- [15] V. Ferey, T. Le Gall, C. Mioskowski, *J. Chem. Soc. Chem. Commun.* **1995**, 487–489.
- [16] A. J. Blake, M. R. Ebden, D. N. A. Fox, W.-S. Li, N. S. Simpkins, *Synlett* **1998**, 189–191.
- [17] S. V. Kessar, P. Singh, K. N. Singh, M. Dutt, *J. Chem. Soc. Chem. Commun.* **1991**, 570–571; b) S. V. Kessar, P. Singh in *Encyclopedia of Reagents for Organic Synthesis*, Vol. 5 (Ed.: L. A. Paquette), Wiley, New York, **1995**, p. 2994.
- [18] E. Vedejs, J. T. Kendall, *J. Am. Chem. Soc.* **1997**, 119, 6941–6942.
- [19] a) L. Lochmann, J. Pospíšil, D. Lím, *Tetrahedron Lett.* **1966**, 257–262; b) M. Schlosser, *Pure Appl. Chem.* **1988**, 60, 1627–1634.
- [20] See references in ref. [8].
- [21] D. Seebach, D. Enders, *Angew. Chem.* **1975**, 87, 1–18; *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 15–32.
- [22] P. Beak, D. B. Beitz, *Chem. Rev.* **1978**, 78, 275–316.
- [23] A. Krief, *Tetrahedron* **1980**, 36, 2531–2640.
- [24] A. I. Meyers, L. M. Fuentes, Y. Kubota, *Tetrahedron* **1984**, 40, 1361–1370.
- [25] a) J. Ren, D. B. Workman, R. R. Squires, *Angew. Chem.* **1997**, 109, 2330–2332; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2230–2232; b) J. Ren, D. B. Workman, R. R. Squires, *J. Am. Chem. Soc.* **1998**, 120, 10511–10522.
- [26] J. M. Van Doren, S. E. Barlow, C. H. DePuy, V. M. Bierbaum, *Int. J. Mass Spectrom. Ion Processes* **1987**, 81, 85–100.
- [27] a) S. T. Graul, R. R. Squires, *Mass Spectrom. Rev.* **1988**, 7, 263–358; b) P. J. Marinelli, J. A. Paulino, L. S. Sunderlin, P. G. Wenthold, J. C.

- Poutsma, R. R. Squires, *Int. J. Mass Spectrom. Ion Processes* **1994**, *130*, 89–105.
- [28] Flowing-afterglow or SIFT-FA mass spectrometers are commercially not available.
- [29] F. Cacace, *Acc. Chem. Res.* **1988**, *21*, 215–222.
- [30] Reviews: a) M. Speranza, *Mass Spectrom. Rev.* **1992**, *11*, 73–117; b) S. Fornarini, *Mass Spectrom. Rev.* **1996**, *15*, 365–389.
- [31] For a review on the gas-phase ion chemistry of protonated benzene and of protonated alkylbenzenes, see D. Kuck, *Mass Spectrom. Rev.* **1990**, *9*, 583–630.
- [32] a) S. Sieber, P. von R. Schleyer, J. Gauss, *J. Am. Chem. Soc.* **1993**, *115*, 6987–6988; b) M. N. Glukhovtsev, A. Pross, A. Nicolaides, L. Radom, *J. Chem. Soc. Chem. Commun.* **1995**, 2347–2348; c) E. del Rio, R. López, T. L. Sordo, *J. Phys. Chem. A* **1997**, *101*, 10090–10094.
- [33] For more recent work on the chemistry of protonated alkylbenzenes, see a) D. Kuck, *Int. J. Mass Spectrom. Ion Processes* **1992**, *117*, 441–455; b) F. Cacace, M. E. Crestoni, S. Fornarini, D. Kuck, *J. Am. Chem. Soc.* **1993**, *115*, 1024–1031; c) S. T. Howard, K. Woźniak, *Chem. Phys. Lett.* **1993**, *212*, 1–4; d) R. S. Mason, C. M. Williams, P. D. J. Anderson, *J. Chem. Soc. Chem. Commun.* **1995**, 1027–1028; e) T. Xu, D. H. Barich, P. D. Torres, J. F. Haw, *J. Am. Chem. Soc.* **1997**, *119*, 406–414; f) D. Kuck, A. Petersen, U. Fastabend, *Int. J. Mass Spectrom. Ion Processes* **1998**, *179/180*, 129–146; g) D. Kuck, U. Fastabend, *Int. J. Mass Spectrom. Ion Processes* **1998**, *179/180*, 147–163; h) M. Tanaka, M. Fujiwara, Q. Xu, H. Ando, T. J. Raeker, *J. Org. Chem.* **1998**, *63*, 4408–4412; i) P. C. Miklis, R. Ditchfield, T. A. Spencer, *J. Am. Chem. Soc.* **1998**, *120*, 10482–10489; j) G. Bouchoux, M. Yáñez, O. Mó, *Int. J. Mass Spectrom.* **1999**, *185/186/187*, 241–251; k) M. Mormann, D. Kuck, *J. Mass Spectrom.* **1999**, *34*, 384–394.
- [34] F. Cacace, M. E. Crestoni, S. Fornarini, *J. Am. Chem. Soc.* **1992**, *114*, 6776–6784.
- [35] a) B. Chiavarino, M. E. Crestoni, C. H. DePuy, S. Fornarini, R. Gareyev, *J. Phys. Chem.* **1996**, *100*, 16201–16208; b) C. H. DePuy, R. Gareyev, S. Fornarini, *Int. J. Mass Spectrom. Ion Processes* **1997**, *151*, 41–45; c) S. Fornarini, M. E. Crestoni, *Acc. Chem. Res.* **1998**, *31*, 827–834.
- [36] a) G. A. Olah, R. H. Schlosberg, D. P. Kelly, G. D. Mateescu, *J. Am. Chem. Soc.* **1970**, *92*, 2546–2548; b) G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, G. D. Mateescu, *J. Am. Chem. Soc.* **1972**, *94*, 2034–2043; c) G. A. Olah, J. S. Staral, G. Ascensio, G. Liang, D. A. Forsyth, G. D. Mateescu, *J. Am. Chem. Soc.* **1978**, *100*, 6299–6308.
- [37] For applications of FT-ICR mass spectrometry in organic chemistry, see J. S. Pyrek, *Synlett* **1999**, 249–266.
- [38] M. Schlosser, J. Porwisiak, F. Mongin, *Tetrahedron* **1998**, *54*, 895–900.
- [39] M. Schlosser, F. Mongin, J. Porwisiak, W. Dmowski, H.-H. Bükler, N. M. M. Nibbering, *Chem. Eur. J.* **1998**, *4*, 1281–1286.
- [40] J. L. Devlin, III, J. F. Wolf, R. W. Taft, W. J. Hehre, *J. Am. Chem. Soc.* **1976**, *98*, 1990–1992.
- [41] G. I. Mackay, R. S. Hemsworth, D. K. Bohme, *Can. J. Chem.* **1976**, *54*, 1624–1642.
- [42] a) S. Ingemann, N. M. M. Nibbering, *J. Chem. Soc. Perkin Trans. 2* **1985**, 837–840; b) See also J. J. Grabowski, P. D. Roy, R. Leone, *J. Chem. Soc. Perkin Trans. 2* **1988**, 1627–1632.
- [43] a) J. B. Cummings, P. Kebarle, *Can. J. Chem.* **1978**, *56*, 1–9; b) J. E. Bartmess, J. A. Scott, R. T. McIver, Jr., *J. Am. Chem. Soc.* **1979**, *101*, 6046–6056.
- [44] a) M. Eckert-Maksić, M. Klessinger, Z. B. Maksić, *J. Phys. Org. Chem.* **1995**, *8*, 435–441; b) M. Eckert-Maksić, M. Klessinger, Z. B. Maksić, *Chem. Eur. J.* **1996**, *2*, 1251–1257; c) Z. B. Maksić, B. Kovačević, D. Kovaček, *J. Phys. Chem. A* **1997**, *101*, 7446–7453.

“Simple” Carbonyls of Ruthenium: New Avenues from the Hieber Base Reaction

Anthony F. Hill*

The rush to develop increasingly more complex and sophisticated transition metal catalysts by ingenious coligand design continues to gather momentum. In this climate it is both refreshing and sobering when results of substantial scientific significance emerge from studies of older and simpler organometallic compounds, which can effectively mediate technologically useful processes. Ultimately, the simpler the system, the more generally applicable are the lessons to be learnt. One such system is provided by the carbonyl chlorides of ruthenium(II), which arise from the carbonylation of alcoholic solutions of commercially available hydrated ruthenium chloride “RuCl₃ · xH₂O”. The resulting yellow solution, described^[1a] as including “species of doubtful composition prepared in situ” finds wide use in the prepara-

tion of numerous complexes of the form [RuCl₂(CO)₂L₂] (L = phosphanes, arsanes, thioethers etc).^[1] Not only do such solutions provide access to the carbonyl chemistry of divalent ruthenium. Bruce and Stone first showed that zinc reduction provided the binary zerovalent carbonyl [Ru₃(CO)₁₂].^[2] This remains the preferred route to this compound, the subsequent chemistry of which has featured in thousands of papers.^[3] This early study provided some key insights, including the isolation of dimeric [Ru₂(μ-Cl)₂Cl₂(CO)₆] (**1**) and the observation that the halide bridges were easily and reversibly cleaved by the weak nucleophile THF to provide *fac*-[RuCl₂(thf)(CO)₃] (**2**). Chloride also reversibly cleaves dimeric **1**, or replaces the labile THF in **2**, to provide the ruthenate *fac*-[RuCl₃(CO)₃][–] (**3**[–]). In the intervening 33 years, the comparative ignorance of the true nature of the interacting species involved in such alcoholic solutions has been more than excused by the enormous synthetic utility. Recent studies, primarily those of Lavigne and co-workers,^[4] have however sought to understand this witches brew, driven in part by the utility of carbonyl halide complexes of divalent ruthenium in various catalytic processes. Amongst these is the water–gas shift

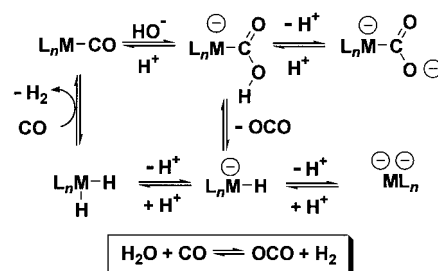
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reaction, and by implication the Hieber base reaction,^[5] the study of which has led to some surprising results. Herein we would like to highlight and contextualize some particularly intriguing results currently emerging.^[6–8]

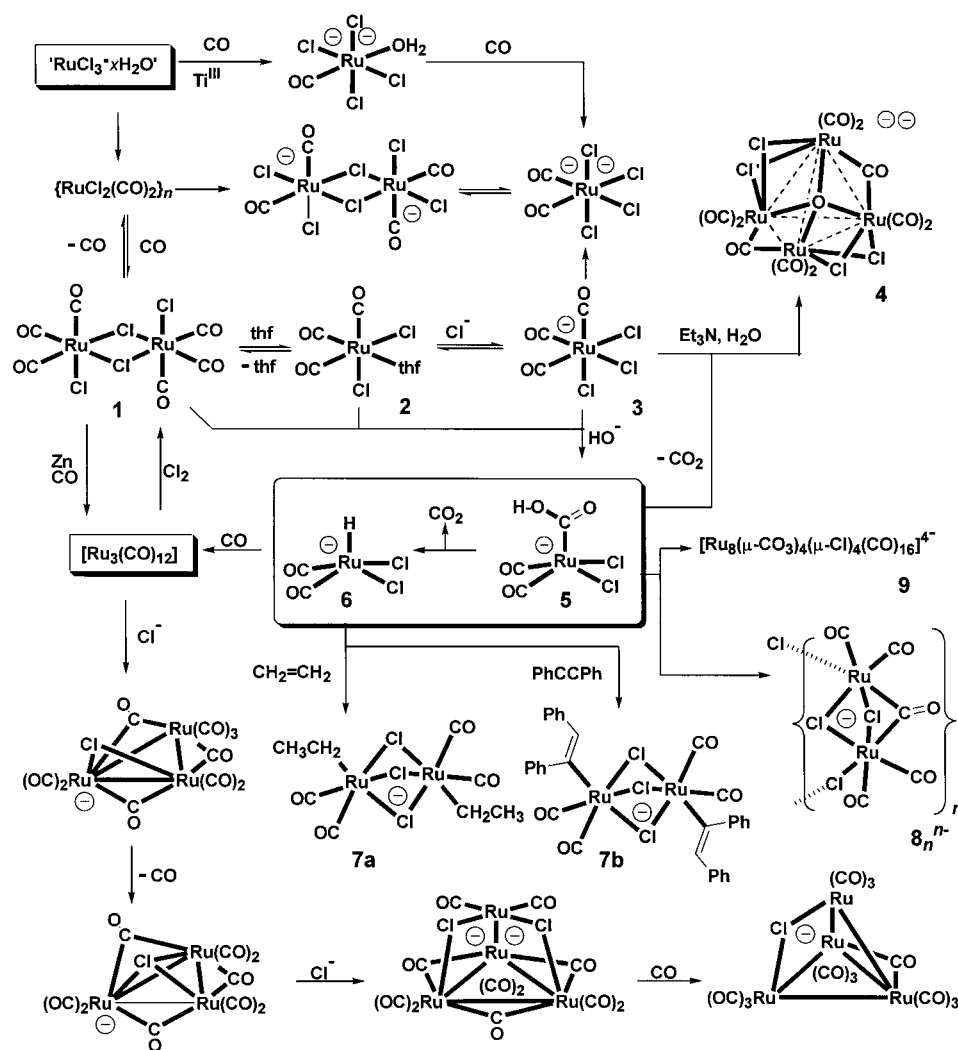
Scheme 1 presents a manifold of well-characterized carbonylchlororuthenium(II) species. Elsewhere can be found the specific conditions devised to favor the predominance or isolation of each species.^[4, 6, 7] The important point however is that each and every one of these species might be considered to be potentially present and operative in catalytic “broths” employing carbonylated ruthenium chloride or mixtures of $[\text{Ru}_3(\text{CO})_{12}]$ and chloride sources. Despite the complexity of this reaction manifold, the study of the individual species and their inter-relationship has been made possible by convenient and reliable routes to each of the components. In particular the carbonyl ruthenate **3**[−] may be conveniently prepared as either the Cs^+ ^[9] or $[\text{PPN}]^+$ salts ($\text{PPN} = (\text{PPh}_3)_2\text{N}$).^[10] The processes that deserve special comment are however the various reactions of **1**, **2**, or $[\text{PPN}]\textbf{3}$ with sources of hydroxide: The conditions are crucial to the progress of the reaction, for example, with water and triethylamine the μ_4 -oxo cluster **4** is obtained. With KOH, however, a (possibly *solvento*-stabilized) hydroxycarbonyl intermediate **5**[−] may be observed at

ambient temperatures, with clear implications for the Hieber base reaction^[5] and the water–gas shift reaction^[11] mediated by divalent ruthenium species.^[12, 13]

Hieber’s “Base reaction” is a fundament of organotransition metal chemistry, having provided the archetypal metal hydrides $\text{K}[\text{HFe}(\text{CO})_4]$ and $[\text{H}_2\text{Fe}(\text{CO})_4]$ ^[5] as well as the key rationale for the metal-catalyzed water–gas shift reaction (WGSR, Scheme 2):^[11] Nucleophilic attack by hydroxide at a carbonyl ligand, with subsequent formation of CO_2 and a metal hydride, can in suitable situations be followed by deprotonation of the metal hydride and overall reduction of the metal center by two units. Alternatively, protonation of



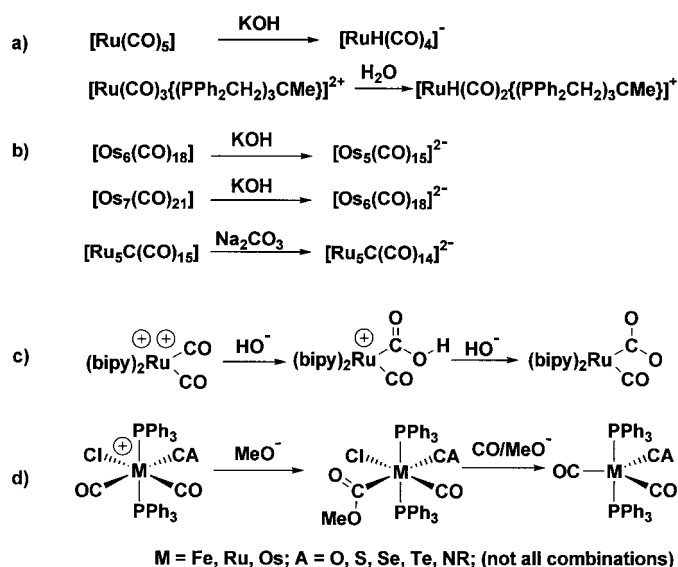
Scheme 2. Metal-mediated water–gas shift reaction (WGSR).



Scheme 1.

the hydrido complex can lead (via a dihydride) to evolution of dihydrogen. Discovered first for iron, this reaction is becoming increasingly conspicuous in the chemistry ruthenium (Scheme 3). Thus, the analogous reaction of $[\text{Ru}(\text{CO})_5]$ with KOH (Scheme 3a) proceeds 30 000 times as fast as that for $[\text{Fe}(\text{CO})_5]$ ^[14] despite a generally held decrease in electrophilicity associated with descending a triad. This protocol finds particularly wide application in the reduction of metal clusters (Scheme 3b)^[15] to provide high nuclearity carbonylates during which CO_2 is liberated. For π -basic and coordinatively saturated metal centers devoid of strong π acids, the possibility arises that CO_2 is retained in the coordination sphere, either as a hydroxycarbonyl group or as $\sigma\text{-CO}_2$ itself (Scheme 3c)^[13] Furthermore, although mechanistically divergent, the use of methoxide as the nucleophile towards CO, can also effect reduction of divalent ruthenium and osmium carbonyl compounds (Scheme 3d).^[16, 17]

The hydroxycarbonyl intermediate $\text{K}[\textbf{5}]$ slowly decarboxy-



Scheme 3. Hieber base reactions with ruthenium and osmium complexes.

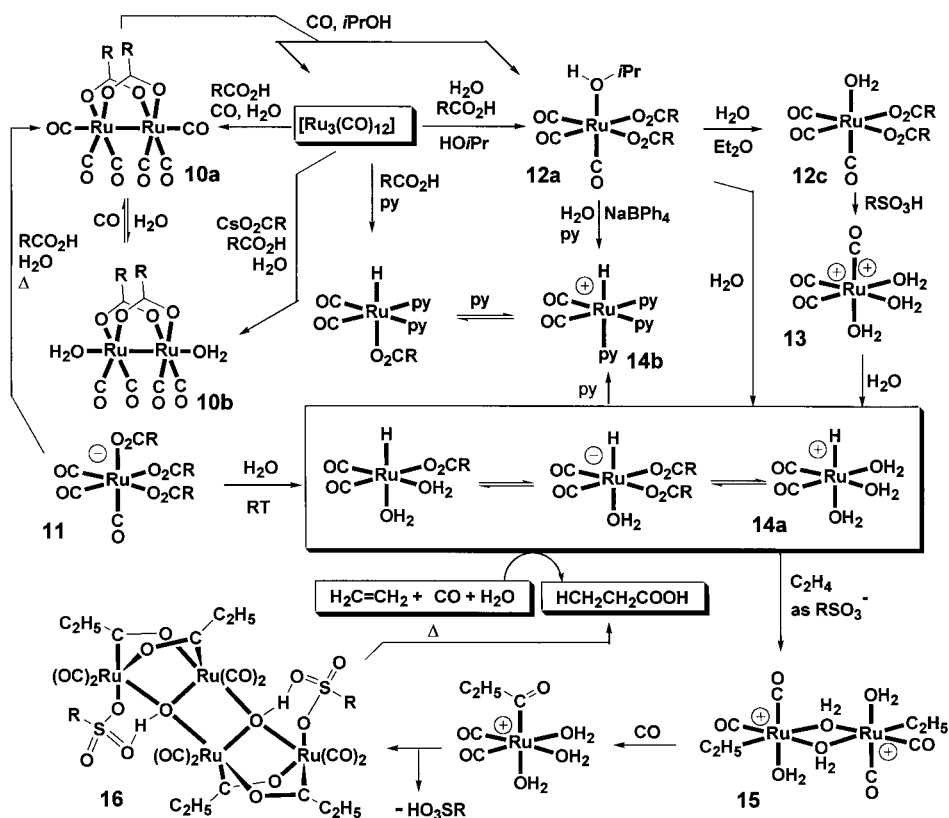
lates when heated to provide a putative hydrido salt $\text{K}[6]$ which has so far defied isolation, due perhaps in part to its strong Brønsted acidity.^[7] Attempts to trap this 16-electron (or possibly solvated or dimeric) complex by carbonylation and formation of $\text{K}[\text{RuHCl}_2(\text{CO})_3]$ perhaps not surprisingly appears to increase the acidity and facile reductive elimination occurs to provide $[\text{Ru}_3(\text{CO})_{12}]$ in excellent yield. Condensing all the steps from “ $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ ” in a one-pot low-pressure procedure provides $[\text{Ru}_3(\text{CO})_{12}]$ directly in 86% yield! The improved access to this already intensely studied compound is highly significant, obviating the use of high-pressure equipment. The assertion that a hydrido complex is indeed involved is however provided by trapping experiments with a range of unsaturated organic compounds: Heating $\text{K}[5]$ in the presence of ethene or toluene provide, respectively, the dinuclear ethyl and stilbenyl complexes $[\text{Ru}_2(\mu\text{-Cl})_3\text{R}_2(\text{CO})_4]^-$ ($\text{R} = \text{CH}_2\text{CH}_2\text{H}$ **7a**, $\text{CPh}=\text{CHPh}$ **7b**) (Scheme 1) which serve as synthetic equivalents in situ for “ $\text{RuCl}(\text{CO})_2\text{R}$ ” in reactions with added ligands, for example, PPh_3 .^[7]

In further studies on the formation of **5**, Lavigne et al. have very recently found a remarkable dependence on conditions and hydroxide source: In concentrated methanol $[\text{Et}_4\text{N}][\text{OH}]$ reacts with **2** to provide the polymeric species $\{[\text{Et}_4\text{N}][\text{Ru}_2(\mu\text{-Cl})_2(\mu\text{-CO})(\text{CO})_4(\mu\text{-Cl})]\}_n$ ($[\text{Et}_4\text{N}][8]$). The repeat unit of this polymer might be described as a $\text{Ru}^{\text{I}}\text{-Ru}^{\text{I}}$ core given that the unique chloro ligand lies equidistant between adjacent diruthenium cores. However, an alternative

mixed-valence $[\text{Ru}^{\text{II}}\text{-Ru}^{\text{0}}]$ description also has instructional merit, that is, one can view the polymer as arising from combination of **3** and “ $\text{Ru}(\text{CO})_2$ ”. Indeed, if the reaction is carried out under an atmosphere of CO, no **8** is observed; rather a mixture of $[\text{Ru}_3(\text{CO})_{12}]$ and $\text{Et}_4\text{N}[\text{3}]$ is obtained. The polymer degrades in acetonitrile to give what is presumed to be a solvated form of the “ $\text{Ru}_2(\mu\text{-Cl})_2(\text{CO})_5(\text{NCMe})_x$ ” anion, for which a rich chemistry may be anticipated.^[8]

A second minor side product is also obtained from $[\text{Et}_4\text{N}]\text{OH}$, **2** (and adventitious Na^+), the yield of which may be increased by the addition of NaHCO_3 . The molecular architecture of the resulting tetraanionic cage **9** can only be described as beautiful, comprising four “ $\text{Ru}_2(\text{CO})_4$ ” units bridged by chloride and carbonate buttresses. The latter arises from CO_2 liberated from the hydroxycarbonyl precursor and if this is purged from the reaction mixture, the formation of **9** is suppressed in favor of the μ -oxo species **4** previously obtained from **3** and moist Et_3N .^[8]

Throughout this chemistry, the role of the chloride ligands has been far from innocent, readily forming bridges in di-, oligo-, and polymeric assemblies (thereby weakly masking potential coordination sites) and as a π -donor presumably moderating the reactivity of the carbonyl ligands. A related “halide-free” chemistry has however emerged from the group of Fachinetti and Funaioli (Scheme 4, $\text{R} = \text{CF}_3$)^[18–20] and the recurrent parallels between the two systems are noteworthy. This chemistry originates from a detailed study of the WGS mediated by $[\text{Ru}_3(\text{CO})_{12}]$ in acidic media ($\text{CF}_3\text{CO}_2\text{H}$, H_2O , diglyme). The species $[\text{Ru}_2(\mu\text{-O}_2\text{CCF}_3)_2(\text{CO})_6]$ (**10a**) and *fac*- $[\text{Ru}(\text{O}_2\text{CCF}_3)_3(\text{CO})_3]^-$ (**11**) underpin the WGS catalytic manifold; however, it is their synthetic utility which perhaps



Scheme 4.

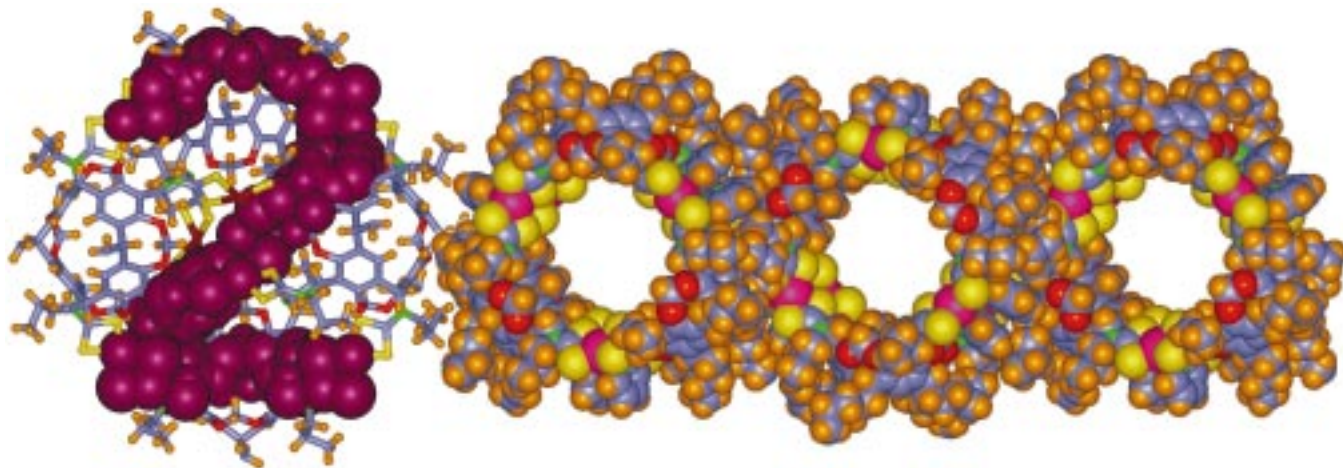
holds the most promise. In the presence of excess trifluoroacetate the former readily disproportionates into the latter and $[\text{Ru}_3(\text{CO})_{12}]$ (recall the implicit carbonylation of **8** to provide **3** and $[\text{Ru}_3(\text{CO})_{12}]$). Under acidic conditions, the latter reacts with water to provide $[\text{Ru}_2(\mu\text{-O}_2\text{CCF}_3)_2(\text{CO})_4(\text{OH}_2)_2]$ (**10b**), hydrogen, and CO_2 . This complex is related to the recently characterized complex $[\text{Ru}_2(\mu\text{-O}_2\text{CCF}_3)_2(\text{CO})_4(\text{NCMe})_2]$ (**10c**), obtained in high yield by Bruce et al. from $[\text{Ru}_3(\text{CO})_{12}]$ and $\text{CF}_3\text{CO}_2\text{H}$ in acetonitrile.^[21] In acid-free THF, the reaction with water appears to give equilibrating hydrido complexes of the form $[\text{RuH}(\text{CO})_2(\text{O}_2\text{CCF}_3)_n\text{L}_{4-n}]^{1-n}$ ($\text{L} = \text{THF}, \text{H}_2\text{O}$). For $n = 1$, thermolysis provides **10b** and hydrogen. A useful substrate to emerge from this work is the complex $[\text{Ru}(\text{O}_2\text{CCF}_3)_2(\text{CO})_3(\text{iPrOH})]$ (**12a**). Although the thf ligand in $[\text{Ru}(\text{O}_2\text{CCF}_3)_2(\text{CO})_3(\text{thf})]$ (**12b**) (obtained by carbonylation of $[\text{Ru}_2(\mu\text{-O}_2\text{CCF}_3)_4(\text{thf})_2]$) is less labile than that of **2**,^[22] the *iPrOH* ligand in **12a** is readily replaced by water to provide the complex $[\text{Ru}(\text{O}_2\text{CCF}_3)_2(\text{CO})_3(\text{OH}_2)]$ (**12c**) simply on recrystallization from moist diethyl ether. This species provides the entry point for a wealth of chemistry of water-soluble organoruthenium compounds, for example, dissolution in acidified (HOTf) water provides the dicationic complex $[\text{Ru}(\text{CO})_3(\text{OH}_2)_3]^{2+}$ (**13**). At higher pH however the carbonyl ligands of this complex are readily attacked by water to provide the hydrido salt *fac*- $[\text{RuH}(\text{CO})_2(\text{OH}_2)_3]\text{OTf}$ (**14a**OTf). As with **4**, **14a** hydrometalates ethene to provide an ethyl derivative; however, in this case water rather than chloride bridges support the adopted dinuclear structure **15**. Carbonylation of **15** results in migratory insertion and formation of the propionyl-bridged complex **16** with coordinated triflate ligands. The tetranuclear assembly is held together by μ_3 -hydroxide bridges, which are intramolecularly hydrogen-bonded to triflate ligands. At high temperatures, however, the propionyl complex generates propionic acid in a catalytic cycle from ethene, CO , water, and hydrogen, which is also mediated by **14a**. The involvement of such thermally robust and acid-stable hydrido, alkyl, and acyl complexes in this system is most impressive.

Further work: From the above it is clear that much has been learnt and remains to be learnt from the study of the “simple” carbonyls of divalent ruthenium, however further directions also present themselves. Kinetic studies on the reactions of KOH with the zerovalent pentacarbonyl complexes $[\text{M}(\text{CO})_5]$ show rates increasing in the order $\text{M} = \text{Fe} \ll \text{Ru} < \text{Os}$.^[14] This trend might reasonably be expected to carry through to the chemistry of the divalent state and therefore make the chemistry of osmium carbonyl chlorides particularly attractive, especially in catalytic applications. Unfortunately at present the synthetic routes to species such as $[\text{Os}_2(\mu\text{-Cl})_2\text{Cl}_2(\text{CO})_6]$ remain far less convenient^[23] than those developed in the ruthenium system. The report of a multi-gram high-yield (83%) synthesis from silica-supported osmium chloride is however encouraging.^[24] Other anionic coligands are also of interest. Parallels have emerged between the chemistries of Lavigne’s chloride and Fachinetti’s trifluoroacetate systems, although at first sight these ligands would appear to have little

in common. The former is soft and π -basic, the latter hard, and yet similar key transformations have been effected. It would therefore seem that there is much scope for coligand variation. Perhaps most timely in this respect is the preparation of carbonyl fluorides, for example, $[\text{Ru}_2(\mu\text{-F})_2\text{F}_2(\text{CO})_6]$ reported by Holloway and Hope.^[25] The potential π and/or Brønsted basicity of coordinated fluoride in such systems offers considerable intrigue (in appropriate solvent systems), perhaps offering a compromise between the properties of chloride and trifluoroacetate ligands. These comments on diversification however in no way distract from the rich organometallic chemistry, which will continue to emerge from the (not so) simple chloro- and trifluoroacetato carbonylruthenium(II) complexes.

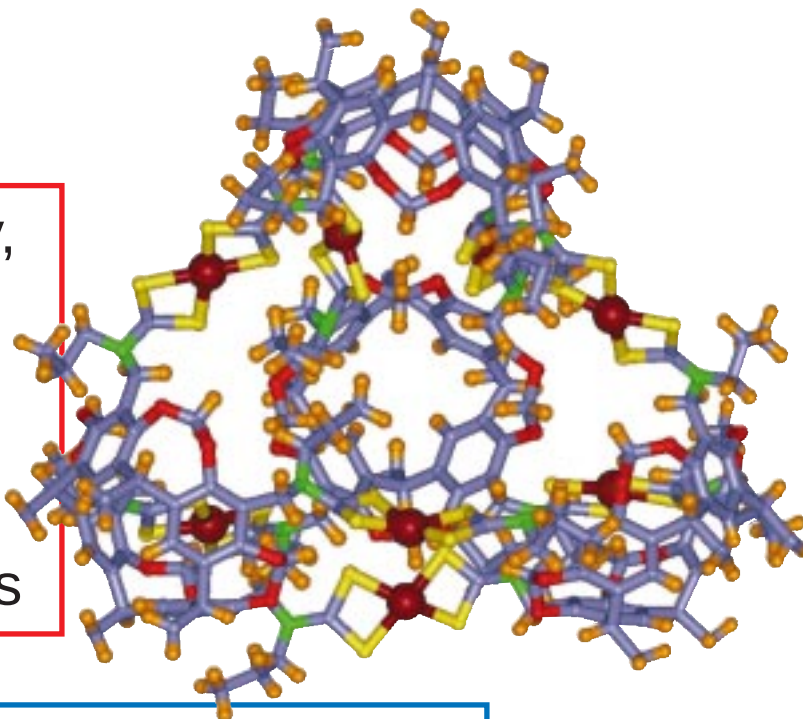
- [1] M. A. Bennett, M. I. Bruce, T. W. Matheson in *Comprehensive Organometallic Chemistry*, Vol. 4 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, pp. 692–694; J. P. Collman, W. R. Roper, *J. Am. Chem. Soc.* **1965**, *87*, 4008.
- [2] M. I. Bruce, F. G. A. Stone, *J. Chem. Soc. A* **1967**, 1238.
- [3] A. F. Hill, A. J. Deeming, R. K. Pomeroy, M. P. Cifuentes, M. G. Humphrey in *Comprehensive Organometallic Chemistry II*, Vol. 7 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1995**.
- [4] G. Lavigne, *Eur. J. Inorg. Chem.* **1999**, 917.
- [5] W. Hieber, E. Becker, *Chem. Ber.* **1930**, *63*, 1405; W. Hieber, H. Vetter *Chem. Ber.* **1931**, *64*, 2340.
- [6] S. Fabre, P. Kalck, G. Lavigne, *Angew. Chem.* **1997**, *109*, 1167; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1092.
- [7] M. Faure, L. Maurette, B. Donnadieu, G. Lavigne, *Angew. Chem.* **1999**, *111*, 539; *Angew. Chem. Int. Ed.* **1999**, *38*, 518.
- [8] L. Maurette, B. Donnadieu, G. Lavigne, *Angew. Chem.* **1999**, *111*, 3919; *Angew. Chem. Int. Ed.* **1999**, *38*, 3707.
- [9] M. J. Cleare, W. P. Griffith, *J. Chem. Soc. A* **1969**, 372.
- [10] N. Lugan, G. Lavigne, J. M. Soulie, S. Fabre, P. Kalck, J. Y. Saillard, J. F. Halet, *Organometallics* **1995**, *14*, 1712.
- [11] P. C. Ford, *Acc. Chem. Res.* **1981**, *14*, 31; P. C. Ford, A. Rokicki, *Adv. Organomet. Chem.* **1988**, *28*, 139.
- [12] D. Choudhury, D. J. Cole-Hamilton, *J. Chem. Soc. Dalton Trans.* **1982**, 1855; D. J. Cole-Hamilton, *J. Chem. Soc. Chem. Commun.* **1980**, 1213.
- [13] H. Tanaka, H. Nagao, S.-M. Peng, K. Tanaka, *Organometallics* **1992**, *11*, 1450.
- [14] D. C. Gross, F. C. Ford, *Inorg. Chem.* **1982**, *21*, 1703.
- [15] G. R. John, B. F. G. Johnson, J. Lewis, *J. Organomet. Chem.* **1979**, *169*, C9; A. G. Cowie, B. F. G. Johnson, J. Lewis, P. R. Raithby, *J. Organomet. Chem.* **1986**, *306*, C63.
- [16] W. Hieber, V. Frey, P. John, *Chem. Ber.* **1967**, *101*, 1961.
- [17] K. R. Grundy, W. R. Roper, *J. Organomet. Chem.* **1976**, *113*, C45; W. R. Roper, *J. Organomet. Chem.* **1986**, *300*, 167.
- [18] G. Fachinetti, T. Funaioli, F. Marchetti, *J. Organomet. Chem.* **1995**, *498*, C20.
- [19] G. Fachinetti, T. Funaioli, L. Lecci, F. Marchetti, *Inorg. Chem.* **1996**, *35*, 7217.
- [20] T. Funaioli, C. Cavazza, F. Marchetti, G. Fachinetti, *Inorg. Chem.* **1999**, *38*, 3361.
- [21] M. I. Bruce, B. W. Skelton, A. H. White, N. N. Zaitseva, *Aus. J. Chem.* **1999**, *52*, 621.
- [22] A. J. Lindsay, G. Wilkinson, M. Motevalli, M. B. Hursthouse, *J. Chem. Soc. Dalton Trans.* **1987**, 2723.
- [23] L. A. W. Hales, R. J. Irving, *J. Chem. Soc. A* **1967**, 1932; W. A. Herrmann, E. Herdtweck, A. Schaefer, *Chem. Ber.* **1988**, *121*, 1907; W. Hieber, H. Stallmann, *Chem. Ber.* **1942**, *75*, 1472; R. Psaro, C. Dossi, *Inorg. Chim. Acta* **1983**, *77*, L255.
- [24] D. Roberto, R. Psaro, R. Ugo, *Organometallics* **1993**, *12*, 2292.
- [25] K. S. Coleman, J. H. Holloway, E. G. Hope, *J. Chem. Soc. Dalton Trans.* **1997**, 1713.

Nanoscale Molecular Hosts and Containers



Zinc(II) ions assemble molecular loops from calixresorcarene ligands

More remarkably, copper(III) ions assemble a molecular tetrahedron of calixresorcarenes



Find out more about this new family of nanosized hosts on the following pages

Resorcarene-Based Nanoarchitectures: Metal-Directed Assembly of a Molecular Loop and Tetrahedron**

O. Danny Fox, Michael G. B. Drew, and Paul. D. Beer*

*Dedicated to Professor Jean-Marie Lehn
on the occasion of his 60th birthday*

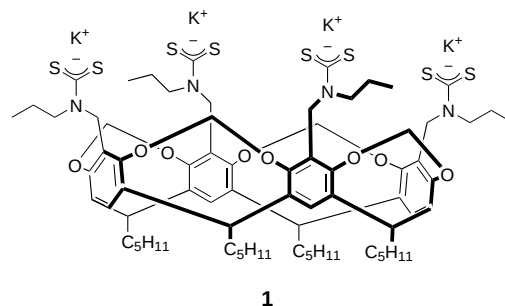
Nature employs both covalently bonded and self-assembled protein shells to store, protect, and transport inorganic and organic molecules. Both naturally occurring and synthetic molecular containers offer the possibility of synthesizing and/or stabilizing novel molecules and materials within their frameworks.^[1] Metal ions in conjunction with ligands are particularly suited to the assembly of molecular architectures and may confer upon the resulting structures a variety of properties—such as charge, magnetism, color, and chemical and redox activity—that are much more difficult to attain with purely organic molecules.^[2] Because assembly of such molecules with labile metal ions is often a thermodynamically driven process,^[3] yields of self-assembled containers can often far exceed those of containers created by formation of covalent bonds.^[4] Frequently, these assembly-driven processes can be controlled, for example, by templation of the host architecture around guest molecules or ions.

Calixarene-based molecules can be multiply functionalized with a variety of ligating moieties, and their bowl shape lends them amenable to formation of host structures suitable for the binding of guest molecules.^[5] Although there are now numerous examples of hydrogen-bonded, self-assembled calixarene-based dimers,^[6] the synthesis of larger molecular containers involving assembly of multiple units is still very much in its infancy.^[7] Dimeric, calixarene-based molecular capsules formed by metal-induced self-assembly processes have been synthesized,^[8] and a recent example has been shown to bind guest molecules as a function of pH value.^[9]

Here we present preliminary findings concerned with the design and synthesis of metal-assembled molecular containers whose structures can be varied by choice of metal ion and its respective oxidation state(s). We detail the synthesis of nanosized molecular structures assembled from dithiocarbamate–resorcarene ligand units and copper or zinc ions. The dithiocarbamate unit is a most versatile ligand with a rich history of coordination chemistry, but remarkably has not yet been exploited in the field of self-assembly.^[10] The ability of this ligand to stabilize metal ions in a range of oxidation states and coordination geometries offers plenty of opportunity for

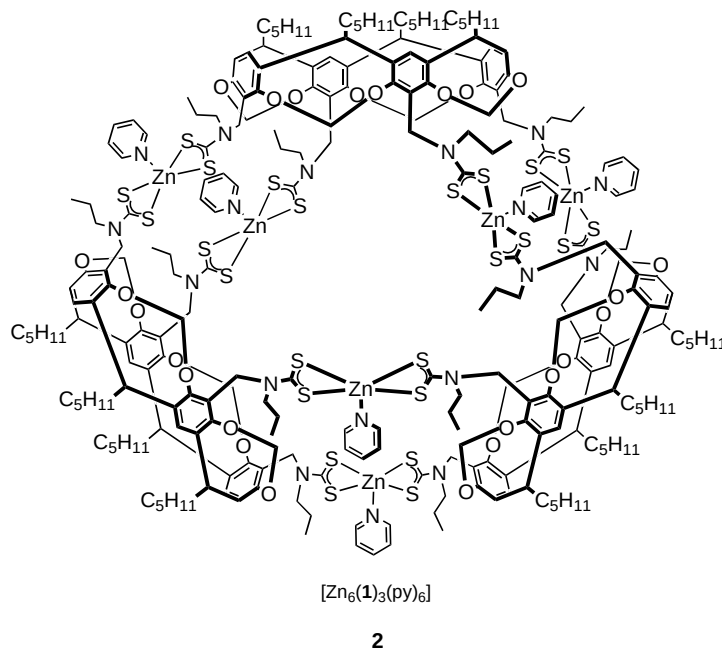
the generation of novel self-assembled molecular architectures with unique properties.

Dithiocarbamate (dtc) **1** is prepared by treatment of a solution of the parent resorcarene secondary amine^[18] in ethanol/water with carbon disulfide and potassium hydroxide. This bowl-shaped ligand is functionalized with four *N*-propyl(dtc) ligating moieties and possesses a potential C_4 axis. Although the potassium salt of **1** could be isolated by



removal of the solvent, in all cases polynuclear metal complexes were prepared directly by treatment of **1** in ethanol/water with metal(II) acetate to afford the crude compounds as powders.

Recrystallization of the zinc(II) complex from pyridine(py)/water gives large, yellow, prismatic crystals of molecular loop $[Zn_6(\mathbf{1})_3(\text{py})_6] \cdot 7.5 \text{ EtOH}$ (**2** · 7.5 EtOH). The structure of this



hexanuclear zinc(II) complex is shown in Figure 1. Nanosized complex **2** is, to the best of our knowledge, the first structure of a metal-assembled, trimeric, calixarene-based molecule and the first example of a calixarene-based molecular loop or ring.

There is one independent zinc atom and the species has crystallographic 32 symmetry. The three resorcarene cups provide the corners for an equilateral molecular triangle with two zinc ions positioned at the midpoints of each side.^[11] The zinc(II) ions are five-coordinate, with two bidentate dtc

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[**] This work was supported by AWE Aldermaston. We thank Dr. N. Rees for MALDI-TOF mass spectrometry, and the EPSRC and University of Reading for funds for the Image Plate System.

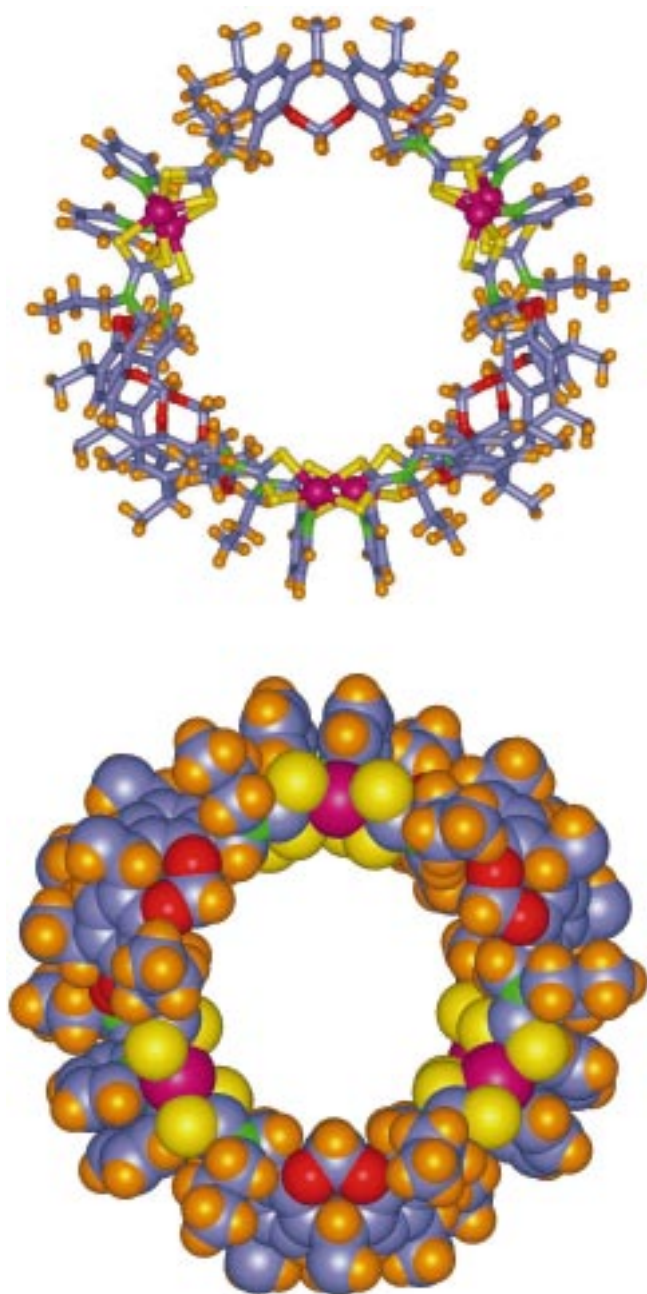


Figure 1. Molecular structure of zinc(II)-assembled molecular loop **2**. Top: Ball-and-stick representation; bottom: CPK representation. In both pictures the *n*-butyl chains from the base of the resorcarene have been omitted for clarity. Zn: pink, S: yellow, O: red, N: green, C: blue, H: orange.

moieties forming the square plane (Zn–S 2.424(2)–2.520(2) Å); the fifth, axial site is occupied by a pyridine molecule (Zn–N 2.086(6) Å), which pulls the metal ion above the square plane by 0.58 Å. Two metal–ligand bridges are formed between adjacent resorcarenes from a pair of non-interacting NCS₂–Zn–S₂CN moieties on opposite sides of the bowl. Adjacent zinc atoms are 6.61 Å apart; across the cavity opposite zinc atoms are 14.69 Å apart. The sides of an equilateral triangle (defined by carbon atoms close to the base of each resorcarene bowl) are 19.1 Å in length (see Figure 4).^[12] Although based on a triangle of resorcarene cups, space-filling models reveal the cavity to be circular; the

diameter of this circle is approximately 16.4 Å. The cavity contains 7.5 ethanol molecules (not shown), but apart from these guest molecules appears mostly unoccupied. In the solid state each trimeric resorcarene loop is surrounded by six neighbors. Interestingly, the packing of these loops in the crystal lattice generates a “molecular honeycomb” (Figure 2).

Characteristic but unexpectedly broad resonances due to the resorcarene structure are observed in the ¹H NMR

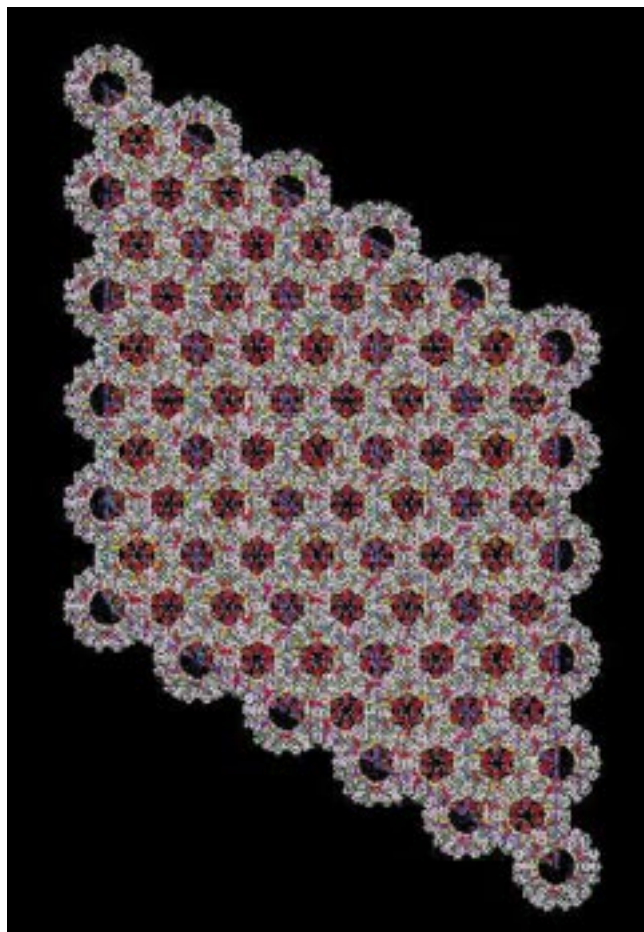
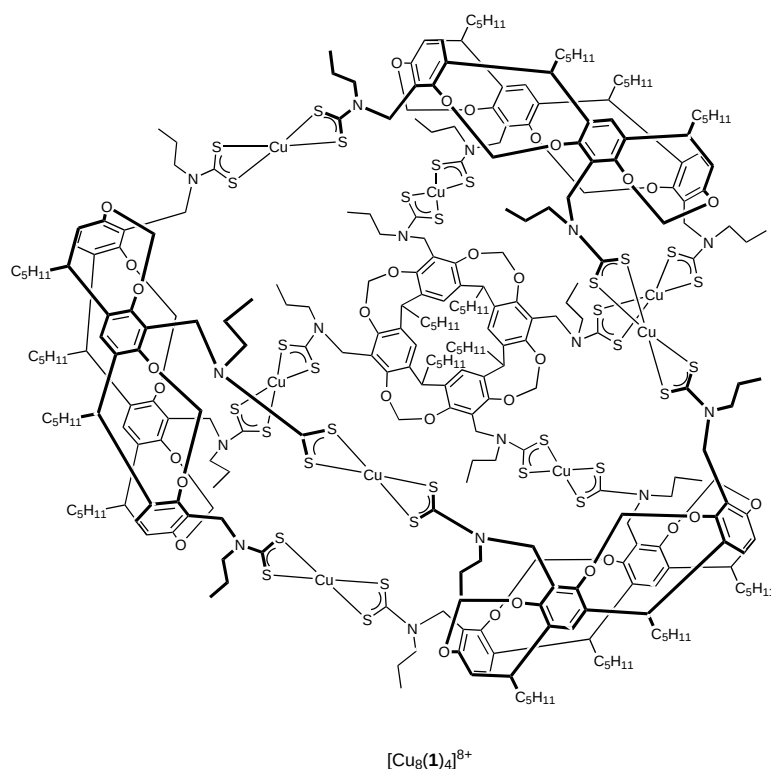


Figure 2. View down the unique *c* axis in the crystal structure of **2**, showing the “molecular honeycomb” formed by the packing of the individual loops. The cavity is sparsely occupied by a few disordered solvent molecules.

spectrum of **2** ([D₈]toluene, 23 °C), which sharpen considerably on heating to 80 °C. We attribute this broadening to slow rotation around the C–N bonds of the Zn(dtc)₂ units, resulting in the presence of numerous stereoisomers (*syn* or *anti*) within the molecular aggregate.^[10, 13] Investigation of **2** by MALDI-TOF mass spectrometry gave only ions corresponding to fragmentation of the trimeric resorcarene structure into monomeric species, for example 1597 [(1–H⁺)Zn₃]⁺; 1621 [(1–2H⁺)Zn₃Na]⁺.

Treatment of **1** with copper(II) acetate provided an intermediate copper(II) complex **3**, which was oxidized to the octanuclear copper(III) complex [Cu₈(**1**)₄][I₃]₇[I]·6H₂O (**4**) by treatment with iodine; complex **4** was isolated as a mixed triiodide/iodide salt.^[14] The structure of octacation [Cu₈(**1**)₄]⁸⁺ in **4** (which displays *S*₄ symmetry) is shown in Figure 3. We believe **4** to contain the first example of a metal-assembled,



tetrameric resorcarene structure to be crystallographically characterized. Four resorcarene ligands lie at the apices of a distorted tetrahedron, and are connected to each other by eight copper(III) ions.^[15] To form a tetrahedral array, geometrical requirements dictate that at two sides of the tetrahedron two copper ions are coordinated to the same resorcarene. The gross structural effect of this is to distort the symmetry of the molecule, twisting the cups of the resorcarenes away from the line of the apices and resulting in a flattening of the tetrahedron (Figure 4). The sides of the tetrahedron differ therefore, with two being 25.0 and four being 19.5 Å in length. The assembly of **4** is, to our knowledge, the first example of copper(III) in the role of self-assembly. Indeed the synthesis of an octanuclear copper(III) complex is in itself unusual.

Crystallographically there are two unique copper(III) ions present in **4**. Each copper(III) ion is chelated by two bidentate dtc moieties in an approximately square-planar fashion. The C–S bond distances (2.11(2)–2.47(2) Å) are consistent with those reported previously in mononuclear $[\text{Cu}^{\text{III}}(n\text{Bu}_2\text{-dtc})_2][\text{I}_3]$ complexes.^[16, 17] The variance in Cu–S bond lengths is most probably a consequence of stress forces applied to the metal–ligand bonds due to the imperfect arrangement of the four resorcarene units. Seven triiodide and one iodide anions are associated with the cationic octamer. There are weak apical interactions between the copper centers and the triiodide anions (Cu2–I 3.26, Cu1–I 3.19 Å). Interestingly for Cu1 a triiodide anion bridges between two adjacent copper centers (both Cu1) of a tetrahedron, generating a Cu–I(I₂)–Cu complex, with a much shorter Cu⋯Cu distance (4.98 Å). Notably, both ends of the linear triiodide molecule are coordinated by copper ions, and

this links the tetrahedra to each other through the crystal lattice.

Magnetic susceptibility measurements (250–300 K) determined that crystals of **4** are diamagnetic. This is consistent with the pseudo-square-planar nature of the

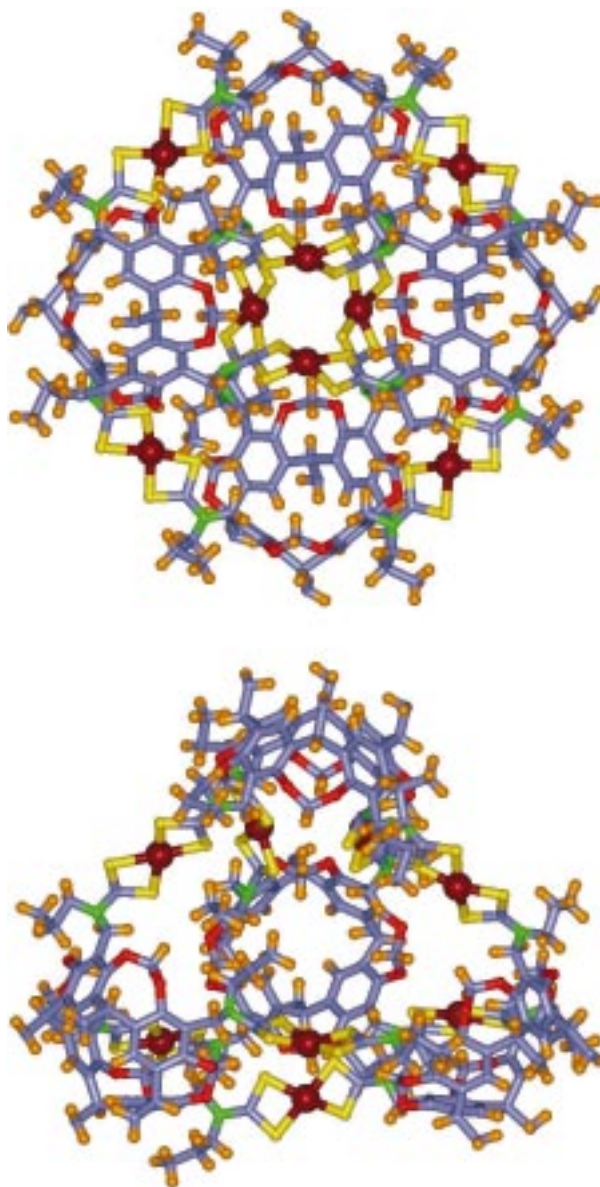


Figure 3. Two views of the molecular structure of the octacation $[\text{Cu}_8(\mathbf{1})_4]^{8+}$ in **4** shown as ball-and-stick representations. The *n*-butyl chains from the base of the resorcarene are omitted for clarity. Cu: dark red, S: yellow, O: red, N: green, C: blue, H: orange.

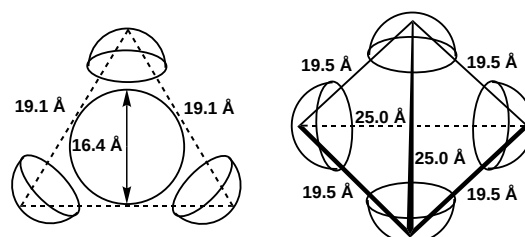


Figure 4. Cartoon representations of the geometrical shapes formed by structures **2** (left) and **4** (right).

d⁸ copper(III) centers, and more importantly shows that oxidation of all copper(II) ions occurs. Complex **4** is insoluble in nonpolar solvents, and upon dissolution in polar or protic solvents such as pyridine or methanol **4** is reduced back to a copper(II) complex. Spontaneous reduction of [Cu^{III}(dtc)₂][I₃] complexes in polar solvents has been reported previously.^[16] The ¹H NMR spectra of **4** prepared in situ by oxidation of **3** with iodine in CDCl₃ or C₆D₆ give resonances that are characteristic of the resorcarene structure but, like those of **2**, are broad and uninformative.

If **4** is observed down one of the four possible C₃ axes, a portal suitable for guest inclusion can clearly be discerned. The size of each portal can be crudely defined as an approximate equilateral triangle with copper atoms occupying the corners. The Cu...Cu distances—that is, the sides of this triangle—are approximately 14 Å. This is clearly a large enough gateway through which a large guest molecule could potentially pass. The center of the tetrahedron (at 0, 0, 1/2) is a crystallographic S₄ site and has eight copper neighbors, four at 7.283 Å and the remaining four at 10.19 Å. The Cu...Cu distances across the tetrahedron can reach as high as 20.4 Å, clearly demonstrating the large size of the cavity.

In conclusion, we have demonstrated the facile, metal-assembled synthesis of trimeric and tetrameric resorcarene host architectures and characterized their solid-state structures. Clearly, a number of factors are involved in the assembly processes including the choice of metal, its oxidation state, and possibly the nature of the anion. Furthermore, we conjecture that the incorporation of redox-active metal–ligand moieties within these nanohosts confers upon them a range of novel physical properties that may allow them to sense, report, and possibly even facilitate chemical reaction of their guest substrates.

Experimental Section

The parent secondary amine tetrakis[(propylamino)methyl]resorcarene was prepared following the method of Boerrigter et al.^[18]

2: To solution of tetrakis[(propylamino)methyl]resorcarene (1.0 g, 0.92 mmol) and potassium hydroxide (0.216 g, 3.96 mmol) in ethanol/water (100 mL/50 mL) was added carbon disulfide (0.294 g, 4.0 mmol), and the solution stirred for 2 h.^[22] Zinc(II) acetate hydrate (0.41 g, 2.0 mmol) was added and the mixture allowed to stir overnight. The white precipitate that formed was removed by filtration and recrystallized from dichloromethane/ethanol. Crystals suitable for X-ray structure analysis were grown by slow vapor diffusion of water into a solution of **2** in pyridine (0.95 g, 62%). Crystals of **2** appear to desolvate on removal from mother liquor. Elemental analysis calcd for [Zn₆(**1**)₃(py)₆](C₂₄₆H₃₁₈N₁₈O₂₄S₂₄Zn₆): C 58.24, H 6.32, N 4.97; found: C 58.29, H 6.62, N 5.23.

Crystallographic data for [Zn₆(**1**)₃(py)₆].7.5EtOH (**2**·7.5EtOH; C₂₆₁H₃₆₃N₁₈O_{31.5}S₂₄Zn₆): *M*_r = 5418.3, rhombohedral, space group *R*3̄c, *a* = 36.98(4), *c* = 56.52(6) Å, *V* = 66 945 Å³, *Z* = 6, ρ_{calcd} = 0.806 g cm^{−3}, *F*(000) = 17 226, μ = 0.470 mm^{−1}; of 23 468 data measured on a Mar Research Image Plate with MoK_α radiation (λ = 0.71073 Å; *T* = 293 K, θ_{max} = 26.03°), 11 762 were independent (*R*(int) = 0.0853). Data analysis was carried out with the XDS program.^[19] The structure was determined by direct methods. Non-hydrogen atoms were included with anisotropic thermal parameters, and hydrogen atoms in calculated positions. A total of 44 distance constraints were included for the alkyl chains. No absorption correction was applied. The structure was refined on *F*² with Shelx97^[20] to give *R*1 = 0.1033 and *wR*2 = 0.2847 for 4279 data with *I* > 2σ(*I*) and *R*1 = 0.2012 and *wR*2 = 0.3350 for all data.^[21]

4: To a solution of tetrakis[(propylamino)methyl]resorcarene (1.0 g, 0.92 mmol) and potassium hydroxide (0.216 g, 3.96 mmol) in ethanol/water

(100 mL/50 mL) was added carbon disulfide (0.294 g, 4.0 mmol), and the solution stirred for 2 h.^[22] Copper(II) acetate (0.41 g, 4.0 mmol) was added, and the mixture allowed to stir overnight. The fine, dark brown powder that formed was removed by filtration and recrystallized from dichloromethane/ethanol to give **3** (0.88 g, Iodine (40 mg, 0.157 mmol) in toluene (20 mL) was added dropwise over 20 min to a stirred solution of **3** (50 mg) in chloroform (20 mL). The resulting red-brown solution was filtered, then allowed to stand and after two weeks gave black prismatic crystals of **4** (42 mg). Elemental analysis calcd for [Cu₈(**1**)₄][I₃]₇[I]·6H₂O (C₂₈₈H₃₉₆I₂₂N₁₆O₃₈S₃₂Cu₈): C 38.36, H 4.43, N 2.49; found: C 37.94, H 4.30, N 2.15.

Crystallographic data for [Cu₈(**1**)₄][I₃]₇[I]·6H₂O (**4**; C₂₈₈H₃₉₆I₂₂N₁₆O₃₈S₃₂Cu₈): *M*_r = 9036.15, tetragonal, space group *P*4₂1c, *a* = 32.09(4), *c* = 23.91(3) Å, *V* = 24 626 Å³, *Z* = 2, ρ_{calcd} = 1.219 g cm^{−3}, *F*(000) = 8908, μ = 1.90 mm^{−1}; of 24 807 data measured on a Mar Research Image Plate with MoK_α radiation (λ = 0.71073 Å; *T* = 293 K, θ_{max} = 22.58°), 10 192 were unique (*R*(int) = 0.0919). The data analysis was carried out with XDS.^[19] The structure was determined by direct methods. Only the iodine atoms were refined anisotropically. The three triiodide anions were refined with occupancies of 1.0, 0.65, and 0.10, respectively. In addition there was an iodide atom with a population parameter of 0.25. A total of 125 distance constraints proved necessary for convergence, primarily over the alkyl chains. The phenyl rings were refined as rigid groups. No absorption correction was applied. The structure was refined on *F*² with Shelx^[20] to give *R*1 = 0.1450 and *wR*2 = 0.3522 for 3229 data with *I* > 2σ(*I*) and *R*1 = 0.2400 and *wR*2 = 0.3942 for all data.^[21]

Received: August 23, 1999 [Z13910]

- [1] a) T. Douglas, M. Young, *Nature* **1998**, 393, 152–155; b) D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem.* **1991**, 103, 1048–1051; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1024–1027.
- [2] Recent reviews: a) R. W. Saalfrank, B. Demleitner in *Transition Metals in Supramolecular; Perspectives in Supramolecular Chemistry* (Ed.: J. P. Sauvage), Wiley-VCH, Weinheim, **1999**, 5, 1–51; b) R. W. Saalfrank, I. Bernt, *Curr. Opin. Solid State Mater. Sci.* **1998**, 3, 407–413; c) M. Fujita, *Chem. Soc. Rev.* **1998**, 27, 417–425; d) C. J. Jones, *Chem. Soc. Rev.* **1998**, 27, 289–299; e) B. Linton, A. D. Hamilton, *Chem. Rev.* **1997**, 97, 1669–1680; f) P. N. W. Baxter in *Comprehensive Supramolecular Chemistry*, Vol. 9 (Eds.: J. P. Sauvage, M. W. Hosseini), Pergamon, Oxford, **1996**, 165–211.
- [3] M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi, K. Ogura, *Nature* **1995**, 378, 469–471.
- [4] D. J. Cram, M. J. Cram in *Container Molecules and Their Guests, Monographs in Supramolecular Chemistry* (Ed.: J. F. Stoddart), The Royal Society of Chemistry, Cambridge, **1994**, and references therein.
- [5] D. M. Roundhill, *Prog. Inorg. Chem.* **1995**, 43, 533–592.
- [6] M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, 97, 1647–1668, and references therein.
- [7] L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, 389, 469–472.
- [8] a) E. Dalcanele, P. Jacopozzi, *Angew. Chem.* **1997**, 109, 665–667; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 613–615; b) K. Fujimoto, S. Shinkai, *Tetrahedron Lett.* **1994**, 35, 2915–2918.
- [9] O. D. Fox, N. K. Dalley, R. G. Harrison, *J. Am. Chem. Soc.* **1998**, 120, 7111–7112.
- [10] D. Coucouvanis, *Prog. Inorg. Chem.* **1979**, 26, 301–469.
- [11] Recent examples of triangular based complexes: a) J. R. Hall, S. J. Loeb, G. K. H. Shimizu, G. P. A. Yap, *Angew. Chem.* **1998**, 110, 130–133; *Angew. Chem. Int. Ed.* **1998**, 37, 121–123; b) R. D. Schenbeck, L. Randacio, E. Zangrando, B. Lippert, *Angew. Chem.* **1998**, 110, 128–130; *Angew. Chem. Int. Ed.* **1998**, 37, 119–121; c) D. Whang, K. M. Park, J. Heo, P. Ashton, K. Kim, *J. Am. Chem. Soc.* **1998**, 120, 4899–4900.
- [12] The triangle is defined by three carbon atoms situated at the base of the resorc[4]arene ligand (C28a, C28b, and C28e).
- [13] Q. J. McCubbin, F. J. Stoddart, T. Welton, A. J. P. White, D. J. Williams, *Inorg. Chem.* **1998**, 37, 3753–3758.
- [14] To date, we have been unsuccessful in our attempts to obtain crystals of **3** suitable for an X-ray structure determination.
- [15] a) D. L. Caulder, K. N. Raymond, *J. Chem. Soc. Dalton Trans.* **1999**, 1185–1200, and references therein; b) C. Bruckner, R. E. Powers, K. N. Raymond, *Angew. Chem.* **1998**, 110, 1937–1940; *Angew. Chem.*

- Int. Ed.* **1998**, 37, 1837–1839; c) J. S. Fleming, K. L. V. Mann, C. A. Carraz, E. Psillakis, J. C. Jeffery, J. A. McCleverty, M. D. Ward, *Angew. Chem.* **1998**, 110, 1315–1318; *Angew. Chem. Int. Ed.* **1998**, 37, 1279–1281; d) R. W. Saalfrank, R. Burak, A. Breit, D. Stalke, R. Herbst-Irmer, J. Daub, M. Porsch, E. Bill, M. Muther, A. X. Trautwein, *Angew. Chem.* **1994**, 106, 1697–1699; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1621–1623.
- [16] a) J. G. Wijnhoven, T. E. M. van den Hark, P. T. Beurskens, *J. Cryst. Mol. Struct.* **1972**, 2, 189–196; b) G. M. Larin, G. A. Zvereva, P. A. Kozmin, T. B. Larina, M. D. Svazhskaya, *Izv. Akad. Nauk SSSR Neorg. Mater.* **1984**, 20, 530–533; *Inorganic Materials (Engl. Transl.)* **1984**, 20, 451.
- [17] R. M. Golding, C. M. Harris, K. J. Jessop, W. C. Tennant, *Aust. J. Chem.* **1972**, 25, 2567–2576.
- [18] H. Boerrigter, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1997**, 62, 7148–7155.
- [19] W. Kabsch, *J. Appl. Crystallogr.* **1988**, 21, 916.
- [20] SHELXL, Program for Crystal Structure Refinement, G. M. Sheldrick, Universität Göttingen, **1997**.
- [21] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-133532 (**2**) and CCDC-133533 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [22] At this point, removal of the solvent under reduced pressure affords the potassium salt of the dtc ligand [**K**₄] [**1**]: ¹H NMR (300 MHz, [D₆]DMSO): δ = 7.47 (4H, s, ArH), 5.95 (4H, d, OCH₂O outer), 5.18 (8H, s, ArCH₂), 4.67 (4H, t, ArCHCH₂H), 4.15 (4H, d, OCH₂O inner), 2.2–2.4 (8H, br. m, CH₂), 1.05–1.25 (40H, br. m, CH₂), 0.81 (12H, t, CH₃), 0.55 (12H, t, CH₃); ES-MS (positive-ion): *m/z* calcd for [C₇₂H₉₆N₄O₈S₈K₅]⁺: 1595.23; found: 1595.51.

Carbohydrates Exhibit a Distinct Preferential Solvation Pattern in Binary Aqueous Solvent Mixtures**

Aleksey Vishnyakov, Göran Widmalm, and Aatto Laaksonen*

Many substances are readily soluble in solvent mixtures but not in the pure components and vice versa.^[1] Some examples of such solvents are binary mixtures of water, alcohols, acetonitrile, and dimethyl sulfoxide (DMSO), including both aqueous and nonaqueous mixtures of them. Selective solvation of ions from salts in mixed solvents is another, early

discovered, property. The classic example is the heteroselective solvation of the ions of silver nitrate in a water–acetonitrile mixture, as demonstrated in 1958 by Strehlow and Koeppe in a Hittorf experiment.^[2] They found that in an equimolar solvent mixture, the nitrate anions were mainly solvated by the water molecules, while the silver cations were approximately four times more solvated by acetonitrile than by water molecules, although acetonitrile is generally known to solvate cations poorly. The unusual solvation properties of some binary liquid mixtures can, to a large extent, be related to a strong deviation from the ideality of Raoult's law. For example, the guide “like dissolves like” is challenged in the mixture of the highly polar molecules water and acetonitrile. This particular mixture exhibits a liquid–liquid separation, with an upper critical point at –1 °C at 38 mol % of acetonitrile. Both IR measurements^[3, 4] and computer simulations^[5, 6] have confirmed the existence of “micro-heterogeneities” and conglomerate water structures at higher acetonitrile concentrations. The often peculiar properties of liquid mixtures have fascinated many, including Mendeleev, who studied the nonideal behavior of water–alcohol mixtures some 130 years ago.^[7] The ions of salts are not the only examples of selectively solvated species in mixed solvents. Many amphiphilic^[8] and biomolecular systems^[1] are better dissolved in mixtures, as a result of preferential solvation.

We have studied a model disaccharide molecule (α -D-Manp-(1→3)- β -D-Glcp-OMe, **1**) in a mixture of DMSO and water. The solvent mixture is not needed for the purpose of increasing solubility, since disaccharides easily dissolve in both water and DMSO. Our emphasis is to study the resulting preferential solvation of the disaccharide and to learn about the behavior of the 1:3 DMSO–water molar mixture used. We would stress that the characteristic properties of the solvent mixture itself are very different from those of either water or DMSO. Based on neutron diffraction^[9] and computer simulation studies,^[10, 11] it has been suggested that DMSO–water mixtures contain complexes with either two or three water molecules attached to one DMSO molecule, held together by hydrogen bonds, as shown schematically in Figure 1. Near to its astonishingly low freezing point of –62 °C (roughly 80 °C below the freezing point of pure DMSO), the 1:3 mixture of DMSO and water behaves essentially like a one-component system.^[12] Our own molecular dynamics (MD) simulations of this 1:3 DMSO–water, both at +15 and –50 °C, confirm that hydrogen-bonded associates (Figure 1) are formed. Besides being a popular cryosolvent, DMSO–water mixtures have been used in applications ranging from antibacterial activity to membrane permeability.^[13] Most of these effects are, however, still not well understood. The solvation of carbohydrates in the DMSO–water mixture should be of some broader interest, not least because this group of biomolecules is associated with cell membranes and is involved in processes such as cell–cell recognition.^[14]

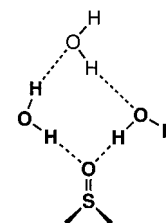


Figure 1. Schematic representation of a 1:3 DMSO–water complex in the binary mixture, observed in MD simulations of the mixture.

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[**] This work has been supported by the Swedish Natural Science Research Council (NFR), the Nordic Minister Council, and the Swedish Institute.

MD simulations have been very helpful in the investigation of water structures around carbohydrates.^[15] From these studies, a complex and highly anisotropic hydration structure has been reported. We have recently studied **1** solvated in water and in a 1:3 DMSO–water mixture^[16] using MD and compared the simulation results to data from NMR measurements.^[17] One important purpose of the previous study was to critically evaluate several sets of force-field models for the disaccharide–DMSO–water system, which involves many different types of competing intermolecular interactions.^[16] In the present work we have carried out a new simulation with a larger system and used the force fields previously found to agree best with the experiment regarding the overall reorientational motion, proton–proton distances, and the conformation of the disaccharide. Simulations were carried out in an NPT ensemble at 1 atm pressure and at 288 K. The total simulated time was 1.3 ns, and reported properties were averaged over the last 1.0 ns.

In the present study, throughout the 1 ns simulation, the *trans*-glycosidic torsional angles φ ($H1_m-C1_m-O3_g-C3_g$) and ψ ($H3_g-C3_g-O3_g-C1_m$), where m and g denote mannose and glucose residues, respectively, stayed in a stable conformation with their librational motion close to -33° and $+56^\circ$, respectively. The resulting *trans*-glycosidic $H1_m-H3_g$ proton–proton distance of 2.41 Å agrees very well with the experimental value of 2.45 Å by Mäler and coworkers.^[17] In this conformation, an intramolecular inter-residue hydrogen bond is formed between the hydroxymethyl (CH_2OH) group in the mannosyl residue and a hydroxyl group in the glucosyl residue, namely, from $HO6_m$ as a donor to $O2_g$ as an acceptor (Figure 2).

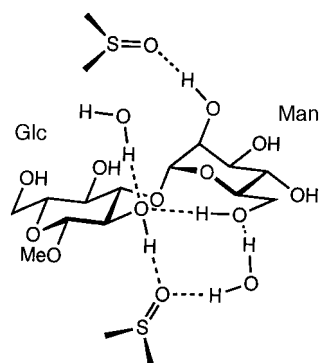


Figure 2. Schematic representation of the disaccharide **1**. Preferential solvation by the binary DMSO–water mixture, identified from MD simulations, is shown with a hydrogen bonded associate of solvent molecules together with an intramolecular hydrogen bond. In addition, a water molecule acting as a hydrogen bond donor and a DMSO molecule preferentially solvate the hydroxyl groups of the solute molecule.

The characteristic features of the solvation structure around the disaccharide stem from the rich variety of solute–solvent hydrogen bonds. Due to the large number of hydroxyl groups, able to serve both as hydrogen bond donors and acceptors, carbohydrates generally impose a strong anisotropic structuring on the surrounding associated solvent. Our disaccharide is no exception. In addition to a well-defined first solvation shell, we can even observe the second shell around it. Water and DMSO both compete as hydrogen bond acceptors, but only water can serve as a hydrogen bond donor to the oxygen atoms of the hydroxyl groups. This gives a clear preference for water to enter the first solvation shell. The DMSO:water molar ratio in the first shell was estimated to 1:5, which is considerably lower than the overall molar ratio of 1:3 in the

bulk solvent. The composition of the second shell is close to that of the surrounding bulk solvent.

Details on the structure of the first solvation shell can be obtained from the radial distribution functions (RDFs), calculated between the solvent molecules and each oxygen atom of **1**. The oxygen–oxygen RDFs for $O4_m$ and $O2_g$ and the oxygen atom of the solvent (both water and DMSO) are shown in Figure 3. All RDFs between the hydroxyl groups and the oxygen atoms of the solvents exhibit a pronounced first peak due to hydrogen bonding. There is, however, a clear competition between water and DMSO as proton acceptors to the hydroxyl groups. We can see that the $O4_m$ oxygen atom prefers water molecules, while $O2_g$ dominantly selects DMSO as a proton acceptor.

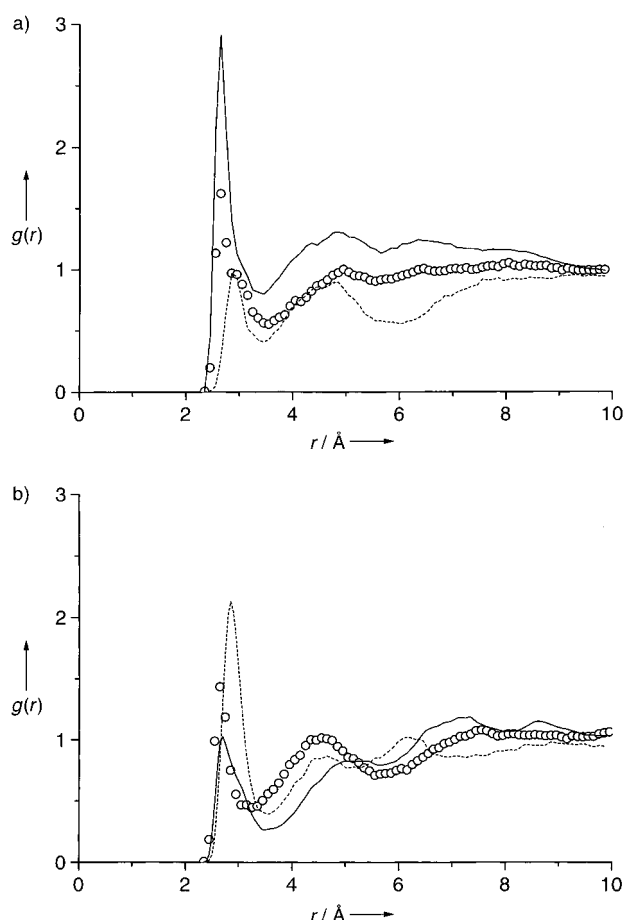


Figure 3. Oxygen–oxygen RDFs for two different oxygen atoms of **1** ($O4_m$ (a), $O2_g$ (b)) and the oxygen atom of the solvent (water (—), DMSO (---)) in the water–DMSO solution. In addition the RDFs for $O_{sugar}-O_{water}$ in the α -D-Manp-(1 $\rightarrow$ 3)- β -D-Glcp-OMe–water system are represented by circles.^[16]

The traditional analysis of solvation structure using the RDF method can be extended by the use of the three-dimensional spatial distribution function (SDF).^[18] This has been done for the two-component solvent DMSO–water around **1** (Figure 4). Although the resulting first solvation shell has the same characteristic structure as that formed by water molecules in a pure aqueous solution,^[16] a distinct preferential solvation pattern can be identified close to the

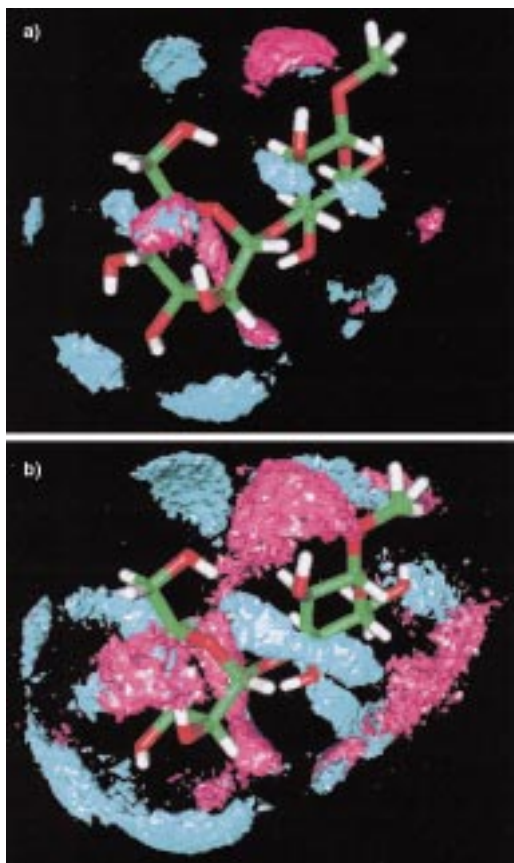


Figure 4. Time-averaged positions of each atom of **1** in a reference coordinate system, and contoured surfaces showing high, positive deviation of the solvent oxygen atom density from the average values. The colour intensity is a function of the probability of finding a certain atom in a certain place related to the average number density. In (a) the intensity is 12.0 and in (b) the intensity is 6.0. Atomic coloring is green for carbon, red for oxygen, and white for hydrogen. Isointensity contours colors are blue for water oxygen atoms and pink for DMSO oxygen atoms. The figures are produced with the "gOpenMol" package.^[19]

different hydroxyl groups. For example, DMSO acts as a hydrogen bond acceptor and solvates predominantly the regions close to HO_{2g} and HO_{2m} (see also Figure 2). Water, acting as a hydrogen bond donor, hydrates selectively the regions around O_{6m} and O_{2g}. The SDFs obviously provide a very detailed picture of solvation. Various graphical representations and techniques to analyze them are given by Bergman and co-workers.^[20]

Another interesting feature is that DMSO, while acting as a hydrogen bond acceptor to the HO_{2g} hydroxyl group, can simultaneously act as an acceptor for a specific water molecule, which is in turn hydrogen bonded to O_{6m}. This leads to a remarkable hydrogen bonded associate, involving two hydroxyl groups of the disaccharide and one molecule each of water and DMSO (see Figure 2). To investigate the relative stability of these associates, we can compare association times^[21] for the oxygen atoms of the solvent attached to the hydroxyl groups. In most cases these were found to be slightly below 10 ps for both water and DMSO. The association time for the O_{2g}-O_{DMSO} pair, however, was found to be between 20 and 30 ps. For the O_{6m}-O_{water} pair it was between 10 and 20 ps. For a comparison, the rotational correlation

times for water and DMSO in the binary solvent mixture are 2 ps and 3 ps, respectively. Thus, these hydrogen-bonded associates survive several rotational correlation time periods. Furthermore, similar associates with water molecules are present in the bulk solvent.

To summarize, we have shown that MD simulations can be used further to obtain detailed information about important solution properties. By combining the information obtained from using the traditional RDFs and the three-dimensional SDFs with the association times for the individual hydrogen bonds, we can see the different parts of disaccharide **1** preferentially solvated by either water or DMSO. We can also see that in some parts there is a clear competition between the components.

Received: June 24, 1999 [Z13625]

- [1] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, **1988**.
- [2] H. Strehlow, H.-M. Koepp, *Z. Elektrochem. Ber. Bunsen-Ges. Phys. Chem.* **1958**, *62*, 373–378.
- [3] D. Jamroz, J. Stangret, J. Lindgren, *J. Am. Chem. Soc.* **1993**, *115*, 6165–6168.
- [4] J. E. Bertie, Z. Lan, *J. Phys. Chem. B* **1997**, *101*, 4111–4119.
- [5] H. Kovacs, A. Laaksonen, *J. Am. Chem. Soc.* **1991**, *113*, 5596–5605.
- [6] D. L. Bergman, A. Laaksonen, *Phys. Rev. E* **1998**, *58*, 4706–4715.
- [7] D. I. Mendelev, PhD thesis, St. Petersburg University (Russia), **1865**.
- [8] K. V. Pervushin, Yu. V. Orekhov, A. I. Popov, L. Yu. Musina, A. S. Arseniev, *Eur. J. Biochem.* **1994**, *219*, 571–583.
- [9] J. A. Glasel, *J. Am. Chem. Soc.* **1970**, *92*, 372–375.
- [10] I. I. Vaisman, M. L. Berkowitz, *J. Am. Chem. Soc.* **1992**, *114*, 7889–7896.
- [11] I. A. Borin, M. S. Skaf, *J. Chem. Phys.* **1999**, *110*, 6412–6420.
- [12] D. H. Rasmussen, A. P. MacKenzie, *Nature* **1968**, *220*, 1315–1317.
- [13] S. W. Jacobs in *Dimethyl Sulfoxide* (Eds.: E. E. Rosenbaum, D. C. Wood), Marcel Dekker, New York, **1971**.
- [14] *Glycosciences* (Eds.: H.-J. Gabius, S. Gabius), Chapman and Hall, London, **1997**.
- [15] Q. Liu, J. W. Brady, *J. Am. Chem. Soc.* **1996**, *118*, 12276–12286.
- [16] A. Vishnyakov, G. Widmalm, J. Kowalewski, A. Laaksonen, *J. Am. Chem. Soc.* **1999**, *121*, 5403–5412.
- [17] L. Mäler, G. Widmalm, J. Kowalewski, *J. Phys. Chem.* **1996**, *100*, 17103–17110.
- [18] I. M. Svishechev, P. G. Kusalik, *Science* **1994**, *265*, 1219–1221.
- [19] L. Laaksonen, "gOpenMol", version 1.21. Center of Scientific Computations, Espoo, Finland. <http://laaksonen.csc.fi/gopenmol/gopenmol.html>.
- [20] D. L. Bergman, L. Laaksonen, A. Laaksonen, *J. Mol. Graphics Modell.* **1997**, *15*, 301–306.
- [21] A. P. Lyubartsev, A. Laaksonen, *J. Phys. Chem.* **1996**, *100*, 16410–16418.

Thermoregulated Optical Properties of Peptidic Pseudorotaxanes**

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The importance of self-assembly in biological processes has led many chemists to design and build superstructures assembled through noncovalent interactions.^[1] Thus, catenanes, rotaxanes, and pseudorotaxanes have been prepared using a variety of different approaches.^[2] The main objective of this scientific effort is the development of nanoscale supramolecules with entirely new and specific properties. It is noteworthy, however, that polypeptides have not been used in such supramolecular devices, even though many researchers have reported the use of peptides in the preparation of receptors, enzyme mimics, artificial ion channels, and dendrimers.^[3] Herein, we describe the preparation and the unusual optical properties of the first synthetic pseudorotaxanes involving a chiral peptidic framework.^[4]

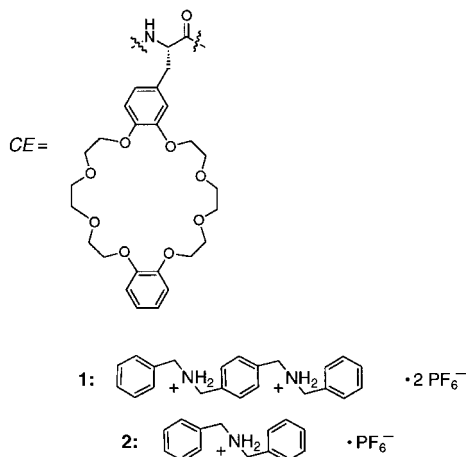
The bis-crown peptide **A**, incorporating two amino acids modified with a crown ether (dibenzo-24-crown-8), was designed and synthesized according to a procedure we have developed.^[5] The heptapeptide features a terminal *tert*-butoxycarbonyl (Boc) protective group, a leucine unit, then the first crown ether substituted amino acid, the three amino acid groups (-X-Y-Z-), the second crown ether-amino acid, and ends with leucine *n*-propylamide. The lateral dibenzo-24-crown-8 has been shown to form "threaded" complexes with polyammonium ions, such as **1**, that have been fully characterized.^[6]

A peptide-diammonium host-guest complex of 1:1 stoichiometry between **A** and **1** with PF₆⁻ counterions (**[A·1]**) has been successfully prepared in two different ways. In one approach, **A** is dissolved in CH₂Cl₂ and then **1** is added. After a brief sonication period, the suspension was stirred for 10

A, B: Boc-Leu-CE-X-Y-Z-CE-Leu-NH-*n*Pr

A: X, Y, Z = Leu

B: X = Ile, Y = Pro, Z = Ala



hours. In another approach, an aqueous solution of **1** was extracted by a solution of **A** in CH₂Cl₂. In both cases, the solvent was removed under vacuum and the resulting products were analyzed. Electrospray (ES) mass spectrometry confirmed the existence of the 1:1 complex. A doubly charged molecular ion, corresponding to **[A·1]** lacking PF₆⁻, is observed in the spectra (Figure 1). However, no trace of either a 2:1 complex or a singly charged 1:1 complex were evident. These observations suggest strongly that the supramolecular species is indeed a pseudorotaxane involving the cooperative action of the two crown moieties.

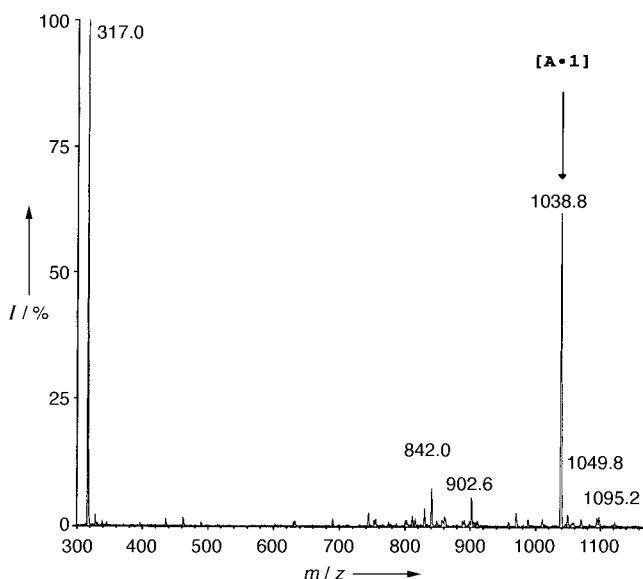


Figure 1. ES mass spectrum of complex **[A·1]**. The peak indicated by the arrow is doubly charged, and corresponds to the mass of the complex lacking two PF₆⁻ counterions (2078).

NMR spectroscopy further corroborates this conclusion. Differences between the spectra of free and **1**-complexed peptide **A** (Figure 2) support the proposal of increased order within the peptide backbone upon the addition of **1**. Moreover, one can observe characteristic peaks for the benzylic methylene protons of complexed polyammoniums ions around $\delta = 4.7$,^[7] along with signals for deshielded α -carbon

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[**] This work was financially supported by the NSERC of Canada, the Fonds FCAR du Québec, and the Université Laval. We thank Dr. Jack Wang and Mrs. Doreen Wen (University of Toronto) for mass spectrometry analysis, and Dr. Matthew C. T. Fyfe (UCLA) for supplying samples of **1**.

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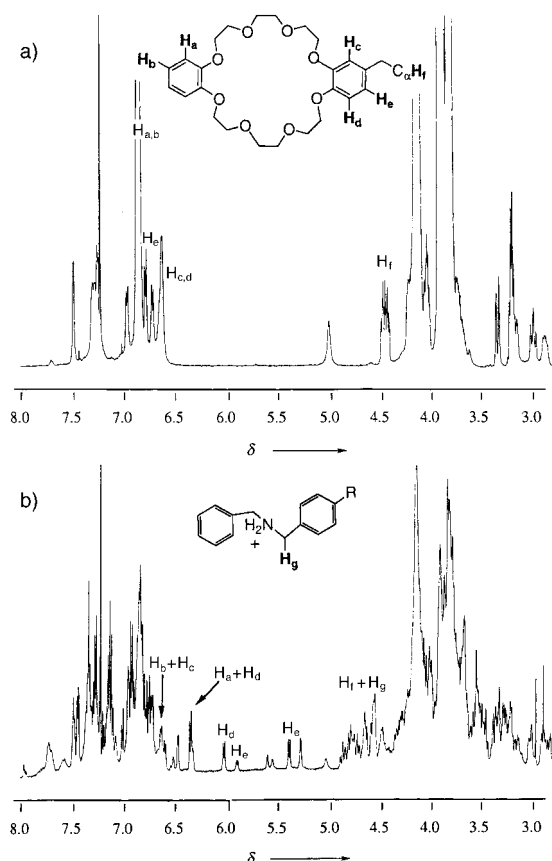


Figure 2. 500 MHz NMR spectra (CDCl_3) of a) free peptide **A** with labeled signals of the crown ether and b) complex **[A·1]** with labeled signals of the polyammonium guest. This partial assignment is based upon TOCSY experiments.

protons of the crown ether substituted amino acids. In addition, some small peaks between $\delta = 5.4$ and 6.7 can be assigned to signals of the aromatic protons of the **1**-complexed crown ether that are significantly shifted upfield. Similar observations have already been reported for related systems.^[8]

Additional evidence for the formation of a 1:1 pseudorotaxane is provided by circular dichroism (CD) studies. Free peptide **A** in MeCN is characterized by a CD curve (Figure 3a) with a maximum at 190 nm and a minimum at around 206–207 nm, indicative of partly formed helical conformations.^[9] Addition of 1 equivalent of **1** results in **[A·1]** complexation, inducing a noteworthy conformational constraint on the peptidic backbone. This is displayed by a dramatic change in the CD curve (Figure 3a) with a maximum at 203 nm and two minima at 194 nm and 233 nm, characteristic of β -turn structures.^[10] Upon heating the MeCN solution slow decomplexation occurs (Figure 3b). At 75 °C, peptide **A** appears mainly uncomplexed and displays a CD curve similar to that of the free peptide. Once the solution is cooled to 25 °C, the complex reforms as shown by the CD curve, to recover its original geometry in the process. This result indicates that the formation of the pseudorotaxane is thermodynamically favored. Moreover, addition of two equivalents of dibenzylammonium **2** to peptide **A** had no effect on its conformation, further supporting that conformational changes observed with **1** result from the formation of a pseudorotaxane involving the two crown side chains.

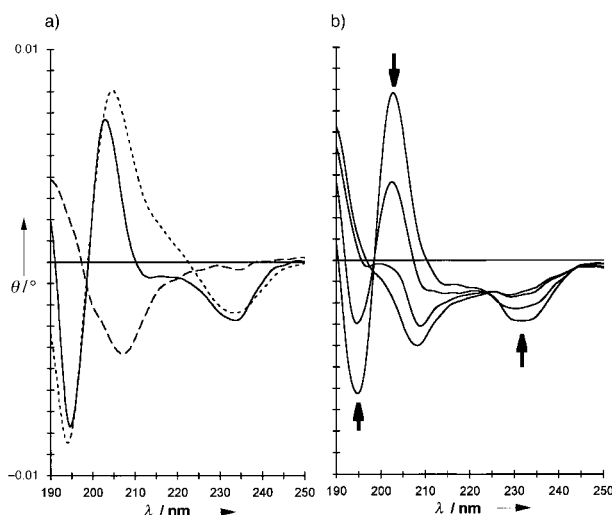


Figure 3. CD studies in MeCN for a) peptide **A** (---), complex **[A·1]** (—), and complex **[B·1]** (····) at 25 °C; b) complex **[A·1]** at 25, 45, 65, and 75 °C. The arrows indicate the modifications occurring in the curves upon increasing temperature.

Analysis of the CD data yielded a binding constant (K_a) of 2640 M^{-1} in MeCN for the complexation process.^[11] This value is much larger than 420 M^{-1} obtained with dibenzo-24-crown-8 and dibenzylammonium,^[7] suggesting a strong cooperative action of the two crown side chains of **A** in the binding phenomenon.

To support the β -turn conformation of the peptidic chain in **[A·1]**, we have designed the analogous heptapeptide **B**, incorporating a proline residue to impose a conformational constraint to the peptidic backbone. Upon addition of **1** to a solution of **B** in MeCN, the CD curve for **[B·1]** superimposes on the curve for **[A·1]** (Figure 3a). The observation of a maximum at 205 nm, and two minima at 194 nm and 233 nm corroborates the proposed turn structure adopted by the peptides once complexed. Modeling studies substantiate the rotaxane-induced conformational change.^[12] As seen in Figure 4, when the backbone of **A** is under a type II β -turn



Figure 4. Representation of pseudorotaxane complex **[A·1]** after potential energy minimization.^[12] Crown ethers, diammonium **1**, and peptide chain are shown in red, blue, and tan respectively. The black ribbon emphasizes the β -turn structure between ^4Leu – ^5Leu of the central triad.

structure, the two crown moieties are nicely oriented to form a threaded complex with **1**. On the possible turn structures, the one having ⁴Leu-⁵Leu at *i*+1, *i*+2 positions gave the most stable structure for the complex.^[13]

In conclusion, we have prepared peptidic pseudorotaxanes [**A**·**1**] and [**B**·**1**] through self-assembly under thermodynamically controlled conditions. These supramolecular systems display thermoregulated optical properties that could make them useful for the development of optical devices. Future work will focus on the applications of these supramolecular systems, as well as on the preparation of receptors with different amino acids by a combinatorial approach, permitting the molecular engineering of novel materials with unique properties.

Received: September 1, 1998
Revised: October 15, 1999 [Z12364]

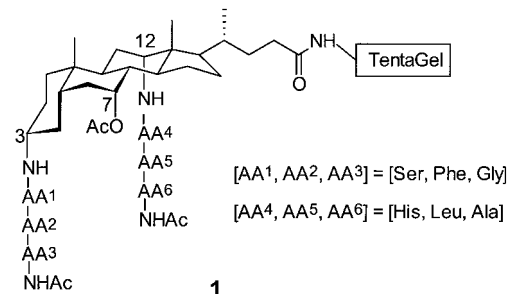
- [1] D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242–1286; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154–1196, and references therein.
- [2] a) P. R. Ashton, S. E. Boyd, C. G. Claessens, R. E. Gillard, S. Menzer, J. F. Stoddart, M. S. Tolley, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1997**, *3*, 788–798; b) R. Jäger, F. Vögtle, *Angew. Chem.* **1997**, *109*, 966–980; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 930–944; c) J.-P. Sauvage, C. O. Dietrich-Buchecker, J.-C. Chambron in *Comprehensive Supramolecular Chemistry*, Vol. 9 (Ed.: J.-M. Lehn), Pergamon, Oxford, **1996**, p. 43; d) D. G. Hamilton, J. E. Davies, L. Prodi, J. K. M. Sanders, *Chem. Eur. J.* **1998**, *4*, 608–620.
- [3] For reviews, see: a) N. Voyer, *Top. Curr. Chem.* **1996**, *184*, 1–37; b) N. Voyer, J. Lamothe, *Tetrahedron* **1995**, *34*, 9241–9284.
- [4] Recently, Leigh reported the formation of an achiral rotaxane and molecular shuttle incorporating a Gly-Gly dipeptide: a) D. A. Leigh, A. Murphy, J. P. Smart, M. Z. Slawin, *Angew. Chem.* **1997**, *109*, 752–756; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 728–732; b) S. A. Lane, D. A. Leigh, A. Murphy, *J. Am. Chem. Soc.* **1997**, *119*, 11 092–11 093.
- [5] a) N. Voyer, J. Roby, D. Deschênes, J. Bernier, *Supramol. Chem.* **1995**, *5*, 61–69; b) N. Voyer, B. Guérin, *Tetrahedron* **1994**, *4*, 989–1010; c) N. Voyer, *J. Am. Chem. Soc.* **1991**, *113*, 1818–1821.
- [6] a) P. R. Ashton, M. C. T. Fyfe, P. T. Glink, S. Menzer, J. F. Stoddart, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1997**, *119*, 12 514–12 524; b) P. R. Ashton, P. T. Glink, J. F. Stoddart, P. A. Tasker, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1996**, *2*, 729–736.
- [7] P. R. Ashton, E. J. T. Chrystal, P. T. Glink, S. Menzer, C. Schiavo, N. Spencer, J. F. Stoddart, P. A. Tasker, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1996**, *2*, 709–728.
- [8] P. R. Ashton, R. Ballardini, V. Balzani, M. Gómez-López, S. E. Lawrence, M. V. Martínez-Díaz, M. Montalti, A. Piersanti, L. Prodi, J. F. Stoddart, D. J. Williams, *J. Am. Chem. Soc.* **1997**, *119*, 10 641–10 651.
- [9] M. C. Manning, *Biocatalyst Design for Stability and Specificity*, American Chemical Society, Washington, DC, **1993**, chap. 3.
- [10] R. W. Woody, *Peptides, Polypeptides, and Proteins*, Wiley, New York, NY, **1986**, pp. 339–350.
- [11] Measured at 45 °C and assuming the formation of 1:1 complex only. M. P. Mack, R. R. Richardson, R. A. Palmer, R. G. Ghirardelli, *J. Am. Chem. Soc.* **1976**, *98*, 7830–7832.
- [12] Modeling was performed using MOE software from the Chemical Computing Group (www.chemcomp.com) using a CVFF-91 force field.
- [13] It is likely that the most stable structure of [**A**·**1**] shown in Figure 4 is accompanied by one or more other β -turn complexes in solution. This would explain the difficulties in crystallizing [**A**·**1**] and discrepancies in the NMR integrations.

Application of Combinatorial Procedures in the Search for Serine-Protease-Like Activity with Focus on the Acyl Transfer Step**

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The attainment of the selectivities and efficiencies of enzymes remains a major goal in organic chemistry.^[1] The efficiency of the serine protease α -chymotrypsin in cleaving peptide bonds, relative to the uncatalyzed hydrolysis, serves as an illustrative example.^[2] Although notable progress has been made in the development of synthetic hydrolases,^[3] the real challenge, the cleavage of nonactivated amides, still remains. Several years ago we embarked on a long-term program aimed at the development of synthetic hydrolases with the focus on gaining a better understanding of the enzymatic process. In particular we developed non-peptidic organic molecules possessing an array of functional groups in a suitable geometry for eventual hydrolytic activity.^[4] In contrast to that work, in which a carefully designed molecule was targeted, we describe herein the first results of a study in which serine-protease activity is searched by combinatorial techniques.^[5]

Our long term goal is to develop a system that is characterized by three independent peptidic chains, each containing one of the three active residues^[6] of the classic triad (Ser, His, and Asp), and possessing serine-protease-like activity. As a first step towards this goal we describe here: 1) the mix-split synthesis of the library **1** containing 729 (3⁶) members, in which the two most important catalytic residues

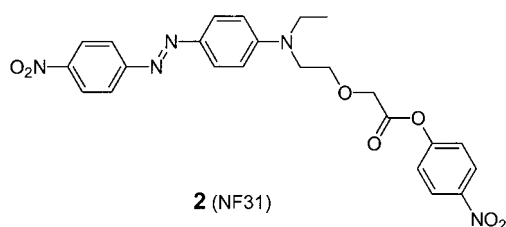


Ser and His are each incorporated into one of the two tripeptidic chains generated on a steroidal scaffold, 2) the screening of the solid-phase-bound library for reaction with the test substrate **2** (NF31) as a model for the first step of the

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[**] This research was supported by FWO-Vlaanderen (G.0051.98), GOA (GOA96009), and TMR (ERBFMRXCT 960011). We thank Prof. Dr. S. Hoste (Gent) for the use of the microscopic camera.

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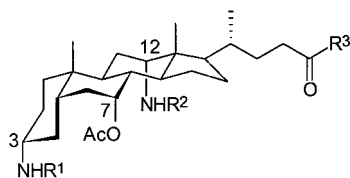


enzymatic mechanism (see below), and 3) the identification of three active sequences **1a–c** by recursive deconvolution (Table 1).

Table 1. Sequences from the hexapeptide library **1** as identified by recursive deconvolution.

Sequence	AA ¹	AA ²	AA ³	AA ⁴	AA ⁵	AA ⁶
1a	Gly	Phe	Ser	Leu	His	Ala
1b	Phe	Ser	Phe	Leu	His	Ala
1c	Ser	Ser	Phe	Leu	His	Ala
1d	Ser	Phe	Ser	Leu	His	Ala

After attachment of the cholic acid derivative **3** (Alloc = allyloxycarbonyl, Boc = *tert*-butoxycarbonyl) to TentaGel-NH₂ (TG-NH₂),^[7] the hexapeptide library was constructed following the split-mix protocol using a set of three amino acids (Ser(*OrtBu*), Phe, Gly) in the combinatorial construction of the first chain and another set of three amino acids (His(*Trt*), Ala, Leu) in the construction of the second chain (*Trt* = trityl = triphenylmethyl).^[8] All peptide couplings except one were effected in a classical way using amino acids



- 3:** R¹ = Alloc, R² = Boc, R³ = OH
4: R¹ = Alloc, R² = Boc, R³ = NH-TG
5: R¹ = AA¹-AA²-AA³-NHAc, R² = Boc, R³ = NH-TG
6: R¹ = AA¹-AA²-AA³-NHAc, R² = H, R³ = NH-TG

protected with the 9*H*-fluoren-9-ylmethoxycarbonyl (Fmoc) group and *N,N'*-diisopropylcarbodiimide/1-hydroxy-1*H*-benzotriazole (DIC/HOBt) methodology. The two peptide strands were attached in succession. After deprotection of the Alloc group in **4**, the first strand was constructed on the free amino group at C-3 and then capped with acetylimidazole to yield **5**. Early attempts at coupling the first amino acid of the second peptide chain with the free amino group at C-12 of **6** (obtained after acid removal of the Boc group of **5**) failed because of steric encumbrance. In this particular case the coupling reagent 1-hydroxy-7-azabenzotriazole was used instead.^[9]

The choice of a suitable substrate for discovering relevant activity is critical. Indeed, not only should its structure allow for easy detection of an active member within the library, but reaction should also occur by a mechanism that is related to the enzymatic process. It occurred to us that the activated

ester **2** could be a suitable substrate for that purpose.^[10] Indeed, it is very reactive towards amines, including sterically hindered ones, and not readily cleaved by primary alcohols.^[11] In practice, when **2** was exposed to TG-NH₂, TG-Ser-NHAc, and TG-His-NHAc under standard screening conditions (exposure of 10 mg beads to 50 μ L of a 0.002 M solution of **2** in 800 μ L CH₃CN, RT, overnight, followed by thorough rinsing with DMF and CH₂Cl₂) the appearance of deep red beads was only observed in the case of TG-NH₂ (Figure 1a); Ser- and His-bound substrates normally do not react to a

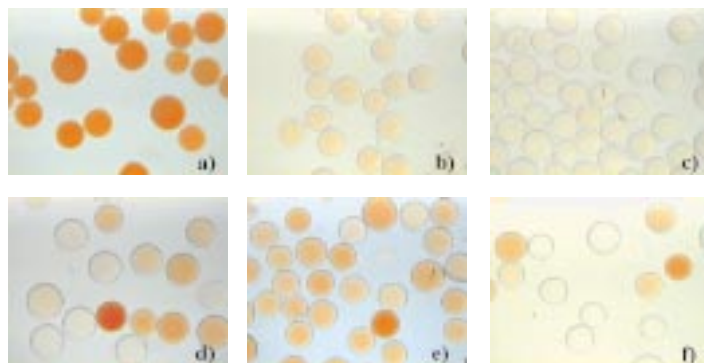


Figure 1. Top: TentaGel beads after reaction with **2**: a) TG-NH₂, b) TG-His-NHAc, c) TG-Ser-NHAc. Bottom: the three sublibraries after reaction with **2**: d) Ala-sublibrary, e) His-sublibrary, f) Leu-sublibrary.

major extent (Figure 1b, c), so any observed reactivity could reveal a mechanism in which both amino acid residues are involved. The library was screened under standard conditions at the stage of the last sublibraries in which the identity of the sixth capped amino acid is known to be Ala, His, or Leu. Each pool containing a total of 243 different members was screened separately and hits were observed in each sublibrary (Figure 1d–f). Inspection of Figure 1d reveals clearly the Ala-sublibrary to be the most promising one in view of discovering a unique sequence. As expected, the testing of the sublibraries at the protected amino acid stage (for example, Ser(*OrtBu*) and His(*Trt*)) did not lead to any hits.

The identification of the most active member(s) within the Ala-sublibrary was performed using recursive deconvolution.^[12] Figure 2 illustrates the procedure that led to the discovery of the sequence Ala-His-Leu as the preferred AA₆-AA₅-AA₄ tripeptidic chain. After selection of Ala as the sixth amino acid (Figure 1d), three new sublibrary pools, each containing 81 different sequences, were constructed in which the identity of the fifth amino acid was known. The testing of these separate pools clearly revealed His as the preferred fifth amino acid (Figure 2a). In the same way Leu was selected as the last amino acid of the first tripeptidic chain after the testing of three new sublibraries, each now containing 27 different members (Figure 2b). The same procedure was used to unravel the AA₃-AA₂-AA₁ chain. It is typical of the deconvolution procedure that choices are more difficult to make while proceeding towards the full identification of an active member. Indeed, the relative increase of the number of active members in the newly created pools leads to a more-even distribution of the color among the beads. Three active members, **1a–c**, were eventually identified (Table 1).

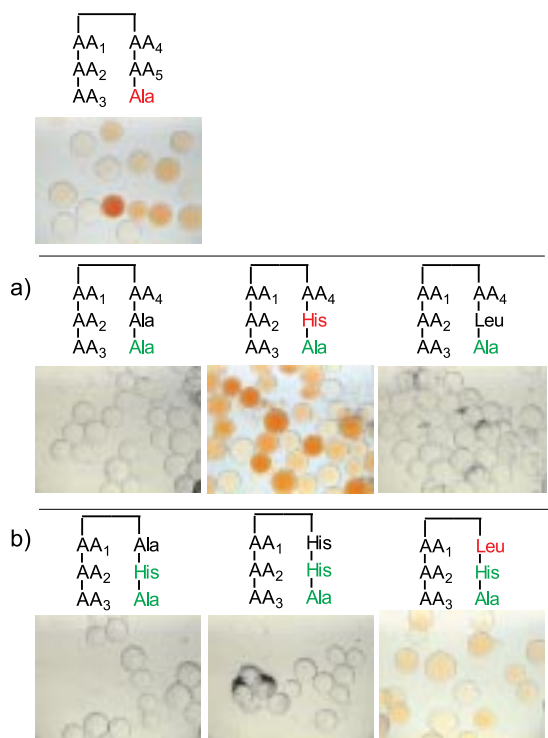


Figure 2. The deconvolution procedure for the identification of the first peptidic strand of the Ala-sublibrary; a) three newly created sublibraries, each containing 81 members that allow the identification of AA₃ as His, b) three newly created sublibraries, each containing 27 members that allows the identification of AA₄ as Leu.

A major advantage of the recursive deconvolution procedure resides in the numerous resyntheses of structurally biased libraries that need to be performed. Indeed, not only are active members within the library resynthesized so that they become available for separate testing, inactive members are also obtained that can serve as control substrates. Sequence **1d** (Table 1) is illustrative in this context: it contains both His and Ser residues, only differs from **1a** in the identity of the first amino acid, and yet is inactive under the standard screening conditions (Figure 3).

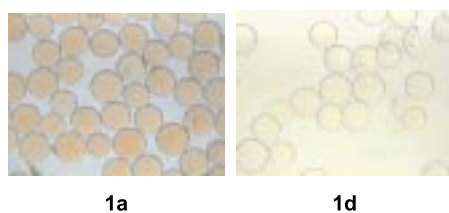


Figure 3. The active sequence **1a** and the non-active sequence **1d** after exposure to **2** (10 mg beads, 850 μ L of a 12×10^{-5} M solution in CH₃CN).

As far as the mechanism of the above process is concerned several aspects need to be clarified. In view of the thorough rinsing procedure (**2** is soluble in CH₂Cl₂ and DMF) there can be no doubt about the covalent nature of the binding of the chromogenic acyl residue to the library component. However, it is difficult at this stage to differentiate unambiguously between acylated-His or esterified-Ser substances. Therefore the three above colored pools **1a–c** were each subjected to mild hydrolysis conditions (H₂O/DMF, 45 °C, 5 days); in each case the red color was retained, which indicated the ester

nature of the covalent linkage.^[13] The well studied mechanism of peptide hydrolysis by the serine protease α -chymotrypsin proceeds by the transfer of the acyl part of the amide to the Ser residue, which is assisted by His (and by Asp although the exact role of the latter is still a matter of debate)^[14] followed by hydrolysis of the acylated enzyme by water by essentially the same but inverse mechanism. In this context the observed reactivity in our study is related to the first step of the enzymatic mechanism, namely the acyl-transfer step. The latter can still involve general base catalysis or nucleophilic catalysis, mechanisms that imply the participation of both Ser and His residues.^[15] At the present stage it is not possible to determine the origin of the difference in reactivity between the active sequences **1a–c** and the inactive sequence **1d**. An attractive explanation would consist in a geometrical arrangement involving the Ser and His residues of **1a–c** that allows for cooperative participation, a process that is not possible for **1d**, although this remains to be proven. Also at this point it is not possible to assess the role, if any, of the solid support in the process.

As far as the de-acylation step is concerned we were fortunate to observe that when the colored pools obtained from **1a–c** were subjected to more forceful hydrolytic conditions (H₂O/DMF, 65 °C, 48 h), the beads originating from **1a** and **1b** became colorless, while those derived from **1c** remained red (Figure 4). This suggests that a different

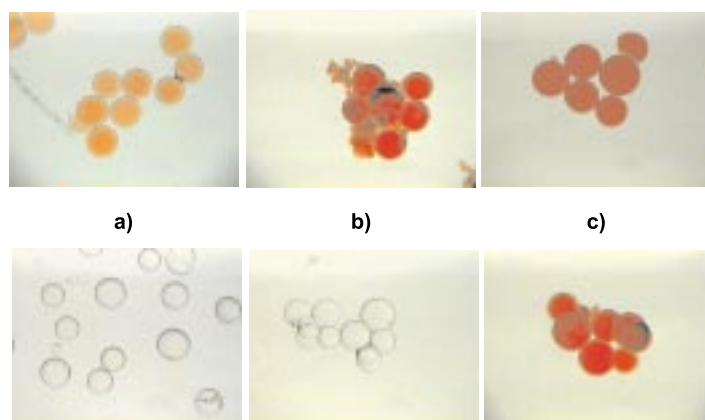


Figure 4. Top: the active sequences after exposure to **2** (10 mg beads, 1 mL of a 2×10^{-3} M solution in CH₃CN): a) **1a**, b) **1b**, c) **1c**. Bottom: the same acylated (**2**) sequences after reaction with H₂O/DMF (65 °C, 48 h).

mechanism may be operating in the de-acylation step. The possibility that the Ser-His couple is involved in both the acylation and the de-acylation stages is of special interest in view of the eventual development of a truly catalytic system.

In summary, we have described the discovery of a few peptide sequences characterized by the presence of both Ser and His that cause the unusual cleavage of an activated *p*-nitrophenyl ester. The discovery rests on the combinatorial mix-split technique for the construction of the hexapeptide library, on the visual detection of active members, and on the identification of the active sequences using recursive deconvolution.

Received: July 8, 1999 [Z13692]

- [1] Y. Murakami, J. Kikuchi, Y. Hisaeda, O. Hayashida, *Chem. Rev.* **1996**, 96, 721–758.
- [2] A. J. Kirby, *Angew. Chem.* **1996**, 108, 770–790; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 707–734.
- [3] K. W. Hahn, W. A. Klis, J. M. Stewart, *Science* **1990**, 248, 1544–1547. For recent examples of artificial hydrolases not involving Ser, see a) J. Suh, S. S. Hah, *J. Am. Chem. Soc.* **1998**, 120, 10088–10093; b) L. Baltzer, K. S. Broo, H. Nilsson, J. Nilsson, *Bioorg. Med. Chem.* **1999**, 7, 83–91.
- [4] A. Madder, P. J. De Clercq, *J. Org. Chem.* **1998**, 63, 2548–2559.
- [5] For a recent combinatorial approach in the discovery of catalysts for phosphate hydrolysis, see D. A. Héroult, A. Berkessel, *Angew. Chem.* **1999**, 111, 99–102; *Angew. Chem. Int. Ed.* **1999**, 38, 102–105.
- [6] D. M. Blow, *Acc. Chem. Res.* **1976**, 9, 145–152.
- [7] J. F. Barry, A. P. Davis, M. N. Pérez-Payan, M. R. J. Elsegood, R. F. W. Jackson, C. Gennari, U. Piarulli, M. Gude, *Tetrahedron Lett.* **1999**, 40, 2849–2852.
- [8] a) A. Furka, F. Sebestyen, M. Asgedom, G. Dibo, *Int. J. Pept. Protein Res.* **1991**, 37, 487–493; b) K. S. Lam, S. E. Salmon, E. M. Hersch, V. J. Hruby, W. M. Kazmierski, R. J. Knapp, *Nature* **1991**, 354, 82–84; c) R. A. Houghten, C. Pinilla, S. E. Blondelle, J. R. Appel, C. T. Dooley, J. H. Cuervo, *Nature* **1991**, 354, 84–86.
- [9] L. A. Carpino, *J. Am. Chem. Soc.* **1993**, 115, 4397–4398.
- [10] NF31 refers to Nadia Farcy, see A. Madder, N. Farcy, N. G. C. Hosten, H. De Muynck, P. J. De Clercq, J. Barry, A. P. Davis, *Eur. J. Org. Chem.* **1999**, 11, 2787–2791.
- [11] For example, no transesterification of **2** is observed when treated with an excess of MeOH (RT, 12 h, CH₃CN).
- [12] a) E. Erb, K. D. Janda, S. Brenner, *Proc. Natl. Acad. Sci. USA* **1994**, 91, 11 422–11 426; b) S. M. Freier, D. A. M. Konings, J. R. Wyatt, D. J. Ecker, *J. Med. Chem.* **1995**, 38, 344–352; c) D. A. M. Konings, J. R. Wyatt, D. J. Ecker, S. M. Freier, *J. Med. Chem.* **1996**, 39, 2710–2719; d) L. Wilson-Lingardo, P. W. Davis, D. J. Ecker, N. Hébert, O. Acevedo, K. Sprinkle, T. Brennan, L. Schwarcz, S. M. Freier, J. R. Wyatt, *J. Med. Chem.* **1996**, 39, 2720–2726.
- [13] 50% cleavage of acetylimidazole is already observed in MeOH after 1 h at RT.
- [14] S. C. Zimmerman, J. S. Korthals, K. D. Cramer, *Tetrahedron* **1991**, 47, 2649–2660.
- [15] The mechanism for the hydrolysis of *p*-nitrophenyl esters by serine proteases is still under discussion, see a) D. M. Quinn, J. P. Elrod, R. Ardis, P. Friesen, R. L. Schowen, *J. Am. Chem. Soc.* **1980**, 102, 5358–5365; b) R. A. Hess, A. C. Hengge, W. W. Cleland, *J. Am. Chem. Soc.* **1998**, 120, 2703–2709.

A Self-Complexing [2]Catenane

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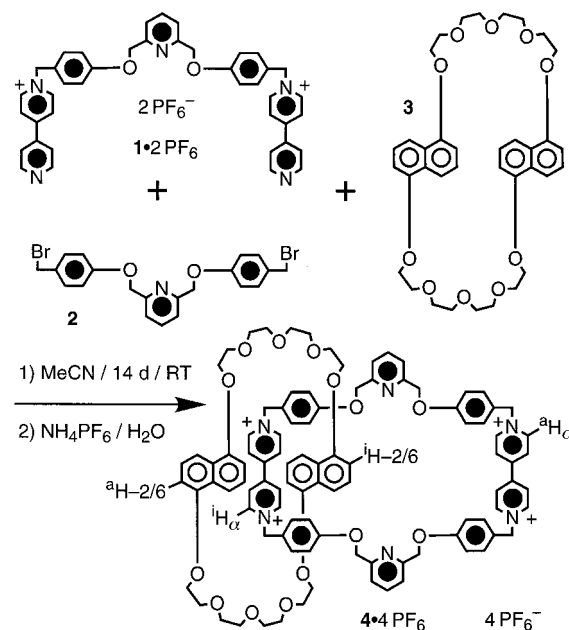
Molecules capable of recognizing one or more identical copies of themselves can be employed for the noncovalent synthesis^[1] of supermolecules and/or supramolecular arrays. Indeed, self-replicating systems,^[2] self-assembling capsules,^[3]

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and supramolecular polymers^[4,5] have all been developed successfully by employing appropriate self-complementary molecules as precursors. Consequently, we contemplated the possibility of synthesizing receptor molecules incorporating mechanically interlocked^[6] components by modifying the design of some [2]catenanes^[7] such that they acquire receptor characteristics. These [2]catenanes incorporate a 1,5-dioxynaphthalene-based macrocyclic polyether component interlocked with cyclobis(paraquat-4,4'-biphenylene)^[8] and are able to bind^[7] π -electron-deficient and π -electron-rich substrates. These recognition phenomena have already been exploited in the synthesis of a “rotacatenane”^[7b] composed of a 1,5-dioxynaphtho[38]crown-10 moiety interlocked with cyclobis(paraquat-4,4'-biphenylene)^[8] and with a third acyclic polyether component containing a 1,5-dioxynaphthalene ring system threaded through the cavity of the bipyridinium-based cyclophane and stoppered by bulky groups.

To generate self-complementary [2]catenanes, we have lengthened and introduced some flexibility into the spacers separating the bipyridinium units in the tetracationic cyclophane component. By inserting a 2,6-bis(oxymethyl)pyridine unit between the two phenylene rings of the 4,4'-bitolyl spacers, the size of the cavity associated with cyclobis(paraquat-4,4'-biphenylene) can be enlarged and enriched with hydrogen bonding acceptors—namely, the nitrogen and oxygen atoms of the 2,6-bis(oxymethyl)pyridine unit. Here, we report the template-directed synthesis of a self-complementary [2]catenane and the formation of a supramolecular homodimer composed of two mutually interpenetrating [2]catenanes both in solution and in the solid state.

Reaction of **1**·2PF₆ and **2**^[9] in the presence of the 1,5-dioxynaphthalene-based macrocyclic polyether **3** gives the [2]catenane **4**·4PF₆ in 18% yield after counterion exchange (Scheme 1), together with small amounts of a [3]catenane incorporating one tetracationic cyclophane and two macrocyclic polyether components.



Scheme 1. The template-directed synthesis of the [2]catenane **4**·4PF₆.

The X-ray structural analysis^[10] of $4 \cdot 4\text{PF}_6$ reveals that the macrocyclic polyether encircles one of the bipyridinium units of the tetracationic cyclophane (Figure 1). The structure is

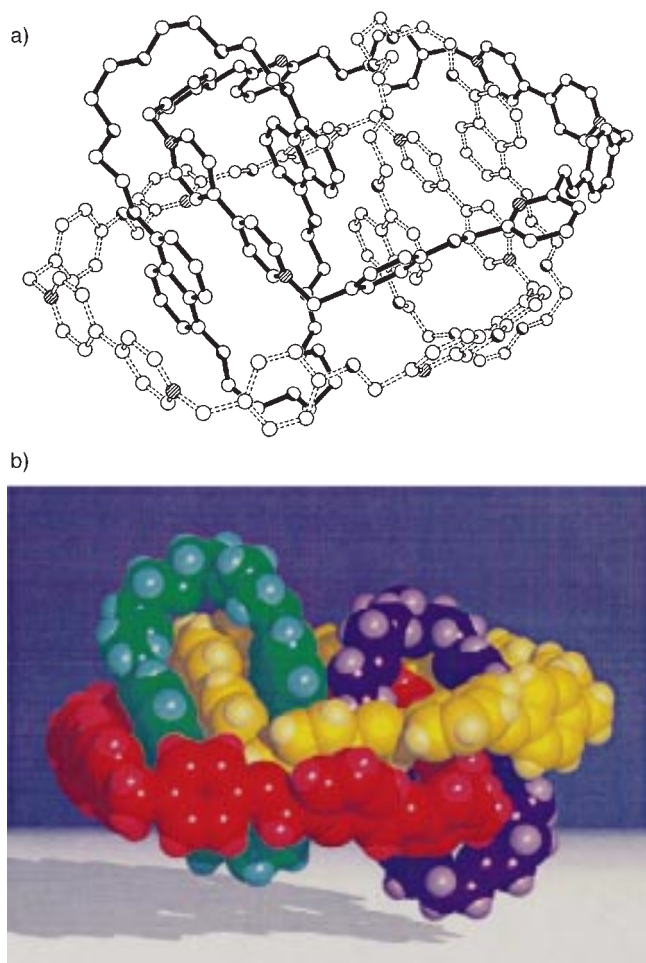


Figure 1. a) Ball-and-stick and b) space-filling representations of one of the supramolecular dimers formed by the [2]catenane 4^{4+} in the solid state. One of the [2]catenanes is made up of the components colored green and yellow, and the other of the components colored red and mauve.

stabilized by $\pi \cdots \pi$ stacking interactions between the bipyridinium unit and the 1,5-dioxynaphthalene ring systems.^[11] The only other interactions of note are a pair of C–H $\cdots$ O hydrogen bonds between one of the methylene hydrogen atoms adjacent to the “inside” bipyridinium unit and the polyether oxygen atoms.^[12] The most interesting feature of this [2]catenane is the open conformation adopted by the cyclophane component. As a consequence, there is a large central void between the inside 1,5-dioxynaphthalene ring system and the “alongside” bipyridinium unit, which are separated by about 14 Å. This void becomes occupied as a result of the mutual interpenetration of centrosymmetrically related pairs of [2]catenanes to form a supramolecular homodimer. The resulting superstructure is stabilized by $\pi \cdots \pi$ stacking interactions between 1) the alongside 1,5-dioxynaphthalene ring system of one [2]catenane and the alongside bipyridinium unit of the other, and between 2) one of the phenoxy rings adjacent to the inside bipyridinium unit

in one [2]catenane and one of the pyridyl spacers in the other, and vice versa.^[13] These noncovalent bonds are supplemented by a C–H $\cdots$ π interaction between one of the *peri* hydrogen atoms of the alongside 1,5-dioxynaphthalene ring system in one [2]catenane and one of the phenoxy rings adjacent to the alongside bipyridinium unit of the other.^[14] The inside pair of 1,5-dioxynaphthalene ring systems are aligned parallel, but offset, such that there is no $\pi \cdots \pi$ overlap. However, there are a pair of C–H $\cdots$ π interactions between one of the β -methylene hydrogen atoms associated with the inside 1,5-dioxynaphthalene ring system of one [2]catenane and the inside 1,5-dioxynaphthalene ring system of the other, and vice versa.^[15] Pairs of dimers form stepped stacks with the alongside bipyridinium unit of one dimer positioned parallel, but offset, to its counterpart in the next. The area of overlap is small but the interplanar separation short (ca. 3.4 Å).

The ^1H NMR spectrum of $4 \cdot 4\text{PF}_6$ (Figure 2 a; $T = 185\text{ K}$, $(\text{CD}_3)_2\text{CO}$) shows only one signal for the α -protons $^a\text{H}_\alpha$ of the alongside bipyridinium unit, indicating that the rotation of this unit around its N $\cdots$ N axis is fast on the ^1H NMR time scale. By contrast, the rotation of the inside bipyridinium unit around its N $\cdots$ N axis and that of the inside 1,5-dioxynaphthalene ring system around its O $\cdots$ O axis are slow. As a result, the α -protons $^i\text{H}_\alpha$ of the inside bipyridinium unit give rise to two sets of signals in the ^1H NMR spectrum (Figure 2 a). Upon warming of the solution, one or both processes become fast on the ^1H NMR time scale, and the two sets of signals for $^i\text{H}_\alpha$ coalesce into one (Figure 2 b, c). With the coalescence treatment^[16] a free energy of activation $\Delta G_c^\ddagger$ of 9.3 kcal mol^{-1} was calculated

at a coalescence temperature T_c of 195 K. Upon a further increase in temperature, the circumrotation of the tetracationic cyclophane through the cavity of the macrocyclic polyether becomes fast. As a result, the two sets of signals for $^a\text{H}_\alpha$ and $^i\text{H}_\alpha$ coalesce into one (Figure 2 d–g). A $\Delta G_c^\ddagger$ value of $13.5\text{ kcal mol}^{-1}$ was determined at a T_c of 288 K. At 185 K the circumrotation of the macrocyclic polyether through the cavity of the tetracationic cyclophane becomes slow and two distinct signals are observed (Figure 3 a) for the

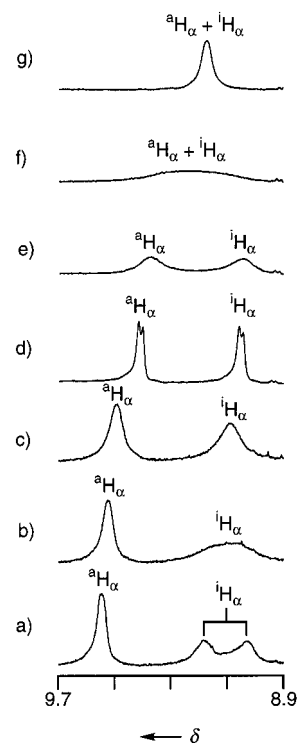


Figure 2. Portion of the ^1H NMR spectra of the [2]catenane $4 \cdot 4\text{PF}_6$ recorded in $(\text{CD}_3)_2\text{CO}$ at a) 185, b) 195, c) 208, d) 252, e) 274, f) 288, and g) 309 K. The limiting frequency separation $\Delta\nu$ for the two signals associated with the protons $^i\text{H}_\alpha$ in a) is 62 Hz, and the derived rate constant k_c at the coalescence temperature is 82 s^{-1} . For the two signals associated with the protons $^a\text{H}_\alpha$ and $^i\text{H}_\alpha$ in c), $\Delta\nu = 143\text{ Hz}$ and $k_c = 317\text{ s}^{-1}$.

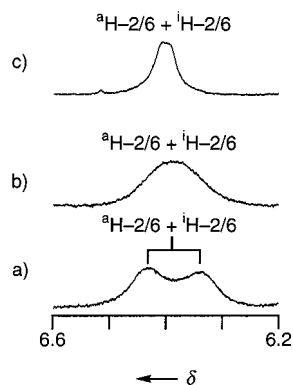


Figure 3. Portion of the ^1H NMR spectra of the [2]catenane $4 \cdot 4\text{PF}_6$ recorded in $(\text{CD}_3)_2\text{CO}$ at a) 185, b) 190, and c) 208 K. The limiting frequency separation $\Delta\nu$ for the two signals associated with the protons $^a\text{H}_{2/6}$ and $^i\text{H}_{2/6}$ in a) is 37 Hz, and the derived rate constant k_c at the coalescence temperature is 82 s^{-1} .

20 M^{-1} ($-\Delta G^\circ = 1.1 \text{ kcal mol}^{-1}$) for the dimerization process was determined^[17] by nonlinear curve fitting of the plot of $\Delta\delta_0$ against c .

Thus, we have established that the [2]catenane $4 \cdot 4\text{PF}_6$ forms a homodimeric superstructure both in solution and in the solid state as a result of a combination of intercatenane $\pi \cdots \pi$ and $\text{C-H} \cdots \pi$ interactions. This homodimer is composed of a total of four macrocyclic components held together by two mechanical bonds and a range of cooperative non-covalent bonds. The intriguing recognition properties of this novel class of [2]catenane receptors offers the potential for the design and synthesis of even more intricate molecular and supramolecular systems incorporating interlocked components. This remarkable and unique example of self-recognition is reminiscent of the dimerization of certain glycopeptides whose antibiotic activity is promoted upon self-recognition.^[18]

Experimental Section

$4 \cdot 4\text{PF}_6$: A solution of $1 \cdot 2\text{PF}_6$ ^[9] (0.28 g, 0.3 mmol), **2** (0.15 g, 0.3 mmol), and **3** (0.59 g, 0.9 mmol) in dry MeCN (25 mL) was stirred for 14 d at ambient temperature. The solvent was evaporated off under reduced pressure and the residue was purified by column chromatography (SiO_2 , 2 M $\text{NH}_4\text{Cl}/\text{MeOH}/\text{MeNO}_2$ (7/2/1, v/v/v)). The resulting purple solid was dissolved in H_2O and a large excess of NH_4PF_6 was added. The resulting precipitate was isolated by filtration, washed with H_2O , and dried to afford $4 \cdot 4\text{PF}_6$ as a purple powder (12 mg, 18%). M.p. $> 200^\circ\text{C}$; FAB-MS: m/z : 2018 $[\text{M} - \text{PF}_6]^+$, 1872 $[\text{M} - 2\text{PF}_6]^+$, 1728 $[\text{M} - 3\text{PF}_6]^+$; ^1H NMR (400 MHz, CD_3CN , 25°C): $\delta = 8.76$ (8H, brs), 7.71–7.52 (16H, m), 7.49 (2H, t), 7.24 (4H, d), 7.10 (8H, brs), 6.57 (4H, t), 6.37 (8H, d), 5.72 (8H, s), 5.09 (8H, s), 3.92–3.71 (32H, m); ^{13}C NMR (125.7 MHz, CD_3CN , 25°C): $\delta = 160.6$, 157.1, 154.0, 145.5, 132.9, 132.2, 130.1, 126.7, 126.2, 121.8, 116.7, 113.8, 106.1, 72.0, 71.7, 71.6, 70.9, 68.9, 65.3.

Received: August 13, 1999 [Z13875]

- [1] a) D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242–1286; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1155–1196; b) M. C. T. Fyfe, J. F. Stoddart, *Acc. Chem. Res.* **1997**, *30*, 393–401; c) M. C. T. Fyfe, J. F. Stoddart, *Adv. Supramol. Chem.* **1999**, *5*, 1–53.
- [2] a) G. von Kiedrowski, *Bioorg. Chem. Front.* **1993**, *3*, 113–146; b) J. Rebek, Jr., *Angew. Chem.* **1990**, *102*, 261–272; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 245–255; c) S. Hoffmann, *Angew. Chem.* **1992**, *104*, 1032–1035; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1013–1016; d) L. E. Orgel, *Nature* **1992**, *358*, 203–209; e) E. A. Winter, M. M. Conn, J. Rebek, Jr., *Acc. Chem. Res.* **1994**, *27*, 198–203; f) L. E. Orgel, *Acc. Chem. Res.* **1995**, *28*, 109–118; g) S. Kauffman, *Nature* **1996**, *382*, 496–497; h) D. H. Lee, K. Severin, M. R. Ghadiri, *Curr. Opin. Chem. Biol.* **1997**, *1*, 491–496; i) A. Luther, R. Brandsch, G. von Kiedrowski, *Nature* **1998**, *396*, 245–248.
- [3] a) J. L. Atwood, K. T. Holman, J. W. Steed, *Chem. Commun.* **1996**, 1401–1407; b) L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469–472; c) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1668; d) R. G. Chapman, J. C. Sherman, *Tetrahedron* **1997**, *53*, 15911–15945; e) L. J. Barbour, G. W. Orr, J. L. Atwood, *Nature* **1998**, *393*, 671–673; f) J. Rebek, Jr., *Acc. Chem. Res.* **1999**, *32*, 278–286; g) A. Jasat, J. C. Sherman, *Chem. Rev.* **1999**, *99*, 931–967.
- [4] a) P. R. Ashton, I. Baxter, S. J. Cantrill, M. C. T. Fyfe, P. T. Glink, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **1998**, *110*, 1344–1347; *Angew. Chem. Int. Ed.* **1998**, *37*, 1294–1297; b) P. R. Ashton, I. W. Parsons, F. M. Raymo, J. F. Stoddart, A. J. P. White, D. J. Williams, R. Wolf, *Angew. Chem.* **1998**, *110*, 2016–2019; *Angew. Chem. Int. Ed.* **1998**, *37*, 1913–1916; c) N. Yamaguchi, D. S. Nagvekar, H. W. Gibson, *Angew. Chem.* **1998**, *110*, 2518–2520; *Angew. Chem. Int. Ed.* **1998**, *37*, 2361–2364; d) N. Yamaguchi, H. W. Gibson, *Angew. Chem.* **1999**, *111*, 195–199; *Angew. Chem. Int. Ed.* **1999**, *38*, 143–147.
- [5] a) K. Hirotsu, T. Higuchi, K. Fujita, T. Ueda, A. Shinoda, T. Imoto, I. Tabushi, *J. Org. Chem.* **1982**, *47*, 1143–1144; b) J. L. Sessler, A. Andrievsky, P. A. Gale, V. Lynch, *Angew. Chem.* **1996**, *108*, 2954–2957; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2782–2785; c) A. Zanotti-Gerosa, E. Solari, L. Giannini, A. Chiesa-Villa, C. Rizzoli, *Chem. Commun.* **1996**, 119–120; d) M. Dimitrius, A. Terzius, A. W. Coleman, C. de Rango, *Carbohydr. Res.* **1996**, *282*, 125–135; e) I. Baxter, A. Ben-Haida, H. M. Colquhoun, P. Hodge, F. H. Kohnke, D. J. Williams, *Chem. Commun.* **1998**, 2213–2214.
- [6] For books and reviews on molecules incorporating interlocked components, see a) J.-C. Chambron, C. O. Dietrich-Buchecker, J.-P. Sauvage, *Top. Curr. Chem.* **1993**, *165*, 131–162; b) H. W. Gibson, M. C. Bheda, P. T. Engen, *Prog. Polym. Sci.* **1994**, *19*, 843–945; c) D. B. Amabilino, J. F. Stoddart, *Chem. Rev.* **1995**, *95*, 2725–2828; d) M. Belohradsky, F. M. Raymo, J. F. Stoddart, *Collect. Czech. Chem. Commun.* **1996**, *61*, 1–43; e) M. Belohradsky, F. M. Raymo, J. F. Stoddart, *Collect. Czech. Chem. Commun.* **1996**, *61*, 527–557; f) M. Fujita, K. Ogura, *Coord. Chem. Rev.* **1996**, *148*, 249–264; g) R. Jäger, F. Vögtle, *Angew. Chem.* **1997**, *109*, 986–988; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 930–944; h) S. A. Nepogodiev, J. F. Stoddart, *Chem. Rev.* **1998**, *98*, 1959–1976; i) M. Fujita, *Acc. Chem. Res.* **1999**, *32*, 53–61; j) D. A. Leigh, A. Murphy, *Chem. Ind.* **1999**, 178–183; k) G. A. Breault, C. A. Hunter, P. C. Mayers, *Tetrahedron* **1999**, *55*, 5265–5293; l) *Molecular Catenanes, Rotaxanes and Knots* (Eds.: C. O. Dietrich-Buchecker, J.-P. Sauvage), Wiley-VCH, Weinheim, **1999**; m) F. M. Raymo, J. F. Stoddart, *Chem. Rev.* **1999**, *99*, 1643–1664.
- [7] a) D. B. Amabilino, P. R. Ashton, V. Balzani, S. E. Boyd, A. Credi, J. Y. Lee, S. Menzer, J. F. Stoddart, M. Venturi, D. J. Williams, *J. Am. Chem. Soc.* **1998**, *120*, 4295–4307; b) D. B. Amabilino, P. R. Ashton, J. A. Bravo, F. M. Raymo, J. F. Stoddart, A. J. P. White, D. J. Williams, *Eur. J. Org. Chem.* **1999**, 1295–1302.
- [8] a) P. R. Ashton, S. Menzer, F. M. Raymo, G. K. H. Shimizu, J. F. Stoddart, D. J. Williams, *Chem. Commun.* **1996**, 487–490; b) M. Asakawa, P. R. Ashton, S. Menzer, F. M. Raymo, J. F. Stoddart, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1996**, *2*, 877–893.
- [9] The bis(hexafluorophosphate) salt $1 \cdot 2\text{PF}_6$ was prepared by treating the dibromide **2** with 4,4'-bipyridine. The dibromide **2** was synthesized in three steps by 1) allowing methyl 4-hydroxybenzoate to react with 2,6-bis(hydroxymethyl)pyridine ditosylate (tosylate = toluene-4-sulfonate), 2) reducing the ester groups, and 3) brominating the resulting hydroxymethyl groups.

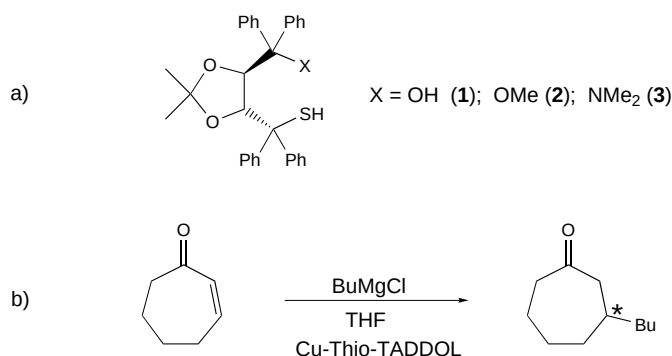
- [10] Crystal data for $4 \cdot 4\text{PF}_6 \cdot [\text{C}_{98}\text{H}_{98}\text{N}_6\text{O}_{14}][\text{PF}_6]_4 \cdot 4\text{MeCN} \cdot 2.5\text{H}_2\text{O}$, $M_r = 2373.0$, triclinic, space group $P\bar{1}$ (no. 2), $a = 13.567(1)$, $b = 17.762(2)$, $c = 24.924(3)$ Å, $\alpha = 74.41(1)$, $\beta = 87.72(1)$, $\gamma = 73.23(1)^\circ$, $V = 5534.5(9)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.424$ g cm⁻³, $\mu(\text{Cu}_{\text{K}\alpha}) = 15.8$ cm⁻¹, $F(000) = 2458$, $T = 193$ K; red rhombs, $0.56 \times 0.35 \times 0.32$ mm, Siemens P4 rotating anode diffractometer, graphite-monochromated $\text{Cu}_{\text{K}\alpha}$ radiation, ω scans, 16246 independent reflections. The structure was solved by direct methods. The major-occupancy non-hydrogen atoms of the [2]catenane and of the hexafluorophosphate counterions, as well as the full-occupancy non-hydrogen atoms of the included solvent molecules, were refined anisotropically (the others isotropically) using full-matrix least squares based on F^2 to give $R_1 = 0.096$, $wR_2 = 0.243$ for 9537 independent observed reflections ($|F_o| > 4\sigma(|F_o|)$), $2\theta \leq 120^\circ$) and 1507 parameters. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-132674. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [11] The mean interplanar separations between the inside and alongside 1,5-dioxynaphthalene ring systems and the inside bipyridinium unit are 3.37 and 3.32 Å, respectively.
- [12] The C $\cdots$ O and H $\cdots$ O distances and the C–H $\cdots$ O angles are 3.29 Å, 2.38 Å, 158° and 3.30 Å, 2.44 Å, 148° , respectively.
- [13] The mean interplanar separations between the interacting 1,5-dioxynaphthalene and bipyridinium units and between the phenoxy and pyridyl rings are 3.42 and 3.67 Å, respectively.
- [14] The H $\cdots$ π distance and the C–H $\cdots$ π angle are 2.95 Å and 139° .
- [15] The H $\cdots$ π distance and the C–H $\cdots$ π angle are 2.77 Å and 132° . C–H $\cdots$ π interactions of this type have been observed previously; see, for example, a) M. Asakawa, P. R. Ashton, W. Hayes, H. M. Janssen, E. W. Meijer, S. Menzer, D. Pasini, J. F. Stoddart, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1998**, 120, 920–931; b) P. R. Ashton, S. E. Boyd, A. Brindle, S. J. Langford, S. Menzer, L. Pérez-García, J. A. Preece, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White, D. J. Williams, *New J. Chem.* **1999**, 23, 587–602.
- [16] I. O. Sutherland, *Annu. Rep. NMR Spectrosc.* **1971**, 4, 71–235.
- [17] K. A. Connors, *Binding Constants*, Wiley, New York, **1987**.
- [18] a) J. P. Waltho, D. H. Williams, *J. Am. Chem. Soc.* **1989**, 111, 2475–2480; b) M. Schäfer, T. R. Schneider, G. M. Sheldrick, *Structure* **1996**, 4, 1509–1515; c) P. J. Loll, A. E. Bevivino, B. D. Korty, P. H. Axelsen, *J. Am. Chem. Soc.* **1997**, 119, 1516–1522; d) G. M. Sheldrick, E. Paulus, L. Vétesy, F. Hahn, *Acta Crystallogr. Sect. B* **1995**, 51, 89–98; e) M. Schäfer, E. Pohl, K. Schmidt-Bäse, G. M. Sheldrick, R. Hermann, A. Malabarba, M. Nebuloni, G. Pelizzi, *Helv. Chim. Acta* **1996**, 79, 1916–1924; f) D. H. Williams, B. Bardsley, *Angew. Chem.* **1999**, 111, 1264–1286; *Angew. Chem. Int. Ed.* **1999**, 38, 1172–1193.

X-Ray, Molecular Diffusion, and NOESY NMR Studies of Chiral, Tetranuclear Cu^I Catalysts Based on Monodentate Thiol Analogues of TADDOL**

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Dieter Seebach*

Chiral Lewis acid catalysts, and specifically homogeneously catalyzed conjugate addition reactions based on copper complexes, have been studied extensively in recent years.^[1–3] Frequently, the metal is introduced as a simple salt, and occasionally as a preformed chelate complex. There is relatively little known about the structures of the metal complex intermediates which develop during the catalysis, especially when several metal centers are present.^[4]

One of our groups^[5] has reported on the enantioselective 1,4-addition of Grignard reagents to enones using CuCl and the thiols **1–3**. These ligands are O,S and N,S analogues of TADDOL a versatile and synthetically accessible chiral auxiliary.^[6] During our investigations it was found that thiol **1** gives rise to preferential formation of (–)-(S)-3-butylcycloheptanone, whereas **2** or **3** afford mainly (+)-(R)-3-butylcycloheptanone from cycloheptenone and BuMgCl (Scheme 1).^[5]



Scheme 1. a) Thiol-TADDOL ligands **1–3**. b) Copper-catalyzed conjugate addition: e.r. = 92:8 (with **1**), e.r. = 8:92 (with **2** or **3**).

We report here on a novel catalyst intermediate which is shown to be a tetranuclear, monodentate copper thiolate complex—that is, the second donor atom of the TADDOL

derivative is not complexed. This is unprecedented in that it is commonly thought that such auxiliaries act as bidentate ligands. Moreover, we suggest a) that this species retains its tetranuclear structure in solution upon addition of a model substrate, based on NMR diffusion measurements and b) that the selectivity inversion is based on structural differences in the tetranuclear species as shown by 2D ¹H NOE NMR spectroscopy.

The unexpected inversion in stereoselectivity as a function of auxiliary prompted us to determine the relationship between the enantiopurity of the product and that of the ligands **1** and **2**^[7] (Figure 1). The observed deviation from linearity is modest; nevertheless, these results suggest that

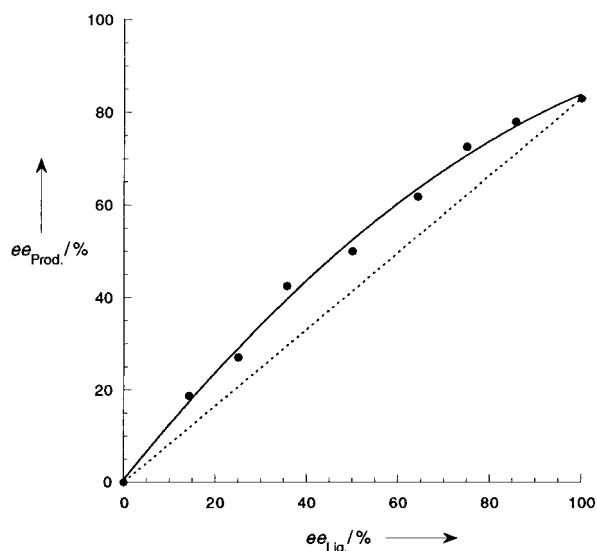
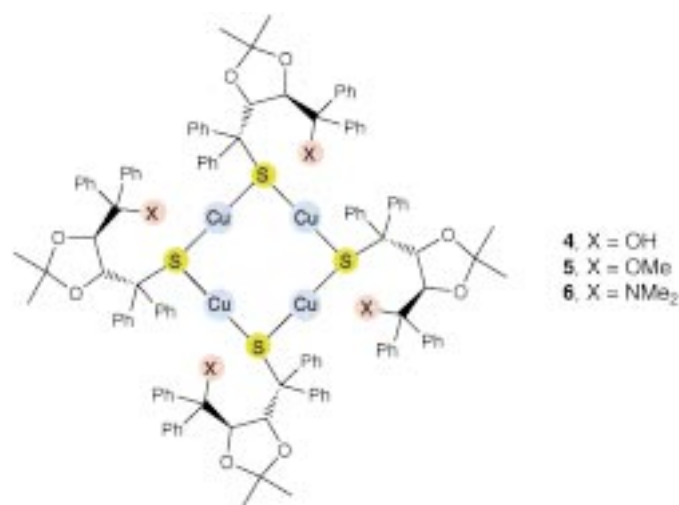


Figure 1. Observed positive nonlinear effect (NLE) for the copper-catalyzed 1,4-addition of BuMgCl to cycloheptenone using ligand **1**. A weaker, but still positive NLE, is observed with ligand **2**.^[5]

more than one ligand (and perhaps several metals) might be involved in the catalysis.^[8] Since higher molecular weight copper thiolates used in catalysis are isolable,^[9] we considered the copper coordination chemistry of **1–3**. Reaction of these auxiliaries with BuLi followed by addition of CuCl affords the tetranuclear copper thiolate complexes **4–6** in good yields.



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[**] TADDOL = α, α', α' -tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol.

Complex **4** can also be obtained—as an air-stable, crystalline material—by heating CuCl, **1**, and Et₃N at reflux in MeOH.

Complexes **4–6** show the same reactivity and selectivity previously observed for the in situ procedures.^[5] Consequently, they are either precursors or catalytically active species in this conjugate addition.

The solid-state structure of **4** was determined by X-ray diffraction methods (Figure 2). The complex contains a butterfly-type arrangement of the Cu₄S₄ core, although the

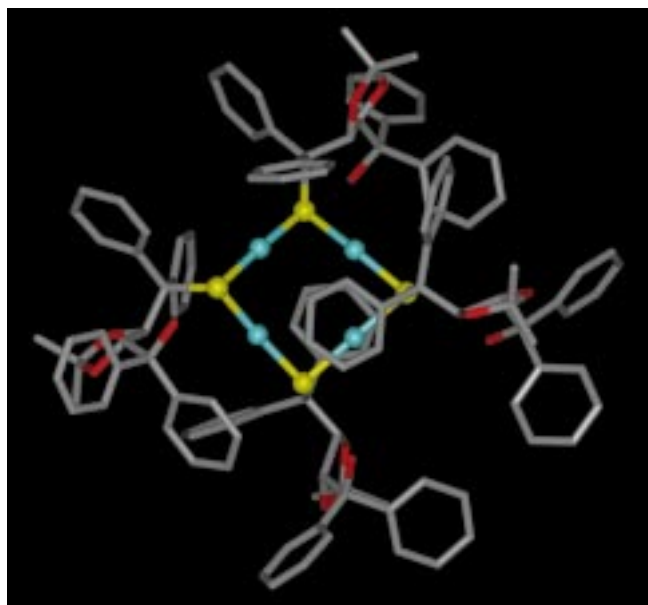


Figure 2. Structure of the tetranuclear Cu complex **4** based on X-ray diffraction data. The H atoms have been omitted for clarity; O atoms are indicated in red, S atoms in yellow, and Cu atoms in blue. The view has been generated with the program insight II (v. 98.0).

four metal atoms lie almost in a plane. Two Cu–Cu separations are relatively short (ca. 2.8 Å), and two are somewhat longer (ca. 3.0 Å). Each of the copper atoms is coordinated to two bridging thiolate sulfur donors (Cu–S 2.14–2.19 Å, S–Cu–S ca. 166 and ca. 177°), thus leaving each Cu^I center coordinatively unsaturated.^[10] The oxygen atom of the OH group is not complexed, based both on the very long O···Cu distances in the structure (3.9–4.3 Å) and the NMR signal observed for the OH proton in solution ($\delta \approx 8.7$). Consequently, this TADDOL-derived thiol is functioning as a monodentate and not a bidentate ligand for Cu^I. The same conclusion is reached for **5** and **6** based on NMR studies. We know of no documented example of a “successful” bidentate chiral auxiliary which functions as a monodentate ligand in enantioselective catalysis. The solid-state data show two different ligand environments per tetranuclear complex, and for the OMe analogue **5** this has been confirmed in solution by ¹H NMR measurements at 213 K.

In an attempt to prepare models related to our copper chemistry, we allowed **4–6** to react with an excess of *tert*-butylisocyanide in [D₈]THF to afford the corresponding isocyanide complexes **7–9**. These new compounds, generated in situ, show exchange of the isocyanide ligands in solution; however, ¹H NMR pulsed-gradient diffusion measure-

ments^[11, 12] on **7–9** reveal that these are also tetranuclear species (Figure 3). Diffusion measurements reflect molecular motion in solution and thus are sensitive to molecular weight. We used the measured diffusion data for the ligands **1** and **2**, which exist as a hydrogen-bonded dimer and monomer,

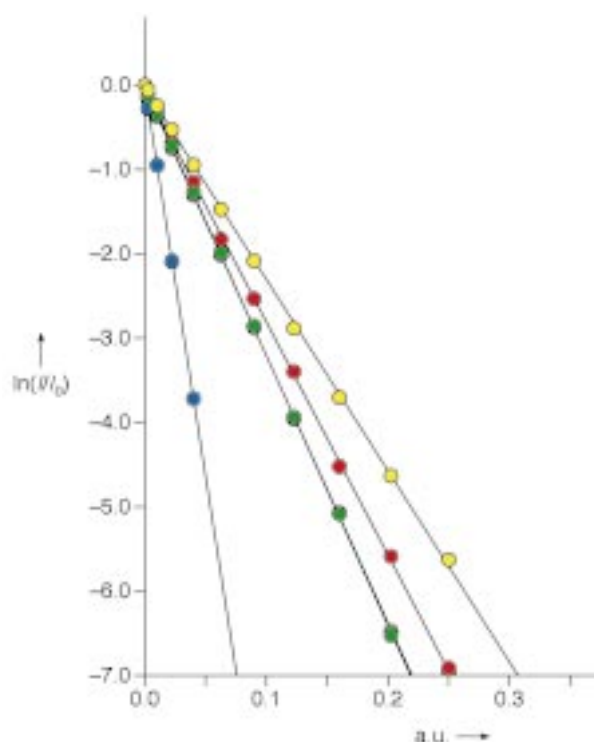


Figure 3. Results of the diffusion measurements using pulsed-field gradients^[11] for the isocyanide complex **7** (yellow), the ligand **1** (red), ligand **2** (green), and solvent THF (blue). The slopes are proportional to the diffusion coefficient (*D*) and to the hydrodynamic radii of **7**, **1**, **2**, and THF. The y axis represents a measure of the relative spin-echo signal intensity, and the x axis represents the square of the gradient amplitude in arbitrary units (a.u.).

respectively, as reference for **7–9**. The results confirm that **4–6** do not degrade to mononuclear species in the presence of additional ligands. To the best of our knowledge, this represents the first application of NMR diffusion measurements for the determination of the aggregation state^[13] of transition metal catalysts.

Despite the exchange, the residence time of the isocyanide donor in **7–9** is sufficient such that ¹H NOE NMR spectroscopy^[14] detects a variety of contacts from the complexed thiolate ligand to the *tert*-butyl group of the isocyanide (Figure 4). Analysis of these spectra suggests a different structure for **7** relative to **8** (and **9**). For **7** the NOE data clearly point to a structure in which the noncomplexed OH-containing section of the molecule has been rotated so as to bring the OH and *ortho* phenyl protons of one of the two rings in close proximity to the Cu center (Scheme 2). This is in contrast to the NOESY data for **8** and **9**, which suggest that the methoxy and dimethylamino groups remain remote from the metal.^[15] These structural differences create a different chiral environment around the copper atom and may be the source of the observed stereochemical inversion noted above.

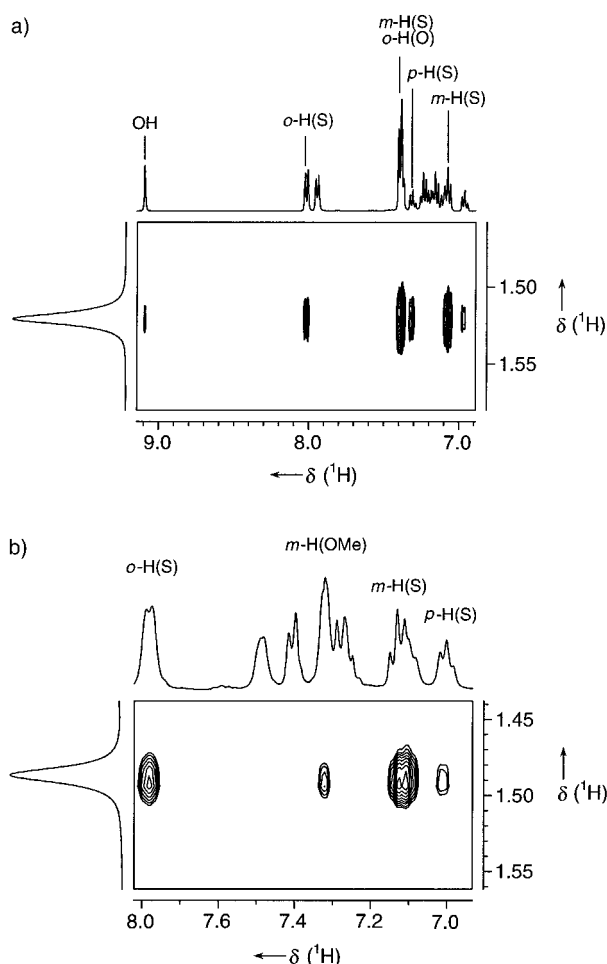
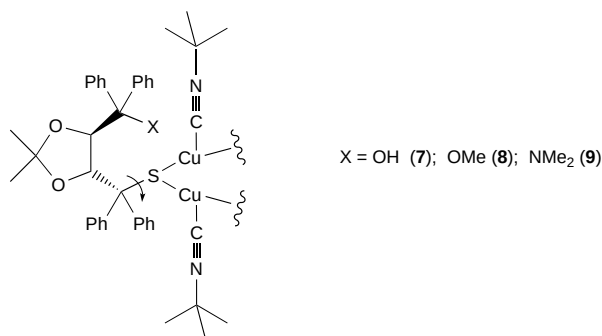


Figure 4. Sections of the NOESY NMR spectrum for the isocyanide complexes **7** (a) and **8** (b). In (a) there are NOEs from the OH proton and the *ortho*-phenyl protons of one of the phenyl rings of the $\text{Ph}_2\text{C}(\text{OH})$ moiety to the methyl protons of the isocyanide. In (b) the only strong NOEs arise from the *ortho*-phenyl protons of one of the proximate $\text{Ph}_2\text{C}(\text{S})$ rings to the methyl protons of the isocyanide. The dynamics for **7** are slightly different than for **8**. The letters in parenthesis (O, S, and OMe) refer to aryl protons of the $\text{Ph}_2\text{C}(\text{OH})$, $\text{Ph}_2\text{C}(\text{S})$, and $\text{Ph}_2\text{C}(\text{OMe})$ groups, respectively (400 MHz, $[\text{D}_8]\text{THF}$, ambient temperature, $\tau = 650\text{--}800\text{ ms}$).



Scheme 2. Fragment showing the rotation around the C–S bond. This rotation brings the OH group and the corresponding phenyl rings closer to the isocyanide ligand.

Concluding, we find that the Cu-catalyzed enantioselective conjugate addition with ligands **1–3** proceeds via a tetranuclear species which uses an unprecedented monodentate complexation mode. Diffusion measurements are shown to be

valuable for the determination of the aggregation state of organocopper complexes in solution.

Experimental Section

Crystal structure analysis of **4**: $\text{C}_{124}\text{H}_{116}\text{Cu}_4\text{O}_{12}\text{S}_4 + \text{C}_{6.75}$, $M_r = 2261.64$, colorless crystal ($0.3 \times 0.26 \times 0.08\text{ mm}^3$). Suitable crystals were obtained from THF/hexane at 5°C . A single crystal was sealed in a glass capillary and cooled to -35°C . A data set covering a full sphere up to $2\theta = 46.50^\circ$ was collected on a Siemens SMART platform diffractometer equipped with a CCD detector ($\text{MoK}\alpha$ radiation, graphite monochromator, ω scans with 0.3° step width). Data reduction and corrections for Lorentz polarization and absorption ($\mu = 0.761\text{ mm}^{-1}$, min./max. transmission 0.9416/0.8038) were performed using the programs SAINT^[16] and SADABS.^[17] The structure was solved by direct methods and refined by full-matrix least squares (versus F^2) with the SHELXTL program package:^[17] orthorhombic, space group $P2_12_12_1$; $a = 20.768(3)$, $b = 40.580(6)$, $c = 15.467(2)\text{ \AA}$, $V = 13035(3)\text{ \AA}^3$; $Z = 4$; of 69777 reflections, 18575 were independent ($R_{\text{int}} = 0.1135$); $R1 = 0.0707$, $wR2 = 0.1625$ for 1388 parameters and 12070 reflections with $I > 2\sigma(I)$. The residual electron density was 0.447 and $-0.416\text{ e \AA}^{-3}$. All non-hydrogen atoms, except the atoms belonging to disordered solvent molecules, were refined with anisotropic thermal parameters for each group, and all hydrogen atoms were placed at calculated positions and refined with common isotropic thermal parameters for each group. Several disordered solvent molecules were described with partially occupied C atom positions. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-125017. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: July 19, 1999 [Z13744]

- Review articles on stereoselective synthesis involving Cu derivatives: a) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, 92, 771–806; b) N. Krause, A. Gerold, *Angew. Chem.* **1997**, 109, 194–213; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 186–204; c) A. Alexakis in *Transition Metal Catalysed Reactions* (Eds.: S.-I. Murahashi, S. G. Davies), IUPAC Blackwell Science, Oxford, **1999**, pp. 303–316.
- a) K. H. Ahn, R. B. Klassen, S. J. Lippard, *Organometallics* **1990**, 9, 3178–3181; b) M. Spescha, G. Rihs, *Helv. Chim. Acta* **1993**, 76, 1219–1230; c) A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, 4, 2427–2430; d) G. van Koten, *Pure Appl. Chem.* **1994**, 66, 1455–1462; e) Q.-L. Zhou, A. Pfaltz, *Tetrahedron* **1994**, 50, 4467–4478; f) M. Kanai, K. Tomioka, *Tetrahedron Lett.* **1995**, 36, 4275–4278; g) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem.* **1997**, 109, 2733–2736; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2620–2623; h) A. K. H. Knöbel, I. H. Escher, A. Pfaltz, *Synlett* **1997**, 1429–1431; i) A. Alexakis, J. Vastra, J. Burton, C. Benhaim, P. Mangeney, *Tetrahedron Lett.* **1998**, 39, 7869–7872; j) Y. Nakagawa, M. Kanai, Y. Nagaoka, K. Tomioka, *Tetrahedron* **1998**, 54, 10295–10307; k) M. Yan, L.-W. Yang, K.-Y. Wong, A. S. C. Chan, *Chem. Commun.* **1999**, 11–12.
- Recent review on copper-catalyzed conjugate addition: N. Krause, *Angew. Chem.* **1998**, 110, 295–297; *Angew. Chem. Int. Ed.* **1998**, 37, 283–285.
- a) E. Nakamura, S. Mori, K. Morokuma, *J. Am. Chem. Soc.* **1997**, 119, 4900–4910; b) K. Nilsson, T. Andersson, C. Ullenius, A. Gerold, N. Krause, *Chem. Eur. J.* **1998**, 4, 2051–2058; c) J. Canisius, A. Gerold, N. Krause, *Angew. Chem.* **1999**, 111, 1727–1730; *Angew. Chem. Int. Ed.* **1999**, 38, 1644–1646.
- a) D. Seebach, G. Jaeschke, A. Pichota, L. Audergon, *Helv. Chim. Acta* **1997**, 80, 2515–2519; b) the preparation of **2** and its application in catalysis has not yet been reported: D. Seebach, A. Pichota, unpublished results.
- a) D. Seebach, A. K. Beck, M. Hayakawa, G. Jaeschke, F. N. M. Kühnle, I. Nägeli, A. B. Pinkerton, P. B. Rheiner, R. O. Duthaler,

- P. M. Rothe, W. Weigand, R. Wünsch, S. Dick, R. Nesper, M. Wörle, V. Gramlich, *Bull. Soc. Chim. Fr.* **1997**, 134, 315–331; b) D. Seebach, A. Pichota, A. K. Beck, A. B. Pinkerton, T. Litz, J. Karjalainen, V. Gramlich, *Org. Lett.* **1999**, 1, 55–58.
- [7] The enantiopurity of the catalyst was obtained by mixing appropriate amounts of the ligand with *R,R* and *S,S* configuration.
- [8] Nonlinear effects in asymmetric catalysis have been described in detail: a) D. Guillauneux, S.-H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, 116, 9430–9439; b) M. Reggelin, *Nachr. Chem. Tech. Lab.* **1997**, 45, 392–396; c) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, 110, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, 37, 2923–2959.
- [9] D. M. Knotter, G. van Koten, H. L. van Maanen, D. M. Grove, A. L. Spek, *Angew. Chem.* **1989**, 101, 351–352; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 341–342.
- [10] Selected examples of polynuclear Cu complexes with thiolate ligands: a) W. Clegg, C. D. Garner, J. R. Nicholson, P. R. Raithby, *Acta Crystallogr. Sect. C* **1983**, 39, 1007–1009; b) D. M. Knotter, A. L. Spek, G. van Koten, *J. Chem. Soc. Chem. Commun.* **1989**, 1738–1740; c) B. Becker, W. Wojnowski, K. Peters, E. M. Peters, H. G. von Schnering, *Polyhedron* **1990**, 9, 1659–1666; d) D. M. Knotter, H. L. van Maanen, D. M. Grove, A. L. Spek, G. van Koten, *Inorg. Chem.* **1991**, 30, 3309–3317; e) D. M. Knotter, D. M. Grove, W. J. J. Smeets, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **1992**, 114, 3400–3410; f) Review article on Cu^I compounds: C. E. Holloway, M. Melnik, *Rev. Inorg. Chem.* **1995**, 15, 147–387.
- [11] P. Stilbs, *Prog. Nucl. Magn. Reson.* **1987**, 19, 1–45.
- [12] All the diffusion measurements were carried out at 400 MHz by dissolving the sample in [D₈]THF at 20 °C and using the standard Stejskal–Tanner sequence.^[18] The shape for the gradients was rectangular and their strength was varied in the course of the experiment. The pulse length was 5 ms and the time between the two gradients (Δ) was 75 ms.
- [13] The aggregation state of organocopper compounds in solution has been determined by others methods: a) R. G. Pearson, C. D. Gregory, *J. Am. Chem. Soc.* **1976**, 98, 4098–4104; b) E. C. Ashby, J. J. Watkins, *J. Am. Chem. Soc.* **1977**, 99, 5312–5317; c) A. Gerold, J. T. B. H. Jastrzebski, C. M. P. Kronenburg, N. Krause, G. van Koten, *Angew. Chem.* **1997**, 109, 778–780; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 755–757; d) H. Huang, C. H. Liang, J. E. Penner-Hahn, *Angew. Chem.* **1998**, 110, 1628–1630; *Angew. Chem. Int. Ed.* **1998**, 37, 1564–1566; e) B. H. Lipshutz, J. Keith, D. J. Buzard, *Organometallics* **1999**, 18, 1571–1574.
- [14] Applications in transition metal complexes: a) P. S. Pregosin, R. Salzmänn, *Coord. Chem. Rev.* **1996**, 155, 35–68; b) P. S. Pregosin, G. Trabesinger, *J. Chem. Soc. Dalton Trans.* **1998**, 727–734.
- [15] It is likely that OH deprotonation and subsequent Mg^{II} complexation will prove to be important in determining the stereochemical course of the reaction.
- [16] SAINT, Version 4, Siemens Analytical X-ray Systems, Inc., Madison, Wisconsin, USA.
- [17] a) SADABS, G. Sheldrick, Göttingen, **1997**; b) SHELXTL program package, Version 5.1, Bruker AXS, Inc., Madison, Wisconsin, USA.
- [18] E. O. Stejskal, J. E. Tanner, *J. Chem. Phys.* **1965**, 42, 288–292.

Acetyl Substitution of the O-Specific Caryan from the Lipopolysaccharide of *Pseudomonas (Burkholderia) caryophylli* Leads to a Block Pattern**

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Most of the O-specific polysaccharides of lipopolysaccharides (LPS) from Gram-negative bacteria represent heteropolysaccharides furnished with repeating units that comprise between two and eight monosaccharidic residues.^[1] A large variety of sugars has been identified in such O-specific polysaccharides, which additionally may be phosphorylated, methylated, substituted by amino acids, or acetylated. Especially the last decoration has been frequently identified; it is always present in nonstoichiometric amounts. The acetylation takes place in later steps of O-specific polysaccharide biosynthesis and has been discussed as a microheterogenic property of LPS. In some cases, homopolysaccharides have been identified as O-specific polysaccharides which are mainly furnished from (amino-)deoxy sugars that may be N- and/or O-acylated, thus resulting in rather hydrophobic molecules.^[2, 3] However, the influence of O-acetyl groups on the conformation of O-specific polysaccharides in general and on the establishment of O-antigenic conformational epitopes has not been investigated.

Few bacteria possess LPS that contain two different O-specific polysaccharides. In particular, this phenomenon is typical for *Burkholderia*,^[3] a genus that comprises species which are pathogenic either to humans or plants. *Pseudomonas (Burkholderia) caryophylli* is a phytopathogenic bacterium responsible for the wilting of carnation.^[4] Its LPS contain two linear homopolysaccharides as O-specific polysaccharides that are built up by two novel and rather peculiar monosaccharides. The major LPS portion possesses a polysaccharide termed caryophyllan, consisting of α -(1→7)-linked caryophyllose (3,6,10-trideoxy-4-C-(D-glycero-1-hydroxyethyl)-D-erythro-D-gulo-decose).^[5–7] The minor LPS portion contains a polysaccharide named caryan, built up from β -(1→7)-linked caryose (4,8-cyclo-3,9-dideoxy-L-erythro-D-ido-nonose).^[7, 8] These O-specific polysaccharides are thought to be involved

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[**] This work was supported in the framework of the VIGONI program by the Deutscher Akademischer Austauschdienst (O.H.) and the Conferenza Permanente dei Rettori delle Università Italiane (M.P., C.D.C., A.M.). The 750-MHz NMR spectra were obtained using a Varian Unity Inova spectrometer of the Danish Instrument Center for NMR Spectroscopy of Biological Macromolecules.

in bacteria–plant interactions and, thus, to represent important virulence factors. Here we report that the caryan is acetylated in an unusual pattern, which may have an impact on the interaction between the LPS and the plant surface.

The lipid A free caryan (molecular mass 38 kDa) was prepared from LPS by mild acid hydrolysis and purification using gel-permeation chromatography. The 1D ^1H NMR spectrum of the sample (Figure 1) revealed the presence of O-acetyl groups (signals at $\delta = 2.17$ and 2.18), a feature that

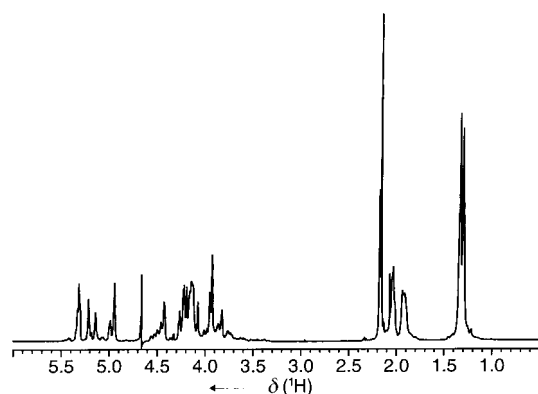


Figure 1. The 1D ^1H NMR spectrum of the acetylated caryan from LPS of *Pseudomonas (Burkholderia) caryophylli*. The spectrum was recorded in D_2O at 750 MHz and 37 °C.

had not been detected before. To exclude the possibility of migration and loss of acetyl groups under acidic conditions, milder hydrolysis conditions of LPS were applied, either by reducing the time of hydrolysis in 1 % acetic acid to one hour or by hydrolysis in 100 mM sodium acetate buffer containing 1 % SDS (pH 4.4, 100 °C, 2 h).^[9] The 1D ^1H NMR spectra revealed in all cases the same acetylation pattern in the caryan. Methylation analysis of the caryan identified exclusively 7-substituted caryose, in accordance with earlier data.^[8]

Chemical shifts obtained by NMR spectroscopy were assigned using 2D homo- and heteronuclear experiments at 750 MHz (^1H ; Table 1). In the ^1H NMR spectrum of the non-acetylated caryan, the small coupling constant ($^3J_{\text{H1,H2}} < 4$ Hz) indicates a synclinal orientation of the protons H1 and H2, that is, the β configuration of the glycosidic linkage. The caryose monosaccharide gives rise to two unconnected spin systems, H1/H3 and H5/H7. Each of these spin systems can be assigned using 2D COSY and TOCSY NMR spectra. Furthermore, the protons of the methyl group (H9) are not connected by spin–spin coupling to any of the other protons. However, both separate spin systems can be connected through NOE contacts and long-range ^1H , ^{13}C coupling constants. The interpretation of the NOE cross-peaks requires a simple molecular modeling study, as is described in detail below for acetylated polysaccharide.

Table 1. ^1H and ^{13}C NMR data for de-O-acetylated (D) and acetylated (A) caryan from the LPS of *Pseudomonas (Burkholderia) caryophylli*.^[a]

Unit	Chemical shift δ ($^1\text{H}/^{13}\text{C}$)									
	1	2	3 _{ax}	3 _{eq}	4	5	6	7	8	9
D										
d-d-d	5.218 (96.2)	4.155 (64.6)	2.055 (30.4)	1.909 –	– (78.2)	4.271 (74.3)	4.219 (77.7)	3.953 (87.6)	– (78.7)	1.30 (15.7)
td	5.186	4.127	2.334	2.093	–	4.429	4.060	4.325	–	1.30
β -red	4.942	3.966	1.993	1.791	–	–	–	–	–	–
α -red	4.559	3.854	1.838	2.111	–	–	–	–	–	–
A										
1, a-a-a	4.944 (97.1)	4.127 (64.6)	2.036 (30.4)	1.933 –	– (78.6)	4.425 (73.7)	5.309 (79.4)	3.922 (87.0)	– (79.3)	1.32 (15.7)
2, a-a-d	5.144 (97.5)	4.162 (64.4)	2.042 (30.4)	1.944 –	– (78.6)	4.496 (73.7)	5.324 (79.4)	3.928 (87.0)	– (79.3)	1.32 (15.7)
3, d-a-a	4.953 (97.1)	4.131 (64.6)	2.036 (30.4)	1.933 –	– (78.6)	4.453 (73.8)	5.323 (79.4)	4.079 (85.9)	– (79.3)	1.30 (15.7)
4, d-a-d	5.144 (97.4)	4.162 (64.6)	2.042 (30.4)	1.944 –	– (78.6)	4.526 (73.8)	5.336 (79.4)	4.075 (85.9)	– (79.3)	1.30 (15.7)
5, d-d-d	5.218 (96.2)	4.152 (64.6)	2.051 (30.4)	1.911 –	– (78.2)	4.272 (74.3)	4.225 (77.7)	3.954 (87.6)	– (78.7)	1.30 (15.7)
6, d-d-a	4.985 (96.4)	4.111 (64.6)	2.029 (30.4)	1.898 –	– (78.2)	4.200 (74.3)	4.248 (77.7)	3.980 (87.6)	– (78.7)	1.30 (15.7)
7, a-d-d	5.207 (96.2)	4.148 (64.6)	2.044 (30.4)	1.905 –	– (78.2)	4.194 (74.2)	4.215 (77.7)	3.830 (89.1)	– (78.7)	1.34 (15.7)
8, a-d-a	5.000 (96.4)	4.116 (64.6)	2.029 (30.4)	1.898 –	– (78.2)	4.194 (74.2)	4.191 (77.7)	3.822 (89.1)	– (78.7)	1.34 (15.7)
td-d	5.186 (96.2)	4.127 (64.6)	2.334 (30.4)	2.099 –	– (72.1)	4.432 (76.8)	4.064 (76.8)	4.330 (78.1)	– (78.1)	1.32 (15.7)
ta-d	–	–	–	–	–	4.356	5.417	4.009	–	–
ta-a	–	–	–	–	–	4.420	5.436	4.012	–	–
β -red	4.942	3.966	1.993	1.791	–	–	–	–	–	–
α -red	4.466	3.824	1.794	2.079	–	–	–	–	–	–

[a] The spectra were recorded at 750 MHz (^1H) and 188.6 MHz (^{13}C) in D_2O at 37 °C. The ^1H NMR data are given for each type in the first row, the ^{13}C NMR data in the second (in parentheses). The coupling constants could not be measured accurately and only the following estimates were possible: $J_{\text{H1,H2}}$ small, $J_{\text{H2,H3ax}}$ large, $J_{\text{H2,H3eq}}$ small, $J_{\text{H5,H6}}$ large, $J_{\text{H6,H7}}$ medium. The residue observed in the NMR spectra is shown in boldface. A = acetylated caryan; a = 6-O-acetylated monomer; α -red = α -configured reducing end; β -red = β -configured reducing end; D = de-O-acetylated caryan; d = non-acetylated monomer; t = terminal. Signals of the O-acetyl group: ^1H NMR: $\delta = 2.17$ (a-a-a, a-a-d), and 2.18 (d-a-a, d-a-d); ^{13}C NMR: $\delta = 20.0$ (a-a-a, a-a-d, d-a-a, d-a-d).

The structure of the repeating unit is confirmed by the long-range coupling constants which link the two ^1H spin systems by connectivities from H9 to C4 and C7 and from H3_{eq} to C4. The glycosidic linkage is clearly proven by the long-range connectivities between H1 and C7 and between C7 and H1. The high quality of the spectra obtained from high-field NMR experiments allows also the identification of the nonreducing terminal residue, which is characterized by chemical shifts at $\delta = 4.060$ (H6) and 4.325 (H7). The comparison with the corresponding shifts for the glycosylated residues ($\delta = 4.219$ and 3.953, respectively) shows a clear glycosylation effect. The signal for the residue at the nonreducing end possesses an relative intensity of approximately 0.5 % relative to that of the residues in the chain. This value is in good agreement with the determined average molecular mass of 38 kDa, corresponding to an average degree of polymerization of approximately 180 monosaccharide units. With regard to the reducing end it is only possible to assign the signals for H1, H2 and the two H3 protons with an $\alpha:\beta$ ratio of approximately 2:3.

A more complex problem is posed by the structural elucidation of the acetylated polysaccharide. The NMR data (Table 1) indicate that several different caryose residues occur which differ in their position in the caryan and in their acetyl substitution. As for the non-acetylated caryan, two independent spin systems were identified for each type of residue (H1/H3 and H5/H7). In the 750-MHz ^1H NMR spectra of the acetylated polysaccharide, eight such spin systems were identified which could all be connected by cross-peaks obtained in a NOESY experiment (Table 2); the cross-peaks result from the close contact between H3_{ax} and H5. Likewise,

H9 could be assigned by similar cross-peaks between H7 and H9. These assignments were confirmed by long-range $^{13}\text{C},^1\text{H}$ spin-spin couplings in an HMBC experiment. The spin systems 1–8 (Table 3) identified eight different caryose units, four that are acetylated at O6 (type 1–4) and four that are not (types 5–8). Acetylation at O6 was proven by the down-field chemical shifts observed for H6 and C6, compared to those of unsubstituted caryose, and was confirmed by long range $^{13}\text{C},^1\text{H}$ spin-spin couplings between H6 and the carbonyl carbon atom.

Table 3. Spin systems identified in the acetylated caryan.

Type	Spin system ^[a]	Type	Spin system ^[a]
1:	a-a-a (25 %)	5:	d-d-d (20 %)
2:	a-a-d (12 %)	6:	d-d-a (10 %)
3:	d-a-a (12 %)	7:	a-d-d (10 %)
4:	d-a-d (6 %)	8:	a-d-a (5 %)

[a] The amounts are given as a percentage, as identified by integration of the NMR signals. a = 6-O-acetylated monomer; d = non-acetylated monomer. The residue observed in the NMR spectrum is shown in boldface.

The linkages between the eight different residues were assigned with data obtained from NMR spectra at 750 MHz. The dipole-dipole correlations observed in a NOESY spectrum identified the sequence of the residues (Figures 2 and 3, Table 2). Important NOE connectivities are those between H1 of the glycosyl donor and H6 and H7 of the glycosylated residue. The NOESY spectrum in Figure 2a shows that a type 1 residue (**a-a-a**, a = acetylated caryose; the residue under consideration is in boldface) is linked to another acetylated caryose (cross-peak between H1 of the residue under consideration and H7 of another acetylated residue). Likewise, the H1 signal of a type 2 caryose (**a-a-d**, d = non-acetylated residue) gave a corresponding NOE signal for a non-acetylated residue. For both type 1 and 2 residues, the residue at the nonreducing end was identified as the acetylated residue, owing to NOE connectivities between H1 of an acetylated residue and H6 and H7 of the glycosylated residue. Similarly, types 3–8 can be assigned. Figure 2b shows that the sequential assignment of acetylated types 1–4 can additionally be obtained by the identification of NOE contacts between H5 of the glycosylating residue and H7 of the glycosylated residue. It should be noted that the NOE signal between H5 and H7 within the same residue is clearly differentiated by a TOCSY spectrum.

The sequence information obtained by NOE contacts was confirmed by long-range $^{13}\text{C},^1\text{H}$ couplings observed in an HMBC experiment. For most of the eight residue types, chemical shifts for C7 are distinct and allow assignment of the long-range connectivities to H1 of the glycosylating residue. Based on the proportion of the eight structure types, as estimated from integration of the 1D ^1H NMR spectra, the ratio of acetylated to non-acetylated residues is approximately one to one.

The assignment of the residue sequence is only possible since the acetyl group at O6 affects not only the chemical shifts of H6 and the proximal H5 and H7, but also that of H1 in the glycosylating residue (compare the corresponding chemical shifts of, for example, residues of types 1 and 2 (**a-a-a** and

Table 2. NOE contacts observed for the acetylated caryan.^[a]

Type(s)	Monomer(s)	NOE contacts ^[b]
<i>intraresidual</i>		
1–4	-a-	H1–H2 (s), H2–H3 _{eq} (s), H2–H3 _{ax} (s), H3 _{ax} –H5 (s), H3 _{ax} –H9 (s), ^[c] H3 _{eq} –H9 (s), H5–H6 (m), H5–H7(m), H6–H7 (m)
5–8	-d-	H1–H2 (s), H2–H3 _{eq} (s), H2–H3 _{ax} (s), H3 _{ax} –H5 (s), H3 _{ax} –H9 (s), ^[c] H3 _{eq} –H9 (s), H5–H7(m), H6–H7 (m)
<i>interresidual towards the reducing end</i>		
1+3	-a-a	H1–H6a (s), H1–H7a (m), H3 _{ax} –H9 (s), ^[c] H5–H7a (m), H5–H9 (m)
6+8	-d-a	H1–H6a (s), H1–H7a (m), H3 _{ax} –H9 (s), ^[c] H5–H7a (m), H5–H9 (m)
2+4	-a-d	H1–H6a (s), H1–H7a (m), H3 _{ax} –H9 (s), ^[c] H5–H7a (m), H5–H9 (m)
5+7	-d-d	H1–H6a (s), H1–H7a (m), H3 _{ax} –H9 (s), ^[c] H5–H7a (m), H5–H9 (m)
<i>interresidual towards the nonreducing end</i>		
1+2	a-a-	H6–H1a (s), H7–H1a (m), H7–H5a (m), H9–H3 _{ax} a (s), ^[c] H9–H5a (m)
7+8	d-a-	H6–H1a (s), H7–H1a (m), H7–H5a (m), H9–H3 _{ax} a (s), ^[c] H9–H5a (m)
3+4	a-d-	H6–H1a (s), H7–H1a (m), H7–H5a (m), H9–H3 _{ax} a (s), ^[c] H9–H5a (m)
5+6	d-d-	H6–H1a (s), H7–H1a (m), H7–H5a (m), H9–H3 _{ax} a (s), ^[c] H9–H5a (m)

[a] The NOE contacts are divided into strong (s), medium (m), and weak (w). a = 6-O-acetylated monomer; d = non-acetylated monomer. [b] For the interresidual NOEs, the first ^1H is from the residue in boldface. [c] Sum of intra- and interresidual NOE contacts.

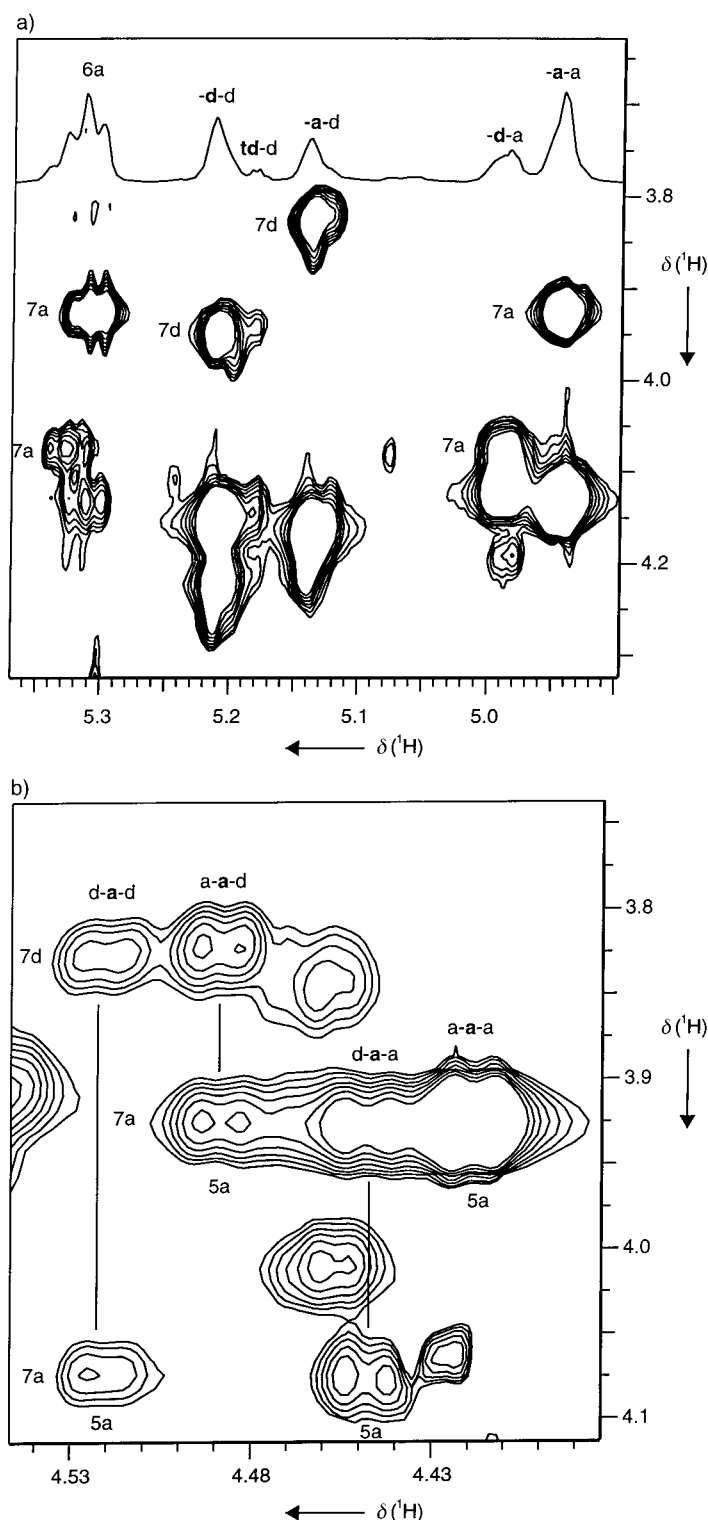


Figure 2. Sections of the NOESY spectrum (40 ms) of the acetylated caryan. a) Regions showing the sequential connectivities between the anomeric H1 and H7 of the adjacent residue; b) region showing the intra- and interresidual NOE connectivities between H5 of acetylated residues and H7 of adjacent residues. The NOE contacts between H1 and H6 are not shown in this section. td = terminal non-acetylated monomer.

a-a-d) and 5 and 6 (d-d-d and d-d-a)). Such substantial effects through space are well described for carbonyl/ester functionalities, which have a large anisotropic effect on chemical shifts. Generally, smaller effects are seen for ^{13}C chemical shifts.

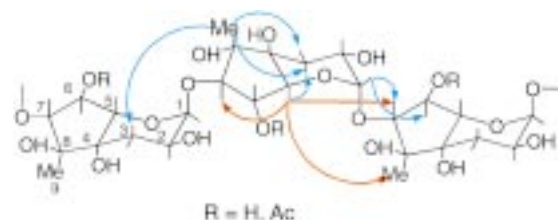


Figure 3. Trisaccharide structures representing structure types 1–8 and important NOE connectivities. Only NOE connectivities for the middle residue are shown; trivial NOEs between vicinal ^1H pairs are not included. Important NOE contacts from H5 to other protons are shown in red.

As in the case of the non-acetylated caryan, the NMR data of the terminal residues can be assigned. For the unsubstituted nonreducing end residue that is linked to another non-acetylated residue, a complete assignment was possible. For the other types of terminal residues, only a part of the chemical shifts could be assigned owing to overlapping of signals.

The strong NOE signals observed between H3_{ax} and H9, which are important for the assignment of the configuration of the caryose monosaccharide, could lead to a wrong assignment for the repeating unit of the polysaccharide, as it would indicate a diaxial arrangement. At the same time a strong NOE contact is observed between H3_{eq} and H9, indicating an equatorial orientation of H9. This can be explained by modeling a larger structure with an equatorial orientation of H9, where a fairly short distance is seen between H9 and H3_{eq} of the adjacent residue. Thus, the observed NOE contact between H9 and H3_{ax} reflects the sum of NOE signals between intra- and interresidual protons. Furthermore, it is in agreement with an equatorial orientation of H9 and with the overall configuration of the isolated monomer, as described previously.^[8]

The minimum-energy conformation of the acetylated trisaccharide is shown in Figure 4. It can clearly be seen how acetylation of O6 accounts for significant effects on the



Figure 4. Stick representation of a minimum-energy conformation of the acetylated trisaccharide a-a-a, based on the identified NOE connectivities as described in the text and summarized in Table 2.

chemical shift of H1 of the glycosylating residue. Molecular modeling of larger structures indicated that the linear sequence does not result in any significant long-range interaction. Thus, the overall conformation is determined by local interactions between adjacent residues. Therefore, it

may not be possible to determine by NMR spectroscopy the length of stretches of structures 1–8. Surprisingly, a comparison of the conformations of the acetylated and non-acetylated stretches (modeled in trisaccharide sequences) gave only small differences, indicating that the two conformations do not differ much.

In conclusion, we have characterized the acetylation pattern of the O-specific caryan of LPS from *Pseudomonas (Burkholderia) caryophylli*. Considering the amounts of units 1–8, we propose a model of a repeating unit of the caryan that comprises smaller areas of both acetylated and non-acetylated caryose residues (Figure 5). Thus, acetylation occurs mainly



Figure 5. Proposed structure of the repeating unit of the caryan from *Pseudomonas (Burkholderia) caryophylli*. The repeating unit is built up from 19 caryose residues. The acetylation/deacetylation pattern reflects the occurrence of units 1–8, as given in Table 3. For clarity, units 1–8 are depicted using different colors. Acetylated areas (A) are followed by non-acetylated areas (D); in both cases, the chains are not very long and comprise about 4–5 caryose residues. Furthermore, “erraneous” acetylation may occur, leading to units 4 and 8.

blockwise. The biosynthesis of such an acetylation pattern and its impact on the biological properties of the caryan are not yet understood. However, the acetylation should increase the hydrophobicity of the polysaccharide, which may be important for the interaction between the bacteria and plant cell surface molecules.

Experimental Section

General: The content of caryose and caryophyllose was identified by GC and GC-MS of the corresponding alditol acetates or acetylated methyl glycosides. The caryan was methylated according to the procedure of Hakomori.^[10] Methylation analysis was achieved using GC-MS (Hewlett-Packard 5890, SPB-5 capillary column (0.25 mm × 30 m, Supelco), temperature program: 150 °C for 5 min, then 5 °C min⁻¹ to 300 °C) after hydrolysis of the methylated caryan, reduction with NaBD₄, and acetylation with acetic anhydride in pyridine at 120 °C for 20 min.

Isolation of acetylated caryan: A portion (100 mg) of the LPS mixture^[7] was placed on a Sephadex G-100 column (3 × 100 cm, Pharmacia), eluted with 0.2 M NaCl, 1 mM EDTA, 10 mM Tris-HCl, 0.25% (v/v) sodium deoxycholate, and 0.02% (w/v) NaN₃ in water. Three fractions were detected using a differential refractometer (Knauer) and were dialyzed first against 0.2 M NaCl, 1 mM EDTA, 10 mM Tris-HCl, and 0.02% (w/v) NaN₃ in water (3 d), then against 0.2 M NaCl in water (3 d), and finally against water (3 d). After lyophilization, the fractions were analyzed by sodium dodecylsulphate polyacrylamide gel electrophoresis (SDS-PAGE, 10% gel): The first fraction (4 mg, 4%) contained a polysaccharide which was not detectable by SDS-PAGE and which is currently being investigated. The other two fractions 2 (63 mg, 63% of LPS) and 3 (27 mg, 27% of LPS) contained different proportions of the two LPSs, that is, one possessing the caryophyllose and the second possessing the caryose O-specific polysaccharide. Owing to the acid lability of the glycosidic linkage of caryophyllose, fractions 2 and 3 (90 mg) were hydrolyzed (2 mL of 1% aqueous acetic acid, 100 °C, 2 h). The lipid A (sediment) and the mixture of caryan and hydrolysis products (supernatant) were collected by ultracentrifugation (100,000 × g, 4 °C, 1 h). The last fraction was lyophilized (yield: 50 mg, 50% of crude LPS) and separated on a Sephadex G-50 column (3 × 50 cm, Pharmacia) with pyridine/acetic acid/water (4/10/1000 v/v/v; pH 4.5) as

eluent; the separation was monitored with a differential refractometer. The fraction eluting in the void volume contained pure caryan (10 mg, 10% of crude LPS), whereas fractions that eluted later contained mainly oligomers of caryophyllose.

Deacetylation of the caryan: The caryan (5 mg) was dissolved in 10 mM NaOH (1 mL) and left at 20–22 °C for 16 h. The solution was neutralized with Dowex 50 WX8 (H⁺) and lyophilized (yield: 4.1 mg).

Size determination: The caryan (1 mg) was dissolved in 50 mM NH₄HCO₃ (0.5 mL) and separated by chromatography on a Sephacryl S300HR column (1 × 30 cm, Pharmacia) with 50 mM NH₄HCO₃ as eluent (0.4 mL min⁻¹) and monitored with a differential refractometer. The column was calibrated using dextran standards (molecular masses: 670, 150, 80, 12, and 5 kDa).

NMR spectroscopy: NMR spectroscopy was carried out at 500 and 750 MHz using Varian UNITY INOVA 500 and 750 spectrometers. Samples were prepared in D₂O (0.6 mL), and spectra were obtained at 37 °C. The chemical shifts are given relative to those of acetone ($\delta = 2.225$ for ¹H and 31.4 for ¹³C). Homo- and heteronuclear experiments were carried out as described previously,^[11] with the exception that NOESY data were obtained with mixing times of 40 ms.

Molecular modeling: Molecular modeling was carried out using the CVFF force field in the Discover program.^[12] The caryose residue was constructed using standard bond lengths and angles in the Insight II program (MSI, San Diego). Molecular dynamics simulations were performed for the trisaccharide fragments in a water box with side length of 40 Å for up to 400 ps and with a step length of 1 fs. Full coordinates were saved every 2 ps.

Received: May 26, 1999

Revised: September 20, 1999 [Z13465]

- [1] U. Mamat, U. Seydel, D. Grimmecke, O. Holst, E. T. Rietschel in *Comprehensive Natural Products Chemistry*, Vol. 3 (Eds.: D. Barton, K. Nakanishi, O. Meth-Cohn, B. M. Pinto), Elsevier, Oxford, **1998**, pp. 179.
- [2] Y. Y. Knirel, N. K. Kochetkov, *Biochemistry (Engl. Transl.)* **1994**, *59*, 1325–1383.
- [3] P.-E. Jansson in *Endotoxin in Health and Disease* (Eds.: H. Brade, D. C. Morrison, S. Opal, S. Vogel), Marcel Dekker, New York, **1999**, p. 155.
- [4] L. K. Jones, *Phytopathology* **1941**, *31*, 199.
- [5] M. Adinolfi, M. M. Corsaro, C. De Castro, R. Lanzetta, M. Parrilli, A. Evidente, P. Lavermicocca, *Carbohydr. Res.* **1995**, *267*, 307–311.
- [6] M. Adinolfi, M. M. Corsaro, C. De Castro, A. Evidente, R. Lanzetta, L. Mangoni, M. Parrilli, *Carbohydr. Res.* **1995**, *274*, 223–232.
- [7] C. De Castro, A. Evidente, R. Lanzetta, P. Lavermicocca, E. Manzo, A. Molinaro, M. Parrilli, *Carbohydr. Res.* **1998**, *307*, 162–172.
- [8] M. Adinolfi, M. M. Corsaro, C. De Castro, A. Evidente, R. Lanzetta, A. Molinaro, M. Parrilli, *Carbohydr. Res.* **1996**, *284*, 111–118.
- [9] M. Caroff, A. Tacken, L. Szabo, *Carbohydr. Res.* **1988**, *175*, 273–282.
- [10] S. Hakomori, *J. Biochem.* **1964**, *51*, 205–208.
- [11] E. V. Vinogradov, B. O. Petersen, J. E. Thomas-Oates, J. Ø. Duus, H. Brade, O. Holst, *J. Biol. Chem.* **1998**, *273*, 28122–28131.
- [12] A. T. Hagler, S. Lifson, R. Dauber, *J. Am. Chem. Soc.* **1979**, *101*, 5122–5130.

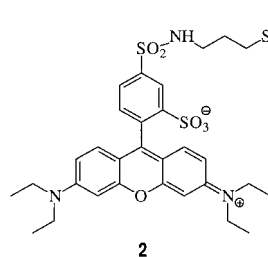
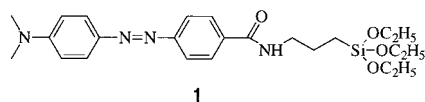
Anchoring of Functional Dye Molecules in MCM-41 by Microwave-Assisted Hydrothermal Cocondensation**

Matthias Ganschow, Michael Wark, Dieter Wöhrle,* and Günter Schulz-Ekloff

The encapsulation of organic dye molecules in molecular sieves leads to composite materials with novel optical properties, which enable potential applications as pigments or as materials for optical data storage, frequency doubling, microlasing, gas sensing, or photocatalysis.^[1] In molecular sieves with cages whose diameters are below 1.5 nm, dye molecules can be incorporated such that they are stable against extraction by in situ synthesis (ship in the bottle) or inclusion through crystallization.^[2]

The mesoporous host Si-MCM-41 used in this investigation is a member of the class of M41S materials with hexagonally arranged cylindrical pores,^[3] and is formed by a template-assisted liquid crystal process. The structure-directing micelles are built by cationic organic surfactant molecules, for example cetyltrimethylammonium bromide (CTAB).^[4] The surfactant molecules inside the pore structure can be burnt off by calcination at 873 K or removed by extraction.^[3, 5] The wide channellike pores of MCM-41 (about 3 nm in diameter) enable the inclusion of relatively large chromophores; these are, however, either extracted or destroyed during removal of the template.^[6]

Especially applications in photocatalysis or optical sensing require stability against extraction, which can only be achieved by covalent anchoring of the dyes onto the walls of MCM-41. A suitable method is the cocondensation of modified triethoxysilyl anchor groups with tetraethoxysilane



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[**] The project was funded by the Deutsche Forschungsgemeinschaft (Schwerpunkt "Nanoporöse Kristalle"; AZ: SCHU 426/10-2). We gratefully acknowledge Dr. M. Wendschuh-Josties and A. Toltz (University of Bremen) for measuring the X-ray diffractograms and the scanning electron micrographs (SEM).

(TEOS).^[7] To our knowledge, this method has not been applied for the encapsulation of functional dyes before. In this investigation the photochromic azo dye **1** and the fluorescent laser dye **2** were chosen as examples. 4-[(4-Dimethylamino-phenyl)azo]benzoic acid and sulforhodamine B reacted with (3-aminopropyl)triethoxysilane to form the compounds **1** and **2**.

The crystallization inclusion was performed in a microwave oven^[2a, 8] to reduce the reaction times to 20 min. This ensures that no dye degrades during the hydrothermal synthesis of the Si-MCM-41 host. In scanning electron micrographs (SEM) Si-MCM-41 particles with a uniform morphology and a narrow particle size distribution were observed independent on the loading with dye molecules (Figure 1). Comparable uniformity has been described for Si-MCM-48.^[9]

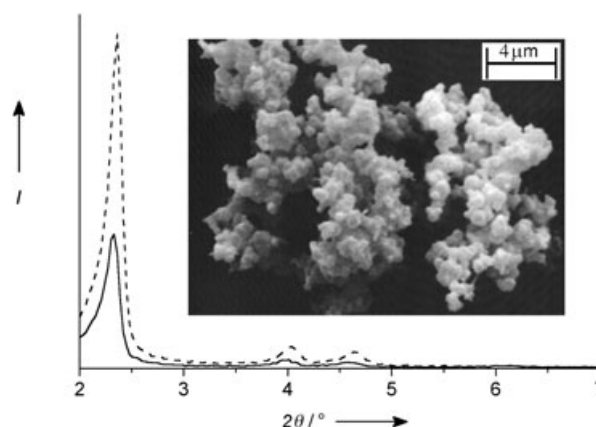


Figure 1. X-ray diffractograms of template-containing (—) and template-free (---) Si-MCM-41 loaded with **1** as well as a scanning electron micrograph of Si-MCM-41 with **1**.

With the azo dye **1** light yellow to dark orange powders are obtained depending on the amount of dye added to the synthesis gel (Figure 2). The dye cannot be washed out of the pores, neither with water nor by extraction with hot ethanol for several days. In contrast, dye molecules without anchor groups are removed within a few minutes. Owing to the high

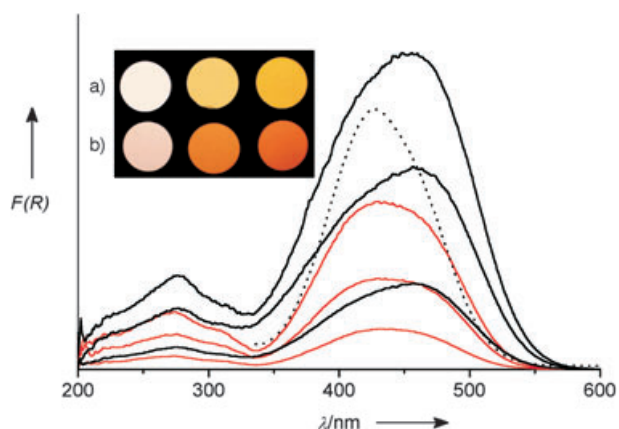


Figure 2. Diffuse-reflectance UV/Vis spectra of template-containing (red) and template-free (black) Si-MCM-41 with **1** covalently anchored in different concentrations (addition of 125, 75, and 25 mg of **1**); for comparison the spectrum of **1** in ethanol is shown (····). The inset shows the colors of dye-loaded Si-MCM-41 samples (addition of 6, 50, and 125 mg of **1**) with template (a) and template-free (b).

stability of the anchored dye molecules, the template molecules can be removed with an aqueous 1M HCl solution at 343 K. Even in the case of template-free samples, no dye could be removed by extraction with ethanol, which indicates that the anchoring amide bonds are stable against acid.

The X-ray diffractograms of the samples, with and without template molecules, show the four to five reflections (Figure 1) that are typical for Si-MCM-41.^[3] Since there are no indications in the X-ray diffractograms for a widening of the pores with progressing dye loading, it can be assumed that the diameter of the micelles remains unchanged independent of the presence of dye molecules.

The removal of the template leads to a decrease in the electron density in the pores. This results not only in an increase in the intensity of the X-ray reflections^[10] (Figure 1), but also in a strong increase in the tinctorial strength of the samples due to changes in the refractive index. In diffuse-reflectance UV/Vis spectra an increase in the Kubelka–Munk values ($F(R)$ values) by a factor of about two and a red shift of the most intense band by 30 nm are observed (Figure 2). In analogy to a change of the solvent, the removal of the surfactant molecules alters the chemical environment of the dye molecules. The resulting strong influence on the reflectance of the samples proves that the dye molecules are located inside the pore system and excludes an exclusive anchoring on the external surface, which represents only 5% of the total surface.

The anchoring of the rhodamine dye **2** leads to analogous results. The products possess a slight to dark pink color (Figure 3). The removal of the template again results in an increase in the $F(R)$ values. Owing to the anchoring the intensity of the shoulder at 520 nm is enhanced in comparison to the band at 556 nm. Usually this behavior characterizes the formation of dimers.^[11] Since, however, in contrast to the behavior in solution, the intensity ratio of the two bands does not change significantly with increasing dye concentration, a monomeric incorporation of the dye molecules is more probable. The increase in intensity of the band at 520 nm can occur due to strong interactions with the host, which facilitate excitation in higher oscillation modes (0–1 excitation).

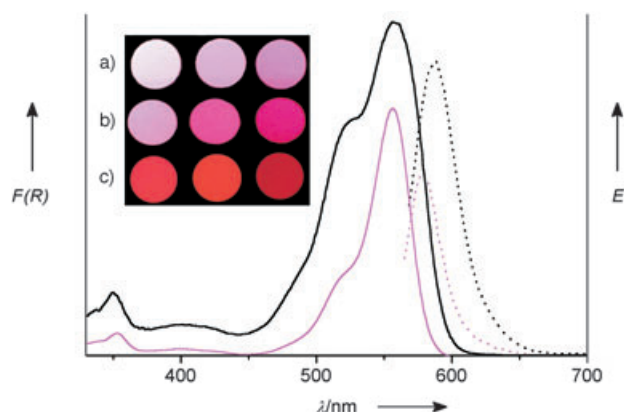


Figure 3. UV/Vis (solid line) and emission spectra (dotted line) of **2** in ethanol (violet) and covalently anchored to Si-MCM-41 (black). The inset shows the colors of dye-loaded Si-MCM-41 samples (addition of 6, 18, and 75 mg of **2**) with template (a), template-free (b), and under illumination with UV light (fluorescence, c).

Contrary to the situation in $\text{AlPO}_4\text{-5}$,^[2c] no limit for inclusion was observed in the investigated concentration range for **1** and **2** (Figure 4). The amount of encapsulated dye increases linearly with the available concentration.

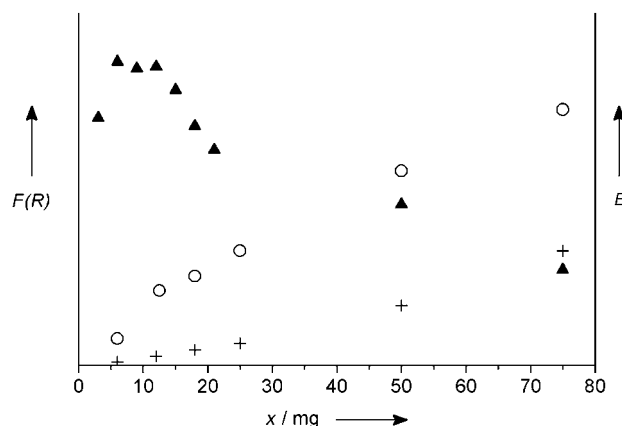


Figure 4. $F(R)$ values (dye **1** = $\circ$, dye **2** = $\blacktriangle$) and emission, E (fluorescence, dye **2** = $\blacktriangle$) of dye-loaded Si-MCM-41 as a function of the amount of dye x added to the synthesis gel.

Owing to the monomeric incorporation of **2** in Si-MCM-41 an intense orange fluorescence is found (Figure 3). The emission maximum is continuously red-shifted with increasing dye concentration; the Stokes shift amounts to 31–39 nm for Si-MCM-41 with template and 32–47 nm for template-free samples. In analogy to the situation in solution the fluorescence intensity passes through a maximum with increased dye loading (Figure 4). Since there are no indications for a formation of dimers in the diffuse-reflectance spectra, it is assumed that the red-shift and the decrease in fluorescence intensity result from a radiationless energy transfer, which is known as Förster quenching.^[12] The critical Förster distance of chromophores—that is, the distance which leads to a 50% decrease of the maximal fluorescence intensity—is about 8 nm.^[2c] From Figure 4 it is apparent that the fluorescence decreases to 50% if 50 mg (0.07 mmol) of dye are added to 2.4 g of TEOS in the synthesis gel. Under consideration of the observed monomeric anchoring onto the inner surface of Si-MCM-41 (BET value $\approx 1050 \text{ m}^2 \text{ g}^{-1}$) an average distance of the dye molecules of 6–7 nm is valid, which is in fair agreement with the literature data, demonstrating again the uniformity of the incorporation.

The microwave-assisted covalent bonding of functional dyes in Si-MCM-41 by hydrothermal cocondensation is reported here for the first time. The short synthesis time (minutes) facilitates the inclusion of dyes that degrade under conventional hydrothermal conditions. A uniform monomeric anchoring of the dye molecules on the inner surface of the Si-MCM-41 host of high quality was proven by X-ray diffraction, diffuse-reflectance UV/Vis, and fluorescence data.

Experimental Section

The azo dye **1** was synthesized from *N,N*-dimethylaniline and 4-aminobenzoic acid.^[13] The azo dye (1 mmol) was suspended in CH_2Cl_2 (15 mL), and (3-aminopropyl)triethoxysilane (1.5 mmol), *p*-toluenesulfonic acid (0.05 mg), and dicyclohexylcarbodiimide (DCC, 1.1 mmol) were added. The suspension was stirred in an ice bath for 5 h. The solvent was removed,

and the mixture purified by chromatography on silica gel ($\text{CHCl}_3/\text{acetonitrile/ethanol}$ 40/2/1). Characterization was carried out by mass spectrometry and UV/Vis and NMR spectroscopy.

To synthesize the rhodamine dye **2** sulforhodamine B acid chloride (0.40 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled in an ice bath. Pyridine (100 μL) and (3-aminopropyl)triethoxysilane (181 mg) were added, and the mixture was stirred for 24 h. The product was precipitated in *tert*-butyl methyl ether, intensively washed, and characterized by mass spectrometry and UV/Vis and NMR spectroscopy.

For the synthesis of the dye-loaded Si-MCM-41 water (24 g), NH_3 (3 g, 25%), and 1-butanol (230 μL) were mixed. Portions (6–125 mg) of the dyes were dissolved in TEOS (2.4 g) in an ultrasonic bath. The two solutions were combined under stirring and CTAB (1.4 g) in water (6 g) was slowly added over 15 min. Subsequently, the synthesis gel was placed in a teflon autoclave and heated under continuous stirring in a microwave oven (MLS 1200, Milestone) for 5 min at 403 K (480 W) and then at 373 K (60 W) for 15 min. The isolated product was washed in water and ethanol several times. To remove the template Si-MCM-41 (250 mg) was stirred for 12 h in an aqueous 1 M HCl solution (100 mL) at 343 K and washed afterwards with water and ethanol.

Received: July 5, 1999

Revised: September 9, 1999 [Z13673]

- [1] a) J. Caro, G. Finger, J. Kornatowski, J. Richter-Mendau, L. Werner, B. Zibrowius, *Adv. Mater.* **1992**, *4*, 273–276; b) M. Ehrl, F. W. Deeg, C. Bräuchle, O. Franke, A. Sobbi, G. Schulz-Ekloff, D. Wöhrle, *J. Phys. Chem.* **1994**, *98*, 47–52; c) G. Ihlein, F. Schüth, U. Vietze, O. Krauß, F. Laeri, *Adv. Mater.* **1998**, *10*, 1117–1118; d) D. E. de Vos, F. Thibault-Starzyk, P. P. Knops-Gerrits, R. F. Parton, P. A. Jacobs, *Macromol. Symp.* **1994**, *80*, 157–184.
- [2] a) D. Wöhrle, G. Schulz-Ekloff, *Adv. Mater.* **1994**, *6*, 875–880; b) C. Schomburg, D. Wöhrle, G. Schulz-Ekloff, *Zeolites* **1996**, *97*, 232–236; c) M. Bockstette, D. Wöhrle, I. Braun, G. Schulz-Ekloff, *Microporous Mesoporous Mater.* **1998**, *23*, 83–96; d) G. A. Ozin, *Adv. Mater.* **1994**, *6*, 71–76.
- [3] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710–712.
- [4] W. Zhou, J. Klinowski, *Chem. Phys. Lett.* **1998**, *292*, 207–212.
- [5] O. Groeger, G. Engelhardt, *Abstr. Pap. 11th German Zeolite Meeting* (Stuttgart) **1999**, PO35.
- [6] a) M. Wark, A. Ortlam, M. Ganschow, G. Schulz-Ekloff, D. Wöhrle, *Ber. Bunsen-Ges. Phys. Chem.* **1998**, *102*, 1548–1553; b) S. Ernst, R. Gläser, M. Selle, *Stud. Surf. Sci. Catal.* **1997**, *105*, 1021; c) I. Honma, H. S. Zhou, *Adv. Mater.* **1998**, *10*, 1532–1536; d) M. Ganschow, D. Wöhrle, G. Schulz-Ekloff, *J. Porphyrins Phthalocyanines* **1999**, *3*, 299–309.
- [7] C. E. Fowler, B. Lebeaus, S. Mann, *Chem. Commun.* **1998**, 1825–1826.
- [8] a) C.-G. Wu, T. Bein, *Chem. Commun.* **1996**, 925–926; b) S. E. Park, D. S. Kim, J. S. Chang, W. Y. Khim, *Catal. Today* **1998**, *44*, 301–308.
- [9] M. Grün, K. K. Unger, A. Matsumoto, K. Tsutsumi, *Microporous Mesoporous Mater.* **1999**, *27*, 207–216.
- [10] B. Marler, U. Oberhagemann, S. Vortmann, H. Gies, *Microporous Mater.* **1996**, *6*, 375–383.
- [11] K. Kemnitz, K. Yoshihara, *J. Phys. Chem.* **1991**, *95*, 6095–6099.
- [12] H. G. O. Becker, *Einführung in die Photochemie*, 1st ed., Deutscher Verlag der Wissenschaften, Berlin, **1991**.
- [13] H. Zollinger, *Diazo Chemistry I*, 1st ed., VCH, Weinheim, **1994**.

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- [2] a) D. Wöhrle, G. Schulz-Ekloff, *Adv. Mater.* **1994**, *6*, 875–880; b) C. Schomburg, D. Wöhrle, G. Schulz-Ekloff, *Zeolites* **1996**, *97*, 232–236; c) M. Bockstette, D. Wöhrle, I. Braun, G. Schulz-Ekloff, *Microporous Mesoporous Mater.* **1998**, *23*, 83–96; d) G. A. Ozin, *Adv. Mater.* **1994**, *6*, 71–76.
- [3] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710–712.
- [4] W. Zhou, J. Klinowski, *Chem. Phys. Lett.* **1998**, *292*, 207–212.
- [5] O. Groeger, G. Engelhardt, *Abstr. Pap. 11th German Zeolite Meeting* (Stuttgart) **1999**, PO35.
- [6] a) M. Wark, A. Ortlam, M. Ganschow, G. Schulz-Ekloff, D. Wöhrle, *Ber. Bunsen-Ges. Phys. Chem.* **1998**, *102*, 1548–1553; b) S. Ernst, R. Gläser, M. Selle, *Stud. Surf. Sci. Catal.* **1997**, *105*, 1021; c) I. Honma, H. S. Zhou, *Adv. Mater.* **1998**, *10*, 1532–1536; d) M. Ganschow, D. Wöhrle, G. Schulz-Ekloff, *J. Porphyrins Phthalocyanines* **1999**, *3*, 299–309.
- [7] C. E. Fowler, B. Lebeaus, S. Mann, *Chem. Commun.* **1998**, 1825–1826.
- [8] a) C.-G. Wu, T. Bein, *Chem. Commun.* **1996**, 925–926; b) S. E. Park, D. S. Kim, J. S. Chang, W. Y. Khim, *Catal. Today* **1998**, *44*, 301–308.
- [9] M. Grün, K. K. Unger, A. Matsumoto, K. Tsutsumi, *Microporous Mesoporous Mater.* **1999**, *27*, 207–216.
- [10] B. Marler, U. Oberhagemann, S. Vortmann, H. Gies, *Microporous Mater.* **1996**, *6*, 375–383.
- [11] K. Kemnitz, K. Yoshihara, *J. Phys. Chem.* **1991**, *95*, 6095–6099.
- [12] H. G. O. Becker, *Einführung in die Photochemie*, 1st ed., Deutscher Verlag der Wissenschaften, Berlin, **1991**.
- [13] H. Zollinger, *Diazo Chemistry I*, 1st ed., VCH, Weinheim, **1994**.

Immobilization of TADDOL with a High Degree of Loading on Porous Silica Gel and First Applications in Enantioselective Catalysis**

Alexander Heckel and Dieter Seebach*

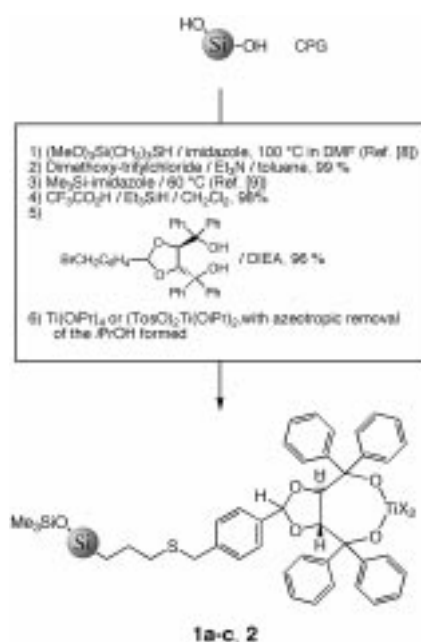
The immobilization of organic compounds (and enzymes)^[1] on (or in) highly porous SiO_2 instead of organic polymers (for example, by cross-linking copolymerization)^[2–4] for solid-phase synthesis and catalysis has the following advantages:^[5, 6] the material has a rigid structure and does not swell in solvents; hence it can be used both at high or low temperatures and at high pressures; depending on the porosity, the degree of loading with functional groups can be high; the surface of the silica can be rendered hydrophobic; the support is chemically inert—except to strong alkali and fluoride.

For comparison with TADDOL ligands grafted onto Merrifield resin or immobilized in polystyrene^[3, 4] we have now grafted a TADDOL derivative onto two commercially available CPGs (controlled-pore glass)^[7] with different pore sizes, made the surface hydrophobic, and finally loaded the TADDOL moieties with titanates (Scheme 1, Table 1). The resulting material (**1a–c** and **2**) has been tested in the Lewis acid-mediated enantioselective addition of Et_2Zn to benzaldehyde and in the [3 + 2]cycloaddition of diphenylnitrone to *N*-crotonoyl-1,3-oxazolidin-2-one^[12] (both reactions show a linear relationship between the enantiomeric purities of TADDOL and product; see Equation (1) and (2) in Scheme 2).^[3, 13, 14]

As shown in Scheme 2 we have achieved virtually the same conversion, diastereo- (% *ds*) and enantioselectivities (% *es*) with the CPG-bound Ti-TADDOLates as in the homogeneous phase, under otherwise identical conditions. Much more important are the results obtained in the multiple use of the CPG-bound Ti-TADDOLates (Figures 1 and 2): 1) As with the polystyrene-bound catalyst^[4] there is a slight decrease in enantioselectivity with multiple uses. 2) However, a high loading (up to 0.32 mmol TADDOL per g) does not have a negative effect on selectivity, here. This is a most welcome feature since the percentage of supporting material in the total mass of the heterogeneous catalyst can thus be kept low. 3) To our surprise, the material can be washed with $\text{HCl}/\text{H}_2\text{O}$ /acetone, dried, and reloaded with titanate, for example, after 10 or even 20 catalytic runs, and the selectivities observed are as good as in the beginning. This means that the loss of catalytic activity was not a consequence of a loss of TADDOL moieties or surface hydrophobization, but rather of impurities that could be removed by washing with acid.^[15, 16] 4) The rate

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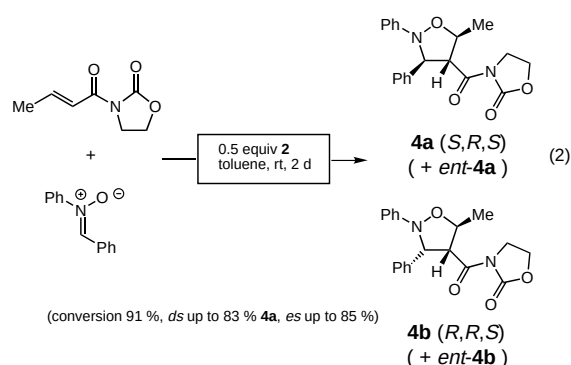
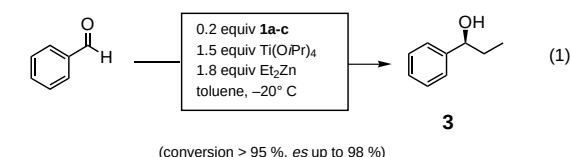
[**] A.H. gratefully acknowledges a Kekulé Stipendium from the Stiftung Stipendien-Fonds des Verbandes der chemischen Industrie e.V. (Frankfurt) and the BMBF. We also thank Grace and Witco GmbH for their generous donation of CPG and Et_2Zn , respectively.



Scheme 1. Synthesis of the CPG-bound TADDOL derivatives **1a–c** and **2** (X = OTos, OiPr). The reaction was monitored quantitatively by the determination of free SH groups^[10] or by the cleavage and subsequent quantitative determination of the stable dimethoxytrityl cations formed.^[11] For a semi-quantitative control of the hydrophobization a solution of Methyl Red in benzene was used.^[5] The yields given refer to the synthesis of the 200 Å material, the TADDOL derivative used is described in ref. [3] DIEA = diisopropylethylamine (Hünig base; Tos = toluene-4-sulfonyl).

Table 1. Specification of the TADDOL derivatives **1** and **2** immobilized on CPG

	X	Loading [mmol g ⁻¹]	Pore size [Å]
1a	OiPr	0.32	200
1b	OiPr	0.08	200
1c	OiPr	0.12	500
2	OTos	0.32	200



Scheme 2. First applications of the CPG-bound TADDOL derivatives **1a–c** and **2**. The addition of Et₂Zn to PhCHO in solution and in the presence of 0.2 equiv TADDOL gives > 99 % conversion and 98 % *es*. Under homogeneous conditions Jørgensen et al. found 86 % conversion, 85 % *ds*, and 92.5 % *es* in the [3+2]cycloaddition with a comparable TADDOL derivative.^[12]

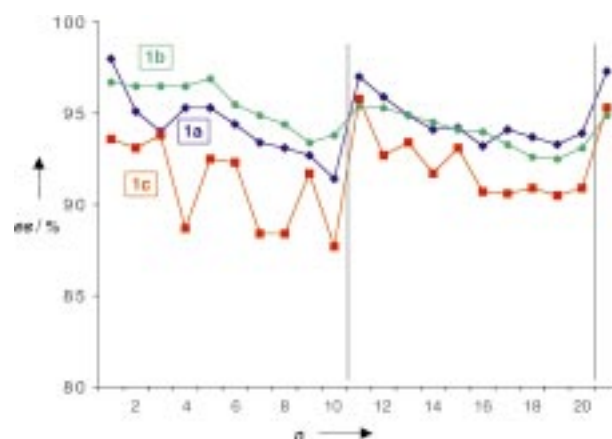


Figure 1. Enantioselectivities obtained in multiple uses of the heterogeneous TADDOL derivatives **1a–c** in the addition of Et₂Zn to benzaldehyde (the *es* value (%) is the percentage of (*S*)-**3** determined by gas chromatography). The contents of the reaction flask were mixed on a shaking machine. After the 10th and 20th catalytic cycle the catalyst was washed with HCl/H₂O/acetone, dried, and re-loaded with titanate. Otherwise the catalyst was only washed with toluene under protective gas between consecutive catalytic cycles. *n* = catalytic cycle.

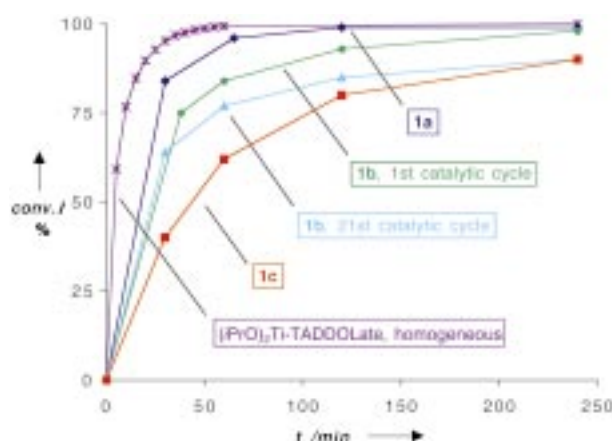


Figure 2. Reaction rates of the addition of Et₂Zn to benzaldehyde with the heterogeneous TADDOL derivatives **1a–c** and comparison with the reaction rate in homogenous solution. The 21st cycle with **1b** was done after the second washing (compare with Figure 1).

of addition of Et₂Zn to benzaldehyde is only slightly lower with the highly loaded CPG **1a** than a reaction with homogeneous Ti-TADDOLate. Furthermore, the rate in the 21st run using the lower-loaded material **1b**—after the second washing procedure—was almost the same as in the first run (Figure 2). 5) Good reproducibility in the [3+2]cycloaddition is also possible when the catalyst is re-used (Equation 2 in Scheme 2). However, the heterogeneous catalyst has to be washed after every use in this case, as described above. Only a small loss of activity is observed after four runs.

Chiral Lewis acids usually have a high molecular weight and often a large quantity (5 to over 100 mol %) has to be employed.^[17] Therefore, immobilization and re-use is very important. This fact, the possible high degree of loading on porous silica gel, its constant volume, and the stability in washing procedures are motivation for further investigations in this field. These include the testing of different types of reactions (especially under conditions where the use of

polystyrene derivatives is problematic), immobilizing different ligands, and immobilizing dendritically modified ligands in the sol–gel process.

Received: August 11, 1999 [Z13861]

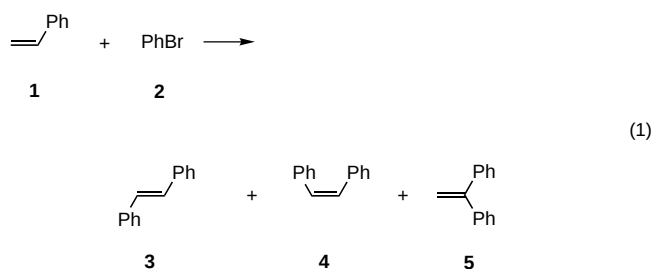
Phosphane-Free Palladium-Catalyzed Coupling Reactions: The Decisive Role of Pd Nanoparticles**

Manfred T. Reetz* and Elke Westermann

- [1] a) W. Keim, B. Driessen-Hölscher in *Handbook of Heterogeneous Catalysis, Vol. 1* (Eds.: G. Ertl, H. Knözinger, J. Weitkamp), Wiley-VCH, Weinheim, **1997**, pp. 231–240; b) M. T. Reetz, A. Zonta, J. Sempelkamp, *Angew. Chem.* **1995**, *107*, 373–376; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 301–303.
- [2] H. U. Blaser, B. Pugin in *Chiral Reactions in Heterogeneous Catalysis* (Eds.: G. Jannes, V. Dubois), Plenum, New York, **1995**, pp. 33–57, and references therein.
- [3] D. Seebach, R. E. Marti, T. Hintermann, *Helv. Chim. Acta* **1996**, *79*, 1710–1740, and references therein.
- [4] H. Sellner, D. Seebach, *Angew. Chem.* **1999**, *111*, 2039–2041; *Angew. Chem. Int. Ed.* **1999**, *38*, 1918–1920, and references therein.
- [5] J. F. Biernat, P. Konieczka, B. J. Tarbet, J. S. Bradshaw, R. M. Izatt in *Separation and Purification Methods, Vol. 23(2)* (Eds.: P. C. Wankat, C. J. van Oss, J. D. Henry), Marcel Dekker, New York, **1994**, pp. 77–348, and references therein.
- [6] A. Choplin, F. Quignard, *Coord. Chem. Rev.* **1998**, *180*, 1679–1702.
- [7] The CPG used was provided by Grace GmbH (In der Hollerhecke 1, D-67547 Worms, Germany (www.grace.com)) and has the following batch numbers: SP2-8319.01 (200 Å), SP18-9042 (500 Å).
- [8] J. N. Kinkel, K. K. Unger, *J. Chromatogr.* **1984**, *316*, 193–200.
- [9] K. D. McMurtrey, *J. Liq. Chromatogr.* **1988**, *11*, 3375–3384.
- [10] a) G. L. Ellman, *Arch. Biochem. Biophys.* **1959**, *82*, 70–77; b) R. D. Badley, W. T. Ford, *J. Org. Chem.* **1989**, *54*, 5437–5443.
- [11] B. S. Sproat, M. J. Gait in *Oligonucleotide Synthesis. A practical approach* (Ed.: M. J. Gait), IRL Press, Oxford, **1984**, pp. 83–115.
- [12] K. V. Gothelf, I. Thomsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **1996**, *118*, 59–64.
- [13] B. Schmidt, D. Seebach, *Angew. Chem.* **1991**, *103*, 1383–1385; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1321–1323.
- [14] C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959.
- [15] When TADDOL immobilized on CPG was used without hydrophobization poor results were obtained in the addition of Et₂Zn to PhCHO.
- [16] The treatment with aqueous acid clearly does not cause clogging of the pores by TiO₂/ZnO, but, rather, appears to have a positive effect on reproducibility (see right part of the curves in Figure 1).
- [17] Reviews: a) R. Dahinden, A. K. Beck, D. Seebach in *Encyclopaedia of Reagents for Organic Synthesis, Vol. 3* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 2167–2171; b) H. Yamamoto, A. Yanagisawa, K. Ishihara, S. Saito, *Pure Appl. Chem.* **1998**, *70*, 1507–1512; c) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290–1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1237–1256; d) S. Kobayashi, *Pure Appl. Chem.* **1998**, *70*, 1019–1026; e) K. Mikami, *Pure Appl. Chem.* **1996**, *68*, 639–644.

The number of examples of Pd-catalyzed C–C bond forming reactions continues to rise, for example, in the area of Heck, Suzuki, and Stille coupling reactions.^[1] One of the most common catalysts is [Pd(PPh₃)₄], but precatalysts such as PdX₂ in the presence of excess PPh₃, which reduces Pd^{II} to Pd⁰, are also used. In addition to new types of catalysts or precatalysts such as Pd–carbene complexes^[2] or phosphapalladacycles,^[3] simple Pd salts such as PdCl₂ or Pd(OAc)₂ in the *absence* of stabilizing phosphane ligands are increasingly being used in Heck and Suzuki reactions.^[1] Preparatively significant examples are the Jeffery system^[4] in which Pd(OAc)₂ in the presence of an excess of a phase-transfer catalyst such as *n*Bu₄N⁺Cl[–] is used, or Pd(OAc)₂ in an aqueous medium.^[5] In both cases aryl iodides are usually employed as the arylating agent. In the case of the industrially more interesting aryl bromides, Pd(OAc)₂ (or PdCl₂) with or without *N,N*-dimethylglycine (DMG) as an additive is currently one of the cheapest and most active catalysts.^[6] How can such simple phosphane-free catalyst systems be understood, given that it is generally assumed that phosphanes exert a stabilizing and activating effect?^[1] We report here a mechanistic study^[7] supported by transmission electron microscopy (TEM) which points to the involvement of intermediary Pd nanoparticles as colloids in such systems.

First the Heck reaction of styrene (**1**; 12 mmol) with bromobenzene (**2**; 10 mmol) at 130 °C in *N*-methylpyrrolidinone (NMP; 10 mL) was studied. Our previously reported catalyst system with [PdCl₂(C₆H₅CN)₂] (1.5 mol %)/DMG as the precatalyst and sodium acetate (20 mmol) as the base was used.^[6] As expected, essentially complete conversion with formation of the Heck products **3–5** in a ratio of 96:1:3 was observed over 6 h [Eq. (1)].



The course of the reaction was monitored by periodically taking samples and analyzing them by gas chromatography. Parallel to these analyses, the samples were studied by TEM.

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[**] E.W. thanks the Fonds der Chemischen Industrie for a doctoral stipendium. We thank Dr. M. Maase for help in the analysis of TEM images.

The reaction begins after an induction period of about one hour (Figure 1).^[8] We found that only samples that were taken after the induction period contained Pd colloids. They have an average particle size of 1.6 nm (Figure 2). The fact that not all samples contain Pd nanoparticles rules out the unlikely possibility of colloid formation following sample withdrawal. Since the samples were directly deposited on carbon film

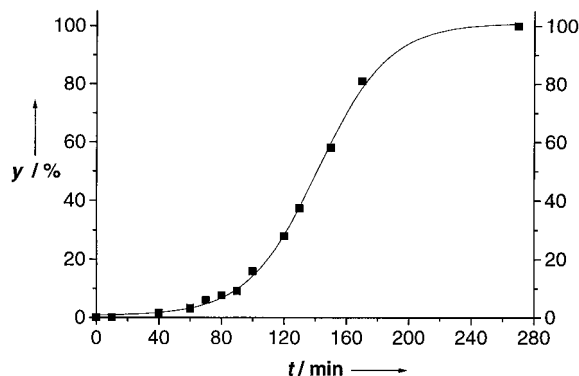


Figure 1. Plot of yield *y* versus time for the Heck reaction of styrene (**1**) with bromobenzene (**2**) at 130 °C in NMP; catalyst: [PdCl₂(C₆H₅CN)₂] (1.5 mol %)/DMG.

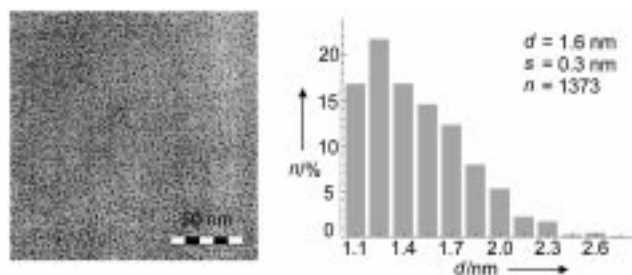


Figure 2. TEM image (left) of a typical sample of a Pd colloid formed in the reaction of **1** with **2** in the presence of [PdCl₂(C₆H₅CN)₂]/DMG as precatalyst. The size distribution of the nanoparticles (right) appears unsymmetrical because the TEM instrument does not detect particles smaller than 1 nm; *d* = average diameter; *s* = standard deviation; *n* = number of particles.

coated TEM grids by dip-coating without workup, the process can be viewed as “in situ” TEM analysis. We assume that [PdCl₂(C₆H₅CN)₂] undergoes rapid ligand exchange with NaOAc to form Pd(OAc)₂, which undergoes thermolytic decomposition at 130 °C with formation of Pd⁰ in the form of a colloid.^[9] This is corroborated by our recent observation that thermolysis of Pd(OAc)₂ at 100 °C (3 h) in the likewise polar solvent propylene carbonate (PC) quantitatively affords PC-stabilized Pd colloidal particles 8–10 nm in size.^[10] Such relatively large preformed thermostable colloids are capable of catalyzing Heck reactions.^[10]

A similar TEM study was carried out with ethyl acrylate (**6**; 10 mmol) and iodobenzene (**7**; 5 mmol) under Jeffery conditions^[4] (12.5 mmol NaOAc; 5 mmol *n*Bu₄N⁺Br[−]; 0.25 mmol Pd(OAc)₂; 5 mL dimethylacetamide (DMA); 50 °C/1 h; > 95 % conversion) [Eq. (2)]. The reaction starts immediately

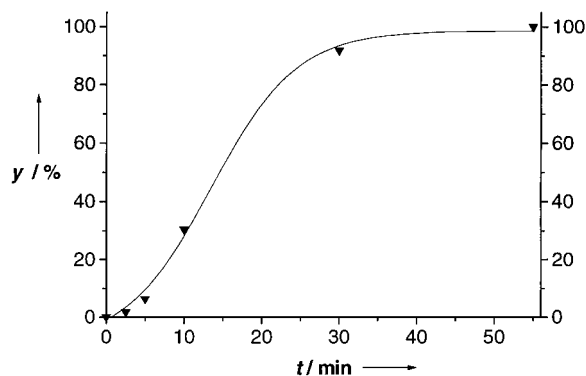
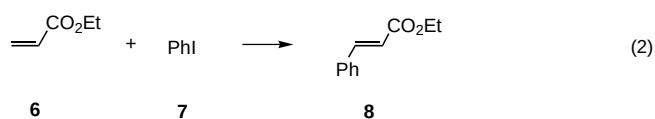


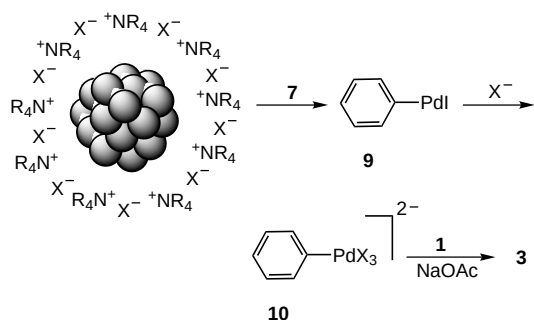
Figure 3. Plot of yield *y* versus time for the Heck reaction of ethyl acrylate (**6**) with iodobenzene (**7**) under Jeffery conditions at 50 °C in DMA; catalyst: Pd(OAc)₂ (5 mol %)/*n*Bu₄N⁺Br[−].

without an induction period and proceeds continuously (Figure 3).

The TEM images of the samples that were used for GC product analysis all showed the presence of Pd colloids with an average particle size of 1.6 nm. It has long been known that chemical or electrochemical reduction of transition metal salts in the presence of ammonium salts leads to R₄N⁺X[−]-stabilized colloids.^[11] Recently, we achieved the size-selective preparation of R₄N⁺(RCO₂[−])-stabilized Pd colloids simply by heating Pd salts such as Pd(NO₃)₂ or PdCl₂ in the presence of tetraalkylammonium carboxylates R₄N⁺(RCO₂[−]) at 60 °C without any additional reducing agents. In this redox-controlled process, the carboxylate anions RCO₂[−] induce electron transfer to Pd^{II} with formation of Pd⁰ as a colloid, and methane, ethane, and CO₂ as inert side products.^[12] Hence, it is likely that under Jeffery conditions, R₄N⁺X[−]-stabilized Pd colloids are formed and then function as in situ catalysts. Indeed, in previous studies it was demonstrated that preformed R₄N⁺X[−]-stabilized Pd colloids are catalytically active.^[13] Differences in catalytic activity of in situ generated Pd colloids and preformed analogues may be due to different cluster sizes, impurities, or aging processes in the case of the preformed colloids, a hypothesis that needs to be examined in greater detail. For example, the Heck reaction of unactivated aryl bromides with catalysis by preformed R₄N⁺X[−]-stabilized Pd colloids gives low yields,^[13b] whereas the coupling of **2** with **6** under Jeffery conditions proceeds smoothly (**2** (1 mmol); **6** (2 mmol); NEt₃ (2.5 mmol); *n*Bu₄N⁺Cl[−] (1 mmol); NMP/molecular sieve 4 Å; 130 °C/15 h: 100 % conversion (81 % yield of **8**) or 86 % conversion (70 % yield of **8**) with NaOAc as base).

Although the appearance of Pd colloids in the present cases occurs simultaneously with the initiation of the Heck reaction, this cannot be viewed as definitive proof for the actual participation of nanoparticles in the catalytic cycle. To shed light on this question, the reaction of a preformed Pd colloid with the stoichiometric amount of iodobenzene (**7**) was studied in the absence of an olefin.

If the hypothetical role of Pd colloids in the catalytic cycle were correct, then oxidative insertion of Pd into the C–I bond with formation of phenylpalladium species **9** (or **10**) and concomitant dissolution of the Pd colloid would be expected (Scheme 1). An *n*Oct₄N⁺(HCO₂[−])-stabilized Pd colloid^[12]

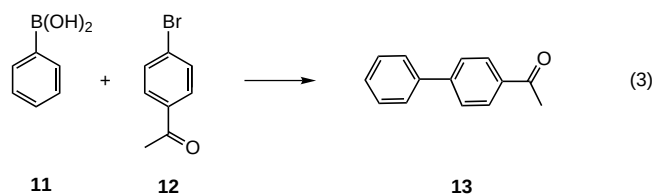


Scheme 1.

(average particle size 2.2 nm) was allowed to react with the calculated amount of iodobenzene (**7**) at room temperature (25 h) in NMP/THF (1/1) and at 70 °C for 2.5 h with stirring. The black color typical of Pd colloids changed to dark red. The reaction was monitored by UV/Vis spectroscopy, which revealed the continuous decrease of the broad plasmon band in the range 400–650 nm typical of transition metal colloids,^[14] as well as the gradual appearance of a new band at 450 nm. The ¹³C NMR spectrum at the end of the reaction shows a set of signals in the aromatic region at δ = 127.5, 127.8, 129.2 and 141.1,^[15] which is clearly different from the signals of iodobenzene (δ = 94.7, 128.1, 130.9, 139.1). The signal at δ = 141.1 appears in a range which is typical for Pd-bound C atoms of arylpalladium compounds.^[16] Differentiating between **9** and the more likely anionic species of type **10** (which are known to occur as phosphane adducts)^[1, 17] is not trivial. Dimeric structures are also possible.^[18] Decisive is the proof of the participation of the species in the actual Heck reaction. Upon adding styrene **1** and NaOAc to the red solution at 70 °C, the Heck product **3** was indeed formed (Scheme 1). In the case of the analogous stoichiometric reaction of the preformed Pd colloid with chlorobenzene under the same conditions no reaction took place, that is, no dissolution of the Pd colloid occurred, as shown by UV/Vis and TEM studies.

Finally, the reaction of styrene (**1**) with bromobenzene (**2**) was investigated with two other catalyst systems. According to TEM analyses, the conventional reaction with Pd(OAc)₂/4PPh₃ as catalyst^[1] (2 mol %) in NMP as solvent at 130 °C did not lead at any time to Pd colloid formation. The same applies to the reaction with the phosphapalladacycle *trans*-di(μ -aceto)-bis[*o*-(di-*o*-tolylphosphanyl)benzyl]dipalladium as the precatalyst.^[3]

The use of simple Pd salts as precatalysts in the Suzuki coupling is also increasing.^[1, 5c, 19] We therefore studied the Pd(OAc)₂-catalyzed reaction of phenylboronic acid (**11**) with *p*-bromoacetophenone (**12**), which afforded the coupling product **13** in 93% yield (1 mol% Pd(OAc)₂; 2.5 equiv NaHCO₃; DMF; 10 h/130 °C) [Eq. (3)]. The TEM images showed the presence of Pd nanoparticles, which in this case



were a little smaller (1.3 nm) than those in the Heck reactions. Control experiments showed previously that preformed Pd colloids catalyze the Suzuki reaction.^[13a]

Our studies point to the involvement of in situ generated nanosized Pd colloids in three preparatively significant phosphane-free catalyst systems based on simple Pd salts, namely, Pd(OAc)₂/DMG, Pd(OAc)₂/(*n*Bu)₄N⁺Cl[−] and Pd(OAc)₂. It is therefore likely that other phosphane-free Heck reactions and related C–C bond-forming processes in the presence of Pd salts without special ligands are also catalyzed by nanosized Pd colloids. Indeed, this suspicion was previously voiced in the case of Pd(OAc)₂-catalyzed Ullmann reactions.^[20]

Although the systems described here involve colloidal solutions of Pd nanoparticles, processes of this kind do not belong to the traditional area of homogeneous catalysis.^[21] Rather, catalysis is likely to occur at defect sites, steps, and kinks on the surface of the colloidal metal particles,^[13a, 14] a process that is more closely related to heterogeneous catalysis.^[22, 23]

Received: August 11, 1999 [Z13860]

- [1] a) J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, **1995**; b) A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, *106*, 2473–2506; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379–2411; c) S. Bräse, A. de Meijere in *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 99–166; d) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; e) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; f) T. N. Mitchell in *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 167–202; g) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React. N. Y.* **1997**, *50*, 1–652; h) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047–1062; i) R. C. Larock, *J. Organomet. Chem.* **1999**, *576*, 111–124; j) G. Dyker, *Chem. Ber.* **1997**, *130*, 1567–1578; k) A. F. Littke, G. C. Fu, *J. Org. Chem.* **1999**, *64*, 10–11; l) M. S. Stephan, A. J. J. M. Teunissen, G. K. M. Verzijl, J. G. de Vries, *Angew. Chem.* **1998**, *110*, 688–690; *Angew. Chem. Int. Ed.* **1998**, *37*, 662–664.
- [2] a) W. A. Herrmann, C. Köcher, *Angew. Chem.* **1997**, *109*, 2256–2282; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162–2187; b) W. A. Herrmann, C.-P. Reisinger, M. Spiegler, *J. Organomet. Chem.* **1998**, *557*, 93–96; c) C. M. Zhang, J. K. Huang, M. L. Trudell, S. P. Nolan, *J. Org. Chem.* **1999**, *64*, 3804–3805; d) D. S. McGuinness, K. J. Cavell, B. W. Skelton, A. H. White, *Organometallics* **1999**, *18*, 1596–1605.
- [3] W. A. Herrmann, V. P. W. Böhm, C.-P. Reisinger, *J. Organomet. Chem.* **1999**, *576*, 23–41.
- [4] a) T. Jeffery, M. David, *Tetrahedron Lett.* **1998**, *39*, 5751–5754; b) T. Jeffery, *Tetrahedron* **1996**, *52*, 10113–10130.
- [5] a) I. P. Beletskaya, *Pure Appl. Chem.* **1997**, *69*, 471–476; b) W. A. Herrmann, C.-P. Reisinger in *Aqueous-Phase Organometallic Catalysis: Concepts and Applications* (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1998**, pp. 383–392; c) N. A. Bumagin, V. V. Bykov, *Tetrahedron* **1997**, *53*, 14437–14450; d) J. P. Genet, M. Savignac, *J. Organomet. Chem.* **1999**, *576*, 305–317.
- [6] M. T. Reetz, E. Westermann, R. Lohmer, G. Lohmer, *Tetrahedron Lett.* **1998**, *39*, 8449–8452.
- [7] Other studies concerning the mechanism^[1, 4] of the Heck reaction: a) C. Amatore, A. Jutand, *J. Organomet. Chem.* **1999**, *576*, 254–278; b) B. L. Shaw, *New J. Chem.* **1998**, 77–79; c) F.-G. Zhao, B. M. Bhanage, M. Shirai, M. Arai in *Reaction Kinetics and the Development of Catalytic Processes* (Eds.: G. F. Froment, K. C. Waugh), *Stud. Surf. Sci. Catal.*, Vol. 122, Elsevier, Amsterdam, **1999**, pp. 427–430; d) F.-G. Zhao, B. M. Bhanage, M. Shirai, M. Arai, *J. Mol. Catal. A* **1999**, *142*, 383–388; e) A. F. Shmidt, A. Khalaika, *Kinet. Catal.* **1998**, *39*,

- 803–809; *Kinet. Katal.* **1998**, 39, 875–881; f) A. F. Shmidt, A. Khalaika, L. O. Nindakova, E. Y. Shmidt, *Kinet. Katal.* **1998**, 39, 200–206; *Kinet. Katal.* **1998**, 39, 216–222; g) W. A. Herrmann, C. Broßmer, K. Öfele, M. Beller, H. Fischer, *J. Organomet. Chem.* **1995**, 491, C1–4; h) G. T. Crisp, *Chem. Soc. Rev.* **1998**, 27, 427–436.
- [8] In other cases the induction period is shorter.
- [9] In the thermolysis of Pd(OAc)₂, the ligand (acetate) serves as the reductant, a process which generates Pd⁰ in addition to methane, ethane, and CO₂.^[10, 12]
- [10] M. T. Reetz, G. Lohmer, *Chem. Commun.* **1996**, 1921–1922.
- [11] a) J. Kiwi, M. Grätzel, *J. Am. Chem. Soc.* **1979**, 101, 7214–7217; b) Y. Sasson, A. Zoran, J. Blum, *J. Mol. Catal.* **1981**, 11, 293–300; c) M. Boutonnet, J. Kizling, P. Stenius, G. Maire, *Colloids Surf.* **1982**, 5, 209–225; d) N. Toshima, T. Takahashi, H. Hirai, *Chem. Lett.* **1985**, 1245–1248; e) M. Boutonnet, J. Kizling, R. Touroude, G. Maire, P. Stenius, *Appl. Catal. A* **1986**, 20, 163–177; f) K. Meguro, M. Torizuka, K. Esumi, *Bull. Chem. Soc. Jpn.* **1988**, 61, 341–345; g) J. Wiesner, A. Wokaun, H. Hoffmann, *Prog. Colloid Polym. Sci.* **1988**, 76, 271–277; h) N. Satoh, K. Kimura, *Bull. Chem. Soc. Jpn.* **1989**, 62, 1758–1763; i) H. Bönemann, W. Brijoux, R. Brinkmann, E. Dinjus, T. Jousen, B. Korall, *Angew. Chem.* **1991**, 103, 1344–1346; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1312; j) N. Toshima, T. Takahashi, *Bull. Chem. Soc. Jpn.* **1992**, 65, 400–409; k) M. T. Reetz, S. A. Quaiser, *Angew. Chem.* **1995**, 107, 2461–2463; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2240–2241; l) M. T. Reetz, W. Helbig, S. A. Quaiser, U. Stimming, N. Breuer, R. Vogel, *Science* **1995**, 267, 367–369.
- [12] M. T. Reetz, M. Maase, *Adv. Mater.* **1999**, 11, 773–777.
- [13] a) M. T. Reetz, R. Breinbauer, K. Wanninger, *Tetrahedron Lett.* **1996**, 37, 4499–4502; b) M. Beller, H. Fischer, K. Kühlein, C.-P. Reisinger, W. A. Herrmann, *J. Organomet. Chem.* **1996**, 520, 257–259.
- [14] J. S. Bradley in *Clusters and Colloids* (Ed.: G. Schmid), VCH, Weinheim, **1994**, pp. 459–544.
- [15] In addition to these four signals, another small signal appears at $\delta = 128.8$, which could not be assigned.
- [16] G. P. Cestari, Dissertation, Universität Düsseldorf (Germany), **1999**.
- [17] a) C. Amatore, A. Jutand, L. Mottier, *Eur. J. Inorg. Chem.* **1999**, 7, 1081–1085; b) F. Paul, J. Patt, J. F. Hartwig, *Organometallics* **1995**, 14, 3030–3039; c) K. J. Klabunde, J. Y. F. Low, *J. Am. Chem. Soc.* **1974**, 96, 7674–7680; d) F. E. Goodson, T. I. Wallow, B. M. Novak, *J. Am. Chem. Soc.* **1997**, 119, 12441–12453.
- [18] a) G. P. F. van Strijdonck, M. D. K. Boele, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1999**, 1073–1076; b) M. T. Reetz, G. Lohmer, R. Schwickardi, *Angew. Chem.* **1998**, 110, 492–495; *Angew. Chem. Int. Ed.* **1998**, 37, 481–483, and references therein.
- [19] a) T. I. Wallow, B. M. Novak, *J. Org. Chem.* **1994**, 59, 5034–5037; b) M. Moreno-Mañas, F. Pajuelo, R. Pleixats, *J. Org. Chem.* **1995**, 60, 2396–2397; c) D. Badone, M. Baroni, R. Cardamone, A. Iellini, U. Guzzi, *J. Org. Chem.* **1997**, 62, 7170–7173.
- [20] G. Dyker, A. Kellner, *J. Organomet. Chem.* **1998**, 555, 141–144.
- [21] Mechanistic discussion of homogeneous versus heterogeneous catalysis: a) J. Schwartz, *Acc. Chem. Res.* **1985**, 18, 302–308; b) Y. Lin, R. G. Finke, *Inorg. Chem.* **1994**, 33, 4891–4910.
- [22] J. M. Thomas, W. J. Thomas, *Principles and Practice of Heterogeneous Catalysis*, Wiley-VCH, Weinheim, **1997**.
- [23] By nature our studies say nothing about the question whether the observed 1.3–1.6 nm sized Pd colloids are the actual catalysts, or whether they function as a “reservoir” or “donor” of smaller and possibly more reactive fragments.

The Tetrakis(carbonyl)dioxosmium(vi) Cation: *trans*-[OsO₂(CO)₄]^{2+*}

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Superacidic reaction media,^[1, 2] in particular the Lewis superacid SbF₅ and the conjugate Brønsted Lewis superacid HF/SbF₅, have allowed in recent years the generation of a substantial number of previously unknown homoleptic metal carbonyl cations,^[3] for example the octahedral cations [M(CO)₆]²⁺ (M = Fe,^[4] Ru, Os^[5]). Thermally stable salts are generally obtained with the superacid anion [Sb₂F₁₁]⁻.^[6] Observations made during the synthesis of [Os(CO)₆][Sb₂F₁₁]₂ by reductive carbonylation of either Os(SO₃F)₃,^[5] OsF₆,^[7] or OsO₄^[8] provide the motivation for this study: In the IR spectra of the products an additional band of varied intensity is observed at 2253 cm⁻¹ in addition to the intense CO stretching band (F_{1u}) of [Os(CO)₆]²⁺ at 2190 cm⁻¹. Since the highest intensities of the band at 2253 cm⁻¹ are found in samples prepared from OsO₄,^[8] we have modified the reaction conditions and intend to show that the high wave-number band can be attributed to the new cation *trans*-[OsO₂(CO)₄]²⁺.

When the reaction temperature is reduced from 60–90 °C^[5] to room temperature and available CO is limited to a modest excess (about 1.4-fold), a yellow product is formed after 10 days. This product is free of [Os(CO)₆][Sb₂F₁₁]₂ according to the vibrational spectrum. The only volatile product, CO₂, is formed in a molar ratio of approximately 1:1 (based on OsO₄), as estimated from the intensity of $\nu_{as}(\text{CO}_2)$ in the gas-phase IR spectrum.

The new compound, tentatively identified as [OsO₂(CO)₄]-[Sb₂F₁₁]₂, is extremely sensitive to moisture and turns black in air within seconds. Upon heating in a sealed tube above 80 °C, decomposition to an inhomogeneous violet material and the release of CO are noted. All attempts to obtain single crystals of [OsO₂(CO)₄][Sb₂F₁₁]₂ and affect a separation from any

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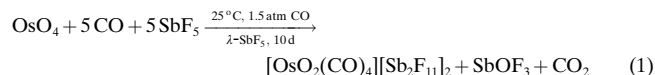
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[**] Financial support by the Deutsche Forschungsgemeinschaft, the Schweizer Nationalfonds, the Fonds der Chemischen Industrie and the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged. We thank Dr. G. Balzer, Universität Hannover, for recording ¹³C MAS NMR spectra.

solid by-products through recrystallization from anhydrous HF or HF/SbF₅ were unsuccessful. In HF decomposition to [Os(CO)₆][Sb₂F₁₁]₂^[5] with formation of a dark blue solution (possibly OsF₅^[9]) occurs within seconds even at –50 °C. In HF/SbF₅ (1:1 to 1:5) the solubility is lower. Solutions are stable at room temperature for several hours, and crystalline [Os(CO)₆][Sb₂F₁₁]₂ is eventually obtained from these solutions.

Based on the evidence discussed above, the formation reaction suggested is that shown in Equation (1):



There are three problems with this formulation:

1) A satisfactory elemental analysis is not obtained for this very reactive material, and the mass balance and redox balance (CO₂ determination) are very approximate with errors of 10–20 %.

2) Although the vibrational spectrum of SbOF₃ is known,^[10] due to extensive overlap with bands of the [Sb₂F₁₁][–] anion, only a single IR band at 407 cm^{–1} can be attributed to this species. (The observed bands below 800 cm^{–1} are listed in the Experimental Section.)

3) At room temperature and with reaction times of 10 days, the reaction is incomplete, and some unchanged OsO₄ is pumped off from the product mixture, which may account for the poor mass balance. Any increase in the reaction temperature results in the formation of substantial amounts of [Os(CO)₆][Sb₂F₁₁]₂.

While there is some uncertainty regarding the formation of [OsO₂(CO)₄][Sb₂F₁₁]₂, the identity of the cation and its octahedral geometry with *trans* oxygen atoms are clearly established by vibrational spectroscopy. The frequencies of

the IR and Raman bands for *trans*-[OsO₂(CO)₄]²⁺ are listed in Table 1 together with estimated intensities and assignments in point group *D*_{4h}. They are compared to calculated data for gaseous *trans*-[OsO₂(CO)₄]²⁺, obtained from gradient-corrected density functional calculations at the BP86/ECP2 level in analogy to an earlier study.^[11] The corresponding vibrational data for *trans*-[OsO₂(CN)₄]^{2–}^[12] are listed as well. Salts of the *trans*-tetracyanodioxosmate(vi) anion have been known since 1928^[13] as members of the large family of osmyl complexes.^[14, 15] As can be seen in Table 1, there is very good agreement between observed and calculated data for both *trans*-[OsO₂(CO)₄]²⁺ and isoelectronic *trans*-[OsO₂(CN)₄]^{2–}.^[12]

The vibrational spectrum of [OsO₂(CO)₄]²⁺ has a number of unusual features:

1) As with other metal carbonyl cations,^[3] the wavenumbers of CO stretching vibrations are unusually high. The stretching force constant *f*_{CO}, obtained according to the Cotton–Kraihanzel approximation,^[16] is with 20.7 × 10² Nm^{–1} comparable to a reported *f*_{CO} value of 20.64 × 10² Nm^{–1} for square-planar [Pt(CO)₄]²⁺.^[17] [Sb₂F₁₁][–] is the anion in both complex salts. The implication is that the cations Pt²⁺ and *trans*-OsO₂²⁺ exhibit comparable Lewis acidities towards CO. Slightly higher *f*_{CO} values are reported only for [Ir(CO)₆]³⁺ (20.8 × 10² Nm^{–1})^[18] and [Hg(CO)₂]²⁺ (21.0 × 10² Nm^{–1}).^[19] Evidently in all four complex cations CO is predominantly σ-bonded and the CO ligand is strongly polarized.^[3]

2) The three CO stretching vibrations of *trans*-[OsO₂(CO)₄]²⁺ follow the selection rules for the point group *D*_{4h}, but the band separations of 11 and 27 cm^{–1} for ν₁(A_{1g}) – ν₂(B_{1g}) and ν₁(A_{1g}) – ν₁₆(E_u), respectively, are smaller than the corresponding Δν values of 27 and 45 cm^{–1} for [Pt(CO)₄]²⁺.^[17] Even smaller band separations of 6 and 19 cm^{–1} are reported for the corresponding CN stretching

Table 1. Experimental and calculated vibrational data for *trans*-[OsO₂(CO)₄]²⁺ and *trans*-[OsO₂(CN)₄]^{2–}.^[a]

Assignment (X = O, N)	[OsO ₂ (CO) ₄] ²⁺			[OsO ₂ (CN) ₄] ^{2–}		
	experimental ν _{IR} [cm ^{–1}]	experimental ν _{Raman} [cm ^{–1}]	calculated ^[b]	experimental ^[c] ν _{IR} [cm ^{–1}]	experimental ^[c] ν _{Raman} [cm ^{–1}]	calculated ^[b]
ν ₁ , A _{1g} , ν(CX)		2280 {20}	2259 {100} ^[d]		2166 {vs}	2155 {100} ^[e]
ν ₈ , B _{1g} , ν(CX)		2269 {16}	2242 {87}		2160 {s}	2144 {63}
ν ₁₆ , E _u , ν(CX)	2253 (100)		2228 (100) ^[f]	2147 (s)		2136 (19)
ν ¹³ (CX) ^[h]	2210 (2.7)			–		
ν ₂ , A _{1g} , ν(OsO)		855 {38}	872 {18}		880 {vs}	869 {11}
ν ₅ , A _{2u} , ν(OsO)	851 (79)		857 (28)	832 (vs)		824 (100) ^[e]
ν ₁₇ , E _u , δ(OsCX)	485 ^[i] (100)		488 (24)	461 (w)		460 (6)
ν ₆ , A _{2u} , δ(OsCX)	462 (45)		465 (11)	442 (vw)		433 (0.9)
ν ₁₂ , B _{2u} , δ(OsCX)	–		437 (0)	–		410 (0)
ν ₁₀ , B _{2g} , δ(OsCX)		411 ^[j]	412 {0.0}		424 {m}	399 {0.8}
ν ₁₄ , E _g , δ(OsCX)		411 {5}	409 {0.2}		407 {w}	406 {0.02}
ν ₃ , A _{1g} , ν(OsC)		378 {5}	363 {5}		377 {w}	384 {3}
ν ₉ , B _{1g} , ν(OsC)		353 {1}	348 {0.7}		364 {w}	377 {1}
ν ₄ , A _{2g} , δ(OsCX)		–	304 {0}		–	304 {0}
ν ₁₈ , E _u , ν(OsC)	– ^[k]		275 (2)	357 (s)		319 (70)
ν ₁₉ , E _u , δ(OOsO)	– ^[k]		227 (7)	261/246 (s)		228 (22)
ν ₁₅ , E _g , δ(COsO)		183 {100}	149 {6}		189/183 {vs}	177 {5}
ν ₂₀ , E _u , δ(COsC)	–		88 (0.5)	115 (sh)		93 (5)
ν ₇ , A _{2u} , δ(COsC)	–		87 (0.1)	130 (s)		105 (12)
ν ₁₁ , B _{2g} , δ(COsC)		128 {43}	86 {3}		127 {s}	93 {3}
ν ₁₃ , B _{2u} , δ(COsC)	–		68 (0)	–		82 (0)

[a] The relative intensity of a vibration is given after the wavenumber (parentheses for IR-active vibrations and curly brackets for Raman-active vibrations). [b] DFT calculations at the BP86/ECP2 level. [c] [Me₄N]⁺ salt.^[12] [d] Absolute Raman intensity = 188.1. [e] 457.6 Å⁴ amu^{–1}. [f] Absolute IR intensity = 249.1. [g] 242.7 kmol^{–1}. [h] [OsO₂(CO)₃(¹³CO)]²⁺. [i] Hidden by a anion band at 493 cm^{–1}. [j] Together with ν₁₄. [k] Hidden by δSbF vibrations (230–346 cm^{–1}).

vibrations in $trans\text{-}[\text{OsO}_2(\text{CN})_4]^{2-}$ ^[12] and for linear $[\text{Hg}(\text{CO})_2]^{2+}$, where $\nu_s(\text{CO})$ and $\nu_{as}(\text{CO})$ are separated by only 3 cm^{-1} .^[19]

3) A very similar small band separation of 4 cm^{-1} is observed for the two characteristic OsO_2 stretching vibrations in $trans\text{-}[\text{OsO}_2(\text{CO})_4]^{2+}$. This unusually small separation is consistently reproducible in various preparations. In $trans\text{-}[\text{OsO}_2(\text{CN})_4]^{2-}$ a separation of 48 cm^{-1} is observed (see Table 1), which is more typical for neutral or anionic osmyl complexes.^[14, 15] The very close proximity of Raman- and IR-active OsO_2 vibrations in the cation could suggest the presence of a single OsO group. However, the OsO stretching vibrations in complexes of this type are commonly found around 1000 cm^{-1} .^[14] In addition the observed strict planarity of the $\text{Os}(\text{CO})_4$ moiety, in compliance with the mutual exclusion rule, would be difficult to explain for an $[\text{OsO}(\text{CO})_4]$ complex.

To understand these unusual observations better, we have calculated the vibrational spectra of two isoelectronic species, molecular $[\text{WO}_2(\text{CO})_4]$, which has been observed previously in an Ar matrix,^[20] and the still unknown $[\text{ReO}_2(\text{CO})_4]^+$. The calculated and available experimental wavenumbers for the CO and MO stretching vibrations for the three isosteric species are listed in Table 2 together with the band separation $\Delta\nu$.

Table 2. Calculated and experimental wavenumbers (in cm^{-1}) of the CO and MO stretching vibrations in the isosteric complexes $\text{WO}_2(\text{CO})_4$, $[\text{ReO}_2(\text{CO})_4]^+$, and $[\text{OsO}_2(\text{CO})_4]^{2+}$.

Assignment	$[\text{WO}_2(\text{CO})_4]$		$[\text{ReO}_2(\text{CO})_4]^+$		$[\text{OsO}_2(\text{CO})_4]^{2+}$	
	calcd ^[a]	exp. ^[b]	calcd ^[a]		calcd ^[a]	exp. ^[c]
$\nu(\text{CO}) (A_{1g})$	2133	2160	2209		2259	2280
$\nu(\text{CO}) (B_{1g})$	2073		2174		2242	2269
$\nu(\text{CO}) (E_u)$	2059	2096	2158		2228	2253
$\Delta\nu(\text{CO})$ ^[d]	60/74	−/64	35/51		17/31	11/27
$\nu(\text{MO}_2) (A_{1g})$	818	850	866		872	855
$\nu(\text{MO}_2) (A_{2u})$	719	751	807		857	851
$\Delta\nu(\text{MO}_2)$	99	99	59		15	4

[a] DFT calculations at the BP86/ECP2 level. [b] Ref. [20]. [c] This work. [d] $\nu(\text{CO}) (A_{1g}) - \nu(\text{CO}) (B_{1g}) / \nu(\text{CO}) (A_{1g}) - \nu(\text{CO}) (E_u)$.

tions $\Delta\nu$. With increasing nuclear charge and oxidation state of the central metal the separation between the two MO stretching vibrations (A_{1g} and A_{2u}) gradually decreases. In a similar manner, the band separation between the two $\nu(\text{CO})$ vibrations (A_{1g} and E_u) decreases; however, the trend is less pronounced. It appears that the reduced electron density on osmium in $[\text{OsO}_2(\text{CO})_4]^{2+}$ compared to the other two isoelectronic species or other osmyl complexes^[14, 15] is responsible for smaller interaction force constants, resulting in narrow band spacings in the MO and CO stretching region. A similar argument can be used to explain the very small separation of 3 cm^{-1} for the CO vibrations of linear $[\text{Hg}(\text{CO})_2]^{2+}$. Differences between calculated and experimental wavenumbers (Tables 1 and 2) are usually small and result from systematic errors in the DFT calculations,^[11] anharmonicity effects, or interionic interactions in the solid state.

To provide further evidence for the existence of $[\text{OsO}_2(\text{CO})_4]^{2+}$ and for its proposed structure, we carried out additional syntheses with ^{13}C -enriched CO and ^{18}O -enriched OsO_4 . We subsequently recorded, in addition to the vibrational spectra, ^{13}C magic angle spinning (MAS) NMR and

UV/Vis spectra. In the ^{13}C NMR spectrum of $[\text{OsO}_2(\text{CO})_4][\text{Sb}_2\text{F}_{11}]_2$ the isotropic chemical shift is $\delta_c = 134$ with a linewidth of about 5 ppm. The relatively narrow resonance line observed is a strong indication for the high symmetry of the cation (D_{4h}) and its diamagnetism. All osmyl complexes with a d^2 electron configuration are diamagnetic,^[14, 15] which is explained by a tetragonal distortion of the octahedral coordination due to the linear O-Os-O moiety.^[21]

The ^{13}C chemical shift of $\delta = 134$ for $trans\text{-}[\text{OsO}_2(\text{CO})_4]^{2+}$ is very similar to the value of $\delta = 137$ reported for $[\text{Pt}(\text{CO})_4]^{2+}$.^[17] This observation, together with the nearly identical CO stretching force constants f_{CO} discussed above and the strong similarity of the vibrational spectra of both $trans\text{-}[\text{OsO}_2(\text{CO})_4]^{2+}$ and $[\text{Pt}(\text{CO})_4]^{2+}$,^[17] suggests a strictly square-planar arrangement of the four CO ligands in both cations. This has recently been confirmed for $[\text{Pt}(\text{CO})_4]^{2+}$ by the determination of the molecular structure of its $[\text{Sb}_2\text{F}_{11}]^-$ salt.^[22] The ^{13}C chemical shift of $trans\text{-}[\text{OsO}_2(\text{CO})_4]^{2+}$ falls between those of $[\text{Os}(\text{CO})_6]^{2+}$ ($\delta = 147$)^[19] and $[\text{Ir}(\text{CO})_6]^{3+}$ ($\delta = 121$)^[18]; the chemical shift for the iridium complex is the smallest value so far observed for metal carbonyl cations and their derivatives.^[3] For the isoelectronic species $trans\text{-}[\text{OsO}_2(\text{CN})_4]^{2-}$ ^[23] and $[\text{Os}(\text{CN})_6]^{4-}$ ^[24] δ_c values of 120 and 142.5 are reported, which correlate well with the ^{13}C chemical shifts for $trans\text{-}[\text{OsO}_2(\text{CO})_4]^{2+}$ and $[\text{Os}(\text{CO})_6]^{2+}$.

Since $trans\text{-}[\text{OsO}_2(\text{CO})_4][\text{Sb}_2\text{F}_{11}]_2$ is unstable in HF and to a lesser extent also in HF-SbF_5 , we have not been able to measure UV/Vis spectra in solution. Instead a diffuse reflectance spectrum is obtained on yellow $trans\text{-}[\text{OsO}_2(\text{CO})_4][\text{Sb}_2\text{F}_{11}]_2$ (Figure 1). However, without reliable extinction coefficients, nothing definitive regarding the nature of the

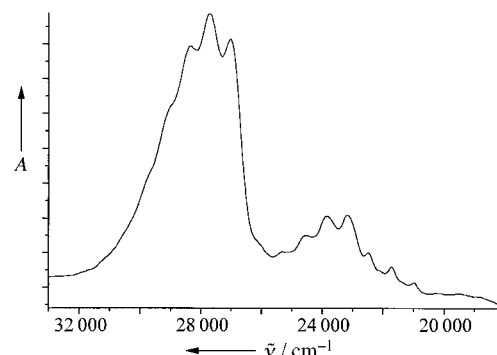


Figure 1. UV Vis spectrum (diffuse reflexion) of $[\text{OsO}_2(\text{CO})_4][\text{Sb}_2\text{F}_{11}]_2$.

observed electronic transitions can be said, and only qualitative, descriptive comments are appropriate. The spectrum observed is similar to that reported for $[\text{NMe}_4]_2\text{-}[\text{OsO}_2(\text{CN})_4]$.^[25] Two of the bands have a vibrational fine structure with vibrational wavenumbers of about 730 cm^{-1} , similar to the $[\text{OsO}_2(\text{CN})_4]^{2-}$ anion.^[25] The origins of the two bands (0–0 transition) at $23\,100$ and $26\,900\text{ cm}^{-1}$ are red-shifted by about 3000 cm^{-1} relative to the bands of $[\text{OsO}_2(\text{CN})_4]^{2-}$.

In spite of some limitations to the interpretation of the UV/Vis spectra, together with vibrational spectra, DFT calculations, and ^{13}C NMR-MAS spectra they permit the unambiguous identification of the new $trans\text{-}[\text{OsO}_2(\text{CO})_4]^{2+}$ cation. The spectroscopic properties correlate very well not only with

those of isoelectronic $\text{trans-[OsO}_2(\text{CN})_4]^{2-}$,^[12, 25] but also with those of the homoleptic carbonyl cations $[\text{Os}(\text{CO})_6]^{2+}$ ^[5] and, particularly, square-planar $[\text{Pt}(\text{CO})_4]^{2+}$.^[17, 22]

The new superelectrophilic^[26] cation $\text{trans-[OsO}_2(\text{CO})_4]^{2+}$ is unusual for two reasons:

1) It is the first oxo derivative of a homoleptic metal carbonyl cation. $\text{trans-[OsO}_2(\text{CO})_4]^{2+}$ joins a small but growing group of cations such as $[\text{M}(\text{CO})_5\text{Cl}]^{2+}$ ($\text{M} = \text{Rh}, \text{Ir}$),^[27] $[\text{W}(\text{CO})_6(\text{FSbF}_5)]^+$,^[28] and polymeric $[\{\text{Mo}(\text{CO})_4\}_2(\text{cis-}\mu\text{-F}_2\text{SbF}_4)_3]^+$.^[29] All are generated in superacids, have been structurally characterized, and have $[\text{Sb}_2\text{F}_{11}]^-$ as counterion. With a number of superacidic media^[1, 2] and very versatile synthetic routes available,^[3] it should be possible to add more cationic derivatives with the atoms N, O, or F as ligands to this list.

2) $\text{trans-[OsO}_2(\text{CO})_4]^{2+}$ is the first cationic metal carbonyl complex with the metal in the formal oxidation state +6. Previously the highest oxidation state of the central metal was +4. Examples include the matrix molecule $[\text{WO}_2(\text{CO})_4]^{20}$ and the pentahalo-monocarbonyl-metalate(IV) anions $[\text{PtCl}_5(\text{CO})]^-$,^[30] $[\text{OsCl}_5(\text{CO})]^-$,^[31] and $[\text{OsF}_5(\text{CO})]^-$.^[32]

Experimental Section

A 50-mL glass flask fitted with a PTFE valve and a magnetic stirring bar was dried by heating in vacuo and charged with OsO_4 (0.116 g, 0.46 mmol). SbF_5 (6.34 g, 20 mmol) was added by condensation in vacuo, and the CO pressure was adjusted to 1.5 bar (3.3 mmol). The initially clear solution was vigorously stirred at room temperature. After several days the solution became turbid, and after 10 days a yellow suspension formed. At room temperature all volatile components were removed in vacuo, and a finely powdered, yellowish solid (0.612 g) was obtained. Vibrational bands observed below 800 cm^{-1} : IR: $\tilde{\nu} = 760$ (m), 704 (vs), 655 (vs), 601 (m), 490 (sh), 407 (m), 346 (m), 311 (s), 276 (s), 240 (vs); Raman: 675 (vs), 645 (m), 605 (m), 296 (s), 232 (m) cm^{-1} .

Received: June 11, 1999 [Z13546]

- [1] G. A. Olah, G. K. S. Prakash, J. Sommer, *Superacids*, Wiley, New York, **1985**, and references therein.
- [2] T. A. O'Donnell, *Superacids and Acidic Melts as Inorganic Chemical Reaction Media*, VCH, Weinheim, **1993**.
- [3] H. Willner, F. Aubke, *Angew. Chem.* **1997**, *109*, 2506–2530; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2402–2425.
- [4] E. Bernhardt, B. Bley, R. Wartchow, H. Willner, E. Bill, P. Kuhn, I. H. T. Sham, M. Bodenbinder, R. Bröchler, F. Aubke, *J. Am. Chem. Soc.* **1999**, *121*, 7188–7200.
- [5] C. Wang, B. Bley, G. Balzer-Jöllenbeck, A. R. Lewis, S. C. Siu, H. Willner, F. Aubke, *J. Chem. Soc. Chem. Commun.* **1995**, 2071–2072.
- [6] D. Zhang, S. J. Rettig, J. Trotter, F. Aubke, *Inorg. Chem.* **1996**, *35*, 6113–6130.
- [7] C. Bach, Dissertation, Universität Hannover, **1999**.
- [8] B. Bley, Dissertation, Universität Hannover, **1997**.
- [9] a) G. B. Hargreaves, R. D. Peacock, *J. Chem. Soc.* **1960**, 2618–2620. b) G. H. Cady, G. B. Hargreaves, *J. Chem. Soc.* **1961**, 1568–1574.
- [10] K. Dehnicke, J. Weidlein, *Z. Anorg. Allg. Chem.* **1966**, *342*, 225–232.
- [11] V. Jonas, W. Thiel, *Organometallics* **1998**, *17*, 353–360.
- [12] W. Preetz, C. Sartori, *Z. Naturforsch. B* **1988**, *43*, 94–98.
- [13] F. Krauss, G. Schrader, *J. Prakt. Chem.* **1928**, *120*, 36–40.
- [14] W. P. Griffiths, *Comprehensive Coordination Chemistry*, Vol. 4 (Ed.: G. Wilkinson), Pergamon, Oxford, **1987**, pp. 519–619.
- [15] W. P. Griffiths, *The Chemistry of the Rarer Platinum Metals (Os, Ru, Ir and Rh)*, Interscience, New York, **1967**, p. 72.
- [16] F. A. Cotton, C. S. Kraihanzel, *J. Am. Chem. Soc.* **1962**, *84*, 4432–4438.
- [17] G. Hwang, C. Wang, F. Aubke, M. Bodenbinder, H. Willner, *Can. J. Chem.* **1993**, *71*, 1532–1536.

- [18] C. Bach, H. Willner, C. Wang, S. J. Rettig, J. Trotter, F. Aubke, *Angew. Chem.* **1996**, *108*, 2104–2106; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1974–1976.
- [19] M. Bodenbinder, G. Balzer-Jöllenbeck, H. Willner, R. J. Batchelor, F. W. B. Einstein, C. Wang, F. Aubke, *Inorg. Chem.* **1996**, *35*, 82–92.
- [20] J. A. Crayston, M. J. Almond, A. J. Downs, M. Poliakoff, J. J. Turner, *Inorg. Chem.* **1984**, *23*, 3051–3056.
- [21] K. A. K. Lott, M. R. C. Symons, *J. Chem. Soc.* **1960**, 973–976.
- [22] M. Bodenbinder, R. Bröchler, S. J. Rettig, J. Trotter, B. von Ahsen, H. Willner, V. Jonas, W. Thiel, F. Aubke, unpublished results.
- [23] A. Abou-Hamdan, A. Roodt, A. E. Merbach, *Inorg. Chem.* **1998**, *37*, 1278–1288.
- [24] J. J. Pesek, W. R. Mason, *Inorg. Chem.* **1979**, *18*, 924–928.
- [25] C. Sartori, W. Preetz, *Z. Naturforsch. A* **1988**, *43*, 239–247.
- [26] The term superelectrophile is chosen to identify metal carbonyl cations with complex charges of +2 and +3; it was first introduced by Olah: G. A. Olah, *Angew. Chem.* **1993**, *105*, 805–826; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 767–788.
- [27] H. Willner, C. Bach, R. Wartchow, C. Wang, S. J. Rettig, J. Trotter, V. Jonas, W. Thiel, F. Aubke, *Inorg. Chem.*, in press.
- [28] R. Bröchler, M. Bodenbinder, I. H. T. Sham, S. J. Rettig, J. Trotter, H. Willner, F. Aubke, *Inorg. Chem.*, submitted.
- [29] R. Bröchler, D. Freidank, M. Bodenbinder, I. H. T. Sham, H. Willner, S. J. Rettig, J. Trotter, F. Aubke, *Inorg. Chem.* **1999**, *38*, 3684–3687.
- [30] D. B. Dell'Amico, F. Calderazzo, F. Marchetti, S. Merlino, *J. Chem. Soc. Dalton Trans.* **1982**, 2257–2260.
- [31] M. Höhling, W. Preetz, *Z. Naturforsch. B* **1997**, *52*, 978–980.
- [32] E. Bernhardt, W. Preetz, *Z. Anorg. Allg. Chem.* **1998**, *624*, 694–700.

A Facile Route to Group 13 Difluorodiorganometalates: $[\text{nBu}_4\text{N}][\text{R}_2\text{MF}_2]$ ($\text{M} = \text{Al}, \text{Ga}, \text{In}$)*

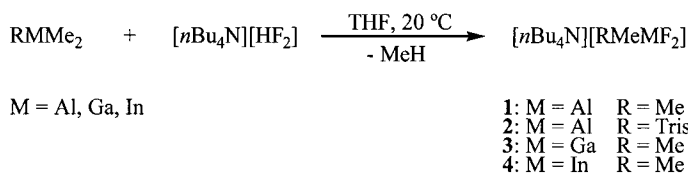
Herbert W. Roesky,* Andreas Stasch, Hagen Hatop, Carsten Rennekamp, David H. Hamilton, Mathias Noltemeyer, and Hans-Georg Schmidt

Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

Group 13 difluorodiorganometalates have been known since 1955;^[1] however, only a few of these were spectroscopically and structurally characterized.^[2] Furthermore, the synthesis of these anions was not straightforward. We describe herein the synthesis, X-ray crystal structure,^[3] and NMR and IR spectroscopic characterization of some difluorodiorganometalates $[\text{nBu}_4\text{N}][\text{R}_2\text{MF}_2]$ ($\text{M} = \text{Al}, \text{Ga}, \text{In}$). The synthesis of these compounds is accomplished through protonolysis of trialkyl derivatives of Group 13 metals with tetra-*n*-butylammonium hydrogen difluoride (TBADF) at room temperature,^[4] which induces elimination of methane and addition of two fluoride ions. The compounds **1–4** are obtained as colorless, rhombic crystals (Scheme 1).

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[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Witco GmbH, the Alexander von Humboldt Foundation, and the Fonds der Chemischen Industrie.



Scheme 1. Synthesis of **1–4**. Tris = (Me₃Si)₃C.

Compounds **1**, **3**, and **4** are isomorphous and crystallize in the monoclinic space group *P*₂₁/*n* (Figure 1). Compound **2** crystallizes in the monoclinic space group *P*₂₁/*c* (Figure 2). The metal center of these anions has a distorted tetrahedral

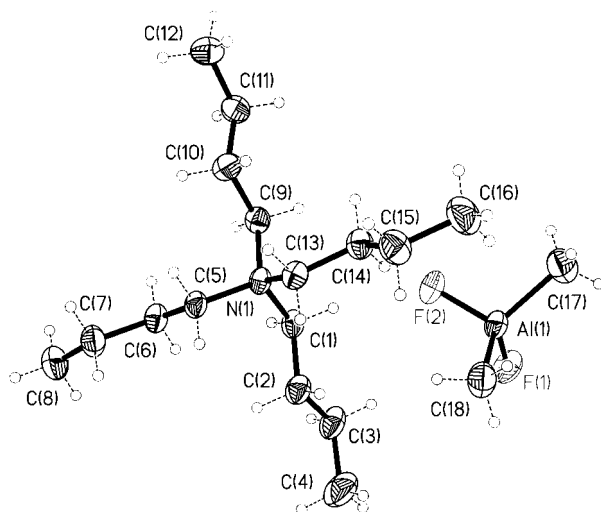


Figure 1. Molecular structure of **1**. Compounds **3** and **4** are isomorphous. Selected bond lengths [Å] and angles [°]: **1**: Al(1)–F(1) 1.7109(13), Al(1)–F(2) 1.7130(13), Al(1)–C(17) 1.965(2), Al(1)–C(18) 1.972(2); F(1)–Al(1)–F(2) 103.23(7), F(1)–Al(1)–C(17) 108.60(10), F(2)–Al(1)–C(17) 108.64(9), F(1)–Al(1)–C(18) 108.74(9), F(2)–Al(1)–C(18) 109.60(8), C(17)–Al(1)–C(18) 117.13(10); **3**: Ga(1)–F(2) 1.838(2), Ga(1)–F(1) 1.839(2), Ga(1)–C(18) 1.966(4), Ga(1)–C(17) 1.972(4); F(2)–Ga(1)–F(1) 98.74(10), F(2)–Ga(1)–C(18) 107.2(2), F(1)–Ga(1)–C(18) 108.27(14), F(2)–Ga(1)–C(17) 107.4(2), F(1)–Ga(1)–C(17) 107.0(2), C(18)–Ga(1)–C(17) 125.1(2); **4**: In(1)–F(1) 2.040(2), In(1)–F(2) 2.047(2), In(1)–C(18) 2.148(4), In(1)–C(17) 2.152(4); F(1)–In(1)–F(2) 95.68(8), F(1)–In(1)–C(18) 105.61(13), F(2)–In(1)–C(18) 105.47(15), F(1)–In(1)–C(17) 106.71(12), F(2)–In(1)–C(17) 105.45(14), C(18)–In(1)–C(17) 132.09(15).

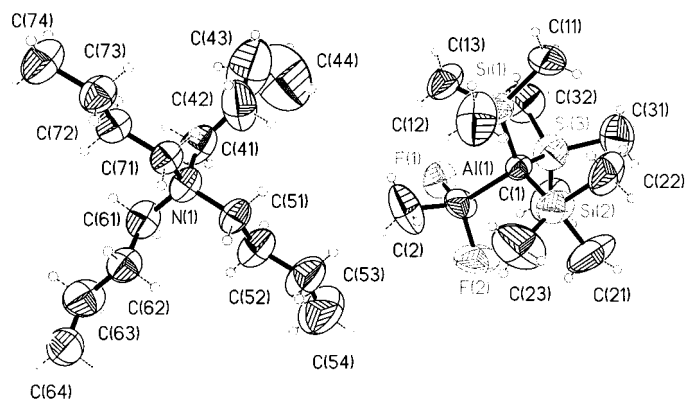


Figure 2. Molecular structure of **2**. Selected bond lengths [Å] and angles [°]: Al(1)–F(2) 1.680(5), Al(1)–F(1) 1.702(5), Al(1)–C(2) 1.945(11), Al(1)–C(1) 2.010(6); F(2)–Al(1)–F(1) 106.0(3), F(2)–Al(1)–C(2) 106.4(5), F(1)–Al(1)–C(2) 107.0(4), F(2)–Al(1)–C(1) 109.0(3), F(1)–Al(1)–C(1) 110.6(3), C(2)–Al(1)–C(1) 117.2(4).

coordination environment. The average Al–F bond length in **1** (1.712 Å) and **2** (1.690 Å) is somewhat longer than normal Al–F single bonds (1.65 Å). The C–Al–C bond angle of **2** is nearly identical to that of **1** despite the presence of a more sterically demanding ligand in **2**; in addition, the F–Al–F bond angle is actually larger in **2** (106.0°) than in **1** (103.23°). The bond lengths and angles for **3** (Ga–F 1.838 and 1.839 Å, F–Ga–F 98.74°, C–Ga–C 125.1°) are similar to those obtained for Cs[Me₂GaF₂]^[2] (Ga–F 1.827 and 1.838 Å, F–Ga–F 96.7°, C–Ga–C 127.8°). The average In–F bond length in **4** is 2.044 Å, and the F–In–F and C–In–C bond angles are 95.68° and 132.09°, respectively.

The signals in the ¹⁹F NMR spectra occur at δ = –154.8 ([D₈]THF) for **1** and δ = –145.9 (C₆D₆) for **2** as expected. Compound **3** displays a singlet at δ = –164.8 (CD₃CN), while the signal for Cs[Me₂GaF₂] occurs at δ = –149.6 (CD₃CN). The signal in the ¹⁹F NMR spectrum for **4** is observed at δ = –180.9. As expected, the ¹⁹F NMR resonances shift progressively to higher field in the series Al, Ga, In. The ²⁷Al NMR signal for **1** (δ = 123.8) is typical for four-coordinate aluminum compounds. The ²⁷Al NMR resonance can be resolved as a triplet (*J* = 120 Hz) after Gaussian multiplication.

Compounds **1–4** all produce the expected signals of the metalates in the FAB (negative-ion) mass spectrum next to the signals for the matrix (3-nitrobenzyl alcohol (NBA)). The IR spectrum for **1** shows two absorptions at 742 and 651 cm^{–1}, attributable to Al–F bond stretches. The comparable bands for **3** occur at 518 and 494 cm^{–1}, while those for **4** are found at 450 and 430 cm^{–1}. Within the group (Al, Ga, In), the frequency of the metal–fluorine bond stretches decreases as expected.

While **1** reacts with water with evolution of gas, **3** and **4** are stable to moisture and exhibit no decomposition upon exposure to water. After an excess of D₂O was added, no decomposition could be detected after one day, as observed by the ¹H NMR signals for the methyl groups on the metal center. In contrast, Cs[Me₂GaF₂] was reported to be sensitive to hydrolysis.^[2]

The fluoride transfer with TBADF is simple to carry out, and has also been demonstrated with the fluorination of trisubstituted silanes.^[5] This might also be extended to organotransition metal compounds.

Experimental Section

All manipulations were performed under a dry and oxygen-free nitrogen atmosphere. Glassware was heated and cooled under vacuum. Solvents were dried by appropriate methods, saturated with nitrogen, and freshly distilled. Gas evolution was measured by a mercury manometer. Melting points were determined with capillaries sealed under nitrogen and are not corrected.

1: A solution of TBADF (1.09 g, 3.86 mmol) in THF (4 mL) was added dropwise to a solution of AlMe₃ (1.95 g of a 15% solution in hexane, 4.06 mmol) in THF (5 mL) at room temperature, and the mixture was stirred for 30 min. Crystallization at –24 °C for two weeks yielded 1.16 g (3.44 mmol, 89%) of **1** as rhombic crystals. M.p. 90 °C; ¹H NMR (250 MHz, [D₈]THF, TMS): δ = –1.25 (t, *J* = 2.4 Hz, 6H, AlCH₃), 1.00 (t, *J* = 7.3 Hz, 12H, CH₃), 1.41 (qt, *J* = 7.5 Hz, 8H, C^{3/7/11/15}H₂), 1.71 (tt, *J* = 7.5 Hz, 8H, C^{2/6/10/14}H₂), 3.35 (m, 8H, C^{1/5/9/13}H₂); ¹³C NMR (126 MHz, [D₈]THF, TMS): δ = –10 to –9.5 (br, AlCH₃), 14.01 (CH₃), 20.56 (C^{3/7/11/15}H₂), 24.69 (C^{2/6/10/14}H₂), 59.19 (C^{1/5/9/13}H₂); ¹⁹F NMR (235 MHz, [D₈]THF, CFCl₃): δ = –154.82 (s); ²⁷Al NMR (65.2 MHz, CD₃CN, AlCl₃): δ = 123.8 (s, *W*_{1/2} =

327 Hz, after Gaussian multiplication: $t, J = 120$ Hz); IR (KBr, nujol): $\tilde{\nu} = 1571, 1491, 1308, 1261, 1172, 1154, 1095, 887, 802, 742, 651, 466$ cm⁻¹; MS (EI): m/z (%): 242 (17, Bu₄N), 142 (100, Bu₂NCH₂); negative-ion FAB-MS (NBA matrix): m/z (%): 95 (70, Me₂AlF₂); elemental analysis calcd for C₁₈H₄₂AlF₂N (337.51): C 64.1, H 12.5, N 4.2; found: C 62.8, H 12.1, N 4.2.

2: A solution of TrisAlMe₂·THF (3.00 g, 8.32 mmol) was added dropwise to a solution of TBADF (2.34 g, 8.32 mmol) in THF (40 mL) at room temperature, and the mixture was stirred for 12 h. The solvent was removed in vacuo, and the residue was redissolved in toluene (30 mL). The solution was then filtered, and recrystallization at 0 °C for 3 d yielded 4.20 g (7.00 mmol, 84 %) of **2** as rhombic crystals. M.p. 108 °C; ¹H NMR (200 MHz, C₆D₆, TMS): $\delta = -0.29$ (t, $J = 2.8$ Hz, 3H, AlCH₃), 0.69 (s, 27H, Me₂Si), 0.91 (t, $J = 6.5$ Hz, 12H, CH₃), 1.12–1.31 (m, 16H, C^{3/7/11/15}H₂, C^{2/6/10/14}H₂), 2.91 (m, 8H, C^{1/5/9/13}H₂); ¹⁹F NMR (235 MHz, C₆D₆, CFCl₃): $\delta = -145.93$ (s); ²⁹Si NMR (79.5 MHz, C₆D₆, TMS): $\delta = -3.71$ (t, $J = 1.5$ Hz, Me₂Si); IR (KBr): $\tilde{\nu} = 2965, 2898, 2878, 1488, 1466, 1382, 1243, 1179, 1029, 869, 787, 754, 741, 709, 680, 664, 640, 575, 316$ cm⁻¹; EI-MS: m/z (%): 242 (100, Bu₄N), 100 (4, Bu(Me)NCH₂); negative-ion FAB-MS (NBA matrix): m/z (%): 311 (100, Tris(Me)AlF₂), 231 (9, Tris); elemental analysis calcd for C_{30.5}H₇₀AlF₂NSi₃ (600.13; crystallized with 0.5 molecules of C₇H₈): C 61.0, H 11.8, Al 4.5, F 6.3, N 2.3; found: C 61.8, H 11.5, Al 3.4, F 5.5, N 2.8.

3: GaMe₃ (1.71 g, 14.9 mmol) was cooled to -196 °C, and THF (10 mL) was added. The solution was warmed to -30 °C, and a solution of TBADF (4.08 g, 14.5 mmol) in THF (10 mL) was added dropwise. The mixture was then stirred for 30 min. Crystallization at 4 °C for 3 d yielded 4.35 g (11.4 mmol, 79 %) of **3** as rhombic crystals. M.p. 132 °C; ¹H NMR (500 MHz, CD₃CN, TMS): $\delta = -0.74$ (s, 6H, GaCH₃), 0.96 (t, $J = 7.3$ Hz, 12H, CH₃), 1.34 (qt, $J = 7.5$ Hz, 8H, C^{3/7/11/15}H₂), 1.60 (tt, $J = 7.5$ Hz, 8H, C^{2/6/10/14}H₂), 3.09 (m, 8H, C^{1/5/9/13}H₂); ¹³C NMR (126 MHz, CD₃CN, TMS): $\delta = -6.63$ (s, GaCH₃), 13.80 (CH₃), 20.35 (C^{3/7/11/15}H₂), 24.42 (C^{2/6/10/14}H₂), 59.36 (C^{1/5/9/13}H₂); ¹⁹F NMR (235 MHz, CD₃CN, CFCl₃): $\delta = -164.76$ (s); IR (KBr, nujol): $\tilde{\nu} = 1576, 1494, 1261, 1181, 1152, 1109, 1024, 887, 802, 563, 518, 494$ cm⁻¹; EI-MS: m/z (%): 242 (34, Bu₄N), 142 (100, Bu₂NCH₂), 101 (19, Me₂Ga), 99 (29, Me₂Ga); negative-ion FAB-MS (NBA matrix): m/z (%): 139 (25, Me₂GaF₂), 137 (38, Me₂GaF₂); elemental analysis calcd for C₁₈H₄₂F₂GaN (380.25): C 56.9, H 11.1, Ga 18.3, N 3.7; found: C 57.0, H 10.6, Ga 18.3, N 3.7.

4: A solution of TBADF (0.931 g, 3.31 mmol) in THF (5 mL) was added dropwise to a solution of InMe₃ (1.06 g of a 50 % solution in diethyl ether, 3.30 mmol) in THF (5 mL) at room temperature. A white precipitate formed immediately upon the addition of the TBADF and subsequently redissolved upon further addition of TBADF. The mixture was stirred for 30 min after the addition was complete. Crystallization at room temperature for 3 h yielded 0.470 g (1.10 mmol, 33 %) of **4** as rhombic crystals. M.p. 147 °C; ¹H NMR (500 MHz, [D₈]THF, TMS): $\delta = -0.56$ (s, 6H, InCH₃), 0.99 (t, $J = 7.4$ Hz, 12H, CH₃), 1.41 (qt, $J = 7.4$ Hz, 8H, C^{3/7/11/15}H₂), 1.73 (tt, $J = 7.5$ Hz, 8H, C^{2/6/10/14}H₂), 3.47 (m, 8H, C^{1/5/9/13}H₂); ¹³C NMR (126 MHz, [D₈]THF, TMS): $\delta = -7.35$ (br, InCH₃), 14.08 (CH₃), 20.66 (C^{3/7/11/15}H₂), 24.84 (C^{2/6/10/14}H₂), 59.22 (C^{1/5/9/13}H₂); ¹⁹F NMR (235 MHz, [D₈]THF, CFCl₃): $\delta = -180.87$ (s); IR (KBr, nujol): $\tilde{\nu} = 1582, 1495, 1306, 1262, 1153, 1144, 1107, 1053, 1025, 888, 803, 738, 693, 507, 450, 430$ cm⁻¹; EI-MS: m/z (%): 242 (50, Bu₄N), 142 (100, Bu₂NCH₂), 115 (14, In); negative-ion FAB-MS (NBA matrix): m/z (%): 183 (18, Me₂InF₂); elemental analysis calcd for C₁₈H₄₂F₂InN (425.35): C 50.8, H 9.9; found: C 50.8, H 9.6.

Received: June 28, 1999 [Z13637]

- [1] a) K. Ziegler, E. Holzkamp, R. Köster, H. Lehmkuhl, *Angew. Chem.* **1955**, 67, 213; b) K. Ziegler, R. Köster, *Liebigs Ann. Chem.* **1957**, 608, 1; c) B. Neumüller, *Coord. Chem. Rev.* **1997**, 158, 69; d) B. R. Jagirdar, E. F. Murphy, H. W. Roesky, *Prog. Inorg. Chem.* **1999**, 48, 351.
[2] a) B. Neumüller, F. Gahlmann, *Chem. Ber.* **1993**, 126, 1579; b) M. R. Kopp, T. Kräuter, B. Werner, B. Neumüller, *Z. Anorg. Allg. Chem.* **1998**, 624, 881; c) M. R. Kopp, B. Neumüller, *Z. Anorg. Allg. Chem.* **1998**, 624, 1393.
[3] Crystal structure analysis: The data were collected on a Stoe Siemens four-circle diffractometer with MoK α radiation on rapidly cooled crystals suspended in oil with profile optimized $2\theta/\omega$ scans. The structures were solved using direct methods (SHELXS-97) and refined on F^2 (SHELXL-97).^[6] A psi-scan absorption correction was used for **3**

and **4** – **1**: C₁₈H₄₂AlF₂N, $M_r = 337.51$, monoclinic, space group $P2_1/n$, $a = 10.744(2)$, $b = 12.124(2)$, $c = 17.203(3)$ Å, $\beta = 96.09(3)^\circ$, $V = 2228.1(7)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.006$ Mg m⁻³, $F(000) = 752$, $\lambda = 0.71073$ Å, $\mu(\text{MoK}\alpha) = 0.105$ mm⁻¹, $T = -123$ °C, crystal size $0.7 \times 0.7 \times 0.2$ mm³. Of the 9616 reflections collected ($7.0 \leq 2\theta \leq 50.0^\circ$), 3921 were independent; max./min. residual electron density $237/-187$ e nm⁻³, $R1 = 0.0431$ ($I > 2\sigma(I)$) and $wR2 = 0.1187$ (all data). – **2**: C_{30.5}H₇₀AlF₂NSi₃ (including 0.5 molecules of toluene), $M_r = 600.13$, monoclinic, space group $P2_1/c$, $a = 17.618(3)$, $b = 12.917(2)$, $c = 17.681(3)$ Å, $\beta = 101.32(2)^\circ$, $V = 3945.1(12)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.010$ Mg m⁻³, $F(000) = 1332$, $\lambda = 0.71073$ Å, $\mu(\text{MoK}\alpha) = 0.170$ mm⁻¹, $T = -60$ °C, crystal size $0.8 \times 0.8 \times 0.6$ mm³. Of the 9891 reflections collected ($7.0 \leq 2\theta \leq 45.0^\circ$), 5134 were independent; max./min. residual electron density $1373/-426$ e nm⁻³, $R1 = 0.1204$ ($I > 2\sigma(I)$), $wR2 = 0.3726$ (all data). – **3**: C₁₈H₄₂F₂GaN, $M_r = 380.25$, monoclinic, space group $P2_1/n$, $a = 10.8088(11)$, $b = 12.0465(11)$, $c = 17.336(2)$ Å, $\beta = 96.73(1)^\circ$, $V = 2241.7(4)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.127$ Mg m⁻³, $F(000) = 824$, $\lambda = 0.71073$ Å, $\mu(\text{MoK}\alpha) = 1.241$ mm⁻¹, $T = -70$ °C, $0.7 \times 0.6 \times 0.2$ mm³. Of the 3265 reflections collected ($7.0 \leq 2\theta \leq 45.0^\circ$), 2924 were independent; max./min. residual electron density $499/-387$ e nm⁻³, $R1 = 0.0398$ ($I > 2\sigma(I)$), $wR2 = 0.1156$ (all data). – **4**: C₁₈H₄₂F₂InN, $M_r = 425.35$, monoclinic, space group $P2_1/n$, $a = 10.8943(12)$, $b = 11.984(2)$, $c = 17.483(3)$ Å, $\beta = 96.20(1)^\circ$, $V = 2269.2(6)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.245$ Mg m⁻³, $F(000) = 896$, $\lambda = 0.71073$ Å, $\mu(\text{MoK}\alpha) = 1.055$ mm⁻¹, $T = -70$ °C, crystal size $0.90 \times 0.80 \times 0.40$ mm³. Of the 6863 reflections collected ($7.0 \leq 2\theta \leq 45.0^\circ$), 3985 were independent; max./min. residual electron density $666/-722$ e nm⁻³, $R1 = 0.0371$ ($I > 2\sigma(I)$), $wR2 = 0.0960$ (all data). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-127535 (**1**), -127536 (**2**), -127537 (**3**), -127538 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [4] D. Landini, H. Molinari, M. Penso, A. Rampoldi, *Synthesis* **1988**, 953.
[5] D. Albanese, D. Landini, M. Penso, *Tetrahedron Lett.* **1995**, 36, 8865.
[6] G. M. Sheldrick, SHELX-97, Program for Crystal Structure Refinement, Universität Göttingen, **1997**.

Palladium-Catalyzed Intermolecular Controlled Insertion of Benzyne-Benzyne-Alkene and Benzyne-Alkyne-Alkene—Synthesis of Phenanthrene and Naphthalene Derivatives

Eiji Yoshikawa and Yoshinori Yamamoto*

Alkynes are frequently used as a substrate for the transition metal catalyzed inter- and intramolecular carbometalation reaction.^[1] However, arynes have hardly been utilized in transition metal catalyzed organic synthesis, although stoichiometric reactions of zirconium-benzyne and nickel-benzyne complexes were studied.^[2] Quite recently, Castedo and his co-workers reported the efficient palladium-catalyzed cyclotrimerization of arynes^[3a] and cocyclization of arynes with alkynes.^[3b] During our continuing studies on the catalytic

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hydro- and/or carbopalladation of allenes,^[4a] enynes,^[4b] methyl-enecyclopropanes,^[4c] and alkynes^[4d, e] it occurred to us that arynes may be utilized as a partner in catalytic carbopalladation. It is well known that aryl- and vinyl-palladium complexes readily undergo intra- and intermolecular carbopalladation with alkynes by, for example, a Heck-type reaction. However, to the best of our knowledge, there is no report on the intermolecular carbopalladation of π -allyl palladium complexes with alkynes, although several examples of the corresponding intramolecular reactions are known.^[5, 6] We now report that benzyne is actually very reactive as a carbopalladation partner of π -allyl palladium chloride: the palladium-catalyzed reaction of allyl chlorides **2** with benzyne precursor **1** produces phenanthrene derivatives **3**, along with their minor regioisomers **4**, in good yields [Eq. (1), Table 1].

After a series of optimization experiments on the reaction of allyl chloride **2a** we settled on the following two best methods: Method A: the reaction of allyl chloride **2** (1.0 equiv) and benzyne precursor **1** (2.0 equiv) in the presence of $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (2.5 mol %), dppf (5 mol %), and CsF (4.0 equiv) in $\text{CH}_3\text{CN}/\text{THF}$ (1/1) at 60°C gave **3a** in 69% yield (entry 1). Method B: the reaction of allyl chloride **2**

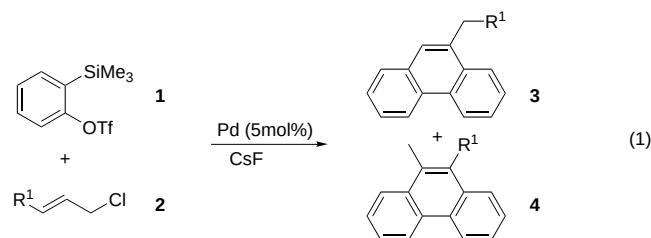


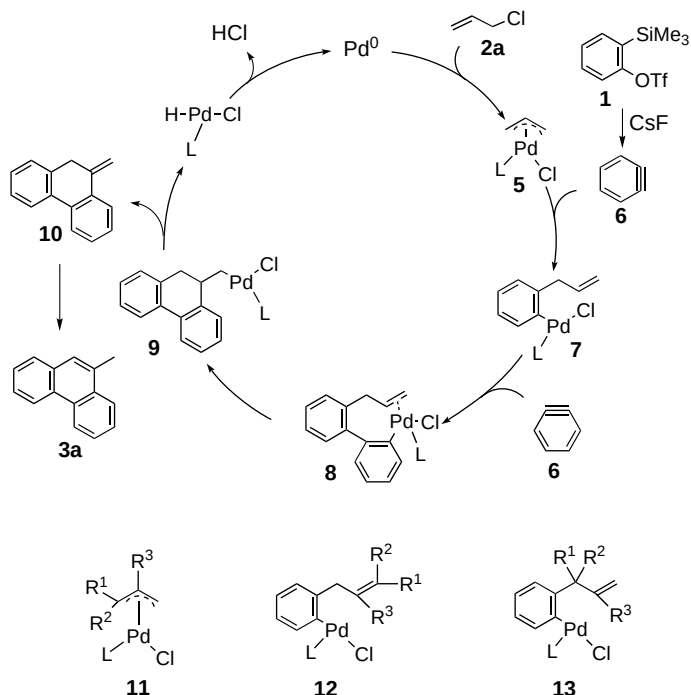
Table 1. Palladium-catalyzed reaction of **1** with **2**.

Entry	2	Method ^[a]	Product	Yield [%] ^[b] (3 : 4) ^[c]
1		A		69
2	2a	B	3a	70
3		A		66 (58:42)
4	2b	B	3b + 4b	70 (70:30)
5		A	3b + 4b	70 (65:35)
6		B	—	—
7		A		44 (80:20)
8	2e	B	3e + 4e	68 (>95:5)
9		A		56 (70:30)
10	2f	B	3f + 4f	71 (73:27)

[a] for a description of the methods see the text. [b] Isolated yield based on **2**. [c] Ratio determined by ^1H NMR spectroscopy on the crude product.

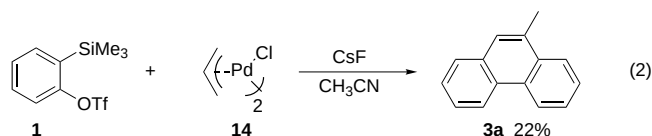
(1.0 equiv) and benzyne precursor **1** (4.0 equiv) in the presence of $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (2.5 mol %) and CsF (8.0 equiv) in CH_3CN at 80°C gave **3a** in 70% yield (entry 2).^[7] The catalytic system of $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ with PPh_3 or dppe gave slightly lower yields, and the other catalysts such as $\{(\eta^3\text{-allyl})\text{palladium chloride}\}_2$ and $[\text{Pd}(\text{PPh}_3)_4]$ were not so effective. The reaction of crotyl chloride (**2b**) with **1** under the conditions of Method A gave a 58:42 mixture of **3b** and **4b** in 66% combined yield (entry 3). The ratio of **3b** to **4b** increased up to 70:30 under the conditions of Method B (entry 4). The reaction of α -methyl allyl chloride **2c** gave a 65:35 mixture of **3b** and **4b** in 70% yield (entry 5). It should be noted that the isomer ratio of the products obtained from the reaction of **2c** is almost same as that of **2b**. Methyl allyl chloride **2d** did not produce phenanthrene derivatives at all (entry 6).^[8] The reaction of prenyl chloride (**2e**) under the conditions of Method A gave an 80:20 mixture of **3e** and **4e** in 44% yield (entry 7). However, the isomer ratio and the chemical yield increased up to greater than 95:5 and 68% yield, respectively, under the conditions of Method B (entry 8). The reaction of cinnamyl chloride (**2f**) afforded an approximately 7:3 mixture of **3f** and **4f** under the conditions of both Methods, but Method B gave a higher chemical yield than Method A (entries 9 and 10).

A plausible mechanism for this unprecedented intermolecular benzyne-benzyne-alkene insertion reaction is shown in Scheme 1. Initially π -allyl palladium chloride **5** would be formed from Pd^0 and **2a**. Benzyne **6**, which is generated from the reaction of CsF and **1**,^[3c] would insert into **5** to afford the aryl palladium intermediate **7**. In the case of substituted allylic chlorides **2b**, **c**, **e**, **f**, two regioisomers **12** and **13** would be produced at this stage. A second benzyne insertion into **7** would produce **8** and subsequent carbopalladation to the alkene would afford the cyclized intermediate **9**. A β -hydride

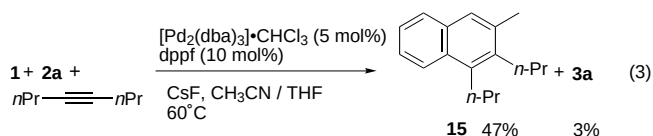


Scheme 1. Proposed mechanism for the palladium-catalyzed benzyne-benzyne-alkene insertion cascade. L = phosphane ligand.

elimination from **9** would give the phosphane-substituted HPdCl species and **10**. The latter would then undergo isomerization to 9-methylphenanthrene (**3a**). In the case of the substituted allylic chlorides benzyne (**6**) would react predominantly at the less-substituted terminus of the π -allyl chloride complex **11** to produce **12** preferentially over its regioisomer **13**. Accordingly, **3b**, **e**, **f** were in general formed predominantly over their isomers **4b**, **e**, **f**, respectively. The formation of **4e** strongly supports the β -elimination-rearrangement processes (**9** $\rightarrow$ **10** $\rightarrow$ **3**) in the proposed mechanism; the rearrangement of the double bond of **4e** to form the phenanthrene ring is not possible. As is apparent from the result of the experiment with **2d**, the carbopalladation step (**8** $\rightarrow$ **9**) is hampered if there is a substituent at the 2-position (for example, $R^3 = \text{Me}$) of **11**. As mentioned above the lack of an example for the intermolecular carbopalladation of π -allyl palladium complexes toward alkynes was strange for us. Accordingly, the reaction of the π -allyl palladium chloride dimer **14** with 4-octyne was examined under various reaction conditions. However, no addition products were obtained, instead the starting materials were recovered. On the other hand, the reaction of **14** (1 equiv) with **1** (1 equiv) in the presence of CsF (2 equiv) in CH_3CN at room temperature gave **3a** in 22% yield [Eq. (2)]. This result clearly indicates a very high reactivity of the benzyne triple bond, compared to the ordinary triple bond, toward the π -allyl–Pd bond.



Encouraged by the successful controlled insertion of benzyne-benzyne-alkene, we next examined the controlled insertion of benzyne-alkyne-alkene. The reaction of **1** (1 equiv), **2a** (1 equiv), and 4-octyne (2 equiv) under slightly modified conditions^[9] of Method A gave **15** in 47% yield along with small amounts (3%) of **3a** [Eq. (3)]. As mentioned



above, π -allyl palladium chloride (**5**) would be very sluggish toward the insertion into the ordinary alkyne, 4-octyne, to give **7** at the first stage of carbopalladation. The second stage of carbopalladation would take place through the Heck-type arylpalladation, so that 4-octyne could participate selectively in this step.

It is now clear that the benzyne triple bond is highly reactive toward carbopalladation processes, and the controlled carbopalladation enables the production of phenanthrene and naphthalene derivatives from π -allyl palladium species. The reactions of benzyne with other organopalladium derivatives are currently under investigation.

Experimental Section

The general procedures for the conversions of the allylic chlorides are described using allyl chloride **2a**.

Method A: **2a** (32.6 μL , 0.4 mmol) was added to a suspension of anhydrous CsF (243 mg, 1.6 mmol), $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (10.4 mg, 0.01 mmol), and dppf (11 mg, 0.02 mmol) in CH_3CN (1 mL) and THF (1 mL), and the mixture was stirred at room temperature for a few minutes. Benzyne precursor **1** (182.8 μL , 0.8 mmol) was added and the resulting mixture was stirred at 60°C for 1 day. The mixture was cooled to room temperature, extracted with diethyl ether, dried with MgSO_4 , and concentrated. The product was purified by column chromatography on silica gel to give **3a** in 69% yield (53.1 mg).

Method B: **2a** (32.6 μL , 0.4 mmol) was added to a suspension of anhydrous CsF (486 mg, 3.2 mmol) and $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (10.4 mg, 0.01 mmol) in CH_3CN (2 mL) and the mixture was stirred at room temperature for 15 min. Four equivalents of **1** (365.6 μL , 1.6 mmol) were added and the mixture was stirred at 80°C for 3 h. The same work-up procedure as above was used, and **3a** was obtained in 70% yield (53.9 mg).

Received: June 28, 1999 [Z13646]

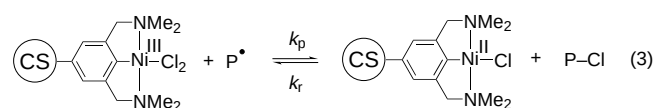
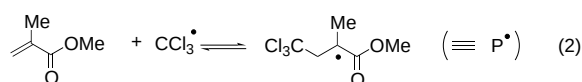
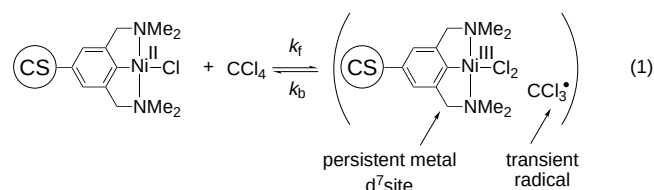
- [1] a) "Transition Metal Organometallics in Organic Synthesis": L. S. Hegedus, in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W. Able, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, pp. 1–977; b) N. E. Schore, *Chem. Rev.* **1988**, 88, 1081–1119.
- [2] a) "Transition Metal Alkyne Complexes: Zirconium–Benzyne Complexes": S. L. Buchwald, R. D. Broene in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W. Able, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, pp. 771–784; b) M. A. Bennett, E. Wenger, *Chem. Ber.* **1997**, 130, 1029–1042; c) For nickel-catalyzed cyclization reactions with strained double bonds, see H. Hashmi, K. Polborn, G. Szeimies, *Chem. Ber.* **1989**, 122, 2399–2401.
- [3] a) D. Peña, S. Escudero, D. Pérez, E. Guitián, L. Castedo, *Angew. Chem.* **1998**, 110, 2804–2806; *Angew. Chem. Int. Ed.* **1998**, 37, 2659–2661; b) D. Peña, D. Pérez, E. Guitián, L. Castedo, *J. Am. Chem. Soc.* **1999**, 121, 5827–5828; c) Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, 1211–1214.
- [4] a) Y. Yamamoto, M. Al-Masum, N. Asao, *J. Am. Chem. Soc.* **1994**, 116, 6019–6020; b) M. M. Slater, V. Gevorgyan, S. Saito, Y. Yamamoto, *Chem. Commun.* **1996**, 17–18; c) N. Tsukada, Y. Yamamoto, *Angew. Chem.* **1997**, 109, 2588–2590; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2477–2479; d) I. Kadota, A. Shibuya, Y. S. Gyoung, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, 120, 10262–10263; e) N. Tsukada, A. Shibuya, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **1997**, 119, 8123–8124.
- [5] a) "Transition Metal Allyl Complexes: Intermolecular Alkene and Alkyne Insertion": W. Oppolzer, in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W. Able, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, **1995**, pp. 905–921; b) W. Oppolzer, *Angew. Chem.* **1989**, 101, 39; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 38; c) R. Keese, R. Gridetti-Grept, B. Herzog, *Tetrahedron Lett.* **1992**, 33, 1207–1210; d) R. C. Larock, K. Takagi, J. P. Burkhart, S. S. Hersherberger, *Tetrahedron*, **1986**, 42, 3759–3762; e) Y. Inoue, K. Ohuchi, T. Kawamata, J. Ishiyama, S. Imaizumi, *Chem. Lett.* **1991**, 835–836.
- [6] The insertion reaction of alkynes into π -allyl nickel complexes is known: a) F. Camps, J. M. Moretó, L. Pagès, *Tetrahedron* **1992**, 48, 3147–3162; b) J. Montgomery, E. Oblinger, A. V. Savchenko, *J. Am. Chem. Soc.* **1997**, 119, 4911–4920; c) G. G. Gómez, J. M. Moretó, *J. Am. Chem. Soc.* **1999**, 121, 878–879.
- [7] Significant amounts of triphenylene (20–30%) were produced as a by-product in Method B (entry 2), but only a trace amount of it was detected in Method A (entry 1).
- [8] An unidentified compound having m/z 282 was obtained. This molecular weight corresponds to a molecule composed of three benzyne and one $\text{CH}_2=\text{CH}(\text{CH}_3)\text{CH}_2$ unit.
- [9] A mixture of $[\text{Pd}_2(\text{dba})_3] \cdot \text{CHCl}_3$ (5 mol%), dppf (10 mol%), and CsF (0.8 mmol) in CH_3CN (1 mL) and THF (1 mL) was treated with **1** (0.4 mmol) at 60°C for 1 day. Further CsF (0.8 mmol) was then added and the resulting mixture was stirred at 60°C for 1 day.

The “Dendritic Effect” in Homogeneous Catalysis with Carbosilane-Supported Arylnickel(II) Catalysts: Observation of Active-Site Proximity Effects in Atom-Transfer Radical Addition**

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Gerard van Koten*

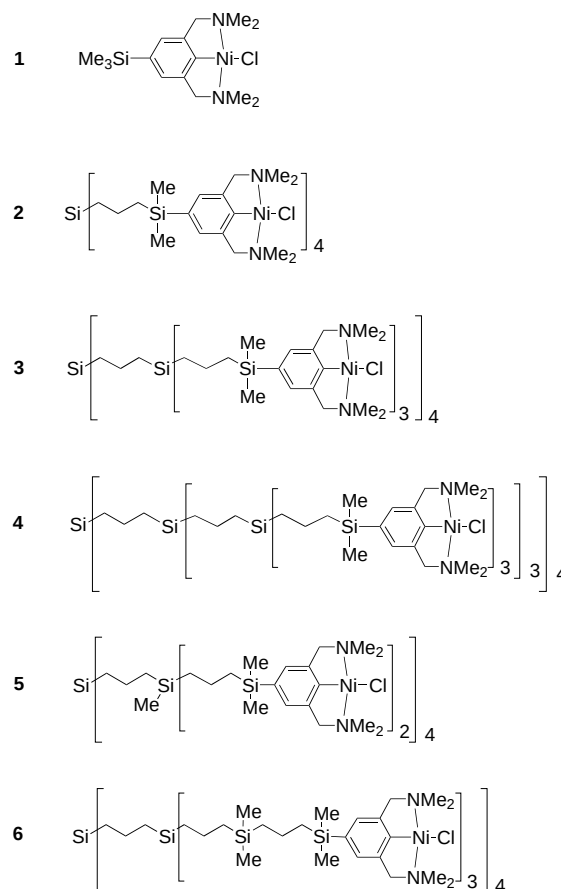
A promising application of (metallo)dendritic macromolecules^[1] is their use in homogeneous catalysis.^[2] Because of their size and well-defined molecular architecture, they may easily be recovered from reaction mixtures and so combine the advantages of homogeneous and heterogeneous catalysis. We have obtained such multimetallic catalytic materials,^[2a, 3, 4] by attaching potentially N,C,N-chelating aryldiamine ligands [2,6-{CH₂NMe₂}₂C₆H₃][−] (“NCN”),^[5] coordinated to a variety of transition metals, to the exterior of carbosilane dendrimers. The nickel-containing catalysts are active in atom-transfer radical addition (ATRA) reactions,^[6] for example the Kharasch addition reaction.^[7] In our original design,^[2a] the d⁸ [Ni^{II}(NCN)] catalytic sites were connected to the carbosilane (CS) support by long-chain carbamate linkers, and each nickel center acted as a single-site catalyst (Scheme 1).^[8]

To study the effect of the nature and length of the carbamate linkers on the catalytic activity, we connected the



Scheme 1. Postulated key intermediate steps in the Kharasch addition reaction catalyzed by the [Ni^{II}(NCN)] complexes. Abbreviations: *k_f* = forward reaction, *k_b* = back reaction, *k_p* = forward product-forming reaction, *k_r* = back “radical-reforming” reaction.

[Ni^{II}(NCN)] complexes directly to the silicon atoms of the CS support and varied the structure of the support (Scheme 2). We here present the first direct evidence for the existence of a “dendritic effect” in redox catalysis^[9] with CS-supported metal catalysts.



Scheme 2. Schematic structures of the mononuclear reference compound **1** and the different generations of catalytically active, nickel-centered carbosilane dendrimers **2–6**.

The nickel dendrimers^[10] (Scheme 2) were prepared by polyolithiation of the CS-ligand precursors and subsequent transmetalation with [NiCl₂(PEt₃)₂]. This gave the orange, oxidation-sensitive nickel derivatives **1–6** (with molecular weights up to ≈ 15 kD) in moderate to good yields (32–86 %). A disadvantage of this procedure is that not all NCN groups become metalated.^[11]

We have used materials **1–4** as catalysts in the Kharasch addition of CCl₄ to methyl methacrylate (MMA) under standard reaction conditions (see Table 1 and Experimental Section). The data show a marked decrease in catalytic activity with increasing generation number (Figure 1). During the catalytic runs with G1-Ni₁₂ (**3**) and G2-Ni₃₆ (**4**), purple to brown precipitates formed which had lost catalytic activity.^[12] We believe that in these precipitates the Ni^{II} sites are (partly) irreversibly oxidized to Ni^{III} sites (the [Ni^{III}X₂(NCN)] complexes are purple/brown and much less soluble than their Ni^{II} analogues). The formation of these precipitates indicates that the back reaction of the Ni^{III} site with the product radical P[•] (Equation (3) in Scheme 1) or with the initial radical •CCl₃ (Equation (1) in Scheme 1) becomes less efficient with time.

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[**] This research was financially supported (A.W.K.) by the Council for Chemical Sciences (CW) of the Netherlands Organization for Scientific Research (NWO). We thank Cees Versluis and Anca van der Kerk for spectrometric studies and Dr. Martin Lutz and Dr. Anthony L. Spek for the crystallographic studies.

Table 1. Catalytic and kinetic data for **1** and the CS–nickel(II) dendritic catalysts **2–6** in the Kharasch addition of CCl_4 to MMA.^[a]

Compound	t [h]	Conversion [%] ^[b]	TOF ^[c]	TTN (per Ni)
1	0.25	15	163	277 ^[d]
	2	91		
G0-Ni ₄ 2	0.25	9	98	272 ^[d]
	2	79		
G1-Ni ₁₂ 3	0.25	3	39	56 ^[d]
	2	17		
G2-Ni ₃₆ 4	0.25	0.2	2	9 ^[d]
	2	1.0		
G1'-Ni ₈ 5	0.25	5	47	253 ^[e]
	2	27		
G1''-Ni ₁₂ 6	0.25	8	85	257 ^[e]
	2	54		

[a] In all catalytic runs the concentration of nickel was kept constant. [b] Selectivity for the formation of the 1:1 adduct of methyl methacrylate and CCl_4 is >99%. Conversion calculated from the formation of the 1:1 addition product as determined with GC analysis using dodecane as an internal standard. [c] Per nickel center per hour; during the first 15 min. [d] After 4 h. [e] After ca. 22 h.

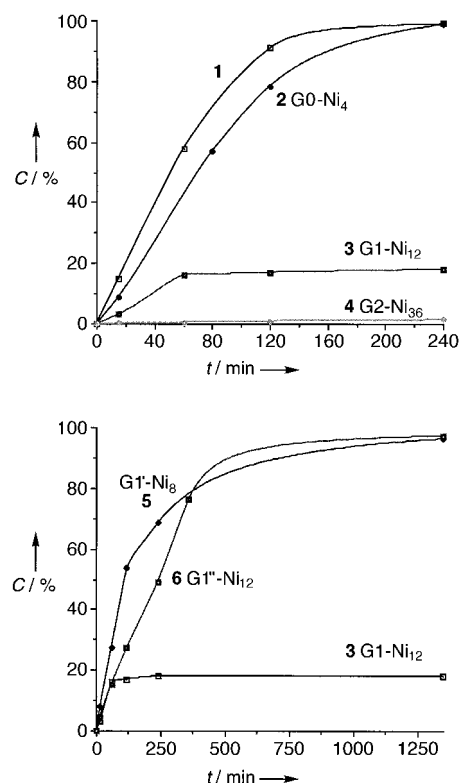


Figure 1. Catalytic activity of the nickel compounds **1–6** in the Kharasch addition of CCl_4 to MMA. C = conversion.

This inhibitive effect could be mimicked by treatment of model compound **1** with CCl_4 in the absence of MMA and (co-)solvent. This leads to the formation of a paramagnetic, brown compound which was identified by X-ray crystal structure analysis as $[\text{Ni}^{\text{III}}\text{Cl}_2\{\text{C}_6\text{H}_2-2,6-(\text{CH}_2\text{NMe}_2)_2-4\text{-SiMe}_3\}]$.^[13] The only organic product formed was C_2Cl_6 , probably by coupling of two CCl_3 radicals. For each C_2Cl_6 molecule formed in this way, two equivalents of the Ni^{III} site remain which in this case cannot be recycled into the Ni^{II} complex.

Molecular modeling (MM2) shows that in **3** the nickel sites are much closer (closest distances about 8–11 Å) than in **2**

(average distance about 19 Å). The Ni–Ni distance in the [G2] dendrimer **4** will certainly be even smaller.^[14] This suggests that the catalyst deactivation observed in **3** and **4** is caused by proximity effects in which the Ni^{III} sites interact with neighboring Ni^{II} sites (forming mixed-valence complexes) rather than with the transient radicals in solution. A related “dendritic effect” has recently been reported by Enomoto and Aida.^[15]

In order to test this hypothesis, two further [G1] dendrimers were synthesized: one G1'-Ni₈ species which contains fewer branches than **3** (**5**, Scheme 2) and one with an extra $(\text{CH}_2)_3\text{SiMe}_2$ tether, G1''-Ni₁₂ (**6**). In both dendrimers there is less congestion at the CS surface, and the proximity effect between the Ni^{II} sites should be smaller. When **5** and **6** were tested under the same standard conditions as given for **1–4** (see Table 1), both catalysts indeed showed a marked return of activity per metal atom. In fact, the total turnover numbers per nickel site were comparable to those of **1** and **2** (see Figure 1). These results support the view that the effectiveness of the reaction between the Ni^{III} site and the product radical $\text{P}^\bullet$ in the series **2** (G0) > **3** (G1) > **4** (G2) is lowered by the increasing proximity of the Ni centers. What might happen is that in **3** and **4** a competing inner-sphere electron transfer occurs along the surface of the CS support between adjacent Ni^{II} and Ni^{III} centers (see Figure 2). Fabbrizzi et al. reported on a related redox-driven intramolecular anion translocation between a nickel and a copper metal center.^[16] In materials with high density of nickel, this would result in the formation of mixed-valence nickel sites which have a lower catalytic activity than single Ni^{II} sites.

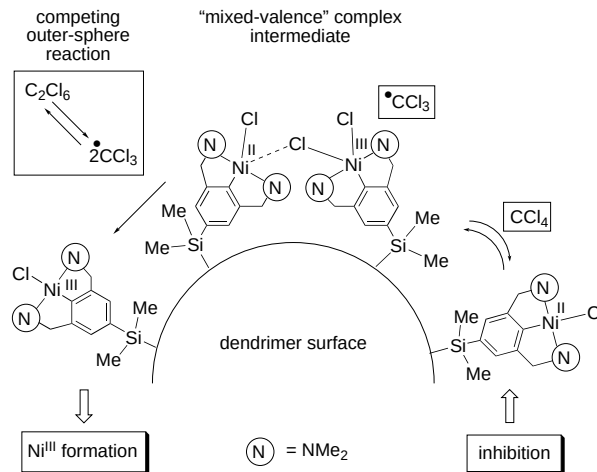


Figure 2. Schematic representation of the deactivation processes on the CS surface of the dendrimers **3** and **4**.

In summary, the catalytic activity of the nickelated dendrimers **2–6** is greatly affected by “surface congestion”, and thus the carbosilane support plays a pivotal role in active-site accessibility. The decrease in the catalytic activity observed with **3** or **4** is ascribed to formation of a mixed-valence $\text{Ni}^{\text{II}}/\text{Ni}^{\text{III}}$ complex on the dendrimer periphery that competes for reaction with substrate radicals. These results support earlier work on metal-center accessibility as a key to metallodendrimer reactivity.^[15]

Experimental Section

Standard catalytic system: Prior to use, a mixture of MMA (28 mmol), CCl₄ (104 mmol), and dodecane (internal standard, 8.9 mmol) was degassed thoroughly using the freeze-pump-thaw method. The catalyst (ca. 9.1×10^{-5} mol) in CH₂Cl₂ (ca. 10 mL) was then added at room temperature under an inert atmosphere. The reaction was monitored by withdrawing samples for GC analysis at regular time intervals.

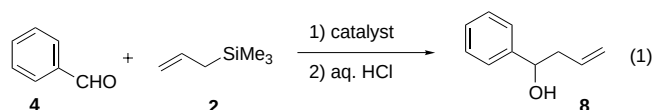
Received: July 20, 1999 [Z13757]

- [1] For recent reviews on dendritic molecules, see a) G. R. Newkome, C. N. Moorefield, F. Vögtle, *Dendritic Molecules-Concepts, Synthesis, Perspectives*, VCH, Weinheim, **1996**; b) "Dendrimers": N. Feuerbacher, F. Vögtle, *Top. Curr. Chem.* **1998**, *197*, 1–18; c) M. A. Hearshaw, J. R. Moss, *Chem. Commun.* **1999**, 1–8.
- [2] See for example: a) J. W. J. Knapen, A. W. van der Made, J. C. De Wilde, P. W. M. N. van Leeuwen, P. Wijkens, D. M. Grove, G. van Koten, *Nature* **1994**, *372*, 659; b) M. T. Reetz, G. Lohmer, R. Schwickardi, *Angew. Chem.* **1997**, *109*, 1559–1562; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1526–1529.
- [3] A. W. Kleij, H. Kleijn, J. T. B. H. Jastrzebski, W. J. J. Smeets, A. L. Spek, G. van Koten, *Organometallics* **1999**, *18*, 268–276.
- [4] A. W. Kleij, H. Kleijn, J. T. B. H. Jastrzebski, A. L. Spek, G. van Koten, *Organometallics* **1999**, *18*, 277–285; b) R. A. Gossage, J. T. B. H. Jastrzebski, J. van Ameijde, S. J. E. Mulders, A. J. Brouwer, R. M. J. Liskamp, G. van Koten, *Tetrahedron Lett.* **1999**, *40*, 1461–1464.
- [5] G. van Koten, *Pure Appl. Chem.* **1989**, *61*, 1681, and references therein; b) M. P. H. Rietveld, D. M. Grove, G. van Koten, *New J. Chem.* **1997**, *21*, 751.
- [6] The nickelated systems are also active in controlled radical polymerization (ATRP). See: a) T. E. Patten, J. Xia, T. Abernathy, K. Matyjaszewski, *Science* **1996**, *272*, 866–868; b) C. Granel, P. Dubois, R. Jérôme, P. Teyssié, *Macromolecules* **1996**, *29*, 8576–8582; c) "Controlled Radical Polymerization": K. Matyjaszewski, *ACS Symp. Ser.* **1998**, 685.
- [7] L. A. van de Kuil, H. Luitjes, D. M. Grove, J. W. Zwikker, J. G. M. van de Linden, A. M. Roelofsen, L. W. Jenneskens, W. Drenth, G. van Koten, *Organometallics* **1994**, *13*, 468–477.
- [8] a) L. A. van de Kuil, D. M. Grove, R. A. Gossage, J. W. Zwikker, L. W. Jenneskens, W. Drenth, G. van Koten, *Organometallics* **1997**, *16*, 4985–4994; b) R. A. Gossage, L. A. van de Kuil, G. van Koten, *Acc. Chem. Res.* **1998**, *31*, 423–431, and references therein.
- [9] C. Valério, J. L. Fillaut, J. Ruiz, J. Guittard, J. C. Blais, D. Astruc, *J. Am. Chem. Soc.* **1997**, *119*, 2588–2589.
- [10] Similar protocols have been used for the synthesis of related multiplatinated systems.^[3] The nickelated dendrimers **2–6**, as well as their ligand precursors, have been characterized by NMR techniques (¹H, ¹³C, ²⁹Si), mass spectrometry (FAB, MALDI-TOF), and microanalyses. Full experimental data will be reported elsewhere.
- [11] Nickel incorporation was found to be in the range of 80–89%. This incomplete nickel incorporation (estimated by ¹H and ¹³C NMR spectroscopy, elemental analyses, as well as mass spectrometry) can be ascribed to partial hydrolysis of the C–Li bond(s) during workup. However, this aspect does not hamper the use of these metallodendrimers in catalytic applications. Further details will be reported in a full paper.
- [12] Catalytic deactivation of polymeric materials with a high loading of the [NiX(NCN)] complexes has also been observed. See: L. A. van de Kuil, D. M. Grove, J. W. Zwikker, L. W. Jenneskens, W. Drenth, G. van Koten, *Chem. Mater.* **1994**, *6*, 1675–1683.
- [13] The X-ray crystal structure determination of **7** will be reported in a forthcoming paper. The structural features of **7** are comparable with that of related [Ni^{III}X₂(NCN)] species. See, for example: D. M. Grove, G. van Koten, R. Zoet, N. W. Murall, A. Welch, *J. Am. Chem. Soc.* **1983**, *105*, 1379–1380.
- [14] We were unable to perform molecular modeling of the G2 derivative **4** with our software (CAChe, MM2) because of the large size of the molecule.
- [15] M. Enomoto, T. Aida, *J. Am. Chem. Soc.* **1999**, *121*, 874–875.
- [16] L. Fabbri, F. Gatti, P. Pallavicini, E. Zambbarbieri, *Chem. Eur. J.* **1999**, *5*, 682–690.

Aluminum Bis(trifluoromethylsulfonyl)amides: New Highly Efficient and Remarkably Versatile Catalysts for C–C Bond Formation Reactions**

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Lewis acids are powerful tools in many different reactions such as Diels–Alder reactions, aldol synthesis, and the Sakurai reaction. The aim is now to develop more-reactive Lewis acidic species that catalytically promote these synthetically valuable transformations.^[1] Metal triflates (triflate = OTf) are employed as Lewis acids to promote important carbon–carbon bond formation reactions since the trifluoromethylsulfonyl (Tf) group is one of the strongest neutral electron-withdrawing groups.^[1, 2] However, a major limitation of the known metal triflates is the synthesis of highly valuable homoallyl alcohols (for example, **8**) by the Lewis acid promoted reaction of aldehydes with inexpensive and non-toxic allyl trimethylsilane [Eq. (1)]. The formation of such homoallyl alcohols necessitates the use of allyl tin reagents instead.^[3, 4]



Attempts to develop more reactive Lewis acidic species for this transformation by modification of the triflate ion with more electron-withdrawing counterions have failed.^[5] Herein we report the first successful development of new versatile catalysts derived from the superacid bis(trifluoromethylsulfonyl)amine (Tf₂NH)^[6] that promote allylation and other important reactions with unprecedented efficiency.

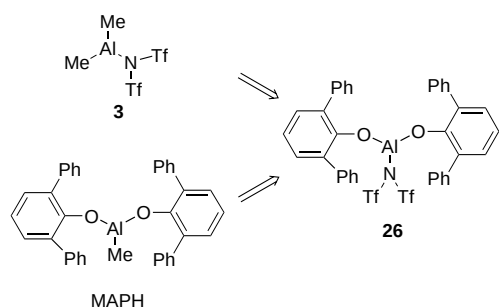
Recently, ytterbium triflate (Yb(OTf)₃) was shown to promote the reaction between aldehydes and allyl tributyltin reagents but that allyl silanes were unaffected by this reagent.^[7] Attempts to develop a more-reactive Lewis acid by modification of the triflate ions with the more electron-withdrawing counterion bis(trifluoromethylsulfonyl)amide (bistriflylamide) failed.^[5] The desired homoallyl alcohol **8** was only formed in trace amounts and generated TMSNTf₂ (TMS = trimethylsilyl) as a side product, which is believed to be the actual promoter for this reaction. This proposal is supported by our finding that catalytic amounts of TMSNTf₂^[8] or Tf₂NH (**1**), which generates TMSNTf₂ in situ through reaction with **2**, form **8** in moderate yield along with substantial amounts of undesired products (Table 1, entries 1 and 2).

Similar results were obtained when (iPrO)₂Ti(NTf₂)₂^[9] and Al(NTf₂)₃^[9] were employed (Table 1, entries 3 and 4). These

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[**] This work has been supported by the Ministry of Education, Science, and Culture of the Japanese Government. A.M. thanks the European Union and Japan Society for the Promotion of Science (EU/JSPS) for the award of a postdoctoral scholarship.

that catalyze the reaction with loss of selectivity.^[13b] A successful achievement of a chemoselective aldol reaction would indicate and favor a Lewis acid catalyzed reaction mechanism over a reaction pathway catalyzed by reactive silyl species. Aluminum 2,6-diphenylphenoxides such as methylaluminum bis(2,6-diphenylphenoxide) (MAPH) have been shown to be suitable for the recognition of less-hindered aldehydes. Thus, compound **26** (Scheme 2) should be suitable for this purpose.^[16, 17]



Scheme 2. Design of a catalyst for the chemoselective aldol reaction.

As expected, treatment of an equimolar mixture of hexanal (**6**) and trimethylacetaldehyde (**7**) with **17** in the presence of 5 mol % of **3** effected only a moderate preference for the less-hindered aldehyde (Table 3, entry 1). In marked contrast, the reaction of **17** promoted by **26** yielded the aldol product of the

Table 3. Chemoselective aldol reactions.^[a]

Entry	Aldehyde	Cat.	Ratio ^[b]
1	CHO vs. CHO	3	74:26 (–)
2	CHO vs. CHO	26	99:1 (84 %)
3	CHO vs. CHO	26	57:43 (–)
4	CHO vs. CHO	26	93:7 (79 %)
5	CHO vs. CHO	26	99:1 (84 %)
6	CHO vs. CHO	26	92:8 (67 %)

[a] Aldehydes (1 equiv each), **17** (1 equiv), 5 mol % catalyst, CH₂Cl₂, –78 °C. Desilylation: 1N HCl/THF [b] Determined by ¹H NMR analysis. The yield is given in parentheses.

less-hindered aldehyde in 84 % yield, and only trace amounts of the trimethylacetaldehyde-derived product were detected by ¹H NMR analysis (Table 3, entry 2). Table 3 further demonstrates that **26** is able to promote the highly selective functionalization of a variety of substrates and exhibits the scope of this process as well as its limitations. While **26** fails to differentiate between hexanal and cyclohexanecarboxaldehyde, higher selectivity is found when the more-hindered 2-phenylpropionaldehyde is employed instead (Table 3, entries 3 and 4). Furthermore, **26** is able to perform the chemoselective aldol reaction between cyclohexanecarboxaldehyde and trimethylacetaldehyde or 2-phenylpropionalde-

hyde (Table 3, entries 5 and 6, respectively). These findings indicate that the bulky aluminum reagent **26** acts as a highly reactive Lewis acid when it promotes the presented reactions, and thus selectivity can be introduced by suitable ligands.

In conclusion, we have developed a new class of aluminum bis(trifluoromethylsulfonamido)amides as highly reactive and versatile Lewis acidic catalysts for a variety of important C–C bond forming reactions. In addition, we were able to design a ligand scaffold in a rational approach to ensure the selective recognition and activation of a desired substrate, thus indicating that the aluminum species act directly as reactive Lewis acids. Considering the wide applications found for strong electron-withdrawing counterions such as triflates, there is a high probability that metal bistriflylamides will prove to be valuable in the development of new Lewis acids for important organic transformations. The correlation of the catalytic ability of aluminum bistriflylamides with the electronic and steric properties of the ligand sphere should allow the development of Lewis acidic catalysts for enantioselective processes.

Experimental Section

Me₂AlNTf₂ (**3**) was readily prepared by treatment of Me₃Al (100 µL of 0.5 M solution in toluene) with 1 equivalent of commercially available Tf₂NH (100 µL of 0.5 M solution in CH₂Cl₂) in CH₂Cl₂ (4.0 mL) at room temperature (gas evolution) for 30 min with rigorous exclusion of air and moisture and was used without further purification.

Typical procedure for the reaction of aldehydes with allyl trimethylsilane: Benzaldehyde (**4**, 100 µL, 1.00 mmol) and allyl trimethylsilane (**2**, 175 µL, 1.10 mmol) were added at –20 °C under argon to a solution of Me₂AlNTf₂ (**3**, 0.05 mmol) in CH₂Cl₂ (4.0 mL). After stirring the reaction mixture for 3 h, 1N HCl (2.0 mL) and THF (2.0 mL) were added and the reaction was allowed to warm to room temperature. The reaction mixture was stirred for 30 min, poured into NaHCO₃ solution, and extracted with diethyl ether. The combined organic extracts were dried over MgSO₄, concentrated, and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/10) to give **8** (138 mg, yield 93 %) as a colorless liquid that shows identical spectral and analytical data with those in ref. [18]

Received: August 26, 1999 [Z13927]

- Recent books: a) *Lewis Acids Reagents* (Ed.: H. Yamamoto), Oxford University Press, New York, **1999**; b) M. Santelli, J.-M. Pons, *Lewis Acids and Selectivity in Organic Synthesis*, CRC Press, New York, **1996**. c) Review: Y. Yamaguchi in *Comprehensive Organic Synthesis*, Vol 2 (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, p. 325.
- a) P. J. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85; b) P. J. Stang, M. R. White, *Aldrichchimica Acta*, **1983**, 16, 15. For applications of various metal triflates in catalysis see ref. [1].
- For general reviews for allylation of aldehydes, see a) J. A. Marshall, *Chem. Rev.* **1996**, 96, 31; b) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, 93, 2207; c) W. R. Roush in *Comprehensive Organic Synthesis*, Vol 2 (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**.
- For successful approaches using allyl silanes, see chiral (acyloxy)boranes: K. Ishihara, M. Mouri, Q. Gao, T. Maruyama, K. Furuta, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, 115, 11490; chiral Ti^{IV} complexes: D. R. Gauthier, E. M. Carreira, *Angew. Chem.* **1996**, 108, 2521; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2363.
- A. Isshi, O. Kotera, T. Saeki, K. Mikami, *Synlett* **1997**, 1145.
- I. A. Koppel, R. W. Taft, F. Anvia, S.-Z. Zhu, L.-Q. Hu, K.-S. Sung, D. D. DesMarteau, L. M. Yagupolski, Y. L. Yagupolski, N. V. Ignatev, N. V. Kondratenko, A. Y. Volkonskii, V. M. Vlasov, R. Notario, P.-C. Maria, *J. Am. Chem. Soc.* **1994**, 116, 3047.

- [7] a) H. C. Aspinall, A. F. Browning, N. Greeves, P. Ravenscroft, *Tetrahedron Lett.* **1994**, 35, 4639; b) H. C. Aspinall, N. Greeves, E. G. McIver, *Tetrahedron Lett.* **1998**, 39, 9283.
- [8] B. Mathieu, L. Ghosez, *Tetrahedron Lett.* **1997**, 38, 5497.
- [9] K. Mikami, O. Kotera, Y. Motoyama, H. Sakaguchi, M. Maruta, *Synlett* **1996**, 171.
- [10] A. Bottoni, A. L. Costa, D. Di Tommaso, I. Rossi, E. Tagliavini, *J. Am. Chem. Soc.* **1997**, 119, 12131.
- [11] A side product formed in substantial amounts at -20°C was identified as the aldehyde cyclic trimer. See S. E. Denmark, N. G. Almstead, *Tetrahedron* **1992**, 48, 5565.
- [12] a) Y. Nishigaichi, Y. Hanano, A. Takuwa, *Chem. Lett.* **1998**, 33, and references therein; b) A. Yanagisawa, Y. Nakatsuka, H. Nakashima, H. Yamamoto, *Synlett* **1997**, 933, and references therein; c) Y. Nishigaichi, M. Fujimoto, A. Takuwa, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2581; d) D. Seyferth, J. Porner, *J. Org. Chem.* **1980**, 45, 1722.
- [13] a) Reviews: R. Mahrwald, *Chem. Rev.* **1999**, 99, 1095; E. M. Vogel, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, 111, 1671; *Angew. Chem. Int. Ed.* **1999**, 38, 1571; b) T. K. Hollis, B. Bosnich, *J. Am. Chem. Soc.* **1995**, 117, 4570, and references therein.
- [14] Cross-aldol reaction with activated trialkylsilylsulfonates: M. Oishi, S. Aratake, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, 120, 8271; by Reformatsky-type reactions: a) M. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **1977**, 99, 7705; b) L. Weissjohan, H. Wild, *Synthesis* **1997**, 512.
- [15] $\text{Sc}(\text{OTf})_3$: S. Kobayashi, I. Hachiya, M. Araki, *Synlett* **1993**, 472; $\text{TMSCl}/\text{SnCl}_2$: N. Iwasawa, T. Mukaiyama, *Chem. Lett.* **1987**, 463; Ph_3COTf : S. Kobayashi, M. Murakami, T. Mukaiyama, *Chem. Lett.* **1985**, 953.
- [16] MAPH is not catalytically active under the reaction conditions employed. For chemoselective recognition by stoichiometric amounts of MAPH, see K. Maruoka, S. Saito, A. B. Conception, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, 115, 1183; for use of other aluminum 2,6-diphenylphenoxides, see a) A. Marx, H. Yamamoto, *Synlett* **1999**, 584; b) T. Ooi, Y. Kondo, K. Maruoka, *Angew. Chem.* **1998**, 110, 3213; *Angew. Chem. Int. Ed.* **1998**, 37, 3039; c) K. Maruoka, S. Saito, H. Yamamoto, *Synlett* **1994**, 439.
- [17] **26** was generated by treatment of MAPH (see ref. [16]) with one equivalent of Ti_2NH (gas evolution) and was used without further purification.
- [18] K. Iseki, Y. Kuroki, M. Takahashi, Y. Kobayashi, *Tetrahedron* **1997**, 53, 3513.

Ordered Two-Dimensional Monolayers of Au_{55} Clusters**

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Highly ordered structures of nanoparticles exhibit attractive physical properties for future nanoelectronics.^[1–5] Metal particles of 1–4 nm in size are of particular interest because of their special electronic properties, as characterized by their quantum size behavior;^[6] their electrons are no longer in a quasi-delocalized three-dimensional state, but are trapped in

a “zero-dimensional space”. Ligand-stabilized metal clusters turned out to be ideal objects for studying these effects. With its two freely mobile electrons $[\text{Au}_{55}(\text{PPh}_3)_{12}\text{Cl}_6]$ represents something like a “last metal”.^[7]

Ordered arrangements of such quantum dots allow correlated single electron tunneling (SET)^[8,9] at room temperature, which has been proposed as a fundamental idea of future nanoelectronics. The realization of such new systems, which require well-defined planar arrays of uniform metal clusters, might open the door to a new generation of computers with a storage capacity raised by a factor of 10^5 – 10^6 relative to the present state of the art.

Many research groups focus their efforts on reaching this goal.^[10–14] Andres et al. reported on perfect layers of alkylthiol-protected gold particles with diameters of 3.7 nm.^[15] Another method for generating ordered two-dimensional layers was described by Möller et al. who prepared gold colloids in ordered polymer micelles.^[16] In the past we carried out intensive research on the preparation of monolayers by the chemical fixation of ligand-stabilized metal clusters on modified substrates,^[17–20] however, we could only observe particles that were at best, densely packed, but not well ordered.

Herein we report the first successful preparation of two-dimensional (2D) hexagonal and cubic lattices of Au_{55} clusters on polymer films by self-assembly. The monolayers were prepared by dipping a poly(ethyleneimine)-covered, carbon-coated copper grid (for transmission electron microscopy) into an aqueous solution of $[\text{Au}_{55}(\text{Ph}_2\text{PC}_6\text{H}_4\text{SO}_3\text{H})_{12}\text{Cl}_6]$ clusters (Figure 1). Classical acid–base reactions take place because of the NH functions on the poly(ethyleneimine) (PEI). The strong interactions between clusters and the surface prevent mechanical removal, for example, by washing.

The characterization of the cluster arrangements was performed by transmission electron microscopy (TEM) at

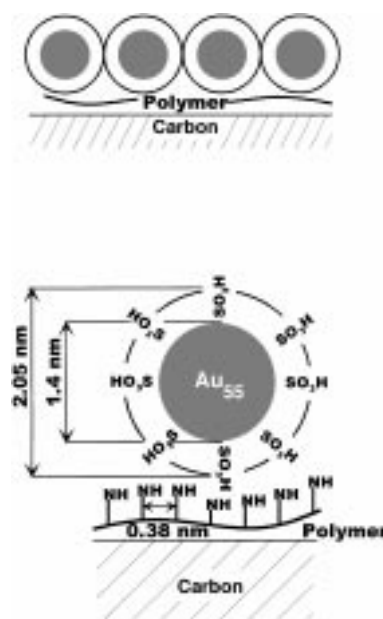


Figure 1. Schematic cross-section of a Au_{55} monolayer on a PEI-modified, carbon-coated copper grid and a magnification of the contact area with characteristic values.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 452) and the Fonds der Chemischen Industrie. The authors also gratefully acknowledge the MSWWF, Nordrhein-Westfalen for financial support. We thank Prof. W. Heitz, University of Marburg, for providing us with polymer samples.

200 kV. This method allows the study of larger areas compared with scanning probe microscopy methods such as tunneling microscopy (STM) or atomic force microscopy (AFM). Most of the clusters were found in ordered arrangements of up to a few μm^2 and in two different types (Figure 2).

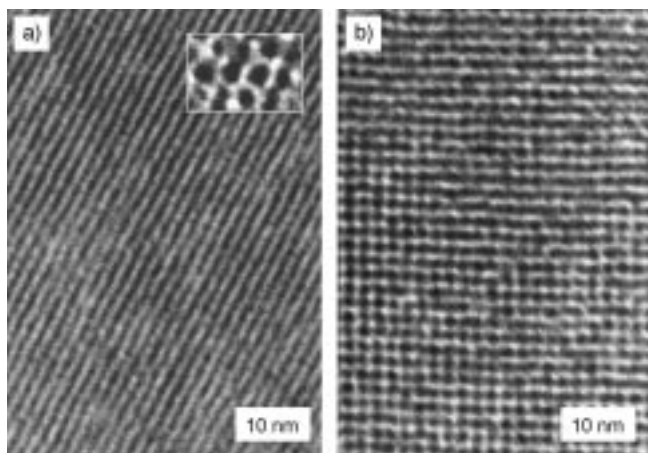


Figure 2. TEM images of Au_{55} monolayers showing a hexagonal (a) and a cubic (b) structure. The magnified insert in (a) shows single clusters in the hexagonal form.

The hexagonal form, the one most expected for an ordered monolayer, was observed, with distances between the rows of 1.87 nm along the (111) direction (Figure 2a). The generation of hexagonal arrangements is already known for bigger colloids.^[15] Unprecedentedly, there is a cubic orientation with rows 2.05 nm apart (Figure 2b). These layers give an idea of the possibilities of future quantum dot arrangements if routine fabrication is developed. In Figures 3a and 3b both cases are illustrated. Both values correspond, as expected, very well with the cluster size of 2.1 nm.^[21] Note, that the Au_{55} clusters have a metallic core of 1.4 nm in diameter and a ligand shell of 2×0.35 nm thickness. Consequently, both lattices are formed by Au_{55} clusters with intact ligand shells.

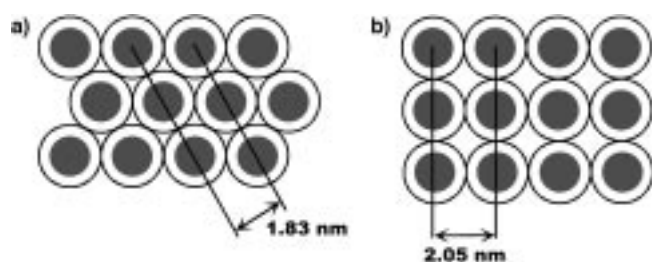


Figure 3. Sketch of both observed cluster superstructures: hexagonal (a) and cubic (b)

Although we have made many attempts in the past few years to assemble two dimensional clusters on PEI-modified substrates, we never observed such perfect structures.^[18] Both STM and AFM imaging only showed areas of metal particles that were partially densely packed, but not well ordered. We attributed the lack of perfect assembling to the strong chemical bonds between the functionalized surface and the clusters. It is assumed that a two-dimensional ordering process

only takes place if the particles are at least slightly movable on the surface so that they can rearrange. Andres et al. have shown that nonfixed colloids are able to build perfect two-dimensional structures, which is in contrast to those that are chemically absorbed to the surface.^[15] Two important questions arise from this observation: why is there a two-dimensional crystallization in spite of the strong chemical fixation, and why is there a hexagonal as well as a cubic pattern of particles?

The reason for this behavior must be attributable to the influence of the polymer, since numerous cluster samples on substrates without this polymer have been investigated by TEM before, but such large ordered domains have never been observed. In the current experiment we used a PEI with the lower molecular weight of 60 000 instead of the 600 000 used in former experiments, so as to avoid the coiling of the polymer on the surface.

Although polymer monolayers are irregular it is known that under special conditions some polymers are partially crystalline.^[22, 23] Decher et al. have demonstrated by X-ray scattering experiments that after drying the polymer multilayers up to four Bragg peaks could be observed, which could be traced back to crystalline areas. An X-ray structure analysis of linear PEI with a low molecular weight (3000) by Chatani et al. also confirmed the presence of crystalline structures. This PEI exists in two distinct crystalline phases, depending on the water content. In both hydrates the polymer chains are planar zigzag and hydrogen bonds seem to have an important influence on the stabilization of the crystal lattices. The phase with the higher water content (12 water molecules per unit cell) offers a more “open structure” with a change in the position of the NH groups. If the existence of crystalline islands in a monolayer of PEI is assumed, then the hypothesis that these two phases act as a template that might direct clusters arising in certain positions seems justified. Such effects have been confirmed by epitaxy experiments.^[24–26] Blaadred et al. have demonstrated a template-directed crystallization of colloids that leads to an epitaxial growth of thin crystalline layers.^[27]

Another observation supports the hypothesis that the polymer acts as structure-determining template: during current investigations of the interactions between various rodlike polymers and clusters we combined poly(1,4-phenyleneethynylene) derivatives and PPh_3 -stabilized palladium clusters. TEM investigations showed small ordered areas of Pd_{55} clusters. Although 80 % of the cluster material we used consisted of larger particles, only the 1.2 nm fraction formed hexagonally ordered structures from very dilute solutions.^[28] Assuming that the polymer forms lamellar aggregates, described as a concentration dependent behaviour,^[29] these prestructures probably forced the clusters to crystallize.

In conclusion, the results can be considered as a successful first step in two dimensional arrangements of metal quantum dots by chemical fixation of ligand-stabilized Au_{55} clusters on a polymer-modified surface. The transmission electron micrographs exhibited highly ordered hexagonal and cubic orientations, which could be attributed to the influence of the polymers. Although further investigations are necessary to optimize these procedures to generate well-defined systems

over long range, these preliminary results are promising for applications in nanoelectronics. The investigation of the electronic properties of the novel monolayers need much effort and has just been started.

Experimental Section

[Au₅₅(Ph₂PC₆H₄SO₃H)₁₂Cl₆] monolayers: the synthesis of [Au₅₅(Ph₂PC₆H₄SO₃Na)₁₂Cl₆] has been described elsewhere.^[30] To replace the Na⁺ ions by protons the clusters were dissolved in desalinated water and treated with an ion exchanger for 30 min. The polymer monolayer was prepared by dipping a carbon-coated copper grid (Plano) into a 10⁻⁵ M aqueous solution of PEI (60000) for 1 h. After washing the coated grid with 10 mL desalinated water and drying in air the monolayer of the gold clusters was prepared by immersing the grid into a 2.6 × 10⁻⁶ M aqueous solution of [Au₅₅(Ph₂PC₆H₄SO₃H)₁₂Cl₆] for 24 h. Careful cleaning with 10 mL desalinated water and drying in air yielded the monolayers. The samples were characterized by transmission electron microscopy (Philips CM200FEG) at 200 kV.

Received: July 12, 1999 [Z13710]

- [1] U. Kreibig, M. Vollmer, *Optical Properties of Metal Clusters*, Springer, Berlin, **1995**.
- [2] G. Schmid in *Clusters and Colloids—From Theory to Application* (Ed.: G. Schmid), VCH, Weinheim, **1994**.
- [3] U. Simon, G. Schön, G. Schmid, *Angew. Chem.* **1993**, *105*, 264; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 250.
- [4] G. Schmid, M. Bäuml, M. Geerkens, I. Heim, C. Osemann, T. Sawitowski, *Chem. Soc. Rev.* **1999**, *28*, 179.
- [5] G. Schmid, M. Bäuml, I. Heim, F. Müller, M. Kröll, T. Sawitowski, *J. Cluster Sci.* **1999**, *10*, 223.
- [6] *Physics and Chemistry of Metal Cluster Compounds. Model Systems for Small Metal Particles. Series on Physics and Chemistry of Material with low-dimensional Structures* (Ed. J. de Jongh), Reidel, Dordrecht, **1994**.
- [7] G. Schön, U. Simon, *Coll. Polym. Sci.* **1995**, *273*, 101; G. Schön, U. Simon, *Coll. Polym. Sci.* **1995**, *273*, 202.
- [8] D. V. Averin, A. N. Korotkov, K. K. Likharev, *Phys. Rev. B* **1991**, *44*, 199.
- [9] A. N. Korotkov, R. H. Chem, K. K. Likharev, *J. Appl. Phys.* **1995**, *78*, 2520.
- [10] Z. L. Wang, A. Harfenist, I. Vezmar, R. L. Whetten, J. Bentley, N. D. Evans, K. B. Alexander, *Adv. Mater.* **1998**, *10*, 808.
- [11] L. F. Chi, S. Rakers, M. Hartig, H. Fuchs, G. Schmid, *Thin Solid Films* **1998**, *327–329*, 520.
- [12] R. L. Whetten, J. T. Khoury, M. M. Alvarez, S. Murthy, I. Vezmar, Z. L. Wang, P. W. Stephens, C. L. Cleveland, W. D. Luedtke, U. Landman, *Adv. Mater.* **1996**, *8*, 428.
- [13] Z. L. Wang, *Adv. Mater.* **1998**, *10*, 13.
- [14] L. Motte, F. Billoudet, M. P. Pileni, *J. Phys. Chem.* **1995**, *99*, 16425.
- [15] R. P. Andres, J. D. Bielefeld, J. I. Henderson, D. B. Janes, V. R. Kolagunta, C. P. Kubiak, W. J. Mahoney, R. G. Osifchin, *Science* **1996**, *273*, 1690.
- [16] S. T. Selvan, J. P. Spatz, H. A. Klok, M. Möller, *Adv. Mater.* **1998**, *10*, 132.
- [17] S. Peschel, G. Schmid, *Angew. Chem.* **1995**, *107*, 1568; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1442.
- [18] G. Schmid, S. Peschel, *New J. Chem.* **1998**, 669.
- [19] G. Schmid, S. Peschel, T. Sawitowski, *Z. Anorg. Allg. Chem.* **1997**, *623*, 719.
- [20] S. Peschel, PhD Thesis, Universität Essen, **1997**.
- [21] G. Schmid, *Chem. Rev.* **1992**, *92*, 1709.
- [22] G. Decher, Y. Lvov, J. Schmitt, *Thin Solid Films* **1994**, *244*, 772.
- [23] Y. Chatani, H. Tadokoro, T. Saegusa, H. Ikeda, *Macromolecules* **1981**, *14*, 315.
- [24] F. Burmeister, C. Schäfle, B. Keilhofer, C. Bechinger, J. Boneberg, P. Leiderer, *Adv. Mater.* **1998**, *10*, 495.
- [25] E. Kim, Y. Xia, G. M. Whitesides, *Adv. Mater.* **1996**, *8*, 245.
- [26] H. W. Deckman, J. H. Dunsmuir, S. Garoff, J. A. McHenry, D. G. Peiffer, *J. Vac. Sci. Technol. B* **1988**, *6*, 333.
- [27] A. van Blaaderen, R. Ruel, P. Wiltzius, *Nature* **1997**, *385*, 321.
- [28] G. Schmid, N. Beyer, unpublished results.
- [29] W. Heitz, personal communication.
- [30] G. Schmid, R. Boese, R. Pfeil, F. Bandermann, S. Meyer, G. H. Calis, J. W. van der Velden, *Chem. Ber.* **1981**, *114*, 3634.

Controlling Electronic Communication in Ethynylated-Polypyridine Metal Complexes**

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*Dedicated to Professor Jean-Marie Lehn
on the occasion of his 60th birthday*

The design of photoactive, molecular-scale devices is a topical subject that has led to detailed examination of numerous elaborate supermolecules. An important, and unresolved, issue concerns how best to interlock the various components into an ordered array that permits controlled transfer of stored information along the molecular axis. In principle, this problem can be overcome by careful manipulation of the energetics of the photoactive terminals and of the connecting framework, provided information transfer occurs by a superexchange mechanism.^[1] Earlier work has shown that this latter requisite is met for intramolecular triplet energy transfer within alkynylene-bridged metal polypyridine complexes.^[2] Indeed, extremely fast electron exchange occurs from a triplet-excited ruthenium(II) bis(2,2':6',2''-terpyridine) (Ru-terpy) terminal to a corresponding osmium(II)^[3] or iron(II) terminal^[4] along a polyalkynylene bridge, with the rate of transfer being almost insensitive to the length of the connector. This situation is ideal for rapid transfer but inappropriate for leaking information at a required rate. Other studies have shown, however, that the electronic conductivity of polyalkynes can be modulated by incorporating aromatic units in the carbon chain.^[5] We have now adopted this strategy as a means to build photoactive dyads possessing similar geometries but displaying disparate rates of intramolecular electron exchange.

For a chromophore to support slow electron exchange it must possess a long-lived excited state. Thus, the triplet lifetime ($\tau_T = 0.6$ ns) of $[\text{Ru}(\text{terpy})_2]^{2+}$ in deoxygenated acetonitrile at 20 °C is too short for the chromophore to participate in electron-exchange reactions unless the reactants are closely coupled, and the luminescence quantum yield (Φ_L) is very low. Interconnection of two such Ru-terpy units through a butadiynylene bridge,^[6] giving **RR1**, extends the triplet lifetime to 720 ns, thereby allowing slow electron transfer to compete with nonradiative deactivation, and raises the emission probability (Table 1). Insertion of a phenyl ring at the center of the butadiynylene bridge,^[7] giving **RR2**,

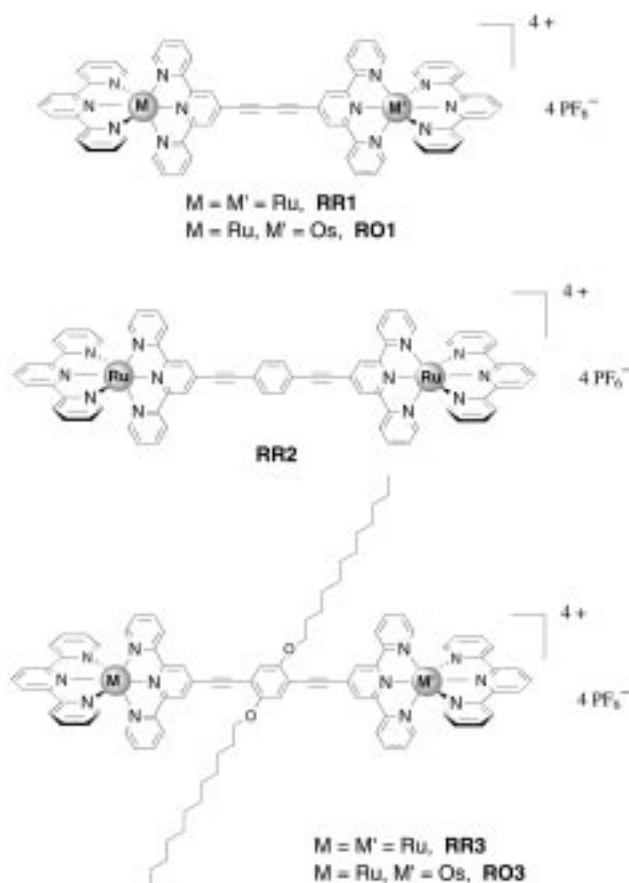


Table 1. Photophysical properties recorded for the metallo-fragments present in the various ruthenium(II) polypyridine complexes in deoxygenated acetonitrile at 20 °C.

Compd	λ_L [nm] ^[a]	Φ_L ^[b]	τ_T [ns] ^[c]	E_T [cm ⁻¹] ^[d]
$[\text{Ru}(\text{terpy})_2]^{2+}$	650	< 0.0001	0.6	16280
RR1	735	0.0023	720	14600
RR2	685	0.0026	110	15400
RR3	693	0.0028	135	15230
RR4	702	0.0040	475	15050
R4	696	0.0035	415	15220
$[\text{Ru}(\text{bpy})_3]^{2+}$	627	0.062	980	16950
RR5	653	0.050	820	16570
RR6 ^[e]	661	0.050	6700	16320

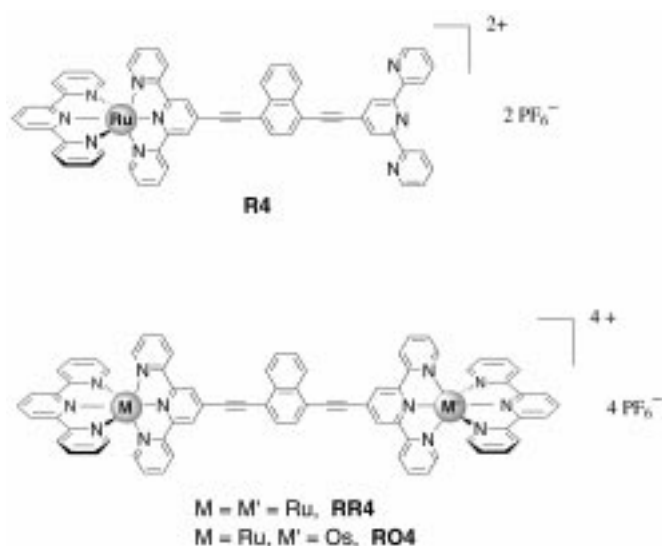
[a] Emission maximum derived by spectral curve fitting, ± 2 nm. [b] Emission quantum yield, $\pm 8\%$. [c] Triplet lifetime, $\pm 5\%$. [d] Triplet energy derived by spectral curve fitting, ± 50 cm⁻¹. [e] Refers to the "Ru(bpy)" fragment since the triplet state localized on the naphthalene-based connector ($E_T = 16100$ cm⁻¹) does not emit under these conditions but shares a common lifetime ($\tau_T = 6.7$ μ s).

shortens the triplet lifetime, reduces the emission probability, and raises the triplet energy (E_T), although the photophysical properties remain vastly superior to those of the parent. This is because of a mismatch in the energy and spatial distribution of LUMOs on the alkyne and phenyl units, which curtails extended delocalization of the promoted electron. Functionalization of the phenyl ring with 2,5-dialkoxy groups (**RR3**) causes a small increase in both triplet lifetime and emission quantum yield, while slightly lowering the triplet energy (Table 1). Replacing the phenyl ring with a naphthalene residue, forming **RR4**, prolongs the triplet lifetime to 475 ns,

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[**] This work was partially supported by the Centre National de la Recherche Scientifique and by the ECPM. All nanosecond laser flash photolysis studies were carried out at the PICR-FRRF, Manchester (UK), and we are grateful to the staff of the FRRF for their technical expertise. Financial support for operating the FRRF and to cover travel expenses was provided by the European Union.

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due to improved blending of the relevant LUMOs, and raises the emission probability (Table 1). The problems associated with the central phenyl ring are thereby overcome and the photophysical properties of **RR4** are almost as attractive as those of **RR1**, with the added benefit that the central unit can now be derivatized.

The triplet decay profile recorded for **RR4** in deoxygenated acetonitrile following excitation with a 10-ns laser pulse at 532 nm is mono-exponential at low laser intensity, but becomes dual-exponential as the laser intensity is increased (Figure 1). The shorter lived component has a lifetime of

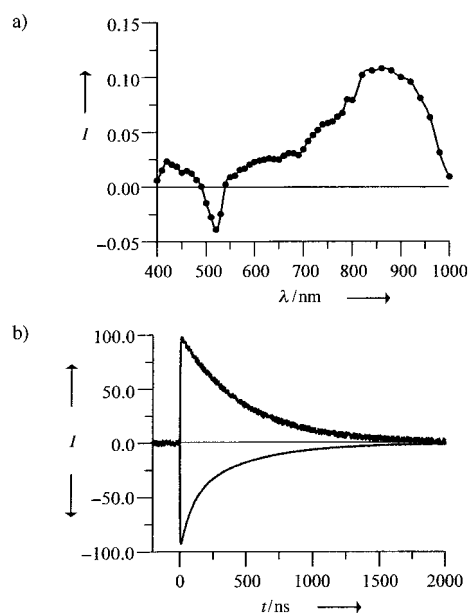
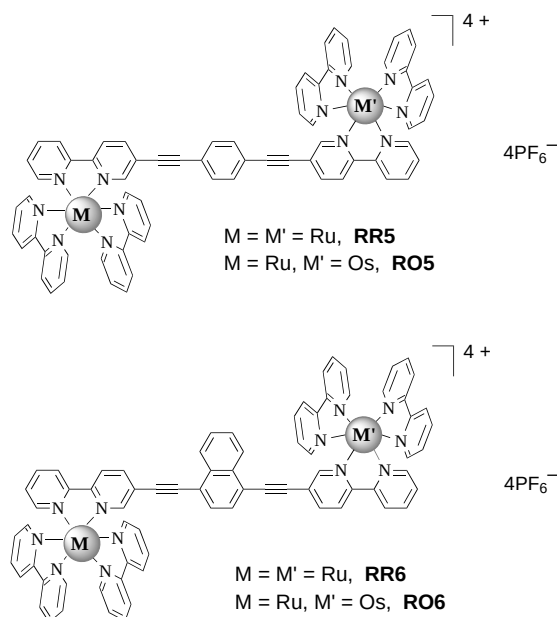


Figure 1. a) Differential absorption spectrum recorded for the triplet excited state of **RR4** in deoxygenated acetonitrile at 20 °C. The intense bleaching seen around 510 nm indicates that the triplet state is localized on the Ru-terpy chromophore. The spectral profile remains independent of laser intensity. b) Decay profiles of **RR4** recorded at 700 nm following excitation at low (upper trace) and high laser intensity (lower trace); the lower trace is inverted for clarity of presentation. At low power the decay curve corresponds to a single exponential component having a lifetime of 475 ns. The profile recorded at high power corresponds to two successive first-order ($2A \rightarrow A \rightarrow B$) processes having lifetimes of 90 and 475 ns. I = intensity.

(90 ± 5) ns, while the slower component retains a lifetime of (475 ± 15) ns. Identical decay profiles are observed by both transient absorption and time-resolved emission techniques, but decay profiles recorded for the mononuclear complex **R4** remain mono-exponential at all laser intensities. The transient absorption spectrum recorded for **RR4** (Figure 1) is independent of laser intensity. The simplest interpretation of these observations is that both Ru-terpy terminals are simultaneously promoted to the triplet state at high laser intensity, and that the shorter lived component corresponds to intramolecular triplet-triplet annihilation. The two Ru-terpy chromophores present in **RR2** and **RR3** can be simultaneously promoted to the triplet manifold, but triplet-triplet annihilation does not take place within the available time frame since decay profiles remain mono-exponential at high intensities. The effect observed with **RR4**, therefore, arises because the naphthalene-based connector both stabilizes the triplet state and promotes electron exchange on the relevant time scale. For **RR1**, it was not possible to simultaneously populate both triplet states at any laser intensity, perhaps because triplet annihilation is complete within the 10-ns laser pulse.

Relative to $[\text{Ru}(\text{bpy})_3]^{2+}$ ($\text{bpy} = 2,2'$ -bipyridyl), the triplet lifetime and emission probability of **RR5** are slightly reduced because of the lower triplet energy (Table 1). For the



naphthalene-bridged system **RR6**, the triplets localized on the connector ($E_T = 16110 \text{ cm}^{-1}$) and on the Ru-bpy terminal ($E_T = 16320 \text{ cm}^{-1}$) are in thermal equilibrium at room temperature, although only the metal complex emits in deoxygenated acetonitrile at 20 °C. The equilibrium mixture strongly favors the naphthalene-like triplet (75 %) and decays by first-order kinetics with a lifetime of (6.7 ± 0.2) μs in deoxygenated acetonitrile. Thus, the triplet lifetime of the Ru-bpy terminal, present in the equilibrium mixture, exceeds that of $[\text{Ru}(\text{bpy})_3]^{2+}$ by a factor of about seven.

In the butadiynylene-linked mixed-metal complex **RO1** intramolecular triplet energy transfer (i.e., Ru $\rightarrow$ Os) is very

fast,^[3] occurring with a rate constant k_{ET} of $3.7 \times 10^{10} \text{ s}^{-1}$ in deoxygenated acetonitrile at 20 °C. Insertion of a central phenyl ring, as in **RO3**, lowers this rate constant by a factor of about 300, while a central naphthalene unit, as in **RO4**, provides for a rate intermediate between these extreme values (Table 2). The average distance^[8] separating the metal centers (d) varies somewhat among these compounds while the energy gap (ΔE_{TT}) between triplets localized on the Ru-terpy donor and Os-terpy acceptor^[9] is relatively small. In fact, this modest energy gap, taken together with the long inherent triplet lifetime of the Os-terpy fragment, might be expected to facilitate reverse triplet energy transfer (i.e., Os $\rightarrow$ Ru) in **RO3** and **RO4**.

It is convenient to describe the rate constant for through-bond energy transfer (k_{D}) in terms of the Fermi golden rule [Eq. (1)],^[10] where FC refers to the Franck–Condon weight-

$$k_{\text{D}} = \frac{2\pi}{\hbar} |V_{\text{DA}}|^2 FC \quad (1)$$

ed density of states and V_{DA} is the electronic coupling matrix element for electron exchange. The Franck–Condon factor can be calculated by reference to luminescence spectra recorded for the appropriate mononuclear Ru and Os complexes,^[10] thereby allowing an estimation of the matrix element (Table 2). To relate k_{D} to the experimentally determined k_{ET} [Eq. (2)] it is necessary to allow for Förster-

$$k_{\text{ET}} = k_{\text{D}} + k_{\text{F}} \quad (2)$$

type coulombic energy transfer, but the rate constant for this process (k_{F}) is readily calculated from spectral characteristics of the relevant mononuclear complexes.^[11]

The derived rates are compiled in Table 2 and indicate that, because of the poor emission characteristics of the Ru-terpy fragment, Förster-type energy transfer is negligible in these systems. As such, the derived k_{ET} values reflect the magnitude of electronic coupling between the reactants, and it is seen that the central aromatic unit imposes a severe barrier for through-bond electronic interactions. In part, this barrier arises from the extended length of the connector, but there is also a substantial difference between the value of V_{DA} derived for **RO3** and **RO4**, for which the metal–metal separation remains identical. Note the qualitative correspondence between k_{ET} for the Ru/Os complexes and τ_{T} measured for the binuclear Ru-terpy complexes. It is apparent that both

parameters are controlled by electronic factors associated with the polyalkynylene connector.

The superexchange mechanism allows for virtual population of the triplet state localized on the connector such that V_{DA} can be expressed in the form of Equation (3),^[1] where ΔE_{DS} is the energy gap between triplet states localized on the connector and donor and α is the product of atomic orbital coefficients describing coupling between 1) donor and connector, 2) successive subunits within the connector, and 3) connector triplet, and acceptor.

$$V_{\text{DA}} = \frac{\alpha^2}{\Delta E_{\text{DS}}} \quad (3)$$

The various ΔE_{DS} values are available from emission spectroscopy, thereby enabling estimation of the connectivity term α (Table 2). Coupling along the butadiynylene bridge is extremely effective, offsetting the relatively large energy gap between donor and connector, and conducive for fast electron exchange. A central aromatic unit imposes a severe drop in the degree of connectivity along the molecular axis, and this must arise because of poor electronic coupling between alkynylene and aromatic fragments, although similar α values are found for both phenylene and naphthalene spacers. The faster rate and higher value of V_{DA} found for **RO4** relative to **RO3** can now be ascribed to the relative ΔE_{DS} values, bearing in mind that the triplet energy of the naphthalene-based connector is much lower than that of the phenylene-bridged system.^[12]

Again, comparison can be made with the corresponding 2,2'-bipyridyl-based systems, and it is seen that intramolecular triplet energy transfer across a central phenylene spacer is about sevenfold faster for **RO5** than for **RO3** (Table 2). This rate enhancement can be traced to the fact that both V_{DA} and α are higher for the 2,2'-bipyridyl-based system. Although there is a small difference between ΔE_{DS} values derived for these two compounds, the faster rate of energy transfer found for **RO5** stems mainly from improved blending of orbitals along the connector. The situation is more complicated for the naphthalene-bridged 2,2'-bipyridyl-based system **RO6** since energy transfer proceeds by intermediate population of the triplet localized on the connector. In fact, energy transfer from the connector triplet to the Os-bpy terminal ($k_{\text{ET}} = 1.7 \times 10^{10} \text{ s}^{-1}$) intercepts reversible triplet energy transfer between the Ru-bpy terminal and the connector, for which both forward ($k_{\text{ET}} = 1.1 \times 10^{10} \text{ s}^{-1}$) and reverse steps

Table 2. Parameters relating to triplet energy transfer in the various mixed-metal Ru-Os dyads, with reference to measurements made in deoxygenated acetonitrile at 20 °C.

Compd	Process ^[a]	k_{ET} [μs^{-1}] ^[b]	k_{F} [μs^{-1}]	k_{D} [μs^{-1}]	ΔE_{TT} [cm^{-1}]	λ_{TT} [cm^{-1}] ^[c]	d [Å]	FC [cm^{-1}] ^[d]	V_{DA} [cm^{-1}] ^[e]	ΔE_{DS} [cm^{-1}]	α [cm]
RO1	Ru $\rightarrow$ Os	37 000	30	37 000	890	1700	15.5	4.6×10^{-5}	26.0	5670	385
RO3	Ru $\rightarrow$ Os	116	2	114	730	1400	19.8	1.3×10^{-4}	0.9	6000	70
RO4	Ru $\rightarrow$ Os	1060	1	1059	700	1400	19.8	1.2×10^{-4}	2.7	1480	65
RO5	Ru $\rightarrow$ Os	800	8	792	2995	2285	18.1	2.0×10^{-4}	2.0	5400	100
RO6	Ru $\rightarrow$ N	10 900	< 1	10 900	305	1455	18.1	6.6×10^{-5}	11.8	na ^[f]	na
RO6	N $\rightarrow$ Os	17 000	< 1	17 000	2335	1200	18.1	$1.8 \times 10^{[f]}$	8.9	na	na

[a] Direction of triplet energy transfer, N refers to naphthalene. [b] Experimental rate constant for electron exchange, $\pm 10\%$. [c] Total reorganization energy accompanying triplet energy transfer, $\pm 100 \text{ cm}^{-1}$. [d] Franck–Condon weighted density of states calculated from spectroscopic properties recorded for appropriate mononuclear complexes, $\pm 5\%$. [e] Matrix element for electron exchange, $\pm 10\%$. [f] na = not applicable.

($k_{\text{ET}} = 2.4 \times 10^9 \text{ s}^{-1}$) can be evaluated by time-resolved emission spectroscopy.^[13]

It is instructive to compare the times required to populate the Os-based acceptor in **RO4** and **RO6** (Figure 2) as a means to assess the benefits of a two-step, energy-transfer process with respect to direct (long-range) transfer.^[14] Thus, the maximum yield of the Os-terpy triplet state attainable by

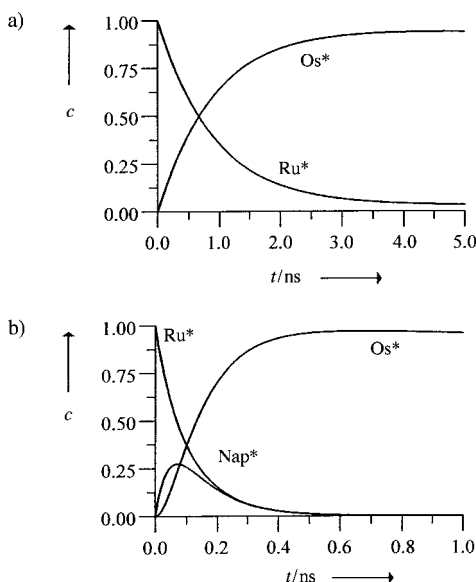


Figure 2. a) Kinetic simulation for **RO4** showing how the concentration c of triplet states localized on Ru-terpy (Ru^*) and Os-terpy terminals (Os^*) vary with time t following selective excitation of the Ru-terpy unit. The long tail seen in the decay of Ru^* is due to reverse energy transfer from Os^* . b) Corresponding simulation for **RO6** showing intermediate population of the triplet state localized on the naphthalene-based connector (Nap^*). Simulations were based on the experimentally determined rate constants.

energy transfer in **RO4** corresponds to 94% of the initially populated Ru-terpy triplet and is reached after 4.8 ns. For **RO6**, the maximum yield of Os-bpy triplet is 97% and is reached after only 670 ps. The two-step mechanism, in this case, is much faster than long-range (i.e., 20 Å) transfer. This finding indicates the benefit of having an intermediary relay but also shows that, in a properly designed system, long-range energy transfer can be competitive.

Electron exchange in mixed-metal Ru/Os polypyridine complexes is an established subject. Remarkably, the fastest and the slowest rates of triplet energy transfer between terpy-based terminals have been measured for systems built around alkyne connectors. The degree of electronic interaction between the metallo terminal and an alkyne is readily modulated by inserting an aromatic unit into the carbon chain, and this has similar effects on both the triplet lifetime and on the rate of electron exchange in binuclear complexes. An unusual effect of the alkyne connector is that it perturbs terminal Ru-terpy and Os-terpy units to different degrees, such that the resultant triplet energy gap ΔE_{TT} becomes sufficiently small to facilitate reversible triplet energy transfer along the molecular axis. By prolonging the triplet lifetime and providing a favorable pathway for electron exchange, the diethynylated naphthalene connector permits

slow energy-transfer steps to compete with nonradiative deactivation of the excited state. Thus, the first example of triplet–triplet annihilation in a ruthenium(II) polypyridine complex is described. Finally, our approach allows the triplet energy of the connector to be sited slightly above or below that of the donor. By way of **RO4** and **RO6**, this provides the first opportunity to compare long-range and successive short-range energy-transfer steps in structurally related molecular systems.

Experimental Section

All new complexes were prepared by complexation of the ditopic ligands with appropriate metal precursors; $[\text{Ru}(\text{terpy})(\text{dmsO})\text{Cl}_2]$ (dmsO = dimethyl sulfoxide) for terpy-based compounds and $[\text{Ru}(\text{bpy})_2\text{Cl}_2] \cdot 2\text{H}_2\text{O}$ for bpy-based complexes. The resultant complexes were purified by chromatography over alumina, followed by double recrystallization. The purity of each new compound was shown to be greater than 98% by spectroscopic and elemental analyses (see the Supporting Information for details). Photophysical measurements were made with a variety of laser excitation sources. For the symmetrical binuclear complexes, the laser excitation wavelength was 532 nm (FWHM = 25 ps or 10 ns), and triplet-state properties were monitored by both transient absorption and time-resolved emission spectroscopy. Kinetics for energy-transfer processes were established by time-correlated, single-photon counting studies following excitation with a frequency-doubled Ti:SAPPHIRE laser (FWHM = 0.3 ps). Emission from either the Ru- or Os-based chromophore was separated with a high-resolution, dual monochromator system before being sampled with a microchannel plate phototube. The time resolution of this instrument, after deconvolution of the instrumental response function, was about 25 ps. Kinetic information was also established by transient absorption spectroscopy following laser excitation at 440 nm (FWHM = 0.35 ps). All experiments were carried out in deoxygenated acetonitrile at 20 °C.

Received: July 1, 1999 [Z13665]

- [1] a) H. McConnel, *J. Chem. Phys.* **1961**, 35, 508; b) J. R. Miller, J. V. Beitz, *J. Chem. Phys.* **1981**, 74, 6746.
- [2] R. Ziessel, M. Hissler, A. El-ghayoury, A. Harriman, *Coord. Chem. Rev.* **1998**, 178–180, 1251.
- [3] V. Grossshenny, A. Harriman, R. Ziessel, *Angew. Chem.* **1995**, 107, 1211; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1100.
- [4] V. Grossshenny, A. Harriman, R. Ziessel, *Angew. Chem.* **1995**, 107, 2921; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2705.
- [5] M. P. Samanta, W. Tian, S. Datta, J. I. Hendersen, C. P. Kubiak, *Physical Review B—Condensed Matter* **1996**, 53, 7626.
- [6] A. C. Benniston, V. Grossshenny, A. Harriman, R. Ziessel, *Angew. Chem.* **1994**, 106, 1956; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1884.
- [7] M. Hissler, A. El-ghayoury, A. Harriman, R. Ziessel, *Angew. Chem.* **1998**, 110, 1804; *Angew. Chem. Int. Ed.* **1998**, 37, 1717.
- [8] Molecular dimensions used here and in the Förster-type calculations were determined from structures simulated with computer molecular dynamics (ZINDO-S parameters) after full-energy minimization using the AMBER force field.
- [9] Triplet energy levels were derived by fitting the luminescence spectra recorded for the relevant mono- or binuclear complexes at room temperature, and for the free ligands at various temperatures, to the spectral curve-fitting analysis described in ref. [10]. For more details, see A. Harriman, F. M. Romero, R. Ziessel, A. C. Benniston, *J. Phys. Chem.* **1999**, 103, 5399.
- [10] Z. Murtaza, D. K. Graff, A. P. Zipp, L. A. Worl, W. E. Jones, Jr., W. D. Bates, T. J. Meyer, *J. Phys. Chem.* **1994**, 98, 10504.
- [11] In calculating the orientation factor it has been assumed that the lowest energy triplet states correspond to charge transfer from the metal center to the ethynylated ligand. This gives a total of 18 and 12 active transition dipoles out of the overall 36 transition dipoles for terpy- and bpy-based systems, respectively. Orientation factors and

center-to-center distances were calculated from the computer-simulated structures, and the overlap integral, calculated from emission and absorption spectra, was assumed to contain 36 equal contributions. For more details, see V. Grosshenny, A. Harriman, M. Hissler, R. Ziessel, *J. Chem. Soc. Faraday Trans.* **1996**, 92, 2223.

- [12] The triplet energies of the ditopic ligands used to assemble complexes **RO3** and **RO4** were derived to be 21 400 and 16 700 cm⁻¹, respectively, from room-temperature emission spectra recorded in micellar media. The triplet energy for the ditopic ligand present in **RO1** was found to be 20 270 cm⁻¹ from phosphorescence spectra recorded at 77 K. Triplet energies for the bpy-based ditopic ligands relevant to **RO5** and **RO6** were measured to be 21 970 and 16 100 cm⁻¹, respectively, from room-temperature emission spectra recorded in micellar media.
- [13] H. Heitele, P. Finckh, S. Weeren, F. Pöllinger, M. E. Michel-Beyerle, *J. Phys. Chem.* **1989**, 93, 5173.
- [14] These values were derived from a compartmental kinetic analysis, allowing for reversible energy transfer, by solving the successive differential equations and using experimentally determined rate constants.

[Ti(CO)₄(η^3 -BH₄)]⁻ and [Ti(CO)₄(η^5 -C₄H₄N)]⁻: The First Zerovalent Metal Complexes Containing η^3 -Borohydride and Pyrrolyl Ligands**

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*Dedicated to Professor Heinrich Nöth
on the occasion of his 70th birthday*

Metal borohydrides are an important class of substances that are known for practically all metals throughout the periodic table. Most contain metals in positive formal oxidation states.^[1] Indeed, only two well-defined examples of zerovalent metal borohydrides have been reported, and both of these contain bidentate borohydride ligands: [Mo(CO)₄(η^2 -BH₄)]⁻^[2] and [Cr(CO)₄(η^2 -BH₄)]⁻.^[3a] We now report on the new zerovalent metal borohydride [Ti(CO)₄(η^3 -BH₄)]⁻ (**1**), the first to contain titanium and a tridentate borohydride ligand.

The synthetic route to this borohydride complex also appears to be unprecedented, that is, the reaction of BH₃·THF with a mononuclear metal carbonyl anion.^[4a] Prior reactions of this type provided only M–BH₃^[4b] or M– η^2 -B₂H₅ complexes.^[5] The above-mentioned Group 6 zerovalent metal carbonyl borohydride complexes were obtained as pure products by treatment of an appropriate metal carbonyl with

borohydride salts.^[2, 3a] Complex **1** is a very labile species and appears to be the most reactive isolable synthon for neutral {Ti(CO)₄}, a highly unsaturated 12-electron fragment (see below).

Treatment of a slurry of [K([15]crown-5)₂][Ti(CO)₆]^[3b] with BH₃·THF (10 equiv, unoptimized) in THF at –60 °C provided a very air-sensitive red solution. After careful separation of non-carbonyl by-products, deep red, pure, solid [K([15]crown-5)₂]-**1** was isolated in 38 % yield (see Experimental Section) as a thermally stable substance at room temperature. By an analogous procedure [K([18]crown-6)]-**1** was obtained in 15 % yield as orange-red microcrystals.^[6]

Spectroscopic properties of both salts are virtually identical for the anionic component and are described here in detail for the [K([15]crown-5)₂]⁺ salt. The IR spectra in THF show two peaks (1945(m), 1811(s) cm⁻¹) in the ν (CO) region that have the same pattern as observed for other titanium tetracarbonyl complexes in THF, including [Ti(CO)₄(η^5 -C₅H₅)]⁻ (**2**; $\tilde{\nu}$ (CO) = 1921 (m), 1779 cm⁻¹ (s)).^[7a] The ν (CO) values of **1** are the highest reported for any titanium tetracarbonyl complex and suggest that [BH₄]⁻ is the weakest donor presently known to stabilize this Ti⁰ unit. The IR spectra of Nujol mulls of **1** in the ν (BH) region show bands at 2495 (m), 2132 (vw), and 2058 cm⁻¹ (w), which have a pattern diagnostic of tridentate borohydride ligands.^[1a] The borohydride signals observed in the ¹H ($\delta_{\text{H}} = -3.60$, 1:1:1:1 quartet, $J_{\text{B,H}} = 85$ Hz) and ¹¹B NMR spectra ($\delta_{\text{B}} = -6.42$, binomial quintet, $J_{\text{H,B}} = 87$ Hz) at 23 °C are consistent with the presence of a highly fluxional BH₄ group, as expected on the basis of prior studies.^[1a] As the temperature was lowered, the 1:1:1:1 quartet in the ¹H NMR spectrum broadened and coalesced at –63 ± 5 °C. At –95 °C the slow exchange limit was reached, and two broad singlets of relative intensity 3:1 were present at $\delta_{\text{H}} = -4.87$ and 0.044, respectively, the weighted average of which is in satisfactory agreement with the resonance position at 23 °C. This study corroborated the presence of a η^3 -BH₄ ligand in **1** and allowed the free energy of activation of the bridging/terminal hydrogen (H_t/H_b) exchange process to be calculated as 8.8 ± 0.2 kcal mol⁻¹ by standard procedures.^[7b] This barrier is somewhat lower than the corresponding $\Delta G^\ddagger$ of 10.0 ± 0.2 kcal mol⁻¹ reported for [Mo(CO)₄(η^2 -BH₄)]⁻, the only other borohydride carbonyl complex for which this value is known.^[2]

A single-crystal X-ray diffraction study on the [K(18-crown-6)]⁺ salt confirmed the existence of **1** in the solid state.^[8] Two independent anions with nearly identical structures were present in the unit cell, and that shown in Figure 1 will be described in some detail here. All hydrogen atoms of the borohydride ligand were visible in the difference map after the remaining anisotropic refinement was complete. The linear H_t-B-Ti skeleton (179(2)°), three short Ti–H distances (av 2.02(4) Å), and the associated short Ti–B distance (2.158(7) Å) are all indicative of a η^3 -BH₄–Ti interaction. Slightly longer Ti–B distances in tridentate borohydride Ti^{IV} complexes have been reported, including [Ti(OAr)₃(η^3 -BH₄)] (Ar = 2,6-*i*Pr₂C₆H₃; 2.20(1) Å^[9a]), and [Ti(BP)₂(η^3 -BH₄)₂] (BP = a biphenoxo dianion; 2.19(1) Å^[9b]). The coordinated borohydride ligand is essentially tetrahedral, with an average B–H_b distance of 1.11(2) Å, which does not significantly differ

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[**] Highly Reduced Organometallics, Part 51. This work was supported by the U.S. National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank John K. Seaburg for conducting preliminary studies in this area and Christine Lundby for expert assistance in the preparation of the manuscript. Part 50: M. V. Barybin, V. G. Young, Jr., J. E. Ellis, *J. Am. Chem. Soc.*, **1999**, 121, 9237.

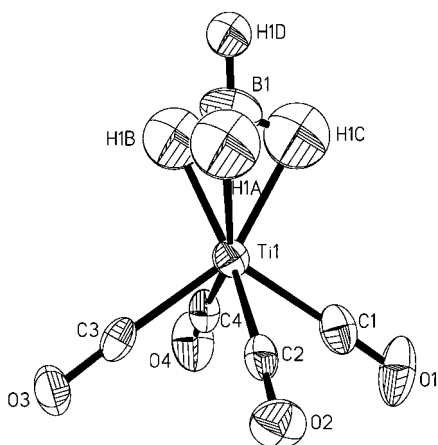


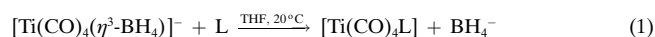
Figure 1. Molecular structure of **1** showing the labeling scheme (50% probability thermal ellipsoids; hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: Ti–C1 1.996(5), Ti–C2 1.997(5), Ti–C3 2.000(5), Ti–C4 2.016(6), C1–O1 1.173(5), C2–O2 1.178(5), C3–O3 1.172(5), C4–O4 1.174(6), Ti–B 2.158(7), B–H1A 1.10(2), B–H1B 1.11(2), B–H1C 1.12(2), B–H1D 1.08(2), Ti–H1A 2.05(4), Ti–H1B 1.97(4), Ti–H1C 2.04(4); Ti–C1–O1 178.2(4), Ti–C2–O2 177.8(4), Ti–C3–O3 177.1, Ti–C4–O4 176.8(4).

from the B–H_i distance (1.08(2) Å). Also, all H–B–H angles are in the narrow range of 108(2)–112(2)°, which is consistent with the presence of a relatively unperturbed tetrahedral borohydride group.

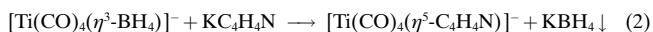
Interestingly, structures of the Ti(CO)₄ units in **1** and **2** are nearly superimposable, despite substantial electronic and structural differences in the donor ligands. For example, in **1** the average Ti–C and C–O distances (1.994(5) and 1.164(5) Å, respectively) as well as the *cis*- and *trans*-OC–Ti–CO angles (72(2) and 112.6(4)°, respectively) are experimentally indistinguishable from the corresponding values in **2** (Ti–C 2.00(1), C–O 1.174(5) Å; *cis*-OC–Ti–CO 72(1), *trans*-OC–Ti–CO 112.7(8)°).^[7a] These structural data are consistent with the idea that the η³-BH₄[−] group is effectively isolobal with η⁵-C₅H₅[−] in these complexes. Although the isolobal nature of η³-BH₄[−] and η⁵-C₅H₅[−] was previously recognized in complexes containing a high-valent metal center, such as [Sc(η³-BH₄)₃] and [Sc(η⁵-C₅H₅)₃],^[10] **1** and **2** are the first pair of metal carbonyl complexes that show this feature.

The asymmetric unit contains two [K([18]crown-6)] counterions that form infinite polymers with the anions through the carbonyl oxygen atoms, O1 and O3. The average K⋯O (carbonyl) and K⋯O (crown ether) distances of 2.80(4) and 2.80(3) Å, respectively, are essentially the same but are significantly longer than the average K⋯O (THF) distance of 2.69(4) Å in [K([18]crown-6)(thf)₂]⁺.^[11] This suggests that the K⁺–O_{carbonyl} interactions are weak at best. Indeed, the overall structure of the anion appears to be essentially unperturbed by this binding. For example, the formally “bridging” carbonyl ligands C1O1 and C3O3 are structurally identical to the other CO groups of **1**.

Treatment of **1** with a variety of nucleophiles at 20 °C in THF invariably results in rapid loss of [BH₄][−] and quantitative formation of previously known zerovalent titanium carbonyl complexes [Eq. (1); L = C₃H₅[−], C₅Me₅[−],^[7a] Ph₃C[−],^[12a]



HBPz₃[−],^[12b] tacn, Me₃tacn^[13]. Although reactions of other transition metal borohydride complexes with nucleophiles often result in formation of the respective nucleophile–borane adducts and metal hydrides,^[3a, 9, 14] no evidence for the generation of titanium hydrides was obtained in any of the reactions of **1** examined to date. The utility of **1** in the synthesis of new complexes was demonstrated by its facile reaction with the pyrrolyl anion to give the first (η⁵-pyrrolyl)titanium complex [Ti(CO)₄(η⁵-C₄H₄N)][−] (**3**) [Eq. (2)].



Pure orange microcrystalline **3** was isolated in 52% yield as a thermally stable [K([15]crown-5)₂]⁺ salt. Spectroscopic properties of **3** (see Experimental Section) are entirely consistent with the proposed formulation. Also, a single-crystal X-ray structural characterization of the corresponding bis(triphenylphosphane)iminium salt was carried out.^[15] Although pyrrolyl complexes of metals in formally positive oxidation states are now fairly common,^[16] including η¹-pyrrolyl complexes of Group 4 metals^[17] and the long-known neutral [Mn(CO)₅(η⁵-C₄H₄N)], the only previous example of a half-sandwich metal carbonyl complex containing a pyrrolyl ligand,^[18] **3** is presently the only known zerovalent metal complex to contain this ligand. Extensions of this research to other early transition metals and studies on the general reactivity patterns of **1** and **3** are in progress.

Experimental Section

[K([15]crown-5)₂]-**1**: A cold (−60 °C) solution of BH₃·THF in THF (1.0 M, 20.0 mL, 20.0 mmol) was added to a finely divided suspension of [K([15]crown-5)₂][Ti(CO)₆]·pyridine (2.50 g, 2.00 mmol) in THF (95 mL), and the mixture was stirred under an atmosphere of argon while slowly being warmed to 10 °C over a period of 16 h. The mixture was then cooled to −60 °C and filtered at this temperature. Following removal of solvent in vacuo (temperature of solution should not exceed 10 °C), cold diethyl ether (0 °C, 150 mL) was added to precipitate the product. The latter was taken up in cold THF (−50 °C) containing 1 mL of [15]crown-5 and filtered again at −60 °C. All but about 4 mL of THF was removed. Slow addition of cold diethyl ether (0 °C, 100 mL) to the resulting concentrated filtrate (0 °C) provided a powdery solid. This was isolated by filtration, washed with cold diethyl ether (0 °C, 3 × 10 mL), and dried in vacuo at room temperature to give 0.494 g (38% yield) of a deep red powder, which provided satisfactory elemental analyses for unsolvated [K([15]crown-5)₂]-**1**. Elemental analysis calcd (%) for C₂₄H₄₄O₁₄BKTi: C 44.05, H 6.78; found: C 43.74, H 6.92; m.p. 115–118 °C (decomp); IR (CH₂Cl₂): ν̄ = 1947 (m), 1806 cm^{−1} (s) (CO); ¹H NMR (300 MHz, [D₈]THF, 0 °C, TMS): δ = 3.53 (s, 40H, [15]crown-5), −3.60 (1:1:1:1 quartet, J_{B,H} = 85 Hz, 4H, BH₄); ¹³C{¹H} NMR (75 MHz, [D₈]THF, 0 °C, TMS): δ = 291.7 (s, CO), 69.2 (s, [15]crown-5); ¹¹B NMR (96.2 MHz, [D₈]THF, 0 °C, BF₃·OEt₂): δ = −6.42 (quintet, J_{H,B} = 87 Hz; BH₄). Attempts to grow X-ray quality crystals of [K([15]crown-5)₂]-**1** were unsuccessful, but suitable red-violet needles of [K([18]crown-6)]-**1**, obtained by the procedure outlined above, were grown from THF/pentane at 4 °C over 7 d.

[K([15]crown-5)₂]-**3**: A solution of pyrrolylpotassium (0.153 g, 1.45 mmol) in THF (200 mL) was added to [K([15]crown-5)₂]-**1** (0.306 g, 0.468 mmol) in cold THF (−50 °C, 10 mL) with stirring. The color of the reaction mixture immediately changed from red to orange. After 10 min the solution was cooled to −70 °C and filtered at −70 °C, and all but about 3 mL of solvent was removed in vacuo. Addition of cold diethyl ether (0 °C, 200 mL) resulted in formation of an orange solid. The latter was recrystallized from THF/diethyl ether to provide air-sensitive orange microcrystals

(0.170 g, 52 % yield). Elemental analysis calcd (%) for $C_{28}H_{44}O_{14}NKTi$: C 47.66, H 6.28, N 1.99; found: C 47.43, H 6.27, N 2.06; m.p. 124–125 °C (decomp); IR (THF): $\bar{\nu}$ = 1930 (m), 1793 cm^{-1} (s) (CO); ^1H NMR (300 MHz, $[D_8]THF$, 0 °C, TMS): δ = 6.16 (m, 2H, pyrrolyl), 5.40 (m, 2H, pyrrolyl), 3.62 (s, 40H, [15]crown-5); $^{13}C\{^1H\}$ (75 MHz, $[D_8]THF$, 0 °C, TMS): δ = 289 (s, CO), 114 (s, pyrrolyl), 99 (s, pyrrolyl), 69 (s, [15]crown-5).

Received: July 30, 1999 [Z13810]

- [1] a) T. J. Marks, J. R. Kolb, *Chem. Rev.* **1977**, 77, 263; b) B. D. James, M. G. H. Wallbridge, *Prog. Inorg. Chem.* **1970**, 11, 99.
- [2] S. W. Kirtley, M. A. Andres, R. Bau, G. W. Grynkeiwich, T. J. Marks, D. L. Tipton, B. R. Whittlesey, *J. Am. Chem. Soc.* **1977**, 99, 7154.
- [3] a) M. Y. Darensbourg, R. Bau, M. W. Marks, R. R. Burch, Jr., J. C. Deaton, S. Slater, *J. Am. Chem. Soc.* **1982**, 104, 6961; b) K.-M. Chi, S. R. Frerichs, S. B. Philson, J. E. Ellis, *J. Am. Chem. Soc.* **1988**, 110, 303.
- [4] a) Previously it was shown that the dinuclear hydrido complex $[HMo_2(CO)_{10}]^-$ in the presence of I^- reacted with equimolar amounts of $BH_3 \cdot THF$ to give $[Mo(CO)_4(\eta^2-BH_4)]^-$ and $[Mo(CO)_5]^-$; [2] b) G. W. Parshall, *J. Am. Chem. Soc.* **1964**, 86, 361.
- [5] a) G. Medford, S. G. Shore, *J. Am. Chem. Soc.* **1978**, 100, 3953; b) T. J. Coffy, G. Medford, J. Plotkin, G. J. Long, J. C. Huffman, S. G. Shore, *Organometallics* **1989**, 8, 2404; c) T. J. Coffy, S. G. Shore, *J. Organomet. Chem.* **1990**, 394, C27.
- [6] In a related reaction, $[Fe(CO)_4]^{2-}$ was shown to react with $BH_3 \cdot THF$ to give equimolar amounts of $[Fe(CO)_4(\eta^2-B_2H_5)]^-$ and $K[BH_4]$. [5b] Although anionic $M-BH_3$ complexes [4b] are likely intermediates in both this reaction and that involving the titanate, in neither case were any intermediates observed. The two reactions provide quite a contrast, however, since in the case of Fe free $[BH_4]^-$ is formed, while the Ti-mediated reaction affords coordinated $[BH_4]^-$.
- [7] a) B. A. Kelsey, J. E. Ellis, *J. Am. Chem. Soc.* **1986**, 108 5016; b) G. Binsch in *Dynamic Nuclear Magnetic Resonance Spectroscopy* (Eds.: L. M. Jackman, F. A. Cotton), Academic Press, New York, **1975**, chap. 3.
- [8] a) Crystal data for $[K([18]crown-6)]_2$: $C_{42}H_{60}K_2N_{12}O_{22}Ti_2$, M_r = 1118.92, monoclinic, space group $P2_1/c$, a = 15.496(3), b = 15.374(3), c = 11.245(2) Å, β = 91.02(3)°, V = 2678.4(0) Å³, Z = 2, ρ_{calcd} = 1.387 g cm⁻³, $F(000)$ = 1168, $\mu(Mo_{K\alpha})$ = 0.530 mm⁻¹, λ = 0.71073 Å, T = 173(2) K; 9448 reflections were measured on a Siemens SMART CCD area detector diffractometer and yielded 4499 unique data ($2\theta_{max}$ = 50°, R_{int} = 0.0309, semi-empirical absorption corrections). The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 with statistical weighting, anisotropic displacement parameters, and constrained isotropic H atoms to give $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{1/2} = 0.1411$ on all data, conventional $R = 0.0611$ on F values of 4424 reflections having $F_o^2 > 2\sigma(F_o^2)$, goodness of fit $S = 0.983$ for all F^2 values and 558 refined parameters. Largest difference peak/hole 0.345/−0.330 e Å⁻³. All calculations were performed on SGI INDY R4400-SC or Pentium computers with the SHEXTL-Plus program suite; b) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-132492. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] a) H. Nöth, M. Schmidt, *Organometallics* **1995**, 14, 4601; b) F. Corazza, C. Floriani, A. Chiesi-Villa, C. Guastini, *Inorg. Chem.* **1991**, 30, 145.
- [10] a) M. Mancini, P. Bougeard, R. C. Burns, M. Mlekuz, B. G. Sayer, J. I. A. Thompson, M. J. McGlinchey, *Inorg. Chem.* **1984**, 23, 1072; b) Y. Oishi, T. A. Albright, H. Fujimoto, *Polyhedron* **1995**, 14, 2603. This paper discusses the electronic properties of the unknown $[Mn(CO)_4(BH_4)]$. It is noteworthy that $[Mn(CO)_3(\eta^3-BH_4)]$, which would be analogous to $[Mn(CO)_3(\eta^5-C_5H_5)]$, is also unknown.
- [11] J. K. Seaburg, P. J. Fischer, V. G. Young, Jr., J. E. Ellis, *Angew. Chem.* **1998**, 110, 163; *Angew. Chem. Int. Ed.* **1998**, 37, 155.
- [12] a) P. J. Fischer, K. A. Ahrendt, V. G. Young, Jr., J. E. Ellis, *Organometallics* **1998**, 17, 13; b) K.-M. Chi, S. R. Frerichs, B. K. Stein, D. W. Blackburn, J. E. Ellis, *J. Am. Chem. Soc.* **1988**, 110, 163; $HBpZ_3$ = hydridotris(1-pyrazolyl)borate.
- [13] J. E. Ellis, A. J. DiMaio, A. L. Rheingold, B. S. Haggerty, *J. Am. Chem. Soc.* **1992**, 114, 10676; $tacn$ = 1,4,7-triazacyclononane; Me_3tacn = 1,4,7-trimethyl-1,4,7-triazacyclononane.
- [14] a) M. L. Luetkens, J. C. Huffman, A. P. Sattelberger, *J. Am. Chem. Soc.* **1985**, 107, 3361; b) J. E. Gozum, G. S. Girolami, *J. Am. Chem. Soc.* **1991**, 113, 3829, and references therein.
- [15] Details of the structure and structural characterization will be described elsewhere: P. J. Fischer, V. G. Young, Jr., J. E. Ellis, unpublished results. Crystal data for $[(Ph_3P)_2N]_3$: $C_{44}H_{34}N_2O_4P_2Ti$, M_r = 764.57, monoclinic, space group $P2_1$, red plate, a = 10.6547(2), b = 12.6892(3), c = 13.9628(4) Å, β = 98.483(1)°, Z = 2, R = 0.0502, with GOF on F^2 of 1.066.
- [16] a) M. Rakowski Du Bois, K. G. Parker, C. Ohman, B. C. Noll, *Organometallics* **1997**, 16, 2325, and references therein; b) see also ref. [8] of J. R. Perera, M. J. Heeg, H. B. Schlegel, C. H. Winter, *J. Am. Chem. Soc.* **1999**, 121, 4536.
- [17] R. V. Bynum, W. E. Hunter, R. D. Rogers, J. L. Atwood, *Inorg. Chem.* **1980**, 19, 2368.
- [18] a) K. K. Joshi, P. L. Pauson, A. R. Qazi, W. H. Stubbs, *J. Organomet. Chem.* **1964**, 1, 471; b) R. B. King, A. Efraty, *J. Organomet. Chem.* **1969**, 20, 264.

A Metamagnetic Two-Dimensional Molecular Material with Nickel(II) and Azide**

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Until a few years ago, the main aim of magnetochemical research was to show that molecular magnetism could lead to the development of new magnetic materials.^[1] One strategy for the design of molecular-based magnets involves assembling transition metal ions in one-, two-, or three-dimensional networks. We are currently studying materials formed from the interaction of transition metal ions with the azido ligand. The azido bridge is a versatile and efficient magnetic coupler; it may transmit either antiferro- or ferromagnetic interactions. Working with Ni^{II} salts and diamines as blocking ligands, for a Ni/diamine ratio of 1/1 four positions in the coordination sphere of the nickel are free. These positions can be occupied by four azido bridges. The most remarkable species obtained to date are the neutral polymeric compounds $[Ni(\mu-N_3)_2(\text{diamine})]_n$: three one-dimensional systems showing global ferromagnetic behavior and metamagnetism at low temperature,^[2] five one-dimensional complexes with alternating end-on (EO) and end-to-end (EE) azido bridges in different sequences showing global anti-ferromagnetic behavior,^[3–6]

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[**] This work was supported by the Spanish Dirección General de Investigación Científica y Técnica (project PB96-0163).

and one two-dimensional sheet showing global antiferromagnetic behavior and a canting phenomenon at low temperature (50 K) that gives the complex the characteristics of a molecular magnet.^[7] Here, we report the synthesis, structure, and magnetic properties of $[\text{Ni}(\mu\text{-N}_3)_2(\text{N,N}\text{-Et}_2\text{-N'}\text{-Me-en})]_n$ (**1**; $\text{N,N}\text{-Et}_2\text{-N'}\text{-Me-en} = \text{N,N}$ -diethyl- N' -methylethylenediamine), which is the first example of a metamagnetic two-dimensional molecular material with Ni^{II} and azide, featuring short-range, intralayer, ferromagnetic behavior and weak interlayer antiferromagnetic interactions. The crystal structure analysis^[8] reveals parallel sheets of nickel atoms linked by EO and EE azido bridges (Figure 1). Each nickel atom is in a

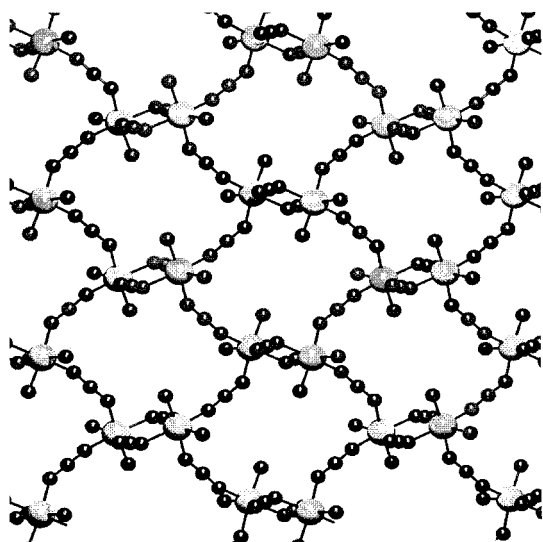


Figure 1. Layer structure of **1**. Dinuclear nickel units, bridged by two EO azido bridges, are linked to four equivalent units by means of four single EE azido bridges. For clarity, only the N atoms of the amine ligands are shown.

distorted octahedral NiN_6 environment and is linked to three other nickel atoms: through two EO azido bridges to one nickel atom and through two EE bridges in a *cis* position to two nickel atoms. Each Ni^{II} ion completes its coordination by binding one bidentate $\text{N,N}\text{-Et}_2\text{-N'}\text{-Me-en}$ ligand. The Ni-N bond lengths range between 2.09 and 2.15 Å, which is characteristic of these complexes. The Ni-N-Ni angle of 100.46° lies within the range of reported values.^[2, 4, 5] All the EE fragments are equivalent and the coordination of the azido bridge is asymmetric; the two Ni-N-N angles are 136.9° and 144.2° , and the $\text{Ni-N}_3\text{-Ni}$ torsion angle is 110.44° .

The cryomagnetic behavior of **1** is shown in Figure 2. At room temperature $\chi_{\text{M}}T$ is the same ($1.44 \text{ cm}^3 \text{ K mol}^{-1}$) for all values of the applied field. This value increases monotonically with cooling to 60 K. As the temperature is lowered further $\chi_{\text{M}}T$ increases more and more rapidly, reaching a maximum value around 16 K, before decreasing at lower temperatures. The maximum value of $\chi_{\text{M}}T$ is field dependent, but the temperature for the maximum $\chi_{\text{M}}T$ remains unchanged. The magnetic behavior, except for the decreasing $\chi_{\text{M}}T$ below 16 K, suggests an intramolecular ferromagnetic interaction between adjacent Ni^{II} ions. These results can be explained by considering the structure. The interaction between the nickel atoms

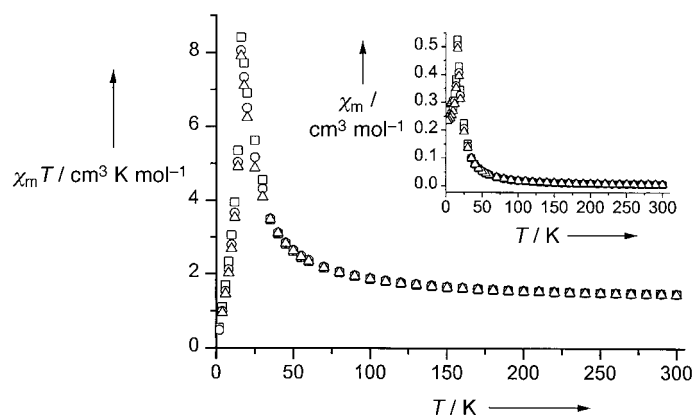


Figure 2. Plot of $\chi_{\text{M}}T$ versus temperature at three values of the applied field ($\square$: 500 G, $\circ$: 1000 G, $\triangle$: 2000 G). Inset: Plot of χ_{M} versus temperature.

through the EO azido bridges, according to the structural parameters and literature data,^[9, 10] must be ferromagnetic. For the interaction through the EE azido ligand, previous studies^[11, 12] show that the value of the superexchange coupling depends mainly on the Ni-N-N angle α and on the $\text{Ni-N}_3\text{-Ni}$ torsion angle θ . Considering the Ni-N-N angle, the maximum antiferromagnetic coupling would be expected for $\alpha = 108^\circ$. For greater values, the interaction must decrease and reach accidental orthogonality at $\alpha = 165^\circ$. Taking into account the torsion angle, the maximum superexchange is found for $\theta = 180^\circ$ or 0° and diminishes gradually to an expected minimum of zero for a torsion angle of $\theta = 90^\circ$. To our knowledge all compounds with an EE azido bridge and a Ni^{II} ion are antiferromagnetic with the exception of two compounds: one is a dinuclear nickel(II) cryptate,^[13] in which the Ni-N-N angles are 165.8° and 157.6° ; the other is a one-dimensional compound,^[14] in which the torsion angle is 75.7° . For **1** the values of the Ni-N-N angles deviate from 108° , and the torsion angle is close to 90° , in the range where the antiferromagnetic contribution is minimized to favor the ferromagnetic contribution.

The magnetic behavior of **1**, with the abrupt increase in the value of $\chi_{\text{M}}T$ on cooling, a maximum around 16 K, and decreasing $\chi_{\text{M}}T$ below this temperature, suggests a three-dimensional antiferromagnetic ordering of the ferromagnetic layers.^[15] Further support for this comes from magnetization versus applied field plots at three temperatures (Figure 3). All curves have the sigmoidal shape (more markedly at lower temperatures) expected for a metamagnet: initially the magnetization increases slightly with increasing field strength because of antiferromagnetic interlayer interactions, subsequently it increases abruptly for a phase transition to a ferromagnetic state, and finally it reaches a saturation magnetization plateau.

The magnetization was also measured in the range of 3–20 K (Figure 4). The field-cooled magnetization (FCM), measured under an applied field of 10 G, increases rapidly on cooling to 16 K and then diminishes. This behavior is typical of metamagnetic ordering. When the applied field was switched off at 3 K, there remained a remnant magnetization (RM), that decreased upon warming. The zero-field-cooled magnetization (ZFCM), measured upon warming under an

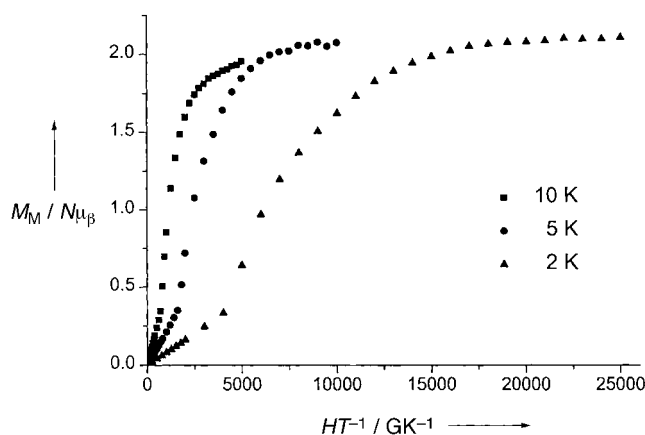


Figure 3. Magnetization versus applied field at three temperatures.

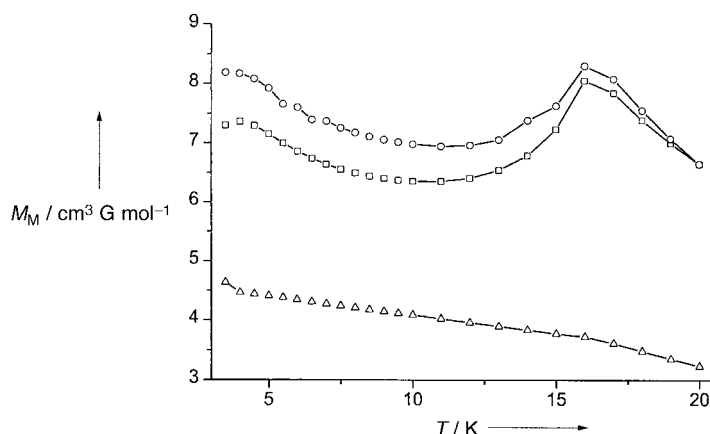


Figure 4. Plots of FCM (○), ZFCM (◻), and RM (Δ) versus temperature at an applied field of 10 G.

applied field of 10 G, shows a maximum at 16 K and decreases rapidly as the temperature is increased further.

The present example is a new demonstration of the versatility of the azido bridge for building molecular-based materials. The magnetic measurement shows, for the first time in a Ni^{II} azido compound, an intralayer ferromagnetic interaction. Finally, the interlayer antiferromagnetic interaction gives rise to metamagnetic behavior. In order to complete the magnetic studies, measurements at alternating current, and of the FCM at different field strengths are now in progress.

Experimental Section

A solution of *N,N*-Et₂-*N'*-Me-en (0.26 g, 2 mmol) in DMF/EtOH (1/1, 10 mL) was added to a solution of Ni(NO₃)₂·6H₂O (0.58 g, 2 mmol) in DMF/EtOH (20 mL). Solid NaN₃ (0.26 g, 2 mmol) was added slowly. The clear dark green solution was filtered to remove any impurities and left to stand undisturbed at room temperature. Single green crystals of **1** were collected after two weeks.

- [1] *Molecular-Based Magnetic Materials: Theory, Techniques and Applications* (Eds.: M. M. Turnbull, T. Sugimoto, L. K. Thompson) ACS Symp. Ser. **1996**, 644.
- [2] J. Ribas, M. Monfort, C. Diaz, C. Bastos, X. Solans, *Inorg. Chem.* **1994**, 33, 484–489.
- [3] J. Ribas, M. Monfort, B. Kumar-Gosh, X. Solans, M. Font-Bardía, *J. Chem. Soc. Chem. Commun.* **1995**, 2375–2376.
- [4] J. Ribas, M. Monfort, I. Resino, X. Solans, P. Rabu, F. Maingot, M. Drillon, *Angew. Chem.* **1996**, 108, 2671–2673; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2520–2522.
- [5] G. Viau, M. G. Lombardi, G. De Munno, M. Julve, F. Lloret, J. Faus, A. Caneschi, J. M. Clemente-Juan, *Chem. Commun.* **1997**, 1195–1196.
- [6] J. Ribas, M. Monfort, B. Kumar-Gosh, X. Solans, *Angew. Chem.* **1994**, 106, 2177–2179; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 2087–2089.
- [7] J. Ribas, M. Monfort, X. Solans, M. Drillon, *Inorg. Chem.* **1994**, 33, 742–745.
- [8] Crystal data (C₇H₁₇N₈Ni): monoclinic, space group *P*2₁/*c*, *a* = 10.0375(13), *b* = 8.6285(6), *c* = 13.7710(14) Å, β = 95.941(14)°, *V* = 1186.3(2) Å³, ρ_{calcd} = 1.523 g cm⁻³; Stoe Image Plate diffractometer, MoK_α radiation λ = 0.71073 Å, *T* = 293 K; 8174 measured (2.8 ≤ θ ≤ 25°) and 2092 independent reflections used in the refinement; Lorentz polarization but no absorption corrections (μ = 1.551 mm⁻¹). The structure was solved by direct methods by using SHELXS97 and refined with SHELXL97, 145 parameters. H computed and refined isotropically, *R*(on *F*) = 0.017, ω*R*(on *F*²) = 0.009, residual electron density 0.066 e Å⁻³. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-121920. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] O. Castell, R. Caballol, V. M. García, K. Handrick, *Inorg. Chem.* **1996**, 35, 1609–1615.
- [10] E. Ruiz, J. Cano, S. Alvarez, P. Alemany, *J. Am. Chem. Soc.* **1998**, 120, 11 122–11 129.
- [11] A. Escuer, R. Vicente, J. Ribas, M. Salah el Fallah, X. Solans, M. Font-Bardía, *Inorg. Chem.* **1994**, 33, 1842–1847.
- [12] R. Cortés, K. Urtiaga, L. Lezama, J. L. Pizarro, A. Goñi, M. I. Arriortua, T. Rojo, *Inorg. Chem.* **1994**, 33, 4009–4015.
- [13] A. Escuer, C. J. Harding, Y. Dussart, J. Nelson, V. McKee, R. Vicente, *J. Chem. Soc. Dalton Trans.* **1999**, 223–227.
- [14] C. S. Hong, Y. Do, *Angew. Chem.* **1999**, 111, 153–155; *Angew. Chem. Int. Ed.* **1999**, 38, 193–194.
- [15] H. Miyasaka, N. Matsumoto, H. Okawa, N. Re, E. Gallo, C. Floriani, *J. Am. Chem. Soc.* **1996**, 118, 981–994.

Received: May 27, 1999

Revised: September 13, 1999 [Z13474]

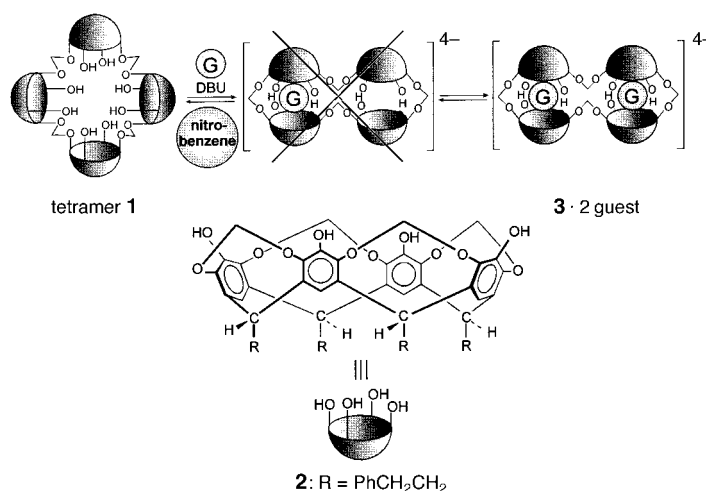
Bis-Capsules: Cooperative Reversible Encapsulation of Two Molecules in Adjacent Separate Chambers**

Naveen Chopra, Christoph Naumann, and John C. Sherman*

The study of discrete species that reversibly or irreversibly encapsulate small molecules in solution has captured the attention of numerous researchers in the past decade. The first such species were carceplexes, which permanently entrap guests within their confines.^[1] Next were hemicarceplexes, which form kinetically stable complexes in solution, but can release guests without rupture of covalent bonds.^[1b, c, 2] Most recently created were systems that reversibly encapsulate small molecules; these are often called capsules.^[3] Current efforts are underway to create larger and higher order encapsulating species.^[3, 4] We recently reported the first bis-carceplex, where two carceplexes are covalently linked such that one guest molecule is entrapped in each of two adjacent but physically separate chambers.^[4] We report here the corresponding first bis-capsule^[3c] and demonstrate that it forms cooperatively and that the guests can communicate with one another.

The bis-carceplex had been prepared from tetramer **1** by bridging the phenols using CH_2BrCl ,^[4] just as two molecules of tetrol **2** had been bridged to give the prototypical mono-carceplex.^[5] In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), two tetrols were linked by charged hydrogen bonds to yield a reversible capsule.^[6] Under similar conditions, tetramer **1** should be predisposed to form bis-capsule **3**·2 guest (Scheme 1). The ^1H NMR spectra of tetramer **1** and DBU are broad in $[\text{D}_5]\text{nitrobenzene}$ at 373 K, but addition of pyrazine yields a new set of sharp host signals as well as a new signal at $\delta = 5.10$, which we assign to encapsulated pyrazine. Integration yields a ratio of one host (four bowls) to two guest molecules, and the symmetry of the spectrum is similar to that of the bis-carceplex^[4] (Figure 1 shows the ^1H NMR spectrum of **3**·2 CDCl_3 ; see below). Analogous results were obtained using methyl acetate (MeOAc) as guest.

The observation of a single set of signals for the host–guest complex in the presence of a single guest suggests the species corresponding to a 1:1 ratio of host to guest (middle structure in Scheme 1) is not formed in significant quantities at equilibrium. The proposed instability of such a species is



Scheme 1. In the presence of DBU, **1** changes configuration to encapsulate two guest molecules and form **3**·2 guest.

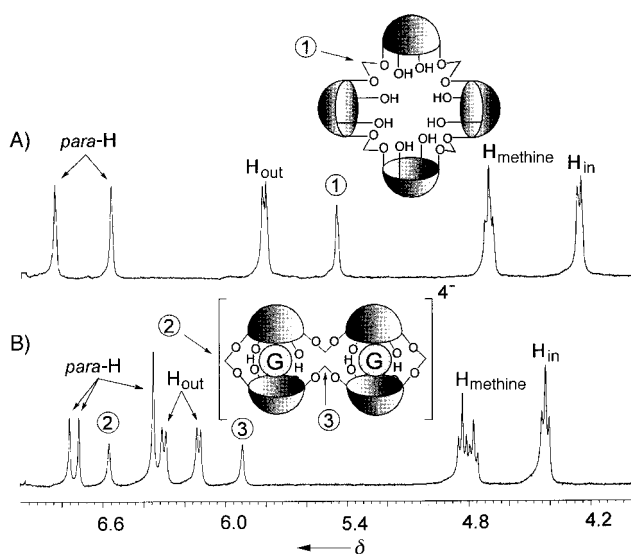


Figure 1. ^1H NMR spectra (400 MHz) of A) tetramer **1** (2.7 mm in $\text{CD}_3\text{OD}/\text{CDCl}_3$ (5/95)) and B) bis-capsule **3**·2 CDCl_3 (2.7 mm tetramer **1**, 11.9 mm DBU in CDCl_3). H_{in} and H_{out} refer to the diastereotopic intra-bowl acetals; para-H refers to H para to OH , O^- , or inter-bowl acetal. The C_4 axis of symmetry in **1** is clearly lost in **3**·2 CDCl_3 .

supported by the following experiment: Recording the ^1H NMR spectra in the presence of mixtures of pyrazine and MeOAc yields a third set of host and guest signals that we assign to the mixed bis-capsule **3**·pyrazine·MeOAc. Integration of all host and guest signals indicates that all capsules are filled. The signals of the guest molecules are shifted by -0.9 , $+0.19$, and $+0.16$ ppm^[7] from their positions in the corresponding bis-capsules **3**·2 pyrazine and **3**·2 MeOAc (see the Supporting Information for full NMR data). Such large $\Delta\delta$ for hetero- versus homo-bis-capsules suggest that it is highly unlikely that all host and guest signals for 1:1 and 1:2 host–guest species would coincide (indeed, the asymmetry of the 1:1 complex alone would not likely yield such simple NMR spectra as those observed). We conclude that the 1:1 complex is not formed to an appreciable extent under any conditions, presumably because it is thermodynamically unfavored; thus formation of the bis-capsules is highly cooperative.^[8] Exami-

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[**] We thank NSERC of Canada and the NIH (GM56104-01) for funding. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial funding. Warm thanks are given to Bob Chapman for helpful discussions and critical reading of the manuscript. We thank Mark Thachuk for help with the K_{rel} calculations.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

nation of Correy–Pauling–Koltun (CPK) models reveals that clamping down of two adjacent bowls of tetramer **1** about a guest forces the remaining two bowls to clamp down due to the short tether between the capsules. Because of the extreme rigidity of the bowls, the clamping would result in an empty cavity (nitrobenzene is too large to fit in such a cavity), which is clearly not going to be thermodynamically stable. Indeed, neither empty mono-capsules nor empty mono-carcerands have ever been observed in the tetrol system.^[5, 6, 9] These results are also consistent with the broad NMR signals obtained in [D₅]nitrobenzene. In the absence of a suitable guest, no well-defined capsules can form, and only aggregates are observed. Similar results have been obtained for the tetrol system.^[6]

Unlike nitrobenzene, chloroform can fit inside the tetrol-based capsules (Figure 1).^[6] Addition of MeOAc to a ¹H NMR sample containing tetramer **1** and DBU in CDCl₃ gave rise to two sets of complexed MeOAc signals ($\delta = -0.57/-2.13$ and $\delta = -0.41/-1.97$). With excess MeOAc, exclusively the latter set of signals is observed, and integration yields 2 MeOAc:1 host; thus we assign this latter signal set to bis-capsule **3**·2 MeOAc and the former signal set to bis-capsule **3**·MeOAc·CDCl₃.^[10]

We have determined the relative guest affinities (K_{rel}) for tetrol-based capsules by performing competition experiments.^[6] Similarly, K_{rel} can be determined for **3**·2 guest. A ¹H NMR sample of tetramer **1** (1.61 mM), DBU (8 mM), and MeOAc (32.2 mM) in CDCl₃ at 298 K showed a mixture of the bis-capsule compounds **3**·2 CDCl₃, **3**·CDCl₃·MeOAc, and **3**·2 MeOAc, in a ratio of 1:4.7:8.6 at equilibrium (Figure 1). From these data, K_{rel} was determined to be 1300.^[11] The corresponding K_{rel} for MeOAc:CDCl₃ in the tetrol-based capsule is 72000 in [D₅]nitrobenzene at 298 K.^[6b] The general trend in guest selectivity holds, as MeOAc is a far better guest in both systems. There is a discrepancy factor of 55 between these data, which may be in part a solvent effect, but such variation is common to non-C₄-symmetric capsules derived from tetrol **2**.^[12] The inter-capsule tether in the bis-capsule may force a small separation between the bowls in each capsule, thus creating a slightly larger cavity, which would better accommodate the larger CDCl₃, and thus diminish the selectivity for MeOAc. The bis-capsule does appear to have a larger cavity than the tetrol system, as MeOAc has restricted motion in the tetrol system,^[6b] but moves freely within the bis-capsules above ambient temperatures.

Communication between guests in adjacent capsules is evident by the difference in chemical shifts of the guests when their neighbor is changed. Table 1 lists the $\Delta\delta$ values for MeOAc in various hetero-bis-capsules. The overall range of these values is 0.31, which is large considering that the pairs of guests are physically separated by two molecular walls. The two sets of $\Delta\delta$ (one for each methyl group of MeOAc) parallel each other, suggesting that the communication is a global one and is not local to one bowl or part thereof. The communication is most likely transmitted through conformational fluctuations as follows: The bowls clamp down tightly on small guests, but are forced to open somewhat when surrounding larger guests.^[5, 9, 13] Since the two capsules are

Table 1. Values of $\Delta\delta$ for MeOAc in bis-capsule **3**·guest·MeOAc in CDCl₃ at 298 K.^[a]

Guest	CH ₃ CO ₂ CH ₃	CH ₃ CO ₂ CH ₃
DMS ^[b]	+0.15	+0.13
1,4-dioxane	+0.15	+0.12
pyrazine	+0.13	+0.11
[D ₆]acetone	+0.05 (+0.09)	+0.03 (+0.07)
DMSO	+0.09	+0.06
MeOAc	0	0
[D ₆]benzene	−0.06 (−0.03)	−0.06 (−0.03)
THF	−0.11	−0.11
CDCl ₃	−0.16	−0.16

[a] $\Delta\delta = \delta(\mathbf{3} \cdot \text{MeOAc} \cdot \text{guest}) - \delta(\mathbf{3} \cdot 2 \text{ MeOAc})$. Values corrected for solvent effects are given in parentheses, as large volumes of these guests were used (**3**·2 MeOAc was used as an internal reference). [b] DMS = dimethyl sulfide.

linked by a short tether, the partial opening of one pair of bowls perturbs the clamping or opening of the other pair. This is consistent with the trend observed in Table 1: The better,^[5, 9] smaller guests generally yield relative downfield shifts in the neighboring MeOAc, while the larger, poorer guests tend to impart upfield shifts. Thus, partial opening of one capsule may allow the other capsule to clamp down more tightly on MeOAc and cause a greater upfield shift. The same trend holds for the guest signals in other complexes: $\delta(\mathbf{3} \cdot \text{MeOAc} \cdot \text{pyrazine}) - \delta(\mathbf{3} \cdot 2 \text{ pyrazine}) = -0.9$ in [D₅]nitrobenzene and $\delta(\mathbf{3} \cdot \text{MeOAc} \cdot \text{CHCl}_3) - \delta(\mathbf{3} \cdot 2 \text{ CHCl}_3) = +0.32$ in CDCl₃/CHCl₃ (1/1), where the MeOAc neighbor allows stronger clamping on the better guest (pyrazine), but weaker clamping on the poorer guest (CHCl₃).

In summary, we have presented the first side-to-side bis-capsules, where guest molecules are reversibly encapsulated in adjacent, but physically separate, chambers. Formation of the bis-capsules is cooperative, as no 1:1 host:guest species was observed. Unprecedented communication between the guest molecules is evident by the neighbor-dependent chemical shifts of encapsulated guests. Such communication may find application in switching devices or as sensors.

Received: May 17, 1999

Revised: August 30, 1999 [Z13431]

- [1] a) D. J. Cram, S. Karbach, Y. H. Kim, L. Baczyński, G. W. Kalley-meyn, *J. Am. Chem. Soc.* **1985**, *107*, 2575–2576; see also: D. J. Cram, *Angew. Chem.* **1988**, *100*, 1041–1052; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009–1020; b) D. J. Cram, J. M. Cram, *Container Compounds and Their Guests*, Royal Society of Chemistry, Cambridge, **1994**; c) J. C. Sherman, *Tetrahedron* **1995**, *51*, 3395–3422; d) A. Jasat, J. C. Sherman, *Chem. Rev.* **1999**, *99*, 931–967.
- [2] M. E. Tanner, C. B. Knobler, D. J. Cram, *J. Am. Chem. Soc.* **1990**, *112*, 1659–1660.
- [3] a) R. Wyler, J. de Mendoza, J. Rebek, Jr., *Angew. Chem.* **1993**, *105*, 1820; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1699–1701; b) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647–1688, and references therein; c) for intriguing polymeric capsules linked tail-to-tail rather than side-to-side, see R. K. Castellano, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 3657–3663; d) J. Yoon, D. J. Cram, *Chem. Commun.* **1997**, 2065–2066.
- [4] N. Chopra, J. C. Sherman, *Angew. Chem.* **1997**, *109*, 1828–1830; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1727–1729.
- [5] J. C. Sherman, C. B. Knobler, D. J. Cram, *J. Am. Chem. Soc.* **1991**, *113*, 2194–2204.

- [6] a) R. G. Chapman, J. C. Sherman, *J. Am. Chem. Soc.* **1995**, *117*, 9081–9082; b) R. G. Chapman, G. Olovsson, J. Trotter, J. C. Sherman, *J. Am. Chem. Soc.* **1998**, *120*, 6252–6260.
- [7] The value -0.9 is $\delta(\text{pyrazine in } \mathbf{3} \cdot \text{pyrazine} \cdot \text{MeOAc}) - \delta(\text{pyrazine in } \mathbf{3} \cdot 2\text{pyrazine})$. The value $+0.19$ is $\delta(\text{CH}_3\text{COCH}_3 \text{ in } \mathbf{3} \cdot \text{pyrazine} \cdot \text{MeOAc}) - \delta(\text{CH}_3\text{COCH}_3 \text{ in } \mathbf{3} \cdot 2\text{MeOAc})$. The value $+0.16$ is $\delta(\text{CH}_3\text{COCH}_3 \text{ in } \mathbf{3} \cdot \text{pyrazine} \cdot \text{MeOAc}) - \delta(\text{CH}_3\text{COCH}_3 \text{ in } \mathbf{3} \cdot 2\text{MeOAc})$.
- [8] For encapsulation of two or more guest molecules in a single large chamber, see a) F. C. Tucci, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 4928–4929; b) R. Meissner, X. Garcias, S. Mecozzi, J. Rebek, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 77–85; c) T. Heinz, D. Rudkevich, J. Rebek, Jr., *Nature* **1998**, *394*, 764–766; d) J. Kang, J. Rebek, Jr., *Nature* **1997**, *385*, 50–52; e) J. Kang, J. Santamaria, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 7389–7390; f) N. Chopra, J. C. Sherman, *Angew. Chem.* **1999**, *111*, 2109–2111; *Angew. Chem. Int. Ed.* **1999**, *38*, 1955–1957.
- [9] a) R. G. Chapman, N. Chopra, E. D. Cochien, J. C. Sherman, *J. Am. Chem. Soc.* **1994**, *116*, 369–370; b) R. G. Chapman, J. C. Sherman, *J. Org. Chem.* **1998**, *63*, 4103–4110.
- [10] The ^1H NMR spectra of **1** and DBU in $\text{CHCl}_3/\text{CDCl}_3$ (1/1) at 298 K gave signals for encapsulated CHCl_3 ($\delta = 5.04$); thus the free species is $\mathbf{3} \cdot 2\text{CHCl}_3$. Upon addition of MeOAc, a new signal for encapsulated CHCl_3 ($\delta = 5.36$) appears, in addition to the new signals of encapsulated MeOAc and host; integration yields $\mathbf{3} \cdot \text{MeOAc} \cdot \text{CHCl}_3$. Cooperativity appears at first to be lost in CDCl_3 , but this is because the second capsule is actually filled with CDCl_3 , which is “invisible” in the ^1H NMR spectra. See the Supporting Information for plots of $[\mathbf{3} \cdot 2\text{CDCl}_3]$, $[\mathbf{3} \cdot \text{MeOAc} \cdot \text{CDCl}_3]$, and $[\mathbf{3} \cdot 2\text{MeOAc}]$ as a function of $[\text{MeOAc}]_{\text{initial}}$.
- [11] The formation of all complexes reported here is reversible; equilibrium is reached in minutes in $[\text{D}_5]\text{nitrobenzene}$ at 373 K and in 24 h in CDCl_3 at 298 K. For calculations of K_{rel} , $[\mathbf{1}]_{\text{initial}} = 1.61 \text{ mM}$; $[\text{MeOAc}]_{\text{initial}} = 32.2 \text{ mM}$; $[\text{CDCl}_3] = 12.5 \text{ M}$; $[\mathbf{3} \cdot \text{CDCl}_3 \cdot \text{MeOAc}] = 0.525 \text{ mM}$; $[\mathbf{3} \cdot 2\text{MeOAc}] = 0.972 \text{ mM}$; $[\mathbf{3} \cdot 2\text{CDCl}_3] = 0.113 \text{ mM}$; $[\text{MeOAc}]_{\text{free}} = 29.7 \text{ mM}$. $K_{\text{rel}} = [\text{cap} \cdot \text{MeOAc}][\text{CDCl}_3]/[\text{cap} \cdot \text{CDCl}_3][\text{MeOAc}]$, where cap = any capsule; for example, $[\text{cap} \cdot \text{MeOAc}] = [\mathbf{3} \cdot \text{CDCl}_3 \cdot \text{MeOAc}] + 2[\mathbf{3} \cdot 2\text{MeOAc}]$. See the Supporting Information for the derivation of this equation.
- [12] R. G. Chapman, J. C. Sherman, *J. Am. Chem. Soc.* **1998**, *120*, 9818–9826.
- [13] R. G. Chapman, J. C. Sherman, *J. Am. Chem. Soc.* **1999**, *121*, 1962–1963.

A Two-Step Spin Crossover in $[(\text{TPA})\text{Fe}^{\text{III}}(\text{cat})]\text{BPh}_4^{*}$

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In our studies of mimics for intradiol catechol dioxygenase^[1] we synthesized $[(\text{TPA})\text{Fe}(\text{cat})]\text{BPh}_4$ (**1**, TPA = tris(2-pyridylmethyl)amine, cat = catechololate dianion), a close analogue of $[(\text{TPA})\text{Fe}(\text{DBC})]\text{BPh}_4$ (**2**, DBC = 3,5-di-*tert*-butyl-

catechololate dianion) prepared first by Que et al.^[2] The latter, in the presence of O_2 , gives a nice example of intradiol dioxygenase activity with cleavage of the intradiol C–C bond.^[2a] As a routine check of the spin state, we measured the magnetic susceptibility of **1** as a function of temperature and discovered that it exhibits a spin crossover,^[3] and moreover one in two steps. We report here the preliminary study of this unusual phenomenon.

Elemental analysis confirmed that complex **1** is consistent with the formula $[(\text{TPA})\text{Fe}(\text{cat})]\text{BPh}_4$ and is unsolvated. The UV/Vis spectrum of **1** in acetonitrile/DMF (9/1) contains two broad ligand–metal charge transfer (LCMT) bands with maxima at 502 nm ($2680 \text{ M}^{-1} \text{ cm}^{-1}$) and 808 nm ($3890 \text{ M}^{-1} \text{ cm}^{-1}$), similar to those observed in other iron(III)-catecholato complexes.^[2b] It may be inferred from this result that the cat ligand chelates the iron(III) ion in an analogous manner to DBC in **2**.^[2a] The structure we propose for **1** is represented in Figure 1.

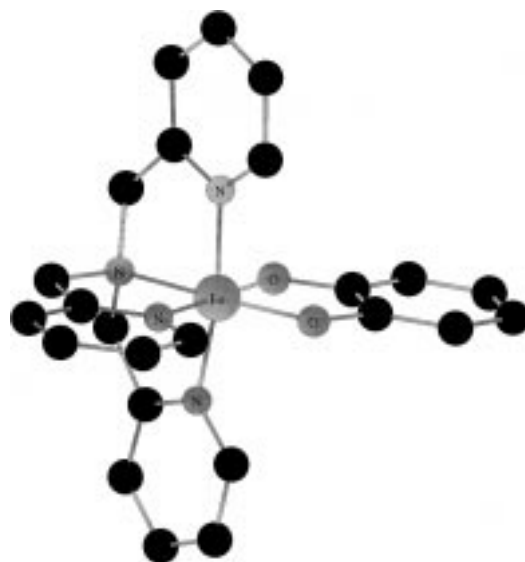


Figure 1. Proposed structure for the $[(\text{TPA})\text{Fe}(\text{cat})]^+$ ion.

The temperature dependence of $\chi_{\text{M}}T$ (χ_{M} = molar magnetic susceptibility) of a microcrystalline sample of **1** (Figure 2) provides evidence for a spin crossover between $S = \frac{1}{2}$ (low spin) and $S = \frac{5}{2}$ (high spin) states of the iron(III) ion.^[4, 5] The expected value of $\chi_{\text{M}}T$ for the high-spin iron(III) ion is $4.375 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$. As the room temperature value of $\chi_{\text{M}}T$ is $4.14 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$, it is expected that most of the iron(III) ions are in the $S = \frac{5}{2}$ state. From the data it can be estimated that about 3% of the molecules are in the low-spin state at room temperature. The value of $\chi_{\text{M}}T$ is $0.49 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$ at 45 K and stays nearly independent of temperature down to 5 K. This value is characteristic of low-spin iron(III) ions and hence of a complete spin conversion at low temperature. These data recorded at decreasing and increasing temperatures did not show any hysteresis effect. Between 45 and 175 K, the $\chi_{\text{M}}T$ versus T curve reveals that the spin-crossover phenomenon takes place in two distinct steps centered at 79 and 106 K (Figure 2, inset). A rather abrupt transformation is observed between 45 and 94 K (80% of the conversion occur within

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[**] Financial supports from the research fund TMR of the European Union (Contracts ERB-FMRX-CT 98-0199) and from the CNRS are gratefully acknowledged.

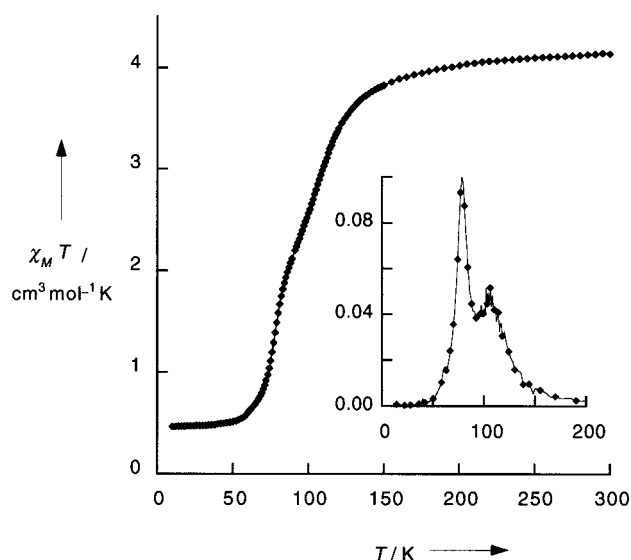


Figure 2. Variation of $\chi_M T$ with temperature for **1**. Inset: The first derivative of the $\chi_M T$ versus T curve.

an approximate 27 K range). Around 94 K ($\chi_M T = 2.32 \text{ cm}^3 \text{ mol}^{-1} \text{ K}$), the transition curve presents an intermediate inflexion point corresponding to a high-spin fraction of about 48 %. The spin crossover at higher temperatures is smoother. The fact that this magnetic behavior was found with different solid samples originating from different preparations allows us to discard the hypothesis of a 1:1 mixture of two crystalline phases exhibiting spin-crossover processes at different temperatures.

Two-step spin-crossover processes have been reported only in a few scarce iron(II) and iron(III) complexes.^[6, 7] One possible origin of this peculiar behavior is the existence of two nonequivalent sites in the unit cell. For some of these compounds^[6b, c, 7] the crystallographic structures at different temperatures substantiated this explanation. The complexes in the two local environments give rise to different spin-crossover processes. To address the origin of the magnetic behavior reported here, efforts are now directed to obtain crystals of **1** suitable for structural determination by X-ray diffraction.

The EPR spectra of **1** in the solid state have been recorded as a function of temperature (Figure 3). At 2.2 K the spectrum ($g_{\parallel} = 1.91$, $g_{\perp} = 2.18$) is characteristic of a low-spin axial iron(III) species.^[4b, 8] This result demonstrates that the low-spin phase corresponds to a low-spin iron(III) catecholate complex. A possible low-spin iron(II) semiquinonate complex is ruled out because no radical-type signal was observed. At higher temperatures, a signal appears at low field while the low-spin signal disappears. It can be inferred from the magnetic data that this low-field signal, broadened by spin-spin interactions, is due to the high-spin fraction. The breadth of the signal forbids the evaluation of the zero-field splitting parameters. At low field and low temperatures, weak resonances are detected that we assigned to high-spin ferric impurities. Under the EPR experimental conditions the signals from these impurities are amplified, which means that they are present in a small

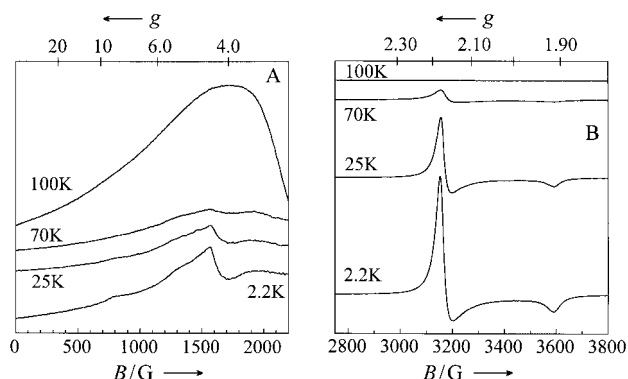


Figure 3. X-band EPR spectra of a powder sample of **1** as a function of temperature (2.2–100 K). A) Low-field region: gain = 10^4 , frequency modulation = 100 kHz, amplitude modulation = 9.466 G, microwave power = $2 \times 10^1 \text{ mW}$; B) high-field region: gain = 10^3 , frequency modulation = 100 kHz, amplitude modulation 4.744 G, microwave power = $5.02 \times 10^{-3} \text{ mW}$.

amount only and hence could not be detected with magnetic measurements.

The magnetic susceptibility of **2**, recorded as a function of the temperature, shows a very smooth spin-crossover process.^[9] This result could be due to the bulkiness of the *tert*-butyl groups which would reduce the cooperativity by keeping molecules separated.

We are now studying this two-step spin-crossover process of **1** by other spectroscopic methods. In particular, we are interested in the analysis of the intense LMCT bands throughout the temperature range of the spin crossover. Chemical variations of this iron(III) catecholate complex will be explored in order to modulate features of the associated spin-crossover process.

Experimental Section

TPA was prepared following the described procedure^[10] but extracted with toluene and recrystallized from *n*-hexane rather than precipitated with HClO_4 .

The synthesis of **1** was performed under an argon atmosphere. Catechol (56 mg, 0.50 mmol) was dissolved in CH_3OH (5 mL) and deprotonated by Et_3N (139 μL , 1 mmol); the solution was added to a mixture of FeCl_3 (80 mg, 0.49 mmol) and TPA (150 mg, 0.51 mmol) in methanol (15 mL). A dark blue, microcrystalline powder was precipitated by adding NaBPh_4 (170 mg, 0.49 mmol) in methanol and collected by filtration (yield 55 %). Elemental analysis: $\text{C}_{22}\text{H}_{17}\text{BF}_6\text{FeN}_4\text{O}_2$ (%): calcd: C 74.49, H 5.47, B 1.42, Fe 7.23, N 7.24; found: C 74.19, H 5.20, B 1.40, Fe 7.15, N 7.39.

Magnetic susceptibility measurements were carried out with a Quantum Design SQUID magnetometer (Model MPMS5S) calibrated against a palladium standard. The independence of the susceptibility value with regard to the applied magnetic field was checked at room temperature. EPR spectra were recorded at several temperatures with a Bruker ESP 300 X-band spectrometer equipped with a Bruker ESR 910 cryostat.

Received: July 21, 1999 [Z13762]

- [1] a) P. Mialane, E. Anxolabéhère-Mallart, G. Blondin, A. Nivorojkine, J. Guilhem, L. Tchertanova, M. Cesario, N. Ravi, E. Bominaar, J. J. Girerd, E. Münck, *Inorg. Chim. Acta* **1997**, 263, 367; b) P. Mialane, L. Tchertanova, F. Banse, J. Sainton, J. J. Girerd, *Inorg. Chem.*, in press; c) P. Mialane, PhD thesis, University of Paris-XI-Orsay (France), **1997**.
- [2] a) H. G. Jang, D. D. Cox, L. Que, Jr., *J. Am. Chem. Soc.* **1991**, 113, 9200; b) D. D. Cox, S. J. Benkovic, L. M. Bloom, F. C. Bradley, M. J. Nelson, L. Que, Jr., D. E. Wallick, *J. Am. Chem. Soc.* **1988**, 110, 2026.

- [3] P. Gütllich, A. Hauser, H. Spiering, *Angew. Chem.* **1994**, *106*, 2109; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2024.
 [4] a) M. F. Tweedle, L. J. Wilson, *J. Am. Chem. Soc.* **1976**, *98*, 16, 4824; b) M. D. Timken, D. N. Hendrickson, E. Sinn, *Inorg. Chem.* **1985**, *24*, 3947.
 [5] W. O. Koch, V. Schünemann, M. Gerdan, A. X. Trautwein, H. J. Krüger, *Chem. Eur. J.* **1998**, *4*, 686.
 [6] a) C. P. Köhler, R. Jakobi, E. Meissner, L. Wiehl, H. Spiering, P. Gütllich, *J. Phys. Chem. Solids* **1990**, *51*, 239; b) D. Boinnard, A. Bousseksou, A. Dworking, J. M. Savariault, F. Varret, J. P. Tuchagues, *Inorg. Chem.* **1994**, *33*, 271; c) Y. Garcia, PhD thesis, University of Bordeaux I (France), **1999**; d) J. A. Real, H. Bolvin, A. Bousseksou, A. Dworkin, O. Kahn, F. Varret, J. Zarembowitch, *J. Am. Chem. Soc.* **1992**, *114*, 4650.
 [7] V. V. Zelentsov, *Sov. Sci. Rev. Sect. B.* **1987**, *10*, 485.
 [8] C. Kim, K. Chen, J. Kim, L. Que, Jr, *J. Am. Chem. Soc.* **1997**, *119*, 5964.
 [9] A. J. Simaan, unpublished results.
 [10] B. G. Gafford, R. A. Holwerda, *Inorg. Chem.* **1989**, *28*, 60.

O–H...Pt^{II}: Hydrogen Bond with a Strong Dispersion Component**

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In the past decade, crystallographic and spectroscopic evidence has accumulated showing that d⁸ metal ions such as platinum(II) are capable of acting as hydrogen-bond acceptors.^[1,2] One may ask whether water could undergo similar hydrogen bond like interactions with solvated platinum complexes. We report here an ab initio study, at the Møller-Plesset second-order perturbation (MP2) level, of the interaction between a water molecule and two platinum(II) complexes [Pt(NH₃)₄]²⁺ (**1**) and *trans*-[Pt(OH)₂(NH₃)₂] (**2**). Our calculations indicate that a linear HO–H...Pt interaction is stabilized by a strong dispersion component. In the case of the HO–H...Pt(NH₃)₄²⁺ interaction, the dispersion component considerably reduces the electrostatic repulsion, while for the HO–H...Pt(OH)₂(NH₃)₂ approach, it adds to the electrostatic attraction, giving rise to a hydrogen bond like interaction with a dissociation energy of about 4 kcal mol^{–1}. It is suggested for the previously reported complex *cis*-[PtBr₂(gly-N)₂]·H₂O (gly = NH₂CH₂COOH) that a similar hydrogen bond between a water molecule and an uncharged platinum central atom occurs in the solid state. Therefore, not

only in anionic but also in electrically neutral platinum(II) complexes can the platinum atom act as a hydrogen-bond acceptor.

Two approaches of a water molecule to **1** or **2** along the z axis (defined as the normal to the platinum coordination plane through the Pt atom) were considered: approach I with the O atom oriented toward Pt and approach II with the O–H vector directed toward Pt, as shown for complex **2** in Figure 1.

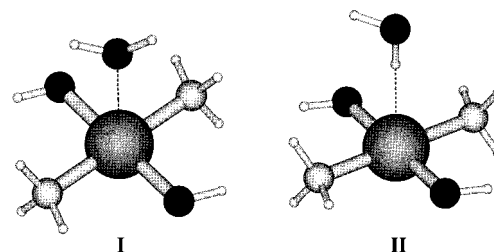


Figure 1. Approaches of H₂O, using complex **2** as an example. Approach I: O atom directed toward Pt; approach II with O–H vector directed toward Pt.

The interaction energies at the Hartree–Fock (E_{HF}) and at the MP2 (E_{MP2}) levels were evaluated as the difference between the total energy of the two interacting species and the sum of the total energies of the individual molecules, corrected for the basis set superposition error. In addition, an estimate of the electrostatic component (E_{ES}) was obtained as the sum of Coulomb terms $q_i q_j / r_{ij}$ between atomic charges determined by optimizing the fit to the MP2 electrostatic potential of the isolated molecules. To an approximation, the interaction energy E_{MP2} can be considered to be the sum of the electrostatic (E_{ES}), exchange-repulsion (E_{EX}), polarization (E_{POL}), and charge-transfer (E_{CT}) components, plus the contribution of electron correlation effects E_{CORR} ^[4–6] (Eq. 1).

$$E_{\text{MP2}} = E_{\text{ES}} + E_{\text{EX}} + E_{\text{POL}} + E_{\text{CT}} + E_{\text{CORR}} \quad (1)$$

It is common practice to associate the interaction energy determined at the Hartree–Fock level E_{HF} with the sum $E_{\text{ES}} + E_{\text{EX}} + E_{\text{POL}} + E_{\text{CT}}$.^[5] The difference $E_{\text{MP2}} - E_{\text{HF}}$ can be therefore used as an estimate for E_{CORR} . In Figure 2, the interaction energies E_{MP2} , E_{HF} , and E_{ES} are plotted against the Pt...O separation, together with the differences $E_{\text{MP2}} - E_{\text{HF}}$ and $E_{\text{HF}} - E_{\text{ES}}$.

Approach I (Figure 2a, b): In approach I, both E_{HF} and E_{MP2} curves quite closely follow the E_{ES} curve at long and intermediate distances, indicating that the interaction is mainly determined by electrostatic (long-range) and exchange-repulsion (short-range) energy. For the approach I/1 the electrostatic energy is negative, giving rise to a profound (–11 kcal mol^{–1}) energy minimum at a Pt...O distance of about 3.3 Å, whereas approach I/2 is purely repulsive. Agreement with the deep minimum for approach I/1 is found in the Cambridge Crystallographic Data Centre (CCDC), which contains several entries of dicationic platinum(II) tetraamine complexes with axial water ligands at distances between 3 and 3.5 Å. The structure of [Pt(py)₄]Cl₂·3H₂O (py = pyridine), determined by neutron diffraction,^[7] (Figure 3) for example, features a square-planar PtN₄ coordination, which is extended

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[**] We are indebted to Drs. J. Langlet, P. Pyykkö, A. Pullman, J. Caillet, and C. Giessner-Prettre for stimulating discussions and helpful comments. Computer time from the IDRIS center of CNRS is gratefully acknowledged.

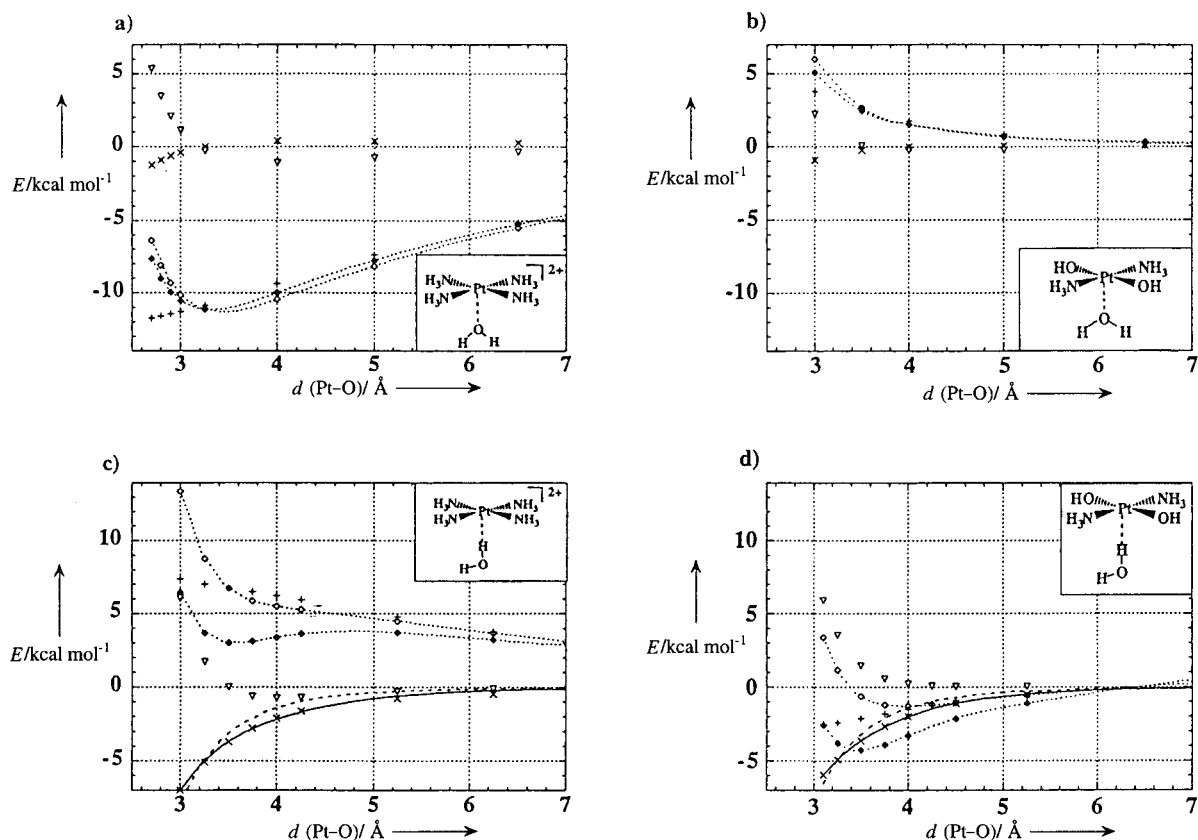


Figure 2. Plots of the interaction energy and its components E_{HF} (---◇---), E_{MP2} (---◆---), E_{ES} (+), $E_{\text{HF}} - E_{\text{ES}}$ (▽), $E_{\text{MP2}} - E_{\text{HF}}$ (×), and fits to the $E_{\text{MP2}} - E_{\text{HF}}$ curves using a single $-C_6d^{-6}$ term (----) and a Buckingham function $Ce^{-\alpha(d-d_0)} - C_6d^{-6}$ ($d_0 = 3.5$ Å) (—). Approaches: a) I/1; b) I/2; c) II/1; d) II/2.

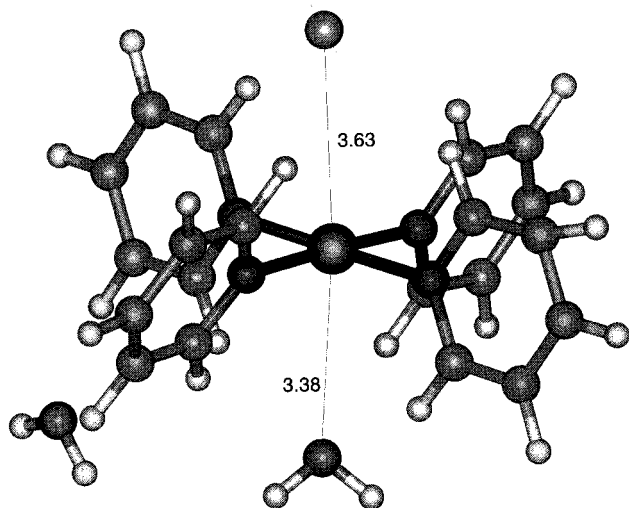


Figure 3. Crystal structure of $[\text{Pt}(\text{py})_4]\text{Cl}_2 \cdot 3\text{H}_2\text{O}$ (CCDC entry CIWKEY01).^[7, 28] Distances are in Å.

to a pseudo-octahedron by axial chloride and water ligands. Water is coordinated to platinum through the oxygen lone pairs with a $\text{Pt} \cdots \text{O}$ distance of 3.38 Å, close to the optimum distance of 3.3 Å that we calculated for the $\text{H}_2\text{O} \cdots \text{Pt}(\text{NH}_3)_4^{2+}$ (I/1) interaction.

Approach II (Figure 2c, d): In contrast to approach I, the E_{HF} and E_{MP2} curves differ considerably in approach II,

indicating that E_{CORR} is much more important. The E_{MP2} curves show pronounced minima at a $\text{Pt} \cdots \text{O}$ distance of about 3.5 Å, which were not observed in the E_{HF} curves. The electrostatic components of the approaches II/1 and II/2 have inverted signs with respect to the approaches I/1 and I/2. Thus, for approach II/1 the E_{MP2} energy is positive throughout, in spite of the local minimum at about 3.5 Å. In contrast, for approach II/2, this minimum corresponds to a bound state with a dissociation energy of about 4 kcal mol⁻¹. Importantly, the $E_{\text{MP2}} - E_{\text{HF}}$ curves, which provide an estimate for E_{CORR} , are almost superimposable for II/1 and II/2. This indicates that E_{CORR} is independent of the charge on the platinum complex and suggests that dispersion energy is the main contributor to E_{CORR} . Ionic contributions to E_{CORR} , which have been shown to be significant, for example, in the case of water clusters,^[8] and second-order induction terms would be expected to be different for II/1 and II/2, and can therefore play only a minor role. Figures 2c, d show that the $E_{\text{MP2}} - E_{\text{HF}}$ curves fit poorly to a $-C_6d^{-6}$ function, but they fit perfectly to a Buckingham function $Ce^{-\alpha(d-d_0)} - C_6d^{-6}$ ($d_0 = 3.5$ Å). The need for a *positive* exponential term suggests that apart from the pure dispersion energy E_{DISP} proportional to d^{-6} , we have a significant dispersion-exchange cross-term $E_{\text{DISP-EX}}$. A similar partial compensation of E_{DISP} by an $E_{\text{DISP-EX}}$ term has been found in other weakly bound systems such as hydrogen-bonded clusters of H_2O , NH_3 , and HF molecules,^[9] as well as clusters of gold(i) complexes displaying *aurophilic* attrac-

tion.^[10] Higher order terms to E_{DISP} , proportional to d^{-8} , d^{-10} , and so forth, whose minor contributions cannot be a priori excluded, have a *negative* sign.

The observation of a bound state at a Pt...O distance of about 3.5 Å for approach II/2 is particularly interesting, since it indicates that not only anionic but even uncharged platinum(II) complexes should undergo hydrogen bonding like associations. The CCDC lists a large number of uncharged and anionic platinum complexes with water of crystallization, and we searched for examples that showed indications of HO–H...Pt hydrogen bonding. This search revealed that water in platinum complex crystals overwhelmingly prefers hydrogen-bonding contacts with ligand atoms to those with the platinum central atom.^[11] Nevertheless, Figure 4 shows the crystal structure of the complex *cis*-[PtBr₂(gly-N)₂]·H₂O^[12] in which we believe HO–H...Pt hydrogen

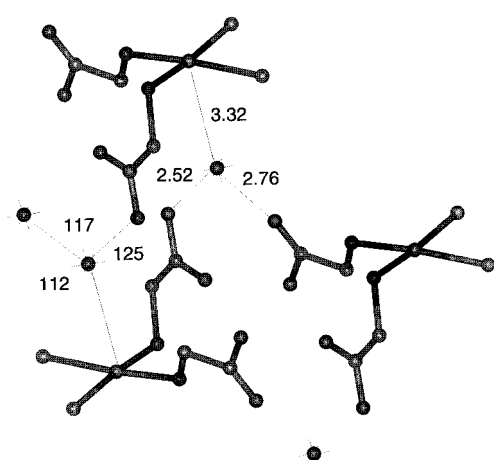


Figure 4. Crystal packing of *cis*-[PtBr₂(gly-N)₂]·H₂O (CCDC entry BGLYPT^[12, 28]). Distances are in Å, angles in degrees.

bonding does occur. In this structure, the oxygen atom of water lies 3.32 Å above the platinum atom, the Pt...O vector subtending an angle of 82° with the mean PtBr₂N₂ plane. Apart from the short contact to platinum, the oxygen atom of the water molecule forms a hydrogen bond with a glycine hydroxy group of a second complex molecule (O...O 2.52 Å), and one with a carbonyl oxygen atom of a third molecule (O...O 2.76 Å). The carbonyl and hydroxy groups of the uncoordinated carboxylates are clearly distinguished in the crystal structure. Since the hydrogen atoms could not be localized the use of crystal structure analysis alone does not allow one to conclude that the second hydrogen atom of the water molecule points towards the platinum center. However, our calculations for the approach between the electrically neutral complex **2** and water strongly suggest that such is the case, since the coordination of platinum by hydrogen (approach II) is attractive, whereas that by the lone pair of electrons of oxygen (approach I) is repulsive.

Although no Morokuma analysis^[13] of the HF energy was performed, some qualitative statements about the size of E_{POL} and E_{CT} can be made from the differential $E_{\text{HF}} - E_{\text{ES}}$ curves. The polarization energy is expected to be considerably stronger for the cationic complex **1** than for the uncharged

species **2**. In fact, the $E_{\text{HF}} - E_{\text{ES}}$ curves, which represent the sum $E_{\text{EX}} + E_{\text{POL}} + E_{\text{CT}}$, show shallow minima (ca. -1 kcal mol^{-1}) at a Pt...O distance of about 4 Å for both approaches of water to complex **1** (Figure 2a, c), whereas the analogous curves for complex **2** (Figure 2b, d) show virtually no minima at all. This suggests that the contributions of E_{POL} to the water interaction of complex **1** are rather small, and those of species **2** are negligible. Furthermore, the absence of minima in the $E_{\text{HF}} - E_{\text{ES}}$ curves in Figure 2b, d indicates that the E_{CT} component is insignificant throughout.

Some of the best characterized H...Pt hydrogen bonds reported so far are N–H...Pt bonds from a quaternary ammonium group to a formally monoanionic platinum atom.^[1, 2] In these complexes the strong electrostatic attraction enhances the binding interaction. Calculations on the model system $\text{NH}_4^+ \cdots [\text{PdCl}(\text{CH}_3)_2(\text{NH}_3)]^-$ at the CAS-SCF level did not reveal any significant orbital interactions,^[14] in agreement with our results for the HO–H...Pt interaction, which suggest that stabilization due to electron transfer is small. (However, the orbital interaction is sufficient to give rise to $^{195}\text{Pt} - ^1\text{H}$ spin–spin coupling which was detected in some cases.^[2, 3, 15]) Intramolecular O–H...Pt hydrogen bonding has been reported for the anions $[\text{Pt}(\text{C}_6\text{F}_5)_3\text{L}]^-$ (L = 8-hydroxyquinoline, 8-hydroxyquinoline).^[3] Our calculations presented in this work suggest that the O–H...Pt interaction has a non-negligible dispersion component. This dispersion component significantly contributes to the energetics of interactions between water and platinum(II) and should therefore be taken into account in force-field studies of solvated platinum(II) complexes.

One referee pointed out that the value of about 4 kcal mol^{-1} determined for E_{CORR} of the HO–H...Pt interaction at the energy minimum may be exaggerated because MP2 calculations are known to overestimate the correlation contributions, and suggested a single-point CCSD or CCSD(T) calculation as a check. While it is correct that MP2 calculations generally yield too high estimates for E_{CORR} , we wish to emphasize that CCSD(T) and especially CCSD calculations may *underestimate* the correlation energy. For instance, supermolecular MP2 calculations on Xe₂ by Runeberg and Pyykkö overestimated the dissociation energy much less heavily (thanks to compensation of errors) than CCSD and CCSD(T) calculations underestimated it.^[16] A refinement of our value for E_{CORR} could consist in a series of correlated calculations, such as MP2, MP3, MP4, CCSD, and CCSD(T), as applied by Pyykkö et al to the model system $[\{\text{HAu}(\text{PH}_3)_2\}_2]$.^[17] Such a series would hopefully converge towards the correct value of E_{CORR} . Such a project was clearly out of the scope of the present paper.

Computational Methods

MP2 calculations^[18] were performed using GAUSSIAN94^[19] on a Cray C98 computer. The Dolg–Pélissier pseudopotential/pseudorbital basis set including two polarization f orbitals^[20, 21] was used for Pt, whereas the N, O, and H atoms were represented by the 6-311++G(2p,2d) all-electron basis. The geometries of **1**, **2**, and H₂O were optimized at the MP2 level using the same orbital bases, except that the f orbitals of Pt were excluded. D_{2h} symmetry was imposed to **1**, C_{2h} to **2**, and C_{2v} to H₂O. For the water interaction calculations with **1** and **2**, H₂O was oriented to lie in the bisector

of the N-Pt-N and N-Pt-O angles for approaches I and II, respectively, as shown for **2** in Figure 1. To assess the effect of nuclear relaxation, we re-optimized the geometry of **2** during H₂O approach II at the E_{MP2} minimum (Pt...O 3.5 Å). The energy gain from nuclear relaxation amounted to $-0.05 \text{ kcal mol}^{-1}$ and was considered negligible. The geometry of the systems was therefore not re-optimized. The basis set superposition error (BSSE) was evaluated using the counterpoise method^[22, 23] for the approaches I/2 and II/2. For the interactions of **1**, the BSSE was assumed to be the same as for the corresponding approach of **2** at the same Pt...O distance. The atomic charges used for the estimation of E_{ES} were determined from fits to the MP2 electrostatic potential for the isolated species using the Merz–Kollman routine^[24] implemented in GAUSSIAN94, with a van der Waals radius of 2.3 Å for Pt. A check calculation using the CHELPG routine^[25] yielded only slightly different E_{ES} curves. The CCDC crystal structures (Figures 3, 4) were drawn using the program Insight II.^[26]

Received: May 28, 1999

Revised: September 10, 1999 [Z13481]

- [1] L. Brammer, J. M. Charnock, P. L. Goggin, R. J. Goodfellow, A. G. Orpen, T. F. Koetzle, *J. Chem. Soc. Dalton Trans.* **1991**, 1789–1798.
- [2] P. S. Pregosin, H. Rüegger, F. Wombacher, G. van Koten, D. M. Grove, I. C. M. Wehman-Ooyevaar, *Magn. Reson. Chem.* **1992**, *30*, 548–551.
- [3] J. M. Casas, L. R. Falvello, J. Forníes, A. Martín, A. J. Welch, *Inorg. Chem.* **1996**, *35*, 6009–6014.
- [4] P. Hobza, R. Zahradník, *Chem. Rev.* **1988**, *88*, 871–897.
- [5] A. D. Buckingham, P. W. Fowler, J. M. Hutson, *Chem. Rev.* **1988**, *88*, 963–988.
- [6] The physical meaning of the individual components is as follows: E_{ES} is the electrostatic interaction of the unperturbed charge distributions of the individual molecules placed at the given distance; E_{POL} is the stabilization arising from relaxation of the electrons of one molecule due to the electric field of the other molecule, without orbital interactions taking place; E_{CT} is the interaction energy due to transfer of electrons from occupied orbitals of one molecule to unoccupied orbitals of the other molecule.
- [7] C. H. Wei, B. E. Hingerty, W. R. Busing, *Acta Crystallogr. Sect. C* **1989**, *45*, 26–30.
- [8] M. Schütz, G. Rauhut, H.-J. Werner, *J. Phys. Chem.* **1998**, *102*, 5997–6003.
- [9] J. Langlet, J. Caillet, M. Caffarel, *J. Chem. Phys.* **1995**, *103*, 8043–8057.
- [10] N. Runeberg, M. Schütz, H.-J. Werner, *J. Chem. Phys.* **1999**, *110*, 7210–7215.
- [11] For instance, the crystal structure of the dihydrate of **2** reveals a network of hydrogen bonds connecting the hydroxide ligands of platinum with the crystal water molecules.^[27] No short Pt...O contacts occur in this structure. One factor generally favoring the ligands over the platinum central atom as hydrogen-bonding acceptors is certainly their good accessibility at the edges of the complex.
- [12] I. A. Baidina, N. V. Podberezskaya, S. V. Borisov, N. A. Shestakova, U. F. Kyklina, G. D. Mal'chikov, *Zh. Strukt. Khim.* **1979**, *20*, 548–551.
- [13] K. Morokuma, *Acc. Chem. Res.* **1977**, *10*, 294–300.
- [14] I. C. M. Wehman-Ooyevaar, D. M. Grove, H. Kooijman, P. van der Sluis, A. L. Spek, G. van Koten, *Inorg. Chem.* **1992**, *31*, 5484–5493.
- [15] D. Hedden, D. M. Roundhill, W. C. Fultz, A. L. Rheingold, *Organometallics* **1986**, *5*, 336–343.
- [16] N. Runeberg, P. Pykkö, *Int. J. Quantum Chem.* **1997**, *66*, 131–140.
- [17] P. Pykkö, N. Runeberg, F. Mendizabal, *Chem. Eur. J.* **1997**, *3*, 1451–1457.
- [18] C. Möller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618–622.
- [19] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian Inc., Pittsburgh, PA, USA **1995**.

- [20] D. Andrae, U. Häussermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, *77*, 123–141.
- [21] J. Kozelka, J. Bergès, *J. Chim. Phys. Phys. Chim. Biol.* **1998**, *95*, 2226–2240.
- [22] S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553–566.
- [23] F. B. van Duijneveldt, J. G. C. M. van Duijneveldt-van de Rijdt, J. H. van Lenthe, *Chem. Rev.* **1994**, *94*, 1873–1885.
- [24] B. H. Besler, K. M. Merz, Jr., P. A. Kollman, *J. Comput. Chem.* **1990**, *11*, 431–439.
- [25] C. M. Breneman, K. B. Wiberg, *J. Comput. Chem.* **1990**, *11*, 361–373.
- [26] Insight II, Biosym/MSI, San Diego, CA, USA **1996**.
- [27] J. Arpalähti, R. Sillanpää, K. J. Barnham, P. J. Sadler, *Acta Chem. Scand.* **1996**, *50*, 181–184.
- [28] F. H. Allen, O. Kennard, *Chemical Design Automation News* **1993**, *8*, 1–37.

Investigations of Thin Films with Amphiphilic Dendrimers Bearing Peripheral Fullerene Subunits**

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Dedicated to Dr. Antoine Skoulios
on the occasion of his 65th birthday

The preparation and study of fullerene derivatives are being intensively pursued, with the aim of generating new supramolecular assemblies and advanced materials.^[1] Incorporation of fullerenes into thin ordered films appears as an important issue in the applications of this carbon allotrope.^[2] However, monolayers of fullerene itself at the air–water interface are difficult to achieve due to strong fullerene–fullerene interactions and three-dimensional aggregation, and all attempts to create defined Langmuir–Blodgett (LB) multilayers of fullerenes have failed.^[3, 4] Whereas functionalization of the fullerene sphere with hydrophilic addends leads to significant improvements,^[4, 5] fullerene derivatives with good spreading characteristics and reversible compression/expansion behavior are quite rare.^[6, 7] In a collaborative work among the research groups of Diederich, Stoddart, Echegoyen, and Leblanc, dendrimers with a fullerene core and peripheral acylated glucose units have been investigated.^[6] These derivatives show reversible behavior of fullerene monolayers in successive compression/decompression cycles, the dendritic portion preventing the irreversible aggregation

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[**] This work was supported by the CNRS. We thank Dr. A. Skoulios for helpful discussions and L. Oswald for technical help.

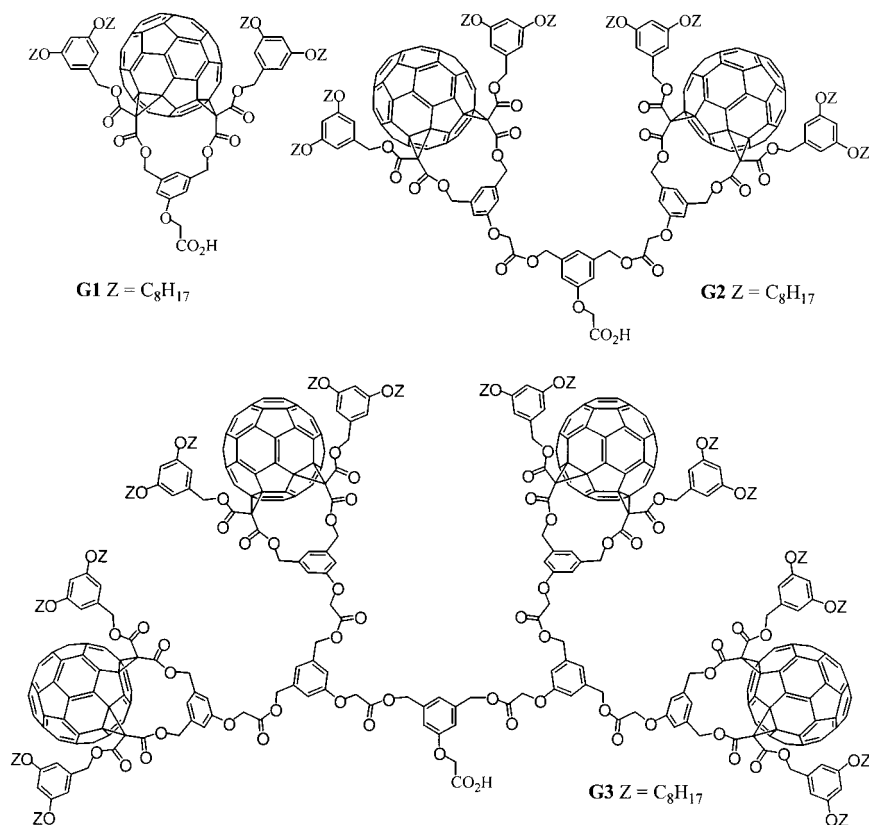
Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

of the fullerene moieties. We have recently shown that the encapsulation of the fullerene sphere in a cyclic addend also prevents the aggregation encountered with amphiphilic fullerene derivatives.^[7] As a part of this research, we now report on investigations of Langmuir and LB films of the amphiphilic dendrimers with peripheral fullerene units **G1**–**G3**.^[8] Whereas Langmuir films with dendrimers have been reported, the incorporation of dendrimers in LB films has been

up to $\Pi \approx 20 \text{ mN m}^{-1}$, the collapse of the film indicated by a change of compressibility, while the **G2** film begins to collapse around 30 mN m^{-1} . These isotherms are perfectly reversible upon multiple compression–decompression cycles and no hysteresis is observed as long as the collapse pressure is not exceeded. The molecular areas for **G1**–**G3**, extrapolated to zero pressure, are $140 \pm 7 \text{ \AA}^2$, $310 \pm 15 \text{ \AA}^2$, and $560 \pm 30 \text{ \AA}^2$, respectively. The values are in the expected 1:2:4 proportion

given the structure of the dendrimers, and are in good agreement with the values estimated by molecular modeling.

The spreading behavior of **G1**–**G3** shows no significant dependence on compression speed or temperature up to 50°C . Observation of the Langmuir films by Brewster angle microscopy (BAM) shows high-quality films for all compounds (Figure 2). When the surface pressure reaches $\Pi \approx 10 \text{ mN m}^{-1}$, and as long as the films do not enter the collapse regime $\Pi \approx 20 \text{ mN m}^{-1}$, only homogeneous surfaces were observed. Figure 2a shows a BAM image of the **G1** film at a molecular area $A \approx 180 \text{ \AA}^2$. All the water surface is covered with molecules, except for small circular domains (black regions), which shrink and disappear when $A \approx 140 \text{ \AA}^2$. Figure 2b shows the films become uniform. The stripes that can be seen are interferences due to the laser light. Contrary to **G1**, **G2** and



scarcely considered.^[6,9] Compounds **G1**–**G3** are all able to form stable Langmuir films at the air–water interface, and a reversible compression/decompression behavior has been observed for all compounds. The Langmuir films of **G1** and **G3** were transferred, forming LB films with high efficiency, in spite of a molecular mass of $7704.6 \text{ g mol}^{-1}$ (**G3**).

Compounds **G1**–**G3** form high-quality Langmuir films at the air–water interface. Isotherms taken at 20°C are depicted in Figure 1. Compounds **G1** and **G3** can withstand pressures

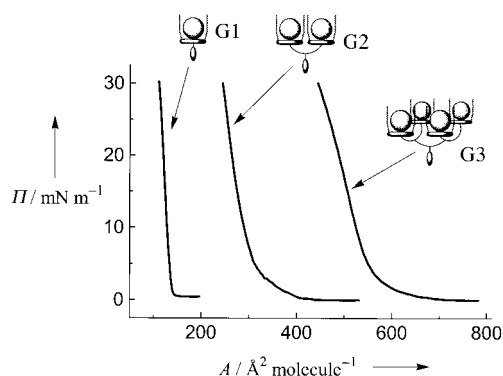


Figure 1. Pressure (Π)–area (A) isotherms for **G1**, **G2**, and **G3** (shown schematically) at 20°C .

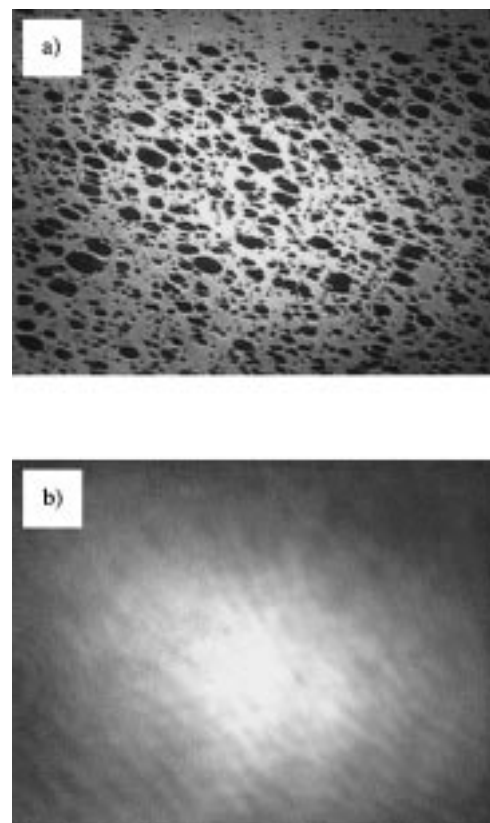


Figure 2. Brewster angle microscopy images for **G1** at $A \approx 180 \text{ \AA}^2$ (a), $A \approx 150 \text{ \AA}^2$ (b).

G3 do not spread uniformly and the molecules spontaneously form islands which are almost defectless. Upon compression, these islands coalesce, yielding good-quality films (the BAM picture of the **G2** and **G3** films at the end of the compression looks exactly like the picture depicted in Figure 2b for **G1**). We emphasize that in spite of the fact that the **G2** and **G3** molecules seem to aggregate when they are spread on water, the isotherms are perfectly reversible as long as Π remains below 20 mN m^{-1} .

Although we could not succeed in transferring the **G1**–**G3** monolayers on hydrophilic substrates, we have been able to easily transfer **G1** and **G3** onto silicon or glass substrates covered with a monolayer of octadecyltrichlorosilane. The transfer ratios (TR) for the first layer were 1.0 ± 0.05 for **G1** and 0.8 ± 0.1 for **G3**, while subsequent layers had a slightly smaller TR (0.9 for **G1** and 0.7 for **G3**). Since the Langmuir films were stable, this should indicate defects were present. Nevertheless, all LB films had a very good appearance, with a uniform brown color for the multilayer films. Films of **G1** gave the best results, followed by **G3**. It was not obvious that a large molecule such as **G3** would allow for the processing of LB films. Compound **G2** could not be transferred by the vertical dipping method (LB), due, we believe, to the lack of rotational symmetry of this molecule. Effectively, **G1** and **G3** are cone-shaped, while **G2** is fanlike. A monolayer of **G2** was deposited on a hydrophilic silicon substrate by the Langmuir–Schaefer (LS) method.^[10]

Figure 3 shows the grazing X-ray patterns for two LB films of **G1**. The monomolecular film shows only two Kiessig fringes, the best fit giving a thickness of $21.0 \pm 0.5 \text{ Å}$ and a roughness of about 4 Å . The expected average layer thickness

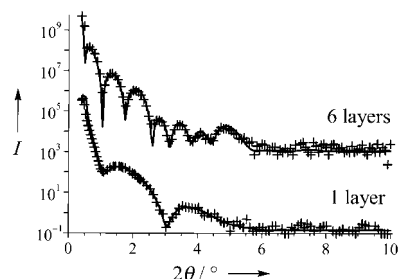


Figure 3. Grazing incidence X-ray patterns for LB films of **G1** (6 layers: upper curve; 1 layer: lower curve), together with the best fit (continuous line) to the data. Overall thickness and film roughness, as deduced from the fits, are $21.0 \pm 0.5 \text{ Å}$ and 4 Å for the 1-layer film, and $104 \pm 1 \text{ Å}$ and 6 Å for the 6-layer film (see text). Not all data points are plotted and the upper curve has been shifted for clarity.

was found to be somewhat smaller than 21 Å for the multilayer films, which is surprising since all layers have the same quality and an almost constant transfer ratio. This apparent contradiction is solved if the overall thickness of multilayer films is measured as a function of the number of layers. Odd layers (downstroke) increase the film thickness by 21 Å , whereas even layers (upstroke) increase by only 17 Å . We believe that this indicates that the molecules of even layers do not deposit atop odd ones, but partially wedge themselves in between (Figure 4). Molecular modeling shows this is indeed reasonable, and suggests that intermolecular

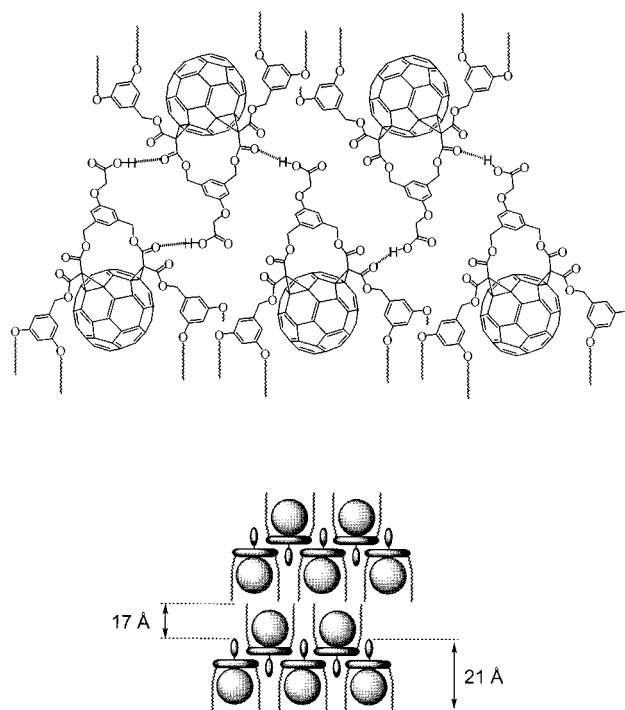


Figure 4. Schematic model of the structure of the multilayer LB films.

hydrogen bonds could take place as schematically depicted in Figure 4 providing additional stabilization of the films. The IR spectra of the multilayer films of **G1** show a signal at 3340 cm^{-1} , in good agreement with the presence of such hydrogen bonds.^[11]

For multilayer films, the presence of low-angle Kiessig fringes indicate that the overall quality of the films is good. Atomic force microscope (AFM) observations using the tapping mode performed on a 13-layer LB film showed, on average, only one defect higher than 5 nm on a $1.25 \times 1.25 \mu\text{m}^2$ area (see Supporting Information). Even if the inner structure of thick films is more poorly defined due to rather high roughness, the feature around $2\theta \approx 5^\circ$ in the X-ray pattern of the 6-layer film indicates the emergence of a Bragg peak. This peak corresponds to an average layer spacing of $\approx 18 \text{ Å}$, in agreement with simulations of the electronic density along the z axis calculated according to the model proposed in Figure 4. The broadness of the peak can be ascribed to the small number of layers. Lastly, a plot of the UV/Vis absorbance, obtained from the spectra of the LB films against the layer number, results in a straight line, indicating effective stacking of the layers. In fact, the **G1** films could be considered as self-healing, a subsequent layer being able to compensate for an imperfect previous one, leading to a macroscopically homogeneous film.

In conclusion, we have shown that fullerene-based amphiphilic dendrimers can form stable Langmuir films and some of them can be readily transferred onto solid substrates, yielding high-quality LB films. The preparation of mixed LB films using those fullerene-based derivatives and amphiphilic conjugated oligomers is now under investigation for photovoltaic applications. Special emphasis is placed on the control of the film morphology for a better understanding of the photovoltaic device performances.

Experimental Section

The synthesis of **G1–G3** has been recently reported.^[8]

Langmuir and LB films: Spreading solutions were prepared by dissolving **G1–G3** in CHCl_3 (1.0–3.0 mg mL^{-1}). Stock solutions proved stable for several months at room temperature. Stock solution (50 μL) was spread on the water surface with a microsyringe, and the film was left for 15–20 min to equilibrate before the compression was started. Data were collected with a KSV LB5000 system (KSV Instruments, Helsinki, Finland) using a symmetrical compression Teflon trough and hydrophilic barriers in a dust-free environment. The whole setup was in a Plexiglas enclosure resting on a vibration-free table, and the trough temperature was controlled to $\pm 0.1^\circ\text{C}$. All isotherms were taken at 20°C unless otherwise specified. Ultra pure water ($\rho = 18.2 \text{ M}\Omega\text{cm}^{-1}$) obtained from a Milli-RO3 Plus system combined with a Milli-Q185 Ultra Purification system from Millipore was used for the subphase. Surface pressure was measured by the Wilhelmy plate method. The monolayers were compressed with speeds ranging from 1.2 to 10 $\text{\AA}^2\text{molecule}^{-1}\text{min}^{-1}$, with almost no incidence of the barrier velocity on the observed behavior.

LB films were obtained by transfer on glass slides or silicon wafers (100) rendered hydrophobic through silanization of the surface with octadecyltrichlorosilane. The vertical dipping method was used for **G1** and **G3**, while **G2** could only be transferred with the horizontal (LS) method. Dipping parameters were not very stringent and usually kept around the following values: trough $30\text{--}40^\circ\text{C}$, dipping speed $\approx 0.5\text{--}4 \text{ mm min}^{-1}$. Transfers were performed at surface pressures 12, 15, and 22 mN m^{-1} for **G1**, **G2**, and **G3**, respectively. It has been possible to build Y-type multilayer films of **G1** and **G3**.

Grazing incidence X-ray analysis (GIXA): The studies of LB films were performed on a X'PERT-MPD device (Philips), equipped with a programmable divergence slit ($1/32^\circ$), a Soller slit collimator, a flat Ge monochromator, and proportional Xe detector. A nickel-filtered $\text{Cu}_{\text{K}\alpha}$ line ($\lambda = 0.1542 \text{ nm}$) was used.

All measurements were recorded immediately after the film transfer, but the diffraction patterns remained stable for as long as several weeks without special care being taken for the storage of the film.

BAM: BAM was performed using a BAM2plus (Nanofilm Technologies GmbH) illuminated by an Ar laser. Images were recorded on a CCD camera of field $620 \mu\text{m} \times 500 \mu\text{m}$.

Received: May 17, 1999

Revised: August 26, 1999 [Z13426]

- [1] A. Hirsch, *The Chemistry of the Fullerenes*, Thieme, Stuttgart, **1994**; F. Diederich, C. Thilgen, *Science* **1996**, 271, 317–323; M. Prato, *J. Mater. Chem.* **1997**, 7, 1097–1109; L. Echegoyen, L. E. Echegoyen, *Acc. Chem. Res.* **1998**, 31, 593–601.
- [2] L. B. Gan, D. J. Zhou, C. P. Luo, C. H. Huang, T. K. Li, J. Bai, X. S. Zhao, X. H. Xia, *J. Phys. Chem.* **1994**, 98, 12459–12461; D. A. Leigh, A. E. Moody, F. A. Wade, T. A. King, D. West, G. S. Bahra, *Langmuir* **1995**, 11, 2334–2336; C. A. Mirkin, W. B. Caldwell, *Tetrahedron* **1996**, 52, 5113–5130, and references therein; P. Wang, Y. Maruyama, R. M. Metzger, *Langmuir*, **1996**, 12, 3932–3937; M. I. Sluch, I. D. W. Samuel, A. Beedy, M. C. Petty, *Langmuir* **1998**, 14, 3343–3346; Y. Huang, Y. Zhao, L. Gan, C.-H. Huang, N. Wu, *J. Colloid Interface Sci.* **1998**, 204, 277–283.
- [3] For examples, see Y. S. Obeng, A. J. Bard, *J. Am. Chem. Soc.* **1991**, 113, 6279–6280; T. Nakamura, H. Tachibana, M. Yumura, M. Matsumoto, R. Azumi, M. Tanaka, Y. Kawabata, *Langmuir* **1992**, 8, 4–6; R. Back, R. B. Lennox, *J. Phys. Chem.* **1992**, 96, 8149–8152; J. Milliken, D. D. Dominguez, H. H. Nelson, W. R. Barger, *Chem. Mater.* **1992**, 4, 252–254; F. Diederich, J. Effing, U. Jonas, L. Jullien, T. Plesnivý, H. Ringsdorf, C. Thilgen, D. Weinstein, *Angew. Chem.* **1992**, 104, 1683–1686; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 1599–1602.
- [4] U. Jonas, F. Cardullo, P. Belik, F. Diederich, A. Gügel, E. Harth, A. Herrmann, L. Isaacs, K. Müllen, H. Ringsdorf, C. Thilgen, P. Uhlmann, A. Vasella, C. A. A. Waldruff, M. Walter, *Chem. Eur. J.* **1995**, 1, 243–251, and references therein.

- [5] For examples, see L. M. Goldenberg, G. Williams, R. M. Bryce, A. P. Monkman, M. C. Petty, A. Hirsch, A. Soi, *J. Chem. Soc. Chem. Commun.* **1993**, 1310–1312; M. Maggini, A. Karisson, L. Pasimeni, G. Scorrano, M. Prato, L. Valli, *Tetrahedron Lett.* **1994**, 35, 2985–2988; C. J. Hawker, P. M. Saville, J. W. White, *J. Org. Chem.* **1994**, 59, 3503–3505; M. Maggini, L. Pasimeni, M. Prato, G. Scorrano, L. Valli, *Langmuir* **1994**, 10, 4164–4166; S. Ravaine, F. Le Pecq, C. Mingotaud, P. Delhaes, J. C. Hummelen, F. Wudl, L. K. Patterson, *J. Phys. Chem.* **1995**, 99, 9551–9557; C. C. Zhu, Y. Xu, Y. Q. Liu, D. B. Zhu, *J. Org. Chem.* **1997**, 62, 1996–2000.
- [6] F. Cardullo, F. Diederich, L. Echegoyen, T. Habicher, N. Jayaraman, R. M. Leblanc, J. F. Stoddart, S. Wang, *Langmuir* **1998**, 14, 1955–1959.
- [7] J.-F. Nierengarten, C. Schall, J.-F. Nicoud, B. Heinrich, D. Guillon, *Tetrahedron Lett.* **1998**, 39, 5747–5750.
- [8] J.-F. Nierengarten, D. Felder, J.-F. Nicoud, *Tetrahedron Lett.* **1999**, 40, 269–272.
- [9] For examples of Langmuir films of dendrimers, see P. M. Saville, J. W. White, C. J. Hawker, K. L. Wooley, J. M. J. Fréchet, *J. Phys. Chem.* **1993**, 97, 293–294; O. Karthaus, K. Ijro, M. Shimomura, *Langmuir* **1996**, 12, 6714–6716; A. P. H. J. Schenning, C. Elissen-Roman, J.-W. Weener, M. W. P. L. Baars, S. J. van der Gaast, E. W. Meijer, *J. Am. Chem. Soc.* **1998**, 120, 8199–8208; Z. Bo, X. Zhang, X. Yi, M. Yang, J. Shen, Y. Rehn, S. Xi, *Polym. Bull. (Berlin)* **1997**, 38, 257–264; J. P. Kampf, C. W. Frank, E. E. Malmström, C. J. Hawker, *Langmuir* **1999**, 15, 227–233; S. J. E. Mulders, A. J. Brouwer, P. Kimkes, E. J. R. Sudhölter, R. M. J. Liskamp, *J. Chem. Soc. Perkin Trans. 2* **1998**, 1535–1538; R. Roy, J. M. Kim, *Angew. Chem.* **1999**, 111, 380–384; *Angew. Chem. Int. Ed.* **1999**, 38, 369–372.
- [10] This method is generally used for the transfer of highly viscous or rigid polymeric films on a substrate, see A. Ulman, *Ultrathin Organic Films*, Academic Press, Orlando, **1991**.
- [11] R. M. Silverstein, G. C. Bassler, T. C. Morrill, *Spectrometric Identification of Organic Compounds*, 4th ed., Wiley, New York, **1981**, pp. 120–121; D. L. Pavia, G. M. Lampman, G. S. Kriz, *Introduction to Spectroscopy*, Saunders College, Philadelphia, **1979**, pp. 46–60.

Acetamidoglycosylation with Glycal Donors: A One-Pot Glycosidic Coupling with Direct Installation of the Natural C(2)-N-Acetylamino Functionality**

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The 2-*N*-acetylamino-2-deoxy class of carbohydrates is ubiquitous among biologically important complex oligosaccharides and glycoconjugates, including, inter alia, glycosaminoglycans, peptidoglycans, and blood group antigens.^[1] As a result, the efficient preparation of this group of glycosides

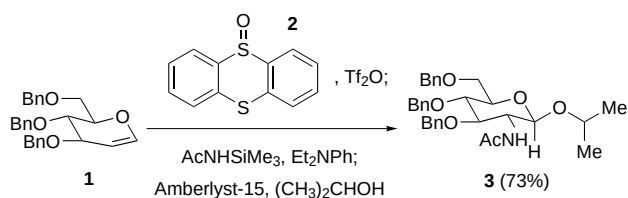
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[**] This research was supported by Glaxo Wellcome Inc., the Alfred P. Sloan Foundation, and the Arnold and Mabel Beckman Foundation (BYI). L.G.H., Jr. gratefully acknowledges a predoctoral fellowship from the National Science Foundation.

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has been a major focus in carbohydrate synthesis.^[2] At present, however, only a handful of methods exist for the introduction of a nitrogen substituent onto the C2-position of a carbohydrate substrate. The most direct synthetic routes usually involve methods of glycal activation in which various *N*-acetylamino precursor functionalities are introduced at the C2-position. Among these are the methods developed by Lemieux et al. for the introduction of oxime^[3] and azide^[4] groups at C2, the sulfonamidoglycosylation procedure of Danishefsky et al.,^[5] the phosphoramidoglycosylation strategy of Descotes and Lafont,^[6] the Fitzsimmons–Leblanc protocol for the formation of pyrano-oxadiazine [4 + 2] cycloadducts,^[7] and most recently the use of activated manganese nitrido complexes by Carrier and co-workers for the introduction of a C2-trifluoroacetamido substituent.^[8] These methods,^[9] although effective in the transfer of nitrogen to the glycal donor, must also entail further functional group manipulations in order to install the naturally occurring acetamido group at C2 as well as to form the glycosidic bond with the desired glycosyl acceptor. We now report a novel method for nitrogen transfer that efficiently effects the direct installation of the native C2-*N*-acetylamino functionality onto glycal donors and, additionally, allows glycosidic coupling with various glycosyl acceptors in an overall one-pot acetamidoglycosylation procedure. In this protocol, a new sulfonium reagent derived from thianthrene-5-oxide (**2**) is employed for glycal activation.

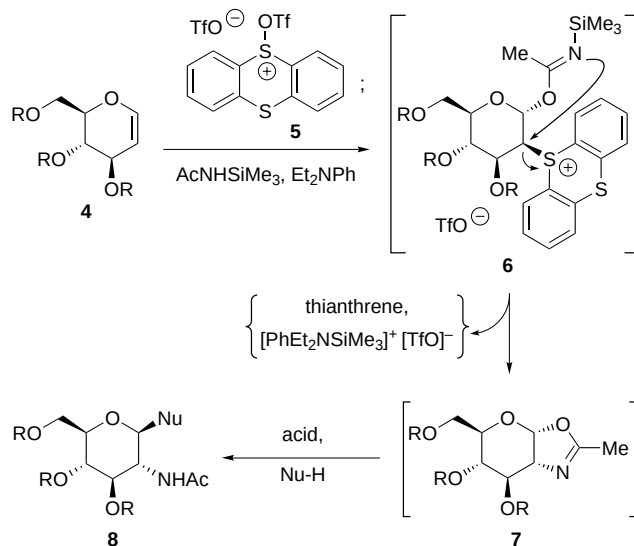
Our acetamidoglycosylation reaction using glycal donors involves an exceedingly simple procedure, exemplified by the glycosylation of 2-propanol with tri-*O*-benzyl-D-glucal (**1**) to generate isopropyl 2-*N*-acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**3**, Scheme 1). In this protocol,



Scheme 1. Acetamidoglycosylation of 2-propanol.

triflic anhydride (2 equiv) is added to a solution of glucal **1** (1 equiv) and thianthrene-5-oxide^[10] (**2**, 2 equiv) in a mixture of chloroform and dichloromethane (4:1) at -78°C . Following an initial activation period of 10 min, the acid scavenger *N,N*-diethylaniline (4 equiv) and solid *N*-trimethylsilyl-acetamide (*N*-TMS-acetamide, 3 equiv) were added sequentially, and the reaction mixture was stirred at 23°C for 2 h. Amberlyst-15 acidic resin and the glycosyl acceptor (2-propanol, 3 equiv) were then added, leading to the formation of the isopropyl glycoside **3** in 73% yield.

Such a transformation could proceed by way of the reaction pathway proposed in Scheme 2, in which the initial step involves low-temperature activation of thianthrene-5-oxide with triflic anhydride to generate thianthrene bis(triflate) (**5**) in situ.^[11] Electrophilic activation of the enol ether functionality in **4** by **5** would lead to the formation of a pyranoside intermediate incorporating an oxocarbenium triflate func-



Scheme 2. Proposed reaction pathway for acetamidoglycosylation.

tionality at C1 and a thianthrene sulfonium moiety at C2.^[12] The introduction of the acetamido group proceeds upon addition of the acid scavenger *N,N*-diethylaniline^[13] and *N*-TMS-acetamide. A key function of the *N*-trimethylsilyl protecting group in this amide reagent is to provide steric shielding at the nitrogen atom to favor initial addition of the amide oxygen atom onto C1 of the activated glycal, thereby generating the putative acetimidate intermediate **6**.^[14] Subsequent intramolecular displacement of the C2-thianthrene-sulfonium moiety by the imidate nitrogen accompanied by loss of the *N*-TMS protective group (either as TMSOTf or more likely as its *N,N*-diethylaniline adduct) would generate the bicyclic dihydrooxazole (oxazoline) intermediate **7**. Acid-mediated oxazoline ring-opening in the presence of a glycosyl acceptor would then afford the desired glycoside **8** in the final stage of the acetamidoglycosylation.

Using this procedure several glycosylations were performed with a series of selectively protected glycal donors (Table 1). It is worth highlighting that the yield in each of these one-pot operations is the result of glycal activation, nitrogen transfer by oxazoline formation, oxazoline ring-opening, and glycosidic bond formation. Thus, the acetamidoglycosylation of simple alkyl alcohols (e.g., 2-propanol, benzyl alcohol, dihydrocholesterol; entries 1,^[15] 2, 4, 5, 6, 8, 9, and 11) as well as of the carbohydrate acceptor methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside^[16] (entries 3, 7, and 10) led to the formation of the corresponding C2-acetamidoglycosides and C2-acetamidodisaccharides directly from protected glycal donors. In addition, glycal protective groups such as benzyl, triisopropylsilyl,^[17] and allyl^[18] ethers (entries 1–4, 8–11), as well as the acid-labile isopropylidene ketal (entries 5–7), can be used in this glycosylation process. The examples with 6-*O*-allyl-3,4-di-*O*-benzyl-D-glucal (entries 8–10) illustrate the propensity of the thianthrene sulfoxide/triflic anhydride reagent combination to selectively react with the glycal enol ether functionality in the presence of simple alkenes. Moreover, relatively mild Lewis acids such as MgI_2 or LiClO_4 can be employed in the place of Amberlyst-15 in certain cases (entries 5 and 6) for

Table 1. Acetamidoglycosylation with glycal donors.

Entry	Donor	Product (Yield)
1		 69%
2		 70%
3		 60%
4		 54%
5 ^[a]		 66%
6 ^[b]		 69%
7		 45%
8		 57%
9		 63%
10		 55%
11 ^[c]		 45%

[a] MgI_2 (1.1 equiv) was used for oxazoline ring-opening instead of Amberlyst-15. [b] LiClO_4 (2.2 equiv) was used for oxazoline ring-opening instead of Amberlyst-15. [c] Glycosylation was performed with 5 equiv of glycosyl acceptor.

the final stage of the reaction (oxazoline ring-opening) in order to minimize unwanted removal of acid-labile protective groups. Finally, direct acetamidoglycosylation with galactal donors can be accomplished (e.g., 3,4,6-tri-*O*-benzyl-D-galactal, entry 11) albeit in moderate overall yield, presumably a

result of the lability of the galactal-derived oxazoline intermediate which is generated in situ (vide infra).

In these reactions, an excess of both the sulfoxide and the triflic anhydride reagent (2 equiv) is required to maximize yields, as this presumably ensures rapid and complete activation of the glycal at low temperature. As a result, the subsequent reagents (TMS-NHAc and glycosyl acceptor) are also employed in a mild excess; however, virtually all of the excess acceptor can be recovered at the end of the reaction. Overall, the yields of these acetamidoglycosylation reactions are comparable to existing methods for nitrogen transfer to glycals, which would still require additional steps for N-protective group exchange and glycosidic bond formation.

Several points are worth noting with respect to the proposed reaction pathway outlined in Scheme 2. First, it is presumed that the addition of thianthrene bis(triflate) (**5**) occurs onto the β -face of **4**. Although this mode of activation may appear sterically unfavorable, the stereoselective addition of electrophilic reagents onto the β -face of glycals leading to 1,2-transdial-*substituted* pyranosides (as in **6**) is certainly preceded as illustrated by numerous examples in the halosulfonamidation of glycals.^[5] Second, the reagent thianthrene-5-oxide (**2**) is believed to undergo reduction to form thianthrene during the course of the C2-*N*-acetamido transfer process. Indeed, in these acetamidoglycosylation reactions, 0.7–0.9 equivalents of thianthrene was isolated as a principal by-product, which is consistent with the proposed reaction cascade. Finally, the bicyclic oxazoline intermediate **7** is invoked as an intermediate in the acetamidoglycosylation process. When activation of 3,4,6-tri-*O*-benzyl-D-glucal (**1**) (thianthrene-5-oxide, Ti_2O ; TMSNHA, PhNEt_2) is performed in CDCl_3 , ^1H NMR analysis of the reaction mixture clearly shows the oxazoline **9**^[19] (Figure 1) as the principal

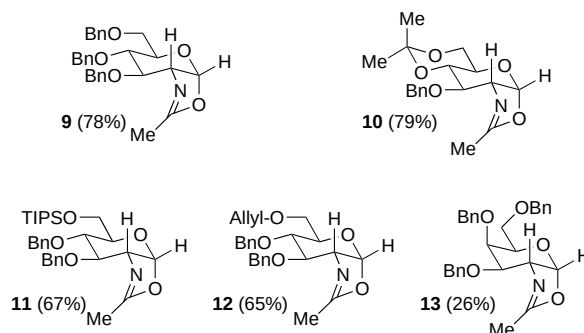


Figure 1. Isolated oxazoline intermediates.

carbohydrate species in solution. Moreover, oxazoline intermediates **9**, **10**, **11**,^[20] **12**,^[20] and **13** can be isolated prior to the introduction of the acid and glycosyl acceptor (Figure 1), lending support to the proposed reaction pathway in Scheme 2. (The poor yield of the galactal-derived oxazoline **13** is a result of its increased hydrolytic lability compared with **9**–**12** in the purification process).^[21] Although these observations do not preclude the possibility of formation of a reactive 1,2-*N*-acetyl aziridine intermediate in situ, such a species has not been detected in our acetamidoglycosylation reaction. Efforts are currently underway to investigate the mechanistic

details of the glycal activation process, as well as extending the method to the introduction of other C2-nitrogen functionalities.

In summary, a new method for C2-aza-glycosylation with glycal donors has been developed. The method involves a novel process for nitrogen transfer to glycals that: 1) employs thianthrene-5-oxide and triflic anhydride as a new reagent combination for glycal activation; and 2) effects, for the first time, the direct installation of the naturally occurring C2-*N*-acetylamino functionality onto glycal donors in conjunction with glycosidic coupling to various glycosyl acceptors in an overall one-pot procedure.

Experimental Section

Representative acetamidoglycosylation procedure:

Dihydrocholesteryl 2-*N*-acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy- β -D-glucopyranoside: Triflic anhydride (81 μ L, 0.480 mmol, 2.0 equiv) was added to a solution of tri-*O*-benzyl-D-glucal (100 mg, 0.240 mmol, 1 equiv) and thianthrene-5-oxide (112 mg, 0.480 mmol, 2.0 equiv) in a mixture of chloroform and dichloromethane (5 mL; 4:1) at -78°C . The reaction mixture was stirred at this temperature for 10 min, followed by the sequential addition of *N,N*-diethylaniline (152 μ L, 0.960 mmol, 4.0 equiv) and solid *N*-TMS-acetamide (72 mg, 0.552 mmol, 2.3 equiv). The reaction mixture was immediately warmed to 23°C and was stirred at this temperature for 2 h. The solution was cooled to -78°C , Amberlyst-15 (145 mg) and dihydrocholesterol (280 mg, 0.720 mmol, 3.0 equiv) were added, and the mixture was then stirred at 23°C for 17 h. The reaction was filtered, and the filtrate was partitioned between dichloromethane (80 mL) and saturated aqueous sodium chloride solution (100 mL). The aqueous phase was further extracted with dichloromethane (70 mL). The combined organic layers were dried (sodium sulfate) and concentrated, and the residue was purified by silica gel flash column chromatography to afford dihydrocholesteryl 2-*N*-acetylamino-3,4,6-tri-*O*-benzyl-2-deoxy- β -D-glucopyranoside (144 mg, 70% yield) as a white solid. M.p. $176\text{--}177^{\circ}\text{C}$; TLC (silica gel) $R_f = 0.39$ (20% ethyl acetate in benzene); $[\alpha]_D^{20} = +27.8$ ($c = 1.0$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3): $\delta = 7.33\text{--}7.27$ (m, 13H), 7.21–7.19 (m, 2H), 5.55 (d, $^3J(\text{H,H}) = 7.3$ Hz, 1H; NH), 5.01 (d, $^3J(\text{H,H}) = 8.0$ Hz, 1H; H1), 4.83 (d, $^3J(\text{H,H}) = 11.5$ Hz, 1H), 4.79 (d, $^3J(\text{H,H}) = 11.0$ Hz, 1H), 4.66 (d, $^3J(\text{H,H}) = 11.5$ Hz, 1H), 4.61 (d, $^3J(\text{H,H}) = 12.3$ Hz, 1H), 4.58 (d, $^3J(\text{H,H}) = 10.9$ Hz, 1H), 4.55 (d, $^3J(\text{H,H}) = 12.1$ Hz, 1H), 4.26 (dd, $^3J(\text{H,H}) = 9.9$, 8.2 Hz, 1H), 3.75 (dd, $^3J(\text{H,H}) = 9.9$, 1.7 Hz, 1H), 3.68 (m, 1H), 3.56 (m, 3H), 3.18 (dt, $^3J(\text{H,H}) = 9.9$, 7.8 Hz, 1H), 1.96 (m, 1H), 1.91–1.76 (m, 2H), 1.84 (s, 3H), 1.70–1.43 (m, 7H), 1.36–0.92 (m, 21H), 0.89 (d, $^3J(\text{H,H}) = 6.6$ Hz, 3H), 0.87 (d, $^3J(\text{H,H}) = 2.3$ Hz, 3H), 0.85 (d, $^3J(\text{H,H}) = 2.5$ Hz, 3H), 0.77 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3): $\delta = 170.35$, 138.61, 138.31, 138.12, 128.46, 128.41, 128.33, 127.94, 127.86, 127.74, 127.72, 127.71, 127.55, 98.07, 80.31, 79.03, 78.75, 74.75, 74.67, 74.59, 73.35, 69.13, 58.22, 56.45, 56.25, 54.35, 44.65, 42.57, 40.02, 39.50, 37.03, 36.15, 35.77, 35.53, 35.45, 34.57, 32.06, 29.43, 28.76, 28.24, 28.00, 24.19, 23.80, 23.63, 22.81, 22.55, 21.20, 18.65, 12.26, 12.04; FTIR (neat film): $\bar{\nu}$ 3286, 3064, 3031, 2932, 2866, 1655, 1557, 1496, 1453, 1373, 1311, 1118, 1072, 1027 cm^{-1} ; HRMS (FAB $^+$): m/z : calcd for $\text{C}_{56}\text{H}_{80}\text{NO}_6$ ($M \sim \text{H}^+$) 862.5986; found 862.5988.

Received: August 16, 1999 [Z13882]

- [6] D. Lafont, G. Descotes, *Carbohydr. Res.* **1988**, 175, 35–48.
- [7] a) Y. Leblanc, B. J. Fitzsimmons, J. P. Springer, J. Rokach, *J. Am. Chem. Soc.* **1989**, 111, 2995–3000; b) B. J. Fitzsimmons, Y. Leblanc, N. Chan, J. Rokach, *J. Am. Chem. Soc.* **1988**, 110, 5229–5231; c) B. J. Fitzsimmons, Y. Leblanc, J. Rokach, *J. Am. Chem. Soc.* **1987**, 109, 285–286.
- [8] J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, *J. Am. Chem. Soc.* **1997**, 119, 3179–3180.
- [9] For additional methods, see a) E. Kozłowska-Grams, G. Descotes, *Can. J. Chem.* **1982**, 60, 558–563; b) H. Driguez, J.-P. Vermees, J. Lessard, *Can. J. Chem.* **1978**, 56, 119–130; c) J. Das, R. R. Schmidt, *Eur. J. Org. Chem.* **1998**, 1609–1613.
- [10] Readily prepared by the treatment of commercially available thianthrene with one equivalent of *m*-chloroperoxybenzoic acid at 0°C .
- [11] For reports on the activation of the sulfoxide functionality with triflic anhydride, see a) V. G. Nenajdenko, P. V. Vertelezkij, I. D. Gridnev, N. E. Shevchenko, E. S. Balenkova, *Tetrahedron* **1997**, 53, 8173–8180; b) J. B. Hendrickson, S. M. Schwartzman, *Tetrahedron Lett.* **1975**, 273–276; c) M. D. Coburn, H. H. Hayden, *Synthesis* **1986**, 490–492; d) E. J. Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.* **1996**, 118, 9202–9203; e) B. A. Garcia, J. L. Poole, D. Y. Gin, *J. Am. Chem. Soc.* **1997**, 119, 7597–7596; f) V. Di Bussolo, Y.-J. Kim, D. Y. Gin, *J. Am. Chem. Soc.* **1998**, 120, 13515–13516; g) D. Kahne, S. Walker, Y. Cheng, D. Van Engen, *J. Am. Chem. Soc.* **1989**, 111, 6881–6882; h) L. Yan, D. Kahne, *J. Am. Chem. Soc.* **1996**, 118, 9239–9248; i) D. Crich, S. Sun, *J. Org. Chem.* **1997**, 62, 1198–1199.
- [12] For an example of glycal activation with sulfonium reagents, see S. Ramesh, N. Kaila, G. Grewal, R. W. Franck, *J. Org. Chem.* **1990**, 55, 5–7.
- [13] The use of other acid scavengers such as triethylamine, diisopropylethylamine, and *N*-methylmorpholine led to poor yields of the glycoside products.
- [14] Additionally, the *N*-TMS protective group significantly increases the solubility of the amide reagent at low temperature.
- [15] The analytical data for the product of the acetamidoglycosylation of benzyl alcohol with **1** in entry 1 was found to be identical in all respects to that previously reported. See: A. Mbongo, C. Fréchet, D. Beaupère, R. Uzan, G. Demailly, *Carbohydr. Res.* **1993**, 246, 361–370.
- [16] H. Hashimoto, K. Asano, F. Fujii, J. Yoshimura, *Carbohydr. Res.* **1982**, 104, 87–104.
- [17] The glucal donor in entry 4 was prepared from the 3,4-di-*O*-benzylation (NaH, BnBr) of 6-*O*-triisopropylsilyl-D-glucal. For a related procedure, see D. M. Gordon, S. J. Danishefsky, *J. Am. Chem. Soc.* **1992**, 114, 659–663.
- [18] The glucal donor in entries 8–10 was synthesized by the 6-*O*-allylation (NaH, Allyl-Br) of 3,4-di-*O*-benzyl-D-glucal. For a preparation of 3,4-di-*O*-benzyl-D-glucal, see R. A. Alonso, G. D. Vite, R. E. McDevitt, B. Fraser-Reid, *J. Org. Chem.* **1992**, 57, 573–584.
- [19] The analytical data for oxazoline **9** was found to be identical in all respects to that previously reported. See: A. Vasella, C. Witzig, *Helv. Chim. Acta* **1995**, 78, 1971–1982.
- [20] The gluco-oxazolines **11** and **12** were each isolated as diastereomeric mixtures containing minor amounts of their corresponding manno-oxazoline stereoisomers in diastereomeric ratios of 9:1 and 10:1, respectively.
- [21] The intermediates **9–13** were isolated by chromatography on Et₃N-neutralized silica gel to minimize oxazoline hydrolysis.

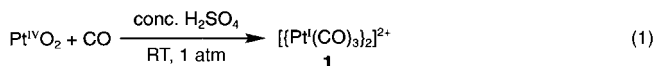
- [1] a) R. A. Dwek, *Chem. Rev.* **1996**, 96, 683–720; b) *Synthetic Oligosaccharides, Indispensable Probes for the Life Sciences* (Ed.: P. Kovac), ACS Symposium Series 560, American Chemical Society, Washington DC, **1994**.
- [2] J. Banoub, P. Boullanger, D. Lafont, *Chem. Rev.* **1992**, 92, 1167–1195.
- [3] R. U. Lemieux, T. L. Nagabhushan, *Can. J. Chem.* **1968**, 46, 401–403.
- [4] R. U. Lemieux, R. M. Ratcliffe, *Can. J. Chem.* **1979**, 57, 1244–1251.
- [5] a) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, 108, 1482–1522; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1380–1419; b) D. A. Griffith, S. J. Danishefsky, *J. Am. Chem. Soc.* **1991**, 113, 5863–5864; c) D. A. Griffith, S. J. Danishefsky, *J. Am. Chem. Soc.* **1990**, 112, 5811–5819.

[[Pt(CO)₃]₂]²⁺: The First Homoleptic, Dinuclear, Cationic Platinum(II) Carbonyl Complex Formed in Concentrated Sulfuric Acid**

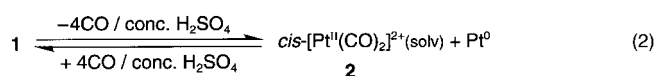
Qiang Xu,* Yoshie Souma, Brian T. Heaton,* Chacko Jacob, and Kan Kanamori

In the last ten years there has been a rapid development in the preparation and structural characterization of homoleptic metal carbonyl cations of late transition metals, following the discovery that they can be prepared in superacid media. This area has recently been reviewed^[1] and, apart from the CO-bridged dinuclear palladium(II) complex [Pd₂(μ-CO)₂](SO₃F)₂^[2a] and the unstable dinuclear mercury(II) carbonyl cation [Hg₂(CO)₂]²⁺,^[2b] all the complexes are monomeric with values of $\tilde{\nu}(\text{CO})$ significantly higher than 2143 cm⁻¹, the value for free CO.^[3] In the 1970s the homoleptic, anionic platinum carbonyl clusters [Pt₃(CO)₆]_n²⁻ (*n* = 1–6, ≈ 10)^[4a] and [Pt₁₉(CO)₁₂(μ₂-CO)₁₀]⁴⁻,^[4b] in which the Pt atoms are bridged by CO ligands, were reported. In 1993 the first homoleptic carbonyl complex of platinum(II), [Pt(CO)₄][Pt(SO₃F)₆], was isolated from the incomplete reduction of Pt(SO₃F)₄ with CO at 25 °C.^[5a] Subsequently, the complex [Pt(CO)₄][Sb₂F₁₁]₂ was prepared by solvolysis of *cis*-[Pt(CO)₂(SO₃F)₂], which is formed by complete reduction of Pt(SO₃F)₄ with CO^[5b] in liquid SbF₅.^[5c] Both the vibrational and NMR spectra of [Pt(CO)₄]²⁺ and *cis*-[Pt(CO)₂(SO₃F)₂] are entirely consistent with a square-planar coordination due to Pt adopting a +2 oxidation state.

We now report on the preparation and spectroscopic characterization of the first homoleptic, dinuclear, cationic platinum(II) carbonyl complex, [[Pt(CO)₃]₂]²⁺ (**1**), in which the Pt atoms are bound by a direct Pt–Pt bond. This unusual complex is formed as a result of the reductive carbonylation of PtO₂ by CO in concentrated sulfuric acid at room temperature and atmospheric pressure. The reaction takes about two weeks to complete [Eq. (1)], producing a colorless solution of



1. Prolonged (ca. 1 d) evacuation of a solution of **1** in concentrated H₂SO₄ results in disproportionation and the exclusive formation of *cis*-[Pt(CO)₂]²⁺(solv) (**2**), but slow reformation of **1** occurs on addition of CO [Eq. (2)]. Both **1** and **2** are extremely sensitive to moisture, exposure results in immediate decomposition to platinum metal.



The formulation of **1** as a dimer is shown from both ¹³C and ¹⁹⁵Pt NMR studies at natural abundance and 99% ¹³CO enrichment (Table 1). According to NMR simulations the observed spectra are in agreement with the presence of a T-shaped Pt(CO)₃ group and the presence of ¹⁹⁵Pt–¹⁹⁵Pt spin–spin coupling (550.9 Hz).

Furthermore, in the Raman spectrum of **1**, there is clear evidence for a very strong, sharp band due to $\tilde{\nu}(\text{Pt}–\text{Pt})$ at

Table 1. Spectroscopic properties of **1**, **2**, and related complexes.

Compound	$\tilde{\nu}(\text{CO})_{\text{IR}}$ [cm ⁻¹]	$\tilde{\nu}(\text{CO})_{\text{Raman}}$ [cm ⁻¹]	$\delta(^{13}\text{C})$	$\delta(^{195}\text{Pt})$	¹ <i>J</i> (Pt,C) [Hz]	Ref.
[[Pt(CO) ₃] ₂] ²⁺ 1 ^[a]	2195, 2186, 2174	2233, 2209, 2194, 2173 ^[b]	158.7, ^[c] 166.3 ^[d]	– 211.0	1595.7, ^[c] 1281.5 ^[d,e]	[f]
<i>cis</i> -[Pt(CO) ₂] ²⁺ (solv) 2 ^[a]	2218, 2182	2219, 2182	133.7	957.9	1907.3	[f]
<i>cis</i> -[Pt(CO) ₂ (SO ₃ F) ₂] ^[g]	2219, 2185	2218, 2181	131		2011	[5b]
<i>cis</i> -[Pt(CO) ₂ Cl ₂] ^[h]	2178, 2137	2172, 2131	151.6		1576	[10]
[Pt(CO) ₄][Sb ₂ F ₁₁] ₂ ^[g]	2244	2289, 2267	137		1550	[5c]

[a] In conc. H₂SO₄. [b] $\tilde{\nu}(\text{Pt}–\text{Pt})_{\text{Raman}} = 165 \text{ cm}^{-1}$. [c] For ¹³C_A; see Figure 1 for labeling scheme. [d] For ¹³C_B. [e] Other coupling constants [Hz]: ¹*J*(Pt,Pt') = 550.9, ²*J*(Pt,C_A) = – 26.2, ²*J*(Pt,C_B) = 199.6, ²*J*(C_A,C_B) = 0, ³*J*(C_A,C_A) = 0, ³*J*(C_A,C_B) = 0, ³*J*(C_B,C_B) = 19.8. [f] This paper. [g] In the solid state. [h] Spectroscopic data listed were obtained in benzene.

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[**] The authors acknowledge Prof. T. Eguchi for his continuous support and helpful discussions. Q.X. is grateful to Drs. K. Mogi and Y. Ichihashi for valuable help and discussions. B.T.H. thanks the EPSRC for support and Dr. J. A. Iggo for helpful discussions.

165 cm⁻¹, which is strongly polarized ($\rho \approx 0.25$). An EXAFS study on **1** shows the presence of a Pt–Pt bond of 2.674 Å, which is approximately 0.1 Å shorter than the Pt–Pt distance in Pt foil.^[6] IR and Raman results of **1** (Table 1) are consistent with a structure of *D*_{2d} symmetry (Figure 1), with only terminal CO groups and a direct Pt–Pt bond. According to calculations at the B3LYP level the conformation adopted by this molecule has a dihedral angle of exactly 90°. This structure is related to the structure of [[PtCl₂(CO)]₂]²⁻ which contains two slightly distorted T-shaped PtCl₂(CO)

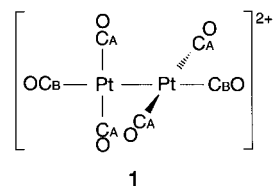


Figure 1. Schematic structure of [[Pt(CO)₃]₂]²⁺ (**1**), along with the labeling scheme for the carbonyl groups.

groups with a dihedral angle of 60° between the two planes and in which both CO groups are *cisoid* (length of the Pt–Pt bond 2.584 Å).^[7a] Other related, crystallographically characterized dinuclear platinum carbonyl species include $[\{\text{PtCl}(\text{CO})(\text{PrBu}_2\text{Ph})\}_2]$ ^[7b] and $[\{\text{Pt}(\text{C}_6\text{F}_5)(\text{CO})(\text{PPh}_3)_2\}_2]$,^[7c] which have dihedral angles of 70.1° and 78.6°, and Pt–Pt distances of 2.628 and 2.599(Å), respectively. Preliminary reports have also appeared for $[\{\text{PtCl}(\text{CO})(\text{PPh}_3)_2\}_2]$ ^[8] and, in all cases, the carbonyl groups are *cis* and the two phosphanes are *trans* to the Pt–Pt bond.

It has been shown that there is no correlation of $d(\text{Pt}–\text{Pt})$ with $^1J(\text{Pt},\text{Pt}')$ in closely related dinuclear platinum complexes.^[8] It is worth noting that $^1J(\text{Pt},\text{Pt}')$ for **1** is 550.9 Hz, while the values for $[\{\text{PtCl}_2(\text{CO})\}_2]^{2-}$ (5250 Hz)^[9] and $[\{\text{PtCl}(\text{CO})(\text{PPh}_3)_2\}_2]$ (760 Hz)^[8] are widely different, although other related coupling constants are similar (see Table 1 and refs. [8, 9]).

Prolonged evacuation of **1** results in disproportionation and formation of **2** through loss of CO [see Eq. (2)]. In this case, ^{13}C and ^{195}Pt NMR measurements on unenriched and 99% ^{13}C -enriched **2** show that there are two magnetically equivalent carbonyl groups per platinum with no $^{195}\text{Pt}–^{195}\text{Pt}$ coupling; **2** is thus a monomer. We presently favor a square-planar platinum(II) center with two CO ligands in a *cis* configuration, consistent with both IR and Raman measurements; the CO stretching frequencies are close to those for *cis*- $[\text{Pt}(\text{CO})_2(\text{SO}_3\text{F})_2]$,^[5b] but higher than those for *cis*- $[\text{Pt}(\text{CO})_2\text{Cl}_2]$.^[10] It is difficult to be sure whether the other two coordination sites on platinum are occupied by a bidentate SO_4^{2-} or by two monodentate $\text{SO}_4^{2-}/\text{HSO}_4^-$ groups since it is impossible to obtain any useful IR or Raman data in the sulfato region. However, when **1** is in concentrated H_2SO_4 , it seems more probable that the other two sites are occupied by monodentate HSO_4^- groups as recently found for silver(I).^[11]

The discovery of **1** suggests that homoleptic cationic carbonyl complexes of late transition metals in low oxidation states can be formed in media which are less acidic than the superacids that have been used previously. We found that this unusual dinuclear platinum carbonyl complex, **1**, exhibits high catalytic activity for the carbonylation of olefins;^[12] future studies will investigate the detailed reaction mechanism of this catalytic activity and attempts will be made to obtain **1** as a crystalline salt.

Experimental Section

Standard canula transfer techniques were used for all sample manipulations. NMR spectra were recorded in D_2SO_4 at room temperature on a Bruker AMX 200. The ^{13}C chemical shifts were referenced to external tetramethylsilane (TMS), and ^{195}Pt chemical shifts were referenced to 42.8 MHz at such a magnetic field that the protons in external TMS resonate at exactly 200 MHz. NMR simulations were carried out using gNMR 4.1 (Cherwell Scientific, Oxford, UK). Infrared spectra were obtained on thin films between two silicon discs on a JASCO FT/IR-230 spectrometer. Raman spectra were recorded on a Nicolet FT-Raman 960 spectrometer.

1: PtO_2 (2 mmol) in 96% H_2SO_4 (10 mL) was vigorously stirred for 2 weeks under ^{12}CO at constant pressure (1 atm), whereupon the dark colloidal suspension became colorless. The resulting solution is very moisture sensitive. Complex **1** with 99% ^{13}CO was prepared similarly.

2: The IR spectrum of **1** in 96% H_2SO_4 was monitored with time under evacuation (0.001 Torr). When the band for **1** (2174 cm^{-1} for ^{12}CO and 2126 cm^{-1} for ^{13}CO) had disappeared (ca. 1 d), nitrogen was admitted to the solution, which contained only **2** and a black colloidal precipitate of Pt metal. The solution of **2** was transferred under nitrogen by canula and used for all the spectroscopic measurements. This solution is indefinitely stable under a nitrogen atmosphere.

Received: July 29, 1999 [Z13795]

- [1] H. Willner, F. Aubke, *Angew. Chem.* **1997**, *109*, 2506–2530; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2403–2425.
- [2] a) C. Wang, M. Bodenbinder, H. Willner, S. Rettig, J. Trotter, F. Aubke, *Inorg. Chem.* **1994**, *33*, 779–786; b) M. Bodenbinder, G. Balzer-Jöllenbeck, H. Willner, R. J. Batchelor, F. W. B. Einstein, C. Wang, F. Aubke, *Inorg. Chem.* **1996**, *35*, 82–92.
- [3] K. Nakamoto, *Infrared Spectra of Inorganic Compounds and Coordination Compounds*, Wiley, New York, 1st ed., **1963**, p. 72.
- [4] a) G. Longoni, P. Chini, *J. Am. Chem. Soc.* **1976**, *98*, 7225–7231; b) D. M. Washecheck, E. J. Wucherer, L. F. Dahl, A. Ceriotti, G. Longoni, M. Manassero, M. Sansoni, P. Chini, *J. Am. Chem. Soc.* **1979**, *101*, 6110–6112.
- [5] a) G. Hwang, M. Bodenbinder, H. Willner, F. Aubke, *Inorg. Chem.* **1993**, *32*, 4667–4669; b) G. Hwang, C. Wang, M. Bodenbinder, H. Willner, F. Aubke, *J. Fluorine Chem.* **1994**, *66*, 159–166; c) G. Hwang, C. Wang, F. Aubke, H. Willner, M. Bodenbinder, *Can. J. Chem.* **1993**, *71*, 1532–1536.
- [6] K. Mogi, Y. Ichihashi, Q. Xu, unpublished results.
- [7] a) A. Modinos, P. Woodward, *J. Chem. Soc. Dalton Trans.* **1975**, 1516–1520; b) C. Couture, D. H. Farrar, D. S. Fisher, R. R. Gukathasan, *Organometallics* **1987**, *6*, 532–536; c) R. Usón, J. Fornies, P. Espinet, C. Fortuño, M. Tomás, A. J. Welch, *J. Chem. Soc. Dalton Trans.* **1989**, 1583–1587.
- [8] N. M. Boag, J. Browning, C. Crocker, P. L. Goggin, R. J. Goodfellow, M. Murray, J. L. Spencer, *J. Chem. Res. (M)* **1978**, 2962–2983.
- [9] N. M. Boag, P. L. Goggin, R. J. Goodfellow, I. R. Herbert, *J. Chem. Soc. Dalton Trans.* **1983**, 1101–1107.
- [10] J. Browning, P. L. Goggin, R. J. Goodfellow, M. G. Norton, A. J. M. Rattray, B. F. Taylor, J. Mink, *J. Chem. Soc. Dalton Trans.* **1977**, 2061–2067.
- [11] D. B. Dell'Amico, F. Calderazzo, F. Marchetti, *Chem. Mater.* **1998**, *10*, 524–530.
- [12] Q. Xu, Y. Souma, *Top. Catal.* **1998**, *6*, 17–26.

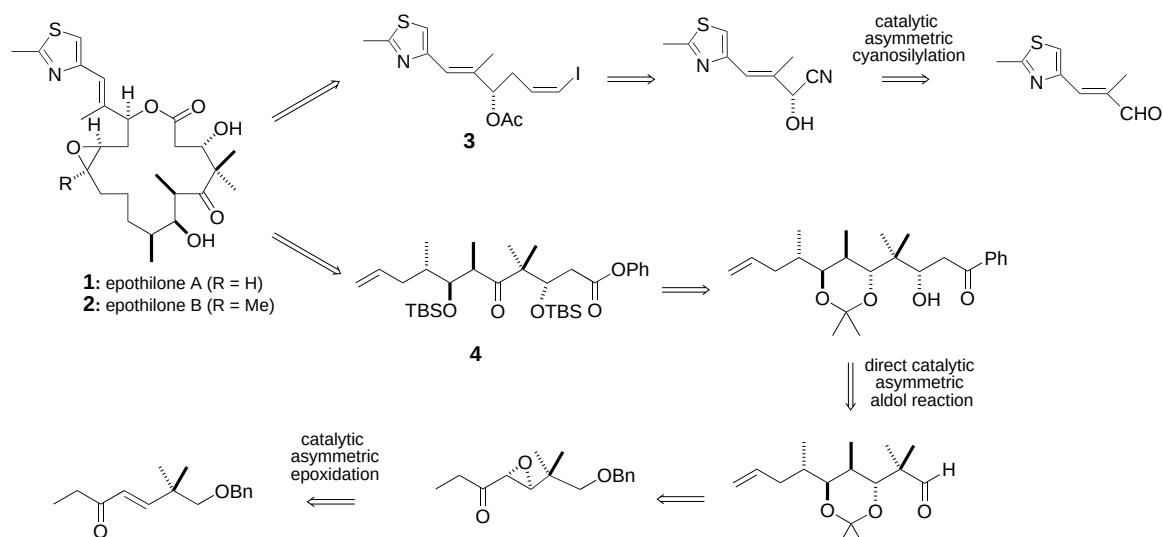
Enantioselective Total Synthesis of Epothilone A Using Multifunctional Asymmetric Catalysts**

Daisuke Sawada and Masakatsu Shibasaki*

Epothilones (see Scheme 1 for epothilones A (**1**) and B (**2**)) show potent antitumor activity by binding and stabilizing microtubules in the same way as taxol, and they are promising drug candidates. Epothilones A and B were isolated from the

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[**] This study was financially supported by CREST. We thank Dr. Motomu Kanai, Yoshitaka Hamashima, and Rie Namme for their support and fruitful discussion.



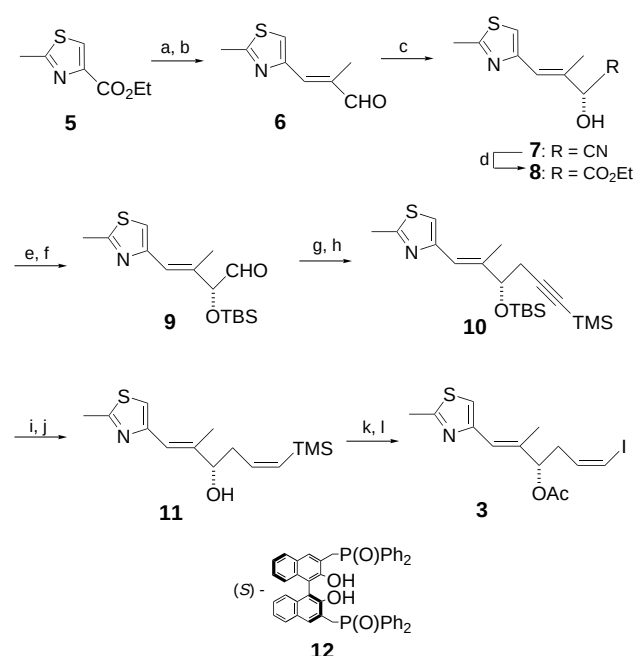
Scheme 1. Retrosynthetic analysis of **1**.

myxobacteria of the genus *Sorangium*, and their structures were determined by Höfle et al.^[1] Highly efficient total syntheses of epothilones were disclosed by the research groups of Danishefsky, Nicolaou, and Schinzer,^[2] but an enantioselective total synthesis using simple asymmetric catalysts has not been achieved.^[3] Herein we report an enantioselective total synthesis of epothilone A (**1**) using multifunctional asymmetric catalyses for direct aldol reaction and cyanosilylation, demonstrating the usefulness of these reactions for the catalytic asymmetric synthesis of complex molecules.

Scheme 1 shows our retrosynthetic strategy. Epothilone A (**1**) was disconnected into two fragments, **3** and **4**. The 16-membered ring of **1** was expected to be constructed by Suzuki coupling of **3** and **4** followed by lactonization. The vinyl iodide **3** could be obtained by a catalytic asymmetric cyanosilylation controlled by a Lewis acid–Lewis base bifunctional catalyst.^[4] The ester **4** could be synthesized by a catalytic asymmetric epoxidation and aldol reaction.^[5, 6]

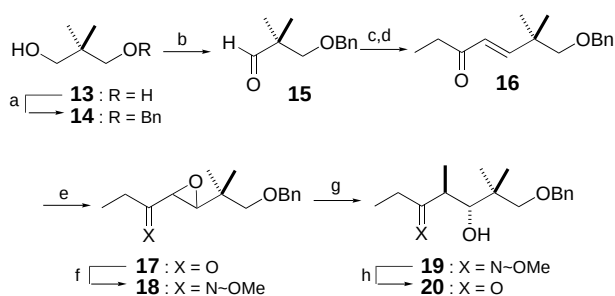
The known ester **5** was converted into aldehyde **6** in two steps for the synthesis of fragment **3** (Scheme 2).^[2b] We then examined a catalytic asymmetric cyanosilylation of **6** using a Lewis acid–Lewis base bifunctional catalyst containing ligand **12** (> 1-g scale).^[4] With use of 10 mol % of the catalyst, cyanohydrin **7** was obtained in excellent yield and enantiomeric excess (97% yield, 99% *ee*) after acid workup.^[7] Conversion of the cyanohydrin into the ester **8** by acidic ethanolysis followed by protection and reduction resulted in the aldehyde **9**. Addition of lithium acetylide to **9** afforded the alcohol product as a mixture of diastereomers, which was directly treated with methyl chloroformate to give the methyl carbonate. Reductive deoxygenation with palladium provided the trimethylsilylalkyne **10**.^[8] Removal of the silyl group, hydrotitanation, and aqueous workup gave (*Z*)-silylalkene **11**, which was easily converted into the vinyl iodide **3**.^[9]

The synthesis of fragment **4** started with commercially available neopentyl glycol **13**. Compound **13** was protected as



Scheme 2. a) DIBAL-H, CH₂Cl₂, –78 °C, 70%; b) Ph₃P=C(Me)CHO, benzene, reflux, 90%; c) Et₂AlCl, ligand **12**, TMSCN, Bu₃P(O), CH₂Cl₂, –40 °C, 97%, 99% *ee*; d) H₂SO₄, EtOH, reflux, 75%; e) *t*BuMe₂SiCl, imidazole, DMF, 99%; f) DIBAL-H, toluene, –78 °C, 87%; g) Me₃SiC≡CLi, THF, –78 °C; then methyl chloroformate, 79%; h) Pd(OAc)₂, Bu₃P, HCO₂NH₄, benzene, 50 °C, 51%; i) AcOH, THF, H₂O, 50 °C, 89%; j) [Ti(O*i*Pr)₄], *i*PrMgCl, Et₂O, –78 → –50 °C, 90%; k) I₂, CH₂Cl₂, 65%; l) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 90%. Bn = benzyl, DIBAL-H = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

monobenzyl ether **14**, which was then oxidized to aldehyde **15** (Scheme 3). The lithium enolate of butanone was allowed to react with **15**, and the resulting alcohol was transformed into enone **16** by the use of trifluoroacetic anhydride and DBU. As planned a catalytic asymmetric epoxidation of **16** was extensively examined.^[5] However, because of the steric hindrance of the quaternary carbon atom in the α -position to the double bond, only small amounts of the epoxide were



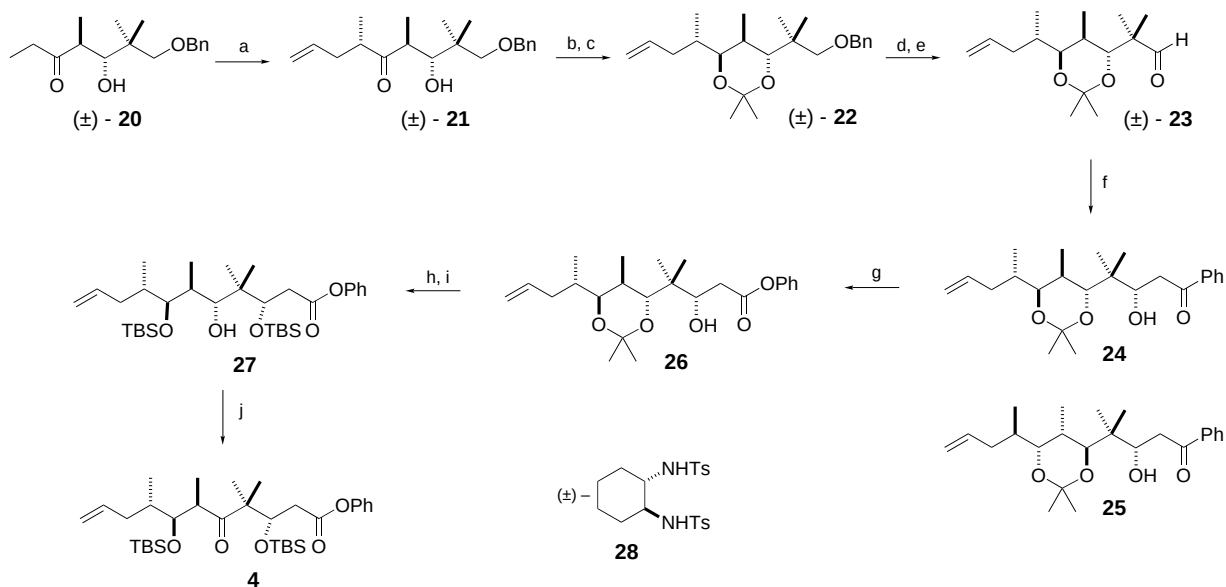
obtained with low *ee* values. This unfortunate result led us to another strategy for the synthesis of optically active **4**. We envisioned that a direct aldol reaction of acetophenone with (±)-**23** (see Scheme 4) promoted by a heteropolymetallic asymmetric catalyst would give the desired **24** by an effective catalyst-controlled process. Toward this end, **16** was oxidized with H₂O₂ to the epoxy ketone **17**, which was then converted into methyloxime **18** (Scheme 3). The epoxide opening to give *anti*-aldol **20** was achieved using cuprate reagent (→**19**) and subsequent reduction with Raney nickel followed by hydrolysis.^[10] To the best of our knowledge, this is a new method to prepare an *anti*-aldol.^[11]

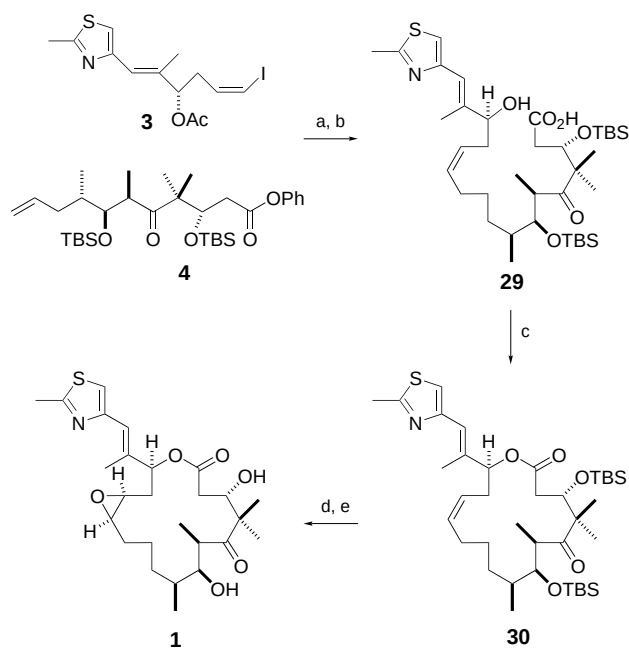
The lithium enolate of aldol **20** was treated with allyl bromide to give **21** as a single stereoisomer (Scheme 4).^[12] Reduction of **21** with Me₄NBH(OAc)₃ provided the desired

diol as the major compound (ca. 7:1), which was then protected as an acetonide (→**22**).^[12] The benzyl group of **22** was cleaved under Birch reduction conditions, and the resulting alcohol was oxidized to aldehyde **23**, which was a key compound for the crucial catalytic resolution. We examined a direct catalytic asymmetric aldol reaction of acetophenone with (±)-**23** using the heteropolymetallic catalyst [LaLi₃{tris(binaphthoxide)}] (LLB) with KOH and H₂O.^[6] Gratifyingly, as expected, the resolution was achieved and the two diastereomers **24** and **25** were formed with high *ee* values in a catalyst-controlled manner using 20 mol % of catalyst (30 % yield, 89 % *ee* for **24**; 29 % yield, 88 % *ee* for **25**; recovery of **23**, 30 %).^[13]

Thus we succeeded in obtaining the two optically active compounds **24** and **25** simultaneously, and therefore a strategy of this type would be useful for exploring the diversity of epothilones in terms of medicinal chemistry. As far as we know, this is the first example of a catalytic resolution of the *racemic* compound in an aldol reaction using a simple asymmetric catalyst.^[2k] The desired compound **24** for the synthesis of epothilone A was transformed into phenyl ester **26** using bis(trimethylsilyl) peroxide (BTSP) and SnCl₄; the terminal olefin remained unchanged.^[14] Deprotection and selective reprotection of hydroxyl moieties gave **27**, which was immediately oxidized to **4** by Dess–Martin periodinane to avoid the undesired cyclization of hydroxy and ester moieties.

Suzuki coupling of fragments **3** and **4** and subsequent hydrolysis under basic conditions afforded the hydroxy acid **29** (Scheme 5).^[2a] Ring closure of **29** under Yamaguchi conditions afforded cyclic compound **30**.^[2d,g,i-k] Finally removal of the two TBS groups and epoxidation of the ring olefin functionality afforded **1**.^[2a,c,i,j]





Scheme 5. a) 9-BBN (2 mol equiv), THF, then [PdCl₂(dppf)] (50 mol %), K₃PO₄, DMF, H₂O, 60 °C, 50%; b) NaOH (aq), MeOH, 84%; c) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, then DMAP, toluene, 88%; d) HF·pyridine, THF, 99%; e) 3,3-dimethyldioxirane, CH₂Cl₂, –35 °C, 49%. 9-BBN = 9-borabicyclo[3.3.1]nonane, DMAP = 4-dimethylaminopyridine, dppf = 1,1'-bis(diphenylphosphanyl)ferrocene.

In summary we have succeeded in an enantioselective total synthesis of epothilone A (**1**) using multifunctional asymmetric catalyses with a direct aldol reaction and cyanosilylation as key steps.

Experimental Section

24, 25: To a stirred solution of KHMDS in toluene (532 µL, 0.266 mmol, 0.5 M) at 0 °C was added a solution of water in THF (590 µL, 0.59 mmol, 1.0 M). The resulting solution was stirred for 20 min at 0 °C, and then (R)-LLB in THF (2.95 mL, 0.295 mmol, 0.1 M) was added and the mixture was stirred at 0 °C for 30 min. The pale yellow solution thus obtained was then cooled to –20 °C, and acetophenone (1.38 mL, 11.8 mmol) was added. The solution was stirred for 20 min at this temperature and then **23** (397 mg, 1.48 mmol) was added and the reaction mixture was stirred for 168 h at –20 °C. The reaction was quenched by addition of 1 N HCl (4 mL), and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (SiO₂, ethyl acetate/hexane 1/30) to give **24** (172 mg, 30%, 89% ee) and **25** (166 mg, 29%, 88% ee).

7: Ligand **12** (447 mg, 0.625 mmol) was placed in a flame-dried flask and dried at 50 °C for 2 h under reduced pressure. Dichloromethane (2 mL) was added, followed by the addition of diethylaluminum chloride in hexane (651 µL, 0.625 mmol, 0.96 M) under argon atmosphere. After the mixture was stirred for 10 min, tributylphosphane oxide (546 mg, 2.5 mmol) in dichloromethane (1.8 mL) was added at room temperature. The resulting mixture was stirred at the same temperature for 1 h to give a clear solution. To this stirred solution of the catalyst was added **6** (1.045 g, 6.25 mmol) in dichloromethane (13.8 mL) at –40 °C. After 30 min TMSCN (1.0 mL, 7.5 mmol) was slowly added over 24 h with a syringe pump. (Because the melting point of TMSCN is 11–12 °C, it should be added dropwise from the top of the flask, where the temperature may be above 15 °C.) The reaction mixture was stirred for 39 h at the same temperature. Trifluoroacetic acid (2.0 mL) was added at –40 °C, and the mixture was stirred vigorously at room temperature for 1 h to hydrolyze the trimethylsilyl ether moiety of the product. After the addition of ethyl acetate (30 mL), the mixture was

stirred for further 30 min. The organic layer was separated and washed with water. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The crude product was further purified by flash chromatography (ethyl acetate/hexane 1/3) to give **7** (1.18 g, 97%, 99% ee).

General procedure for the epoxide opening reaction using a cuprate reagent (see Table 1, entry 1):^[11] To a suspension of CuCN in diethyl ether was added methylolithium in diethyl ether (4.9 mL, 5.36 mmol, 1.1 M) at –78 °C. Then the temperature was gradually raised to 0 °C, and the mixture was stirred for 20 min to give a clear solution. To the solution was added the epoxy-oxime (99.3 mg, 0.54 mmol) in diethyl ether (2.0 mL), and the resulting mixture was stirred for 24 h at the same temperature. Then saturated aqueous NH₄Cl and aqueous NH₃ were added, and the mixture was stirred at room temperature for 1 h. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The crude product was further purified by flash chromatography (ethyl acetate/hexane 1/20) to give the methyloxime alcohol (83 mg, 77%).

Received: September 1, 1999 [Z13949]

- [1] G. Höfle, N. Bedolf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671–1673; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567–1569.
- [2] a) A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2976–2978; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801–2803; b) Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170–172; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166–168; c) D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, *Angew. Chem.* **1997**, *109*, 543–544; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523–524; d) K. C. Nicolaou, F. Sarabia, S. Ninkovic, Z. Yang, *Angew. Chem.* **1997**, *109*, 539–540; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 525–527; e) D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, *109*, 775–777; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 757–759; f) K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268–272; g) K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Trujillo, *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973; h) K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991; i) D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092; j) C. R. Harris, S. D. Kuduk, A. Balog, K. Savin, P. W. Glunz, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 7050–7062; k) S. C. Sinha, C. F. Barbas III, R. A. Lerner, *Proc. Natl. Acad. Sci. USA* **1998**, *146*, 14603–14608; l) review: K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120–2153; *Angew. Chem. Int. Ed.* **1998**, *37*, 2014–2045; m) J. Mulzer, A. Mantoulaidis, E. Ohler, *Tetrahedron Lett.* **1998**, *39*, 8633–8636; n) S. A. May, P. A. Grieco, *J. Chem. Soc. Chem. Commun.* **1998**, 1597–1598; o) D. Schinzer, A. Bauer, J. Schieber, *Synlett* **1998**, 861–864; p) J. D. White, R. G. Carter, K. F. Sundermann, *J. Org. Chem.* **1999**, *64*, 684–685; q) D. Schinzer, A. Bauer, O. M. Böhm, A. Limberg, M. Cordes, *Chem. Eur. J.* **1999**, *5*, 2483–2491; r) D. Schinzer, A. Bauer, J. Schieber, *Chem. Eur. J.* **1999**, *5*, 2492–2500.
- [3] For an enantioselective total synthesis of epothilone A using antibody catalysis, see reference [2k].
- [4] Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641–2642.
- [5] a) M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 2329–2330; b) S. Watanabe, Y. Kobayashi, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *Tetrahedron Lett.* **1998**, *39*, 7353–7356; c) S. Watanabe, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *J. Org. Chem.* **1998**, *63*, 8090; d) K. Daikai, M. Kamaura, J. Inanaga, *Tetrahedron Lett.* **1998**, *39*, 7321–7322.
- [6] a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942–1944; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*,

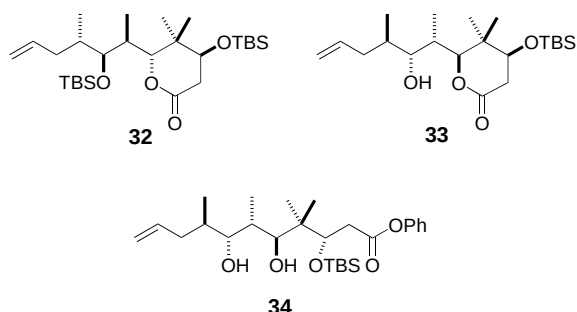
1871–1873; b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178.

- [7] The absolute configuration was determined by Mosher's method; see J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519. The enantiomeric excess was determined by HPLC analysis using DAI-CEL CHIRALPAK AD (2-propanol/hexane 1/100).
- [8] a) T. Mandai, T. Matsumoto, M. Kawada, J. Tsuji, *Tetrahedron Lett.* **1993**, *34*, 2161–2164; b) J. Tsuji, T. Sugiura, I. Minami, *Synthesis* **1987**, 603–606.
- [9] a) K. Harada, H. Urabe, F. Sato, *Tetrahedron Lett.* **1995**, *36*, 3203–3206; b) F. Sato, H. Ishikawa, M. Sato, *Tetrahedron Lett.* **1981**, *22*, 85–88. This method could lead to the fragment for the synthesis of epothilone B (2).
- [10] For related work with oximes, see E. J. Corey, L. S. Melvin, Jr., M. F. Haslanger, *Tetrahedron Lett.* **1975**, 3117–3120.
- [11] We can also prepare *syn*-aldol from *cis*-enone by this method.^[13] Through coupling with the stereocontrolled catalytic asymmetric epoxidation of the *cis*- and *trans*-enones recently developed in our group,^[5] it is possible to prepare *syn*- and *anti*-aldol from *cis*- and *trans*-enones, respectively, with excellent *ee* values (Table 1).

Table 1. Epoxide opening of *cis*-epoxy-oximes by cuprate reagents.

Entry	R ¹	R ²	R ³	Yield [%]
1	methyl	pentyl	methyl	77
2	propyl	pentyl	methyl	72
3	phenethyl	pentyl	methyl	85
4	phenethyl	pentyl	butyl	80
5	phenethyl	pentyl	phenyl	80
6	phenethyl	pentyl	vinyl	50
7	pentyl	phenethyl	methyl	81

- [12] The relative configuration of the alcohol resulting from reduction of **21** with Me₄NBH(OAc)₃ was determined by analyzing the NOE of **22**, and the relative configuration of the methyl group of **22** resulting from allylation of **20** was further determined by transforming **22** into **31** and analyzing the coupling constant between H_a and H_b (10.2 Hz).
- [13] The absolute configurations were determined by Mosher's method,^[8] and the enantiomeric excesses were determined by HPLC analysis using DAI-CEL CHIRALPAK AD (2-propanol/hexane 1/100). The relative configurations were determined by transforming **24** into **32** and **25** into **33** (cyclization of **27** and **34**, respectively), and analyzing their NOEs.



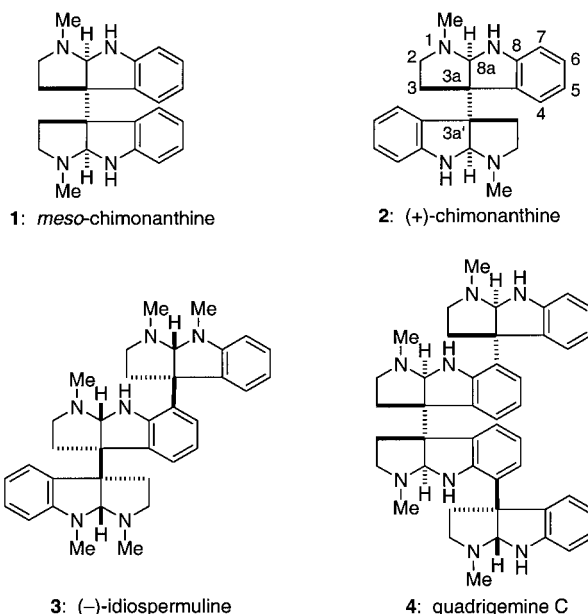
- [14] R. Göttlich, K. Yamakoshi, H. Sasai, M. Shibasaki, *Synlett* **1997**, 971–973.

Enantioselective Construction of Vicinal Stereogenic Quaternary Centers by Dialkylation: Practical Total Syntheses of (+)- and *meso*-Chimonanthine**

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Enantioselective formation of vicinal stereogenic quaternary carbon centers is one of the more formidable challenges in contemporary organic synthesis.^[1, 2] Here we report a powerful method for creating such arrays by reaction of achiral dienolates with a chiral, enantiopure dielectrophile. The method was developed to address the vicinal stereogenic quaternary benzylic carbon centers that are the signature structural feature of indole alkaloids containing the hexacyclic 3a,3a'-bispyrrolidino[2,3-*b*]indoline unit.

The chimonanthines are the simplest members of this family and are found in nature in all three stereochemical motifs: *meso*-chimonanthine (**1**)^[3] and (–)-chimonanthine^[4] from plant sources; (+)-chimonanthine (**2**) from the skin of a Colombian frog^[5] and from plant sources.^[6] In addition, many



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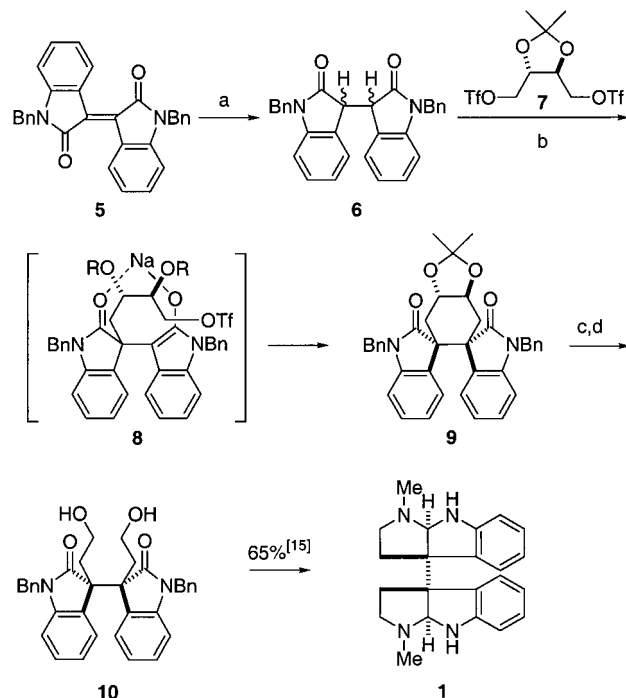
[**] This research was supported by the NIH (grant GM-12389), Bristol-Myers Squibb Pharmaceuticals (graduate fellowship to B.A.S.), the American Cancer Society (postdoctoral fellowship to J.F.L., PF-98-003), and Pfizer (undergraduate research fellowship to J.M.V). NMR and mass spectra were determined at University of California, Irvine with instruments purchased with the assistance of the NSF and NIH shared instrumentation programs. We are grateful to Dr. Joseph Ziller and Dr. John Greaves for their assistance with X-ray and mass spectrometric analyses.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

more complex indole alkaloids contain the 3a,3a'-bispyrrolidino[2,3-*b*]indoline moiety. For example, (–)-idiospermuline (**3**) consists of a (–)-chimonanthine fragment functionalized with one additional pyrrolidinoindoline unit,^[7] while the dodecacyclic alkaloid quadrigemine C (**4**) is proposed to have a *meso*-chimonanthine core functionalized with two pyrrolidinoindoline units of the same absolute stereochemistry.^[8]

Early synthetic efforts directed towards this class of indole alkaloids produced largely the racemic C_2 -symmetric isomers by oxidative dimerization of indole^[9] or oxindole derivatives,^[10] or by dialkylation of dihydroisoidigo.^[11] We have reported a stereoselective approach to *meso*-bispyrrolidinoindoline alkaloids by samarium-mediated reductive dialkylation of an isoidigo,^[12] and more recently a flexible approach to either the *meso* or C_2 isomers using an intramolecular Heck reaction cascade was presented.^[13] Herein we disclose a highly efficient synthesis of 3a,3a'-bispyrrolidino[2,3-*b*]indolines having either *meso* or C_2 symmetry. The approach utilizes the nature of a metal dienolate (chelated or nonchelated) to control the relative configuration, while exploiting the chirality of a tartrate-derived dielectrophile to control absolute stereochemistry.

Isoidigo **5**,^[12] which is available in two steps and 85 % yield from commercially available oxindole and isatin, was converted into the corresponding dihydroisoidigo **6** by reduction with zinc in acetic acid at room temperature (Scheme 1). Alkylation of the disodium dienolate of **6** with 1.1 equiv of ditriflate **7**^[14] in THF at -78°C provided in 92 % yield a single pentacyclic product **9**, having the *cis* relationship of the two spirooxindole groups. The acetonide was removed by exposure of **9** to camphorsulfonic acid (CSA) and MeOH to liberate the cyclohexanediol, which was cleaved with

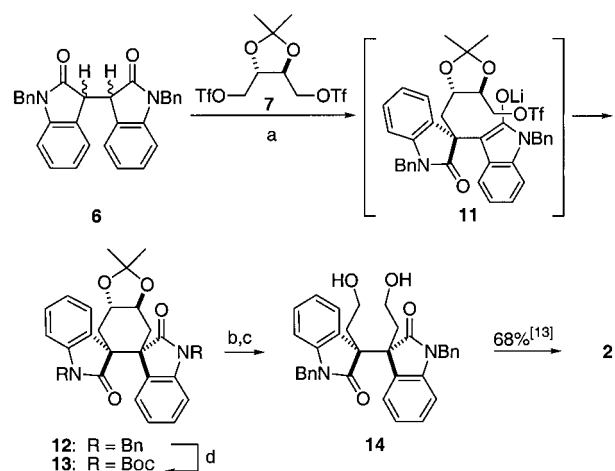


Scheme 1. a) Zn, AcOH, room temperature, 83 %; b) NaHMDS (2.1 equiv), THF, -78°C , 92 %; c) CSA, MeOH/ CH_2Cl_2 , 100 %; d) $\text{Pb}(\text{OAc})_4$, PhH; NaBH_4 , MeOH, 92 %. Bn = benzyl, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, OTf = trifluoromethanesulfonate (triflate),

$\text{Pb}(\text{OAc})_4$, and the resulting labile dialdehyde was reduced with NaBH_4 to provide diol **10**. This intermediate could be converted into *meso*-chimonanthine (**1**) in six steps and 65 % overall yield.^[12, 15]

The critical dialkylation step of the approach to **1** summarized in Scheme 1 is more amenable to scale-up than the related step of our earlier route.^[12] Use of the tartrate-derived dielectrophile **7** avoids problems with competing $\text{S}_{\text{N}}2'$ cyclization that are seen in the reaction of the disodium dienolate of **6** with *cis*-1,4-dichloro-2-butene.^[12] Stereoselection in the second alkylation step is consistent with preferential reaction of chelated intermediate **8**.^[12, 16]

The outcome of the dialkylation reaction was dramatically altered by changing the dienolate counter ion and reaction solvent (Scheme 2). When the reaction of **6** with ditriflate **7** was carried out with LiHMDS (2.1 equiv) in THF containing



Scheme 2. a) LiHMDS (2.1 equiv), THF/DMPU, -78°C , 55 %; b) CSA, MeOH/ CH_2Cl_2 , 100 %; c) $\text{Pb}(\text{OAc})_4$, PhH; NaBH_4 , MeOH, 90 %; d) *t*Bu-Li, Et_2O , -78°C then O_2 ; Boc_2O , DMAP, CH_2Cl_2 , 61 %. Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DMPU = 1,3-dimethylhexahydro-2-pyrimidinone.

10 % DMPU at -78°C , the major product formed was the C_2 -symmetric bisoxindole **12**, which could be isolated in 55 % yield. Under these conditions, the other possible C_2 product was generated in trace amounts only (1–3 %), while isomer **9** having the spirooxindole groups *cis* was formed in 20 % yield. Both of these minor isomers were easily removed from **12** by chromatography.

The relative stereochemistry of **12** was established by removing the benzyl groups with *tert*-butyllithium/oxygen^[17] followed by *N*-acylation with di-*tert*-butyl dicarbonate to provide BOC derivative **13**. Single-crystal X-ray analysis of this derivative established the relative stereochemistry of **12**.^[18] Using the same sequence employed to elaborate **9**, C_2 -symmetric bisoxindole **12** was converted in two steps and 90 % overall yield into **14** ($[\alpha]_{\text{D}}^{23} = +235$, $c = 0.9$ in CHCl_3). This intermediate was processed in six additional steps to complete the first enantioselective total synthesis of (+)-chimonanthine (**2**; 68 % overall yield; $[\alpha]_{\text{D}}^{23} = +274$, $c = 0.5$ in EtOH).^[13, 19]

In summary, the dialkylation approach described herein constitutes a practical way to prepare either the *meso* or enantiopure C_2 stereoisomers of 3a,3a'-bispyrrolidino[2,3-*b*]indolines on large scales. Starting from commercially avail-

able oxindole and isatin, the total syntheses of *meso*- (1) and (+)-chimonanthine (2) were accomplished in 39 and 21% overall yield respectively. The alkylation of the dilithium dienolate of 6 in 10% DMPU/THF is notable in producing one of the two possible C_2 products with high selectivity (20:1). This alkylation reaction is a rare example of high diastereoselectivity arising from the combination a prostereogenic enolate with a chiral electrophile containing an sp^3 carbon center.^[20]

Received: September 2, 1999 [Z13956]

- [1] Recent reviews of asymmetric synthesis of quaternary centers: a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; b) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066.
- [2] For an excellent recent strategy, see R. M. Lemieux, A. I. Meyers, *J. Am. Chem. Soc.* **1998**, *120*, 5453–5457.
- [3] Y. Adjibadé, B. Weniger, J. C. Quirion, B. Kuballa, P. Cabalion, R. Anton, *Phytochemistry* **1992**, *31*, 317–319.
- [4] H. F. Hodson, B. Robinson, G. F. Smith, *Proc. Chem. Soc. London* **1961**, 465–466.
- [5] T. Tokuyama, J. W. Daly, *Tetrahedron* **1983**, *39*, 41–47.
- [6] L. Verotta, T. Pilati, M. Tatò, E. Elisabetsky, T. A. Amador, D. S. Nunes, *J. Nat. Prod.* **1998**, *61*, 392–396.
- [7] R. K. Duke, R. D. Allan, G. A. R. Johnston, K. N. Mewett, A. D. Mitrovic, C. C. Duke, T. W. Hambley, *J. Nat. Prod.* **1995**, *58*, 1200–1208.
- [8] F. Guéritte-Voegelein, T. Sévenet, J. Pusset, M.-T. Adeline, B. Gillet, J.-C. Beloeil, D. Guénard, P. Potier, R. Rasolonjanahary, C. Kordon, *J. Nat. Prod.* **1992**, *55*, 923–930.
- [9] E. S. Hall, F. McCapra, A. I. Scott, *Tetrahedron* **1967**, *23*, 4131–4141.
- [10] a) R. Göschke, J. B. Hendrickson, R. Rees, *Tetrahedron* **1964**, *20*, 565–579; b) C. L. Fang, S. Horne, N. Taylor, R. Rodrigo, *J. Am. Chem. Soc.* **1994**, *116*, 9480–9486.
- [11] T. Hino, S. Yamada, *Tetrahedron Lett.* **1963**, 1757–1760.
- [12] J. T. Link, L. E. Overman, *J. Am. Chem. Soc.* **1996**, *118*, 8166–8167.
- [13] L. E. Overman, D. V. Paone, B. A. Stearns, *J. Am. Chem. Soc.* **1999**, *121*, 7702–7703.
- [14] Ditriflate 7 is available on a large scale by reaction of (+)-2,3-*O*-isopropylidene-L-threitol with triflic anhydride and iPr_3NEt in Et_2O at 0°C. Both enantiomers of this intermediate are available from (+)- and (–)-tartaric acid: E. A. Mash, K. A. Nelson, S. Van Deusen, S. B. Hemperly in *Organic Syntheses*, Vol. 68 (Ed.: J. D. White), Wiley, New York, **1990**, pp. 92–103.
- [15] Diol 10 had previously been converted into *meso*-chimonanthine.^[12] The efficiency of this conversion is increased to 65% by utilizing the conditions we recently developed to convert a related chiral diol into (–)-chimonanthine.^[13]
- [16] Consistent with this interpretation, stereoselection was eroded in the presence of a sodium-selective cryptand (Kryptofix 221).
- [17] R. M. Williams, E. Kwast, *Tetrahedron Lett.* **1989**, *30*, 451–454.
- [18] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134670. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [19] Literature value:^[6] $[\alpha]_D^{25} = +264.5$ ($c = 1.0$ in EtOH).
- [20] a) A recent survey of stereoselective C–C bond formation cites no examples in sections dealing with alkylation reactions with chiral electrophiles; see D. S. Matteson, *Methoden Org. Chem. (Houben-Weyl)* 4th ed. 1996, Vol. E21/2, pp. 1077–1118; b) Interconversion of atropisomers of the dienolates derived from 6 is likely to be slow under the alkylation conditions. Whether the 20:1 selectivity arises solely in the initial alkylation step or is enhanced by selective partitioning of the minor diastereomer in the cyclization step has not yet been determined.

How Strong Is the Coordination Bond between a Histidine Tag and Ni–Nitrilotriacetate? An Experiment of Mechanochemistry on Single Molecules**

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A number of extensively used methods of increasing importance in molecular biology are based on the ability of the nickel(II) ion, when chelated by nitrilotriacetate (nta), to selectively bind proteins containing stretches of consecutive histidine residues (His). Hochuli et al. established this field of applications when they discovered that proteins containing isolated histidines lead to complexes that are less stable than those arising from proteins having two consecutive His tags at one terminus ($2 \times$ His-tag).^[1] Indeed, a stretch of six consecutive His tags ($6 \times$ His-tag) is now commonly appended to the primary sequence of recombinant proteins, making it possible to isolate them selectively from a flow of crude cell lysate by means of a Ni–nta-functionalized chromatographic matrix^[2a,b] and to immobilize them on biosensors for biomolecular interaction analysis.^[3] The stability of the anchoring of the His-tagged proteins is challenged in both cases by the frictional force exerted on them by the flow. Such interplay between external forces and chemical processes can now be transferred to the single-molecule level thanks to recent developments in nanoscale manipulation techniques.^[4, 5] Single-molecule experiments can give crucial insights into binding processes that cannot be accessed by solution methods. In the single-molecule world, bond making and breaking becomes a digital “yes-or-no” process. Determination of binding constants by traditional means provides only information that is averaged on the entire ensemble of the molecules and on the overall time scale of the experiment.

We simulated the process involved in the Ni–nta protein separation techniques by reproducing the approach, binding, stretching, and unbinding under external forces between individual His tags and individual Ni–nta chelating groups in a single-molecule experiment with the scanning force microscope (SFM, see Figure 1).^[6] This experiment revealed that: 1) the probability that the encounters between a $6 \times$ His-tag and a Ni–nta group develop in a stable bond is much higher than that for a $2 \times$ His-tag; 2) both tags can make either of two types of complex with markedly different stabilities and with different “energy landscapes” along their force-driven disso-

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[**] We thank G. Zuccheri (Bologna) for crucial and helpful advice, one referee for his insightful comments and enlightening suggestions, V. Albano and A. Ripamonti (Bologna) for their advice and support, and Biacore AB (Uppsala, Sweden) for providing us with samples of their NTA chip and product information. This work was supported by Programmi Biotecnologie legge 95/95 (MURST 5%), Progetto Biologia Strutturale MURST (ex quota 40%), Progetto CNR MSTA II Biomateriali, and Università di Bologna (Fund for Selected Research Topics).

ciation pathway; and 3) the probability that the $6 \times \text{His}$ -tag forms the more stable complex is much higher than that for the $2 \times \text{His}$ -tag.

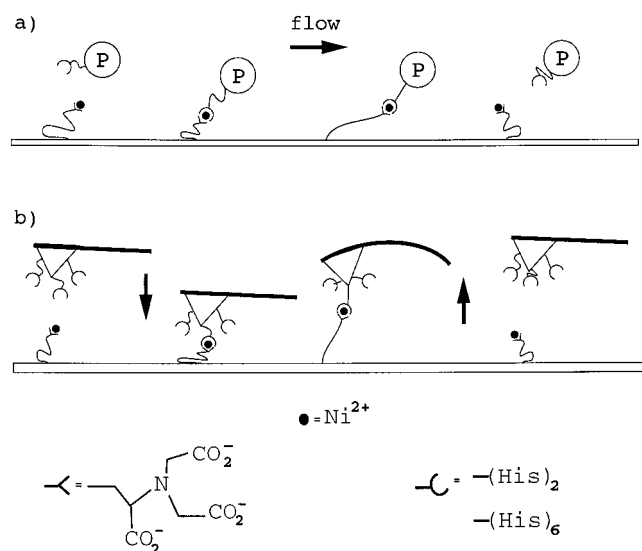


Figure 1. Sketch of the approach, binding, stretching, and unbinding of a) a His-tagged protein (p) under the flow inside an affinity chromatography column or on a biosensor surface and b) a His-tagged peptide covalently bound to an SFM tip in an approach and retraction cycle. (This figure was inspired by Figure 1 in reference[4c]).

A $2 \times \text{His}$ -tagged peptide, $\text{HCys}-(\text{Gly})_6-(\text{His})_2-\text{OH}$, was covalently attached on its Cys end to a gold-coated SFM tip. The tip was brought into proximity to a substrate having exposed Ni-nta groups covalently bound through carboxymethylated dextran linkers, which were attached to a gold surface by an alkane C_{18} chain (sensor chip NTA, Biacore, Sweden). Whenever the $2 \times \text{His}$ -tag of the peptide formed a chelate with a Ni-nta group, a molecular bridge was established between the tip and the substrate. The tip was subsequently retracted at a constant pulling velocity until the bridge broke (see Figure 1b). The force acting on the molecular bridge was monitored from the cantilever deflection, and force versus extension (displacement of the piezo driver) curves were recorded. At a pulling velocity of $1 \mu\text{m s}^{-1}$ only 28% of the approaches led to binding events. The successful events were recognized by unbinding traces with single or multiple sawtooth patterns like those depicted in Figure 2a–c. Each tooth consists of a part with rising deflection followed by a sudden drop. The rising part corresponds to the stretching of a molecular bridge; the drop reflects its breaking and provides an estimate of the rupture force. The distribution of all the rupture forces recorded displays two maxima with different heights: ruptures at about 350 pN occurred more than twice as frequently as those at about 500 pN (Figure 3a). Figure 3b reports the distribution observed when the same experiment was performed with the homologous peptide $\text{HCys}-(\text{Gly})_6-(\text{His})_6-\text{OH}$ which has a $6 \times \text{His}$ -tag. The probability of binding events increased from the

28% of the $2 \times \text{His}$ -tag to 42%. Most of the unbinding traces exhibited a single rupture: the distribution of the forces was very broad and peaked at about 500 pN, the same value as the lower maximum in Figure 2b.

The first critical issue with this type of measurement is to verify that exactly one single polymer chain is picked up by

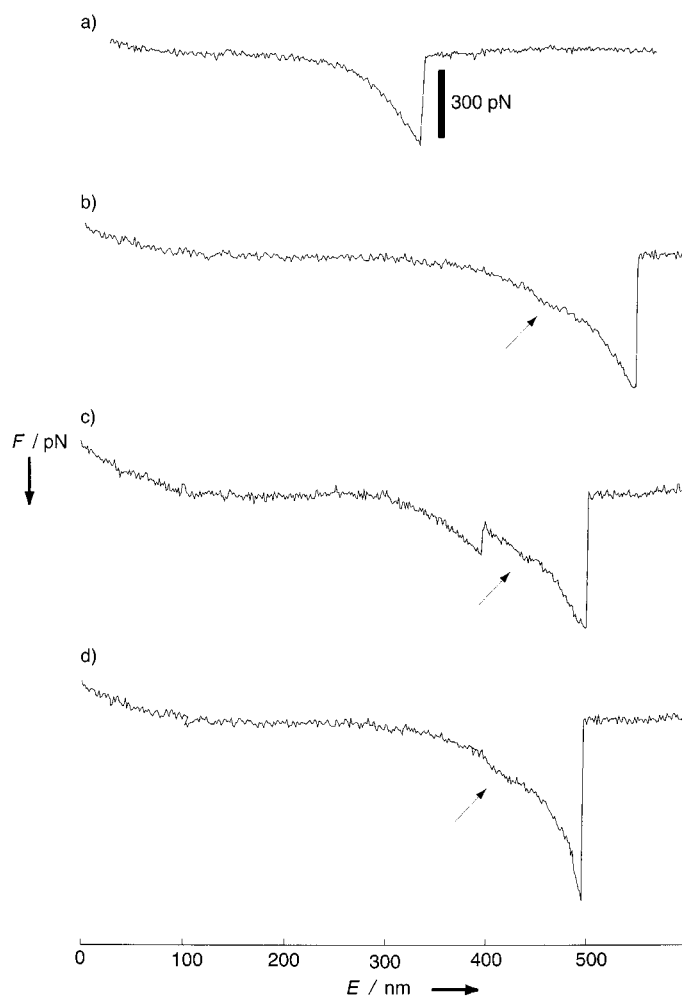


Figure 2. Characteristic shape of the force (F) vs extension (E) unbinding traces associated with the rupture of the coordination bond between His tags and nickel(II)-nta (a–c) and iron(III)-nta (d). Single rupture events (a, b, d) and sequential two-bond ruptures at about 280 and 600 pN (c) are shown. When a conformational transition of the carboxymethylated dextran chain also took place, it was revealed by the plateau at about 300 pN, which is marked by arrows in b–d.

the SFM tip and that only one single binding/unbinding event is measured. We followed both strategies that had been introduced previously to verify this point. 1) When the measured curves are normalized according to the length of each individual force-extension trace (which relates to the length of the single polymer chain upon rupture), their features should overlap perfectly.^[7, 8] In an attempt to verify this for our case we have plotted a set of representative curves in Figure 4. 2) Polysaccharide molecules have a large enthalpic component in their elasticity. They undergo typical conformational transitions that take place at different applied forces.^[4b, 7, 8, 9] Rief et al. characterized this type of transition in

single molecules of carboxymethylated dextran and found that it occurs at about 300 pN.^[7] The same authors utilized the corresponding plateau in the force–extension curve as an internal strain gauge to calibrate the force acting on the system.^[7] We followed the same approach: the traces in which this plateau was clearly evident (e.g. Figure 2b–d) were utilized to check the direct measurements of the spring

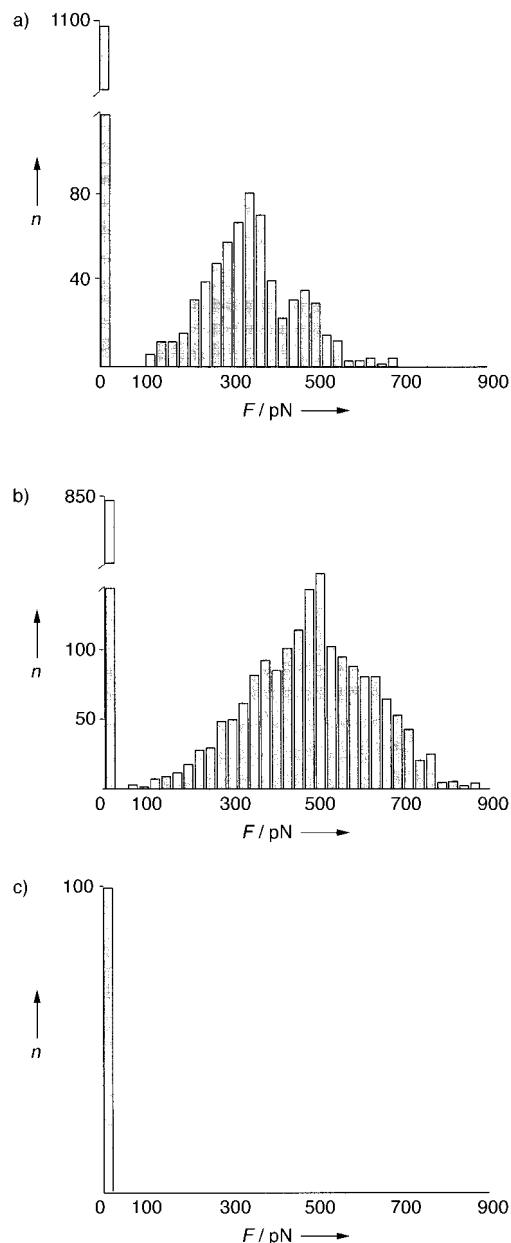


Figure 3. Histogram of the distribution (n , number of events) of all the unbinding forces (F) recorded with the Ni–nta-functionalized substrate and a) the 2xHis-tag and b) the 6xHis-tag. No binding event was recorded when the substrate was depleted of nickel(II) ions (c).

constant of different cantilevers, a determination with quite low precision (see Experimental Section). On the basis of these results we could infer that only single binding/unbinding events had been considered. This conclusion was supported by one further observation: the distribution of the rupture forces (see Figure 3) did not peak on integer multiples of an

elementary force value,^[10] as would be expected if simultaneous ruptures of more than one bond took place. On the other hand, it must be pointed out that none of these individual observations were as clear-cut as they in principle could be. In fact, 1) the plateau was not observed in all traces, and its normalized length was not constant; 2) the superimposition of the normalized curves was not perfect for all traces (see Figure 4); and 3) the data distributions of rupture forces were rather broad. These three observations most likely originate from a nonhomogeneous carboxymethylation of the dextran linkers and from their being not directly anchored to the substrate but to a molecular network. Our experiment should thus be improved by the use of a better defined polymeric linker. Our current data should be used just for comparing the different behaviors of the $2 \times$ His- and $6 \times$ His-tags rather than for assigning the absolute values of the single-bond strengths.

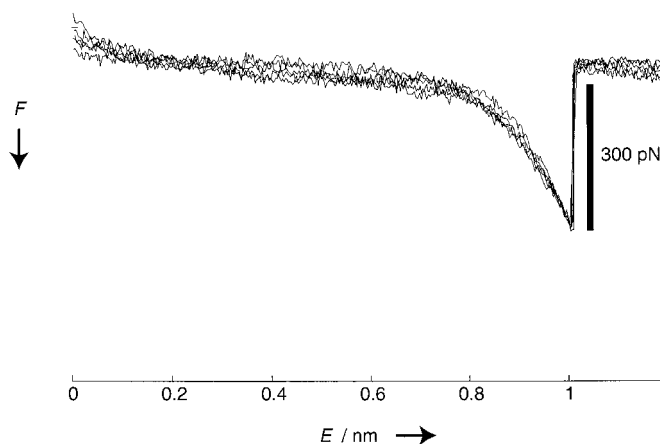


Figure 4. Superimposition of a sample of single-rupture force-extension traces normalized as described in the text.

The second critical issue with this type of measurements is to pinpoint which bond is rupturing. The bond rupture events we observed could be assigned to the Ni–His junction between the polysaccharide and the peptide sides of the system. In fact, the forces for all other bonds along the chains (C–C, C–O, C–S, including the S–Au anchor to the substrate) were recently estimated by Grandbois et al.:^[4b] the weakest is the S–Au bond which, under conditions identical to those in our experiment, was found to be able to withstand forces of up to 1400 pN, far greater than the forces we applied. Our assignment was confirmed by two control experiments. 1) After the substrate was depleted of nickel(II) ions we were operating in a force regime markedly repulsive, and no adhesion between the tip and the substrate was ever observed (Figure 3c). 2) When nta was complexed to a smaller and more charged ion like iron(III), larger rupture forces (up to about 750 pN) were recorded, as expected (see Figure 2d).

We can therefore infer that the two peaks in Figure 3a and b are associated with two different complexes, or even with two classes of complexes. Therefore, when a $2 \times$ His-tag is brought into contact with a Ni–nta group, the less stable complex (or complexes) is formed more frequently. In the

case of a $6 \times$ His-tag the more stable one (or ones) is formed more frequently instead. These two coordination bonds differ not only in stability, but also in the “energy landscape”^[11] of their transition states, as revealed by the study we carried out on the dependence of their rupture forces on the force loading rate (to be published). This parameter, first introduced by Evans and Ritchie,^[12] is equal to the product of the pulling velocity and the “effective” spring constant (the combination in series of the spring constant of the cantilever and of the molecular bridge).

This experiment, although not yet optimized, is casting a new light on our understanding of a bond that forms the basis for more and more important tools for molecular biology. These results make it possible not only to foresee the tremendous possibilities but also the possible problems and pitfalls of this very new and still developing SFM method for studying binding processes.

Experimental Section

The peptide HCys-(Gly)₆-(His)₂-OH was kindly provided by Prof. Peggion (Padova), and HCys-(Gly)₆-(His)₆-OH was synthesized by Tecnogen (Naples, Italy). Both were synthesized by solid-phase methods, and their purity was controlled by HPLC and MALDI-TOF MS. The Ni-nta Biacore chip was depleted of nickel(II) ions by incubation in 0.35 M ethylenediaminetetraacetic acid solution for 2 h; iron(III) or nickel(II) ions were reintroduced by treating the chip with a 100 mM solution of FeCl₃ or NiCl₂ and then rinsing with water. Si₃N₄ AFM cantilevers (DI, Santa Barbara, CA) were metalized by resistive deposition of Ti and then Au 99.99% (thicknesses of 10–15 nm and 30–40 nm, respectively) at 10^{-6} Torr. The tips were then immediately immersed in a 1 mg mL⁻¹ solution of the peptide in phosphate-buffered saline (PBS) at pH 7.4 for 30 min.

The spring constants of the cantilevers were determined from their thermal excitation^[13] with a precision not higher than 30%. Four cantilevers were used for the measurements. The values of their spring constants obtained by this method were in the range of 60 to 120 pN nm⁻¹. Force measurements were carried out in PBS with a Nanoscope III Multimode AFM (DI, Santa Barbara, CA).

Received: June 1, 1999 [Z13499]

- [1] E. Hochuli, H. Döbeli, A. Schacher, *J. Chromatogr.* **1987**, *411*, 177–184.
- [2] a) L. Nieba, A. Kriebler, A. Plückthun, *Anal. Biochem.* **1996**, *234*, 155–165, and references therein; b) A. M. Schmidt, H. N. Müller, A. Skerra, *Chem. Biol.* **1996**, *3*, 645–653.
- [3] J. Crowe, H. Döbeli, R. Gentz, E. Hochuli, D. Stüber, *Methods in Molecular Biology*, Vol. 31, Humana Press, Totowa, NJ, **1994**, pp. 371–387, and references therein.
- [4] a) V. T. Moy, E. L. Florin, H. E. Gaub, *Science* **1994**, *266*, 257–259; b) M. Grandbois, M. Beyer, M. Rief, H. Clausen-Schaumann, H. E. Gaub, *Science* **1999**, *283*, 1727–1730; c) J. Fritz, A. G. Katopodis, F. Kolbinger, D. Anselmetti, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 12283–12288; d) C. Bustamante, C. Rivetti, D. J. Keller, *Curr. Opin. Struct. Biol.* **1997**, *7*, 709–716; e) S. Izrailev, S. Stepaniants, M. Balsera, Y. Oono, K. Schulten, *Biophys. J.* **1997**, *72*, 1568–1581.
- [5] B. Samori, *Angew. Chem.* **1998**, *110*, 2318–2321; *Angew. Chem. Int. Ed.* **1998**, *37*, 2198–2200.
- [6] In this experiment, the unbinding takes place under a rising force and in a time much shorter than those of protein separation processes. These forces are kinetic in nature.^[4d,e, 11] Therefore, in these processes the bond ruptures may occur at lower forces than those we measured.

- [7] M. Rief, F. Oesterhelt, B. Heymann, H. E. Gaub, *Science* **1997**, *275*, 1295–1297.
- [8] H. Li, M. Rief, F. Oesterhelt, H. E. Gaub, *Adv. Mater.* **1998**, *3*, 316–319.
- [9] P. E. Marszalek, A. F. Oberhauser, Y. P. Pang, J. M. Fernandez, *Nature* **1998**, *396*, 661–664.
- [10] E. L. Florin, V. T. Moy, H. E. Gaub, *Science* **1994**, *264*, 415–417.
- [11] R. Merkel, P. Nassoy, A. Leung, K. Ritchie, E. Evans, *Nature* **1999**, *397*, 50–53, and references therein.
- [12] E. Evans, K. Ritchie, *Biophys. J.* **1997**, *72*, 1541–1555.
- [13] E. L. Florin, M. Rief, H. Lehmann, M. Ludwig, C. Dornmair, V. T. Moy, H. E. Gaub, *Biosensors Bioelectronics* **1995**, *10*, 895–901.

Denticity Changes of Hydrotris(pyrazolyl)borate Ligands in Rh^I and Rh^{III} Compounds: From κ^3 - to Ionic “ κ^0 ”-Tp^{***}

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Dedicated to Professor Swiatoslaw Trofimenko

The formally tridentate cyclopentadienyl and hydrotris-(pyrazolyl)borate ligands are important auxiliary ligands in organometallic chemistry.^[1, 2] Most often they act as spectators, and chemical transformation occurs at the metal center or at other coordinated ligands. However, in some instances they may have a noninnocent involvement by means of hapticity changes.

Variations in coordination mode are well documented for the cyclopentadienyl system (Cp').^[3, 4] Casey and co-workers demonstrated some years ago the interconversion of η^5 -C₅H₅, η^1 -C₅H₅, and ionic “ η^0 ”-C₅H₅⁻ compounds in the reaction of [(η^5 -C₅H₅)Re(NO)(CH₃)(PMe₃)] with PMe₃^[5] and proposed an η^3 -C₅H₅ intermediate for the $\eta^5 \rightleftharpoons \eta^1$ exchange. In contrast,

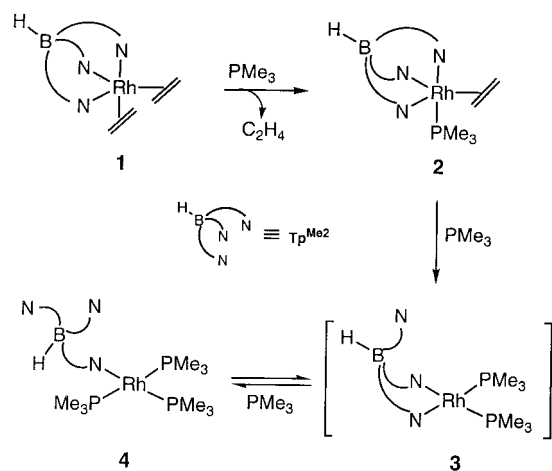
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[**] Financial support from the DGESIC (projects PB96-0824, PB97-0733) and from the Junta de Andalucía is gratefully acknowledged.

the tris(pyrazolyl)borates (Tp') bind predominantly in a facial, tripodal fashion,^[2, 6] that is, κ^3 -N,N',N''-Tp', and examples of κ^2 -Tp'ML_n complexes are rare except among 16-electron, square-planar species.^[2, 7, 8] To our knowledge, the monodentate κ^1 -N-Tp' coordination mode is restricted to a series of closely related Ni complexes of the bulky hydrotris(3-*tert*-butylpyrazolyl)borate anion.^[7, 9] During the course of this work, an interesting Rh compound that displays an unprecedented κ^2 -N,H-Tp' bonding mode was reported by Kalck, Etienne, and co-workers.^[10]

As far as we are aware, direct, unequivocal evidence for an ionic " κ^0 "-Tp'-metal compound has not yet been provided. Moreover, the recent isolation of the salt [Tm₂Bi][Tp₂Na], by addition of NaTp to the purported "[Tm₂BiCl]" (Tm = hydrotris(methimazolyl)borate), was attributed to the proficiency of Tp as a ligand and to its unwillingness to act as a counterion.^[11] Here we report the interconversion of κ^3 -N,N',N''-, κ^2 -N,N'-, κ^1 -N- and " κ^0 "-Tp'-rhodium compounds (Tp' = Tp, Tp^{Me2} (Tp^{Me2} = hydrotris(3,5-dimethylpyrazolyl)borate)). We have authenticated the four coordination modes by X-ray crystallography on Rh^I and Rh^{III} complexes. That concerning the unprecedented " κ^0 " mode is described herein.

Treatment of either [Tp^{Me2}Rh(C₂H₄)₂] (**1**) or [Tp^{Me2}Rh(C₂H₄)(PMe₃)] (**2**)^[12] with an excess of PMe₃ (ca. 5–6 equiv; 20 °C, <1 h) induces quantitative formation of the new complex **4**, isolable as yellow crystals (Scheme 1). The putative intermediate bis-phosphane complex cannot be



Scheme 1. PMe₃-induced variations in the coordination of the Tp^{Me2} ligand in Rh^I complexes.

detected in the course of this reaction, but it can be generated by the slow dropwise addition of one molar equivalent of PMe₃ to solutions of **2**. Compound **3** is always contaminated with small amounts of **2** and **4** and has not been isolated in analytically pure form. Its characterization by spectroscopic methods is, however, straightforward.^[13] Since the reaction of the tris-phosphane complex **4** with the bis-ethene derivative **1** gives a mixture of **2** and **3**, the interconversion of the κ^1 - and κ^2 -Tp^{Me2}Rh^I complexes shown in Scheme 1 is reversible. Complete displacement of the coordinated Tp^{Me2} ligand appears possible, although more forcing conditions are

needed (120 °C, 6 h). Like other [Rh(PMe₃)₄]X (X = BPh₄, PF₆) salts,^[14] [Rh(PMe₃)₄]Tp^{Me2} cannot be isolated and decomposes during workup. This precluded its full characterization.

A single crystal of the tris-phosphane complex **4** was subjected to an X-ray study^[15] (Figure 1). The long Rh...H(B) separation of 2.59(4) Å seems to indicate no significant

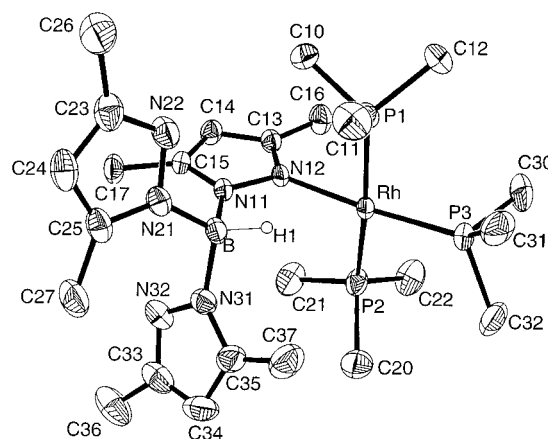
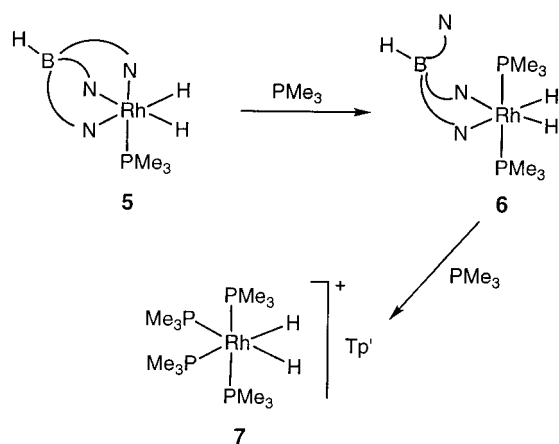


Figure 1. Molecular structure of **4**. Selected bond lengths [Å] and angles [°]: Rh–N12 2.116(2), Rh–P1 2.3209(8), Rh–P2 2.3057(8), Rh–P3 2.2206(9); N12–Rh–P1 86.14(6), N12–Rh–P2 86.89(6), P3–Rh–P2 93.69(3), P3–Rh–P1 92.78(3).

B–H...Rh interaction and therefore κ^1 -Tp^{Me2} coordination. However, in view of the error associated with the determination of this bonding parameter and of the somewhat similar, albeit shorter, Rh...H separation of 2.35(3) Å^[10] in the related complex [(κ^2 -N,H-Tp^{Me2,4-Cl})Rh(CO)(PPh₃)₂] (Tp^{Me2,4-Cl} = hydrotris(3,5-dimethyl-4-chloropyrazolyl) borate), it seems advisable to defer the assignment of the Tp^{Me2} coordination mode in **4** until more data are available. The ³¹P{¹H} NMR spectrum of **4** in [D₈]toluene at 20 °C can be interpreted in terms of an AB₂X spin system (X = ¹⁰³Rh) in which the AB₂ portion almost approaches a first-order situation ($\delta(P_A) = -5.8$, $\delta(P_B) = -14.1$; ²J(P_A,P_B) = 48, ¹J(P_A,Rh) = 158, ¹J(P_B,Rh) = 133 Hz). However, at –80 °C the two *trans* phosphane ligands become inequivalent, and a large ²J(P,P) coupling of 340 Hz can be readily computed by spin-simulation techniques. The low-temperature spectrum is in accord with an asymmetric structure, but in view of literature precedent^[8a, 10, 16–18] the presence in solutions of **4** of isomeric complexes that feature different coordination modes of the Tp^{Me2} ligand (see above) cannot be excluded.

The bis-hydrido complex [(κ^3 -Tp^{Me2})Rh(H)₂(PMe₃)] (**5a**)^[12] undergoes similar reactions when heated in the presence of PMe₃ (Scheme 2). The κ^2 -Tp^{Me2} bis-phosphane compound **6a** is initially formed^[19] (50 °C, 2 h), but additional stirring at 50 °C for 8 h gives a compound formulated as [Rh(H)₂(PMe₃)₄]Tp^{Me2} (**7a**). The NMR parameters of the [Rh(H)₂(PMe₃)₄]⁺ cation of **7a** are identical to those already reported,^[14, 20] and match exactly those corresponding to the species that is generated by the reaction of [Rh(H)₂(PMe₃)₄]Cl^[14] with KTp^{Me2}.



(Tp' = Tp^{Me2}: **5a**, **6a**, **7a**; Tp: **5b**, **7b**)

Scheme 2. Changes in the denticity of Tp and Tp^{Me2} in Rh^{III} hydrido complexes. The reactions proceed at 50 °C for Tp' = Tp^{Me2}, and at room temperature for Tp' = Tp.

Whereas this proposal could not be confirmed by X-ray studies, the analogous complex [Rh(H)₂(PMe₃)₄]Tp (**7b**) of the unsubstituted tris(pyrazolyl)borate ligand can be isolated as white crystals from the reaction of [(κ³-Tp)Rh(H)₂(PMe₃)] (**5b**) with PMe₃ (ca. 5–6 equiv).^[21] As shown in Figure 2, there is no bonding interaction^[22] between the Rh^{III} center and

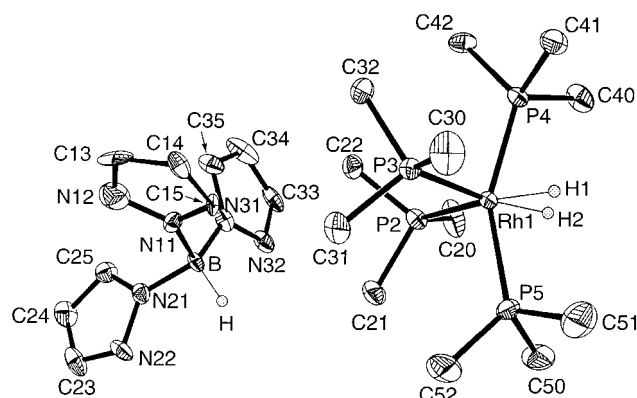


Figure 2. Molecular structure of **7b**. Selected bond lengths [Å] and angles [°]: Rh1–H1 1.57(7), Rh1–H2 1.53(9), Rh1–P(2) 2.362(2), Rh1–P(3) 2.358(2), Rh1–P(4) 2.310(2), Rh1–P(5) 2.296(2); P3–Rh1–P2 98.70(7), P5–Rh1–P4 154.72(7).

the Tp[–] anion; the closest Rh...N contact is to one of the N atoms of the Tp ligand of another asymmetric unit (4.627 Å). It is therefore clear that the overall transformation shown in Scheme 2 provides the first examples of metal salts of the hydrotris(pyrazolyl)borate anions Tp^{1–}. Moreover, our results constitute the first observation of a stepwise change in the denticity of Tp' ligands from κ³ to “κ⁰”. Such changes in Tp' coordination modes may have important implications in stoichiometric and catalytic transformations of M–Tp' compounds.

Before closing, some comments on the application of the ν(B–H)^[17] and δ(¹¹B{¹H})^[18] criteria to ascertain the κⁿ-Tp' denticity in the above complexes appear appropriate. Referring for convenience and simplicity to the Tp^{Me2} derivatives,

the ν(B–H) stretching frequencies of **2** (2518 cm^{–1}) and **3** (2450 cm^{–1}) are in accord with the proposed κ³-Tp^{Me2} (in the case of **2**) and κ²-Tp^{Me2} coordination modes (for **3**). The ¹¹B{¹H} NMR chemical shifts of δ = –8.8 (**2**) and –5.6 (**3**) also point in the same direction.^[18] The situation is, however, more complex for the κ¹-Tp^{Me2} compound **4**. Comparison of its ¹¹B{¹H} chemical shift of δ = –2.0 with those of **2** and **3** shows the trend expected for κ³ → κ² → κ¹ exchange. However, the IR spectrum of **4** (KBr disk, Nujol mull, and solution in THF, in the latter case in the temperature range 20 to –85 °C) contains three bands in the proximity of 2425 (shoulder for spectra in THF), 2390, and 2355 cm^{–1}. It seems reasonable that the proposed κ¹ coordination mode in **4** is only one of several possible isomeric forms, and that other isomers, such as κ²-N,H or κ²-N,N', are responsible for the multiplicity of the ν(B–H) bands. In solution these putative structures could equilibrate rapidly on the NMR time scale. This interesting aspect of the chemistry of **4** is presently under investigation and will be addressed in detail in a full paper. Finally, the “κ⁰” complex **7a** displays ν(B–H) at 2431 cm^{–1} and has a δ(¹¹B) value of about –2.0. Hence, a distinction between the κ¹- and “κ⁰” formulations for our compounds does not appear possible purely on the basis of B–H stretching frequencies and ¹¹B chemical shifts.

Experimental Section

4: A solution of [Tp^{Me2}Rh(C₂H₄)₂] (0.114 g, 0.25 mmol) in THF (15 mL) at –30 °C was treated with a solution of PMe₃ in THF (1.5 mL, 1M, 1.5 mmol). After stirring for 1 h at room temperature, the solution was analyzed by ³¹P NMR spectroscopy, which showed quantitative formation of the title compound. The volatile materials were removed in vacuo, and the residue was dissolved in petroleum ether (20 mL). After filtration and concentration, the solution was cooled to –20 °C, and yellow crystals of **4** were obtained (0.12 g, 42% yield). IR (Nujol): ν̄ = 2425, 2390, 2355, 2335(sh) cm^{–1} (B–H); ¹H NMR (C₆D₆, 25 °C): δ = 5.93, 5.85 (brs, 2:1, 3H, 3 CH_{pz}), 2.40, 2.36, 2.28, 2.18 (brs, 2:1:1:2, 18H, 6 Me_{pz}), 0.96 (m, 27H, 3 PMe₃); ¹³C{¹H} NMR (C₆D₆, 25 °C): δ = 146.6, 143.6, 145.3, 148.1 (2:2:1:1, C_q (pz)), 106.3, 104.6 (2:1, CH_{pz}), 21.4 (d, ¹J(C,P) = 27 Hz, PMe₃), 17.7 (pseudo-t, ¹J(C,P)_{app} = 13 Hz, 2 *trans*-PMe₃), 15.1, 14.1, 12.7, 11.5 (1:2:1:2, Me_{pz}); ³¹P{¹H} NMR (C₆D₆, 25 °C): δ = –5.8 (dt, ¹J(P,Rh) = 158 Hz, ²J(P,P) = 48 Hz), –14.1 (dd, ¹J(P,Rh) = 133 Hz, ²J(P,P) = 48 Hz); ¹¹B{¹H} NMR (C₆D₆, 25 °C): δ = –2.0; elemental analysis calcd for C₂₄H₄₉BN₆P₃Rh: C 45.9, H 7.9, N 13.4; found: C 45.7, H 7.8, N 13.7.

7b: A solution of PMe₃ in THF (0.6 mL, 1M, 0.6 mmol) was added to a solid sample of [TpRh(H)₂(PMe₃)] (0.03 g, 0.07 mmol). The mixture was heated at 50 °C for 30 min, after which ³¹P NMR spectroscopy revealed quantitative transformation into a new compound. The solvent was evaporated in vacuo, and the residue extracted with THF. After filtration and concentration under reduced pressure, the solution was cooled to –20 °C to yield white crystals of **7b** in about 40% yield. IR (Nujol): ν̄ = 2474 (B–H), 1955 cm^{–1} (Rh–H); ¹H NMR ([D₆]acetone, 25 °C): δ = 7.36, 7.28, 5.92 (d, d, t, ¹J(H,H) = 2.0 Hz, 3H each, 9 CH_{TP}), 4.97 (q, 1:1:1:1, ¹J(H,B) = 113.6, 1H, BH), 1.60 (pseudo-t, ¹J(H,P)_{app} = 3.2 Hz, 18H, 2 *trans*-PMe₃), 1.53 (d, ²J(H,P) = 7.0 Hz, 18H, 2 *cis*-PMe₃), –10.57 (dtd, ²J(H,P) = 136.6, 20.2, ¹J(H,Rh) = 15.0 Hz, 2H, 2 Rh–H); ¹³C{¹H} NMR ([D₆]acetone, 25 °C): δ = 138.7, 133.4, 102.6 (CH_{TP}), 25.3 (pseudo-t, ¹J(C,P)_{app} = 17 Hz, 2 *trans*-PMe₃), 21.9 (filled in d, ¹J(C,P)_{app} = 27 Hz, 2 *cis*-PMe₃); ³¹P{¹H} NMR ([D₆]acetone, 25 °C): δ = –13.0 (dt, ¹J(P,Rh) = 96, ²J(P,P) = 27 Hz), 23.9 (dt, ¹J(P,Rh) = 87, ²J(P,P) = 27 Hz); ¹¹B{¹H} NMR ([D₆]acetone, 25 °C): δ = –1.2; elemental analysis calcd for **7b** (C₂₁H₄₈BN₆P₄Rh): C 40.5, H 7.7, N 13.5; found: C 40.2, H 7.5, N 13.6.

Received: August 3, 1999 [Z13823]

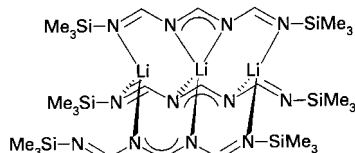
- [1] a) F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, *Advanced Inorganic Chemistry*, Wiley-Interscience, New York, **1999**; b) F. Bottomley, L. Sutin, *Adv. Organomet. Chem.* **1988**, 28, 339; c) R. Poli, *Chem. Rev.* **1991**, 91, 509.
- [2] a) S. Trofimenko, *Chem. Rev.* **1993**, 93, 943; b) G. Parkin, *Adv. Inorg. Chem.* **1995**, 42, 291; c) N. Kitajima, W. B. Tolman, *Prog. Inorg. Chem.* **1995**, 43, 418.
- [3] See, for example: a) H. Werner, H.-J. Kraus, *Angew. Chem.* **1979**, 91, 1013; *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 948; b) B. W. Hames, P. Legzdins, D. T. Martin, *Inorg. Chem.* **1978**, 17, 3644; c) M. D. Butts, R. G. Bergman, *Organometallics* **1994**, 13, 1899; d) W. D. Jones, V. L. Kuykendall, A. D. Selmeczy, *Organometallics* **1991**, 10, 1577.
- [4] J. M. O'Connor, C. P. Casey, *Chem. Rev.* **1987**, 87, 307.
- [5] C. P. Casey, J. M. O'Connor, K. J. Haller, *J. Am. Chem. Soc.* **1985**, 107, 1241.
- [6] For an early discussion of the tendency of Tp' ligands to coordinate in a tridentate fashion and to impose nearly octahedral coordination geometry on the metal center, see a) M. D. Curtis, K. B. Shi, W. M. Butler, *J. Am. Chem. Soc.* **1986**, 108, 1550; b) M. D. Curtis, K. B. Shi, W. M. Butler, J. C. Huffman, *J. Am. Chem. Soc.* **1986**, 108, 3335.
- [7] E. Gutiérrez, S. A. Hudson, A. Monge, M. C. Nicasio, M. Paneque, C. Ruiz, *J. Organomet. Chem.* **1998**, 551, 215.
- [8] a) U. E. Bucher, A. Currao, R. Nesper, H. Rüegger, L. M. Venanzi, E. Younger, *Inorg. Chem.* **1995**, 34, 66; b) R. G. Ball, C. K. Ghosh, J. K. Hoyano, A. D. McMaster, W. A. G. Graham, *J. Chem. Soc. Chem. Commun.* **1989**, 341; c) V. Chauby, C. Serra Le Berre, P. Kalck, J.-C. Daran, G. Commenges, *Inorg. Chem.* **1996**, 35, 6354.
- [9] E. Gutiérrez, S. A. Hudson, A. Monge, M. C. Nicasio, M. Paneque, E. Carmona, *J. Chem. Soc. Dalton Trans.* **1992**, 2651.
- [10] F. Malbosc, P. Kalck, J.-C. Daran, M. Etienne, *J. Chem. Soc. Dalton Trans.* **1999**, 271.
- [11] J. Reglinski, M. D. Spicer, M. Garner, A. R. Kennedy, *J. Am. Chem. Soc.* **1999**, 121, 2317.
- [12] a) M. Paneque, S. Taboada, E. Carmona, *Organometallics* **1996**, 15, 2678; b) A. Monge, M. C. Nicasio, M. Paneque, P. J. Pérez, A. Pizzano, M. L. Poveda, L. Rey, C. Ruiz, S. Sirol, S. Taboada, M. Trujillo, E. Carmona, *Inorg. Chem.*, in press.
- [13] [κ^2 -Tp^{Me2}Rh(PMe₃)₂] (**3**): IR (Nujol mull): $\tilde{\nu}$ = 2450 cm⁻¹ (BH); ³¹P{¹H} NMR (C₆D₆, 25 °C): δ = -2.4 (d, ¹J(P,Rh) = 171 Hz); ¹¹B{¹H} NMR (C₆D₆, 25 °C) δ = -5.6.
- [14] A. R. Jones, F. M. Real, G. Wilkinson, A. M. R. Galas, M. B. Hursthouse, K. M. A. Malik, *J. Chem. Soc. Dalton Trans.* **1980**, 551.
- [15] a) X-ray data for **4**: a crystal having approximate dimensions 0.20 × 0.35 × 0.35 mm was mounted on a Bruker-Siemens Smart CCD diffractometer equipped with a low-temperature device and a normal-focus 2.4-kW sealed-tube X-ray source (Mo_{Kα} radiation, λ = 0.71067 Å) operating at 50 kV and 20 mA. Data were collected over a quadrant by a combination of two exposure sets. Each exposure of 10 s covered 0.3° in ω . The unit cell dimensions were determined by a least-squares refinement on reflections with $I > 2\sigma$ and $6^\circ < 2\theta < 52^\circ$. The crystal-to-detector distance was 6.05 cm. Coverage of the unique set was over 92% complete to at least 23° in θ . The first 50 frames were recollected at the end of the data collection to monitor crystal decay. The intensities were corrected for Lorentzian and polarization effects. Scattering factors for neutral atoms and anomalous dispersion corrections for Rh and P were taken from the *International Tables for X-Ray Crystallography*.^[23] The structure was solved by Multan and Fourier methods. Full-matrix least-square refinement was carried out by minimizing $w(F_o^2 - F_c^2)^2$. Hydrogen atoms were included in their calculated positions, except for that coordinated to B, which was located in a Fourier synthesis and refined isotropically. Refinement was performed on F^2 for all reflections. Weighted R factors (R_w) and all goodness of fits were based on F^2 , and conventional R factors (R) on F . Most of the calculations were carried out with SMART^[24] software for data collection and reduction, and SHELXTL^[24] for structure solution and refinements. Crystal data: M_r = 628.32; monoclinic, space group $P2_1/c$, a = 12.5927(9) Å, b = 12.3861(9) Å, c = 20.773(2) Å, β = 93.6140(10)°, V = 3233.6(4) Å³, Z = 4, ρ_{calcd} = 1.291 g cm⁻³, $F(000)$ = 1320, T = 148(2) K. Of the 9001 reflections collected, 5245 were unique (R_{int} = 0.0223). Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0329, wR_2 = 0.0733. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications nos. CCDC-132889 (**4**) and CCDC-132888 (**7b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [16] Y. Takahashi, M. Akita, S. Hikighi, Y. Moro-oka, *Organometallics* **1998**, 17, 4884.
- [17] M. Akita, K. Ohta, Y. Takahashi, S. Hikichi, Y. Moro-Oka, *Organometallics* **1997**, 16, 4121.
- [18] T. O. Northcutt, R. J. Lachicotte, W. D. Jones, *Organometallics* **1998**, 17, 5148.
- [19] [κ^2 -Tp^{Me2}Rh(H)₂(PMe₃)₂] (**6a**): IR (Nujol): $\tilde{\nu}$ = 2484 (B-H), 2068, 2045 cm⁻¹ (Rh-H); ¹H NMR (C₆D₆, 25 °C): δ = 5.84, 5.74 (s, 2:1, 3 H, 3CH_{pz}), 2.41, 2.32, 2.15, 1.73 (s, 2:2:1:1, 18 H, 6Me_{pz}), 1.13 (d, ²J(H,P) = 5.5 Hz, 9 H, PMe₃), 0.55 (d, ²J(H,P) = 4.8 Hz, 9 H, PMe₃), -17.22 (q, ¹J(H,Rh) = ²J(H,P) = 20.8 Hz, 2 H, 2Rh-H); ¹³C{¹H} NMR (C₆D₆, 25 °C): δ = 151.0, 150.0, 146.0, 141.4 (2:2:1:1, C_q (pz)), 107.0, 105.6 (2:1, CH_{pz}), 19.3 (dd, ¹J(C,P) = 19, ³J(C,P) = 12 Hz; PMe₃), 18.0 (dd, ¹J(C,P) = 17, ³J_{CP} = 11 Hz, PMe₃), 17.0, 14.3, 14.0, 11.3 (2:2:1:1; Me_{pz}); ³¹P{¹H} NMR (C₆D₆, 25 °C): AB part of an ABX spin system centered at δ = -4.0, $J(A,Rh) = J(B,Rh) = 107$ Hz; $J(AB)$ could not be separated from the spectrum because the smallest signals of the AB spin system were not located; ¹¹B{¹H} NMR (C₆D₆, 25 °C): δ = -6.0.
- [20] R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1971**, 93, 2397.
- [21] While this manuscript was being prepared, we learned that related Rh^I complexes containing a " κ^0 "-Tp' group (Tp' = Tp^{Me2}, 4-Cl) can be obtained from [Tp'Rh(CO)₂] and PMePh₂ or Ph₂P(CH₂)₃PPh₂: P. Kalck, personal communication.
- [22] X-ray data for **7b**: the X-ray structural determination of **7b** was carried out on a crystal of approximate dimensions 0.08 × 0.10 × 0.14 mm by the same procedure as for compound **4**^[15a] but in this case data were collected over an hemisphere of the reciprocal space by combination of three exposure sets. The H atoms coordinated to Rh were located in Fourier synthesis and refined isotropically. Crystal data: M_r = 622.25; triclinic, space group $P1$, a = 9.4968(13), b = 9.7223(13), c = 9.8279(13) Å, α = 60.891(2), β = 85.285(2), γ = 80.050(2)°, V = 780.9(2) Å³, Z = 1, ρ_{calcd} = 1.323 g cm⁻³, $F(000)$ = 326, T = 143(2) K. Of the 3680 reflections collected, 3210 were unique (R_{int} = 0.0261). Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0417, wR_2 = 0.0925.^[15b]
- [23] *International Tables for X-Ray Crystallography*, Kynoch Press: Birmingham, U. K., **1974**.
- [24] SHELXTL, Siemens Energy & Automation Inc., Analytical Instrumentation, **1996**.

Synthesis and Structures of 1,3,5,7-Tetraazaheptatrienylsodium and -thallium(I)**

W. Marco Boesveld, Peter B. Hitchcock, Michael F. Lappert,* and Heinrich Nöth

Organolithium compounds are important as reagents in both organic and inorganic chemistry. For this reason their structures have been extensively investigated in solution and in the solid state.^[1] Structures of the heavier alkali metal organic compounds are also attracting increasing interest.^[2] Although the chemistry of thallium(I) compounds bears some resemblance to that of alkali metal analogues, thallium(I) bis(trimethylsilyl)amide was only recently structurally characterized,^[3] whereas the alkali metal bis(trimethylsilyl)amides have been known since the 1960s.^[4] The alkali metal amides have proved their versatility as bulky bases, amido-ligand transfer reagents, polymerization initiators, and in insertion reactions with unsaturated polar organic compounds containing C–O or C–N multiple bonds.

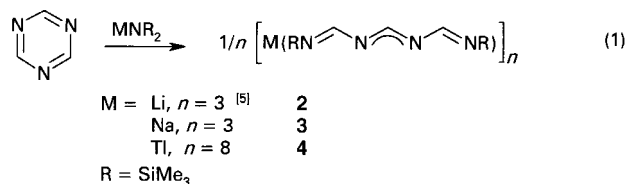
We have described the reaction of $\text{LiN}(\text{SiMe}_3)_2$ with 1,3,5-triazine (**1**) yielding the 1,3,5,7-tetraazaheptatrienyllithium complex **2**, involving both formally an $\alpha \rightarrow \omega$ Me_3Si shift and



2

ring opening.^[5] We now report on the reactions of the corresponding sodium and thallium(I) amides $\text{MN}(\text{SiMe}_3)_2$ ($\text{M} = \text{Na}, \text{Tl}$) with **1**, and the structures of the novel products, 1,3,5,7-tetraazaheptatrienylsodium (**3**) and -thallium(I) (**4**).

1,3,5-Triazine (**1**) was allowed to react at -20°C in tetrahydrofuran with sodium bis(trimethylsilyl)amide, or in toluene with thallium(I) bis(trimethylsilyl)amide, to give a green-gray or black suspension which afforded colorless crystals of **3** or **4** in 70% and 66% yield, respectively [Eq. (1)].



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[**] We thank the European Union for a HCM grant (category 20) for W.M.B. and the Engineering Physical Sciences Research Council for other support.

Compounds **3** and **4** are both air- and moisture-sensitive, and very soluble in hydrocarbons. Each was characterized by elemental analysis, multinuclear NMR spectroscopy, and single crystal X-ray structure analysis.

The X-ray molecular structure of the crystalline sodium complex **3** shows the presence of two crystallographically independent, trinuclear molecules and a disordered cyclohexane molecule in the unit cell. Each of the three-coordinate sodium atoms Na1 and Na3 is in a distorted trigonal planar environment (the sum of the angles being $349.6(2)$ and $349.2(2)^\circ$, respectively); the average Na–N bond length is $2.46 \text{ \AA}$ (Figure 1). The remaining sodium atom Na2 is at the

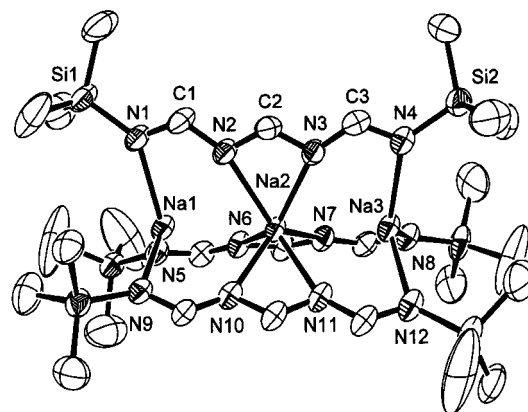


Figure 1. ORTEP representation of **3** with selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: N1–C1 1.275(7), C1–N2 1.380(7), N2–C2 1.316(7), C2–N3 1.311(7), N3–C3 1.360(7), C3–N4 1.269(7), Na1–N1 2.462(5), Na1–N5 2.475(5), Na1–N9 2.440(5), Na2–N2 2.452(5), Na2–N3 2.397(5), Na2–N6 2.432(5), Na2–N7 2.404(5), Na2–N10 2.381(5), Na2–N11 2.466(5); N2–C2–N3 $122.4(5)$, N1–Na1–N5 $118.1(2)$, N1–Na1–N9 $111.3(2)$, N5–Na1–N9 $120.2(2)$, N2–Na2–N3 $56.7(2)$, N2–Na2–N6 $99.3(2)$, N3–Na2–N6 $132.4(2)$.

center of a distorted trigonal prism (the central lithium atom in **2** is at the center of a distorted tetrahedron),^[5] comprising the two triangular faces N2, N10, N6 and N3, N7, N11 (the sum of the angles subtended by each of these atoms at Na2 is $298.1(2)$ and $298.5(2)^\circ$, respectively); the average Na–N bond length is $2.42 \text{ \AA}$, and thus similar to the Na–N bond length in benzamidate systems.^[6] Each organic ligand has very similar bond lengths (also when compared to the ligands in the lithium complex **2**, although in **2** they have slipped with respect to each other);^[5] N1–C1 and N4–C3 are double bonds (ca. $1.27 \text{ \AA}$), C3–N3 and C1–N2 are short single bonds (ca. $1.37 \text{ \AA}$); and N3–C2 and C2–N2 have bond lengths characteristic for a delocalized system (ca. $1.31 \text{ \AA}$).^[7] These assignments are consistent with the coplanarity of the atoms Si1, N1, C1, N2, C2, N3, C3, N4, and Si2; the largest deviation from the mean plane is $0.080 \text{ \AA}$. In summary, we conclude that this novel structural type comprises three sodium cations forming an axis to which the three anionic ligands coordinate. The projection of **3** along its Na–Na–Na axis shows the molecule to have approximate C_3 symmetry (Figure 2). To the best of our knowledge, only two other trinuclear sodium amides, $[\text{Na}\{\mu\text{-N}(\text{SiMe}_3)_2\}]_3$ ^[8] and $[\text{Na}\{\mu\text{-NC}(\text{Me})_2(\text{CH}_2)_3\text{CMe}_2\}]_3$,^[9] and one aryl-ligand complex, $[\text{Na}\{\mu\text{-2,6-(CH}_2\text{NMe}_2)_2\text{C}_6\text{H}_3\}]_3$,^[10] were previously known; each of these three complexes are, unlike trinuclear **3**, divisible into three identical monomeric units.

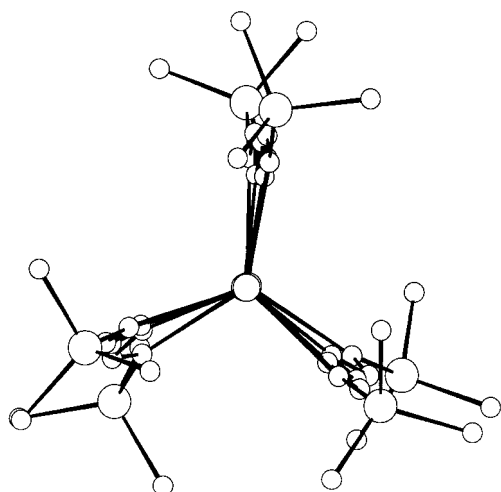


Figure 2. Projection of **3** along its Na-Na-Na axis showing pseudo- C_3 symmetry.

The thermal stability of this trinuclear sodium complex **3** is remarkable. The EI mass spectrum showed the molecular ion and more intense fragment ions corresponding to loss of one ligand; the dinuclear ion was the base peak. The $^{23}\text{Na}\{^1\text{H}\}$ NMR spectrum of **3** at ambient temperature in $[\text{D}_8]\text{toluene}$ showed a signal at $\delta = 25.0$ ($w_{1/2} = 0.36$ kHz) and another centered at $\delta = 9$ ($w_{1/2} = 2.2$ kHz) in a ratio of approximately 1:2, and these signals coalesced at around 98°C . Thus, compound **3**, like **2**,^[5] evidently retains its trinuclear structure in solution and in the gas phase. The excellent coordination of the ligands to the sodium cations is also apparent from the fact that **3**, like **2**, is unresponsive to strongly coordinating, neutral donor molecules, such as tetramethylethylenediamine and pentamethyldiethylenetriamine.

The molecular structure of crystalline **4** consists of two symmetry-related tetranuclear units that form a rather asymmetric and unprecedented structure (Figure 3). The atom Tl1 is four-coordinate (distances to Tl2 3.76; Tl3 3.68; N41 2.59; N63 2.51 Å), Tl2 is three-coordinate (distances to Tl1 3.76; N1 2.655; N25 2.49 Å), Tl3 is five-coordinate (distances to Tl1 3.84; Tl4' 3.89; N45 2.54; N65 2.75; N67 2.60 Å), and Tl4 is three-coordinate (distances to Tl3' 3.57; N5 2.495; N21 2.58 Å). The structure is best described as comprising four units each consisting of two thallium atoms and two $[\{\text{Me}_3\text{SiNC}(\text{H})\text{N}\}_2\text{CH}\}^-$ ligands with Tl–N bond lengths in the unexceptional range of 2.49–2.75 Å. Each ligand bonds to two thallium atoms, and each thallium atom bonds to two ligands, that is, two ligands to Tl1 and Tl3 and two to Tl2 and Tl4. Short internuclear Tl1–Tl2, Tl1–Tl3 and Tl3–Tl4 distances of around 3.76, 3.65, and 3.89 Å, respectively, and additional metal–ligand contacts lead to the formation of a “cluster”. Although polynuclear thallium(I) compounds are well known and often have relatively short Tl...Tl contacts,^[11] only one octanuclear structure, $[\{\text{TlSi}t\text{Bu}\}_8]$, was previously reported.^[12] Recent examples of thallium(I) amides having Tl^I...Tl^I contacts of about 3.7 Å and Tl^I–N bond lengths of about 2.45 Å include $[\{\text{TlN}(\text{SiMe}_3)\text{CH}_2\}_2\text{CH}_2]$ ^[13] and $[\{\text{TlN}(\text{SiMe}_3)\text{CH}_2\}_3\text{CR}']_2$ ($\text{R}' = \text{Me},^{[14]} \text{Ph}^{[15]}$).

The ligand $[\{\text{Me}_3\text{SiNC}(\text{H})\text{N}\}_2\text{CH}\}^-$ coordinates differently to thallium in **4** than to sodium in **3**, in that only N1 and N5,

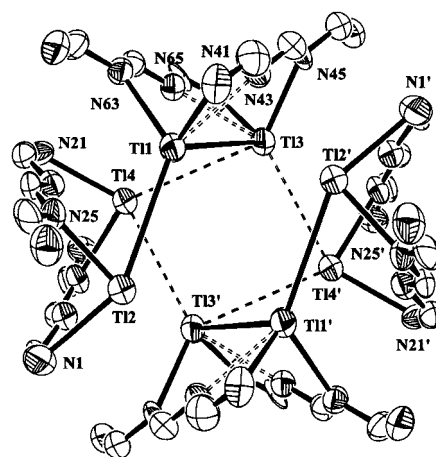


Figure 3. The core of the molecular structure of **4**. Hydrogen atoms and Me_3Si groups are omitted. Selected bond lengths [Å] and angles $^\circ$: Tl1–Tl2 3.7591(9), Tl1–Tl3 3.6788(9), Tl3–Tl4 3.887(1), Tl1...Tl4 3.965(1), Tl2...Tl3' 3.947(1), Tl3...Tl4' 4.000(1), Tl2...Tl4 4.601(2), Tl1–N41 2.592(14), Tl1–N43 2.794(13), Tl1–N63 2.511(10), Tl2–N1 2.65(14), Tl2–N25 2.489(12), Tl3–N45 2.541(11), Tl3–N65 2.747(11), Tl3–N67 2.602(14), Tl4–N5 2.495(12), Tl4–N21 2.582(12), N1–C2 1.24(2), C2–N3 1.38(2), N3–C4 1.332(19), C4–N5 1.335(19), N5–C6 1.38(2), C6–N7 1.253(19); N3–C4–N5 121.6(15), N5–Tl4–N21 89.5(4), N45–Tl3–N67 87.8(4), N63–Tl1–N41 91.0(4), N65–Tl3–N67 50.9(4), Tl1–Tl3–Tl4' 109.8, Tl2–Tl1–Tl3 112.44(2).

but not N7, bind to the metal in **4**. This, however, is not reflected in the intraligand bond lengths which are similar in **2–4**; thus, for **4** the approximate bond lengths for N1–C2 and C6–N7 are 1.25 Å, for C2–N3 and C6–N5 1.38 Å, and for C4–N3 and C4–N5 1.33 Å.

In the ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR solution spectra at ambient temperature, ^{203}Tl or ^{205}Tl couplings were not observed, possibly due to a dynamic exchange process or because Tl–CH interactions were absent.

Each of **2–4** consists of cationic metal atoms and anionic, planar, delocalized $[\{\text{Me}_3\text{SiNC}(\text{H})\text{N}\}_2\text{CH}\}^-$ ligands. Their structures differ, however, due to weak metal–metal interactions present in **4**, but not in **2** or **3**. We expect **3** and **4** to be significant additions to **2** as ligand-transfer reagents for the synthesis of new unusual, highly thermally stable and lipophilic metal complexes.

Experimental Section

3: 1,3,5-Triazine (**1**) (1.07 g, 13.2 mmol) was added to a solution of $\text{NaN}(\text{SiMe}_3)_2$ (2.42 g, 13.2 mmol) in THF (75 mL) at -20°C . The reaction mixture was allowed to warm to ambient temperature and stirred for 4 h. Volatiles were removed in vacuo, and the residue was extracted with pentane (2×200 mL) to give the analytically pure solid **3** (2.46 g, 70%). Recrystallization from hexane yielded colorless single crystals suitable for X-ray structure analysis. Mp $201\text{--}204^\circ\text{C}$ (decomp); elemental analysis $\text{C}_{27}\text{H}_{63}\text{Na}_3\text{N}_2\text{Si}_6$ (%): calcd: C 40.9, H 8.00, N 21.2; found: C 41.3, H 7.97, N 21.2; ^1H NMR (300.13 MHz, C_6D_6 , 293 K): $\delta = 8.30$ (s, 6H), 8.08 (s, 3H), 0.32 (s, 54H, SiMe_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.47 MHz): $\delta = 180.2$ $[\{\text{Me}_3\text{SiNC}(\text{H})\text{N}\}_2\text{CH}\}^-$, 170.9 $[\{\text{Me}_3\text{SiNC}(\text{H})\text{N}\}_2\text{CH}\}^-$, 0.5 (SiMe_3); $^{23}\text{Na}\{^1\text{H}\}$ NMR (66.17 MHz): $\delta = 25.0$ ($w_{1/2} = 0.36$ kHz, 1Na), 9 ($w_{1/2} \approx 2.2$ kHz, 2Na); MS (EI; $M = \text{L}_3\text{Na}_3$): m/z (%): 792 ($[\text{L}_3\text{Na}_3]^+$, 4), 551 ($[\text{L}_2\text{Na}_3]^+$, 44), 287 ($[\text{LNa}_3]^+$, 100).

4: 1,3,5-Triazine (**1**) (1.24 g, 15.3 mmol) was added to a solution of $\text{TlN}(\text{SiMe}_3)_2$ (freshly sublimed, 6.18 g, 17.0 mmol) in toluene at -20°C . The mixture was protected from light, and stirring was continued at ambient temperature for 12 h. The organic layer was filtered and volatiles were

evaporated in vacuo from the filtrate to afford the air-sensitive, analytically pure **4** (4.48 g, 66%). Colorless, single crystals suitable for X-ray structure analysis were obtained from hexane. Elemental analysis $C_{72}H_{168}N_{32}Si_{16}Ti_8$ (%): calcd: C 24.25, H 4.75, N 12.6; found: C 25.9, H 4.80, N 12.4; ^1H NMR (500.13 MHz, $C_6D_5CD_3$, 293 K): δ = 9.72 (s, 2H), 8.45 (s, 1H), 0.21 (s, 18H, $SiMe_3$); $^{13}C\{^1H\}$ NMR (125.76 MHz): δ = 175.5, 167.45, 0.6.

Crystal data for **3**: $C_{27}H_{63}Na_3N_{12}Si_6(C_6H_{12})_{1/2}$, M_r = 835.5, triclinic, space group $P\bar{1}$ (no. 2), a = 10.372(8), b = 22.57(2), c = 23.50(2) Å, α = 92.76(6), β = 102.75(5), γ = 103.25(6)°, V = 5194(7) Å³, Z = 4, ρ_{calcd} = 1.07 g cm⁻³, $\lambda(MoK\alpha)$ = 0.71073 Å, $\mu(MoK\alpha)$ = 2.2 cm⁻¹. Data for a specimen of dimensions 0.4 × 0.4 × 0.4 mm³ were collected at 173(2) K on an Enraf-Nonius CAD-4 diffractometer, 14448 unique reflections for $2^\circ < \theta < 23^\circ$, R_1 = 0.078 (for 9400 reflections with $I > 2\sigma(I)$), wR_2 = 0.235 (all data). In **3** there are two independent molecules of the trimer and one poorly defined cyclohexane solvent molecule. For **4**: $C_{72}H_{168}N_{32}Si_{16}Ti_8$, M_r = 3566.8, monoclinic, space group $C2/c$, a = 15.6556(4), b = 30.3470(9), c = 30.2663(3) Å, β = 96.195(1)°, V = 14295.6(6) Å³, Z = 4, ρ_{calcd} = 1.657 g cm⁻³, $\lambda(MoK\alpha)$ = 0.71073 Å, $\mu(MoK\alpha)$ = 0.9159 cm⁻¹. Data for a specimen of dimensions 0.33 × 0.21 × 0.12 mm³ were collected at 193 K in the hemisphere mode on a Siemens P4 instrument fitted with a CCD area detector, 8557 unique reflections for $4.6^\circ < \theta < 54^\circ$, R_1 = 0.0565 (for 6019 reflections with $I > 2\sigma(I)$), wR_2 = 0.1443 (all data). Each of the structures **3** and **4** was solved by using the heavy atom method and refined with full-matrix least-squares on all F^2 (SHELXL-93 and 97, respectively) with non-hydrogen atoms anisotropic.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133067 and -133068. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received: August 2, 1999 [Z13815]

- [1] *Lithium Chemistry: A Theoretical and Experimental Overview* (Eds.: A.-M. Sapse, P. von R. Schleyer), Wiley, New York, 1995, and references therein.
- [2] a) J. D. Smith, *Adv. Organomet. Chem.* **1999**, *43*, 267; b) E. Weiss, *Angew. Chem.* **1993**, *105*, 1565; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1501.
- [3] K. W. Klinkhammer, S. Henkel, *J. Organomet. Chem.* **1994**, *480*, 167.
- [4] M. F. Lappert, P. P. Power, A. R. Sanger, R. C. Srivastava, *Metal and Metalloid Amides*, Ellis-Horwood, Chichester, 1980.
- [5] W. M. Boesveld, P. B. Hitchcock, M. F. Lappert, *Chem. Commun.* **1997**, 2091; W. M. Boesveld, P. B. Hitchcock, M. F. Lappert, *J. Chem. Soc. Dalton Trans.*, **1999**, 4041.
- [6] D. Stalke, M. Wedler, F. T. Edelman, *J. Organomet. Chem.* **1992**, *431*, C1.
- [7] a) J. Barker, M. Kilner, *Coord. Chem. Rev.* **1994**, *133*, 219; b) F. A. Cotton, J. H. Matonic, C. A. Murillo, *Inorg. Chem.* **1996**, *35*, 498; c) M. Burke-Laing, M. Laing, *Acta Crystallogr. Sect. B* **1976**, *32*, 3216.
- [8] a) J. Knizek, I. Krossing, H. Nöth, H. Schwenk, T. Seifert, *Chem. Ber.* **1997**, *130*, 1053; b) M. Driess, H. Pritzkow, M. Skipinski, U. Winkler, *Organometallics* **1997**, *16*, 5108.
- [9] B. Gehrhus, P. B. Hitchcock, A. R. Kennedy, M. F. Lappert, R. E. Mulvey, P. J. A. Roger, *J. Organomet. Chem.* **1999**, *587*, 88.
- [10] R. den Besten, L. Brandsma, A. L. Spek, J. A. Kanters, N. Veldman, *J. Organomet. Chem.* **1995**, *498*, C6.
- [11] C. Janiak, *Coord. Chem. Rev.* **1997**, *163*, 107.
- [12] B. Krebs, A. Brömmelhaus, *Angew. Chem.* **1989**, *102*, 1726; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1682; B. Krebs, A. Brömmelhaus, *Z. Anorg. Allg. Chem.* **1991**, *595*, 167.
- [13] K. W. Hellmann, L. H. Gade, R. Fleischer, D. Stalke, *Chem. Commun.* **1997**, 527.
- [14] K. W. Hellmann, L. H. Gade, R. Fleischer, T. Kottke, *Chem. Eur. J.* **1997**, *3*, 1801.
- [15] C. H. Galka, L. H. Gade, *Inorg. Chem.* **1999**, *38*, 1038.

Genetic Engineering of *Streptomyces coelicolor* A3(2) for the Enantioselective Reduction of Unnatural β -Keto-Ester Substrates**

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The use of whole cells for the biotransformation of organic substrates is a well-documented technique^[1] which has a number of benefits over conventional, reagent-based methods. For example, bakers' yeast is routinely used for the reduction of β -keto-esters, and the resulting β -hydroxy-esters are obtained with predictably high chemo- and enantioselectivities, under mild and neutral conditions.^[2] With the huge advances made in molecular biology over the last 20 years it has become possible to manipulate microbial biosynthetic pathways at the genetic level.

For a number of years Hopwood et al.^[3] and others^[4] have been studying the genetics of *Streptomyces coelicolor* A3(2), a soil bacterium that produces the dimeric benzoisochromanone antibiotic actinorhodin (**1**). The biosynthesis of **1** proceeds by the polyketide pathway outlined in Scheme 1,^[5] where key features involve a type II minimal *act* polyketide synthase (PKS)—consisting of β -ketoacyl synthase (KS), chain length factor (CLF), and acyl carrier protein (ACP)—and associated aromatase and cyclase enzymes to assemble the naphthol **2**, which undergoes selective reduction to **3** and cyclization to the yellow pigment (*S*)-DNPA (**4**). Recently we have provided definitive proof that the *actVI* genetic region of *S. coelicolor* A3(2) is involved in the stereospecific construction of the pyran ring of **1**.^[6] More specifically it was found that the engineered strain CH999/pIJ5660 (a pRM5-based plasmid^[4b] containing the *act* minimal PKS, aromatase (ARO), and cyclase (CYC) genes as well as the *actVI*-

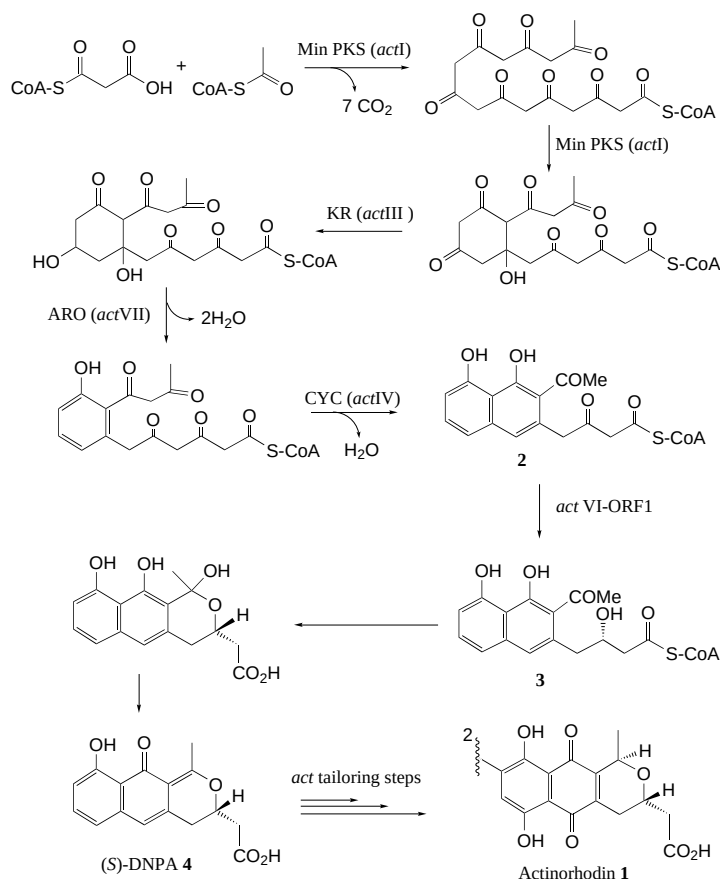
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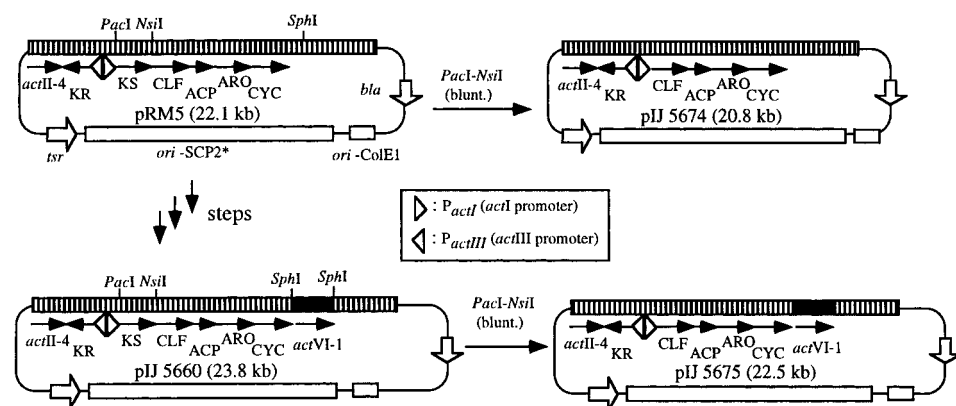
[**] This work was supported by a BBSRC Clean Technology Grant (CT04273; to D.A.H., G.R.S., and K.I.B.-M.), by a Norwich Research Park studentship (C.M.S.), and by the John Innes Foundation (D.A.H.).



Scheme 1. Biosynthesis of actinorhodin (**1**). CoA = coenzyme A.

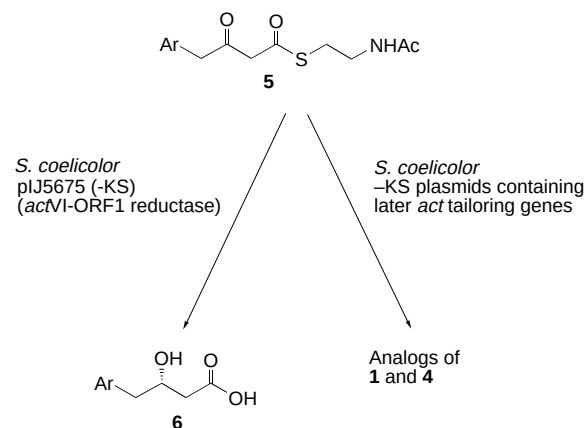
ORF1 gene) produced **4** with complete selectivity. This clearly indicates that the *actVI-ORF1* gene encodes the reductase that selectively reduces C-3 in the β -keto-ester **2**, thus ultimately creating one of the corresponding stereocentres in the pyran ring of **1** (Scheme 1).

Here we describe the construction of pIJ5675, a pRM5-based recombinant plasmid containing the *actVI-ORF1* gene,



Scheme 2. Scheme for the construction of the recombinant plasmids. The starting plasmid, pRM5, is bifunctional for replication in both *E. coli* (ColE1 replicon; *ori-ColE1*) and *Streptomyces* (SCP2* replicon; *ori-SCP2**). Selection marker genes used: *bla* (β -lactamase) for *E. coli*, *tsr* (thiostrepton resistance) for *Streptomyces*. The *act* genes to be expressed: *actII-4* (pathway-specific activator), KR (ketoreductase), KS (β -ketoacyl synthase), CLF (chain length factor), ACP (acyl carrier protein), ARO (aromatase), CYC (cyclase). pIJ5660 was constructed by introducing *actVI-ORF1* gene at the *SphI* site downstream of the CYC as described previously.^[5] KS (–) derivatives of pRM5 and pIJ5660 were constructed in *E. coli* as follows: 1) restriction digests with the unique sites, *PacI* and *NsiI*, to remove the 1.3-kb KS gene; 2) treatment with T4 DNA polymerase to generate blunt ended fragments; 3) blunt-end ligation to afford pIJ5674 and pIJ5675.

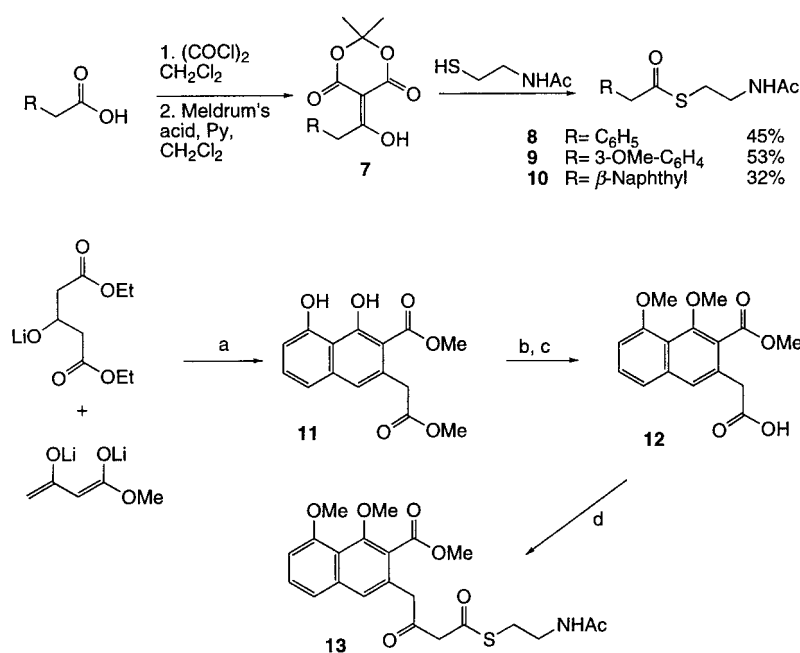
like pIJ5660, but in which a gene (*actI-ORF1*) for the ketosynthase (KS) has been deleted from the minimal *act* PKS gene cluster (Scheme 2). This was carried out with the express aim of feeding unnatural β -keto-ester substrates such as **5** (Scheme 3) so that the action of the *actVI-ORF1* reductase would lead to the stereospecific formation of analogues of **3** (e.g. **6**).^[7] Since pIJ5675 lacks the KS gene involved in the formation of the early polyketide products by the natural pathway shown in Scheme 1 the natural substrate **2** would



Scheme 3. Feeding of the unnatural β -keto-ester substrates **5**.

not be formed and therefore there would be no competition between **2** and unnatural substrates such as **5**. The results reported herein prepare the way for the initiation of a larger, more ambitious program involving the construction of KS-deficient plasmids to which the feeding of unnatural substrates may allow the biosynthesis of functionalized analogues of **4** and eventually **1**.

The *N*-acetylcysteamine (NAC) thioesters were chosen as they are known to be good analogues of SCoA.^[8] The substrates **8–10** were prepared from the corresponding arylacetic acid chlorides using the methodology developed by Gilbert et al.^[9] Thus, treatment of the Meldrum's acid derivatives **7** with *N*-acetylcysteamine leads to the NAC thioesters in reasonable overall yield from the starting acids (Scheme 4). We also sought to prepare the more complex NAC thioester **13**, closely resembled the natural substrate **2** in the actinorhodin pathway. The basic naphthalene core of **13** was easily assembled using the elegant methodology developed by Yamaguchi et al.^[10] and furnished multigram quantities of the diester **11** in an operationally simple, though low yielding step. Protection of the phenolic units followed by selective ester hydrolysis gave the acid ester **12** in excellent yield. Attempts to form **13** by the above



Scheme 4. Synthesis of substrates **8–10** and **13**. a) Ref. [10]; b) MeI, K₂CO₃, acetone, reflux, 88%; c) KOH, MeOH, H₂O, 93%; d) carbonyl diimidazole, THF, 6 h, then 5 equiv of Mg(O₂CCH₂COSCH₂CH₂NHAc)₂ (**14**), THF, room temperature, 8 h, 70% overall.

methodology failed with this more advanced intermediate due to the instability of the acid chloride. An alternative procedure was developed by which the required NAC thioester **13** could be synthesized in high yield by conversion of **12** into the corresponding acyl imidazole^[11] followed by reaction with an excess of the magnesium half thioester salt **14** of *N*-acetylcysteamine (Scheme 4).

The four substrates **8**, **9**, **10**, and **13** were then incubated with mycelium of CH999/pIJ5675 (CH999 is *S. coelicolor* with the natural *act* gene cluster deleted^[4b]) in a liquid YEME medium^[3a] under sterile conditions at 30 °C for two days. After centrifugation and extraction the crude β -hydroxy acids were esterified to aid purification, and the resulting methyl esters

(**15–18**) were purified by column chromatography. The results are summarized in Table 1. The enantioselectivity in each case was determined by NMR spectroscopy using a combination of chiral shift reagents and Mosher ester derivatives.^[12] In all four cases the reduced β -hydroxy esters were obtained with good to excellent enantioselectivity (55–99% *ee*). Particularly noteworthy in that respect is the lactone **18**, which was formed as essentially a single enantiomer by cyclization of the initially formed β -hydroxy acid. This high selectivity is attributed to the close structural similarity between the NAC thioester **13** and the natural substrate of the *actVI*-ORF1 reductase (i.e., **2**).

The molecular structure of **18** was confirmed by X-ray crystallography (Figure 1).^[13] It was also found that *N*-acetylcysteamine thioesters were essential because simple Me or *t*Bu esters were not reduced by CH999/pIJ5675. This indicates that NAC thioesters are required for recognition by the *actVI*-ORF1 reductase and/or they are required for successful transport across the cell membrane. Finally, as a control,

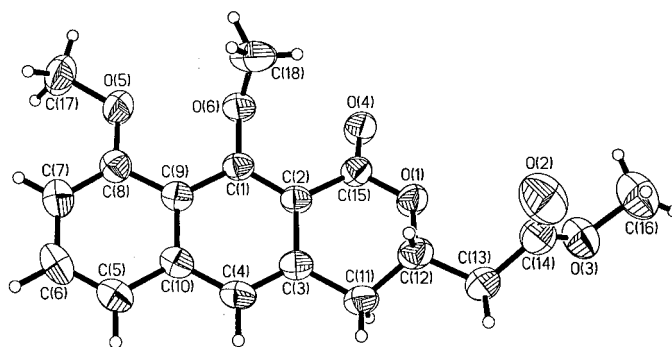


Figure 1. Molecular structure of tricyclic lactone **18** with 50% probability thermal ellipsoids.

Table 1. Enantioselective reduction of NAC thioesters by the recombinant *S. coelicolor* A3(2) strain CH999/pIJ5675.

NAC substrate	Product	Yield [%]	<i>ee</i> [%] ^[a]	$[\alpha]_D^{25}$ ^[b]
		18	85	+ 1.2 (<i>c</i> = 0.9)
		27	74	+ 1.1 (<i>c</i> = 0.8)
		55	55	+ 1.0 (<i>c</i> = 1.77)
		42	99	– 39.2 (<i>c</i> = 1.0)

[a] Determined by ¹H NMR spectroscopy using Mosher ester derivatives and confirmed with a chiral shift reagent (1 mg of substrate per 0.5 ml of CDCl₃; 1 equiv of [Eu(hfc)₃] (hfc = 3-(heptafluoropropyl-hydroxymethylene)-D-camphorate). [b] Concentration in grams per 100 ml of CH₂Cl₂.

the plasmid CH999/pIJ5674 was prepared which lacks both the KS and *actVI*-ORF1 genes (Scheme 2). Feeding of all four substrates (**8**–**10**, **13**) to this strain gave no reduction products. These results are highly significant in that they prove that the *actVI*-ORF1 gene is indeed the source of the reductase responsible for the formation of **15**–**18** and it is the same reductase that plays a role in the biosynthesis of actinorhodin.

In summary, these results establish, for the first time, the feasibility of novel biotransformations based on KS-deficient strains of *S. coelicolor*. We believe that this study has provided the groundwork for the engineering of more elaborate multienzyme constructs that will hopefully allow the biotransformation of simple NAC thioesters into complex, enantiopure, analogues of (*S*)-DNPA (**4**) and actinorhodin (**1**).

Experimental Section

Under sterile conditions a 250-ml conical flask was charged with 50 ml of YEME media, and a suspension of CH999/pIJ5675 spores in glycerol (0.2 ml) was added. In a separate flask the same procedure was repeated with CH999/pIJ5660 as an indicator of secondary metabolite production. The cultures were incubated on an orbital shaker at 30 °C until the indicator had turned dark brown (approx. 2 d). A solution of the NAC thioester **13** (0.15 g, 0.336 mmol) was dissolved in methanol (1 ml) and added to the CH999/pIJ5675 culture, which was shaken for a further 2 d at 30 °C. After centrifugation the supernatant was decanted and acidified to pH 1 with 2 M HCl, saturated with sodium chloride, and extracted with ethyl acetate (2 × 100 ml). The solvent was removed in vacuo to give a brown residue, which was dissolved in anhydrous methanol (1 ml) and then added to a premixed solution of acetyl chloride (0.2 g, 2.54 mmol) in anhydrous methanol (10 ml). The resulting solution was stirred for 15 min, and then the solvent removed in vacuo to give a brown residue. Purification by flash chromatography over silica gel (EtOAc/petroleum ether 30/70) gave the lactone **17** as white solid (46 mg, 42 %). M.p. 210–211 °C (from EtOAc/petroleum ether 40/60); $[\alpha]_D^{25} = -39.2$ ($c = 1.0$ in CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu} = 2956, 2840, 1734, 1624, 1564, 1462 \text{ cm}^{-1}$; $^1\text{H NMR}$ (300 MHz, CDCl_3 , 25 °C, TMS): $\delta = 2.7$ (dd, $^3J(\text{H,H}) = 16$, $^3J(\text{H,H}) = 7 \text{ Hz}$, 1H; $\text{CH}_2\text{CO}_2\text{Me}$), 2.9 (dd, $^2J(\text{H,H}) = 16$, $^3J(\text{H,H}) = 6 \text{ Hz}$, 1H; $\text{CH}_2\text{CO}_2\text{Me}$), 3.1 (ddd, $^2J(\text{H,H}) = 16$, $^3J(\text{H,H}) = 10$, $^4J(\text{H,H}) = 1 \text{ Hz}$, 1H; aryl- CH_2), 3.15 (ddd, $^2J(\text{H,H}) = 16$, $^3J(\text{H,H}) = 3.5$, $^4J(\text{H,H}) = 0.5 \text{ Hz}$, 1H; aryl- CH_2), 3.68 (s, 3H; CO_2Me), 4.0 (s, 6H; $2 \times$ aryl-OMe), 5.9 (m, 1H, $\text{CH}_2\text{CHOCH}_2$), 6.9 (dd, $^3J(\text{H,H}) = 8$, $^4J(\text{H,H}) = 0.5 \text{ Hz}$, 1H; aryl-H), 7.3 (dd, $^3J(\text{H,H}) = 8$, $^4J(\text{H,H}) = 1 \text{ Hz}$, 1H; aryl-H), 7.36 (s, 1H, aryl-H), 7.5 (approx. t, $^3J(\text{H,H}) = 8 \text{ Hz}$; aryl-H); $^{13}\text{C NMR}$ (67.5 MHz, CDCl_3 , 25 °C, CHCl_3): $\delta = 34.2$ (CH_2), 39.3 (CH_2), 52.0 and 56.3 ($2 \times$ aryl-OMe), 63.5 (CO_2CH_3), 73.7 ($\text{CH}_2\text{CHOCH}_2$), 106.6 (aryl-CH), 120.1 (aryl-CH), 121.5 (aryl-CH), 129.7 (aryl-CH), 134.8 (aryl-C), 139.1 (aryl-C), 157.9 (C=O, lactone), 161.7 (aryl-C), 162.0 (aryl-C), 170.1 (C=O, ester); HR-MS: calcd for $\text{C}_{18}\text{H}_{18}\text{O}_6$ (M^+): 330.1103, found: 330.1098.

Received: June 24, 1999 [Z13628]

- [1] H. G. Davies, R. H. Green, D. R. Kelly, S. M. Roberts, *Biotransformations in Preparative Organic Chemistry: The Use of Isolated Enzymes and Whole Cell Systems*, Academic Press, 1989.
- [2] S. Servi, *Synthesis* 1990, 1.
- [3] a) D. A. Hopwood, M. J. Bibb, K. F. Chater, T. Kieser, C. J. Bruton, H. M. Kieser, D. J. Lydiate, C. P. Smith, J. M. Ward, H. Schrempf, *Genetic Manipulation of Streptomyces, A Laboratory Manual*, The John Innes Foundation, Norwich, 1985; b) D. A. Hopwood, *Chem. Rev.* 1997, 97, 2465–2497.
- [4] a) P. L. Bartel, C. B. Zhu, J. S. Lampel, D. C. Dosch, S. P. Connors, J. M. Beale, P. J. Keller, C. Chang, H. G. Floss, *J. Bacteriol.* 1990, 172,

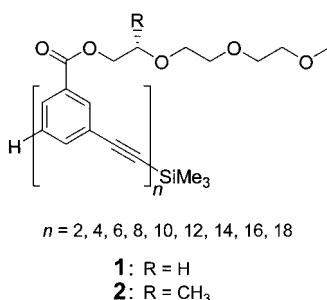
- 4816–4826; b) R. McDaniel, S. Ebert-Khosla, D. A. Hopwood, C. Khosla, *Science* 1993, 262, 1546–1550.
- [5] For the purposes of this study, **2** and **3** are depicted as the free phenol tautomers although they may exist as protein-bound keto forms during biosynthesis: M. A. Fernández-Moreno, M. Martínez, J. L. Cabarello, K. Ichinose, D. A. Hopwood, F. Malpartida, *J. Biol. Chem.* 1994, 269, 24854.
- [6] K. Ichinose, C. M. Surti, T. Taguchi, F. Malpartida, K. I. Booker-Milburn, G. R. Stephenson, Y. Ebizuka, D. A. Hopwood, *Bioorg. Med. Chem. Lett.* 1999, 9, 395.
- [7] Khosla et al. have previously described the conversion of NAC thioesters into erythromycin analogues using an engineered DEBS KS1 null mutant: J. R. Jacobsen, C. R. Hutchinson, D. E. Cane, C. Khosla, *Science* 1997, 277, 367.
- [8] a) D. E. Cane, W. R. Ott, P. C. Prabhakatan, W. Tan, *Tetrahedron Lett.* 1991, 32, 5457; b) A. Jacobs, J. Staunton, A. C. Sutkowski, *J. Chem. Soc. Chem. Commun.* 1991, 1113.
- [9] I. H. Gilbert, M. Ginty, J. A. O'Neill, T. J. Simpson, J. Staunton, C. L. Willis, *Bioorg. Med. Chem. Lett.* 1995, 5, 1587 (see also ref. [8b]).
- [10] M. Yamaguchi, K. Hasebe, H. Higashi, M. Uchida, A. Irie, T. Minami, *J. Org. Chem.* 1990, 55, 1611.
- [11] D. W. Brooks, L. D. L. Lu, S. Masamune, *Angew. Chem.* 1979, 91, 76; *Angew. Chem. Int. Ed. Engl.* 1979, 18, 72.
- [12] Racemates of all four examples were prepared for comparison by NaBH_4 reduction of the methyl β -keto-esters corresponding to **8**–**10** and **13**. The absolute configuration of **15** was assigned by comparing the $[\alpha]_D$ value of (3*S*)-4-phenylbutanoic acid obtained from the feeding study ($+2.6$, $c = 1$) with that of the known (3*R*)-enantiomer (-5.3 , $c = 1$): G. Capozzi, S. Roelens, S. Talami, *J. Org. Chem.* 1993, 58, 7932.
- [13] Data were collected at 293 K on a Rigaku AFC7R diffractometer using graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$) and ω scans, and corrected for Lorentz polarization effects and absorption effects (ψ scans). The structure was solved by direct methods, and refined (isotropic U for all hydrogen atoms, anisotropic for all other atoms) by full-matrix least squares on F^2 (all data). Crystal data for **18** ($\text{C}_{18}\text{H}_{18}\text{O}_6$): colorless block, $0.45 \times 0.25 \times 0.15 \text{ mm}$, orthorhombic, space group $P2_12_12_1$, $a = 14.624(2)$, $b = 16.821(1)$, $c = 6.501(1) \text{ \AA}$, $V = 1599.3(4) \text{ \AA}^3$, $\rho_{\text{calcd}} = 1.372 \text{ Mg m}^{-3}$, $\mu(\text{MoK}\alpha) = 0.103 \text{ mm}^{-1}$, $3.5 < 2\theta < 50^\circ$; of 9946 reflections measured, 2396 were unique; $R_{\text{int}} = 0.0450$, wR_2 (all data) = 0.0742, R_1 ($I > 2\sigma(I)$) = 0.0283, $S = 1.022$, Flack $\chi = 0.0(11)$, largest diff. peak/hole = $0.93/-0.86 \text{ e \AA}^{-3}$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication no. CCDC-127928. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Twist Sense Bias Induced by Chiral Side Chains in Helically Folded Oligomers**

Ryan B. Prince, Luc Brunsveld, E. W. Meijer, and Jeffrey S. Moore*

There is growing interest in the design of synthetic chain molecules that acquire well-defined conformations in solution,^[1–4] analogous to the folded state of proteins or nucleic acids. Toward this end, there remains much to be learned about the structure and dynamics of conformationally ordered polymer molecules, and in particular about how to achieve conformational uniqueness in solution.^[5–7] Studies on solvent–polymer interactions reveal the important role that solvophobicity^[8] can play in driving polymers into compact conformations.^[9] However, it is evident from theoretical studies that the collapsed state of most chain molecules, especially homopolymers, is highly degenerate.^[10, 11] In advancing foldable chain molecules from disordered, collapsed states to conformational uniqueness, it is important to understand how to use weak interactions cooperatively, and how to derive order from both side-chain as well as main-chain interactions.

We have previously shown^[4, 12] that phenylene-ethynylene oligomers (i.e., **1**) can be driven to fold into helical^[13] conformations by solvophobic forces. Recently we also



demonstrated that incorporation of a single chiral binaphthol unit into the backbone induces a bias in the helical twist sense.^[14] However, the kinked binaphthol monomer significantly decreased the stability of the folded conformation. Here we demonstrate that a small, chiral perturbation to the side chain^[15–17] causes a bias to the helical twist sense without

disrupting the conformational stability [Eq. (1)]. These results indicate that side chains can play a role in helping to promote conformational order. Moreover, solvent and thermal denaturation studies monitored by absorption and circular dichroism spectroscopies reveal insight into the cooperative nature of the folding process and the manner in which this conformational order develops. Specifically, these studies show that there is a significant progression in conformational order following the initially formed helical state.



To perform these studies we prepared a series of *m*-phenylene ethynylene oligomers with chiral side chains (**2**). These oligomers are analogous to the previously reported achiral series **1**, except for the introduction of a methyl group at the second carbon atom of each of the side chains. This places the stereochemical information in reasonably close proximity to the aromatic backbone. The chiral unit was derived from L-ethyl lactate, which is readily available in high enantiomeric purity, using standard synthetic transformations.^[18] All oligomers were characterized by ¹H NMR spectroscopy, HPLC, size-exclusion chromatography (SEC), and mass spectrometry and shown to be greater than 99% pure. The synthesis and analytical data of all compounds can be found in the Supporting Information.

UV absorption measurements established the conditions that caused oligomers **2** to adopt a helical conformation. This is revealed from the ratio of absorbances at 287 and 303 nm as we have previously reported (the helical conformation has a significantly lower A_{303}/A_{287} ratio than the random conformation).^[4, 12] It was found that, within experimental error, the conformational transitions of the chiral oligomers **2** displayed the same chain-length and solvent dependence as their achiral counterparts **1**. Thus, the introduction of a methyl group in the side chain did not destabilize the helical state.

Circular dichroism (CD) measurements were performed in order to study the twist sense bias.^[19] In chloroform, chiral oligomers **2** showed no ellipticity in the backbone chromophore (250–400 nm), regardless of chain length and temperature studied. This is not surprising because in chloroform the oligomers are expected to be in a random-coil conformation; hence, there is little possibility for transferring chiral information from the side chains to the backbone.

In sharp contrast to the behavior in chloroform, a remarkable Cotton effect was observed for dilute solutions of oligomers **2** in acetonitrile at room temperature. The ellipticity was dependent on chain length and was zero only for oligomers not long enough to adopt a helical conformation ($n < 10$). As shown in Figure 1, the UV spectrum of **2** ($n = 8$) in acetonitrile exhibits a bandshape characteristic of the random coil conformation and a CD spectrum that displays no ellipticity. However, the UV spectrum of **2** ($n = 18$) in acetonitrile exhibits the bandshape indicative of the helical conformation and a CD spectrum that displays a bisignate Cotton effect. These results suggest that the transfer of chiral information from the side chains to the main chain can only

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[**] This material is based upon work supported by the National Science Foundation (NSF CHE 97-27172). R.B.P. thanks the Lubrizol Corporation for a doctoral fellowship.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

occur once order is present in the backbone. The putative helical conformation likely places the side chains in close proximity, thereby heightening their ability to interact in a cooperative manner to give rise to the diastereomeric preference of one twist sense over the other.

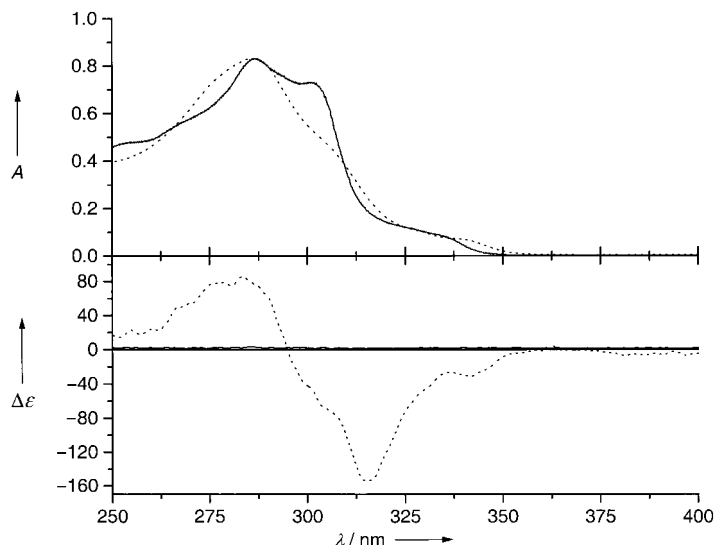


Figure 1. Normalized absorption (top) and CD spectra (bottom) of **2** ($n=8$, solid line; $n=18$, dashed line) in acetonitrile. A = absorbance.

A measure of chiral induction is given by the anisotropy factor $g_{\text{abs}} = \Delta\epsilon/\epsilon$ at 316 nm. Figure 2 shows how g_{abs} varies with chain length for dilute solutions of **2** in acetonitrile at several temperatures. It is evident from this plot that there is a critical chain length below which no chiral induction is observed (i.e., $n < 10$). This coincides with the length needed to form a stable helical conformation for **1**.^[12] It is also apparent that beyond the critical size, the chiral induction grows steadily as the chain lengthens (Figure 2). Also, the chiral induction decreases when the samples are heated. Mixtures of **1** and **2** ($n=18$) showed a linear relationship between ellipticity and mole percent of **2**. This, together with

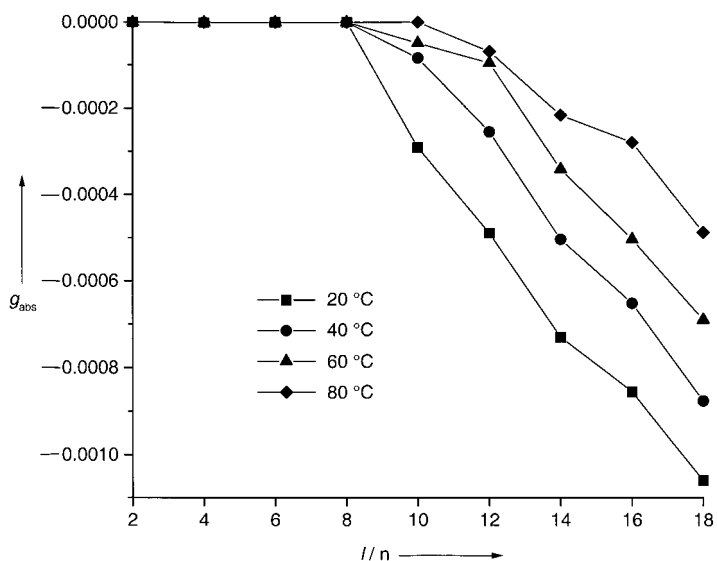


Figure 2. Plot of the chiral induction, expressed in terms of the anisotropy factor $g_{\text{abs}} = \Delta\epsilon/\epsilon$, as a function of chain length l at different temperatures for solutions of **2** in acetonitrile. The data were recorded at 316 nm.

vapor pressure osmometry experiments,^[4] confirms that these are primarily unimolecular phenomena.

Previous studies have shown that the helix–coil transition can be driven by changes in solvent or temperature.^[4, 12] The effect of solvent on oligomers that display a preferential twist sense was monitored by absorption and CD spectroscopies. Typical solvent denaturation curves are shown in Figure 3. The addition of chloroform to dilute solutions of **2** in acetonitrile resulted in an increase in the ratio of absorbances

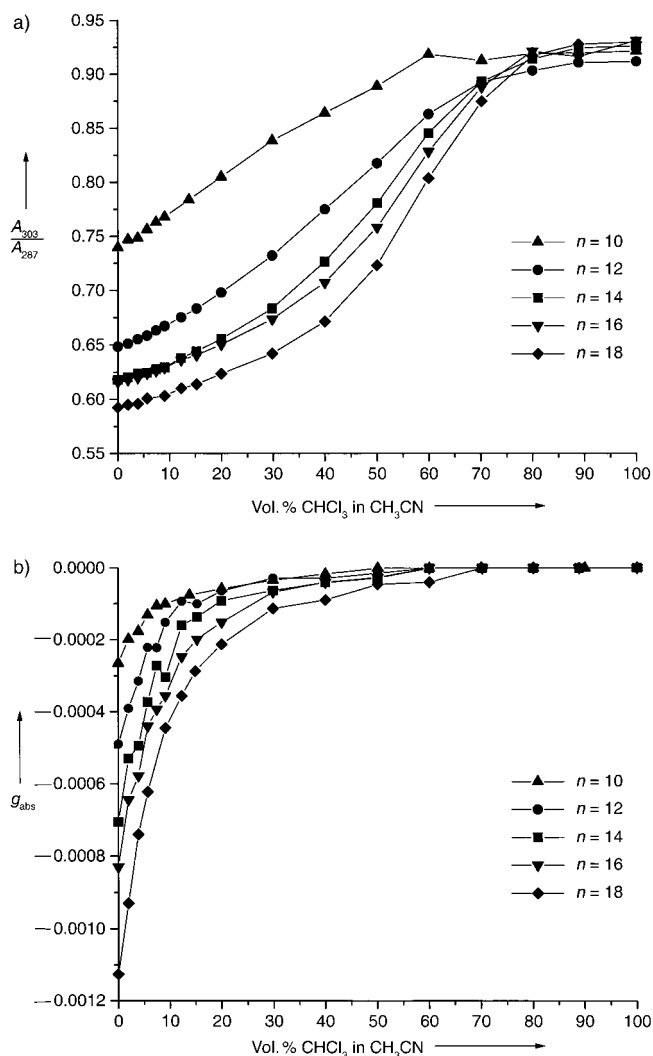


Figure 3. Solvent denaturation curves of **2** measured by a) the UV absorbance ratio A_{303}/A_{287} and b) the circular dichroism (g_{abs} at 316 nm).

at 303 and 287 nm (Figure 3a).^[20] This increase is associated with the loss of helical order as we have previously shown.^[4, 12] When the same solvent denaturation is monitored by CD spectroscopy, it is only at high acetonitrile compositions that a Cotton effect is observed (Figure 3b).^[20] The sudden onset and rapid growth in molar ellipticity at high acetonitrile concentrations is indicative of cooperative interactions.

It should be emphasized that the onset of the twist sense bias occurs at a solvent composition that is well beyond the helix–coil transition as monitored by UV spectroscopy. These different transition behaviors are interesting and may reveal important aspects about the nature of this solvophobically induced organization. It is important to remember that UV

spectroscopy detects the presence of a stable helical conformation, while CD spectroscopy detects the presence of diastereomeric excess. The solvophobicity of the hydrocarbon backbone, which is presumably much larger than that of the polar side chains, could explain why the backbone adopts helical order well before bias is imparted to the helix twist sense. From the CD data, the diastereomeric excess originates at approximately the same chloroform composition regardless of chain length (Figure 3b). Based on this observation it is plausible that ordering of the solvated side chains, a process that lags behind helix formation, is the mechanism by which chirality is transferred to the backbone. The analogy might be made to the "molten globular state" of proteins, a state in which the peptide backbone possesses a native-like conformation while having disordered side chains.^[21, 22]

An alternative way to explain the observed transition behavior is to consider the dynamics and conformational uniqueness of the backbone. At high chloroform compositions (but when the oligomers are still helical, as judged by UV spectroscopy) there are possibly a large number of energetically similar, helical-like backbone conformations that interconvert rapidly. Here the analogy might be made to the "compact denatured state" of proteins, a collapsed form in which there is a broad ensemble of backbone and side-chain conformations even though there is extensive hydrophobic clustering.^[23] The UV spectrum simply fails to provide the needed resolution to distinguish between a well-ordered, conformationally unique backbone and a mixture of helical-like conformers. The dynamics and structural diversity available to the backbone in this conformational state may preclude cooperative interactions among the side chains that give rise to the twist sense bias. Upon increasing the amount of acetonitrile, a smaller set of backbone helical conformations becomes populated, allowing the side chains to order and transfer their chirality to the main chain. Regardless of which of these explanations is correct, the transfer of chirality appears to be a highly cooperative process that requires a progression of conformational order beyond the initially formed helical state. The sharpness of the CD transition points toward a high twist sense bias that obviously cannot be deduced from the magnitude of the Cotton effect.

In conclusion, we have demonstrated that it is possible to bias the twist sense of a solvophobicity driven helical conformation by the attachment of chiral side chains. These results show that the side chains can play more than just an ancillary role in these conformationally ordered oligomers. The diastereomeric bias only appears after the backbone acquires a conformationally ordered state. Solvent denaturation studies showed that a helical conformation is a necessary, but not a sufficient condition for inducing a diastereomeric bias. In particular, the onset of the twist sense bias was shown to lag significantly behind the appearance of helical conformations, possibly because a large ensemble of "collapsed" conformations is initially formed. To further elucidate the nature of the folding and chirality transfer, additional experiments in more polar media will be undertaken.

Received: April 14, 1999
Revised: August 4, 1999 [Z13281]

- [1] R. S. Lokey, B. L. Iverson, *Nature* **1995**, 375, 303–305.
- [2] S. H. Gellman, *Acc. Chem. Res.* **1998**, 31, 173–180.
- [3] D. Seebach, J. L. Matthews, *Chem. Commun.* **1997**, 2015–2022.
- [4] J. C. Nelson, J. G. Saven, J. S. Moore, P. G. Wolynes, *Science* **1997**, 277, 1793–1796.
- [5] P. G. Wolynes, *Nat. Struct. Biol.* **1997**, 4, 871–874.
- [6] J. D. Bryngelson, J. N. Onuchic, N. D. Socci, P. G. Wolynes, *Proteins: Struct. Funct. Genet.* **1995**, 21, 167–195.
- [7] C. M. Dobson, A. Sali, M. Karplus, *Angew. Chem.* **1998**, 110, 908–935; *Angew. Chem. Int. Ed.* **1998**, 37, 868–893.
- [8] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, New York, **1990**.
- [9] C. Williams, F. Bochard, H. L. Frisch, *Ann. Rev. Phys. Chem.* **1981**, 32, 433–451.
- [10] H. S. Chan, K. A. Dill, *Macromolecules* **1989**, 22, 4559–4573.
- [11] C. J. Camacho, D. Thirumalai, *Phys. Rev. Lett.* **1993**, 71, 2505–2508.
- [12] R. B. Prince, J. G. Saven, P. G. Wolynes, J. S. Moore, *J. Am. Chem. Soc.* **1999**, 121, 3114–3121.
- [13] A. E. Rowan, R. J. M. Nolte, *Angew. Chem.* **1998**, 110, 65–71; *Angew. Chem. Int. Ed.* **1998**, 37, 63–68.
- [14] M. S. Gin, T. Yokozawa, R. B. Prince, J. S. Moore, *J. Am. Chem. Soc.* **1999**, 121, 2643–2644.
- [15] F. Ciardelli, S. Lanzillo, O. Pieroni, *Macromolecules* **1974**, 7, 174–179.
- [16] J. S. Moore, C. B. Gorman, R. H. Grubbs, *J. Am. Chem. Soc.* **1991**, 113, 1704–1712.
- [17] M. M. Green, N. C. Peterson, T. Sato, A. Teramoto, R. Cook, S. Lifson, *Science* **1995**, 268, 1860–1866.
- [18] H. M. Janssen, E. Peeters, M. F. van Zundert, M. H. P. van Genderen, E. W. Meijer, *Macromolecules* **1997**, 30, 8113–8128.
- [19] As expected, no ellipticity could be detected for any of the achiral oligomers of series **1** under conditions where the helical conformation is stable. This is explained as the presence of a racemic mixture of left- and right-handed helices.
- [20] All measurements were determined to be independent of time. See the Supporting Information for full details of sample preparation.
- [21] E. I. Shakhnovich, A. V. Finkelstein, *Biopolymers* **1989**, 28, 1667–1680.
- [22] A. V. Finkelstein, E. I. Shakhnovich, *Biopolymers* **1989**, 28, 1681–1694.
- [23] K. A. Dill, D. Stigter, *Adv. Protein Chem.* **1995**, 46, 59–104.

Mixed-Valent Heptairon Complex with a Ground-State Spin Value of $S = 12/2$ Constructed from a Triiron Cluster Ligand**

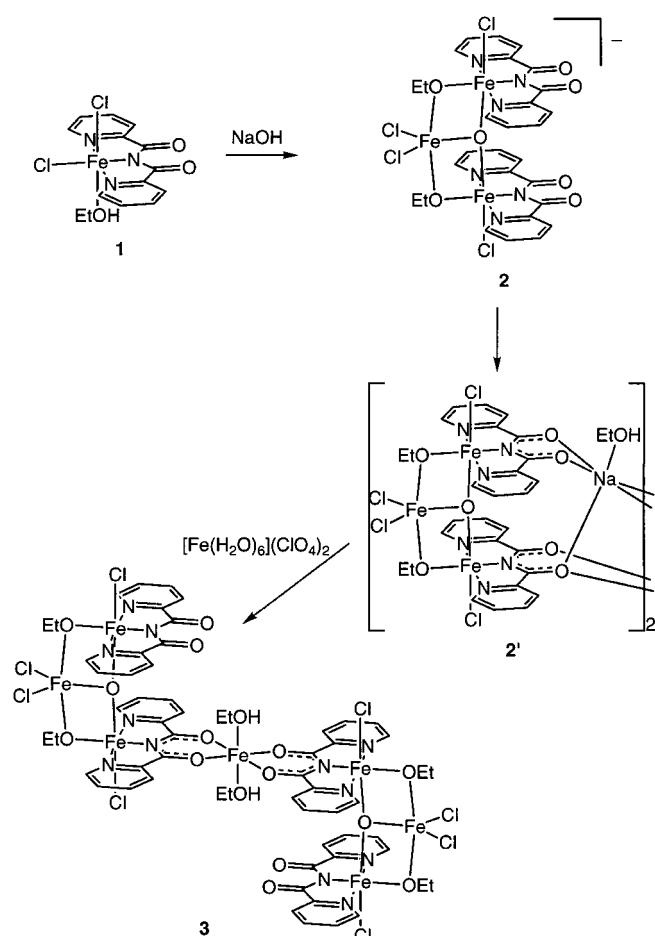
Takashi Kajiwaru and Tasuku Ito*

Complexes assembled from metal-containing subunits^[1–12] have attracted much attention in view of their very interesting structures, for example, ferric wheels,^[1] and properties, for example, molecular-based magnetism,^[2] and multistep, multi-electron redox reactions.^[3] Designing the spatial arrangement

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[**] This work was supported by a Grant-in-Aid for Scientific Research on Priority Area "Metal-Assembled Complexes" (No. 0149102) and the Encouragement of Young Scientists (No. 11740366) from the Ministry of Education, Science, Sports, and Culture, Japan.

of metal ions and tuning the metal–metal interactions are challenging tasks. One beneficial way of constructing metal assemblies is to use “complex ligands” such as metal–cyanide,^[4, 5] metal–oxalate,^[6] metal–thiolate,^[7] metal–oximate,^[8, 9] and metal–oxamide complexes.^[10] In most cases, the resulting multimetal compounds containing complex ligands of these types are either discrete molecules with low nuclearity or dimensional solids, and examples of discrete molecules with high nuclearity are rather rare.^[5, 9, 11] A “metal cluster complex ligand” would be effective in making such a high nuclear compound. We reported recently on novel trinuclear complexes constructed with the bis-bidentate bridging complex ligands $[M(\text{bpca})_2]$ ($M = \text{Fe}^{\text{II}}, \text{Mn}^{\text{II}}$; Hbpca = bis(2-pyridylcarbonyl)amine).^[12] Herein we report on a “cluster complex ligand” containing $[\text{Fe}(\text{bpca})]^{2+}$ moieties that act as ligating sites and leads to a heptairon complex (Scheme 1).



Scheme 1. Preparation of **3** from cluster ligand **2**.

An anionic triiron(III) cluster complex ion, $[\text{Fe}_3(\mu_3\text{-O})(\text{bpca})_2\text{Cl}_4(\text{EtO})_2]^-$ (**2**), was formed and isolated as the sodium salt $[\text{Na}_2(\text{2})_2(\text{EtOH})_2]$ (**2'**) when $[\text{Fe}(\text{bpca})\text{Cl}_2(\text{EtOH})]$ (**1**)^[13] was allowed to react with sodium hydroxide in EtOH. The reaction of **2'** with iron(II) perchlorate in the presence of [18]crown-6 in ethanol/nitromethane afforded the mixed-valent heptairon complex $[\text{Fe}(\text{2})_2(\text{EtOH})_2]$ (**3**), with the ground-state spin value of $S = 12/2$.

The structures of **2'**^[14] and **3**^[14] are shown in Figures 1 and 2, respectively. Both complexes crystallize in the same $P2_1/n$ space group and possess a crystallographic inversion center at

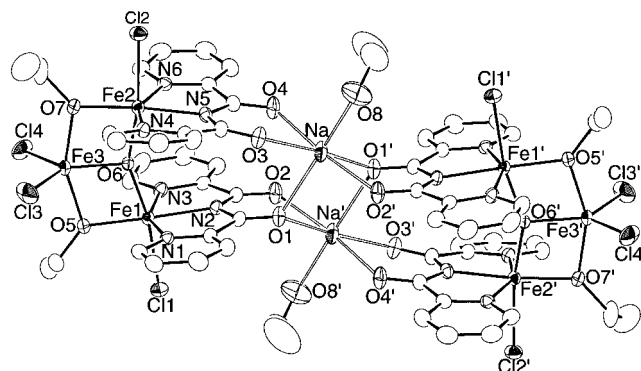


Figure 1. ORTEP drawing of **2'** with thermal ellipsoids at 30% probability. Hydrogen atoms are omitted. Selected distances [Å]: Fe1...Fe2 3.7305(8), Fe1...Fe3 3.0440(7), Fe2...Fe3 3.0320(8), Fe1...Na 6.0116(17), Na...Na' 3.506(4).

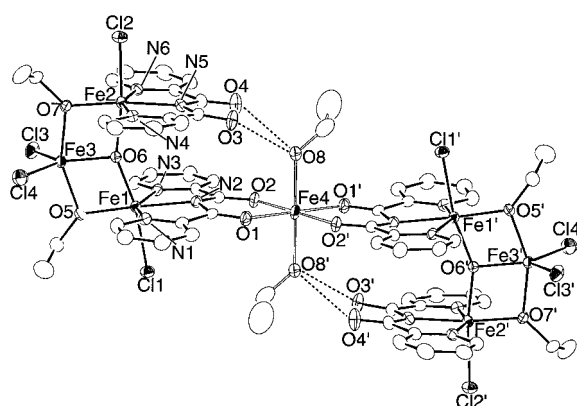


Figure 2. ORTEP drawing of **3** with thermal ellipsoids at 30% probability. Hydrogen atoms are omitted. Selected distances [Å]: Fe1...Fe2 3.7387(9), Fe1...Fe3 3.0439(9), Fe1...Fe4 5.5830(7), Fe2...Fe3 3.0150(9).

the midpoint between the two sodium atoms (**2'**) or on the Fe4 atom (**3**), thus making each half of each molecule crystallographically independent.

Complex **2'** consists of two anionic cluster ligands (depicted with filled bonds), two sodium ions, and coordinating ethanol molecules. The structure can be taken as the coordination of cluster ligand **2** to Na^+ ions. Three iron(III) centers in the cluster ligand form an approximate isosceles triangle with two equal sides of 3.0440(7) (Fe1–Fe3) and 3.0320(8) Å (Fe2–Fe3) and a base of 3.7305(8) Å (Fe1–Fe2). The μ_3 -oxo atom (O6) is bound to three iron atoms at almost the same distances (1.925(2), 1.919(2), and 1.934(2) Å). The Fe1–O6–Fe3 and Fe2–O6–Fe3 angles are 104.13(11) and 103.78(11)°, respectively, while the Fe1–O6–Fe2 angle of 152.07(13)° is much larger. The central iron ion (Fe3) is five coordinate, has two chloro ligands, and possesses a slightly distorted trigonal-bipyramidal geometry. A very similar $\text{Fe}_3^{\text{III}}(\mu_3\text{-O})$ core structure has been found in a hexanuclear ferric complex reported by Christmas et al.^[15] The distances between the iron and donor atoms in **2** are typical of high-spin Fe^{III} complexes. In this moiety four carbonyl groups on two bpca[−] ligands are

disposed toward the same direction and coordinate to sodium ions in a multidentate fashion.

In **3**, two cluster ligands coordinate to an iron(II) ion (Fe4) in a bidentate fashion, and coordination-free carbonyl oxygens (O3 and O4) form hydrogen bonds with a coordinated ethanol molecule ($O \cdots O$ 2.726(5) and 3.165(6) Å, respectively). The structure of the triiron(III) cores in **3** differs slightly from that found in **2'** (Fe1–Fe3 3.0439(9), Fe2–Fe3 3.0150(9) Å; Fe1–O6–Fe3 105.05(14), Fe2–O6–Fe3 101.77(13)°), probably as a result of the interaction with the central iron(II) ion. The divalent iron ion Fe4 is in an octahedral environment with an O_6 donor set at distances in the range of 2.090(3)–2.113(4) Å, which is similar to that found in $[Fe^{II}(H_2O)_2(acac)_2]^{[16]}$ ($acac^-$ = acetylacetonate), although the equatorial and axial coordination bonds are slightly elongated and shortened in **3**, respectively.

Figure 3 shows the magnetic behavior of **2'** and **3**. The $\chi_M T$ value for **2'** decreases continuously as the temperature is lowered. From the structural analysis **2'** can be considered to consist of two well-separated, trinuclear iron(III) cluster units with a closest approach of 12.129(1) Å (Fe1–Fe1'). The

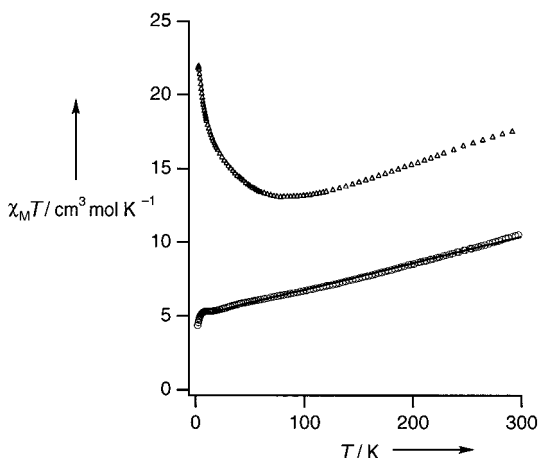


Figure 3. Plots of $\chi_M T$ versus T for **2'** (○, at 5000 G) and **3** (△, at 1000 G). The $\chi_M T$ values are calculated for discrete molecules containing six iron atoms for **2'** and seven iron atoms for **3**. The solid line represents the theoretical fit to the data.

temperature dependence of $\chi_M T$ for **2'** was analyzed by the isolated three-spin model ($H = -2J(S_{Fe1} \cdot S_{Fe3} + S_{Fe2} \cdot S_{Fe3}) - 2J'S_{Fe1} \cdot S_{Fe2}$) with the intertrimer interactions θ . The best fit parameters were calculated using the data in the range 20–300 K to avoid the influence of zero-field interactions, and were determined as $J = -15.2(1) \text{ cm}^{-1}$, $J' = -36.3(2) \text{ cm}^{-1}$, and $\theta = 4.2(1) \text{ K}$ ($2.9(1) \text{ cm}^{-1}$) with $g = 2$ (fixed). Several triiron(III) complexes containing a μ_3 -oxo bridge have been studied for their spin-frustration behavior, and it has been reported that the ground-state spin multiplicity depends on the ratio J/J' .^[15, 17] The ground-state spin value of each triiron(III) unit in our system was calculated to be $S = 3/2$.^[18]

The magnetic behavior of the mixed-valent heptairon complex **3** differs drastically from that of its precursor **2'**. The $\chi_M T$ value for **3** is larger than that of **2'** by roughly 7 emu K mol^{-1} in the range 300–80 K, reaches a minimum around 80 K, and then shows a sharp increase below this

temperature to reach the maximum of 22.0 emu K mol^{-1} at 2 K. This maximum value corresponds to a theoretical value of 21.0 emu K mol^{-1} for the $S = 12/2$ ground state with $g = 2$, which is larger than the value calculated for ferromagnetically coupled high-spin Fe^{II} ions with $S = 4/2$ and two Fe_3^{III} cores with an $S = 3/2$ ground state (see earlier discussion). The dependence of the magnetization on the field is also in accord with the ground state S being equal to or greater than 11/2 (Figure 4). There is not any significant contact among neighboring complexes, and this magnetic behavior arises from interactions within a molecule. The theoretical analysis for **3** has not been carried out because of the complexity of the spin states that arises from seven iron atoms.

It is clear, however, that the central iron(II) ion and two cluster ligands interact strongly to generate a relatively high ground spin state. The ground-state spin of each of cluster ligand unit might be changed in **3**.

We have shown that cluster ligand **2** is very useful in constructing metal assemblies. Ligand **2** can coordinate to a variety of metal ions in a bidentate, tridentate, and even tetradentate fashion. Related studies are now in progress in our laboratories.

Experimental Section

2': A solution of NaOH in EtOH (0.1M, 2.5 mL) was added to a hot solution of $[Fe(bpc)Cl_2(EtOH)]$ (100 mg, 0.25 mmol) in ethanol/nitromethane (1/1, 10 mL). The dark red solution was heated at reflux for 2 h, and the resulting deep orange solution allowed to stand for one day. Complex **2'** crystallized as red-orange prismatic crystals.

3: A suspension of **2'** (40 mg, 0.04 mmol) in ethanol/nitromethane (1/1, 6 mL) was heated gently under an atmosphere of nitrogen until a clear solution was obtained. A solution of [18]crown-6 in ethanol (0.1M, 0.4 mL) was then added. The diffusion of a solution of $[Fe(H_2O)_6](ClO_4)_2$ in ethanol (0.05M, 0.4 mL) into the solution resulted in the color changing from orange to black, and after several hours, **3** crystallized as black prismatic crystals.

Received: August 5, 1999 [Z13834]

- [1] a) S. P. Watton, P. Fuhrmann, L. E. Pence, A. Caneschi, A. Cornia, G. L. Abbati, S. J. Lippard, *Angew. Chem.* **1997**, *109*, 2917; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2774; b) C. Benelli, S. Parsons, G. A. Solan, R. E. P. Winpenny, *Angew. Chem.* **1996**, *108*, 1967; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1825; c) K. L. Taft, C. D. Delfs, G. C. Papaefthymiou, S. Foner, D. Gatteschi, S. J. Lippard, *J. Am. Chem. Soc.* **1994**, *116*, 823.
- [2] a) E. K. Brechin, J. Yoo, M. Nakano, J. C. Huffman, D. N. Hendrickson, G. Christou, *Chem. Commun.* **1999**, 784; b) S. M. J. Aubin, N. R. Dilley, L. Pardi, J. Krzystek, M. W. Wemple, L.-C. Brunel, M. B. Maple, G. Christou, D. N. Hendrickson, *J. Am. Chem. Soc.* **1998**, *120*, 4991; c) S. M. J. Aubin, M. W. Wemple, D. M. Adams, H.-L. Tsai, G. Christou, D. N. Hendrickson, *J. Am. Chem. Soc.* **1996**, *118*, 7746.

- [3] a) T. Ito, T. Hamaguchi, H. Nagino, T. Yamaguchi, H. Kido, I. S. Zavarine, T. Richmond, J. Washington, C. P. Kubiak, *J. Am. Chem. Soc.* **1999**, *121*, 4625; b) H. Kido, H. Nagino, T. Ito, *Chem. Lett.* **1996**, 745.
- [4] For example, see a) M. Ohba, N. Usuki, N. Fukita, H. Okawa, *Angew. Chem.* **1999**, *111*, 1911; *Angew. Chem. Int. Ed.* **1999**, *38*, 1795; b) H. Miyasaka, N. Matsumoto, N. Re, E. Gallo, C. Floriani, *Inorg. Chem.* **1997**, *36*, 670; c) M. S. El Fallah, E. Rentschler, A. Caneschi, R. Sessoli, D. Gatteschi, *Angew. Chem.* **1996**, *108*, 2081; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1947; d) S. Ferlay, T. Mallah, J. Vaissermann, F. Bartolome, P. Veillet, M. Verdaguer, *Chem. Commun.* **1996**, 2481.
- [5] a) K. K. Klausmeyer, T. B. Rauchfuss, S. R. Wilson, *Angew. Chem.* **1998**, *110*, 1808; *Angew. Chem. Int. Ed.* **1998**, *37*, 1694; b) K. V. Langenberg, S. R. Batten, K. J. Berry, D. C. R. Hockless, B. Moubaraki, K. S. Murray, *Inorg. Chem.* **1997**, *36*, 5006; c) R. J. Parker, D. C. R. Hockless, B. Moubaraki, K. S. Murray, L. Spiccia, *Chem. Commun.* **1996**, 2789.
- [6] a) R. Pellaux, H. W. Schmalke, R. Huber, P. Fischer, T. Hauss, B. Ouladdiaf, S. Decurtins, *Inorg. Chem.* **1997**, *36*, 2301; b) C. Mathonnière, C. J. Nuttall, S. G. Carling, P. Day, *Inorg. Chem.* **1996**, *35*, 1201; c) R. P. Farrell, T. W. Hambley, P. A. Lay, *Inorg. Chem.* **1995**, *34*, 757; d) H. Tamaki, Z. J. Zhong, N. Matsumoto, S. Kida, M. Koikawa, N. Achiwa, Y. Hashimoto, H. Okawa, *J. Am. Chem. Soc.* **1992**, *114*, 6974; e) Y. Pei, Y. Journaux, O. Kahn, *Inorg. Chem.* **1989**, *28*, 100.
- [7] a) T. Glaser, T. Beissel, E. Bill, T. Weyhermüller, V. Schünemann, W. Meyer-Klaucke, A. X. Trautwein, K. Wieghardt, *J. Am. Chem. Soc.* **1999**, *121*, 2193; b) T. Glaser, F. Kesting, T. Beissel, E. Bill, T. Weyhermüller, W. Meyer-Klaucke, K. Wieghardt, *Inorg. Chem.* **1999**, *38*, 722; c) C. Krebs, T. Glaser, E. Bill, T. Weyhermüller, W. Meyer-Klaucke, K. Wieghardt, *Angew. Chem.* **1999**, *111*, 370; *Angew. Chem. Int. Ed.* **1999**, *38*, 359.
- [8] a) F. Birkelbach, M. Winter, U. Flörke, H.-J. Haupt, C. Butzlaff, M. Lengen, E. Bill, A. X. Trautwein, K. Wieghardt, P. Chaudhuri, *Inorg. Chem.* **1994**, *33*, 3990; b) C. Krebs, M. Winter, T. Weyhermüller, E. Bill, K. Wieghardt, P. Chaudhuri, *J. Chem. Soc. Chem. Commun.* **1995**, 1913; c) F. Corazza, E. Solari, C. Floriani, A. Chiesi-Villa, C. Guastini, *J. Chem. Soc. Chem. Commun.* **1986**, 1562.
- [9] M. S. Ma, R. J. Angelici, D. Powell, R. A. Jacobson, *Inorg. Chem.* **1980**, *19*, 3121.
- [10] A. Escuer, R. Vicente, J. Ribas, R. Costa, X. Solans, *Inorg. Chem.* **1992**, *31*, 2627.
- [11] N. Matsumoto, Y. Mizuguchi, G. Mago, S. Eguchi, H. Miyasaka, T. Nakashima, J.-P. Tuchagues, *Angew. Chem.* **1997**, *109*, 1964; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1860.
- [12] T. Kajiura, T. Ito, *J. Chem. Soc. Dalton Trans.* **1998**, 3351.
- [13] T. Kajiura, I. Ito, *Acta Crystallogr. Sect. C* **2000**, in press.
- [14] Crystal structure determination of **2**·4CH₃NO₂: An orange crystal (ca. 0.38 × 0.32 × 0.18 mm) was analyzed with a Bruker SMART CCD-based diffractometer at 200 K with MoK_α radiation ($\lambda = 0.71073$ Å). Monoclinic, space group $P2_1/n$, $a = 14.9174(8)$, $b = 15.4925(8)$, $c = 19.8300(11)$ Å, $\beta = 105.4740(10)^\circ$, $V = 4416.7(4)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.593$ g cm⁻³, $\mu(\text{MoK}_\alpha) = 1.289$ mm⁻¹, $F(000) = 2156$. ω -scans, 27813 reflections measured ($2\theta_{\text{max}} = 55^\circ$), of which 9940 were independent and 7236 were observed [$I > 2\sigma(I)$], 545 refined parameters, $R = 0.0510$, $wR2 = 0.1347$, residual electron density max./min. 1.247/−0.569 e Å⁻³, max./min. transmission 0.8014/0.7022. Crystal structure determination of **3**·3CH₃NO₂: A black crystal (ca. 0.32 × 0.28 × 0.15 mm) was analyzed with a Bruker SMART CCD-based diffractometer at 193 K with MoK_α radiation ($\lambda = 0.71073$ Å). Monoclinic, space group $P2_1/n$, $a = 14.6914(9)$, $b = 19.0764(11)$, $c = 15.2417(9)$ Å, $\beta = 91.1990(10)^\circ$, $V = 4270.7(4)$ Å³, $Z = 2$, $\rho_{\text{calc}} = 1.655$ g cm⁻³, $\mu(\text{MoK}_\alpha) = 1.486$ mm⁻¹, $F(000) = 2164$. ω -scans, 26851 reflections measured ($2\theta_{\text{max}} = 55^\circ$), of which 9656 were independent and 5646 were observed [$I > 2\sigma(I)$], 538 refined parameters, $R = 0.0553$, $wR2 = 0.1274$, residual electron density max./min. 0.831/−0.509 e Å⁻³, max./min. transmission 0.8621/0.6109. Data reduction for both compounds was performed with the SAINT software, which corrects for Lorentz and polarization factors as well as decay. Absorption corrections were applied with SADABS supplied by G. Sheldrick (Universität Göttingen). The structures were solved by direct methods with the SHELXS-97 program and refined by the least squares method on F^2 , (SHELXL-97, incorporated in SHELXTL-PC ver-

sion 5.10). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated by geometrical methods and refined as a riding model. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-132694 and CCDC-132695. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [15] C. A. Christmas, H.-L. Tsai, L. Pardi, J. M. Kesselman, P. K. Gantzel, R. K. Chadha, D. Gatteschi, D. F. Harvey, D. N. Hendrickson, *J. Am. Chem. Soc.* **1993**, *115*, 12483.
- [16] M. V. Tsodikov O. V. Bukhtenko, O. G. Ellert, I. A. Petrunenko, A. S. Antsyshkina, G. G. Sadikov, Y. V. Maksimov, Y. B. Titov, V. M. Nobotortsev, *Izv. Akad. Nauk. Ser. Khim.* **1995**, *8*, 1454.
- [17] a) E. Bill, C. Krebs, M. Winter, M. Gerdan, A. X. Trautwein, U. Flörke, H.-J. Haupt, P. Chaudhuri, *Chem. Eur. J.* **1997**, *3*, 193; b) S. M. Gorun, G. C. Papaefthymiou, R. B. Frankel, S. J. Lippard, *J. Am. Chem. Soc.* **1987**, *109*, 4244.
- [18] This result is also supported by the dependence of the magnetization of **2** on the field.

Encoded Helical Self-Organization and Self-Assembly into Helical Fibers of an Oligoheterocyclic Pyridine–Pyridazine Molecular Strand**

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Jean-Claude Homo, and Marc Schmutz

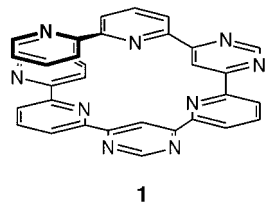
Helices and superhelices are key structural features of proteins, nucleic acids, and oligosaccharides. It is therefore no surprise that helical structures and superstructures have received increasing attention in biomimetic and synthetic supramolecular systems.^[1] Helical organization in synthetic systems has been obtained through covalent conformational restrictions,^[2] metal complexation,^[3] solvophobic effects,^[4] intermolecular interactions,^[5] and nonbonding intramolecular interactions.^[6] Several approaches to the generation of helical entities have been pursued in our group^[7] starting from double-helical metal complexes (helicates),^[8] followed by triple helicates,^[9] circular helicates,^[10] and helically wound, supramolecular liquid crystalline polymers.^[11] More recently

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[**] L.A.C. thanks the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Centre National de la Recherche Scientifique (CNRS), France, for financial support. J.-C.H. and M.S. acknowledge the financial support of INSERM, CNRS, and l'Hôpital Universitaire de Strasbourg.

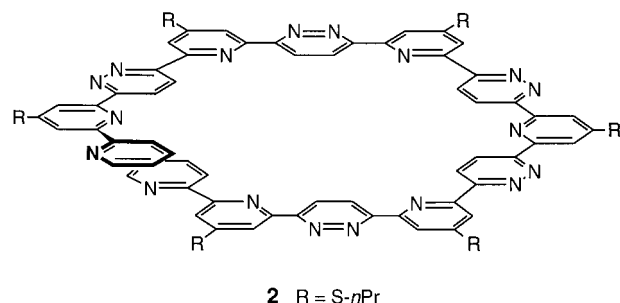
we have introduced a general concept for the strictly enforced generation of helical molecules by intramolecular self-organization of a suitably encoded oligoheterocyclic strand.^[12–14] It is based on the design of *helicity codons* that enforce helical winding of the strand due to the *transoid* conformation imposed around the interheterocyclic bonds. Thus, helical induction was achieved by means of extended sequences of “pyridine–pyrimidine” helicity



codons, which were shown to generate molecular helices presenting one turn, such as **1**,^[12] two turns,^[13] and up to four turns,^[14] with six heterocycles per turn.

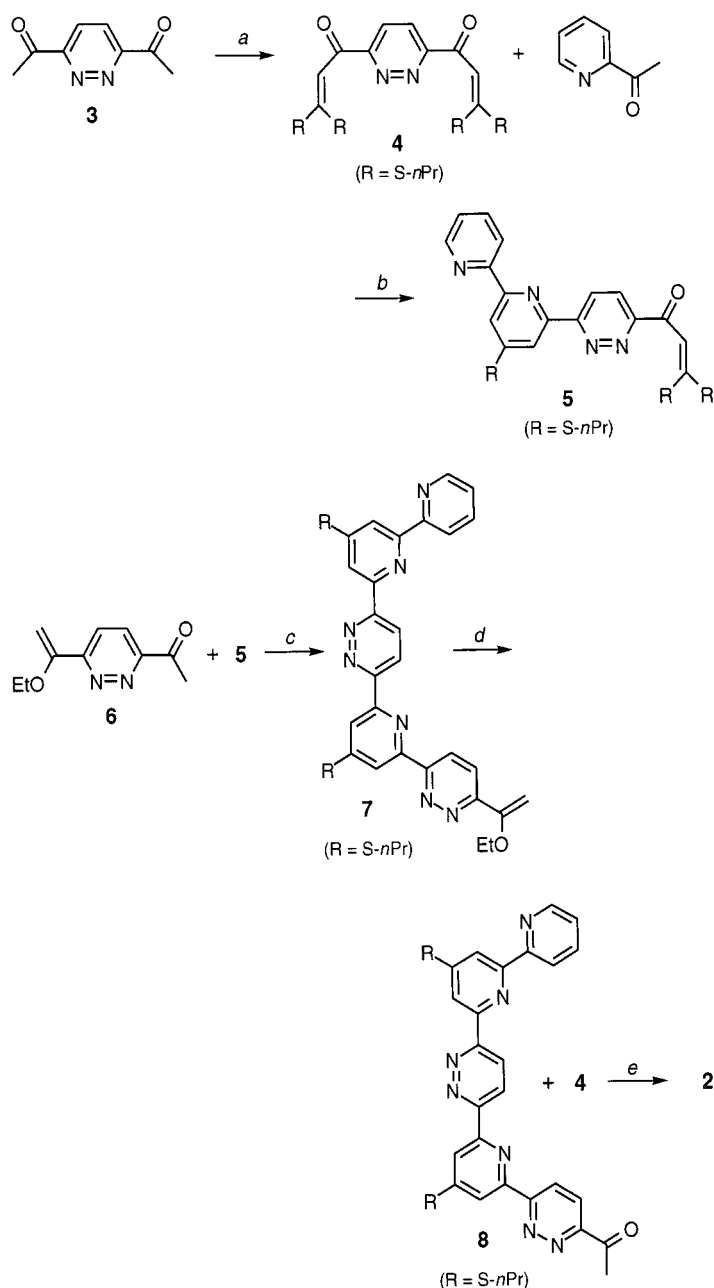
Further steps toward the control of the structural features of molecular and supramolecular

helical species involve the design of other suitable codons, the modification of diameter, the number of residues per turn, and the pitch of the helix, as well as the generation of extended multicomponent entities by self-assembly. The work presented here addresses several of these questions. We describe an isomeric, alternating pyridine–pyridazine heterocyclic strand that, a priori, should yield an hexagonal helical structure (**2**) with twelve heterocycles per turn, an outside diameter of about 25 Å, and a central cavity of about 8 Å across.



Compound **2** was synthesized using the Potts methodology^[15] following the sequence of reactions shown in Scheme 1. 3,6-Diacetylpyridazine (**3**) and 3-acetyl-6-(1-ethoxyvinyl)pyridazine (**6**) were synthesized from 3,6-dichloropyridazine using tributyl-(1-ethoxyvinyl)tin, as previously described for their 4,6-substituted pyrimidine counterparts.^[13b, 16] The bis-Michael acceptor **4**, prepared from **3**, was treated with one equivalent of 2-acetylpyridine to obtain the mono-addition product **5**. The reaction of Michael acceptor **5** with the unsymmetrically substituted pyridazine **6** gave **7**, which was subsequently hydrolyzed to **8** in aqueous acid. Reaction of two equivalents of **8** with the bis-Michael acceptor **4** gave the desired final product **2**. Compound **2** is soluble in chloroform and insoluble in most other common organic solvents. It is sparingly soluble in dichloromethane and pyridine, and forms viscous, birefringent solutions in these solvents.

The planar *transoid* conformer of 2,2'-bipyridine is calculated to be about 25 kJ mol^{−1} lower in energy than the *cisoid* conformer.^[17] This conformational preference may be attributed to: a) weak, favorable interactions between the lone pair of electrons on the nitrogen and the adjacent hydrogen atom on the neighboring heterocycle in the *transoid* conformer,



Scheme 1. a) NaH, CS₂, *n*PrI, DMSO, room temperature (66%); b) 1) NaH, THF/DMSO (2/1), room temperature; 2) NH₄OAc, AcOH, reflux (24%); c) 1) NaH, THF/DMSO (3/1), room temperature; 2) NH₄OAc, AcOH, reflux (33%); d) Acetone/2N HCl (9/1), room temperature (97%); e) 1) NaH, THF/DMSO (6/1), room temperature; 2) NH₄OAc, AcOH, reflux (19%).

b) favorable antiparallel orientation of the nitrogen dipoles in the *transoid* conformer, and c) unfavorable steric interactions between CH sites in the *cisoid* conformer. A pyridine–pyridazine unit would also be expected to favor the *transoid* conformer in a similar way. Molecular modeling, starting from an extended nonhelical form, confirms that the optimal conformation of compound **2** consists of a helical structure having twelve heterocycles per turn with the two terminal pyridine rings overlapping at approximately 3.4 Å (Figure 1). As a further indication of the generality of intramolecular conformational control based on heterocyclic connectivity,

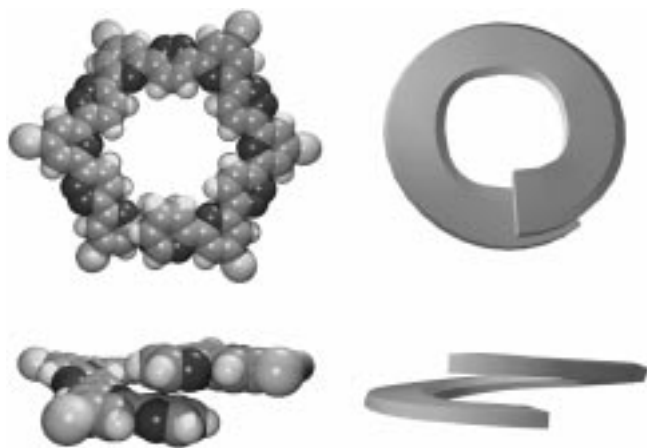


Figure 1. Minimized conformation and schematic representation of compound **2** viewed face on and from the side (propyl groups removed for clarity).

2,3-bis-[6-(2,2'-bipyridyl)]pyrazine has also been shown to adopt a curled conformation with four heterocycles per helical turn.^[18]

Enforced helix formation of compound **2** in solution was confirmed by significant upfield shifts of the proton resonances at positions C4 and C5^[19a] of the terminal pyridine rings (δ = 7.06, 6.53) due to the shielding effects of intramolecular stacking. This marked shielding is diagnostic of helix formation in isomeric pyridine–pyrimidine molecular strands previously studied in our laboratory^[12–14] and is also characteristic for the aromatic termini of helicenes and heterohelicenes.^[20]

Furthermore, all aromatic proton resonances of compound **2** in chloroform were shifted to higher fields as the concentration was increased. This distinct upfield displacement of 0.6–0.8 ppm in a concentration range of 0.1–100 mM at 35 °C was attributed to the formation of molecular assemblies, resulting in diamagnetic anisotropy effects between neighboring molecules. Consequently, the observed shift of the protons at positions C4 and C5 of the terminal pyridine rings has both intra- and intermolecular π – π stacking contributions.^[19b] Self-aggregation was confirmed by vapor-pressure osmometry which gave an apparent molecular weight for compound **2** of about 3600 g mol^{–1} (at 36 °C in chloroform over a concentration range of 2–18 mM). This value is more than twice the actual value of 1453.92 g mol^{–1}. Previous results on the aggregation of phenylacetylene macrocycles have suggested the importance of a preorganized planar geometry to achieve multiple π – π stacking.^[21] Indeed, a pre-organized helical conformation of compound **2** can be envisaged to form self-assembled supramolecular stacks with up to twelve face-to-face π – π interactions between the aromatic heterocycles of neighboring molecules (Figure 2, left).

Self-aggregation of compound **2** was also observed in dichloromethane and pyridine. Low-molecular-weight gels for organic solvents generate elongated aggregates which subsequently assemble into fiberlike structures that form an extended entangled network.^[22] Gel formation induced by compound **2** prompted an investigation by electron microscopy, that revealed the formation of an extensive fiber

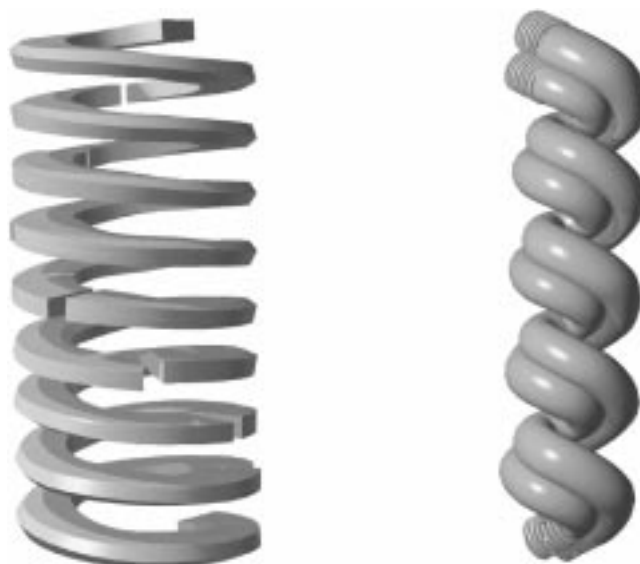


Figure 2. Schematic tentative representations of a self-assembled helical stack of compound **2** (left) and a fiber composed of two coiled-coil self-assembled stacks of compound **2** (right).

network with helical substructures. The freeze-fracture electron micrograph of compound **2** in dichloromethane (1 mg mL^{–1}; Figure 3a) shows uniform fibers with an approximate diameter of 80 Å; these fibres are probably composed of coiled-coil bundles of two or three single supramolecular stacks (Figure 2, right). The chirality observed in the fibers, manifested as helical twisting, could result from favorable

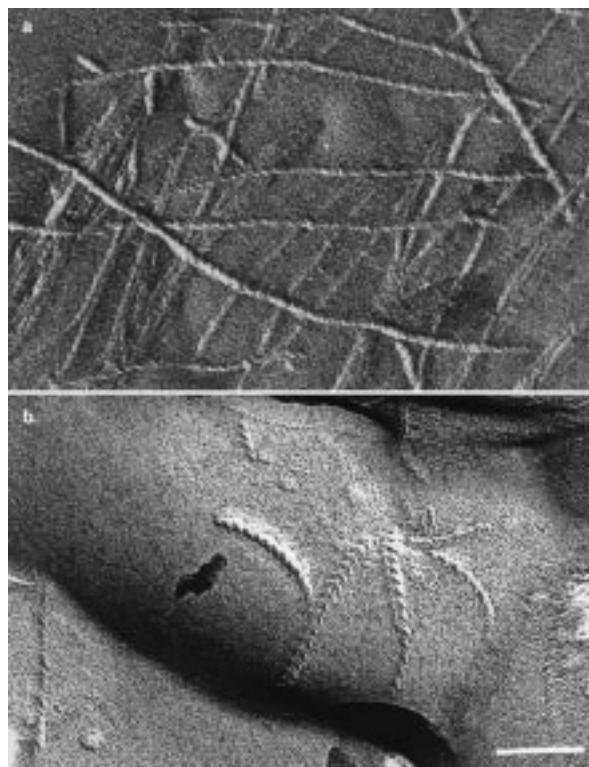


Figure 3. Freeze-fracture electron micrographs of compound **2** in a) dichloromethane and b) pyridine showing fiber network formation with helical textures (scale bar represents 100 nm).

intermolecular π - π stacking interactions from helices of compound **2** of the same helical sense. The molecular helical chirality is consequently translated into supramolecular helicity that is expressed on a nanometer scale. In Figure 3a, a dominance of fibers of same chirality is observed; it may be due to the induction of fiber formation by seeds generated by the breakdown of an initial helical entity caused by the sonication procedure employed. More defined helical structures displaying left- and right-handed helical twists were observed from a birefringent solution of compound **2** in pyridine (2 mg mL⁻¹, Figure 3b), a solvent expected to break intermolecular π - π interactions. The pitch of the helical fibers observed in Figures 3a and 3b is around 115 Å. Networks of fibers of micrometer length subsequently form linear and intertwined macrofibers (Figure 4), yielding a



Figure 4. Freeze-fracture electron micrograph showing molecular aggregation of compound **2** into linear and helical fibers and macrofiber bundles in dichloromethane (scale bar represents 200 nm).

viscous, birefringent organogel in dichloromethane. A solution of compound **2** in pyridine is birefringent but not nearly as viscous as the gel in dichloromethane, and the length of the fibers (and their entanglement) is much greater in dichloromethane than in pyridine. This molecular aggregation into fibers and macrofiber bundles is reminiscent of gels obtained from crown ether substituted phthalocyanines.^[23]

Particularly attractive in this self-organizing/self-assembling system is the formation of bundles of extended molecular channels^[24] comprising tubular (helical) stacks with hollow cores of finite size (ca. 8 Å diameter), thus opening ways for the design of functional polymolecular materials for multichannel ion-active devices.^[25] Further developments towards this end may involve internal functionalization with ion-binding sites.

Analogous to the primary amino acid sequence that encodes the required information for protein folding and assembly, the primary heterocyclic sequence and connectivity encodes for helical self-organization and subsequent self-assembly. Such systems provide access to controlled sequential and hierarchical self-organization processes of well-defined polymolecular architectures at the supramolecular level.

Experimental Section

Physical characterization of compound **2**: m.p. 326.2–329.0 °C (decomp); *R_f* (alumina, CH₂Cl₂): 0.14; ¹H NMR (500.13 MHz, CDCl₃ (29 mm), 55 °C): δ = 8.17–7.77 (m, 26H), 7.06 (m, 2H), 6.53 (m, 2H), 3.06 (t, ³*J* = 7.1 Hz, 4H), 3.02 (t, ³*J* = 7.1 Hz, 4H), 2.98 (t, ³*J* = 7.1 Hz, 4H), 1.88–1.70 (m, 12H), 1.21 (t, ³*J* = 7.4 Hz, 6H), 1.17 (t, ³*J* = 7.4 Hz, 6H), 1.10 (t, ³*J* = 7.4 Hz, 6H); ¹³C NMR (125.77 MHz, CDCl₃ (29 mm), 55 °C): δ = 157.08, 156.60, 156.54, 156.53, 156.50, 154.60, 154.09, 153.25, 153.04, 152.16, 151.32, 151.24, 151.16, 151.14, 148.72, 135.72, 123.99, 123.84, 123.79, 123.74, 123.04, 120.14, 118.36, 118.32, 118.15, 118.03, 118.02, 117.36, 33.22, 33.13, 33.00, 21.80, 21.69, 21.68, 13.91, 13.84, 13.65; IR (KBr, cm⁻¹): $\tilde{\nu}$ = 2960, 2925, 2870, 1577, 1545, 1458, 1390, 1097, 988, 850, 812; UV/Vis (CH₂Cl₂): λ_{max} (ϵ) = 296 (202000); MS (FAB +): *m/z* (%): 1453.5 (100, [*M*⁺]); elemental analysis: C₇₈H₇₂N₁₈S₆ (1453.92): calcd: C 64.44, H 4.99, N 17.34; found: C 64.42, H 5.01, N 17.22.

Molecular modeling was carried out with the MacroModel molecular mechanics program (version 5.5) using the Amber* force field and a standard Monte Carlo search for favorable conformations.

Molecular weight determinations were performed with a Knauer twin-thermister hanging-drop vapor-pressure osmometer operated at 36 °C. The molecular weight of compound **2** was measured in HPLC-grade chloroform over a concentration range of 2–18 mM. A calibration curve was generated by using a polystyrene molecular weight standard (MW = 2430, MN_{VPO} = 2330, polydispersity = 1.06).

Organogels for freeze-fracture transmission electron microscopy were prepared by dissolving compound **2** (0.5–2.0 mg) in dichloromethane or pyridine with heating and bath sonication. The solutions were aged at room temperature for at least 12 h prior to use. Freeze-fracture experiments were performed in an apparatus developed at IGBMC by J.-C. Homo. Gel solutions were sandwiched between two copper specimen holders and frozen in liquid nitrogen. The frozen samples were transferred to the fracture-replication stage which was kept at a vacuum of 10⁻⁸ mbar at –178 °C. Replication was performed immediately after fracturing with about 20 Å platinum/carbon at 45° followed by about 200 Å

carbon at 90°. The replicas were retrieved and cleaned in chloroform, mounted on carbon coated grids and observed with a Philips CM12 electron microscope operating at 100 keV.

Received: August 6, 1999 [Z13840]

- [1] a) A. E. Rowan, R. J. M. Nolte, *Angew. Chem.* **1998**, *110*, 65–71; *Angew. Chem. Int. Ed.* **1998**, *37*, 63–68; b) D. S. Lawrence, T. Jiang, M. Levett, *Chem. Rev.* **1995**, *95*, 2229–2260.
- [2] K. P. Meurer, F. Vögtle, *Top. Curr. Chem.* **1985**, *127*, 1–76.
- [3] a) A. Williams, *Chem. Eur. J.* **1997**, *3*, 15–19; b) C. Piguet, G. Bernardinelli, G. Hopfgartner, *Chem. Rev.* **1997**, *97*, 2005–2062.
- [4] a) J. C. Nelson, J. G. Saven, J. S. Moore, P. G. Wolynes, *Science* **1997**, *277*, 1793–1796; b) R. B. Prince, T. Okada, J. S. Moore, *Angew. Chem.* **1999**, *111*, 245–249; *Angew. Chem. Int. Ed.* **1999**, *38*, 233–236; c) M. S. Gin, T. Yokozawa, R. B. Prince, J. S. Moore, *J. Am. Chem. Soc.* **1999**, *121*, 2643–2644.
- [5] a) C.-Y. Huang, V. Lynch, E. V. Anslyn, *Angew. Chem.* **1992**, *104*, 1259–1261; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1244–1246; b) S. J. Geib, C. Vincent, E. Fan, A. D. Hamilton, *Angew. Chem.* **1993**, *105*, 83–85; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 119–121.
- [6] a) Y. Hamuro, S. J. Geib, A. D. Hamilton, *J. Am. Chem. Soc.* **1997**, *119*, 10587–10593; b) A. Tanatani, H. Kagechika, I. Azumaya, R. Fukutomi, Y. Ito, K. Yamaguchi, K. Shudo, *Tetrahedron Lett.* **1997**, *38*, 4425–4428.
- [7] J.-M. Lehn, *Supramolecular Chemistry. Concepts and Perspectives*, VCH, Weinheim, **1995**.

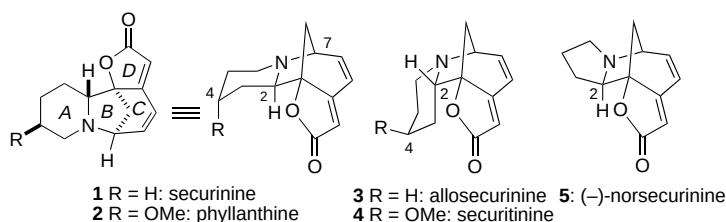
- [8] a) J.-M. Lehn, A. Rigault, J. Siegel, J. Harrowfield, B. Chevrier, D. Moras, *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 2565–2569; b) J.-M. Lehn, A. Rigault, *Angew. Chem.* **1988**, *100*, 1121–1122; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1095–1097.
- [9] R. Krämer, J.-M. Lehn, A. De Cian, J. Fischer, *Angew. Chem.* **1993**, *105*, 764–767; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 703–706.
- [10] a) B. Hasenknopf, J.-M. Lehn, B. O. Kneisel, G. Baum, D. Fenske, *Angew. Chem.* **1996**, *108*, 1987–1990; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1838–1840; b) B. Hasenknopf, J.-M. Lehn, N. Boumediene, A. Dupont-Gervais, A. Van Dorsselaer, B. Kneisel, D. Fenske, *J. Am. Chem. Soc.* **1997**, *119*, 10956–10962.
- [11] a) T. Gulik-Krzywicki, C. Fouquey, J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 163–167; b) N. Kimizuka, S. Fujikawa, H. Kuwahara, T. Kunitake, A. Marsh, J.-M. Lehn, *J. Chem. Soc. Chem. Commun.* **1995**, 2103–2104.
- [12] a) G. S. Hanan, J.-M. Lehn, N. Kyritsakas, J. Fischer, *J. Chem. Soc. Chem. Commun.* **1995**, 765–766; b) G. S. Hanan, U. S. Schubert, D. Volkmer, E. Rivière, J.-M. Lehn, N. Kyritsakas, J. Fischer, *Can. J. Chem.* **1997**, *75*, 169–182.
- [13] a) D. M. Bassani, J.-M. Lehn, G. Baum, D. Fenske, *Angew. Chem.* **1997**, *109*, 1931–1933; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1845–1847; b) D. M. Bassani, J.-M. Lehn, *Bull. Soc. Chim. Fr.* **1997**, *134*, 897–906.
- [14] M. Ohkita, J.-M. Lehn, G. Baum, D. Fenske, *Chem. Eur. J.* **1999**, *12*, 3471–3481.
- [15] a) K. T. Potts, *Bull. Soc. Chim. Belg.* **1990**, *99*, 741–768; b) K. T. Potts, K. A. Gheysen Raiford, M. Keshavarz-K., *J. Am. Chem. Soc.* **1993**, *115*, 2793–2807.
- [16] A. J. Majeed, Ø. Antonsen, T. Benneche, K. Undheim, *Tetrahedron* **1989**, *45*, 993–1006.
- [17] S. T. Howard, *J. Am. Chem. Soc.* **1996**, *118*, 10269–10274.
- [18] F. R. Heitzler, M. Neuburger, M. Zehnder, E. C. Constable, *Liebigs Ann.* **1997**, 297–301.
- [19] a) Assignment of the C4 and C5 protons can be deduced from the presence of multiple ^3J coupling only possible for these protons. b) The association constants calculated from the shifts of the C4 and C5 proton resonances differ from that obtained from the remaining aromatic protons, assuming a simple monomer–dimer equilibrium; this may be due to the fact that intermolecular self-association should increase intramolecular helical self-organization. A value in the 10^3 M^{-1} range may be grossly estimated.
- [20] a) R. H. Martin, N. Defay, H. P. Figeys, M. Flammang-Barbieux, J. P. Cosyn, M. Gelbecke, J. J. Schurter, *Tetrahedron* **1969**, *25*, 4985–4998; b) H. Wynberg, *Acc. Chem. Res.* **1971**, *4*, 65–73.
- [21] A. S. Shetty, J. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **1996**, *118*, 1019–1027.
- [22] J. van Esch, F. Schoonbeek, M. De Loos, E. M. Veen, R. M. Kellogg, B. L. Feringa in *Supramolecular Science: Where It Is and Where It Is Going* (Eds.: R. Ungaro, E. Dalcanele), Kluwer, Dordrecht, **1999**, pp. 233–259.
- [23] H. Engelkamp, S. Middelbeek, R. J. M. Nolte, *Science* **1999**, *284*, 785–788; for another case, see: W. Yang, X. Chai, L. Chi, X. Liu, Y. Cao, R. Lu, Y. Jiang, X. Tang, H. Fuchs, T. Li, *Chem. Eur. J.* **1999**, *5*, 1144–1149.
- [24] a) J.-M. Lehn, J. Malthête, A.-M. Levelut, *J. Chem. Soc. Chem. Commun.* **1985**, 1794–1795; b) N. Khazanovich, J. R. Granja, D. E. McRee, R. A. Milligan, R. Ghadiri, *J. Am. Chem. Soc.* **1994**, *116*, 6011–6012.
- [25] J.-M. Lehn, *Supramolecular Chemistry. Concepts and Perspectives*, VCH, Weinheim, **1995**, chap. 8.

A New Enantioselective Approach to Total Synthesis of the Securinega Alkaloids: Application to (–)-Norsecurinine and Phyllanthine**

Gyoonhee Han, Matthew G. LaPorte, James J. Folmer, Kim M. Werner, and Steven M. Weinreb*

Dedicated to the memory of Professor George Buchi

The securinega alkaloids are a family of approximately 20 tetracyclic compounds produced by several *Securinega* and *Phyllanthus* species of the Euphorbiaceae plant family.^[1] The major securinega alkaloid is securinine (**1**), isolated from the leaves of *Securinega suffruticosa*. Its enantiomer, virosecurinine, is also naturally occurring, as are the antipodes of



several other alkaloids of this class. Allosecurinine (**3**), which is the C2 epimer of **1**, is also a common alkaloid of this group, as is securitinine (**4**). The enantiomer of **3** (viroallosecurinine) is a natural product as well. Some additional common alkaloids of this group are (–)-norsecurinine (**5**), whose (+)-enantiomer is also naturally occurring, and phyllanthine (**2**).

These alkaloids are associated with a wide range of biological activity. Securinine causes central nervous system stimulation and clonic–tonic convulsions in laboratory animals. This activity is due to the alkaloid acting as a γ -amino butyric acid (GABA) receptor antagonist.^[2] These alkaloids have found a sporadic use clinically for such diseases as poliomyelitis, ALS (amyotrophic lateral sclerosis) and chronic aplastic anemia.^[1] Securinine has also been found to be an antimalarial agent^[3] and to have antibacterial activity.^[4]

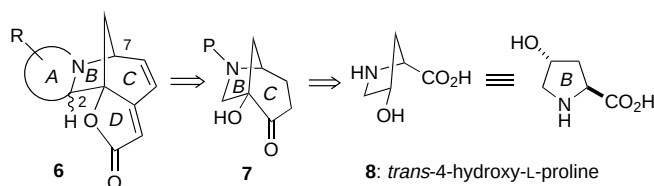
To date there has been only limited synthetic work in this area. A nonstereoselective total synthesis of racemic securinine (**1**) was described by Horii et al. in 1966.^[5] More recently, Heathcock and coworkers devised a clever route to racemic norsecurinine (**5**).^[6] In this synthesis, both the A-ring and the configuration of the C2 atom of **5** were derived from L-proline, although unfortunately optical activity was lost by the racemization of an intermediate. Jacobi et al.^[7] have developed an innovative route to both (+)- and (–)-norsecurinine,

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[**] We are grateful to the National Institutes of Health (GM-32299) for financial support of this research.

starting from L- and D-proline, respectively, once again as a source of the five-membered A-ring and the absolute configuration of the C2 atom. Finally, the Magnus group^[8] has reported an elegant synthesis of racemic norsecurinine via the related securinega alkaloid nirurine, starting from 3-hydroxypyridine.

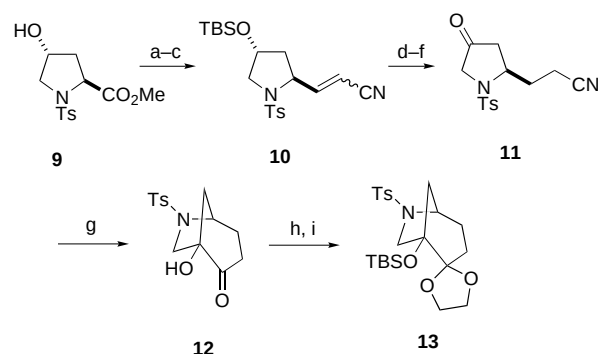
We have been attempting to develop a novel, general strategy for construction of the securinega alkaloids and have established two fundamental design criteria: 1) since most members of this family differ only in the A-ring size and functionality, as well as the C2 configuration (compare **1–5**), the strategy should be flexible enough to allow for the variations in these areas of the molecules; 2) the approach should provide access to both enantiomeric series of alkaloids. With these points in mind, our basic strategy (Scheme 1) was to use readily available *trans*-4-hydroxy-L-proline (**8**) (or the



Scheme 1. Retrosynthetic pathway for securinega alkaloids **6** using 4-hydroxy-L-proline (**8**) as a starting material.

commercially available D-enantiomer) as a source of the alkaloid B-ring and the C7 configuration.^[9] The intent was to first elaborate **8** into a BC-ring fragment like **7**, followed by annulation of the desired A-ring having the appropriate stereogenicity at C2. Finally, the butenolide D-ring would be appended at a late stage to afford the alkaloids **6**. Herein we describe the successful application of this concept to a new enantioselective total synthesis of (–)-norsecurinine (**5**) and the first total synthesis of phyllanthine (**2**).

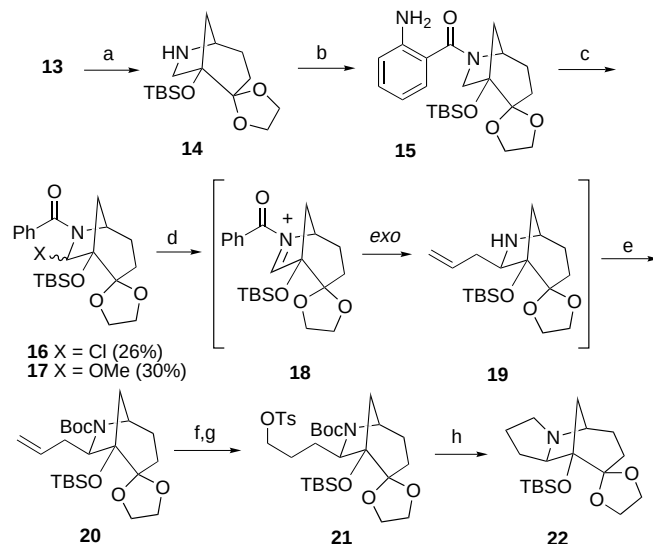
The enantiomerically pure ester **9**, prepared from *trans*-4-hydroxy-L-proline (**8**),^[10] was converted via the α,β -unsaturated nitrile **10** to ketonitrile **11** (Scheme 2). We were pleased to find that exposure of **11** to SmI₂, followed by acidic



Scheme 2. a) TBSCl, imidazole, CH₂Cl₂, 88%; b) DIBAL-H, PhMe, –78 °C → rt, 98%; c) DMSO, (COCl)₂, NEt₃, CH₂Cl₂, –78 °C/Ph₃P=CHCN, CH₂Cl₂, –78 °C → rt, 90% (7:2 *E/Z* mixture); d) 1 atm H₂, 10% Pd-C, EtOAc, 98%; e) Bu₄NF, THF, rt, 100%; f) Jones reagent, acetone, rt, 84%; g) SmI₂, MeOH, THF, –78 °C → rt/H₃O⁺, 78%; h) TBSOTf, iPr₃NEt, CH₂Cl₂, 0 °C → rt, 91%; i) (CH₂O)₂, *p*-TsOH, PhH, reflux, 100%.

hydrolysis, provided the key salemic bicyclic BC-ring system **12** in good yield.^[11] Hydroxyketone **12** was then transformed into protected ketal silyl ether derivative **13**.

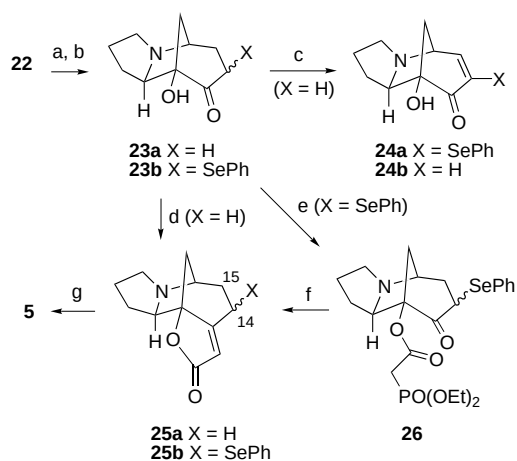
Intermediate **13** was converted to the (–)-norsecurinine ABC-ring synthon as outlined in Scheme 3. The *N*-tosyl group of **13** was removed to afford amine **14**, which was acylated with isatoic anhydride to yield the *ortho*-aminobenzamide



Scheme 3. a) Na, naphthalene, DME, –78 °C, 88%; b) isatoic anhydride, DMAP, MeCN, rt, 87% from **13**; c) NaNO₂, HCl, CuCl, MeOH, rt; d) allylmagnesium bromide, BF₃·Et₂O, THF, –78 → 0 °C; e) (Boc)₂O, NEt₃, CH₂Cl₂, reflux, 68%; f) disiamyl borane, THF, 0 °C → rt/H₂O₂, NaOH; g) TsCl, DMAP, NEt₃, CH₂Cl₂, 71% from **20**; h) 3% HCl, MeOH, 60 °C, 81%.

derivative **15**. In a key step which utilizes our recently reported method,^[12] amide **15** could be regioselectively converted to a mixture of α -chloro- and α -methoxybenzamides **16** and **17**, respectively, in a good combined yield. Subsequent treatment of this mixture with excess allylmagnesium bromide/BF₃·Et₂O stereoselectively afforded the allyl amine **19**, which was transformed without purification into the *tert*-butoxycarbonyl (Boc) derivative **20**. Formation of alkylation product **19** undoubtedly proceeds via the *N*-acyliminium species **18**, which is exclusively *exo*-attacked by the Grignard reagent, followed by debenzoylation by the excess organometallic reagent. The configuration of **20** was established by X-ray analysis of the derivative **25a** (see below). To complete formation of the requisite tricyclic ABC-species, olefin **20** underwent hydroboration, followed by treatment of the resulting primary alcohol with tosylate, giving sulfonate **21**. Removal of the Boc group from **21** resulted in direct in situ cyclization to ketal silyl ether **22**.

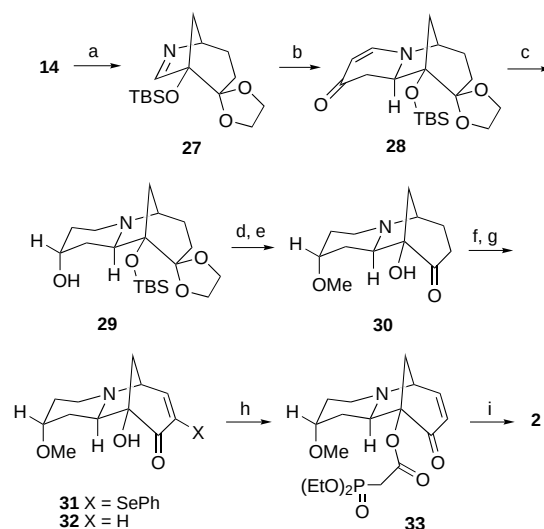
Mild acidic hydrolysis of **22** then led to the pivotal tricyclic α -hydroxy ketone **23a** (Scheme 4). This compound could be reacted with the ketene ylide reagent of Bestmann,^[13] a reaction which is best conducted in this case at high pressure (12 kbar), to afford (+)-14,15-dihydronorsecurinine (**25a**), a naturally occurring minor alkaloid isolated along with (–)-norsecurinine from the root bark of *Securinega virosa*.^[14] The structure of the synthetic alkaloid **25a** was firmly established by an X-ray analysis of its hydrochloride salt.^[15]



Scheme 4. a) 3 N HCl, 95 °C, 74 %; b) PhSeCl, EtOAc, NEt₃, reflux, 60 %; c) PhSeCl, EtOAc, py, reflux, 67 %; d) Ph₃P=C=O, PhMe, CH₂Cl₂, 12 kbar, rt, 89 %; e) (EtO)₂POCH₂CO₂H, CMC, CH₂Cl₂, 0 °C → rt, 88 %; f) K₂CO₃, [18]crown-6, PhMe, 0 °C → rt, 95 %; g) dimethyldioxirane, CH₂Cl₂/Me₂CO, -78 °C, 39 %.

In order to prepare (–)-norsecurinine itself, we next investigated conversion of hydroxy ketone **23a** to the corresponding enone **24b** (Scheme 4). Despite extensive effort we were unable to effect the α -phenylselenation of **23a**, or any hydroxyl-protected derivatives, using standard enolate selenation methods.^[16] On the other hand, we did find that application of an alternate method based on the work of Liotta^[17] (PhSeCl, EtOAc, pyridine, reflux) to substrate **23a** did not afford the anticipated α -selenophenylketone **23b**, but surprisingly gave α -selenophenylene **24a** as the only discernible product. However, we have been unable to remove the selenophenyl group from **24a** to produce the enone **24b**. Interestingly, we also discovered that simply changing the selenation base from pyridine to triethylamine allowed conversion of ketone **23a** to the desired α -phenylselenoketone **23b**. Disappointingly, all attempts to effect elimination of the selenophenyl group from **23b** via the corresponding selenoxide species^[16a] led to a number of decomposition products, probably due to the instability of the resulting enone **24b**. Despite these problems, it was possible to successfully complete the alkaloid total synthesis by converting the keto selenide **23b** to the phosphonate species **26**, which could then be cyclized to butenolide derivative **25b**.^[18] Finally, treatment of the butenolide **25b** with dimethyldioxirane at low temperature led directly to (–)-norsecurinine (**5**) having spectral data identical with those of authentic material.^[16c, 19]

In order to test the generality of our strategy for synthesis of the securinega alkaloids, we have extended the approach to phyllanthine (**2**). Thus, the bicyclic amine **14** could be cleanly oxidized with iodosobenzene^[20] to afford the imine **27** (Scheme 5). We were pleased to find that this imine undergoes an *exo*-stereoselective hetero Diels–Alder reaction with Danishefsky's diene under high pressure (yield ca. 70 %), or more conveniently and efficiently upon catalysis by Yb(OTf)₃,^[21, 22] to afford the tricyclic vinylogous amide **28** after aqueous workup (yield 84 %).^[23] Treatment of **28** with two equivalents of L-selectride effected both conjugate



Scheme 5. a) PhIO, CH₂Cl₂, rt, 87 %; b) Danishefsky's diene, Yb(OTf)₃, MeCN, 84 %; c) L-selectride (2 equiv.), THF, -78 °C, 85 %; d) NaH, MeI, THF, 0 °C → rt, 87 %; e) 3 N HCl, reflux, 78 %; f) (PhSe)₂, SeO₂, MsOH, CH₂Cl₂, 0 °C → rt, 58 %; g) NaI, BF₃·Et₂O, MeCN, 0 °C, 84 %; h) (EtO)₂POCH₂CO₂H, DCC, THF, 0 °C → rt, 67 %; i) K₂CO₃, [18]crown-6, PhMe, 0 °C → rt, 84 %.

reduction and subsequent stereoselective reduction of the ketone group, yielding the axially oriented alcohol **29**. This compound could then be O-methylated and the protecting groups removed by acid hydrolysis to afford hydroxyketone **30**. Attempted application to ketone **30** of the phenylselenation method^[17] used for **23a** (see above) resulted in a complex mixture of products. However, using the selenation procedure reported by Sonoda's group (PhSeSePh, MsOH, SeO₂),^[24] **30** was transformed to the α -phenylselenoenone **31**, which was deselenated in good yield with NaI/BF₃·Et₂O^[25] to provide the required enone **32**. To complete the synthesis, hydroxyenone **32** was esterified to give phosphonate **33**.^[26] Cyclization of **33**, promoted by potassium carbonate/[18]crown-6, then afforded phyllanthine (**2**) which had ¹H and ¹³C NMR data in good accord with those reported for the natural product.^[27]

In summary, we have successfully implemented a new general strategy for enantioselective construction of the securinega alkaloids. Key steps in the total synthesis of (–)-norsecurinine (**5**) include an intramolecular SmI₂-catalyzed ketonitrile coupling and application of our new method for generation of *N*-acylimines.^[12] The total synthesis of phyllanthine (**2**) features a stereoselective imino Diels–Alder reaction for construction of the A-ring.

Received: August 27, 1999 [Z13932]

- For reviews see: a) V. Snieckus, *The Alkaloids*, **1975**, *14*, 425; b) J. A. Beutler, A. N. Brubaker, *Drugs Future* **1987**, *12*, 957.
- D. Rognan, T. Boulanger, R. Hoffmann, D. P. Vercauteren, J.-M. Andre, F. Durant, C.-G. Wermuth, *J. Med. Chem.* **1992**, *35*, 1969.
- H. Weenen, M. H. H. Nkunya, D. H. Bray, L. B. Mwasumbi, L. S. Kinabo, V. A. Kilimali, J. B. Wijnberg, *Planta Med.* **1990**, *56*, 371.
- J. L. Mensah, I. Lagarde, C. Ceschin, G. Michel, J. Gleye, I. Fouraste, *J. Ethnopharmacol.* **1990**, *28*, 129.
- a) S. Saito, H. Yoshikawa, Y. Sato, H. Nakai, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Tamura, *Chem. Pharm. Bull.* **1966**, *14*, 313; b) Z. Horii, T. Imanishi, T. Tanaka, I. Mori, M. Hanaoka, C. Iwata, *Chem. Pharm.*

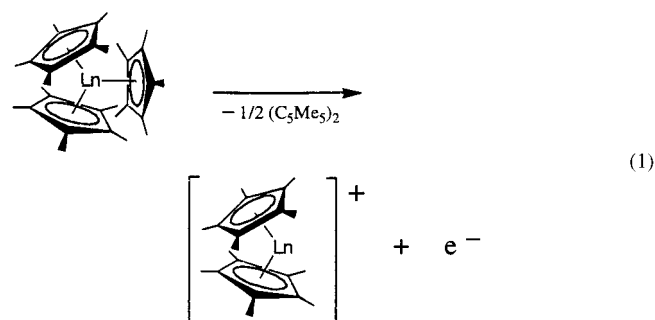
- Bull.* **1972**, *20*, 1768; c) Z. Horii, T. Imanishi, M. Hanaoka, C. Iwata, *Chem. Pharm. Bull.* **1972**, *20*, 1774.
- [6] a) C. H. Heathcock, R. A. Jennings, T. W. von Geldern, *J. Org. Chem.* **1983**, *48*, 3428; b) C. H. Heathcock, T. W. von Geldern, *Heterocycles* **1987**, *25*, 75.
- [7] P. A. Jacobi, C. A. Blum, R. W. DeSimone, U. E. S. Udodong, *J. Am. Chem. Soc.* **1991**, *113*, 5384.
- [8] P. Magnus, J. Rodriguez-Lopez, K. Mulholland, I. Matthews, *Tetrahedron* **1993**, *49*, 8059.
- [9] Interestingly, the Heathcock^[6] and Jacobi^[7] strategies leading to the more common (–)-enantiomer of norsecurinine (**5**) require D-proline whereas our approach to (–)-**5** uses the less-expensive L-amino acid.
- [10] R. H. Andreatta, V. Nair, A. V. Robertson, W. R. J. Simpson, *Aust. J. Chem.* **1967**, *20*, 1493.
- [11] Compare: G. A. Molander, C. N. Wolfe, *J. Org. Chem.* **1998**, *63*, 9031, and references therein. See also: Y. Yamamoto, D. Matsumi, R. Hattori, K. Itoh, *J. Org. Chem.* **1999**, *64*, 3224.
- [12] a) G. Han, M. C. McIntosh, S. M. Weinreb, *Tetrahedron Lett.* **1994**, *35*, 5813; b) S. M. Weinreb, *J. Heterocycl. Chem.* **1996**, *33*, 1437; c) G. Han, M. G. LaPorte, M. C. McIntosh, S. M. Weinreb, *J. Org. Chem.* **1996**, *61*, 9483.
- [13] a) H. J. Bestmann, D. Sandmeier, *Chem. Ber.* **1980**, *113*, 274; b) K. Nickisch, W. Klose, F. Bohlmann, *Chem. Ber.* **1980**, *113*, 2038.
- [14] a) S. Saito, T. Tanaka, K. Kotera, H. Nakai, N. Sugimoto, Z.-I. Horii, M. Ikeda, Y. Tamura, *Chem. Pharm. Bull.* **1964**, *12*, 1520; b) S. Saito, T. Tanaka, K. Kotera, H. Nakai, N. Sugimoto, Z.-I. Horii, M. Ikeda, Y. Tamura, *Chem. Pharm. Bull.* **1965**, *13*, 786.
- [15] We thank Dr. M. Parvez (University of Calgary) for this crystal structure determination. We also are indebted to Dr. C. J. Easton and J. Kelly (Australian National University) for obtaining an ORD spectrum of **25a**, which established that our synthetic material is in the same enantiomeric series as the natural compound.^[14]
- [16] a) H. J. Reich, S. Wollowitz, *Org. React.* **1993**, *44*, 1; b) attempted DDQ or Saegusa oxidations of **23a** and **25a** also failed; c) other selenide oxidants such as *m*-CPBA, O₃, or NaIO₄ gave significantly lower yields of **5**.
- [17] A similar reaction leading directly to an α -selenophenyleneone was described: D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer, H. S. Kezar III, *J. Org. Chem.* **1981**, *46*, 2920. See also: K. B. Sharpless, R. F. Lauer, A. Y. Teranishi, *J. Am. Chem. Soc.* **1973**, *95*, 6137.
- [18] a) Condensation of α -phenylselenoketone **23b** with the Bestmann ketene ylide^[13] gave only a low yield of butenolide **25b**; b) selenides **23b**, **25b** and **26** are mixtures of epimers at C14.
- [19] We are grateful to Professor Peter Jacobi for providing copies of the IR, NMR, CD and mass spectra of authentic norsecurinine.^[7]
- [20] a) P. Muller, D. M. Gilabert, *Tetrahedron* **1988**, *44*, 7171; b) J. Larsen, K. A. Jorgensen, *J. Chem. Soc. Perkin Trans. 2* **1992**, 1213.
- [21] For reviews and lead references to imino Diels–Alder reactions, see: a) D. L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, Orlando, **1987**, ch. 2; b) S. M. Weinreb in *Comprehensive Organic Synthesis*, Vol. 4 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 401.
- [22] Compare: S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1997**, *119*, 10049.
- [23] The crystal structure and configuration of cycloadduct **28** were confirmed by X-ray analysis. We thank Dr. M. Shang (University of Notre Dame) for determining this structure.
- [24] N. Miyoshi, T. Yamamoto, N. Kambe, S. Murai, N. Sonoda, *Tetrahedron Lett.* **1982**, *23*, 4813. See also: M. Watanabe, B. Z. Awen, M. Kato, *J. Org. Chem.* **1993**, *58*, 3923. This procedure is useful for forming an α -phenylselenoketone from a ketone, although direct formation of an α -phenylselenoone as occurred with **30** has apparently not previously been observed.
- [25] This protocol was previously used to dehalogenate an α -bromoone: A. K. Mandal, S. W. Mahajan, *Tetrahedron* **1988**, *44*, 2293.
- [26] Reaction of hydroxy enone **31** with the Bestmann ketene ylide^[13] does not give phyllanthine.
- [27] a) J. Parelo, *Bull. Soc. Chim. Fr.* **1968**, 1117; b) D. Arbain, A. A. Birkbeck, L. T. Byrne, M. V. Sargent, B. W. Skelton, A. H. White, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1863.

Formal Three-Electron Reduction by an f-Element Complex: Formation of [(C₅Me₅)(C₈H₈)U]₂(C₈H₈) from Cyclooctatetraene and [(C₅Me₅)₃U]**

William J. Evans,* Gregory W. Nyce, and Joseph W. Ziller

Reduction reactions involving more than two electrons are not common for metal complexes containing just one metal.^[1] In f-element chemistry, multielectron reductions from mono-metallic species are particularly rare^[2] since the common low-valent ions Th^{III}, U^{III}, Eu^{II}, Yb^{II}, Sm^{II}, and Tm^{II} typically react as one-electron An^{IV}/An^{III} or Ln^{III}/Ln^{II} redox couples.^[3–5] Recently however, we have shown that there is a new way of accomplishing reductive chemistry with f-element complexes by steric crowding^[6,7] and we report here how this method can be coupled with a traditional one-electron redox couple to accomplish multielectron reduction with a mono-metallic uranium complex.

It has recently been discovered that the sterically crowded [(C₅Me₅)₃Ln] complexes (Ln = Sm,^[6] Nd^[7]) can act as one-electron reductants as shown in Equation (1). The reductive reactivity of the [(C₅Me₅)₃Ln] complexes can be rationalized



by the fact that the C₅Me₅[–] ions are not well-stabilized electrostatically in these compounds due to the long Ln–C(C₅Me₅) distances caused by steric congestion. If the redox reaction in Equation (1) is coupled to a one-electron metal-based reduction, for example, the U^{IV}/U^{III} couple^[8] of uranium, then a complex such as [(C₅Me₅)₃U]^[9] could be a two-electron reducing agent. This concept was tested by reacting [(C₅Me₅)₃U] with 1,3,5,7-cyclooctatetraene (C₈H₈). It had been shown that U^{III} complexes would act as one-electron reductants with cyclooctatetraene.^[10] Our efforts to couple that reactivity with sterically induced reduction are reported here.

Reaction of [(C₅Me₅)₃U] with C₈H₈ in a 1:1 stoichiometry formed (C₅Me₅)₂ and a new product, **1**, but residual [(C₅Me₅)₃U] remained at the end of the reaction. Subsequently, it was determined that a 2:3 [(C₅Me₅)₃U]:C₈H₈

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[**] We thank the US National Science Foundation for support of this research.

stoichiometry was optimal for the production of **1** in good yield. The ^1H NMR spectrum of **1** at 25°C contains a resonance attributable to C_5Me_5^- at $\delta = 5.5$ and two resonances attributable to $\text{C}_8\text{H}_8^{2-}$ at $\delta = -41.7$ and -42.2 in a 2:1 ratio, respectively. The $\text{C}_8\text{H}_8^{2-}$ chemical shifts and line widths of **1** are similar to those of other $\text{U}^{\text{IV}}/\text{C}_8\text{H}_8^{2-}$ compounds.^[11] Since neither the NMR, the IR, nor the analytical data were structurally definitive, the complex was examined by X-ray crystallography^[12] and found to be $[(\text{C}_5\text{Me}_5)(\text{C}_8\text{H}_8)\text{U}]_2(\text{C}_8\text{H}_8)$ (**1**) (Figures 1 and 2). The net reaction is shown in Equation (2).

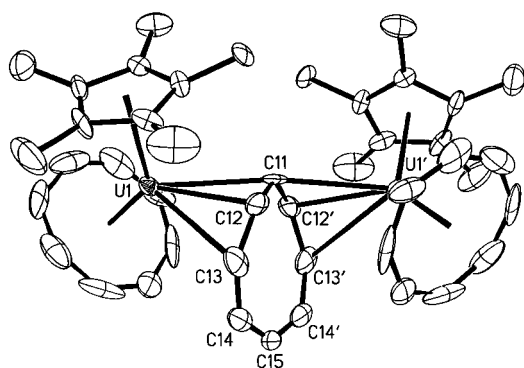


Figure 1. Molecular structure of $[(\text{C}_5\text{Me}_5)(\text{C}_8\text{H}_8)\text{U}]_2(\text{C}_8\text{H}_8)$ (**1**) with thermal ellipsoids drawn at the 50% probability level.

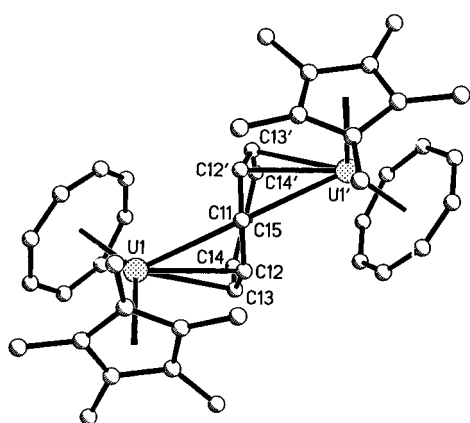
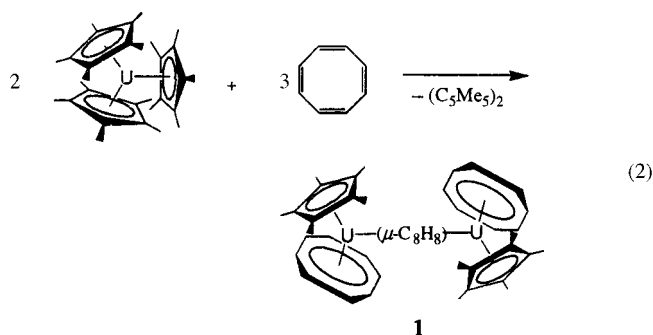


Figure 2. Side view of **1** showing the nonplanarity of the bridging ring. C12 is 0.19 Å out of the average plane of the bridging ring carbon atoms.



Complex **1** contains two mixed ligand bent metallocene units, $[(\text{C}_5\text{Me}_5)(\text{C}_8\text{H}_8)\text{U}]^+$, coordinated to a bridging $\text{C}_8\text{H}_8^{2-}$ moiety. The bridging $\text{C}_8\text{H}_8^{2-}$ moiety is nonplanar as shown in Figure 2 and is bound in an unusual $\eta^3:\eta^3$ fashion in which one

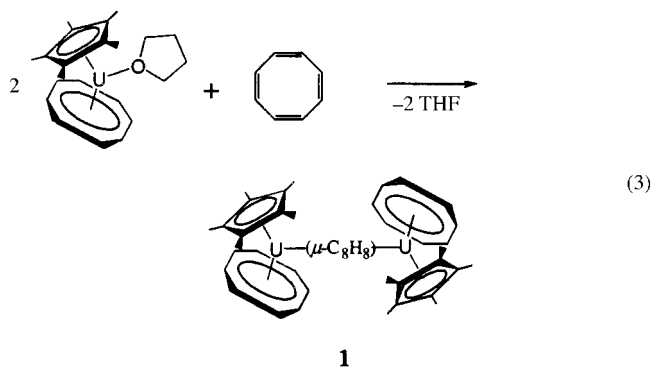
atom is common to both pseudo-allyl moieties. The three unique U–C distances in this bridge have disparate values, U–C12 2.687(17), U–C11 2.878(2), and U–C13 3.00(2) Å, but the difference between the longest and shortest distances is not outside the range observed in allyl f-element complexes,^[13] and the shortest of these distances matches the U–C(terminal C_8H_8) average, 2.68(2) Å. The $\eta^3\text{-C}_8\text{H}_8$ bonding in **1** has similarities to that found in one part of **2**^[14] although



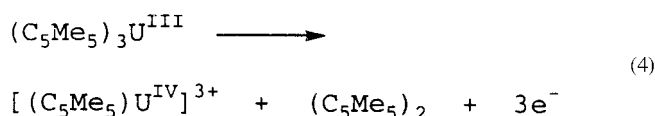
in **2** the bridging $\text{C}_8\text{H}_8^{2-}$ ring is planar. The $\eta^3\text{-C}_8\text{H}_8$ distances in **2** (2.70(2), 2.90(2), and 3.06(2) Å) are also quite similar to those in **1**. Nonplanar $\text{C}_8\text{H}_8^{2-}$ rings have been previously been observed in $[(\text{C}_8\text{H}_8)_3\text{Ti}_2]$ ^[15] and $[(\text{C}_8\text{H}_8)_3\text{Cr}_2]$.^[16] Apparently, the $\eta^3:\eta^3$ mode of attachment in **1** is an acceptable way to fit a bridging $\text{C}_8\text{H}_8^{2-}$ ring between two $[(\text{C}_5\text{Me}_5)(\text{C}_8\text{H}_8)\text{U}]^+$ units. Space-filling models suggest that **1** is sterically crowded.

The U–C(terminal C_8H_8) 2.68(2) Å and U–C(C_5Me_5) 2.80(2) Å average bond lengths are numerically reasonable for a sterically crowded U^{IV} complex,^[17] but comparison with literature values is limited due to the large error limits of the data. For example, the average distance of U–C(terminal C_8H_8) 2.68(2) Å can be compared with the 2.647(4) Å average distance in $[\text{K}(\text{diglyme})]\text{-}[\text{U}(\text{MeC}_8\text{H}_7)_2]$ with trivalent uranium (diglyme = diethylene glycol dimethyl ether).^[18]

Complex **1** is remarkable in several respects. It contains the components of the very stable uranocene molecule $[\text{U}(\text{C}_8\text{H}_8)_2]$ ^[19] yet it does not adopt the uranocene structure. Moreover, complex **1** is the preferred product regardless of the $[(\text{C}_5\text{Me}_5)_3\text{U}]:\text{C}_8\text{H}_8$ stoichiometry between 1:1 and 1:100. Complex **1** is stable for at least two weeks at room temperature in C_6D_6 . It decomposes slowly at 80°C , but it does not decompose to $[\text{U}(\text{C}_8\text{H}_8)_2]$.^[19] Complex **1** is also stable in THF, which raised the possibility that it could be generated from the known U^{III} complex $[(\text{C}_5\text{Me}_5)(\text{C}_8\text{H}_8)\text{U}(\text{thf})]$ ^[20] and C_8H_8 . This reaction does occur to make **1** in quantitative yield as shown in Equation (3).



Examination of the optimal stoichiometry in Equation (2) shows that $[(\text{C}_5\text{Me}_5)_3\text{U}]$ is not a two-electron reductant as originally hypothesized, but rather a three-electron reductant! The net reaction is accomplished through one $\text{U}^{\text{IV}}/\text{U}^{\text{III}}$ and two $(\text{C}_5\text{Me}_5)/(\text{C}_5\text{Me}_5)^-$ couples as shown in Equation (4). Hence this study shows that the one-electron reduction chemistry of sterically crowded $[(\text{C}_5\text{Me}_5)_3\text{Ln}]$ lanthanide



complexes can be generalized to U^{III} and can be coupled to the U^{III} redox chemistry to do multielectron reductions. This also shows that the $\text{C}_8\text{H}_8^{2-}/\text{U}^{\text{IV}}$ components of uranocene can exist in forms other than the very stable parallel ring structure of $[\text{U}(\text{C}_8\text{H}_8)_2]$. This reaction suggests a rich reductive chemistry can be accessed by coupling steric crowding and lower f-element oxidation states.

Experimental Section

All manipulations were performed under an N_2 or Ar atmosphere by glove box or Schlenk techniques.

1: In a THF-free glovebox, 1,3,5,7- C_8H_8 (24 mg, 0.23 mmol) was added to a brown solution of $[(\text{C}_5\text{Me}_5)_3\text{U}]$ (100 mg, 0.155 mmol) in toluene (10 mL). After the brown solution was stirred at room temperature for 4 d, the solvent was removed by rotary evaporation. The gummy brown solid was washed with hexanes and dried under reduced pressure to afford **1** as a dark brown powder (70 mg, 85%). IR (KBr): $\tilde{\nu}$ 3022 m, 2903 s, 2851 m, 1435 w, 1373 w, 1020 w, 902 w, 797 w, 729 sh, 673 sh, 568 w cm^{-1} ; Elemental analysis ($\text{U}_2\text{C}_{44}\text{H}_{54}$): calcd: C 49.91, H 5.14; found: C 49.64, H 4.92; ^1H NMR (400 MHz, $[\text{D}_6]\text{benzene}$, 25 °C): δ = 5.5 (s, C_5Me_5 ; $\Delta\nu_{1/2}$ = 10 Hz, 30H), –41.7 (s, C_8H_8 ; $\Delta\nu_{1/2}$ = 14 Hz, 16H), –42.2 (s, C_8H_8 ; $\Delta\nu_{1/2}$ = 20 Hz, 8H); ^1H NMR (400 MHz, $[\text{D}_8]\text{toluene}$, –100 °C): δ = 14.5 (s, C_5Me_5), –80.8 (s, C_8H_8 , 16H), –87.5 (s, C_8H_8 , 8H); ^{13}C NMR (100 MHz, $[\text{D}_6]\text{benzene}$, 25 °C): δ = 395, 280, 279, –26.

Received: July 6, 1999 [Z13685]

- [1] *Inorganic Reactions and Methods*, Vol. 15 (Ed.: J. J. Zuckerman), VCH, Deerfield Beach, FL, 1986.
- [2] a) D. S. Arney, C. J. Burns, D. C. Smith, *J. Am. Chem. Soc.* **1992**, *114*, 10068–10069; b) D. S. Arney, C. J. Burns, *J. Am. Chem. Soc.* **1993**, *115*, 9840–9841; c) J. G. Brennan, R. A. Andersen, *J. Am. Chem. Soc.* **1985**, *107*, 514–516; d) F. G. N. Cloke, *Chem. Soc. Rev.* **1993**, 17–24.
- [3] L. R. Morss, *Chem. Rev.* **1976**, *76*, 827.
- [4] T. J. Marks, R. D. Ernst in *Comprehensive Organometallic Chemistry* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, chap. 21.
- [5] M. N. Bochkaev, I. L. Fedushkin, A. A. Fagin, T. V. Petrovskaya, J. W. Ziller, R. N. R. Broomhall-Dillard, W. J. Evans, *Angew. Chem.* **1997**, *109*, 123–124; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 133–135.
- [6] W. J. Evans, K. J. Forrestal, J. W. Ziller, *J. Am. Chem. Soc.* **1998**, *120*, 9273–9282.
- [7] W. J. Evans, G. W. Nyce, R. D. Clark, R. J. Doedens, J. W. Ziller, *Angew. Chem.* **1999**, *111*, 1917–1919; *Angew. Chem. Int. Ed.* **1999**, *38*, 1801–1803.
- [8] a) R. G. Finke, Y. Hirose, G. Gaughan, *J. Chem. Soc. Chem. Commun.* **1981**, 232; b) J. G. Brennan, R. A. Andersen, *J. Am. Chem. Soc.* **1985**, *107*, 514–516; c) J. G. Brennan, R. A. Andersen, A. Zalkin, *Inorg. Chem.* **1986**, *25*, 1756–1760; d) J. G. Brennan, R. A. Andersen, A. Zalkin, *Inorg. Chem.* **1986**, *25*, 1761–1765; e) L. R. Avens, D. M. Barnhart, C. J. Burns, S. D. McKee, W. H. Smith, *Inorg. Chem.* **1994**, *33*, 4245–4254.
- [9] W. J. Evans, K. J. Forrestal, J. W. Ziller, *Angew. Chem.* **1997**, *109*, 798–799; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 774–776.
- [10] T. R. Bousie, R. M. Moore, A. Streitwieser, A. Zalkin, J. Brennan, K. A. Smith, *Organometallics* **1990**, *9*, 2010–2016.
- [11] a) $[(\text{C}_8\text{H}_8)_2\text{U}]$, δ = –48.6 ppm. A. Streitwieser, U. Müller-Westerhoff, F. Sonnichsen, F. Mares, D. G. Morrell, K. O. Hodgson, C. A. Harmon, *J. Am. Chem. Soc.* **1973**, *95*, 8644; b) $[(\text{C}_8\text{H}_8)\text{UCl}_2]$, δ = –31.5;^[10] c) $[(\text{C}_5\text{Me}_5)(\text{C}_8\text{H}_8)(\text{NET}_2)]$, δ = –35.78 and $[\text{U}(\text{C}_5\text{Me}_5)(\text{C}_8\text{H}_8)(\text{thf})_2][\text{BPh}_4]$, δ = –32.88. J. C. Berthet, C. Boisson, M. Lance, J. Viger, M.

Nierlich, M. Ephritikhine, *J. Chem. Soc. Dalton. Trans.* **1995**, 3027–3033.

- [12] X-ray quality crystals were grown by slowly cooling a hot toluene solution of **1**. A brown crystal of approximate dimensions $0.03 \times 0.20 \times 0.30$ mm in Paratone oil was mounted on a glass fiber and transferred to a Siemens CCD diffractometer. Crystal data for **1** at 158 K: $\text{C}_{44}\text{H}_{54}\text{U}_2$, monoclinic, space group $C2$, $a = 15.2722(9)$, $b = 9.9717(6)$, $c = 13.8865(8)$ Å, $\beta = 103.7740(10)^\circ$, $V = 2054.0(2)$ Å³, $Z = 2$. At convergence, $wR2 = 0.1978$ and $\text{GOF} = 1.070$ for 210 parameters refined against 4136 unique reflections [as a comparison for refinement against F , $R1 = 0.0725$ for those 3950 reflections with $I > 2.0\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-129637. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [13] W. J. Evans, T. A. Ulibarri, J. W. Ziller, *J. Am. Chem. Soc.* **1990**, *112*, 2314–2324.
- [14] S. R. Ely, T. E. Hopkins, C. W. DeKock, *J. Am. Chem. Soc.* **1976**, *98*, 1624–1625.
- [15] a) H. Briel, G. Wilke, *Angew. Chem.* **1966**, *5*, 942; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 898–899; b) H. Dietrich, H. Dierks, *Angew. Chem.* **1966**, *78*, 943; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 899.
- [16] D. J. Brauer, C. Kruger, *Inorg. Chem.* **1976**, *15*, 2511–2514.
- [17] A. Avdeef, K. N. Raymond, K. O. Hodgson, A. Zalkin, *Inorg. Chem.* **1972**, *11*, 1083–1088.
- [18] T. R. Bousie, D. C. Eisenberg, J. Rigsbee, A. Streitwieser, A. Zalkin, *Organometallics* **1991**, *10*, 1922–1928.
- [19] A. Streitwieser, U. Müller-Westerhoff, *J. Am. Chem. Soc.* **1968**, *90*, 7364.
- [20] A. R. Schake, L. R. Avens, C. J. Burns, D. L. Clark, A. P. Sattelberger, W. H. Smith, *Organometallics* **1993**, *12*, 1497–1498.

Application of Reductive Samarium to the Synthesis of Small Unnatural Peptides**

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Dedicated to Professor Anders Kjær
on the occasion of his 80th birthday

The selective introduction of side chains to a specific glycine residue in a peptide strand represents a challenging task for the preparation of unnatural peptides. Instead of a stepwise approach where commercially available or synthetic amino acids are incorporated by a traditional peptide synthesis, application of a direct peptide modification step is justified by the numerous analogues which may be quickly synthesized from a single and intact peptide. As reactive intermediates, glycine enolates^[1–4] and radicals^[5–7] as well as

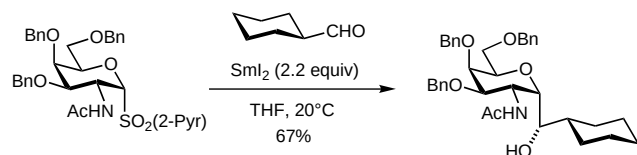
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[**] Financial support from The Danish National Science Foundation (THOR program) and The University of Aarhus is gratefully acknowledged.

glycine cation equivalents^[8,9] have been exploited for the C–C coupling step. The seminal studies by Seebach and co-workers^[11] are the most impressive in this area, demonstrating that linear and cyclic peptides up to 11 units in length can be alkylated at a glycine residue with a polyolithiated peptide enolate. Such enolates are prepared by the low-temperature deprotonation of first the acidic amide protons with lithium diisopropylamide (LDA) followed by one of the α -CH protons of glycine. However, successful deprotonation and alkylation requires that the nitrogen atom of the adjacent amino acid in the C-terminus direction to the arising enolate be N-alkylated. This problem could be resolved by incorporating a removable electron-withdrawing substituent on the glycine α -carbon atom; nevertheless a subsequent reduction step is required for the removal of the activating group.^[1e]

Here we show that reductive samarium of glycine pyridyl sulfides in the presence of carbonyl substrates (Barbier conditions) is a possible alternative for the selective incorporation of carbinol side chains onto glycine residues in peptides. Of particular interest is that alkylation occurs at room temperature in the presence of the amide protons and, more importantly, without the aid of an activating group.

In previous work, we have demonstrated that C-glycosides can be stereoselectively obtained by a samarium diiodide induced Barbier reaction with glycosyl pyridyl sulfones.^[10,11] The key to the success of this reaction lies in the ease of the reduction of the pyridyl sulfone group, which is in part due to the generation of a stabilized anomeric radical.^[12] Pertinent to the present work are the successful carbonyl coupling reactions, which proceed even when the monosaccharide possesses an acetamido group at the C2 position,^[10c,f,g] implying that the organosamarium intermediate displays a higher reactivity for carbonyl coupling rather than internal or external protonation (Scheme 1). These observations under



Scheme 1. Previous results^[10c,f,g] in the SmI_2 -promoted coupling of *N*-acetylgalactosamine pyridyl sulfones with carbonyl compounds. Bn = benzyl, 2-Pyr = 2-pyridyl.

consideration of the fact that α -glycyl radicals display an enhanced stability owing to the captodative effect^[7] suggested that similar glycine derivatives could also undergo reductive samarium and concomitant carbonyl coupling reactions as the glycosyl pyridyl sulfones.

The feasibility of this approach was first assessed with the dipeptide derivative **1a** (Table 1, entry 1). The success of this work requires that a reducible group can be selectively introduced at the α -carbon atom of the glycine residue in the presence of other amino acid units. The previous work by Easton and collaborators concerning selective bromination of dipeptides with *N*-bromosuccinimide (NBS) was therefore significant for our studies.^[5a,b]

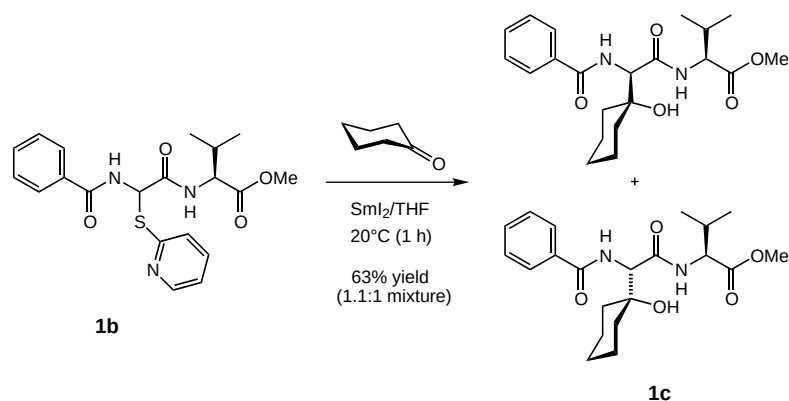
Table 1. Introduction of the pyridyl sulfide group.

Entry	Peptide ^[a]	Pyridyl sulfide (yield) ^[b]
1		 1b , 85%
2		2b , 87%
3		3b , 74%
4		4b , 42%
5		 5b , 48%
6		 6b , 59% ^[c]

[a] For the reaction conditions see the Experimental Section. [b] Yields of isolated product after chromatography on silica gel. [c] Based on recovered starting material (35%).

Hence, bromination of **1a** was achieved by photolysis of the dipeptide with one equivalent of NBS in refluxing dichloromethane for 3 h. The bromide proved to be quite unstable and thus the reaction mixture was immediately treated with 2-sulfanylpuridine (2.0 equiv) and diisopropylethylamine (Hünig's base). In this way, the stable pyridyl sulfide **1b**, as an approximately 1.6:1 diastereomeric mixture, could be isolated in 85% yield after chromatographic separation (Table 1, entry 1). Attempts to oxidize the sulfide to the sulfone were unsuccessful, possibly owing to the sensitivity of the sulfone towards hydrolysis, but this obstacle was of no importance as the glycyl pyridyl sulfide displayed a high reactivity with SmI_2 .

Treatment of a mixture of dipeptide **1b** and cyclohexanone with a solution of blue SmI_2 in THF led to the consumption of two equivalents of the one-electron reducing agent over a period of 1 h. After chromatographic purification, an approximately 1:1 diastereomeric mixture of the dipeptide derivatives **1c** was obtained in an encouraging 63% yield (Scheme 2). This implied that carbonyl coupling is indeed a

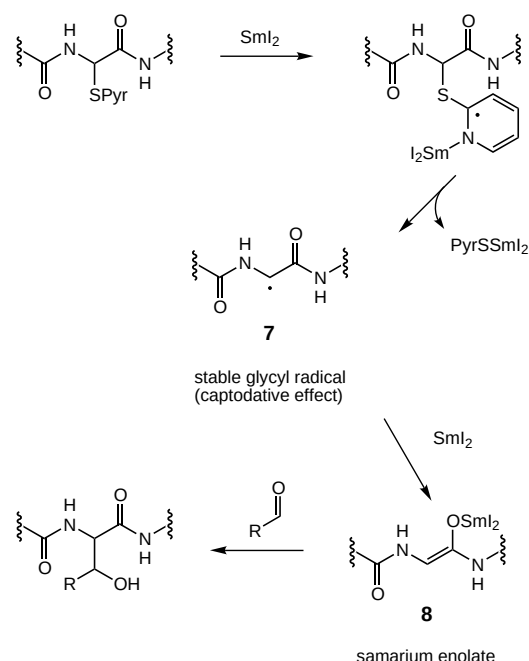


Scheme 2. SmI_2 -induced coupling of dipeptide **1b** with cyclohexanone.

fast event in comparison to either intramolecular or intermolecular protonation involving the two amide groups.

A series of other dipeptides and one tripeptide were then tested in which the glycine residue is located either as a C- or N-terminal residue in the dipeptides **2a–5a** (Table 1, entries 2–5) or as the middle unit of tripeptide **6a** (entry 6), in order to assess the effect of the glycine position on both yields and diastereoselectivities. The pyridyl sulfides **2b–6b** were obtained in good to acceptable yields (42–87 %) using the Easton protocol for bromination. It was pleasing to see that reductive samarium and coupling also proceeded in good yields (43–65 %) to afford the modified dipeptides **2c–5c** as approximately 1:1 diastereomers (Table 2, entries 1, 4–6). The use of *n*-octanal or cyclohexanecarbaldehyde with **2b** furnished inseparable diastereomeric mixtures of **2d** and **2e** (entries 2 and 3), although only three isomers could be seen in the ¹H NMR spectrum. Quite remarkable was the coupling of tripeptide **6b** to cyclohexanone to give the modified peptide **6c** in a good yield of 50 % considering the presence of three amide protons in **6b** (entry 7). In this latter case, a small diastereoselectivity (2:1) was noted for this reaction.^[13]

In all cases, diastereoselectivities at the glycyl α-carbon atom were low. This is somewhat surprising considering the high Lewis acid character of samarium(III) salts and hence their ability to form strong complexes with amides or other carbonyl groups.^[14] The mechanism of this reaction (Scheme 3) proceeds via the stable glycyl radical **7** by the initial reduction of the pyridyl sulfide group by the divalent lanthanide reagent. Further reduction of this carbon radical by a second equivalent of SmI₂ would lead to a Sm^{III} enolate intermediate **8**. The presence of other possible coordination



Scheme 3. A mechanistic proposal for the coupling of pyridyl sulfide containing peptides with carbonyl compounds. Pyr = pyridyl.

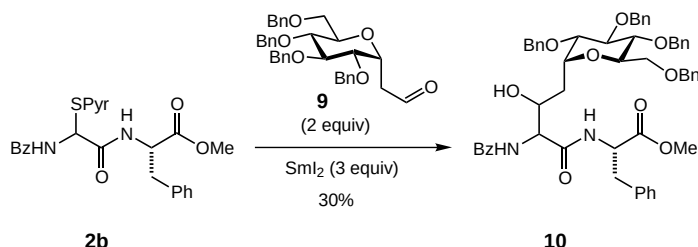
sites for the metal ion may therefore give rise to cyclic enolate structures, where attack of the incoming electrophile could be directed by the distal side-chain substituent of the neighboring amino acid unit.^[10c,f,g, 11, 15] The low selectivity suggests that this is not the case, but it is nevertheless an important feature in the application of this approach for combinatorial chemistry.

Table 2. C-Alkylation of peptides **2b–6b**.

Entry	Pyridyl sulfide	Carbonyl compound ^[a]	Alkylated peptide (yield) ^[b]
1		cyclohexanone	2c , 64 % (1:1)
2	2b (R = CH ₂ Ph)	<i>n</i> -octanal	2d , 60 % (2.2:1.8:1.0)
3	2b (R = CH ₂ Ph)	cyclohexanecarbaldehyde	2e , 57 % (2.0:1.1:1.0)
4	3b (R = CH ₂ CO ₂ Me)	cyclohexanone	3c , 61 % (1:1)
5	4b (R = Me)	cyclohexanone	4c , 43 % (1:1)
6		cyclohexanone	 5c , 45 % (1.1:1)
7		cyclohexanone	 6c , 50 % (2:1)

[a] For the reaction conditions see the Experimental Section. [b] Yields of isolated products after chromatography on silica gel. The numbers in parentheses refer to the diastereomeric ratio as determined by ¹H NMR spectroscopy.

Finally, motivated by the recent interest in the synthesis of C-glycopeptides,^[16] a hydrolytically stable analogue of the parent N- or O-glycoside, we have applied the above methodology as an alternative and direct approach to such compounds, as illustrated with the example in Scheme 4. Hence, the dipeptide derivative **2b** was coupled to the easily accessible aldehyde **9**,^[17] affording the C-glycopeptide **10** in 30% yield as a mixture of diastereomers.



Scheme 4. Preparation of a C-glycopeptide.

In conclusion, we have presented a novel and mild approach to the alkylation of peptides via reductive samarium. Further work is now in progress to identify other conditions which will increase the diastereoselectivities of these reactions, such as modifying the coordination sphere of the lanthanide ion with chiral ligands or the use of other transition metal reductants.

Experimental Section

Pyridyl sulfide formation: 1b: A solution of *N*-bromosuccinimide (65 mg, 0.37 mmol) and dipeptide **1a** (99 mg, 0.34 mmol) in CH_2Cl_2 (4 mL) was irradiated with a 150-W lamp for 3 h. The heat from the lamp was sufficient to maintain refluxing. The solution was then cooled to 0 °C, after which 2-sulfanylpuridine (57 mg, 0.51 mmol) and diisopropylethylamine (89 μL , 0.51 mmol) were added. The reaction mixture was stirred for 3 h at 0 °C, then diluted with CH_2Cl_2 and washed with water ($2 \times$) and brine. The organic phase was dried (MgSO_4) and evaporated to dryness, whereafter the residue was purified by flash chromatography (diethyl ether/pentane 7/3) to afford a diastereomeric mixture (1.6:1) of the pyridyl sulfide **1b** (116 mg, 85%) as a pale yellow oil. ^1H NMR (CDCl_3 , 200 MHz): δ = 0.72 (d, J = 4.5 Hz, 3H), 0.85 (d, J = 4.5 Hz, 3H), 0.97 (d, J = 4.6 Hz, 3H), 1.00 (d, J = 4.6 Hz, 3H), 2.20 (m, 2H), 3.60 (s, 3H), 3.76 (s, 3H), 4.55 (dd, J = 5.8, 3.0 Hz, 1H), 4.60 (dd, J = 5.8, 3.0 Hz, 1H), 6.47 (d, J = 5.0 Hz, 2H), 7.14–7.89 (m, 9H), 8.48 (m, 1H), 8.55 (m, 1H), 9.22 (m, 2H); ^{13}C NMR (50 MHz, CDCl_3): δ = 171.94, 171.64, 169.36, 165.75, 157.88, 149.34, 149.11, 137.08, 136.96, 133.38, 132.16, 128.69, 127.37, 123.57, 120.78, 58.01, 57.75, 54.36, 54.18, 52.31, 52.06, 31.64, 31.12, 19.26, 19.06, 17.77, 17.40.

Peptide alkylation: 1c: A 0.1M solution of SmI_2 in THF (5.5 mL, 0.55 mmol) was added to a stirred solution of pyridyl sulfide **1b** (82 mg, 0.20 mmol) and cyclohexanone (62 μL , 0.60 mmol) in THF (0.5 mL) at 20 °C. After stirring for 1 h, saturated aq. NH_4Cl was added to the reaction mixture, which was then extracted twice with CH_2Cl_2 . The combined organic phases were washed twice with water, dried with MgSO_4 , and evaporated to dryness. Flash chromatography (pentane/EtOAc 3/1) gave dipeptides **1c** (49 mg, 63%) as a colorless solid in a 1:1 diastereomeric mixture. ^1H NMR (CDCl_3 , 200 MHz): δ = 0.90 (d, J = 4.4 Hz, 3H), 0.91 (d, J = 4.4 Hz, 3H), 0.94 (d, J = 4.9 Hz, 3H), 0.97 (d, J = 4.9 Hz, 3H), 1.19–1.86 (m, 20H), 2.21 (m, 2H), 3.64 (s, 3H), 3.76 (s, 3H), 4.46 (dd, J = 5.8, 3.2 Hz, 1H), 4.50 (dd, J = 5.9, 3.3 Hz, 1H), 4.56 (d, J = 5.4 Hz, 1H), 4.59 (d, J = 5.6 Hz, 1H), 6.85 (d, J = 5.8 Hz, 1H), 7.13 (m, 3H), 7.40–7.56 (m, 6H), 7.77–7.84 (m, 4H); ^{13}C NMR (50 MHz, CDCl_3): δ = 175.94, 172.00, 171.54, 168.13, 168.00, 133.75, 132.10, 128.81, 127.28, 73.03, 72.76, 58.31, 57.84, 57.56, 57.41, 52.45, 52.35, 35.67,

35.40, 33.86, 33.59, 30.92, 25.70, 21.89, 21.78, 21.61, 19.23, 19.14, 18.02, 17.70; HR-MS (ES) calcd for $\text{C}_{21}\text{H}_{30}\text{N}_2\text{O}_5\text{Na}$ ($M + \text{Na}$): 413.2052, found: 413.2043.

Received: July 5, 1998 [Z13682]

- [1] For a comprehensive review on the use of peptide enolates by Seebach and co-workers, see D. Seebach, A. K. Beck, A. Studer in *Modern Synthetic Methods*, Vol. 7 (Eds.: B. Ernst, C. Leumann), VCH, Weinheim, **1995**, pp. 1–178; see also a) D. Seebach, H. G. Bossler, G. Gründler, S. Shoda, R. Wenger, *Helv. Chim. Acta* **1991**, *74*, 197; b) D. Seebach, A. K. Beck, H. G. Bossler, C. Gerber, S. Y. Ko, C. W. Murtiashaw, R. Naef, S. Shoda, A. Thaler, M. Krieger, R. Wenger, *Helv. Chim. Acta* **1993**, *76*, 1564; c) H. G. Bossler, D. Seebach, *Helv. Chim. Acta* **1994**, *77*, 1124; d) D. Seebach, O. Bezençon, B. Jaun, T. Pietzonka, J. L. Matthews, F. N. M. Kühnle, W. B. Schweizer, *Helv. Chim. Acta* **1996**, *79*, 588; e) T. Matt, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 1845, and references therein.
- [2] D. J. Ager, D. E. Froen, R. C. Klix, B. Zhi, J. McIntosh, R. Thangarasa, *Tetrahedron* **1994**, *50*, 1975.
- [3] a) M. J. O'Donnell, T. P. Burkholder, V. V. Khau, R. W. Roeske, Z. Tian, *Pol. J. Chem.* **1994**, *68*, 2477; b) M. J. O'Donnell, C. Zhou, W. L. Scott, *J. Am. Chem. Soc.* **1996**, *118*, 6070.
- [4] a) U. Kazmaier, *Angew. Chem.* **1994**, *106*, 1046; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 998; b) U. Kazmaier, *J. Org. Chem.* **1994**, *59*, 6667; c) U. Kazmaier, S. Maier, *Chem. Commun.* **1998**, 2535; d) U. Kazmaier, S. Maier, *J. Org. Chem.* **1999**, *64*, 4575.
- [5] a) C. J. Easton, I. M. Scharfbillig, E. W. Tan, *Tetrahedron Lett.* **1988**, *29*, 1565; b) C. J. Easton, E. W. Tan, M. P. Hay, *J. Chem. Soc. Chem. Commun.* **1989**, 385; c) V. A. Burgess, C. J. Easton, M. P. Hay, *J. Am. Chem. Soc.* **1989**, *111*, 1047.
- [6] A. Papadopoulos, B. Lewall, E. Steckhan, K.-D. Ginzel, F. Knoch, M. Nieger, *Tetrahedron* **1991**, *47*, 563.
- [7] For a recent review on peptide radicals, see C. J. Easton, *Chem. Rev.* **1997**, *97*, 53.
- [8] a) P. Renaud, D. Seebach, *Angew. Chem.* **1986**, *98*, 836; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 843; b) P. Renaud, D. Seebach, *Helv. Chim. Acta* **1986**, *69*, 1704; c) D. Seebach, R. Charczuk, C. Gerber, P. Renaud, H. Berner, H. Schneider, *Helv. Chim. Acta* **1989**, *72*, 401.
- [9] W. Steglich, M. Jäger, S. Jaroch, P. Zistler, *Pure Appl. Chem.* **1994**, *66*, 2167.
- [10] a) D. Mazéas, T. Skrydstrup, J.-M. Beau, *Angew. Chem.* **1995**, *107*, 990; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 909; b) O. Jarreton, T. Skrydstrup, J.-M. Beau, *Chem. Commun.* **1996**, 1661; c) D. Urban, T. Skrydstrup, C. Riche, A. Chiaroni, J.-M. Beau, *Chem. Commun.* **1996**, 1883; d) O. Jarreton, T. Skrydstrup, J.-M. Beau, *Tetrahedron Lett.* **1997**, *38*, 303; e) T. Skrydstrup, O. Jarreton, D. Mazéas, D. Urban, J.-M. Beau, *Chem. Eur. J.* **1998**, *4*, 655; f) D. Urban, T. Skrydstrup, J.-M. Beau, *J. Org. Chem.* **1998**, *63*, 2507; g) L. Andersen, L. M. Mikkelsen, J.-M. Beau, T. Skrydstrup, *Synlett* **1998**, 1393; h) O. Jarreton, T. Skrydstrup, J.-M. Beau, *Chem. Eur. J.* **1999**, *5*, 430; i) S. L. Krintel, J. Jiménez-Barbero, T. Skrydstrup, *Tetrahedron Lett.* **1999**, *40*, 7565.
- [11] For recent reviews on the application of SmI_2 in organic synthesis, see A. Krief, A.-M. Laval, *Chem. Rev.* **1999**, *99*, 745; G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307; G. A. Molander, C. R. Harris, *Tetrahedron* **1998**, *54*, 3321; T. Skrydstrup, *Angew. Chem.* **1997**, *109*, 355; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 345.
- [12] B. Giese, H.-G. Zetz in *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), Marcel Dekker, New York, **1997**, p. 507, and references therein.
- [13] Since only two diastereomers were isolated in the condensation of **6b** with cyclohexanone, it does not appear that epimerization is occurring at the adjacent amino acid moieties under the reaction conditions used.
- [14] See also a) M. Kawatsura, F. Dekura, H. Shirahama, F. Matsuda, *Synlett* **1996**, 373; b) G. A. Molander, J. C. McWilliams, B. C. Noll, *J. Am. Chem. Soc.* **1997**, *119*, 1265.
- [15] Another possible mechanism for product formation involves the addition of the glycol radical onto a SmI_2 -coordinated ketone or aldehyde. The carbonyl group should display a greater reactivity due to a lowered LUMO, while the high-energy oxy radical intermediate formed upon radical addition would be immediately reduced by the

presence of the divalent lanthanide. Nevertheless, evidence against radical-type mechanisms for carbonyl addition reactions have been put forth for other systems. For a discussion on this topic, see D. P. Curran, T. L. Fevig, C. P. Jasperse, M. J. Tottleben, *Synlett* **1992**, 943, and references therein.

- [16] For some recent approaches to the synthesis of C-glycosyl amino acids and peptides, see a) F. Burkhart, M. Hoffmann, H. Kessler, *Angew. Chem.* **1997**, 109, 1240; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1191; b) L. Lay, M. Meldal, F. Nicotra, L. Panza, G. Russo, *Chem. Commun.* **1997**, 1469; c) S. D. Debenham, J. S. Debenham, M. J. Burk, E. J. Toone, *J. Am. Chem. Soc.* **1997**, 119, 9897; d) A. Dondoni, A. Marra, A. Massi, *Chem. Commun.* **1998**, 1741; e) A. Dondoni, A. Marra, A. Massi, *Tetrahedron Lett.* **1998**, 39, 6601; f) A. Dondoni, A. Marra, A. Massi, *Tetrahedron* **1998**, 54, 2827; g) R. N. Ben, A. Orellana, P. Arya, *J. Org. Chem.* **1998**, 63, 4817; h) P. Arya, R. N. Ben, H. Qin, *Tetrahedron Lett.* **1998**, 39, 6131; i) D. Urban, T. Skrydstrup, J.-M. Beau, *Chem. Commun.* **1998**, 955; j) A. J. Pearce, S. Ramaya, S. N. Thorn, G. B. Bloomberg, D. S. Walter, T. Gallagher, *J. Org. Chem.* **1999**, 64, 5453.
- [17] Prepared in two steps from methyl 2,3,4,6-tetra-O-benzyl- α -D-mannopyranoside, by first allylation with allyltrimethylsilane and TMSOTf and then ozonolysis: A. Hosomi, Y. Sakata, H. Sakurai, *Carbohydrate Res.* **1987**, 171, 125.

Antiferromagnetic Coupling in a Gadolinium(III) Semiquinonato Complex**

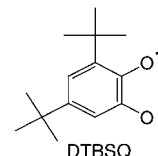
Andrea Caneschi, Andrea Dei, Dante Gatteschi,*
Lorenzo Sorace, and Kira Vostrikova

Rare earth ions have long been exploited to influence the properties of magnets by introducing anisotropic contributions and by changing the compensation temperature.^[1] In general little is known about the nature of the exchange interactions of rare earth ions among themselves and with other magnetic groups, because until recently few simple compounds containing magnetically coupled f-block ions were available. Recently, complexes of lanthanide ions with various paramagnetic ligands, ranging from metal complexes to organic radicals, were reported.^[2–6] In particular gadolinium(III) complexes exhibited ferromagnetic couplings ranging from 0.5 to 10 cm^{−1}. The rather unexpected sign of the coupling was explained by a mechanism in which the magnetic orbitals of the paramagnetic ligands have negligible overlap with the 4f orbitals, but overlap with the empty d and s orbitals of gadolinium polarizes the f electrons with their spins parallel to that of the paramagnetic ligand.^[7,8]

Some exceptions to ferromagnetic coupling were recently reported for copper(II) complexes and nitronyl nitroxide radicals.^[9,10] An antiferromagnetic coupling of 6 cm^{−1} was

observed in a chelating nitronyl nitroxide triazole derivative. This suggests that the observed coupling is actually the sum of two contributions, one from the direct overlap of the magnetic orbitals of the ligands with the f orbitals, which presumably results in antiferromagnetism, and the other from the overlap with the s and d orbitals, which leads to ferromagnetism. The former may become dominant when the radical ligands are stronger donors. Therefore we investigated the coupling of gadolinium(III) with semiquinonates, which are much better ligands than nitroxide-type radicals.

The complex [Gd(Hbpz₃)₂(dtbsq)] · 2CHCl₃ (**1**; Hbpz₃ = hydrotris(pyrazolyl)borate; dtbsq = 3,5-di-*tert*-butylsemiquinonato) was obtained by metathetical reaction between the parent metal benzoato derivative^[11] and 3,5-di-*tert*-butylcatechol in alkaline methanol. Recrystallization from chloroform/hexane yielded blue crystals of **1**.



Cyclic voltammetry experiments in acetonitrile showed that **1** undergoes a reversible one-electron redox process at −0.65 V and an irreversible process at +0.02 V versus ferrocene/ferrocenyl cation (Fc/Fc⁺). Both processes involve the coordinated dioxolene ligand, and the reversible one is assigned to the semiquinonato/catecholato couple, and the irreversible one to the quinone/semiquinonato couple. Given the electrochemical properties of other metal *o*-dioxolene complexes,^[12,13] this behavior is as expected when the different charge density of the metal acceptor is taken into account. The electronic spectrum shows a band at 12600 cm^{−1} and a pattern of bands in the region 26400–28400 cm^{−1}, which were suggested^[12] to be internal transitions of the semiquinonato ligand.

Figure 1 shows the X-ray crystal structure of **1**.^[14] The coordination sphere around gadolinium comprises six nitro-

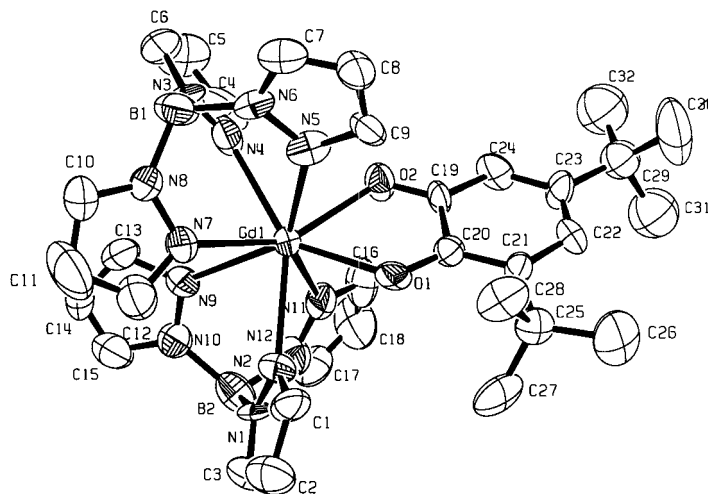


Figure 1. ORTEP view of complex **1** (50% probability thermal ellipsoids); hydrogen atoms and solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: Gd1–O1 2.343(9), Gd1–O2 2.354(12), Gd1–N4 2.48(2), Gd1–N2 2.503(14), Gd1–N11 2.53(2), Gd1–N7 2.53(2), Gd1–N5 2.571(11), Gd1–N9 2.585(14), C19–C20 1.49(2), O1–C20 1.27(2), O2–C19 1.25(2); O1–Gd1–O2 67.7(6), O2–Gd1–N4 81.5(5), O1–Gd1–N2 73.1(5), O1–Gd1–N11 88.8(5), O2–Gd1–N11 73.8(5), N2–Gd1–N11 72.9(6), N4–Gd1–N7 79.5(6), N2–Gd1–N7 78.5(5), O1–Gd1–N5 75.6(4), O2–Gd1–N5 78.7(6), N4–Gd1–N5 72.3(5), N7–Gd1–N5 71.3(6), N4–Gd1–N9 75.4(5), N2–Gd1–N9 74.4(5), N11–Gd1–N9 69.3(5), N7–Gd1–N9 72.1(5).

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[**] This work was supported by the 3MD EU Network (contract no. ERB 4061 PL 97-0197).

gen atoms of pyrazolylborate ligands and two oxygen atoms of the semiquinone. The eight-coordinate Gd atom lies in a distorted square-antiprismatic environment, in which O1, N5, N2, N7 lie approximately on one face, and N9, N4, N11, O2 on the other. The asymmetric unit is the whole molecule, and each molecule crystallizes with two molecule of chloroform. The C–O bond lengths are slightly shorter and the C19–C20 distance slightly longer than those usually observed in semiquinonato metal complexes.^[15]

The magnetic susceptibility of **1** was measured in the temperature range 2–245 K with a SQUID susceptometer in applied magnetic fields of 1000 and 10000 Oe (Figure 2). The χT value at high temperature (ca. 7.9 emu K mol^{−1} at 245 K) is

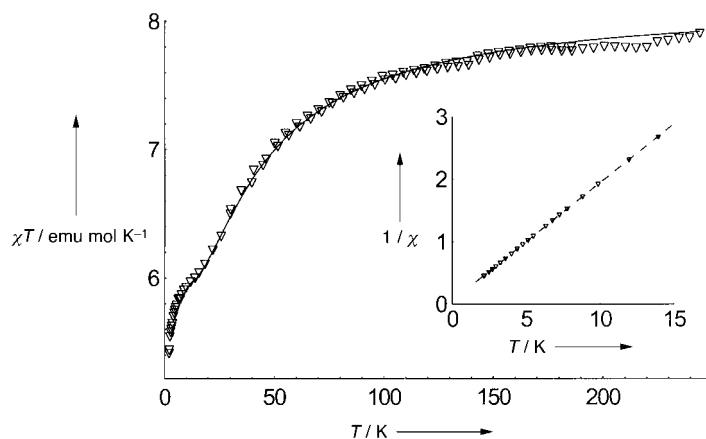


Figure 2. Temperature dependence of χT for **1**. The solid line represents the best-fit curve (see text for parameters). The inset shows the plot of $1/\chi$ versus T at low temperature; the dashed line is the best-fit curve under the assumption of Curie–Weiss behavior.

slightly lower than expected for Curie behavior of uncorrelated spins of 7/2 and 1/2 with $g = 2.00$ (8.25 emu K mol^{−1}); hence, the two centers are still weakly interacting at this temperature. On lowering the temperature, χT decreases, and this suggests antiferromagnetic interactions between the two spin carriers, which give rise to an $S = 3$ ground state and an $S = 4$ excited state. The decrease of χT to a value below that expected for an $S = 3$ state (5.98 emu K mol^{−1}) at $T < 10$ K can be attributed to zero-field splitting (ZFS) effects or to a weak antiferromagnetic interaction between neighboring molecules.

The χT versus T curve in the range 10–245 K was reproduced by assuming antiferromagnetic coupling between the two centers and by using the Hamiltonian $H = -JS_1 \cdot S_2 + g\mu_B \mathbf{H} \cdot \mathbf{S}$. The best fit to the experimental data was obtained with $J = -11.4$ cm^{−1}, $g_{SQ} = 2.00$, $g_{Gd} = 1.99$ (Figure 2).

The possibility that the decrease in χT at low temperature is a ZFS effect was ruled out by the field-dependent magnetization curves up to 7 T, measured at 2.15 K and 4.5 K (Figure 3). The experimental data are reproduced well by the Brillouin function for an $S = 3$ system without any ZFS effects. Preliminary X-band EPR spectra also show evidence for only a small ZFS ($D < 0.2$ cm^{−1}).

The decrease of χT to a value below that expected for an $S = 3$ ground state could then be explained by the existence of

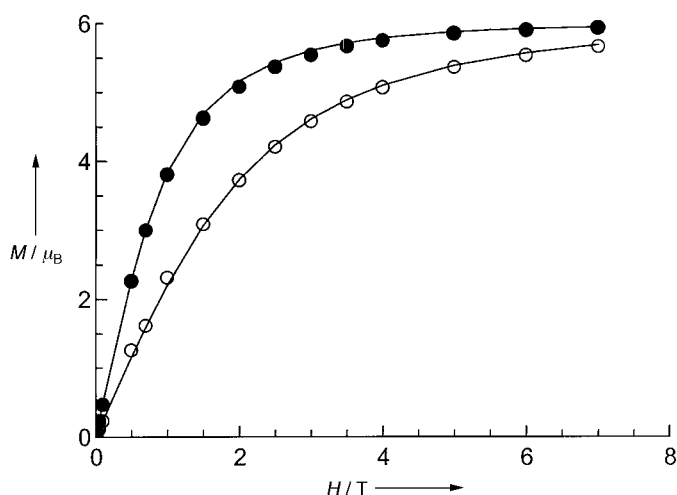


Figure 3. Field-dependent magnetization of **1** at 2.15 K (filled circle) and 4.5 K (empty circle). The lines represent the Brillouin function for an $S = 3$ state at the two temperatures.

small antiferromagnetic interactions between neighboring molecules. The plot of $1/\chi$ versus T in the low temperature range (inset of Figure 2) is in agreement with this hypothesis: it obeys a Curie–Weiss law with a small negative constant θ (−0.28 K) and a C value that compares quite well with what expected for an $S = 3$ state. The small value of θ is in agreement with the large distances between magnetic centers of neighboring molecules (Gd ⋯ Gd 9.64, Gd ⋯ O 7.53, O ⋯ O 7.33 Å).

The observed coupling confirms the prediction that stronger ligands may give rise to effective antiferromagnetic couplings with gadolinium. It is the strongest so far reported, in agreement with the fact that semiquinonato is the strongest paramagnetic ligand so far investigated with gadolinium(III). Comparing this value with those of other ions, such as iron(III), reveals the weakness of the metal–radical interaction for the rare earth element. Values of J for iron(III) semiquinonato complexes are at least about 600 cm^{−1},^[16] that is, more than an order of magnitude larger. However the present results show that moderate couplings can be obtained between rare earth atoms and semiquinonato ligands. We are now investigating the properties of mono-, bis-, and tris-semiquinonato complexes of rare earth elements.

Experimental Section

1: Solid KOH (0.112 g, 2 mmol) was added to a suspension of [Gd(Hbpz₃)₂(PhCOO)] (1.410 g, 2 mmol) and 3,4-di-*tert*-butylcatechol (0.444 g, 2 mmol) in anhydrous methanol (15 mL). The mixture was stirred in air for 20 min, the deep blue-green solution was filtered, and methanol was evaporated under reduced pressure. The precipitate was dissolved in CHCl₃/hexane (1/10; 30 mL), and the solution was filtered and stored for two weeks at about −5 °C. The precipitate was washed with cold hexane and well-shaped blue-green crystals of **1** were obtained. Elemental analysis calcd (%) for [Gd(Hbpz₃)₂(dtbsq)] · 2CHCl₃: C 39.18, H 4.06, N 16.12; found: C 39.40, H 4.15, N 15.98.

Received: July 20, 1999

Revised: September 21, 1999 [Z13752]

- [1] A. H. Morrish, *The Physical Principles of Magnetism*, Wiley, New York, 1965.
- [2] A. Bencini, C. Benelli, A. Caneschi, R. L. Carlin, A. Dei, D. Gatteschi, *J. Am. Chem. Soc.* **1985**, 107, 8128.
- [3] O. Guillou, O. Kahn, R. L. Oushoorn, K. Boubekeur, P. Batail, *Angew. Chem.* **1992**, 104, 658; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 626.
- [4] M. Sakamoto, M. Hashimura, K. Matsuki, N. Matsumoto, K. Inoue, H. Okawa, *Bull. Chem. Soc. Jpn.* **1991**, 64, 3639.
- [5] J. P. Costes, A. Dupuis, J. P. Laurent, *J. Chem. Soc. Dalton Trans.* **1998**, 735.
- [6] C. Benelli, A. Caneschi, D. Gatteschi, J. Laugier, P. Rey, *Angew. Chem.* **1987**, 99, 958; *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 913.
- [7] C. Benelli, A. Caneschi, O. Guillou, L. Pardi, D. Gatteschi, *Inorg. Chem.* **1990**, 29, 1750.
- [8] M. Andruh, I. Ramade, E. Codjovi, O. Guillou, O. Kahn, J. C. Trombe, *J. Am. Chem. Soc.* **1993**, 115, 1822.
- [9] C. Lescop, D. Luneau, E. Beloritzky, P. Fries, M. Guillot, P. Rey, *Inorg. Chem.*, submitted.
- [10] J.-P. Costes, F. Dahan, A. Dupuis, J.-P. Laurent, *Proc. VIth International Conference on Molecular Based Magnets*, Seignosse, **1998**.
- [11] M. J. Mass, C. J. Jones, *J. Chem. Soc. Dalton Trans.* **1990**, 581.
- [12] C. Benelli, A. Dei, D. Gatteschi, L. Pardi, *Inorg. Chem.* **1989**, 28, 1476.
- [13] C. Benelli, A. Dei, D. Gatteschi, H. Gudel, L. Pardi, *Inorg. Chem.* **1989**, 28, 3089.
- [14] Data collection and refinement: Data were collected on a Enraf Nonius CAD 4 four-circle diffractometer with graphite-monochromated Mo $\text{K}\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$), $\omega/2\theta$ scan, 293 K. Intensities were corrected for absorption (ψ scan). The symmetry and systematic absences of the reciprocal lattice were consistent with the orthorhombic space groups $Pca2_1$ (no. 29) and $Pbcm$ (no. 57). The structure could be successfully solved by direct methods (SIR92) only for $Pca2_1$; remaining atoms were identified by successive Fourier difference syntheses with SHELXL93. The structure was refined against F^2 by full-matrix least-squares methods for 4074 independent reflections, of which 2804 with $I > 4\sigma(I)$ were observed, with 12 restraints and 500 parameters. Anisotropic thermal factors were used for 53 of 57 non-hydrogen atoms; 38 hydrogen atoms were placed in calculated positions. Crystal data for **1**: Crystal dimensions $0.15 \times 0.35 \times 0.30 \text{ mm}$; $\text{C}_{34}\text{H}_{42}\text{B}_2\text{Cl}_6\text{GdN}_{12}\text{O}_2$, $M_r = 1042.37$; orthorhombic, space group $Pca2_1$ (no. 29), $a = 19.776(5)$, $b = 12.0690$, $c = 18.975(5) \text{ \AA}$, $\alpha = 90.050(5)$, $\beta = 89.990(5)$, $\gamma = 90.000(5)^\circ$, $V = 4529(3) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.529 \text{ g cm}^{-3}$, $\mu = 1.863 \text{ cm}^{-1}$, $2.66^\circ < \theta < 24.97^\circ$; $F(000) = 2088$, GOF on F^2 1.016; $R1 = 0.0635$ [$I > 4\sigma(I)$], $R1 = 0.1215$ (all data); absolute structure parameter 0.02(3); max./min. residual electron density $2.145/-1.365 \text{ e \AA}^{-3}$, located near gadolinium ion. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-129619. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [15] C. G. Pierpont, C. W. Lange, *Prog. Coord. Chem.* **1993**, 41, 381.
- [16] L. S. Kessel, R. M. Emberson, P. G. Debrunner, D. N. Hendrickson, *Inorg. Chem.* **1980**, 19, 1170.

Improved Electrochemistry in Low-Polarity Media Using Tetrakis(pentafluorophenyl)-borate Salts as Supporting Electrolytes**

Robert J. LeSuer and William E. Geiger*

The widespread nature of electron-transfer reactions provides an impetus to extend electrochemical experiments to new matrix conditions (solvents, temperatures, electrolytes).^[1] The choice of supporting electrolyte is crucial in that the "indifferent salt" affects not only mass transport and solution resistance, but possibly determines the chemical fate of the electrolysis products.^[2, 3] Mann and co-workers have shown, for example, that the oxidation of ruthenocene is a reversible one-electron process when the electrolyte anion is $[\text{B}(\text{C}_6\text{H}_3(\text{CF}_3)_2)_4]^-$, whereas an irreversible two-electron process is found when the more traditional anions $[\text{ClO}_4]^-$, $[\text{BF}_4]^-$, or $[\text{PF}_6]^-$ are used.^[3] We now bring attention to several electrochemical advancements that are possible when tetraalkylammonium salts of the weakly coordinating^[4] anion tetrakis(pentafluorophenyl)borate, $[\text{B}(\text{C}_6\text{F}_5)_4]^-$, are employed in solvents of low dielectric strength. Our results establish that these electrolytes are greatly advantageous for the investigation of electrode processes in such solvents. Voltammetry can now be more accurately performed at conventionally sized electrodes under demanding conditions (e.g., at low temperatures and/or high scan rates) in solvents of very low polarity. The improvements arise from the increased solubilities and dissociation tendencies of cations having a $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ counterion, phenomena that have received attention in the area of homogeneous catalysis.^[4, 5]

We show here that 1) the $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ anion is extremely effective in solubilizing positively charged species produced in anodic reactions and 2) voltammetric measurements are now possible in solvents having very low dielectric constants, including aliphatic ethers.

Addressing the first point, we note that, although dichloromethane is a preferred solvent for oxidation reactions, the precipitation of polycationic products at the electrode often complicates voltammetric scans in this solvent. As a result, studies are often performed in a more polar (but usually more reactive) solvent such as CH_3CN . Examples of this strategy may be found in the study of polyferrocenyl compounds, where precipitation of multiply charged species frequently passivates electrode surfaces in low-polarity solvents.^[6] Product precipitation is avoided with a $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ -containing electrolyte. Figure 1 compares cyclic voltammetry (CV) scans of the triferrocenyl compound **1** in CH_2Cl_2 containing 0.1M $[\text{NBu}_4][\text{PF}_6]$ with those of the same system

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[**] This work was supported by the National Science Foundation (CHE 97-05763) and the Boulder Scientific Co. (gift of $\text{Li}[\text{B}(\text{C}_6\text{F}_5)_4]$). Carolyn Mordas contributed experimental expertise as an NSF-REU-supported undergraduate. We thank Prof. Ian Manners for a sample of **1**.

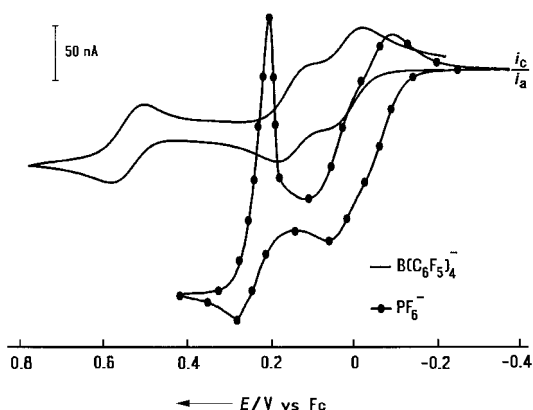
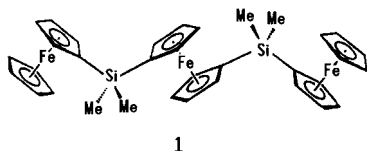


Figure 1. Comparison of cyclic voltammograms (scan rate 0.2 V s^{-1}) of 1.0 mm **1** in CH_2Cl_2 (Pt electrode, 0.5 mm diameter) at ambient temperature with different supporting electrolytes. $\bullet$ — $\bullet$ 0.1 M $[\text{NBu}_4][\text{PF}_6]$; — 0.1 M $[\text{NBu}_4][\text{B}(\text{C}_6\text{F}_5)_4]$. Fc = $\text{Cp}_2\text{Fe}^+/\text{Cp}_2\text{Fe}^0$.

with 0.1 M $[\text{NBu}_4][\text{B}(\text{C}_6\text{F}_5)_4]$. The diffusion-controlled shapes of all three waves for the experiment with $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ media attest to the fact that even the trication **1**³⁺ is soluble, in contrast to the clear evidence of the precipitation



and subsequent cathodic stripping wave on the return sweep (ca. 0.2 V) in $[\text{PF}_6]^-$ -containing media. We have experienced a number of such situations, which will be discussed in more detail in subsequent papers, and it appears that the simplification of anodic processes through solubilization of polycations in $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ -containing media is quite general. We strongly urge the adoption of this or a related anion for voltammetry and electrolyses that must be conducted in low-polarity solvents.

Because the thermodynamic potentials of all three ferrocenyl-centered oxidations of **1** are now directly accessible from the CV scans, the influence of possible ion-pairing interactions on the potentials of the three successive couples may be probed. Observed shifts of $\Delta E_{1/2} = 46 \text{ mV}$ and 116 mV for the $0/1^+$ and $1^+/2^+$ couples, respectively, when going from $[\text{PF}_6]^-$ to $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ media are consistent with increasingly reduced ion pairing of the Fe^{III} centers with the borate anion (compared to hexafluorophosphate) as the ferrocenyl groups are progressively oxidized.^[7]

An example of newly useful electrochemical solvents can be taken from the aliphatic ether family. Diethyl ether is an important reaction medium, but its low dielectric constant (4.3) has severely restricted its use in electrochemistry.^[8] However, $[\text{NBu}_4][\text{B}(\text{C}_6\text{F}_5)_4]$ gives modestly conducting solutions^[9] in this solvent, even at subambient temperatures. Figure 2 shows a CV scan (scan rate 0.005 V s^{-1} , $T = 210 \text{ K}$) of decamethylferrocene at a Pt disk 125 μm in diameter. Under these slow scan conditions a quasi-steady-state voltammogram is obtained with $E_{1/2} = -0.60 \text{ V}$ versus $\text{Cp}_2\text{Fe}^+/\text{Cp}_2\text{Fe}^0$. Although there is ohmic distortion^[10] in this wave, thermody-

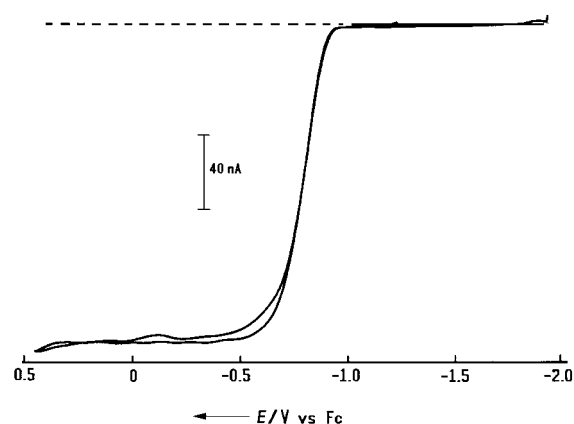


Figure 2. "Steady-state" CV scan (scan rate 0.005 V s^{-1}) of the oxidation of 1.1 mm decamethylferrocene in Et_2O saturated with $[\text{NBu}_4][\text{B}(\text{C}_6\text{F}_5)_4]$ (<25 mm) at 210 K (Pt disk, 0.125 mm diameter). The dashed line gives the zero current value. Fc = $\text{Cp}_2\text{Fe}^+/\text{Cp}_2\text{Fe}^0$.

namic information about the decamethylferrocene/decamethylferrocenium couple is clearly accessible in Et_2O .

Greatly improved performance is achieved in *tert*-butyl methyl ether, in which $[\text{NBu}_4][[\text{B}(\text{C}_6\text{F}_5)_4]$ displays an increased solubility, which leads to a lower solution resistance.^[9] For example, a CV scan of 9,10-anthraquinone in this solvent (Figure 3) exhibits respectable ΔE_p values (ca. 130 mV, scan rate 0.2 V s^{-1} , 2-mm Pt electrode) and clearly demonstrates the generation of both the semiquinone species and the anthraquinone dianion with approximate $E_{1/2}$ values of -1.51 and -1.99 V , respectively, versus $\text{Cp}_2\text{Fe}^+/\text{Cp}_2\text{Fe}^0$.^[11]

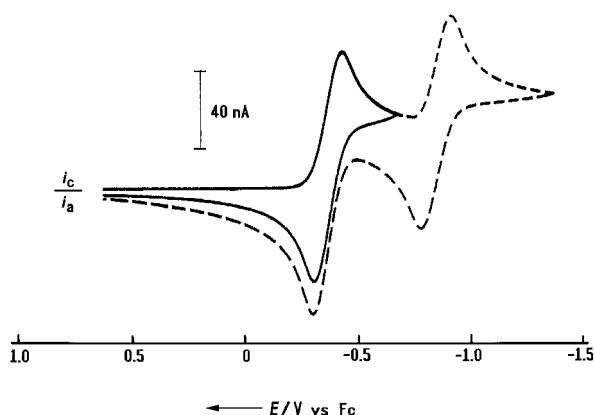


Figure 3. CV scans (scan rate 0.2 V s^{-1}) of 1 mm anthraquinone in *tert*-butyl methyl ether/0.075 M $[\text{NBu}_4][\text{B}(\text{C}_6\text{F}_5)_4]$ at ambient temperature (Pt electrode, 2 mm). The dashed line is obtained when the scan is extended to more negative potentials. Fc = $\text{Cp}_2\text{Fe}^+/\text{Cp}_2\text{Fe}^0$.

The decreased resistivities of low-polarity solvents containing $[\text{NR}_4][\text{B}(\text{C}_6\text{F}_5)_4]$ salts and the concomitant lowering of iR_u (ohmic) losses^[12] also allow voltammograms of greater accuracy to be recorded at conventional electrodes, compared to analogous solutions with the traditional anions. The resistivity of 0.10 M $[\text{NBu}_4][\text{B}(\text{C}_6\text{F}_5)_4]$ in THF at 295 K is $490 \Omega \text{ cm}$, compared to $2300 \Omega \text{ cm}$ for the same concentration of $[\text{NBu}_4][\text{ClO}_4]$.^[9] At a 2-mm Pt disk electrode, the $\text{Cp}_2\text{Co}^+/\text{Cp}_2\text{Co}^0$ couple showed a peak separation of 158 mV in $[\text{ClO}_4]^-$ -containing media (scan rate 0.2 V s^{-1} , 1 mm Cp_2Co^+) compared to a separation of 78 mV in $[\text{B}(\text{C}_6\text{F}_5)_4]^-$ -containing

media under identical conditions (0.1M supporting electrolyte). The latter more closely approaches the value of 61 mV^[13] expected for this system.^[14] The new family of electrolytes raises expectations that faster heterogeneous electron transfer rates may be measured in low-polarity media,^[15] in addition to aiding mechanistic studies through increased accuracy of diagnostic parameters such as peak potentials and voltammetric wave shapes.^[16]

There is no reason to think that [NBu₄][B(C₆F₅)₄] is the optimum supporting electrolyte for all electrochemistry in low-polarity media, and analogues specifically designed to meet the needs of other redox systems are easily envisioned. When combined with ultramicroelectrode technology,^[17] which already minimizes problems of ohmic loss, and advances in the use of very small concentrations of supporting electrolytes,^[18] this family of salts holds significant promise in aiding further advances in applications of electrochemistry.^[19]

Experimental Section

Experiments were carried out under a nitrogen atmosphere using Schlenk or dry-box conditions, and solvents were dried and distilled, except for *tert*-butyl methyl ether, which was used as received (Aldrich, anhydrous). [NBu₄][B(C₆F₅)₄] was prepared by metathesis of an aqueous solution of Li[B(C₆F₅)₄]·*n*Et₂O (*n* = 2–3) (Boulder Scientific Co.) with a solution of [NBu₄]Br in methanol. The precipitate was washed with water, dried under vacuum, and recrystallized several times from CH₂Cl₂/Et₂O (purified yield ca. 70%). Conductance values were obtained with a YSI Model 3200 conductance meter and a conductivity cell with a cell constant of 0.1 cm⁻¹. Voltammetry was performed using a Princeton Applied Research Model 273 potentiostat without ohmic compensation. A standard three-electrode cell configuration was employed using working electrodes composed of polished disks (Pt or glassy C), a Pt wire auxiliary electrode, and a Ag/AgCl reference electrode.

Received: August 30, 1999 [Z13940]

- [1] a) C. D. Baer, C. A. Camaioni-Neto, D. A. Sweigart, A. M. Bond, T. F. Mann, G. A. Tondreau, *Coord. Chem. Rev.* **1989**, 93, 1; b) A. Abbott, *Chem. Soc. Rev.* **1993**, 435; c) A. Fry in *Laboratory Techniques in Electroanalytical Chemistry* (Eds.: P. T. Kissinger, W. R. Heineman), 2nd ed., Marcel Dekker, New York, **1996**, p. 469; d) D. H. Evans, S. A. Lerke in *Laboratory Techniques in Electroanalytical Chemistry* (Eds.: P. T. Kissinger, W. R. Heineman), 2nd ed., Marcel Dekker, New York, **1996**, p. 487; e) R. Cosmo, C. Kautz, K. Meerholz, J. Heinze, K. Müllen, *Angew. Chem.* **1988**, 101, 638; *Angew. Chem. Int. Ed.* **1988**, 28, 604; f) S. Ching, J. T. McDevitt, S. R. Peck, R. W. Murray, *J. Electrochem. Soc.* **1991**, 138, 2308; g) C. R. Carbrera, A. J. Bard, *J. Electroanal. Chem.* **1989**, 273, 147; h) M. Tsionsky, A. J. Bard, M. V. Mirkin, *J. Am. Chem. Soc.* **1997**, 119, 10785.
- [2] N. J. Stone, D. A. Sweigart, A. M. Bond, *Organometallics* **1986**, 5, 2553.
- [3] M. G. Hill, W. M. Lamanna, K. R. Mann, *Inorg. Chem.* **1991**, 30, 4687.
- [4] A. R. Siedle, B. Hanggi, R. A. Newmark, K. R. Mann, T. Wilson, *Macromol. Symp.* **1995**, 89, 299.
- [5] W. E. Piers, T. Chivers, *Chem. Soc. Rev.* **1997**, 345.
- [6] Mixtures of CH₂Cl₂ and CH₃CN have been frequently employed to increase the solubility of both the neutral complexes and their cationic products: a) R. Rulkens, A. J. Lough, I. Manners, S. R. Lovelace, C. Grant, W. E. Geiger, *J. Am. Chem. Soc.* **1996**, 118, 12683; b) B. Grossmann, J. Heinze, E. Herdtweck, F. H. Koehler, H. Noeth, H. Schwenk, M. Spiegler, W. Wachter, B. Weber, *Angew. Chem.* **1997**, 109, 384; *Angew. Chem. Int. Ed.* **1997**, 36, 387.
- [7] A quantitative study of ion-pairing interactions in metallocene (poly)cations is being conducted. The cobaltocenium/cobaltocene couple was used as an internal standard; see a) R. S. Stojanovic, A. M. Bond, *Anal. Chem.* **1993**, 65, 56; b) G. Gritzner, J. Kuta, *Pure Appl. Chem.* **1984**, 56, 461. The difference between *E*_{1/2} for Cp₂Co⁺/Cp₂Co⁰ and Cp₂Fe⁺/Cp₂Fe⁰ was measured as 1.33 V in separate experiments in both electrolytes, enabling the scaling of Figure 1.

- [8] C. K. Mann, *Electroanalytical Chemistry*, Vol. 3 (Ed.: A. J. Bard), Marcel Dekker, New York, **1969**, p. 101. Electrochemistry in ethers is normally performed using lithium-based supporting electrolytes; for leading references, see Z. Wang, B. Huang, R. Xue, L. Chen, X. Huang, *J. Electrochem. Soc.* **1998**, 145, 3346.
- [9] Some other resistivity values: a) *tert*-butyl methyl ether, ambient temperature, 0.075 M [NBu₄][B(C₆F₅)₄], 2.5 KΩ cm; b) diethyl ether, saturated [NBu₄][B(C₆F₅)₄] (<0.025 M), 235 K, 22 KΩ cm; c) THF, 0.1 M [NBu₄][PF₆], ambient temperature, 2.3 KΩ cm.
- [10] The value of *E*_{3/4} – *E*_{1/4} was 112 mV at room temperature and 133 mV at 210 K.
- [11] The electrochemistry of quinones has been reviewed: J. Q. Chambers, *The Chemistry of Quinonoid Compounds*, Part 2 (Ed.: S. Patai), Wiley, London, **1974**. Representative *E*_{1/2} values in nonaqueous solvents: in DMF/0.1 M [NEt₄][ClO₄], –1.33 V vs. Cp₂Fe⁺/Cp₂Fe⁰ for *E*_{1/2}, –2.03 V for *E*_{1/2}; L. Jętko, G. Manning, *J. Electroanal. Chem.* **1970**, 26, 195; see also M. E. Peover, *J. Chem. Soc.* **1962**, 4540.
- [12] D. K. Roe in *Laboratory Techniques in Electroanalytical Chemistry* (Eds.: P. T. Kissinger, W. R. Heineman), 2nd ed., Marcel Dekker, New York, **1996**, p. 195.
- [13] The value of *E*_{pa} – *E*_{pc} for a Nernstian couple displays a minor dependence on the CV switching potential and is predicted to be 61 mV for a system undergoing fast heterogeneous electron transfer kinetics under our recording conditions; see R. S. Nicholson, *Anal. Chem.* **1966**, 38, 1406.
- [14] T. Gennett, D. F. Milner, M. J. Weaver, *J. Phys. Chem.* **1985**, 89, 2787, and references therein.
- [15] D. F. Milner, M. J. Weaver, *Anal. Chim. Acta* **1987**, 198, 245.
- [16] W. E. Geiger in *Laboratory Techniques in Electroanalytical Chemistry* (Eds.: P. T. Kissinger, W. R. Heineman), 2nd ed., Marcel Dekker, New York, **1996**, p. 683.
- [17] A. C. Michael, R. M. Wightman in *Laboratory Techniques in Electroanalytical Chemistry* (Eds.: P. T. Kissinger, W. R. Heineman), 2nd ed., Marcel Dekker, New York, **1996**, p. 367.
- [18] a) S. M. Drew, R. M. Wightman, C. A. Amatore, *J. Electroanal. Chem.* **1991**, 317, 117; b) K. B. Oldham, T. J. Cardwell, J. H. Santos, A. M. Bond, *J. Electroanal. Chem.* **1997**, 430, 39; c) D. Pletcher, H. Thompson, *J. Chem. Soc. Faraday Trans.* **1998**, 94, 3445.
- [19] Note added in proof (December 13, 1999): Voltammograms of titanium complexes have recently been reported in difluorobenzene using 2 mM tetrabutylammonium tetrakis(pentafluorophenyl)borate as the supporting electrolyte: S. Feng, J. Klosin, W. J. Kruper, Jr., M. H. McAdon, D. R. Neithamer, P. N. Kickias, J. T. Patton, D. R. Wilson, *Organometallics* **1999**, 18, 1159.

Combinatorial Synthesis of Four-Helix Bundle Hemoproteins for Tuning of Cofactor Properties**

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The aim of protein design is to create novel proteins with tailored structural and functional properties. Besides a rational approach by site-directed mutations of known proteins, a general strategy is to generate a large pool of different molecules and to screen this library for single substances with the desired properties. This goal is realized by phage display

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[**] This project was supported by the Volkswagen-Stiftung and the BMBF. We thank Patric Hörth for determining the mass spectra.

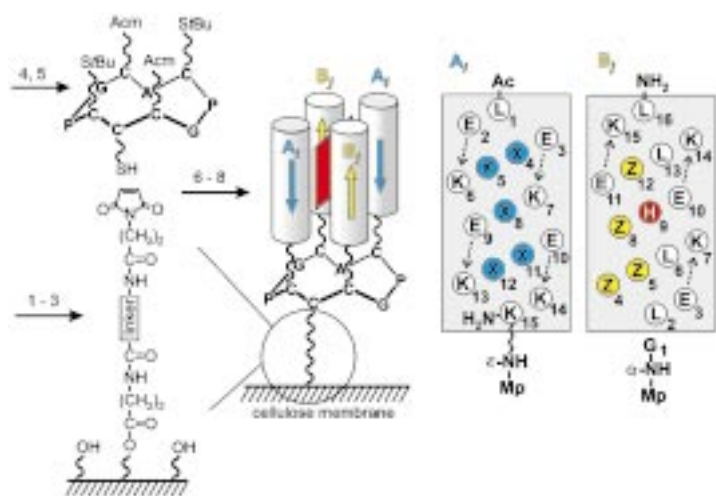
of proteins produced by DNA-based variations and then selection, for example, by their affinity to immobilized ligands^[1] as well as by chemical solid-phase synthesis of libraries with short linear or cyclic peptides.^[2]

Extensive research efforts are being directed towards a de novo design of proteins that provide a wide variability in biomimetic chemistry.^[3] In particular the interaction of synthetic proteins with the cofactor Fe^{III}–protoporphyrin IX (heme) has been studied.^[4] The difficulty in screening physical parameters has limited the studies of variants to rather small numbers.^[5] The assembly of synthetic proteins from antiparallel α -helices on a cyclic peptide is an efficient strategy for the synthesis of predetermined structures.^[6] This method was successfully applied to tailor a synthetic cytochrome b analogue, which was also active in bioelectronic applications when bound to a gold surface^[7] and to metalloproteins capable of light-induced electron transfer.^[8] These studies have focused on the need for an optimized protein environment to control the physical properties of a cofactor. Herein we report the synthesis of a library of hemoproteins from small libraries of peptide building blocks attached to a template that is bound to a cellulose membrane. The strategy is based on a combination of spot synthesis,^[9] the concept of template-assembled synthetic proteins (TASP),^[6] and solid-phase characterization of physical parameters.

A schematic presentation of the protein design^[7,8] and the synthesis is shown in Scheme 1. The cellulose membrane was

variation of residues X_k ($k=4, 5, 8, 11, 12$) and Z_l ($l=4, 5, 8, 12$) in the amphiphilic helices A_i and B_j , respectively; these residues were found by molecular modeling to form the hydrophobic binding pocket of the heme. Since a variation of all the natural amino acids at these nine positions would need 5×10^{11} proteins we have limited the variation to hydrophobic amino acids of different size and a few polar ones, including Gly, Ala, Val, Leu, Ile, Phe, Tyr, and Gln. The 22 different combinations of these amino acids for the shielding helices A_i and the 21 for the binding helices B_j resulted in 462 modular proteins. Finally Fe^{III}–protoporphyrin IX was incorporated into the proteins by incubating the membranes with a solution of the cofactor.

The peptides could be collected at any stage of the synthesis by acid cleavage of the linker from cutout spots. Figure 1 shows the analytical reversed-phase HPLC and mass spectrometry of the final products formed from five different sets



Scheme 1. Stepwise assembly of the cellulose-bound library of synthetic Fe^{III}–protoporphyrin IX modular proteins. The positions of the varied amino acids labeled X_k and Z_l of helices A_i and B_j , respectively, and the heme-ligating histidine are colored. The numbers above the arrows refer to the synthetic steps described in the Experimental Section.

modified with β -alanine, to which a linker and 3-maleimidopropionic acid were coupled. The maleimidopropionyl (Mp) group reacts selectively with the unprotected cysteine residues of the cyclic template. The successive removal of the S*t*Bu and acetamidomethyl (Acm) protecting groups of the cysteine residues and the coupling of the maleimidopropionyl moiety of the helical peptides A_i and B_j ensured the antiparallel orientation of the helix pairs. Small libraries have been synthesized using a parallel peptide synthesizer by

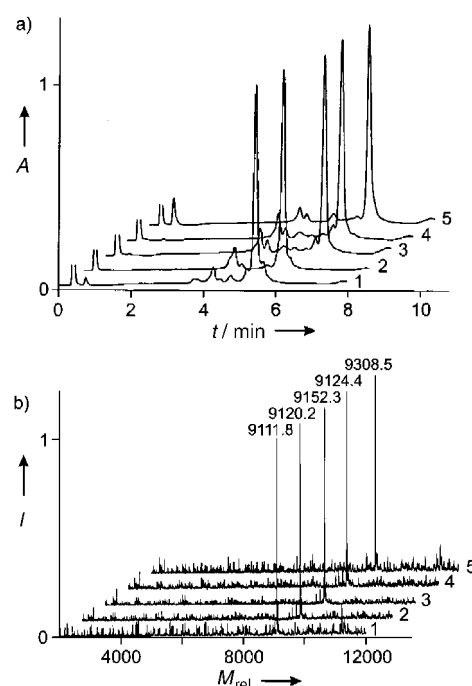


Figure 1. a) Analytical reversed-phase HPLC monitored at 215 nm of four-helix bundle proteins after cleavage of the linker from cutout spots and precipitation with diethyl ether. b) Deconvoluted electrospray mass spectra of the samples used for (a). The traces 1–5 have been recorded with the proteins assembled from helices A_8B_{12} , $A_{13}B_{11}$, $A_{18}B_9$, A_9B_{11} , and A_3B_{12} , respectively. For the varied amino acids see Figure 3. The masses reveal the correct primary structure of the template assembled four-helix bundle proteins.

of helices. Electrospray mass spectrometry was also used to characterize all the helices, the template, several cellulose-assembled test peptides, and the intermediate products. Importantly, no impurities of template-assembled helix bundles with less than four helices were detected (Figure 1 b) and hence the four-helix bundles were pure enough for direct screening. For comparison of the cellulose-bound hemoproteins with their soluble variants two four-helix bundle proteins with helices $A_{10}B_9$ and $A_{10}B_{11}$ (see Figure 3) were assembled on a previously described template^[7b] in milligram quantities and characterized in solution.

Figure 2 shows a picture of a sheet with 42 cellulose-bound proteins with a heme group in the oxidized and the reduced state. The spectra were recorded from the spots of the hemoprotein A₁₀B₉. The protein complexes show typical

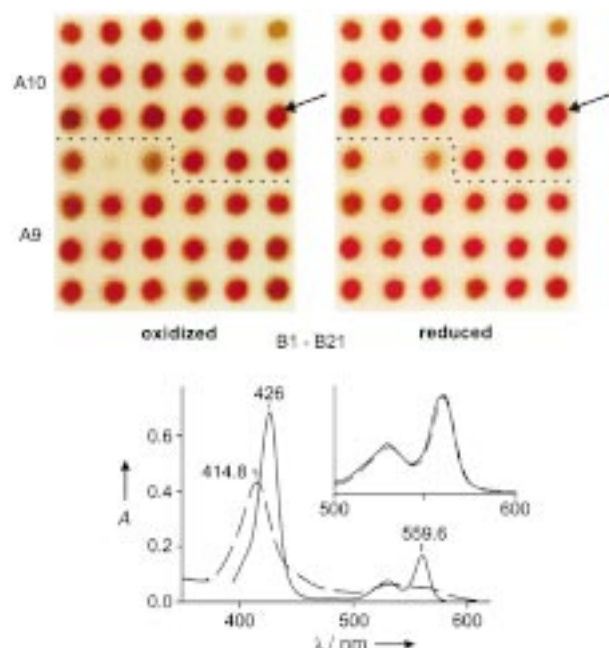


Figure 2. Top: Cellulose membrane with 42 different covalently bound proteins with ligated heme in the oxidized (left) and reduced (right) state. The dashed line indicates the frontier between the proteins with shielding helix A₉ (bottom) and A₁₀ (top). A total of 21 different binding helices B_i were combined with the shielding helices. The arrows indicate the protein used to record the spectra shown below. Bottom: UV/Vis spectra monitored from the cellulose-bound Fe^{III}-protoporphyrin IX protein assembled from helices A₁₀ and B₉ (oxidized state, dashed line) and after addition of dithionite in the reduced state (solid line). Inset: expanded region of the spectrum in the reduced state superimposed with that of a reference protein with the same helices (---).

spectra for bis-histidine-ligated b-type cytochromes with a Soret band at about 414 nm in the oxidized state and at about 427 nm in the reduced state. The complexes display distinct α - and β -bands at about 560 and 530 nm, respectively, in the reduced state. To check the applicability of this solid-phase characterization the spectra of the soluble proteins were compared with those of the corresponding cellulose-bound peptides and found to be superimposable (see inset in Figure 2).

Two of the shielding and two of the binding helices (B₂₀ and B₂₁) were designed to be either nonamphiphilic or non- α -helical. Proteins containing these helices did not bind heme (see the spots in Figure 2) or showed an undefined spectrum of the heme. For the remaining 399 proteins the width at half the maximum intensity of the α -band in the reduced state varied between 14.4 and 20.3 nm with a maximal deviation of 6% in repeated recordings. These complexes were screened for the midpoint potential of the heme group. The midpoint potential was estimated by determining the fraction of total complexes reduced at an ambient potential of –95 mV versus the standard hydrogen electrode (SHE). Figure 3 shows the spectra of two proteins at this potential fitted to the isosbestic

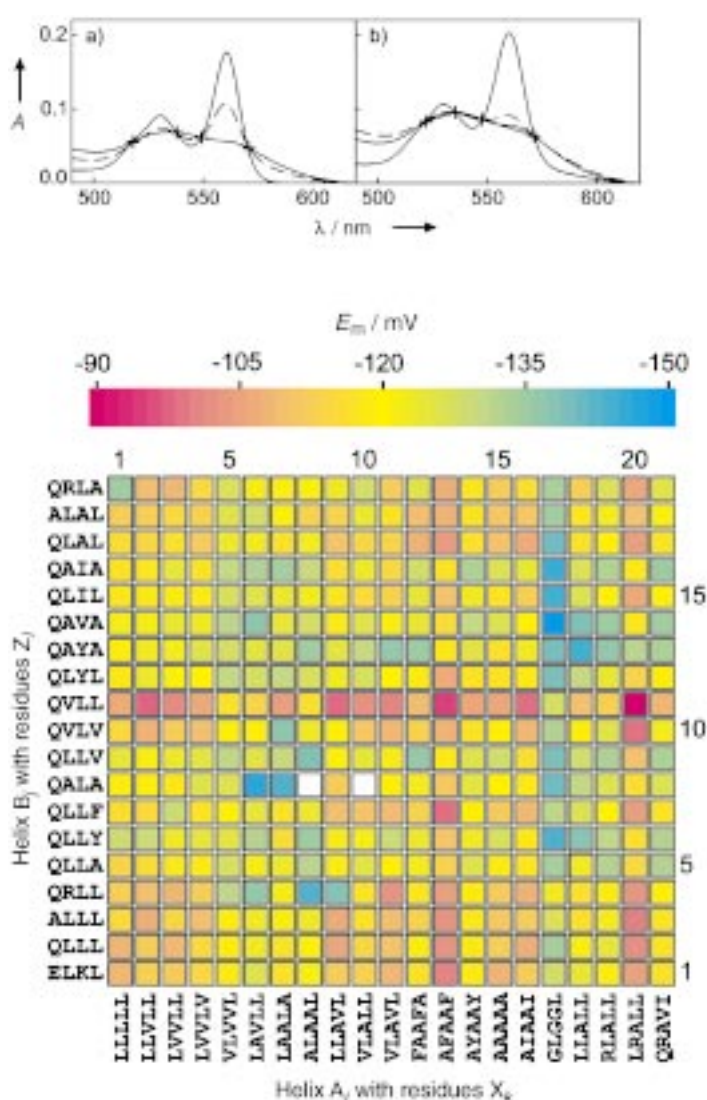


Figure 3. Redox midpoint potentials of cellulose-bound four-helix bundle proteins with inserted Fe^{III}-protoporphyrin IX. Top: Spectra of the proteins with helices A₁₃B₁₇ (left) and helices A₁₇B₁₄ (right) in the oxidized and reduced state (solid lines). The isosbestic points marked by crosses were taken from these spectra and used to normalize the spectrum monitored at –95 mV in the presence of the redox buffer 2,5-dihydroxy-*p*-benzoquinone (4 mM) under argon (---). The respective midpoint potentials of –103 and –148 mV were estimated using the Nernst equation and the reduced fraction at –95 mV by comparing the absorbance of the three spectra at the maximum of the α -band. Bottom: The estimated midpoint potentials of the proteins assembled from helices A_i and B_j are color-coded according to the scale at the top. The amino acids at the positions X_k ($k = 4, 5, 8, 11, 12$) and Z_l ($l = 4, 5, 8, 12$) are given along the axis.

points of the spectra of the oxidized and the reduced protein. The estimated midpoint potentials varied in the range of –90 to –150 mV as summarized in the color-coded diagram in Figure 3. The combinatorial approach was successful in finding proteins that tune the heme to a midpoint potential that is 80 mV more positive than the redox potential of our previously designed heme proteins of about –170 mV^[8] and even more positive than those of other synthetic heme proteins^[4a] that have redox potentials close to the value of –210 mV for histidine/imidazole-coordinated heme in water.^[10] The redox potentials of the two reference proteins

synthesized in solution were both 10 mV more negative than their immobilized counterparts. The heme group could be removed by washing the membrane with DMF. When the heme group was incorporated a second time, a maximal difference of 5% between the two independent redox measurements of 57 modular hemoproteins with shielding helices A₅, A₆, and A₁₉ was found. This does not only show the excellent reproducibility of the repeated use of the cellulose-bound protein library, but also the possibility of successive screening with different cofactors such as other metalloporphyrins or chlorophyll derivatives.

A relationship between the midpoint redox potentials and the varied amino acids is not readily apparent. For example, the change of 20 mV in the midpoint potential by a switch of Val and Leu at the positions Z₅ and Z₁₂ in helices B₉ and B₁₁ is not easy to interpret, but in general the effects of the binding and the shielding helix seem to be additive. Figure 3 indicates the trend that a combination of helices that form complexes with more positive midpoint potentials display the highest values, as for example the combinations of helix B₁₁ with A₁₃ or A₂₀. This observation is consistent with a tight packing of all four helices being needed to exclude water from the heme-binding pocket and favor a high redox potential.^[10] Further analysis of the data using neural networks^[11] is currently in progress and may help to design new variants with even higher midpoint potentials.

A method for the efficient synthesis of large numbers of four-helix bundle proteins from peptide libraries has been described. The parallel solid-phase synthesis has led to spatially separated spots of homogenous protein–heme complexes that could be directly screened for physical properties. Automation with pipetting and screening robots and the extension to a large number of proteins is possible. The reversible binding of cofactors allows the successive screening of the protein library. The range of the detected redox potentials demonstrates the applicability of the described method to tune physical parameters of immobilized de novo proteins. The method is not limited to two different helices and can also be of general use for the synthesis of large numbers of receptorlike molecules, new metalloproteins, or the search for new catalysts.

Experimental Section

The helical peptides were synthesized using a multiple batch solid-phase peptide synthesizer (Advanced ChemTech) with standard 9H-fluorenylmethoxycarbonyl (Fmoc)/benzotriazol-1-yl-*N*-tetramethyluronium tetrafluoroborate (TBTU) protection/activation. 3-Maleimidopropionic acid was coupled to the *N*-terminus of helices B₉ or the ϵ -amino group of the C-terminal lysine of helices A₅.^[8a] All deprotected peptides were purified by preparative reversed-phase HPLC. Cellulose membranes were derivatized with β -alanine (1; Scheme 1).^[9] The 1-hydroxy-1H-benzotriazole (HOBt) ester of the modified Rink linker, *p*-[(*R,S*)- α -[1-(9H-fluorenyl)-methoxyformamido]-2,4-dimethoxybenzyl]-phenoxyacetic acid, was coupled by adding 2 μ L ($\times 2$) of a 0.3 M solution, which resulted in spots of 8 mm diameter (2). Any residual free amino groups were acetylated^[9] and 3-maleimidopropionic acid was coupled to the linker as a symmetrical anhydride (3). Synthesis of the cyclic decapeptide template (4) was as described^[7b] except for an additional trityl-protected cysteine (trityl = triphenylmethyl). The trityl-deprotected (5) template was coupled to each of the spots in 0.3 M sodium-phosphate (pH 7.1)/acetonitrile (2/1, (6)). The deprotection of the *S*tBu groups with dithiothreitol and of the Ac groups

with mercuric acetate under Ar and coupling of the helices (7) were adapted from described procedures.^[8] The synthesis was monitored by cutting out spots of the membrane and cleaving the modified Rink linker by incubation with TFA/CH₂Cl₂/water/triisopropyl silane (50/45/4/1) for 60 min. Fe^{III}–protoporphyrin IX (heme) was incorporated into the cellulose-bound proteins by incubation with 50 μ M heme in 100 mM Tris-HCl (pH 7.5)/DMF (4/1) followed by washing with the solvent ($\times 3$, (8)). The spectra were recorded with a diode-array spectrophotometer (J&M, Germany) by placing light guides on opposite sides of the protein spots with the membrane submerged in buffer in a microtiter plate without wells. The spectra were analyzed automatically by software of local design.

Received: September 24, 1999 [Z14063]

- [1] a) D. R. Liu, P. G. Schultz, *Angew. Chem.* **1999**, *111*, 36–56; *Angew. Chem. Int. Ed.* **1999**, *38*, 36–54; b) G. P. Smith, J. K. Scott, *Methods Enzymol.* **1993**, *217*, 228–257; c) J. Hanes, A. Plückthun, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 4937–4942.
- [2] Reviews from several authors can be found in *Combinatorial Peptide and Nonpeptide Libraries* (Ed.: G. Jung), VCH, Weinheim, **1996**, p. 544.
- [3] a) M. Mutter, S. Vuilleumier, *Angew. Chem.* **1989**, *101*, 551–571; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 535–554; b) J. W. Bryson, S. F. Betz, H. S. Lu, D. J. Suich, H. X. Zhou, K. T. O’Neil, W. F. DeGrado, *Science* **1995**, *270*, 935–941; c) G. Tuchscherer, L. Scheibler, P. Dumy, M. Mutter, *Biopolymers* **1998**, *47*, 63–73.
- [4] a) C. T. Choma, J. D. Lear, M. J. Nelson, P. L. Dutton, D. E. Robertson, W. F. DeGrado, *J. Am. Chem. Soc.* **1994**, *116*, 856–865; b) D. E. Robertson, R. S. Farid, C. C. Moser, J. L. Urbauer, S. E. Mulholland, R. Pidikiti, J. D. Lear, A. J. Wand, W. F. DeGrado, P. L. Dutton, *Nature* **1994**, *368*, 425–432; c) F. Nastro, A. Lombardi, G. Morelli, O. Maglio, G. D’Auria, C. Pedone, V. Pavone, *Chem. Eur. J.* **1997**, *3*, 340–349; d) S. Sakamoto, I. Obataya, A. Ueno, H. Mihara, *J. Chem. Soc. Perkin Trans. 2* **1999**, 2059–2069.
- [5] a) N. R. L. Rojas, S. Kamtekar, C. R. Simons, J. E. McLean, K. M. Vogel, T. G. Spiro, R. S. Farid, M. H. Hecht, *Protein Sci.* **1997**, *6*, 2512–2524; b) B. R. Gibney, F. Rabanal, J. J. Skalicky, A. J. Wand, P. L. Dutton, *J. Am. Chem. Soc.* **1999**, *121*, 4952–4960.
- [6] M. Mutter, E. Altmann, K.-H. Altmann, R. Hersperger, P. Koziej, K. Nebel, G. Tuchscherer, S. Vuilleumier, H. U. Gremlich, K. Müller, *Helv. Chim. Acta* **1988**, *71*, 835–847.
- [7] a) H. K. Rau, W. Haehnel, *Ber. Bunsen-Ges. Phys. Chem.* **1996**, *100*, 2052–2056; b) H. K. Rau, W. Haehnel, *J. Am. Chem. Soc.* **1998**, *120*, 468–476; c) E. Katz, V. Heleg-Shabtai, I. Willner, H. K. Rau, W. Haehnel, *Angew. Chem.* **1998**, *110*, 3443–3447; *Angew. Chem. Int. Ed.* **1998**, *37*, 3253–3256; d) M. Fahnenschmidt, H. K. Rau, R. Bittl, W. Haehnel, W. Lubitz, *Chem. Eur. J.* **1999**, *5*, 2327–2334.
- [8] a) H. K. Rau, N. DeJonge, W. Haehnel, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 11 526–11 531; b) N. DeJonge, H. K. Rau, W. Haehnel, *Z. Phys. Chem.* **1999**, *213*, 175–180.
- [9] R. Frank, *Tetrahedron* **1992**, *48*, 9217–9232.
- [10] G. R. Moore, G. W. Pettigrew, *Cytochromes c: Evolutionary, Structural and Physicochemical Aspects*, Springer, Berlin, **1990**, pp. 309–362.
- [11] a) G. Schneider, P. Wrede, *J. Mol. Evol.* **1993**, *36*, 586–595; b) G. Schneider, W. Schrödl, G. Wallukat, E. Nissen, J. Müller, W. Röspeck, P. Wrede, R. Kunze, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 12 179–12 184.

Complete Carbonylation of $fac-[Tc(H_2O)_3(CO)_3]^+$ under CO Pressure in Aqueous Media: A Single Sample Story!*

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Diagnostic nuclear medicine is one of the prominent fields where radio nuclides of transition metals (e.g. ^{99m}Tc) have played an important role in functional organ imaging for two decades.^[1,2] However, until recently most of the ligand systems produced classical Werner-type compounds, which are thermodynamically very stable but suffer frequently from hydrolysis under physiological conditions. The “second generation” of radiopharmaceuticals, which combine receptor-specific, bioactive molecules with a radioactive isotope, require metal complexes that provide the highest possible stability, and avoid interference of the metal center with the binding site of the biomolecule. Thus, organometallic carbonyl compounds attract considerable attention due to their unique features in terms of kinetic inertness, small size, and in vivo stability.^[3] It has recently been shown that the novel Tc^I organometallic precursor $fac-[^{99m}Tc(H_2O)_3(CO)_3]^+$ (**1**) represents a powerful alternative to Tc^V compounds for the successful labeling of even the smallest molecules under retention of their bioaffinity and selectivity.^[4] The precursor produces very kinetically inert complexes with a variety of mono-, bis-, and tridentate ligand systems.^[5] However, very little is known about the water exchange reaction of the $fac-[Tc(H_2O)_3(CO)_3]^+$ complex, the reactivity of the coordinated CO ligands, or the influence of the functionalities of an entering ligand system on the rate of the substitution reactions. To develop appropriate ligand systems and optimize the labeling conditions of functionalized biomolecules, we believe that it is of critical importance to understand the fundamental behavior of the corresponding metal precursor in aqueous media.

This study of the water and CO exchange rate was performed by using multinuclear NMR (^{13}C , ^{17}O , ^{99}Tc) techniques under normal and moderately pressurized conditions. All the experiments described in this paper were carried out over a period of several weeks using only one single sample of $fac-[Tc(H_2O)_3(CO)_3]^+$. During this period no decomposition of this species was observed (as verified by NMR spectroscopy) although the sample was kept in a highly acidic medium (2M $HClO_4$) and heated to 100 °C.

First, complex **1** was dissolved at 277 K in ^{17}O enriched water (oxygen isotopic composition: ^{16}O 57.9 %, ^{17}O 5 %, ^{18}O 37.1 %). The first ^{17}O NMR spectrum was recorded three minutes after the preparation of the sample and exhibited a single broad peak at $\delta = -52$, which was attributed to the coordinated water molecules in **1**. The signal of the bulk water was suppressed by addition of Mn^{II} (see Experimental Section). No variation of the signal intensity was observed, demonstrating that the water exchange was completed after three minutes at 277 K. When the sample was heated to 363 K, no significant broadening of the signal at $\delta = -52$ (resulting from the exchange between the coordinated and bulk water molecules) was observed. Combining these observations, the estimated half-life of the water exchange rate at 277 K is between 1 s and 1 min. Comparable results were reported for the water *trans* to the CO ligand in $[Ru(H_2O)_5CO]^{2+}$ ($k_{ax} = 3.8 \times 10^{-3} s^{-1}$, $t_{1/2} \approx 3$ min).^[7] For this Ru^{II} complex the CO exchange rate was dependent on the rupture of the $Ru-H_2O_{ax}$ bond.^[8] The half-life for the observed CO exchange was about three days, much longer than the half-life of the water exchange reaction due to the very low concentration of CO in water. As Tc^I and Ru^{II} have an identical electronic configuration (d^6 low spin), the same mechanism for the CO exchange on $fac-[Tc(H_2O)_3(CO)_3]^+$ may be expected. If this is true, and based on the proposed range of the water exchange rate on **1**, a half life of the CO exchange between 1 and 24 h is expected.

To verify this prediction, the Tc solution was transferred into a 10 mm NMR sapphire tube^[9] and pressurized with 4.4 MPa of ^{13}CO . The CO exchange was then monitored by ^{99}Tc NMR spectroscopy (Figure 1 a–d). The substitution of the coordinated ^{12}CO molecules by one, two, and finally three ^{13}CO led to the appearance of a doublet, a triplet, and finally a quadruplet due to the coupling between the Tc center with the coordinated ^{13}CO molecules. The $^1J_{^{99}Tc,^{13}C}$ coupling constant is 354 Hz and is, to our knowledge, the first $^{99}Tc-^{13}C$ coupling constant reported. Moreover, each substitution of one ^{12}CO by one ^{13}CO causes an isotopic shift of $\Delta\delta = -1.05$ per carbon mass unit (-95 Hz at 9.4 T, Figure 1 a–d).

The chemical scheme of the CO exchange on $fac-[Tc(H_2O)_3(CO)_3]^+$ is also shown in Figure 1. The mathematical model describing this type of exchange has already been developed for the ligand exchange on $[Ru(H_2O)_5L]^{2+}$.^[8] The second-order rate constants, k_{CO} , were determined at 277 K and 310 K by fitting the differential equations to the concentrations as a function of time of the different isotopomers of **1** (Figures 1 e and 1 f). The curves in Figure 1 e,f were fitted by using a single rate constant as the adjustable parameter. It is also worth mentioning that the CO exchange on **1** can be monitored at many different temperatures using the same Tc solution by alternatively pressurizing it with ^{13}CO (Figure 1 e) and ^{12}CO (Figure 1 f).

To test for complete carbonylation, the Tc solution was kept for more than two weeks at ambient temperature under 50 bar of ^{13}CO . The ^{99}Tc spectrum recorded after this time revealed three new signals at $\delta = -1050$, -1418 , and -1961 as well as the quartet at $\delta = -869.7$ from **1** (Figure 2 a). The signal at $\delta = -1961$ is a septet, with a coupling constant of 261 Hz and must be the result of the coupling between a Tc center and six

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[**] We thank the Swiss National Foundation for Scientific Research (A.E.M.) and Mallinckrodt Medical Inc. for the support to this work (R.S. and R.A.)

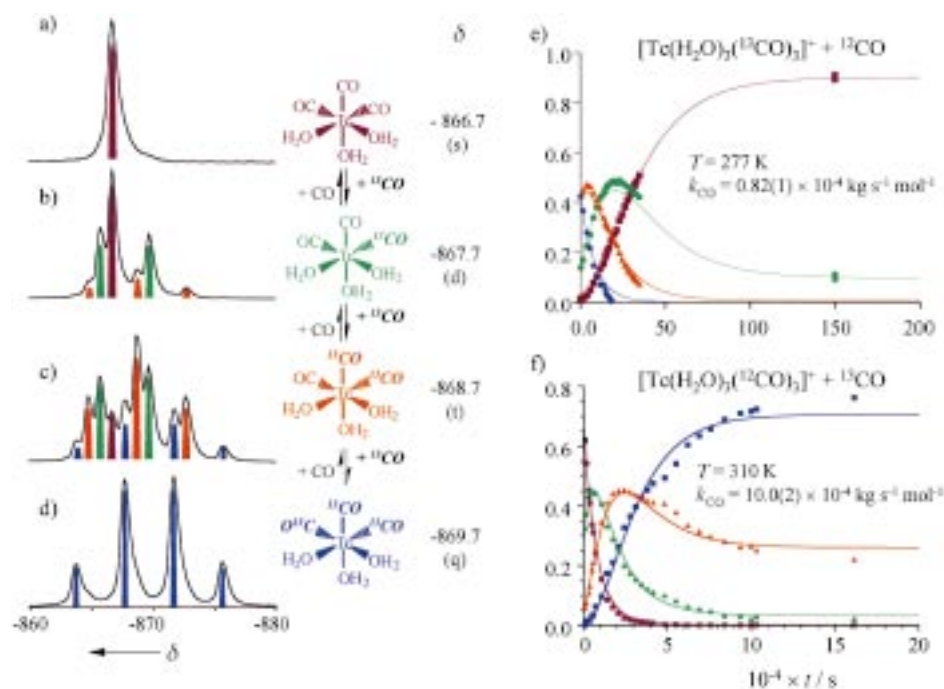


Figure 1. CO exchange on *fac*-[Tc(H₂O)₃(CO)₃]⁺: time dependency of ⁹⁹Tc NMR spectra of a solution containing complex **1** under 44 bar of ¹³CO at 277 K. The spectra were recorded 2 min (a), 4 h (b) and 35 h (c) after applying the ¹³CO pressure; spectrum (d) was recorded after removing all ¹²CO present; evolution of the mole fraction of the different isotopomers of complex **1** under 44 bar of ¹²CO at 277 K (e) and 44 bar of ¹³CO at 310 K (f).

equivalent carbon atoms as in [Tc(¹³CO)₆]⁺. To confirm the presence of [Tc(¹³CO)₆]⁺, the Tc solution was slowly degassed and a ¹³C NMR spectrum was recorded (Figure 2b). Two decets can be seen in the carbonyl region, one at $\delta = 209.7$

[M(CO)₆]ⁿ⁺-type complexes ($n = 1-2$; M = 3d or 4d transition metal in Groups 6–8), the value of the ¹³C NMR chemical shift of **2** ($\delta = 190.2$) was missing. A comparison of this value with that calculated in a density functional study

(¹*J*_{99Tc,13C} = 354 Hz) belonging to [Tc(¹³CO)₃(H₂O)₃], and a smaller one at $\delta = 190.2$ whose coupling constant, ¹*J*_{99Tc,13C} = 261 Hz, is identical to the coupling constant of the septet in the ⁹⁹Tc spectrum. This confirms unambiguously the existence of six equivalent CO ligands coupling with a Tc center, and therefore, the formation of the homoleptic [Tc(CO)₆]⁺ (**2**) complex in aqueous solution.

The synthesis of **2** was already reported in 1965^[10], from solid Tc(CO)₅Cl under 300 bar of CO at 90 °C in presence of AlCl₃. The reaction was performed under anhydrous conditions and the product was characterized only by elemental analysis. In contrast to these rather harsh reaction conditions, we have shown that [Tc(CO)₆]⁺ can be synthesized under relatively mild and even aqueous conditions. We could characterize **2** unambiguously by ⁹⁹Tc and ¹³C NMR techniques. Among the large quantity of data reported for

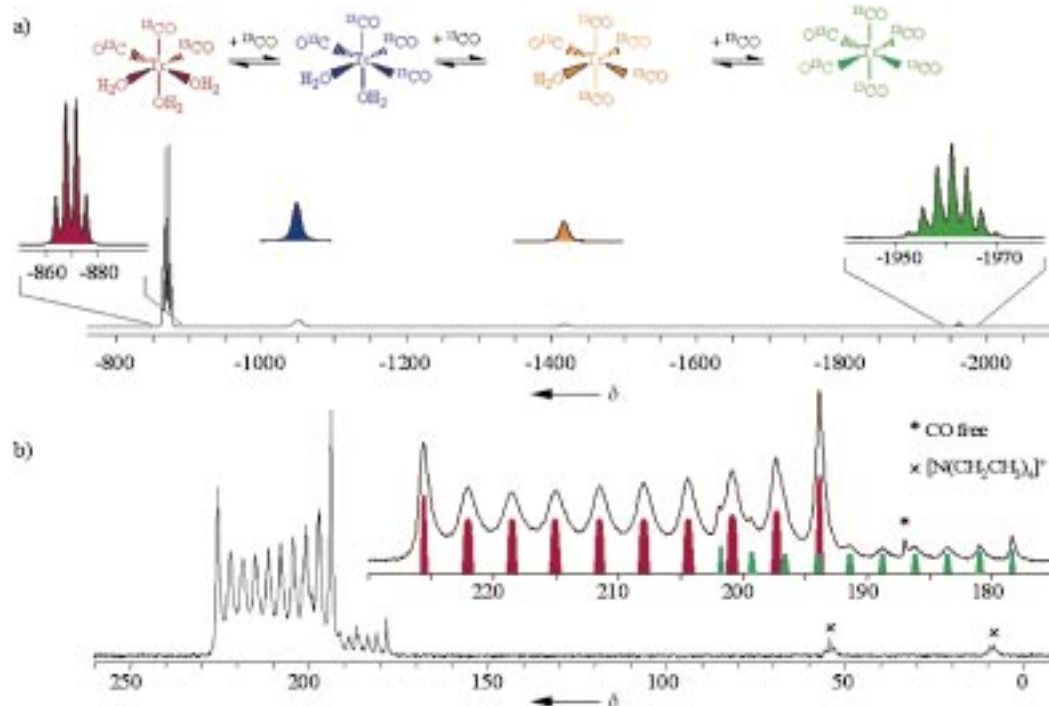


Figure 2. a) ⁹⁹Tc NMR spectrum, recorded at 310 K, of a solution of *fac*-[Tc(H₂O)₃(¹³CO)₃]⁺ kept three weeks under 44 bar of ¹³CO at room temperature; b) ¹³C NMR spectrum recorded at 335 K of the same solution as in (a) after releasing the CO pressure.

($\delta = 193.1$),^[11] confirms the quality of the theoretical studies for these systems.

Since the additional two peaks at $\delta = -1050$ and -1418 in the ^{99}Tc spectra (Figure 2a) are much broader and exhibit no splitting, the assignment of these signals is not readily apparent. It seems reasonable to assume that each substitution of a water molecule by one CO will increase the shielding of ^{99}Tc . Therefore, these two signals can logically be attributed to $[\text{Tc}(\text{H}_2\text{O})_2(\text{CO})_4]^+$ (**3**) and $[\text{Tc}(\text{H}_2\text{O})(\text{CO})_5]^+$ (**4**). The reduced local symmetry of complexes **3** and **4** and the inequivalence of the CO ligands (complicated coupling pattern) explain the broader signals and the impossibility to resolve the coupling pattern.

When the CO pressure was released, the ^{99}Tc NMR peaks of **3** and **4** disappeared within one hour, and the signal of **2** at $\delta = -1961$ within two days at 25°C ; this left only the signal of **1** at $\delta = -867$. The same phenomenon was observed in the ^{13}C spectra. The decrease of the signal at $\delta = 190.2$ was concomitant with an increase of the signals at $\delta = 209.7$ (**1**) and at 187 (free CO). These observations emphasize the high stability of the homoleptic $[\text{Tc}(\text{CO})_6]^+$ complex compared to the tetra- or pentacarbonyl complexes and support our kinetic model to describe the CO exchange on **1**. For the CO exchange for $[\text{Ru}(\text{H}_2\text{O})_5\text{CO}]^{2+}$, the *trans*- $[\text{Ru}(\text{H}_2\text{O})_4(\text{CO})_2]^{2+}$ intermediate was not observed but its existence indirectly demonstrated. In the present study, the signal of the $[\text{Tc}(\text{H}_2\text{O})_2(\text{CO})_4]^+$ intermediate was observed in the ^{99}Tc spectra, confirming the validity of the model.

In this study, many aspects of the reactivity of *fac*- $[\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ were observed by using one single sample. A range for the water exchange rate was determined. A kinetic model was developed to describe the CO exchange and the rate could be monitored by ^{99}Tc NMR spectroscopy at 4°C ($k_{\text{CO}} = (0.82 \pm 0.01) \times 10^{-4} \text{ kg s}^{-1} \text{ mol}^{-1}$) and 37°C ($k_{\text{CO}} = (10.0 \pm 0.02) \times 10^{-4} \text{ kg s}^{-1} \text{ mol}^{-1}$). Moreover, the full aqueous carbonylation of *fac*- $[\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ was unambiguously demonstrated by ^{99}Tc and ^{13}C NMR spectroscopy and the first ^{99}Tc – ^{13}C coupling constant was determined.

Experimental Section

$[\text{NET}_4]_2[\text{TcCl}_3(\text{CO})_3]$ was synthesized according to the literature.^[6] A solution of *fac*- $[\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ (**1**) was prepared as follows: To a suspension of $[\text{NET}_4]_2[\text{TcCl}_3(\text{CO})_3]$ (0.183 g, 0.33 mmol) in dry THF (5 mL) three equivalents of AgPF_6 were added and stirred for 5 h. After filtration of AgCl and NET_4PF_6 , THF was evaporated under N_2 , and aqueous HClO_4 (2 mL, 2 M) was added. To suppress the ^{17}O NMR signal of the bulk water, $\text{Mn}(\text{ClO}_4)_2$ (0.153 g, 0.69 mmol) was added. This solution was mixed at 277 K with ^{17}O -enriched water (1 mL). The final composition of the solution was: **1** 0.11 mol kg^{-1} , $[\text{H}^+] 1.33 \text{ mol kg}^{-1}$, $[\text{ClO}_4^-] 1.78 \text{ mol kg}^{-1}$. To monitor the CO exchange reaction of **1**, the solution was transferred into a sapphire tube^[9] and a pressure of 44 bar of ^{13}CO was applied. After complete exchange, the solution was degassed and shaken for 10 min under 6 bar of N_2 . Then, a pressure of 44 bar of ^{12}CO were applied to monitor the CO exchange at another temperature. This procedure was repeated several times. The CO concentration at 44 bar is $0.044 \text{ mol kg}^{-1}$. The absence of sideproducts of the Tc complexes was checked by ^{99}Tc , ^{17}O , and ^1H NMR after each reaction. NMR spectra (^{99}Tc and ^{13}C) were obtained on a Bruker ARX-400 spectrometer. The ^{13}C and ^{99}Tc NMR chemical shifts are referenced to TMS and TcO_4^- , respectively, and measured with respect to dissolved CO ($\delta = 187$),^[12] and $[\text{Tc}(\text{H}_2\text{O})_3(^{12}\text{CO})_3]^+$ ($\delta = -867$), respectively. The CO exchange was monitored by ^{99}Tc NMR spectroscopy. The spectra were obtained at 90.04 MHz in 500–5000 scans with a spectral

width of 100 kHz, 32 k data points (acquisition time 0.262 s), and a pulse width of 15 μs . New products formed under CO pressure were characterized by ^{99}Tc and ^{13}C NMR spectroscopy. The ^{13}C NMR spectra were recorded at 100.63 MHz in 200–20000 scans, with a spectral width of 41.7 kHz, 64 k data points (acquisition time 5.8 s) and a pulse width of 15 μs . Rate constants were obtained by fitting the kinetic data to appropriate differential equations by a nonlinear optimization procedure with the program SCIENTIST (version 2.0, MicroMath Inc.).

Received: July 23, 1999

Revised: September 21, 1999 [Z13775]

- [1] a) J. Steigman, W. Eckelman, *The Chemistry of Technetium in Medicine, Vol. I*, National Academy Press, Washington D.C., **1992**, pp. 1–180, and references therein; b) S. Jurisson, D. Berning, W. Jia, M. Dangshe, *Chem. Rev.* **1993**, 93, 1137–1156, and references therein.
- [2] a) S. Liu, D. S. Edwards, J. A. Barrett, *Bioconjugate Chem.* **1997**, 8, 621–636; b) S. Vallbhajosula, B. R. Moyer, J. Lister-James, B. J. McBride, H. Lipszyc, H. Lee, D. Bastidas, R. T. Dean, *J. Nucl. Med.* **1996**, 37, 1016–1022; c) A. J. T. George, F. Jamar, M.-S. Tai, B. T. Heelan, G. P. Adams, J. E. McCartney, L. L. Houston, L. M. Weiner, H. Oppermann, A. M. Peters, J. S. Huston, *Proc. Natl. Acad. Sci. USA* **1995**, 92, 8358–8362; d) M. J. Verhaar, P. A. Keep, R. E. Hawkins, L. Robson, J. L. Casey, B. Pedley, J. A. Boden, R. H. Begent, K. A. Chester, *J. Nucl. Med.* **1996**, 37, 868–872.
- [3] a) R. Alberto, R. Schibli, A. Egli, P. A. Schubiger, U. Abram, T. A. Kaden, *J. Am. Chem. Soc.* **1998**, 120, 7987–7988; b) F. Minutolo, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1998**, 120, 4514–4515.
- [4] a) R. Alberto, R. Schibli, P. A. Schubiger, U. Abram, H.-J. Pietzsch, B. Johannsen, *J. Am. Chem. Soc.* **1999**, 121, 6076–6077; b) A. Egli, R. Alberto, L. Tannahill, R. Schibli, U. Abram, A. Schaffland, R. Waibel, D. Tourwé, L. Jeannin, K. Iterbeke, P. A. Schubiger, *J. Nucl. Med.* **1999**, in press.
- [5] a) R. Schibli, R. Alberto, U. Abram, S. Abram, A. Egli, P. A. Schubiger, T. A. Kaden, *Inorg. Chem.* **1998**, 37, 3509–3516; b) R. Alberto, R. Schibli, P. A. Schubiger, U. Abram, T. A. Kaden, *Polyhedron* **1996**, 15, 1079–1089.
- [6] R. Alberto, R. Schibli, A. Egli, P. A. Schubiger, W. A. Herrmann, G. M. Artus, U. Abram, T. A. Kaden, *J. Organomet. Chem.* **1995**, 493, 119–127.
- [7] N. Aebischer, E. Sidorenkova, M. Ravera, G. Laurenczy, D. Osella, J. Weber, A. E. Merbach, *Inorg. Chem.* **1997**, 36, 6009–6020.
- [8] N. Aebischer, R. Churlaud, L. Dolci, U. Frey, A. E. Merbach, *Inorg. Chem.* **1998**, 37, 5915–5924.
- [9] T. Cusanelli, U. Frey, D. T. Richens, A. E. Merbach, *J. Am. Chem. Soc.* **1996**, 118, 5265–5271.
- [10] W. Hieber, F. Lux, C. Herget, *Z. Naturforsch. B* **1965**, 20, 1159–1165.
- [11] G. Laurenczy, L. Helm, A. Ludi, A. E. Merbach, *Helv. Chim. Acta* **1991**, 74, 1236–1238.
- [12] A. W. Ehlers, Y. Ruiz-Morales, E. J. Baerends, T. Ziegler, *Inorg. Chem.* **1997**, 36, 5031–5036.

Femtosecond Dynamics of Dioxygen – Picket-Fence Cobalt Porphyrins: Ultrafast Release of O₂ and the Nature of Dative Bonding**

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The natural systems of hemoglobin and myoglobin form reversible complexes with O₂, which are involved in the transport of O₂ in biological systems. The protein environment surrounding the metal center in these molecules controls the rate of the binding of O₂ and discriminates against poisonous carbon monoxide. Synthetic models of these systems have been designed to optimize the binding of O₂ and include “picket-fence”, “pocket”, “basket-handle”, “picnic-basket”, and “capped” porphyrins.^[1] These models are attractive systems for study because of their high affinities for O₂ at room temperature. Among the issues that can be addressed with these model systems are: 1) the nature of the elementary steps involved in the reactions of O₂ complexes, 2) the influence of hydrogen bonding on the rates of O₂ binding and release, and 3) the geometry of the O₂–metal complex on the time scale of the dynamics.

Herein we report our first study of the femtosecond dynamics of a) a four-coordinate picket-fence cobalt(II) porphyrin in benzene at room temperature, b) its five-coordinate 1-methylimidazole (1-MeIm) adduct (used to enhance the binding of O₂), and c) the six-coordinate O₂ complex of the 1-MeIm adduct (Figure 1). The transient behavior of the two O₂-free porphyrins is very similar to that for cobalt(II) tetraphenylporphyrin. However, a dramatic change in the transient absorption is observed when the porphyrin is oxygenated. These observations indicate the release of the bound O₂ from the active binding site with a total reaction time of 1.9 ± 0.4 ps. We relate such behavior to the nature of the dative cobalt–O₂ bond and the charge redistribution triggered by the direct femtosecond excitation of the complex to the transition state for O₂ release.

In a recent publication^[2] we reported a correlation between the electrocatalytic activity of tetra-ruthenated cobalt porphyrins toward the reduction of O₂^[3,4] and the femtosecond dynamics of their charge transfer states. We have also investigated the femtosecond dynamics of cobalt(II) tetraphenylporphyrin (Co^{II}TPP).^[5] We were drawn to investigate the dynamics of oxygenated cobalt porphyrins since the cobalt center plays a key role in the catalyzed reduction of O₂. The coordination of O₂ to most four-coordinate cobalt(II) porphyrins or five-coordinate amine adducts of cobalt(II) porphyrins is not favorable at room temperature. It has been estimated for the 1-methylimidazole adduct of cobalt(II) tetra(*p*-methoxy-

phenyl)porphyrin that only about 0.8% of the cobalt centers would have O₂ as a sixth ligand in toluene solutions saturated with air.^[6] Although more elaborate types of porphyrins exhibit higher affinities for O₂^[1,7] we were attracted to the original picket-fence cobalt porphyrin (Figures 1 and 2) because its structure is relatively close to our previously examined cobalt tetraphenylporphyrins, it binds O₂ with high affinity at room temperature, and the binding is reversible.

The steady-state absorption spectra of the oxygenated and deoxygenated picket-fence cobalt porphyrin (CoP) are differ-

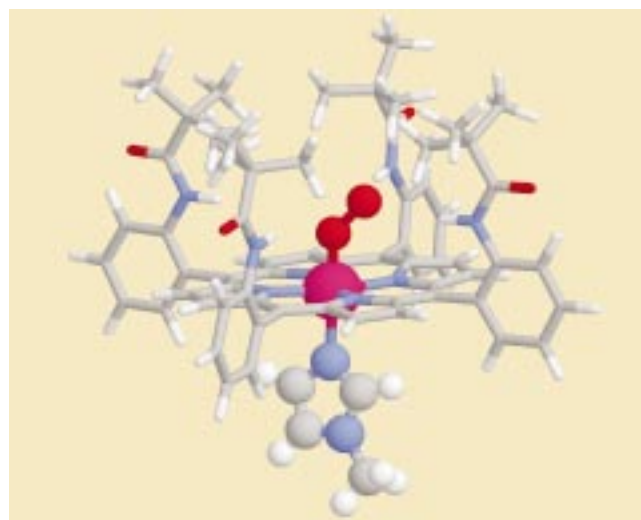


Figure 1. Structural model of the six-coordinate picket-fence cobalt(II) porphyrin examined in this study.

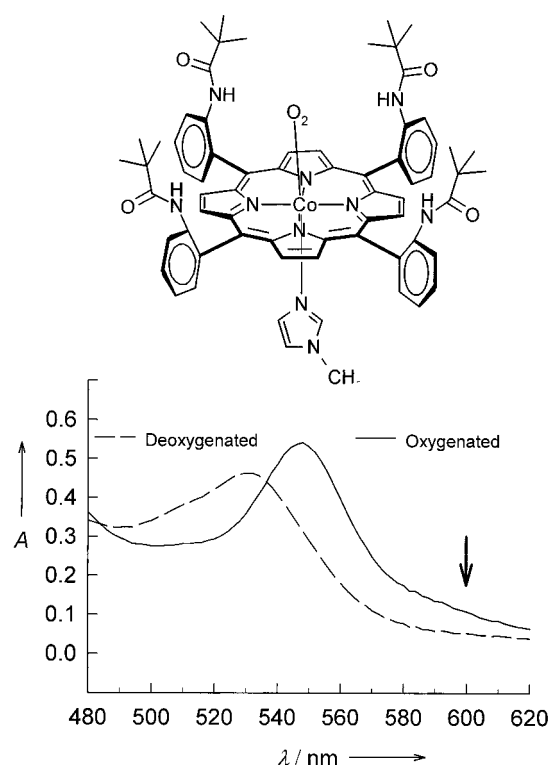


Figure 2. Top: Molecular structure of the model in Figure 1. Bottom: Steady-state absorption spectra of (1-MeIm)–Co^{II}tpivPP in benzene at room temperature: Solutions were equilibrated with 1 atm of argon (dashed curve) or O₂ (solid curve).

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[**] This work was supported by the US National Science Foundation (Laboratory for Molecular Sciences).

ent in that the oxygenated form shows a definite red shift at room temperature (Figure 2). A series of transient absorption measurements using a pump wavelength of 545 nm and a probe wavelength of 600 nm is shown in Figure 3. The upper

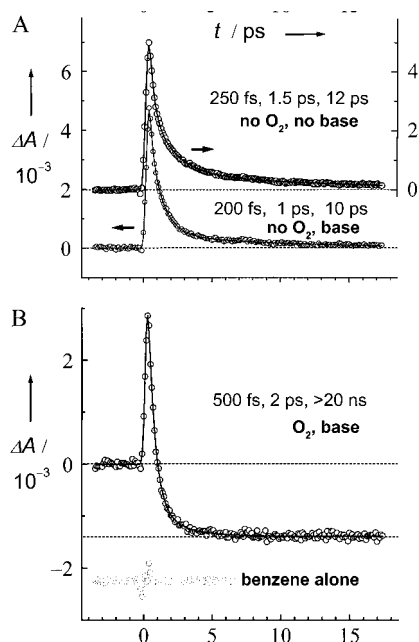


Figure 3. Femtosecond transient absorption at 600 nm of picket-fence cobalt porphyrin in benzene with excitation at 545 nm. A) Transients measured under argon, with and without complexation by (4 mM) 1-MeIm (base); B) Transient measured in 4 mM 1-MeIm under 1 atm of O_2 , and the transient for pure benzene.

trace in Figure 3A is the transient absorption of CoP in benzene at room temperature under 1 atm of argon. The temporal evolution is very similar to that reported previously for $Co^{II}TPP$.^[5] It consists of three exponential decay components (having relative amplitudes of 57%, 34%, and 9%, respectively) with lifetimes indicated in the figure. The measurement was repeated in the presence of 4 mM 1-MeIm (referred to as base, B), which converts more than 98% of the porphyrin into five-coordinate B-CoP,^[8] and resulted in the generation of the second trace in Figure 3A. Although the lifetimes are somewhat shortened, and the relative amplitudes change, the three decay components are still present.

Figure 3B shows the response obtained after the B-CoP + 4 mM 1-MeIm solution was saturated with O_2 , which converts approximately 85% of the porphyrin into B-CoP- O_2 .^[9] Since the absorbance of B-CoP- O_2 at 545 nm is higher than that of B-CoP (see Figure 2), we estimate that about 90% of the photoexcited porphyrin contains coordinated O_2 . The presence of O_2 causes a dramatic change in the transient behavior: following the absorbance increase at $t=0$, there is a substantial bleaching, or decrease in absorbance, at longer times. The long-lived plateau of the bleaching signal is reached within 4 to 5 ps. This plateau does not decay appreciably over the maximum range of our delay time, which indicates a recovery lifetime of at least 20 ns. (A slight (<10%) decrease in this plateau level appears to occur on a time scale of tens of picoseconds).

We performed similar experiments probing at 471 nm. In the absence of O_2 the longest component (with a 10 to 20 ps lifetime) was relatively weak compared to that at 600 nm, which matched the trend observed for $Co^{II}TPP$.^[5] In the presence of O_2 the 471 nm transient was dominated by a 200 fs decay component followed by a long-lived negative plateau similar to that at 600 nm. However, the response was complicated by at least three additional relaxation components. The measurements at 600 nm are unique because they probe only the tail of the Q-band absorption (see Figure 2).

Hoshino concluded from the transient absorption spectrum of CoTPP- O_2 in O_2 -saturated 2-methyltetrahydrofuran at low temperature (140–200 K)^[10] that the product detected on the nanosecond time scale (following photolysis at 532 nm) was ground-state $Co^{II}TPP$, which subsequently recombined (non-geminately) with O_2 on the microsecond time scale. Similarly, in our experiments B-CoP is produced at long times in its ground state. A negative change in the transient absorption at 600 nm, as seen in the transient shown in Figure 3B, is then predicted because the B-CoP complex absorbs only weakly at 600 nm (Figure 2). Lending further support to this assignment of the product is the fact that the spectrum and transient behavior observed prior to the addition of O_2 were fully recovered when the same sample was again placed under argon, which demonstrated that no significant oxidation or other degradation of the porphyrin sample had occurred during the experiments under O_2 saturation.

The fact that the 600 nm absorbance does not recover appreciably on the nanosecond time scale shows that the extent of geminate recombination of O_2 and B-CoP is small. This behavior contrasts with the 43% recombination efficiency reported for O_2 and picket-fence iron porphyrin, B-FeP (B = 1-MeIm), in toluene with excitation at 314 nm.^[11] It is interesting to note that the photoinduced release of CO from myoglobin is characterized by an absence of geminate recombination.^[12] In that case the direct monitoring of the CO has shown that it is released from the metal coordination site and trapped in a pocket of the heme protein within 500 fs. The protein environment surrounding the trapping site then undergoes relaxation with a time constant of 1.6 ps.^[13] However, it is not necessary to invoke such a trapping mechanism in all cases of low geminate recombination since ligand–porphyrin association rates depend strongly on the specific ligand and metal center. The contrast in the geminate recombination of O_2 with B-CoP and B-FeP is consistent with the smaller equilibrium binding of O_2 with B-CoP.^[14, 15]

The nature of the ultrafast dynamics of the O_2 release can now be addressed. The first steps parallel those previously deduced for CoTPP.^[5, 16] Relaxation within the porphyrin system (200 fs, prominent only when probing at 471 nm) precedes porphyrin-to-metal electron-transfer, but the latter occurs at an enhanced rate (500 fs as opposed to 1–2 ps) because of the dative bonding of cobalt and O_2 , as discussed below. (The absence of a clear 200 fs component at 600 nm is understandable because the 600 nm probe is expected to be less sensitive to the initial state than is the 471 nm probe.^[5]) The strong O_2 bonding in the adduct ground state ($\Delta H = -12.2 \text{ kcal mol}^{-1}$)^[14] has significant $Co^{III}-O_2^-$ character and is made possible only through the influence of the base on the

metal center; the behavior of the transient profile seen in Figure 3A shows that the perturbation of the porphyrin system by the base alone is not severe.

The dative bonding of O₂ to cobalt depends critically on the interaction of the d_{z²} orbital on Co with the π* orbital on O₂ (through a σ-type interaction) and on the back-bonding from the metal d-π orbitals to O₂. The noncolinear configuration enhances the σ-bonding, and, because the d_{z²} electron of Co is engaged in bonding, the oxidation state of Co approaches +3.^[17, 18, 19] Following femtosecond excitation the charge transfer from the porphyrin-based π system to the base-metal-O₂ system restores an electron to the cobalt d_{z²} orbital and weakens the metal-O₂ bond. Reverse charge transfer and release of the O₂ can then occur in concert to produce the free porphyrin in its ground state in 2 ps. That this process occurs faster than the 10 ps decay of the charge-transfer state in the absence of oxygen (Figure 3A) may be related to the different natures of the charge-transfer state with and without O₂. The porphyrin-to-metal charge-transfer state of B-CoP has a measurable absorption at 600 nm as evidenced by the 10 ps component in Figure 3A. The fact that no 10 ps decay component appears in the transient of B-CoP-O₂ means that B-CoP was not formed in the excited state, and thus confirms that release of O₂ directly produces the B-CoP complex in its ground state.^[20]

The total reaction time is 2 ps. In general, the release of O₂ involves the breakage of the bond and the reorganization around the active site, as discussed for myoglobin-CO.^[13] It should be noted that the dative character of the bond could lead to two different channels: either homolytic cleavage to release O₂ or heterolytic cleavage to form superoxide. Our results, as in the case of ref. [10], support the homolytic channel: the ground state of B-CoP is d_{z²}¹, similar to the CT state of B-CoP-O₂, while the ground state of the latter is essentially d_{z²}⁰. Our findings may be relevant to other recent studies, including a report of the photoejection of O₂ in less than 2 ps from an oxygenated Co^{II}porphyrin-Al^{III}phthalocyanine aggregate^[21] and studies on oxyhemoproteins (oxyhemoglobin, oxymyoglobin, etc.) in fast spectroscopic experiments by Petrich et al.,^[22] and others, as summarized by Šima.^[23]

In conclusion, excitation of the O₂ adduct of the picket-fence porphyrin within the Q-band leads to ultrafast (2 ps) ejection of O₂, which is a reflection of the influence of charge redistribution within the complex on the O₂-Co dative bond. The entry to the transition state of these systems allows us to study the direct evolution to products and to dissect the elementary steps, similar to what has been achieved in elementary charge-transfer systems.^[24] There is a host of additional experiments to be carried out on these novel models.

Experimental Section

Our laser system has been described in detail elsewhere.^[5] Basically, an amplified 790 nm pulse train (1.8 W, 1 kHz) from a Ti:Sapphire laser was used to pump two optical parametric amplifiers to produce independently tunable pump and probe beams. The pump beam was directed through a variable delay line and a beam chopper and overlapped with the probe beam in a 1 mm path-length glass cell containing the sample solution. The

polarization and power of both beams were adjusted as required (pump power 2 μJ, probe power 50 nJ, magic angle probing), lightly focused (spot size ca. 0.5 mm), and crossed at a small angle (ca. 2°). The probe power was detected after the cell by a photodiode and the gated and integrated signal was normalized to a similarly processed signal from a photodiode sampling the probe power before the cell. The change in absorbance was obtained from the signals with and without pump excitation as determined by the chopper. The total temporal response of the experiments was determined to be 300–350 fs full width at half maximum height.

The picket-fence free base porphyrin, 5,10,15,20-tetrakis(*a,a,a,a*-2-pivalamido-phenyl)porphyrin (*a,a,a,a*-H₂TpivPP), was synthesized by first preparing the 5,10,15,20-tetrakis(2-nitrophenyl)porphyrin in 11% yield by condensing 2-nitrobenzaldehyde with pyrrole in boiling glacial acetic acid according to the procedure of Collman et al.^[25] The crude product was used as obtained in the further reaction in which the nitro groups were converted into the amines by reduction with excess SnCl₂ in concentrated HCl at 65–70 °C.^[25] The crystalline product, 5,10,15,20-tetrakis(2-amino-phenyl)porphyrin (H₂TamPP), isolated in 92% yield, was a mixture of the four atropisomers in statistical abundance (*α,β,α,β*:-*α,α,β,β*:-*α,α,α,α*-atropisomer = 1:2:4:1), as indicated by thin layer chromatography on silica gel with benzene:diethyl ether (1:1). The *α,α,α,α*-atropisomer was obtained in 60% yield by conversion of the random mixture of atropisomers by the silica gel/benzene reflux method,^[26] followed by purification by column chromatography and crystallization from CHCl₃/MeOH mixtures. The 500 MHz ¹H NMR and UV/Vis spectra of *a,a,a,a*-H₂TamPP were in agreement with those previously reported.^[26]

a,a,a,a-H₂TamPP was reacted with pivaloyl chloride and the product was purified by column chromatography on silica gel followed by recrystallization from a CHCl₃/EtOH/heptane mixture to give pure *a,a,a,a*-H₂TpivPP, as confirmed by the 500 MHz ¹H NMR and UV/Vis spectra. The picket-fence cobalt(II) porphyrin, [5,10,15,20-tetrakis(*a,a,a,a*-2-pivalamidophenyl)porphyrinato]cobalt(II) (Co^{II}TpivPP), was prepared by heating a solution of *a,a,a,a*-H₂TpivPP in THF at 50 °C for 2 h with excess anhydrous CoCl₂ and 2,6-lutidine.^[14] The product was purified by chromatography on alumina followed by crystallization from benzene. The 500 MHz ¹H NMR and UV/Vis spectra of *a,a,a,a*-Co^{II}TpivPP were in agreement with those previously reported.^[14, 27] The photo- and thermal isomerization of several picket-fence systems have been studied.^[28] The thermal process is negligible at room temperature and the photochemical process occurs only in long-lived triplet states with very low yields; unlike these systems, Co^{II}TpivPP has an ultrashort excited state lifetime.

Typically, we performed a sequence of four femtosecond transient absorption measurements. We first measured the transient absorption of Co^{II}TpivPP in benzene, freshly passed through a column of alumina, at room temperature and under 1 atm of argon in a 1 mm path-length glass cell (with reservoir, hi-vac valve, and a 24/40 joint adapter closed with septum); the concentration of the porphyrin was adjusted to yield a static absorbance of about 0.2 at 550 nm. 1-Methylimidazole (redistilled) was subsequently added, still under 1 atm of argon, to produce a 4 mM solution. The visible absorption spectrum showed bands at 508 and 530 nm. The transient absorption measurement was then repeated. For the next experiments, O₂ at 1 atm was bubbled through the solution at room temperature until the absorption band at 548 nm (B-CoP-O₂) showed no further change. Preparation of the sample for the final run involved bubbling argon through the solution until the visible absorption spectrum for B-CoP was recovered.

Received: September 23, 1999 [Z14060]

- [1] J. P. Collman, L. Fu, *Acc. Chem. Res.* **1999**, 32, 455–463, and references therein.
- [2] H. Z. Yu, J. S. Baskin, B. Steiger, F. C. Anson, A. H. Zewail, *J. Am. Chem. Soc.* **1999**, 121, 484–485.
- [3] B. Steiger, F. C. Anson, *Inorg. Chem.* **1997**, 36, 4138–4140.
- [4] F. C. Anson, C. Shi, B. Steiger, *Acc. Chem. Res.* **1997**, 30, 437–444.
- [5] H. Z. Yu, J. S. Baskin, B. Steiger, C. Z. Wan, F. C. Anson, A. H. Zewail, *Chem. Phys. Lett.* **1998**, 293, 1–8.
- [6] F. A. Walker, *J. Am. Chem. Soc.* **1973**, 95, 1154–1159.
- [7] C. K. Chang, Y. Liang, G. Avilés, *J. Am. Chem. Soc.* **1995**, 117, 4191–4192.

- [8] Calculated from the thermodynamic data in ref. [14].
- [9] Calculated from the thermodynamic data in ref. [14]. The solubility of O₂ in benzene was taken to be $9.1 \times 10^{-3} \text{ M atm}^{-1}$, see ref. [29].
- [10] M. Hoshino, *Chem. Phys. Lett.* **1985**, *120*, 50–52.
- [11] T. G. Grogan, N. Bag, T. G. Traylor, D. Magde, *J. Phys. Chem.* **1994**, *98*, 13791–13796.
- [12] T. A. Jackson, M. Lim, P. A. Anfinrud, *Chem. Phys.* **1994**, *180*, 131–140.
- [13] M. Lim, T. A. Jackson, P. A. Anfinrud, *Nat. Struct. Biol.* **1997**, *4*, 209–214.
- [14] J. P. Collman, J. I. Brauman, K. M. Doxsee, T. R. Halbert, S. E. Hayes, K. S. Suslick, *J. Am. Chem. Soc.* **1978**, *100*, 2761–2766.
- [15] J. P. Collman, J. I. Brauman, K. S. Suslick, *J. Am. Chem. Soc.* **1975**, *97*, 7185–7186.
- [16] C. D. Tait, D. Holten, M. Gouterman, *Chem. Phys. Lett.* **1983**, *100*, 268–272.
- [17] B. B. Wayland, J. V. Minkiewicz, M. E. Abd-Elmageed, *J. Am. Chem. Soc.* **1974**, *96*, 2795–2801.
- [18] A. Dedieu, M.-M. Rohmer, A. Viellard, *J. Am. Chem. Soc.* **1976**, *98*, 5789–5800.
- [19] I. Bytheway, M. B. Hall, *Chem. Rev.* **1994**, *94*, 639–658, and references therein.
- [20] The B-CoP ground state is relatively transparent at 600 nm, but has a large absorbance at 471 nm (see Figure 2), so processes such as vibrational relaxation and solvation after release of the O₂ may cause a further evolution of the 471 nm absorbance, in addition to the constant background (beyond 5 ps) arising from photo-bleaching of B-Co-O₂. For example, the observed 471 nm dynamics may reflect relaxation of the picket structure surrounding the binding site or a secondary interaction between that structure and the dissociated O₂ that are undetected in the 600 nm data.
- [21] T. Fournier, Z. Liu, T.-H. Tran-Thi, D. Houde, N. Brasseur, C. La Madeleine, R. Langlois, J. E. van Lier, D. Lexa, *J. Phys. Chem. A* **1999**, *103*, 1179–1186.
- [22] J. W. Petrich, C. Poyart, J. L. Martin, *Biochemistry* **1988**, *27*, 4049–4060.
- [23] J. Šima in *Structure and Bonding*, Vol. 84 (Ed.: J. W. Buchler), Springer, Berlin, **1995**, pp. 135–193.
- [24] D. P. Zhong, A. H. Zewail, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 2602–2607, and references therein.
- [25] J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang, W. T. Robinson, *J. Am. Chem. Soc.* **1975**, *97*, 1427–1439.
- [26] J. Lindsey, *J. Org. Chem.* **1980**, *45*, 5215.
- [27] H. Imai, K. Nakata, A. Nakatsubo, S. Nakagawa, Y. Uemori, E. Kyuno, *Synth. React. Inorg. Met. Org. Chem.* **1983**, *13*, 761–780.
- [28] a) R. A. Freitag, J. A. Mercer-Smith, D. G. Whitten, *J. Am. Chem. Soc.* **1981**, *103*, 1226–1228; b) R. A. Freitag, D. G. Whitten, *J. Phys. Chem.* **1983**, *87*, 3918–3925.
- [29] H. L. Clever, R. Battino in *Solutions and Solubilities Part I in Techniques of Chemistry*, Vol. VIII (Ed.: M. R. J. Dack), Wiley, New York, **1975**, pp. 379–441.

Femtosecond Dynamics of Norrish Type-II Reactions: Nonconcerted Hydrogen-Transfer and Diradical Intermediacy**

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Herein we report our first real-time study of the dynamics of Norrish type-II reactions: the intramolecular hydrogen transfer and the reaction of the intermediate, diradical species. The nuclear motions associated with the breakage of C–H and C–C bonds and formation of O–H and C–C bonds are studied for the series 2-pentanone, 2-hexanone, and 5-methyl-2-hexanone, using femtosecond time-resolved mass spectrometry. The time scale for the ultrafast hydrogen atom transfer (70–90 fs) and diradical closure and cleavage (400–700 fs) are obtained from the time evolution of the mass-gated species—the observed and vastly different reaction times indicate the nonconcerted nature of the two steps. Density functional theory (DFT) calculations are also reported to elucidate the energetics along the reaction path, and we address the analogy with the McLafferty rearrangement in ion chemistry.

Norrish type-I^[1] and type-II^[2] reactions are of fundamental importance in photochemistry. The contrast between photochemical and thermal reactions of ketones has been of interest for more than 50 years. Elsewhere, the femtosecond (fs) dynamics of Norrish type-I reactions have been reported.^[3, 4] In these reactions the α -cleavage is the pathway for product formation. In contrast, in Norrish type-II reactions carbonyl compounds containing γ C–H bonds undergo a 1,5-hydrogen shift upon electronic excitation and yield new products by cleavage and cyclization processes. Figure 1 lists the molecular structures of the systems studied here; three have γ C–H bonds and for calibration purposes one does not.

The literature is rich with detailed studies in the solution and gas phases, with primary focus on the photochemistry of the first excited S₁ state.^[2] As noted in these studies the Norrish type-II reaction is deduced, from yield and quenching experiments, to be on the nanosecond time scale and competes with vibrational relaxation and intersystem crossing; there is a barrier for excited singlet reactions of about 4 kcal mol^{−1}. The studies reported here are at higher energy (see Figure 2) and are designed to address the primary ultrafast dynamics without complications from much slower relaxation processes. However, the Norrish type-II elementary processes discussed here are the two described in ref. [2] for the overall mechanism.

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[**] This work was supported by the US Airforce Office of Scientific Research and Office of Naval Research. S.D.F., a postdoctoral fellow of the Fund for Scientific Research-Flanders, acknowledges a Fulbright scholarship and financial support by the Katholieke Universiteit Leuven and by Caltech.

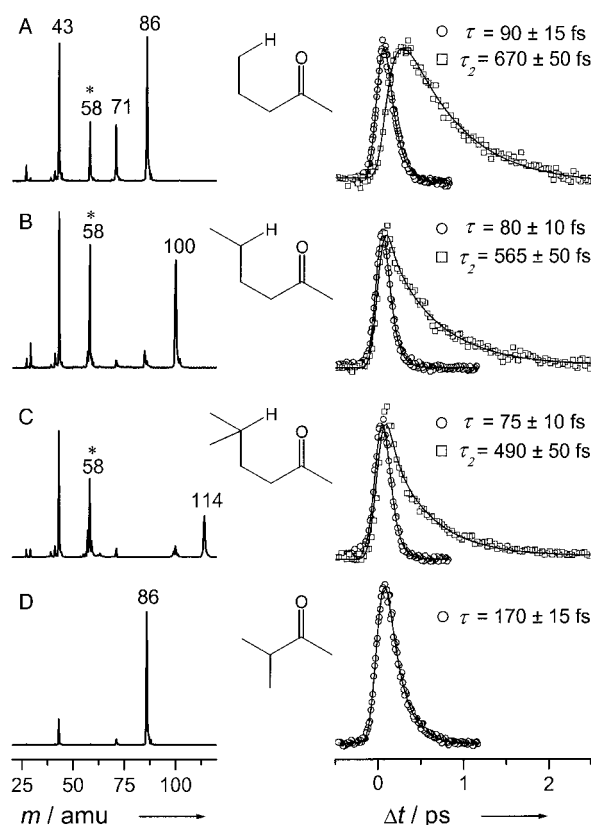


Figure 1. Femtosecond mass spectra (on the left) and transients (on the right): parent (○) and m/z 58 intermediate (□) of A) 2-pentanone, B) 2-hexanone, and C) 5-methyl-2-hexanone. D) is 3-methyl-2-butanone. The theoretical fits are represented as solid curves with the fitted time constant τ representing the decay time of the parent and τ_2 the decay time of the m/z 58 species. The other mass peaks are from the α -cleavage of C–C bonds (for further information see the text).

The fs laser and molecular beam apparatus have been described in detail elsewhere.^[5] Briefly, a fs laser system was integrated to a molecular beam apparatus with the capability of measuring the time-of-flight (TOF) mass spectra. The amplified pulses were typically about 80 fs and the energy was of the order of $150 \mu\text{J pulse}^{-1}$ at 615 nm. For the pump the 615 nm output was frequency doubled. The probe beam, which ionizes the transient species, was passed to a computer-controlled translation stage to generate the time delay. Both pump and probe beams were appropriately attenuated to minimize background signals.

Figure 1 displays the fs mass spectra and transients of A) 2-pentanone, B) 2-hexanone, C) 5-methyl-2-hexanone, and D) 3-methyl-2-butanone. The mass spectra of these molecules are characterized by their parent mass peak at m/z 86, 100, 114, and 86, respectively, and by additional peaks which are the radicals produced by α -cleavage of the C–C bonds. Our observation here of the additional peaks is entirely consistent with previous studies of α -cleavage in methyl alkyl ketones,^[3] in which the fs mass spectra contained a peak at m/z 43 corresponding to the acetyl radical and a peak at m/z ($M - 15$) corresponding to the alkyl carbonyl radical (Norrish type-I). However, all molecules studied here (A, B, and C) show a unique additional peak in the mass spectrum situated at m/z 58. This peak is only present when the molecular structure (A,

B, C) is poised for Norrish type-II reactions, as evident by the absence of the m/z 58 peak in the spectrum of 3-methyl-2-butanone (D), which lacks a hydrogen atom in the γ -position.

By gating the signal at the parent mass and m/z 58, we obtained the transient signals for the corresponding species. The results are shown to the right of Figure 1. A least-squares-fit with proper convolution gives the parent decay time $\tau = 90 \pm 15$ fs, 80 ± 10 fs, and 75 ± 10 fs for 2-pentanone, 2-hexanone, and 5-methyl-2-hexanone, respectively. The rise times of the intermediates are comparable to the decay times of their respective parents. The m/z 58 species decays in 670 ± 50 fs for 2-pentanone (A), 565 ± 50 fs for 2-hexanone (B), and 490 ± 50 fs for 5-methyl-2-hexanone (C).^[6] The decay of the α -cleavage intermediate is different. For example, for A, τ_2 (m/z 71) = 850 ± 50 fs and τ_2 (m/z 43) = 930 ± 50 fs.

The decay of the m/z 58 species is an order of magnitude different from that of the parent, which indicates that its origin is not from ion fragmentation of the parent. Accordingly, the 70–90 fs and 400–700 fs decay times, depending on the molecule, describe the two steps shown in Equation 1. Since the decay of the parent and the rise of the intermediate are similar, the hydrogen transfer, therefore, occurs in 70–90 fs. This is consistent with the time scale observed for intramolecular H-atom transfer (≈ 60 fs) observed in methyl salicylate.^[7]

Figure 2 depicts the reaction pathways of the 2-pentanone diradical intermediate formed after intramolecular hydrogen

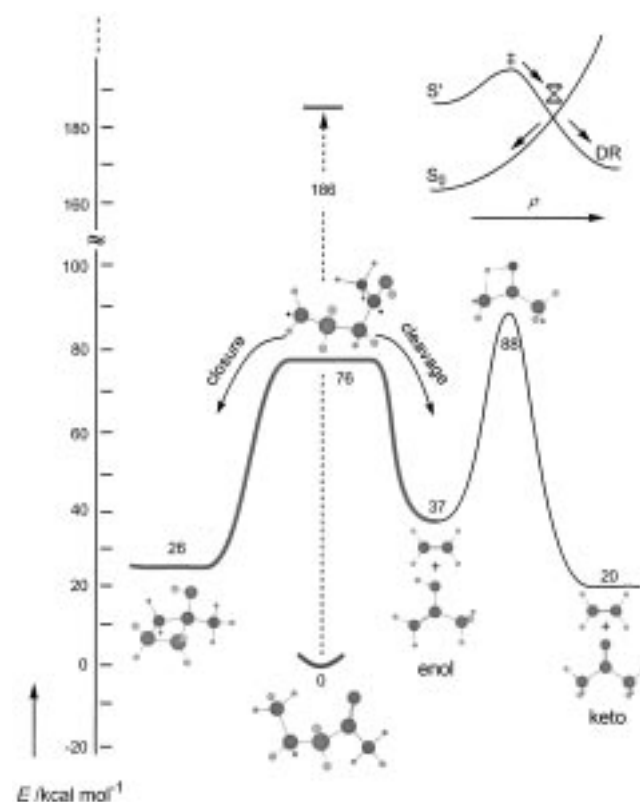
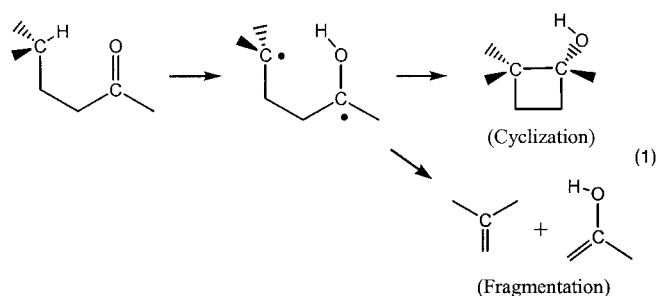


Figure 2. Ground-state potential-energy surface of 2-pentanone showing the possible reaction pathways of the diradical intermediate, which is formed after transfer of the hydrogen atom. The total experimental energy is also indicated.^[17] The structures and energies shown are from density functional theory calculations. The insert reflects the topology of the ground- and excited-state surfaces along the hydrogen transfer reaction coordinate (ρ , γ C–H distance, see text for further information).

transfer. The stationary points were calculated using the spin-unrestricted DFT method at the B3LYP/6-31G* level. As discussed elsewhere^[8, 9] the restricted method was used for all closed-shell species, whereas the unrestricted one was employed for open-shell species. Vibrational frequencies were calculated at the same level of theory in order to characterize the nature of the stationary points and to determine the zero-point energy correction. All calculations were carried out using the Gaussian package.^[10]

Our DFT calculations illuminate several points. First, the calculations show that the β C–C bond of the diradical intermediate is long (1.626 Å), that is, relatively weak. It is, therefore, anticipated that upon ionization the diradical species will easily undergo fragmentation to give the m/z 58 signal in the TOF mass spectrum. Second, once the diradical intermediate is formed, two reaction pathways are possible: the diradical can close the ring to form a cyclobutanol derivative, or it can break the C–C bond in the β position to yield an ethylene derivative and 2-propenol, the enol precursor of acetone [see Eq. (1)]. Third, the interconversion to the keto structure (acetone) involves a high energy barrier (Figure 2) and will not take place on these ultrafast time scales.



Although both cyclization and fragmentation are essentially barrierless (Figure 2), the cleavage of the diradical will be the dominant reaction channel as a consequence of entropy effects, that is, the conformational requirements for ring closure are more demanding than for fragmentation. The 1,4-diradical described above is similar to other diradicals, such as tetramethylene, studied in this laboratory.^[11] It is remarkable that the time scale for the decay is comparable (ca. 700 fs versus 400–700 fs) even though the precursors are entirely different. The entropic effects were shown to be very important; for tetramethylene, which forms ethylene and cyclobutane, fragmentation is a factor of two larger than cyclization.^[11b)]

The decay times (Figure 1) of the diradical intermediates show a systematic trend: the life time decreases with increasing number of alkyl substituents on the γ carbon atom. On the basis of the decrease in the γ C–H bond strength in going from 2-pentanone (98 kcal mol^{−1}) to 2-hexanone (94.5 kcal mol^{−1}), to 5-methyl-2-hexanone (92 kcal mol^{−1}),^[2b)] it is anticipated that the internal energy content of the diradical intermediates of 2-hexanone and 5-methyl-2-hexanone will be higher than in 2-pentanone,^[12] and hence result in somewhat faster dynamics. However, the change in bond energies is small and the potential of the diradical is essentially constant for small

energy changes to make a difference.^[11b)] Thus the increased number of degrees of freedom (18) when two methyl substituents are present and the increase in reaction rates suggest a highly nonstatistical behavior. Since the H-atom transfer is on the fs time scale, it is the reaction directionality that limits the phase space.

These intramolecular hydrogen transfer reactions, which are followed by cyclization or fragmentation, are quite common. In ion chemistry, the McLafferty rearrangement,^[13] as studied by mass spectrometry, is a direct analogue of Norrish type-II reactions. In fact, the electron impact mass spectra are very similar to our fs photoinduced mass spectra. Both the neutral channel (Norrish type-II reaction) and the ionic channel (McLafferty rearrangement: fragmentation of the parent ion) contribute to the overall m/z 58 signal. However, as discussed above, the fs resolution allows us to distinguish unambiguously between both processes: the contribution of the McLafferty rearrangement is reflected by a relatively short decay component, which, as expected, is identical to the neutral parent dynamics. On the other hand, the Norrish type-II reaction dynamics occur on the longer time scales reported in Figure 1. This observation is confirmed by the increase of the short decay component with increasing probe intensity. Moreover, the mass spectrum of 3-methyl-2-butanone, a structural isomer of 2-pentanone, lacks the m/z 58 peak, which is consistent with the fact that only ketones containing the γ C–H atom undergo the Norrish type-II reaction and McLafferty rearrangements, which are separated on the fs time scale.

Given the above experimental observations and theoretical studies, it is interesting to address the ultrafast population of the reaction intermediate (see insert Figure 2) and the nature of orbital correlations. The initial excitation of the ketones with a fs pulse populates a singlet excited surface (S'). Along the reaction coordinate (ρ), which involves the transfer of a γ -hydrogen atom, the molecule crosses a barrier. Based upon ab initio calculations of intermolecular hydrogen transfer reactions,^[14] it is suggested that intramolecular hydrogen transfer reactions of ketones also involve a conical intersection.^[15] The presence of such a conical intersection is consistent with the dominant deactivation path of excited ketones, that is, internal conversion to the ground state, and also with the ultrafast dynamics of the formation of the diradical reaction intermediate. The barrier on an adiabatic singlet excited surface (S') describes the hydrogen transfer when a C–H bond is broken and an O–H bond is formed, which is similar to the H-atom transfer process in malonaldehyde.^[16] Figure 3 gives a simple picture of orbital correlation, together with the calculated (DFT) highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).

In conclusion, this contribution reports the fs dynamics of the elementary steps in Norrish type-II reactions, elucidating the nature of hydrogen atom transfer and the intermediate diradical species that undergoes closure and fragmentation. The energetics are obtained by density functional theory. Only with fs resolution can one dissect the two nonconcerted steps, and examine differences in Norrish type-II and McLafferty rearrangements, which are common in neutral and ion chemistry.

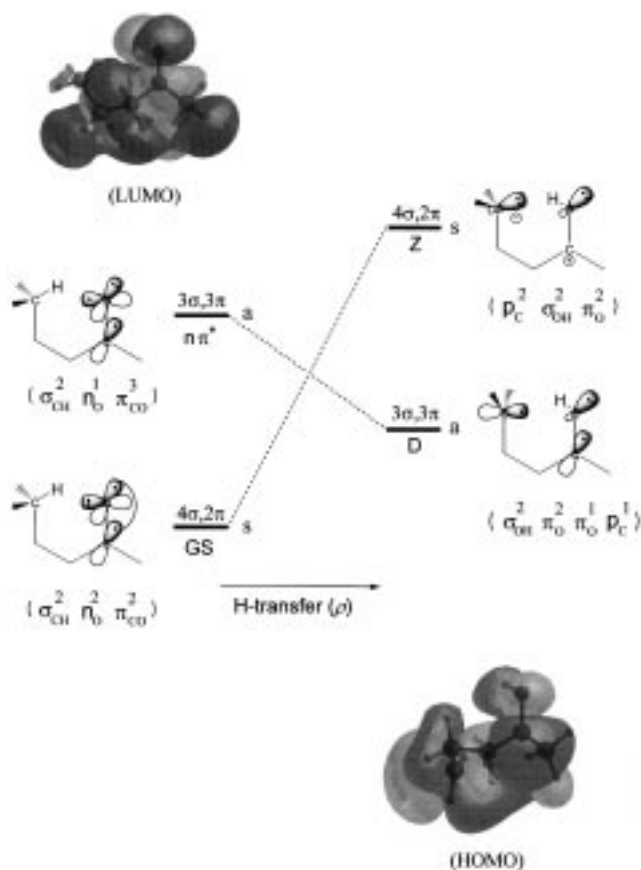


Figure 3. The HOMO and LUMO obtained from our density functional theory calculations, together with simple orbital correlations showing the direct formation of the diradical species. The correlation is with respect to the molecular plane of symmetry. Note that in the optimized geometry calculation of the HOMO and LUMO, this restriction is relaxed as the geometry is not planar.

Received: September 23, 1999 [Z14061]

- [1] a) R. G. W. Norrish, *Trans. Faraday Soc.* **1934**, 30, 103; b) E. K. C. Lee, R. S. Lewis, *Adv. Photochem.* **1980**, 12, 1; c) N. J. Turro, *Modern Molecular Photochemistry*, University Science Books, Sausalito, CA, **1991**, and references therein.
- [2] a) R. G. W. Norrish, *Trans. Faraday Soc.* **1937**, 33, 1521; b) P. J. Wagner, *Acc. Chem. Res.* **1971**, 4, 168, and references therein; c) J. C. Scaiano, *Acc. Chem. Res.* **1982**, 15, 252; d) M. V. Encina, E. A. Lissi, *J. Photochem.* **1975**, 4, 321; e) F. S. Wettack, W. A. Noyes, Jr., *J. Am. Chem. Soc.* **1968**, 90, 3901; f) F. S. Wettack, *J. Phys. Chem.* **1969**, 73, 1167; g) W. N. Nau, J. C. Scaiano, *J. Phys. Chem.* **1996**, 100, 11360, and references therein; h) M. Klessinger, J. Michl, *Excited states and photochemistry of organic molecules*, VCH, New York, **1995**, and references therein.
- [3] a) S. K. Kim, S. Pedersen, A. H. Zewail, *J. Chem. Phys.* **1995**, 103, 477; b) S. K. Kim, A. H. Zewail, *Chem. Phys. Lett.* **1996**, 250, 279; c) S. K. Kim, J. Guo, J. S. Baskin, A. H. Zewail, *J. Phys. Chem.* **1996**, 100, 9202.
- [4] a) S. A. Buzza, E. M. Snyder, D. A. Card, D. E. Folmer, A. W. Castleman, *J. Chem. Phys.* **1996**, 105, 7425; b) T. Shibata, H. Li, H. Katayanagi, T. Suzuki, *J. Phys. Chem. A* **1998**, 102, 3643; c) J. C. Owrtsky, A. P. Baronavski, *J. Chem. Phys.* **1998**, 108, 6652; d) Q. Zhong, L. Poth, A. W. Castleman, *J. Chem. Phys.* **1999**, 110, 192; e) J. C. Owrtsky, A. P. Baronavski, *J. Chem. Phys.* **1999**, 110, 11206.
- [5] A. H. Zewail, *Femtochemistry: Ultrafast Dynamics of the Chemical Bond, Vol. I and II*, World Scientific, Singapore, **1994**, and references therein.
- [6] Note that fragmentation of the parent ion contributes to the transient signal of the intermediate of 2-hexanone and 5-methyl-2-hexanone and this contribution has been accounted for in the fitting procedure.

- [7] J. L. Herek, S. Pedersen, L. Bañares, A. H. Zewail, *J. Chem. Phys.* **1992**, 97, 9046.
- [8] A. A. Scala, E. W.-G. Diau, Z. H. Kim, A. H. Zewail, *J. Chem. Phys.* **1998**, 108, 7933.
- [9] J. Andzelm, C. Sosa, R. A. Eades, *J. Phys. Chem.* **1993**, 97, 4664.
- [10] GAUSSIAN 94 & 98, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman et al., Gaussian Inc., Pittsburgh, **1998**.
- [11] a) S. Pedersen, J. L. Herek, A. H. Zewail, *Science* **1994**, 266, 1359; b) S. De Feyter, E. W.-G. Diau, A. A. Scala, A. H. Zewail, *Chem. Phys. Lett.* **1999**, 303, 249.
- [12] This trend in internal energy content has been confirmed by DFT calculations. The available internal energies of the diradical intermediates are 110, 113, and 116 kcal mol⁻¹ for 2-pentanone, 2-hexanone, and 5-methyl-2-hexanone, respectively.
- [13] a) F. W. McLafferty, *Anal. Chem.* **1956**, 28, 306; b) F. W. McLafferty, F. Turecek, *Interpretation of Mass Spectra*, University Science Books, Sausalito, CA, **1993**.
- [14] a) W. M. Nau, G. Greiner, J. Wall, H. Rau, M. Olivucci, M. A. Robb, *Angew. Chem.* **1998**, 110, 103–107; *Angew. Chem. Int. Ed.* **1998**, 37, 98; b) W. M. Nau, G. Greiner, H. Rau, M. Olivucci, M. A. Robb, *Ber. Bunsen Ges. Phys. Chem.* **1998**, 102, 486.
- [15] W. M. Nau, *Ber. Bunsen Ges. Phys. Chem.* **1998**, 102, 476.
- [16] a) A. L. Sobolewski, W. Domcke, *Chem. Phys. Lett.* **1999**, 300, 533; b) A. L. Sobolewski, W. Domcke, *J. Phys. Chem. A* **1999**, 103, 4494.
- [17] Our total energy (two photons) is similar to that used for acetone (186 kcal mol⁻¹), which leaves an available energy of 110 kcal mol⁻¹ for the diradical. Our absorption spectra of acetone and 2-hexanone (in hexane) are similar. We also measured the power dependence of the parent signal (for example, for 2-pentanone) and found (1.23 ± 0.02) resonant 2-photon behavior. It should be noted that quantum yield measurements only give the fraction of the wave packet population in the fluorescing configuration.^[18]
- [18] a) D. Zhong, E. W.-G. Diau, T. M. Bernhardt, S. De Feyter, J. D. Roberts, A. H. Zewail, *Chem. Phys. Lett.* **1998**, 298, 129; b) M. Chachisvilis, A. H. Zewail, *J. Phys. Chem. A* **1999**, 103, 7408. n0

An EPR Investigation of the Kinetics of Inclusion of a Persistent Radical in Water-Soluble Calix[4]arenes

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A voluminous literature reporting the synthesis and characterization of calixarenes behaving as highly selective receptors for metal cations and organic guest molecules has appeared during the last twenty years^[1]. These calixarenes are

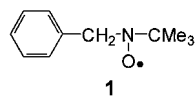
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[**] Financial support from CNR (Rome) and from MURST and the University of Bologna (research project "Free Radicals and Radical Ions in Chemical and Biological Processes") is gratefully acknowledged by M.L. and G.F.P. We also wish to thank Prof. R. Ungaro for helpful discussion.

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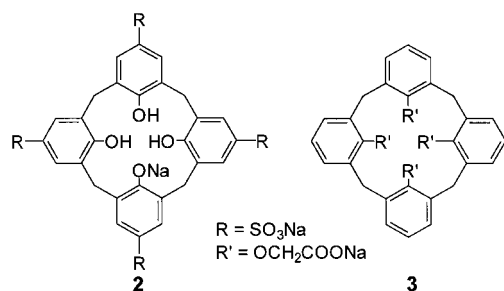
highly selective receptors for metal cations and organic guests. The earliest examples of water-soluble calixarenes were described in the mid 1980s by Ungaro and co-workers^[2] and by Shinkai and co-workers,^[3] while several additional examples have appeared more recently.^[4] The equilibration between host and guest entities in water is a dynamic process taking place at rates higher than the differences in the NMR frequencies. For this reason the experimental NMR spectra appear as averages of those from the free and complexed species, similar to what is observed with inclusion equilibria involving cyclodextrin hosts.^[5]

In contrast to NMR, EPR spectroscopy is characterized by a much faster time scale. When this technique is used to study the complexation of radical species by cyclodextrins (CDs), EPR spectra resulting from the superposition of separate signals from free and complexed species are usually observed.^[6–8] We have recently found that a radical probe particularly suitable for studying inclusion phenomena in aqueous solution by β -CDs is benzyl *tert*-butyl nitroxide (**1**).^[8, 9] The formation of an inclusion complex with this radical was manifested by large spectral changes arising both from the decrease of nitrogen hyperfine splitting, $a(\text{N})$, induced by the less polar environment of the β -CD host cavity, and from the



strongly reduced coupling of the benzylic protons, $a(2\text{H}_\beta)$, due to conformational changes occurring upon complexation. Thus, inclusion into the CD produced a considerable decrease in the overall splitting and significant differences in the resonance fields of the $M_1(2\text{H}_\beta) = \pm 1$ lines for the included and free species. The EPR spectra also showed a strong linewidth dependence on temperature, indicating that the lifetime of **1** in the associated and free form is comparable to the EPR time scale. Analysis of the EPR line shape enabled us to measure the rate constants for the association and dissociation processes.^[9]

Water-soluble calixarenes have been mainly employed to study the inclusion of charged organic species such as tetraalkylammonium cations^[1d, 10] or α -amino acids^[11]. Very little is known on their inclusion properties towards neutral aromatic guest species which, on the other hand, are easily complexed in the solid state.^[1] Here we report the use of benzyl *tert*-butyl nitroxide (**1**) to probe its inclusion in two water-soluble calixarenes—namely, pentasodium 25,26,27,28-tetrahydroxycalix[4]arene-5,11,17,23-tetrakisulfonate (**2**) and tetrasodium 25,26,27,28-tetrakis(carboxymethoxy)-calix[4]arene (**3**).^[12]—and to study the kinetics of the association/dissociation process by analyzing variations in the EPR line shape with temperature.



The EPR spectrum at 298 K of **1**, produced by oxidation of benzyl-*tert*-butylamine (1.0×10^{-3} M) with oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$; 4.8×10^{-4} M) in water, is shown in Figure 1a. The spectrum is easily interpreted on the basis of the coupling of the unpaired electron with the nitrogen nucleus and with

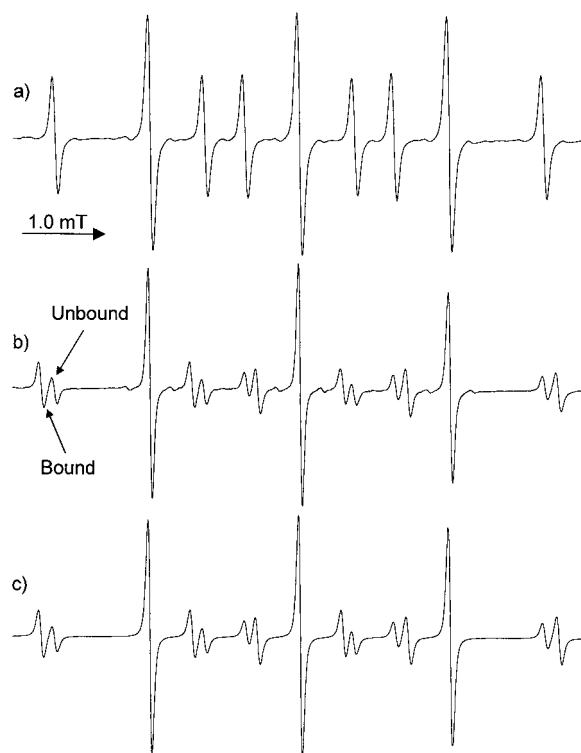
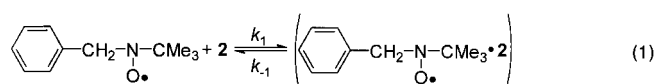


Figure 1. EPR spectra recorded at 294 K of nitroxide **1** (3×10^{-5} M) in water (a) and in water containing 0.1 M calix[4]arene **2** (b). The simulation (c) of spectrum b was performed by using the following data: free nitroxide (38 %, linewidth 0.023 mT, $a(9\text{H}) = 0.015$ mT, $a(\text{N}) = 1.669$ mT, $a(2\text{H}) = 1.064$ mT, $g = 2.0056$); included nitroxide (62 %, linewidth 0.026 mT, $a(9\text{H}) = 0.015$ mT, $a(\text{N}) = 1.686$ mT, $a(2\text{H}) = 1.211$ mT, $g = 2.0056$); rate constant for association $k_1 = 3.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ and for dissociation $k_{-1} = 2.6 \times 10^6 \text{ s}^{-1}$ [See Eq. (1)].

the two equivalent benzylic protons ($a(\text{N}) = 1.669$ mT, $a(2\text{H}) = 1.064$ mT, $g = 2.0056$). In the presence of calix[4]arene **2** (0.1 M), additional signals (Figure 1b) assigned to the radical included in the cavity of **2**, which is in equilibrium with the free nitroxide [Eq. (1)], were observed.



When the absolute concentration of **2** was increased, the ratio between included and free species varied linearly and, for values higher than 0.15 M, the spectrum of the complexed radical **1**, characterized by the spectroscopic parameters $a(\text{N}) = 1.686$ mT, $a(2\text{H}) = 1.211$ mT, and $g = 2.0056$, became dominant. The EPR results were consistent with the formation of 1:1 inclusion complexes of nitroxide **1** with calix[4]arene **2**.

The above-reported data indicate that the hyperfine splitting at nitrogen remains essentially unaffected, while that at

the benzylic protons increases upon inclusion. The similarity of the $a(\text{N})$ values for free and included **1** indicates that the NO group in the complexed radical is exposed to bulk water; it is therefore conceivable that the phenyl moiety is instead selectively bound to the calixarene cavity. On the other hand, the increased splitting of the benzylic proton signals^[13] suggests that inclusion into the calix[4]arene cavity is accompanied by a change either of the preferred conformation adopted by the radical or of the height of the barrier to the internal rotation of the phenyl group.

In the investigated range of temperatures (278–334 K), the EPR spectrum of **1** showed marked selective line-broadening, especially evident on the lines corresponding to $M_I(2\text{H}) = \pm 1$ (Figure 1 b). Such linewidth effects are due to modulation of the proton and, to a smaller extent, nitrogen hyperfine splittings, arising by exchange between the free and included nitroxide.^[9] The rate constants k_1 for the inclusion of **1** by calix[4]arene and k_{-1} for the dissociation of the resulting complex were determined at various temperatures by simulating the exchange-broadened EPR spectra by using well-established procedures^[15] based on the density matrix theory^[16] in the assumption of a two-jump model [see Eq. (1)]. Figure 1 shows, as an example, an experimental spectrum (b) and the corresponding computer simulation (c). The kinetics of the inclusion of **1** by calix[4]arene **2** in water were studied in the temperature range 278–334 K (Figure 2) and the resulting activation parameters $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are reported in Table 1.

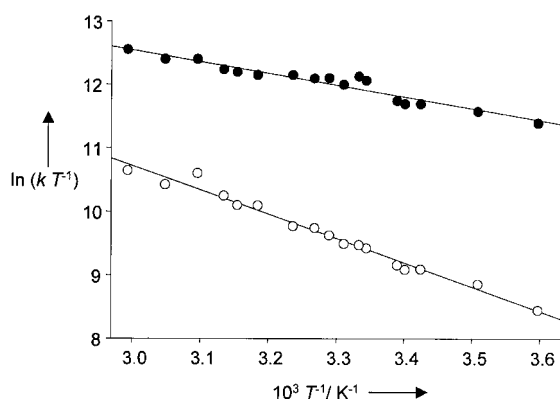


Figure 2. Plot of $\ln(k/T)$ vs. $1000/T$ for the association (●) and dissociation (○) rate constants for inclusion of radical **1** by calix[4]arene **2** in water.

A different behavior was observed when studying the inclusion of nitroxide **1** in calixarene **3**. Although the benzylic proton splittings showed significant variations upon addition of **3** ($a(2\text{H})$ decreased from 1.064 mT in water to 1.030 mT in a 0.14 M solution of **3**), it was not possible to detect separate signals from the free and bound nitroxide. This suggests that, in the present case, the time-averaged spectrum is observed;

this could be due either to fast rates of association and dissociation or to small differences in the spectroscopic parameters of the free and bound species.

An examination of the thermodynamic and kinetic parameters (Table 1) shows that the reaction enthalpy, $\Delta H^\ddagger$, for the inclusion process is negative ($-16.4 \text{ kJ mol}^{-1}$), suggesting that the driving force to complexation is the π – π stabilizing interaction between the phenyl ring of **1** and the aromatic system of the calixarene^[17] or a hydrophobic effect or both. However, the room-temperature value of the affinity constant is small (12.5 M^{-1}) because of the negative entropy of reaction ($-33.9 \text{ J mol}^{-1} \text{ K}^{-1}$) originating from the freezing of the translational degrees of freedom for the guest molecule. It also appears that the difference between the $\Delta S^\ddagger$ for association and ΔS° is small ($-13.4 \text{ J mol}^{-1} \text{ K}^{-1}$), while that between the corresponding enthalpic terms is quite large (31.7 kJ mol^{-1}). This suggests that in the transition state nitroxide and calix[4]arene are already so close that the solvent arrangement around the incipient complex is similar to that of the inclusion compound, rather than that of the separate host and guest molecules. From the large enthalpy of activation, it may be inferred that the phenyl ring of **1** is not yet deep enough inside the calixarene cavity to provide the stabilizing interaction between the guest and host π systems.

In conclusion, water-soluble calixarene hosts form inclusion complexes with the nitroxide radical **1**, the inclusion producing marked differences in the hyperfine splitting constants with respect to the free radical.^[18] The EPR spectra also showed selective line broadening effects due to the exchange between free and included nitroxide, which allowed us to measure, for the first time, the kinetic rate constants and the activation parameters for the inclusion of a neutral molecule in a calixarene host in water.^[19] Even if complementary techniques like UV, NMR, or fluorescence spectroscopy cannot be employed for our probe to check the data, the use of radical **1** for investigating the dynamics of calixarene host–guest interactions and to study structural and medium effects on it, has considerable potential in our view, and should be considered as another method for investigating the kinetics of complexation.^[20] Experiments are currently in progress to check the influence of changing the pH and of adding a cosolvent or inorganic salt on the equilibrium and activation parameters. Moreover, since chiral nitroxides bearing β -hydrogen atoms are readily accessible, the present study can be extended to chiral radical probes.

Experimental Section

Radical **1** was generated by mixing a solution of benzyl-*tert*-butylamine ($4.4 \times 10^{-2} \text{ M}$) in methanol (0.5 mL) and a solution containing oxone (Aldrich; $1.6 \times 10^{-2} \text{ M}$) in water (0.5 mL) with a solution containing variable amounts of calixarene (0.01–0.15 M) in water (20 mL). In all samples the

Table 1. Thermodynamic and kinetic parameters for the inclusion of nitroxide **1** by calix[4]arene **2** in water.

	$\Delta H^\ddagger$ ^[a] [kJ mol ⁻¹]	$\Delta S^\ddagger$ ^[a] [J mol ⁻¹ K ⁻¹]	K^{298} [M ⁻¹]	$\Delta H^\ddagger$ [kJ mol ⁻¹]	$\Delta S^\ddagger$ [J mol ⁻¹ K ⁻¹]	k^{298}
association	-16.4	-33.9	12.5	15.3 ± 2.1 ^[b]	-47.3 ± 7.1	$4.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$
dissociation				31.7 ± 2.3	-13.4 ± 7.5	$3.5 \times 10^6 \text{ s}^{-1}$

[a] Values derived from the measured activation parameters. [b] Errors correspond to twice standard deviations.

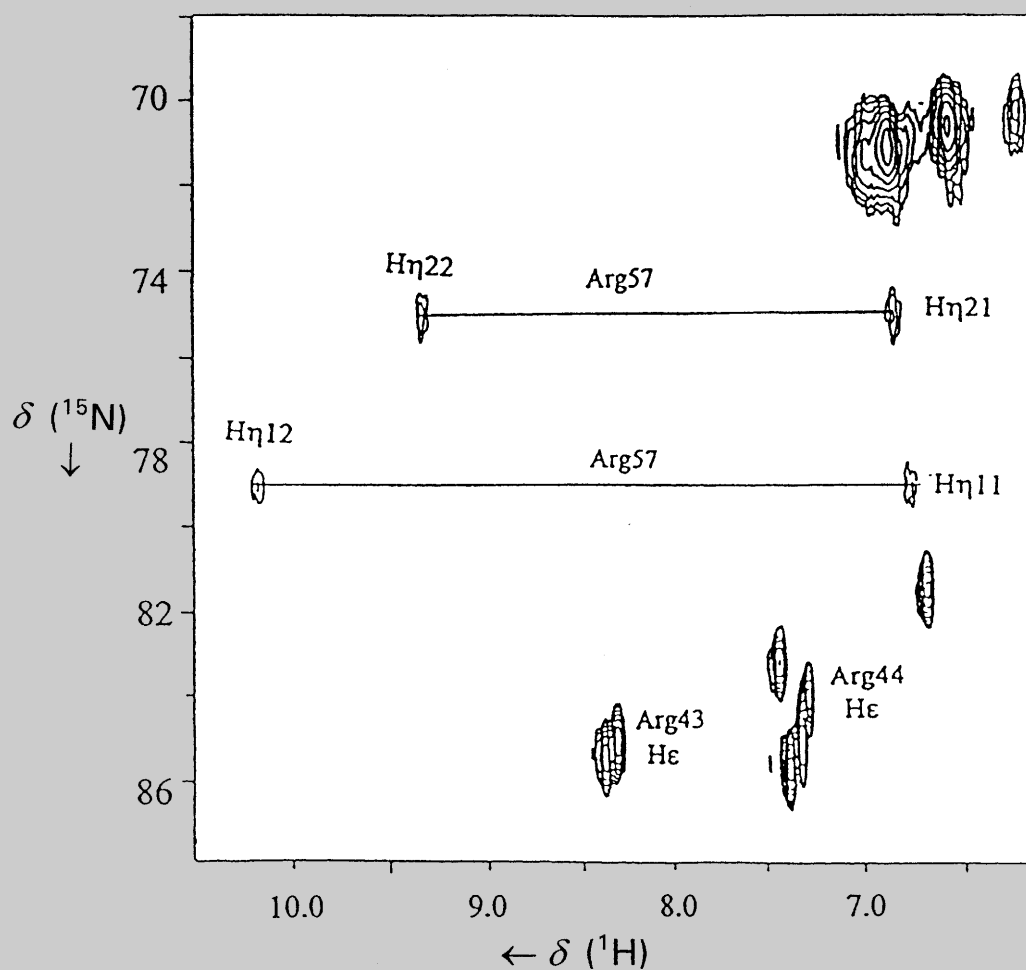
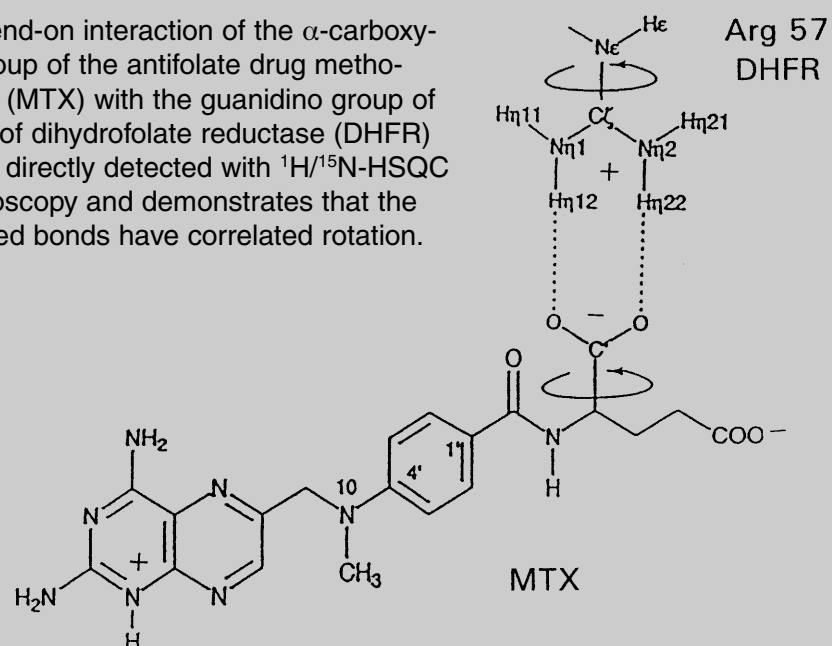
pH was adjusted to 7.4. Samples were then transferred in capillary tubes (1 mm inner diameter) and EPR spectra were recorded using a Bruker ESP300 spectrometer. The instrument settings were as follows: microwave power 5.0 mW, modulation amplitude 0.05 mT, modulation frequency 100 kHz, scan time 180 s. The computed spectra were best-fitted to the experimental ones using a Monte Carlo minimization procedure.^[9, 21] The input data for the minimization program were the number of nonequivalent nuclei, the hyperfine splitting constants of the free and included radical at each temperature, the intrinsic linewidth in the absence of exchange, and the rate constants for the exchange process.

Received: May 28, 1999

Revised: September 6, 1999 [Z134781E]

- [1] For examples, see: a) C. D. Gutsche in *Calixarenes Revisited*, The Royal Society of Chemistry, Cambridge, **1998**; b) A. Ikeda, S. Shinkai, *Chem. Rev.* **1997**, 97, 1713; c) V. Böhmer, *Angew. Chem.* **1995**, 107, 785; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 713; d) A. Pochini, R. Ungaro in *Comprehensive Supramolecular Chemistry*, Vol. 2 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, K. S. Suslik), Pergamon, Oxford, **1996**, p. 103.
- [2] A. Arduini, A. Pochini, S. Reverberi, R. Ungaro, *J. Chem. Soc. Chem. Commun.* **1984**, 981.
- [3] a) S. Shinkai, S. Mori, T. Tsubaki, T. Sone, O. Manabe, *Tetrahedron Lett.* **1984**, 25, 5315; b) S. Shinkai, S. Mori, H. Koreishi, T. Tsubaki, O. Manabe, *J. Am. Chem. Soc.* **1984**, 108, 2409.
- [4] a) S. G. Bott, A. W. Coleman, J. L. Atwood, *J. Am. Chem. Soc.* **1986**, 108, 1709; b) S. Shinkai, K. Araki, O. Manabe, *J. Am. Chem. Soc.* **1988**, 110, 7214; c) S. Shinkai, K. Araki, T. Matduda, N. Nishiyama, H. Ikeda, I. Takasu, M. Iwamoto, *J. Am. Chem. Soc.* **1990**, 112, 9053; d) H. J. Schneider, F. Werner, T. Blatter, *J. Phys. Org. Chem.* **1993**, 6, 588; e) L. Zhang, A. Macias, T. Lu, J. L. Gordon, G. W. Gokel, A. E. Kaifer, *J. Chem. Soc. Chem. Commun.* **1993**, 1017; f) A. Casnati, Y. Ting, D. Berti, M. Fabbì, A. Pochini, R. Ungaro, D. Sciotto, G. G. Lombardo, *Tetrahedron* **1993**, 49, 9815; g) B. L. Poh, C. W. Tan, *Tetrahedron* **1994**, 50, 3453; h) G. Arena, A. Casnati, L. Mirone, D. Sciotto, R. Ungaro, *Tetrahedron Lett.* **1997**, 38, 1999.
- [5] H. J. Schneider, F. Hacket, V. Rüdiger, *Chem. Rev.* **1998**, 98, 1755, and references therein.
- [6] a) J. Martinie, J. Michon, A. Rassat, *J. Am. Chem. Soc.* **1975**, 97, 1818; b) J. Michon, A. Rassat, *J. Am. Chem. Soc.* **1979**, 101, 995.
- [7] a) Y. Kotake, E. G. Janzen, *J. Am. Chem. Soc.* **1992**, 114, 2872; b) Y. Kotake, E. G. Janzen, *J. Am. Chem. Soc.* **1989**, 111, 7319; c) Y. Kotake, E. G. Janzen, *J. Am. Chem. Soc.* **1988**, 110, 3699.
- [8] M. Lucarini, B. P. Roberts, *Chem. Commun.* **1996**, 1577.
- [9] M. Lucarini, B. Luppi, G. F. Pedulli, B. P. Roberts, *Chem. Eur. J.* **1999**, 5, 2048.
- [10] G. Arena, A. Casnati, A. Contino, G. C. Lombardo, D. Sciotto, R. Ungaro, *Chem. Eur. J.* **1999**, 5, 738.
- [11] G. Arena, A. Contino, G. G. Gulino, A. Magrì, F. Sansone, D. Sciotto, R. Ungaro, *Tetrahedron Lett.* **1999**, 40, 1597.
- [12] Compounds **2** and **3** have been synthesized and purified according to the procedure described in reference [4f].
- [13] The magnitude of $a(2H_\beta)$ depends on the time-averaged value of $\cos^2\theta$, where θ is the dihedral angle between the N-C-H $_\beta$ bond and the symmetry axis of the 2p $_z$ orbital on nitrogen containing the unpaired electron.^[14] A larger value of the β -proton splitting in the inclusion compound indicates a decreased tendency of the phenyl group to lie, on average, in the eclipsed position. A more complete discussion about this point can be found in reference [9].
- [14] C. Heller, H. M. McConnell, *J. Chem. Phys.* **1960**, 32, 1535.
- [15] M. Guerra, G. F. Pedulli, M. Tiecco, G. Martelli, *J. Chem. Soc. Perkin Trans. 2* **1974**, 562.
- [16] a) J. H. Freed, G. K. Fraenkel, *J. Chem. Phys.* **1963**, 39, 326; b) A. Hudson, G. R. Luckhurst, *Chem. Rev.* **1969**, 69, 191.
- [17] C. A. Hunter, *Chem. Soc. Rev.* **1994**, 23, 101.
- [18] Other radical probes such as *tert*-butyl diphenylmethyl nitroxide (extensively used by Kotake and Janzen^[7] for studying inclusion phenomena with cyclodextrins) and the water-soluble nitroxide radical TEMPO choline (TEMPO=tetramethylpyrrolidene *N*-oxide), do not show any appreciable change in the hyperfine splitting constants upon addition of calix[4]arene **2** to aqueous solutions.
- [19] Examples of the determination of rate constants of inclusion of neutral molecule in organic solvents have been previously reported. See for instance: T. Szabo; G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, 120, 6193, and references therein.
- [20] M. H. Kleinman, C. Bohne in *Molecular and Supramolecular Photochemistry*, Vol. 1 (Eds.: V. Ramamurthy, K. S. Schanze), Marcel Dekker, New York, **1997**.
- [21] B. Kirste, *J. Magn. Reson.* **1987**, 73, 213.

The end-on interaction of the α -carboxylate group of the antifolate drug methotrexate (MTX) with the guanidino group of Arg57 of dihydrofolate reductase (DHFR) can be directly detected with $^1\text{H}/^{15}\text{N}$ -HSQC spectroscopy and demonstrates that the indicated bonds have correlated rotation.



NMR Studies of Ligand Binding to Dihydrofolate Reductase

James Feeney*

It is just 50 years since Farber and co-workers reported that remission of some childhood leukaemias could be achieved using the folate antagonist aminopterin. Earlier research in several laboratories had identified the antifolate properties of agents based on the 2,4-diaminopyrimidine structure—pioneering work that eventually led to the development of drugs such as trimethoprim (antibacterial) and pyrimethamine (antimalarial). The medical importance of this work was acknowledged in 1988 when Hitchings and Elion shared the Nobel Prize in Physiology and Medicine (with Black) in recognition of their work on inhibitors of purine and pyrimidine metabolism. The target enzyme for the antifolate drugs is dihydrofolate reductase (DHFR) and its discovery by Futterman in 1957 triggered an avalanche of

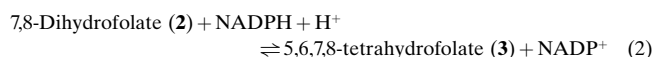
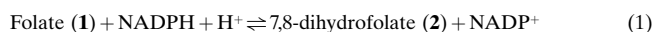
scientific investigations which has continued unabated to the present time. Complexes of DHFR with small molecules became early paradigms for studying drug–receptor interactions and received the attention not only of molecular pharmacologists and biochemists but also of chemists and physicists attracted by the possibility of carrying out investigations at a molecular level on a well-defined system of medical significance. After the discovery of the enzyme, many DHFRs from various sources were purified and subjected to detailed biochemical and biophysical investigation. More than 60 structures of DHFR complexes have now been determined by X-ray crystallography, many of them in the laboratories of Kraut and Matthews. These structures have allowed detailed discussions of the enzyme mechanism

and assisted in the building of structural models of DHFR complexes with novel inhibitors. More recently, NMR spectroscopy has been used to determine the structures of DHFR complexes in solution. The major strengths of the NMR technique have been its unique capabilities for probing specific interactions of enzymes with substrates and substrate analogues, for characterizing the multiple conformations of the complexes, and for measuring rates of a wide range of dynamic processes in these systems. Such studies on complexes of dihydrofolate reductase form the basis of this review.

Keywords: enzymes • NMR spectroscopy • protein dynamics • protein–ligand interactions • protein structures

1. Introduction

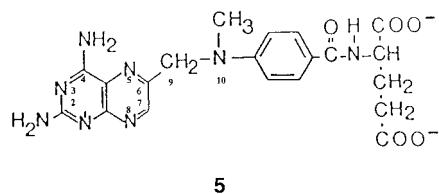
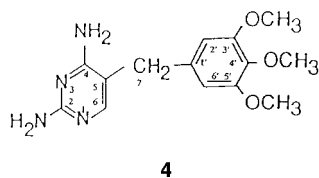
Currently there is a great deal of interest in investigating the molecular recognition processes involved in forming drug–receptor complexes. The driving force for such studies is the presumption that a molecular understanding of the origins of binding specificity might eventually provide a reliable basis for rational drug design. One of the most extensively studied systems is the enzyme dihydrofolate reductase (DHFR) and its interactions with antifolate drugs.^[1–27] This enzyme catalyzes the reduction of folate **1** and dihydrofolate **2** to tetrahydrofolate **3** [Eqs. (1, 2)].



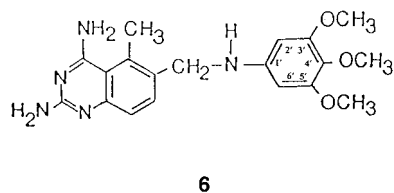
DHFR is an essential cellular enzyme since the final product of the catalysis, tetrahydrofolate, is an important precursor required in several biosynthetic processes involved in the production of purines, pyrimidines, and some amino acids.^[6] DHFR is thus an excellent target for drugs aimed at selectively inhibiting the enzyme in invasive cells. There are several clinically useful antifolate drugs including trimethoprim (**4**, antibacterial), methotrexate (**5**, anticancer), and pyrimethamine (**13**, antimalarial), which act by inhibiting the enzyme in parasitic or malignant cells. Trimethoprim, for example, is 16 500 times more effective as an inhibitor of the bacterial enzymes than the mammalian enzymes.^[5]

Dihydrofolate reductases are generally small proteins (18 000–25 000 Da in most species) and have no disulfide bonds nor metal ion requirements. A fascination with the

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enzyme has dominated the research activities of many scientists and several reviews^[5–12] have chronicled the progress in the field. Many modified DHFRs have been prepared by site-directed mutagenesis and have been studied in order to answer specific questions relating to enzyme catalysis or ligand binding.^[27–31] Extensive binding studies of inhibitors and coenzymes to DHFR from *Lactobacillus casei* have been carried out and examples of measured association constants (K_a values being measured at pH 6.5–7.0) for typical binary complexes are: methotrexate (**5**, $2 \times 10^9 \text{ M}^{-1}$), trimethoprim (**4**, $2 \times 10^7 \text{ M}^{-1}$), trimetrexate (**6**, $\sim 2 \times 10^8 \text{ M}^{-1}$), NADPH ($1 \times 10^8 \text{ M}^{-1}$), and NADP⁺ ($4.5 \times 10^4 \text{ M}^{-1}$).^[32–35]



The formation of the ternary complex with NADPH and a substrate analogue is often accompanied by cooperative (positive or negative) effects where the two ligands influence each others binding.^[34, 35] These effects can be large and influence the binding by as much as a factor of 2000 in some cases. Differences in the cooperative binding of ligands to enzymes from different species can sometimes contribute to the specificity of binding. For example, the specificity of the

binding of trimethoprim to the bacterial enzymes over the mammalian enzymes is partly a result of differences in the cooperativity of the binding with NADPH: the cooperativity factor of 200 observed for the binding to the bacterial enzymes is much reduced in complexes with mammalian enzymes.^[33] Since it is likely that the DHFR-NADPH-inhibitor ternary complex is the therapeutically relevant complex, these affects of the coenzyme on the binding specificity will be of considerable significance in drug design. Although DHFR has been studied comprehensively there are still many unanswered questions relating to the origins of the binding specificity and cooperativity.

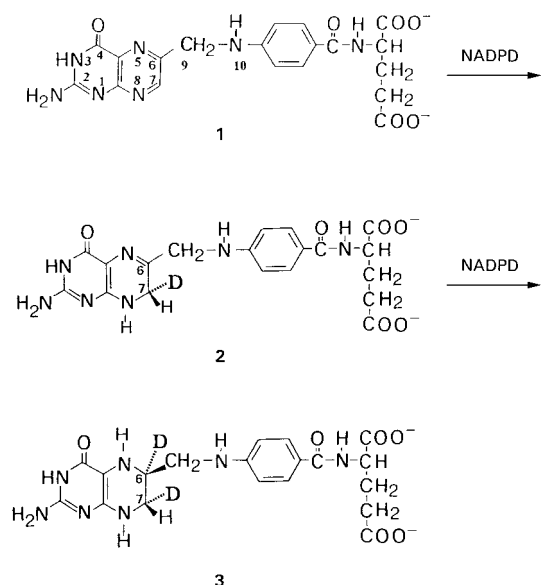
The structures of many DHFR complexes have been determined by X-ray crystallography^[13–16] and such structures have been used to assist in modeling structures of related ligand complexes of DHFR using quantum chemistry calculations.^[36, 37] In recent years advances in NMR methods have enabled structures of moderately-large proteins to be determined and structures of several dihydrofolate reductase complexes have now been reported.^[17–21] However, the major power of the NMR technique is its ability to provide information that is inaccessible by other methods. For example, NMR spectroscopy has proved to be an excellent method for probing specific protein–ligand interactions, multiple conformations, and dynamic processes in protein–ligand complexes.^[22–26]

2. Insights into the Mechanism of Dihydrofolate Reductase

DHFR reduces folate (**1**) first to 7,8-dihydrofolate and then to 5,6,7,8-tetrahydrofolate [Eqs. (1, 2)], with the folate reduction being 100 times slower than the subsequent reduction of 7,8-dihydrofolate in the reaction catalyzed by *L. casei*.^[38] The reduction of 7,8-dihydrofolate involves transfer of the 4-pro-*R* hydrogen atom of NADPH to the C6 position of dihydrofolate.^[39, 40] We have used NMR methods to determine the stereochemistry of this reduction process. For this, we prepared selectively deuterated 5,6,7,8-tetrahydrofolate by reducing folate with *L. casei* DHFR and NADPH specifically deuterated at its 4-pro-*R* position.



James Feeney was born in 1936 in St. Helens, England. He graduated from the University of Liverpool (BSc, 1958; PhD, 1960) and was awarded a DSc by the university in 1975. From 1960–1964 he was a Lecturer in Chemistry at the University of Liverpool. He then joined Varian Associates and subsequently was appointed Director of Varian European Laboratories (1967–1969) in Zurich. Since 1969 he has worked with the Medical Research Council, first at the MRC Molecular Pharmacology Unit, Cambridge (1969–1972) and then at the National Institute for Medical Research, Mill Hill (1972–present). Dr. Feeney is Head of the Molecular Structure Division (since 1989) and Controller of the MRC Biomedical NMR Centre (since 1980) at the National Institute for Medical Research. He is a Visiting Professor at the University of Surrey, a Fellow of the Royal Society of Chemistry, and has an Honorary Doctorate from the University of Roskilde, Denmark.



We then determined the sites of deuteration in the product by comparing the ^1H spectra of the deuterated and non-deuterated tetrahydrofolates. It could be shown that the deuterons which are transferred to the C6 and C7 positions are both added onto the same face of the pterin ring^[41, 42] (see structure **3**). The absolute configuration of the hydrogen atom at the 6-position of tetrahydrofolate was already known to be 6*S* from earlier X-ray crystallographic studies.^[43, 44] Thus, the NMR results for the enzymic deuteration of folate gave the configuration of the added proton at the 7-position as 7*S*, that is, on the same face as the one in the 6-position. In the X-ray structure of the complex of DHFR with methotrexate (**5**, MTX) and NADPH,^[13, 14] the “transferred” proton 4- H_R of NADPH is located near the opposite face of the MTX pteridine ring to that which receives the protons in the folate reduction.^[13, 14, 41–45]

Thus, although methotrexate (**5**) and folate (**1**) have similar structures, differing only at positions C4 and N10, the pteridine ring of **5** binds to DHFR in a different orientation to that of **1**^[41, 42] and 7,8-dihydrofolate.^[13, 43, 45] This behavior has been confirmed in subsequent X-ray^[16] and NMR structural studies,^[27, 46] where the pterin ring in the DHFR–folate complex was found to be turned over by about 180° relative to its orientation in the DHFR–MTX complex. The finding that such similar molecules can bind in very different ways emphasizes the value of carrying out detailed structural studies in evaluating inhibitor design.

The mechanism of protonation of N8 (for folate) and N5 (for dihydrofolate) as the first stage of each reduction step is still not fully understood. Selinsky and co-workers^[47] have examined binary complexes of bovine DHFR with folate and dihydrofolate (labeled with ^{15}N at N5 and ^{13}C at C6) and showed that N5 was not protonated in either of the complexes. Mutagenesis studies modifying Asp27 in *E. coli* DHFR have indirectly implicated this residue in the enzymatic reduction.^[31] Asp27 is the only residue with an ionizable group that is close to the active site (equivalent to Asp26 in *L. casei*

DHFR and Glu30 in human DHFR). The X-ray structure analysis^[16] indicates that this residue is not sufficiently close to either N8 or N5 to be involved in direct protonation. The oxygen atoms of the carboxyl group of the conserved Asp residue are hydrogen bonded to one of the protons in the 2- NH_2 group and to the N3 proton of folate.^[48, 49] Protonation schemes for N8 and N5 have been proposed in which the Asp residue promotes the formation of a protonated enolic form of the pteridine ring as an intermediate prior to reduction at N5 (Cannon and co-workers^[50] have carried out calculations that suggested that the substrate could form an enol tautomer). However, studies of binary complexes of ^{13}C - and ^{15}N -labeled folates show that bound folate exists in the keto form for human and bacterial enzymes.^[46–49] Blakley et al.^[49] have also shown that N3 remains protonated even at pH 9.5 in the folate complex with human DHFR. They noted the predominance of the imino–keto form of bound folate and concluded that protonation schemes involving the enolic forms are unlikely to be correct. Blakley and co-workers^[49] detected no change in the ionization state of the Glu30 carboxylate group over the pH range 5 to 7 in the binary complex of folate with human DHFR and they concluded that ionization of Glu30 is unlikely to be the origin of the observed pH dependence of hydride transfer (apparent $\text{pK} \approx 6.0$).

Similar results were found for the equivalent Asp26 in the complex of *L. casei* DHFR with folate.^[51] Oefner and co-workers^[16] detected a bound water molecule near to N5 in their crystal structure studies of the complex of human DHFR with folate and suggested that this water molecule is a likely candidate for mediating a proton transfer to N5. A similar water molecule has been detected in X-ray^[14] and NMR studies^[54] of the *L. casei* DHFR–MTX–NADPH complex (water molecule 253 shown in Figure 1) and also in NMR studies of human DHFR complexes.^[55] The detection of this long-lived water molecule in solution supports its possible involvement in the proton transfer to N5 of dihydrofolate. A major complication of all these NMR studies is that none of the data has been obtained on the relevant ternary complex containing the substrate and NADPH but rather on related complexes.

Benkovic et al.^[28, 29, 56, 57] and Blakley et al.^[58] have also carried out extensive kinetic studies on several DHFRs. For example, Andrews, Benkovic, and co-workers^[56] have shown that for the *L. casei* enzyme, the dissociation of the product is the rate-limiting step for the steady-state turnover at low pH values. The product, tetrahydrofolate, only dissociates from the enzyme after NADP^+ is replaced by NADPH.

3. Signal Assignments and Nuclear Overhauser Effects

3.1. Assignment of the NMR Signals of the Protein

Multidimensional NMR methods^[59, 60] have been used in combination with isotopically labeled proteins to obtain complete signal assignments for several complexes of DHFR from bacterial^[52, 61–63] and mammalian species.^[21, 53] In our own

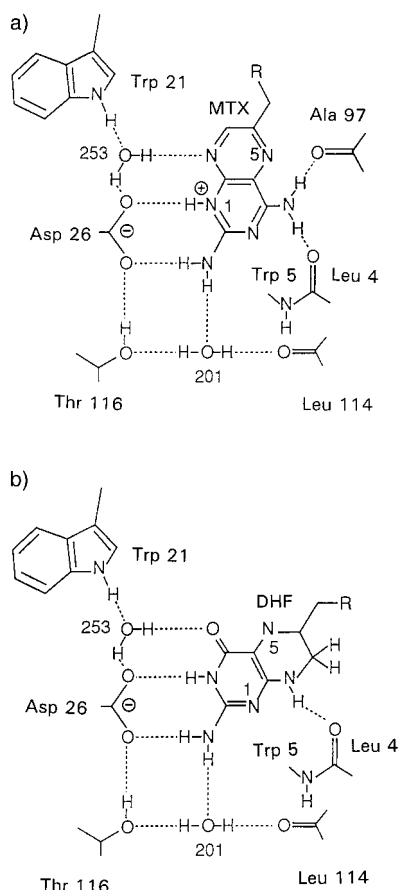
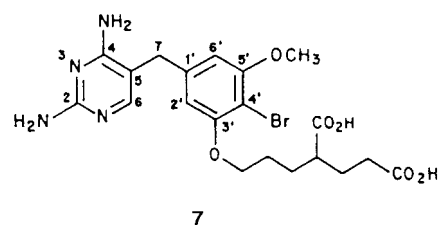


Figure 1. Schematic diagrams showing the location of water molecules 201 and 253 in the a) methotrexate binding site of the *L. casei* DHFR-MTX-NADPH complex as determined by X-ray crystallography^[14] and b) proposed dihydrofolate (DHF) binding site (from Bolin et al.).^[14] Trp 5 has been incorporated into the original figure from Bolin et al.^[14] (Reprinted with permission from Bolin et al.^[4])

NMR studies of complexes of *L. casei* DHFR with **4–7**, the assignments were obtained^[17–20, 61, 62] using samples containing ¹⁵N and ¹³C/¹⁵N uniformly labeled DHFR and specifically labeled ligands.^[61, 62] The availability of over-expressing *E. coli* strains containing the *L. casei* DHFR gene simplifies the preparation of isotopically labeled proteins.^[64] The sequential assignments of the backbone resonances were assigned from 3D TOCSY-HMQC, NOESY-HMQC,^[65] HMQC-NOESY-HMQC,^[66–68] HNCA,^[69] HNHA,^[70] and HNHB experiments,^[71] while 3D ¹³C/¹H HCCH-COSY and HCCH-TOCSY^[72, 73] experiments enabled most of the side-chain resonances to be assigned for the complex with methotrexate (an example of the latter is shown in Figure 2). Once the detailed assignments had been made for the complex of DHFR with methotrexate, it was rela-



tively easy to transfer the assignments to related complexes because of the similarities in the connectivity patterns seen in the 2D spectra of the different complexes.

In the days before the NMR methods for making sequential assignments were available, assignments were often made by using NOE measurements to correlate and assign resonances from nuclei that were close to each other in the crystal structure of the complex.^[76] This method assumes that the solution and crystal structures are similar. Many of the early assignments for complexes of *L. casei* DHFR were made in this way, and they all proved to be in complete agreement with the NMR sequential assignments made subsequently.^[61, 62, 76] The assignment method based on crystal structure information is still a useful approach for very large proteins (> 50 kDa) where scalar coupling correlations between nuclei are difficult to detect.

Selective isotopic labeling of DHFR has been used to simplify spectra and assist in spectral assignments. Several selectively deuterated *L. casei* DHFRs were prepared by biosynthetic incorporation of deuterated amino acids; by comparing spectra of the nondeuterated and selectively deuterated samples, it was possible to detect and assign those ¹H signals which are present in the former and absent in the latter.^[77–82] By examining 2D COSY spectra from DHFR-containing γ -Me-deuterated valine^[78, 79] and α -deuterated valine,^[80] it was possible to assign the signals for the protons normally at the deuterated sites. We have prepared *L. casei* DHFR containing (2S,4R)-[5,5,5-²H₃]leucine^[81] and have made stereospecific assignments for Leu methyl groups by examining the ¹H COSY spectra of the deuterated and nondeuterated samples (see Figure 3).

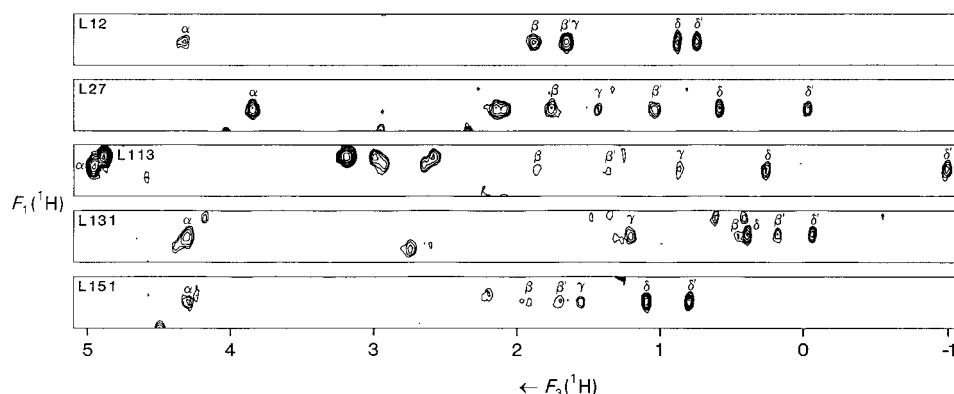


Figure 2. Representative F_1/F_3 strips from the HCCH-TOCSY spectrum of the DHFR-MTX complex taken at the α -carbon shifts (F_2) of five leucine residues. The spectra can be considered as a series of 2D TOCSY^[74, 75] slices ($^1\text{H}(F_1)/^1\text{H}(F_3)$) at different ¹³C chemical shifts (F_2). The labeled cross-peaks are typical of the through-bond correlations seen for the α -protons (F_1) of all 13 leucine residues in DHFR. (Reprinted with permission from Soteriou et al.^[62])

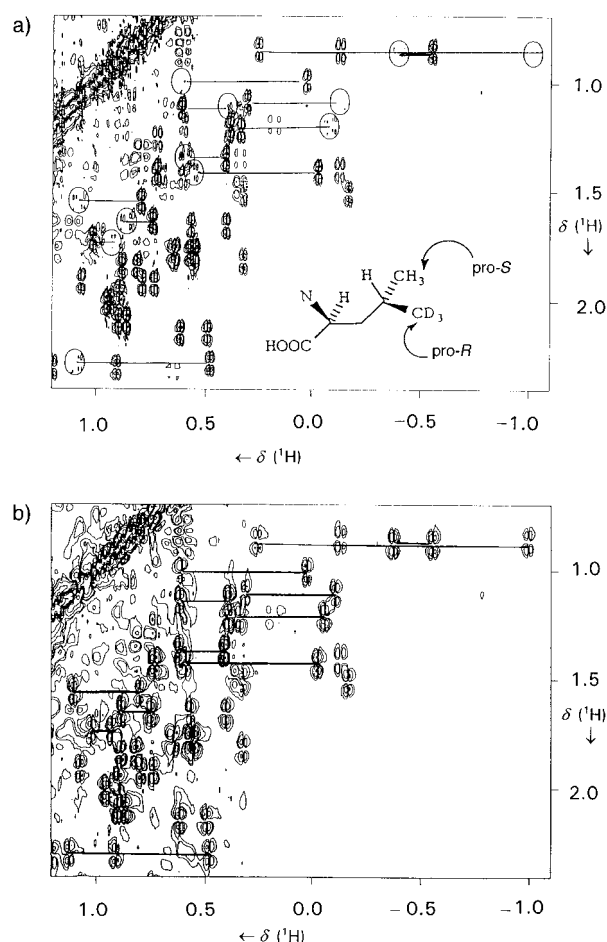


Figure 3. The high-field “aliphatic” region of the 2D DQF-COSY ^1H contour plot for the *L. casei* DHFR–MTX complex recorded at 308 K. a) The complex of the selectively deuterated enzyme incorporating (2*S*,4*R*)-[5,5,5- $^2\text{H}_3$]leucine; b) the complex with the nondeuterated enzyme. The positions of the leucine cross-peaks involving the 4-*pro-R* methyl group are circled in (a) and the methyl pairs from each leucine are joined with lines. (Reprinted with permission from Ostler et al.^[81])

In some experiments, *L. casei* DHFR samples containing several deuterated amino acids were examined.^[79, 82] This is a particularly useful approach for examining aromatic amino acid signals and their NOE connections. The spectrum shown in Figure 4 illustrates the considerable simplification that can be obtained. Spectral simplification can also be achieved by using photochemical CIDNP experiments (CIDNP = chemically induced dynamic nuclear (spin) polarization) experiments to enhance signals from surface-accessible aromatic residues in complexes of DHFR with inhibitors.^[83]

Various ^{13}C - and ^{19}F -containing amino acids have been biosynthetically incorporated into the enzyme and NMR measurements then used to study the effects of ligand binding.^[84–86] A remarkable result was obtained for *L. casei* DHFR containing 6-*F*-Trp, where the fluorine substituents in two of the Trp residues (Trp5 and Trp133) are in sufficiently close proximity to show a through-space ^{19}F - ^{19}F scalar spin–spin coupling.^[84]

3.2. Assignment of the NMR Signals of the Ligands

Ligand nuclei are obviously well placed to provide direct information about the binding site in the complex. Assignments of ligand resonances are crucial for detailed structural studies because they are the starting point for collecting the intermolecular protein–ligand NOEs required for determining distance restraints. For weakly binding ligands ($K_a \leq 10^3 \text{ M}^{-1}$) that show fast exchange behavior between bound and free species the chemical shifts of the bound ligand can easily be calculated from the analysis of the binding curves.^[87, 88] Very tightly bound ligands ($K_a > 10^7 \text{ M}^{-1}$) show slow exchange behavior and give separate signals for the bound and free ligand. These are often assigned by examining isotopically labeled analogues in combination with various experimental procedures. In the simplest experiments the

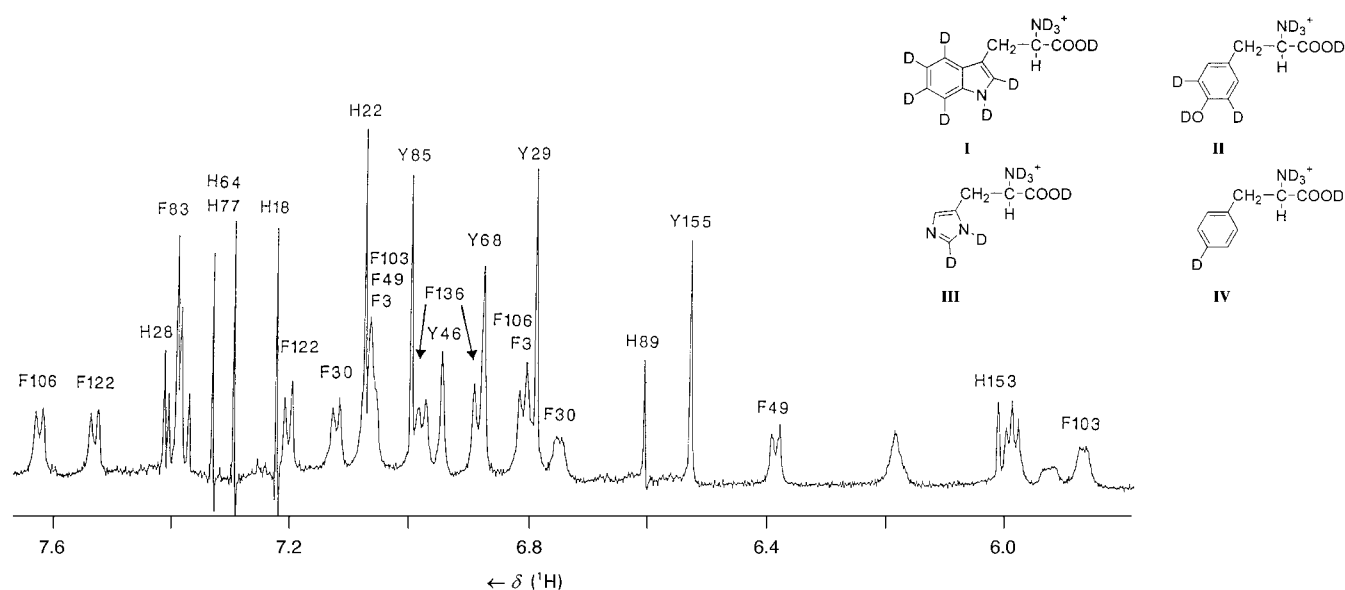


Figure 4. The aromatic region of the resolution-enhanced ^1H spectrum of a selectively deuterated *L. casei* dihydrofolate reductase-methotrexate complex recorded at 600 MHz. The selectively deuterated aromatic amino acids I–IV were incorporated into the DHFR sample. (Reprinted with permission from Birdsall et al.^[82])

complexes formed with the labeled ligands can be examined directly using ^{15}N or ^{13}C NMR spectroscopy: only signals from nuclei at labeled positions are observed and thus the assignment problem is usually trivial. Several studies of this type have been carried out in our laboratory involving isotopically labeled folate,^[89, 90] methotrexate (**5**),^[91] and trimethoprim (**4**).^[92–94] Blakley and co-workers^[49] have also used this approach to examine isotopically labeled folate (**1**) bound to human DHFR and Huang and co-workers have likewise studied *E. coli* DHFR complexes containing labeled **1** and **4**.^[95, 96] Isotope editing or filtering pulse sequences can also be used. Heteronuclear multiple (and single) quantum coherence (HMQC and HSQC) experiments allow the scalar coupled $^1\text{H}/\text{X}$ pairs to be detected selectively (each characterized by both the ^1H and $^{13}\text{C}/^{15}\text{N}$ frequencies, the X nuclei being detected indirectly by the ^1H nucleus).^[97, 98]

For complexes formed with less tightly binding ligands ($K_a \approx 10^6 \text{ M}^{-1}$), the dissociation rates can be sufficiently fast to allow magnetization transfer experiments to connect the separate resonances seen for the bound and free species. Because the assignments in the free ligand are usually known with certainty, the assignments of the connected signals from the bound species can then be made. We have used transfer of magnetization methods to assign signals from NADP⁺,^[100] trimethoprim (**4**),^[101] folate (**1**),^[32, 101] and pyrimethamine^[102] analogues bound to *L. casei* DHFR. During the course of these studies the first transferred NOE experiments for determining intramolecular NOEs in bound ligands were carried out.^[103, 104] In this method cross relaxation (NOE) between two protons in the bound ligand is transferred to the free molecule by exchange between bound and free species. The negative NOEs from the bound state can thus be detected from experiments on the signals of the free ligand in slow exchange with bound species (Figure 5) or on the averaged signals for free and bound ligands when in fast exchange. These NOEs can then be used to determine the conformation of the bound ligand.^[103] Quantitative results are best obtained for systems in fast exchange where the exchange rates are much faster than the relaxation rate of the free proton.^[105]

DHFR complexes formed with ligands containing isotopes such as ^3H , ^{19}F , and ^{31}P have also been examined.^[102, 106–110] For example, ^{19}F NMR has been used to examine complexes of *L. casei* DHFR formed with fluorine-containing pyrimethamines; their simple ^{19}F spectra are ideal for monitoring multiple conformations and dynamic processes in the complexes (see Section 8 on multiple conformations).^[102, 107, 110]

3.3. Ligand–Protein NOE Measurements

Isotope editing experiments, as pioneered by Fesik and co-workers^[97] as well as Otting and Wüthrich,^[146] can be used to assign protein–ligand NOEs. For example, 2D HMQC–NOESY experiments can be used for measuring NOEs from the isotopically labeled ligand to the protein. The 3D NOESY–HMQC experiment is a powerful extension of this approach that allows selective detection of NOEs between ligand protons (attached to ^{13}C or ^{15}N) and neighboring protons in the protein, with the observed NOESY cross-peaks

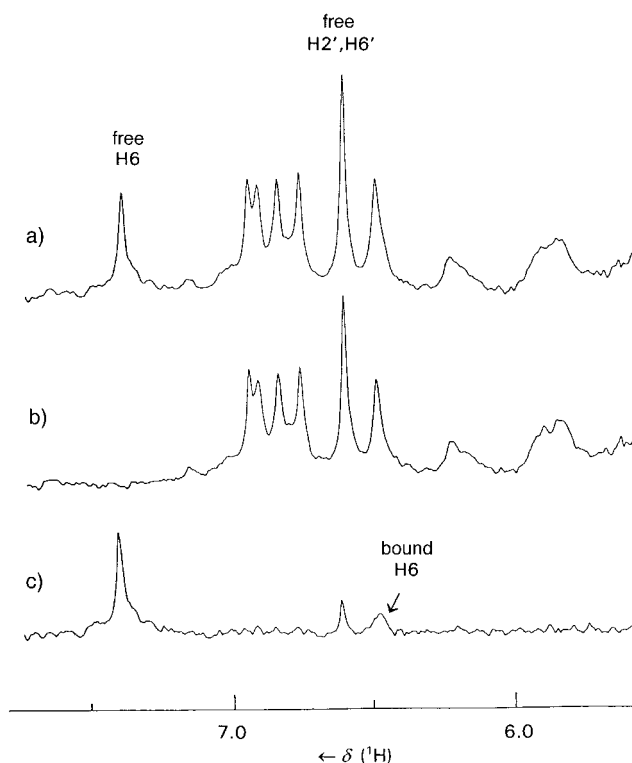


Figure 5. The aromatic region of the 270 MHz ^1H spectrum at 319 K of a selectively deuterated DHFR in the presence of 2.7 equivalents of trimethoprim (**4**). a) Control spectrum without irradiation. b) Spectrum after irradiation at the H6 proton frequency of free trimethoprim. c) Difference spectrum showing a negative NOE to the free H2',H6' signal (at $\delta = 6.61$) and a transfer of magnetization to the bound H6 signal (at $\delta \sim 6.5$). Transferred NOEs^[103, 104] are observed between the H6 and the H2',H6' protons of free trimethoprim in the presence of trimethoprim bound to *L. casei* DHFR: the negative NOEs observed in (b) and (c) on the free H2',H6' signal on irradiation of the free H6 signal are transferred by an exchange of magnetization between bound and free trimethoprim and reflect the negative NOEs between these protons in the bound species. (Reprinted with permission from Cayley et al.^[104])

being dispersed over the chemical shift of the X nucleus. This method considerably simplifies the NOESY spectrum at any particular X frequency and is very useful for examining protein complexes where parts of the 2D NOESY spectrum can suffer from problems of signal overlap.^[98] Using these 2D and 3D approaches we have also examined complexes of *L. casei* DHFR with trimethoprim (**4**) labeled at the [1,3,2-amino- ^{15}N] or [7,4'-OCH $_3$ - ^{13}C] positions,^[17] and have defined details of the trimethoprim binding site from the measured NOEs. The ^{15}N -edited NOEs detected in the 2D HMQC–NOESY $^1\text{H}/^{15}\text{N}$ spectrum of the former complex are shown in Figure 6.^[17]

$^{12}\text{C}/^{13}\text{C}$ -filtered 2D NOESY experiments also provide a means for detecting NOEs from protons in an unlabeled ligand to protons attached to ^{13}C in a ^{13}C -labeled protein: Figure 7 shows the ligand–protein NOE connections involving the N10-CH $_3$ group and the α -CH protons of unlabeled methotrexate bound to ^{13}C -labeled *L. casei* DHFR.^[19] All NOEs between protons attached to ^{13}C have been rejected. Similar experiments using $^{14}\text{N}/^{15}\text{N}$ -filtered NOESY sequences have been used to detect NOEs between NH protons in unlabeled ligands and protons in ^{15}N -labeled DHFR.^[99]

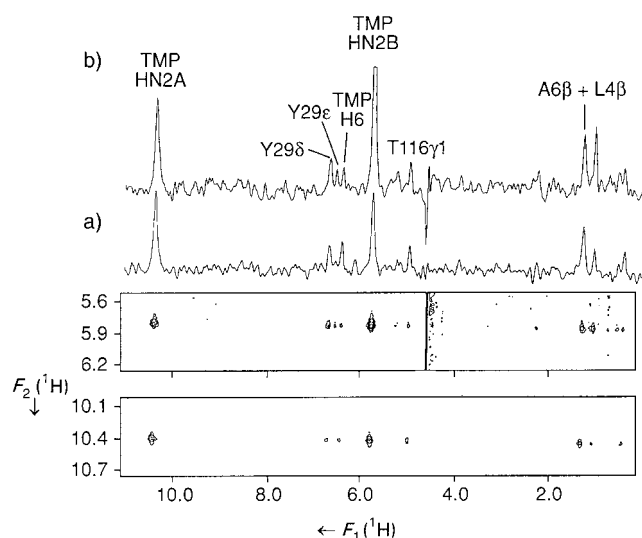


Figure 6. Part of the spectrum from an ^{15}N -edited 2D NOESY experiment on the complex of *L. casei* DHFR with [1,3,2-amino- ^{15}N]trimethoprim (edited at a ^{15}N frequency of $\delta = 59.6$ from external NH_4Cl). The upper traces are the rows at the frequencies of the HN2A and HN2B protons showing both intramolecular NOEs and intermolecular NOEs. (Reprinted with permission from Martorell et al.^[17])

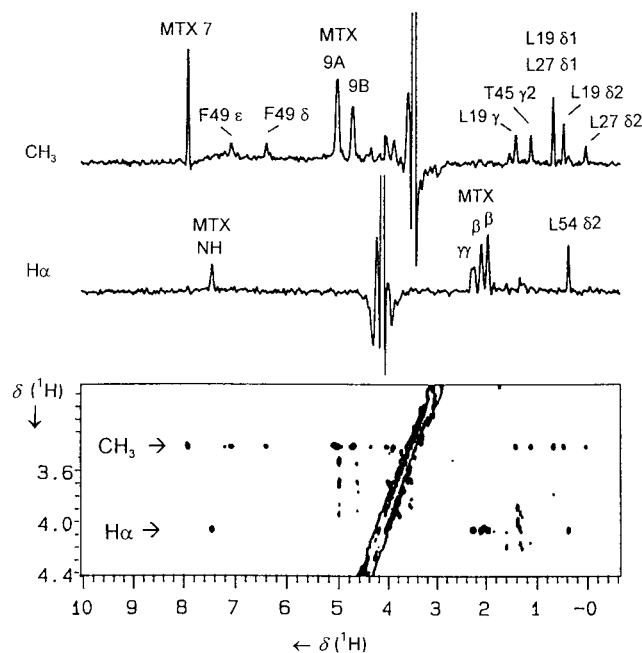


Figure 7. Part of the $^{12}\text{C}/^{13}\text{C}$ -filtered 2D NOESY spectrum acquired with a sample containing unlabeled methotrexate and ^{13}C -labeled *L. casei* dihydrofolate reductase (at 308 K and pH 6.5) showing the NOEs involving the methotrexate N10- CH_3 and $\text{H}\alpha$ protons. (Reprinted with permission from Gargaro et al.^[19])

Figure 8 shows the extensive set of ligand–protein NOEs determined for **5** in its complex with *L. casei* DHFR.

For nonlabeled ligands it is sometimes possible to take advantage of dynamic processes within the bound ligand to assist in making protein–ligand NOE assignments. Several NOEs were obtained with this novel approach by monitoring the effects of temperature on NOE signals that result from dynamic processes in trimethoprim (**4**) bound to DHFR.^[20] At 278 K the trimethoxy ring of bound trimethoprim is flipping

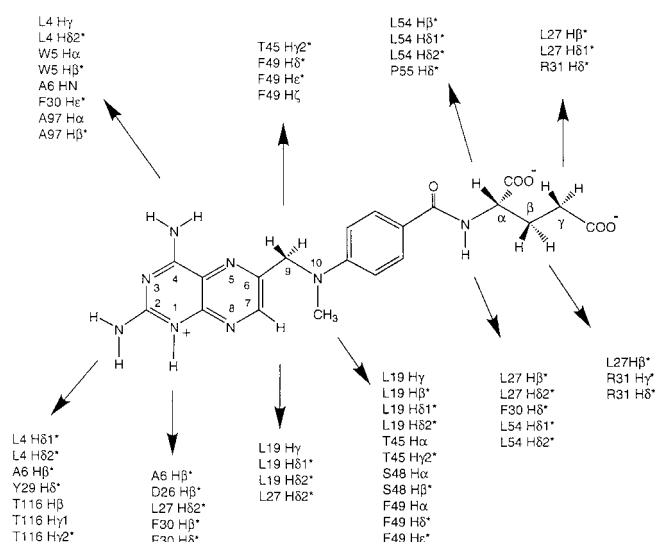


Figure 8. Intermolecular protein–ligand NOEs in the DHFR–methotrexate complex. (Reprinted with permission from Gargaro et al.^[19])

sufficiently slowly to give separate narrow signals for the 3'- and 5'- OCH_3 groups in slow exchange and these give good NOE cross-peaks to protein signals. At higher temperatures the ligand signals broaden because of the increase in flip rate and their NOE cross-peaks disappear, thus allowing the corresponding signals that are observed only in the lower temperature spectrum to be identified as NOEs involving ligand protons.

4. Structure Determinations of DHFR Complexes

In recent years NMR has become a powerful method for determining the structures of proteins in solution.^[59, 111] Once the signal assignments are known it is possible to extract the NOE and coupling constant information from the NMR spectra and to use these to obtain a list of proton–proton distance and angle constraints. Simulated annealing molecular dynamics calculations can then be used to obtain models of protein structures consistent with these constraints.^[112, 113]

We have used these methods to determine the three-dimensional structures of complexes of inhibitors **4–7** with *L. casei* DHFR.^[17–20] Stereospecific assignments and torsion angle constraints were deduced from NOE and coupling constant data using the program AngleSearch.^[114] Several ^{13}C and ^{15}N analogues of trimethoprim (**4**) and methotrexate (**5**) were used to obtain the isotope-edited or isotope-filtered spectra required for defining the protein–ligand NOEs. The structures of the complexes were determined using either conventional simulated annealing molecular dynamics calculations or by using various docking methodologies. For example, the three-dimensional solution structure of the complex of *L. casei* DHFR with the anticancer drug methotrexate (**5**)^[19] was determined using 2531 distance, 361 dihedral angle, and 48 hydrogen bond restraints obtained from analysis of multidimensional NMR spectra. Simulated annealing calculations produced a well-defined family of structures fully consistent with the constraints (Figure 9a).

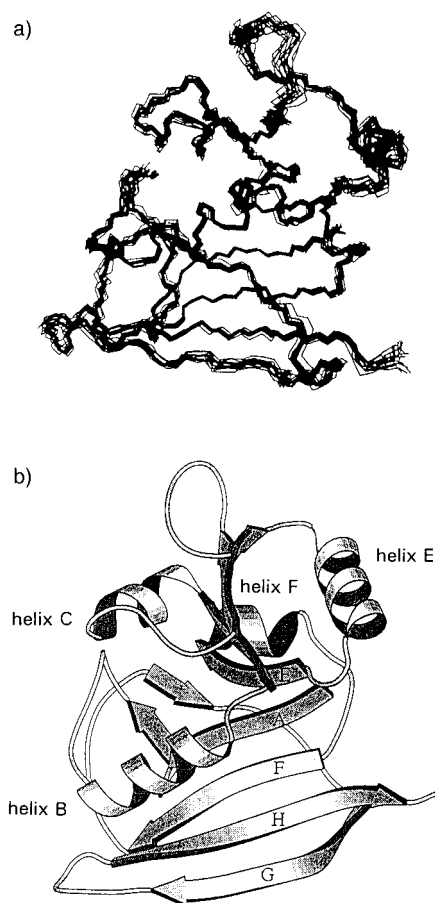


Figure 9. a) Superposition of the backbone atoms of residues 1–162 from the final 21 energy-minimized structures of the *L. casei* DHFR–methotrexate complexes.^[19] b) MOLSCRIPT diagram^[172] of the representative structure of this complex showing the elements of secondary structure. The representative structure is the one closest to the average structure. (Reprinted with permission from Gargaro et al.^[19])

The structure has four α -helices as well as eight β -strands with two other regions, comprising residues 11–14 and 126–127, which also interact with each other in a β -sheet manner (Figure 9b). The overall fold of the binary complex in solution is very similar to that observed in the X-ray studies of the ternary complex of *L. casei* DHFR formed with methotrexate (5) and NADPH^[14] (Figure 10).

To obtain high quality structures of the ligand binding site region it is necessary to have a large number of protein–ligand distance constraints (see Figure 8). In earlier simulation studies^[115] using NMR-type distance constraints (classified as strong, medium, and weak) extracted from an X-ray structure of folate bound to human DHFR,^[16] we found that molecules of this type require at least 50 ligand–protein distance constraints to produce acceptable structures. In the case of the binding site determined for methotrexate (5), the pteridine ring part is very well-defined (see Figure 10), but the structure around the glutamate moiety needed to be improved by including restraints reflecting the previously determined^[116, 117] specific interactions between the glutamate α -carboxylate group with Arg57 and the γ -carboxylate group with His28 (see Section 5). The NADPH binding site appears to be essentially preformed in the binary complex and this

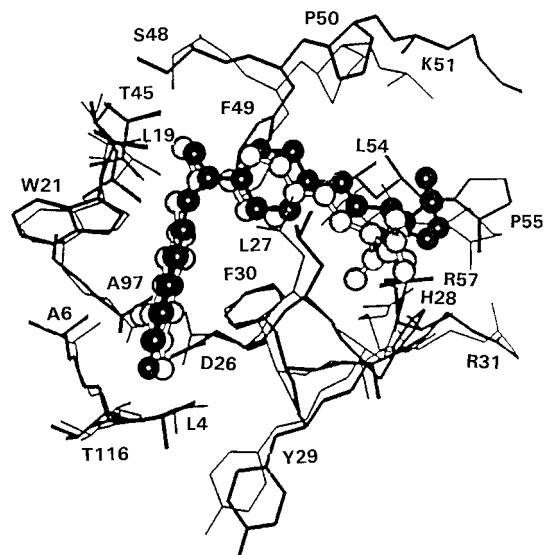


Figure 10. A comparison of the methotrexate binding site in the NMR-determined solution structure (dark lines) in the *L. casei* DHFR–methotrexate structure with that in the crystal structure (light lines) of the ternary complex DHFR–methotrexate–NADPH (crystal data from Bolin et al.).^[14] (Reprinted with permission from Gargaro et al.^[19])

may contribute to the tighter binding of the coenzyme in the presence of methotrexate since no major conformational change is required when NADPH binds to the binary complex.

Structures of other *L. casei* DHFR complexes, such as that with trimetrexate (6), have also been determined and one can begin to make comparisons of the similarities and differences between the modes of binding of different ligands.^[20] Figure 11 shows a superposition of methotrexate (5) and

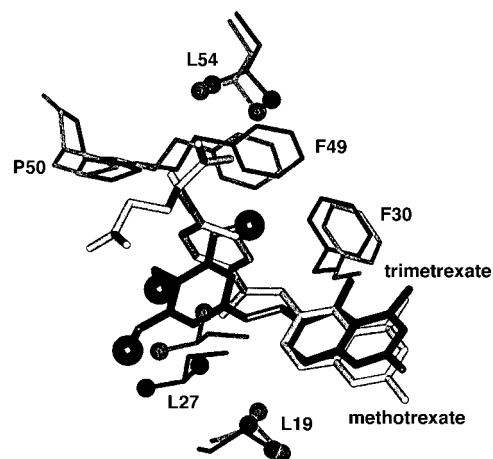


Figure 11. A comparison of the trimetrexate (dark shading) and methotrexate (light shading) binding sites in the structures of their *L. casei* dihydrofolate reductase complexes. The superposition of structures was made over the backbone atoms (N, C α , and C) of all 162 residues in the two structures. Methyl groups are shown as balls. (Reprinted with permission from Polshakov et al.^[20])

trimetrexate (6) in their binding sites in DHFR. It can be seen that the 2,4-diaminopyrimidine moieties of the two drugs bind in the same binding pocket. The remaining parts of the

molecules adapt their conformations such that they can make effective van der Waals interactions with essentially the same set of hydrophobic amino acids, whose side-chain orientations and local conformations are not greatly changed in the two complexes.

In addition to the conventional structural determinations carried out using simulated annealing calculations we have been exploring various methods for docking ligands into a reference protein structure.^[17, 18] The atomic coordinates used for a reference protein are usually obtained from an X-ray structure of a related complex containing the same protein. Recently we have been using NMR-determined structures of a related complex in the docking procedure: in this approach NMR constraints from the reference structure are used rather than the atomic coordinates of the protein.^[118] The method uses a set of experimentally determined values for protein–ligand, ligand–ligand, and protein–protein restraints for residues in or near to the binding site combined with a set of protein–protein restraints involving all the other residues which are taken from the list of restraints previously used to generate the reference structure of a related complex. The binding site residues that are influenced by replacing the reference ligand by the new ligand are determined by monitoring differences in ¹H chemical shifts between the new complex and the reference complex. The method has been validated by showing the excellent agreement between structures of the *L. casei* DHFR–trimetrexate complex calculated by the conventional method using a full experimentally determined set of restraints and that using this new restraint-docking method based on a *L. casei* DHFR–methotrexate reference structure.^[118]

5. Detection of Specific Interactions

Protein–ligand complexes often contain specific interactions between charged groups on the interacting molecules, and NMR spectroscopy has proved to be an excellent method for determining the ionization states of such groups and for monitoring how they are perturbed on forming the complex. Changing the ionization state of a group can result in large changes in the chemical shifts of nearby nuclei and these are particularly easy to characterize for nuclei such as ¹³C, ¹⁵N, and ³¹P. For example, ionization states of phosphate groups can be conveniently measured from ³¹P chemical shift measurements. The 2'-phosphate groups of NADP⁺ and NADPH in the coenzyme complexes of DHFR have been shown to bind in their dianionic forms (for both *L. casei* and *E. coli* DHFR) with the p*K* of the 2'-phosphate in the bound coenzyme group being decreased by at least 3 units compared to its p*K* value in the free species.^[108] The difference $\Delta\delta$ in ³¹P chemical shift between the mono- and dianionic species is about 3.5, which makes it easy to identify the bound form as being in the dianionic state.

More usually, one examines samples that have been specifically labeled with isotopes for such studies. For example, Blakley and co-workers^[49] have used ¹⁵N chemical shift measurements to show that the N3 atom of [2-amino,3-¹⁵N]folate bound to human DHFR exists as the protonated

unionized form even at pH 9.5. In earlier experiments on complexes of [2-¹³C]folate with *Streptococcus faecium* DHFR, the observed ¹³C chemical shifts indicated that the bound folate is in the same protonation state as free folate.^[119]

5.1. Protein Interactions Involving the Pyrimidine Ring of the Inhibitor

A consideration of the crystal structure of the DHFR–methotrexate complex^[14] indicated that a protonated N1 position of the pteridine ring would be sufficiently close to the carboxylate group of the conserved Asp27 to form a hydrogen bond. Cocco and co-workers^[119] have used NMR spectroscopy to characterize this interaction. They examined the ¹³C NMR spectrum of [2-¹³C]methotrexate bound to *S. faecium* DHFR and from measurements of the characteristic ¹³C shift of the C2 carbon atom they showed that the adjacent N1 is protonated in the complex and remains protonated even at pH 10. Thus, by combining results from NMR (to give the protonation state of N1) and X-ray studies (to indicate the interacting residue, Asp27), a more complete picture of this particular interaction could be obtained. Similar experiments have been carried out with *L. casei*^[46] and *E. coli* DHFRs and two *E. coli* mutant enzymes in which Asp27 was replaced by asparagine and serine.^[120] While the p*K* value of methotrexate is greater than 10 in the complex with the wild-type enzyme, the p*K* value is less than 4 in complexes with the mutant enzymes. Cannon and co-workers^[121] have predicted the p*K_a* value for the N1 position in the DHFR–methotrexate complex and their quantum chemistry calculations suggest that N1 remains unprotonated and forms a hydrogen bond with an unionized carboxylate group on the conserved Asp residue, which is in contradiction to the experimental results. While the experimental evidence for N1 protonation appears to be strong, the definitive experiment of examining the DHFR complex with [1-¹⁵N]labeled methotrexate has not yet been carried out: a protonated N1 would be detected as a ¹⁵N and/or ¹H signal with a 90 Hz doublet splitting from ¹H-¹⁵N spin coupling.

Measurements of ¹³C chemical shifts of [2-¹³C]trimethoprim complexed with *L. casei* DHFR have revealed that the pyrimidine N1 is protonated in bound trimethoprim.^[92, 122] Figure 12 shows that the ¹³C chemical shift of the bound species is similar to that of the free protonated N1 species and the p*K* of the bound trimethoprim is decreased by at least 3 p*K* units.

The protonated state of N1 was demonstrated even more directly in ¹H NMR experiments on a complex of [1,3,2-amino-¹⁵N]trimethoprim with the enzyme where it was possible to detect the ¹H signal of the directly bonded N1 proton (the signal was observed at $\delta = 14.4$ and had a 90 Hz doublet splitting characteristic of ¹H-¹⁵N spin coupling).^[92] The ¹⁵N spectra also clearly showed that N1 is protonated (the ¹⁵N chemical shift of N1 changes by $\delta \approx 80$ on protonation).

Hydrogen-bonding interactions involving the 2-NH₂ and 4-NH₂ protons of trimethoprim (**4**) have also been detected by

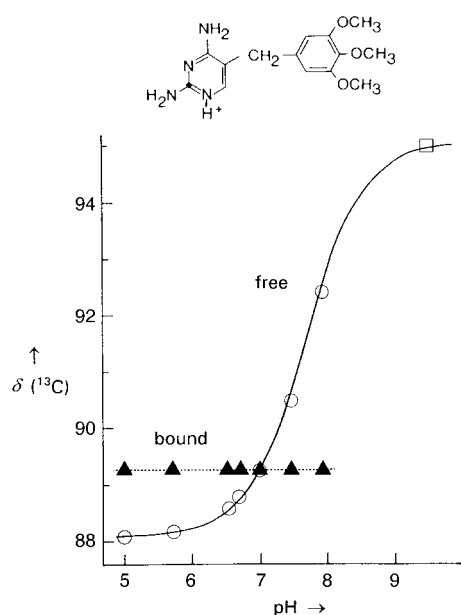


Figure 12. The NMR titration curve (^{13}C chemical shifts versus pH) of $[2-^{13}\text{C}]$ trimethoprim: (○) free ligand; (▲) in its complex with *L. casei* DHFR. The solid line is calculated for a $\text{p}K = 7.70$ and $\Delta\delta = 7.09$. The data point at pH 9.5 (□) was obtained for free trimethoprim in the absence of enzyme. (Reprinted with permission from Roberts et al.^[122])

measuring $^1\text{H}/^{15}\text{N}$ chemical shifts in DHFR complexes with ^{15}N -labeled trimethoprim. Dale and co-workers^[123] used this approach in their studies of a trimethoprim-resistant mutant DHFR (Phe98 → Tyr) from *S. aureus* to show that the 4- NH_2 group of trimethoprim in the complex with the mutant enzyme and NADPH no longer forms a hydrogen bond with the carbonyl oxygen atom of Leu5.

5.2. Protein Interactions Involving the Glutamic Acid Moiety of Folate Analogues

In the crystal structure studies by Matthews and co-workers^[13, 14] on the ternary complex of *L. casei* DHFR with methotrexate (**5**) and NADPH the α -carboxylate group of the glutamic acid moiety of methotrexate is found to be positioned such that it could form an ion pair with the guanidino group of the conserved Arg57 while the γ -carboxylate group was located such that it could interact with the imidazole ring of His28 as shown in Figure 13. We have shown that NMR methods can be used to detect the presence of these interactions in complexes formed with ligands containing carboxylate groups.

5.2.1. Interactions of Arg57 with Ligand Carboxylate Groups

Recent studies of $^1\text{H}/^{15}\text{N}$ signals from arginine residues have proved to be particularly useful for monitoring protein–ligand interactions.^[124–126a] For example, in the $^1\text{H}/^{15}\text{N}$ HSQC spectra of the complex of *L. casei* DHFR with methotrexate, the interaction of the methotrexate α -carboxylate group with the guanidino group of Arg57 can be directly detected by

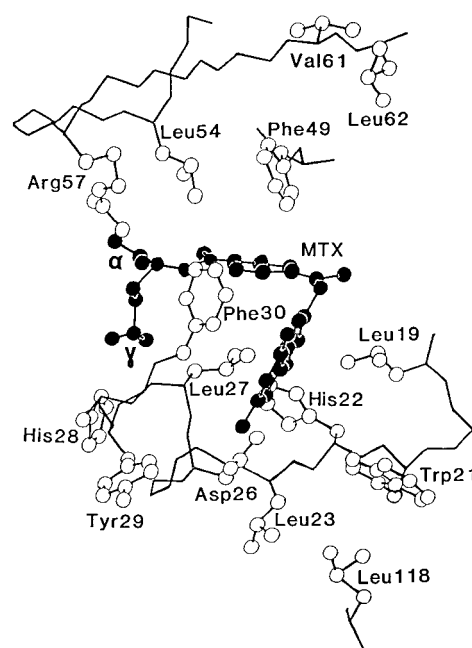


Figure 13. Part of the crystal structure of the *L. casei* DHFR-MTX-NADPH complex (from the data of Bolin et al.^[14]) showing residues around the methotrexate binding site. Heavy atoms of methotrexate are shown as black balls and those of selected side chains as white balls. (Reprinted with permission from Hammond et al.^[159])

using such measurements. In this case, the interaction causes large shift perturbations for two of the guanidino NH^η protons and hindered rotation about the $\text{N}^\epsilon\text{--C}^\zeta$ and $\text{C}^\zeta\text{--N}^\eta$ bonds of the guanidino group (Figure 14a) then results in four separate

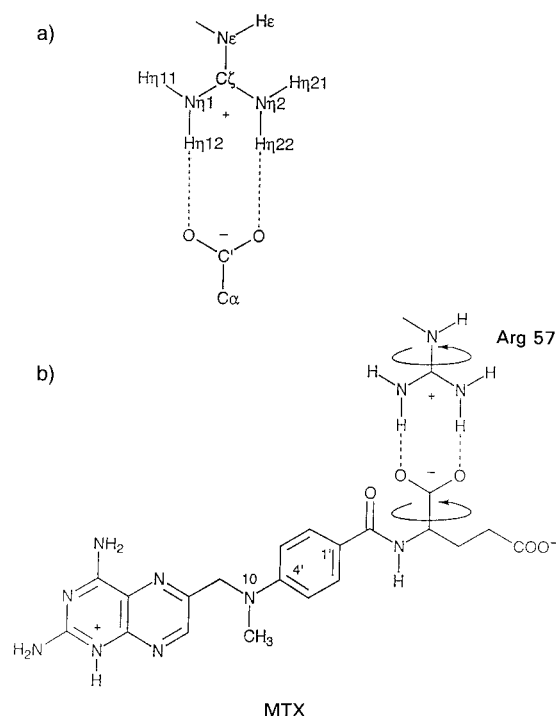


Figure 14. a) Symmetrical end-on interaction of the α -carboxylate oxygen atoms of methotrexate with the guanidino group of Arg57. b) Correlated rotations about the $\text{N}^\epsilon\text{--C}^\zeta$ bond of the Arg57 guanidino group and the $\text{C}^\zeta\text{--C}^\alpha$ bond of the glutamate α -carboxylate group of methotrexate (**5**, MTX) in its complex with *L. casei* DHFR. (Reprinted with permission from Nieto et al.^[125])

signals for the NH^η nuclei being observed in the HSQC spectra (Figure 15). All four signals could be specifically assigned to their particular NH^η protons in Arg57. The large downfield chemical shifts observed for two of these signals indicated that two of the NH^η protons ($\text{NH}^{\eta 12}$ and $\text{NH}^{\eta 22}$) form hydrogen bonds with the charged oxygen atoms of the α -carboxylate group of the glutamate moiety of methotrexate.

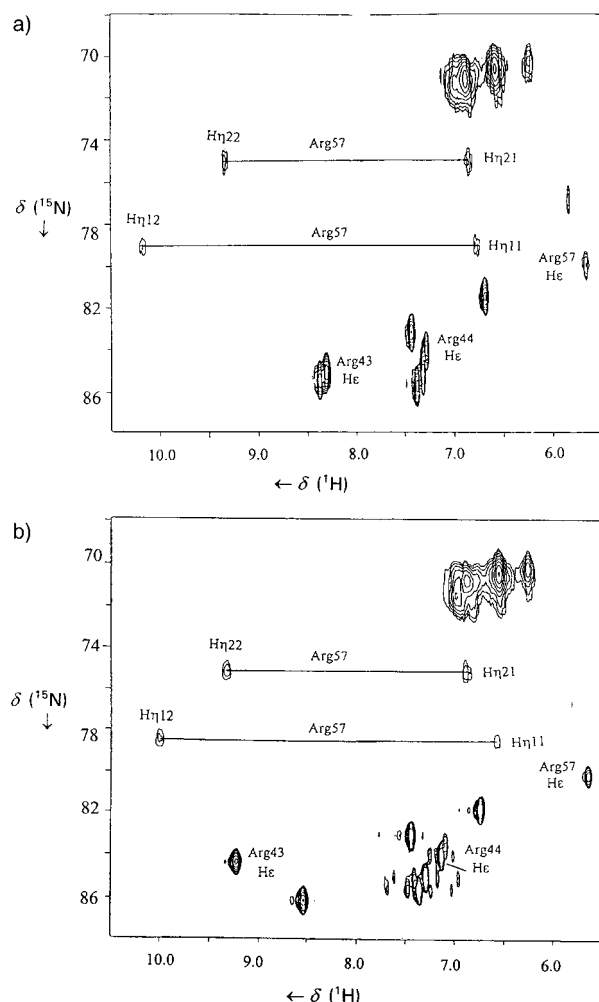


Figure 15. The ^1H - ^{15}N HSQC spectrum of the Arg57 NH^η protons (274 K) from a) the DHFR–methotrexate complex; b) the DHFR-methotrexate-NADPH complex. The chemical shifts indicate a symmetrical end-on interaction of the α -carboxylate oxygen atoms of methotrexate with the guanidino group of Arg57 as indicated in the structure shown in Figure 14a. (Reprinted with permission from Gargaro et al.^[124] and Nieto et al.^[125])

Because only the two centrally situated NH^η protons are involved in the hydrogen bonding, the guanidino group must be forming part of a symmetrical end-on interaction as shown in Figure 14a.^[124] These effects involving Arg57 were not seen for complexes with ligands such as trimethoprim (**4**) that do not contain any carboxylate groups.

The $^1\text{H}/^{15}\text{N}$ HSQC spectrum given in Figure 15 showing the four resolved NH^η signals of Arg57 for the DHFR–methotrexate complex was recorded at 274 K: increasing the temperature caused line-broadening and coalescence of signals as a result of exchange effects.^[125] The rotation rates

for the $\text{N}^\epsilon\text{--C}^\zeta$ and $\text{C}^\zeta\text{--N}^\eta$ bonds were calculated from line-shape analysis and, for the $\text{N}^\epsilon\text{--C}^\zeta$ bond, from 2D zz -HSQC exchange experiments^[126b,c] carried out using a pulse sequence described by Yamazaki and co-workers.^[126a] These experiments allow the observation of the transference of heteronuclear zz -magnetization between the different ^{15}N -labeled sites. Interactions between the methotrexate α -carboxylate group and the Arg57 guanidino group decrease the rotation rates for the $\text{N}^\epsilon\text{--C}^\zeta$ bond by about a factor of 3 and those for the $\text{C}^\zeta\text{--N}^\eta$ bonds by a factor of more than 300 compared with their values in free arginine.^[126a–128]

Surprisingly, the relative rates of rotation about these two bonds are reversed in the protein complexes relative to their values in free arginine (Figure 16). This behavior can readily

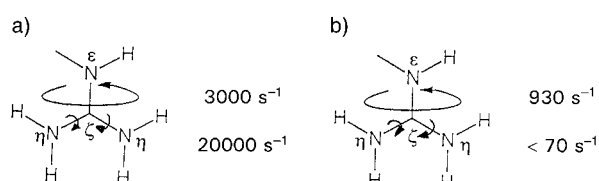


Figure 16. Rotation rates at 313 K for the $\text{N}^\epsilon\text{--C}^\zeta$ and $\text{C}^\zeta\text{--N}^\eta$ bonds in a) free arginine residues; b) Arg57 in the DHFR–methotrexate complex.

be explained if there are correlated rotations about the $\text{N}^\epsilon\text{--C}^\zeta$ bond of the Arg57 guanidino group and the $\text{C}'\text{--C}^\alpha$ bond of the glutamate α -carboxylate group of methotrexate (see Figure 14b). These correlated rotations would allow rotation about the $\text{N}^\epsilon\text{--C}^\zeta$ bond without the need to break the interactions of the NH^η protons with the carboxylate oxygen atoms. The latter interactions would then slow down rotations about the $\text{C}^\zeta\text{--N}^\eta$ bonds preferentially.^[125]

In the $^1\text{H}/^{15}\text{N}$ HSQC spectrum of the DHFR ternary complex formed with methotrexate and NADPH (Figure 15b) the NH^ϵ proton of Arg43 shows a large downfield chemical shift and also a retardation of its rate of proton exchange with water compared with the binary complex with methotrexate.^[124] Resolved signals for the four NH^η protons of Arg43 were not observed. This behavior contrasts with that seen for Arg57 and is consistent with the presence of a side-on interaction of the guanidinium NH^ϵ proton with the charged oxygen atoms of the ribose 2'-phosphate group of NADPH. It was seen earlier that ^{31}P NMR studies indicate that the 2'-phosphate group binds to DHFR in its dianionic form both in solution^[108] and in the solid state.^[129]

5.2.2. Interactions of His28 with Carboxylate Groups

In our previous NMR studies of the ^1H NMR chemical shifts of the imidazole C2 proton of histidine in complexes of the *L. casei* DHFR with methotrexate (**5** and several other ligands containing the glutamic acid moiety) we found that the pK value of His28 was ca. 1 pK unit higher than its value in the ligand-free enzyme (Figure 17)^[130, 131] This value reflects the interaction of His28 with the MTX γ -carboxylate group (Figure 13) and provides an excellent method for monitoring interactions involving His28.^[132] We have used these effects to study complexes of *L. casei* DHFR with the α - and γ -amide

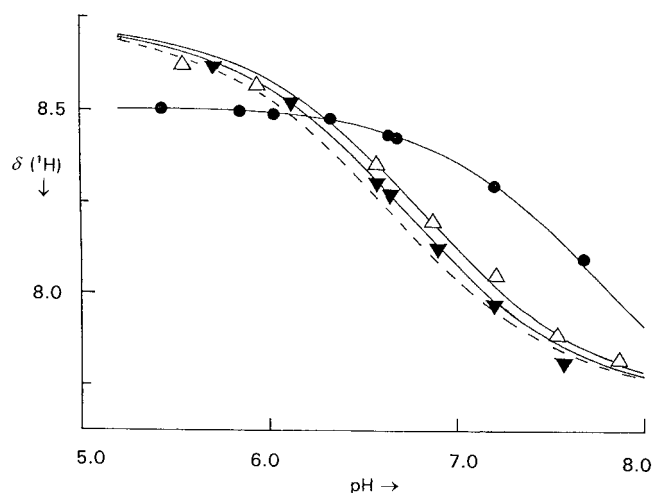
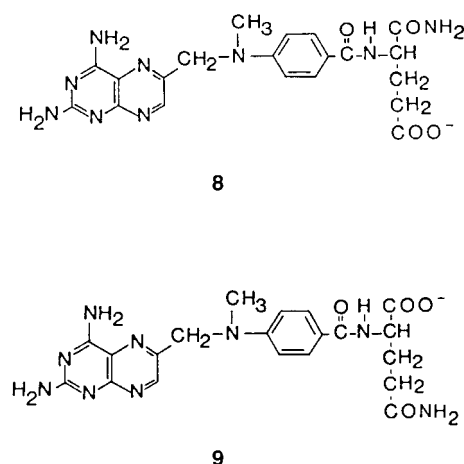


Figure 17. The pH dependence of the chemical shift (^1H , referenced to sodium 2,2-dimethyl-2-silapentane-5-sulphonate) of the C2 protons of His28 in several dihydrofolate reductase complexes. (●) methotrexate (**5**); (▼) methotrexate γ -amide (**10**); (△) methotrexate α -amide (**9**); (---) free enzyme.^[116] (Reprinted with permission from Feeney.^[23])

analogues of methotrexate, **8** and **9**.^[116] The γ -amide and α -amide analogues bind one and two orders of magnitude less tightly to *L. casei* DHFR, respectively, than does methotrexate. For the γ -amide MTX complex with DHFR, the ^1H chemical shifts of the His28 imidazole C2 proton indicated



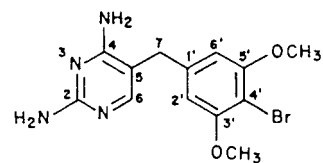
that its pK value is not perturbed from its value in the ligand-free enzyme showing that an ion-pair interaction is not formed (see Figure 17).^[116]

The ^1H NMR spectrum of the α -amide MTX complex with DHFR also showed that the pK of His28 was not perturbed even though the γ -carboxylate group is available for interaction. Thus, modification of the α -carboxylate not only destroys the Arg57 interactions, but also perturbs the overall structure such that the available free γ -carboxylate can no longer form an ion pair with His28. Changes in the shielding of several protons near to the benzoyl ring also accompany the removal of the α - CO_2^- interaction with Arg57. These differences in chemical shift are consistent with a change in the orientation of the benzoyl ring, which results in changes in the ring-current shielding effects at neighboring protons.^[116, 133]

6. Rational Design of Inhibitors

The detailed structural information available for complexes of dihydrofolate reductase^[13–20] has been used in combination with molecular graphics and molecular modeling methods to design improved inhibitors.^[12, 45, 133–144] NMR spectroscopy is proving to be an excellent alternative method to X-ray crystallography^[140] for monitoring the design process by detecting specific interactions between a new inhibitor and the protein, and assessing whether or not the predicted interactions have taken place.^[25, 116, 117, 143]

We have designed improved DHFR inhibitors by preparing analogues of trimethoprim (**4** or brodimoprim **10**, in which a bromo substituent replaces the 4'- OCH_3 group) that have side chains on the O3' position of the benzyl ring to make additional interactions with certain protein residues that are normally involved in substrate binding but not used for binding to **4**. For example, when the 2,4-diaminopyrimidine ring of a brodimoprim analogue is modeled into its binding site in DHFR it is seen that the brodimoprim, unlike folate or methotrexate, cannot make any direct interactions with Arg57 and His28 (Figure 18).^[117]



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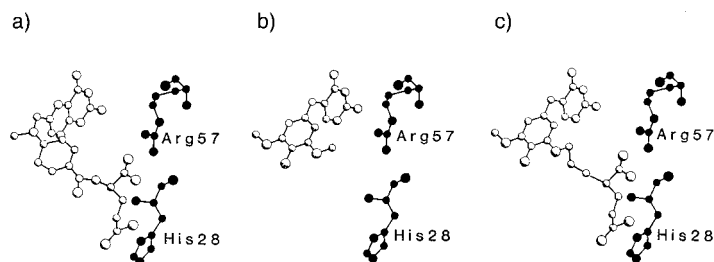
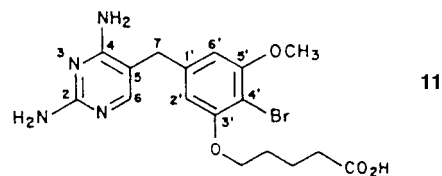
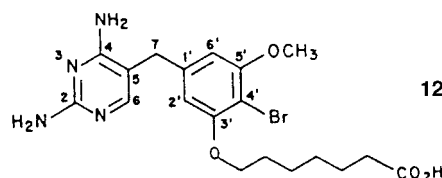


Figure 18. a) Detail from the X-ray crystal structure of the complexes of *L. casei* DHFR with methotrexate (**5**) and NADPH (Bolin et al.^[14]). The proximity of the α - and γ -carboxyl groups of methotrexate to Arg57 and His28 are clearly visible. b) Brodimoprim (**10**) in its bound conformation makes no contacts with these residues. c) A model of the mode of binding of the dicarboxylate derivative **7** of brodimoprim (**10**)^[117] using the crystal structure data of Matthews and co-workers.^[13, 14] (Reprinted with permission from Feeney.^[25])

In collaboration with colleagues from Hoffmann-LaRoche we have synthesized several analogues of brodimoprim (**8**) that were designed to interact with these additional residues.^[117] These rationally designed analogues have an additional side chain containing one or two carboxylate groups aimed at interacting with the Arg57 and/or His28 residues on the protein. The measured inhibition constants for the various analogues (Table 1) provide estimates of their improved binding. The ^1H chemical shifts of the His28 imidazole C2 protons were used to monitor the pK values of His28 residues, and $^1\text{H}/^{15}\text{N}$ chemical shifts of the Arg57 guanidino groups were used to monitor interactions with ligand carboxylate groups in the various DHFR complexes.^[143] These experi-

Table 1. Inhibition constants (K_i) and pK values of His28 for complexes of *L. casei* DHFR with brodimoprim and some of its analogues.

Ligand	K_i [nM]	pK His28
10	11.3	6.80
11	0.2	6.83
12	0.6	6.80
7	< 0.01	7.80

**11****12**

ments allowed us to assess if the ligand side chains are binding in the predicted manner. One example, the carboxybutyl derivative **11**, was designed to interact with the Arg57 residue. The observed perturbations to the $^1\text{H}/^{15}\text{N}$ chemical shifts of the Arg57 guanidino group nuclei are those expected for a symmetrical end-on interaction of the carboxylate group with the Arg57 guanidino protons. This interaction results in four separate NH^i signals in the HSQC spectrum, two of which (one from each NH_2 group) have substantial downfield shifts as a result of hydrogen bonding.^[143] As expected for this analogue, there was no perturbation of the pK value of His28.

Another ligand, the dicarboxy derivative **7**, was designed to interact with both His28 and Arg57. Its complex with DHFR showed an increase in the pK value of His28 of about 1 unit (see Table 1), which indicated that a carboxylate–His28 interaction had been made (see Figure 18). The interaction of a carboxylate group with the Arg57 guanidino group was also confirmed by the appearance of the four NH^i signals in the $^1\text{H}/^{15}\text{N}$ HSQC spectrum, which indicate a symmetrical end-on interaction with the carboxylate oxygen atoms and the presence of hindered rotation within the guanidino group (see Figure 15). The dicarboxyl derivative **7** binds three orders of magnitude more tightly to DHFR than does the parent molecule and retains its specificity of binding with respect to human DHFR.

Some of the other brodimoprim analogues do not bind in the expected manner. For example, the carboxyhexyl derivative **12** (see Table 1), which was designed to achieve the carboxylate–His28 interaction, did not perturb the pK value of His28 even though it binds fairly tightly to the enzyme. Thus, although **12** can reach His28, it appears to prefer to bind at some alternative site. The monitoring of His28 and Arg57 NMR signals clearly provides a convenient and direct method for assessing whether or not a predicted interaction has taken place in these complexes.^[117, 143]

7. Dynamic Processes in Protein–Ligand Complexes

Analysis of ^{15}N and ^{13}C relaxation data can provide information about rapid segmental motions in the enzyme–ligand complexes (rates of 10^9 to 10^{12} s^{-1}), while line-shape analysis and transfer of magnetization experiments can characterize intramolecular motions at much slower rates (rates of 10^0 to 10^4 s^{-1}), typical of those observed for bond rotations in arginine residues, for ring-flipping of aromatic rings, and for breaking and reforming of hydrogen bonds.

7.1. Rapid Motions

Epstein and co-workers^[145] have used ^{15}N relaxation measurements on the complex of *E. coli* DHFR with folate (**1**) to determine the dynamics of the backbone and tryptophan side chain. They found large amplitude motions for the backbone on the pico- and nanosecond time scales in regions of the protein that could be implicated in transition-state stabilization. They concluded that these time-dependent structure variations could be associated with the catalytic properties of the enzyme.^[145] Relaxation time studies on complexes of the *L. casei* enzyme have also been reported.^[20, 93] By analyzing the ^{13}C relaxation times of the C7 carbon atom in $[7,4'\text{-OCH}_3\text{-}^{13}\text{C}_2]$ trimethoprim—bound to *L. casei* DHFR—the overall correlation time (tumbling time) of the molecule was calculated to be 15.4 ns at 295 K. The $4'\text{-OCH}_3$ carbon atom has a sixfold slower relaxation rate. This can be interpreted in terms of additional rapid motions that affect the relaxation of the $4'\text{-OCH}_3$ carbon atom and suggests that the benzyl ring is librating rapidly ($> 10^{10} \text{ s}^{-1}$) over angles of $\pm 30^\circ$.^[93]

7.2. Slow Intramolecular Processes

Examples of bond rotations and correlated rotations have already been discussed for the case of arginine guanidino groups interacting with carboxylate groups in ligands. Correlated rotations have also been seen for the ring-flipping of *para*-substituted aromatic rings in bound ligands. In complexes of *L. casei* DHFR with ligands containing symmetrically substituted aromatic rings, the rings are usually undergoing ring-flipping. NMR spectroscopy is the ideal technique for determining the rates of such processes. In some complexes, such as that with folate (**1**), the rate of ring-flipping is fast enough to ensure that only a single signal is seen for the $2',6'$ -protons (and another for the $3',5'$ -protons) of the benzoyl ring. For other complexes, such as the DHFR–methotrexate complex, the ^1H signals for the corresponding protons have never been detected—probably because of line broadening as a result of exchange processes at the temperatures studied. However, by examining ^{19}F spectra of the complex of $3',5'$ -difluoromethotrexate with DHFR at different temperatures it was possible to characterize the ring-flipping in detail (see Figure 19).^[107]

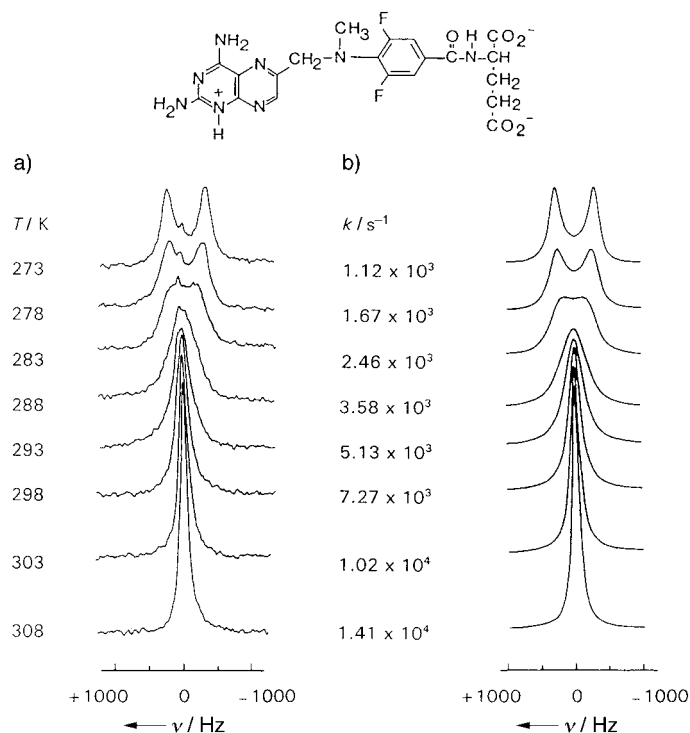


Figure 19. a) The 188.2 MHz ^{19}F NMR spectra of 3',5'-difluoromethotrexate complexed with *L. casei* DHFR examined at a series of temperatures. b) The corresponding calculated spectra and rates of exchange. (Reprinted with permission from Clore et al.^[107])

Two separate signals are seen for the 3',5'-fluorine nuclei at 274 K, and on increasing the temperature the signals broaden and eventually coalesce (at ~ 298 K). A line-shape analysis of this classical 2-site exchange behavior gave the rate of ring-flipping as $7 \times 10^3 \text{ s}^{-1}$ at 298 K for the binary complex and $2 \times 10^4 \text{ s}^{-1}$ at 298 K for the ternary complex with NADPH. In both complexes the ring-flipping motions require correlated rotations about the bonds attached to the 1'- and 4'-positions of the ring. Verma and co-workers^[147] have calculated the possible reaction pathway for the ring-flipping process in this complex.

Rates of ligand ring-flipping have also been determined in complexes of *L. casei* DHFR with trimethoprim (**4**),^[93, 94] pyrimethamine analogues,^[102] and with trimetrexate (**6**).^[20] Line-shape measurements on ^{13}C spectra (and more recently from $^1\text{H}/^{13}\text{C}$ HMQC spectra^[148]) of [3'-OCH₃- ^{13}C]trimethoprim have been used to characterize these rates for the benzyl ring in DHFR complexes with trimethoprim analogues.^[93, 94] For the binary DHFR–TMP complex the rate of ring-flipping is 793 s^{-1} at 298 K. From a consideration of the bound conformation of trimethoprim it could be seen that rotation about the C7–C1' bond (τ_2 in Figure 20) cannot occur without changing the C5–C7 torsion angle (to remove steric interactions between the pyrimidine and benzyl rings). This in turn requires a fluctuation in the protein structure such that the torsion angle about the C5–C7 bond (τ_1 in Figure 20) in bound trimethoprim needs to change by at least 35° in order to remove this steric hindrance and allow the ring-flipping to take place about τ_2 .^[93]

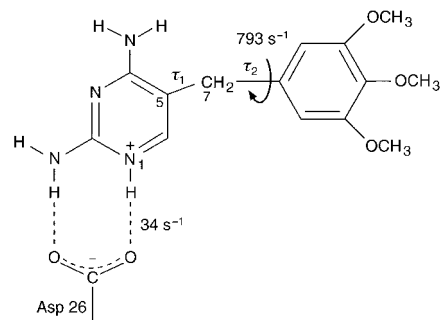


Figure 20. Dynamic processes in the complex of trimethoprim with *L. casei* DHFR measured at 298 K. The lifetime of the complex is 0.5 s at this temperature. The flipping rate was measured from line-shape analyses over a range of temperatures^[148] and corrects the value given in ref. [93].

Analyses of the line widths of NH proton signals measured as a function of temperature provide rates of proton exchange with the solvent. These can be related to the rates of breaking and reforming of hydrogen bonds in cases where hydrogen-bond breaking is a required step before proton exchange with the solvent can take place.^[92] The rate of breaking the hydrogen bond between the trimethoprim pyrimidine N1 proton and the carboxylate oxygen of Asp26 in the DHFR–trimethoprim complex was estimated as 34 s^{-1} at 298 K. At this temperature the dissociation rate for the complex (2 s^{-1}) is much slower than either the frequency of ring-flipping (793 s^{-1}) or the hydrogen-bond breaking (34 s^{-1} , see Figure 20). It is clear that both processes involve the breaking and reforming of protein–ligand interactions many times within the lifetime of the complex. The lifetimes of the partially dissociated species will be very short and complete dissociation would require the events to occur simultaneously or in close succession.

This picture would be consistent with our earlier suggestion concerning a “zipper”-type mechanism for binding and releasing flexible ligands in protein–ligand complexes.^[149] In this model the binding of a flexible ligand to a protein was proposed to occur by the initial formation of a nucleation complex where the ligand is only partially bound and which then undergoes a series of conformational rearrangements that lead to other interactions with the protein forming in a zipper-type process to give the fully bound complex (Figure 21). Dissociation would involve a similar stepwise reversal of the various partially bound states. Such processes would allow for rapid rates of association and dissociation (by partitioning the overall activation energies into a series of smaller values) while retaining the specificity of binding that results from the multi-site interactions between the flexible ligand and the protein.

8. Multiple Conformations

NMR spectroscopy has proved to be a powerful technique for detecting multiple conformations in protein–ligand complexes in solution. In many cases two or more conformations have been detected by the observation of separate NMR spectra for the different forms. The easiest way to detect

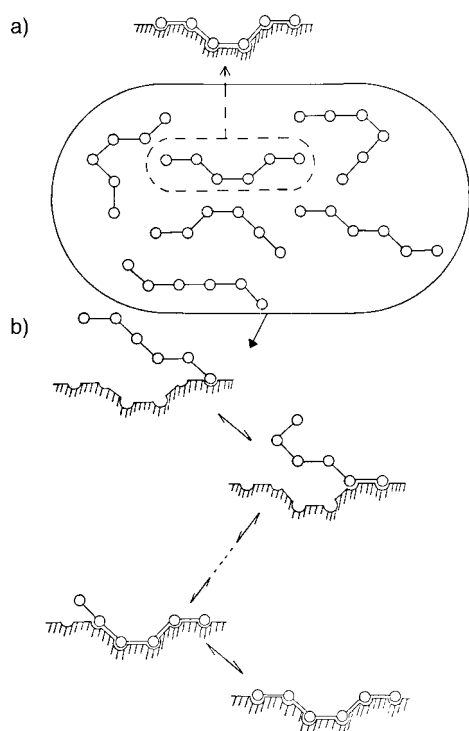


Figure 21. Schematic representation of a) the “lock and key” and b) the “zipper” model for ligand binding. Only those ligands which instantaneously have the correct conformation can bind in the “lock and key” model but essentially all the ligands can bind as in (b), where the final bound conformation is adopted by a step-wise “zipper-type” process. (Reprinted with permission from Burgen et al.^[149])

multiple conformations is by examining NMR spectra from complexes formed with isotopically labeled ligands (^3H , ^{13}C , ^{15}N , ^{19}F), which readily reveal the multiplicity of signals when different conformations are present.

Multiple conformations found in protein–ligand complexes are often caused by the ligand being bound in more than one way. However, they have also been observed in the free enzymes. For example, NMR studies on DHFR from *E. coli* have revealed two distinct conformations which differ in the region of a mobile loop centered on residues 16–20.^[150] Several complexes formed with dihydrofolate reductase from *L. casei*, *E. coli*, and *S. faecium* have been shown by NMR studies to exist as mixtures of conformations.^[79, 90, 94, 103, 151–160] In such cases the relative amounts of the conformers in the equilibrium can be estimated from measurements of the intensity of the NMR signals from the different conformations. The conformational equilibria can sometimes be perturbed by changes in temperature, pH, or structure (for example, changes in the amino acid sequence by site-directed mutagenesis). The rate of interconversion between the conformational states of some complexes can be measured from analysis of the line shapes or, in favorable cases, by transfer of magnetization methods.^[161]

The occurrence of multiple conformations often depends on the source of the enzyme. For example, the complex of the *E. coli* enzyme with methotrexate exists as two conformations^[91, 95, 160] whereas the same complex formed with the *L. casei* enzyme is a well-defined single conformation.^[159] However, for other ligands, such as folate (**1**), it is the

complex with the *L. casei* enzyme^[46, 90, 156, 157] rather than the *E. coli* enzyme^[150] that shows multiple conformations. Multiple conformations have also been reported in X-ray studies, but in these cases it is difficult to assess the affect of crystal-packing forces on the stability of the conformations.^[137]

8.1. Ternary Complexes of *L. casei* DHFR with Trimethoprim and NADP^+

The ternary complex formed by *L. casei* DHFR with trimethoprim and NADP^+ has been shown to exist as a mixture of two almost equally populated conformations (Forms I and II).^[156, 157] These conformations were first detected in the ^1H spectrum of the complex where six of the seven imidazole C2 protons from the histidines gave rise to two separate signals corresponding to the two forms (Figure 22).^[156, 157] The pairs of histidine signals each coalesced

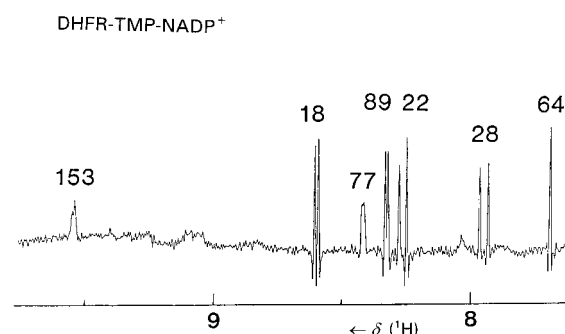


Figure 22. Part of the low-field region of the resolution-enhanced 500 MHz ^1H spectrum of the *L. casei* DHFR-Trimethoprim- NADP^+ complex showing the seven assigned C2-proton signals of histidine, six of which appear as doubled signals because of the presence of two conformations with almost equal populations. (Reprinted with permission from Birdsall et al.^[157])

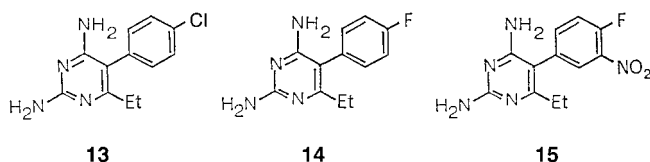
into single lines in a manner typical of a two-site exchange process on raising the temperature and a line-shape analysis at 314 K gave the rate of interconversion (18 s^{-1}) between the two forms.^[156] Detailed ^{13}C and ^{31}P studies have confirmed the presence of the two conformations.^[157] Two similar conformations are also seen in the DHFR-trimethoprim- NADP^+ complex formed with the *E. coli* enzyme.^[96]

A consideration of the measured chemical shifts, coupling constants, and NOEs indicates that although the conformation of the bound trimethoprim is similar in the two forms that of the bound NADP^+ is very different: in Form II, the NADP^+ nicotinamide ring extends out into solution while in Form I it is buried within the protein.^[156, 157] Conformational differences between Forms I and II were also detected in the nicotinamide ribose ring and the pyrophosphate linkages but the adenine ring and its ribose moiety are bound similarly in the two forms.

Complexes of various analogues of TMP and NADP^+ with DHFR were also shown to exist in two conformations with the populations of the two forms depending on the particular structures of the analogues.^[157] Such information provides additional insights in studies of structure–activity relationships.

8.2. Complexes of *L. casei* DHFR with Pyrimethamine Analogues

In some complexes the multiple conformations result from flexible ligands binding in essentially the same binding site but in different conformational states. Examples are found in complexes formed with pyrimethamine analogues (such as **15**) containing asymmetrically substituted aromatic rings where two different rotational isomers of the bound ligand result



from hindered rotation about the pyrimidine–phenyl bond.^[102] We have used NMR spectroscopy to investigate such restricted rotation in complexes of *L. casei* DHFR with the pyrimethamine analogues **13**–**15**.^[102] These analogues are of therapeutic interest both as antimalarial^[162] and potential anti-tumour agents.^[163, 164] The 3'-nitro-4'-fluoropyrimethamine analogue **15** has an asymmetrically substituted aromatic ring and can exist as a mixture of two rotational isomers (an enantiomeric pair; Figure 23).

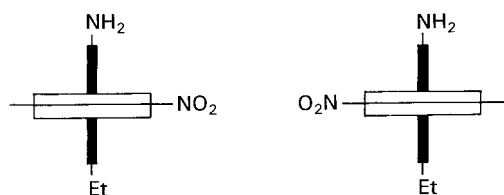


Figure 23. Schematic representation of the two rotational isomers (enantiomers) for 3'-nitro-4'-fluoropyrimethamine (**15**). The planes of the two aromatic rings are shown perpendicular to the plane of the paper and are presented as black and white bars. (Reprinted with permission from Birdsall et al.^[102])

The ^{19}F NMR spectrum of the complex of **15** with DHFR showed two separate ^{19}F signals for the bound ligand, which corresponded to two different conformational states for the complex. The 2D exchange spectrum (Figure 24) shows the two forms have exchange peaks with the free ligand but not with each other.^[102] From intensity measurements, the ratio of the two populations A/B is 0.6/0.4 in the binary complex. In the ternary complex with NADP^+ the preference for binding is reversed with the A/B ratio becoming 0.3/0.7.^[102]

We have used 2D exchange ^1H NMR spectroscopy to connect the signals from the bound species with their corresponding signals in the free ligand for complexes of DHFR formed with ligands **13**–**15** (spectra not shown). In the complex where the ligand has a symmetrically substituted phenyl ring, such as for **13** and **14**, four signals were observed for the four aromatic protons, which indicated that each is shielded differently. This result indicates the presence of hindered rotation about the phenyl–pyrimidine bond, with the phenyl ring taking up a fixed position within its binding

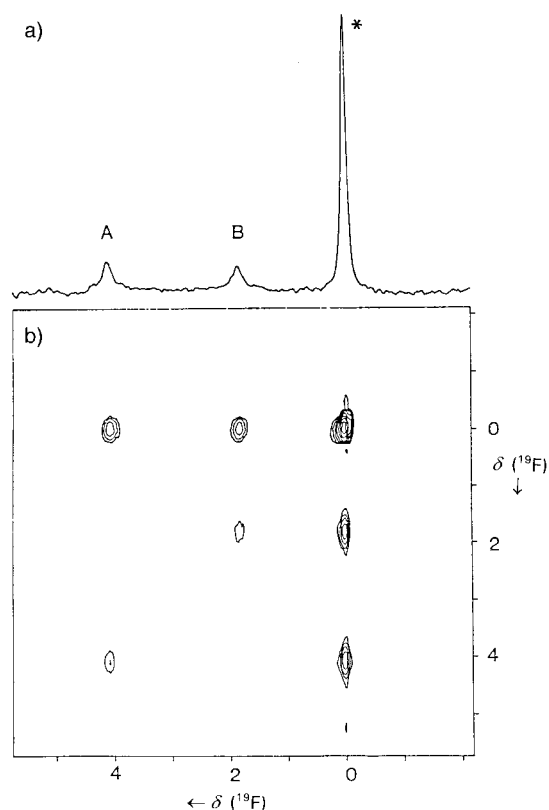


Figure 24. 376 MHz ^{19}F NMR spectra of 1.2 mM DHFR in the presence of excess 3'-nitro-4'-fluoropyrimethamine (**15**) at 308 K, pH 6.5. a) 1D spectrum, b) 2D NOESY exchange spectrum. Both spectra are referenced to the free ligand signal (indicated by an *). Forms A and B are seen to have exchange cross-peaks with the free ligand (magnetization transfer by exchange), but no exchange cross-peaks were observed between the Forms A and B. (Reprinted with permission from Tendler et al.^[102])

site such that each of the four aromatic protons is in a different shielding environment in the protein. DHFR complexes containing pyrimethamine analogues with asymmetrically substituted phenyl rings such as **15** showed two complete sets of signals (three from Form A and three from Form B) for the phenyl protons in the bound ligands. Using X-ray data on related complexes^[140, 165] together with NOE data on the *L. casei* DHFR complex it was possible to assign the ligand phenyl ring protons in bound pyrimethamine that are oriented towards Phe30^[102] and thus assign ligand signals to Forms A and B (Figure 25).

An understanding of the conformational preference for binding Form A in the binary complex of 3'-nitro-4'-fluoropyrimethamine (**15**) with DHFR can be reached by considering the model of the complex shown in Figure 25. In Form A the nitro substituent would be directed towards the vacant nicotinamide ring binding site and this could assist the favored binding. Addition of the NADP^+ to form the ternary complex reverses the preference for Form A, and this is consistent with the expected unfavorable steric interaction between the bulky nitro group and the nicotinamide ring of bound NADP^+ .^[102]

Ternary complexes of DHFR with pyrimethamine analogues and NADP^+ ^[102] were found to have the NADP^+ in two different conformations (Forms I and II),^[156, 157] similar to those seen earlier for the DHFR-trimethoprim- NADP^+

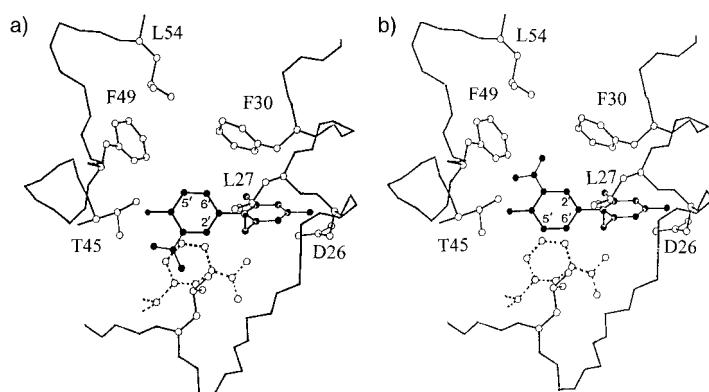


Figure 25. Model of the binding site in the 3'-nitro-4'-fluoropyrimethamine–DHFR complex for a) Form A and b) Form B. The position of the NADP⁺ nicotinamide ring binding site is also indicated as a dotted line structure. The modeling used some crystallographic data from Matthews et al.^[13, 14] (Reprinted with permission from Birdsall et al.^[102])

complex. The results suggest that the two types of conformational states could be correlated with only Forms IB and IIA being populated. This would be consistent with a structure having the nitro substituent oriented towards the vacant site for the nicotinamide ring binding in Form IIA and oriented away from the nicotinamide ring binding site in Form IB (see Figure 25).

8.3. Complexes of *L. casei* DHFR with Folate and NADP⁺

Complexes of *L. casei* DHFR with folate and NADP⁺ provide further examples of ligands that bind in different conformational states to essentially the same binding site in the protein. The ternary complex of *L. casei* DHFR with folate and NADP⁺ has been shown by NMR spectroscopy to have three distinct conformational states, designated Forms I, IIa, and IIb.^[46, 90, 106, 157] Isotopically labeled (³H, ¹³C, and ¹⁵N) folates were used in these NMR studies. For example, multiple ¹³C signals corresponding to the three different forms have been seen in the ¹³C spectrum of the complex of *L. casei* DHFR with NADP⁺ and [4,6,8a-¹³C]folate (**16**) measured at various pH values^[46] (Figure 26).

It can be seen that the populations of these conformational states are pH dependent. At pH 6.8 Forms IIa and IIb are present while at pH 5.5 the ternary complex is almost exclusively in Form I. The NOE measurements at pH 5.2 clearly indicate that the H7 proton of folate is close to the methyl group protons of Leu19 and Leu27 as shown in Figure 27. Similar NOEs were seen in a 2D HMQC–NOESY ¹H/¹³C experiment on the complex with [4,7,8a,9-¹³C]methotrexate where edited NOEs between MTX H7 and the methyl protons of Leu19 and 27 were detected.^[46] Thus the orientation of the pterin ring in Form I is very similar to that of methotrexate in the DHFR–methotrexate complex. As mentioned earlier, this orientation is known to be about 180° from that of the corresponding ring in folate in its catalytically active complex (see Section 2).^[46] NOE data from the DHFR–folate–NADP⁺ complex indicated that Form IIa

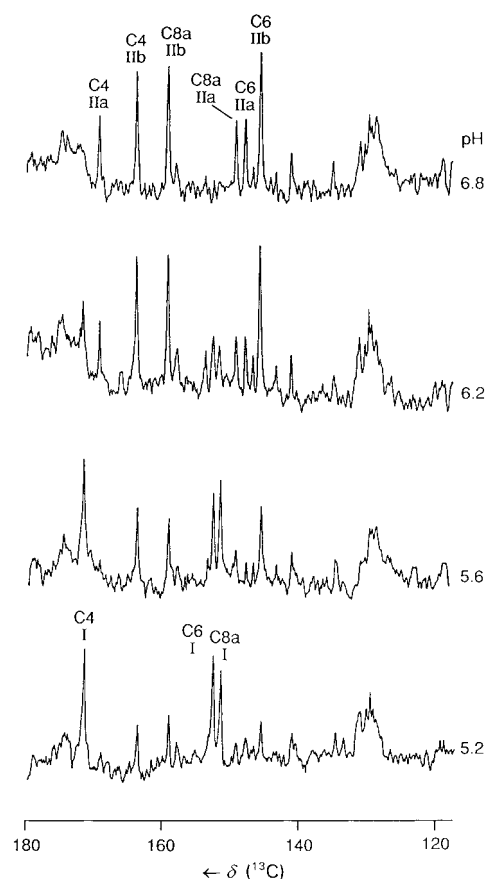
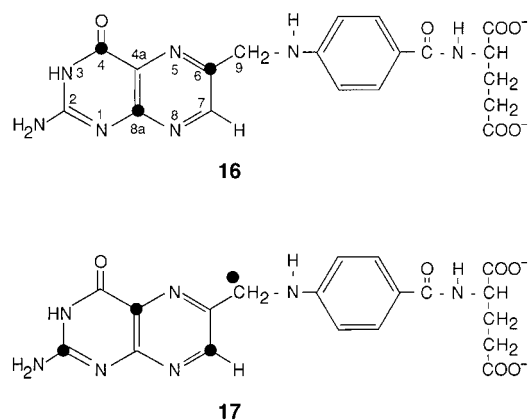


Figure 26. The low-field region of the 100.6 MHz ¹³C NMR spectra at 281 K of the ternary complex of *L. casei* DHFR and NADP⁺ and [4,6,8a-¹³C]folate at different pH values. Signals from the naturally occurring ¹³C in the protein are also observed (at $\delta \sim$ ca. 130, 157, and ca. 175). (Reprinted with permission from Cheung et al.^[46])

has a similar orientation to Form I (and to bound methotrexate (**5**)) but that Form IIb has a different orientation of the pterin ring from that in the methotrexate complex. The H7 proton in Form IIb shows an NOE connection to the Ala97 methyl protons indicating its proximity to these protons but shows no NOEs to the Leu19 and Leu27 methyl protons (see Figure 27). These NOE results have been confirmed by examining the 2D ¹H/¹³C HMQC–NOESY spectra of ¹³C-labeled folates ([4,6,8a-¹³C]folate (**16**) and [2,4a,7,9-¹³C]folate (**17**)) bound to *L. casei* DHFR.^[46]



From a consideration of the crystal structure data obtained by Bolin and co-workers^[14] on the DHFR-MTX-NADPH complex it could be deduced that a “turned over” pteridine ring occupying essentially the same binding site would have its H7 proton close to the methyl protons of Ala97. Thus the major conformational difference between Forms I and IIb is the approximate 180° difference in orientation of the pterin ring in the two forms as illustrated in Figure 27. Form I (and Form IIa) has the pterin ring in the same orientation as the methotrexate complex, and Form IIb has the folate pterin ring turned over by 180° about an axis coincident with the ligand C2-NH₂ bond. In this orientation the catalytic reduction can proceed with the correct stereochemistry and this is referred to as the “active” conformation (Figure 27). In contrast, Forms I and IIa with the methotrexate-like orienta-

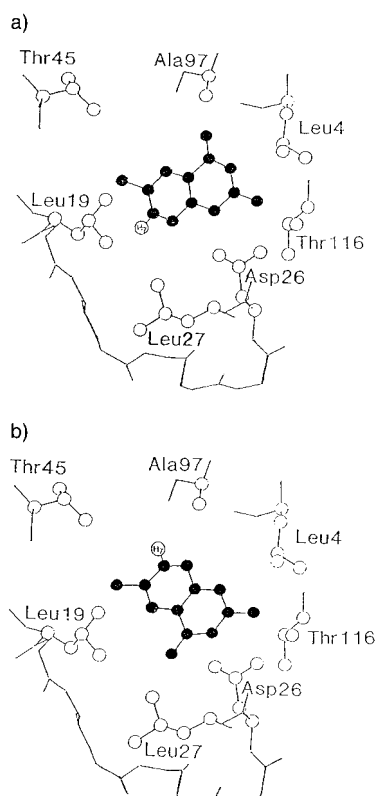
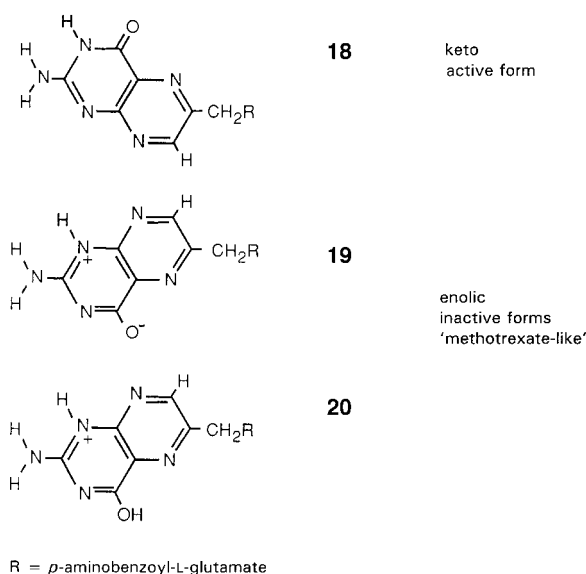


Figure 27. a) Proposed conformation of the pterin ring in the folate–DHFR complex in the “inactive” Forms I and IIa (based on the methotrexate conformation in the crystal structure data of Matthews and co-workers).^[13, 14] b) Proposed conformation of the pterin ring in the folate–DHFR “active” Form IIb (turned over by about 180° compared to the other forms). (Reprinted with permission from Feeney.^[24])

tion of the pterin ring correspond to “inactive” conformations (Figure 27). The folate pterin ring is seen to occupy approximately the same binding site in the different forms.^[46, 157]

NMR studies of ¹³C chemical shifts of bound folate have provided useful information about the tautomeric states in the three forms found in the complex with *L. casei* DHFR. By considering the ¹³C chemical shifts of the labeled, bound folates **16** and **17** it was found that Form IIb is very similar to free folic acid at pH 5.5 for which the structure is known to be in the 4-keto form with N1 unprotonated^[166] (see structure **18**).^[46] This result gives no support to proposed enzyme



mechanisms that require enolic forms as intermediates since only Form IIb has the “active” conformation of its pterin ring. In contrast, the C2 and C4 chemical shifts of bound folate in Form IIa are very different from those of free folic acid, which indicates a possible change in the keto/enol tautomerism or in the N1/N3 protonation states. Studies of model compounds provide estimates of the ¹³C chemical shifts for various tautomeric and ionization states of folate. Comparisons of these with the experimental data for bound folate indicated that while Form IIb is in the keto form, Forms I and IIa exist as enolic forms (see structures **19** and **20**).

¹H NMR studies suggest that N1 is protonated in Forms I and IIa. This observation means that the tautomeric and ionization states in Forms I and IIa at N1 are both very similar to that in methotrexate which has a NH₂ group at the 4-position. Since the pterin ring has been shown to have the same orientation as in the methotrexate–DHFR complex, it is likely that the pterin ring in folate in Forms I and IIa bind to residues in the protein that are the same as those involved in methotrexate binding.

Site-directed mutagenesis studies involving Asp26 have provided direct evidence that this residue is involved in controlling the pH dependence of the conformational equilibrium.^[167, 168] However, recent NMR studies of DHFR–folate–NADP⁺ complexes using Asp-γ-¹³CO₂-labeled DHFR and the mutant Asp26Asn DHFR have shown that the Asp26 residue influences the pH dependence of the equilibrium in an indirect manner by modifying the pK value of the pterin ring of bound folate.^[51] This effect could result from Asp26 being close to the N1 position which is protonated in Forms I and IIa. The observation of multiconformational states in more than 20 different complexes of dihydrofolate reductase suggests that this phenomenon could also be common in other protein–ligand complexes. This is an important finding that has implications not only for understanding complex structure–function relationships but also for assisting in inhibitor design, since each different conformation provides a new starting point for exploring drug design.

9. Summary and Outlook

NMR spectroscopy has been shown to be a powerful technique for providing information about interactions, conformations, and dynamic processes in complexes of dihydrofolate reductase and antifolate drugs. It is likely that the increasing awareness of the capabilities of NMR methods for studying protein–ligand complexes and the wider accessibility of the high-field NMR spectrometers required for this type of work will encourage further research in this general area. The NMR experiments can now be executed with increasing facility and comparative studies of complexes of ligands with DHFRs from different species are becoming easier to carry out. This process should allow questions concerning the origins of ligand-binding specificity to different DHFRs (for example bacterial and mammalian) to be addressed more directly. Structural studies in solution on complexes of target DHFRs from species not yet examined (such as *Plasmodium falciparum* and *P. carinii*) will no doubt be carried out.

Improved methods of structure determination—for example by incorporating chemical shift information—will eventually provide more detailed information about protein–ligand complexes in solution. The recently developed approaches for obtaining structural information using dipolar coupling contributions that result from orienting the molecules in solution (either by using high magnetic field, liquid crystal or phage orienting approaches) should have an important impact on structural studies of DHFR–ligand complexes.^[169] The improved structures should allow the detection of smaller differences in structure between different complexes. Future work should also lead to an improved understanding of the dynamic processes taking place within ligand–protein complexes.

Fesik and co-workers^[170, 171] have suggested a novel method for designing tightly binding enzyme inhibitors that could be applied to DHFR. In this method large numbers of ligands are quickly screened for their potential binding to a target protein by detecting changes in chemical shift in ¹H/¹⁵N HSQC spectra of the ¹⁵N-labeled protein in the presence of batches of ligands. A binding ligand is identified as one that perturbs the protein ¹H/¹⁵N chemical shifts. Once such a binding ligand has been identified, the protein is saturated with this ligand, and the screening continued to find another ligand that binds noncompetitively with the first one. When a suitable second candidate is found, detailed NMR structural work on the ternary complex is undertaken and—on the basis of the structural information obtained—a strategy is developed for chemically linking the weakly binding ligands to produce a high affinity binding ligand. This approach has been used to produce inhibitors with high binding affinity for metalloproteinases such as stromelysin.^[171] A similar approach could be adopted to find new lead compounds as potential inhibitors of dihydrofolate reductase. Such work would best be carried out in industrial laboratories where suitable libraries of compounds are readily available for the screening.

It is clear that DHFR, in addition to its intrinsic pharmacological interest, has proved to be an excellent test-bed for exploring ideas and methods of tackling the problem of

binding specificity and many of the results obtained on this system will have general applicability.

I would like to acknowledge the collaboration of many colleagues in the NMR studies on L. casei DHFR described here, particularly Arnold Burgen, Gordon Roberts, Berry Birdsall, Andrew Cheung, Vladimir Polshakov, Tom Frenkiel, Gill Ostler, and John McCormick. I am especially grateful to Arnold Burgen for stimulating my interests in molecular pharmacology and for initiating the early NMR work on dihydrofolate reductase. Berry Birdsall, Andrew Lane, Eva Hyde, Jürgen Schmidt, and Mark Williams are thanked for their comments on this article.

Received: January 27, 1999 [A 322]

- [1] S. Farber, L. K. Diamond, R. D. Mercer, R. F. Sylvester, Jr., J. A. Wolff, *New. Engl. J. Med.* **1948**, 238, 787–793.
- [2] L. J. Daniel, L. C. Norris, *J. Biol. Chem.* **1947**, 170, 747–756.
- [3] G. H. Hitchings, G. B. Elion, H. Van der Werff, E. A. Falco, *J. Biol. Chem.* **1948**, 174, 765–766.
- [4] S. Futterman, *J. Biol. Chem.* **1957**, 228, 1031–1038.
- [5] G. H. Hitchings, J. A. Burchall, *Adv. Enzymol.* **1965**, 27, 417–468.
- [6] “Chemistry and Biochemistry of Folate”: R. L. Blakley in *Folates and Pterins, Vol. 1* (Eds.: R. L. Blakley, S. J. Benkovic), Wiley, New York, **1984**, chap. 5, pp. 191–253.
- [7] J. R. Bertino, *Cancer Res.* **1963**, 23, 1286–1306.
- [8] F. M. Huennekens, M. J. Osborn, *Adv. Enzymol.* **1959**, 21, 369–446.
- [9] “The comparative biochemistry of dihydrofolate reductase”: J. H. Freisheim, D. A. Matthews in *Folate antagonists as therapeutic agents, Vol. 1* (Eds.: F. M. Sirotnak, J. J. Burchall, W. B. Enslinger, J. A. Montgomery), Academic Press, Orlando, Florida, **1984**, pp. 70–132.
- [10] J. E. Gready, *Adv. Pharmacol. Chemother.* **1980**, 17, 37–102.
- [11] F. M. Huennekens, *Protein Sci.* **1996**, 5, 1201–1208.
- [12] Nobel Lecture (Physiology/Medicine) “Selective inhibitors of dihydrofolate reductase”: G. H. Hitchings, Jr., *In Vitro Cell. Develop. Biol.* **1989**, 25, 303–310; G. H. Hitchings, *Angew. Chem.* **1989**, 101, 903–909; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 879–885.
- [13] D. A. Matthews, R. A. Alden, J. T. Bolin, D. J. Filman, S. T. Freer, R. Hamlin, W. G. J. Hol, R. L. Kisliuk, E. J. Pastore, L. T. Plante, N. Xuong, J. Kraut, *J. Biol. Chem.* **1978**, 253, 6946–6954.
- [14] J. T. Bolin, D. J. Filman, D. A. Matthews, R. C. Hamlin, J. Kraut, *J. Biol. Chem.* **1982**, 257, 13650–13662.
- [15] M. R. Sawaya, J. Kraut, *Biochemistry* **1997**, 36, 586–603, and references therein.
- [16] C. Oefner, A. D’Arcy, F. K. Winkler, *Eur. J. Biochem.* **1988**, 174, 377–385.
- [17] G. Martorell, M. J. Gradwell, B. Birdsall, C. J. Bauer, T. A. Frenkiel, H. T. A. Cheung, V. I. Polshakov, L. Kuyper, J. Feeney, *Biochemistry* **1994**, 33, 12416–12426.
- [18] W. D. Morgan, B. Birdsall, V. I. Polshakov, D. Sali, I. Kompis, J. Feeney, *Biochemistry* **1995**, 34, 11690–11702.
- [19] A. R. Gargaro, A. Soteriou, T. A. Frenkiel, C. J. Bauer, B. Birdsall, V. I. Polshakov, I. L. Barsukov, G. C. K. Roberts, J. Feeney, *J. Mol. Biol.* **1998**, 277, 119–134.
- [20] V. I. Polshakov, B. Birdsall, T. A. Frenkiel, A. R. Gargaro, J. Feeney, *Protein Sci.* **1999**, 8, 1–15.
- [21] J. M. Johnson, E. M. Meiering, J. E. Wright, J. Pardo, A. Rosowsky, G. Wagner, *Biochemistry*, **1997**, 36, 4399–4411.
- [22] “The interaction of substrates and inhibitors with dihydrofolate reductase”: G. C. K. Roberts in *Chemistry and Biology of Pteridines* (Ed.: J. A. Blair), W. de Gruyter, Berlin, **1983**, pp. 197–214.
- [23] “NMR studies of protein ligand interactions”: J. Feeney in *NMR of Biological Macromolecules* (Ed.: S. I. Stassinopoulou), Springer, Berlin, **1994**, pp. 115–154.
- [24] J. Feeney, *Biochem. Pharmacol.* **1990**, 40, 141–152; “NMR studies of dynamic processes and multiple conformations in protein ligand complexes”: J. Feeney in *NMR and Biomolecular Structure* (Eds.: M. Bertino, T. Molinari, A. Niccolai), VCH, Weinheim, **1991**, pp. 189–205.

- [25] "NMR studies of ligand binding to dihydrofolate reductase and their application in drug design": J. Feeney in *NMR in Drug Design* (Ed.: D. Craik), CRC, Boca Raton, FL, **1996**, pp. 275–313.
- [26] "NMR spectroscopy and drug design: lessons from dihydrofolate reductase inhibitors": B. Birdsall in *The Scientific Basis of Antimicrobial Chemotherapy* (Eds.: D. Greenwood, F. O'Grady), Cambridge University Press, Cambridge, **1985**, pp. 267–281.
- [27] B. Birdsall, J. Andrews, G. Ostler, S. J. B. Tendler, W. Davies, J. Feeney, G. C. K. Roberts, H. T. A. Cheung, *Biochemistry* **1989**, *28*, 1353–1362.
- [28] S. J. Benkovic, C. A. Fierke, A. M. Naylor, *Science* **1988**, *239*, 1105–1110.
- [29] S. J. Benkovic, J. A. Adams, C. A. Fierke, A. M. Naylor, *Pteridines Folic Acid Deriv.* **1989**, *1*, 37–43.
- [30] J. Thillet, J. Absil, S. R. Stone, R. Pictet, *J. Biol. Chem.* **1988**, *263*, 12500–12508.
- [31] J. E. Villafranca, E. E. Howell, D. H. Voet, M. S. Strobel, R. C. Ogden, J. N. Abelson, J. Kraut, *Science* **1983**, *222*, 782–788.
- [32] J. Feeney, B. Birdsall, G. C. K. Roberts, A. S. V. Burgen, *NMR in Biology* (Eds.: R. A. Dwek, I. D. Campbell, R. E. Richards, R. J. P. Williams), Academic Press, London, **1977**, pp. 111–124; J. Feeney, B. Birdsall, J. P. Albrand, G. C. K. Roberts, A. S. V. Burgen, P. A. Charlton, D. W. Young, *Biochemistry* **1981**, *20*, 1837–1842.
- [33] D. P. Baccanari, S. Daluge, R. W. King, *Biochemistry* **1982**, *21*, 5068–5075.
- [34] B. Birdsall, E. I. Hyde, A. S. V. Burgen, G. C. K. Roberts, J. Feeney, *Biochemistry* **1981**, *20*, 7186–7195.
- [35] B. Birdsall, A. S. V. Burgen, G. C. K. Roberts, *Biochemistry* **1980**, *19*, 3732–3737; B. Birdsall, A. S. V. Burgen, G. C. K. Roberts, *Biochemistry* **1980**, *19*, 3723–3731.
- [36] C. L. Fisher, V. A. Roberts, A. T. Hagler, *Biochemistry* **1991**, *30*, 3518–3526.
- [37] S. H. Fleischman, C. I. Brooks III, *Proteins Struct. Funct. Genet.* **1990**, *7*, 52–61.
- [38] J. G. Dann, G. Ostler, R. A. Bjur, R. W. King, P. Scudder, P. C. Turner, G. C. K. Roberts, A. S. V. Burgen, *Biochem. J.* **1976**, *157*, 559–571.
- [39] E. J. Pastore, M. Friedkin, *J. Biol. Chem.* **1962**, *237*, 3002–3010.
- [40] M. Y. Lorenson, G. F. Maley, F. Maley, *J. Biol. Chem.* **1967**, *242*, 3332–3344.
- [41] P. A. Charlton, D. W. Young, B. Birdsall, J. Feeney, G. C. K. Roberts, *J. Chem. Soc. Chem. Commun.* **1979**, 922–924.
- [42] P. A. Charlton, D. W. Young, B. Birdsall, J. Feeney, G. C. K. Roberts, *J. Chem. Soc. Perkin Trans. 2* **1985**, 1349–1353.
- [43] "X-ray crystallography studies of the structure of 5,10-methylenetetrahydrofolic acid": J. C. Fontecilla-Camps, C. E. Bugg, C. Temple, J. D. Rose, J. A. Montgomery, R. L. Kisluk in *Chemistry and Biology of Pteridines* (Eds.: R. L. Kisluk, G. M. Brown), Elsevier, New York, **1979**, pp. 235–240.
- [44] J. C. Fontecilla-Camps, C. E. Bugg, C. Temple, J. D. Rose, J. A. Montgomery, R. L. Kisluk, *J. Am. Chem. Soc.* **1979**, *101*, 6114–6115.
- [45] "Dihydrofolate reductases as targets for selective inhibitors": G. R. Hitchings, B. Roth in *Enzyme Inhibitors as Drugs* (Ed.: M. Sandler), Macmillan, London, **1980**, pp. 263–270.
- [46] H. T. A. Cheung, B. Birdsall, T. A. Frenkiel, J. Feeney, *Biochemistry* **1993**, *32*, 6846–6854.
- [47] B. S. Selinsky, M. E. Perlman, R. E. London, C. J. Unkefer, J. Mitchell, R. L. Blakley, *Biochemistry* **1990**, *29*, 1290–1296.
- [48] C. Bystroff, S. J. Oatley, J. Kraut, *Biochemistry* **1993**, *29*, 3263–3277.
- [49] R. L. Blakley, J. R. Appleman, J. H. Freisheim, M. J. Jablonsky, *Arch. Biochem. Biophys.* **1993**, *306*, 501–509.
- [50] W. R. Cannon, B. J. Garrison, S. J. Benkovic, *J. Am. Chem. Soc.* **1997**, *119*, 2386–2395.
- [51] B. Birdsall, M. G. Cassarotto, H. T. A. Cheung, J. Basran, G. C. K. Roberts, J. Feeney, *FEBS Lett.* **1997**, *402*, 157–161.
- [52] C. J. Falzone, S. J. Benkovic, P. E. Wright, *Biochemistry* **1990**, *29*, 9667–9677.
- [53] B. J. Stockman, N. R. Nirmala, G. Wagner, T. J. Delcamp, M. T. DeYarman, J. H. Freisheim, *Biochemistry* **1992**, *31*, 218–229.
- [54] I. P. Gerotheranassis, B. Birdsall, C. J. Bauer, T. A. Frenkiel, J. Feeney, *J. Mol. Biol.* **1992**, *204*, 549–554.
- [55] E. M. Meiering, H. J. Li, T. J. Delcamp, J. H. Freisheim, G. Wagner, *J. Mol. Biol.* **1995**, *247*, 309–325; E. M. Meiering, G. Wagner, *J. Mol. Biol.* **1995**, *247*, 294–308.
- [56] J. Andrews, C. A. Fierke, B. Birdsall, G. Ostler, J. Feeney, G. C. K. Roberts, S. J. Benkovic, *Biochemistry* **1989**, *28*, 5743–5750.
- [57] C. R. Wagner, J. Thillet, S. J. Benkovic, *Biochemistry* **1992**, *31*, 7834–7840.
- [58] G. Maharaj, B. S. Selinsky, J. R. Appleman, M. Perlman, R. E. London, R. L. Blakley, *Biochemistry* **1990**, *29*, 4554–4560.
- [59] K. Wüthrich, *NMR of Proteins and Nucleic Acids*, Wiley, **1986**; K. Wüthrich, *Science* **1989**, *243*, 45–50.
- [60] G. M. Clore, A. M. Gronenborn, *Science* **1991**, *252*, 1390–1399.
- [61] M. D. Carr, B. Birdsall, J. Jimenez-Barbero, V. I. Polshakov, C. J. Bauer, T. A. Frenkiel, G. C. K. Roberts, J. Feeney, *Biochemistry* **1991**, *30*, 6330–6341.
- [62] A. Soteriou, M. D. Carr, T. A. Frenkiel, J. E. McCormick, C. J. Bauer, D. Sali, B. Birdsall, J. Feeney, *J. Biomol. NMR* **1993**, *3*, 535–546.
- [63] S. Altmann, A. M. Labhardt, H. Senn, K. Wüthrich, *J. Biomol. NMR* **1997**, *9*, 445–446.
- [64] J. Andrews, G. M. Clore, R. W. Davies, A. M. Gronenborn, B. Gronenborn, D. Kalderon, P. C. Papadopoulos, S. Schafer, P. F. G. Sims, R. Stancombe, *Gene* **1985**, *35*, 217–222.
- [65] M. Ikura, L. E. Kay, A. Bax, *Biochemistry* **1990**, *29*, 4659–4667.
- [66] T. A. Frenkiel, C. J. Bauer, M. D. Carr, B. Birdsall, J. Feeney, *J. Magn. Reson.* **1990**, *90*, 420–425.
- [67] M. Ikura, A. Bax, G. M. Clore, A. M. Gronenborn, *J. Am. Chem. Soc.* **1990**, *112*, 9020–9022.
- [68] G. M. Clore, A. M. Gronenborn, *Prog. NMR Spectrosc.* **1992**, *23*, 43–92.
- [69] L. E. Kay, M. Ikura, R. Tschudin, A. Bax, *J. Magn. Reson.* **1990**, *89*, 496–514.
- [70] G. W. Vuister, A. Bax, *J. Am. Chem. Soc.* **1993**, *115*, 7772–7777.
- [71] S. J. Archer, M. Ikura, D. A. Torchia, A. Bax, *J. Magn. Reson.* **1991**, *95*, 636–641.
- [72] A. Bax, G. M. Clore, P. C. Driscoll, A. M. Gronenborn, M. Ikura, L. E. Kay, *J. Magn. Reson.* **1990**, *87*, 620–627.
- [73] S. W. Fesik, E. R. P. Zuiderweg, *Quart. Rev. Biophys.* **1990**, *23*, 97–131.
- [74] L. Braunschweiler, R. R. Ernst, *J. Magn. Reson.* **1983**, *53*, 521–528.
- [75] D. G. Davis, A. Bax, *J. Am. Chem. Soc.* **1985**, *107*, 2820–2821.
- [76] S. J. Hammond, B. Birdsall, M. S. Searle, G. C. K. Roberts, J. Feeney, *J. Mol. Biol.* **1986**, *188*, 81–97.
- [77] J. Feeney, G. C. K. Roberts, B. Birdsall, D. V. Griffiths, R. W. King, P. Scudder, A. S. V. Burgen, *Proc. R. Soc. London B* **1977**, *196*, 267–290; D. V. Griffiths, J. Feeney, G. C. K. Roberts, A. S. V. Burgen, *Biochim. Biophys. Acta* **1976**, *446*, 479–485; J. Feeney, G. C. K. Roberts, D. V. Griffiths, J. Thomson, R. W. King, A. S. V. Burgen, *Biochemistry* **1980**, *19*, 2316–2321; J. Feeney, B. Birdsall, J. Akiboye, S. J. B. Tendler, J. Jimenez-Barbero, G. Ostler, J. R. P. Arnold, G. C. K. Roberts, A. Kühn, K. Roth, *FEBS Lett.* **1989**, *248*, 57–61.
- [78] M. S. Searle, S. J. Hammond, B. Birdsall, G. C. K. Roberts, J. Feeney, R. W. King, D. V. Griffiths, *FEBS Lett.* **1986**, *194*, 165–170.
- [79] B. Birdsall, J. Feeney, D. V. Griffiths, S. Hammond, B. J. Kimber, R. W. King, G. C. K. Roberts, M. S. Searle, *FEBS Lett.* **1984**, *175*, 364–368.
- [80] J. Feeney, B. Birdsall, G. Ostler, M. D. Carr, M. Kairi, *FEBS Lett.* **1990**, *272*, 197–199.
- [81] G. Ostler, A. Soteriou, C. M. Moody, J. A. Khan, B. Birdsall, M. D. Carr, D. W. Young, J. Feeney, *FEBS Lett.* **1993**, *318*, 177–180.
- [82] B. Birdsall, J. R. P. Arnold, J. Jimenez-Barbero, T. A. Frenkiel, C. J. Bauer, S. J. B. Tendler, M. D. Carr, J. A. Thomas, G. C. K. Roberts, J. Feeney, *Eur. J. Biochem.* **1990**, *191*, 659–668.
- [83] J. Feeney, G. C. K. Roberts, R. Kaptein, B. Birdsall, A. Gronenborn, A. S. V. Burgen, *Biochemistry* **1980**, *19*, 2466–2472.
- [84] B. J. Kimber, D. V. Griffiths, B. Birdsall, R. W. King, P. Scudder, J. Feeney, G. C. K. Roberts, A. S. V. Burgen, *Biochemistry* **1977**, *16*, 3492–3500; B. J. Kimber, J. Feeney, G. C. K. Roberts, B. Birdsall, A. S. V. Burgen, B. D. Sykes, *Nature* **1978**, *271*, 184–185.
- [85] J. Feeney, J. E. McCormick, C. J. Bauer, B. Birdsall, C. M. Moody, B. A. Starkmann, D. W. Young, P. Francis, R. H. Havlin, W. D. Arnold, E. Oldfield, *J. Am. Chem. Soc.* **1996**, *118*, 8700–8706.

- [86] L. Cocco, B. Roth, C. Temple, J. A. Montgomery, R. E. London, R. L. Blakley, *Arch. Biochem. Biophys.* **1981**, *226*, 567–577; L. Cocco, R. L. Blakley, T. I. Walker, R. E. London, N. A. Matwiyoff, *Biochemistry* **1978**, *17*, 4285–4290.
- [87] G. C. K. Roberts, J. Feeney, A. S. V. Burgen, V. Yuferov, J. Dann, R. Bjur, *Biochemistry* **1974**, *13*, 5351–5357.
- [88] J. Feeney, J. G. Batchelor, J. P. Albrand, G. C. K. Roberts, *J. Magn. Reson.* **1979**, *33*, 519–529.
- [89] B. Birdsall, A. Gronenborn, E. I. Hyde, G. M. Clore, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Biochemistry* **1982**, *21*, 5831–5838.
- [90] B. Birdsall, J. De Graw, J. Feeney, S. J. Hammond, M. S. Searle, G. C. K. Roberts, W. T. Colwell, J. Crase, *FEBS Lett.* **1987**, *217*, 106–110.
- [91] H. T. A. Cheung, B. Birdsall, J. Feeney, *FEBS Lett.* **1992**, *312*, 147–151.
- [92] A. W. Bevan, G. C. K. Roberts, J. Feeney, I. Kuyper, *Eur. Biophys. J.* **1985**, *11*, 211–218.
- [93] M. S. Searle, M. J. Forster, B. Birdsall, G. C. K. Roberts, J. Feeney, H. T. A. Cheung, I. Kompis, A. J. Geddes, *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 3787–3791.
- [94] H. T. A. Cheung, M. S. Searle, J. Feeney, B. Birdsall, G. C. K. Roberts, I. Kompis, S. J. Hammond, *Biochemistry* **1986**, *25*, 1925–1931.
- [95] F.-Y. Huang, Q.-X. Yang, T.-H. Huang, *FEBS Lett.* **1991**, *289*, 231–234.
- [96] F.-Y. Huang, Q.-X. Yang, T.-H. Huang, L. Gelbaum, L. F. Kuyper, *FEBS Lett.* **1991**, *283*, 44–46.
- [97] S. W. Fesik, E. R. P. Zuiderweg, E. T. Olejniczak, R. T. Gampe, Jr., *Biochem. Pharmacol.* **1990**, *40*, 161–167.
- [98] M. Ikura, L. E. Kay, A. Bax, *Biochemistry* **1990**, *29*, 4659–4667.
- [99] B. Birdsall, V. I. Polshakov, J. Feeney, unpublished results.
- [100] E. I. Hyde, B. Birdsall, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Biochemistry* **1980**, *19*, 3738–3746; E. I. Hyde, B. Birdsall, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Biochemistry* **1980**, *19*, 3746–3754; J. L. Way, B. Birdsall, J. Feeney, G. C. K. Roberts, A. S. V. Burgen, *Biochemistry* **1975**, *14*, 3470–3475.
- [101] B. Birdsall, G. C. K. Roberts, J. Feeney, J. G. Dann, A. S. V. Burgen, *Biochemistry* **1983**, *22*, 5597–5604; B. Birdsall, J. Feeney, G. C. K. Roberts, A. S. V. Burgen, *FEBS Lett.* **1980**, *120*, 107–109.
- [102] S. J. B. Tendler, R. J. Griffin, B. Birdsall, M. F. G. Stevens, G. C. K. Roberts, J. Feeney, *FEBS Lett.* **1988**, *240*, 201–204; B. Birdsall, S. J. B. Tendler, J. R. P. Arnold, J. Feeney, R. J. Griffin, M. D. Carr, J. A. Thomas, G. C. K. Roberts, M. F. G. Stevens, *Biochemistry* **1990**, *29*, 9660–9667; J. Feeney, C. J. Bauer, T. Frenkiel, B. Birdsall, M. D. Carr, G. C. K. Roberts, J. R. P. Arnold, *J. Magn. Reson.* **1991**, *91*, 607–613.
- [103] J. P. Albrand, B. Birdsall, J. Feeney, G. C. K. Roberts, A. S. V. Burgen, *Int. J. Biol. Macromol.* **1979**, *1*, 37–41; J. Feeney, B. Birdsall, G. C. K. Roberts, A. S. V. Burgen, *Biochemistry* **1983**, *22*, 628–633.
- [104] P. J. Cayley, J. P. Albrand, J. Feeney, G. C. K. Roberts, E. A. Piper, A. S. V. Burgen, *Biochemistry* **1979**, *18*, 3886–3895.
- [105] A. M. Gronenborn, G. M. Clore, *Biochem. Pharmacol.* **1990**, *40*, 115–119.
- [106] N. Curtiss, S. Moore, B. Birdsall, J. Bloxidge, C. Gibson, J. R. Jones, J. Feeney, *Biochem. J.* **1994**, *303*, 401–405.
- [107] G. M. Clore, A. M. Gronenborn, B. Birdsall, J. Feeney, G. C. K. Roberts, *Biochem. J.* **1984**, *217*, 659–666.
- [108] J. Feeney, B. Birdsall, G. C. K. Roberts, A. S. V. Burgen, *Nature* **1975**, *257*, 564–566; B. Birdsall, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *FEBS Lett.* **1977**, *80*, 313–316; I. P. Gerotheranassis, B. Birdsall, C. J. Bauer, J. Feeney, *Eur. J. Biochem.* **1992**, *204*, 173–177.
- [109] P. J. Cayley, J. Feeney, B. J. Kimber, *Int. J. Biol. Macromol.* **1980**, *2*, 251–255.
- [110] B. Birdsall, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *FEBS Lett.* **1977**, *80*, 313–316.
- [111] M. P. Williamson, T. K. Havel, K. Wüthrich, *J. Mol. Biol.* **1985**, *182*, 295–315.
- [112] A. T. Brünger, X-PLOR 3.1.—A system for X-ray crystallography and NMR. Yale University Press, New Haven, CT **1992**.
- [113] M. Nilges, A. M. Gronenborn, A. T. Brünger, G. M. Clore, *Protein Eng.* **1988**, *2*, 27–38.
- [114] V. I. Polshakov, T. A. Frenkiel, B. Birdsall, A. Soteriou, J. Feeney, *J. Magn. Reson. Ser. X* **1995**, *108*, 31–43.
- [115] M. J. Gradwell, J. Feeney, *J. Biomol. NMR* **1996**, *7*, 48–58.
- [116] D. J. Antonjuk, B. Birdsall, A. S. V. Burgen, H. T. A. Cheung, G. M. Clore, J. Feeney, A. Gronenborn, G. C. K. Roberts, W. Tran, *Br. J. Pharmacol.* **1984**, *81*, 309–315.
- [117] B. Birdsall, J. Feeney, C. Pascual, G. C. K. Roberts, I. Kompis, R. L. Then, K. Muller, A. Kroehn, *J. Med. Chem.* **1984**, *23*, 1672–1676.
- [118] V. I. Polshakov, W. D. Morgan, B. Birdsall, J. Feeney, *J. Biomol. NMR* **1999**, *14*, 115–122.
- [119] L. Cocco, J. P. Groff, C. Temple, Jr., J. A. Montgomery, R. E. London, N. S. Matwiyoff, R. L. Blakley, *Biochemistry* **1981**, *20*, 3972–3978.
- [120] R. E. London, E. E. Howell, M. S. Warren, J. Kraut, *Biochemistry* **1986**, *25*, 7229–7235.
- [121] W. R. Cannon, B. J. Garrison, S. J. Benkovic, *J. Mol. Biol.* **1997**, *271*, 656–668.
- [122] G. C. K. Roberts, J. Feeney, A. S. V. Burgen, S. Daluge, *FEBS Lett.* **1981**, *131*, 85–88.
- [123] G. E. Dale, C. Broger, A. D'Arcy, P. G. Hartman, R. DeHoogt, S. Jolidon, I. Kompis, A. M. Labhardt, H. Langen, H. Locher, M. G. P. Page, D. Stuber, R. L. Then, B. Wipf, C. Oefner, *J. Mol. Biol.* **1997**, *266*, 23–30.
- [124] A. R. Gargaro, T. A. Frenkiel, P. M. Nieto, B. Birdsall, V. I. Polshakov, W. D. Morgan, J. Feeney, *Eur. J. Biochem.* **1996**, *238*, 435–439.
- [125] P. M. Nieto, B. Birdsall, W. D. Morgan, T. A. Frenkiel, A. R. Gargaro, J. Feeney, *FEBS Lett.* **1997**, *405*, 16–20.
- [126] a) T. Yamazaki, S. M. Pascal, A. U. Singer, J. D. Forman-Kay, L. E. Kay, *J. Am. Chem. Soc.* **1995**, *117*, 3556–3564; b) G. Wagner, G. Bodenhausen, N. Muller, M. Rance, O. W. Sorensen, R. R. Ernst, K. Wüthrich, *J. Am. Chem. Soc.* **1985**, *107*, 6440–6446; c) G. Wider, D. Neri, K. Wüthrich, *J. Biomol. NMR* **1991**, *1*, 93–98.
- [127] R. J. Smith, D. H. Williams, K. James, *J. Chem. Soc. Chem. Commun.* **1989**, 682–683.
- [128] G. D. Henry, B. D. Sykes, *J. Biomol. NMR* **1995**, *5*, 59–66.
- [129] I. P. Gerotheranassis, P. J. Barrie, B. Birdsall, J. Feeney, *Eur. J. Biochem.* **1996**, *235*, 262–266.
- [130] B. Birdsall, D. V. Griffiths, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Proc. R. Soc. London B* **1977**, *196*, 251–265.
- [131] A. M. Gronenborn, B. Birdsall, E. I. Hyde, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Biochemistry* **1981**, *20*, 1717–1722.
- [132] P. Wyeth, A. Gronenborn, B. Birdsall, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Biochemistry* **1980**, *19*, 2608–2615.
- [133] C. E. Johnson, F. A. Bovey, *J. Chem. Phys.* **1958**, *29*, 1012–1014.
- [134] D. R. Seeger, D. B. Cosulich, J. M. Smith, M. E. Hultquist, *J. Am. Chem. Soc.* **1949**, *71*, 1753–1758.
- [135] B. J. Roth, C. C. Cheng, *Prog. Med. Chem.* **1982**, *19*, 1–58.
- [136] K. A. Ohemeng, B. J. Roth, *Med. Chem.* **1991**, *30*, 3518–3526.
- [137] V. Cody, N. Galitsky, J. R. Luft, W. Pangborn, A. Rosowsky, R. L. Blakley, *Biochemistry* **1997**, *36*, 13897–13903.
- [138] C. D. Selassie, Z. X. Fang, R. L. Li, C. Hansch, G. Debnath, T. E. Klein, R. Langridge, B. T. Kaufman, *J. Med. Chem.* **1989**, *32*, 1895–1905.
- [139] B. J. Roth, *Fed. Proc.* **1986**, *45*, 2765–2772.
- [140] L. F. Kuyper, B. Roth, D. P. Baccanari, R. Ferone, C. R. Beddell, J. N. Champness, D. K. Stammers, J. G. Dann, F. E. Norrington, D. J. Baker, P. J. Goodford, *J. Med. Chem.* **1982**, *25*, 1120–1122.
- [141] C. Hansch, *Drug Intell. Clin. Pharm.* **1982**, *16*, 391–396.
- [142] B. J. Roth, E. Aig, *J. Med. Chem.* **1987**, *30*, 1998–2004.
- [143] W. D. Morgan, B. Birdsall, P. M. Nieto, A. R. Gargaro, J. Feeney, *Biochemistry* **1999**, *38*, 2127–2134.
- [144] R. J. Breckenridge, *Experientia* **1991**, *147*, 1148–1161.
- [145] D. M. Epstein, S. J. Benkovic, P. E. Wright, *Biochemistry* **1995**, *34*, 11037–11048.
- [146] G. Otting, K. Wüthrich, *J. Magn. Reson.* **1989**, *85*, 586–594.
- [147] C. S. Verma, S. Fischer, L. S. D. Caves, G. C. K. Roberts, R. E. Hubbard, *J. Phys. Chem.* **1996**, *100*, 2510–2518.
- [148] V. I. Polshakov, B. Birdsall, J. Feeney, *Biochemistry* **1999**, *38*, 15962–15969.
- [149] A. S. V. Burgen, G. C. K. Roberts, J. Feeney, *Nature* **1975**, *253*, 753–754.

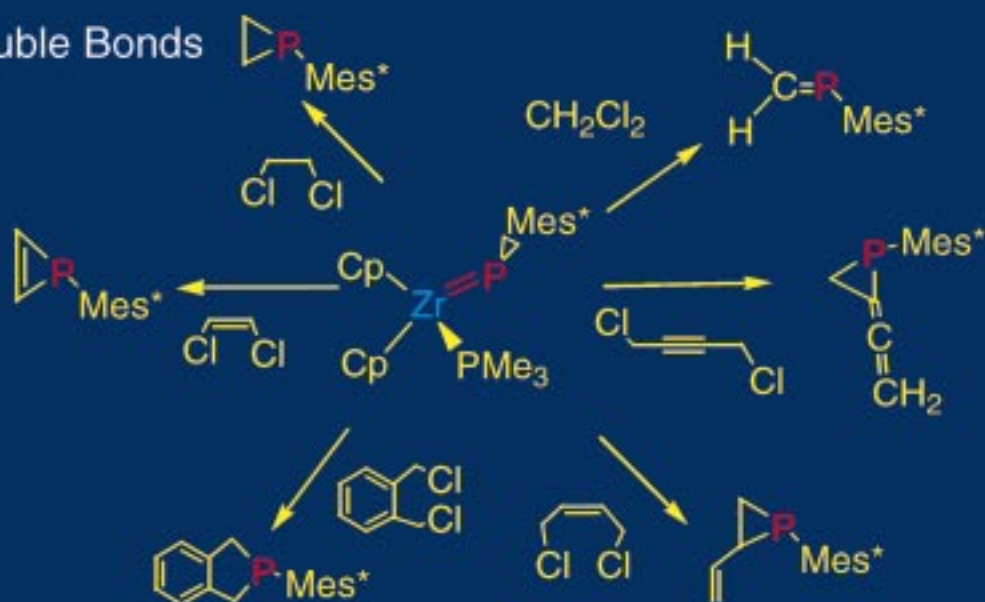
- [150] L. Li, C. J. Falzone, P. E. Wright, S. J. Benkovic, *Biochemistry* **1992**, *31*, 7826–7833.
- [151] B. Birdsall, A. Gronenborn, G. M. Clore, E. I. Hyde, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Pteridines Folic Acid Deriv.* **1982**, 563–566.
- [152] B. Birdsall, A. Gronenborn, G. M. Clore, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Biochem. Biophys. Res. Commun.* **1981**, *101*, 1139–1144.
- [153] “Dihydrofolate reductase: interactions with the coenzyme NADPH”: J. Feeney, B. Birdsall, G. C. K. Roberts, A. S. V. Burgen in *NMR in Biology* (Eds.: R. A. Dwek, I. D. Campbell, R. E. Richards, R. J. P. Williams), Academic Press, London, **1977**, pp. 111–124.
- [154] J. P. Groff, R. E. London, L. Cocco, R. L. Blakley, *Biochemistry* **1981**, *20*, 6169–6178.
- [155] M. Johnson, E. M. Meiering, J. E. Wright, J. Pardo, A. Rosowsky, G. Wagner, *Biochemistry* **1997**, *36*, 4399–4411.
- [156] A. M. Gronenborn, B. Birdsall, E. I. Hyde, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Nature* **1981**, *290*, 273–274.
- [157] A. M. Gronenborn, B. Birdsall, E. I. Hyde, G. C. K. Roberts, J. Feeney, A. S. V. Burgen, *Mol. Pharm.* **1981**, *20*, 145–153; B. Birdsall, A. W. Bevan, C. Pascual, G. C. K. Roberts, J. Feeney, A. Gronenborn, G. M. Clore, *Biochemistry* **1984**, *23*, 4733–4742; B. Birdsall, J. Feeney, S. J. B. Tendler, S. J. Hammond, G. C. K. Roberts, *Biochemistry* **1989**, *28*, 2297–2305.
- [158] R. E. London, G. P. Groff, R. L. Blakley, *Biochem. Biophys. Res. Commun.* **1979**, *86*, 779–786.
- [159] S. J. Hammond, B. Birdsall, J. Feeney, M. S. Searle, G. C. K. Roberts, H. T. A. Cheung, *Biochemistry* **1987**, *26*, 8585–8590.
- [160] C. J. Falzone, P. E. Wright, S. J. Benkovic, *Biochemistry* **1991**, *30*, 2184–2191.
- [161] G. M. Clore, G. C. K. Roberts, A. Gronenborn, B. Birdsall, J. Feeney, *J. Magn. Reson.* **1981**, *45*, 151–161.
- [162] B. T. Hill, L. A. Price, *Cancer Treat. Rev.* **1980**, *7*, 95–112.
- [163] E. A. Bliss, R. J. Griffin, M. F. G. Stevens, *J. Chem. Soc. Perkin Trans. I* **1987**, 2217–2228.
- [164] R. J. Griffin, M. A. Meek, C. H. Schwalbe, M. F. G. Stevens, *J. Med. Chem.* **1989**, *32*, 2468–2474.
- [165] D. J. Baker, C. R. Beddell, J. N. Champness, P. J. Goodford, F. E. A. Norrington, B. Roth, D. K. Stammers in *Chemistry and Biology of Pteridines* (Ed.: J. D. Blair), W. de Gruyter, Berlin, **1982**, pp. 545–549.
- [166] R. L. Blakley, *The Biochemistry of Folic Acid and Related Pteridines*, North–Holland, Amsterdam–London, **1969**.
- [167] M. A. Jimenez, J. R. P. Arnold, J. Andrews, J. A. Thomas, G. C. K. Roberts, B. Birdsall, J. Feeney, *Protein Eng.* **1989**, *2*, 627–631.
- [168] J. Basran, M. G. Casarotto, I. L. Barsukov, G. C. K. Roberts, *Biochemistry*, **1995**, *34*, 2872–2882.
- [169] J. H. Prestegard, *Nat. Struct. Biol. NMR Suppl.* **1998**, 517–522.
- [170] S. B. Shuker, P. J. Hajduk, R. P. Meadows, S. W. Fesik, *Science* **1996**, *274*, 1531–1534.
- [171] P. J. Hajduk, G. Sheppard, D. G. Nettesheim, E. T. Olejniczak, S. B. Shuker, R. P. Meadows, D. H. Steinman, G. M. Carrera, P. A. Marcotte, J. Severin, K. Walter, H. Smith, E. Gubbins, R. Simmer, T. F. Holzman, D. W. Morgan, S. K. Davidsen, J. B. Summers, S. W. Fesik, *J. Am. Chem. Soc.* **1997**, *119*, 5818–5827.
- [172] P. Kraulis, *J. Appl. Crystallogr.* **1991**, *24*, 946–950.

Zirconium-Phosphorus Chemistry

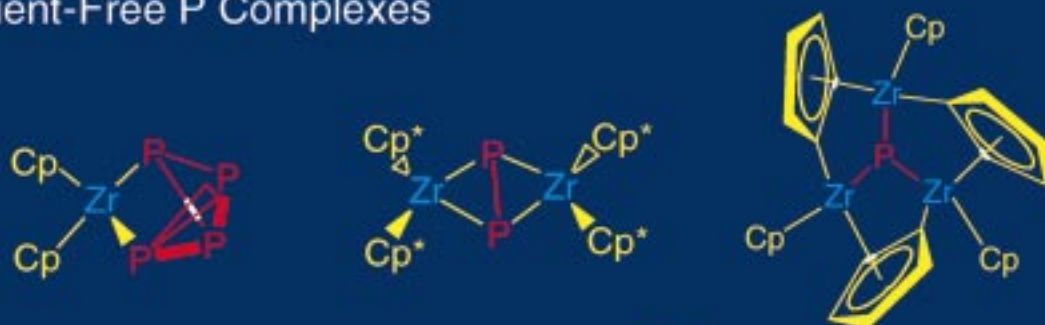
Zr-P Single Bonds



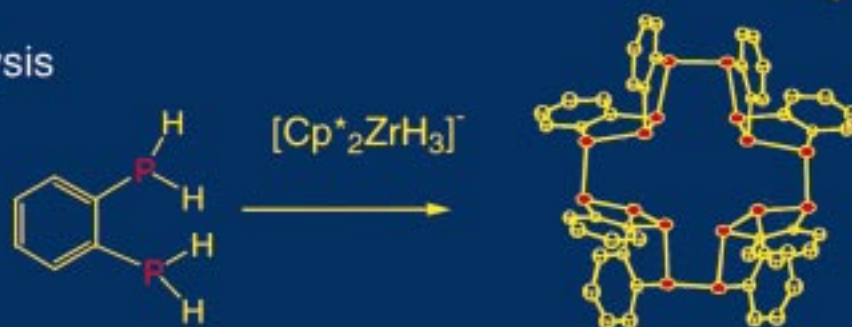
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Substituent-Free P Complexes



Catalysis



Zirconium – Phosphorus Chemistry: Strategies in Syntheses, Reactivity, Catalysis, and Utility

Douglas W. Stephan*

The extension of the principles of organometallic chemistry to applications in metal-mediated syntheses of main group compounds is an emerging subdiscipline that is drawing much current attention. This review focuses on a subset of this area, specifically the utility of Zr–P compounds in organophosphorus chemistry. Until the early 1980s only a handful of compounds containing Zr–P bonds were known, and virtually nothing was known about their reactivity. In the past fifteen years

this area has developed dramatically. Early emphasis was on the synthesis and reactivity of complexes containing Zr–P single bonds. Subsequently, synthetic strategies for compounds containing Zr–P double bonds, phosphazirconacycles, and Zr complexes of substituent-free phosphorus were developed. Each of these classes of Zr–P compounds exhibits a unique reactivity that often permits the stoichiometric syntheses of unprecedented organophosphorus compounds. Moreover, in

recent studies this reactivity has been exploited in catalytic syntheses of organophosphorus oligomers. Overall, the rich chemistry of Zr–P compounds and their utility in the preparation of phosphorus compounds illustrate the potential of this organometallic approach to the synthesis of main group compounds.

Keywords: homogeneous catalysis • phosphorus • P ligands • zirconium

1. Introduction

The battery of stoichiometric and catalytic synthetic strategies that are based on organometallic chemistry hinges on the principles of synthesis and reactivity of metal–carbon bonds. In the past ten years, there have been growing efforts to broaden the range of application of organometallic chemistry to include main group elements. These endeavors led to the characterization of a number of structurally unprecedented compounds, yet metal-mediated syntheses of main group compounds have only just begun to emerge. We and others have contributed to this hybrid field of main group/transition metal organometallic chemistry by focusing on the potential of Zr–P compounds. Upon commencement of these studies in the 1980s, the known Zr–P chemistry was very limited, and the reactivity of compounds containing Zr–P σ bonds was virtually unexplored. This review recounts developments in both the syntheses and reactivity of Zr–P complexes. Synthetic strategies for compounds containing Zr–P double bonds, phosphazirconacycles, and Zr complexes

of substituent-free phosphorus are described. These classes of Zr–P derivatives demonstrate unique reactivity, often applicable to stoichiometric syntheses of unprecedented organophosphorus compounds. More recently, Zr–P chemistry has been extended to catalytic syntheses of organophosphorus oligomers. This progression from synthesis and reactivity to application in organophosphorus chemistry illustrates the potential of organometallic reagents in the synthesis of compounds of the main group elements.

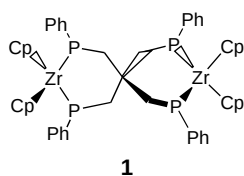
2. Synthesis and Reactivity of Zirconium Phosphanido and Phosphanato Complexes

The challenge addressed by early research was simply the development of synthetic methodologies for the preparation of species containing Zr–P σ bonds. Several approaches are described below. A detailed account of structural and spectroscopic data of some of these compounds formed part of an earlier review.^[1]

2.1. Halide Metathesis

Zr–P chemistry began with the pioneering efforts of Issleib and Häckert.^[2] The reaction of $[\text{Cp}_2\text{MX}_2]$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$) with

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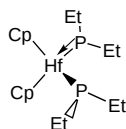


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LiPR_2 was reported to give the Ti^{III} and Zr^{III} dimers $[\{\text{Cp}_2\text{M}(\mu\text{-PR}_2)\}_2]$ ($\text{R} = \text{Et}, \text{Bu}$) and the by-product P_2R_4 . In the following year, Ellerman and Poersch described the first $\text{Zr}^{\text{IV}}\text{-P}$ compound

1, derived from the reaction of $[\text{Cp}_2\text{ZrCl}_2]$ and $[\text{NaP}(\text{Ph})\text{CH}_2]_4\text{C}$ in liquid ammonia.^[3]

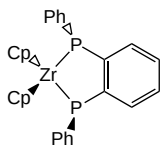
These early papers prompted much of what was to follow in the 1980s. Baker et al. reported the synthesis of complexes of the form $[\text{Cp}_2\text{M}(\text{PR}_2)_2]$ ($\text{M} = \text{Zr}, \text{Hf}$; $\text{R} = \text{Et}, \text{Cy}, \text{Ph}$) in 1983.^[4] These species could be reduced to the Zr^{III} analogues



2

$[\text{Na}(\text{thf})_x][\text{Cp}_2\text{Zr}(\text{PR}_2)_2]$. X-ray structural data for **2** revealed unequal Hf-P bond lengths (2.488(1), 2.682(1) Å), and this confirmed the ability of phosphorus to act as a π donor to give a formally 18-electron Hf center. Variable-temperature NMR data revealed a barrier to rotation about the Hf-P double bond of 6.0(2) kcal mol⁻¹ in $[\text{Cp}_2\text{Hf}(\text{PCy}_2)_2]$. In the

same year, Baker et al. also described a variety of homoleptic compounds, including $[\text{Li}(\text{dme})_n][\text{M}(\text{PCy}_2)_5]$ ($\text{M} = \text{Zr}, \text{Hf}$; $\text{dme} = 1,2\text{-dimethoxyethane}$) and $[\text{Li}(\text{dme})_n][\text{M}(\text{PCy}_2)_4]$ ($\text{M} = \text{Ti}, \text{Zr}$), which were derived from the metathesis of LiPCy_2 with appropriate THF adducts of metal halides.^[5] Similar synthetic procedures gave a variety of silylphosphanido complexes of the form $[(\text{C}_5\text{H}_4\text{R})_2\text{M}(\text{X})_{2-n}(\text{P}(\text{SiMe}_3)_2)_n]$

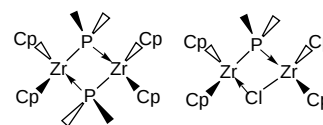


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($\text{R} = \text{H}, \text{SiMe}_3$; $\text{M} = \text{Zr}, \text{Hf}$; $\text{X} = \text{Cl}, \text{Me}$), and a number of primary phosphanido complexes were prepared from lithium phosphanides and the corresponding metallocene dihalide or methylmetallocene halide.^[6-11] The chelate complex **3** was prepared by the reaction of $[\{1,2\text{-(PPh)}_2\text{C}_6\text{H}_4\}\{\text{Li}(\text{tmeda})\}_2]$ ($\text{tmeda} = N,N,N',N'\text{-tetramethylethylenediamine}$)

with $[\text{Cp}_2\text{ZrCl}_2]$.^[12-14]

As mentioned above, Issleib et al. established in 1966 that electron-rich lithium phosphanides can reduce Zr^{IV} and Ti^{IV} .^[2] However, it was not until 1988 that Gambarotta et al. reported the first X-ray structural data for the Zr^{III} dimers **4** and **5**.^[15] We subsequently reported structural and magnetic studies on $[\{\text{Cp}_2\text{M}(\mu\text{-PET}_2)\}_2]$ ($\text{M} = \text{Ti}, \text{Zr}$),^[16] and Hey-Haw-

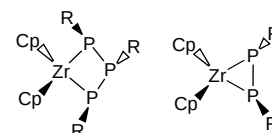


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kins et al. structurally characterized $[\{\text{Cp}_2\text{Zr}(\mu\text{-PHR})\}_2]$ ($\text{R} = t\text{Bu}, \text{adamantyl}$).^[17] Theoretical studies on dinuclear Zr^{III} complexes led to the controversial proposal of “superlong” metal-metal bonds. Ab initio and Hartree-Fock-Slater calculations were used to support the notion that metal-metal bonds exist in these dimers, despite the fact that the metal atoms are separated by more than 3.5 Å.^[18-20]

As early as 1972 Issleib et al. reported the synthesis of Ti and Zr complexes of the type $[\text{Cp}_2\text{M}(\text{PPhPPhPPh})]$ from $[\text{Cp}_2\text{MX}_2]$ and $\text{Li}_2\text{P}_4\text{Ph}_4$.^[21] In 1981, Köpf and Voigtländer described the complexes $[\text{Cp}_2\text{M}(\text{PRPRPR})]$ ($\text{M} = \text{Ti}, \text{Zr}, \text{Hf}$; $\text{R} = \text{Ph}, \text{Et}, \text{Me}$),^[22] but it was not until 1988 that Hey et al. reported the first crystal structure of $[\text{Cp}_2\text{Hf}(\text{PPhPPhPPh})]$, derived from the metathetical reaction of the corresponding metallocene dihalide with LiPPhPh .^[23] The analogous compounds $[\text{Cp}_2\text{M}(\text{PRPRPR})]$ ($\text{M} = \text{Zr}, \text{Hf}$; $\text{R} = \text{Ph}, \text{Cy}$) were prepared in a similar manner.^[24-26] In contrast, Benac and Jones showed that reactions of



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LiPHR ($\text{R} = \text{Ph}, t\text{Bu}$) with various metallocene dihalides lead to several products, including **6**, **7**, $[\text{Cp}_2\text{M}(\text{PR-PR})]$, and $[\{\text{Cp}_2\text{M}(\mu\text{-PRH})\}_2]$; this implies that electronic and steric factors determine the reaction course.^[27] Subsequently, a crystal structure of the diphosphanato derivative $[(\eta^5\text{-C}_5\text{Me}_4\text{Et})_2\text{-Zr}(\text{PMesPMes})]$ ($\text{Mes} = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$), an analogue of **7**, was reported by Kurz and Hey-Hawkins.^[28]

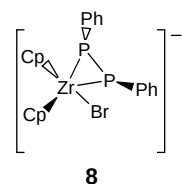
2.2. P-H Bond Activation

The tendency of phosphanido reagents to reduce Zr^{IV} to Zr^{III} prompted the quest for alternative synthetic pathways to



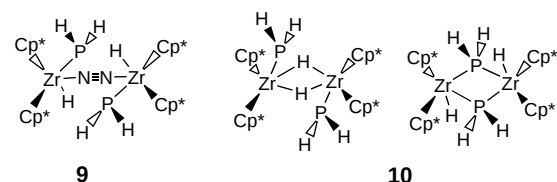
Doug Stephan was born in 1953 in Hamilton, ON, Canada where he completed his undergraduate studies in Chemistry at McMaster University in 1976. As an NSERC of Canada Scholar, he completed his graduate work on studies of catalytic asymmetric synthesis in 1980 at the University of Western Ontario under the aegis of Professor N. C. Payne. In the following two years, he held a NATO postdoctoral Fellowship at Harvard University in the laboratories of R. H. Holm. In 1982 he became an Assistant Professor at the University of Windsor, where he was subsequently promoted through the ranks to Professor in 1992. He has served on the NSERC of Canada grant selection committee and is currently on the editorial boards of the Canadian Journal of Chemistry and Organometallics. In 1995 he spent a DFG-supported sabbatical in the laboratories of Professor G. Erker in Münster. Generally, his research interest focuses on the synthesis and applications of Zr-P and Ti-S compounds in both stoichiometric and catalytic reactions as well as the development of new olefin polymerization catalysts.

Zr–P bonds. While strategies based on P–H bond activation offer potential routes to Zr–P double bonds (see Section 3.3), some pathways to Zr phosphanido and phosphanato complexes have been discovered. For example, the triphosphanato complex $[\text{Cp}_2\text{Zr}(\text{PPhPPHPPh})]$ was obtained from the reaction of PhPH_2 with $[\text{Cp}_2\text{ZrMe}_2]$.^[23] Other complexes of the type $[\text{Cp}_2\text{Zr}(\text{PRPRPR})]$ ($\text{R} = \text{Ph}, \text{Cy}$) were obtained by



oxidative addition of P–H bonds to Zr^{II} , generated in situ by reaction of $[\text{Cp}_2\text{ZrCl}_2]$ with Mg .^[24] Addition of bromide ion to such a reaction mixture led to the interception of the anionic di-phosphanato species **8**.^[24]

Marsh et al. reported further studies on oxidative addition of phosphane to Zr^{II} species.^[29] Reaction of $[(\text{Cp}^*\text{Zr}(\text{N}_2))_2(\mu\text{-N}_2)]$ ($\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) with PH_3 led to the stepwise formation of **9** and two isomers of **10**. The latter complex reacts with alkenes at higher temperatures to liberate the corresponding alkylphosphane and $[\text{Cp}_2^*\text{Zr}(\text{H})_2]$.



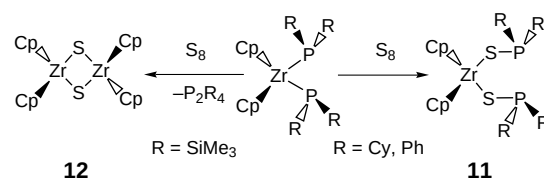
Alternatively, acidolysis of metal hydrides by primary or secondary phosphanes yields phosphanido complexes. Thus, Vaughan and Hillhouse prepared phosphanido complexes of the type $[\text{Cp}_2^*\text{HfH}(\text{PHR})]$ and $[\text{Cp}_2^*\text{HfH}(\text{PR}_2)]$ from $[\text{Cp}_2^*\text{HfH}_2]$ with concurrent elimination of H_2 .^[6]

2.3. Reactivity

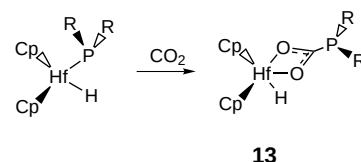
Initial reactivity studies by Wade et al. probed the chemistry of the complexes $[\text{Cp}_2\text{M}(\text{PR}_2)_2]$ with a variety of protic (alcohols, thiols, phosphanes, H_2O) or halogen-containing (Ph_2PCl , Me_3SiCl , MeI) reagents.^[30] In general, such reactions lead to facile Zr–P bond scission with the liberation of the corresponding phosphane. Similarly, aminolysis of $[\text{Cp}_2\text{ZrCl}(\text{P}(\text{SiMe}_3)_2)]$ by aniline gave $[\text{Cp}_2\text{ZrCl}(\text{NHPh})]$ and the corresponding secondary phosphane.^[31] Attempts to replace the halide ion in $[\text{Cp}_2\text{ZrCl}(\text{PR}_2)]$ by reaction with AlMe_3 , Me_3SiN_3 , or LiOR resulted in displacement of the phosphanido group and the liberation of phosphane or LiPR_2 .^[7]

Despite the demonstrated lability of the Zr–P bond, one of our early reports revealed insertion chemistry of Zr–P bonds. The reaction of the complexes $[\text{Cp}_2\text{Zr}(\text{PR}_2)_2]$ ($\text{R} = \text{Ph}, \text{Cy}$) with S_8 gave **11**.^[32] In contrast, the more sterically crowded phosphanido complex $[\text{Cp}_2\text{Zr}\{\text{P}(\text{SiMe}_3)_2\}_2]$ gave **12** and unidentified phosphorus products.^[33]

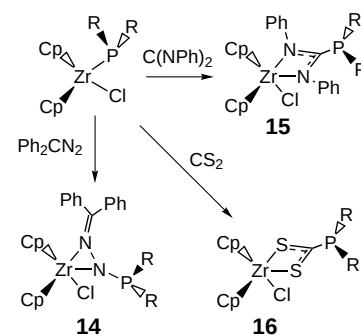
Hf–P bond scission was observed in the reactions of $[\text{Cp}_2^*\text{HfH}(\text{PR}_2)]$ with H_2 , CO , and C_2H_4 , which led to the liberation of phosphane and formation of $[\text{Cp}_2^*\text{Hf}(\text{H})_2]$,



$[\text{Cp}_2^*\text{Hf}(\text{CO})_2]$, and $[\text{Cp}_2^*\text{Hf}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)]$, respectively. In contrast, CO_2 inserts into the Hf–P bond of $[\text{Cp}_2^*\text{HfH}(\text{PR}_2)]$ to give **13**.^[6]



Subsequent studies showed that a variety of reagents such as Ph_2CN_2 , $\text{C}(\text{PhN})_2$, and CS_2 insert into the Zr–P bond of $[\text{Cp}_2\text{ZrCl}(\text{PR}_2)]$ ($\text{R} = \text{SiMe}_3$) to give **14**,^[34] **15**,^[35] and **16**.^[33]



Complex **17**^[36, 37] (Figure 1) was generated by insertion of P_4 into the Zr–P bonds of $[\text{Cp}_2\text{Zr}\{\text{P}(\text{SiMe}_3)_2\}_2]$. The reaction of $[(\eta^5\text{-C}_5\text{Me}_4\text{Et})_2\text{ZrCl}(\text{PHCy})]$ with PhNCS and CS_2 gave the insertion products **A** ($\text{Cp}' = \eta^5\text{-C}_5\text{Me}_4\text{Et}$) and **B** (an analogue of **16**).^[38] Similarly, the compounds **C** (an analogue of **14**), **D** ($\text{R} = \text{Ph}, i\text{Pr}$; an analogue of **15**), and **E** ($\text{Cp}' = \text{C}_5\text{H}_4\text{Me}$) were obtained by insertion of Ph_2CN_2 , $\text{C}(\text{NR})_2$ ($\text{R} = \text{Ph}, i\text{Pr}$), and PhNC , respectively, into the Zr–P bonds of the corresponding phosphanido complexes.^[34, 39, 40] The analogous insertion of phenylacetylene afforded **18**,^[41] and further substitution with

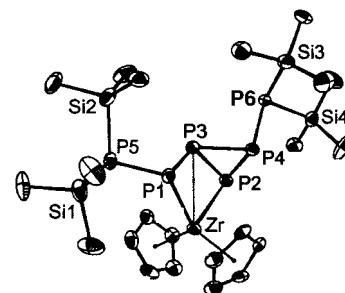
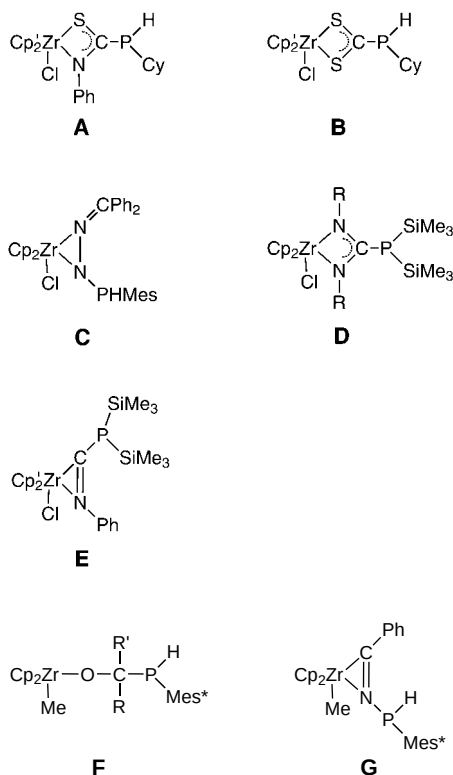
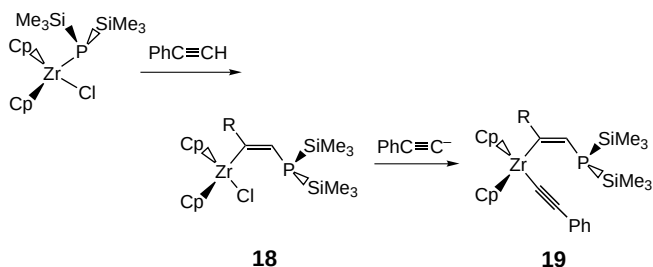


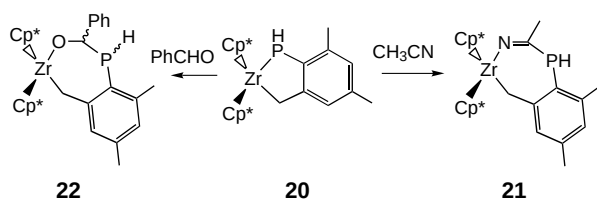
Figure 1. X-ray structure of $[\text{Cp}_2\text{Zr}\{\text{PP}(\text{SiMe}_3)_2\text{PP}(\text{SiMe}_3)_2\text{P}\}]$ (**17**); reproduced with permission of The Royal Society of Chemistry.^[36, 37]



phenylacetylide anion gave **19**.^[42] We showed that ketones, aldehydes, and nitriles also insert into the Zr–P bonds of $[\text{Cp}_2\text{ZrMe}(\text{PHMes}^*)]$ ($\text{Mes}^* = 2,4,6\text{-}t\text{Bu}_3\text{C}_6\text{H}_2$) to give products of the type **F** ($\text{R} = \text{Ph}$; $\text{R}' = \text{Ph}, \text{H}$) and **G**.^[11] In a similar

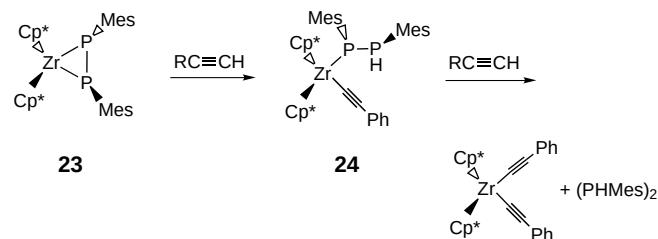


fashion, the chelate phosphanido complex **20** undergoes insertion of acetonitrile and benzaldehyde into the Zr–P bond to give **21** and **22**, respectively.^[43, 44]

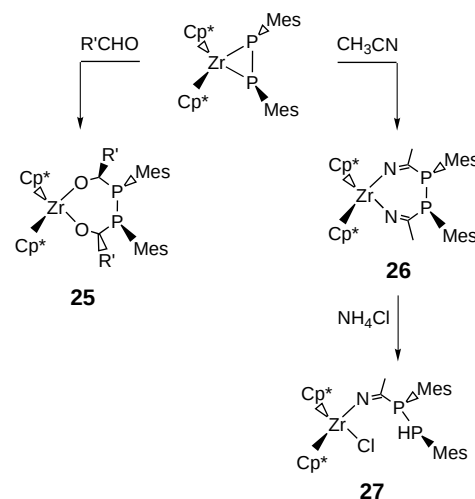


Di- and triphosphanato complexes also exhibit facile Zr–P acidolysis and insertion reactions. For example, hydrolysis of $[\text{Cp}_2\text{Zr}\{\text{PPh}_2\}_2]$ gave the diphosphanes $(\text{PHR})_2$.^[27] Acidolysis

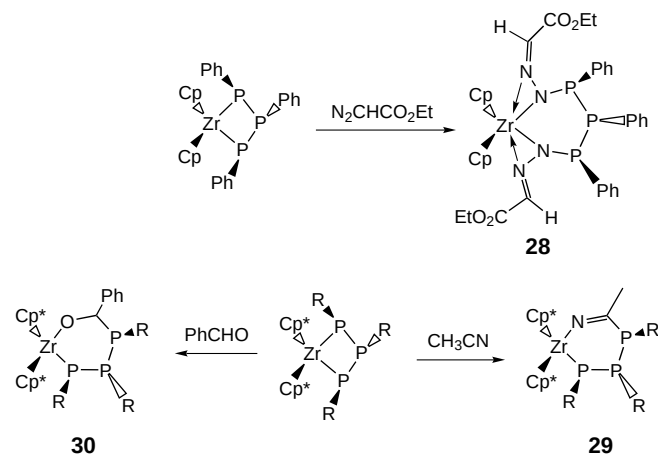
of the diphosphanato complex **23** by primary phosphanes gave the corresponding bis-phosphanido complexes and liberated the substituted diphosphane $(\text{PHMes})_2$.^[44] Similarly, treatment of **23** with diiodomethane gave $[\text{Cp}_2^*\text{ZrI}_2]$ and an unidentified phosphorus product, while treatment with acetone afforded the dienolato complex $[\text{Cp}_2^*\text{Zr}\{\text{OC}(\text{CH}_2)_2\text{CH}_3\}_2]$. Acidolysis of **23** by phenylacetylene yields sequentially **24** and $[\text{Cp}_2^*\text{Zr}(\text{CCPh})_2]$.



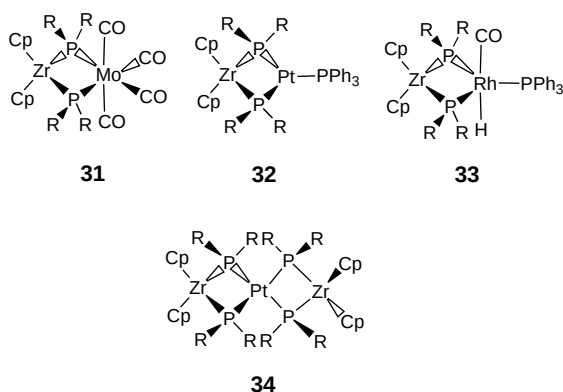
Insertion of nitriles and aldehydes into diphosphanato complexes gives **25** and **26**, and subsequent protolysis of the latter with NH_4Cl liberates the nitrile and provides **27**, which bears a pendent diphosphane group. Double insertion of



diazooacetate into the Zr–P bonds of the triphosphanato complex $[\text{Cp}_2\text{Zr}(\text{PPhPPhPPh})]$ affords **28**.^[45] In the case of $[\text{Cp}_2^*\text{Zr}(\text{PPhPPhPPh})]$, aldehydes and nitriles insert only once to give the unsymmetrical six-membered ring complexes **29** and **30**.^[44]



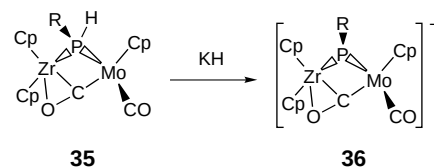
Another avenue for reactivity of zirconium phosphanido complexes was predicated on the basis that the donor ability of the lone pair of electrons on phosphorus would permit such complexes to act as metalloligands towards later transition metals to afford phosphorus-bridged early–late heterometallic complexes.^[46] As early as 1977, Stelzer et al. reported the formation of $[\text{Cp}_2\text{Zr}(\mu\text{-PRR}')_2\text{Mo}(\text{CO})_4]$ by the displacement of labile ligands on Mo by the Zr phosphanido moiety.^[47, 48] In the 1980s a number of groups exploited this concept to prepare a variety of Zr and Hf doubly phosphanido bridged complexes of the type $[\text{Cp}_2\text{M}(\mu\text{-PR}_2)_2\text{M}'\text{L}_n]$. Various bridging phosphanido groups ($\text{R} = \text{Ph}$, Et, Cy, SiMe_3) and a variety of late transition metal moieties ($\text{M}'\text{L}_n$) were included. Among them were $\text{Mo}(\text{CO})_4$ (see **31**), $\text{Cr}(\text{CO})_4$, $\text{W}(\text{CO})_4$, $\text{Fe}(\text{CO})_3$, $\text{Ni}(\text{CO})_2$, $\text{Fe}(\text{NO})_2$, $\text{Ni}(\text{PPh}_3)$, $\text{Pd}(\text{PR}_3)$, $\text{Pt}(\text{PPh}_3)$ (see **32**), $\text{Rh}(\text{indenyl})$, $\text{RhH}(\text{PPh}_3)(\text{CO})$ (see **33**), $\text{IrH}(\text{PPh}_3)(\text{CO})$, $\text{Ni}(\text{cod})$ ($\text{cod} = 1,5\text{-cyclooctadiene}$), and $\text{ReH}(\text{CO})_3$.^[49–59] The trimetallic complexes **34** ($\text{M} = \text{Zr}$, Hf; $\text{M}' = \text{Ni}$, Pd, Pt), in which two early transition metal phosphanido moieties are coordinated to a central late transition metal center, were prepared by a similar method.^[56]



The two metal centers in the doubly phosphanido bridged heterobimetallic complexes did not show cooperative reactivity. Rather, the inclusion of the early-transition metalloligand provides only a limited ancillary effect. For example, complexes $[\text{Cp}_2\text{Zr}(\mu\text{-PR}_2)_2\text{Pt}(\text{PPh}_3)]$ exhibited typical ligand substitution reactions and failed to undergo oxidative addition reactions.^[54, 55] This diminished reactivity was attributed to weak dative Pt–Zr interactions. Such donor–acceptor interactions were described on the basis of extended Hückel molecular orbital calculations.^[56] Similarly, $[\text{Cp}_2\text{Zr}(\mu\text{-PR}_2)_2\text{RhH}(\text{CO})(\text{PPh}_3)]$ (**33**) was shown to act as a catalyst precursor in the hydroformylation of 1-hexene.^[58] While the reaction rate is considerably lower than that of typical monometallic Rh complexes, it is noteworthy that the selectivity for terminal aldehydes is dramatically increased.

Attempts to prepare complexes in which the early and late transition metal centers cooperatively activate a substrate led to the isolation of the singly phosphanido bridged heterobimetallic complexes $[\text{Cp}_2\text{Zr}(\mu\text{-PR}_2)(\mu\text{-CO})\text{MoCp}(\text{CO})]$, which are readily prepared by the reaction of $[\text{Cp}_2\text{Zr}(\text{PR}_2)_2]$ with $[\text{CpMo}(\text{CO})_3\text{H}]$ or $[\text{CpMo}(\text{CO})_3]_2$.^[60] In the first case, Zr–P bond cleavage affords PHR_2 as by-product, while in the

latter reaction, Mo–Mo bond reduction occurs concurrently with the oxidation of one of the phosphanido ligands to P_2R_4 . Related singly phosphanido bridged heterobimetallic species were obtained directly from the redox reaction of the Zr^{III} complexes $[\{\text{Cp}_2\text{Zr}(\mu\text{-PR}_2)_2\}_2]$ with $[\{\text{CpMo}(\text{CO})_3\}_2]$.^[61] While structural data for the complexes $[\text{Cp}_2\text{Zr}(\mu\text{-PR}_2)(\mu\text{-CO})\text{MoCp}(\text{CO})]$ show considerable C–O bond activation, as indicated by the C–O bond lengths ($\text{R} = \text{Ph}$: 1.230(5) Å; $\text{R} = \text{Et}$: 1.226(4) Å), attempts to effect further reaction of the $\eta^1\text{-}\eta^2$ carbonyl fragment were unsuccessful.^[60] The related complex **35** undergoes deprotonation to generate the phosphinidene-bridged heterobimetallic anionic species **36**.^[62] The reversibility of this deprotonation was demonstrated by deuterium labeling at phosphorus.



More recent studies have rekindled interest in heterobimetallic complexes, as the complexes $[\text{Cp}_2\text{Zr}\{\mu\text{-P}(\text{SiMe}_3)_2\}\text{Ni}(\text{CO})_2]$ and $[(\eta^5\text{-C}_5\text{H}_4\text{R})_2\text{Zr}\{\mu\text{-P}(\text{C}_6\text{H}_2\text{iPr}_3)_2\}\text{M}(\text{CO})_4]$ ($\text{R} = \text{Me}$, H; $\text{M} = \text{Mo}$, Cr) are active catalysts for the polymerization of ethylene.^[63–66]

3. Synthetic Strategies Towards and Reactivity of Zr–P Double Bonds

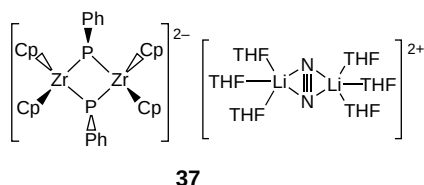
Species containing terminal Zr–P double bonds were viewed both as a synthetic challenge and a means to expand the range of Zr–P chemistry. This approach was concurrently developed for different metals (Mo, W, Ta) by the groups of Lappert, Cowley, Schrock, and Wolczanski.^[67–70] Several of the initial synthetic routes to Zr–P double bonds were frustrated by the high reactivity of the putative Zr phosphinidene intermediates. Nonetheless, the isolation and study of a stable zirconocene phosphinidene complex was ultimately achieved.

3.1. Halide Elimination

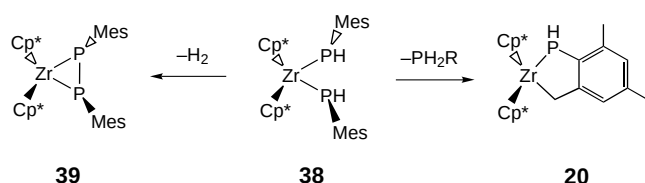
In early attempts to generate early transition metal phosphinidene complexes, Vaughan and Hillhouse treated $[\text{Cp}_2^*\text{HfX}(\text{PHR})]$ with a variety of bases, including KH, $n\text{BuLi}$, and $\text{NaN}(\text{SiMe}_3)_2$.^[6] In one case, a single species exhibiting a singlet ^{31}P NMR signal at $\delta = 376$ was observed in solution. Although this promising result was suggestive of a phosphinidene species, this compound could not be isolated free of impurities, and consequently the formulation remained uncertain. In a similar vein, Arif and Cowley reported that the compound $[\text{Cp}_2\text{ZrCl}\{\text{P}(\text{SiMe}_3)\text{Mes}^*\}]$ failed to eliminate Me_3SiCl even under thermal or photochemical duress.^[71]

3.2. Halide Replacement Reactions

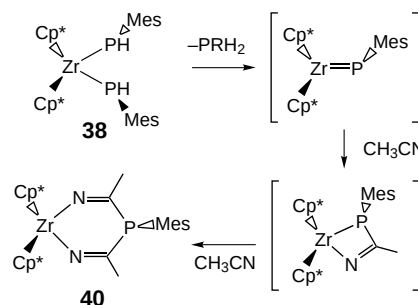
The most direct and, in retrospect, most naive strategy, involved reaction of the metallocene dihalides with Li_2PR . Such phosphanediides are strong reducing reagents and effect Zr-P bond formation with concurrent reduction to Zr^{III} . The resulting salts contain phosphinidene-bridged dianions $[\{\text{Cp}_2\text{Zr}(\mu\text{-PR})\}_2]^{2-}$.^[62] For $\text{R} = \text{Ph}$, crystallographic data confirmed the formulation of the dianion and also revealed an issue of peripheral interest. The Li cations in this salt are bridged in an unprecedented side-on manner by an N_2 molecule.^[72] The extreme lability of the N_2 ligand in this species, even in the solid state, was consistent with the observed N–N distance of 1.06(1) Å. Subsequent studies by Bazhenova et al. confirmed the incorporation of N_2 in the solid state but disputed the formulation by suggesting that N_2 was partially reduced.^[73] This was in contrast to our formulation for the complex **37**. Moreover, the proposal of a mixed-valent $\text{Zr}^{\text{IV}}/\text{Zr}^{\text{III}}$ formulation is inconsistent with our observation of a half-field transition in the EPR spectrum, as well as the lability of the N_2 ligand.^[72]



Reduction of Zr^{IV} can be avoided by alteration of the reaction conditions and use of sterically demanding substituents. For example, a simple halide replacement reaction provides the Zr^{IV} bis-phosphanido complex **38**. In benzene, this species is unstable with respect to elimination of phosphane and undergoes degradation into a mixture of **39** and **20**.^[43, 44] The formation of these products supported the



proposal of an intermediate Zr phosphinidene species $[\text{Cp}_2^*\text{Zr}=\text{PR}]$, generated by elimination of one equivalent of RPH_2 . This transient Zr phosphinidene complex undergoes P–H or C–H addition to give the two observed products. Further evidence of the generation of a Zr phosphinidene intermediate was obtained from the reaction of LiPHMe_3 with $[\text{Cp}_2^*\text{ZrCl}_2]$ in DME. Spectroscopic data supported the formation of a LiCl adduct of the zirconium phosphinidene complex $[\text{Cp}_2^*\text{Zr}(\text{PMe}_3)\text{LiCl}(\text{dme})]$.^[44] Moreover, the degradation of **38** in the presence of two equivalents of MeCN yields **40**; this confirms the intermediacy of a phosphinidene species.^[43, 44]



The above approach was used with the more sterically demanding lithium phosphanide LiPHMe_3^* in an effort to stabilize the terminal phosphinidene species. While reaction of $[\text{Cp}_2^*\text{ZrCl}_2]$ with one equivalent of the lithium reagent gave $[\text{Cp}_2^*\text{Zr}(\text{PHMe}_3^*)\text{Cl}]$, a second equivalent resulted in no further reaction. Presumably further substitution is precluded by steric congestion.^[74] In marked contrast, $[\text{Cp}_2\text{ZrCl}_2]$ reacts with two equivalents of LiPHMe_3^* . Loss of phosphane from the intermediate bis-phosphanido complex in the presence of PMe_3 afforded the first terminal Zr phosphinidene complex **41** (Figure 2), albeit in 40% yield.^[44] The disparity of the ^{31}P NMR chemical shifts ($\delta = 792, -12$) of the two phosphorus atoms in **41** are consistent with the structural data, which confirm the presence of a Zr–P double bond (2.505(4) Å).^[44] Moreover, this illustrates the subtle balance of steric features necessary to facilitate formation of a stable Zr phosphinidene complex and yet preclude further reaction.

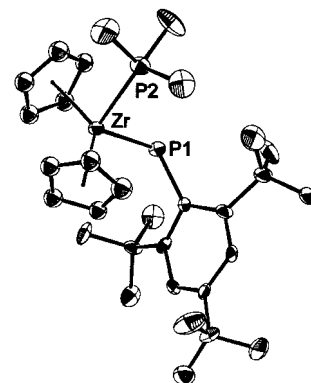


Figure 2. X-ray structure of $[\text{Cp}_2\text{Zr}(\text{PMe}_3^*)(\text{PMe}_3)]$ (**41**); reprinted with permission of *Organometallics*, copyright© American Chemical Society 1993.^[44]

Of related interest is the reaction of $[\text{Cp}_2\text{Zr}(\text{PHMe}_3^*)\text{Cl}]$ with excess KH in THF, from which the novel anionic phosphinidene hydride salt **42** (Figure 3) was obtained in low yield. This can be formally viewed as the KH-stabilized adduct of the terminal phosphinidene complex.^[74]

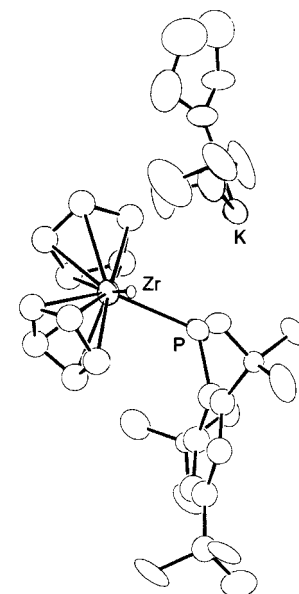
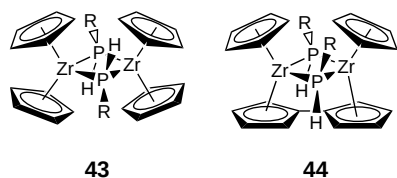


Figure 3. X-ray structure of $[\text{K}(\text{thf})_2][\text{Cp}_2\text{ZrH}(\text{PMe}_3^*)]$ (**42**); reprinted with permission of *Organometallics*, copyright© American Chemical Society 1995.^[74]

3.3. P–H Bond Activation

Although the above synthetic strategies proved successful in the interception of a terminal phosphinidene species, alternative routes were sought to more readily gain access to terminal phosphinidene complexes. Oxidative addition of the P–H bonds of primary phosphanes to low-valent Zr compounds was envisioned as proceeding via a phosphide–hydride intermediate which could lose H₂ to give a Zr phosphinidene moiety. However, experiments revealed that such a view is oversimplified. In fact, the course of the reaction depends both on the zirconium reagent and the phosphane.

Generation of Zr^{II} by the Negishi method with BuLi and reaction with RPH₂ (R = Ph, Cy, SiPh₃) affords Zr^{III} phosphanido-bridged dimers of the type **43** and/or **44**.^[75] In the case of (Ph₃Si)PH₂, in addition to these products, a small amount of the phosphinidene-bridged dimer [Cp₂Zr₂(μ-PHR)(μ-PR)(μ-C₁₀H₈)] was also isolated. It is proposed that these reactions proceed through a mononuclear phosphinidene intermediate which is reduced in the course of C–H or Zr–H bond additions to the Zr–P double bond.^[62]



Reduction of [Cp₂ZrCl₂] by Mg in the presence of phosphanes also provides the phosphanido-bridged dimers [[Cp₂Zr(μ-PHR)]₂] (R = Cy, SiPh₃). More sterically demanding substituents preclude formation of such Zr^{III} species. For example, use of MesPH₂ in the above reaction affords the phosphinidene-bridged complex **45**. However, in the analogous reaction of Mes*PH₂, P–H, P–C, and C–H bond activation provided the P-capped trimer **46**^[74, 76] (Figure 4).

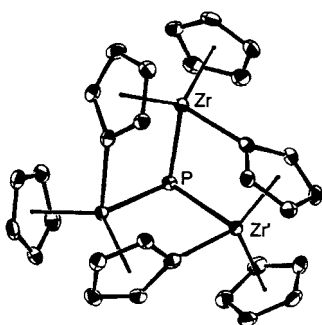
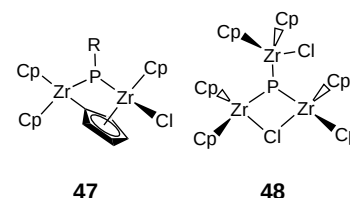


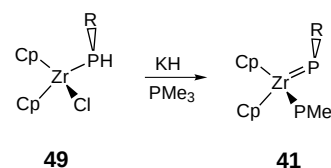
Figure 4. X-ray structure of [[Cp₂Zr(μ-C₅H₄)]₃(μ₃-P)] (**46**); reprinted with permission of *Organometallics*, copyright© American Chemical Society 1992.^[76]

Reduction of [Cp₂*ZrCl₂] and [Cp₂ZrCl₂] by Mg in the presence of PhPH₂ yielded the triphosphanato derivatives [Cp₂*Zr(PPhPPhPPh)] and [Cp₂Zr(PPhPPhPPh)], respectively.

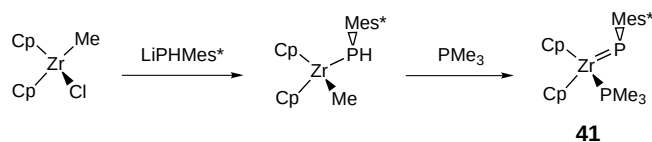
Schwartz's reagent [[Cp₂Zr(H)Cl]_n] reacts with P–H bonds to give a variety of products, depending on the nature of the primary phosphane.^[77] The Zr^{III} dimers [[Cp₂Zr(μ-PHR)]₂] and **47** are obtained in relatively low yields from reactions with PhPH₂ and Ph₃SiPH₂, respectively. In the case of MesPH₂, reaction with [[Cp₂Zr(H)Cl]_n] gives the phosphinidene-bridged species **45** directly. Addition of an excess of [[Cp₂Zr(H)Cl]_n] to Mes*PH₂ effects partial reduction and invokes P–C bond cleavage to afford the unusual complex [[Cp₂Zr]₂(μ₃-P)(μ₂-Cl)(Cp₂ZrCl)] (**48**), in which the central phosphorus atom has planar geometry.^[77]



Addition of a base to primary phosphanido complexes is another avenue for exploring P–H reactivity. Treatment of [Cp₂ZrCl(PHR)] (**49**; R = Mes, Mes*) with KH in the presence of PMe₃ invokes P–H bond cleavage and formation of the base-stabilized terminal phosphinidene complexes [Cp₂Zr(PR)(PMe₃)] in approximately 40% yield.^[44] These

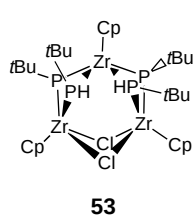
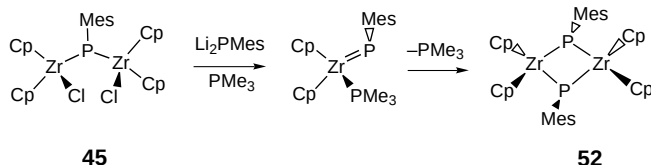
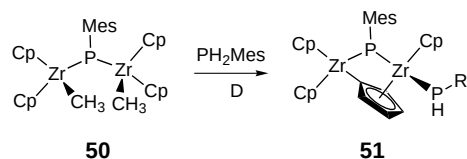


species are reactive, and isolation and complete characterization was only possible for the complex incorporating the Mes* substituent on phosphorus. A preferable route to this complex is the reaction of LiPHMes* with [Cp₂Zr(Me)Cl]. The intermediate phosphanido methyl complex gradually loses methane over 12 h at 25 °C in the presence of PMe₃ to provide the terminal phosphinidene complex **41** in quantitative yield.^[78]



The analogous approach with sterically less demanding phosphanides takes an alternative pathway.^[11] Reaction of [Cp₂Zr(Me)Cl] with LiPHMes yields [Cp₂ZrMe(PHMe)], which dimerizes with loss of phosphane to give [(Cp₂ZrMe)₂(μ-PMe)] (**50**). This compound is obtained directly from the thermal reaction of the corresponding phosphane with [Cp₂ZrMe₂]. With an additional equivalent of phosphane, **50** undergoes cyclopentadienyl C–H bond activation to give the phosphinidene-bridged complex **51**. The

mesityl analogue of **41** is generated from the reaction of **45** with Li_2PMe_3 in the presence of PMe_3 , but the product is not isolable, as it loses PMe_3 to give the insoluble phosphinidene-bridged dimer **52**.



Recently, Hey-Hawkins et al. extended P–H bond activation to mono-cyclopentadienyl Zr complexes.^[79] Treating LiPHtBu with $[(\text{CpZrCl}_3)_n]$ results in a redox reaction in which Zr is partially reduced and the phosphinido group is oxidized to $(\text{PHtBu})_2$. Among the products, the phosphinidene derivative **53** was obtained in low yield and crystallographically characterized.

3.4. Reactivity of Zirconium Phosphinidene Complexes

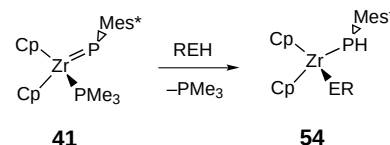
While the reactivity of bridging phosphinidene complexes has received limited attention, the facile, high-yield synthesis of the terminal zirconocene phosphinidene complex **41** permitted a more exhaustive examination of its reactivity. In accord with expectations based on the analogy of terminal Zr phosphinidene moieties to carbenes, such species proved to be highly reactive. Several classes of reactions have been uncovered. In the case of terminal Zr phosphinidene complexes, these reactions demonstrate their viability as synthons for a variety of organophosphorus compounds.

3.5. Protonation and Alkylation

Initial studies on the reactivity of Zr phosphinidene complexes focused on bridging phosphinidene complexes. Protonation and methylation of the dianions $[(\text{Cp}_2\text{Zr})_2(\mu\text{-PR})_2]^{2-}$ was readily achieved in a stepwise manner to afford the monoanionic and neutral phosphanido-bridged dimers $[(\text{Cp}_2\text{Zr})_2(\mu\text{-PR})(\mu\text{-PHR})]^-$ and $[(\text{Cp}_2\text{Zr}(\mu\text{-PR}'))_2]$ ($\text{R}' = \text{H}, \text{Me}$).^[62] Protonation of the dianion was reversed by KH , similar to the interconversion of the phosphanido-bridged heterobimetallic complex **35** and the phosphinidene-bridged species **36**.

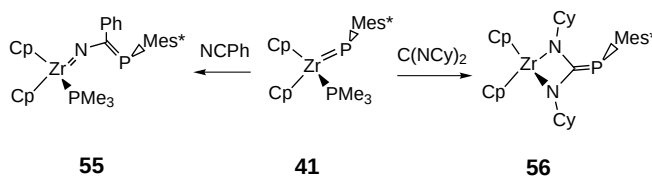
3.6. Additions to $\text{Zr}=\text{P}$ Bonds

Phenol, thiophenol, aniline, and phosphanes add to **41** to afford complexes of the type **54** ($\text{ER} = \text{OPh}, \text{SPh}, \text{NHPh}, \text{PHR}$).^[80]



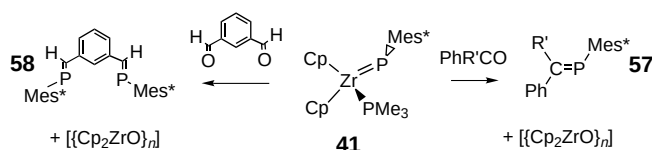
3.7. Insertion Reactions

Benzonitrile and dicyclohexylcarbodiimide react with **41**.^[78] In the former case, the net result was insertion of the nitrile into the $\text{Zr}=\text{P}$ bond with intramolecular phosphinidene-group transfer to the C atom of the nitrile to give **55**. The reaction with dicyclohexylcarbodiimide proceeds by cycloaddition and subsequent rearrangement to give **56**. While these reactions are in effect insertions of the substrate between Zr and P, there are also examples of intramolecular phosphinidene group transfer.



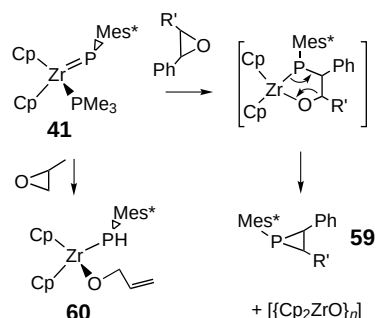
3.8. Phosphinidene Group Transfer Reactions

Reaction of **41** with ketones and aldehydes such as benzophenone or benzaldehyde proceeds in a facile manner in THF solution at room temperature.^[78] The double-bond metathesis reaction affords the phosphalkene **57** and the zirconocene oxide $[(\text{Cp}_2\text{ZrO})_n]$. Separation of the products is simple owing to the insolubility of the zirconocene oxide. In a similar manner, this reaction was applied in the synthesis of **58** from $\text{C}_6\text{H}_4(\text{CHO})_2$. It is noteworthy that while the conven-

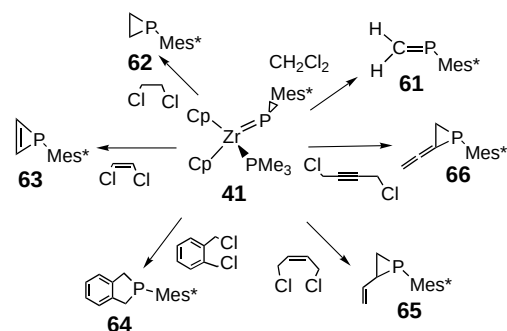


tional organic synthesis of this bis-phosphalkene provides a mixture of the *E* and *Z* isomers, the preparation from **41** affords only the *E* isomer in 86% yield of isolated product. Similar metathesis reactions with phenyl isothiocyanate afford the zirconocene sulfide dimer $[(\text{Cp}_2\text{Zr}(\mu\text{-S}))_2]$ and the heterophosphallene $\text{PhN}=\text{C}=\text{PMe}_3^*$. Again, the insolubility of the Zr by-products makes product isolation simple. A limitation of this approach is demonstrated by the analogous reaction with cyclohexanone. In this case, enolization provides a proton source and results in the formation of the

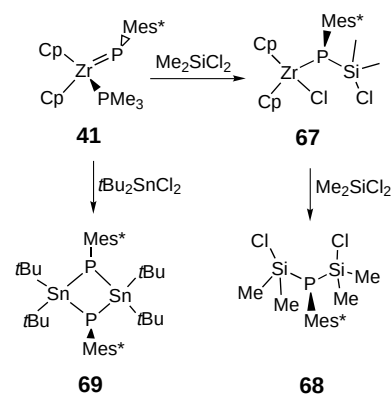
complex $[\text{Cp}_2\text{Zr}(\text{PHMes}^*)(\text{OC}_6\text{H}_9)]$. A similar situation is also observed in the reactions of **41** with epoxides. Phenyl- and 1,2-diphenyloxirane react cleanly with P/O exchange to give the corresponding phosphirane **59** ($\text{R} = \text{H}, \text{Ph}$) and zirconocene oxide. In contrast, propylene oxide gives $[\text{Cp}_2\text{Zr}(\text{PHMes}^*)(\text{OC}_3\text{H}_5)]$ **60** as a result of the existence of an enol form.^[78]



Reaction of **41** with *gem* dihalides such as CH_2Cl_2 and CHCl_3 also provides access to the corresponding phosphalkene **61** and $\text{H}(\text{Cl})\text{C}=\text{PMes}^*$ with concurrent formation of $[\text{Cp}_2\text{ZrCl}_2]$.^[78] In the case of CHCl_3 , the *cis* and *trans* isomers of the phosphalkene were obtained in a 1:2 ratio. This approach also allowed the preparation of the phosphirane **62**, the phosphirene **63**, and the phospholane **64** from the appropriate organic dihalides. In a similar manner, the substituted phosphiranes **65** and **66** were obtained from the analogous reactions of 1,4-dichloro-2-butene and 1,4-dichloro-2-butyne, respectively.^[78] It is noteworthy that related substituted phosphiranes have also been recently prepared by acidolysis of bicyclic zirconacyclopentadiene phosphiranes derived from zirconocene-mediated cyclization of dialkynylphosphanes.^[81]



Phosphinidene-group transfer to main group elements has also been achieved.^[78] The silicon halide Me_2SiCl_2 adds to the phosphinidene complex **41** to give **67**, but this species did not eliminate $[\text{Cp}_2\text{ZrCl}_2]$ to form a phosphasilene. Instead, **67** reacts with excess Me_2SiCl_2 to yield the disilylphosphane **68**. In contrast, reactions of dialkyl metal dihalides R_2MCl_2 ($\text{R} = \text{Ge}, \text{Sn}$) or dialkyltin sulfides with **41** were employed to prepare $(\text{Me}_2\text{MPMes}^*)_2$ ($\text{M} = \text{Ge}, \text{Sn}$) and **69** with the concurrent formation of $[\text{Cp}_2\text{ZrCl}_2]$ or $[\{\text{Cp}_2\text{Zr}(\mu\text{-S})\}_2]$, respectively. Attempts to increase the steric bulk of substituents on Sn to facilitate the formation of a terminal Sn phosphinidene species resulted in no reaction, despite the use of more forcing conditions.

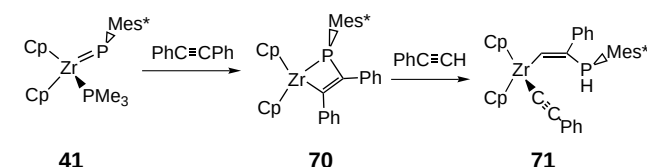


4. Phosphazirconacycles: Synthesis and Reactivity

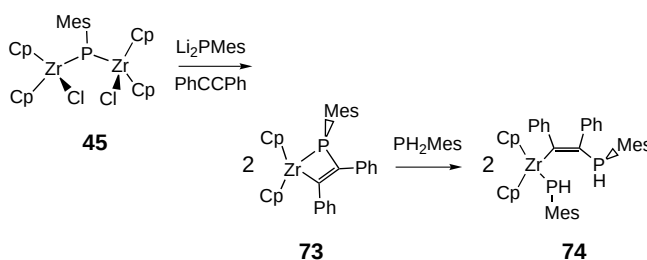
Another approach to reactive Zr–P compounds and thus to a variety of organophosphorus derivatives involves the use of phosphazirconacycles. While we have exploited reactions of Zr phosphinidene complexes to access such compounds, others have utilized reactions of phosphalkynes and to a lesser extent phosphanylmethanides.

4.1. Cycloadditions to Zr Phosphinidene Complexes

Substituted acetylenes undergo [2+2] cycloadditions with **41** to provide the four-membered metallacycles **70**.^[82, 83] These additions are reversible, and hence in the presence of a second acetylene, an equilibrium mixture of the two metallacycles is obtained. Primary acetylenes do not undergo such exchange; instead, they protonate the P atom to give the ring-opened complex **71**.

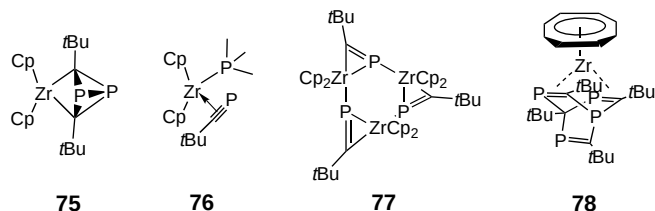


The analogous metallacycle **72** incorporating the sterically less demanding mesityl substituent was obtained from the reaction of $[\text{Cp}_2\text{Zr}(\text{Me})\text{Cl}]$ with LiPHMes in the presence of diphenylacetylene.^[82] Complex **73** was synthesized by the reaction of **45** with Li_2PMes in the presence of diphenylacetylene. Subsequent reaction of **73** with MesPH_2 effects ring-opening protonation at phosphorus to give **74**.

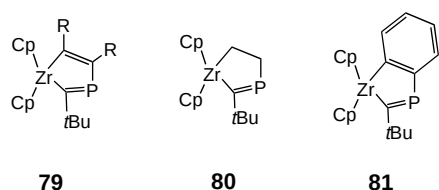


4.2. Phosphaalkyne-Based Metallacycles

The reaction of phosphaalkynes with transition metals has been extensively explored by Binger et al.^[84, 85] The first Zr phosphaalkyne derivative **75** was prepared in 1987 by the reaction of $[\text{Cp}_2\text{Zr}]$ with $t\text{BuC}\equiv\text{P}$.^[86] Structural characterization revealed the novel bicyclic structure. Binger also described the isolation of **76** and its subsequent reaction with BEt_3 to give the trimeric species **77**.^[84] More recently, Binger et al. showed that reaction of $[\text{Zr}(\text{cot})_2]$ (cot = cyclooctatetraene) with $t\text{BuC}\equiv\text{P}$ affords the unusual complex **78**.^[87] The

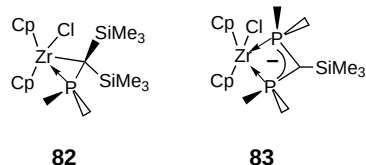


proposed mechanism for the formation of this species involves oxidative coupling, cycloaddition, and 1,2-addition reactions. This view is supported in part by the isolation and characterization of related Ti, Hf, and V complexes.^[88–91] Complex **76** also reacts with acetylenes and olefins to give the metallacycles **79** and $[\text{Cp}_2\text{Zr}(\text{CH}_2\text{CH}_2\text{P}=\text{C}t\text{Bu})]$ (**80**). The benzyne complex $[\text{Cp}_2\text{Zr}(\text{C}_6\text{H}_4)]$ reacts with phosphaalkyne to give the metallacycle **81**,^[92] while Mathey et al. prepared the analogous phosphabenzynes complex.^[93]



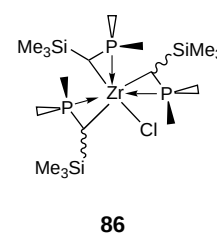
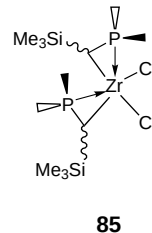
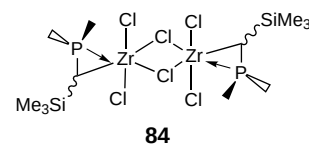
4.3. Phosphanylmethanido Complexes

In 1988, Karsch et al. reported that reaction of $[\text{Cp}_2\text{ZrCl}_2]$ with $\text{Li}[\text{C}(\text{SiMe}_3)_2\text{PMe}_2]$ and $\text{Li}[\text{C}(\text{PR}_2)_2]$ affords **82** and **83**, respectively, with three- and four-membered chelate rings.^[94–98] Karsch et al. also reported complexes of the types **84–86** and $[\text{ZrCl}_2\{\text{C}(\text{SiMe}_3)_2(\text{PMe}_2)_2\}]$, all obtained by reactions of ZrCl_4 with phosphanylmethanides.^[99]



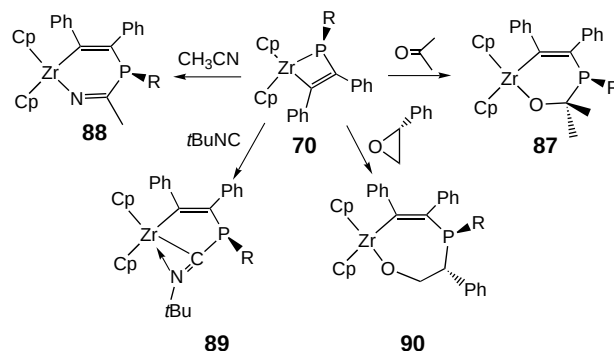
4.4. Reactivity

Phosphazirconacycles exhibit reactivity patterns similar to those of Zr phosphanido complexes. However, such compounds can also act as unique synthetic precursors for novel organophosphorus compounds.



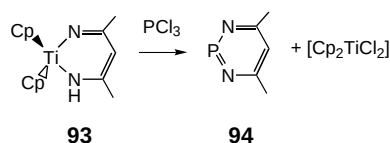
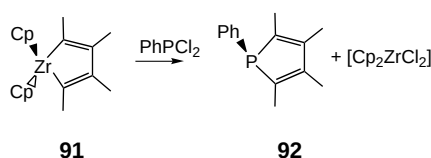
4.5. Insertion Reactions

Phosphazirconacycles undergo insertion reactions to effect ring expansion. Ketones, aldehydes, nitriles, isonitriles and epoxides insert into the Zr–P bond of the metallacycles **70**.^[82, 83] This expands the ring to five, six, and seven members in complexes such as **87–90**. The acetone-insertion product **87** reacts with benzaldehyde to replace acetone with benzaldehyde in the metallacycle. Kinetic data reveal that loss of acetone is the rate-limiting step; this suggests the intermediacy of a zirconocene alkylidene complex that is generated by a retro-[4+2] cycloaddition.



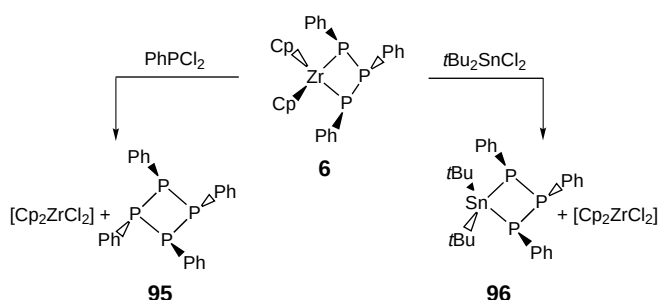
4.6. Metallacycle-Transfer Reactions

Of greater utility from the perspective of organophosphorus chemistry are reactions in which Zr is replaced by other elements. Fagan and Nugent first reported this concept in 1988.^[100, 101] By employing the Zr-containing compounds, metallacycle transfer to phosphorus was effected. The reactions of **91** or $[\text{Cp}_2\text{Zr}(\text{CH}_2\text{CMe}_2)_2]$ with PhPCl_2 gave the organophosphorus compound **92** and $\text{PhP}(\text{CH}_2\text{CMe}_2)_2$ in 85 and 67% yield, respectively, with concurrent formation of $[\text{Cp}_2\text{ZrCl}_2]$. A similar report by Tumas et al. in 1990 described the preparation of phospho- and arsacyclobutenes by reaction of $[\text{Cp}_2\text{Ti}(\text{CH}_2\text{C}(\text{Ph})=\text{CPh})]$ with PhECl_2 (E = P, As).^[102] In the same vein, Mathey et al. recently described the reaction of the Ti-based metallacycle **93** with PCl_3 , which yields $[\text{Cp}_2\text{TiCl}_2]$ and **94**.^[103] This methodology has been used in a

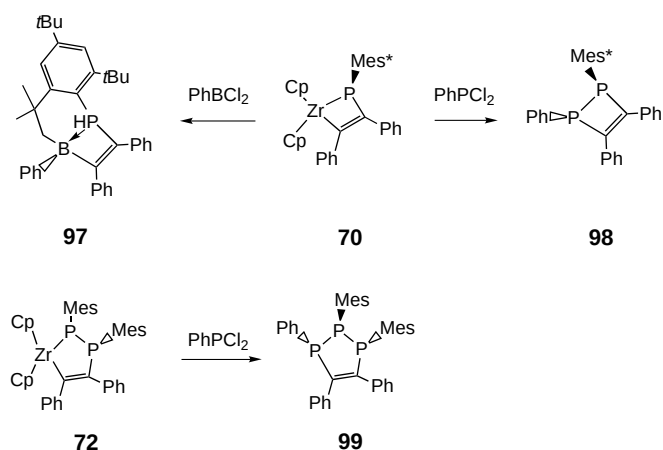


series of elegant preparations of various functionalized diazaphosphinines.

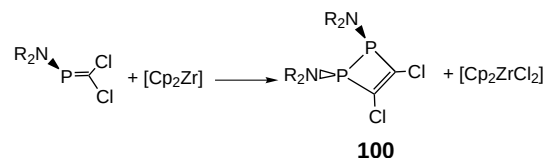
The principle of metal atom replacement can be applied to a variety of phosphazirconacycles as well. The reaction of **6** with PhPCl₂ provides a facile route to **95**, whereas reaction with *t*Bu₂SnCl₂ gives **96** cleanly.^[104]



In a similar manner, the metallacycle **70** reacts with PhBCl₂ to generate the intermediate phosphaboracyclobutene, which undergoes C–H bond activation to give **97**. The analogous reaction with PhPCl₂ gives the diphosphacyclobutene **98**. Similarly, reaction of PhPCl₂ with **72** yields the triphosphacyclopentene **99**.^[104] These latter two reactions afford rare

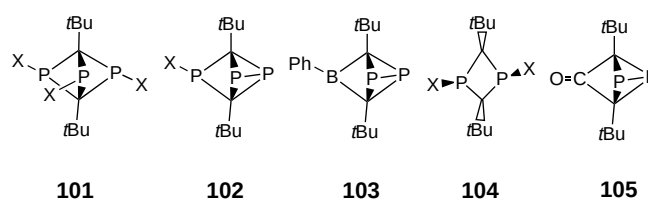


examples of di- and triphosphacycles in which the substituents on phosphorus can be specifically varied. Related 3,4-dihalo-1,2-dihydro-1,2-diphosphetes **100** were prepared by Majoral et al., who used zirconocene to couple dichlorophosphaalkenes.^[105] The proposed mechanism involves coordination of the phosphaaalkene, oxidative addition of C–Cl, and subsequent elimination of [Cp₂ZrCl₂].

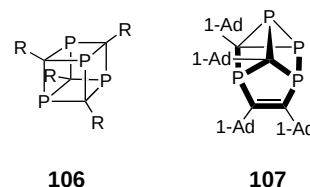


4.7. Reactions of Phosphaalkyne Complexes

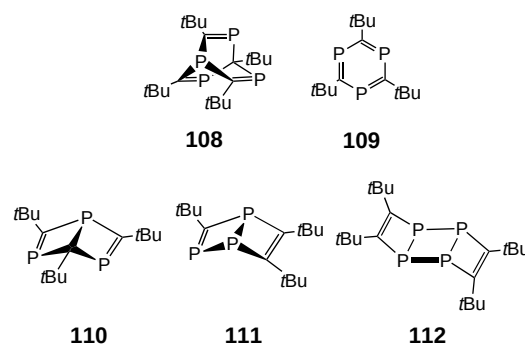
Complex **76** is a highly reactive species that acts as a synthon for a number of unusual and unique organophosphorus compounds. In an initial report, reaction with PCl₅ or PBr₃ was shown to give the tricyclic species **101**.^[106] In the case of X = Cl the formulation was confirmed by X-ray crystallography. Related reactions affording the cyclic compounds **102**–**104** were also reported.^[84] The reaction of [Cp₂Ti(CO)₂] with the phosphaaalkyne gave the tricyclic species **105**.^[107]



Binger et al. also showed that the reaction of **76** with Cl₃CCl₃ gives the tetraphosphacubanes (RCP)₄ (R = *t*Bu, CMe₂Et, 1-adamantyl (1-Ad)) **106** in 70% yield.^[108] With R = adamantyl, the tetracyclic compound **107** was also obtained. Crossover experiments were consistent with the suggestion that the corresponding diphosphetes and their Diels–Alder dimers act as intermediates.^[109]

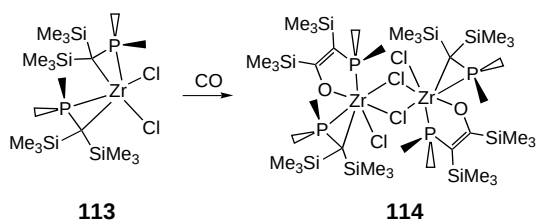


Treatment of **78** with Cl₃CCl₃ liberates the 1,3,5,7-tetraphosphabarrelene **108**.^[87] Related Ti and Hf chemistry affords access to several other novel phosphacycles, including the 1,3,5-triphosphabenzene **109**, the Dewar-1,3,5-triphosphabenzene **110**, the Dewar-1,2,4-triphosphabenzene **111**, and the cyclic dimer of a 1,2-diphosphete **112**.^[88]



4.8. Reactions of Phosphanylmethanido Complexes

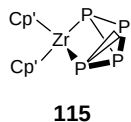
Karsch et al. described the reaction of carbon monoxide with **113**, which is thought to proceed by CO insertion into the Zr–C bond followed by silyl group transfer to give the dimeric complex **114**.^[99]



5. Synthesis and Reactivity of Zirconium Complexes Containing Substituent-Free Phosphorus

5.1. Synthesis

Another class of Zr–P derivatives worthy of investigation are those containing substituent-free phosphorus. Similar to **17**,^[110] a variety of complexes containing elemental phosphorus as ligands have been studied extensively by Scherer et al.^[111, 112] Oxidative addition of P₄ to [Cp₂Zr(CO)₂] gave the complexes **115** (Cp' = Cp*, 1,3-*t*Bu₂C₅H₃).^[113]



The above-mentioned serendipitous preparation of **46** and **48** spurred our own interest in naked-phosphorus compounds of zirconium.^[74, 76] Treatment of [Cp₂Zr(PHMe*)Cl] with an excess of KH results in P–C and P–H bond activation.^[74, 114] This reaction yields both paramagnetic and diamagnetic products. The minor product of this reaction is the paramagnetic complex **116** (Figure 5).^[114] This mixed-valent dimer

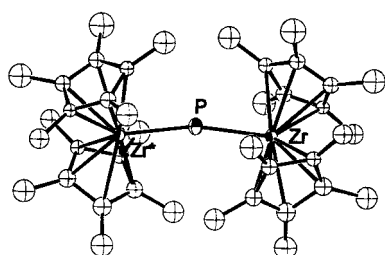


Figure 5. X-ray structure of [(Cp₂Zr)₂(μ-P)] (**116**); reprinted with permission of *Organometallics*, copyright© American Chemical Society 1995.^[74]

contains two Zr centers which are linearly bridged by a single phosphorus atom. The major diamagnetic product was formulated as **117** on the basis of spectroscopic, mass spectrometric, and analytical data. This formulation was supported by an alternative synthesis: Reaction of [(Cp₂Zr(N₂))₂(μ-N₂)] with an excess of Mes*PH₂ proceeds smoothly with P–H and C–H activation to give **118** in high yield. This complex can be deprotonated with KH to give **119**,

which reacts with [Cp₂*ZrCl₂] to give **117**. It is noteworthy that reaction of **117** with excess phosphane and KH results in further incorporation of substituent-free phosphorus atoms and formation of **120** (Figure 6). This species forms an infinite ladder structure of P and bridging K atoms in the solid state.^[74, 114]

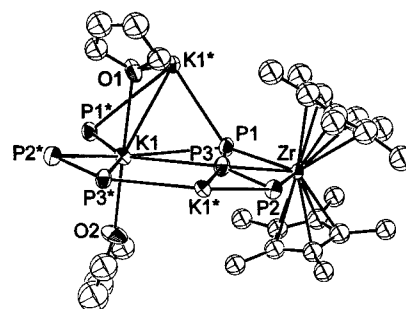
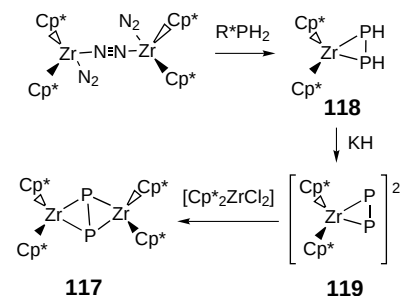
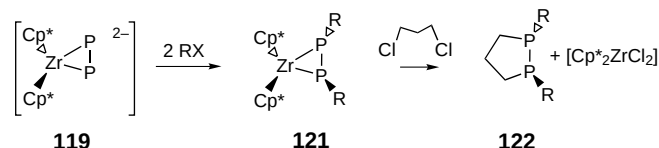


Figure 6. X-ray structure of [K(thf)_{1.5}][Cp₂*Zr(P₃)] (**120**); reprinted with permission of *Organometallics*, copyright© American Chemical Society 1995.^[74]



5.2. Reactivity

The reactivity of Zr complexes with substituent-free phosphorus ligands has received only limited attention. They can be viewed as synthons for organophosphorus compounds for which no limitations are imposed by initially present substituents. Thus, one can contemplate a series of reactions in which desired substituents are introduced sequentially. In preliminary studies, we have explored the reactions of **119**.^[115] This compound reacts stoichiometrically with two equivalents of alkyl halides such as benzyl chloride or cyclohexyl chloride to yield complexes of the type **121**. Subsequent reaction with dichloropropane yields cyclic diphosphanes **122** and [Cp₂*ZrCl₂].



6. Catalytic Dehydrocoupling Reactions

In 1995, we reported the synthesis of the novel potassium salt of the zirconocene trihydride anion.^[116] Subsequently, the efficient and almost quantitative synthesis of the Li

polymerization chemistry. Elaboration of the catalytic syntheses with Zr catalysts potentially offers new routes to a wider variety of novel phosphorus compounds. Moreover, unprecedented oligomers and polymers containing phosphorus may provide unique new materials. While metal-mediated syntheses of main group compounds in general terms has only begun to be uncovered, the chemistry of Zr–P compounds stands out as a subset that richly illustrates this potential.

Received: September 22, 1998

Revised: January 28, 1999 [A 304]

- [1] E. Hey-Hawkins, *Chem. Rev.* **1994**, 94, 1661.
- [2] K. Issleib, H. Häckert, *Z. Naturforsch. B* **1966**, 21, 519.
- [3] J. Ellerman, P. Poersch, *Angew. Chem.* **1967**, 79, 380; *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 355.
- [4] R. T. Baker, J. F. Whitney, S. S. Wreford, *Organometallics* **1983**, 2, 1049.
- [5] R. T. Baker, P. J. Krusic, T. H. Tulip, J. C. Calabrese, S. S. Wreford, *J. Am. Chem. Soc.* **1983**, 105, 6763.
- [6] G. A. Vaughan, G. L. Hillhouse, *Organometallics* **1989**, 8, 1760.
- [7] L. Weber, G. Meine, R. Boese, N. Augart, *Organometallics* **1987**, 6, 2484.
- [8] F. Lindenberg, E. Hey-Hawkins, *J. Organomet. Chem.* **1992**, 435, 291.
- [9] E. Hey-Hawkins, S. Kurz, G. Baum, *Z. Naturforsch. B* **1995**, 50, 239.
- [10] S. Kurz, E. Hey-Hawkins, *J. Organomet. Chem.* **1994**, 479, 125.
- [11] T. L. Breen, D. W. Stephan, *Organometallics* **1996**, 15, 4509.
- [12] R. Bohra, P. B. Hitchcock, M. F. Lappert, W.-P. Leung, *J. Chem. Soc. Chem. Commun.* **1989**, 728.
- [13] H. Kopf, V. Richtering, *J. Organomet. Chem.* **1988**, 346, 355.
- [14] E. Hey, *J. Organomet. Chem.* **1989**, 378, 375.
- [15] M. Y. Chiang, S. Gambarotta, F. Von Bohuis, *Organometallics* **1988**, 7, 1864.
- [16] D. G. Dick, D. W. Stephan, *Can. J. Chem.* **1991**, 69, 1146.
- [17] E. Hey-Hawkins, S. Kurz, J. Sieler, G. Baum, *J. Organomet. Chem.* **1995**, 486, 229.
- [18] B. Benard, M. M. Rohmer, *J. Am. Chem. Soc.* **1992**, 114, 4785.
- [19] M.-M. Rohmer, M. Benard, *Organometallics* **1991**, 10, 157.
- [20] R. L. Dekock, M. A. Peterson, L. E. L. Reynolds, L.-H. Chen, E. J. Baerends, P. Vernooijs, *Organometallics* **1993**, 12, 2794.
- [21] K. Issleib, F. Krech, *Angew. Chem.* **1972**, 84, 582; *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 527.
- [22] H. Kopf, R. Voigtlander, *Chem. Ber.* **1981**, 114, 2731.
- [23] E. Hey, S. G. Bott, J. L. Atwood, *Chem. Ber.* **1988**, 121, 561.
- [24] J. Ho, T. L. Breen, A. Ozarowski, D. W. Stephan, *Inorg. Chem.* **1994**, 33, 865.
- [25] K. Fromm, G. Baum, E. Hey-Hawkins, *Z. Anorg. Allg. Chem.* **1992**, 615, 35.
- [26] E. Hey, *Z. Naturforsch. B* **1988**, 43, 1271.
- [27] B. L. Benac, R. A. Jones, *Polyhedron* **1989**, 8, 1774.
- [28] S. Kurz, E. Hey-Hawkins, *J. Organomet. Chem.* **1993**, 462, 203.
- [29] S. Nielsen-Marsh, R. J. Crowte, P. G. Edwards, *J. Chem. Soc. Chem. Commun.* **1992**, 699.
- [30] S. R. Wade, M. G. H. Wallbridge, G. R. Willey, *J. Chem. Soc. Dalton Trans.* **1983**, 2555.
- [31] F. Lindenberg, E. Hey-Hawkins, G. Baum, *Z. Naturforsch. B* **1995**, 50, 1359.
- [32] L. Gelmini, D. W. Stephan, *Organometallics* **1987**, 6, 1515.
- [33] E. Hey, M. F. Lappert, J. L. Atwood, S. G. Bott, *J. Chem. Soc. Chem. Commun.* **1987**, 421.
- [34] E. Hey, M. F. Lappert, J. L. Atwood, S. G. Bott, *Polyhedron* **1988**, 7, 2083.
- [35] E. Hey-Hawkins, F. Lindenberg, *Z. Naturforsch. B* **1993**, 48, 951.
- [36] E. Hey, M. F. Lappert, J. L. Atwood, S. G. Bott, *J. Chem. Soc. Chem. Commun.* **1987**, 597.
- [37] E. Hey-Hawkins, M. F. Lappert, J. L. Atwood, S. G. Bott, *J. Chem. Soc. Dalton Trans.* **1991**, 939.
- [38] U. Segerer, E. Hey-Hawkins, *Polyhedron* **1997**, 16, 2537.
- [39] E. Hey, U. Muller, *Z. Naturforsch. B* **1989**, 44, 1538.
- [40] F. Lindenberg, J. Sieler, E. Hey-Hawkins, *Polyhedron* **1996**, 15, 1459.
- [41] E. Hey-Hawkins, F. Lindenberg, *Chem. Ber.* **1992**, 125, 1815.
- [42] F. Lindenberg, E. Hey-Hawkins, *Z. Anorg. Allg. Chem.* **1995**, 621, 1531.
- [43] Z. Hou, D. W. Stephan, *J. Am. Chem. Soc.* **1992**, 114, 10088.
- [44] Z. Hou, T. L. Breen, D. W. Stephan, *Organometallics* **1993**, 12, 3158.
- [45] E. Hey, F. Weller, *Chem. Ber.* **1988**, 121, 1207.
- [46] D. W. Stephan, *Coord. Chem. Rev.* **1989**, 95, 41.
- [47] G. Johannesen, O. Stelzer, *Chem. Ber.* **1977**, 110, 3438.
- [48] O. Stelzer, E. Unger, *Chem. Ber.* **1977**, 110, 3430.
- [49] L. Gelmini, L. C. Matassa, D. W. Stephan, *Inorg. Chem.* **1985**, 24, 2585.
- [50] M. G. B. Drew, S. R. Wade, M. G. H. Wallbridge, G. R. Willey, *J. Chem. Soc. Dalton Trans.* **1986**, 713.
- [51] T. S. Targos, R. P. Rosen, R. R. Whittle, G. L. Geoffroy, *Inorg. Chem.* **1985**, 24, 1375.
- [52] R. T. Baker, T. H. Tulip, S. S. Wreford, *Inorg. Chem.* **1985**, 24, 1379.
- [53] S. A. Yousif-Ross, A. Wojcicki, *Inorg. Chim. Acta* **1990**, 171, 115.
- [54] L. Gelmini, D. W. Stephan, *Inorg. Chim. Acta* **1986**, 111, L17.
- [55] L. Gelmini, D. W. Stephan, *Inorg. Chem.* **1986**, 25, 1222.
- [56] R. T. Baker, W. C. Fultz, T. B. Marder, I. D. Williams, *Organometallics* **1990**, 9, 2357.
- [57] R. T. Baker, T. H. Tulip, *Organometallics* **1986**, 5, 839.
- [58] L. Gelmini, D. W. Stephan, *Organometallics* **1988**, 7, 849.
- [59] P. Y. Zheng, D. W. Stephan, *Can. J. Chem.* **1989**, 67, 1584.
- [60] P. Y. Zheng, T. T. Nadasdi, D. W. Stephan, *Organometallics* **1989**, 8, 1393.
- [61] D. G. Dick, D. W. Stephan, *Organometallics* **1990**, 9, 1910.
- [62] J. Ho, Z. Hou, R. J. Drake, D. W. Stephan, *Organometallics* **1993**, 12, 3145.
- [63] F. Lindenberg, T. Shribman, J. Sieler, E. Hey-Hawkins, M. S. Eisen, *J. Organomet. Chem.* **1996**, 515, 19.
- [64] F. Lindenberg, T. Gelbrich, E. Hey-Hawkins, *Z. Anorg. Allg. Chem.* **1995**, 621, 771.
- [65] U. Senff, S. Kurz, E. Hey-Hawkins, *Z. Anorg. Allg. Chem.* **1997**, 623, 1255.
- [66] T. Shribman, S. Kurz, U. Senff, F. Lindenberg, E. Hey-Hawkins, M. S. Eisen, *J. Mol. Catal.* **1998**, 129, 191.
- [67] P. B. Hitchcock, M. F. Lappert, W. P. Leung, *J. Chem. Soc. Chem. Commun.* **1987**, 1282.
- [68] A. H. Cowley, R. L. Geerts, C. M. Nunn, *J. Am. Chem. Soc.* **1987**, 109, 6523.
- [69] C. C. Cummins, R. R. Schrock, W. M. Davis, *Angew. Chem.* **1993**, 105, 758; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 756.
- [70] J. B. Bonanno, P. T. Wolczanski, E. B. Lobkovski, *J. Am. Chem. Soc.* **1994**, 116, 11159.
- [71] A. M. Arif, A. H. Cowley, C. M. Nunn, M. Pakalski, *J. Chem. Soc. Chem. Commun.* **1987**, 994.
- [72] J. Ho, R. J. Drake, D. W. Stephan, *J. Am. Chem. Soc.* **1993**, 115, 3792.
- [73] T. A. Bazhenova, A. V. Kulikov, A. F. Shestakov, A. E. Shilov, M. Y. Antipin, K. A. Lyssenko, Y. T. Struchkov, V. D. Makhayev, *J. Am. Chem. Soc.* **1995**, 117, 12176.
- [74] M. C. Fermin, J. Ho, D. W. Stephan, *Organometallics* **1995**, 14, 4247.
- [75] J. Ho, D. W. Stephan, *Organometallics* **1991**, 10, 3001.
- [76] J. Ho, D. W. Stephan, *Organometallics* **1992**, 11, 1014.
- [77] J. Ho, R. Rousseau, D. W. Stephan, *Organometallics* **1994**, 12, 1918.
- [78] T. L. Breen, D. W. Stephan, *J. Am. Chem. Soc.* **1995**, 117, 11914.
- [79] C. Frenzel, E. Hey-Hawkins, U. Muller, I. Strenger, *Z. Anorg. Allg. Chem.* **1997**, 623, 277.
- [80] T. L. Breen, D. W. Stephan, *Organometallics* **1997**, 16, 365.
- [81] A. Mahieu, Y. Miquel, A. Igau, B. Donnadieu, J.-P. Majoral, *Organometallics* **1997**, 16, 3086.
- [82] T. L. Breen, D. W. Stephan, *Organometallics* **1996**, 15, 5729.
- [83] T. L. Breen, D. W. Stephan, *J. Am. Chem. Soc.* **1996**, 118, 4204.
- [84] P. Binger in *Multiple Bonds and Low Coordination in Phosphorus Chemistry* (Eds.: M. Regitz, O. J. Scherer), Thieme, New York, **1990**, p. 90.

- [85] P. Binger, B. Biedenbach, A. T. Herrmann, F. Langhauser, P. Betz, R. Goddard, C. Krüger, *Chem. Ber.* **1990**, *123*, 1617.
- [86] P. Binger, B. Biedenbach, C. Krüger, M. Regitz, *Angew. Chem.* **1987**, *99*, 798; *Angew. Chem. Int. Ed.* **1987**, *26*, 764.
- [87] P. Binger, G. Glaser, B. Gabor, R. Mynott, *Angew. Chem.* **1995**, *107*, 114. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 81.
- [88] P. Binger, G. Glaser, S. Albus, C. Krüger, *Chem. Ber.* **1995**, *128*, 1261.
- [89] R. Milczarek, W. Rüsseler, P. Binger, K. Jonas, K. Angermund, C. Krüger, M. Regitz, *Angew. Chem.* **1987**, *99*, 957; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 908.
- [90] P. Binger, S. Leininger, J. Stannek, B. Gabor, R. Mynott, J. Bruckmann, C. Krüger, *Angew. Chem.* **1995**, *107*, 2411; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2227.
- [91] P. Binger, S. Leininger, K. Günther, U. Bergstrasser, *Chem. Ber.* **1997**, *130*, 1491.
- [92] P. Binger, R. Biedenbach, M. Mynott, M. Regitz, *Chem. Ber.* **1988**, *121*, 1455.
- [93] P. Rosa, P. Le Floch, L. Ricard, F. Mathey, *J. Am. Chem. Soc.* **1997**, *119*, 9417.
- [94] H. H. Karsch, B. Deubelly, J. Hofmann, U. Pieper, G. Muller, *J. Am. Chem. Soc.* **1988**, *110*, 3654.
- [95] N. E. Schore, S. J. Young, M. M. Olmstead, P. Hofmann, *Organometallics* **1983**, *2*, 1769.
- [96] N. E. Schore, H. Hope, *J. Am. Chem. Soc.* **1980**, *102*, 4251.
- [97] H. H. Karsch, B. Deubelly, G. Grauvogl, J. Lachmann, G. Muller, *Organometallics* **1992**, *11*, 4245.
- [98] H. H. Karsch, G. Grauvogl, B. Deubelly, G. Muller, *Organometallics* **1992**, *11*, 4238.
- [99] H. H. Karsch, G. Grauvogl, M. Kawecki, P. Bissinger, O. Kumberger, A. Schier, U. Muller, *Organometallics* **1994**, *13*, 610.
- [100] P. J. Fagan, W. A. Nugent, *J. Am. Chem. Soc.* **1988**, *110*, 2310.
- [101] P. J. Fagan, W. A. Nugent, J. C. Calabrese, *J. Am. Chem. Soc.* **1994**, *116*, 1880.
- [102] W. Tumas, J. A. Suriano, R. L. Harlow, *Angew. Chem.* **1990**, *102*, 89; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 75.
- [103] N. Avarvari, P. Le Floch, L. Ricard, F. Mathey, *Organometallics* **1997**, *16*, 4089.
- [104] T. L. Breen, D. W. Stephan, *Organometallics* **1997**, *16*, 365.
- [105] N. Cenac, A. Chrostowska, J.-M. Sotiropoulos, B. Donnadiou, A. Igau, G. Pfister-Guillouzo, J.-P. Majoral, *Organometallics* **1997**, *16*, 4551.
- [106] P. Binger, T. Wettling, R. Schneider, F. Zurmühlen, U. Bergstrasser, J. Hoffmann, G. Maas, M. Regitz, *Angew. Chem.* **1988**, *100*, 873; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 207.
- [107] A. Barron, A. H. Cowley, S. W. Hall, C. N. Nunn, *Angew. Chem.* **1988**, *100*, 873; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 837.
- [108] T. Wettling, B. Geissler, R. Schneider, S. Barth, P. Binger, M. Regitz, *Angew. Chem.* **1992**, *104*, 761; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 758.
- [109] B. Geissler, T. Wettling, S. Barth, P. Binger, M. Regitz, *Synthesis* **1994**, 1337.
- [110] E. Hey, M. F. Lappert, J. L. Attwood, S. G. Bott, *J. Chem. Soc. Chem. Commun.* **1987**, 421.
- [111] O. J. Scherer, *Comments Inorg. Chem.* **1987**, *6*, 1.
- [112] O. J. Scherer, *Angew. Chem.* **1990**, *102*, 1137; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1104.
- [113] O. J. Scherer, M. Swarowsky, H. Swarowsky, G. Wolmershauser, *Angew. Chem.* **1988**, *100*, 738. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 694.
- [114] M. C. Fermin, J. Ho, D. W. Stephan, *J. Am. Chem. Soc.* **1994**, *116*, 6033.
- [115] D. W. Stephan, unpublished results.
- [116] M. C. Fermin, D. W. Stephan, *J. Am. Chem. Soc.* **1995**, *117*, 12645.
- [117] N. Etkin, A. J. Hoskin, D. W. Stephan, *J. Am. Chem. Soc.* **1997**, *119*, 11420.
- [118] N. Etkin, M. C. Fermin, D. W. Stephan, *J. Am. Chem. Soc.* **1997**, *119*, 2954.
- [119] S. Xin, H. G. Woo, J. F. Harrod, E. Samuel, A. M. Lebus, *J. Am. Chem. Soc.* **1997**, *119*, 5307.
- [120] R. Shu, L. Hao, J. F. Harrod, H.-G. Woo, E. Samuel, *J. Am. Chem. Soc.* **1998**, *120*, 12988.

New Pathways in Plastics Recycling

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Plastics waste is today recovered, reprocessed, or used as raw material or fuel in a number of processes. Current legislation in Germany has acted as a driving force for the recycling of plastic waste. The book *Recycling and Recovery of Plastics* by Brandrup^[1] provides a review of the various methods and processes. Mechanical treatment to recyclates or incineration with energy utilization lie at the forefront of economic interest. Except for energy utilization no satisfactory solutions have yet been found for contaminated or mixed plastics or, in particular, composite plastics since articles made from such old plastic materials usually exhibit unsuitable mechanical properties. On the other hand, in view of the large and still strongly growing quantities of plastic produced, plastic waste represents a significant source of raw materials, one which until now has been inadequately exploited for the production of valuable chemical products. This form of raw material utilization could offer economic advantages and reflect recycling philosophy, for in this way the material cycle is closed.

Polyolefins in particular, which in quantity terms represent the largest group of plastics, are frequently used as packaging material and rapidly reappear as waste. Because they consist only of carbon and hydrogen atoms they are also called "solid oil".

Consequently many research groups in universities and industry have in the past investigated not only direct recycling but also the use of plastics as raw materials when the polymer molecules are degraded into small, organic base materials which can be purified by distillation or other methods.

However, because of chemical and technical problems as well as economic and legal factors, all processes for recycling of mass-produced plastics as raw materials have not been cost effective until now. Catalytic degradative reactions, such as those recently published by Dufaud and Basset,^[2] Uemichi et al.,^[3] and Pifer and Sen^[4] have now provided a new stimulus.

Particularly spectacular is the selective degradation of polyethylene with zirconium hydride catalysts at only 150 °C upon addition of hydrogen, as described by Dufaud and Basset.^[2] Reversal of the polymerization by Ziegler catalysts occurs, leading to short-chain hydrocarbons. This result is

illustrative of the effort devoted to recovery of the corresponding monomers from the plastic waste where possible.

Unfortunately the monomers cannot easily be recovered quantitatively from mass-produced plastics, including polyethylene (PE) and polypropylene (PP). In contrast, monomer recovery from specialty plastics such as polymethylmethacrylate (PMMA), polystyrene (PS), and polytetrafluorethylene (PTFE) has already been carried out successfully in high yields. In certain cases this method has been used technically when valuable monomers increased the profitability. Chemical research is therefore directed at recovering the respective monomer in high yield and purity.

The Current Status of Plastics Recycling as a Source of Raw Materials

Because of the low cost effectiveness of recycling plastics for raw materials there have been few technical applications until now. Therefore plastic waste is still mainly

- dumped (total loss of materials and energy);
- materially recycled, usually to products of lesser value (loss of quality), particularly if plastic mixtures are used;
- thermally recycled in municipal waste incineration plants or steel works (material loss).

In the case of bulk plastics the methods currently developed for recycling as raw materials have found few industrial applications. Nevertheless scientific interest in this topic remains undaunted. The reasons are clear:

- Considerable economic interest in the complete degradation of plastics and the recovery of high-value products exists because of high dumping costs and legal requirements for recycling.
- The unsolved chemical problems present a challenge to modern scientists. Particular aspects are the inertness of the polyolefins and the thermodynamic limitations to polymer reversal.

Separation and purification of plastic mixtures will be critical for recycling as raw materials. In a few cases monomer recovery has been remarkably successful with specialty plastics and has been used technically on a larger scale. Thus, up to 97% of monomer was recovered from PMMA in a fluidized bed process at 450 °C.^[5] A conversion of the plants that currently run the depolymerization in lead baths over to this process is planned. Polystyrene may also be extensively depolymerized to monomers at 550 °C; in addition to 77% styrene, 13% oligomers are also formed. The purity achieved

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at present is still too low, however, to allow economic operation.

The pyrolysis of PTFE is remarkable. In the past only 16 % of the monomer could be recovered. Recently by optimization of a fluidized bed process and at a cleavage temperature of 605 °C 78 % tetrafluoroethene, 5 % hexafluoropropene, and 4 % perfluorocyclobutane were obtained.^[6] Fluidization with water vapor was critical for the high yields of these usable fluoroolefins.

In addition to thermal cleavage, solvolysis (alcoholysis) of the important polyester polyethylene terephthalate (PET) to terephthalic acid derivatives and glycol has been used technically.^[1]

The technical implementation of chemical recycling relies fundamentally on well-proven process concepts. Pyrolysis is carried out either as a melt continuous in stirred tank reactors, in a fluidized bed, or in a rotary kiln, while solvolysis is normally undertaken in a stirred vessel under pressure. A problem with all processes is the contamination of used plastic and the uniformity of type of the materials used. In this context high proportions of PVC still cause difficulty because of the formation of HCl and corrosion, although there has been no lack of attempts at dehalogenation. Composites, particularly those with metals, can impair reutilization. Used, mixed, and contaminated plastics must therefore normally be mechanically treated and, to a lesser extent, also thermally pretreated.

One interesting possibility for the separation of plastics mixtures could be the staged pyrolysis investigated by Bockhorn: Different components are depolymerized or destroyed one after the other with a temperature program.^[7] The development potential of this method has yet to be established.

Catalysts in Recycling Polyolefins for Raw Materials

Polyolefins prepared from olefins such as PE and PP are kinetically relatively inert and more closely resemble paraffins in their chemical behavior. Until now there has been no way to degrade these polyolefins selectively at low temperatures to give homogeneous hydrocarbon products (especially olefins).

In contrast thermal cleavage (pyrolysis) is a well-established method for the degradation of polyolefins. Under severe reaction conditions (> 450 °C) cleavage of the polymer chain occurs as the primary reaction with sufficient speed—considerable amounts of heat must be mustered to cleave the C–C bond. The radical fragments formed undergo complicated and less selective secondary reactions that are difficult to control under the conditions of the primary reaction and are in effect analogous to the reactions of crude oil cracking. The product spectrum of pyrolysis is determined primarily by these secondary reactions, so that special efforts have been made to direct the reaction through the use of catalysts.

As always, the action of the catalyst is based on the formation of reactive intermediates to reduce the activation energy of the corresponding partial reaction and thus increase the rate of reaction. The enthalpy of bond cleavage cannot be influenced by the catalysts. In the degradation of polyolefins it

is reasonable to use the same or similar catalysts that were used in their preparation. From a mechanistic viewpoint reversal of the Ziegler–Natta polymerization is, according to the principle of microreversibility, theoretically possible. However, for thermodynamic reasons this reaction is limited because selective transfer of the relatively high depolymerization enthalpy to the reactants is difficult.

In this context Dufaud and Basset have succeeded in activating the C–C bond in PE catalytically with a strongly electrophilic Ziegler–Natta catalyst and cleaving it by the action of hydrogen at 150 °C.^[2] A zirconium monohydride—obtained by condensation of tetraneopentylzirconium with the silanol groups on the surface of a partially dehydroxylated aluminosilica gel and subsequent hydrogenation with H₂—was used as catalyst. Dufaud and Basset suggest two structures which are characterized by the close spatial relationship of the zirconium hydride to the silicon dihydride or aluminum hydride (Figure 1). This compound is able to polymerize

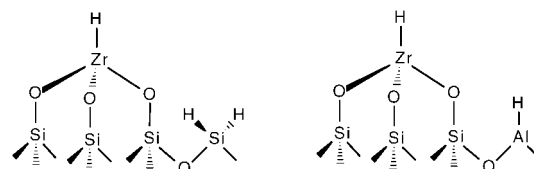


Figure 1. Suggested structures for zirconium hydride on aluminosilica gel (according to Dufaud and Basset).^[2]

ethene as well as propene. The polymer thus formed and bound to the catalyst could be cleaved hydrogenolytically to lower alkanes under a hydrogen atmosphere at 150 °C. After 15 h the polymer was completely degraded to ethane and methane. Not only polymer generated in situ, but also normal commercial polyethylene was degraded in the same way. Initially oligomers were formed which were then further cleaved to lower alkanes.

The mechanism proposed by Dufaud and Basset is based on endothermic β -alkyl transfer and subsequent exothermic hydrogenation (Figure 2). It is clear that this degradation reaction is not a “true” depolymerization (i.e., retro-polymerization) where starting from an active end only monomers are cleaved. Formally regarded this is a statistical chain cleavage which, because of the involvement of hydrogen, may even be considered to be a retro-polycondensation. Nevertheless, this discovery is remarkable since for the first time a catalyst has been found that is actively involved in the primary reaction. Even if in this case no monomers were obtained, catalytic monomer recovery is a large step closer. The specific production of olefins with suitable input of cleavage energy is the main problem for the realization of retro-polymerization.

Another possibility for the application of catalysts is to use cracking or superacid catalysts that are well-known for crude-oil processing, and to test their suitability for plastic pyrolysis.^[8] For example, zeolite catalysts which frequently exhibit active metal centers may be used. It is no wonder, therefore, that more recent work on plastics degradation has been concerned with similar systems. Uemichi et al. have inves-

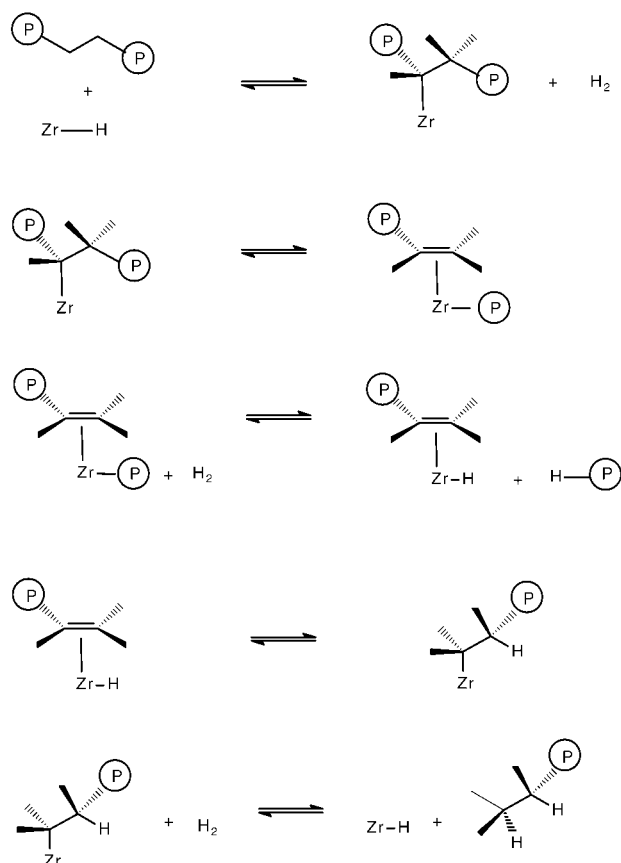


Figure 2. Mechanism of the hydrogenolysis of polyethylene (according to Dufaud and Basset).^[2] (P) = polymer chain.

tigated the catalytic degradation of low-density polyethylene (LDPE) with different catalysts.^[3] Here, a PE melt was passed slowly into a fixed-bed reactor heated to 525 °C through which helium is passed. The resulting products were captured and analyzed. In contrast to the non-catalyzed reaction, aromatic oils were formed in large amounts depending upon the catalyst, but rarely olefins. The high pyrolysis temperature of 400–525 °C showed clearly that secondary reactions are effectively catalyzed by this route, the primary reaction, however, proceeds largely unaltered.

Ibrahim and Seehra have investigated by ESR spectroscopy the cleavage of PE/PP mixtures in the presence of sulfur the

zeolite HZSM-5, and nickel/molybdenum on Al₂O₃.^[9] In this way they determined the number of radicals formed in relation to temperature and catalyst. They found that upon addition of sulfur or sulfur with NiMo/Al₂O₃ radicals were formed at temperatures as low as 280 and 240 °C, respectively. In contrast, with pure PE/PP or upon addition of HZSM-5 the radicals could only be observed at 360 °C. The number of radicals formed upon addition of sulfur was several times higher than without catalyst addition, but significantly lower when other catalysts were used. The precise nature of the effect of sulfur addition is still unclear. The action of HZSM-5 and NiMo/Al₂O₃ is attributed to the hydrogenation of the free radicals.

Unusual methods which initiate the partial oxidative decomposition of plastics by the action of nitrogen oxides and oxygen should not go unmentioned. Pifer and Sen were able to show, for example, that at 170 °C small amounts of valuable organic acids could be obtained from a number of different polyolefins.^[4] This cannot be an example of catalysis because NO_x and O₂ do not emerge from the reaction unscathed. Instead, it is better to use the term initiation. However, the principle is interesting because the carbon chain is cleaved at low temperatures.

Even though the promising developments for polyolefins and plastic mixtures described here still have to find industrial application, they do show a way by which raw materials obtained by recycling lead to more valuable products and hence to an improvement in the cost efficiency of the processes.

- [1] *Recycling and Recovery of Plastics* (Ed.: J. Brandrup), 1st ed., Hanser/Gardner, München, **1996**.
- [2] V. Dufaud, J.-M. Basset, *Angew. Chem.* **1998**, *110*, 848–852; *Angew. Chem. Int. Ed.* **1998**, *37*, 806–810.
- [3] Y. Uemichi, K. Takuma, A. Ayame, *Chem. Commun.* **1998**, 1975–1976.
- [4] A. Pifer, A. Sen, *Angew. Chem.* **1998**, *110*, 3500–3502; *Angew. Chem. Int. Ed.* **1998**, *37*, 3306–3308.
- [5] a) J. R. MacCallum, *Makromol. Chem.* **1965**, *83*, 137–147; b) W. Kaminsky, J. Franck, *J. Anal. Appl. Pyrolysis* **1991**, *19*, 311–318.
- [6] C. M. Simon, W. Kaminsky, *Polym. Degrad. Stab.* **1998**, *62*, 1–7.
- [7] H. Bockhorn, A. Hornung, U. Hornung, *J. Anal. Appl. Pyrolysis* **1998**, *46*, 1–14.
- [8] a) W. Ding, J. Liang, L. L. Anderson, *Fuel Process. Technol.* **1997**, *5*, 47–62; b) D. W. Park, E. Y. Hwang, J. R. Kim, J. K. Choi, Y. A. Kim, N. C. Woo, *Polym. Degrad. Stab.* **1999**, *65*, 193–198.
- [9] M. M. Ibrahim, M. S. Seehra, *Energy Fuels* **1997**, *11*, 926–930.

Oxygen and Osmium—A New Alliance for Dihydroxylations?

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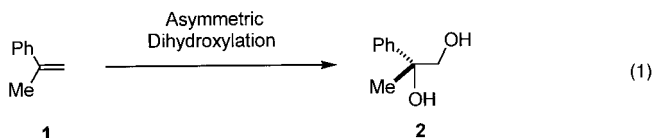
In the industrial production of monomers and chemical intermediates selective oxidation processes are used a great deal and, therefore, there is a great interest in these reactions. Although many of these processes are well established, there is still a need for further improvements, especially in the functionalization of nonactivated carbon–carbon double bonds.

Although the activation of oxygen is one of the main issues in biochemistry^[1] as well as in homogeneous catalysis,^[2] the use of molecular oxygen as a cooxidant in osmium-catalyzed dihydroxylation reactions has been ignored up until recently. However, publications now show increasing activity in this field of research.^[3]

The oxidation of alkenes by osmium tetroxide has been well known for a long time and osmium is one of the most efficient transition metals for catalytic dihydroxylations. It is not just the possibility of an asymmetric version of this reaction that has attracted synthetic^[4] and theoretical^[5] chemists. Several cooxidants have been investigated in osmium-catalyzed dihydroxylations to replace the ferricyanide in the reoxidation of Os^{VI} to Os^{VIII}.^[6] It was shown early on that oxygen can be used for this purpose, but the reoxidation is highly pH-dependent.^[7] Usually these oxidations led to carboxylic acids but, under certain conditions, diols can be obtained.^[8] Although it was already known that oxygen can add to several osmium complexes,^[9] dioxygen is activated by this coordination and recently the first stable oxo complexes of osmium have been isolated.^[10]

Krief and Colaux-Castillo have used selenoxides as cooxidants for Os^{VI}.^[11] Earlier work by Krief's group had shown that the corresponding selenides can be easily oxidized by

[Eq. (1)].^[13] It is remarkable that even air can be used in this reaction, instead of oxygen, with almost equal efficiency.



More direct is the approach from Beller et al. His team optimized the reaction conditions of the osmium-catalyzed dihydroxylation with oxygen as cooxidant and applied this method to the asymmetric version as well.^[14] The drawback of overoxidation, described earlier for this system,^[7] was solved by using a biphasic system. Careful investigation of the pH dependence of the reaction showed that at low pH no significant amount of diol was formed, probably because of the instability of the Os^{VI} state below pH 8. High conversions were found at pH 10.4.

As this is a ligand-accelerated reaction,^[15] higher yields are obtained by using additional ligands. These can be either achiral, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), or chiral ligands, such as (DHQD)₂PHAL. The selectivities are slightly lower than in the Sharpless and Krief procedures, probably due to the higher reaction temperature of 50 °C. If the reaction is performed at lower temperatures, or with lower oxygen pressures, the conversions are unsatisfactory. On the other hand, by using higher oxygen, or even air, pressures (3–5 bar), the catalyst loading can be lowered to 0.05 mol % and high selectivities can still be obtained.^[16] The procedures of the different groups and their results for the dihydroxylation of α -methylstyrene (**1**) are summarized in Table 1.

Table 1. Comparison of the conditions for the reaction **1** $\rightarrow$ **2**.^[a]

	[K ₂ OsO ₂ (OH) ₄]/ (DHQD) ₂ PHAL	K ₂ CO ₃	Cooxidant (quantity)	Solvent	T [°]	Yield [%]	ee [%]
Sharpless	0.2/1	300	K ₃ Fe(CN) ₆ (300)	<i>t</i> BuOH/H ₂ O	0	90	94
Krief	0.4/1.1	30	PhSeCH ₂ Ph (8), ¹ O ₂	<i>t</i> BuOH/H ₂ O	12	89	96
Beller	0.5/1.5	—	O ₂	<i>t</i> BuOH/phosphate buffer	50	96	80

[a] Quantities given in mol %.

singlet oxygen, which is generated by irradiation in the presence of a sensitizer.^[12] Therefore, the resulting selenoxides serve as an oxygen carrier in this reaction. By dihydroxylation of α -methylstyrene (**1**) in the presence of a chiral ligand 1,4-bis(dihydroquinidinyl)phthalazine [(DHQD)₂PHAL], diol **2** was obtained in similar selectivity and yield to that originally described by Sharpless using the AD-mix- β

The Beller group also extended their procedure to other, functionalized alkenes and obtained good to high selectivities with good yields. Interestingly, even tri- or tetrasubstituted alkenes can be dihydroxylated without the addition of methanesulfonamide, a requisite reagent in the Sharpless procedure for these alkenes.^[16] The procedure developed by Krief and co-workers was also applied to other alkenes, and selectivities similar to the Sharpless procedure were obtained.^[17]

Dioxygen is often used as a versatile cooxidant but usually only one oxygen atom is transferred during these oxidation reactions, leaving the other oxygen atom behind in a

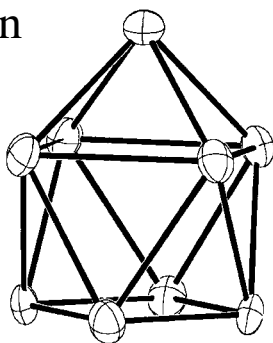
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stoichiometric side product. This can be observed in various transition metal catalyzed reactions, as well as in enzymatic transformations. This is also true for the Krief procedure where water is generated as a stoichiometric side product.

In one of the first atom-efficient oxidation reactions, in which both oxygen atoms from dioxygen were incorporated into the substrate, ruthenium porphyrin catalysts were used for epoxidations of alkenes.^[18] The Beller procedure runs along these lines, using both oxygen atoms for the dihydroxylation in an atom-efficient way. This procedure opens up perspectives for a preparation of diols without the production of side products—even on an industrial scale.

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- [1] *Active Oxygen in Biochemistry* (Eds.: J. S. Valentine, C. S. Foote, A. Greenberg, J. F. Liebman), Blackie, London, **1995**.
- [2] *The Activation of Dioxygen and Homogeneous Catalytic Oxidation* (Eds.: D. H. R. Barton, A. E. Martell, D. T. Sawyer), Plenum, New York, **1993**; M. Akita, Y. Moro-oka, *Catal. Today* **1998**, *44*, 183–188; Y. Moro-oka, *Catal. Today* **1998**, *45*, 3–12.
- [3] Functionalizations of alkenes with oxygen are possible also without any metal catalyst: T. Iwahama, S. Sakaguchi, Y. Ishii, *Chem. Commun.* **1999**, 727–728, and references therein.
- [4] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
- [5] A. J. DelMonte, J. Haller, K. N. Houk, K. B. Sharpless, D. A. Singleton, T. Strassner, A. A. Thomas, *J. Am. Chem. Soc.* **1997**, *119*, 9907–9908; P. Norrby, T. Rasmussen, J. Haller, T. Strassner, K. N. Houk, *J. Am. Chem. Soc.* **1999**, *121*, 10186–10192.
- [6] J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 1123–1125; S. Torii, P. Liu, N. Bhuvaneshwari, C. Amatore, A. Jutand, *J. Org. Chem.* **1996**, *61*, 3055–3060.
- [7] J. Périchon, S. Palous, R. Buvet, *Bull. Soc. Chim. Fr.* **1963**, 982–988.
- [8] J. F. Cairns, H. L. Roberts, *J. Chem. Soc. C* **1968**, 640–642; Celanese Corp., GB-B 1028940, **1966** [*Chem. Abstr.* **1966**, *65*, 3064f].
- [9] M. A. Esteruelas, E. Sola, L. A. Oro, U. Meyer, H. Werner, *Angew. Chem.* **1988**, *100*, 1621–1622; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1563–1564; A. Mezzetti, E. Zangrando, A. Del Zotto, P. Rigo, *J. Chem. Soc. Chem. Commun.* **1994**, 1597–1598.
- [10] T. Y. Bartucz, A. Golombek, A. J. Lough, P. A. Maltby, R. H. Morris, R. Ramachandran, M. Schlaf, *Inorg. Chem.* **1998**, *37*, 1555–1562; P. Barthazy, M. Wörle, A. Mezzetti, *J. Am. Chem. Soc.* **1999**, *121*, 480–481, and references therein.
- [11] A. Krief, C. Colaax-Castillo, *Tetrahedron Lett.* **1999**, *40*, 4189–4192.
- [12] L. Hevesi, A. Krief, *Angew. Chem.* **1976**, *88*, 413; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 381.
- [13] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. Jeong, H. Kwong, K. Morikawa, Z. Wang, D. Xu, X. Zhang, *J. Org. Chem.* **1992**, *57*, 2768–2771.
- [14] C. Döbler, G. Mehlretter, M. Beller, *Angew. Chem.* **1999**, *111*, 3211–3212; *Angew. Chem. Int. Ed.* **1999**, *38*, 3026–3028.
- [15] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159–1171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059–1070.
- [16] C. Döbler, M. Beller, personal communication.
- [17] A. Krief, personal communication.
- [18] J. T. Groves, R. Quinn, *J. Am. Chem. Soc.* **1985**, *107*, 5790–5792.
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Counterintuitive to the known behavior of *nido* clusters, two-electron oxidative polymerization of *nido*- Ge_9^{4-} provides chains of vertex-linked *nido*- Ge_9^{4-} clusters.

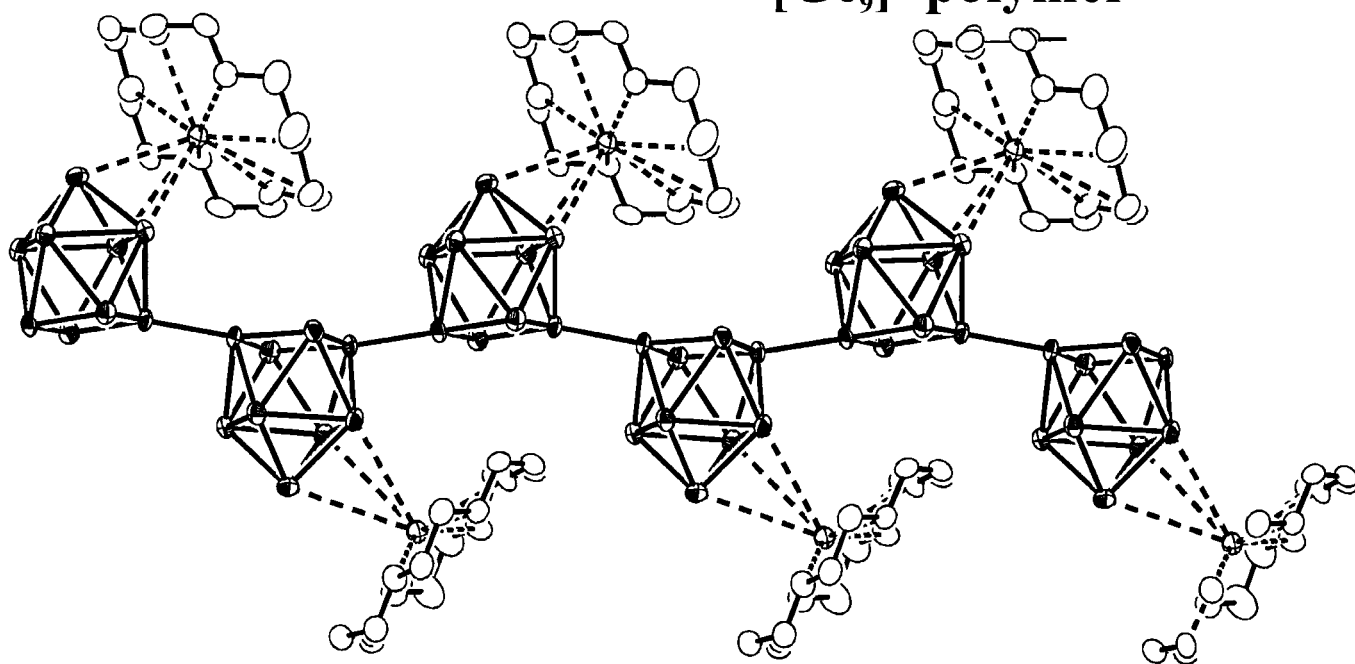


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$[\text{Ge}_9]^{4-}$ cluster



$[\text{Ge}_9]^{2-}$ polymer



An Unprecedented $_{\infty}[\text{Ge}_9]^{2-}$ Polymer: A Link between Molecular Zintl Clusters and Solid-State Phases**

Craig Downie, Zhongjia Tang, and Arnold M. Guloy*

Understanding relationships between the geometry, properties, and reactivity of small semiconductor clusters and bulk materials is a problem of fundamental and technological importance.^[1] One basic question is how properties and structures of small molecular clusters evolve when going to bulk materials. Although the step-wise growth of large transition metal clusters has been clearly elucidated, similar routes to main group semiconductor clusters are scarce.^[2] Moreover, evidence for the direct synthesis of bulk solid elemental semiconductors by kinetic-controlled cluster assembly and reactions has been lacking or inconclusive.^[1, 3] Progress toward this goal has been slow mainly due to the lack of unequivocal structural and mechanistic relationships between solid-state phases and their relevant cluster derivatives.

Members of a unique family of “naked” metal cluster ions, collectively known as Zintl ions, have been isolated from solution and characterized. They represent one end of the cluster-to-solid spectrum.^[4] In particular, Group 14 homopolyatomic anionic clusters may be considered as close derivatives of the technologically important elements. Hence, chemical and physical studies of novel Zintl cluster ions may provide valuable clues to understanding the evolution of molecular clusters into nanophases and bulk solid-state structures of Si, Ge, Sn, and Pb.^[1, 5]

Numerous Zintl cluster ions have been isolated and classified.^[4] Use of sequestering agents has led to several isolable homopolyatomic germanium anions such as Ge_9^{n-} ($n = 2, [6] 3, [7] 4^{[6]}$), Ge_5^{2-} ,^[8] Ge_{10}^{2-} ,^[7a] and Ge_{18}^{6-} .^[9] A different synthetic route also provided $[\text{Ge}_6\{\text{Cr}(\text{CO})_5\}_6]^{2-}$, which features an octahedral *closo*- Ge_6^{2-} unit.^[10] It should be noted that the nine-atom *nido*- Ge_9^{4-} clusters are remarkably resilient and are stable in solution and in the solid state.^[4c, 6, 11] Moreover, oxidation of *nido*- Ge_9^{4-} clusters resulted in the formation of related cluster species such as the paramagnetic radical Ge_9^{3-} , Ge_{18}^{6-} dimers, and *closo*- Ge_9^{2-} . Recent questions about the nature of Ge_9^{n-} clusters have been posed addressed at the validity of the disproportionation allocation of charges in $[\text{K}([2.2.2]\text{crypt})]_6\text{Ge}_9\text{Ge}_9$ into Ge_9^{2-} and Ge_9^{4-} .^[4c, 6, 12] Our investigation, focused on the isolation and characterization of *closo*- Ge_9^{2-} clusters, has led to the synthesis of a unique polymeric Zintl anion. Herein we report the synthesis as well as the crystal and electronic structures of $[\text{K}([18]\text{crown-6})]_2\text{Ge}_9 \cdot \text{en}$ (en = ethylenediamine), which fea-

tures an unprecedented polymer of vertex-linked *nido*- Ge_9^{2-} clusters. The polymer can be considered as being formed from a two-electron oxidative polymerization of *nido*- Ge_9^{4-} polyhedral clusters.

The title compound $[\text{K}([18]\text{crown-6})]_2\text{Ge}_9 \cdot \text{en}$ (**1**) was prepared by allowing binary alloys, having nominal composition “ KGe_4 ”, to react with crown ether [18]crown-6 in neat ethylenediamine and toluene. Careful use of slow diffusion techniques, over a two-week period, resulted in the formation and growth of transparent light blue-green crystals of **1**, which were investigated by single-crystal X-ray diffraction. Although the use of non-cryptand sequestering agents in the isolation of Zintl anions has been suggested, there has only been one report on the successful use of crown ethers in this regard—the isolation and characterization of $[\text{K}([18]\text{crown-6})]_3\text{KSn}_9$.^[13]

Compound **1** crystallizes in the noncentric orthorhombic space group $P2_12_12_1$.^[14] The asymmetric unit consists of one Ge_9^{2-} monomer, two types of $[\text{K}([18]\text{crown-6})]^+$ complex ions, and one solvent molecule. The crystal structure (Figure 1) features zigzag chains of $_{\infty}[\text{Ge}_9^{2-}]$ anions that lie along

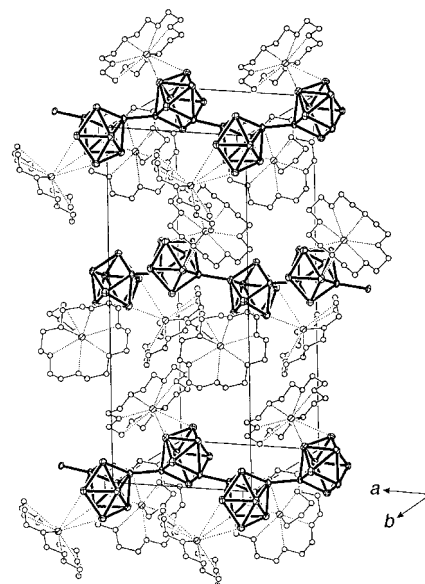


Figure 1. A view of the unit cell of **1**. Non-germanium atoms are represented as circles (K = crossed; C, O, N = open). Ellipsoids for germanium atoms are drawn at 50% probability. For clarity, only one orientation of the disordered [18]crown-6 molecule of the “noncapping” cation is drawn.

the 2_1 screw axes along *a*. The polymer of unligated clusters is illustrated as an “up” and “down” chain arrangement of Ge_9 clusters, with one diagonal of the cluster basal planes lying along the polymer axis. The polymer is completed by intercluster *exo* bonds that link the basal vertices of neighboring polyhedral clusters. The *exo* bonds (2.486(1) Å) are comparable to known Ge–Ge single bonds,^[15a] and form an angle of 171° with each cluster base.

The complex cations $[\text{K}([18]\text{crown-6})]^+$ serve as “face-capping” and “spacer” units that effectively surround and isolate each anionic polymer. One type of cation caps the apical triangular faces of a polyhedral cluster unit in the polar

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[**] This work was supported by the Petroleum Research Fund and the NSF (CAREER Award, DMR-9733587), and made use of MRSEC/TCSUH facilities at the University of Houston supported by the NSF (DMR-9632667). We also thank Dr. J. Korp for help with the crystallography.

chains (Figure 2) and reflect the lack of an inversion center in the crystal structure. The remaining noncapping complex cations, which exhibit configurational disorder of the crown ether, are coordinated by solvent molecules and serve as spacers.^[14] The resulting distance between the axes of nearest neighboring polymers is over 14 Å.

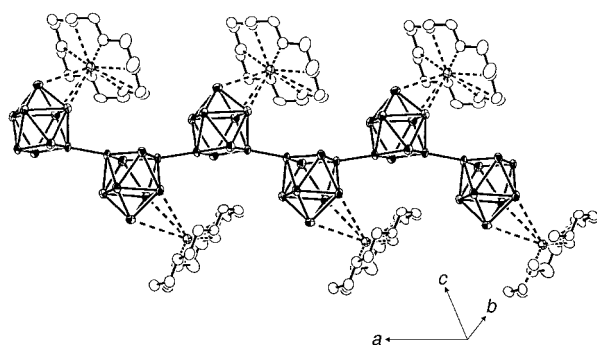


Figure 2. View of a section of the polymeric anion chain and "capping" $[K([18]\text{crown-6})]^+$ cations of **1**. All thermal ellipsoids are drawn at 50% probability.

The Ge_9^{2-} cluster unit (Figure 3) closely resembles a monocapped square antiprism that is distorted to C_{2v} symmetry. The observed Ge–Ge bond lengths within the cluster range from 2.552(1) to 2.864(1) Å and compare well with the distances for the isolated *nido*- Ge_9^{4-} cluster.^[6, 11] The longest

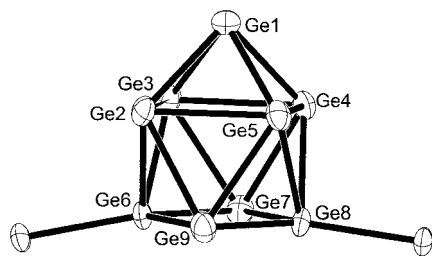


Figure 3. ORTEP representation of one $[\text{Ge}_9]^{2-}$ cluster unit of the polymeric anion. Ellipsoids are drawn at 50% probability. The *exo*-bonded atoms have been added. Bond lengths [Å] within the cluster: Ge1–Ge2 2.601, Ge1–Ge3 2.585, Ge1–Ge4 2.577, Ge1–Ge5 2.588, Ge2–Ge3 2.864, Ge2–Ge5 2.705, Ge2–Ge6 2.620, Ge2–Ge9 2.625, Ge3–Ge4 2.734, Ge3–Ge6 2.615, Ge3–Ge7 2.658, Ge4–Ge5 2.855, Ge4–Ge7 2.627, Ge4–Ge8 2.622, Ge5–Ge8 2.633, Ge5–Ge9 2.639, Ge6–Ge7 2.563, Ge6–Ge9 2.552, Ge7–Ge8 2.554, Ge8–Ge9 2.554. The *exo*-bond distance, Ge6–Ge8, is 2.486 Å. The standard deviation for all distances is 0.001 Å.

cluster edges are located at the nearly rectangular cluster "waist", with the face-capping cation closest to the longest edge of the cluster waist. The accompanying angular distortions from ideal C_{4v} symmetry are most noticeable at the basal planes. A rhomboidal distortion of the basal planes is depicted by a contraction along the chain axis, resulting in basal angles of 102.5° and 77.5° at the *exo*-bonded and nonbonded vertices, respectively. The distortion also results in basal diagonal distances of 3.194(1) Å and 3.942(1) Å between *exo*-bonded vertices and nonbonded vertices, respectively. However, the planarity of the basal plane remains intact.

On the basis of cluster bond distances and angles, the point symmetry of the cluster unit is close to C_{2v} and can be derived from a "compression" of a base diagonal in a C_{4v} monocapped square antiprism. The distortion contrasts the well-described

geometric transformation of nine-atom *nido* clusters, which is accompanied by a "butterfly" distortion of the cluster base.^[4c, 6, 12] The slight distortions from ideal C_{2v} geometry may be attributed to the effects of the face-capping $[K([18]\text{crown-6})]^+$ ion and close packing of the noncentric lattice. Application of Wade's rules of electron counting^[15b] to the Ge_9^{2-} cluster unit leads to the following distribution: 38 total e^- – 14 lone-pair e^- – 2 *exo*-bond e^- = 22 skeletal bond e^- , effectively yielding an electron count for a *nido* cluster.

The surprising formation of the polymeric anion is counterintuitive to known two-electron oxidation behavior of *nido* clusters and contrasts the existence of an isoelectronic *closo*- Ge_9^{2-} cluster.^[4, 16] Moreover, synthesis of elemental clusters through the reduction of metal salts has been clearly established.^[2, 17] The addition of [2.2.2]crypt to an aliquot portion of " $K\text{Ge}_4$ " in solution results in high-yield formation of $[K([2.2.2]\text{crypt})]_2\text{Ge}_9$ with *closo*- Ge_9^{2-} clusters.^[16] The unique polymerization implies that energy barriers between different geometric conformations of the monomeric cluster are small. Moreover, the electronic and geometric resiliency of *nido*- Ge_9^{4-} is emphasized. These factors and the packing effects of the disclike shape of the cations allow for the formation of bonds between *nido* clusters.

Theoretical calculations on related nine-atom *nido* clusters show that the HOMO states are mainly derived from cluster orbitals at the basal vertices.^[18] Consequently, this correlates with the oxidative formation of *exo* bonds between basal *trans* vertices in the polymer. Whereas isolated Zintl cluster ions are mainly associated with Groups 14 and 15, extended structures of clusters that exhibit classical deltahedral bonds have been entirely allied with Zintl phases containing "electron-deficient" triels (Group 13).^[4c, 19] Hence, polymeric $[K([18]\text{crown-6})]_2\text{Ge}_9$ nicely bridges the electronic and structural gap between isolated Zintl cluster anions and the extended structures of Zintl phases.

Extended-Hückel band calculations performed on a $[\text{Ge}_9^{2-}]$ polymer indicate a direct band gap of 2.86 eV. The electronic states immediately above and below the Fermi level (E_f) are 4p-based cluster antibonding and bonding states and do not exhibit significant band dispersion. Intercluster bonding states derived from basal atoms are stabilized, and lie 2–3 eV below E_f . Corresponding antibonding states are destabilized and lie more than 5 eV above E_f . Moreover, the increased 4s–4p hybridization of the *exo*-bonded atoms correlates with the observed increase in the basal bond angles. The semiconducting "bare" metal polymer satisfies descriptions for a quantum-wire structure, predicted to exhibit unique optical and electronic properties associated with quantum confinement.^[20] Preliminary optical absorption measurements indicate the material is strongly photoluminescent, consistent with the calculated band gap. Detailed investigations on the optical, SHG (Secondary Harmonic Generation), and spectroscopic properties of the novel material are currently in progress.

Experimental Section

All manipulations and reactions were carried out under an argon atmosphere. All solvents were degassed, distilled, and dried accordingly. The crown ether was oven- and vacuum-dried before use.

A sample (0.104 g) of the binary alloy "KGe₄", prepared by high-temperature reactions of pure elements (Aldrich) within sealed Nb tubing, was dissolved in neat en (5 mL), forming a dark green solution. A separate solution of [18]crown-6 (0.048 g, 0.182 mmol) in neat toluene (4 mL) was slowly added and layered on the alloy solution. Formation of transparent light blue-green rodlike crystals was observed after two weeks. The moisture-sensitive crystals were preserved in mother liquor and were found to be of compound **1** (yield 30–40 %).

Received: September 7, 1999 [Z13981]

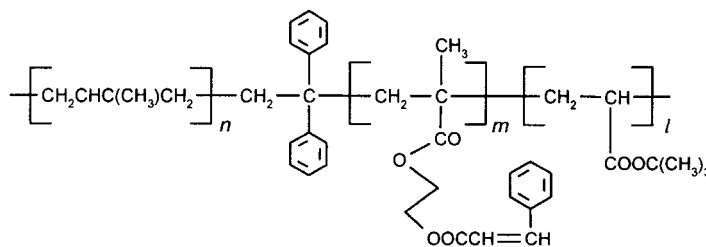
- [1] a) L. E. Brus, P. F. Szajowski, W. L. Wilson, T. D. Harris, S. Schuppler, P. H. Citrin, *J. Am. Chem. Soc.* **1995**, *117*, 2915; b) K. M. Ho, A. A. Shvartsbyrg, B. Pan, Z.-Y. Lu, C.-Z. Wang, J. G. Wacker, J. L. Fye, M. F. Jarrold, *Nature* **1998**, *392*, 582.
- [2] a) M. J. Wagner, J. L. Dye in *Comprehensive Supramolecular Chemistry*, Vol. 1 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, J.-M. Lehn), Pergamon, Oxford, **1996**; b) G. Schmid, *Cluster and Colloids*, VCH, Weinheim, **1994**.
- [3] a) M. L. Steigerwald in *Inorganometallic Chemistry* (Ed.: T. P. Fehlner), Plenum, New York, **1992**, pp. 333–358; b) M. O. Watanabe, T. Miyazawa, T. Kanayama, *Phys. Rev. Lett.* **1998**, *81*, 5362.
- [4] a) J. D. Corbett, *Struct. Bonding (Berlin)* **1997**, *87*, 157; b) H.-G. von Schnering, *Angew. Chem.* **1981**, *93*, 44; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 33.
- [5] a) R. A. Bley, S. M. Kauzlarich, *J. Am. Chem. Soc.* **1996**, *118*, 12461; b) L. Brus, *J. Phys. Chem.* **1994**, *98*, 3575.
- [6] C. H. E. Belin, J. D. Corbett, A. Cisar, *J. Am. Chem. Soc.* **1977**, *99*, 7163.
- [7] a) C. Belin, H. Mercier, V. Angilella, *New J. Chem.* **1991**, *15*, 931; b) T. F. Fässler, M. Hunziker, *Inorg. Chem.* **1994**, *33*, 5380.
- [8] J. Campbell, G. J. Schröbilgen, *Inorg. Chem.* **1997**, *36*, 4078.
- [9] L. Xu, S. C. Sevov, *J. Am. Chem. Soc.* **1999**, *121*, 9245.
- [10] P. Kirchner, G. Huttner, K. Heinze, G. Renner, *Angew. Chem.* **1998**, *110*, 1754; *Angew. Chem. Int. Ed.* **1998**, *37*, 1664.
- [11] a) V. Queneau, S. C. Sevov, *Angew. Chem.* **1997**, *109*, 1818; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1754; b) H. G. von Schnering, M. Baitinger, U. Bolle, W. Carrillo-Cabrera, J. Curda, Y. Grin, F. Heinemann, J. Llanos, K. Peters, A. Schmeding, M. Somer, *Z. Anorg. Allg. Chem.* **1997**, *623*, 1037; c) M. Somer, W. Carrillo-Cabrera, E. M. Peters, K. Peters, H. G. von Schnering, *Z. Anorg. Allg. Chem.* **1998**, *624*, 1915.
- [12] T. F. Fässler, U. Schutz, *Inorg. Chem.* **1999**, *38*, 1866.
- [13] T. F. Fässler, R. Hoffmann, *Angew. Chem.* **1999**, *111*, 526; *Angew. Chem. Int. Ed.* **1999**, *38*, 543.
- [14] Crystal structure data for **1**: *M_r* = 1320.24, orthorhombic, space group *P2₁2₁2₁* (no. 19), *a* = 11.2796(7), *b* = 14.7049(9), *c* = 27.8321(17) Å, *V* = 4616.4(5) Å³, *Z* = 4, *ρ* = 1.900 g cm⁻³, *μ* = 6.003 mm⁻¹, *λ* = 0.71073 Å (MoK_α), *2θ_{max}* = 46.5°; of 20849 total reflections, 6629 were independent and 6605 were observed (> 3σ₁); 455 total variables; final *R* indices *R*1 = 0.0328, *wR*2 = 0.0772 (*I* > 4σ(*I*)) and *R*1 = 0.0488, *wR*2 = 0.0978 (all data). The analysis, using a Siemens SMART diffractometer equipped with a CCD area detector, was carried out at -50 °C. Empirical absorption correction was applied on a hemisphere of data, and redundant reflections were averaged. The structure was solved by direct methods and refined by full-matrix least-squares calculations. One of the two crown ether molecules is disordered over two different positions (50:50). The potassium atom K2 attached to it binds to an en solvent molecule, which is also disordered. Owing to disorder, the exact amount of en cannot be determined. One en molecule per K2 atom was assumed for all the calculations. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133996. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [15] a) W. B. Pearson, *The Crystal Chemistry and Physics of Metals and Alloys*, Wiley, New York, **1972**; b) K. Wade, *Adv. Inorg. Chem. Radiochem.* **1976**, *18*, 1.
- [16] Z. Tang, C. Downie, A. M. Guloy, unpublished results.

- [17] a) J. R. Heath, *Science* **1992**, *258*, 1131; b) L. Brus, *Adv. Mater.* **1993**, *5*, 286.
- [18] a) L. Lohr, *Inorg. Chem.* **1981**, *20*, 4229; b) J. Campbell, D. A. Dixon, H. P. A. Mercier, G. J. Schröbilgen, *Inorg. Chem.* **1995**, *34*, 5798.
- [19] a) C. Belin, M. Tillard-Charbonnel, *Prog. Solid State Chem.* **1993**, *22*, 59; b) J. K. Burdett, E. Canadell, *J. Am. Chem. Soc.* **1990**, *112*, 7207; c) Z. Xu, A. M. Guloy *J. Am. Chem. Soc.* **1998**, *120*, 7349.
- [20] a) T. Ogawa, T. Takagahara, *Phys. Rev. B* **1991**, *43*, 14325; b) F. Rossi, E. Molinari, *Phys. Rev. Lett.* **1996**, *76*, 3642.

Block Copolymer Nanotubes**

Sean Stewart and Guojun Liu*

The preparation of nanometer-sized structures with well-defined shape and narrow size distribution, "nanostructures", has attracted much attention mainly to meet the demand for smaller electronic devices.^[1] Nanostructures are also useful in the preparation of strong nanocomposite materials or sensors that may imitate enzymes in molecular recognition. Nanostructures of block copolymers^[2] are interesting because they span the size range from 5 to 500 nm and fill the gap between nanostructure sizes obtainable from traditional lithographic techniques and those from small-molecule self-assembly processes. In this communication we report the preparation of solvent-dispersible nanotubes from a triblock copolymer, polyisoprene-*block*-poly(2-cinnamoyl ethyl methacrylate)-*block*-poly(*tert*-butyl acrylate), PI-*b*-PCEMA-*b*-PtBA (**1**), with 130 isoprene, 130 CEMA, and 800 tBA units.



1, PI-*b*-PCEMA-*b*-PtBA

Although there have been many reports in the past decade on the preparation and study of nanotubes, our nanotubes are unique in composition and properties. Excluding those dealing with nanochannels formed in inorganic oxides,^[3–6] glass,^[7] metals,^[8] or polymer matrices,^[9, 10] the majority of publications in the past eight years have been on carbon^[11–14] or metal

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[**] G.L. thanks the Natural Sciences and Engineering Research Council of Canada and S.S. thanks the University of Calgary for financial support. Partial financial support from the Petroleum Research Fund, administered by the American Chemical Society, is also gratefully acknowledged.

oxide nanotubes.^[15, 16] Nanotubes have been reported to derive from lipids,^[17] amino acids,^[18, 19] tubulin templates,^[20] organic precursors,^[21, 22] or polymers.^[23, 24] For polymeric nanotube preparation, alumina membranes with cylindrical pores were used as the template.^[23] The resultant tubes are generally made of conductive polymers and are not dispersible in any solvents. More recently Eisenberg and co-workers^[24] reported tubule formation due to the self-assembly of polystyrene-*block*-poly(ethylene oxide) in water. The tubules were not crosslinked and are different from our nanotubes not only in preparation methodology but also in their structural stability in different solvents.

The approach utilized here, illustrated in Figure 1, is similar to that used extensively in our research group for the preparation of nanochannels in thin films,^[9, 25] nanofibers,^[26, 27] and hollow^[28, 29] or shaved^[30] nanospheres. This approach has



Figure 1. Schematic presentation of the process involved in the preparation of nanotubes. The PCEMA shell is photocrosslinked (dark gray to light gray), then ozonolysis decomposes the PI core (black to white). The PrBA corona chains (wavy lines) render solvent dispersibility to the nanotubes.

also been utilized by Lee et al.^[10] for the preparation of porous films and Huang et al.^[31] for the preparation of hollow nanospheres from diblocks. The approach involves molecular design, block copolymer synthesis, self-assembly of block copolymers, the interlocking of the self-assembled nanostructure by crosslinking the shell, and the selective domain degradation, “nanosculpturing”, of the crosslinked nanostructure. The triblock self-assembly occurred in methanol to form cylindrical micelles with a PI core, a PCEMA shell, and a PrBA corona. Cylindrical structure interlocking was achieved by photocrosslinking the PCEMA shell. Nanotubes of PCEMA-*block*-PrBA (**2**) were obtained by degrading the PI core of crosslinked micelles of **1**.

The precursor to the triblock was synthesized by anionic polymerization with the detailed procedure described elsewhere.^[32–35] The triblock **1** was characterized by light scattering (LS), ¹H NMR, and gel-permeation chromatography (GPC) (Table 1). LS was used to determine the molar mass of the PI block. NMR analysis of the triblock yielded monomer ratios $n/m/l = 1.00/0.97/6.0$. GPC analysis suggests narrow molar mass distributions for both the PI block and **1** as a whole.

Formation of cylindrical micelles from **1** in methanol was confirmed by transmission electron microscopy (TEM) results shown in Figure 2a. The cylinders have a diameter of about

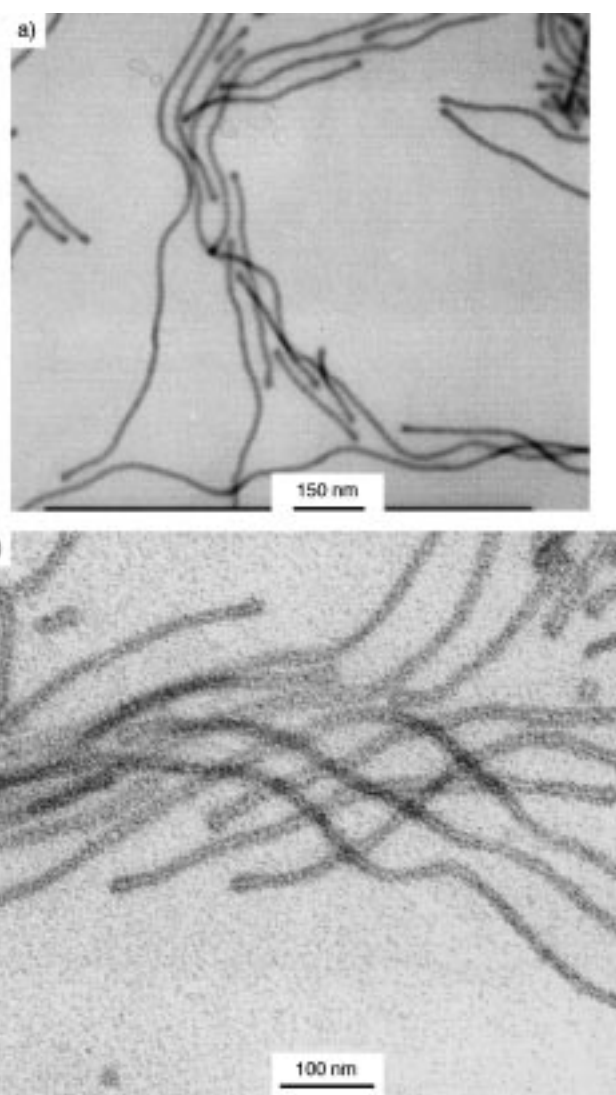


Figure 2. TEM images of a) cylindrical micelles of **1** and b) nanotubes **2**. The micelles were stained with OsO₄, the nanotubes with RuO₄.

22 nm with a dark-gray core-shell structure. Since PrBA is soluble in methanol and is not stained by OsO₄, the PrBA has formed an “invisible” corona. The core and shell of micelles of **1** (Figure 2a) should consist of PI and PCEMA. PI should look darker, as demonstrated by Ding and Liu,^[36] under these conditions because each gram of PI contains approximately four times more stain-susceptible double bonds than PCEMA. The cylinders reach micrometer lengths but with a broad length distribution.

Although there have been many studies of ABC triblock copolymer morphology in the solid state,^[37] the study of their morphologies in block-selective solvents has been rare.^[29, 38–40] This may represent the second report of cylindrical micelle

Table 1. Characteristics of the polymers.

Sample	dn/dc [mL g ⁻¹]	$\bar{M}_w$ (LS) [g mol ⁻¹]	PI block $\bar{M}_w/\bar{M}_n$ (GPC)	1,4-PI [%]	n	m	Triblock l	$\bar{M}_w/\bar{M}_n$ (GPC)
1	0.104	9.0×10^3	1.05	92	130	130	800	1.08
1'	0.104	20×10^3	1.06	93	290	220	770	1.30

formation of a triblock copolymer in a block-selective solvent following Yu and Eisenberg.^[38]

The crosslinking of the cylindrical micelles of **1** to produce **2** was achieved by irradiating the sample with UV light (500 W Hg lamp) that had passed through a 260 nm cut-off filter. The filter was used to minimize light absorption by PI and its consequent crosslinking. The loss of CEMA double bonds was followed by absorbance decrease from either IR (1631 cm^{-1}) or UV (274 nm) where the converted CEMA groups absorb negligibly. PCEMA crosslinked due to the dimerization of CEMA groups from different chains in the shell.^[41, 42] A typical CEMA conversion of 40 to 50 % was used for locking the cylindrical micelle structure. PCEMA crosslinking did not perturb the structure of the cylindrical micelles as judged from TEM images. The crosslinking, however, made the structure immutable as demonstrated by the stability not only in methanol but also in THF, CHCl_3 , and CH_2Cl_2 which dissolves PI, *Pt*BA, and uncrosslinked PCEMA.

Due to the structural stability of the crosslinked micelles and the fact that PCEMA crosslinking stabilized but did not change the micelle morphology, it was more convenient to use the crosslinked micelles or nanofibers for demonstrating their core-shell corona structure. This was done using ^1H NMR spectroscopy and TEM. When a nanofiber sample of **1** was analyzed by NMR in CDCl_3 , no signals were observed from the PCEMA block and the intensity of the PI peaks was substantially reduced relative to that of the *Pt*BA signals. The absence of PCEMA signals suggests PCEMA crosslinking and lowered mobility of PCEMA chain segments. The enhanced signals of *Pt*BA relative to PI suggest that the *Pt*BA chains exist in a relatively unhindered environment, such as in the corona. Signals were seen from PI because PI is a rubbery polymer at room temperature and segmental motion was possible in the PI phase of the nanofibers.

For the TEM study, another triblock **1'** (Table 1) was used because this sample had an overall higher molar mass, and formed much larger straight or branched cylindrical micelles (Figures 3 a and 3 b), thus facilitating the differentiation of the various sub-domains. Unfortunately, this sample had a greater polydispersity arising presumably from nonuniform chain growth due to the high viscosity of the mixture at the later stage of the polymerization. Also, **1'** formed mainly branched rather than straight cylindrical micelles due to the different relative block lengths. Despite these differences, the straight or branched cylindrical micelles formed from this triblock should have the same core-shell-corona structure as **1** due to their similar preparation.

Like the cylindrical micelles of **1**, the branched cylindrical micelles of **1'** have distinctively a dark PI core and gray PCEMA shell in the TEM images independent of the staining by OsO_4 (Figure 3 a) or RuO_4 (Figure 3 b). The presence of an unstained *Pt*BA layer was confirmed by the following experiment. After spraying from CH_2Cl_2 and staining with OsO_4 , the crosslinked branched or straight cylindrical micelles of **1'** had a diameter of approximately 65 nm. This value increased to about 79 nm when the sample was sprayed from a trimethylsilyl iodide solution in CH_2Cl_2 . The diameter of the cross-linked micelles increased, because trimethylsilyl iodide stained the *Pt*BA corona through reaction (1).

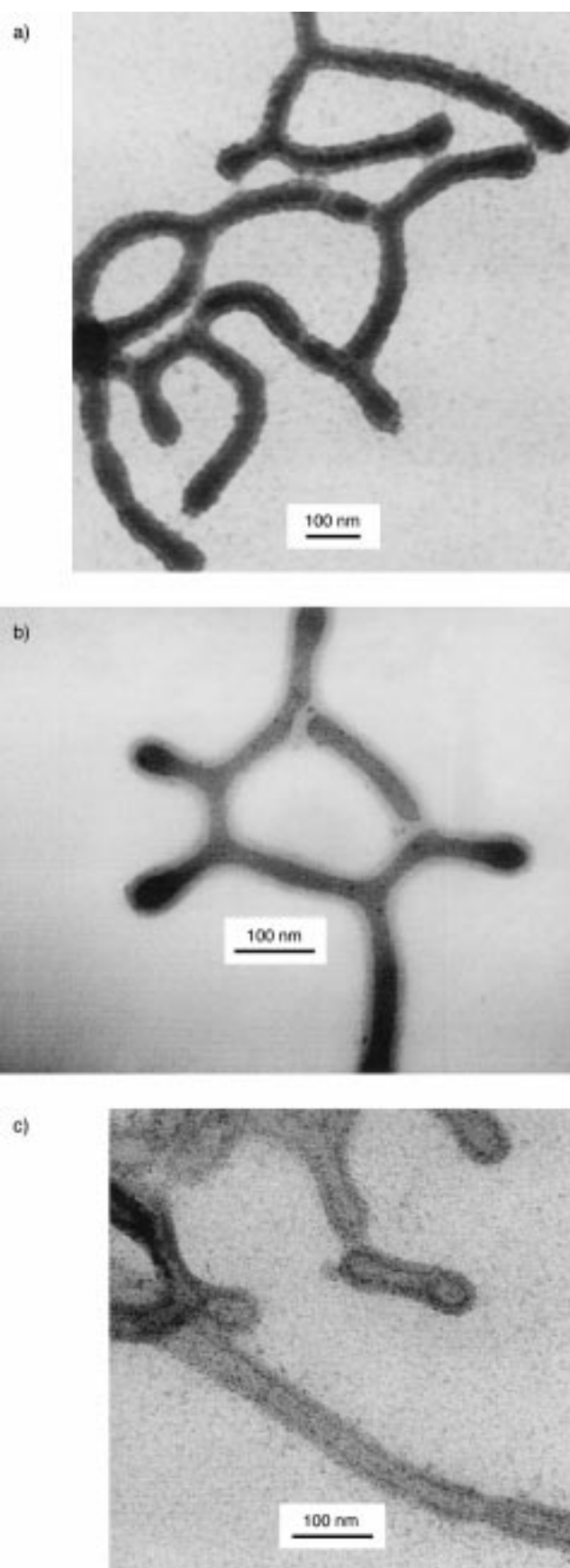
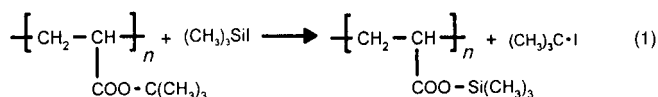


Figure 3. TEM images of straight or branched cylindrical micelles of **1'** stained with a) OsO_4 and b) RuO_4 . Shown in c) is the TEM image of nanotubes **2'** stained with RuO_4 .



The PI block of nanofibers (**1** or **1'**) was decomposed by ozonolysis to form nanotubes (**2** or **2'**, respectively). The complete decomposition of the PI block is demonstrated by the almost quantitative disappearance of the characteristic IR absorption for double bonds at 1631 cm^{-1} (Figure 4). Shown

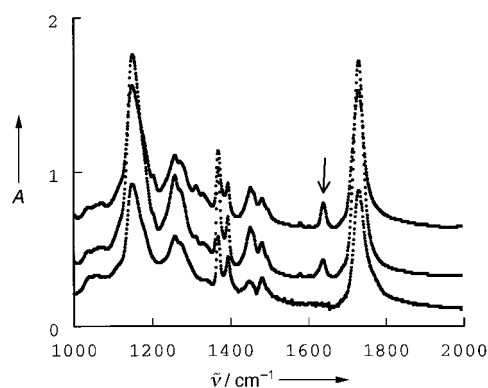


Figure 4. Comparison between the FTIR spectra of micelles of **1** (top), crosslinked micelles of **1** (middle), and nanotubes **2** (bottom).

in Figures 2b and 3c are TEM images of such straight **2** or branched **2'** nanofibers stained with RuO_4 . Comparing Figures 3b and 3c, a light stripe in the center of each cylinder in Figure 3c unambiguously suggests the formation of nanotubes. A similar light stripe can be seen in each cylinder in Figure 2b but it is not as clear due to its small size.

The formation of nanotubes from **1** was also confirmed from a rhodamine B (RB) loading experiment. RB loading was achieved by refluxing either nanofibers of **1** or nanotubes **2** with a RB solution in methanol (ca. 10 %) for 24 h and then evaporating off the methanol. RB impregnated the tubes and fibers presumably to eliminate a concentration gradient between the bulk phase and the fiber or tube phase. The distinct IR absorption peaks at 1590 and 845 cm^{-1} for RB and *tert*-butyl groups of the nanotubes and nanofibers, respectively, were used to estimate RB loading density. Under the same conditions, each gram of nanotube or nanofiber was impregnated with 0.065 and 0.021 g of RB, respectively. The much higher RB loading for the nanotubes suggests the presence of a hollow space left behind by PI degradation. Since the mass ratio of PI to PCMA and PtBA in the triblock **1** is 0.066 , the excess loading density of 0.044 g g^{-1} for the nanotube **2** relative to that of the nanofiber of **1** suggests the high utilization of the hollow space in **2**. This high space utilization is possible because of methanol evaporation. As methanol evaporates, the RB concentration increases until it reaches the saturation limit. After that, RB crystallizes inside and outside of the tube. The crystallization of RB inside the tube will decrease the local RB concentration and lead to the diffusion of more RB into the tube. This process continues until all the methanol evaporates.

The loading of RB into the nanotube hollow space is evident from the TEM image shown in Figure 5. A sample

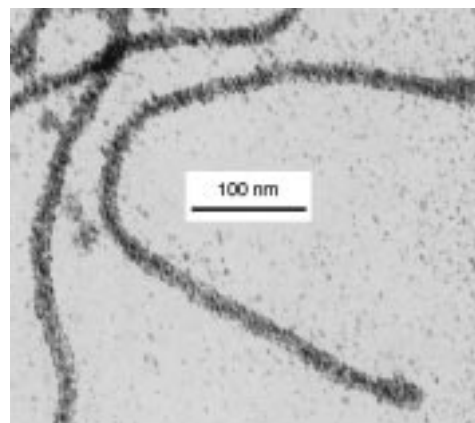


Figure 5. TEM image of nanotubes **2** loaded with rhodamine B, and stained with RuO_4 .

from the reflux of **2** with RB in methanol was aspirated onto a carbon-coated copper grid. The grid was equilibrated with a drop of water for 20 s to dissolve most of the free RB on the grid or adsorbed on the nanotube outer surfaces, and this excess water was removed by adsorption onto filter paper. The RB-loaded **2** was stained with RuO_4 , and the TEM image of the cylinders do not show the light stripes in agreement with RB filling of the nanotubes.

In summary, we have demonstrated cylindrical micelle formation in methanol from sample **1**. The cylindrical micelles consisted of a PtBA corona, PCMA shell, and PI core. Nanotubes **2** were obtained after PCMA crosslinking and PI core degradation. The potential of using molecules **2** as microvials has been demonstrated by RB loading. Other potential applications of **2** include the use as templates for metal or semi-conductor nanowire production. Such insulated nanowires should be of use in nanometer-sized electronic devices. Nanotube **2** can also be pyrolyzed to yield carbon or metal-carbide nanotubes, which could be useful in nanocomposite preparation.^[1]

Experimental Section

The polymerization of isoprene was performed in dry hexane (1 d). A slight excess of diphenyl ethylene over *sec*-butyl lithium was added to convert the polyisoprene anion to the terminal diphenyl ethylene anion and an aliquot of the PI block was taken for molar mass determination. After the introduction of THF by cryodistillation, the second monomer 2-trimethylsiloxyethyl methacrylate (HEMA-TMS) was polymerized at -78°C for 2 h, then the third monomer *t*BA for 4 h. Polymerization was terminated by the addition of methanol. The methanol also hydrolysed the trimethylsilyl group from HEMA-TMS to yield poly(2-hydroxyethyl methacrylate), PHEMA. PI-*b*-PHEMA-*b*-PtBA was purified by precipitation from methanol/water ($\approx 7/3$) at ca. -10°C . **1** was obtained by reacting PI-*b*-PHEMA-*b*-PtBA with excess cinnamoyl chloride in pyridine overnight at room temperature. Polymer **1** was purified by repeated precipitation from methanol/water (see above). Residual PI homopolymer in the triblock was removed through three extractions with hexanes (room temperature, 1 d). The extracted sample was dissolved in THF and added into a large excess of methanol; once the THF evaporated, the micellar sample was finally added into ice to induce precipitation.

The specific refractive index increment dn/dc of the PI block in cyclohexane at 488 nm was determined to be 0.104 g mL^{-1} . The molar masses of the PI blocks were determined from a Brookhaven Model 9025 light-scattering instrument. The GPC analysis was performed using a Waters HT-4 ultra-styragel column and polystyrene as calibrant.

To prepare cylindrical micelles, triblock copolymer (100 mg) was dissolved in THF (≈ 2 mL), the THF was evaporated and the sample dried at 85°C for 2 h. Methanol (50 mL) was added to redisperse the polymer.

To prepare nanotubes, ozone generated (Welsback generator) was bubbled into a nanofiber solution in CH_2Cl_2 at -78°C for 10 min. Excess ozone was purged with nitrogen. An excess of trimethylphosphite was added and the mixture was stirred for 3 h at -78°C to reduce the ozonides formed to low molar mass aldehyde or ketone groups.^[43]

TEM images were obtained using a Hitachi-7000 instrument operated at 100 kV. TEM specimens were prepared by aspirating a liquid sample onto a carbon-coated Cu grid and staining with OsO_4 or RuO_4 . For staining PtBA with $(\text{CH}_3)_3\text{SiI}$, nanofibers of **1** were mixed with a 0.14 M $(\text{CH}_3)_3\text{SiI}$ solution in CH_2Cl_2 for 1 h, followed by aspirating onto a carbon-coated copper grid. Excess $(\text{CH}_3)_3\text{SiI}$ was removed with a drop of dry CH_2Cl_2 and adsorption onto tissue.

For RB impregnation, nanotubes or nanofibers (40 mg) were mixed with RB (470 mg) and methanol (6 mL). The mixture was refluxed for 24 h. Then the methanol was evaporated. The remaining solid was suspended in water, filtered, and washed repeatedly with hot water before drying. The dried RB-loaded nanotube or nanofiber aggregates were ground with KBr for FTIR measurements.

Received: March 18, 1999

Revised: October 4, 1999 [Z13187]

- [1] G. M. Chow, K. E. Gonsalves, *Nanotechnology—Molecularly Designed Materials* (ACS Symp. Ser. **1996**, 622).
- [2] G. Liu, *Curr. Opin. Colloid Interface Sci.* **1998**, 3, 200.
- [3] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, 359, 710.
- [4] For a review, see J. Y. Ying, C. P. Mehnert, M. S. Wong, *Angew. Chem.* **1999**, 111, 58; *Angew. Chem. Int. Ed.* **1999**, 38, 56.
- [5] C. R. Martin, *Science* **1994**, 266, 1961.
- [6] P. Hoyer, *Langmuir* **1996**, 12, 1411.
- [7] D. H. Pearson, R. J. Tonucci, *Science* **1995**, 270, 68.
- [8] H. Masuda, K. Fukuda, *Science* **1995**, 268, 1466.
- [9] G. Liu, J. Ding, *Adv. Mater.* **1998**, 10, 69.
- [10] J.-S. Lee, A. Hirao, S. Nakahama, *Macromolecules* **1989**, 22, 2602.
- [11] S. Iijima, *Nature* **1991**, 354, 56.
- [12] S. Iijima, T. Ichihashi, *Nature* **1993**, 363, 603.
- [13] A. Thess, R. Lee, P. Nikolaev, H. Dai, P. Petit, J. Robert, C. Xu, Y. H. Lee, S. G. Kim, A. G. Rinzler, D. T. Colbert, G. E. Scuseria, D. Tomanek, J. E. Fischer, R. E. Smalley, *Science* **1996**, 273, 483.
- [14] For a review, see S. Subramoney, *Adv. Mater.* **1998**, 10, 1157.
- [15] T. Kasuga, M. Hiramatsu, A. Hoson, T. Sekino, K. Niihara, *Langmuir* **1998**, 14, 3160.
- [16] B. C. Satishkumar, A. Govindaraj, E. M. Voli, L. Basumallic, C. N. R. Rao, *J. Mater. Res.* **1997**, 12, 604.
- [17] J. M. Schnur, *Science* **1993**, 262, 1669.
- [18] N. Khazanovich, J. R. Granja, D. E. McRee, R. A. Milligan, M. R. Ghadiri, *J. Am. Chem. Soc.* **1994**, 116, 6011.
- [19] J.-H. Fuhrhop, D. Spiroski, C. Boettcher, *J. Am. Chem. Soc.* **1995**, 115, 1600.
- [20] M. Mertig, R. Kirsch, W. Pompe, *Appl. Phys. A* **1998**, 66, 723.
- [21] A. Harada, J. Liu, M. Kamachi, *Nature* **1993**, 364, 516.
- [22] M. F. M. Roks, R. J. M. Nolte, *Macromolecules* **1992**, 25, 5398.
- [23] J. P. Spatz, B. Lorenz, K. Weishaupt, H. D. Hochheimer, V. P. Menon, R. V. Parthasarathy, C. R. Martin, J. Bechtold, P.-H. Hor, *Phys. Rev. Lett.* **1994**, 50, 14888.
- [24] K. Yu, A. Eisenberg, *Macromolecules* **1998**, 31, 3509.
- [25] G. Liu, J. Ding, A. Guo, M. Herfort, D. Bazett-Jones, *Macromolecules* **1997**, 30, 1851.
- [26] G. Liu, L. Qiao, A. Guo, *Macromolecules* **1996**, 29, 5508.
- [27] G. Liu, *Adv. Mater.* **1997**, 9, 437.
- [28] J. Ding, G. Liu, *Chem. Mater.* **1998**, 10, 537.
- [29] S. Stewart, G. Liu, *Chem. Mater.* **1999**, 11, 1049.
- [30] J. Tao, G. Liu, J. Ding, M. Yang, *Macromolecules* **1997**, 30, 4084.
- [31] H. Huang, E. E. Remsen, T. Kowalewski, K. L. Wooley, *J. Am. Chem. Soc.* **1999**, 121, 3805.

- [32] J. Ding, G. Liu, *J. Phys. Chem.* **1998**, 102, 6107.
- [33] F. Henselwood, G. Liu, *Macromolecules* **1997**, 30, 488.
- [34] G. Wang, F. Henselwood, G. Liu, *Langmuir* **1998**, 14, 1554.
- [35] G. Liu, J. Ding, S. Stewart, *Angew. Chem.* **1999**, 111, 884; *Angew. Chem. Int. Ed.* **1999**, 38, 835.
- [36] J. Ding, G. Liu, *Macromolecules* **1997**, 30, 655.
- [37] For a review, see F. S. Bates, G. H. Fredrickson, *Phys. Today* **1999** (February), 32.
- [38] K. E. Yu, A. Eisenberg, *Macromolecules* **1998**, 31, 5546.
- [39] J. Kriz, B. Masar, J. Pleštil, Z. Tuzar, H. Pospisil, D. Doskocilova, *Macromolecules* **1998**, 31, 41.
- [40] C. S. Patrickios, C. Forder, S. P. Armes, N. C. Billingham, *J. Polym. Sci. Part A: Polym. Chem.* **1997**, 35, 1181.
- [41] J. E. Guillet, *Polymer Photophysics and Photochemistry—An Introduction to the Study of Photoprocesses in Macromolecules*, Cambridge University Press, Cambridge, **1985**.
- [42] A. Guo, G. Liu, J. Tao, *Macromolecules* **1996**, 29, 2487.
- [43] See, for example: S. H. Pine, J. B. Hendrickson, D. J. Cram, G. S. Hammond, *Organic Chemistry*, 4th ed., McGraw-Hill, New York, **1980**.

A Dicubane-Like Tetrameric Nickel(II) Azido Complex**

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Over the last few years, considerable research has been directed at the preparation of molecule-based magnets, especially nanoscale magnets in which each microcrystal behaves as a single domain. A method of preparing nanomagnets involves single molecules having ground electronic states with a large number of unpaired electrons.^[1] A variety of blocking organic ligands has been used for the preparation of these cluster compounds, most of which provide oxo bridges between metal centers.^[2]

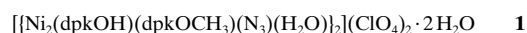
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[**] This work was supported by the Basque Government (PI 96/39), the University of the Basque Country (UPV 130.310-EB017/95), and the Spanish M.E.C. (DGES) (PB97/0637). Z.E.S. thanks the Spanish Government for a doctoral fellowship. We thank Dr. M. Salah El Fallah for his collaboration in the magnetic measurements.

An efficient way to generate interactions between metal centers involves the use of pseudohalide ligands, among which the azide anion is one of the most interesting mediators of molecular magnetism.^[3] A large number of compounds with this ligand, from dimers to three-dimensional networks, have been characterized so far.^[4–12] Since the azido ligand can mediate antiferromagnetic interactions when it bridges end-to-end^[10] and ferromagnetic interactions when it bridges end-on,^[6, 9, 13] this variety of molecular architectures gives rise to a broad range of magnetic couplings. Antiferro- or ferromagnetic, alternating (even in the sign), and canted systems have been obtained. In the case of the very scarce cubane-like systems, those exhibiting μ -1,1-azido bridges are ferromagnetic.^[8]

As mentioned above, in most of the clusters for nanomagnets the intermetallic connections are oxo bridges. The di-2-pyridylketone (dpk) ligand has been extensively used as a blocking ligand as it has three potential donor sites (the two pyridyl N atoms and the O atom of the carbonyl group) which give rise to different coordination modes.^[14] Additionally, this ligand occasionally undergoes metal-promoted hydration to give a *gem*-diol,^[15] which can coordinate in protonated or deprotonated form. Solvolysis reactions could be expected with other solvents and would widen the range of structural arrangements. The simultaneous use of dpk and azide ligands might enhance the formation of intermetallic bridges. Here we report on a ferromagnetic tetranuclear complex **1**, the structure of which can be described as a dicubane unit with two missing vertices.



The X-ray crystal structure of **1** (Figure 1)^[16] consists of centrosymmetric tetranuclear units in which the nickel(II) ions are connected by the ligands N_3 , dpkOH, and dpkOCH₃.

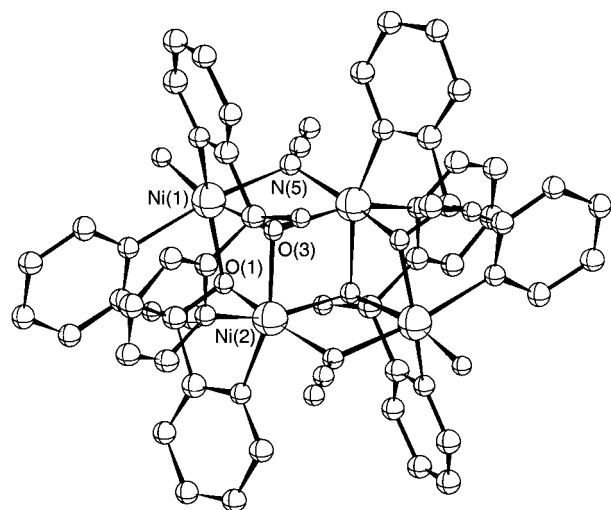


Figure 1. Molecular structure of **1** (H atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: Ni(1)–N(5) 2.110(7), Ni(1)–O(1) 2.032(5), Ni(1)–O(3) 2.124(5), Ni(2a)–N(5) 2.076(6), Ni(2)–O(1) 2.120(5), Ni(2)–O(3) 2.014(5); Ni(1)–N(5)–Ni(2a) 101.8(3), Ni(1)–O(1)–Ni(2) 94.7(2), Ni(1)–O(3)–Ni(2) 95.1(2), Ni(1)–O(3)–Ni(2a) 99.2(2); symmetry code (a): $-x, -y, -z$.

(dpkOH and dpkOCH₃ result from solvolysis of the dpk ligand) to give a face-shared dicubane-like core with two missing vertices. The Ni^{II} ions exhibit a slightly distorted octahedral [NiN₃O₃] environment, in which the Ni–N distances range from 2.024(6) (dpk) to 2.110(4) Å (N₃), and the Ni–O distances from 2.014(5) to 2.124(5) Å. The end-on azido bridges have N–Ni–N angles of 101.8(2)°, and the Ni–O–Ni angles range from 94.7(2) to 100.6(2)°. The Ni⋯Ni distance for the combination of azido and oxo bridges is 3.248(2) Å, while those for doubly oxo-bridged Ni atoms are 3.054(1) and 3.133(2) Å.

The variation of the molar magnetic susceptibility χ_m was investigated for **1** in the temperature range 1.8–300 K. The product $\chi_m T$ continuously increases with decreasing temperature from 2.6 cm³ mol^{−1} K (room temperature) to a maximum of 5.35 cm³ mol^{−1} K at 12 K, after which $\chi_m T$ rapidly decreases and tends to zero (Figure 2). This behavior is characteristic of

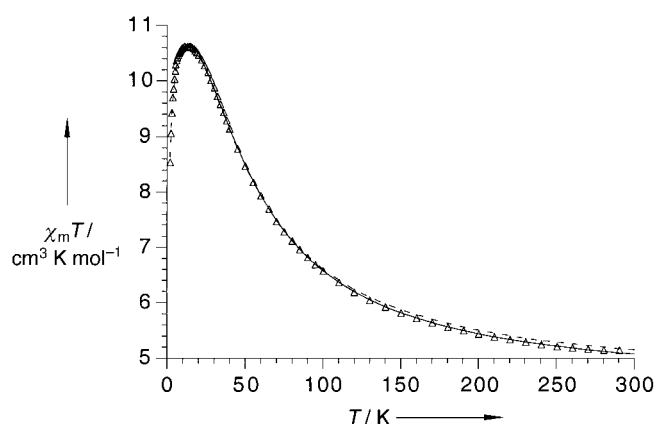


Figure 2. Temperature dependence of $\chi_m T$ for **1**. The solid line corresponds to the best fit (see text) with four different J values, the dashed line corresponds to the fit with J_A , J_B , and D .

a system with ferromagnetic interactions. The sudden decrease in $\chi_m T$ is associated with the characteristic zero-field splitting (ZFS) of the Ni^{II} ion (intermolecular interactions are zero or negligible because the tetranuclear units are isolated by the ClO_4^- counterions). For this case, where four different J values exist, an analytical expression is not available. However, the eigenvalues of the spin states can be obtained in numerical form from a full-matrix diagonalization^[17] of the Hamiltonian [Eq. (1)].

$$H = -J_1(S_1S_2 + S_3S_4) - J_2(S_2S_3 + S_4S_1) - J_3(S_2S_4) - J_4(S_1S_3) \quad (1)$$

The numbering of the spins follows the numbering of the nickel atoms in Figure 3 (J_4 correlates the atoms 1 and 3). The best-fit parameters^[17] obtained for values up to the maximum in the $\chi_m T$ curve were $J_1 = 18.0$, $J_2 = 15.3$, $J_3 = 27.1$, $J_4 = -1.6$ cm^{−1}, $g = 2.1$ with $R = 6.4 \times 10^{-5}$ (solid line in Figure 2). Due to the similarity of the J_1 and J_2 values, the approximations $J_1 = J_2 = J_A$, $J_3 = J_B$, and $J_4 = 0$ can be made to fit the experimental data to the coupling constants and to take into account the effect of the ZFS of the $S = 4$ ground state that was observed in the $\chi_m T$ curve at low temperature. Then the

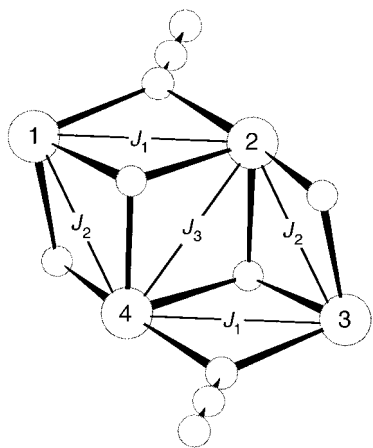


Figure 3. Coupling pattern of the four Ni atoms in **1**.

Hamiltonian reduces to Equation (2). The best-fit parameters obtained in this case were $J_A = 14.7$, $J_B = 29.1 \text{ cm}^{-1}$, $D = -0.068 \text{ cm}^{-1}$, $g = 2.12$ with $R = 2.8 \times 10^{-5}$ (dashed line in Figure 2).

$$H = -J_A(S_1S_2 + S_3S_4 + S_2S_3 + S_4S_1) - J_B(S_2S_4) - D[S_z^2 - S(S+1)/3] \quad (2)$$

We investigated the variation of the magnetization M with the applied magnetic field H for **1** in the range 0–7 T at 5 K (Figure 4). The magnetization reaches the saturation value

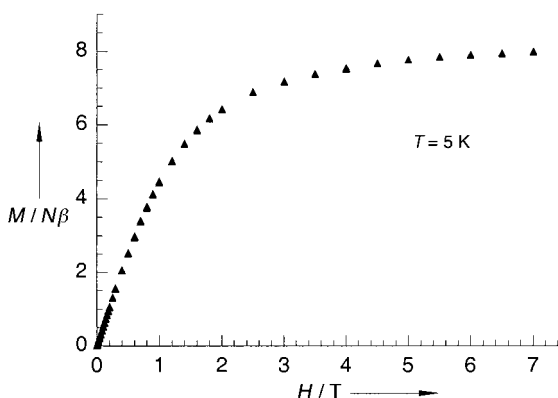


Figure 4. Field dependence of the magnetization M at 5 K for **1**.

expected for a tetranuclear ferromagnetic nickel(II) compound, that is, $N\beta g/2$ (≈ 8). The magnetic behavior of **1** can be explained by the existence of end-on azido bridges with angles close to 100° , which give rise to moderately strong ferromagnetic interactions that are added to the ferromagnetic interactions associated with the oxo bridges. Otherwise, the two ferromagnetically coupled μ -azido- μ -oxo Ni_2 units would couple antiferromagnetically to give $S = 0$, irrespective of the relative magnitude of the different J values.

The combination of dpk and azido ligands is a good strategy for obtaining “cubane-like” systems. The resulting compound **1** has an unusual tetranuclear dicubane-type molecular structure. The bridging ligands connecting the nickel(II) ions provide global ferromagnetic exchange interactions.

Experimental Section

Caution: Azido and perchlorate complexes of metal ions are potentially explosive. Only a small amount of material should be prepared and it should be handled with care.

Compound **1** was synthesized by slow addition of a methanolic solution (25 mL) of dpk (0.184 g, 1 mmol) to an aqueous/methanolic solution (25 mL) prepared by mixing $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (0.366 g, 1 mmol) and NaN_3 (0.065 g, 1 mmol). The reaction was carried out with continuous stirring at 45°C . Green prismatic crystals appeared after allowing the resulting solution to stand at room temperature for two weeks. Yield: 0.220 g (62% based on nickel); elemental analysis calcd for $\text{C}_{23}\text{H}_{24}\text{N}_7\text{O}_{10}\text{ClNi}_2$: Ni 16.5, N 13.8, C 38.8, H 3.4; found: Ni 16.7, N 14.1, C 38.9, H 3.5; IR (KBr pellet): $\tilde{\nu} [\text{cm}^{-1}]$: 2200 (s, $\nu_{\text{as}}(\text{N}_3)$), 1328 (w, $\nu_s(\text{N}_3)$), 1610 (s, $\nu(\text{CO})$), 1540 (w, pyridyl stretch), 1020 (m, pyridyl breathing), 757 (m, pyridyl C–H), 1098–1125 (m, $\nu_3(\text{ClO}_4)$), 630 (s, $\nu_4(\text{ClO}_4)$); UV/Vis diffuse reflectance spectrum: $\tilde{\nu} [\text{cm}^{-1}]$: 9520 (ν_1), 15380 (ν_2), 25000 (ν_3) from $^3\text{A}_{2g}$ to $^3\text{T}_{2g}$, $^3\text{T}_{1g}(\text{F})$, and $^3\text{T}_{1g}(\text{P})$, respectively.

Received: April 23, 1999

Revised: September 29, 1999 [Z13307]

- [1] D. P. Goldberg, A. Caneschi, C. D. Delfs, R. Sessoli, S. J. Lippard, *J. Am. Chem. Soc.* **1995**, *117*, 5789; A. K. Powell, S. L. Heath, D. Gatteschi, L. Pardi, R. Sessoli, G. Spina, F. D. Giallo, F. J. Pieralli, *J. Am. Chem. Soc.* **1995**, *117*, 2491; A. L. Barra, A. Caneschi, D. Gatteschi, R. Sessoli, *J. Am. Chem. Soc.* **1995**, *117*, 8855.
- [2] S. L. Castro, Z. Sun, C. M. Grant, J. C. Bellinger, D. N. Hendrickson, G. J. Christou, *J. Am. Chem. Soc.* **1998**, *120*, 2365.
- [3] R. Cortés, L. Lezama, F. A. Mautner, T. Rojo in *Molecule-Based Magnetic Materials* (Eds.: M. M. Turnbull, T. Sugimoto, L. K. Thomson), ACS Book Series, Washington, **1996**, pp. 187–200.
- [4] D. M. Duggan, D. N. Hendrickson, *Inorg. Chem.* **1973**, *12*, 2422; J. Commarmond, P. Plumeré, J. M. Lehn, Y. Agnus, R. Louis, R. Weiss, O. Kahn, I. Morgenstern-Badarau, *J. Am. Chem. Soc.* **1982**, *104*, 6330; P. Chaudhuri, M. Guttman, D. Ventur, K. Weighardt, B. Nuber, J. Weiss, *J. Chem. Soc. Chem. Commun.* **1985**, 1618; T. Rojo, L. Lezama, R. Cortés, J. L. Mesa, M. I. Arriortua, G. Villeneuve, *J. Magn. Magn. Mater.* **1990**, *83*, 519; R. Cortés, M. K. Urtiaga, L. Lezama, J. I. R. de Larramendi, M. I. Arriortua, T. Rojo, *J. Chem. Soc. Dalton Trans.* **1993**, 3685, and references therein.
- [5] R. Vicente, A. Escuer, J. Ribas, M. S. El Fallah, X. Solans, M. Font-Bardía, *Inorg. Chem.* **1993**, *32*, 1920; J. Ribas, M. Monfort, C. Diaz, C. Bastos, X. Solans, *Inorg. Chem.* **1994**, *33*, 484.
- [6] J. Ribas, M. Monfort, C. Diaz, C. Bastos, X. Solans, *Inorg. Chem.* **1993**, *32*, 3557.
- [7] J. Ribas, M. Monfort, R. Costa, X. Solans, *Inorg. Chem.* **1993**, *32*, 695.
- [8] M. A. Halcrow, J. C. Huffman, G. Christou, *Angew. Chem.* **1995**, *107*, 971; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 889.
- [9] R. Cortés, L. Lezama, J. L. Pizarro, M. I. Arriortua, X. Solans, T. Rojo, *Angew. Chem.* **1994**, *106*, 2520; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2488.
- [10] C. G. Pierpont, D. N. Hendrickson, D. M. Duggan, F. Wagner, E. K. Barefield, *Inorg. Chem.* **1975**, *14*, 604; A. Escuer, R. Vicente, J. Ribas, M. S. El Fallah, X. Solans, M. Font-Bardía, *Inorg. Chem.* **1993**, *32*, 3727; R. Cortés, M. K. Urtiaga, L. Lezama, J. L. Pizarro, A. Goñi, M. I. Arriortua, T. Rojo, *Inorg. Chem.* **1994**, *33*, 4009.
- [11] J. Ribas, M. Monfort, X. Solans, M. Drillon, *Inorg. Chem.* **1994**, *33*, 742; M. A. S. Goher, F. A. Mautner, *Croat. Chem. Acta* **1990**, *63*, 559; R. Cortés, L. Lezama, J. L. Pizarro, M. I. Arriortua, T. Rojo, *Angew. Chem.* **1996**, *108*, 1934; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1810.
- [12] F. A. Mautner, R. Cortés, L. Lezama, T. Rojo, *Angew. Chem.* **1996**, *108*, 96; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 78.
- [13] R. Cortés, J. L. Pizarro, L. Lezama, M. I. Arriortua, T. Rojo, *Inorg. Chem.* **1994**, *33*, 2697.
- [14] J. A. R. Navarro, M. A. Romero, M. J. Salas, M. Quirós, E. R. T. Tiekink, *Inorg. Chem.* **1997**, *36*, 4988; M. C. Feller, R. Robson, *Aust. J. Chem.* **1968**, *21*, 2919; A. Basu, T. G. Kasar, N. Y. Sapre, *Inorg. Chem.* **1998**, *27*, 4539; A. Basu, A. R. Sapre, N. Y. Sapre, *J. Chem. Soc. Dalton Trans.* **1987**, 1797.

- [15] N. Okabe, M. Koizumi, *Acta Crystallogr. C: Cryst. Struct. Commun.* **1998**, 54, 288; R. Faure, H. Loiseleur, G. Thomas-David, *Acta Crystallogr. B: Struct. Crystallogr. Cryst. Chem.* **1973**, 29, 1890; S. L. Wang, J. W. Richardson, S. J. Brigg, R. A. Jacobson, W. P. Jensen, *Inorg. Chim. Acta* **1986**, 111, 67.
- [16] X-ray structure analysis: Enraf-Nonius CAD-4 diffractometer. Unit cell parameters were determined from automatic centering of 25 reflections ($4 < 2\theta < 60^\circ$) and refined by least-squares methods. Data were collected with graphite-monochromatized $\text{MoK}\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$) by using the ω scan technique. Lorentzian, polarization, and extinction corrections were made. The structure was solved by direct methods and successive Fourier difference syntheses with the SHELXL-93 computing program. Crystal data for **1**: $\text{C}_{23}\text{H}_{24}\text{ClN}_7\text{Ni}_2\text{O}_{10}$ ($M_r = 711.36$), monoclinic, space group $P2_1/c$, $a = 13.456(3)$, $b = 10.906(2)$, $c = 19.990(7) \text{ \AA}$, $\beta = 91.59(3)$, $V = 2932.4(13) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 1.611 \text{ g cm}^{-3}$, $\mu = 14.40 \text{ cm}^{-1}$, $F(000) = 1456$. The refinements by full-matrix least-squares methods gave final $R1(F_o) = 0.074$, $wR2(F_o^2) = 0.184$ and $S = 0.999$ for 7643 reflections with $I \geq 2\sigma(I)$ and 389 variables. All non-hydrogen atoms were refined anisotropically. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-102206. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [17] The calculations were made with the computer program CLUMAG, which uses the irreducible tensor operator formalism (ITO): D. Gatteschi, L. Pardi, *Gazz. Chim. Ital.* **1993**, 123, 231.

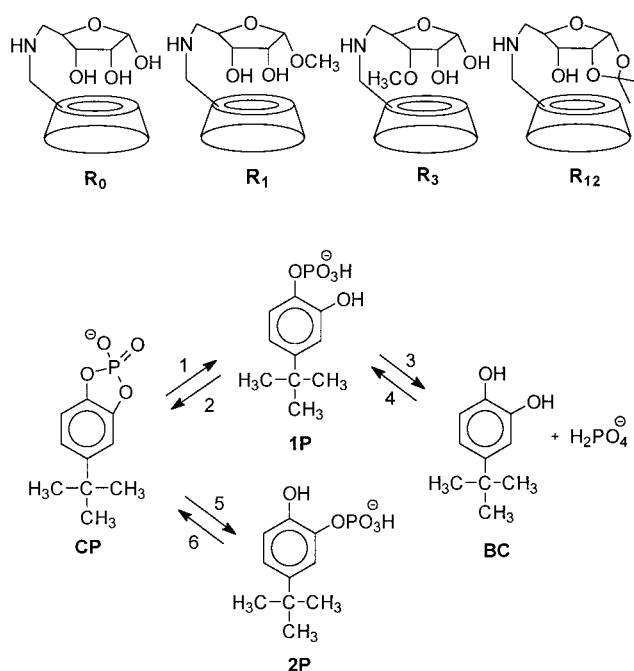
5-(β -Cyclodextrinylamino)-5-Deoxy- α -D-Riboses as Models for Nuclease, Ligase, Phosphatase, and Phosphorylase**

Man Jung Han,* Kyung Soo Yoo, Ji Young Chang, and Tae-Kyu Ha

The synthesis and activity testing of enzyme models have drawn attention to the elucidation of enzyme structures and mechanisms.^[1] Several models have been synthesized and their activities have been tested for nuclease, ligase, phosphatase, and phosphorylase.^[2] We recently reported that ribose-containing polymers show catalytic activity for the cleavage of DNA.^[3] The study of various polymer structures strongly suggested that the *vic-cis*-diol groups of the ribose rings play a key role in the catalysis, which is surprising

because there are plenty of biopolymers containing ribose rings. This prompted us to further study the mechanism of action by synthesizing enzyme models containing riboses capping β -cyclodextrin (CD) and then performing model reactions with phosphate substrates. The models showed catalytic activity for the hydrolysis of phosphodiester (nuclease activity), the hydrolysis of phosphomonoester (phosphatase activity), the esterification of phosphomonoester to phosphate diester (ligase activity), and the phosphorylation of alcohols with phosphate ions (phosphorylase activity).

6-Monotosyl- β -cyclodextrin was prepared as described in the literature.^[4] It was treated with 5-amino-5-deoxy-1,2-*O*-isopropylidene- α -D-ribose to yield 5-(β -cyclodextrinylamino)-5-deoxy-1,2-*O*-isopropylidene- α -D-ribose (**R**₁₂), which was hydrolyzed to form 5-(β -cyclodextrinylamino)-5-deoxy- α -D-ribose (**R**₀) (Scheme 1). The derivatives **R**₁ and **R**₃, in



Scheme 1. β -Cyclodextrinyl compounds and reactions of phosphate esters.

which 1-OH and 3-OH of the ribose ring are blocked by methyl groups, were synthesized by similar methods.^[5] The *N*-methylpyridinium salt of the cyclic phosphate (**CP**)^[5] and the 1-phosphate (**1P**) and 2-phosphate (**2P**) of 4-*tert*-butylcatechol (**BC**) were also synthesized as substrates (Scheme 1). Compounds **BC**^[6] and **CP** are well known to form inclusion complexes with CD, and CD capped with imidazole has been investigated as a nuclease model using **CP** as substrate.^[2]

Reactions 1 (and 5), 2, 3, and 4 (Scheme 1) are the model reactions for nuclease, ligase, phosphatase, and phosphorylase, respectively. The rates of the reactions were measured at pH 7.4 (Tris buffer), ionic strength (μ) of 0.2 (KCl), and 25°C by HPLC in the presence of the cyclodextrinyl compounds (4 mM) and the substrates (0.4 mM). This concentration ratio was chosen for the activity measurements since no significant rate acceleration was observed by further increasing the concentration of the former compound.

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[**] This work was supported by the Korean Science and Engineering Foundation and the Korean Ministry of Education. The computer center of ETH Zürich is also gratefully acknowledged for the use of computing facilities.

The hydrolysis rates of **CP** were measured in the buffer alone and also in the presence of ribose, CD, **R**₀, **R**₁, **R**₃, or **R**₁₂. The time-dependent concentration changes of **CP** are shown in Figure 1 a. The hydrolysis was accelerated by **R**₀, **R**₁, and **R**₃ in the order of **R**₀ > **R**₃ > **R**₁, whereas ribose, CD, and **R**₁₂ showed no catalytic activity above the activity of the buffer,

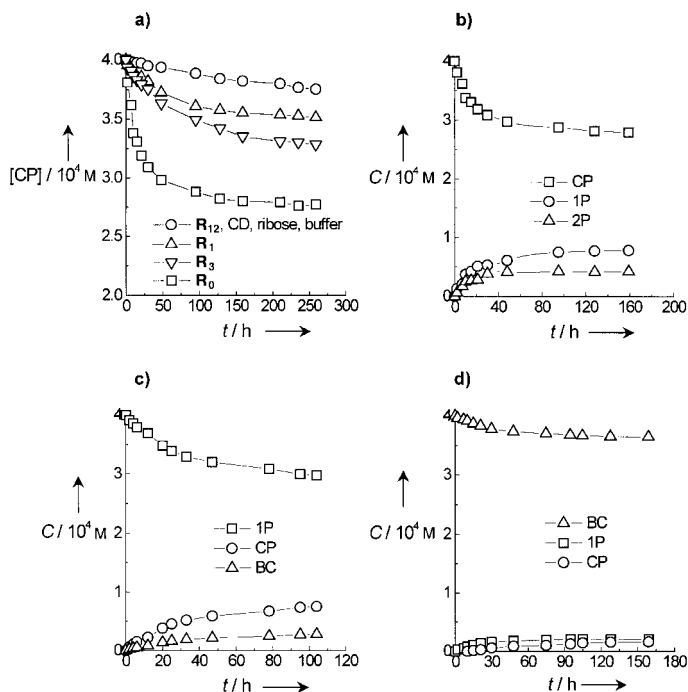


Figure 1. Concentration changes versus time: a) for hydrolysis of cyclic phosphate (**CP**) in Tris buffer solution (○) and in the presence of ribose (○), CD (○), **R**₁₂ (○), **R**₁ (△), **R**₃ (▽), and **R**₀ (□); b) for the reaction of **CP** (□) → **1P** (○) + **2P** (△) catalyzed by **R**₀; c) for the reaction of **1P** (□) → **CP** (○) + **BC** (△) catalyzed by **R**₁; d) for the reaction of **BC** (△) → **1P** (□) → **CP** (○) catalyzed by **R**₃. (For reaction conditions, see the Experimental Section.)

indicating clearly that the *vic-cis*-diol groups of riboses on CDs are essential for the catalysis. As the reactions were pseudo-first-order, the rate constants for the hydrolysis were obtained by plotting logarithmic concentrations of **CP** against time and were found to be 10.7, 1.41, and 2.03 × 10^{−3} h^{−1} for **R**₀, **R**₁, and **R**₃. These were, respectively, 33, 4.4, and 6.3 times faster than for the uncatalyzed reaction (3.2 × 10^{−4} h^{−1}). The hydrolysis products of **CP** were found to be **1P** and **2P** as previously reported.^[2] The reactions in the presence of the cyclodextrinyl compounds (**R**₀, **R**₁, and **R**₃) reached equilibrium after extended times, that is, the reactions are reversible. In the hydrolysis of **CP** in the presence of **R**₀ (Figure 1b), the concentration of **CP** decreased while **1P** and **2P** simultaneously formed.^[7] After 120 hours the reactions reached equilibrium.

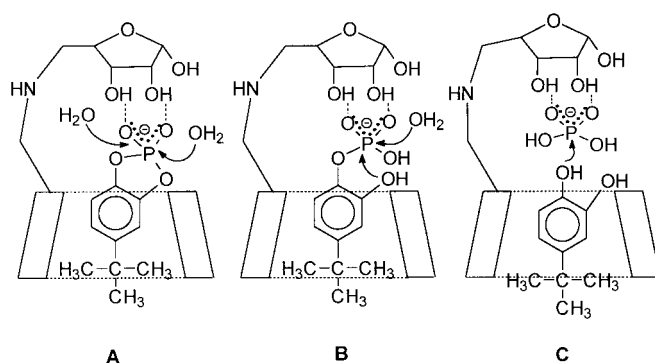
When **1P** was mixed with **R**₀, **R**₁, or **R**₃ in Tris buffer solution at pH 7.4, cyclization to **CP** and hydrolysis to **BC** occurred simultaneously. Compound **1P** was found to be stable in the buffer solution and in the presence of CD or **R**₁₂ under the same conditions. No significant reaction was found after one month. The concentration changes of the starting material and the products in the reaction of **1P** in the presence

of **R**₁ are shown in Figure 1c. The reaction reached equilibrium after 100 hours. Similar reactions occurred in the presence of **R**₀ or **R**₃.^[8]

When **BC**, cyclodextrinyl compounds (**R**₀, **R**₁, or **R**₃), and KH₂PO₄ were mixed in the mole ratio of 1:10:15 at pH 7.4 (Tris buffer), esterification to form **1P** occurred, which was followed by cyclization to yield **CP**. In order to make this reaction first order, phosphate was added in excess. These reactions did not occur in the buffer solution or in the presence of CD or **R**₁₂. The concentration change in the presence of **R**₃ versus time of the reaction is plotted in Figure 1d. Phosphate compound **1P** formed immediately at the beginning of the reaction and then **CP** began to form. The reaction reached equilibrium after 140 hours. Similar reactions occurred in the presence of **R**₀ and **R**₁.^[9]

In order to investigate whether the *sec*-amino groups on the cyclodextrinyl compounds contribute to the catalysis as a general base or, more likely at the operating pH of 7.4, as a general acid, we synthesized 6-monomethylamino-β-cyclodextrin as a model compound. The reactions with **CP**, **1P**, and **BC** were repeated in the presence of the 6-monomethylamino-β-cyclodextrin (instead of the enzyme models **R**₀, **R**₁, and **R**₃) using the same conditions, and the rates of reaction were measured. The rate constant for the hydrolysis of **CP** was found to be 3.38 × 10^{−4} h^{−1}, nearly the same as that of the uncatalyzed reaction (3.23 × 10^{−4} h^{−1}), and reactions 2, 3, and 4 (Scheme 1) did not occur, indicating that the *sec*-amino groups do not participate in the catalysis.

Based on the experimental results described above, the mechanism of action can be postulated as follows: the *vic-cis*-diols form hydrogen bonds with the two phosphoryl oxygen atoms of the phosphate group when the substrate is in the CD cavity of **R**₀. This activates the phosphorus atom to be attacked by nucleophiles (H₂O or [−]OH) as shown in Scheme 2. In the case of hydrolysis of **CP** (Scheme 2A), water could attack either side of the activated phosphate to form **1P** or **2P**. The hydrolysis and esterification of **1P** (Scheme 2B) occur when water or the 2-OH group of **1P** attack the phosphorus atom



Scheme 2. Action mechanisms of β-cyclodextrinyl compounds. The 2,3-*cis*-diol of ribose forms hydrogen bonds with the two phosphoryl oxygen atoms of the phosphate to activate the phosphorus atom for attack by nucleophiles (H₂O or OH of catechol). a) The phosphorus atom of **CP** is attacked by H₂O to form **1P** or **2P**. b) The hydrolysis and esterification of **1P** occur when H₂O attacks the phosphorus atom to break the P–O ester bond or the 2-OH group of **1P** attacks to eliminate the OH group of the phosphate, respectively. c) The phosphorylation of **BC** occurs by nucleophilic attack of the 1-OH group of **BC** to the phosphorus atom to eliminate the OH group from the phosphate.

and either break the P–O ester bond or cause the OH group of the phosphate to leave, respectively. The phosphorylation of **BC** (Scheme 2C) occurs by nucleophilic attack of the 1-OH group of **BC** at the activated phosphorus atom with the OH group of the phosphate as the leaving group. Since the cleavage of **CP** is occasionally regioselective, depending on the directions of hydrogen bonds and attacking nucleophiles,^[2] **2P** is not formed for the reactions shown in Figure 1c and d.

For catalytic activity, two hydrogen bonds should be formed simultaneously between the *vic-cis*-diols of ribose and the two phosphoryl oxygen atoms of the phosphate group. The order of catalytic activity, $R_0 > R_3 > R_1$, seems to depend on the extent of hydrogen bond formation; in the case of R_0 , hydrogen bonds can be formed either by the 1,2- or the 2,3-diol of the ribose so its activity is the highest. As the arm connecting ribose to CD in cyclodextrinyl compounds is rather short and in a *trans* position to the diols, the 1,2-diol is probably more easily accessible to the phosphate than the 2,3-diol and thus, the activity of R_3 was higher than that of R_1 . The 1-OH of **BC** (Scheme 2C) protrudes toward the phosphate so that **1P** was formed more favorably than **2P**.

The formation of strong hydrogen bonds was also born out by a theoretical study of the interactions between 3,4-*cis*-dihydroxytetrahydrofuran (DHTHF) and $H_2PO_4^-$, and DHTHF and HPO_4^{2-} . Quantum-chemical calculations using density functional theory at the B3LYP/6-31 + G** level and also at the MP2/6-31 + G** level of theory^[10] showed that: 1) the hydrogen bond distances are rather short (1.76 Å and 1.52 Å for the $H_2PO_4^-$ and HPO_4^{2-} adducts, respectively), 2) the dissociation energies of the hydrogen bonds are quite large (19.3 and 42.5 kcal mol⁻¹), and 3) the red shifts of the OH-stretching frequencies of DHTHF in the adducts are also very large (up to 300 and 650 cm⁻¹, respectively). The reduction of the charge density at the phosphate sites was found to be appreciable (0.057 and 0.191 electrons).

As the synthetic ribose-containing polymers have shown nuclease activity,^[3] biopolymers containing riboses may have similar enzyme activities. One of the typical biopolymers containing riboses with *vic-cis*-diols is poly(ADP-ribose) formed from NAD⁺ in chromatin. However, its functions are not clear so far; since its discovery in 1966,^[11] it has been suggested to be involved in numerous biological reactions.^[12] Poly(ADP-ribose) forms during apoptosis^[13] and DNA replication, transcription, and repair,^[14] when nuclease, ligase, phosphatase and/or phosphorylase actions will be required. Further study on the enzyme functions of naturally occurring biopolymers having riboses with free *vic-cis*-diols is necessary.

Experimental Section

Reaction of 6-monotosyl- β -cyclodextrin (0.5 g, 3.88 mmol) with 5-amino-5-deoxy-1-*O*-methyl-D-ribose (0.15 g, 7.76 mmol) or 5-amino-5-deoxy-3-*O*-methyl-1,2-*O*-isopropylidene- α -D-ribose (0.15 g, 7.51 mmol) in DMF (5 mL) gave 5-(β -cyclodextrinylamino)-5-deoxy-1-*O*-methyl- α -D-ribose (R_1 , yield: 72.4%) and 5-(β -cyclodextrinylamino)-5-deoxy-3-*O*-methyl-1,2-*O*-isopropylidene- α -D-ribose (R_{12} , yield: 74.9%), respectively. The latter compound was hydrolyzed in 1N HCl to result in 5-(β -cyclodextrinylamino)-5-deoxy- α -D-ribose (R_0 , yield: 79.5%). 4-*tert*-Butylcatechol-1-phosphate (**1P**) and 2-phosphate (**2P**) were obtained by separation of the hydrolysis products of the cyclic phosphate of 4-*tert*-butyl catechol (**CP**)

with the aid of preparative liquid chromatography with 0.025M KCl aqueous solution as the eluent. 6-Monomethylamino- β -cyclodextrin was synthesized by a reaction of 6-monotosyl- β -cyclodextrin (1 g, 0.78 mmol) with aqueous 40 wt % of methylamine (0.72 mL, 0.93 mmol) for 48 h at room temperature (yield: 41.5%, m. p.: 219–220 °C).

Cyclodextrinyl compounds (4×10^{-3} M) and phosphates (4×10^{-4} M) were dissolved in Tris-buffer solution (pH 7.4) with an ionic strength of 0.2 (KCl) in a vial, which was immersed in a water bath at 25 ± 0.1 °C. Aliquots (80 μ L) of the reaction solution were taken by microsyringe at defined time intervals and injected into a Waters liquid chromatograph with UV detector at 285 nm (eluent: 0.025M KCl, flow rate: 0.8 mL min⁻¹). The concentrations of the reactants and products were evaluated by peak areas, which were corrected by the extinction coefficients of the compounds ($\epsilon = 2460$ for **CP**, 3500 for **1P**, 3490 for **2P**, 2310 for **BC** at 285 nm and pH 7.4).

Received: May 3, 1999

Revised: October 12, 1999 [Z13367]

- [1] A. J. Kirby, *Angew. Chem.* **1996**, *108*, 770–790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 707–724.
- [2] a) R. Breslow, J. B. Doherty, G. Guillot, C. Lipsey, *J. Am. Chem. Soc.* **1978**, *100*, 3227–3229; b) R. Breslow, P. Bovy, C. L. Hersch, *J. Am. Chem. Soc.* **1980**, *102*, 2115–2117.
- [3] a) M. J. Han, K. S. Yoo, T. J. Cho, J. Y. Chang, Y. J. Cha, S. H. Nam, *Chem. Commun.* **1997**, 163–164; b) M. J. Han, K. S. Yoo, K. H. Kim, G. H. Lee, J. Y. Chang, *Macromolecules* **1997**, *30*, 5408–5415.
- [4] I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka, K. Yamamura, *J. Am. Chem. Soc.* **1977**, *99*, 7100–7102.
- [5] T. A. Khwaja, C. B. Resse, J. C. M. Stewart, *J. Chem. Soc.* **1970**, 2092–2100.
- [6] R. Breslow, A. Graff, *J. Am. Chem. Soc.* **1993**, *115*, 10988–10989.
- [7] The rate constants k_1 and k_5 were measured to be 6.5 and 4.1 when catalyzed by R_0 , 0.87 and 0.54 by R_1 and 1.17 and 0.89×10^{-3} h⁻¹ by R_3 , respectively.
- [8] The rate constants k_2 and k_3 were found to be 28.4 and 11.6 when catalyzed by R_0 , 4.35 and 1.59 by R_1 , and 5.99 and 2.77×10^{-3} h⁻¹ by R_3 , respectively.
- [9] The rate constant k_4 was measured to be 10.2, 2.6, and 4.1×10^{-3} h⁻¹ when catalyzed by R_0 , R_1 , and R_3 , respectively.
- [10] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) J. A. Pople, J. S. Binkley, R. Seeger, *Int. J. Quantum Chem. Symp.* **1976**, *10*, 1–19.
- [11] a) P. Chambon, J. D. Weill, J. Doly, M. T. Strosser P. Mandel, *Biochem. Biophys. Res. Commun.* **1966**, *25*, 638; b) T. Sugimura, S. Sugimura, S. Hasegawa, Y. Kawamura, *Biochim. Biophys. Acta* **1967**, *138*, 438.
- [12] a) K. Ueda, O. Hayaishi, *Ann. Rev. Biochem.* **1985**, *54*, 73–100; b) D. Lautier, J. Laguerre, J. Thibodeau, L. Mennard, G. G. Poirier, *Mol. Cell Biochem.* **1993**, *122*, 171–193; c) R. Alvarez-Gonzalez, G. Pacheco-Rodriguez, H. Mendoza-Alvarez, *Mol. Cell Biochem.* **1994**, *138*, 33–37; d) H. Maruta, N. Matsumura, S. Tamura, *Biochem. Biophys. Res. Commun.* **1997**, *236*, 265–269.
- [13] C. M. Simbulan-Rosenthal, D. S. Rosenthal, S. Iyer, A. H. Boulares M. E. Smulson, *J. Biol. Chem.* **1998**, *273*, 13703–13712.
- [14] a) M. Malanga, F. R. Althaus, *J. Biol. Chem.* **1994**, *269*, 17691–17696; b) M. S. Satoh, G. G. Poirier, T. Lindahl, *Biochemistry* **1994**, *33*, 7099–7106.

Reducing Molecular Shuttling to a Single Dimension**

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Many of the properties of organic materials that are of technological interest are fundamentally different than those of wholly inorganic systems. Amongst them are phenomena which originate from specific submolecular movements, for example, the solitonic behavior of electron transport in conjugated polyacetylenic semiconductors, where the doped molecules localize the extra particle over several unsaturated C–C bonds and an applied electric field makes the charge move along the chain.^[1] Effectively a set of single and double bonds travel as a wave from one end of the molecule to the other, inextricably linking submolecular motion to a macroscopic phenomenon. Other remarkably complicated dynamic processes can arise in organic systems with unusual molecular-level architectures.^[2–4] The mechanically interlocked components of catenanes and rotaxanes, for example, possess unique degrees of freedom with respect to each other that might be exploitable in nanoscale devices or “molecular machinery”.^[2–h,i] However, great care must be taken when extrapolating ideas about motion from the macroscopic world to the molecular level, where the principle of microscopic reversibility and quantum effects operate.^[3] As a result of the large masses involved, and perhaps because of the lack of a better framework, the dynamic behavior of mechanically interlocked systems has previously only been considered in a nearly classical context.^[4]

Here we describe the “shuttling” process (translation of the macrocycle between specific sites along the axis of the thread in rotaxanes with two or more “stations”^[5]) starting from a simple quantum-mechanical model, that is, the double minimum potential, which is used to calculate average kinetic energies and rate constants and finally, through the use of the partition function, the free energies of activation. This motion is particularly exciting because of its possible utility in switchable systems, where properties differ depending upon which station is occupied by the macrocycle, or in “nanomanipulations”, in which shuttling could be used to fetch or deliver small molecules or clusters of atoms attached reversibly to the macrocycle. The success of the treatment provides

a further tool for designing functional rotaxanes. It shows that at energies slightly above the activation barrier to shuttling, the probability density of the wavefunctions are largest in zones where they are small at lower energies. Effectively, therefore, just above the shuttling energy barrier the degree of occupancy of the stations and the route of shuttling are exchanged! Application of this model to peptide-based molecular shuttles, where information is available regarding the relationship between rates of shuttling and the distance between stations, shows good agreement between the calculated free energy barriers and rate constants and those obtained experimentally from temperature-dependent dynamic NMR studies.

In its lowest energy state, the macrocycle in a molecular shuttle (e.g. **1**) is located preferentially at one of the stations by intercomponent noncovalent bonding.^[2h,i, 5] Whilst in the absence of threading movement of a macrocycle is unrestricted in all directions, in a shuttle translation of the macrocycle is essentially limited to along the vector of the thread. An actual quantum-mechanical calculation of this one-dimensional motion requires the description of the potential energy term, which is taken as the linear combination of a quadratic and a quartic term. The low dimensionality is justified by the timescale of the motion, which is several orders of magnitude slower than for the other molecular-level movements.

The generic double-minimum potential was selected using “Occam’s razor”. The most well known of such potentials is the quartic potential, which adds to the harmonic part (ax^2) a quartic component (bx^4). For certain ratios of coefficients a and b the potential energy curve forms two equivalent minima. Other functions use additional parameters and complicate unnecessarily the investigation without modifying the conclusions. The same potential is successful in simulating long-standing experimental results such as the inversion tunneling of ammonia.^[6] A similar double-minimum potential has been recently used to analyze the Cope rearrangement,^[7] which is a problem of ultrafast double minimum potential, as opposite to this very slow one. A potential with a seesaw-type behavior with the presence of multiple secondary minima could be introduced, but this is unnecessary for the issue addressed here. The present choice can also be thought as an average over all the possible shuttling pathways.

In the Schrödinger equation [Eq. (1)] m is the reduced mass, and E_i and ψ_i are the energies of the levels and the

$$\left(-\frac{\hbar^2}{8\pi^2 m dx^2} + ax^2 + bx^4\right)\psi_i = E_i\psi_i \quad (1)$$

corresponding eigenfunctions (in a molecular orbital treatment, they would be the molecular orbitals). Variation of a and b affects the dynamics of the system, and they are adjusted with the intent of reproducing the observed rate constant of shuttling at room temperature k_{298} . This is estimated by thermal averaging of the microcanonical rates $k(E_i)$ [Eq. (2)], where $E_i > E_{\text{barrier}}$ (that is, only the levels

$$k(E_i) = \frac{2}{mL^2} \langle T \rangle \quad (2)$$

above the barrier are considered), L is the distance between the turning points of the potential, and T is the kinetic energy.

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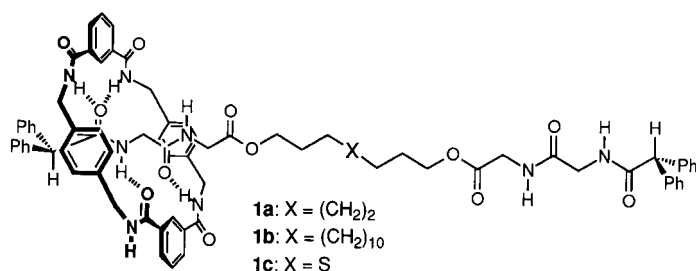
[**] This work was partly supported by the TMR initiative of the European Union (contract FMRX-CT97-0097). F.Z. also acknowledges partial support from MURST (project “Dispositivi Supramolecolari”). D.A.L. is an EPSRC Advanced Research Fellow (AF/982324). We would also like to thank one of the referees for his/her very helpful comments.

Equation (2) gives an upper value of the rate constants because the use of the kinetic energy implies squared velocities and, for any quantity q , $\langle q^2 \rangle \geq \langle q \rangle^2$. The free energy of activation $\Delta G^\ddagger$ was obtained using the transition state theory (TST)^[8] relation in Equation (3), where Q is the partition function defined in Equation (4) (in this approach and within TST the partition function at the transition state is unity).

$$\Delta G^\ddagger = E_{\text{barrier}} + k_B T \ln Q_{\text{min}} \quad (3)$$

$$Q = \sum_i e^{-\frac{E_i}{k_B T}} \quad (4)$$

In Table 1, the experimental rate constants and the Eyring-derived free activation energies for the peptide rotaxanes **1a–c** are shown. These systems were selected because of the



versatility of the self-assembly reaction by which they are produced^[5k, 9] and because recent work with solutions showed that elongation of the shuttling route by more than 10 Å only affects the shuttling frequency by one order of magnitude.^[5k] In these two-station rotaxanes, the shuttling action might be thought of as commencing through the detachment of the ring from the hydrogen-bond network present at the station. The shuttle can then travel—subject to few additional constraints—all the way to the other station. The experimental free energies of activation $\Delta G^\ddagger$ and rate constants k depend weakly on the molecular structure and strongly on the solvent used, and confirm the intuitive picture that once the hydrogen bonds are broken, most of the effort is done. In agreement with a purely mechanical model, a longer chain length corresponds to a slower frequency of shuttling. However, that chemistry is not solely mechanics and with barriers of about 10 kcal mol^{−1} diffusion is only one component of the shuttling motion.

Table 1 also provides the calculated rate constants as a function of the “walked” length. In the calculations, the length of the path was fixed, effectively reducing the number of fitting parameters to one. There is good agreement between

experimental and calculated rates. The data for models 1–3 allow a disentanglement of the effect of route elongation on entropy and shuttling motion. The increase in the distance between the minima by 8 Å (without modification of ΔE ; models 1 and 2) increases $\Delta G^\ddagger$ by 0.34 kcal mol^{−1} and decreases by nearly 50 % the rate. The remaining variation (model 3) necessary to achieve agreement with the experiment can be explained by slight variations of the transition state due to the addition of eight CH₂ groups.

The agreement between experiment and theory proves that the assumptions of the present model are reasonable and that 1) the shuttling motion can be separated from the other degrees of freedom and 2) the effective coordinate of shuttling can be described quite simply as a double-minimum potential. The further agreement of experimental and calculated activation free energies is also quite encouraging. The mechanical, expected, effect is now turned into a real chemical kinetics effect derived from the density of states per unit of energy. The increase in the density of states results in a larger value for $\Delta G^\ddagger$ despite the presence of a constant energy barrier (this is the difference between the minima and the maximum of the potential). The higher density of states found by the calculations for the longer shuttling pathway (Figure 1) can be understood if one considers that even in the particle-in-a-box model an increase of the size of the box—that is, elongation of the chain—gives more densely packed

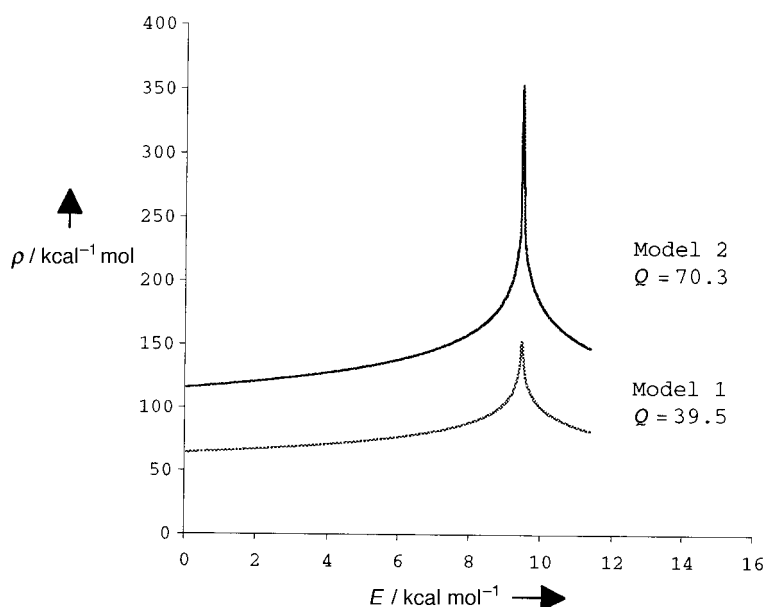


Figure 1. Density of states in models 1 and 2. Notice the cusp behavior, intrinsic to the solution of the quantum-mechanical equation.

Table 1. Experimental^[5k] and quantum-mechanical energy barriers [kcal mol^{−1}] and frequencies [s^{−1}] for the shuttling of peptide rotaxanes **1a–c**.

Rotaxane	Frequency _{exp}	$\Delta G^\ddagger_{\text{exp}}$	Model	Route [Å] ^[a]	ΔE	Frequency _{calcd}	$\Delta G^\ddagger_{\text{calcd}}$
1a	37 000	11.2 ± 0.3	1	10.0 (14.14)	9.49	37 121	11.67
			2	18.0 (25.45)	9.49	20 032	12.01
1b	5200	12.4 ± 0.3	3	18.0 (25.46)	10.39	5213	12.87
1c	62 000	10.9 ± 0.3	4	10.0 (14.14)	9.19	62 721	11.37

[a] The distance between the minima; the distance between the turning points is given in parentheses. The potential energy was $V_n = a_n x^2 + b_n x^4$ ($n = 1, 2, 3, 4$; $a_1 = -0.527476$, $b_1 = 1.05495 \times 10^{18}$, $a_2 = -0.162801$, $b_2 = 0.100495 \times 10^{18}$, $a_3 = -0.178240$, $b_3 = 0.110025 \times 10^{18}$, $a_4 = -0.510802$, $b_4 = 1.02160 \times 10^{18}$; units are a_n in J m^{−2}, b_n in J m^{−4}).

levels. The cusp behavior at $E = E_{\text{barrier}}$ is a quantum-mechanical effect that could not have been anticipated without solution of Equation (1). The closer to one another the levels are, the more readily are they thermally populated or, in other words, the larger is the partition function Q and hence $\Delta G^\ddagger$. As one may have expected, therefore, addition of CH_2 groups in the peptide rotaxanes does not change the intrinsic barrier of the shuttling and, importantly, the mechanical model is here substituted by a kinetic one whose parameters can be obtained by molecular calculations.

The agreement of the model calculations warrants a more detailed investigation of the quantum system, whose features become of fundamental importance to the overall understanding of the behavior of molecular shuttles. Figure 2 shows

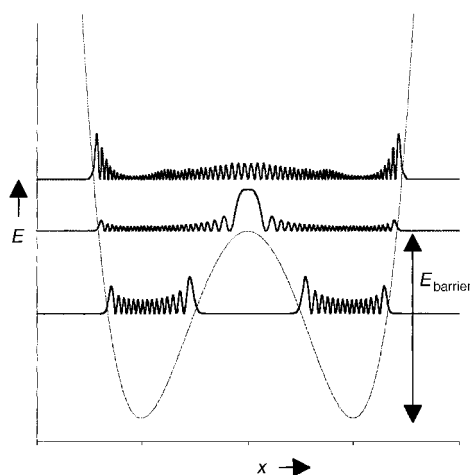


Figure 2. Potential energy curve and square of the wavefunction for three selected levels: At energies lower than the barrier, the ring sits at either one of the stations, at energies just above the barrier, the degree of occupancy of route and stations are reversed. At higher energies, the probability resembles that of a classic oscillator and population of the low energy stations is again favored. x = position.

the squares of the wavefunctions of three energy levels where the behavior of the shuttle changes significantly. At low energies, probed only at low temperatures, the system is localized as expected at the minima; that is, the shuttle is statistically located at either one of the stations. However, when the barrier is overcome, the highest probability of finding the macrocycle moves away from the minima, and it is most likely to be found at the top of the barrier. Effectively, the populations of the stations and spacer unit of the thread are switched in this energy regime. This finding must not be taken to mean that the probability becomes localized at the center of the route as the temperature increases, but the realization that the macrocycle becomes preferentially located somewhere along the thread besides the ground-state stations should clearly be borne in mind when considering possible conditions where rotaxanes could be used in nanomanipulations or devices. At higher energies, the probability distribution again resembles closely the classical one with maxima at the two turning points.

The shuttling motion in rotaxanes is in many respects a complicated classical motion which can, however, as shown

here, be reduced to a one-dimensional quantum-mechanically based one. The picture that emerges has many similarities with that of a cart rolling along a roller coaster shaped like the double-minimum potential depicted in Figure 2. At energies below the transition state, the cart/macrocycle sits around one of the two minima; when its energy is barely sufficient to overcome the barrier, it spends the longest time passing over it and the greatest probability is to find it at or near the top of the barrier; when the energy is much higher, the turning points, where the classical particle has to slow down, are where it is preferentially located! (We thank one of the referees for this analogy.) The kinetics of the process can be similarly appraised from the model. A longer spacer means that the ring takes a longer time to walk; however, the mechanical analogy cannot be carried too far because kinetics with a barrier of more than 10 kcal mol^{-1} is not only a matter of diffusion. The variation of the rate constants is therefore explained in terms of an increase in the activation free energy with the chain elongation. This, in turn, is a typically quantum-mechanical effect caused by the increase of the density of states per unit of energy with the shuttling route.

Received: May 6, 1999
Revised: October 8, 1999 [Z 13376]

- [1] a) W. P. Su, J. R. Schrieffer, A. J. Heeger, *Phys. Rev. Lett.* **1979**, *42*, 1698–1701; b) W. P. Su, J. R. Schrieffer, A. J. Heeger, *Phys. Rev. B* **1980**, *22*, 2099–2111; c) M. J. Rice *Phys. Lett. A* **1979**, *71*, 152–154.
- [2] a) K. Mislow, *Chemtracts: Org. Chem.* **1989**, *2*, 151–174. b) T. C. Bedard, J. S. Moore, *J. Am. Chem. Soc.* **1997**, *117*, 10662–10671; c) G. de Santis, L. Fabbrizzi, D. Iacopino, P. Pallavicini, A. Perotti, A. Poggi, *Inorg. Chem.* **1997**, *36*, 827–832; d) I. Willner, *Acc. Chem. Res.* **1997**, *30*, 347–356; e) A. Ikeda, T. Tsudera, S. Shinkai, *J. Org. Chem.* **1997**, *62*, 3568–3574; f) R. Deans, A. Niemz, E. C. Breinlinger, V. M. Rotello, *J. Am. Chem. Soc.* **1997**, *119*, 10863–10864; g) A. N. Stevens, C. J. Richards, *Tetrahedron Lett.* **1997**, *38*, 7805–7808; h) V. Balzani, M. Gómez-López, J. F. Stoddart, *Acc. Chem. Res.* **1998**, *31*, 405–414; i) J.-P. Sauvage, *Acc. Chem. Res.* **1998**, *31*, 611–619; j) P. D. Boyer, *Angew. Chem.* **1998**, *110*, 2424–2436; *Angew. Chem. Int. Ed.* **1998**, *37*, 2296–2307; k) J. E. Walker, *Angew. Chem.* **1998**, *110*, 2438–2450; *Angew. Chem. Int. Ed.* **1998**, *37*, 2308–2319; l) J. C. Skou, *Angew. Chem.* **1998**, *110*, 2452–2461; *Angew. Chem. Int. Ed.* **1998**, *37*, 2320–2328.
- [3] a) R. P. Feynman, R. B. Leighton, M. Sands, *The Feynman Lectures on Physics, Vol. I*, Addison-Wesley, Reading, MA, USA, **1963**, chap. 46. b) T. R. Kelly, I. Tellitu, J. P. Sestelo, *Angew. Chem.* **1997**, *109*, 1969–1972; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1866–1868; c) A. P. Davis, *Angew. Chem.* **1998**, *110*, 953–954; *Angew. Chem. Int. Ed.* **1998**, *37*, 909–910.
- [4] See, for example: a) R. Ballardini, V. Balzani, A. Credi, C. L. Brown, R. E. Gillard, M. Montali, D. Philp, J. F. Stoddart, M. Venturi, A. J. P. White, B. J. Williams, D. J. Williams, *J. Am. Chem. Soc.* **1997**, *119*, 12503–12513; b) D. A. Leigh, A. Murphy, J. P. Smart, M. S. Deleuze F. Zerbetto, *J. Am. Chem. Soc.* **1998**, *120*, 6458–6467; c) M. S. Deleuze, D. A. Leigh, F. Zerbetto, *J. Am. Chem. Soc.* **1999**, *121*, 2364–2379.
- [5] a) P.-L. Anelli, N. Spencer, J. F. Stoddart, *J. Am. Chem. Soc.* **1991**, *113*, 5131–5133; b) P. R. Ashton, R. A. Bissell, N. Spencer, J. F. Stoddart, M. S. Tolley, *Synlett* **1992**, 914–918; c) P. R. Ashton, R. A. Bissell, R. Górski, D. Philp, N. Spencer, J. F. Stoddart, M. S. Tolley, *Synlett* **1992**, 919–922; d) P. R. Ashton, R. A. Bissell, N. Spencer, J. F. Stoddart, M. S. Tolley, *Synlett* **1992**, 923–926; e) R. A. Bissell, E. Córdova, A. E. Kaifer, J. F. Stoddart, *Nature* **1994**, *369*, 133–137; f) A. C. Benniston, A. Harriman, V. M. Lynch, *J. Am. Chem. Soc.* **1995**, *117*, 5275–5291; g) A. C. Benniston, *Chem. Soc. Rev.* **1996**, *25*, 427–435; h) J.-P. Collin, P. Gavinã, J.-P. Sauvage, *Chem. Commun.* **1996**, 2005–2006; i) P. R.

- Ashton, R. Ballardini, V. Balzani, S. E. Boyd, A. Credi, M. T. Gandolfi, M. Gómez-López, S. Iqbal, D. Philp, J. A. Preece, L. Prodi, H. G. Ricketts, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White, D. J. Williams, *Chem. Eur. J.* **1997**, *3*, 152–170; j) P.-L. Anelli, M. Asakawa, P. R. Ashton, R. A. Bissell, G. Clavier, R. Górski, A. E. Kaifer, S. J. Langford, G. Mattersteig, S. Menzer, D. Philp, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, M. S. Tolley, D. J. Williams, *Chem. Eur. J.* **1997**, *3*, 1113–1135; k) A. S. Lane, D. A. Leigh, A. Murphy, *J. Am. Chem. Soc.* **1997**, *119*, 11092–11093; l) H. Murakami, A. Kawabuchi, K. Kotoo, M. Kunitake, N. Nakashima, *J. Am. Chem. Soc.* **1997**, *119*, 7605–7606; m) C. Gong, T. E. Glass, H. W. Gibson *Macromolecules* **1998**, *31*, 308–313.
- [6] F. Zerbetto, M. Z. Zgierski, *Chem. Phys.* **1989**, *130*, 45–54, and references therein.
- [7] H. Quast, M. Seefelder, *Angew. Chem.* **1999**, *111*, 1132–1126; *Angew. Chem. Int. Ed.* **1999**, *38*, 1064–1067.
- [8] a) R. C. Gilbert, S. C. Smith, *Theory of Unimolecular and Recombination Reactions*, Blackwell Scientific Publications, Oxford, **1990**; b) M. J. Pilling, P. W. Seakins *Reaction Kinetics*, Oxford University Press, Oxford, **1995**.
- [9] a) D. A. Leigh, A. Murphy, J. P. Smart, A. M. Z. Slawin, *Angew. Chem.* **1997**, *109*, 752–756; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 728–731; b) W. Clegg, C. Gimenez-Saiz, D. A. Leigh, A. Murphy, A. M. Z. Slawin, S. J. Teat, *J. Am. Chem. Soc.* **1999**, *121*, 4124–4129.

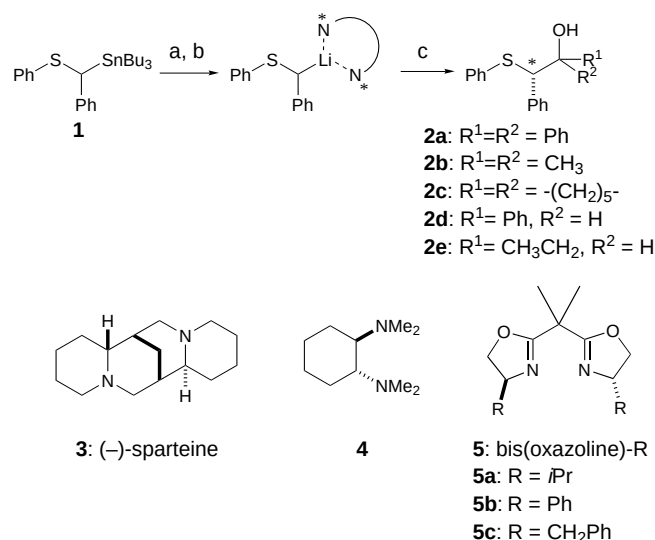
Enantioselective Reactions of Configurationally Unstable α -Thiobenzylolithium Compounds**

Shuichi Nakamura, Ryo Nakagawa,
Yoshihiko Watanabe, and Takeshi Toru*

Asymmetric induction that arises from organolithium substrates complexed to chiral ligands has emerged as an efficient and powerful method. Since Hoppe et al. showed a high enantioenrichment could be achieved in a lithiation reaction to provide α -oxygen-substituted dipole-stabilized carbanions,^[1] the enantioselective reactions of dipole-stabilized α -heterocarbanions have been the subject of extensive studies.^[2] These reactions generally afford products with high enantioselectivity through asymmetric deprotonation. However, α -thiocarbanions do not give products with such enantioselectivity,^[3] possibly because these carbanions are configurationally unstable and rapidly racemize even at temperatures as low as -78°C .^[4–6] Racemization of the α -selenocarbanions also occurs,^[4, 7] but Hoffmann et al. have

succeeded in achieving good enantioselectivities through a dynamic thermodynamic resolution in the reactions of non-dipole-stabilized α -selenocarbanions.^[8] More recently, Nakai and Tomooka's group has reported highly enantioselective reactions of α -oxyorganolithium compounds.^[9] Enantioselective reactions of α -thiocarbanions using asymmetrically deprotonated η^6 -arene(tricarbonyl)chromium complexes have been reported.^[10] There are, however, no reports on the intermolecular enantioselective reaction of α -sulfenyl carbanions derived from primary benzyl sulfides. The α -sulfenyl carbanion may be more unstable than the α -selenocarbanion,^[4] and a high level of chiral induction could be realized through the asymmetric substitution process^[2a] that is controlled either by the intermediate lithium carbanion/chiral ligand complex or by the transition state of the complex–electrophile interaction. We report herein the first highly stereoselective asymmetric substitution reactions of primary α -sulfenyl carbanions.

First we examined the reaction of α -lithio aryl benzyl sulfides with various electrophiles in cumene.^[11] α -Lithiobenzyl phenyl sulfide was prepared from phenyl α -(tributylstannyl)benzyl sulfide (**1**) since reactions starting with benzyl phenyl sulfide often gave products with high stereoselectivity but in yields of less than 40%. Several chiral ligands, (–)-sparteine (**3**), (1*R*,2*R*)-*N,N,N',N'*-tetramethylcyclohexane-1,2-diamine (**4**), and 2,2-bis[2-[(4*S*)-substituted-1,3-oxazolynyl]]-propanes^[12] **5a–c**, were examined (Scheme 1). The yields and enantioselectivities obtained in these reactions are shown in Table 1.



Scheme 1. a) *n*BuLi (1.15 equiv), cumene, -78°C ; b) chiral ligand (1.2 equiv), 1 h; c) electrophile, temperatures used are given in Table 1.

Ligands **3** and **4** provided the thio alcohol **2a** in low enantioselectivity from the reaction of lithiated **1** with benzophenone. The results are noteworthy since these chiral ligands often give high enantioselectivities in the reactions of α -heterocarbanions.^[1, 2, 8] However, bisoxazolines showed excellent chiral induction. In particular, **5a** gave (*S*)-thio alcohols **2a**, **2b**, and **2c** in the reactions of lithiated **1** with

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[**] This work was partly supported by a Grant-in-Aid for Scientific Research (No. 1650890) from the Ministry of Education, Science, and Culture of Japan.

Table 1. Reaction of lithiated **1** with electrophiles in the presence of chiral ligands **3–5**.

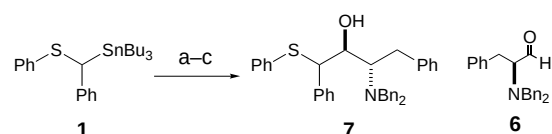
Ligand	Electrophile	T [°C]	Product	Yield [%]	ee [%] ^[a,b]	[α] _D ^[c]
3	Ph ₂ CO	–78	2a	93	8 (<i>R</i>)	–
4	Ph ₂ CO	–78	2a	8	10 (<i>S</i>)	–
5a	Ph ₂ CO	–78	2a	79	99 (<i>S</i>)	–45.1
5b	Ph ₂ CO	–78	2a	60	66 (<i>S</i>)	–
5c	Ph ₂ CO	–78	2a	17	59 (<i>S</i>)	–
5a	CH ₃ COCH ₃	–78	2b	53	98 (<i>S</i>)	–
5a	CH ₃ COCH ₃	–95	2b	71	> 99 (<i>S</i>)	+250.0
5a	cyclohexanone	–78	2c	54	91 (<i>S</i>)	–
5a	cyclohexanone	–95	2c	100	98 (<i>S</i>)	+202.3
5a	PhCHO	–78	2d	99 ^[d]	81 (<i>syn</i>) ^[e]	–
					> 99 (<i>anti</i>) ^[e]	–
5a	CH ₃ CH ₂ CHO	–78	2e	51 ^[f]	96 (<i>syn</i>)	–
					97 (<i>anti</i>)	–

[a] The enantiomeric excess was determined by HPLC. [b] The absolute configuration was determined by HPLC by comparison with the spectra of the authentic compounds prepared by different routes. [c] T = 20–27 °C, c = 0.29–0.52 g per 100 mL of CHCl₃. [d] *syn:anti* = 61:39. [e] The enantiomeric excess was determined by HPLC after oxidation with *m*CPBA to give the sulfone. [f] *syn:anti* = 38:62.

benzophenone, acetone, and cyclohexanone at –78 °C in 99, 98, and 91 % *ee*, respectively. The enantioselectivity increased as the reaction temperature was lowered. The reactions of **1** with benzaldehyde and propanal gave mixtures of *syn* and *anti* isomers in ratios of 61:39 and 38:62, respectively, and each isomer was produced with high enantioselectivity. In all these reactions **5a** was recovered quantitatively without any loss of enantiomeric purity.

The reaction proceeded with high stereoselectivity starting not only with benzyl phenyl sulfide but also with the racemic stannyl sulfide. The Sn/Li exchange is known to occur with complete retention of configuration at the sp³ carbanion center^[13] and thus, the racemic carbanion is formed from **1**. Hence the chiral induction does not rely upon the configuration of the carbanion but occurs at a late stage of the pathway, in other words, through an asymmetric substitution, in which the enantiodetermining step is either a dynamic kinetic or dynamic thermodynamic resolution.

The configurational instability of the α-lithio benzyl phenyl sulfide/ligand complex was confirmed by the reactions with (*dl*)- and (*S*)-2-(*N,N*-dibenzylamino)-3-phenylpropanals^[14] (**6**) in cumene according to the method reported by Hoffmann et al. (Scheme 2, Table 2).^[7, 15] The reaction of the racemic carbanion with a chiral aldehyde should afford the product in a diastereoisomer ratio of 50:50 provided that the complex of



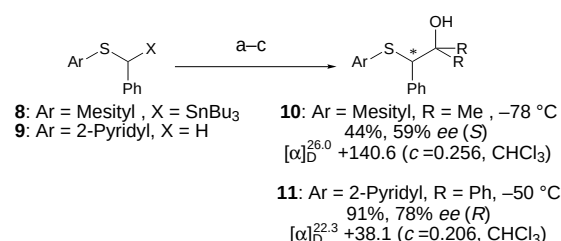
Scheme 2. a) *n*BuLi (1.15 equiv), cumene, –78 °C; b) ligand (1.2 equiv), –78 °C, 1 h; (d) *dl*-**6** or (*S*)-**6**, –78 °C.

Table 2. The configurational stability of lithiated **1**.

Ligand	Aldehyde	Yield [%]	Ratio
TMEDA	(<i>dl</i>)- 6	90	58:42
TMEDA	(<i>S</i>)- 6	88	61:39
5a	(<i>S</i>)- 6	90	80:20

anorganolithium compound and a ligand is configurationally stable. However, the reaction with the chiral aldehyde gave **7** in a ratio of 61:39, which is essentially the same as the ratio obtained in the reaction of a racemic aldehyde with *N,N,N',N'*-tetramethylethylenediamine (TMEDA). The diastereomer ratio was 80:20 when **5a** and the chiral aldehyde were used. These results show that the complex formed between the lithium carbanion with a ligand such as TMEDA or **5a** is configurationally unstable at –78 °C, and hence, the enantioselective outcome of the reaction with **1** should arise through a dynamic kinetic resolution. This proposal is also supported by the fact that higher enantioselectivity was attained from the reaction at lower reaction temperatures.

We also studied the enantioselective reaction of other α-lithio aryl benzyl sulfides. The reactions of benzyl mesityl sulfide (**8**) and benzyl 2-pyridyl sulfide (**9**) gave **10** and **11** in 59 and 78 % *ee*, respectively (Scheme 3). The enantioselectivity



Scheme 3. Lithiation of **8** and **9** followed by the reaction with electrophiles. a) *n*BuLi (1.15 equiv), cumene, –78 °C; b) **5a** (1.2 equiv), 1 h; c) electrophile, temperatures used are given in the scheme.

of the reaction starting with **8** was lower than that obtained from **1**. This is probably because the α-sulphenyl carbanion from **8** is configurationally more stable than the one from **1**.^[16] Surprisingly, the enantioselective reaction of **9** with **5a** gave **11**, which has stereochemistry opposite to that obtained in the reaction of **1**. The nitrogen atom from the pyridyl group is also incorporated in the complex, such that the lithium cation is fully coordinated by the carbanion along with three nitrogen atoms from the bisoxazoline ligand and the pyridyl group. We suppose that the stereoselection is induced at this point by the energy difference of the intermediate complexes. The attack of an electrophile on the carbanion occurs from the direction opposite to the lithium cation to give the *R* isomer.^[17]

Experimental Section

General procedure:^[18] A solution of *n*BuLi (0.165 mmol) in hexane was added to a solution of **1** (70.5 mg, 0.144 mmol) in cumene (1.0 mL) at –78 °C. The solution was stirred for 10 min and then **5a** (45.3 mg, 0.173 mmol) added. After the reaction mixture had been stirred for 1 h, a solution of an electrophile (0.187 mmol) in cumene (0.5 mL) was added, and the reaction mixture was stirred for an additional 1 h at –78 °C. Standard work-up and purification by column chromatography gave **2**.

Received: June 18, 1999 [Z13586]

[1] For a review, see D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316, and references therein.

[2] a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552–560; b) N. C. Faibish, Y. S. Park, S. Lee, P. Beak, *J. Am. Chem. Soc.* **1997**, *119*, 11561–11570; G. A. Weisen-

- burger, N. C. Faibish, D. J. Pippel, P. Beak, *J. Am. Chem. Soc.* **1999**, *121*, 9522–9530, and references therein.
- [3] a) B. Kaiser, D. Hoppe, *Angew. Chem.* **1995**, *107*, 344; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 323–325; b) T. Shinozuka, Y. Kikori, M. Asaoka, H. Takei, *J. Chem. Soc. Perkin Trans. 1* **1995**, 119–120.
- [4] a) R. W. Hoffmann, M. Julius, F. Chemla, T. Ruhland, G. Frenzen, *Tetrahedron* **1994**, *50*, 6049–6060; b) R. W. Hoffmann, R. K. Dress, T. Ruhland, A. Wenzel, *Chem. Ber.* **1995**, *128*, 861–870.
- [5] High configurational stability has been achieved only through in situ trapping or intramolecular rearrangement, see a) P. G. McDougal, B. D. Condon, M. D. Laffosse, Jr., A. M. Lauro, D. VanDerveer, *Tetrahedron Lett.* **1988**, *29*, 2547–2550; b) P. G. McDougal, B. D. Condon, *Tetrahedron Lett.* **1989**, *30*, 789–790; c) H. J. Reich, M. D. Bowe, *J. Am. Chem. Soc.* **1990**, *112*, 8994–8995; d) K. Brickmann, R. Brückner, *Chem. Ber.* **1993**, *126*, 1227–1239.
- [6] An example of a dipole-stabilized α -thiobenzyl lithium compound that is configurationally stable in diethyl ether is known, see D. Hoppe, B. Kaiser, O. Stratmann, R. Fröhlich, *Angew. Chem.* **1997**, *109*, 2872–2874; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2784–2786.
- [7] T. Ruhland, R. Dress, R. W. Hoffmann, *Angew. Chem.* **1993**, *105*, 1487; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1467–1468.
- [8] a) W. Klute, R. Dress, R. W. Hoffmann, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1409–1411; b) R. W. Hoffmann, W. Klute, R. K. Dress, A. Wenzel, *J. Chem. Soc. Perkin Trans. 2* **1995**, 1721–1726; c) R. W. Hoffmann, W. Klute, *Chem. Eur. J.* **1996**, *2*, 694–700.
- [9] For enantioselective reactions of nondipole-stabilized α -oxycarbanions in the presence of bisoxazolines, see a) N. Komine, L. Wang, K. Tomooka, T. Nakai, *Tetrahedron Lett.* **1999**, *40*, 6809–6812; b) K. Tomooka, L. Wang, N. Komine, T. Nakai, *Tetrahedron Lett.* **1999**, *40*, 6813–6816. We are grateful to Prof. K. Tomooka for helpful discussions.
- [10] a) S. E. Gibson (née Thomas), P. Ham, G. R. Jefferson, M. H. Smith, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2161–2162; b) A. Ariffin, A. J. Blake, R. A. Ewin, N. S. Simpkins, *Tetrahedron: Asymmetry* **1998**, *9*, 2563–2566. For α -oxycarbanions see also: c) R. A. Ewin, N. S. Simpkins, *Synlett* **1996**, 317–318; d) S. E. Gibson (née Thomas), P. C. V. Potter, M. H. Smith, *Chem. Commun.* **1996**, 839–840; e) S. E. Gibson (née Thomas), P. C. V. Potter, M. H. Smith, *Chem. Commun.* **1996**, 2757–2758; f) R. A. Ewin, A. M. MacLeod, D. A. Price, N. S. Simpkins, A. P. Watt, *J. Chem. Soc. Perkin. Trans. 1* **1997**, 401–415.
- [11] Reactions in diethyl ether or THF gave **2** with much lower stereoselectivity.
- [12] For enantioselective reactions using bis-oxazolines, see a) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; b) S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, *J. Am. Chem. Soc.* **1994**, *116*, 8797–8798; c) M. Nakamura, M. Arai, E. Nakamura, *J. Am. Chem. Soc.* **1995**, *117*, 1179–1180; d) D. M. Hodgson, G. P. Lee, *Tetrahedron: Asymmetry*, **1997**, *8*, 2303–2306. e) K. Tomooka, N. Komine, T. Nakai, *Tetrahedron Lett.* **1998**, *39*, 5513–5516; f) V. Schulze, R. W. Hoffmann, *Chem. Eur. J.* **1999**, *5*, 337–344; g) T. Kambara, K. Tomioka, *Chem. Pharm. Bull.* **1999**, *47*, 720–721.
- [13] a) W. C. Still, C. Sreekumar, *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202; b) J. S. Sawyer, A. Kucerovy, T. L. Macdonald, G. J. McGarvey, *J. Am. Chem. Soc.* **1988**, *110*, 842–853. There is a reaction with partial inversion, see J. Clayden, J. H. Pink, *Tetrahedron Lett.* **1997**, *38*, 2565–2568.
- [14] M. T. Reetz, M. W. Drewes, A. Schmitz, *Angew. Chem.* **1987**, *99*, 1186–1188; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141–1143.
- [15] a) R. Hirsch, R. W. Hoffmann, *Chem. Ber.* **1992**, *125*, 975–982; b) R. W. Hoffmann, M. Bewersdorf, *Liebigs Ann. Chem.* **1992**, 643–653. Configurational instability of the α -lithiobenzyl phenyl sulfide in THF has been verified, see R. W. Hoffmann, T. Ruhl, J. Harbach, *Liebigs Ann. Chem.* **1992**, 725–730.
- [16] The barrier to racemization for the α -seleno- and α -thiocarbanions having a bulky aryl group such as the duryl or mesityl group is known to be significantly higher than for those with a phenyl group, see refs.[3b, 5d]
- [17] This hypothesis relies on several reactions involving the Hoffmann test as well as MO calculations and will be discussed in detail in due course.
- [18] All complexes formed from the carbanions and the chiral ligands were soluble in cumene.

Hydroxy-Directed, SmI₂-Induced Conversion of Carbohydrates into Carbocycles**

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Recently, we established that the configuration of the hydroxy groups in a starting material has a powerful influence in facilitating the reductive couplings promoted by samarium(II) iodide^[1] and in controlling the stereochemical outcome.^[2,3] All of these hydroxy-directed carbon–carbon bond formation reactions proceed in good yields and provide access to highly functionalized molecules with excellent stereocontrol. Furthermore, the sense of the diastereoselectivity was in full accordance with a chelation-control model. We have now discovered that this new methodology allows the stereoselective construction of polyoxygenated six-membered carbocycles from carbohydrate templates. During the last decade, organic chemists have been very interested in the transformation of carbohydrates to carbocycles.^[4] Although most current approaches involve a radical methodology, only a limited number of SmI₂-mediated annulations of five-membered ring carbocycles from carbohydrates have been reported.^[5]

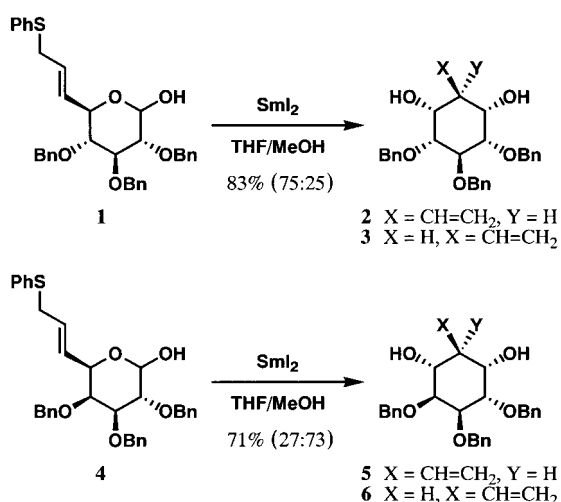
As shown in Scheme 1, the six-membered ring carbocycles can be accessed from the allyl sulfides **1** and **4**, which are prepared from methyl β -D-glucopyranoside and β -D-galactopyranoside by simple carbohydrate manipulations.^[6] When **1** was allowed to react directly with SmI₂ (2.5 equiv) at room temperature in THF/MeOH (5/1), the ring-closing reaction proceeded with complete stereochemical control to furnish the *cis*-1,3-cyclohexanediols **2** and **3** in a 75:25 ratio and in excellent yield. Similarly, the *cis*-1,3-cyclohexanediols **5** and **6** (27:73) were exclusively obtained through the SmI₂-mediated reaction of **4**.^[9] Apparently, the corresponding δ -hydroxy aldehydes **7** and **8** must be generated in equilibrium processes before the self-terminating 6-*exo-trig* ketyl–olefin cyclization mediated by SmI₂ (Scheme 2).^[10] This new annulation process is of considerable synthetic utility not only because of the observed high diastereoselectivity but also because of the exceptional synthetic versatility of the cyclization products.

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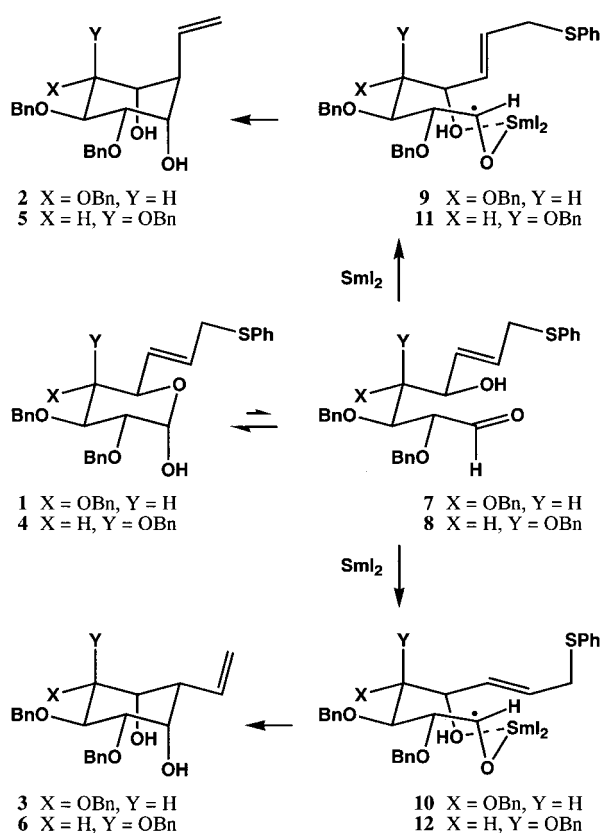
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[**] The present work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (no.09231201) from The Ministry of Education, Science, Sports and Culture of the Japanese Government. The authors are greatly indebted to Professor Dennis P. Curran (University of Pittsburgh) for helpful discussions.

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Scheme 1. Cyclizations to form six-membered rings. Bn = benzyl.

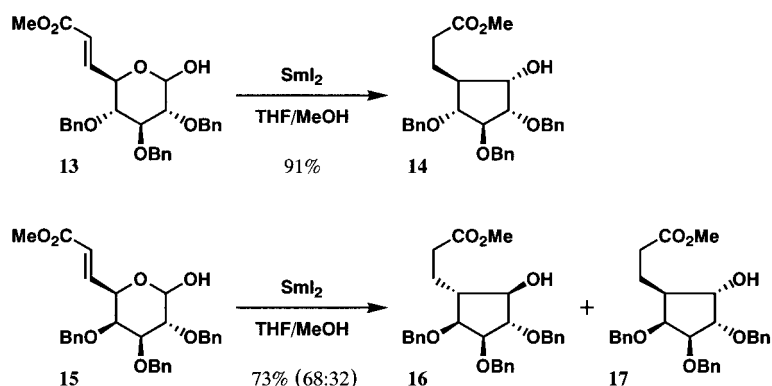


Scheme 2. The chelation-control model.

In the cyclization products **2**, **3**, **5**, and **6**, the two hydroxy groups are situated *cis* to the new six-membered rings (Scheme 2). Thus, the high stereoselectivity can be again explained by assuming a chelation-control model.^[2] After the single-electron reduction of the aldehyde part of **7** or **8**, chelation of the Sm^{III} cation attached to the resulting ketyl radical with the δ -hydroxy group of **7** or **8** gives the requisite species for the construction of the cyclic ketyl intermediate. The ketyl radical center adds to the olefinic part through the plausible transition states **9** and **10** or **11** and **12**. The β -scission reaction of the cyclic radical intermediates with a second

equivalent of SmI₂ in turn leads to the *cis*-1,3-cyclohexanediol products **2** and **3** or **5** and **6**, respectively.

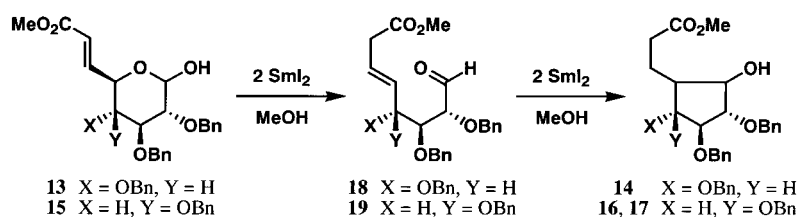
In stark contrast, the five-membered ring carbocycles were constructed with complete chemoselectivity through a similar SmI₂-induced cyclization of the corresponding α,β -unsaturated methyl esters **13** and **15** (Scheme 3).^[6] Direct treatment



Scheme 3. Cyclizations to form five-membered rings.

of **13** with SmI₂ (5.0 equiv) at 0 °C in THF/MeOH (15/1) provided the cyclopentanol **14** as the sole product in excellent yield. The same cyclization of **15** affected exclusive formation of the cyclopentanol **16** and **17** (68:32).^[9]

When 2.5 equiv of SmI₂ are added to **13** at –40 °C in THF/MeOH (15/1), the β,γ -unsaturated methyl ester **18** was obtained (Scheme 4). Furthermore, coupling cyclization of



Scheme 4. The pathway involving ring opening and ketyl–olefin coupling.

18 with 2.5 equiv of SmI₂ at 0 °C in THF/MeOH (15/1) produced **14** as a single stereoisomer in 87 % yield. Therefore, the SmI₂-mediated reductive cyclizations of **13** and **15** may involve sequential ring-opening and ketyl–olefin annulation reactions. Thus, the ring-cleavage reactions of tetrahydropyran with SmI₂ are initiated by the single-electron reduction of the α,β -unsaturated ester moiety of **13** or **15**, forming the intermediate β,γ -unsaturated methyl ester **18** or **19**.^[11] The SmI₂-promoted 5-*exo-trig* ketyl–olefin cyclization of **18** or **19** generated in situ affords the observed cyclopentanol products **14** or **16** and **17**, respectively.

Received: June 22, 1999 [Z13601]

[1] Samarium(II) iodide has evolved as a unique, single-electron reducing reagent for inducing reductive couplings to effectively form carbon–carbon bonds under exceedingly mild conditions; reviews: a) H. B. Kagan, M. Sasaki, J. Collin, *Pure Appl. Chem.* **1988**, *60*, 1725; b) H. B. Kagan, *New J. Chem.* **1990**, *14*, 453; c) G. A. Molander, *Chem. Rev.*

- 1992, 92, 29; d) G. A. Molander, *Org. React. N. Y.* **1994**, 46, 211; e) G. A. Molander, R. H. Harris, *Chem. Rev.* **1996**, 96, 307.
- [2] a) T. Kan, F. Matsuda, M. Yanagiya, H. Shirahama, *Synlett* **1991**, 391; b) M. Kito, T. Sakai, K. Yamada, F. Matsuda, H. Shirahama, *Synlett* **1993**, 158; c) T. Kan, S. Hosokawa, S. Nara, M. Oikawa, S. Ito, F. Matsuda, H. Shirahama, *J. Org. Chem.* **1994**, 59, 5532; d) M. Kawatsura, F. Matsuda, H. Shirahama, *J. Org. Chem.* **1994**, 59, 6900; e) M. Kawatsura, K. Hosaka, F. Matsuda, H. Shirahama, *Synlett* **1995**, 729; f) F. Matsuda, *J. Synth. Org. Chem. Jpn.* **1995**, 53, 987; g) M. Kawatsura, F. Dekura, H. Shirahama, F. Matsuda, *Synlett* **1996**, 373; h) M. Kito, T. Sakai, N. Haruta, H. Shirahama, F. Matsuda, *Synlett* **1996**, 1057; i) M. Kawatsura, E. Kishi, M. Kito, T. Sakai, H. Shirahama, F. Matsuda, *Synlett* **1997**, 479; j) F. Matsuda, M. Kawatsura, F. Dekura, H. Shirahama, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2371.
- [3] Recently, SmI₂-mediated 5- and 6-*exo-trig* cyclizations stereocontrolled by hydroxy groups were reported: G. A. Molander, C. P. Losada, *J. Org. Chem.* **1997**, 62, 2934.
- [4] Review: R. J. Ferrier, S. Middleton, *Chem. Rev.* **1993**, 93, 2779.
- [5] a) E. J. Enholm, A. Trivellas, *J. Am. Chem. Soc.* **1989**, 111, 6463; b) E. J. Enholm, H. Satici, A. Trivellas, *J. Org. Chem.* **1989**, 54, 5841; c) E. J. Enholm, A. Trivellas, *Tetrahedron Lett.* **1994**, 35, 1627; d) J. L. Chiara, J. Marco-Contelles, N. Khair, P. Gallego, C. Destable, M. Bernabé, *J. Org. Chem.* **1995**, 60, 6010; e) J. L. Chiara, S. Martínez, M. Bernabé, *J. Org. Chem.* **1996**, 61, 6488; f) J. Marco-Contelles, P. Gallego, M. Rodríguez-Fernández, N. Khair, C. Destable, M. Bernabé, A. Martínez-Grau, J. L. Chiara, *J. Org. Chem.* **1997**, 62, 7397; g) I. S. de Gracia, H. Dietrich, S. Bobo, J. L. Chiara, *J. Org. Chem.* **1998**, 63, 5883; h) A. Chénédé, P. Pothier, M. Sollogoub, A. J. Fairbanks, P. Sinaï, *J. Chem. Soc. Chem. Commun.* **1995**, 1373; i) J. J. C. Grové, C. W. Holzapfel, D. B. Williams, *Tetrahedron Lett.* **1996**, 37, 1305; j) J. J. C. Grové, C. W. Holzapfel, D. B. Williams, *Tetrahedron Lett.* **1996**, 37, 5817; k) J. J. C. Grové, C. W. Holzapfel, *Tetrahedron Lett.* **1997**, 38, 7429; l) Z. Zhou, S. M. Bennett, *Tetrahedron Lett.* **1997**, 38, 1153; m) S. M. Bennett, R. K. Biboutou, Z. Zhou, R. Pion, *Tetrahedron* **1998**, 54, 4761; n) A. Boiron, P. Zillig, D. Faber, B. Giese, *J. Org. Chem.* **1998**, 63, 5877; o) J. M. Aurrecoechea, B. López, *Tetrahedron Lett.* **1998**, 39, 2857.
- [6] The α,β -unsaturated ester **13** and sulfide **1** were synthesized from methyl 2,3,4-tri-*O*-benzyl- β -D-glucopyranoside, which was prepared according to the known method^[7] starting with methyl β -D-glucopyranoside. First, **13** was synthesized by 1) Swern oxidation of the C6 hydroxy group of methyl 2,3,4-tri-*O*-benzyl- β -D-glucopyranoside, 2) Wittig reaction with Ph₃P=CHCO₂Me, 3) acetolysis of the anomeric methoxy group with Ac₂O,^[8] and 4) removal of the acetoxy group. The sulfide **1** was prepared from **13** by 1) protection of the anomeric hydroxy group of **13** as its *tert*-butyldimethylsilyl ether group, 2) reduction of the methoxycarbonyl group with *i*Bu₂AlH, 3) chlorination, 4) substitution with NaSPh, and 5) desilylation. Following the same procedure, the α,β -unsaturated ester **15** and sulfide **4** were derived from methyl β -D-galactopyranoside.
- [7] B. Bernet, A. Vasella, *Helv. Chim. Acta* **1979**, 62, 1990.
- [8] O. Duclos, A. Duréault, J. C. Depeyaz, *Tetrahedron Lett.* **1992**, 33, 1059.
- [9] The stereostructures of cyclohexanediols **2**, **3**, **5**, and **6** and cyclopentanols **14**, **16**, and **17** were confirmed by 2D COSY and 2D NOESY experiments.
- [10] We reported the stereoselective cyclization mediated by SmI₂ using allyl sulfides as ketyl radical acceptors: T. Kan, S. Nara, S. Ito, F. Matsuda, H. Shirahama, *J. Org. Chem.* **1994**, 59, 5111.
- [11] a) G. A. Molander, B. E. La Belle, G. Hahn, *J. Org. Chem.* **1986**, 51, 5259; b) E. J. Enholm, J. A. Schreier, *J. Org. Chem.* **1995**, 60, 1110.

Luminescence of Novel Neodymium Sulfonylamine Complexes in Organic Media**

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Neodymium(III)-containing solids are the most popular luminescent materials for application in laser systems.^[1] Inorganic Nd^{III} compounds such as oxides, fluorides, phosphates, and their mixed matrices were investigated for the capability of high power laser radiation by controlling the Nd^{III} density in matrices. The construction of strongly luminescent Nd^{III} materials in organic media would be desirable for developing applications in novel organic Nd^{III} devices, such as organic liquid lasers, optical-fiber polymers, organic electroluminescent devices, and near-IR immunoassays.^[2] However, the energy gap theory shows that the presence of C–H or O–H bonds in the vicinity of Nd^{III} leads to effective radiationless transitions by vibrational excitation of C–H or O–H bonds, and this results in negligible emission quantum yields.^[3] Suppression of such vibrational excitation in the Nd^{III} system requires deuteration of C–H and O–H bonds or replacement of C–H bonds with C–F bonds in ligating molecules, and the use of deuterated solvents with low vibrational frequencies. By using these strategies, various researchers recently observed effective emission in certain organic/Nd^{III} systems.^[4] However, an emission quantum yield on the order of 10^{−5} was never observed in solvents that contain H atoms. Here we report on the luminescence of novel Nd^{III} complexes and the first observation of enhanced luminescence of Nd^{III} in a solvent of high vibrational frequency, namely, undeuterated acetone, by using bis(perfluoroalkylsulfonfyl)amines as bulky ligands with low vibrational frequencies.

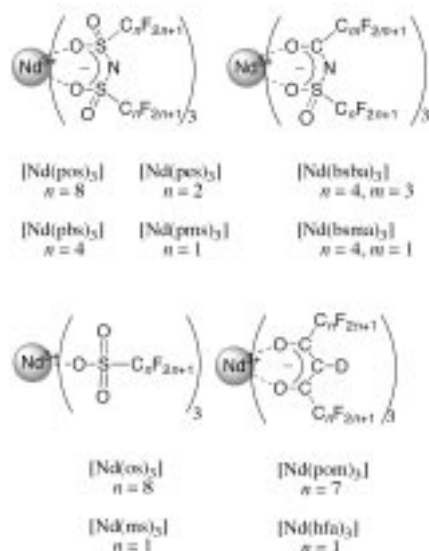
Bis(perfluorooctylsulfonfyl)amine (posH) was synthesized by treating the corresponding perfluorooctylsulfonfylamine with perfluorooctylsulfonfyl fluoride in the presence of triethylamine (TEA) as base in THF, followed by acidification with 10% aqueous H₂SO₄. [Nd(pos)₃] was prepared by treating posH with neodymium oxide in water. For comparison, we prepared [Nd(pbs)₃] (pbs = bis-perfluorobutylsulfo-

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[**] We thank Prof. T. Yamanaka and Dr. Y. Fujimoto (Institute of Laser Engineering, Osaka University). We also appreciate the help of Professor S. Fukuzumi (Department of Material and Life Science, Osaka University) in the quenching measurement with oxygen. This work was supported in part by the ASAHI GLASS foundation.

nylaminate), [Nd(pes)₃] (pes = bis-perfluoroethylsulfonylamine), [Nd(pms)₃] (pms = bis-perfluoromethylsulfonylamine), [Nd(bsba)₃] (bsba = *N*-perfluorobutylsulfonylperfluorobutylamine),^[5] [Nd(bsma)₃] (bsma = *N*-trifluoromethylsulfonylperfluorobutylamine),^[5] [Nd(os)₃] (os = perfluorooctylsulfonate) and [Nd(ms)₃] (ms = perfluoromethylsulfonate) by similar methods. [Nd(pom)₃] (pom = bis(perfluorooctanoyl)-[D]methanato) and [Nd(hfa)₃] (hfa = hexafluoro[3-*D*]acetylacetonato) were prepared according to the procedure described elsewhere.^[4a-c] All the Nd^{III} complexes (see Scheme 1)



Scheme 1. Neodymium(III) complexes investigated in this study.

were characterized by ¹H (when the compound contains hydrogen atoms), ¹⁹F, and ¹³C NMR spectroscopy; IR spectroscopy; elemental analysis; and differential scanning calorimetry (DSC). Water of crystallization was determined by elemental analysis and DSC (Table 1).

Samples for measurements of the luminescence of Nd^{III} in organic media were prepared under deoxygenated conditions because oxygen molecules can affect the transition lumines-

cence of f orbitals.^[4c] Solutions (0.05 M) of the Nd^{III} complexes were prepared in 1 mL of a solvent under 10⁻³ torr and then transferred to a quartz cell for optical measurements.^[4c] Solutions in quartz cells (optical path length 10 mm) were excited at 585 nm (⁴I_{9/2} → ²G_{7/2}) with a spectrometer (JASCO, SS-25). A Ge detector was used to detect emission in the near-infrared region (band path 4 mm). The spectra presented here were corrected for detector sensitivity and lamp intensity. The emission quantum yields were determined by standard procedures with an integrating sphere and quartz cells (optical path length 1 mm).^[4c] Emission lifetimes were determined by using a Q-switched Nd:YAG laser (Spectra-Physics Quanta-Ray PCR-2) and a Si photodiode (Hamamatsu Photonics S3759). Samples were excited by the second harmonic (532 nm) of the fundamental nanosecond pulse. The emission from the sample was measured by using low-cut optical filters (HOYA, R66 and R68) that were placed in front of the detector. Quenching of the excited state by dioxygen was investigated by introducing oxygen gas (99%, 760 torr) into the [Nd(pos)₃]/[D₆]acetone and [Nd(pms)₃]/[D₆]acetone systems.

The emission quantum yields of the Nd^{III} complexes in [D₆]DMSO, [D₆]acetone, and undeuterated acetone are listed in Table 1. [Nd(pos)₃], [Nd(pbs)₃], and [Nd(bsba)₃] produced emissions with respectable quantum efficiency in undeuterated acetone, whereas the emission of other complexes was not observable in undeuterated acetone under the same instrumental conditions. The emission spectrum of [Nd(pos)₃] in undeuterated acetone had the typical shape of an Nd^{III} emission with a branching ratio in the three transitions similar to that observed for [Nd(hfa)₃] in [D₆]DMSO (Figure 1).^[4c] The quantum yield was 3.0 ± 0.5%. This is the first observation of the effective emission of the Nd^{III} complex in an organic solvent with C–H bonds.

The quantum efficiency of [Nd(pos)₃] in acetone was comparable to those in [D₆]acetone and [D₆]DMSO. However, the emission efficiency of other complexes was affected by solvent, and the quantum yield in [D₆]acetone was much lower (≤ 1.2%). These results indicate that the Nd^{III} ion in [Nd(pos)₃] is shielded due to the strong coordination of pos,

Table 1. Emission quantum yields and lifetimes of Nd^{III} complexes in organic media.

Complex	<i>n</i> H ₂ O	Chain length	Emission quantum yields [%]			Lifetime [μs] [D ₆]acetone
			[D ₆]DMSO	[D ₆]acetone	acetone	
[Nd(pos) ₃]	0	<i>n</i> = 8	3.3	3.2	3.0	13 (12) ^[a]
[Nd(pbs) ₃]	0	<i>n</i> = 4	3.3	2.5	0.8	2.0
[Nd(pes) ₃]	2	<i>n</i> = 2	3.3	1.0	< 0.01	–
[Nd(pms) ₃]	2	<i>n</i> = 1	3.3	0.8	< 0.01	–
[Nd(bsba) ₃]	0	<i>n</i> = 4, <i>m</i> = 3	3.3	1.1	0.8	2.0
[Nd(bsma) ₃]	2	<i>n</i> = 4, <i>m</i> = 1	3.3	0.8	< 0.01	1.9
[Nd(os) ₃]	6	<i>n</i> = 8	3.3	1.2	< 0.01	2.0
[Nd(ms) ₃]	6	<i>n</i> = 1	3.3	1.1	< 0.01	4.0
[Nd(pom) ₃]	0	<i>n</i> = 7	3.2 ^[b]	0.8 ^[c]	< 0.01	–
[Nd(hfa) ₃]	2	<i>n</i> = 1	1.1	0.3	< 0.01	1.7
[Nd(NO ₃) ₃]	6	<i>n</i> = 0	3.3	< 0.01	< 0.01	< 0.1

[a] The value in parentheses is the lifetime in undeuterated acetone. [b] The [Nd(hfa)₃]/DMSO system should have a symmetrical, rigid, and bulky shell composed of six inner-coordinating DMSO molecules and three weakly outer-coordinating hfa molecules.^[4b] The smaller quantum yield of [Nd(hfa)₃] in [D₆]DMSO is thought to be due to vibrational excitation from Nd^{III} to outer-coordinating C=O sites of hfa. The coordination structure of [Nd(pom)₃] in [D₆]DMSO is similar to that of [Nd(hfa)₃] in DMSO; however, the quantum yield of Nd(pom)₃ in [D₆]DMSO was 3.2% due to prevention of energy migration.^[4b] [c] [Nd(pom)₃] was insoluble in [D₆]acetone. The quantum yield of [Nd(pom)₃] in [D₆]acetone was estimated by using the quantum yield of [Nd(poa)₃] (poa = tris(perfluorooctanoyl)acetic acid).^[4e]

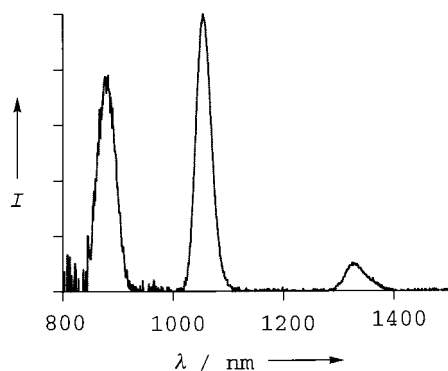


Figure 1. Emission spectrum of 0.05 M $[\text{Nd}(\text{pos})_3]$ in undeuterated acetone (880 nm: $^4\text{F}_{3/2} \rightarrow ^4\text{I}_{9/2}$, 1054 nm: $^4\text{F}_{3/2} \rightarrow ^4\text{I}_{11/2}$, 1325 nm: $^4\text{F}_{3/2} \rightarrow ^4\text{I}_{13/2}$). Excitation at 585 nm. The unsymmetrical shape of the $^4\text{F}_{3/2} \rightarrow ^4\text{I}_{13/2}$ transition is due to Stark splitting of the crystal field.

and acetone molecules appear to be unable to interact with the Nd^{III} ion. The Ω_2 parameter of the Judd–Ofelt analysis was $0.09 \times 10^{-20} \text{ cm}^2$ in undeuterated acetone. This result suggests that the geometrical structure of $[\text{Nd}(\text{pos})_3]$ in undeuterated acetone is symmetrical and free of coordinated solvent. To evaluate the stronger coordination of pos relative to pom, MO calculations were performed on $[\text{Nd}(\text{pos})_3]$ and $[\text{Nd}(\text{pom})_3]$ with the CAChe system (MM2/PM3). The electron density on the O atoms of the sulfonylamine was -0.74 , much more negative than those of pem (-0.29), water (-0.33), and acetone (-0.28). This supports the much stronger interaction of Nd^{III} with bis(perfluoroalkylsulfonyl)amines than with β -diketonates.^[6]

The Nd^{III} complexes possessing two long-chain perfluoroalkyl groups are always free of water of crystallization according to DSC analysis. Weakly coordinating acetone and water molecules cannot be incorporated into the coordination sphere of Nd^{III} when it is covered by bulky perfluoroalkyl groups. The emission of the complexes of bis-sulfonylamine is superior to those of the complexes of ligands with carbonyl groups ($[\text{Nd}(\text{bsba})_3]$ and $[\text{Nd}(\text{pom})_3]$). These facts can be rationalized by Frank–Condon factor (FC) calculations on the coordinating groups. Sulfonyl groups have lower FC values ($\text{FC}_{\text{S-O}} = 0.0031$) than ligands having carbonyl groups ($\text{FC}_{\text{C-O}} = 0.015$).^[7]

A series of Nd^{III} complexes of bis(perfluoroalkylsulfonyl)amine ligands gave the order of the quantum yields of $[\text{Nd}(\text{pos})_3] > [\text{Nd}(\text{pbs})_3] > [\text{Nd}(\text{pes})_3] > [\text{Nd}(\text{pms})_3]$ in $[\text{D}_6]$ -acetone, and this indicates that the introduction of long-chain perfluoroalkyl groups is important for enhanced emission. We already reported that $[\text{Nd}(\text{pom})_3]$ emits in fluid systems more efficiently than $[\text{Nd}(\text{hfa})_3]$ due to suppression of cross relaxation as nonradiative energy transfer by maintaining the distance between the two Nd^{III} ions at the limit of diffusional collision.^[3b] This should also hold for $[\text{Nd}(\text{pos})_3]$. In contrast, the quantum yield of $[\text{Nd}(\text{os})_3]$ (1.2%) is comparable to that of $[\text{Nd}(\text{ms})_3]$ (1.1%). The monodentate ligand, os, results in an Nd^{III} coordination sphere covered by three perfluorooctyl groups, which are not sufficient to prevent the incorporation of acetone molecules and energy migration leading to cross relaxation in fluid systems.

Emission lifetimes of the Nd^{III} complexes in $[\text{D}_6]$ -acetone are listed in Table 1. The lifetime of $[\text{Nd}(\text{pos})_3]$ is much longer than those of other Nd^{III} complexes. However, the lifetimes were not proportional to the quantum yields. These results may be ascribed to the effect of geometrical parameters of the coordination environment of the Nd^{III} ion on the emission rate.^[4h] The emission lifetime of $[\text{Nd}(\text{pos})_3]$ in undeuterated acetone was comparable with that in $[\text{D}_6]$ -acetone (Table 1). Interestingly, the emission in $[\text{D}_6]$ -acetone was not quenched by oxygen, although the singlet oxygen emission can be observed in the case of $[\text{Nd}(\text{pms})_3]$ under the same conditions.^[4e]

All the complexes except $[\text{Nd}(\text{hfa})_3]$ gave the same quantum efficiency in $[\text{D}_6]$ -DMSO as $[\text{Nd}(\text{NO}_3)_3]$. This appears to be attributable to predominant coordination of $[\text{D}_6]$ -DMSO to Nd^{III} . We previously reported that strongly coordinating DMSO molecules can penetrate into the inner coordination sphere of $[\text{Nd}(\text{hfa})_3]$ in DMSO to give a twelve-coordinate complex with three DMSO and three hfa ligands.^[4h] The predominant coordination of $[\text{D}_6]$ -DMSO molecules in the inner sphere of the Nd^{III} complexes may explain the uniform emission quantum efficiency (see footnote to Table 1).

In summary, to maintain the effective emission of Nd^{III} in a matrix of high vibrational frequency, the coordination sphere of Nd^{III} should consist of strongly coordinating, bulky ligands with low vibrational frequencies, that is, there are three criteria for luminescence: 1) suppression of vibrational excitation, 2) prevention of nonradiative cross relaxation at diffusional collision, and 3) suppression of solvent incorporation in the emitting Nd^{III} complex.

Experimental Section

posH: white crystal. ^{19}F NMR (270 MHz, $[\text{D}_6]$ -acetone, 25°C , hexafluorobenzene): $\delta = -79.51$ (t, 6F, CF_3), -111.59 (d, 4F, CF_2), -118.43 (s, 4F, CF_2), -120.10 (m, 12F, C_2F_6), -121.06 (s, 4F, CF_2), -124.59 (s, 4F, CF_2); IR (KBr): $\tilde{\nu} = 1373, 1237, 1206, 1151 \text{ cm}^{-1}$; elemental analysis calcd for $\text{C}_{16}\text{H}_{10}\text{O}_4\text{S}_2\text{N}_4\text{F}_{34}$: C 19.58, H 0.10, N 1.43; found: C 18.54, H 0.20, N 1.50. pbsH was also prepared and identified by the same methods. pesH, pmsH, os and ms were obtained from Fluka Chemika.

Received: June 22, 1999

Revised: October 12, 1999 [Z13605]

- [1] F. Gan, *Laser Materials*, World Scientific, Singapore, **1995**, p. 209.
- [2] Organic Nd^{III} devices have not been reported yet. For other lanthanide devices, see a) H. Samelson, A. Lempicki, C. Brecher, V. Brophy, *Appl. Phys. Lett.* **1964**, *5*, 173–174; b) J. Kido, K. Hongawa, K. Nagai, K. Okuyama, *Appl. Phys. Lett.* **1994**, *65*, 2124–2126; c) T. Kobayashi, S. Nakatsuka, T. Iwafuji, K. Kuriki, N. Imai, T. Nakamoto, C. D. Claude, K. Sasaki, Y. Koike, Y. Okamoto, *Appl. Phys. Lett.* **1997**, *71*, 2421–2423.
- [3] G. Stein, E. Würzberg, *J. Chem. Phys.* **1975**, *62*, 208–213.
- [4] a) Y. Hasegawa, K. Murakoshi, Y. Wada, S. Yanagida, J. Kim, N. Nakashima, T. Yamanaka, *Chem. Phys. Lett.* **1996**, *248*, 8–12; b) Y. Hasegawa, K. Murakoshi, Y. Wada, J. Kim, N. Nakashima, T. Yamanaka, S. Yanagida, *Chem. Phys. Lett.* **1996**, *260*, 173–177; c) Y. Hasegawa, Y. Kimura, K. Murakoshi, Y. Wada, J. Kim, N. Nakashima, T. Yamanaka, S. Yanagida, *J. Phys. Chem.* **1996**, *100*, 10201–10205; d) A. Beeby, S. Faulkner, *Chem. Phys. Lett.* **1997**, *266*, 116–122; e) M. H. V. Werts, J. W. Hofstraat, F. A. J. Geurts, J. W. Verhoeven, *Chem. Phys. Lett.* **1997**, *276*, 196–201; f) M. Iwamuro, Y. Hasegawa, Y. Wada, K. Murakoshi, T. Kitamura, N. Nakashima, T. Yamanaka, S.

- Yanagida, *Chem. Lett.* **1997**, 1067; g) M. Iwamuro, Y. Hasegawa, Y. Wada, K. Murakoshi, T. Kitamura, N. Nakashima, T. Yamanaka, S. Yanagida, *J. Lumin.* **1998**, 79, 29–38; h) Y. Hasegawa, M. Iwamuro, Y. Wada, K. Murakoshi, R. Arakawa, N. Nakashima, T. Yamanaka, S. Yanagida, *Bull. Chem. Soc. Jpn.* **1998**, 71, 2573–2581; i) F. J. Steemers, W. Verboom, J. W. Hofstra, F. A. J. Geurts, D. N. Reinhoudt, *Tetrahedron Lett.* **1998**, 39, 7583–7586; j) Y. Hasegawa, K. Sogabe, Y. Wada, T. Kitamura, N. Nakajima, S. Yanagida, *Chem. Lett.* **1999**, 35.
- [5] K. Sogabe, Y. Hasegawa, Y. Wada, T. Kitamura, S. Yanagida, unpublished results.
- [6] Calculations were performed by extracting an N–H or α -CH proton from pesH and pemH (bis(perfluoroethanoyl)methane), respectively, and then coordinating one oxygen atom of each ligand to a Tl^{III} ion. The structures were optimized by MM2. The charge density was determined by using PM3. The charge distributions were quite similar to each other and support the structure of $[Nd(pes)_3]$ as seen in Scheme 1. Strong interaction between pms and alkali metal ions was also revealed by Hartree–Fock calculations. See also R. Arnaud, D. Benrabah, J.-Y. Sanchez, *J. Phys. Chem.* **1996**, 100, 10882–10891.
- [7] S. Yanagida, Y. Hasegawa, K. Murakoshi, Y. Wada, N. Nakashima, T. Yamanaka, *Coord. Chem. Rev.* **1998**, 171, 461–480.

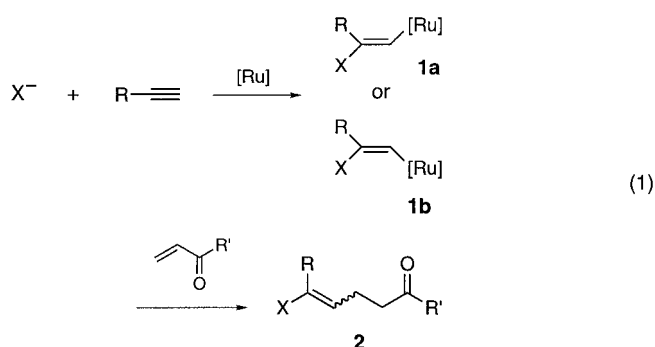
A Mechanistic Dichotomy Leading to a Ruthenium-Catalyzed *cis*-Addition for Stereoselective Formation of (*Z*)-Vinyl Bromides**

Barry M. Trost* and Anthony B. Pinkerton

Addition reactions of alkenes and alkynes catalyzed by transition metals normally lead either to a *cis* or to a *trans* product (excluding stereorandom processes). A situation wherein both mechanistic pathways are energetically accessible with the same catalyst system has not been described. In our exploration of ruthenium-catalyzed three-component couplings, we have discovered such a mechanistic duality, which has led to the *cis*-bromoalkylation of alkynes. Vinyl bromides are extremely useful as cross-coupling partners in a variety of transition metal catalyzed processes^[1] and as precursors to organolithium and related organometallic compounds. However, there are difficulties of selectivity during their preparation. Poor stereoselectivity in the addition of HBr to alkynes or in the bromination–dehydrobromination processes in the case of alkenes limits the utility of these classic protocols. Olefination reactions^[2] and stoichiometric bromination of carbon–metal bonds^[3, 4] are the main pathways for the more selective preparation of vinyl bromides. More efficient methods, notably wherein such entities are created

by simple additions,^[5] become an important objective. Our earlier work demonstrated the viability of (*E*)-vinyl chloride formation via a three-component coupling,^[6] presumably through a *trans*-chlororuthenation followed by olefin insertion into the metal–halide bond. The availability of a nonhalogen-bearing ruthenium complex as a useful catalyst induced us to consider the development of a stereoselective synthesis of vinyl bromides. This led to a geometrically complementary process compared to our earlier study with chloride wherein tri- and tetra-substituted (*Z*)-vinyl bromides are available by a three-component coupling.

Initial experiments using $[CpRu(cod)Cl]^{[7]}$ (Cp = cyclopentadienyl, cod = cycloocta-1,4-diene) gave competitive vinyl chloride formation (the chloride source is the catalyst) even at high concentration of bromide salts [Eq. (1)]. The



development of a bromo-alkylation reaction led us to turn to a halide-free ruthenium complex, $[CpRu(CH_3CN)_3]PF_6$,^[8] as a potential catalyst [Eq. (2), MVK = methyl vinyl ketone].

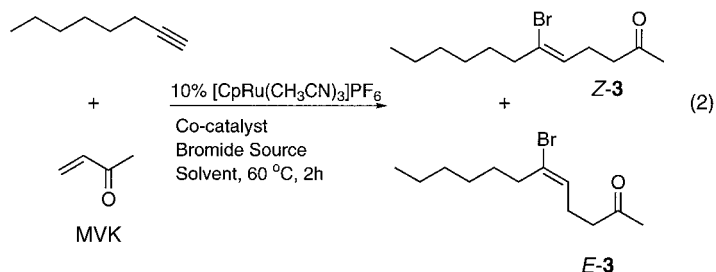


Table 1 summarizes the initial studies for optimizing cocatalyst concentration, bromide source, and solvent for these reactions. Improved yields were achieved upon switching from dimethylformamide (DMF) to an acetone/DMF mixture as solvent (entry 3 versus 2). In this mixture a more soluble bromide source, such as tetramethylammonium bromide instead of ammonium bromide, gave more of the (*Z*)-product, but in lower yields (entry 4 versus 3). In acetone alone the (*Z*)-product was formed with very high selectivity, albeit in even lower yields (entries 5 and 6). Adding DMF to acetone increased the yield but lowered the geometrical selectivity drastically (entries 7 and 8). Switching to a bromide source fully soluble in acetone, lithium bromide, gave high yields as well as high selectivities (entry 9); further, only 1.5 equivalents of the salt were necessary (entry 10). Entries 1, 11, and 12 show the vital nature of the co-catalyst for high yields as well as higher selectivities, an effect that has been observed previously.^[6]

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[**] We thank the National Science Foundation and the General Medical Sciences Institute of the National Institutes of Health (NIH) for their generous support of our work. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California at San Francisco, supported by the NIH Division of Research Resources. A.B.P. was supported, in part, by a fellowship from Glaxo-Wellcome.

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Table 1. Selected optimization experiments for (Z)-vinyl bromide formation [Eq. (2)].^[a]

Entry	Co-catalyst (mol %)	Bromide source (equiv)	Solvent	Yield of 3 [%]	Z/E ^[b]
1	SnBr ₂ (15)	NH ₄ Br (3)	DMF	13	1/3.3
2	SnBr ₄ (15)	NH ₄ Br (3)	DMF	54	1/2.1
3	SnBr ₄ (15)	NH ₄ Br (3)	acetone/DMF 1/1	71	1/2.3
4	SnBr ₄ (15)	N(CH ₃) ₄ Br (3)	acetone/DMF 1/1	54	4.0/1
5	SnBr ₄ (15)	N(CH ₃) ₄ Br (3)	acetone	35	15/1
6	SnBr ₄ (15)	NH ₄ Br (3)	acetone	40	10/1
7	SnBr ₄ (15)	NH ₄ Br (3)	acetone/DMF 2/1	62	1/2.2
8	SnBr ₄ (15)	NH ₄ Br (3)	acetone/DMF 4/1	56	1.4/1
9	SnBr ₄ (15)	LiBr (3)	acetone	81	4.0/1
10	SnBr ₄ (15)	LiBr (1.5)	acetone	88	6.6/1
11	SnBr ₄ (5)	LiBr (1.5)	acetone	54	6.7/1
12	none	LiBr (1.5)	acetone	22	4.2/1

[a] All reactions run according to Equation (2) with a 1:1.5 ratio of alkyne to MVK and a concentration of 0.5 M in alkyne. [b] Determined by ¹H NMR spectroscopy or GC.

NOE experiments established the geometry of the isomers, and the overall structures were confirmed by spectral data.^[9] The products were found not to isomerize under the reaction conditions.

With the optimized set of conditions (Table 1, entry 10) a range of substrates was examined. The reactions were run according to Equation (3) and the results are summarized in Table 2. There is excellent chemoselectivity, and the alkyne can be a nitrile (entries 2 and 6), an alcohol, including propargylic alcohols (entries 3, 4, 8, and 9), a phthalimide (entry 5) and an ester (entry 7). Other enones than MVK are also effective as coupling partners (entries 6–8).

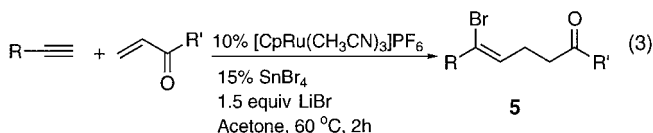
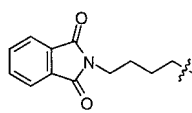
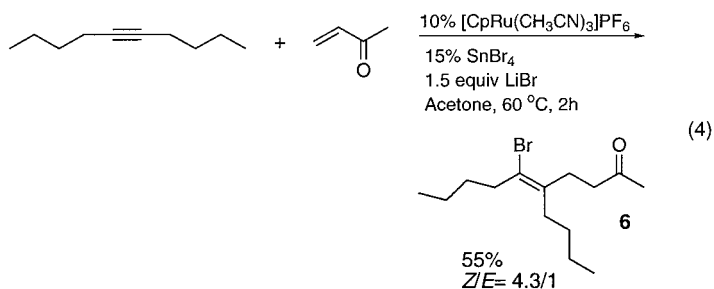


Table 2. Examples of ruthenium-catalyzed (Z)-vinyl bromide formation.^[a]

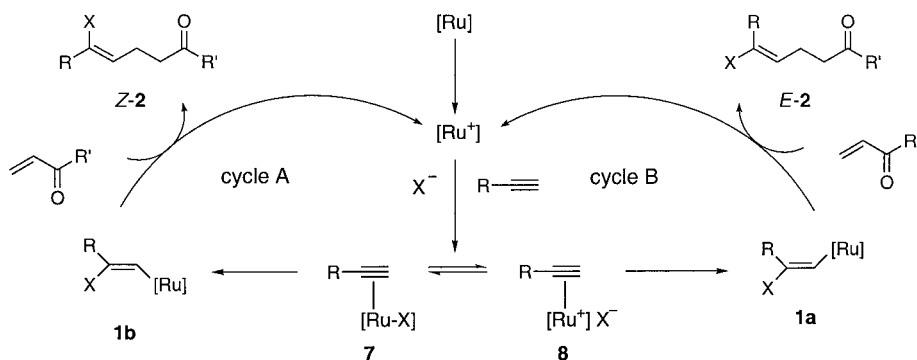
Entry	R-	R'	Yield of 5 [%]	Z/E ^[b]
1	CH ₃ (CH ₂) ₅ -	-CH ₃	88	6.6/1
2	NC(CH ₂) ₃ -	-CH ₃	90	3.3/1
3	CH ₃ CH(OH)CH ₂ -	-CH ₃	82	6.0/1
4	CH ₃ CH(OH)-	-CH ₃	64	11.0/1
5		-CH ₃	67	3.6/1
6	NC(CH ₂) ₃ -		77	4.7/1
7	AcO(CH ₂) ₄ -		78	5.0/1
8	CH ₃ CH(OH)CH ₂ -		81	5.8/1
9	HO(CH ₂) ₉ -	-CH ₃	92	5.1/1

[a] All reactions run according to Equation (3) with a 1:1.5 ratio of alkyne to the vinyl ketone. [b] Determined by ¹H NMR spectroscopy or GC.

As shown in Equation (4), disubstituted alkynes also participate, giving stereospecifically a tetra-substituted vinyl bromide. However, regiochemical issues arise when such alkynes are not symmetrically substituted.



A hypothetical mechanism is shown in Scheme 1. Initial formation of a cationic ruthenium species leads to coordina-



Scheme 1. Proposed mechanism for the ruthenium-catalyzed, stereoselective synthesis of vinyl bromides. Selection of cycle A or B is dependent upon the nature of the solvent and the concentration of halide in solution.

tion by the alkyne and the halide either covalently attached (**7**) or as an ion pair (**8**). The former would lead to a *cis*-haloruthenation (cycle A),^[10] giving rise to intermediate **1b**, while the latter would give a *trans*-haloruthenation^[11] (cycle B) to **1a**. Insertion of the enone would then lead to the Z or E isomer of **2** from **1b** or **1a**, respectively. Three observations support this mechanism. First, use of a less polar solvent, acetone rather than DMF, should favor the neutral **7** over the charged species **8**, and consequently lead to more of the (Z)-product stemming from a *cis*-bromoruthenation. Second, increasing bromide ion concentration, by switching to more soluble bromide sources such as tetramethylammonium or lithium bromide, or simply adding more of the bromide source, shifts the equilibrium between **7** and **8** towards **7** and favors cycle A, to give more (Z)-product, as observed. Finally, substrates that contain good coordinating groups for ruthenium, such as nitriles (Table 2, entry 2), lead to more of the E product—in agreement with the fact that in this case the ruthenium center is more coordinatively saturated and thus disfavors the formation of **7**.

The role of the co-catalyst is thought to be both as a Lewis acid, to activate the enone, as well as a stabilizing entity to prevent deactivation of the ruthenium catalyst. However, the exact nature of its effect is unclear at this point. It should be noted that the ruthenium enolate, formed initially by addition of either **1a** or **1b** to the vinyl ketone, does not undergo β-hydrogen elimination to compete with protonation.

In conclusion, this method represents a novel, efficient and selective synthesis of (*Z*)-vinyl bromides through a simple addition.^[12] The ability to obtain both *trans*- and *cis*-haloalkylation of alkynes is synthetically useful as well as mechanistically intriguing. Current work is focused on further elucidation of the mechanism and expansion of the scope of the reaction.

Received: July 2, 1999 [Z13668]
Revised: October 4, 1999

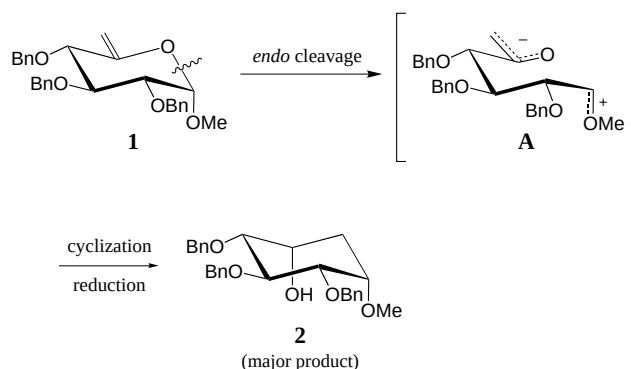
- [1] For examples see: *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, L. S. Hegehus), Pergamon, Oxford, **1995**; N. A. Saccomano in *Comprehensive Organic Synthesis*, Vol. 1 (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon, Oxford, **1991**, pp. 193–201.
- [2] Some examples: S. H. Pine, *Org. React.* **1994**, *43*, 1; D. A. Ager, *Org. React.* **1990**, *38*, 1; B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863.
- [3] D. S. Matteson, *Tetrahedron* **1989**, *45*, 1859.
- [4] E. Takada, S. Hara, A. Suzuki, *Tetrahedron Lett.* **1993**, *34*, 7067.
- [5] B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.
- [6] B. M. Trost, A. B. Pinkerton, *J. Am. Chem. Soc.* **1999**, *121*, 1988.
- [7] For previous use of this catalyst in our group see: B. M. Trost, A. Indolese, T. J. J. Müller, B. Treptow, *J. Am. Chem. Soc.* **1995**, *117*, 615; B. M. Trost, T. J. J. Müller, J. Martinez, *J. Am. Chem. Soc.* **1995**, *117*, 1888; B. M. Trost, M. Portnoy, H. Kurihara, *J. Am. Chem. Soc.* **1997**, *119*, 836.
- [8] T. P. Gill, K. R. Mann, *Organometallics* **1982**, *1*, 485.
- [9] All new compounds have been characterized spectroscopically, and elemental composition has been established by combustion analysis or high resolution mass spectrometry; see Supporting Information.
- [10] For several examples of *cis*-halometalations see: H. Dietl, H. Reinheimer, J. Moffatt, P. M. Maitlis, *J. Am. Chem. Soc.* **1970**, *92*, 2276; K. Kaneda, T. Uchiyama, Y. Fujiwara, T. Imanaka, S. Teranishi, *J. Org. Chem.* **1979**, *44*, 55; R. Hua, S. Shimada, M. Tanaka, *J. Am. Chem. Soc.* **1998**, *120*, 12365.
- [11] For a *trans*-chloroalkylation see: Z. Wang, X. Lu, *Chem. Commun.* **1996**, 535. For a stoichiometric *cis*-chlororuthenation of acetylenedicarboxylates see: P. R. Holland, B. Howard, R. J. Mawby, *J. Chem. Soc. Dalton Trans.* **1983**, 231.
- [12] M. Hulce, M. J. Chapdelaine in *Comprehensive Organic Synthesis*, Vol. 4 (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1991**, pp. 279–287.

Carbocyclic Ring Closure of Unsaturated S-, Se-, and C-Aryl Glycosides

Matthieu Sollogoub, Jean-Maurice Mallet, and Pierre Sinay*

The glycoside-to-carbocycle transformation^[1] provides an attractive route for the synthesis of functionalized carbocycle derivatives from readily available sugar precursors. Usually these transformations rely on the cleavage of the glycosidic acetal functionality to liberate the reactive carbonyl group that undergoes carbocyclization.^[1b] The disadvantage of these approaches is the loss of the aglycon. Furthermore it is impossible to apply this method to sugars bearing unusual aglycons, particularly C-glycosides, where no acetal functionality is present. Herein, we report the first direct transformation of hex-5-eno S-, Se-, and C-glycosides into carbocycles with retention of the aglycon.

We reported that hex-5-enopyranosides such as **1** undergo reductive rearrangement with triisobutylaluminum (TIBAL) to afford highly substituted cyclohexane derivatives such as **2**,^[2] where both the aglycon moiety and anomeric configuration are retained^[3] (Scheme 1). The key step in this transformation is the *endo* cleavage of the glycosidic bond to give a stabilized carbocationic intermediate **A**, which then recycles and undergoes reduction to afford the observed major product **2**.

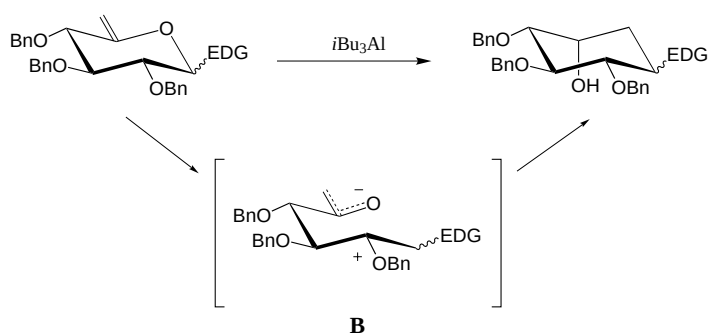


Scheme 1. The key step of the TIBAL-promoted rearrangement: *endo*-glycosidic cleavage (the detailed mechanism of this process is not known). Bn = benzyl.

We assumed that it should be possible to replace the methoxy group by other electron-donating groups that would stabilize the analogous carbocationic intermediate **B** and therefore promote *endo* cleavage (Scheme 2). However, when the known C-glucoside **3**^[4] was treated with five equivalents of TIBAL at 50 °C, we failed to observe the desired carbocycle

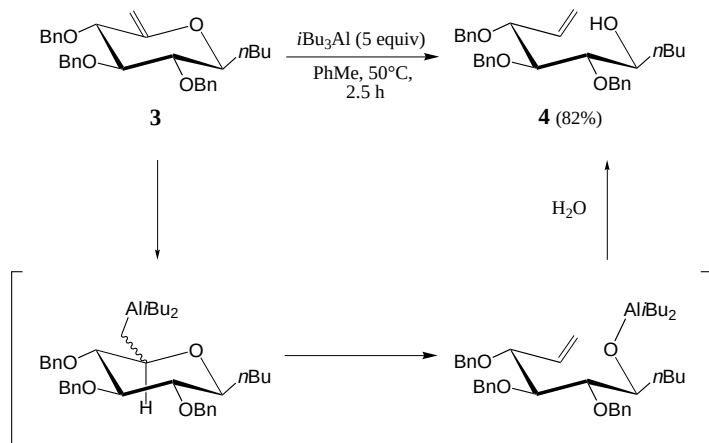
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Scheme 2. Putative mechanism for the general sugar-to-carbocycle rearrangement promoted by TIBAL. EDG = electron-donating group.

and instead isolated the known open-chain product **4**^[4] in 82% yield (Scheme 3, the physical and spectroscopic data of the rearrangement products are given in the Supporting Information). Product **4** is the result of an overall reductive cleavage of the endocyclic C5–O bond, a reaction which has

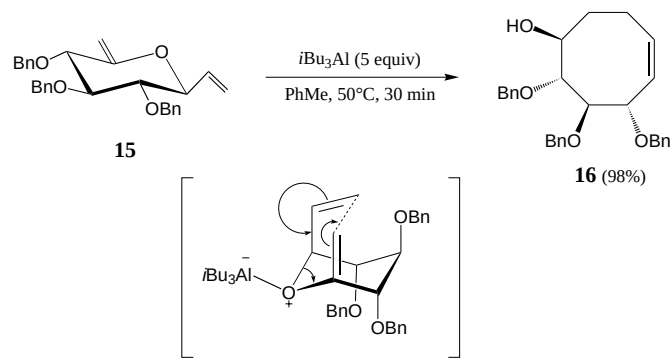


Scheme 3. Formation of **4** by a postulated hydroalumination–elimination mechanism.

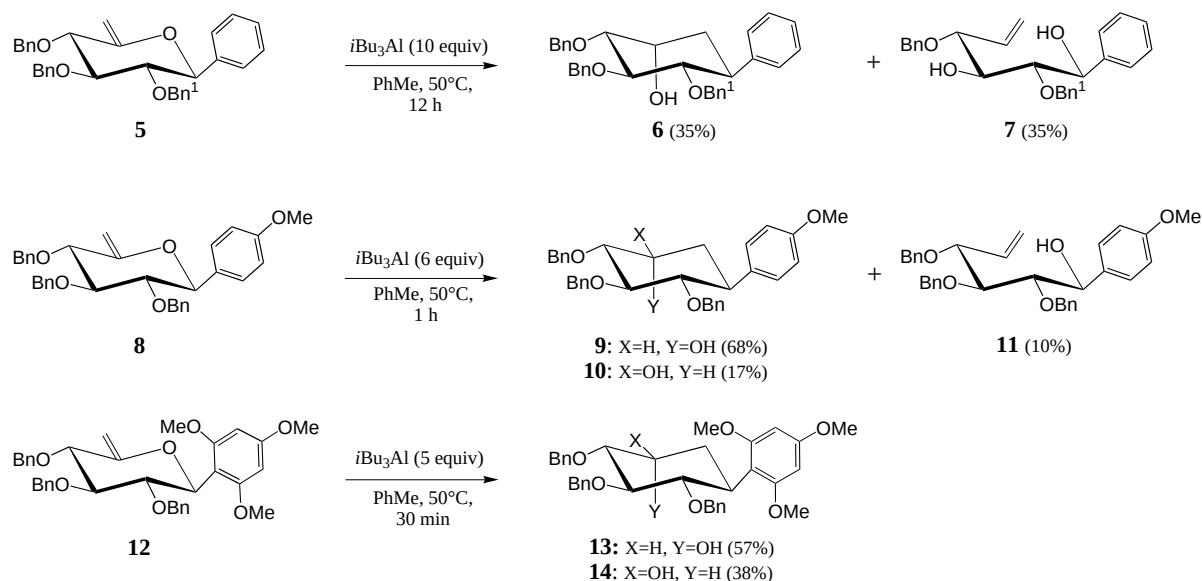
already been described for simple enol ethers.^[5] An hydroalumination–elimination mechanism, as shown in Scheme 3, may explain this process.

In light of this observation we proposed that only stronger stabilization of the carbenium intermediate **B** (Scheme 2) would kinetically favor *endo* cleavage and subsequent rearrangement over competitive hydroalumination–elimination. Indeed, reaction of the C-phenyl glycoside **5**^[6] resulted in the desired cyclohexane **6** (35%) along with the open-chain by-product **7** (35%; Scheme 4). The increased electron-donating ability of the *para*-methoxyphenyl group in **8**^[7] further biased the reaction towards rearrangement, and the desired carbocycles **9** and **10** were isolated in 85% yield as a 4:1 mixture along with only 10% of the open-chain product **11**. Finally, reaction of the trimethoxyphenyl derivative **12**^[8] afforded exclusively the carbocyclization products **13** and **14** in 95% yield as an inseparable mixture (3:2); no traces of the open-chain product were detected.

In the case of the C-vinyl glycoside **15**,^[9] no six-membered ring was observed as a product of carbocyclization. Instead Claisen rearrangement catalyzed by TIBAL^[10] afforded cyclo-octene **16** in 98% yield (Scheme 5). Thiem and Wershkun



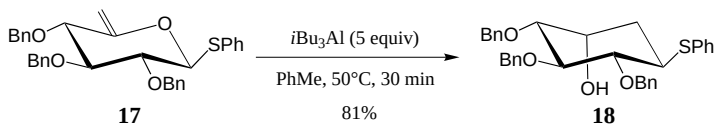
Scheme 5. TIBAL-catalyzed Claisen rearrangement of the C-vinyl glycoside **15**.



Scheme 4. TIBAL-promoted rearrangement of **5**, **8**, and **12**. Increasing electron-donating ability of the substituent at C1 favors carbocyclization over reductive cleavage of the endocyclic C5–O bond.

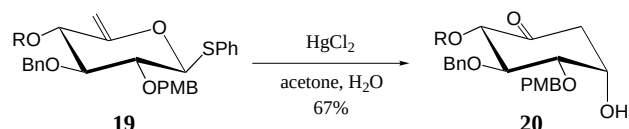
applied the thermal variant of this reaction to sugars under more forcing conditions.^[11]

The reaction of the thiophenyl substrate **17**^[12] with five equivalents of TIBAL at 50 °C also gave the desired carbocycle **18** in 81 % yield (Scheme 6). In contrast, the Ferrier-II^[13] reaction has been applied^[14] to the thiophenyl derivative **19** to



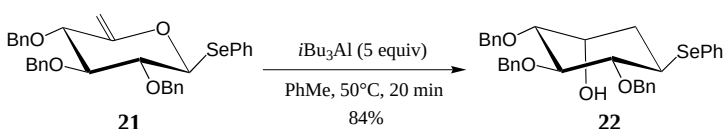
Scheme 6. Application of the TIBAL-promoted rearrangement to a thiophenyl glucoside.

give the hydroxy ketone **20** (i.e., with loss of the thiophenyl moiety, Scheme 7). However, in our case the sulfur atom stabilizes the carbenium intermediate (**B**, EDG = SPh in Scheme 2) to afford the cyclohexane with retention of the thiophenyl functionality, as predicted. This example illustrates the fundamental difference between the TIBAL-promoted rearrangement and the Ferrier-II reaction.



Scheme 7. Application of the Ferrier-II rearrangement to a thiophenyl glucoside.^[14] PMB = *para*-methoxybenzyl; R = substituted monosaccharide.

Similarly, the same conditions were applied to the selenophenyl glucoside **21**^[15] which was converted into the cyclohexane **22** (84 %; Scheme 8).



Scheme 8. Application of the TIBAL-promoted rearrangement to a selenophenyl glucoside.

In conclusion we have demonstrated that the TIBAL-promoted rearrangement of unsaturated glycosides (5-hex-enopyranosides) into carbocycles is generally applicable to carbohydrates, provided the aglycon is sufficiently electron donating in nature (O-, S-, Se-, and C-glycosides). We are currently exploring further suitable systems known to stabilize cations and also the wider application of this rearrangement in non-carbohydrate systems.

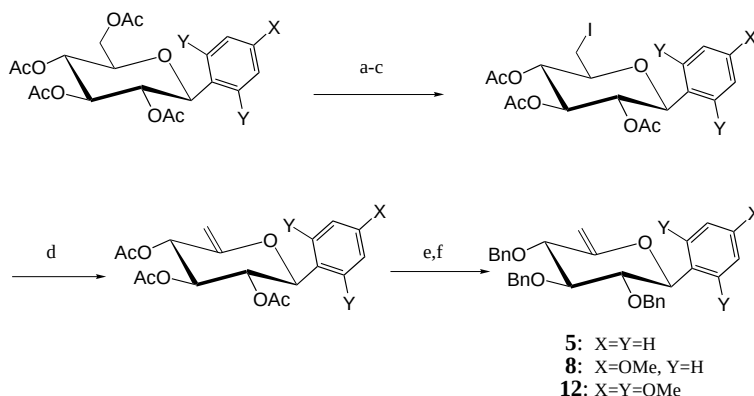
Experimental Section

TIBAL (0.9 mL, 0.9 mmol, 1M in toluene) was added to a stirred solution of **12** (100 mg, 0.17 mmol) in anhydrous toluene (1 mL) at room temperature under argon. The reaction mixture was heated at 50 °C for 30 min, when TLC (EtOAc/

cyclohexane 3/7) indicated no starting material (*R*_f = 0.5) and a major product (*R*_f = 0.3). The mixture was cooled to room temperature, and water (2 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL) and washed with water (10 mL). Combined extracts were dried (MgSO₄) and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent, EtOAc/cyclohexane 3/7) to afford an inseparable mixture of the two isomers **13** and **14** as an oil (95 mg, 95 %).

Received: July 8, 1999 [Z13694]

- [1] a) R. J. Ferrier, S. Middleton, *Chem. Rev.* **1993**, 93, 2779–2831; b) P. Sinaÿ, P. Dalko, *Angew. Chem.* **1999**, 111, 819–823; *Angew. Chem. Int. Ed.* **1999**, 38, 773–776.
- [2] S. K. Das, J.-M. Mallet, P. Sinaÿ, *Angew. Chem.* **1997**, 109, 513–516; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 493–496.
- [3] We successfully applied this methodology for the direct synthesis of disaccharide mimetics by replacing the aglycon methoxy group with monosaccharide substituents: A. J. Pearce, M. Sollogoub, J.-M. Mallet, P. Sinaÿ, *Eur. J. Org. Chem.* **1999**, 2103–2117.
- [4] D. Rouzaud, *Thèse de troisième cycle*, Université Paris-Sud Orsay (France), **1985**.
- [5] P. Pino, P. Lorenzi, *J. Org. Chem.* **1966**, 31, 329–331.
- [6] Prepared according to Scheme 9 from the known (2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)benzene; see C. D. Hurd, R. P. Holysz, *J. Am. Chem. Soc.* **1950**, 72, 1732–1735.
- [7] Prepared according to Scheme 9 from the known (2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)anisole; see P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiechi, A. Scala, *J. Chem. Soc. Chem. Commun.* **1987**, 16, 1245–1246.
- [8] Prepared according to Scheme 9 from the known 2,4,6-trimethoxy-2-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)benzene; see R. A. Eade, H.-P. Pham, *Aust. J. Chem.* **1979**, 32, 2483–2493.
- [9] Prepared by debenzoylation and subsequent benzylation of the benzoylated compound.^[11]
- [10] L. A. Paquette, D. Friedrich, R. D. Rogers, *J. Org. Chem.* **1991**, 56, 3841–3849.
- [11] B. Werschkun, J. Thiem, *Angew. Chem.* **1997**, 109, 2905–2906; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2793–2794.
- [12] Prepared according to literature procedures^[2] from the known phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-*D*-glucopyranoside; see P. J. Pfaffli, S. Hixson, L. Anderson, *Carbohydr. Res.* **1972**, 23, 195–206.
- [13] R. J. Ferrier, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1455–1458.
- [14] N. Sakairi, M. Hayashida, A. Amano, H. Kuzuhara, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1301–1313.
- [15] Prepared according to literature procedures^[2] from the known phenyl 2,3,4-tri-*O*-benzyl-1-seleno-β-*D*-glucopyranoside; see E. Perrin, PhD thesis, Université Pierre et Marie Curie Paris 6 (France), **1996**.



Scheme 9. Preparation of unsaturated C-aryl glucosides. Reagents: a) MeONa, MeOH; b) I₂, PPh₃, DMF; c) Ac₂O, pyridine; d) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), THF, reflux; e) MeONa, MeOH; f) BnBr, NaH, DMF.

Boron–Carbon Order in CeB₂C₂**

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Infinite, planar, π -conjugated systems are of interest for their electronic properties and intercalation chemistry. Graphite and BN both contain hexagonal networks of fused aromatic 6π -electron rings, with alternating B and N atoms in the latter case.^[1] However, the isoelectronic BC[−] sheets found in CaB₂C₂ and LnB₂C₂ (Ln = lanthanide, Y) were found to contain 4.8² nets of fused 4π and 8π rings stacked directly above one another with the cations between the eight-membered rings of successive layers.^[2–5] This structure has a basic tetragonal cell with $a \approx 3.8$ and $c \approx 4$ Å (the interplanar spacing). The only nonisostructural analogue is ScB₂C₂, which contains a planar arrangement of five- and seven-membered rings.^[6]

Two important structural features of the LnB₂C₂-type structures were uncertain. The first is whether the B and C atoms are a) paired or b) alternate within the eight-membered rings (Figure 1). The latter arrangement has an enlarged

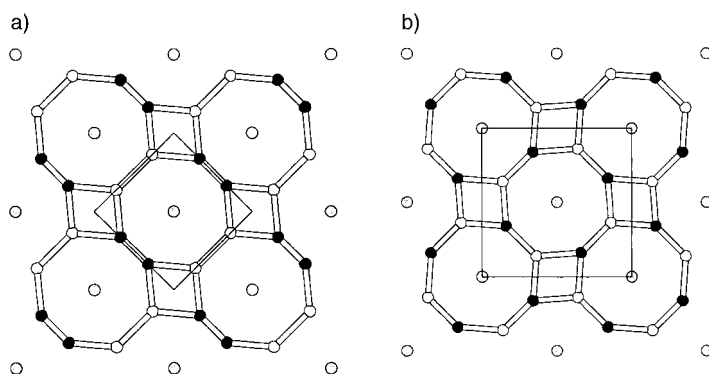


Figure 1. Alternative models for the BC[−] planes in CeB₂C₂ with the unit cells (Ce: grey, B: white, C: black). Type (a) contains bonded B–B and C–C pairs, whereas only B–C bonds are present in type (b).

tetragonal cell with $a' \approx \sqrt{2}a$. The second uncertainty is whether the B/C atoms in successive layers are stacked directly or alternate in the z direction, which doubles the c -axis periodicity. Published single-crystal X-ray diffraction studies on YB₂C₂,^[3] CaB₂C₂,^[4] and LaB₂C₂^[5] reported that the layers are of type (a) and alternate in the z direction to give an $a \times a \times 2c$ tetragonal cell. However, calculations of the BC[−] layer band structure by Burdett et al.^[7] using extended Hückel theory indicate that arrangement (b) should be more stable as

it produces a large band gap of approximately 2.8 eV. The authors of this paper concluded that “a careful reexamination of the LnB₂C₂ structures is warranted”.

As part of a study of the low-temperature electronic and magnetic properties of the LnB₂C₂ compounds, we performed a definitive structure determination on CeB₂C₂ using powder neutron diffraction. This is preferable even to single-crystal X-ray methods, as the X-ray diffraction is dominated by the heavy Ce atom and gives almost no contrast between B and C. The isotopes of natural boron, which consists of 20% ¹⁰B and 80% ¹¹B, scatter neutrons quite differently. ¹⁰B is strongly neutron absorbing and has a small coherent scattering length of $b \approx 0.4$ fm, whereas ¹¹B is nonabsorbing and has a scattering length (6.66 fm) almost equal to that of carbon (6.65 fm). We therefore carried out neutron diffraction experiments on two samples of polycrystalline CeB₂C₂. One contained natural boron ($b = 5.40$ fm) and provided good contrast between B and C at the expense of strong sample absorption, while the second sample was prepared with 99.1% ¹¹B to give good counting statistics although no B/C contrast is present. The sample preparation, diffraction experiments, and details of the refinement are described in the Experimental Section.

The powder neutron diffraction patterns of the two CeB₂C₂ samples show superstructure peaks (indicated by arrows in Figure 2a) that are all indexed on a tetragonal $\sqrt{2}a \times \sqrt{2}a \times c$ unit cell. No doubling of the c axis was observed. The

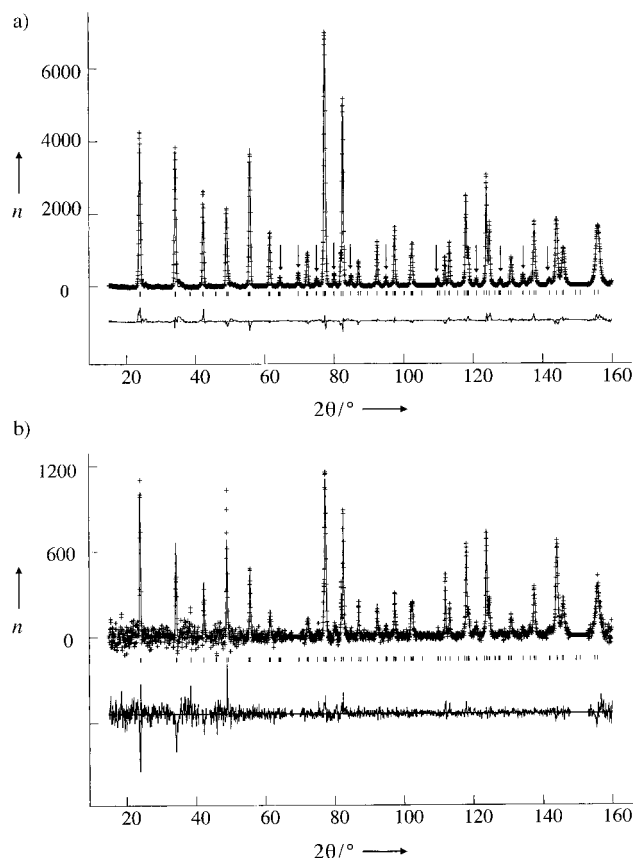


Figure 2. Observed, calculated, and difference neutron diffraction profiles for CeB₂C₂ samples containing 99% enriched ¹¹B (a) and natural boron (b). The backgrounds of approximately 240 counts in (a) and approximately 400 counts in (b) have been subtracted from the plots for ease of comparison. Peaks indicating the enlarged cell (Figure 1b) are indicated by arrows on profile (a).

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[**] We acknowledge EPSRC for neutron beamtime, EPSRC and ICI Katalco for a studentship for J.V.D., and the Ministry of Education, Science, Sports and Culture, Japan, for a Grant-in-Aid for Scientific Research on Priority Areas No. 288.

arrangement in Figure 1b is confirmed by the Rietveld fits to the two profiles; no significant scrambling of the B/C atoms was found when their site occupancies were refined. The refined coordinates and derived distances and angles are given in Table 1. Figure 1b shows the [001] projection of the

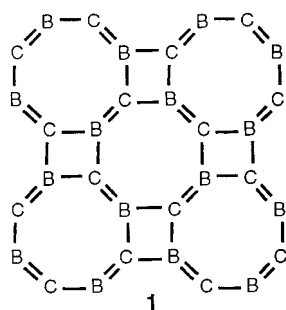
Table 1. Atomic parameters and bond lengths [Å] and angles [°] with multiplicities for the ^{11}B -enriched CeB_2C_2 sample at 15 K.

Atom	Site	x	y	z	U_{iso} [Å ²]
Ce	2(a)	0	0	0	0.0003(2)
B	4(h)	0.36107(9)	0.13894	0.5	0.0027(2)
C	4(h)	0.16060(8)	0.33940	0.5	0.0030(2)
Ce–B	$\times 8$	2.8402(2)	C–B–C	$\times 2$	130.86(2)
Ce–C	$\times 8$	2.7952(2)	C–B–C	$\times 1$	98.28(4)
B–C	$\times 2$	1.6220(6)	B–C–B	$\times 2$	139.14(2)
B–C	$\times 1$	1.5312(9)	B–C–B	$\times 1$	81.72(4)

The cell is tetragonal, space group $P4/mbm$, with $a = 5.39803(3)$ and $c = 3.84641(3)$ Å.

CeB_2C_2 structure. The information contained in both profiles contributed to the model. The superstructure intensities in the ^{11}B pattern reflect the difference between the pseudosymmetry-related light-atom coordinates (i.e., B: x and C: y) and enables their values to be determined precisely, while the contrast in the natural B pattern assigns the sites to B and C.

This neutron diffraction study demonstrates that the four- and eight-membered rings in the CeB_2C_2 structure consist of alternating B and C atoms, as predicted by Burdett et al.^[7] Two types of B–C bonds are present: long bonds (1.62 Å) common to the four- and eight-membered rings, and short bonds (1.53 Å) unique to the eight-membered rings. The difference between these distances shows that the π bonding



within the layers is predominantly as described by the idealized arrangement of single and double bonds in **1**. The layers essentially consist of fused cyclobutane- and cyclooctatetraene-like rings in which the bond angles are significantly distorted from the ideal values of 90 and 135°. As a result, the Ce atoms located above the centers of the eight-membered rings have slightly shorter contacts to C (2.80 Å) than to B (2.84 Å) in keeping with the greater electronegativity of carbon. These distances are comparable to the mean Ce–C distance of 2.74 Å in the $[\text{Ce}(\text{C}_8\text{H}_8)]^-$ anion.^[8] The Ce atoms are packed in an almost perfect simple cubic array; the Ce–Ce distances of 3.82 Å in the ab plane and 3.85 Å parallel to c are longer than those of 3.64 Å in cubic close-packed Ce metal but still enable metallic Ce–Ce bonding to occur (see below).

A surprising feature of the CeB_2C_2 structure is that the B/C atoms in successive layers are stacked directly above each other. An alternating arrangement along c would be expected from electrostatic principles and is observed in BN.^[1] The coordination of the layers to the Ce atoms may favor the direct stacking structure through hybridization of the $\text{BC}^- \pi$ and Ce d electron states.

The large band gap calculated for the observed arrangement (b) of the BC^- layers prevents more than two electrons being donated from each cerium atom to the borocarbide layer. The charge distribution is thus described as $\text{Ce}^{3+}\text{B}_2\text{C}_2^{2-}\text{e}^-$ with the surplus electron in the Ce metal d band. This is supported by the high metallic conductivity of CeB_2C_2 ; the resistivity (measured in the [110] direction on a single crystal by the conventional four-probe dc method) falls from 48 mΩ cm at 300 K to 2 mΩ cm at 4 K. Further evidence for metal–metal interactions comes from our magnetic neutron diffraction studies on other LnB_2C_2 compounds. The $\text{Ln} = \text{Tb}–\text{Tm}$ phases display both commensurate and sinusoidally modulated incommensurate magnetic structures at low temperatures, characteristic of RKKY interactions between localised $4f^n$ configurations mediated by the conduction electrons. Full details of these magnetic structures will be published elsewhere.

Experimental Section

Polycrystalline samples of CeB_2C_2 were prepared by arc-melting 3-g pellets of the powdered elements (99.9% Ce, submicron 99.999% graphite, <2 μm 96% amorphous boron) on a water-cooled copper hearth in an argon atmosphere. The samples were remelted several times to improve homogeneity. Powder neutron diffraction patterns were collected on instrument D2b at the ILL, Grenoble. The samples were placed in a vanadium can (diameter 10 mm) within a He cryostat. The profile was recorded in the range $2\theta = 0–160^\circ$ with a neutron wavelength of 1.5943 Å. Data were collected from the natural-boron sample at 4 K for 5 h and from the ^{11}B sample at 15 K for 6 h. An absorption correction was applied to the data from the natural-boron sample. Rietveld analysis^[9] with the GSAS package^[10] enabled both profiles to be fitted simultaneously with a single set of atomic positions. Small regions of the natural-boron profile were excluded due to the presence of an unidentified second phase, and because of scattering from the cryostat, the region between $2\theta = 148$ and 153° was excluded for both samples. The final model gave $R_{\text{wp}} = 8.1$, $R_p = 6.5$, $R_F = 13.7\%$ for the natural-boron sample, $R_{\text{wp}} = 7.1\%$, $R_p = 5.3\%$, $R_F = 6.4\%$ for the ^{11}B sample, and an overall $\chi^2 = 9.6$.

Received: July 13, 1999 [Z13720]

- [1] R. S. Pease, *Acta Crystallogr.* **1952**, 5, 356.
- [2] a) P. K. Smith, P. W. Gilles, *J. Inorg. Nucl. Chem.* **1967**, 29, 375–382; b) N. A. Fishel, H. A. Eick, *J. Inorg. Nucl. Chem.* **1969**, 31, 891–893; c) J. Bauer, J. Debuigne, *C. R. Acad. Sci. Ser. C* **1972**, 274, 1271–1275; d) E. T. Bezruk, L. Ya. Markovskii, *Zh. Prikl. Khim. Moscow* **1972**, 45, 3–6; e) P. K. Smith, PhD thesis, University of Kansas (USA), **1964**.
- [3] J. Bauer, H. Nowotny, *Monatsh. Chem.* **1971**, 102, 1129–1145.
- [4] T. Bréant, D. Pensec, J. Bauer, J. Debuigne, *C. R. Acad. Sci. Ser. C* **1978**, 287, 261–264.
- [5] J. Bauer, O. Bars, *Acta Crystallogr. Sect. B* **1980**, 36, 1540–1544.
- [6] G. S. Smith, Q. Johnson, P. C. Nordine, *Acta Crystallogr.* **1965**, 19, 668.
- [7] J. K. Burdett, E. Canadell, T. Hughbanks, *J. Am. Chem. Soc.* **1986**, 108, 3971–3976.
- [8] K. O. Hodgson, K. N. Raymond, *Inorg. Chem.* **1972**, 11, 3030.
- [9] H. M. Rietveld, *J. Appl. Crystallogr.* **1969**, 2, 65–71.
- [10] A. C. Larson, R. B. Von Dreele, *Los Alamos Laboratory Rep. No.* La-UR-86-748, **1987**.

Direct Experimental Evidence for the $\text{H}_2\text{O}^+\text{O}_2^-$ Charge Transfer Complex: Crucial Support to Atmospheric Photonucleation Theory**

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At the end of the nineteenth century water-vapor photonucleation was thoroughly investigated by Wilson,^[1] who observed the formation of droplets upon UV irradiation of supersaturated air and discovered that oxygen plays a role. Although photonucleation, and its atmospheric relevance, has since been the subject of numerous studies,^[2] its mechanism remained poorly understood, until Byers Brown^[3] proposed a theory based on the excitation by a UV photon of a collision complex ($\text{H}_2\text{O} \cdot \text{O}_2$) to a charge transfer (CT) complex ($\text{H}_2\text{O}^+\text{O}_2^-$). Owing to its large dipole moment, the complex acts as an effective nucleation center, attracting the polar water molecules and promoting the formation of a cluster ("Wilson cluster"). Ab initio^[4] and modeling studies^[5] provide a sound theoretical foundation to the Byers Brown mechanism, which has so far suffered from a complete lack of experimental evidence for the occurrence of its pivotal intermediate, the CT complex. Here, we report direct experimental evidence for its existence as an isolated species with a lifetime exceeding 0.5 μs in the gas phase. Apart from being of interest to the chemistry of water clusters, this result has a direct bearing on the water-vapor photonucleation in the atmosphere.

To clarify our experimental strategy, it is useful to contrast the salient features of the $\text{H}_2\text{O}/\text{O}_2$ pairs bound by van der Waals (vdW) or CT interactions, as described by the most recent and reliable theoretical analysis.^[4c] The energy separation between the two species is computed to amount to 5.75 eV, corresponding to an excitation wavelength of 215.6 nm. The vdW collision complex is characterized by a large separation of H_2O and O_2 and by an essentially repulsive interaction between them, whereas in the CT complex the $\text{H}_2\text{O}^+/\text{O}_2^-$ separation is much shorter and the binding energy (BE) very large, as expected for the charged fragments of a zwitterion whose dipole moment is computed to be 6.04 D. Furthermore, there is a reasonably good agreement between the calculated UV spectrum of the vdW complex and the experimentally observed photonucleation spectrum.

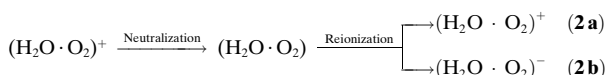
The large difference between the BE of the $\text{H}_2\text{O}/\text{O}_2$ pair in the vdW complex and the BE of the $\text{H}_2\text{O}^+/\text{O}_2^-$ pair in the CT complex suggested that the most promising experimental approach could be based on neutralization–reionization (NR) mass spectrometry. This well-established technique^[6] is endowed with the ability, essential in the case of interest, of

discriminating between strongly bound neutral species, such as the CT complex, and very weakly bound species, such as the vdW water–oxygen complex. The latter would be undetectable by NR mass spectrometry because the energy deposition in the high-energy neutralizing collisions is far too large to result in species with microsecond lifetimes, which are the only ones observed in NR experiments.^[7]

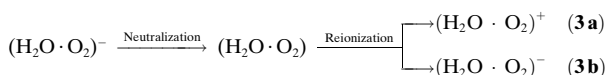
Our experimental approach can be outlined as follows. Charged water–oxygen adducts (i.e. $(\text{H}_2\text{O} \cdot \text{O}_2)^+$ or $(\text{H}_2\text{O} \cdot \text{O}_2)^-$ ions) were produced by well-established ion–molecule reactions in the chemical ionization (CI) source of a multi-sector mass spectrometer. The ions were accelerated to energies of 4–8 kV and mass selected before undergoing two consecutive collision events in two separate cells located along the beam path and containing suitable target gases. A fraction of the ions was neutralized in the first cell by electron transfer reactions, for example according to Equation (1), where M denotes a target gas molecule, accompanied by fragmentation processes. The parent ions that escaped neutralization, the fragment ions, and in general all charged species were removed by a deflecting electrode, leaving a beam containing only fast-moving neutral species to enter the second gas cell. Here reionization occurred either by collision-induced electron loss from the neutral species, yielding cations ($^+\text{NR}^+$ variant), or by electron transfer from a molecule of the target gas ($^+\text{NR}^-$ variant), yielding anions.



In either cases, the reionized species were energy selected and their mass spectra recorded. Detection of a "recovery" signal, a peak of the mass-to-charge ratio (m/z 50) of the original ions, would demonstrate that they survived sequence (2) and hence that the $(\text{H}_2\text{O} \cdot \text{O}_2)$ neutral species must have a lifetime exceeding the time interval of the order of one microsecond between the neutralization and the reionization events.



The same scheme applies, with obvious modifications, to the experiments involving the $(\text{H}_2\text{O} \cdot \text{O}_2)^-$ ion, where detection of a recovery signal at a mass-to-charge ratio of 50 from sequence (3) would provide independent evidence for the existence of the neutral species of interest.



Both the $^+\text{NR}^+$ and $^+\text{NR}^-$ spectra display significant recovery peaks at m/z 50 and the same peaks are also displayed by the $^-\text{NR}^+$ and $^-\text{NR}^-$ spectra (Figure 1). Although the evidence from these NR experiments appeared hardly questionable, the importance of the problem suggested a confirmatory test to make the conclusions irrefutable. To this end, $^{18}\text{O}_2$ and H_2^{18}O were used to prepare $(\text{H}_2^{16}\text{O} \cdot ^{18}\text{O}_2)^+$ and $(\text{H}_2^{18}\text{O} \cdot ^{16}\text{O}_2)^+$ adducts with m/z ratios of 54 and 52, respectively, whose NR spectra, illustrated in Figure 2, are fully consistent with those of the unlabeled species.

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[**] This work was supported by the University of Rome, the Italian National Research Council (CNR) and the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST).

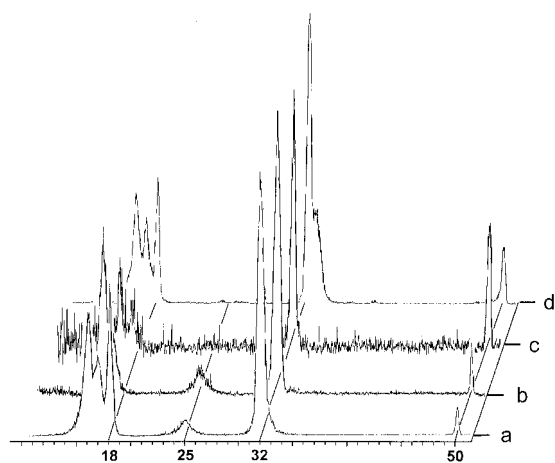


Figure 1. a) $+NR^+$ spectrum, b) $+NR^-$ spectrum of the $(H_2O \cdot O_2)^+$ ion [Eq. (2)], c) $-NR^-$ spectrum, d) $-NR^+$ spectrum of the $(H_2O \cdot O_2)^-$ ion [Eq. (3)] (m/z 50). Note the recovery peak at the same m/z ratio from all the sequences.

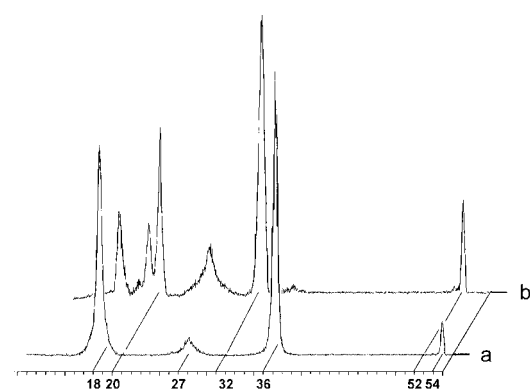


Figure 2. $+NR^+$ spectra of a) the $(H_2O \cdot ^{18}O_2)^+$ ion (m/z 54), b) the $(H_2^{18}O \cdot O_2)^+$ ion (m/z 52), both displaying recovery peaks at the expected m/z ratios.

In a separate set of experiments, the fragmentation pattern of the cations from the reionization process was examined by neutralization–reionization/collisionally-activated dissociation (NR/CAD) mass spectrometry utilizing the TOF analyzer. The cation, which is formed from the reionization of the unlabeled neutral species, decomposes exclusively into O_2^+ (m/z 32), without detectable formation of the OH^+ fragment, a result consistent with the expected H_2O-O_2 connectivity. The only fragments formed from the dissociation of the $(H_2^{16}O \cdot ^{18}O_2)^+$ and $(H_2^{18}O \cdot ^{16}O_2)^+$ recovery ions from the reionization of the corresponding neutral species are $^{18}O_2^+$ (m/z 36) and $^{16}O_2^+$ (m/z 32), respectively, without detectable formation of the isotopically mixed $^{16}O^{18}O^+$ fragment (m/z 34).

The summary of the experimental results is that a neutral $(H_2O \cdot O_2)$ species does exist in the isolated state, and that its lifetime exceeds $0.5 \mu s$, the minimum flight time from the neutralization to the reionization cell of our apparatus for a 50 Da molecule traveling at the speed corresponding to a kinetic energy of 8 keV.

Regarding the nature and the bonding of the neutral species detected, we preliminarily note that the energy deposited into the neutral species by the 8 keV neutralizing collisions

prevents survival of neutral species located in shallow energy wells; the detection limit of NR mass spectrometry corresponds to a energy well depth of the order of 10 kcal mol^{-1} .^[7] It follows that a sizable barrier must exist for the dissociation of the observed species, be it an H_2O_3 molecule or some $H_2O \cdot O_2$ adduct. As to covalently bound species, the only conceivable candidate, the HO_3H molecule, can safely be excluded, based on the following considerations. First, it is extremely unlikely that ionic species of the H-O-O-O-H connectivity can be formed upon the mere clustering of O_2^+/O_2^- ions with water in the CI source. Second, the NR/CAD spectrum of the $(HO_3H)^+$ ion from the reionization of HO_3H would be expected to contain a peak for the HO^+ fragment, which was not detected. Finally, the lack of the isotopically mixed $^{16}O^{18}O^+$ fragment in the NR/CAD spectra of the $(H_2^{18}O \cdot ^{16}O_2)^+$ and $(H_2^{16}O \cdot ^{18}O_2)^+$ ions from the reionization of the corresponding neutral species suggests that the oxygen atoms undergo no scrambling, and that the constituent water and oxygen units retain their distinct identity throughout the entire neutralization–reionization sequence.

These results strongly support the existence of a metastable $H_2O \cdot O_2$ adduct that cannot be matched by the vdW collision complex that is formed by H_2O and O_2 molecules and in which the interaction is theoretically characterized as repulsive.^[4c] More generally, the theory of intermolecular interactions predicts that the BE of any conceivable adducts formed by neutral, ground-state H_2O and O_2 molecules is many orders of magnitude less than required to survive the neutralization event.^[8] It follows that such weakly bound species would invariably dissociate in the picosecond timeframe, and hence would be undetectable by NR mass spectrometry. Based on the above considerations, the neutral species observed must be identified as a metastable adduct formed by *excited* H_2O and O_2 molecules, whose excess energy with respect to the ground state is easily available at the expense of the translational energy of the parent projectile ion.^[9] Among such species, the $(H_2O^+O_2^-)$ CT complex, located 5.75 eV above the ground-state vdW complex,^[4c] is by far the most likely candidate. Indeed, apart from $(H_2O^+O_2^-)$ being the only excited adduct identified theoretically by the systematic exploration of the H_2O/O_2 system, the BE of its charged fragments is very large,^[4c] well above the limit required for detection by NR mass spectrometry.^[10] Of course, the CT complex, although stable with respect to dissociation into its charged fragments, can be short-lived owing to fast intramolecular processes, such as fluorescence and intersystem crossing. So far, the lifetime of the CT complex has not been calculated theoretically, but certain spectroscopic features led to an estimated 10^{-9} – 10^{-6} s range.^[4b] The lifetime deduced from the present results approaches the upper limit of the above interval, which reinforces the role of the CT complex as a nucleation center, allowing sufficient time for the polar water molecules to organize into a Wilson cluster.

Experimental Section

The experiments were performed with a multisector mass spectrometer of the EBE-TOF configuration (ZAB Spec oa-TOF, VG Micromass Ltd., Manchester, UK), modified by addition of two pairs of collision gas cells and a low-temperature CI source equipped with a thoriated filament.

Typical CI source conditions were as follows: source temperature 100 °C; repeller voltage 0.0 V; ion-extraction voltage 8 kV; source pressure 0.1–0.3 Torr. The NR experiments were performed in the first of the collision cells positioned between the magnet and the second electrostatic analyzer, using Xe or CH₄ as the neutralizing colliders, at a pressure adjusted to achieve a 80 % transmittance. Reionization was achieved utilizing O₂ as the collider, approximately at the same transmittance. Any ions remaining after the first collision event were deflected from the primary neutral beam using a high-voltage electrode (1 kV), whose efficiency was checked by suitable control experiments. The NR spectra were averaged over 20–50 acquisitions to achieve a satisfactory signal-to-noise ratio.

The gases were of research grade from commercial sources with a stated purity exceeding 99.95 mol % and were used without further purification. Ozone was prepared from dry O₂ in a commercial ozonizer, collected in a silica trap at 77 K and recovered by controlled warming of the trap. ¹⁸O₂ and H₂¹⁸O (>99 % ¹⁸O atom %) were obtained from Isotec (Miamisburg, USA). The (H₂O·O₂)⁺ ion was prepared by hydration of O₂⁺ in the positive O₂/CI of water^[11]. Much higher yields were achieved by displacement of O₃ by H₂O in the O₃⁺ complex^[12], a very efficient process as demonstrated by kinetic experiments performed utilizing a Fourier-transform ion-cyclotron resonance mass spectrometer (47e Apex, Bruker Spectrospin AG, Bremen, Germany). The (H₂O·O₂)[−] ion was prepared by hydration of O₂[−] in the negative CI of moist oxygen.^[13]

Received: July 22, 1999

Revised: September 29, 1999 [Z13767]

Efficient Hydrolysis of RNA by a PNA – Diethylenetriamine Adduct**

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A few years ago, Komiyama et al. reported^[1] that a hybrid composed of diethylenetriamine (DETA) anchored to the 5'-end of DNA by means of a urethane bond (Figure 1a) hydrolyzed linear RNA selectively at the 3'-side of cytosine 22 (C22, marked with an arrow) to give a 22-mer RNA fragment

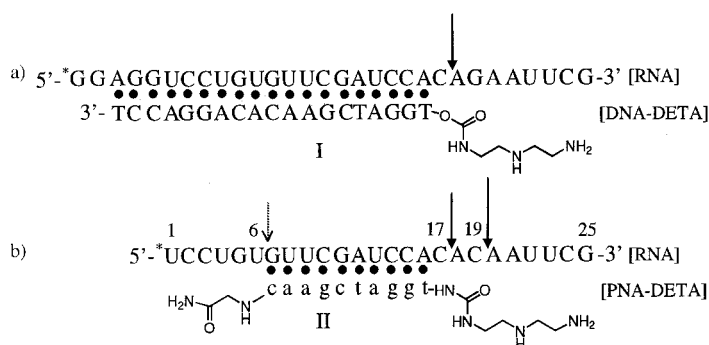


Figure 1. a) Complex **I** of RNA and DNA-DETA as employed by Komiyama et al.; b) complex **II** of RNA and PNA-DETA. Arrows indicate cleavage positions of RNA for hydrolysis by DNA-DETA or PNA-DETA. Nucleotide units are written in uppercase, PNA units in lowercase.

with a 3'-phosphate terminus. This selective scission was ascribed to intramolecular acid–base cooperation of an ammonium ion and a neutral amine in the ethylenediamine moiety [N(CH₂)₂NH₂] of the DNA-DETA adduct.^[2] Interestingly, the total conversion for the RNA hydrolysis was only 10 mol % after incubation of the RNA·DNA-DETA complex **I** (Figure 1a) at pH 8 for 4 h at 50 °C. The relatively low conversion of the RNA substrate may be attributed to less effective hydrogen bonding in complex **I**. We surmised that a higher conversion could be attained by decreasing significantly the freedom in dangling motion of the duplex in the complex.

It is generally accepted that peptide nucleic acids (PNAs)^[3] nicely mimic the physical properties of DNA. Thus, PNAs hybridize sequence specifically to RNA (DNA). They bind, however, more strongly to RNA (DNA)^[4] due to the presence of a neutral polyamide backbone. The latter features, together

- [1] C. T. R. Wilson, *Philos. Trans. R. Soc. London A* **1899**, 192, 403.
- [2] a) F. J. M. Farley, *Proc. R. Soc. London A* **1951**, 207, 527; b) W. A. Hoppel, D. E. Dinger, *J. Atmos. Sci.* **1973**, 30, 331; c) H. Reiss, D. C. Marvin, R. H. Heist, *J. Colloid Interface Sci.* **1977**, 58, 155; d) D. Clark, J. F. Noxon, *Science* **1971**, 174, 941; e) F. C. Wen, T. McLaughlin, J. L. Katz, *Phys. Rev. A* **1982**, 26, 2235.
- [3] W. Byers Brown, *Chem. Phys. Lett.* **1995**, 235, 94.
- [4] a) W. Byers Brown, M. A. Vincent, K. Trollope, I. H. Hillier, *Chem. Phys. Lett.* **1992**, 192, 213; b) W. Byers Brown, I. H. Hillier, A. J. Masters, I. J. Palmer, H. V. Dos Santos, M. Stein, M. A. Vincent, *Faraday Discuss. Chem. Soc.* **1995**, 100, 253; c) I. J. Palmer, W. Byers Brown, I. H. Hillier, *J. Chem. Phys.* **1996**, 104, 3198.
- [5] H. V. Dos Santos, S. J. Vaughn, E. V. Akhmatkaya, M. A. Vincent, A. J. Masters, *J. Chem. Soc. Faraday Trans.* **1997**, 93, 2781.
- [6] a) D. V. Zagorevskij, J. L. Holmes, *Mass Spectrom. Rev.* **1994**, 13, 133; b) C. A. Schalley, G. Hornung, D. Schröder, H. Schwarz, *Chem. Soc. Rev.* **1998**, 27, 91.
- [7] The 6 kcal mol^{−1} value recently reported in the case of H₂OO survival is to be regarded as a lower limit, see: D. Schröder, C. A. Schalley, N. Goldberg, J. Hrůsák, H. Schwarz, *Chem. Eur. J.* **1996**, 2, 1235, and references therein.
- [8] J. O. Hirschfelder, C. F. Curtiss, R. B. Bird, *Molecular Theory of Gases and Liquids*, Wiley, New York, **1964**.
- [9] a) J. L. Holmes, *Mass Spectrom. Rev.* **1989**, 8, 513; b) N. Goldeberg, H. Schwarz, *Acc. Chem. Res.* **1994**, 27, 347.
- [10] Other conceivable candidates would be neutral species formed in ⁺NR⁺ and [−]NR[−] experiments in highly excited, long-lived Rydberg-states, see: a) G. Herzberg, *Annu. Rev. Phys. Chem.* **1987**, 38, 27. However, their role is denied by the results of our ⁺NR[−] and [−]NR[−] experiments, since electron attachment to a Rydberg-state species is expected to be difficult, see ref. [7].
- [11] N. G. Adams, D. K. Bohme, D. B. Dunkin, F. C. Fehsenfeld, E. E. Ferguson, *J. Chem. Phys.* **1970**, 52, 3133.
- [12] F. Cacace, R. Cipollini, G. de Petris, F. Pepi, M. Rosi, A. Sgamellotti, *Inorg. Chem.* **1998**, 37, 1398.
- [13] J. D. Payzant, P. Kerbarle, *J. Chem. Phys.* **1972**, 56, 3482.

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[**] This work was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO). We thank Hans van den Elst for synthesizing the RNA sequence and recording the mass spectra.

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with the fact that PNAs resist biodegradation,^[5] were an incentive to replace the DNA–DETA adduct in complex **I** by a PNA–DETA adduct as in complex **II** (Figure 1 b).

As part of an ongoing program^[6] towards the design and use of antisense probes based on PNA, we here report the preparation and ribonucleolytic properties of a PNA attached by means of a urea bond to DETA.

Based on the RNA substrate employed by Komiyama et al. (Figure 1 a), a 25-mer RNA (Figure 1 b) containing a 10-mer sequence (i. e. G7–A16) complementary to the adduct, as well as two potential neighboring C–A scission sites^[7] adjacent to A16, was chosen as the target RNA. The RNA 25-mer, prepared according to a well-established solid-phase approach,^[8] was ³²P-labeled at the 5'-end using adenosine 5'-[γ -³²P]-triphosphate and T4 polynucleotide kinase. The PNA–RNA complex in which the diethylenetriamine moiety in PNA **11** is replaced by an acetyl group (PNA–Ac) showed a *T*_m of 69 °C (pH 7, 100 mM NaCl), indicating that the PNA–DETA adduct forms a sufficiently stable duplex with the target RNA.

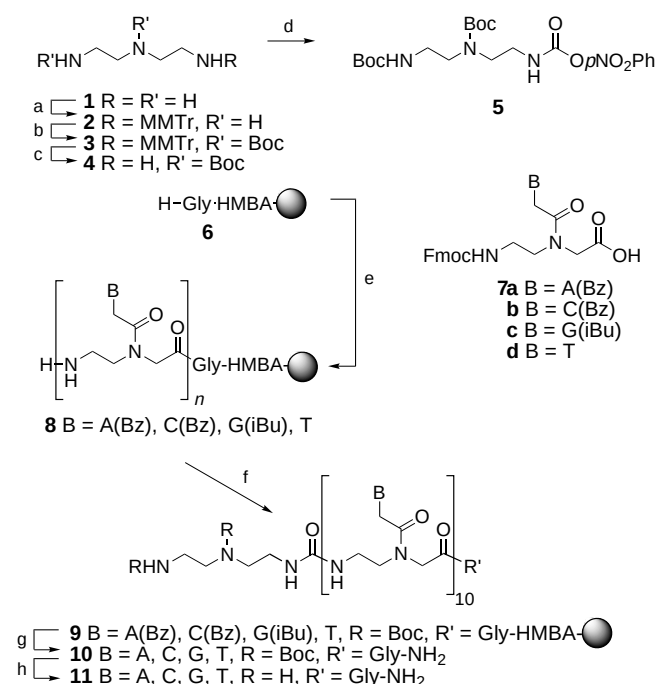
The construction of the 10-mer PNA–DETA adduct **11** commences with the four-step transformation of DETA (**1**) into the *N,N'*-Boc-protected and activated derivative **5** (Scheme 1). Treatment of excess **1** in dichloromethane with MMTrCl (see Scheme 1 for abbreviations) led to the isolation of the crude mono-MMTr derivative **2**. Treatment of the latter with excess Boc₂O in dioxane gave, after purification on silica gel, the fully protected derivative **3**. Removal of the *N*-MMTr group of **3** with TFA in the presence of the scavenger

*n*Bu₃SnH resulted, after extraction, in the isolation of the crude free amine **4**. Reaction of **4** with *para*-nitrophenyl chloroformate led, after purification on silica gel, to the activated derivative **5** in an overall yield of 42 %.

At this stage, the PNA decamer complementary to the G7–A16 stretch of the RNA in complex **II** was assembled following a well-established solid-phase synthesis.^[6] Thus, sequential elongation of glycine anchored by an ester bond to functionalized polystyrene beads (i. e. **6** in Scheme 1) with Fmoc/*N*-acyl-protected building blocks **7a–d**^[9] under the agency of the coupling reagent HATU and subsequent reaction of the resulting resin-bound 10-mer PNA **8** with excess **5** in the presence of DIPEA for 16 h at 20 °C gave immobilized **9** (see Experimental Section). Removal of the *N*-acyl protecting groups from the nucleobases in **9** and concomitant release from the solid support was effected by ammonolysis (NH₃/MeOH) to give, after purification by reversed-phase high-performance liquid chromatography (RP-HPLC), the homogeneous *N,N'*-Boc protected PNA–DETA adduct **10**. Treatment of the latter adduct with TFA (75 %) resulted in the isolation of the fully deprotected PNA–DETA adduct **11**, the homogeneity and identity of which was firmly established by RP-HPLC and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

Having the 10-mer PNA–DETA adduct **11** and the 25-mer RNA in hand, we examined the ribonucleolytic behavior of **11** by degrading the target 25-mer RNA at 40 °C in a Tris·HCl (10 mM) buffer containing NaCl (100 mM) and EDTA (0.1 mM) at pH 7. In this respect, it is of interest to note that the pH is one unit below that required for optimal cleavage of the phosphodiester bonds in RNA by intramolecular acid–base cooperation. The hydrolysates were analyzed by electrophoresis on 20 % denaturing polyacrylamide gel.

A typical electrophoresis pattern is presented in Figure 2. Cursory inspection of the traces in lanes 4–8 shows, after a



Scheme 1. a) Monomethoxytrityl chloride (MMTrCl), CH₂Cl₂; b) Boc₂O (di-*tert*-butyldicarbonate), dioxane, 73 % (2 steps); c) 5 % trifluoroacetic acid (TFA), Bu₃SnH, CH₂Cl₂, 91 %; d) *p*NO₂PhOC(O)Cl, Et₃N, CH₂Cl₂, 63 %; e) stepwise elongation with **7a–d**; f) **5**, *N,N*-diisopropylethylamine (DIPEA), DMF; g) NH₃/MeOH, 50 °C; h) 75 % TFA, H₂O. Boc = *tert*-butoxycarbonyl, Fmoc = fluorene-9-ylmethoxycarbonyl, HMBA = *para*-hydroxymethylbenzoic acid. The polystyrene support is represented by shaded circles.

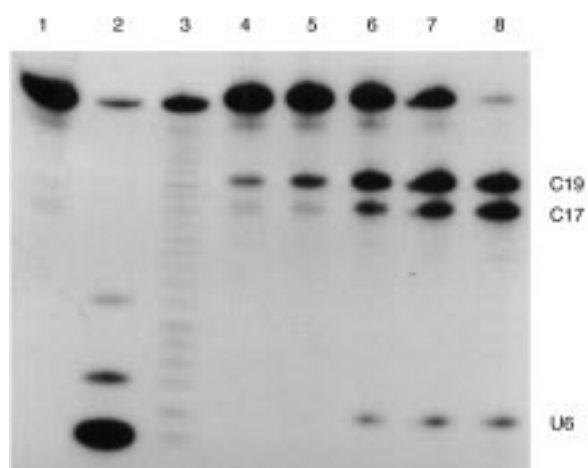


Figure 2. Autoradiograph for the cleavage of the 5'-labeled RNA 25-mer in Tris·HCl buffer at pH 7 and 40 °C in the presence of EDTA (0.1 mM). Lane 1: PNA–DETA (*t* = 0); lane 2: T1 digestion; lane 3: alkaline hydrolysis ladder; lane 4: PNA–DETA (*t* = 1 h); lane 5: PNA–DETA (*t* = 2 h); lane 6: PNA–DETA (*t* = 4 h); lane 7: PNA–DETA (*t* = 8 h); lane 8: PNA–DETA (*t* = 24 h). [RNA]₀ = 60 nM, [PNA–DETA] = 2 μM. EDTA = ethylenediaminetetraacetic acid, Tris = tris(hydroxymethyl)aminomethane.

lapse of 24 h, the presence of two major 5'-end labeled RNA fragments. Comparison of the mobility of the two cleavage products with T1 digestion (lane 2) and alkaline hydrolysis (lane 3) of the target RNA (lane 1) revealed that both fragments resulted from hydrolysis at the 3'-side of C17 and C19, respectively. The total conversion for the RNA hydrolysis was approximately 29 mol % after 4 h at 40 °C, as gauged by densitometry (Figure 3). It is also worthwhile mentioning that the cleavage of the phosphodiester bond in close proximity of the duplex structure in complex **II** is relatively less efficient (see, for instance, Figure 3). A similar preference for the more distant cleavage site was also reported in other, closely related studies.^[7a,b, 10]

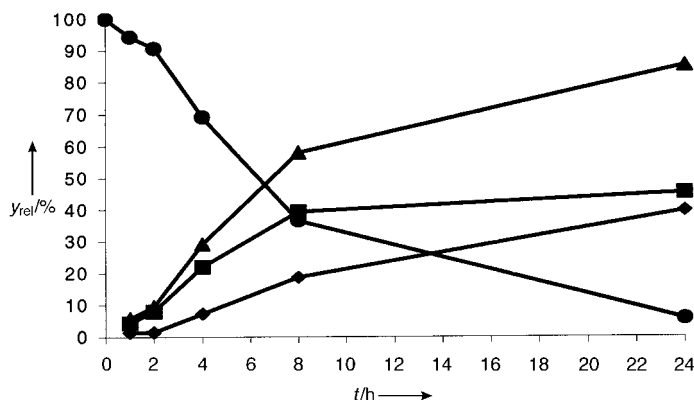


Figure 3. Relative amounts (y) of intact and cleaved RNA at different reaction times. Intact RNA 25-mer (●), fragment 1 (RNA 19-mer) (■), fragment 2 (RNA 17-mer) (◆), summed amount of fragments 1 and 2 (▲).

In contrast with the latter observations, no scission was observed when the 10-mer PNA-Ac was used instead of the PNA-DETA conjugate **11**. The same holds for incubation of the 25-mer RNA with diethylenetriamine in the presence or absence of the PNA-Ac decamer, thus illustrating the sequence specificity of RNA hydrolysis by the PNA-DETA adduct **11**.

Apart from the two main cleavage products an additional minor degradation product, resulting from scission after U6, could be observed upon prolonged incubation (see lanes 6–8). Since participation of the glycinamide in the cleavage is ruled out by the inactivity of the PNA-Ac, the formation of the latter fragment may indicate that the spatial arrangement of the RNA·PNA-DETA complex **II** positions the ethylenediamine residue of the PNA-DETA in close proximity (i. e. approximately one helical turn) to the phosphodiester bond between U6 and G7 in the RNA substrate.

These results show for the first time that a PNA-based adduct cleaves an RNA sequence specifically at micromolar concentration under physiological conditions. An additional but nonetheless essential feature of this type of adduct is the fact that almost complete conversion of RNA can be attained (see e. g. Figure 3) with a relatively short stretch of PNA, thus obviating the need for an excessively long sequence of DNA to reach the same goal.^[11] In this respect, we note that our PNA approach nicely complements the recently reported selective cleavage of HIV-1 TAR-RNA with a peptide-cyclen conjugate.^[12] In summary, the ease of preparing artificial

nucleases based on PNA will be of great interest for the future design of other types of chemical nucleases.

Experimental Section

Solid-phase synthesis of PNA-DETA adduct **11:** All solvents (Biosolve, DNA synthesis grade) were used as received. Solid-phase synthesis was performed on a Pharmacia Gene Assembler using highly cross-linked polystyrene beads as the solid support (loading: 26–28 $\mu\text{mol g}^{-1}$) on a 1 μmol scale. The support was functionalized with a glycine moiety attached to a *para*-hydroxymethylbenzoic acid linker. Assembly of the PNA part was established using solutions of 0.3 M monomers **7a–d**, 0.3 M DIPEA and 0.3 M HATU (*O*-(azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) in acetonitrile/dimethylformamide (1/1 v/v). Prior to coupling, the monomers were preactivated for 1 min by mixing equal amounts of the PNA monomer (15 equiv per μmol support), HATU and DIPEA solutions. The protocol for one PNA chain extension cycle consisted of 1) wash: acetonitrile/dimethylformamide (1/1 v/v), 2.5 mL; 2) coupling: PNA + HATU + DIPEA in acetonitrile/dimethylformamide (1/1 v/v), 15 min; 3) wash: acetonitrile/dimethylformamide (1/1 v/v), 2.5 mL; 4) capping: Ac₂O/lutidine/*N*-methylimidazole/tetrahydrofuran (1/1/1/7 v/v/v/v), 2.0 mL; 5) wash: acetonitrile/dimethylformamide (1/1 v/v), 2.5 mL; 6) Fmoc removal: 20% piperidine in acetonitrile/dimethylformamide (1/1 v/v), 3 min; 7) wash: acetonitrile/dimethylformamide (1/1 v/v), 2.5 mL. After the last elongation step, the solid support was transferred to a separate reaction vessel, and a solution of **5** (12 mg, 25 μmol) and diisopropylethylamine (5 μL) in dimethylformamide (0.5 mL) was added. After mixing for 16 h, the reagents were drained from the vessel, and the solid support was washed with dimethylformamide (2 mL) followed by dichloromethane (2 mL). At this stage, the oligomers were cleaved from the support with concomitant deprotection of the exocyclic amino groups by treatment with methanolic ammonia (1.5 mL) at 50 °C for 16 h. RP-HPLC purification and analysis were carried out on a Jasco HPLC system equipped with a LiChrospher 100 RP-18 end-capped column (10.0 $\times$ 250 mm and 4.0 $\times$ 250 mm, respectively). Gradient elution was performed at 40 °C by building up a gradient starting with buffer A (0.1% TFA in water) and applying buffer B (0.1% TFA in acetonitrile/water, 9/1 v/v) with a flow rate of 1.0 mL min⁻¹. The Boc groups of purified **10** were removed by treatment with 75% TFA. Homogeneous deprotected PNA-DETA adduct **11** was obtained after freeze-drying. The identity and homogeneity of oligomers **10** and **11** were confirmed by MALDI-TOF MS and RP-HPLC. **10**: MALDI-TOF MS: m/z : 3139.1 [$M+H$]⁺, 3160.2 [$M+Na$]⁺; calcd for C₁₂₅H₁₆₅N₆₅O₃₅: m/z : 3138.1. **11**: MALDI-TOF MS: m/z : 2939.6 [$M+H$]⁺, 2962.3 [$M+Na$]⁺; calcd for C₁₁₅H₁₄₉N₆₅O₃₁: m/z : 2937.9.

RNA degradation with PNA-DETA adduct **11:** All buffers were made from highly purified Milli Q water and were sterilized before use. Labeled RNA 25-mer and PNA-DETA were mixed in Tris·HCl buffer (10 mM, pH 7) containing NaCl (100 mM) and EDTA (0.1 mM) to give the following concentrations: [RNA] = 60 nM, [PNA-DETA] = 2 μM . The samples (70 μL) were incubated at 40 °C. After incubation, the RNA was immediately precipitated by addition of 3 M NaOAc (pH 5, 7 μL), EtOH (225 μL), and 10 $\mu\text{g mL}^{-1}$ tRNA (1 μL). The precipitated RNA was recovered by centrifugation, and was then dried and redissolved in 5 μL water and 5 μL loading buffer. The solutions were heated at 80 °C for 1 min, centrifuged and analyzed on a 20% denaturing electrophoresis gel.

Received: July 22, 1999 [Z13768]

- [1] M. Komiyama, T. Inokawa, K. Yoshinari, *J. Chem. Soc. Chem. Commun.* **1995**, 77–78.
- [2] a) K. Yoshinari, K. Yamazaki, M. Komiyama, *J. Am. Chem. Soc.* **1991**, 113, 5899–5901; b) M. Komiyama, K. Yoshinari, *J. Org. Chem.* **1997**, 62, 2155–2160.
- [3] P. E. Nielsen, M. Egholm, R. H. Berg, O. Buchardt, *Science* **1991**, 254, 1497–1500.
- [4] M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, P. E. Nielsen, *Nature* **1993**, 265, 566–568.

- [5] V. V. Demidov, V. N. Potaman, M. D. F. Kamenetskii, M. Egholm, O. Buchardt, S. H. Sonnichsen, P. E. Nielsen, *Biochem. Pharmacol.* **1994**, *48*, 1310–1313.
- [6] a) A. C. van der Laan, N. J. Meeuwenoord, R. S. Oosting, R. Brands, E. Kuyl-Yeheskiely, J. H. van Boom, *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 295–297; b) A. C. van der Laan, R. Brill, R. G. Kuimelis, E. Kuyl-Yeheskiely, J. H. van Boom, *Tetrahedron Lett.* **1997**, *38*, 2249–2252; c) A. C. van der Laan, P. Havenaar, R. S. Oosting, E. Kuyl-Yeheskiely, E. Uhlmann, J. H. van Boom, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 663–668; d) J. C. Verheijen, A.-M. M. van Roon, A. C. van der Laan, G. A. van der Marel, J. H. van Boom, *Nucleosides Nucleotides* **1999**, *18*, 493–508; e) J. C. Verheijen, G. A. van der Marel, J. H. van Boom, S. F. Bayly, M. R. Player, P. F. Torrence, *Bioorg. Med. Chem.* **1999**, *7*, 449–455.
- [7] C–A sites in RNA are known to be particularly susceptible to hydrolysis through intramolecular acid–base cooperation. See: a) M. Komiyama, T. Inokawa, T. Shiiba, N. Takeda, K. Ysohinari, M. Yashiro, *Nucleic Acids Symp. Ser.* **1993**, *29*, 197–198; b) V. Vlassov, T. Abramova, T. Godovikova, R. Giegé, V. Silnikov, *Antisense Nucleic Acid Drug Dev.* **1997**, *7*, 39–42; c) V. V. Vlassov, G. Zuber, B. Felden, J.-P. Behr, R. Giegé, *Nucleic Acids Res.* **1995**, *23*, 3161–3167; d) M. A. Podyminigin, V. V. Vlassov, R. Giegé, *Nucleic Acids Res.* **1993**, *21*, 5950–5956.
- [8] R. T. Pon in *Methods in Molecular Biology, Protocols for Oligonucleotides and Analogs*, Vol. 20 (Ed.: S. Agrawal), Humana Press, Totowa, NJ, **1993**, chap. 19.
- [9] F. Bergmann, W. Bannwarth, S. Tam, *Tetrahedron Lett.* **1995**, *36*, 6823–6826.
- [10] V. Silnikov, G. Zuber, J.-P. Behr, R. Giegé, V. Vlassov, *Phosphorus Sulfur Silicon* **1996**, *109–110*, 277–280.
- [11] R. Häner, J. Hall, *Antisense Nucleic Acid Drug Dev.* **1997**, *7*, 423–430, and references therein.
- [12] K. Michaelis, M. Kalesse, *Angew. Chem.* **1999**, *111*, 2382–2385; *Angew. Chem. Int. Ed.* **1999**, *38*, 2243–2245.

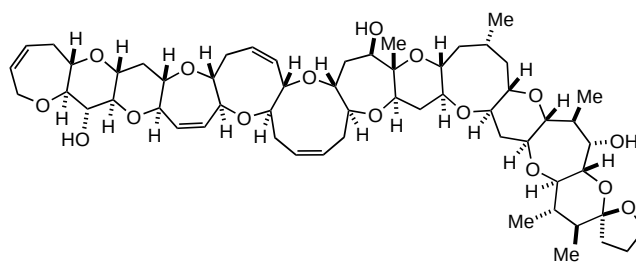


Figure 1. The structure of CTX-3C.

targets, providing a stimulus for the development of many new reactions and strategies for the construction of polycyclic systems.^[3] This work has culminated in the recent total syntheses of brevetoxins A and B, completed by Nicolaou and co-workers,^[4] as well as several syntheses of the smaller congener hemibrevetoxin B.^[5]

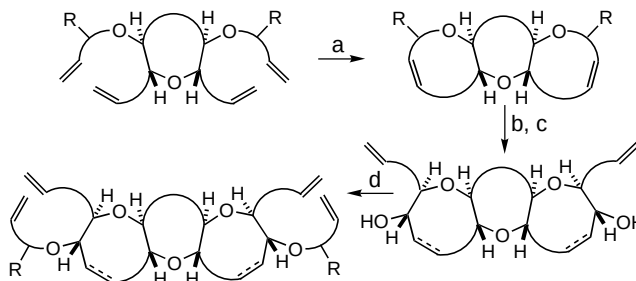
We recently presented a powerful strategy for the construction of subunits found in the brevetoxins and ciguatoxins. Catalytic ring-closing metathesis (RCM)^[6] reactions of enol ethers,^[7a,b] allylic ethers,^[7c,d] or alkynyl ethers^[7e] were promoted by the Schrock catalyst [2,6-*i*Pr₂C₆H₃NMo{OC(CF₃)₂-Me}₂CHCMe₂Ph] (**1**)^[8] or the Grubbs catalyst [Cl₂{(C-C₆H₁₁)₃P}₂-RuCHPh] (**2**)^[9] leading to the formation of cyclic ethers.^[10] Stereoselective elaboration of the RCM products then gave fully functionalized, saturated or unsaturated, cyclic ethers suitable for conversion into polyoxacyclic units of the type found in the natural products.^[7d]

We now report a new strategy for polycyclic ether assembly, the essence of which is illustrated in Scheme 1.^[11] We envisaged the construction of rings in a two-directional

Synthesis of Polycyclic Ethers by Two-Directional Double Ring-Closing Metathesis**

J. Stephen Clark* and Olivier Hamelin

Neurotoxic marine polycyclic ethers of the brevetoxin and ciguatoxin family continue to be interesting synthetic targets as a consequence of their architectural complexity and potent biological activity.^[1] They constitute a major challenge in terms of medium-size ring construction as illustrated by CTX-3C (Figure 1).^[2] This ciguatoxin contains a total of 13 rings and possesses a daunting combination of saturated and unsaturated medium-sized rings. The size of the brevetoxins and ciguatoxins, coupled with their structural and stereochemical complexity, has made them irresistible synthetic



Scheme 1. Strategy for the synthesis of polycyclic ethers using two-directional RCM reactions. a) Ring-closing metathesis; b) ring functionalization; c) side-chain functionalization; d) side-chain introduction.

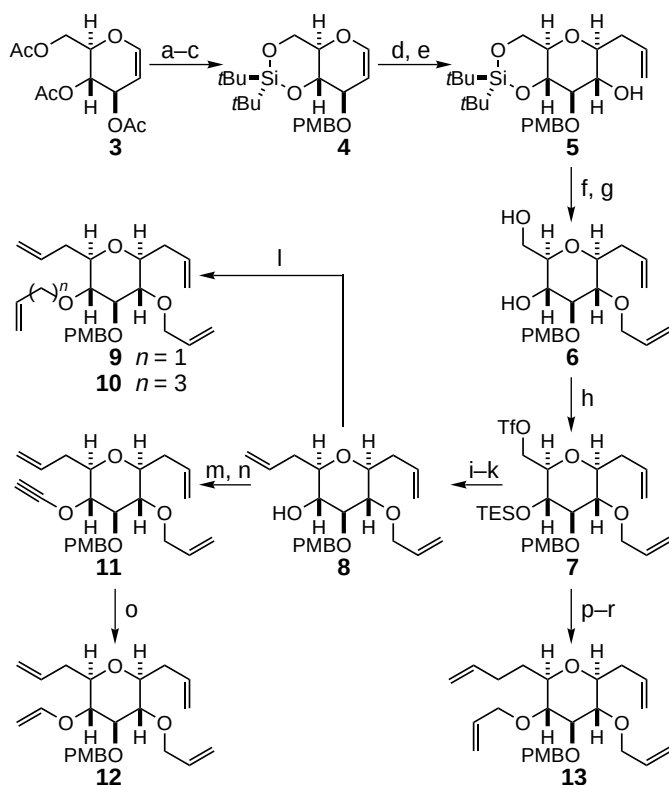
manner by performing double RCM reactions of allylic ethers, enol ethers, or alkynyl ethers, or any combination thereof.^[12] We expected that the reaction would be of general applicability, permitting the preparation of tricyclic ethers with any permutation of ring sizes. Elaboration of the tricyclic products, using our recently described methods,^[7b] followed by side-chain functionalization would then provide appropriately functionalized systems for iteration of the two-directional ring-closure sequence.

The precursors were prepared as shown in Scheme 2. Treatment of commercially available tri-*O*-acetyl-D-glucal (**3**) with sodium methoxide afforded D-glucal, which was converted into 4,6-*O*-di-(*tert*-butyl)silanediy-D-glucal accord-

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[**] The European Commission is gratefully acknowledged for the award of a Marie-Curie Fellowship to O.H. as part of the TMR Programme. We thank Dr. A. J. Blake and Dr. P. Cooke for performing the X-ray crystallographic analysis of compound **14**.

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Scheme 2. Preparation of cyclization precursors for two-directional RCM reactions. a) NaOMe, MeOH, RT, 92–100%; b) $t\text{Bu}_2\text{Si}(\text{OTf})_2$ (1.05 equiv), DMF, pyridine -40°C , 92%; c) PMBOC(NH)CCl₃ (2.5 equiv), PPTS, CH₂Cl₂, reflux, 94%; d) Me₂CO₂, Me₂CO, CH₂Cl₂, 0°C ; e) CH₂CHCH₂MgBr (3 equiv), ZnCl₂ (3 equiv), THF/Et₂O (2/1), $-78 \rightarrow 5^\circ\text{C}$, 73% over 2 steps (>20:1); f) NaH (1.6 equiv), CH₂CHCH₂Br (1.15 equiv), $n\text{Bu}_4\text{NI}$, [18]crown-6, THF, RT; g) TBAF (5 equiv), THF, RT, 81% over 2 steps; h) Tf₂O (1.15 equiv), TESOTf (1.5 equiv), 2,6-lutidine (5 equiv), CH₂Cl₂, -78°C ; i) Me₃SiCCl₃ (6 equiv), THF/HPMA (6/1), $-78^\circ\text{C} \rightarrow \text{RT}$; j) TBAF (3 equiv), THF, RT, 82% over 3 steps; k) H₂, Lindlar catalyst, EtOAc, RT, 83%; l) NaH, CH₂CH(CH₂)_nBr ($n=1, 3$), $n\text{Bu}_4\text{NI}$, [18]crown-6, THF, RT, 90% **9**, 81% **10**; m) KH (5 equiv), Cl₂CCHCl (1.3 equiv), THF, $-78^\circ\text{C} \rightarrow \text{RT}$; n) $n\text{BuLi}$ (5 equiv), Et₂O, $-78 \rightarrow -20^\circ\text{C}$, 82% over 2 steps; o) H₂, 5% Pd/BaSO₄, pyridine, RT, 70%; p) CH₂CHCH₂MgBr (5 equiv), CuBr (0.78 equiv), Et₂O, 0°C , 91% over 2 steps; q) TBAF (1.2 equiv), THF, RT, 90%; r) NaH (2 equiv), CH₂CHCH₂Br (1.5 equiv), $n\text{Bu}_4\text{NI}$, THF, RT, 85%. RT=room temperature, PMB=*p*-methoxybenzyl, PPTS=pyridinium *p*-toluenesulfonate, TBAF=tetrabutylammonium fluoride, Tf₂O=trifluoromethanesulfonic anhydride, TESOTf=triethylsilyl trifluoromethanesulfonate, HMPA=hexamethyl phosphoramide.

ing to the procedure of Hoberg.^[13] The free secondary hydroxyl group was then protected as the *p*-methoxybenzyl (PMB) ether to afford the dihydropyran **4**.^[14] Epoxidation of the enol ether using dimethyldioxirane gave an unstable glacial epoxide.^[15] Immediate treatment of the epoxide with allylmagnesium bromide in the presence of zinc chloride provided the alcohol **5** in a highly diastereoselective manner (>20:1 as indicated by NMR analysis).^[16] Allylation of the free hydroxyl group and subsequent removal of the silicon protecting group delivered the diol **6** in good yield. One-pot triflate formation at the primary hydroxyl site and protection of the secondary hydroxyl group as the triethylsilyl (TES) ether afforded the triflate **7**.^[5d] Introduction of the side chain was accomplished by treatment of triflate **7** with lithium

trimethylsilylacetylide.^[10f] Removal of the silicon protecting groups and subsequent Lindlar hydrogenation delivered the alcohol **8**.

The RCM precursors selected for study were prepared from the triflate **7** and the alcohol **8**. The bis-allyl ether **9** and the precursor **10** were obtained by deprotonation of the alcohol **8** and treatment of the resulting sodium alkoxide with allyl bromide and 5-bromopent-1-ene, respectively. The alkynyl ether **11** was prepared from **8** using the procedure of Greene and co-workers,^[17] which we recently employed in the preparation of related compounds.^[7e] Hydrogenation of the alkynyl ether **11** then afforded the enol ether **12** in good yield.^[18] The final precursor required for our study, the bis-allyl ether **13**, was prepared in a direct and efficient manner by copper-catalyzed addition of allylmagnesium bromide to the triflate **7**,^[19] removal of the TES protecting group, and conversion of the free hydroxyl group into the allyl ether.

The two-directional double RCM reactions of the precursors **9**–**13** were investigated and the relative efficacy of the molybdenum catalyst **1** and the ruthenium catalyst **2** was compared in each case (Table 1). The double allylic ether RCM reaction of the *meso* substrate **9**, when performed with either of the catalysts, led to the efficient formation of two seven-membered rings. The resulting crystalline tricyclic ether

Table 1. Double RCM reactions of substrates **9**–**13** mediated by complexes **1** and **2**.

Substrate	Catalyst ^[a]	Yield [%] ^[b]	Product
9	1 (35 mol %)	85	
9	2 (25 mol %)	88	
10	1 (50 mol %)	21	
10	2 (30 mol %)	65	
11	2 (15 mol %)	50	
12	1 (20 mol %)	63	
12	2 (30 mol %) ^[c]	71	
13	1	— ^[d]	
13	2 (20 mol %)	77	

[a] Reaction conditions: complex **1** in benzene at room temperature or 55°C , complex **2** in dichloromethane at room temperature or reflux. [b] Yield of product after chromatographic purification. [c] Reaction performed in benzene at reflux. [d] A complex mixture of products was isolated.

14 was obtained in good yield, and its structure was confirmed by X-ray analysis. Treatment of the homologous compound **10** with the catalyst **2** resulted in formation of a seven-membered and a nine-membered ring by allylic ether and alkene RCM, yielding tricyclic ether **15** in good yield. Treatment of the same substrate with the molybdenum catalyst **1** provided the product in inferior yield. Simultaneous allylic ether and enyne RCM reactions were accomplished upon treatment of the substrate **11** with catalyst **2**, and the diene **16**, which corresponds to the ABC ring system found in CTX-3C (Figure 1), was produced in reasonable yield. Treatment of the substrate **12** with either catalyst **1** or **2** led to simultaneous RCM of an allylic ether and an enol ether, and afforded the product **17** in good yield. The success of the ruthenium-catalyzed reaction is particularly noteworthy because enol ethers are not usually good substrates for the catalyst **2**.^[20] Finally, formation of a seven- and an eight-membered ring by double RCM was accomplished by treatment of the substrate **13** with the catalyst **2** to yield product **18**.

Our results demonstrate that it is possible to build outwards from a single ring in a two-directional manner by performing double RCM reactions. In all cases the yields of the *trans*-fused tricyclic ethers ranged from good to excellent, and no bridged cyclic ethers, arising from the other possible intramolecular double RCM manifold, were isolated.^[12d] It is remarkable that higher yields were obtained when the ruthenium catalyst **2** was used instead of the generally more reactive molybdenum catalyst **1**.

This efficient and flexible two-directional strategy for the construction of *trans*-fused polyoxacyclic frameworks is currently being utilized to construct subunits of the brevetoxins and ciguatoxins.

Received: July 23, 1999

Revised: October 11, 1999 [Z13772]

- [1] For a review concerning marine toxins, see T. Yasumoto, M. Murata, *Chem. Rev.* **1993**, 93, 1897.
- [2] M. Satake, M. Murata, T. Yasumoto, *Tetrahedron Lett.* **1993**, 34, 1975.
- [3] For some examples of methods developed for the synthesis of polycyclic ether frameworks, see a) K. C. Nicolaou, C.-K. Hwang, D. A. Nugiel, *J. Am. Chem. Soc.* **1989**, 111, 4136; b) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, C.-K. Hwang, *J. Am. Chem. Soc.* **1989**, 111, 5330; c) K. C. Nicolaou, C.-K. Hwang, B. E. Marron, S. A. DeFrees, E. A. Couladouros, Y. Abe, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, 112, 3040; d) M. Zárraga, J. D. Martín, *Tetrahedron Lett.* **1991**, 32, 2249; e) Y. Yamamoto, J. Yamada, I. Kadota, *Tetrahedron Lett.* **1991**, 32, 7069; f) M. Sasaki, H. Fuwa, M. Inoue, K. Tachibana, *Tetrahedron Lett.* **1998**, 39, 9027; g) J. D. Rainier, S. P. Allwein, *Tetrahedron Lett.* **1998**, 39, 6901.
- [4] a) K. C. Nicolaou, *Angew. Chem.* **1996**, 108, 644; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 589; b) K. C. Nicolaou, Z. Yang, G. Shi, J. L. Gunzner, K. A. Agrios, P. Gärtner, *Nature* **1998**, 392, 264; c) K. C. Nicolaou, J. L. Gunzner, G. Shi, K. A. Agrios, P. Gärtner, Z. Yang, *Chem. Eur. J.* **1999**, 5, 646.
- [5] a) K. C. Nicolaou, K. R. Reddy, G. Skokotas, F. Sato, X.-Y. Xiao, C.-K. Hwang, *J. Am. Chem. Soc.* **1993**, 115, 3558; b) I. Kadota, P. Jung-Youl, N. Koumura, G. Pollaud, Y. Matsukawa, Y. Yamamoto, *Tetrahedron Lett.* **1995**, 36, 5777; c) M. Morimoto, H. Matsukura, T. Nakata, *Tetrahedron Lett.* **1996**, 37, 6365; d) Y. Mori, K. Yaegashi, H. Furukawa, *J. Org. Chem.* **1998**, 63, 6200; e) I. Kadota, Y. Yamamoto, *J. Org. Chem.* **1998**, 63, 6597.
- [6] For reviews concerning ring-closing metathesis reactions, see a) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, 28, 446; b) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, 109, 2124; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2036; c) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371; d) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, 54, 4413.
- [7] a) J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, 38, 123; b) J. S. Clark, J. G. Kettle, *Tetrahedron* **1999**, 55, 8231; c) J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, 38, 127; d) J. S. Clark, O. Hamelin, R. Hufton, *Tetrahedron Lett.* **1998**, 39, 8321; e) J. S. Clark, G. P. Trevitt, D. Boyall, B. Stammen, *Chem. Commun.* **1999**, 2629.
- [8] R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, 112, 3875.
- [9] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem.* **1995**, 107, 2179; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2039.
- [10] For other examples of the use of RCM reactions in the preparation of subunits found in the brevetoxins and ciguatoxins, see a) K. C. Nicolaou, M. H. D. Postema, C. F. Claiborne, *J. Am. Chem. Soc.* **1996**, 118, 1565; b) M. T. Crimmins, A. L. Choy, *J. Org. Chem.* **1997**, 62, 7548; c) M. Delgado, J. D. Martín, *Tetrahedron Lett.* **1997**, 38, 6299; d) T. Oishi, Y. Nagumo, M. Hirama, *Synlett* **1997**, 980; e) T. Oishi, Y. Nagumo, M. Hirama, *Chem. Commun.* **1998**, 1041; f) M. Sasaki, T. Noguchi, K. Tachibana, *Tetrahedron Lett.* **1999**, 40, 1337; g) M. Delgado, J. D. Martín, *J. Org. Chem.* **1999**, 64, 4798.
- [11] For an example of two-directional polyoxacycle construction, see J. L. Ravelo, A. Reguerio, E. Rodríguez, J. de Vera, J. D. Martín, *Tetrahedron Lett.* **1996**, 37, 2869.
- [12] For examples of double ring-closing metathesis reactions, see a) G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, 115, 9856; b) S.-H. Kim, W. J. Zuercher, N. B. Bowden, R. H. Grubbs, *J. Org. Chem.* **1996**, 61, 1073; c) W. J. Zuercher, M. Hashimoto, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, 118, 6634; d) M. Lautens, G. Hughes, *Angew. Chem.* **1999**, 111, 160; *Angew. Chem. Int. Ed.* **1999**, 38, 129; e) C. Baylon, M.-P. Heck, C. Mioskowski, *J. Org. Chem.* **1999**, 64, 3354.
- [13] J. O. Hoberg, *Carbohydr. Res.* **1997**, 300, 365.
- [14] N. Nakajima, K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, 29, 4139.
- [15] R. L. Halcomb, S. J. Danishefsky, *J. Am. Chem. Soc.* **1989**, 111, 6661.
- [16] a) W. M. Best, V. Ferro, J. Harle, R. V. Stick, D. M. G. Tilbrook, *Aust. J. Chem.* **1997**, 50, 463; b) D. A. Evans, B. W. Trotter, B. Côté, *Tetrahedron Lett.* **1998**, 39, 1709; c) J. D. Rainier, S. P. Allwein, *J. Org. Chem.* **1998**, 63, 5310.
- [17] A. Moyano, F. Charbonnier, A. E. Greene, *J. Org. Chem.* **1987**, 52, 2919.
- [18] N. Kann, V. Bernardes, A. E. Greene, *Org. Synth.* **1997**, 74, 13.
- [19] H. Kotsuki, I. Kadota, M. Ochi, *Tetrahedron Lett.* **1989**, 30, 1281.
- [20] a) O. Fujimura, G. C. Fu, R. H. Grubbs, *J. Org. Chem.* **1994**, 59, 4029; b) C. F. Sturino, J. C. Y. Wong, *Tetrahedron Lett.* **1998**, 39, 9623.

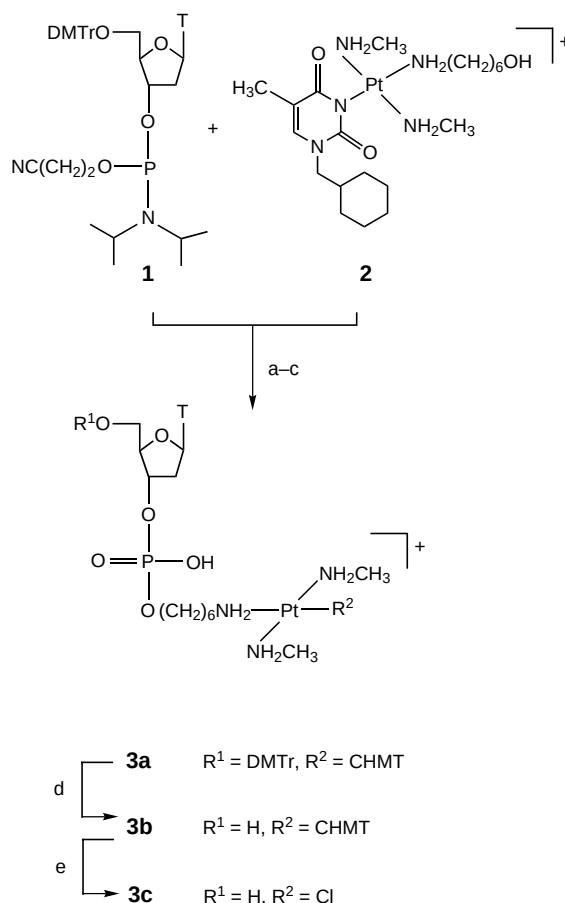
Solid-Phase Synthesis of a Monofunctional *trans*-a₂Pt^{II} Complex Tethered to a Single-Stranded Oligonucleotide**

Kathrin S. Schmidt, Dmitri V. Filippov,
Nico J. Meeuwenoord, Gijs A. van der Marel,
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Jan Reedijk*

Single-stranded oligonucleotides bind with high selectivity to complementary sequences within DNA or RNA. This important feature allows regulation of gene expression at the stage of transcription (antigene strategy) or translation (antisense strategy).^[1] Effectuation of this idea in combating cancer and AIDS seems promising.^[2, 3] So far the general applicability of this concept is, however, hampered by the observation that the adducts of oligonucleotides with DNA or RNA do not fully survive the replication and transcription machinery.^[4, 5]

Model studies indicated that cross-linking of an oligonucleotide and its target by a *trans*-a₂Pt^{II} species (a = NH₃ or amine) is a potential solution to this problem.^[6] The implementation of this concept in the antigene and antisense strategy is limited due to the lack of an efficient synthesis of selectively platinated oligonucleotides. For instance, the reaction of an oligonucleotide with a Pt^{II} species does not proceed regioselectively, resulting in tedious and time-consuming purification of the end product. On the other hand, incorporation of preplatinated nucleotide building blocks in an oligonucleotide by solid-phase DNA synthesis appears to be more rewarding in achieving specific and sequence-independent platination.^[7, 8] Unfortunately, the preparation of *trans*-a₂Pt^{II}-modified oligonucleotides by this method is accompanied by the formation of an inactivated species, which excludes cross-linking with target molecules.^[8]

Here we report a novel solid-phase approach to an oligonucleotide-tethered monofunctional *trans*-Pt^{II} complex with cross-linking ability. The newly synthesized *trans*-Pt^{II} building unit **2** (Scheme 1), in which the Pt^{II} center is inter alia coordinated to 1-amino-hexan-6-ol (AHOL) and 1-*N*-cyclohexylmethylthymine (CHMT), was designed to execute essential chemical manipulations en route to the target compound (i.e., **9** in Scheme 2). Thus, the primary hydroxyl group of the AHOL ligand served to tether **2** through a phosphate bond to the 5'-terminus of immobilized DNA.



Scheme 1. a) *o*-NPT; b) I₂/collidine; c) 25% aq. NH₃; d) 80% aq. AcOH; e) DCl (pD 2.2). DMTr = 4,4'-dimethoxytrityl.

Moreover, the presence of the cyclohexylmethyl moiety, instead of a methyl group,^[9] would enhance the solubility of **2** in organic solvents. Apart from this, it was essential to establish whether the Pt^{II} center in **2** would be compatible with the solid-phase synthesis of DNA. The latter prerequisite is of primary importance in effecting exchange of the CHMT ligand by a chloro ligand,^[9] thus giving access to a monofunctionally platinated, single-stranded oligonucleotide in the final stage of the synthesis.

The viability of our strategy was explored first by executing the following solution-phase experiment (Scheme 1): Compound **2** was condensed with 5'-O-DMTr-dT-3'-phosphoramidite (**1**) under the influence of 5-(*ortho*-nitrophenyl)-1-*H*-tetrazole (*o*-NPT) to give, after oxidation of the intermediate phosphite, the corresponding phosphotriester derivative. Removal of the β -cyanoethyl group by treatment with concentrated aqueous ammonia resulted, after purification by reverse-phase HPLC, in the isolation of the homogeneous compound **3a**. The identity of **3a** was firmly established by ¹H, ³¹P, and ¹⁹⁵Pt NMR spectroscopy as well as LC-MS. It was also verified that **3a** survived the forced ammonolysis conditions (6 h at 50 °C) usually applied for the removal of *N*-acyl protecting groups of deoxynucleoside building units, clearly indicating that **2** is fully compatible with the DNA synthesis protocol. Transformation of **3a** into the required chloro derivative **3c** could be realized by the following two-step

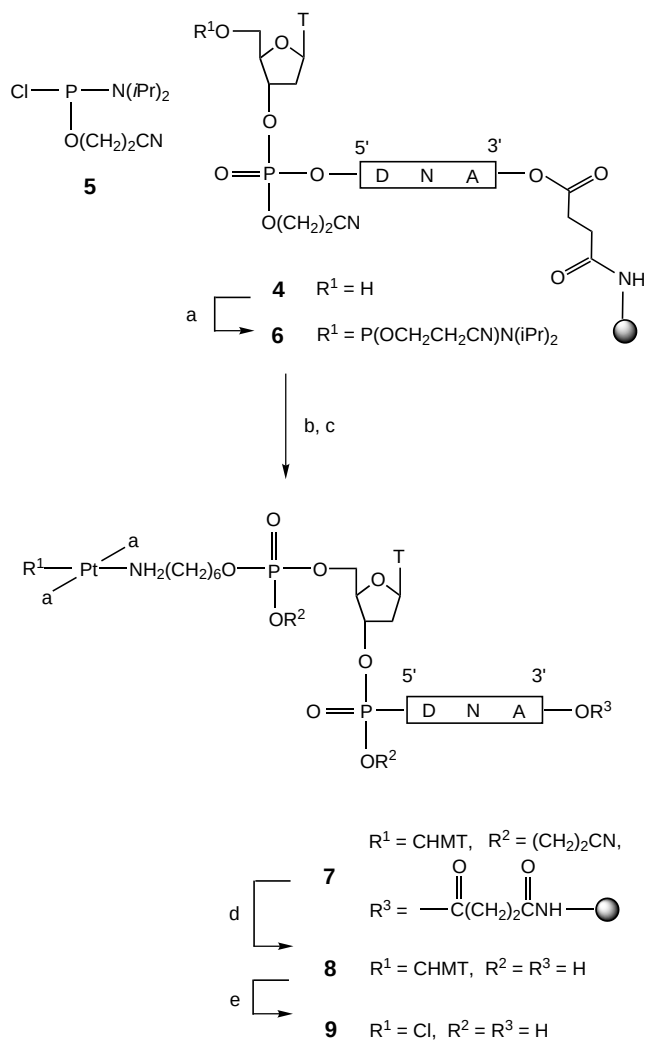
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[**] a = NH₃ or amine. This work was supported by the DAAD (Doktorandenstipendium im Rahmen des gemeinsamen Hochschulsonderprogramms III von Bund und Ländern) and performed in the framework of the BIOMED project BMHA-CT97-2485.

process: Detritylation of **3a** under the influence of aqueous acetic acid gave, after purification, **3b** in a nearly quantitative yield. Exchange^[9] of the CHMT ligand of **3b** with diluted HCl (pD 2.2, 96 h, 40 °C) proceeded smoothly and quantitatively to afford homogeneous **3c**, as evidenced by ¹H NMR and LC-MS.

At this stage, tetrathymidylic acid **4** (Scheme 2) immobilized by a 3'-O-succinyl bond to controlled pore glass (CPG) was phosphitylated^[10] with the bifunctional reagent **5**. The newly formed 5'-amidite **6** was then coupled with **2** under the



Scheme 2. a) Bifunctional reagent **5**, triethylamine; b) **2**, *o*-NPT; c) I₂/collidine; d) 25% aq. NH₃; e) aq. HCl (pH 2.3). DNA = d(TTT), T = thymine.

influence of *o*-NPT to afford, after oxidation (I₂/collidine), immobilized **7**. Subjecting **7** to concentrated aqueous ammonia led to decyanoethylation and concomitant release from the solid support to give **8** in an estimated yield of 34%, as gauged by HPLC in combination with electrospray-ionization mass spectrometry. The structure of **8** was substantiated independently by transformation into the corresponding chloro-coordinated product **9**. Thus, treatment of purified (reverse-phase HPLC) **8** with diluted hydrochloric acid (pH 2.3, 40 °C, 48 h) led to the exclusive formation of the

monofunctional *trans*-Pt^{II} oligonucleotide **9**, as evidenced by LC-MS.

The methodology described here shows for the first time^[11] that a monofunctional *trans*-Pt^{II} complex tethered to a homopyrimidine oligodeoxynucleotide can be constructed by a solid-phase approach, thus opening the way to the future design of a new class of useful chemical nucleic acids probes and antigene reagents. Although the yield of the condensation of **2** with the immobilized DNA fragment **4** (i.e., conversion of **4** into **7** in Scheme 2) is not yet fully optimized, sufficient material can be attained to examine in detail the cross-linking ability of the monofunctional *trans*-Pt^{II} oligonucleotide complex with DNA. Moreover, the possible occurrence of depurination^[12] in the acid-mediated (HCl, pH 2.3) exchange process (i.e., conversion of **8** into **9** in Scheme 2) may be prevented using a slightly more acid-labile temporary ligand. Both aspects are currently under investigation and will be reported in due course.

Experimental Section

2: 1-*N*-Cyclohexylmethylthymine was prepared according to a slightly modified published procedure^[13] and converted into its potassium salt.^[14] *trans*-[(NH₂CH₂)₃PtCl(CHMT)], obtained by a slight modification of a published procedure,^[15] was stirred with 1-amino-hexan-6-ol (1 equiv) in methanol/water (1/1) at 60 °C for 72 h to give crystalline **2** in 60% yield.

3a: To a solution of **2** (13.5 μmol) in dioxane was added amidite **1** (13 μmol) and *o*-NPT (53.5 μmol) in acetonitrile. After 10 min an aqueous solution of I₂/collidine was added. The solvents were removed and the residue dissolved in 1000 μL of methanol containing 200 μL of concentrated aqueous ammonia. After 10 h at 20 °C, the sample was freeze-dried and purified by reverse-phase HPLC (Alltima C18 column, 50 mmol of aqueous ammonium bicarbonate/acetonitrile buffer, gradient: 40 → 70% acetonitrile) to give **3a**. ¹⁹⁵Pt NMR (CD₃OD): δ = -2621; ³¹P NMR (CD₃OD): δ = 0.18; the complete assignment of the nonexchangeable protons was corroborated by a ¹H, ¹H COSY experiment; ESI-MS: *m/z*: 1201.5 [*M*⁺].

Automated DNA synthesis: Immobilized d(TTTT) (0.2 μmol) was synthesized on a Gene Assembler (Pharmacia) following a standard protocol,^[16] phosphitylated,^[10] and allowed to react with **2** (15 μmol, 0.05 M solution in dioxane/acetonitrile (1/1)) in the presence of *o*-NPT (30 μmol, 0.2 M solution in acetonitrile). Decyanoethylation and release from the solid support were effected by treatment of crude **7** with concentrated aqueous ammonia for 12 h at 20 °C.

LC-MS analysis was carried out on a PE Sciex API 165 mass unit connected to a Jasco HPLC system. HPLC analysis was performed using a Merck LiChrosphere 100 RP18 column (pore size 5 μm, diameter 4 mm, length 250 mm) and 10 mM aqueous ammonium acetate/acetonitrile (gradient: 5 → 50% acetonitrile) buffer. Apart from **8** (*m/z*: 1812 [*M*⁺], 906 [*M*²⁺]; *t*_r = 12.50 min), also tetrathymidylic acid (*m/z*: 1155.6 [*M*⁺]; *t*_r = 7.10 min) and its corresponding 5'-amidate (*m/z*: 1318.5 [*M*⁺]; *t*_r = 10.13 min) were present in nearly equal amounts (33% each).

Received: August 9, 1998 [Z13848]

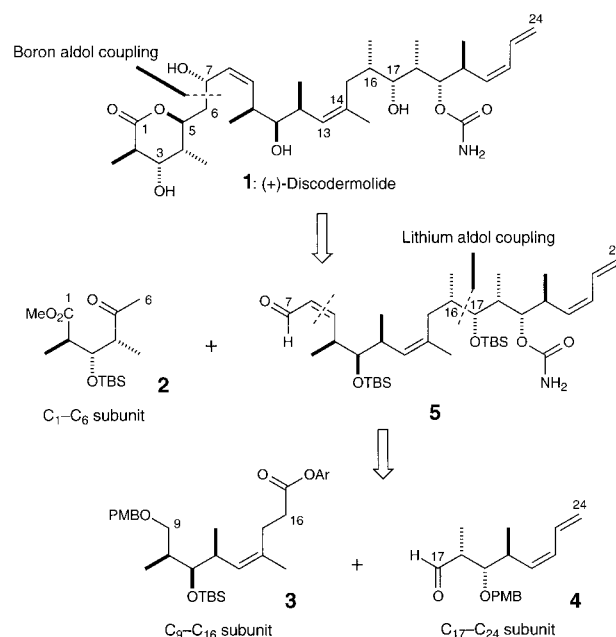
- [1] P. C. Zamecnik, M. L. Stephenson, *Proc. Natl. Acad. Sci. USA* **1978**, 75, 280–284.
- [2] A. de Mesmaeker, R. Häner, P. Martin, H. E. Moser, *Acc. Chem. Res.* **1995**, 28, 366–374, and references therein.
- [3] M. D. Matteucci, R. Wagner, *Nature* **1996**, 384, 20–22, and references therein.
- [4] N. T. Thuong, C. Hélène, *Angew. Chem.* **1993**, 105, 697–723; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 666–690.
- [5] G. E. Plum, D. S. Pilch, S. F. Singleton, K. J. Breslauer, *Annu. Rev. Biophys. Biomol. Struct.* **1995**, 24, 319–350.

- [6] B. Lippert, M. Leng in *Topics in Biological Inorganic Chemistry, Vol. 1 (Metallopharmaceuticals 1)* (Eds.: M. J. Clarke, P. J. Sadler), Springer, Berlin, **1999**, pp. 117–142, and references therein.
- [7] R. Manchanda, S. U. Dunham, S. J. Lippard, *J. Am. Chem. Soc.* **1996**, *118*, 5144–5145.
- [8] J. Schliepe, U. Berghoff, B. Lippert, D. Cech, *Angew. Chem.* **1996**, *108*, 705–707; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 646–648.
- [9] Removal of the 1-*N*-cyclohexylmethylthymine ligand is more efficient than reported for 1-*N*-methylthymine: U. Berghoff, K. Schmidt, M. Janik, G. Schröder, B. Lippert, *Inorg. Chim. Acta* **1998**, *269*, 135–142.
- [10] S. B. Rajur, J. Robles, K. Wiederholt, R. G. Kuimelis, L. W. McLaughlin, *J. Org. Chem.* **1997**, *62*, 523–529.
- [11] Recently the synthesis of a thymine-tethered Pt^{IV} complex has been reported: S. Ren, L. Cai, B. M. Segal, *J. Chem. Soc. Dalton Trans.* **1999**, 1413–1422. The authors present, however, no evidence sustaining the compatibility of this complex with automated DNA synthesis.
- [12] J. A. Zoltewicz, D. F. Clark, T. W. Sharpless, G. Grahe, *J. Am. Chem. Soc.* **1970**, *92*, 1741–1750.
- [13] D. T. Browne, J. Eisinger, N. J. Leonard, *J. Am. Chem. Soc.* **1968**, *90*, 7302–7323.
- [14] C. J. L. Lock, P. Pilon, B. Lippert, *Acta Crystallogr. Sect. B* **1979**, *35*, 2533–2537.
- [15] O. Krizanovic, M. Sabat, R. Beyerle-Pfnür, B. Lippert, *J. Am. Chem. Soc.* **1993**, *115*, 5538–5548.
- [16] M. J. Gait in *An Introduction to Modern Methods of DNA Synthesis* (Ed.: M. J. Gait), IRL, Oxford, **1984**, pp. 1–22.

Total Synthesis of the Antimicrotubule Agent (+)-Discodermolide Using Boron-Mediated Aldol Reactions of Chiral Ketones**

Ian Paterson,* Gordon J. Florence, Kai Gerlach, and Jeremy P. Scott

Discodermolide (**1**) is a unique polyketide isolated in 1990 by Gunasekera et al. at the Harbor Branch Oceanographic Institute, Florida, from the Caribbean sponge *Discodermia dissoluta*.^[1] Structurally (Scheme 1), it bears 13 stereogenic centers, a tetrasubstituted δ -lactone (C₁–C₅), one di- and one tri-substituted *Z*-alkene, a carbamate moiety, and a terminal *Z*-diene. Discodermolide displays potent activity as an anti-mitotic agent, with a similar mechanism of action to taxol (paclitaxel), namely by stabilizing microtubules and promoting the polymerization of tubulin.^[2] It inhibits the growth of human breast cancer cells in vitro, as well as paclitaxel-resistant ovarian and colon cancer cells, and other multidrug



Scheme 1. Retrosynthetic analysis. Ar = 2,6-dimethylphenyl.

resistant cells.^[3] Hence, discodermolide is a particularly promising candidate for development in cancer chemotherapy, but its use is severely limited by its scarce supply (0.002 % w/w isolation yield)^[1] from the rare sponge source.

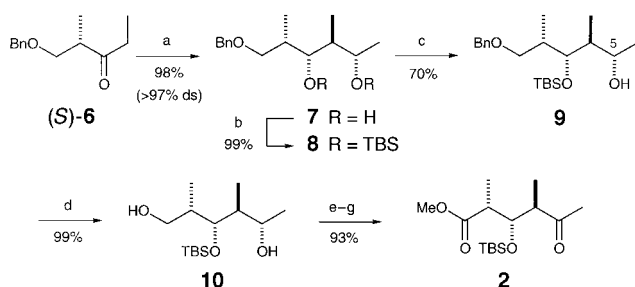
To date, two total syntheses of the natural (+)-discodermolide and three syntheses of the antipodal (–)-discodermolide have been reported,^[4] together with various synthetic approaches.^[5] Schreiber and co-workers^[4a] have synthesized both antipodes and established the absolute configuration, as well as preparing a number of structural analogues.^[4b] Despite these impressive efforts, there is still a pressing demand for developing a more practical and efficient synthetic route to (+)-discodermolide.

Herein, we describe a highly convergent total synthesis, which has the potential to provide useful quantities of (+)-discodermolide. Notably, our route is entirely different from earlier syntheses and is based on a novel aldol-coupling strategy, which also employs aldol reactions of chiral ketones to construct the three key subunits **2**, **3**, and **4** (Scheme 1). Our retrosynthetic analysis is based on a C₆–C₇ disconnection which leads back to the (C₁–C₆) methyl ketone **2** and the enal **5**. Further disassembly of **5** gives the (C₉–C₁₆) ester **3** and the (C₁₇–C₂₄) aldehyde **4**.

As shown in Scheme 2 the synthesis of the C₁–C₆ subunit **2** began with a boron-mediated *anti*-selective aldol reaction between the readily available^[6] ethyl ketone (*S*)-**6** and acetaldehyde. The intermediate aldolate was reduced in situ with LiBH₄ to give diol **7** (98 %, >97 % diastereoselectivity (ds)).^[6a] Protection as the bis-*tert*-butyldimethylsilyl (TBS) ether **8**, followed by methanolysis using catalytic CSA in MeOH/CH₂Cl₂ at 0 °C, gave C₅-alcohol **9** in 70 % yield, together with starting material and diol **7**, which were recycled accordingly. After debenzoylation, diol **10** was converted into subunit **2** by sequential double Swern oxidation, NaClO₂ oxidation, and esterification. This three-step operation was carried out without chromatography in 93 % yield. The

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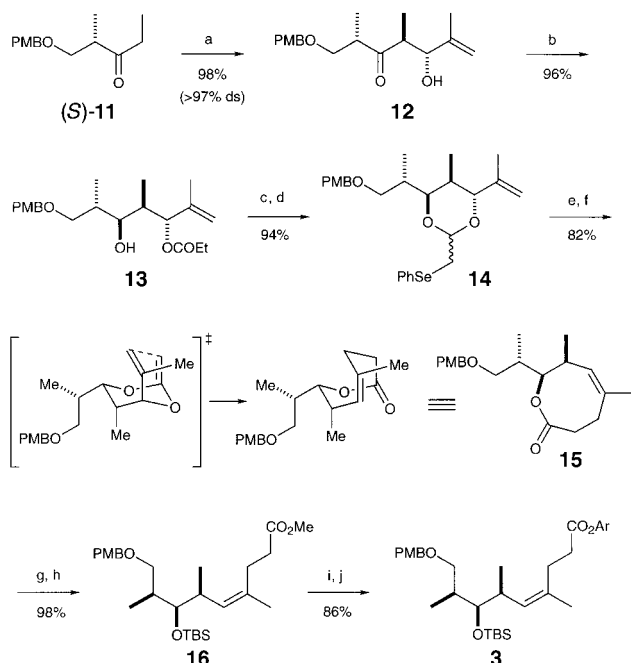
[**] We thank the EPSRC (Grants GR/M46686 and L41646, and studentships for G.J.F. and J.P.S.), the DFG (postdoctoral fellowship for K.G.), Merck, and Novartis for support, and Dr. S. P. Gunasekera (Harbor Branch Oceanographic Institute) for kindly providing a sample of natural (+)-discodermolide. We also thank Prof. A. B. Holmes (Cambridge) for helpful discussions regarding the Claisen rearrangement chemistry and Dr. P. A. Wallace for contributions to early studies.



Scheme 2. Synthesis of the C₁-C₆ subunit (**2**). a) 1) (cHex)₂BCl, Et₃N, Et₂O, 0 °C, 3 h; MeCHO, -78 → -27 °C, 16 h; 2) LiBH₄, -78 °C, 3 h; 3) H₂O₂(30% aq)/MeOH, NaOH(10% aq), 0 °C, 2 h; b) TBSOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 2 h; c) CSA, MeOH/CH₂Cl₂, 0 °C, 8 h; d) 20% Pd(OH)₂/C, H₂, EtOH, 20 °C, 20 h; e) 1) (COCl)₂, DMSO, CH₂Cl₂, -78 °C, 1.5 h; 2) Et₃N, -78 → -20 °C, 20 min; f) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*BuOH, H₂O, 20 °C, 2 h; g) CH₃N₂, Et₂O, 20 °C, 5 min. Bn = benzyl, cHex = cyclohexyl, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, CSA = camphorsulfonic acid.

synthesis can be conveniently performed on a multigram scale with the overall yield of **2** being 62% over the seven steps.

It was of special interest to have a solution in hand to establish the *Z*-configuration of the C₁₃-C₁₄ trisubstituted alkene in discodermolide with complete selectivity (Scheme 3). Commonly used methods such as Wittig olefinations give varying degrees of selectivity. On the basis of the work of Holmes et al., a Claisen-type ring expansion was used advantageously to achieve this alkene substitution pattern

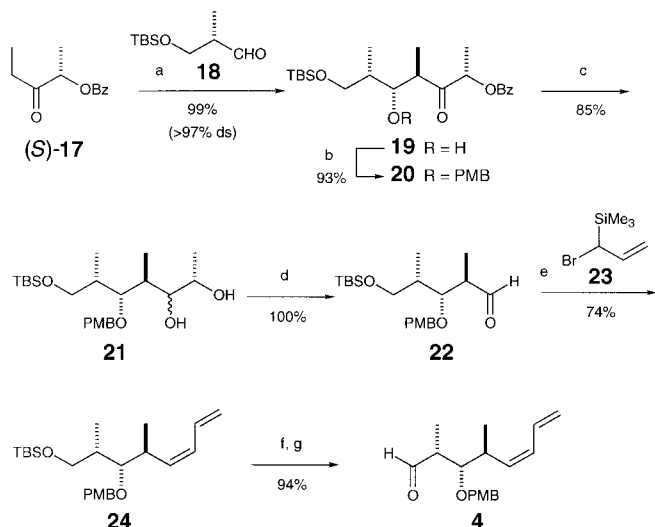


Scheme 3. Synthesis of the C₉-C₁₆ subunit (**3**). a) 1) (cHex)₂BCl, Et₃N, Et₂O, 3 h; CH₂=C(Me)CHO, -78 → -27 °C, 16 h; 2) H₂O₂(30% aq)/MeOH, pH7 buffer, 0 °C, 2 h; b) SmI₂, EtCHO, THF, -10 °C, 2.5 h; c) K₂CO₃, MeOH, 20 °C, 3 h; d) PhSeCH₂CH(OEt)₂, toluene, cat. PPTS, reflux, 4.5 h; e) NaIO₄, NaHCO₃, MeOH/H₂O, 20 °C, 2 h; f) DBU, CH₂=C(OMe)OTBS, xylenes, reflux, 6 h; g) NaOMe, MeOH, 0 °C, 1 h; h) TBSOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 1.5 h; i) KOH(1M aq), MeOH, reflux, 1 h; j) 2,6-dimethylphenol, DCC, 4-DMAP, CH₂Cl₂, 20 °C, 16 h. PPTS = pyridinium *para*-toluenesulfonate, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DCC = *N,N'*-dicyclohexylcarbodiimide, 4-DMAP = 4-*N,N*-dimethylaminopyridine.

and simultaneously introduce a carbonyl group attached to C₁₆, to enable a later aldol coupling.^[7] The synthesis of the aryl ester **3** started from the ethyl ketone (*S*)-**11** (that is, the *para*-methoxybenzyl (PMB) equivalent of (*S*)-**6**; available in 3 steps and 80% yield from methyl (*S*)-3-hydroxy-2-methylpropionate).^[8] Using our standard conditions,^[6b,c] the boron-mediated *anti*-selective aldol reaction between (*S*)-**11** and methacrolein gave adduct **12** in high diastereoselectivity (>97% ds) and 99% yield.

An Evans–Tishchenko reduction with SmI₂ and propionaldehyde formed exclusively the corresponding 1,3-*anti*-diol (96%) protected as the mono-propionate **13**.^[9] Saponification with K₂CO₃ in MeOH, followed by transacetalization with phenylselenyl acetaldehyde diethyl acetal,^[10] provided a mixture of diastereomeric acetals **14** in 94% yield, which were oxidized with NaIO₄ and submitted directly to the rearrangement conditions. Elimination of the selenoxide took place in refluxing xylenes (0.01M) in the presence of DBU giving an intermediate ketene acetal, which underwent Claisen rearrangement smoothly to give the lactone **15** in 82% yield together with 10% of the recyclable seleno acetals **14**. The exclusive formation of the *Z*-alkene can be attributed to the preferred chairlike transition state shown in Scheme 3. Next, the 8-membered lactone **15** was converted in a four-step sequence (85% overall) by methanolysis and TBS protection of the resultant hydroxy ester into **16**, followed by saponification and esterification with 2,6-dimethylphenol by using Steglich's protocol,^[11] to give the required subunit **3** (61% overall yield for 9 steps on a multigram scale).

The preparation of the remaining C₁₇-C₂₄ subunit **4** is shown in Scheme 4. The boron-mediated aldol reaction between the lactate-derived ketone (*S*)-**17** and aldehyde **18** gave the corresponding adduct **19** in excellent yield and with *anti* selectivity (99%, >97% ds).^[12] Protection as the PMB ether



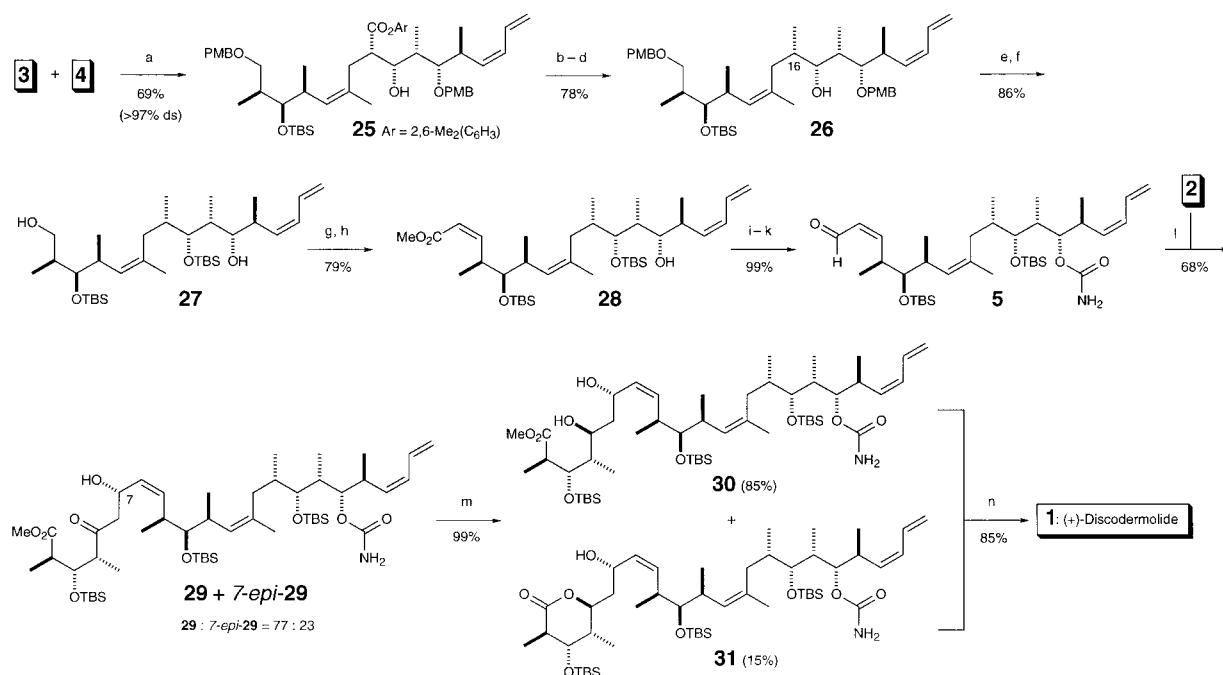
Scheme 4. Synthesis of the C₁₇-C₂₄ subunit (**4**). a) 1) (cHex)₂BCl, Et₃N, Et₂O, 3 h; **18**, -78 → -27 °C, 16 h; 2) H₂O₂(30% aq)/MeOH, 0 °C, 1 h; b) PMBTCA, cat. TfOH, THF, 20 °C, 9 h; c) LiAlH₄, THF -78 → -27 °C, 3 h; d) NaIO₄, MeOH, 20 °C, 30 min; e) 1) CrCl₃, THF, 20 °C, 16 h; 2) KH, THF, 0 °C, 1.5 h; f) CSA (0.2 equiv), MeOH/CH₂Cl₂, 20 °C, 5 h; g) DMP, CH₂Cl₂, 20 °C, 15 min. Bz = benzoyl, PMBTCA = *para*-methoxybenzyl trichloroacetimidate, TfOH = trifluoromethanesulfonic acid, DMP = Dess–Martin periodinane.

under acidic conditions gave **20**, which was reduced with LiAlH_4 to provide diols **21**. NaIO_4 -mediated oxidative cleavage gave the aldehyde **22** in preparation for the introduction of the *Z*-diene moiety. This sequence was achieved in a two-step procedure, following our previously established protocol by using a Nozaki–Hiyama reaction.^[5] Addition of the aldehyde **22** and allylic bromide **23** to a suspension of CrCl_2 in THF produced an intermediate β -hydroxy silane, which on treatment with KH underwent a Peterson-type *syn* elimination to generate the required *Z*-diene **24** in 74 % yield (*Z/E* > 98:2). Deprotection with CSA in $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (94 %), followed by Dess–Martin oxidation, gave aldehyde **4**. The overall yield of **4** is 54 % for 8 steps carried out on a multigram scale.

Now, having all three major subunits in hand, we turned to coupling these together while at the same time installing the three stereogenic centers at C_7 , C_{16} , and C_{17} (Scheme 5). The Heathcock-type ester **3** was enolized with LiTMP at -100°C to give exclusively the *E*-enolate.^[13] The subsequent *anti*-selective aldol reaction with the C_{17} – C_{24} aldehyde **4** gave the Felkin–Anh adduct **25** in 69 % yield and high diastereoselectivity (> 97 % ds). A three-step sequence of reduction with LiAlH_4 , selective sulfonation in the presence of the secondary C_{19} -alcohol, followed by an additional LiAlH_4 reduction, gave the deoxygenated product **26** with the C_{16} -methyl group in place (78 % yield; all reactions gave 95–100 % yield based on recovered starting materials). Protection of the remaining alcohol with a TBS group and a double deprotection with DDQ provided the diol **27** (86 % yield). Selective oxidation of

the primary alcohol in the presence of the secondary C_{19} -alcohol was achieved using TEMPO in CH_2Cl_2 at 20°C .^[14] The crude aldehyde obtained was converted directly into the *Z*-enoate **28** by using the Still modification of the Horner–Wadsworth–Emmons procedure (79 % yield for two steps).^[15] At this stage, the carbamate moiety was installed following a modification of the Kocovsky protocol.^[4e, 16] A chemoselective reduction using DIBAL–H at -78°C and subsequent Dess–Martin oxidation produced the enal **5**.

The final coupling step between methyl ketone **2** and aldehyde **5** required the correct introduction of the C_7 -stereocenter. Model studies had revealed that boron-mediated aldol reactions with **2** and γ -chiral *Z*-enals, related structurally to **5**, gave unexpectedly high levels of 1,4-stereoselection from the aldehyde component in the *undesired* sense.^[17] Gratifyingly, the inherent facial bias of the *Z*-enal **5** was overturned by carrying out this boron aldol coupling under reagent control using (+)- Ipc_2BCl to give 77 % diastereoselectivity in favor of the desired (*7S*)-adduct **29** (52 %).^[18] Notably, this is the first case in which this reagent system has been used successfully in a triple asymmetric induction situation to achieve the desired stereocontrol in a mismatched aldol coupling.^[19] A hydroxyl-directed reduction^[20] of **29** with $\text{Me}_4\text{NBH}(\text{OAc})_3$ provided the 1,3-*anti*-diol **30** together with pre-lactonized **31** in quantitative combined yield. Finally, global deprotection and concomitant lactonization was achieved in one pot by reaction of **30** and **31** with $\text{HF}\cdot\text{py}$ in THF to provide (+)-discodermolide (**1**) in 85 % yield. The spectroscopic data of the synthetic material were in



Scheme 5. Subunit coupling and total synthesis of (+)-discodermolide (**1**). a) **3**, LiTMP , LiBr , THF, -100°C ; **4**, 7 min; b) LiAlH_4 , THF, -30°C , 3 h; c) 2,4,6- $\text{Me}_3(\text{C}_6\text{H}_2)\text{SO}_2\text{Cl}$, Et_3N , CH_2Cl_2 , 20°C , 24 h; d) LiAlH_4 , THF, -10°C , 3 h; e) TBSOTf , Et_3N , CH_2Cl_2 , 20°C , 24 h; f) DDQ, $\text{CH}_2\text{Cl}_2/\text{pH 7 buffer}$, 20°C , 16 h; g) cat. TEMPO, BAIB, CH_2Cl_2 , 20°C , 4 h; h) $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, [18]c-6, K_2CO_3 , PhMe, $-20 \rightarrow 0^\circ\text{C}$, 2 h; i) 1) $\text{Cl}_3\text{CC}(\text{O})\text{NCO}$, CH_2Cl_2 , 20°C , 1 h; 2) K_2CO_3 , MeOH, 20°C , 1 h; j) DIBAL–H, CH_2Cl_2 , -78°C , 1.5 h; k) DMP, CH_2Cl_2 , 20°C , 1 h; l) 1) **2**, (+)- Ipc_2BCl , Et_3N , Et_2O , 1.5 h; **5**, $-78 \rightarrow -27^\circ\text{C}$, 16 h; 2) H_2O_2 (30% aq)/MeOH, pH 7 buffer, 0°C , 1 h; m) $\text{Me}_4\text{NBH}(\text{OAc})_3$, MeCN/AcOH, $-25 \rightarrow 20^\circ\text{C}$, 16 h; n) $\text{HF}\cdot\text{py}$, THF, 20°C , 16 h. LiTMP = lithium 2,2,6,6-tetramethylpiperidide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TEMPO = 2,2,6,6-tetramethyl-1-piperidinoxyl, BAIB = [bis(acetoxy)iodo]benzene, [18]c-6 = [18]crown-6, KHMDS = potassium bis(trimethylsilyl)amide, DIBAL–H = diisobutylaluminum hydride, *Ipc* = isopinocampheyl, py = pyridine.

excellent agreement to those of a natural sample (^1H and ^{13}C NMR, IR, TLC, $[\alpha]_{\text{D}}^{20} = +13.0$ ($c = 1.09$, MeOH).

In conclusion, this total synthesis of (+)-discodermolide proceeds in 27 steps and 7.7% overall yield for the longest linear sequence starting from commercial methyl (S)-3-hydroxy-2-methylpropionate. The three key subunits were synthesized efficiently using boron-mediated *anti*-selective aldol reactions of chiral ketones (S)-6, (S)-11, and (S)-17. This synthesis has the potential to provide useful quantities of (+)-discodermolide, which will allow detailed biological evaluation, as well as offering a variety of options for analogue chemistry.

Received: September 13, 1999 [Z14006]

- [1] S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, *J. Org. Chem.* **1990**, *55*, 4912 (Corrigendum: *J. Org. Chem.* **1991**, *56*, 1346).
- [2] a) E. ter Haar, R. J. Kowalski, E. Hamel, C. M. Lin, R. E. Longley, S. P. Gunasekera, H. S. Rosenkranz, B. W. Day, *Biochemistry* **1996**, *35*, 243; b) S. L. Schreiber, J. Chen, D. T. Hung, *Chem. Biol.* **1996**, *3*, 287.
- [3] a) R. J. Kowalski, P. Giannakakou, S. P. Gunasekera, R. E. Longley, B. W. Day, E. Hamel, *Mol. Pharmacol.* **1997**, *52*, 613; b) R. Balachandran, E. ter Haar, M. J. Welsh, S. G. Grant, B. W. Day, *Anti-Cancer Drugs* **1998**, *9*, 67.
- [4] a) J. B. Nerenberg, D. T. Hung, P. K. Somers, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 12621; b) D. T. Hung, J. B. Nerenberg, S. L. Schreiber, *J. Am. Chem. Soc.* **1996**, *118*, 11054; c) A. B. Smith, III, Y. Qui, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **1995**, *117*, 12011; d) S. S. Harried, G. Yang, M. A. Strawn, D. C. Myles, *J. Org. Chem.* **1997**, *62*, 6098; e) J. A. Marshall, B. A. Johns, *J. Org. Chem.* **1998**, *63*, 7885.
- [5] a) D. L. Clark, C. H. Heathcock, *J. Org. Chem.* **1993**, *58*, 5878; b) I. Paterson, S. P. Wren, *J. Chem. Soc. Chem. Commun.* **1993**, 1790; c) J. M. C. Golec, S. D. Jones, *Tetrahedron Lett.* **1993**, *34*, 8159; d) P. L. Evans, J. M. C. Golec, R. J. Gillespie, *Tetrahedron Lett.* **1993**, *34*, 8163; e) J. M. C. Golec, R. J. Gillespie, *Tetrahedron Lett.* **1993**, *34*, 8167; f) I. Paterson, A. Schlapbach, *Synlett* **1995**, 498; g) M. Miyazawa, S. Oonuma, K. Maruyama, M. Miyashita, *Chem. Lett.* **1997**, 1191; h) M. Miyazawa, S. Oonuma, K. Maruyama, M. Miyashita, *Chem. Lett.* **1997**, 1193; i) J. A. Marshall, Z.-H. Lu, B. A. Johns, *J. Org. Chem.* **1998**, *63*, 817; j) D. A. Evans, D. P. Halstead, B. D. Allison, *Tetrahedron Lett.* **1999**, *40*, 4461; k) S. A. Filla, J. J. Song, L. Chen, S. Masamune, *Tetrahedron Lett.* **1999**, *40*, 5449; l) A. M. Misske, H. M. R. Hoffmann, *Tetrahedron* **1999**, *55*, 4315.
- [6] a) I. Paterson, M. V. Perkins, *Tetrahedron Lett.* **1992**, *33*, 801; b) I. Paterson, J. M. Goodman, M. Isaka, *Tetrahedron Lett.* **1989**, *30*, 7121; c) I. Paterson, R. D. Norcross, R. A. Ward, P. Romea, M. A. Lister, *J. Am. Chem. Soc.* **1994**, *116*, 11287.
- [7] J. R. Harrison, A. B. Holmes, I. Collins, *Synlett* **1999**, 972.
- [8] I. Paterson, E. A. Arnott, *Tetrahedron Lett.* **1998**, *39*, 7185.
- [9] D. A. Evans, A. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447.
- [10] a) M. Petrzilka, *Helv. Chim. Acta* **1978**, *61*, 3075; b) J. W. Burton, J. S. Clark, S. Derrer, T. C. Stork, J. G. Bendall, A. B. Holmes, *J. Am. Chem. Soc.* **1997**, *119*, 7483.
- [11] a) B. Neises, W. Steglich, *Angew. Chem.* **1978**, *90*, 556; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522; b) G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.
- [12] I. Paterson, D. J. Wallace, C. J. Cowden, *Synthesis* **1998**, 639.
- [13] It was crucial to lower the temperature to -100°C in order to suppress partial decomposition of the lithium enolate. a) S. H. Montgomery, M. C. Pirrung, C. H. Heathcock, *Org. Synth. Coll. Vol.* **1990**, *7*, 190; b) M. C. Pirrung, C. H. Heathcock, *J. Org. Chem.* **1980**, *45*, 1727; c) I. Paterson, *Tetrahedron Lett.* **1983**, *24*, 1311.
- [14] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974.
- [15] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405.
- [16] P. Kocovsky, *Tetrahedron Lett.* **1986**, *27*, 5521.

- [17] I. Paterson, G. J. Florence, unpublished results.
- [18] a) I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, R. D. Norcross, *Tetrahedron* **1990**, *46*, 4663; b) I. Paterson, R. M. Oballa, R. D. Norcross, *Tetrahedron Lett.* **1996**, *37*, 8581.
- [19] For a review of asymmetric aldol reactions using boron enolates, see C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1.
- [20] a) D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560; b) A. K. Saxena, P. Mangiaracina, *Tetrahedron Lett.* **1983**, *24*, 273.

Cofactor-Bound Cross-Linked Enzyme Crystals (CLEC) of Alcohol Dehydrogenase**

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The use of dehydrogenases in organic synthesis is often limited by the intrinsic instability of enzymes and their nicotinamide cofactors.^[1] The protein part of the molecule can be efficiently stabilized by several techniques such as directed evolution,^[2] immobilization,^[3] and protein crystallization and cross-linking.^[4] The latter approach has turned out to be especially efficient in producing robust and productive biocatalysts for chemical synthesis.^[5] Here, we expand this approach to the stabilization of the cofactor part of the dehydrogenase molecule. Horse liver alcohol dehydrogenase (HLADH) was crystallized in the presence of reduced nicotinamide adenine dinucleotide (NADH), and the resulting crystals were treated with glutaraldehyde to yield the cross-linked enzyme crystals (CLECs). The crystallized and cross-linked HLADH was first introduced by Lee et al., and it demonstrated good activity (26% of that in solution) and an increased stability of the cross-linked crystals in the presence of zinc salts.^[6] In this work, we use this system to address two main questions: 1) Is a cofactor more stable when bound inside the enzyme crystal? 2) Is it possible to regenerate a cofactor using a coupled substrate system, thus making HLADH-NADH-CLEC a useful catalyst for organic synthesis?

The activity of soluble enzyme and various HLADH-CLEC preparations was compared in the reduction of 6-methyl-5-hepten-2-one (**1**) in the presence of isopropanol for cofactor regeneration (Scheme 1). The results, presented in Table 1, afford several conclusions. The HLADH-NADH-CLECs exhibit higher activity when HLADH is cocrystallized with a cofactor and an inhibitor, DMSO. In this case, the resulting complex exhibited 64% of the activity of the soluble enzyme in the absence of an exogenous cofactor. DMSO seems to be

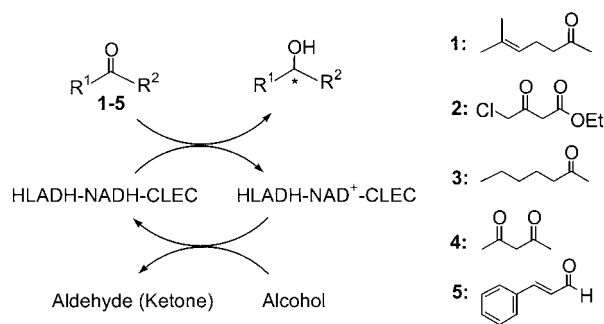
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[**] This work was funded by the NIH (grant 5R44GM51781).

Table 1. Activity of soluble HLADH and various HLADH-NADH-CLEC in the reduction of 6-methyl-5-heptene-2-one (**1**) with and without addition of an exogenous cofactor.

Enzyme	with added NADH		without added NADH	
	[$\mu\text{mol min}^{-1}\text{mg}$]	[%]	[$\mu\text{mol min}^{-1}\text{mg}$]	[%]
soluble HLADH	14.0	100	0	0
HLADH-NAD(H)-CLEC-I ^[b]	12.9	92	8.9	64
HLADH-NAD(H)-CLEC-II ^[c]	9.6	69	2.5	18
HLADH-CLEC ^[d]	2.1	15	0	0

[a] The activity was based on a 2-h reaction time. [b] Prepared in the presence of both NADH and DMSO. [c] Prepared in the presence of NADH only. [d] Prepared in the absence of both NADH and DMSO.



Scheme 1. Reductions catalyzed by HLADH-NADH-CLEC.

necessary in maintaining the optimal HLADH conformation in the crystal.^[6, 7]

As expected, HLADH-CLEC, which was prepared in the absence of a cofactor, had no catalytic activity in the reaction without added NADH. The addition of exogenous NADH increased the activity of both HLADH-NADH-CLEC and HLADH-CLEC. This effect was especially profound for CLECs crystallized in the presence of NADH, or NADH and DMSO, reaching 69 and 92 % of the activity of the soluble enzyme, respectively.

HLADH-NADH-CLEC-I (Table 1) was then applied to the reduction of several additional ketones **1–4** (Scheme 1). The degree of conversion in these reactions depends on the substrate structure, while the enantioselectivity and stereochemical preference of the soluble HLADH remains unchanged (Table 2).

The ability of the CLECs to maintain the bound cofactor was assayed by incubating the HLADH-NADH-CLEC at a concentration of 30 mg mL⁻¹ (dry weight) in 50 mM 2-[[tris-(hydroxymethyl)methyl]amino]1-ethanesulfonic acid (TES) buffer (pH 7.5) containing 10 % ethanol, at 40 °C for 48 hours in a stirred cell. Following incubation, the CLECs were removed from the solution by filtration and the supernatant

Table 2. Reduction of ketones **1–4** catalyzed by HLADH-NADH-CLEC-I.

Ketones	Conversion [%] ^[a] ee [%]	Stereochemistry of the product	Ref.
1	25.5	96	<i>S</i> [5d]
2	55.8 ^[b]	98	<i>R</i> [7]
3	26.7	98	<i>S</i> [8]
4	5.8 ^[c]	> 98	<i>S</i>

[a] Conversion based on 20 hour reaction. [b] The product was exclusively ethyl 3-hydroxy-4-chlorobutyrate. [c] The product was exclusively 4-hydroxy-2-pentanone.

was assayed spectrophotometrically at 280 nm for protein and at 340 nm ($\epsilon = 6230 \text{ M}^{-1}\text{cm}^{-1}$) for NADH. Only background absorbance was detected indicating that neither protein nor cofactor leach from the CLEC.

The data on both activity and leaching are consistent with structural studies which indicated that in the presence of cofactor, HLADH undergoes a large conformational change from an open form to a closed form.^[7] The catalytic and coenzyme binding domains in each subunit rotate against each other, enclosing the cofactor and thereby preventing its dissociation from the holoenzyme after the crystals are cross-linked. The very low activity of HLADH-CLEC, even in the presence of the exogenous cofactor (Table 1), can be explained by the markedly different conformation of apo- and holoenzymes and the difficulty the cofactor has accessing the binding center of the apoenzyme in the CLEC form. The fact that the addition of exogenous NADH increases activity in all cases indicates that some cofactor binding sites in the crystalline HLADH remain vacant. In addition, it is known that about 4 % of the enzyme surface is covered by the bound cofactor.^[10] It is also possible that a portion of surface-bound NADH was lost during the processing of the crystals. It is worth mentioning that NADH transport in and out of the crystal may proceed differently in different dehydrogenases. For instance, lactate dehydrogenase crystallized in the absence of a cofactor exhibited 30 % of the activity of the soluble enzyme in the presence of the exogenous NADH.^[11]

To understand whether the cofactor is protected from inactivation within a protein crystal, the oxidized form of nicotinamide adenine dinucleotide (NAD⁺) and NADH were incubated in different aqueous buffers (pH 6–8 at 30 °C; Figure 1), and the integrity of the cofactor was measured enzymatically by addition of fresh HLADH and a substrate (see the Experimental Section). Under these conditions the half-life ($t_{1/2}$) of the cofactors ranges from 2.6 d for NADH in phosphate buffer at pH 6 to 10.7 d in TES/2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES) buffer at pH 6 for NAD⁺.

Next, we determined the stability of HLADH under the same conditions (Figure 2). The half-life of the soluble HLADH turned out to be close to 14 d regardless of the buffer used. The residual activity of HLADH was assayed in the presence of freshly added NADH and thus the data reflect the stability of the HLADH, not the cofactor. In contrast to the soluble enzyme and cofactor, the HLADH-NADH-CLEC complex retained its full activity after three months of incubation at 30 °C (Figure 2), indicating that not only the

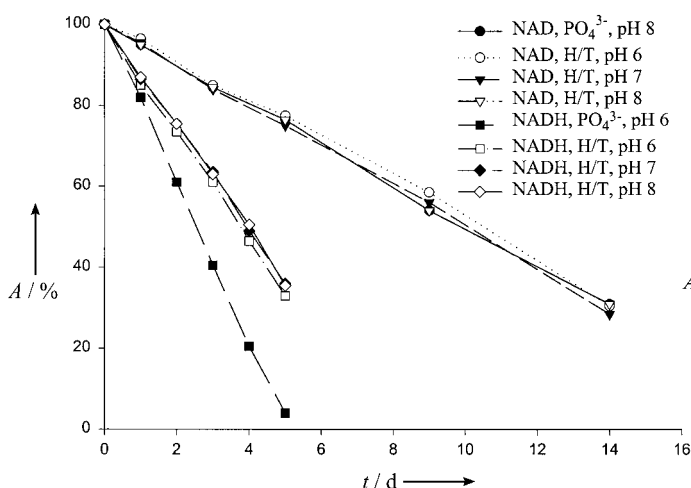


Figure 1. Stability of NAD⁺ and NADH in phosphate buffer and HEPES/TES (H/T) buffer at 30°C. (For details, see the Experimental Section.)

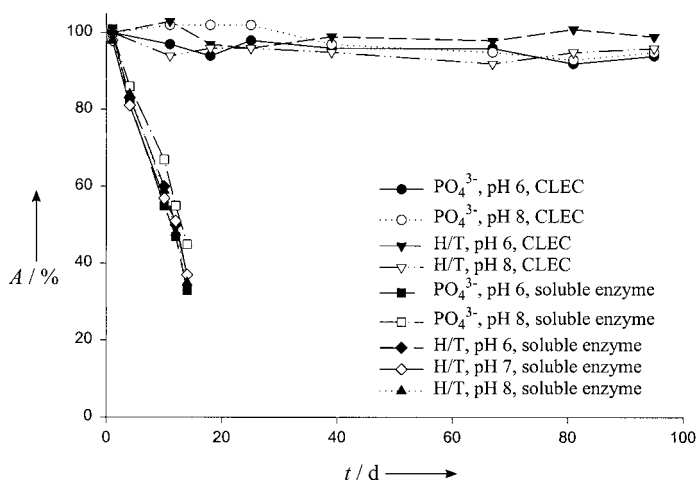


Figure 2. Stability of soluble HLADH and HLADH-NADH-CLEC in buffer at 30°C. (For details, see the Experimental Section.)

enzyme, but also the cofactor was protected by the crystal environment.

Similar to many hydrolases, HLADH in a CLEC form exhibits high stability towards organic solvents and elevated temperature (Figure 3). Soluble enzyme was rapidly inactivated at 40°C in the presence of 25% 2-propanol ($t_{1/2} = 4$ h). At lower temperature (25°C) the half-life of soluble enzyme was extended to 24 h. In contrast, HLADH-NADH-CLEC-I was stable for 96 h in 25% isopropanol at 25°C, maintaining almost full activity for 48 h, and had a half-life of more than 4 d at 40°C.

The stability of HLADH-NAD(H)-CLEC toward organic solvents is important because high concentrations of isopropanol, as well as ethanol or 1,4-butanediol, can be used for cofactor regeneration in a coupled substrate system (Scheme 1).^[12] We found that HLADH-NADH-CLEC-I retained full activity for 2 d in 90% isopropanol at 25°C. Therefore, high concentrations of alcohols can be used for the regeneration of cofactor in a reaction catalyzed by HLADH-NADH-CLEC-I. In contrast, soluble HLADH precipitated and lost activity immediately under the same conditions.

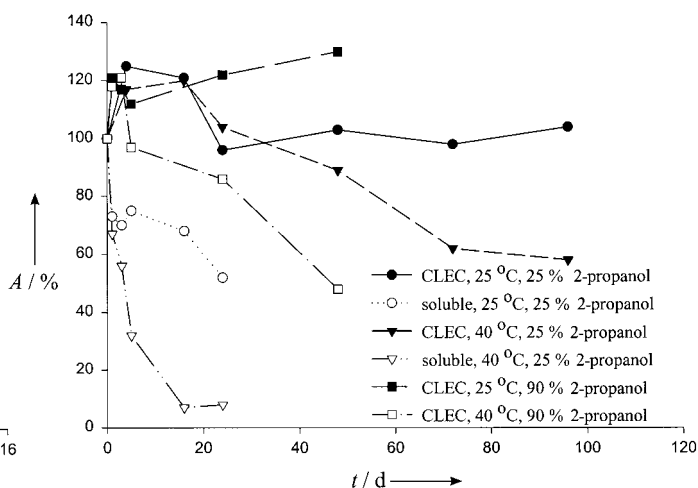


Figure 3. Stability of soluble HLADH and HLADH-NADH-CLEC-I at 25°C and 40°C in 25% and 90% isopropanol. (For details, see the Experimental Section.)

The ability of the bound cofactor to be recycled inside HLADH-NADH-CLEC was demonstrated in the reduction of cinnamaldehyde (**5**) using 1,4-butanediol to regenerate the cofactor (Scheme 1). A 10 mm × 10 cm column (Pharmacia C) was packed with 50 mg (dry weight) of HLADH-NADH-CLEC-I, and a total amount of 15 mmol of cinnamaldehyde (**5**) was reduced to cinnamyl alcohol. The catalyst had retained nearly full activity when the experiment was terminated. To calculate the cofactor total turnover number (TTN) we assumed that the total protein as measured by dry weight was active enzyme (water content and active-site inactivation were assumed to be negligible). This assumption suggested there was 1.2 μmol of NADH bound to 50 mg of HLADH-NADH-CLEC (given two active sites per enzyme molecule and a holoenzyme molecular weight of 80000). Under these conditions the CLEC yielded a turnover number for cofactor regeneration of greater than 12000. Given the conservative assumptions used in calculating TTN, we were extremely encouraged by the performance of the HLADH-NADH-CLEC since it suggests great potential for a much higher level of catalyst productivity.

Experimental Section

Enzyme crystallization: HLADH was crystallized by a method modified from Lee et al.^[6] Enzyme crystals were recovered by low-speed centrifugation and dissolved in a buffer solution of 0.2 M NaCl/50 mM TES (pH 7.5). Insoluble precipitate was removed by filtration and the soluble enzyme was dialyzed exhaustively against 50 mM TES buffer (pH 7.5). Following equilibration (18 h) the dialysis bags (12000 molecular weight cut off (MWCO) containing 5 mL of enzyme solution (11 mg mL⁻¹) were dialyzed against 50 mM TES buffer (pH 7.5) containing 5% DMSO, 0.5 mg mL⁻¹ NADH, and 8% 2-methyl-2,4-pentanediol (MPD) at 4°C. The MPD concentration was increased by increments of 2% at intervals of 30 min to 1 h until the final MPD concentration was 22%. Crystallization was observed beginning at 16% MPD. Greater than 90% of the enzyme was recovered in crystalline form after 48 h incubation.

Cross-linking of enzyme crystals: HLADH crystals were cross-linked in 1-mL reaction volumes containing 10 mg mL⁻¹ protein crystals, 1.0% glutaraldehyde, 5% DMSO, 0.5 mg mL⁻¹ NADH, and 100 mM TES buffer (pH 7.5). Cross-linking was allowed to proceed for 4 h with stirring. Residual glutaraldehyde and DMSO were removed by exhaustive washing

with TES buffer (pH 7.5) containing 20% ethanol. The HLADH cross-linked crystals were stored in 50 mM TES buffer (pH 7.5).

Stability of NAD⁺ and NADH in buffer: Solutions (20 mM) of NAD⁺ or NADH were incubated at 30 °C in 50 mM TES/HEPES buffer at pH 6, pH 7 and pH 8. Additionally, 20 mM NAD⁺ or NADH was incubated at 30 °C in 25 mM sodium phosphate buffer at pH 6 and pH 8. Incubations were performed in duplicate. Active cofactor was quantified enzymatically. A 100-μL aliquot of 20 mM cofactor solution was removed at intervals and added to 900 μL of TES buffer (50 mM, pH 7.5) at 30 °C containing 10 μmol substrate and 2 mg of HLADH. The substrate for reduced cofactor was cinnamaldehyde and the substrate for oxidized cofactor was cinnamyl alcohol. Moles of product formed were measured by HPLC and assumed to be proportional to moles of active cofactor added to the reaction. (HPLC conditions: 15 cm Rainin C₁₈ microsphere 5 μm 300 Å column; mobile phase: acetonitrile/water = 1/1; flow rate: 0.5 mL min⁻¹; monitoring at 260 nm; retention time = 2.38 (cinnamyl alcohol); 2.97 min (cinnamaldehyde). Standard curves were constructed from known quantities of cofactor. Data is presented as a percentage of the initial cofactor quantity (20 μmol).

Stability of HLADH in buffer: HLADH (2 mg mL⁻¹) was incubated at 30 °C in 50 mM HEPES/TES buffer at pH 6, pH 7, and pH 8 and also in 25 mM phosphate buffer at pH 6 and pH 8. Aliquots (50 μL) were removed at intervals and enzyme activity was measured in a cosubstrate assay of 20 mM cinnamaldehyde, 1.5 M isopropanol, and 100 mM NAD⁺ in 50 mM HEPES/TES buffer at 30 °C. The rate of product formation was measured by HPLC. Data is presented as a percentage of the initial activity.

Stability of HLADH-NADH-CLEC in buffer: HLADH-NADH-CLEC (10 mg mL⁻¹) was incubated at 30 °C in 50 mM HEPES/TES buffer at pH 6 and pH 8 and in 25 mM phosphate buffer at pH 6 and pH 8. Aliquots (50 μL) were removed at intervals and enzyme activity was measured in a cosubstrate assay of 20 mM cinnamaldehyde and 1.5 M isopropanol in 50 mM HEPES/TES buffer at 30 °C. The rate of product formation was measured by HPLC. Data is presented as a percentage of the initial activity.

General procedure for reductions: A suspension of substrate (20 μL) in a mixture of isopropanol (0.2 mL) and phosphate buffer (2 mL, pH 7.0) was incubated with 200 μL of CLEC or soluble HLADH at room temperature with and without adding 0.3 mg of NADH. The conversion was determined by GC analysis. Conditions for GC analysis: Cyclodex B capillary GC 25 m × 0.25 mm column, thickness: 0.25 μm (J & W Scientific, Folsom, CA), flow rate: He, 1 mL min⁻¹; temperature program: initial: 90 °C for 10 min, gradient rate: 2–5 °C min⁻¹, final: 160 °C for 0 min).

HLADH-NADH-CLEC-I catalyzed multi-cycle reaction of cinnamaldehyde: A slurry of CLEC (10 mL, 50 mg dry weight) and 0.5 g of silica gel in a solution containing 100 mM Tris HCl and 0.1 mM ZnCl₂ (pH 9.0) was packed in a 10 mm × 10 cm column (Pharmacia C). A solution of 200 mM 1,4-butanediol and 10 mM cinnamaldehyde in 100 mM Tris HCl and 0.1 mM ZnCl₂ buffer (pH 9.0) was pumped through the column at a flow rate of approximately 15 mL h⁻¹ at ambient temperature. Conversion of aldehyde was measured by HPLC analysis using a 15-cm Rainin C₁₈ microsphere 5 μm 300 Å column (mobile phase: acetonitrile/water = 1/1; flow rate: 0.5 mL min⁻¹; monitoring at 260 nm; retention time: 2.38 min (product); 2.97 min (substrate)). A total substrate volume of 3.22 L passed through the column before the experiment was stopped.

Received: August 17, 1999 [Z13893]

- [1] a) C.-H. Wong, G. M. Whitesides, *J. Am. Chem. Soc.* **1981**, *103*, 4890–4899; b) C.-H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon, **1994**, chap. 3, pp. 131–195.
- [2] C. Schmidt-Dannert, F. H. Arnold, *Trends Biotechnol.* **1999**, *17*, 135–136.
- [3] V. V. Mozhaev, *Trends Biotechnol.* **1993**, *11*, 88–95.
- [4] Recent reviews: a) A. L. Margolin, *Trends Biotechnol.* **1996**, *14*, 223–230; b) T. Zelinski, H. Waldmann, *Angew. Chem.* **1997**, *109*, 746–748; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 722–724; c) J. J. Lalonde, *CHEMTECH* **1997**, *27*, 38–45; d) D. Haring, P. Schreier, *Curr. Opin. Chem. Biol.* **1999**, *3*, 35–38.
- [5] a) N. L. St. Clair, M. A. Navia, *J. Am. Chem. Soc.* **1992**, *114*, 7314–7316; b) J. J. Lalonde, C. P. Govardhan, N. K. Khalaf, O. G. Martinez, K. J. Visuri, A. L. Margolin, *J. Am. Chem. Soc.* **1995**, *117*, 6845–6852;

- c) R. A. Persichetti, N. L. St. Clair, J. P. Griffith, M. A. Navia, A. L. Margolin, *J. Am. Chem. Soc.* **1995**, *117*, 2732–2737; d) Y.-F. Wang, K. Yakovlevsky, B. Zhang, A. L. Margolin, *J. Org. Chem.* **1997**, *62*, 3488–3495; e) L. Z. Vilenchik, J. P. Griffith, N. St. Clair, M. A. Navia, A. L. Margolin, *J. Am. Chem. Soc.* **1998**, *120*, 4290–4294.
- [6] K. M. Lee, M. Blaghen, J.-P. Samama, J.-F. Biellmann, *Bioorg. Chem.* **1986**, *14*, 202.
- [7] a) H. Eklund, C. I. Branden, *J. Biol. Chem.* **1979**, *254*, 3458–3461; b) H. Eklund, J. P. Samama, L. Wallen, C. I. Branden, A. Akeson, T. A. Jones, *J. Mol. Biol.* **1981**, *146*, 561–587; c) H. Eklund, B. V. Plapp, J. P. Samama, C. I. Branden, *J. Biol. Chem.* **1982**, *257*, 14349–14358; d) H. Eklund, J. P. Samama, T. A. Jones, *Biochemistry* **1984**, *23*, 5982–5996.
- [8] C.-H. Wong, D. G. Drueckhammer, H. M. Sweers, *J. Am. Chem. Soc.* **1985**, *107*, 4028.
- [9] E. Keinan, E. K. Jafeli, K. K. Seth, R. Lamed, *J. Am. Chem. Soc.* **1986**, *108*, 162.
- [10] H. Eklund, *Pharmacol. Biochem. Behav.* **1983**, *18*, 73–81.
- [11] S. B. Sobolov, M. D. Leonida, A. Bartoszko-Malik, K. I. Voivodov, F. McKinney, J. Kim, A. J. Fry, *J. Org. Chem.* **1996**, *61*, 2125.
- [12] W. Hummel, M.-R. Kula, *Eur. J. Biochem.* **1989**, *184*, 1–13.

In₈(C₆H₃-2,6-Mes₂)₄ (Mes = C₆H₂-2,4,6-Me₃): A Metal-Rich Main-Group Cluster with a Distorted Cubane Structure**

Barrett E. Eichler, Ned J. Hardman, and Philip P. Power*

The reaction between indium monochloride and the bulky lithium terphenyl (Et₂O)LiC₆H₃-2,6-Trip₂^[1] (Trip = C₆H₂-2,4,6-*i*Pr₃) was recently reported to yield the monomeric compound InC₆H₃-2,6-Trip₂.^[2a] This compound and its thallium analogue^[2b] are unique examples of one-coordinate metal atoms in the solid state. Reactions of InCl or TlCl with less crowded lithium terphenyls are expected to lead to more highly aggregated structures, which may involve interesting metal–metal interactions. This class of compounds is of considerable current interest in Group 13 metal chemistry.^[3] We therefore investigated the reactions of InCl with lithium terphenyls of various sizes.^[4] Initial work focused on the less crowded ligand C₆H₃-2,6-Mes₂^[5] (Mes = C₆H₂-2,4,6-Me₃). Here we report that the reaction of LiC₆H₃-2,6-Mes₂ with InCl leads to the unusual cluster species In₈(C₆H₃-2,6-Mes₂)₄ (**1**) rather than the projected stoichiometric aggregates of formula (InC₆H₃-2,6-Mes₂)_n (*n* ≥ 2).

Compound **1** was synthesized by treating a suspension of InCl in THF with LiC₆H₃-2,6-Mes₂ at about –78 °C. Red crystals of **1** were isolated in approximately 25% yield after recrystallization from hexane. The X-ray crystal structure^[6] of **1** (Figure 1) shows that in the solid state the compound has a

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[**] This work was supported by the National Science Foundation.

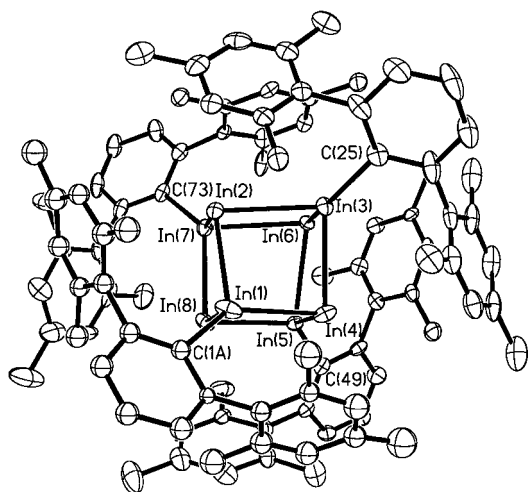


Figure 1. Schematic drawing of **1** (H atoms omitted for clarity). Selected bond lengths [Å] and angles [°]: In(1)–In(2) 2.8754(13), In(1)–In(4) 2.8814(13), In(1)–In(8) 2.9328(13), In(1)–C(1A) 2.216(18); In(2)–In(1)–In(4) 89.02(3), In(2)–In(1)–In(8) 73.59(3), In(4)–In(1)–In(8) 75.57, In(1)–In(2)–In(3) 81.28(3), In(1)–In(2)–In(7) 106.54(4), In(3)–In(2)–In(7) 104.96(3).

distorted cubane arrangement of eight indium atoms. However, only four of the metal atoms carry a terphenyl substituent. The geometrical distortions in the In_8 array result in approximate D_{2d} local symmetry, similar to that of several other cubane compounds.^[7] The structure may be regarded as consisting of two interpenetrating tetrahedra of four $\text{InC}_6\text{H}_3\text{-2,6-Mes}_2$ units and four indium atoms. It seems probable that each $\text{InC}_6\text{H}_3\text{-2,6-Mes}_2$ moiety donates two electrons to In–In bonding in the In_8 unit, whereas each unsubstituted indium atom supplies one electron, and the remaining two valence electrons are accommodated in a nonbonding orbital that is mostly 5s in character. Thus, twelve electrons may be available for cluster bonding in this scheme. Although the formal In–In bond order in the cube is predicted to be 0.5, the average In–In distance is 2.915(26) Å (range 2.857(4)–2.966(4) Å), which is comparable to In–In single-bond lengths in some R_2InInR_2 ^[8] species and is considerably shorter than the In–In distances (3.25, 3.38 Å) in indium metal.^[9] The average In–C distance in **1** of 2.205(12) Å is shorter than those of 2.260(7) and 2.250(5) Å in $\text{InC}_6\text{H}_3\text{-2,6-Trip}_2$ ^[2a] and $[\text{InC}(\text{SiMe}_3)_3]_4$, respectively.^[10]

The shortening of In–C bonds on complexation of InR units with the metal atoms was commented upon previously^[2a] and it may be connected with changes in metal orbital hybridization or metal charge. For example, if in the case of **1**, the $\text{InC}_6\text{H}_3\text{-2,6-Mes}_2$ units behave as electron donors to the indium atoms, ionic character would develop across the In–In bond, that is, $\text{In}^{\delta-}\text{-In}^{\delta+}\text{-C}_6\text{H}_3\text{-2,6-Mes}_2$. This should result in a shortening of the In–C bonds consistent with experimental observations. Interestingly, there are no other close interactions between the metal atoms and the ligands. The closest approaches of the centroids of *ortho*-mesityl rings to the unsubstituted indium atoms In(2), In(4), In(6), and In(8) are in the range 3.631–4.036 Å. These may be compared to the corresponding distances of 2.83 and 2.89 Å in the contact ion pair complex $[\text{In}(\text{mesitylene})_2][\text{InBr}_4]$.^[11] Clearly, the “solva-

tion” of the unsubstituted indium atoms in **1** by the *ortho*-mesityl groups is very weak. This suggests that the stability of **1** depends upon the steric protection afforded to the In_8 core by the $\text{C}_6\text{H}_3\text{-2,6-Mes}_2$ substituents rather than dipolar interactions between the *ortho*-mesityl groups and the indium atoms. This conclusion is also consistent with the proposed ionic character of the In–In bonds, which gives rise to negative charge at the unsubstituted indium atoms and hence reduced likelihood of interactions between the mesityl groups and these centers.

At present few neutral, donor-free, cluster compounds of heavier Group 13 elements are known.^[12] For indium, apart from the tetraorganodimetallic species mentioned above, there are the weakly dimerized complex (In–In 3.631(2) Å) $[\text{In}(\eta^5\text{-C}_5(\text{CH}_2\text{Ph})_5)]_2$,^[13] the tetrameric $[\text{In}\{\text{C}(\text{SiMe}_3)_3\}]_4$ ^[10] (In–In 3.002(1) Å), and the weakly bonded hexamer $[\text{In}(\eta^5\text{-C}_5\text{Me}_5)]_6$ ^[14] (In–In 3.942(1)–3.963(1) Å), all of which have a substituent on each indium atom. In addition, there is the unusual complex $\text{In}(\text{InTrip}_2)_3$ ^[8d], in which the central metal atom is bound to three $\text{In}(\text{Trip})_2$ groups. Stoichiometrically, however, the complexes most relevant to **1** are the recently reported clusters $\text{In}_{12}[\text{Si}(\text{tBu})_3]_8$ ^[15] and $\text{In}_8[\text{Si}(\text{tBu})_3]_6$.^[16] The In_{12} cluster can be described as a *conjuncto*-indane composed of two distorted octahedral $\text{In}_6[\text{Si}(\text{tBu})_3]_4$ moieties which are linked by In–In bonds across the two unsubstituted indium atoms in each octahedral unit. The particular stability of $\text{In}_{12}[\text{Si}(\text{tBu})_3]_8$, whose In–In bond lengths are similar to those in **1**, was attributed to steric effects of the $\text{Si}(\text{tBu})_3$ groups, which completely obscure the surface of the In_{12} array from attack. A space-filling model of **1** (Figure 2) clearly shows that the $\text{C}_6\text{H}_3\text{-2,6-Mes}_2$ ligand accomplishes the same end for the In_8 array in **1**. The structure of $\text{In}_8[\text{Si}(\text{tBu})_3]_6$ bears an even closer resemblance to **1** in that also it has an In_8 cubane core. In this case the core is stretched along a diagonal and may be classified as a doubly capped octahedral compound. Similarly, **1** can be described as a tetracapped tetrahedron. The structural data for these three clusters, analogues of which are unknown in boron chemistry, indicate that, in principle at least, it should be possible to control the size and geometry of indium clusters by means of the steric properties of the

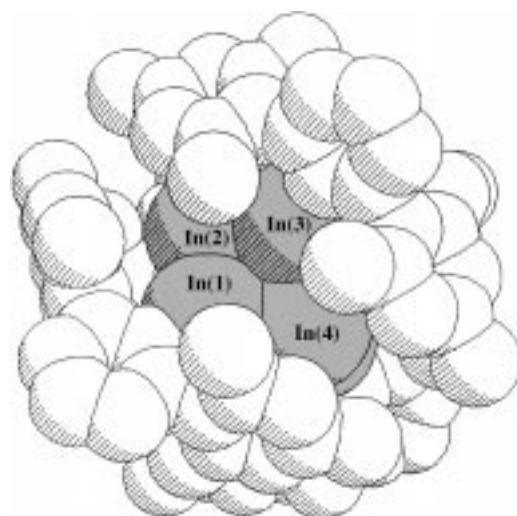


Figure 2. Space-filling drawing of **1** illustrating the steric protection of the In_8 core by the $\text{C}_6\text{H}_3\text{-2,6-Mes}_2$ ligands.

substituents on the indium atoms. The synthesis and structure of **1** also suggest that the extrusion of part of the ligand array in simple clusters such as R_2MMR_2 ($M = Ga, In$) or $(InR)_n$ to give higher clusters that incorporate unsubstituted metal atoms may be a general phenomenon in these sterically crowded species. Another distinctive feature of the synthesis of **1** is that an In^I compound was employed as starting material. This already has a 1:1 metal:ligand ratio and is closer stoichiometrically to the more highly aggregated cluster product **1** than are the higher valent starting materials, which usually carry two substituents per metal atom. It now seems likely that further examples of these interesting species will be isolated not only for indium but also for the other Group 13 metals.

Experimental Section

Under anaerobic and anhydrous conditions, a pale yellow solution of $LiC_6H_3-2,6-Mes_2$ (1.60 g, 4.99 mmol) in THF (20 mL) was cooled to ca. $-78^\circ C$ and added dropwise to a yellow suspension of $InCl$ (0.82 g, 5.5 mmol) in THF (5 mL) at ca. $-78^\circ C$. The solution became dark orange-brown upon addition and was stirred for 30 min. The solution was warmed to $-15^\circ C$, and the THF was removed under reduced pressure. The orange-brown solid was extracted with hexanes (100 mL) and gravity filtered through a Celite pad. The volume of the orange-brown solution was reduced to 30 mL. Cooling to ca. $0^\circ C$ for 12 h produced dark brown crystals of **1** (0.55 g, 0.25 mmol, 36.8% yield based on $InCl$). M.p. $207-210^\circ C$; ^1H NMR (399.77 MHz, C_6D_6 , $25^\circ C$, TMS): $\delta = 0.88$ (t, hexane), 1.22 (m, hexane), 1.88 (s, 24H, *p*-Me, Mes), 2.12 (brs, 24H, *o*-Me, Mes), 2.29 (brs, 24H, *o*-Me, Mes), 6.75 (d, $^3J(H, H) = 7.2$ Hz, 8H, *m*- C_6H_3), 6.86 (s, *m*-Mes, 16H), 7.05 (t, $^3J(H, H) = 7.2$ Hz, 4H, *p*- C_6H_3); $^{13}C\{^1H\}$ NMR (100.53 MHz, C_6D_6 , $25^\circ C$, TMS): $\delta = 21.29$ (*p*-Me, Mes), 21.65 (*o*-Me, Mes), 129.28 (*m*-Mes), 136.59 (*m*- C_6H_3), 137.13 (*o*-Mes), 137.23 (*p*- C_6H_3), 141.53 (*p*-Mes), 144.97 (*i*-Mes), 148.77 (*o*- C_6H_3), 189.88 (*i*- C_6H_3); UV/Vis (hexanes): $\lambda_{max}(\epsilon) = 305$ sh (1000).

Received: August 30, 1999 [Z13942]

- [1] B. Schiemenz, P. P. Power, *Organometallics* **1998**, *15*, 958.
- [2] a) S. T. Haubrich, P. P. Power, *J. Am. Chem. Soc.* **1998**, *120*, 2202; b) M. Niemeyer, P. P. Power, *Angew. Chem.* **1998**, *110*, 1291; *Angew. Chem. Int. Ed.* **1998**, *37*, 1277.
- [3] W. Uhl, *Angew. Chem.* **1993**, *105*, 1449; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1386; C. Dohmeier, D. Loos, H. Schnöckel, *Angew. Chem.* **1996**, *108*, 141; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 129.
- [4] B. T. Twamley, S. T. Haubrich, P. P. Power, *Adv. Organomet. Chem.* **1999**, *44*, 1.
- [5] K. Ruhlandt-Senge, J. J. Ellison, R. J. Wehnschulte, F. Pauer, P. P. Power, *J. Am. Chem. Soc.* **1993**, *115*, 11353.
- [6] Crystal data for **1** (190 K) with $Mo_{K\alpha}$ ($\lambda = 0.71073 \text{ \AA}$) radiation: $a = 14.0174(5)$, $b = 15.5917(5)$, $c = 23.7818(8) \text{ \AA}$, $\alpha = 92.047(1)$, $\beta = 104.734(1)$, $\gamma = 107.703(1)^\circ$, $Z = 2$, space group $P\bar{1}$, $R_1 = 0.052$ for 7389 data with $I > 2\sigma(I)$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-135535. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [7] For example: K. S. Hagen, J. G. Reynolds, R. H. Holm, *J. Am. Chem. Soc.* **1981**, *103*, 4054; B.-K. Teo, J. C. Calabrese, *J. Am. Chem. Soc.* **1975**, *97*, 1256.
- [8] a) W. Uhl, M. Layh, W. Hiller, *J. Organomet. Chem.* **1989**, *368*, 139; b) R. D. Schluter, A. H. Cowley, D. A. Atwood, R. A. Jones, M. R. Bond, C. J. Carrano, *J. Am. Chem. Soc.* **1993**, *115*, 2070; c) N. Wiberg, K. Amelunxen, H. Nöth, H. Schmidt, H. Schwenk, *Angew. Chem.*

- 1996**, *108*, 110; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 65; d) P. J. Brothers, K. Hübler, U. Hübler, B. C. Noll, M. M. Olmstead, P. P. Power, *Angew. Chem.* **1996**, *108*, 2528; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2355.
- [9] A. F. Wells, *Structural Inorganic Chemistry*, 5th ed., Clarendon, Oxford, **1984**, p. 1278.
- [10] W. Uhl, A. Jantschak, W. Saak, M. Kaupp, R. Wartchow, *Organometallics* **1998**, *17*, 5009.
- [11] J. Ebenhöch, G. Müller, J. Riede, H. Schmidbaur, *Angew. Chem.* **1984**, *96*, 367; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 386.
- [12] Some prominent recent examples for Al and Ga are given in: A. Ecker, L. Weckert, H. Schnöckel, *Nature* **1997**, *387*, 379; C. Klemp, R. Koppe, E. Weckert, H. Schnöckel, *Angew. Chem.* **1999**, *111*, 1851; *Angew. Chem. Int. Ed.* **1999**, *38*, 1740; W. Kostler, G. Linti, *Angew. Chem.* **1997**, *109*, 2758; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2644.
- [13] H. Schumann, C. Janiak, F. Görlitz, J. Loebel, A. Dietrich, *J. Organomet. Chem.* **1989**, *363*, 243.
- [14] O. T. Beachley, R. Blom, M. R. Churchill, J. Fettingner, J. C. Pazik, L. Victoriano, *J. Am. Chem. Soc.* **1986**, *108*, 4666.
- [15] N. Wiberg, H.-W. Lerner, H. Nöth, W. Ponikwar, *Angew. Chem.* **1999**, *111*, 887; *Angew. Chem. Int. Ed.* **1999**, *38*, 839.
- [16] N. Wiberg, T. Blank, A. Purath, G. Stösser, H. Schnöckel, *Angew. Chem.* **1999**, *111*, 2745; *Angew. Chem. Int. Ed.* **1999**, *38*, 2563.

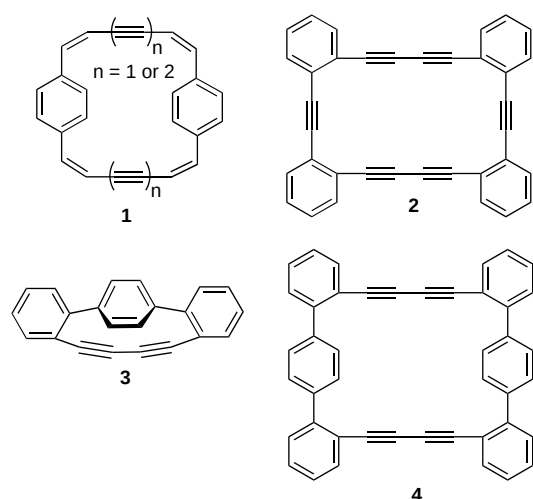
The Synthesis of a Novel Strained Diyneparacyclophane and Its Dimer by Metal-Mediated Coupling**

Shawn K. Collins, Glenn P. A. Yap, and Alex G. Fallis*

Diverse families of cyclophanes^[1] and assorted cage compounds^[2] with novel structures and properties continue to be topics of wide-spread interest.^[3] Earlier, we reported the synthesis of a novel class of enediyne cyclophanes by sequential palladium- or copper-mediated coupling.^[4] In contrast to normal $[n.m]$ paracyclophanes, the rotation of the benzene ring in these molecules is not restricted by the bridging bonds. Consequently they were christened revolv-eneynes **1** as the aromatic rings rotate freely, with "skipping rope"-type properties, in which the bridging units and one aromatic ring may swing around each other. The unsaturated bonds in these bridges impart a helical twist to the structures. As a result, they possess helical chirality, a property that is shared with related D_2 -symmetric olefinic paracyclophanes.^[5] In a related area, we^[6] and others^[7] have attempted to extend these syntheses to multibridged systems in order to prepare potential precursors to fullerenes such as C_{60} , but with limited success. However, Vollhardt and co-workers^[8] have demonstrated that **2** decomposed explosively to form carbon anions when heated, and cobalt alkyne complexes afforded carbon nanotubes.

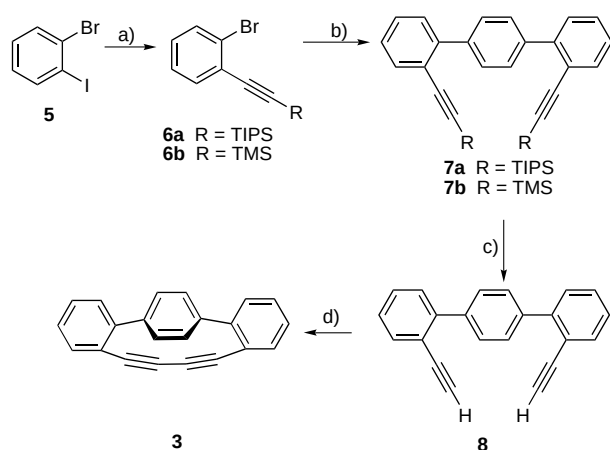
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[**] We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this research. S. K. Collins thanks NSERC for a Graduate Scholarship.



Herein we report an extension of our initial investigations which culminated in the synthesis of the strained diyne system **3** in 90% yield. Modification of the coupling conditions afforded the corresponding dimer **4** which is the benzenoid analogue of **1** for $n=2$. A variety of related bis-acetylene systems are also known^[9] and the relevant bond angles are compared with those of **3** and **4**.

The synthesis of **3** is outlined in Scheme 1 and commenced with commercially available 1-bromo-2-iodobenzene (**5**).



Scheme 1. Synthesis of strained cyclophane **3**. a) TMSA (or TIPS), $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$, CuI , THF, DEA, 55 °C, 15 h, 90% for $\text{R}=\text{TMS}$, 80% for $\text{R}=\text{TIPS}$; b) 1) $n\text{BuLi}$, THF, -78 °C, 30 min, 2) ZnBr_2 , THF, 0 °C, 15 min, 3) $[\text{Pd}(\text{PPh}_3)_4]$, 1,4-dibromobenzene, THF, 65 °C, 15 h, 90% for $\text{R}=\text{TMS}$, 80% for $\text{R}=\text{TIPS}$; c) For $\text{R}=\text{TIPS}$: TBAF, THF, 3 h, 100%; for $\text{R}=\text{TMS}$: K_2CO_3 , MeOH, THF, H_2O , 3 h, 100%; d) $\text{Cu}^{\text{II}}(\text{OAc})_2$ (6 equiv), pyridine/diethyl ether 3/1, 90 °C, 3 h, 90%.

Selective reaction at the iodine center by palladium(0)-mediated coupling in the presence of copper iodide with triisopropylsilyl- or trimethylsilylacetylene provided the phenyl acetylenes **6a** and **6b**^[10] in yields of 80 and 90%, respectively. The most efficient procedure for the coupling of **6a** with 1,4-dibromobenzene involved the use of an organozincate generated in situ by halogen–metal exchange with $n\text{BuLi}$ followed by transmetalation with ZnBr_2 . Subsequent addition of tetrakis(triphenylphosphane)palladium(0) and 1,4-dibromobenzene followed by a 15-hour reflux afford-

ed the silyl-protected derivatives **7** (80–90% yield). This organozinc protocol^[11] was superior to traditional tributyl- or trimethyltin coupling methods because it avoided the difficult chromatographic separations encountered from the co-elution of alkyltin byproducts and the phenylacetylenes. Removal of the triisopropylsilyl protecting groups was accomplished by treatment with tetra- n -butylammonium fluoride in THF, although traces of triisopropylsilyl protecting groups complicated the separation. Removal of the trimethylsilyl groups was accomplished efficiently with K_2CO_3 in THF/MeOH/ H_2O at 21 °C, thus protection using the trimethylsilyl was preferred. The diacetylene **8**, was then subjected to oxidative coupling using $\text{Cu}^{\text{II}}(\text{OAc})_2$ ^[12] and by refluxing in pyridine/diethyl ether (3/1). A single product was isolated in 90% yield whose spectral features suggested it was the monomer **3**^[17] and not the anticipated dimer **4** which would be formed from an intermolecular coupling. Thus the strained system **3** from the intramolecular coupling of the terminal acetylenes formed preferentially. In order to understand this preference various reaction conditions were examined, as summarized in Table 1.

Table 1. Effect of oxidative-coupling conditions on product ratios.

Coupling conditions ^[a]	Yields [%]	
	3	4
90 °C, 3 h	90	0
21 °C, 3 d	43–58	18–26
21 °C, 3 d (protected from light)	54	17–21

[a] $\text{Cu}^{\text{II}}(\text{OAc})_2$, 6 equiv; pyridine/diethyl ether 3/1.

Variation of the reaction temperature afforded considerable control over the ratio of inter- versus intramolecular coupling. Reactions protected from light produced emerald green solutions, while in reactions left unprotected the solution remained the characteristic sapphire blue of the $\text{Cu}^{\text{II}}(\text{OAc})_2$, although the total yields and product mixtures were similar. $\text{Cu}^{\text{I}}/\text{O}_2$ mediated couplings,^[7, 13] in contrast, gave a complex “soup” of products with no trace of **3**, although a disappointing 10% yield of the dimer **4** was isolated.

Crystals of the dimer **4**^[17] suitable for X-ray analysis were grown from a dichloromethane/methanol solution. It was anticipated that the unsaturated bonds in the bridges would impart a helical twist to the molecule as observed previously for the revolenynes. Thus, the two central benzene rings were expected to be aligned in an overlapping manner, superimposed on each other but slightly offset. The crystal structure analysis revealed the dimer, which co-crystallized with dichloromethane in a 2:1 ratio, was indeed helical but the spatial arrangement of the “outer” rings created two “arms” (Figure 1).^[14] This stereochemical relationship appears to result from a twisting of the molecule to facilitate through-space alignment between two of the “outer” benzene rings of the bridges. This creates a pincer-like structure,^[15] with one molecule of dichloromethane within the cavity of every second molecule dispersed uniformly throughout the lattice of the crystal. The helical conformation of the dimer helps to relieve strain within the acetylene bonds. The bond angles at the four triple bonds are as follows: $\text{C}(19)\text{--}\text{C}(20)\text{--}\text{C}(21)$ 177.7°, $\text{C}(20)\text{--}\text{C}(21)\text{--}\text{C}(22)$ 177.1°, $\text{C}(41)\text{--}\text{C}(42)\text{--}\text{C}(43)$ 175.9°, $\text{C}(42)\text{--}\text{C}(43)\text{--}\text{C}(44)$ 178.7°.

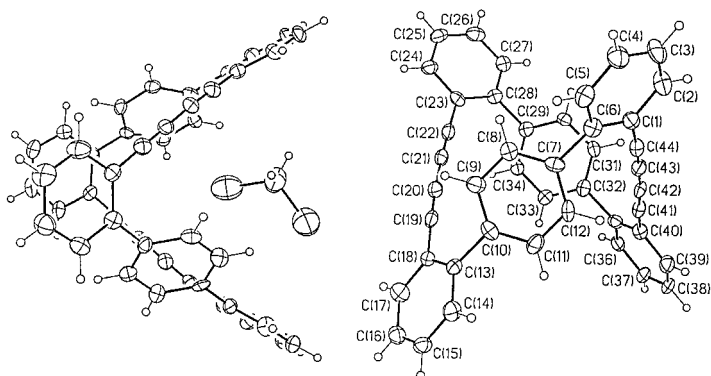
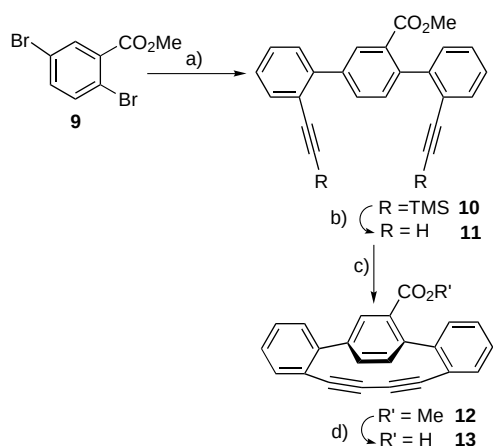


Figure 1. Structure of **4** in the crystal: view from the side with a co-crystallized molecule of dichloromethane (left), and from above without a molecule of dichloromethane (right).

Several attempts to crystallize **3** were unsuccessful and resulted in the formation of a material assumed to be a polymer. In order to assign the structure of **3** unambiguously, a new analogue was synthesized containing a carboxylic acid group. This facilitated crystallization, allowed X-ray structural analysis of the crystal, and provided insight into the hydrogen bonding of the acid dimers in the crystal. The acid **13** was assembled using a parallel set of reactions (Scheme 2) to those



Scheme 2. Synthesis of the carboxylic acid cyclophane derivative **13**. a) 1) **6b**, *n*BuLi, THF, -78°C , 30 min, 2) ZnBr_2 , THF, 0°C , 15 min, 3) $[\text{Pd}(\text{PPh}_3)_4]$, methyl 2,5-dibromobenzoate, THF, 65°C , 15 h, 80%; b) K_2CO_3 , MeOH, THF, H_2O , 3 h, 99%; c) $\text{Cu}^{\text{II}}(\text{OAc})_2$ (6 equiv), pyridine/diethyl ether 3/1, 90°C , 3 h, 64%; d) LiOH, H_2O , MeOH, 50°C , 3 h, 25%.

described above. The organozinc derivative of **6b** (Scheme 2) was prepared as previously and the solution treated with tetrakis(triphenylphosphane)palladium(0) and methyl 2,5-dibromobenzoate (reflux, 15 h) to afford **10**^[17] in 80% yield. Removal of the trimethylsilyl groups and oxidative coupling with $\text{Cu}^{\text{II}}(\text{OAc})_2$ in refluxing pyridine/diethyl ether (3/1) gave **12**^[17] in 64% yield. Saponification of the methyl ester with lithium hydroxide required warming to reflux in methanol over 3 h to produce the carboxylic acid **13** in a modest 25% yield. More vigorous conditions and alternative bases (KOH, NaOH) caused decomposition. The carboxylic acid crystal-

lized from dichloromethane as monoclinic crystals for X-ray analysis.^[14]

Figure 2 illustrates the influence of the free acid group which, as expected, forms hydrogen bonded dimers through intermolecular association. This clearly establishes the structure of both **3** and **13**.^[15] The inherent strain in this unique ring

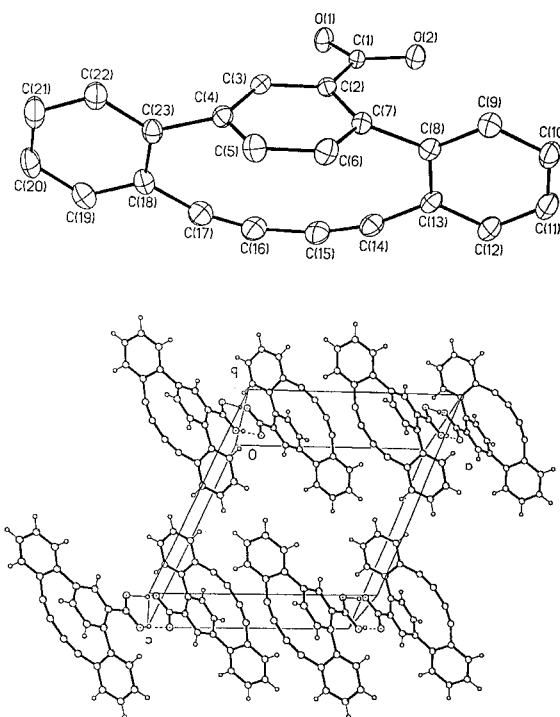


Figure 2. Structure of **13** in the crystal (top) and intermolecular hydrogen bonding within the lattice (bottom).

system is reflected in the deviation from planarity observed between the two outer benzene rings which lie perpendicular to the central ring and the connecting bonds. The bond between C(7)–C(8) is bent 17.8° out of the plane of the central ring, while the C(4)–C(23) bond is distorted by 18.7° . The acetylene bonds are also strained as the angles C(14)–C(15)–C(16) and C(15)–C(16)–C(17) are 163.7° and 163.5° , respectively. However, the carbon–carbon bond lengths fall within the normal range. The corresponding bond angles in a related [4.4]orthocyclophane bisdiyne system prepared by Zhou, Carroll, and Swager^[9b] were 165.8° and 166.7° , respectively, while the [3.4]paracyclophane diynes synthesized by Ueda, Katayama, and Tanaka^[9d] are also bowed, but the deformation is less, with bond angles of 172.8° and 173.9° , respectively.

In conclusion, this palladium-coupling sequence provided a rapid route to novel benzene–diyne bridged cyclophanes that possess interesting geometric features. It is anticipated that current investigations will lead to more highly functionalized systems with unique properties, capable of binding transition metals^[16] and acting as multidentate ligands when heteroatoms are present. In addition, with appropriate functionality, these methods will provide access to novel liquid crystals.

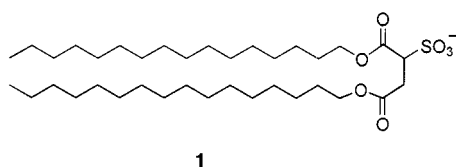
Received: August 17, 1999 [Z13894]

- [1] a) *Top. Curr. Chem.* **1983**, 113; *Top. Curr. Chem.* **1983**, 115; b) *Cyclophanes*, Vols. I, II (Eds.: P. M. Keehn, S. M. Rosenfeld), Academic Press, New York, **1983**; c) F. Diederich, *Cyclophanes*, Royal Society of Chemistry, Cambridge, UK, **1991**; d) F. Vögtle, *Cyclophane Chemistry*, Wiley, New York, **1993**; e) *Top. Curr. Chem.* **1994**, 172; f) G. J. Bodwell, *Angew. Chem.* **1996**, 108, 2221–2224; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2085–2088; g) A. de Meijere, B. König, *Synlett* **1997**, 1221–1232.
- [2] a) C. Seel, F. Vögtle, *Angew. Chem.* **1992**, 104, 542–563; *Angew. Chem. Int. Ed. Engl.* **1992**, 31, 528–549; b) *Frontiers in Supramolecular Organic Chemistry and Photochemistry* (Eds.: H. J. Schneider, H. Dürr), VCH, Weinheim, **1991**.
- [3] a) B. König, *Top. Curr. Chem.* **1998**, 196, 96–136; b) T. Tsuji, *Adv. Strained Interesting Org. Mol.* **1999**, 7, 103–152; c) *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**.
- [4] M. A. Romero, A. G. Fallis, *Tetrahedron Lett.* **1994**, 35, 4711–4714.
- [5] D. Malaba, A. Djebli, L. Chen, E. A. Zarate, C. A. Tessier, W. J. Youngs, *Organometallics* **1993**, 12, 1266–1276.
- [6] A. G. Fallis, *Can. J. Chem.* **1999**, 77, 159–177.
- [7] a) Y. Rubin, T. C. Parker, S. I. Khan, C. L. Holliman, S. W. McElvany, *J. Am. Chem. Soc.* **1996**, 118, 5308–5309; b) Y. Rubin, *Chem. Eur. J.* **1997**, 3, 1009–1016; c) Y. Tobe, N. Nakagawa, K. Naemura, T. Wakabayashi, T. Shida, Y. Achiba, *J. Am. Chem. Soc.* **1998**, 120, 4544–4545; d) Y. Rubin, T. C. Parker, S. J. Pastor, S. Jalisatgi, C. Bouille, C. L. Wilkins, *Angew. Chem.* **1998**, 110, 1353–1356; *Angew. Chem. Int. Ed.* **1998**, 37, 1226–1229.
- [8] a) R. Boese, A. J. Matzger, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1997**, 119, 2052–2053; b) P. I. Dosa, C. Erben, V. S. Iyer, K. P. C. Vollhardt, I. M. Wasser, *J. Am. Chem. Soc.* **1999**, 121, 10430–10431.
- [9] a) L. Guo, J. D. Bradshaw, C. A. Tessier, W. J. Youngs, *J. Chem. Soc. Chem. Commun.* **1994**, 243–244; b) Q. Zhou, P. J. Carroll, T. M. Swager, *J. Org. Chem.* **1994**, 59, 1294–1301; c) H. Hopf, P. G. Jones, P. Bubenitschek, C. Werner, *Angew. Chem.* **1995**, 107, 2592–2594; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2367–2368; d) H. Ueda, C. Katayama, J. Tanaka, *Bull. Chem. Soc. Jpn.* **1981**, 54, 891–896.
- [10] Compound **6b** is now commercially available from Aldrich.
- [11] S. Sengupta, V. Snieckus, *J. Org. Chem.* **1990**, 55, 5680–5683.
- [12] a) G. Eglington, W. McRae, *Adv. Org. Chem.* **1963**, 4, 225–338; b) O. M. Behr, G. Eglington, A. R. Galbraith, R. A. Raphael, *J. Chem. Soc.* **1960**, 3614–3625.
- [13] a) A. S. Hay, *J. Org. Chem.* **1960**, 25, 1275–1276; b) A. S. Hay, *J. Org. Chem.* **1962**, 27, 3320–3321.
- [14] X-ray crystal structural analyses: Dimer **4**: crystal size $0.30 \times 0.04 \times 0.04$ mm³, orthorhombic, space group *Pbca*, scan range $3.96 < 2\theta < 41.98^\circ$, $a = 15.201(5)$, $b = 20.611(6)$, $c = 21.317(6)$ Å, $V = 6679(3)$ Å³, $Z = 8$, $\rho_{\text{calcd}} = 1.268$ g cm⁻³, $\mu = 0.226$ mm⁻¹, 3586 unique reflections at -80°C , of which 3586 were taken as observed [$I_o > 2.00\sigma(I)$], $R = 0.1125$, $R_w = 0.2685$; monomer **13**: crystal size $0.20 \times 0.20 \times 0.20$ mm³, monoclinic, space group *P2₁/c*, scan range $5.3 < 2\theta < 57.28^\circ$, $a = 12.879(4)$, $b = 10.168(3)$, $c = 13.466(4)$ Å, $\beta = 114.545(4)^\circ$, $V = 1604.2(8)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.326$ g cm⁻³, $\mu = 0.084$ mm⁻¹, 3482 unique reflections at -80°C , of which 3482 were taken as observed [$I_o > 2.00\sigma(I)$], $R = 0.0563$, $R_w = 0.0983$ (this value is a consequence of the traces of polymer that appear to adhere to the crystal surface). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-133375 (**4**) and CCDC-133376 (**13**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [15] For an example of “pincer”-shaped molecules, see R. Rathore, S. V. Lindeman, J. K. Kochi, *Angew. Chem.* **1998**, 110, 1665–1667; *Angew. Chem. Int. Ed.* **1998**, 37, 1585–1587.
- [16] J. Schulz, F. Vögtle in ref. [1e], pp. 41–86.
- [17] Physical data for the new compounds. **3**: White solid, m. p. 167–170 °C; ¹H NMR (200 MHz, CDCl₃): $\delta = 7.39$ (m, 9 H), 7.72 (m, 3 H); ¹³C NMR (50 MHz, CDCl₃): $\delta = 84.1, 98.1, 124.8, 126.4, 126.9, 127.4, 128.7, 129.8, 141.5, 150.9$; IR (CHCl₃): $\tilde{\nu} = 2965, 2921, 1508, 1457, 1260, 1099, 1019$ cm⁻¹; MS (70 eV): m/z (%): 276 (100), 248 (6), 198 (1), 162 (10), 137 (14), 99 (2), 70 (2), 31 (6); HRMS for C₂₂H₁₂: calcd: 276.0940; found: 276.0938. **4**: Yellow solid, m. p. 257–260 °C; ¹H NMR (500 MHz, CDCl₃): $\delta = 7.27$ (m, 4 H), 7.36 (m, 8 H), 7.53 (s, 8 H), 7.58 (d, $J = 7.4$ Hz, 4 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 76.7, 81.3, 120.4, 127.1, 128.8, 129.2, 129.5, 133.7, 139.3, 145.2$; IR (CHCl₃): $\tilde{\nu} = 3055, 3029, 2924, 2854, 2216, 1468, 1439, 1220, 840$ cm⁻¹; MS (FAB): m/z (%): 551 (3), 461 (1), 391 (1), 369 (1), 338 (1), 277 (5), 246 (5), 219 (3). **10**: Pale yellow solid, m. p. 113–116 °C; ¹H NMR (500 MHz, CDCl₃): $\delta = 0.02$ (s, 9 H), 0.11 (s, 9 H), 3.66 (s, 3 H), 7.30 (m, 4 H), 7.40 (m, 3 H), 7.48 (dm, 1 H), 7.58 (dm, 1 H), 7.83 (dd, $J = 2.0, 7.9$ Hz, 1 H), 8.20 (d, $J = 1.8$ Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = -0.40, -0.32, 51.9, 97.6, 98.1, 103.8, 104.4, 121.5, 122.3, 126.9, 127.3, 128.4, 128.4, 128.9, 129.3, 130.3, 130.7, 130.8, 131.6, 132.4, 133.4, 139.6, 141.0, 143.0, 145.0, 167.5$; IR (CHCl₃): $\tilde{\nu} = 3006, 2957, 2156, 1722, 1474, 1437, 1312, 1248, 1208, 1118$ cm⁻¹; MS (70 eV): m/z (%): 480 (23), 465 (25), 435 (23), 407 (6), 391 (10), 376 (32), 348 (54), 333 (30), 319 (13), 303 (20), 289 (30), 263 (16), 225 (10), 201 (7), 147 (7), 89 (43), 73 (100), 59 (36); HRMS for C₃₀H₃₄O₂Si₂: calcd: 480.1942; found: 480.1927; elemental analysis for C₃₀H₃₄O₂Si₂: calcd: C 74.95, H 6.71; found: C 75.05, H 6.65. **12**: Yellow solid, m. p. 143–146 °C; ¹H NMR (500 MHz, CDCl₃): $\delta = 3.66$ (s, 3 H), 7.24 (m, 2 H), 7.33 (m, 3 H), 7.45 (m, 3 H), 7.69 (d, $J = 6.8$ Hz, 1 H), 7.73 (d, $J = 7.1$ Hz, 1 H), 7.95 (d, $J = 1.7$ Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃): $\delta = 51.8, 83.3, 84.8, 97.9, 98.0, 123.1, 124.9, 126.4, 126.9, 127.0, 127.2, 127.8, 128.6, 128.8, 130.9, 132.0, 132.3, 133.4, 142.1, 142.7, 149.4, 150.5, 166.4$; IR (CHCl₃): $\tilde{\nu} = 2999, 2954, 2858, 2169, 1720, 1436, 1308, 1213, 1140$ cm⁻¹; MS (70 eV): m/z (%): 334 (35), 303 (4), 274 (41), 218 (1), 143 (30), 112 (12), 69 (100), 40 (16); HRMS for C₂₄H₁₄O₂: calcd: 334.0094; found: 334.1018.

Molecular Dispersion of Chains in the Mixed-Valence Complexes $[M(en)_2][MCl_2(en)_2]$ (M : Pt, Pd, Ni) and Anionic Amphiphiles in Organic Media**

Nobuo Kimizuka,* Sang Ho Lee, and Toyoki Kunitake

Controlled manipulation of inorganic nanostructures under the influence of organic molecular assemblies is an important area of current research in nanochemistry.^[1, 2] Though there are many artificially built inorganic nanostructures known to date^[1] they are normally insoluble and exist only as basic structural motifs in solid materials. The linear halogen-bridged platinum complexes $[Pt(en)_2][PtCl_2(en)_2](ClO_4)_4$ (en = ethylenediamine) represent one of the pseudo one-dimensional inorganic systems that have been extensively characterized in crystalline samples.^[4] These one-dimensional chains exist only in the crystalline state, and dissolution in water results in dissociation into single molecular complexes. We recently devised an approach to isolate and to solubilize one-dimensional platinum complexes into organic media by transforming them into lipophilic supramolecular assemblies.^[3] The introduction of anionic lipid **1** as a counterion enabled the one-dimensional complex $[Pt(en)_2][PtCl_2(en)_2]$ to become soluble in organic media through the formation of mesoscopic supramolecular assemblies.^[3] Herein we describe



a generalization of our approach by the use of mixed valent palladium and heterometallic complexes. The morphology of the aggregates, spectral characteristics, and thermal stability of these assemblies in chloroform are discussed.

Ternary supramolecular complexes were prepared by mixing aqueous solutions of mixed-valence complexes $[Pd(en)_2][PdCl_2(en)_2](ClO_4)_4$, $[Pd(en)_2][PtCl_2(en)_2](ClO_4)_4$, and $[Ni(en)_2][PtCl_2(en)_2](ClO_4)_4$ (12.7 mM, 1 mL), with the aqueous bilayer membrane **1** (in the Na^+ form, 12.7 mM, 4 mL) at room temperature. The highly colored precipitates of $[Pd(en)_2][PdCl_2(en)_2](1)_4$ (dark green), $[Pd(en)_2][PtCl_2(en)_2](1)_4$ (yellow), and $[Ni(en)_2][PtCl_2(en)_2](1)_4$ (red) that formed immediately were washed with deionized water (5 mL, $\times 3$) and ethanol (3 mL, $\times 2$), and then dried in vacuo. The stoichiometry of these complexes was confirmed by elemental

analysis. The observed colors are different from those of the corresponding ethylenediamine complexes and are ascribed to intervalence electron transfer transitions ($M^{II} \rightarrow M^{IV}$) within chloro-bridged complexes.^[4, 5] Therefore, it is apparent that the mixed-valence structures are maintained in the lipid complexes. These ternary complexes are readily dispersed in chloroform by ultrasonication, without any loss of color from the solids. The maintenance of the absorption arising from intervalence electron transfer in chloroform has been also observed for the platinum complex $[Pt(en)_2][PtCl_2(en)_2](1)_4$,^[3] and thus the complexation of polyions with anionic amphiphiles provides a general route for solubilizing halogen-bridged mixed-valence complexes in organic media.

Figure 1 shows transmission electron micrographs of solutions of $[Pd(en)_2][PdCl_2(en)_2](1)_4$ (a), $[Pd(en)_2][PtCl_2(en)_2](1)_4$ (b), and $[Ni(en)_2][PtCl_2(en)_2](1)_4$ (c) in chloroform. These samples are not stained, and the dark images are ascribed to

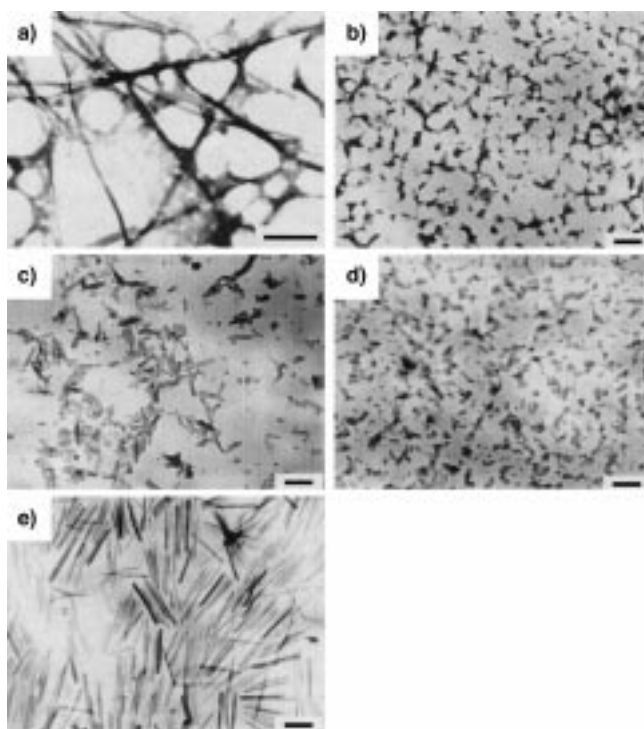


Figure 1. Transmission electron micrographs of solutions of the following complexes in chloroform: a) $[Pd^{II}(en)_2][Pd^{IV}(en)_2Cl_2](1)_4$, b) $[Pd^{II}(en)_2][Pt^{IV}(en)_2Cl_2](1)_4$, c) $[Ni^{II}(en)_2][Pt^{IV}(en)_2Cl_2](1)_4$, d) $[Pd^{II}(en)_2][Pd^{IV}(en)_2Cl_2](1)_4$ heated at 60 °C, e) $[Pd^{II}(en)_2][Pt^{IV}(en)_2Cl_2](1)_4$ after cooling the 60 °C sample. The scale bars represent 100 nm. Samples are not stained.

metal components in the mixed-valent complexes. The palladium complex displayed rodlike structures with widths of 60–120 nm and lengths of 2.5–17 μm (a), while the heterometallic complex of $[Pd(en)_2][PtCl_2(en)_2](1)_4$ showed only irregular nanostructures (b). Fragmented tapes are seen for $[Ni(en)_2][PtCl_2(en)_2](1)_4$ (c), which resembles that observed for the platinum complex $[Pt(en)_2][PtCl_2(en)_2](1)_4$.^[3] It is noteworthy that changes in the metal species remarkably influence the aggregate morphology.

Figure 2 shows the UV/Vis spectra obtained for the four complexes. These colored dispersions were stable over a period of one month. The absorption maxima of these

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[**] This work was partly supported by a Grant-in-Aid for COE Research "Design and Control of Advanced Molecular Assembly Systems" from the Ministry of Education, Science, Sports, and Culture, Japan (No. 08CE2005). S.H.L. thanks the Korea Science and Engineering Foundation (KOSEF).

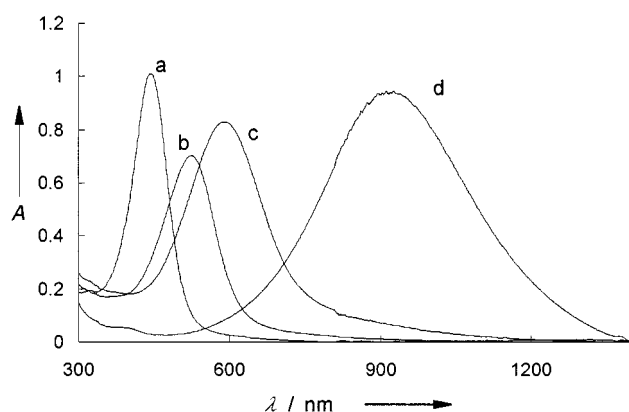


Figure 2. UV/Vis spectra of solutions of the following complexes in chloroform ($[M^{II}] = [M^{IV}] = 0.3 \text{ mM}$, 1 mm cell, 20°C): a) $[\text{Pd}^{\text{II}}(\text{en})_2][\text{Pt}^{\text{IV}}(\text{en})_2(\text{Cl})_2](\mathbf{1})_4$, b) $[\text{Ni}^{\text{II}}(\text{en})_2][\text{Pt}^{\text{IV}}(\text{en})_2(\text{Cl})_2](\mathbf{1})_4$, c) $[\text{Pt}^{\text{II}}(\text{en})_2][\text{Pt}^{\text{IV}}(\text{en})_2(\text{Cl})_2](\mathbf{1})_4$, d) $[\text{Pd}^{\text{II}}(\text{en})_2][\text{Pd}^{\text{IV}}(\text{en})_2(\text{Cl})_2](\mathbf{1})_4$.

solutions are located at $\lambda_{\text{max}} = 443 \text{ nm}$ (2.80 eV, $\epsilon = 33733 \text{ M}^{-1}\text{cm}^{-1}$, a), 524 nm (2.37 eV, $\epsilon = 21833 \text{ M}^{-1}\text{cm}^{-1}$, b), 590 nm (2.10 eV, $\epsilon = 27667 \text{ M}^{-1}\text{cm}^{-1}$, c), and 910 nm (1.36 eV, $\epsilon = 31567 \text{ M}^{-1}\text{cm}^{-1}$, d). These absorption bands are not present for the component ethylenediamine complexes, and are ascribed to intervalence electron transfer transitions along the chloro-bridged chains. These absorption peaks are apparently dependent on the combination of the mixed-valent metal ions, which indicates that the electronic structure in these supramolecular assemblies is tunable. The series of charge-transfer bands are in the same order as that reported for the corresponding perchlorates in the crystalline state (reflectance spectra:^[4, 5] Pd/Pt: 385 nm (3.22 eV), Ni/Pt: 440 nm (2.82 eV), Pt/Pt: 456 nm (2.72 eV), Pd/Pd: 605 nm (2.05 eV)), but are considerably red shifted. The intervalence electron transfer absorption energy of halogen-bridged mixed-valent Pt complexes is known to decrease with increasing distances between Pt^{II} and Pt^{IV} centers.^[4, 6] As these lipid complexes display identical colors both in the powdery state and in chloroform solution the observed red shifts in solution must reflect lengthened metal(II)–metal(IV) distances in the one-dimensional chains, which probably arise from the presence of large organic counterions.

As the aggregate diameters observed by electron microscopy (Figure 1) are much larger than the molecular length of **1**, the observed structures must be comprised of aggregates of the unit supramolecular polyion complex, which is schematically shown in Figure 3. Long alkyl chains of **1** act as

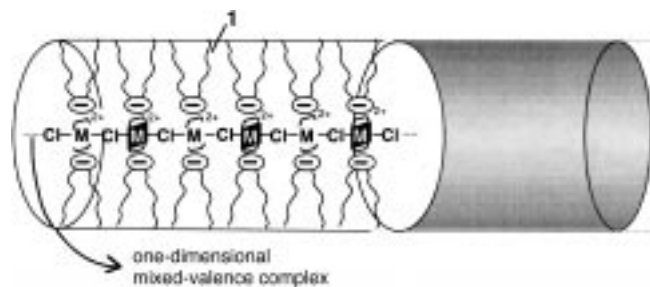


Figure 3. Schematic representation of the structural unit of $[\text{M}^{\text{II}}(\text{en})_2][\text{M}^{\text{IV}}(\text{en})_2(\text{Cl})_2](\mathbf{1})_4$ dispersed in chloroform. Aggregation of this structural unit provides the observed nanostructures.

solvophilic moieties in this structural unit, while the polyion complex moiety serves as a solvophobic moiety, and this combination gives rise to an amphiphilic supramolecular structure in organic media.^[7]

The thermal stability of these supramolecular assemblies in chloroform was subsequently investigated. In the case of a solution of $[\text{Pd}(\text{en})_2][\text{PdCl}_2(\text{en})_2](\mathbf{1})_4$ in chloroform ($2.5 \times 10^{-5} \text{ M}$) a temperature change from 5 to 55°C resulted in a decrease in absorbance by approximately 35%, and this was accompanied by a blue shift in the spectrum to 878 nm (Figure 4a). The initial intensity of the absorption was

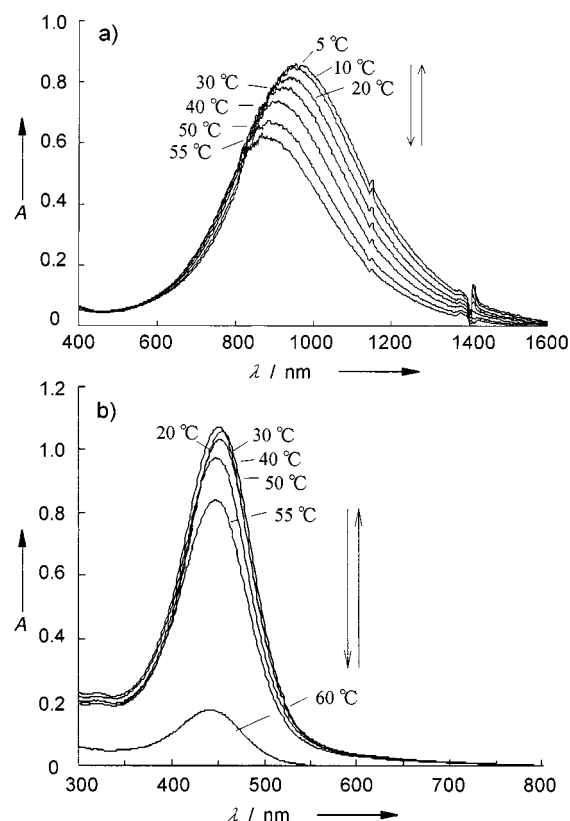


Figure 4. Temperature dependence of the UV/Vis spectra of a) $[\text{Pd}^{\text{III}}(\text{en})_2][\text{Pd}^{\text{IV}}(\text{en})_2(\text{Cl})_2](\mathbf{1})_4$, 0.25 mM in chloroform, 1 cm cell, b) $[\text{Pd}^{\text{III}}(\text{en})_2][\text{Pt}^{\text{IV}}(\text{en})_2(\text{Cl})_2](\mathbf{1})_4$, 0.4 mM in chloroform, 1 mm cell.

recovered upon cooling the solution to 5°C . An electron micrograph of $[\text{Pd}(\text{en})_2][\text{PdCl}_2(\text{en})_2](\mathbf{1})_4$, which was prepared by dropping a solution of the aggregate in chloroform at 60°C onto a carbon-coated copper mesh, was devoid of the rodlike nanostructures. It, instead, consisted of irregular aggregates that resemble that of $[\text{Pd}(\text{en})_2][\text{PtCl}_2(\text{en})_2](\mathbf{1})_4$ at 20°C (Figure 1d). Though we can not exclude the possibility that the irregular structure is formed as a result of a rapid evaporation of the warm chloroform, it is more likely that the rodlike nanostructure is destroyed as a consequence of partial dissociation of the linear coordination chain into molecular complexes of $[\text{Pd}(\text{en})_2](\mathbf{1})_2$ and $[\text{PdCl}_2(\text{en})_2](\mathbf{1})_2$. In accordance with the observed spectral recovery, the rodlike nanostructure was reformed upon cooling the heated solution (data not shown). When the temperature was further raised to 60°C , however, recovery of absorption after cooling became

poor (ca. 18% of the initial intensity). This result can be ascribed to the smaller stability of $[\text{Pd}^{\text{IV}}\text{Cl}_2(\text{en})_2]$ at elevated temperatures, with the complex being readily reduced to a $\text{Pd}^{\text{II}}(\text{en})_2$ species by oxidation of the coordinating chloride ion.^[8]

In the case of $[\text{Ni}(\text{en})_2][\text{PtCl}_2(\text{en})_2](\mathbf{1})_4$ in chloroform ($3 \times 10^{-4} \text{ M}$), the recovery of intervalence electron transfer absorption after heating was inferior to that observed for $[\text{Pd}(\text{en})_2][\text{PtCl}_2(\text{en})_2](\mathbf{1})_4$. Only approximately 50% of the initial intensity was recovered after cooling the 60°C solution to room temperature. However, reversible thermochromism was observed for $[\text{Pd}(\text{en})_2][\text{PtCl}_2(\text{en})_2](\mathbf{1})_4$ in chloroform ($4 \times 10^{-4} \text{ M}$). When a solution of this complex was heated to 60°C (Figure 4b), the UV absorption decreased to 17% of the initial intensity without changing the peak position. The original intensity was restored upon cooling to room temperature, and this reversible change was possible even after three thermal cycles. Figure 1e shows an electron micrograph of $[\text{Pd}(\text{en})_2][\text{PtCl}_2(\text{en})_2](\mathbf{1})_4$ after cooling. Rectangular nanocrystals (length: ca. 1400–2000 nm, width: ca. 80–200 nm) are abundant. These nanostructures are more developed than those before the heat treatment (Figure 1b). It is clear that this regular supramolecular structure is formed by self-assembly of thermally dissociated component complexes.

In conclusion, it is established that formation of amphiphilic supramolecular assemblies is a general route to stabilize one-dimensional, halogen-bridged mixed-valent complexes in organic media. The combination of metal ions significantly alters their spectral properties and morphologies, which gives rise to a wide spectrum of one-dimensional electronic systems in the solution phase. These new findings offer a new basis for research on molecular wires.

Experimental Section

The synthesis of sodium dihexadecyl sulfosuccinate (Na-**1**) was described previously.^[9] Ethylenediamine complexes and chloro-bridged mixed-valence complexes were prepared according to the literature.^[10] Elemental analyses (calcd (found)): $[\text{Pd}(\text{en})_2][\text{Pt}(\text{en})_2\text{Cl}_2](\mathbf{1})_4$ ($\text{C}_{152}\text{H}_{308}\text{N}_8\text{O}_{28}\text{S}_4\text{Cl}_2\text{PdPt}$): C 57.11 (56.80), H 9.71 (9.68), N 3.51 (3.45); $[\text{Ni}(\text{en})_2][\text{PtCl}_2(\text{en})_2](\mathbf{1})_4$ ($\text{C}_{152}\text{H}_{308}\text{N}_8\text{O}_{28}\text{S}_4\text{Cl}_2\text{NiPt}$): C 57.97 (57.31), H 9.86 (9.81), N 3.56 (3.45); $[\text{Pt}(\text{en})_2][\text{PtCl}_2(\text{en})_2](\mathbf{1})_4$ ($\text{C}_{152}\text{H}_{308}\text{N}_8\text{O}_{28}\text{S}_4\text{Cl}_2\text{Pt}_2$): C 55.57 (55.06), H 9.45 (9.38), N 3.41 (3.32); $[\text{Pd}(\text{en})_2][\text{Pd}(\text{en})_2\text{Cl}_2](\mathbf{1})_4$ ($\text{C}_{152}\text{H}_{308}\text{N}_8\text{O}_{28}\text{S}_4\text{Cl}_2\text{Pd}_2$): C 58.74 (58.11), H 9.99 (10.09), N 3.61 (3.52). UV/Vis absorption spectra were obtained using a JASCO V-570 spectrophotometer. Transmission electron microscopy (TEM) was conducted on a Hitachi H-600 instrument. Samples were readily dispersed in chloroform (0.3 mm) by ultrasonication (Branson Sonifier Model 185) for 0.5–1 min at 0°C , and were dropped on a carbon-coated Cu grid. The Cu meshes were subjected to TEM observation with an acceleration voltage of 75 kV and magnifications of 5000–20000.

Received: June 23, 1999 [Z 13616]

- [1] G. A. Ozin, *Adv. Mater.* **1992**, *4*, 612–649.
- [2] N. Kimizuka, T. Kunitake, *Adv. Mater.* **1996**, *8*, 89–91.
- [3] N. Kimizuka, N. Oda, T. Kunitake, *Chem. Lett.* **1998**, 695–696.
- [4] H. Okamoto, M. Yamashita, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2023–2039, and references therein.
- [5] Y. Wada, T. Mitani, M. Yamashita, T. Koda, *J. Phys. Soc. Jpn.* **1985**, *54*, 3143–3153.
- [6] H. Okamoto, T. Mitani, K. Toriumi, M. Yamashita, *Mater. Sci. Eng. B* **1992**, *13*, L9–L14.

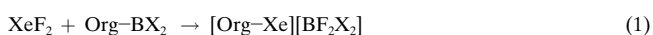
- [7] Amphiphilicity directed supramolecular assembly in organic media: N. Kimizuka, T. Kawasaki, K. Hirata, T. Kunitake, *J. Am. Chem. Soc.* **1995**, *117*, 6360–6361.
- [8] F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, 4th ed., Wiley, New York, **1980**, chap. 22.
- [9] T. Kunitake, Y. Okahata, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1877–1879.
- [10] F. Basolo, J. C. Bailar, B. R. Tarr, *J. Am. Chem. Soc.* **1950**, *72*, 2433–2438.

The First Organoxenon(IV) Compound: Pentafluorophenyldifluoroxenonium(IV) Tetrafluoroborate**

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The preparative chemistry of the noble gases is based on their binary fluorides. Of the compounds derived from the three known xenon fluorides XeF_2 , XeF_4 , and XeF_6 , relatively few Xe^{IV} species have been prepared to date.^[1] The bonding systems that have been observed are limited to $\text{Xe}^{\text{IV}}\text{--F}$ and $\text{Xe}^{\text{IV}}\text{--O}$ compounds (XeF_4 , $[\text{XeF}_3]^+$, $[\text{XeF}_5]^-$, XeOF_2 , $[\text{XeOF}_3]^-$, $\text{Xe}(\text{OTeF}_5)_4$, $\text{XeF}_3(\text{OIOF}_4)$). Important aspects of the reactivity of the parent compound XeF_4 are its fluoride-donor and -acceptor and oxidative-fluorinating abilities. The latter is intermediate to those of the other xenon fluorides: $\text{XeF}_6 > \text{XeF}_4 > \text{XeF}_2$. The fluoride-donor ability of XeF_4 is much lower than that of either XeF_2 or XeF_6 .

Since 1989 an increasing number of organoxenon(II) compounds have been prepared, mainly in the form of cationic xenonium compounds $[\text{OrgXe}][\text{X}]$ ($\text{Org} = \text{aryl}$,^[2] alkenyl,^[3] and alkynyl^[4]) but also as molecular species such as $\text{C}_6\text{F}_5\text{XeCl}$.^[5] In most cases the $\text{Xe}^{\text{II}}\text{--C}$ bond formation occurs through nucleophilic substitution with organoboranes [xenoborylation: Eq. (1)] and in some specific cases through electrophilic substitution on electron-poor aromatic compounds [xenonylation: Eq. (2)].^[6]

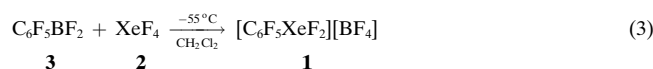


We have now been able to apply an optimized form of the xenoborylation procedure successfully to XeF_4 . Because of

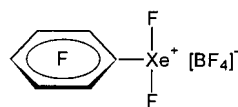
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[**] The preliminary investigations for this work were supported by the German–Slovenian Joint Project “Versuche zur ersten Synthese von Xenon(IV)-Kohlenstoff Verbindungen”. We acknowledge the National Science and Engineering Council of Canada (postdoctoral fellowship for N.L.), the Fonds der Chemischen Industrie, and the Ministry of Science and Technology of the Republic of Slovenia for financial support.

the increased oxidation potential of XeF₄ compared to XeF₂, oxidatively resistant reactants and by-products with electron-poor organic groups were required. The use of B(C₆F₅)₃, which was successful in the fluoroaryl substitution of XeF₂,^[7] had to be ruled out because the nucleophilic and easily oxidizable anion [(C₆F₅)₂BF₂][−] results from the aryl transfer. The problem of oxidizable by-products was overcome by using the recently accessible C₆F₅BF₂,^[8] which yields [BF₄][−] as the by-product. Furthermore the Lewis acidity of C₆F₅BF₂ is appropriate for the fluoroaryl substitution on XeF₄ (sufficient polarization of the hypervalent F–Xe–F bond, but no complete abstraction of a fluoride ion). If the reaction conditions are too acidic, oxidation of the aromatic system takes place. In addition to using the right aryl transfer reagent the solvent also had to be carefully selected. The basic solvent MeCN hindered the nucleophilic substitution to the point that no product **1** could be observed. Dichloromethane is a suitable solvent for strongly oxidizing nonmetal fluorides, based on previous work on fluoroaryl substitution on BrF₃^[9] and BrF₅.^[10] Additionally CH₂Cl₂ greatly facilitates the isolation of insoluble saltlike products. Pentafluorophenylboron difluoride (**3**) reacts smoothly with a suspension of xenon tetrafluoride (**2**) in CH₂Cl₂ at −55 °C to yield the first organoxenon(IV) compound, pentafluorophenyldifluoroxenonium(IV) tetrafluoroborate (**1**), in nearly quantitative yield [Eq. (3)]. Salt **1** is a yellow solid which decomposes above about −20 °C. It is insoluble in CH₂Cl₂ and dissolves well in MeCN, forming a bright yellow solution.



The Xe atom in the [C₆F₅XeF₂]⁺ cation is surrounded by two nonbonding and three bonding electron pairs, for which the VSEPR model predicts a φ -trigonal-bipyramidal arrangement resulting in a T-shaped molecular geometry (Scheme 1). The cation is isoelectronic with neutral C₆F₅IF₂. A comparison of the ¹⁹F NMR spectroscopic data of the two species shows a significant high-frequency shift for the *p*- and *m*-F atoms in the aromatic part of the cation, even in basic solution (Table 1).



Scheme 1. Salt **1** with the T-shaped arylxenonium(IV) cation.

The ¹⁹F NMR spectrum of salt **1** in a 1:1 mixture of CH₃CN and CD₃CN at −40 °C consists of resonances at −29.54 (XeF₂), −125.51 (*o*-F), −134.97 (*p*-F), −153.44 (*m*-F), and −149.01 ppm ([BF₄][−]). The XeF₂ resonance shows satellites corresponding to one-bond scalar coupling to ¹²⁹Xe (26.44 % natural abundance; *I* = 1/2) with ¹*J*(¹⁹F,¹²⁹Xe) = 3893 Hz. This ¹*J* value is comparable to that of XeF₄ itself (¹*J*(¹⁹F,¹²⁹Xe) = 3908 Hz); however, the resonance of **1** is more shielded than that of **2** in MeCN at −40 °C (δ = −19.08). The ¹²⁹Xe NMR spectrum of **1** (CH₃CN/CD₃CN 1/1) consists of a triplet at δ = −1706.5 (¹*J*(¹²⁹Xe,¹⁹F) = 3892 Hz), which is significantly shielded compared to that of XeF₄ (δ = 316.9, ¹*J*(¹²⁹Xe,¹⁹F) = 3895 Hz; MeCN, 24 °C).^[11] This difference in chemical shifts between **1** and **2** is consistent with that observed between [C₆F₅Xe]⁺ (δ = −3807.8) and XeF₂ (δ = −1784.5). The

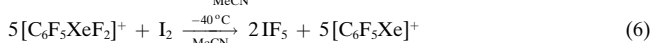
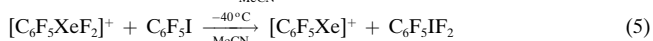
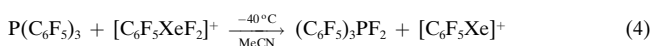
Table 1. ¹²⁹Xe, ¹⁹F, ¹³C, and ¹¹B NMR data of **1**.^[a]

¹²⁹ Xe NMR: δ = −1706.5 (t, $\tau_{1/2}$ = 206 Hz, ¹ <i>J</i> (¹²⁹ Xe, ¹⁹ F) = 3892 Hz)
¹⁹ F NMR: δ = −29.54 (s, $\tau_{1/2}$ = 20 Hz, 2F, XeF ₂ with ¹²⁹ Xe satellites, ¹ <i>J</i> (¹⁹ F, ¹²⁹ Xe) = 3893 Hz), −125.51 (m, ^[b] 2F, <i>o</i> -F), −134.97 (m, ^[b] 1F, <i>p</i> -F), −153.44 (m, 2F, <i>m</i> -F), −149.01 (s, $\tau_{1/2}$ = 82 Hz, 4F, [BF ₄] [−])
¹³ C NMR: δ = 121.86 (m, C-1), 143.28 (dd, ¹ <i>J</i> (¹³ C, ¹⁹ F) = 268.5 Hz, ² <i>J</i> (¹³ C, ¹⁹ F) = 16.2 Hz, C-2,6) 138.25 (dm, ¹ <i>J</i> (¹³ C, ¹⁹ F) = 267.8 Hz), 148.54 (dm, ¹ <i>J</i> (¹³ C, ¹⁹ F) = 273.8 Hz)
¹¹ B NMR: δ = −1.21 (s, $\tau_{1/2}$ = 18 Hz)
for comparison:
[C ₆ F ₅ Xe] ⁺ : ^[c]
¹⁹ F NMR: δ = −125.15 (2F, <i>o</i> -F), −141.86 (1F, <i>p</i> -F), −154.69 (2F, <i>m</i> -F)
C ₆ F ₅ IF ₂ : ^[c]
¹⁹ F NMR: δ = −123.02 (2F, <i>o</i> -F), −144.55 (1F, <i>p</i> -F), −156.87 (2F, <i>m</i> -F), −161.24 (2F, IF ₂)

[a] Measured with a Bruker AVANCE-DRX-500 instrument; δ (Xe) relative to XeOF₄, 24 °C; δ (F) relative to CCl₃F with C₆F₆ as internal standard; δ (C) relative to TMS with the respective solvent as a internal standard; δ (B) relative to BF₃·OEt₂. Information on the signal multiplicity, the coupling constant *J* [Hz], and the signal assignment are given in parentheses after the δ values. [b] Unresolved signal. [c] Data from the conversion of **1** with C₆F₅I, measured with a Bruker WP-80-SY instrument.

¹³C NMR spectrum of the same solution of **1** at −40 °C shows resonances at δ = 121.86 (C-1), 143.28 (C-2,6), 138.25 (C-3,5), and 148.54 (C-4). A singlet at δ = −1.21 ($\tau_{1/2}$ = 18 Hz) was observed in the ¹¹B NMR spectrum.

The preliminary data on the reactivity of the [C₆F₅XeF₂]⁺ cation in salt **1** clearly show the oxidative-fluorinating power of the XeF₂ fragment. The phosphane P(C₆F₅)₃ was oxidized by [C₆F₅XeF₂]⁺ to the phosphorane (C₆F₅)₃PF₂ [Eq. (4)]. Oxidation of the iodine atom in C₆F₅I requires strong oxidizing agents such as F₂,^[12] XeF₂,^[13] ClF, ClOCF₃, Cl₂O,^[14] or HNO₃/(CF₃CO)₂O.^[15] C₆F₅I reacts with **1** in MeCN to form C₆F₅IF₂ [Eq. (5)].



The oxidative-fluorinating ability of [C₆F₅XeF₂]⁺ under moderate conditions (coordinating solvent MeCN) is so large that the molecule I₂ was oxidized to IF₅ [Eq. (6)].

Experimental Section

All experiments were carried out under careful exclusion of moisture (dry argon atmosphere) in FEP traps (FEP = tetrafluoroethylene–hexafluoropropylene copolymer).

A solution of **3** (140 μ mol) in CH₂Cl₂ (400 μ L) at −78 °C was added to a cold suspension of **2** (117 μ mol) in CH₂Cl₂ (400 μ L) at −78 °C. The mixture was then warmed to −55 °C while stirring, resulting in the formation of a yellow solid. After 45 min at −55 °C the mother liquor was decanted and the solid dissolved in CH₃CN/CD₃CN (1/1, 400 μ L, −45 °C; Table 1).

Reactions of **1**: Yellow solutions of **1** in MeCN (approx. 30 μ mol) were treated at −40 °C with excess amounts of reagent (P(C₆F₅)₃ as a solution in MeCN, C₆F₅I as a liquid, and I₂ as a solid). The course of the reaction was followed by ¹⁹F NMR spectroscopy. The main product of the reaction with I₂ was IF₅, observed as a doublet (I(F_{eq})₄) at δ = 4.10 and a quintet (IF_{ax}) at δ = 52.80 with a coupling constant ²*J*(F,F) of 83.5 Hz.

The NMR data from the reaction with C₆F₅I show the presence of the excess of C₆F₅I as well as equimolar amounts of C₆F₅IF₂ and [C₆F₅Xe]⁺ (Table 1).

After the reaction with the phosphane the solvent was distilled off at -30°C under vacuum, the molecular organic compounds were extracted with CH_2Cl_2 at -30°C , and the solid residue was dissolved in MeCN (main product: $[\text{C}_6\text{F}_5\text{Xe}][\text{BF}_4]$ (Table 1)). The extract of the reaction with the phosphane was characterized by ^{19}F NMR spectroscopy: $\delta = 1.32$ (d hept., $^1J(\text{F},\text{P}) = 694.5$, $^4J(\text{F},\text{F}) = 16.3$, 2 F; PF_2), -132.73 (6 F, *o*-F), -146.50 (3 F, *p*-F), -159.48 (6 F, *m*-F); GC-MS (70 eV): *m/z* (%): 570 (5) $[\text{M}^+]$, 551 (3) $[\text{M}^+ - \text{F}]$, 403 (100) $[\text{M}^+ - \text{C}_6\text{F}_5]$.

Received: August 26, 1999 [Z13929]

- [1] J. H. Holloway, E. G. Hope, *Adv. Inorg. Chem.* **1999**, 46, 51–100, and references therein.
- [2] a) D. Naumann, W. Tyrre, *J. Chem. Soc. Chem. Commun.* **1989**, 47–50; b) H.-J. Frohn, S. Jakobs, *J. Chem. Soc. Chem. Commun.* **1989**, 625–627.
- [3] a) H.-J. Frohn, V. V. Bardin, *J. Chem. Soc. Chem. Commun.* **1993**, 1072–1074; b) H.-J. Frohn, V. V. Bardin, *Chem. Commun.* **1999**, 919–920.
- [4] V. V. Zhdankin, P. J. Stang, N. S. Zefirov, *J. Chem. Soc. Chem. Commun.* **1992**, 578–579.
- [5] H.-J. Frohn, T. Schroer, G. Henkel, *Angew. Chem.* **1999**, 111, 2751–2753; *Angew. Chem. Int. Ed.* **1999**, 38, 2554–2556.
- [6] D. Naumann, W. Tyrre, R. Gnann, D. Pfolk, *J. Chem. Soc. Chem. Commun.* **1994**, 2651–2653.
- [7] H.-J. Frohn, St. Jakobs, G. Henkel, *Angew. Chem.* **1989**, 101, 1534–1536; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1506–1507.
- [8] H.-J. Frohn, H. Franke, P. Fritzen, V. V. Bardin, *J. Organomet. Chem.*, in press.
- [9] H.-J. Frohn, *J. Fluorine Chem.* **1998**, 89, 59–63.
- [10] H.-J. Frohn, W. Breuer, *J. Fluorine Chem.* **1990**, 47, 301–315.
- [11] K. O. Christe, E. C. Curtis, D. A. Dixon, H. P. Mercier, J. C. P. Sanders, G. J. Schrobilgen, *J. Am. Chem. Soc.* **1991**, 113, 3351–3361.
- [12] M. Schmeisser, K. Dahmen, P. Sartori, *Chem. Ber.* **1970**, 103, 307–311.
- [13] L. M. Yagupol'skii, V. V. Lyalin, V. V. Orda, L. A. Alekseeva, *Zh. Org. Khim.* **1970**, 6, 329–332; *J. Org. Chem. (USSR)* **1970**, 6, 317–319.
- [14] H.-J. Frohn, J. Helber, *J. Fluorine Chem.* **1980**, 16, 568.
- [15] M. Schmeisser, K. Dahmen, P. Sartori, *Chem. Ber.* **1967**, 100, 1633–1637.

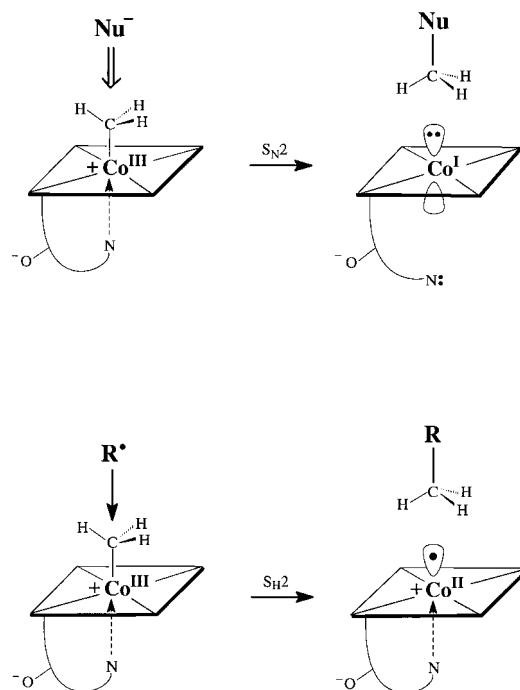
Methylcorrinoids Methylate Radicals—Their Second Biological Mode of Action?*

Hervé Mosimann and Bernhard Kräutler*

Dedicated to Professor Rolf Thauer
on the occasion of his 60th birthday

The vitamin B_{12} derivative methylcobalamin (**1**), as well as related methylcorrinoids, are fundamentally important organometallic cofactors of methylation reactions.^[1] The known enzymatic reactions with **1** depend on the heterolytic organometallic reactivities of methyl- Co^{III} -corrins and Co^{I} -corrins and the methylations proceed by nucleophilic substitution

steps (Scheme 1, top).^[2, 3] Extensive investigations of the B_{12} -dependent methionine synthase have indeed shown that the methyl transfer reactions occur by two nucleophilic substitution steps and convert homocysteine and N^5 -methyltetrahydrofolate (with net retention) into methionine and tetrahydrofolate.^[4]



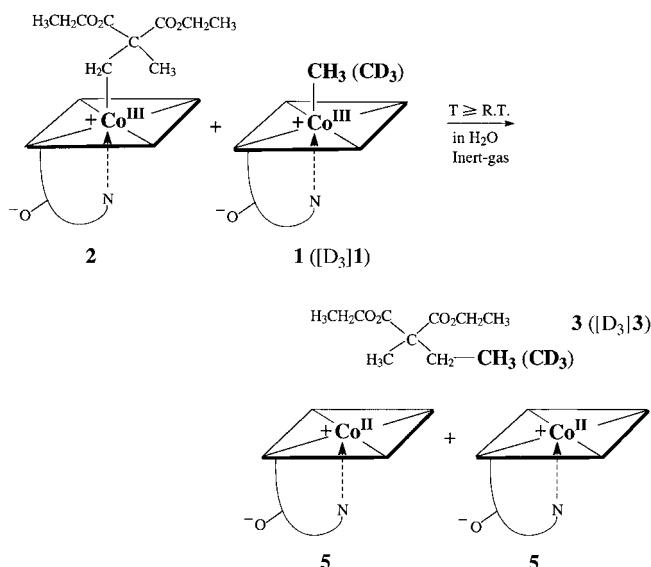
Scheme 1.

Recent biosynthetic investigations on archaeobacterial lipids^[5a] and the antibiotics bottromycin,^[5b] thienamycin,^[6a] and thiostrepton^[6b] provided evidence for unprecedented biological methylation reactions (and other alkylations) at saturated and inactivated carbon centers. In these methylation reactions methyl groups that originate from methionine are incorporated with net retention into the products.^[5, 6] Arigoni and co-workers have considered a radical mechanism involving methylcorrin cofactors for these methylation reactions.^[5a] Herein we report the first experiments that establish the (very efficient!) methylation of alkyl radicals by **1** (see Scheme 1, bottom).

Heating an oxygen-free aqueous solution of 2'-bis(ethoxycarbonyl)propylcobalamin (**2**)^[7] and methylcobalamin (**1**)^[1, 8] (**1**:**2** = 1.6:1) at 70°C for about 5 h (at pH 7, with protection from light) completely decomposed the organocobalamin **2**. The organic decomposition products obtained after oxidation of the reaction mixture with air (in the dark and with the addition of potassium cyanide) were analyzed after extraction with deuteriochloroform.^[9] The 200 MHz ^1H NMR spectrum of the product exhibited signals for a 4.6:1 mixture of 2-ethyl-2-methylmalonic acid diethyl ester (**3**) and of 2,2-dimethylmalonic acid diethyl ester (**4**), with a combined yield amounting to approximately 70 % (Scheme 2). In an analogous experiment using trideuteromethylcobalamin ($[\text{D}_3]\textbf{1}$) instead of **1** a combined yield of approximately 70 % of $[\text{D}_3]\textbf{3}$ and **4** was obtained as a 4.7:1 mixture (degree of deuteration of $[\text{D}_3]\textbf{3}$: $95 \pm 5\%$ from NMR studies). Storage of a deoxy-

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[**] We thank Prof. D. Arigoni for discussions that induced the present project. We are grateful to the Swiss National Science Foundation (H.M.) and to the Austrian National Science Foundation (FWF-Project No. 12639) for financial support.



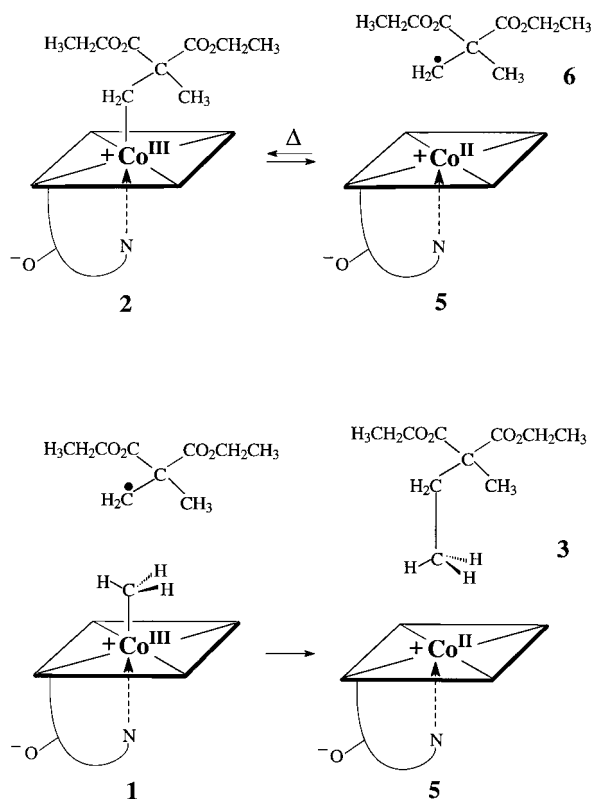
Scheme 2.

generated aqueous solution of **2** and **1** at room temperature and in the absence of light for about 17 h led to the decomposition of about 30 % of **2** and to the formation of an approximately 3:1 mixture of **3** and **4**.

The organometallic vitamin B₁₂ derivative **2** is thermally labile and decomposes even at room temperature to cob(II)alamin (**5**) and the 2-bisethoxycarbonylpropyl radical (**6**).^[7, 10] The effective half-life of **2** at 27 °C in an oxygen-saturated, neutral aqueous solution is about 50 min, which is in qualitative agreement with earlier experiments.^[7] However, **2** remains practically intact in a strictly oxygen-free aqueous solution (25 °C, pH 7), even after 20 h (UV/Vis). In a similar experiment **2** was completely decomposed after 7 h at 70 °C to Co^{II}-corrins (>90 %, UV/Vis) and to 2,2-dimethylmalonic acid diethyl ester (ca. 40 %).^[11] In contrast, aqueous solutions of methylcobalamin (**1**) are stable for a practically unlimited time at room temperature (in the absence of nucleophiles and in the dark). In the presence of the radical trap 2,2,6,6-tetramethyl-piperidinyl-1-oxyl (TEMPO) **1** is decomposed with an effective half-life of only about 4 h at 130 °C (in ethylene glycol).^[12] Compound **1** thermolytically decomposes at 200 °C with formation of methane and ethane (ca. 1:1).^[13]

Our experimental results can be explained by a decomposition of the thermolabile **2** in the presence of **1** to the Co^{II}-corrin **5** and to the 2-bisethoxycarbonylpropyl radical (**6**), which abstracts the cobalt-bound methyl group of **1**, to produce the methylation product **3** (Scheme 3).

The proposed abstraction of the cobalt-bound methyl group of methylcobalamin (**1**) by a primary alkyl radical (**6**) can be estimated from homolytic bond dissociation energies (BDE) to be a very exothermic reaction step ($\Delta H \approx -48 \text{ kcal mol}^{-1}$).^[14] Our experiments indicate that the abstraction of the organometallically bound methyl group of **1** by the radical **6** competes effectively with the recombination reaction of **6** with the Co^{II}-corrin **5** (this recombination to **2** is also strongly exothermic and presumably nearly diffusion-controlled.^[16]) We explain the formation of **3** from **1** and **2** by the substitution of the cobalt–corrin moiety of **1** by the alkyl radical **6**. Such

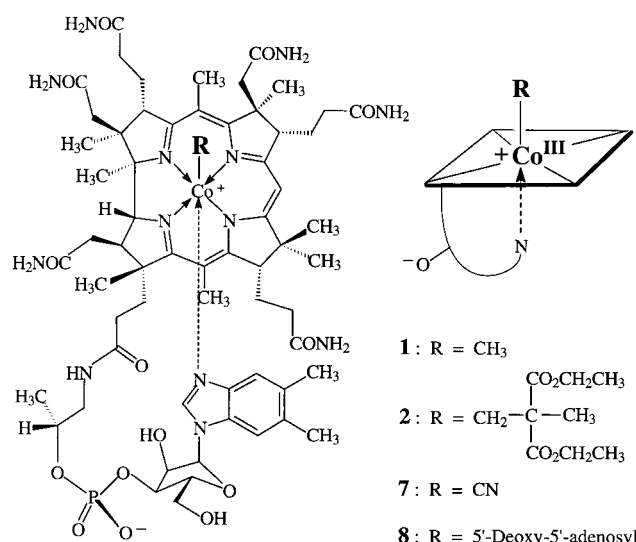


Scheme 3.

an intermolecular, homolytic substitution reaction by a (short-lived, organic) radical at a saturated carbon atom directly bound to a metal center is without precedence,^[17] but corresponding reactions of (persistent) metal radicaloids (such as Co^{II}-complexes, etc.) are known.^[18, 19] The occurrence of related intramolecular mechanisms was suggested to be responsible for the formation of (substituted) cycloalkanes from organometallic, bridged B₁₂ dimers,^[20] as well as from hexenyl cobaloximes.^[18] Homolytic substitution reactions at carbon centers, when examined more closely, were found to take place with stereochemical inversion of configuration.^[17, 18]

As a result of its characteristic low homolytic (Co–C)–BDE^[12] **1** has the reactivity of a “latent” (persistent) methyl radical towards radicals^[19, 21] and, similar to coenzyme B₁₂ (**8**, a “reversibly functioning source of an alkyl radical”),^[23] should be considered a partner in biological radical reactions. The enzymatic transfer of a methyl group from **1** to a carbon-centered radical should proceed with inversion of the configuration of the methyl group (and should therefore occur with net retention of configuration from methionine). In the known cases of unusual biosynthetic C-methylation reactions the configuration of the methyl group in the methylation product is the same as the one in methionine, the biosynthesis precursor.^[5, 6] Our investigations thus support the suggested participation of methylcorrins in biosynthetic methylations of carbon radicals.^[5]

The property of efficient radical methylation agent should, therefore, be added to the characteristic organometallic reactivities of methylcobalamin (**1**), the known biologically important methylation agent of nucleophiles.^[2, 4] Methylcor-



rinoids are to be considered also as “latent methyl radicals” and are cofactors suitable for homolytic biosynthetic methylation reactions.

Experimental Section

Trideuteromethylcob(III)alamin ([D₃]**1**): Prepared according to Tollinger et al.^[8] but using trideuteromethyl iodide instead of [¹³C]methyl iodide. Degree of deuteration was determined as 98 ± 5 % from ¹H NMR and FAB-MS studies.

2'-Bis(ethoxycarbonyl)propylcobalamin (**2**): An oxygen-free solution of aquocobalamin chloride (200 mg, 0.145 mmol) in aqueous 0.1 M LiClO₄ (5 mL, <10 ppm O₂) was reduced (UV/Vis) in a glove box at a mercury electrode to give cob(I)alamin (−1.1 V versus a 0.1 N calomel reference (0.1 NCE), consumption: 2.06 F mol^{−1}). An 0.5 M aqueous solution of *p*-toluene sulfonic acid (0.520 mL) and 2-bromomethyl-2-methylmalonic acid diethyl ester (0.178 mL)^[25a] (0.867 mmol) in methanol (1 mL) were then added in the dark. The electrolysis was continued at −1.0 V versus 0.1 NCE for 2.5 h. The solvents were removed at room temperature. The residue was dissolved in a little methanol and precipitated with acetone. The precipitate was washed with acetone and dried to give **2-H**⁺ (as the tosylate, 231 mg, 94 % yield) as an orange coloured solid (still containing 5 % aquocobalamin). UV/Vis (H₂O, pH 2): λ_{max} (lg ε) = 451 s (3.76), 421 (3.78), 296 s (4.17), 285 (4.23), 266 (4.30); ¹H NMR (500 MHz, D₂O, pD 2): δ = 9.10 (s, 1H), 7.55 (d, 2H), 7.41 (s, 1H), 7.35 (s, 1H), 7.22 (d, 2H), 7.04 (s, 1H), 6.40 (d, 1H), 4.82 (dd, 1H), 4.66 (dd, 1H), 4.62 (m, 1H), 4.58 (d, 1H), 4.21–4.15 (m, 1H), 4.07 (d, 1H), 3.92–3.85 (m, 2H), 3.80–3.72 (m, 4H), 3.64 (dd, 1H), 3.43 (d, 1H), 3.18 (dd, 1H), 3.06 (dd, 1H), 2.77–2.64 (m, 3H), 2.45–2.08 (m, 10H), 2.27 (s, 6H), 2.24 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.04–1.89 (m, 5H), 1.80–1.60 (m, 4H), 1.75 (s, 3H), 1.53 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H), 1.29 (d, 1H), 1.15 (s, 3H), 1.03 (d, 3H), 0.95 (t, 3H), 0.86 (t, 3H), 0.54 (d, 1H), 0.50 (s, 3H), −0.07 (s, 3H); FAB-MS (*o*-nitrobenzyl alcohol (NOBA) matrix): *m/z* (%): 1518.5/1517.5/1516.5 (17/22/28) [*M*+H⁺]; 1331.5/1330.5/1329.4 (38/76/100) [*M*+H⁺ − C₅H₅O₄].

Thermolysis of **2** in presence of methylcobalamin (**1**): **2-H**⁺ (30.0 mg containing 17 % water, 0.0135 mmol) was dissolved in hydrochloric acid (3 mL, 10 mM). The solvents were removed and the solid residue was dried. Similarly **1** (29.0 mg, 0.0216 mmol) was dissolved in water (5 mL) and then dried. Both compounds were then dissolved in phosphate buffer (4 mL, 0.1 M, pH 7) in the dark and in the glove box, and the deoxygenated mixture was heated in the dark at 70 °C for 5 h. Oxygen-saturated water (2 mL) and 0.5 M aqueous KCN (0.054 mL) were then added and the mixture was extracted with CDCl₃ (3 × 0.6 mL). The extract was dried by passing through a plug of dried cotton wool. Analysis by 200 MHz ¹H NMR spectroscopy identified the product as a 4.6:1 mixture of 2-ethyl-2-methylmalonic acid diethyl ester (**3**)^[25b] and 2,2-dimethyl-malonic acid diethyl ester (**4**).^[25c] The total yield (ca. 70 %) was estimated by comparison with the signal of the residual CHCl₃ in CDCl₃ (standardized against

anthracene). **3**: ¹H NMR (200 MHz, CDCl₃):^[25b] δ = 4.19 (q, *J* = 7.1, OEt), 1.92 (q, *J* = 7.5, Et-C(2)), 1.39 (s, CH₃-C(2)), 1.25 (t, *J* = 7.1, OEt), 0.88 (t, *J* = 7.5, Et-C(2)).

Thermolysis of **2** and trideuteromethylcobalamin ([D₃]**1**): The reaction was carried out as above, but with [D₃]**1** instead of **1**, and gave 2-(2,2,2-trideuteroethyl)-2-methylmalonic acid diethyl ester ([D₃]**3**) and **4** (4.7:1, 71 %). [D₃]**3**: ¹H NMR (200 MHz, CDCl₃): δ = 4.19 (q, *J* = 7.1, OEt), 1.89 (brs, Et-C(2)), 1.39 (s, CH₃-C(2)), 1.25 (t, *J* = 7.1, OEt).

Received: June 25, 1999 [Z13632]

- [1] W. Friedrich, *Vitamin B₁₂ und verwandte Corrinoides*, Vol. III/2 of *Fermente, Hormone und Vitamine* (Ed.: R. Ammon, W. Dirscherl), Georg Thieme, Stuttgart, **1975**.
- [2] J. M. Pratt, *Inorganic Chemistry of Vitamin B₁₂*, Academic Press, New York, **1972**.
- [3] B. Kräutler in *Vitamin B₁₂ and B₁₂ Proteins* (Eds.: B. Kräutler, D. Arigoni, B. T. Golding), WILEY-VCH, Weinheim, **1998**, pp. 3–43.
- [4] a) C. L. Drennan, S. Huang, J. T. Drummond, R. G. Matthews, M. L. Ludwig, *Science* **1994**, *266*, 1669–1674; b) M. L. Ludwig, R. G. Matthews, *Annu. Rev. Biochem.* **1997**, *66*, 269–313.
- [5] a) P. Galliker, O. Gräther, M. Rümmler, W. Fitz, D. Arigoni in *Vitamin B₁₂ and B₁₂ Proteins* (Eds.: B. Kräutler, D. Arigoni, B. T. Golding), WILEY-VCH, Weinheim, **1998**, pp. 447–458; b) L. Kellenberger, D. Holmes, B. Martinoni, D. Arigoni, *Chimia* **1996**, *50*, 344.
- [6] a) D. R. Houck, K. Kobayashi, J. M. Williamson, H. G. Floss, *J. Am. Chem. Soc.* **1986**, *108*, 5365–5366; b) P. Zhou, D. O'Hagan, U. Mocek, Z. Zeng, L.-D. Yuen, T. Frenzel, C. J. Unkefer, J. M. Beale, H. G. Floss, *J. Am. Chem. Soc.* **1989**, *111*, 7274–7276.
- [7] J. H. Grate, J. W. Grate, G. N. Schrauzer, *J. Am. Chem. Soc.* **1982**, *104*, 1588–1594.
- [8] M. Tollinger, T. Dérer, R. Konrat, B. Kräutler, *J. Mol. Catal. A* **1997**, *116*, 147–155.
- [9] The aqueous fraction of a similar experiment contained vitamin B₁₂ (**7**) and **1** in the ratio 1.7:1.0 (¹H NMR).
- [10] In acidic solutions **2** is protonated at the nucleotide base to give **2-H**⁺, which tends to decompose more than 100 times less rapidly than **2**.
- [11] The NMR data provided no evidence for the existence of products derived from a rearrangement of **6** to a methylsuccinyl radical (for studies with **6** and with related radicals in solution, see S. Wollowitz, J. Halpern, *J. Am. Chem. Soc.* **1988**, *110*, 3112–3120).
- [12] B. D. Martin, R. G. Finke, *J. Am. Chem. Soc.* **1992**, *114*, 585–592.
- [13] G. N. Schrauzer, J. W. Sibert, R. J. Windgassen, *J. Am. Chem. Soc.* **1968**, *90*, 6681–6688.
- [14] (Co-C)-BDE (**1**) ≈ 37 kcal mol^{−1}; [12] (C-C)-BDE (**3**) ≈ 85 kcal mol^{−1}.^[15]
- [15] A. J. Gordon, R. A. Ford in *The Chemist's Companion*, Wiley, New York, **1972**.
- [16] J. F. Endicott, G. J. Ferraudi, *J. Am. Chem. Soc.* **1977**, *99*, 243–245.
- [17] J. C. Walton, *Acc. Chem. Res.* **1998**, *31*, 99–107.
- [18] M. D. Johnson, *Acc. Chem. Res.* **1983**, *16*, 343–349.
- [19] B. Kräutler, *Helv. Chim. Acta* **1987**, *70*, 1268–1278.
- [20] B. Kräutler, T. Dérer, P. Liu, W. Mühlecker, M. Puchberger, K. Gruber, C. Kratky, *Angew. Chem.* **1995**, *107*, 66–69; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 84–86.
- [21] The observation of ethane as the main product of the photolysis^[13] and of the reductive electrolysis^[22] of **1** was rationalized by dimerization of methyl radicals.^[13, 22] Our results suggest an alternative consideration, namely of a direct reaction of methyl radicals with the intact methylcorrinoid (**1**).
- [22] K. A. Robinson, E. Itabashi, H. B. Mark, Jr., *Inorg. Chem.* **1982**, *21*, 3571–3573.
- [23] J. Halpern, *Science* **1985**, *227*, 869–875.
- [24] Co^{II}-corrinoids (such as **5**, the biologically important radical traps)^[3] then may act, in a complementary way, in homolytic demethylations of reactive (radicaloid) methylating agents.^[8, 19]
- [25] a) Y. Murakami, Y. Hisaeda, T. Ozaki, T. Tashiro, T. Ohno, Y. Tani, Y. Matsuda, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 311–324; b) F. Björklund, J. Boutelje, S. Gatenbeck, K. Hult, T. Norin, P. Szmulik, *Tetrahedron* **1985**, *41*, 1347–1352; c) L. Kiriazis, E. Kalatzis, N. E. Alexandrou, *J. Heterocycl. Chem.* **1989**, *26*, 155–160.

Enzymatic Synthesis of Neoglycopeptide Building Blocks**

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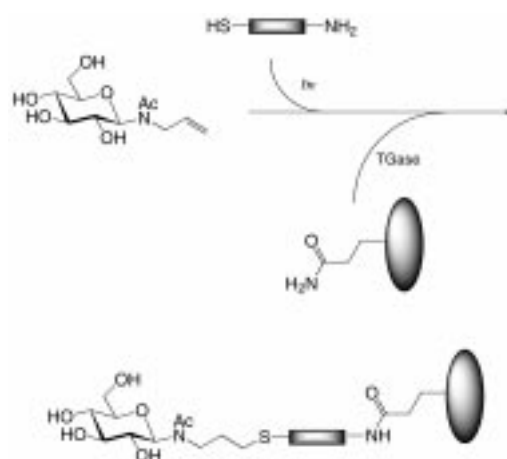
Cellular interactions triggered by glycostructures are imperative for the smooth functioning of an organism. On the other hand, and far less beneficial, such structures serve as anchors for pathogenic organisms harmful to the host. Both these functions imply uses for such structures in biomedical applications and therefore, the need for unlimited and facile access to a library of glycopeptide structures is evident. Ideally, saccharide and peptide should be prepared in parallel, to a certain degree.

Transglutaminase (glutaminy-peptide γ -glutamyl transferase, TGase, EC 2.3.2.13) is an acyl transferase that catalyzes the amidation reaction of primary amines with the γ -carboxamide residue of glutamine. Previous research in this area is illustrated by a few key papers and patents: the enzyme has been used to synthesize high molecular weight emulsifiers,^[1] for protein immobilization,^[2] to cross-link trypsin/ α -amylase mixtures after preabsorption on DEAE-type ion-exchange resins (DEAE = diethylaminoethyl),^[3] to prepare hapten-protein conjugates for ELISA (enzyme-linked immunosorbent assay) assays,^[4] and to synthesize high molecular weight peptidoglucans.^[5]

We report here on a regioselective procedure for the synthesis of N-linked-neoglycopeptides, leaving the core sugar conformation intact. Amino functionalization is achieved on the saccharide, after N-glycosylation using allylamine, by photoinduced coupling of cysteamine (2-aminoethanthiol) to the double bond (Scheme 1).

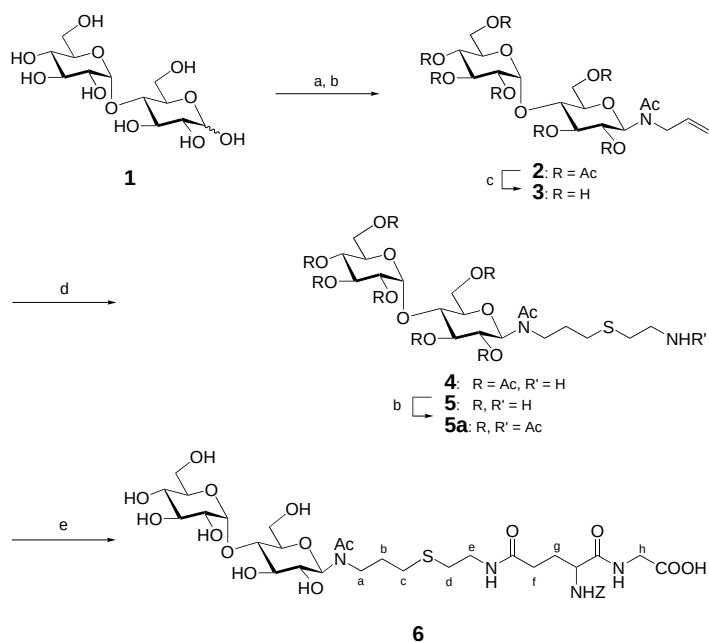
Whereas in most biotechnical applications cross-linking has been brought about by transaminase acting on ϵ -amino groups of lysine, the question here arose whether the amino group could also be attached through a spacer linkage to the anomeric center of a glycoside. Such a construction would mimic the Asn-glycoside linkage of N-linked glycoproteins, and it would require the least modification of the saccharide part (Asn = asparagine).

To qualify as a versatile chemo-enzymatic procedure the reaction should: 1) be performed in aqueous media, 2) allow for a wide range of substrates, 3) not depend on cofactors, like the *in vitro* route which uses dolichyl phosphates in peptide glycosylation does, and 4) be feasible on a preparative scale.



Scheme 1. Rationale of the spacer-transglutaminase approach.

The chosen model compound maltose (**1**), was allowed to react with allylamine^[6] and subsequently acetylated to yield the stable peracetylated β -configured anomer **2** (Scheme 2). Upon irradiation (254 nm) of a mixture of **2** and cysteamine



Scheme 2. Chemoenzymatic synthesis of the neoglycopeptide **6**: a) $\text{CH}_2\text{CHCH}_2\text{NH}_2$, room temperature, 72 h; b) Ac_2O /pyridine (1/2), DMAP (85% yield from maltose); c) MeONa/MeOH , pH 10 (90%); d) cysteamine hydrochloride (5 equiv), MeOH , $h\nu$ (254 nm), argon, 8 h (80%); e) compound **5** (30 mM), Z-Gln-Gly (30 mM), TGase (20 g l^{-1}), phosphate buffer ($\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$ 0.2 M, pH 6), 50 °C, shaken for several hours (60%). DMAP = 4-dimethylaminopyridine, Z-Gln-Gly = benzyloxycarbonyl-glutamine-glycine, TGase = transglutaminase.

hydrochloride in methanol,^[7–10] the peracetylated thioether **4** was obtained in 80% yield. This compound was prone to acyl migration, and therefore allylglycosamine **2** was deacetylated prior to the photoaddition reaction to yield a stable compound **3**. After the photochemical step, **3** furnished the unprotected spacer modified disaccharide **5**.

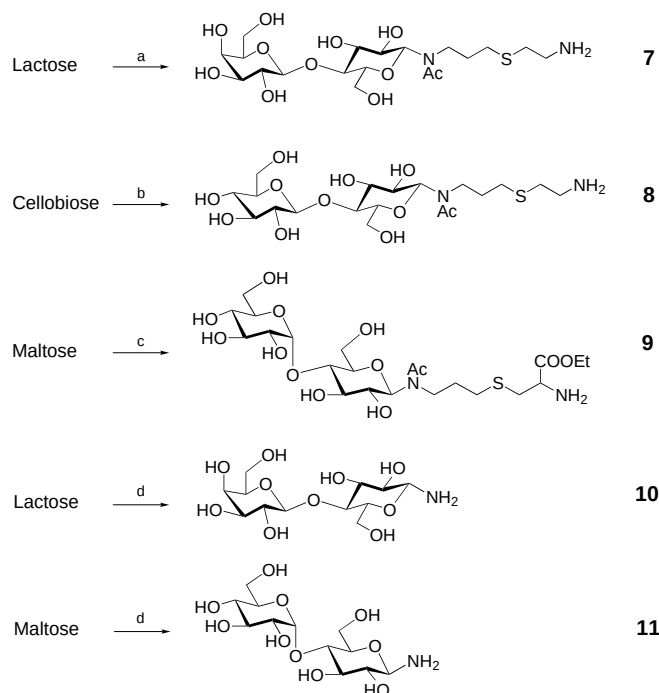
The spacer requirements were evaluated by estimating the relative activities of compounds **4**, **5**, **7**, **8**, **9**, **10**, and **11**

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[**] This work has enjoyed generous financial support from Unilever Research Vlaardingen, which is gratefully acknowledged. Microbial transglutaminase (EC 2.3.2.13) was a kind gift from Ajinomoto Co. Europe, Hamburg.

(Scheme 3) relative to hydroxylamine (100%). *N*-Acetyl-[4-*O*- α -D-glucopyranosyl]- β -D-glucopyranosyl]-3-thio(2-aminoethyl)aminopropane (**5**) was accepted as a substrate by the



Scheme 3. Synthesis of additional artificial substrates for TGase. a) 4 steps, 79% from lactose; b) 4 steps, 78% from cellobiose; c) 4 steps, 65% from maltose; d) NH_4HCO_3 (saturated solution), 40 °C, 4 d.

enzyme with a relative activity of 21% (Table 1) and, as expected, the per-*O*-acetylated counterpart **4** was almost inactive. Compounds **7** and **8**, prepared from lactose and cellobiose following the same procedure as for the synthesis of **5**, also proved to be good substrates for the TGase with relative activities comparable to that found for compound **5** (19 and 18%). The lack of activity for **9** may be attributed to the hindrance and the electronic situation of the amine, whereas either the instability at pH 6 or the lack of spacer yielded both lactosamine **10** and maltosamine **11**^[12, 13] inactive. This research demonstrates that the primary amino spacer arm, rather than the nature of the sugar backbone, determines the recognition by the enzyme, allowing this method to be applied to a variety of saccharides.

Table 1. Evaluation of the spacer requirements.

Compound	Relative activity ^[a] [%]
NH_2OH	100
4	1
5	21
7	19
8	18
9	0
10	0
11	0

[a] Relative activities [$V_0^{\text{Obs}}/V_0^{\text{NH}_2\text{OH}}$] of compounds **4**, **5**, **7**, **8**, **9**, **10** and **11** were estimated against hydroxylamine (standard, 100%). Liberated NH_3 was detected by the glutamate dehydrogenase/reduced nicotinamide adenine dinucleotide phosphate (GLDH/NADPH) assay.^[11]

For the preparative scale transacylation, compound **5** was allowed to react with the dipeptide benzyloxycarbonyl-glutamine-glycine (*Z*-Gln-Gly) and Tgase^[14] in a buffered solution (pH 6), at 50 °C.^[15, 16] The characterization of compound **6** (Table 2), after work-up, proved the covalent cross-linking between the saccharide and the peptide.

Table 2. Selected physical data for compounds **2**, **5**, **5a**, and **6**.

2: ^1H NMR (300 MHz, CDCl_3): δ = 5.86 (d, $J_{1,2}$ = 9.5 Hz; H-1), 5.74 (dddd; $\text{CH}=\text{CH}_2$), 5.36 (d, $J_{1,2}$ = 4 Hz; H-1'), 5.34 (dd $\sim$ t, $J_{2,3}$ = 9, $J_{3,4}$ = 9 Hz; H-3), 5.34 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 9.6 Hz; H-3'), 5.10 (d; $\text{CH}=\text{CH}_2$), 5.01 (dd $\sim$ t, $J_{4,5}$ = 10, $J_{3,4}$ = 9.6 Hz; H-4'), 4.87 (dd $\sim$ t, $J_{1,2}$ = 9.5, $J_{2,3}$ = 9 Hz; H-2), 4.82 (dd, $J_{2,3}$ = 10.4, $J_{1,2}$ = 4 Hz; H-2'), 4.40 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6a}$ = 2.5 Hz; H-6'a), 4.20 (dd, $J_{6a,6b}$ = 12.3, $J_{5,6b}$ = 4 Hz; H-6'b), 4.15 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 4 Hz; H-6'a), 4.03 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6b}$ = 2.5 Hz; H-6'b), 3.92 (m_c, $J_{4,5}$ = 10, $J_{3,4}$ = 9, $J_{5,6b}$ = 4, $J_{5,6a}$ = 2.5 Hz; H-4, H-5'), 3.75 (m_c, $J_{5,6a}$ = 4, $J_{5,6b}$ = 2.5 Hz; H-5, $\text{CH}_2-\text{CH}=\text{CH}_2$); ^{13}C NMR (75 MHz, CDCl_3): δ = 171.00–170.00 (8 $\times$ C=O), 135.17 ($\text{CH}=\text{CH}_2$), 117.43 ($\text{CH}=\text{CH}_2$), 96.00 (C-1'), 80.34 (C-1), 76.27 (C-3), 74.98 (C-5), 73.04 (C-4), 71.32 (C-2), 70.49 (C-2'), 69.80 (C-3'), 69.03 (C-4'), 68.55 (C-5'), 62.99 (C-6), 61.95 (C-6'), 24.87 ($\text{CH}_2-\text{CH}=\text{CH}_2$), 22.00–21.00 (8 $\times$ COCH_3); MS (ESI): m/z : 740 [$M+\text{Na}$]⁺

5: White powder (80% yield); MS (ESI): m/z : 523 [$M+\text{Na}$]⁺, 501 [$M+\text{H}$]⁺. For analytical purposes, **5** was peracetylated to form **5a**

5a: ^1H NMR (600 MHz, CDCl_3): δ = 5.39 (d, $J_{1,2}$ = 4 Hz; H-1'), 5.30 (m_c, $J_{2,3}$ = 10.5, $J_{1,2}$ = 9.7, $J_{3,4}$ = 9.7, $J_{3,4}$ = 9.1 Hz; H-2, H-3, H-3'), 5.00 (t, $J_{1,2}$ = 9.7, $J_{3,4}$ = 9.7, $J_{4,5}$ = 9.7 Hz; H-1, H-4'), 4.80 (dd, $J_{2,3}$ = 10.5, $J_{1,2}$ = 4 Hz; H-2'), 4.48 (dd, $J_{6a,6b}$ = 12.5 Hz; H-6b), 4.19 (dd, $J_{6a,6b}$ = 12.1, $J_{5,6b}$ = 4.1 Hz; H-6'b), 4.16 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 4 Hz; H-6a), 4.02 (dd, $J_{6a,6b}$ = 12.1, $J_{5,6a}$ = 2.5 Hz; H-6'a), 3.98 (dd, $J_{3,4}$ = 9.1, $J_{4,5}$ = 9.1 Hz; H-4), 3.90 (m_c, $J_{4,5}$ = 9.7, $J_{5,6b}$ = 4.1, $J_{5,6a}$ = 2.5 Hz; H-5'), 3.72 (m_c, $J_{4,5}$ = 9.1, $J_{5,6a}$ = 4 Hz; H-5), 3.35 (m_c; CH_2 (e)), 2.59 (m_c; CH_2 (d)), 2.42 (m_c; CH_2 (a)), 2.15–1.88 (m; 9 $\times$ COCH_3), 1.83 (m_c, 1H; CH_2 (c)), 1.71 (m_c, 3H; CH_2 (c), CH_2 (b)); ^{13}C NMR (150 MHz, CDCl_3): δ = 171.60–169.30 (9 $\times$ COCH_3), 95.49 (C-1'), 85.26 (C-1), 75.91, 75.67 (C-2 + C-3), 74.63 (C-5), 69.95 (C-2'), 69.37 (C-4'), 69.14 (C-3'), 68.54 (C-5'), 62.45 (C-4), 62.40 (C-6), 61.33 (C-6'), 38.43 (CH_2 (e)), 31.72 (CH_2 (d)), 30.31 (CH_2 (c)), 29.17 (CH_2 (a)), 28.43 (CH_2 (b)), 23.10–20.43 (9 $\times$ COCH_3); MS (ESI): m/z : 859 [$M+\text{Na}$]⁺, 837 [$M+\text{H}$]⁺

6: ^1H NMR (600 MHz, D_2O): δ = 7.41 (m_c; aromatic-Hs), 5.38 (d; H-1'), 5.15, 5.07 (each d, each 1H; CH_2-Ph), 4.98 (d, $J_{1,2}$ = 8.5 Hz; H-1), 4.12 (m_c; CH (Gln)), 3.90–3.45 (m, $J_{6a,6b}$ or $J_{6a,6b}$ = 12.0, $J_{3,4}$ or $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.5, $J_{1,2}$ = 8.5 Hz; CH_2 (f), CH_2 (g), CH_2 (h), H-2, H-2', H-3, H-3', H-4', H-5, H-5', H-6, H-6'), 3.40 (dd, $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.5 Hz; H-4), 3.31 (m_c; CH_2 (e)), 2.64 (m_c; CH_2 (d)), 2.52 (m_c; CH_2 (a)), 2.34 (m_c; CH_2 (c)), 1.87 (m_c; CH_2 (b)); ^{13}C NMR (150 MHz, D_2O): δ = 175.16–175.53 (5 $\times$ C=O), 136.12 (aromatic-C), 128.70–127.69 (5 $\times$ aromatic-CH), 99.57 (C-1'), 86.73 (C-1), 77.19–69.20 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5', 2 $\times$ CH_2), 67.17 (CH_2-Ph), 60.73, 60.36 (C-6 + C-6'), 43.33 (CH_2), 38.42 (CH_2 (e)), 31.87 (CH_2 (c)), 29.10 (CH_2 (d)), 27.85 (CH_2 (a)), 27.12 (CH_2 (b)); MS (ESI): m/z : 865 [$M+\text{H}+2\text{Na}$]⁺ (daughter 757 [$(M-\text{OCH}_2\text{Ph})+2\text{Na}$]⁺), 859 [$M+\text{K}$]⁺ (daughter 751 [$(M-\text{OCH}_2\text{Ph})+\text{K}$]⁺), 843 [$M+\text{Na}$]⁺ (daughter 735 [$(M-\text{OCH}_2\text{Ph})+\text{Na}$]⁺), 819 [$M-\text{H}$]⁻ (daughter 711 [$(M-\text{OCH}_2\text{Ph})-\text{H}$]⁻).

In conclusion, a practical combined approach towards new glycoprotein structures has been worked out, which requires minor modifications of the saccharide and thereby conserves the spatial arrangement of the sugar functionality. By combining both photochemical linking and enzymatic acyl transfer, a double regiochemical control can be exerted on the glycoside as well as on the peptide. Finally, this procedure should be applicable to the synthesis of neoglycopeptide building blocks and the synthesis of multivalent glycoside ligands on a suitably arranged protein scaffold.

Received: August 9, 1999 [Z13846]

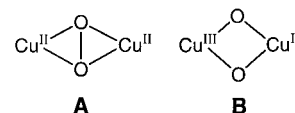
- [1] A. Kato, T. Wada, K. Kobayashi, K. Seguro, M. Motoki, *Agric. Biol. Chem.* **1991**, 55, 1027–1027.
- [2] M. Motoki, H. Aso, K. Seguro, N. Nio, *Agric. Biol. Chem.* **1987**, 51, 997–1002.
- [3] Y. Kanata, E. Ishikawa, M. Motoki, *Agric. Biol. Chem.* **1992**, 56, 1323–1324.
- [4] A. Josten, M. Mensel, F. Spener, *Anal. Biochem.* **1998**, 258, 202–208.
- [5] S.-C. B. Yan, F. Wold, *Biochemistry* **1984**, 23, 3759–3765.
- [6] W. Spevak, F. Dasgupta, C. J. Hobbs, J. O. Nagy, *J. Org. Chem.* **1996**, 61, 3417–3422.
- [7] R. T. Lee, Y. C. Lee, *Carbohydr. Res.* **1974**, 37, 193–201.
- [8] R. Roy, C. A. Laferriere, A. Gamian, H. J. Jennings, *J. Carbohydr. Chem.* **1987**, 6, 161–165.
- [9] R. Roy, *J. Chem. Soc. Chem. Commun.* **1988**, 1058–1060.
- [10] C. Kieburg, M. Dubber, T. K. Lindhorst, *Synlett* **1997**, 1447–1449.
- [11] Sigma Diagnostics, ammonia detection kit [No 171-A].
- [12] L. M. Likhoshesterov, O. S. Novikova, V. A. Derevitskaja, N. K. Kotchetkov, *Carbohydr. Res.* **1986**, 146, C1–C5.
- [13] L. Urge, E. Kollat, M. Hollosi, I. Laczkó, K. Wroblewski, J. Thurin, L. Otvos, Jr., *Tetrahedron Lett.* **1991**, 32, 3445–3448.
- [14] The commercial transglutaminase, produced by a fermentation method and stabilized in maltodextrin (ratio of protein to carbohydrate was not specified by supplier) was used without any further purification. The microbial enzyme (TGase) is reported to be Ca^{2+} -independent.
- [15] F. Lipmann, L. C. Tuttle, *J. Biol. Chem.* **1945**, 21–28.
- [16] J. E. Folk, P. W. Cole, *J. Biol. Chem.* **1965**, 240, 2951–2960; J. E. Folk, P. W. Cole, *J. Biol. Chem.* **1966**, 241, 5518–5525.

Aliphatic Hydroxylation by a Bis(μ -oxo)dicopper(III) Complex**

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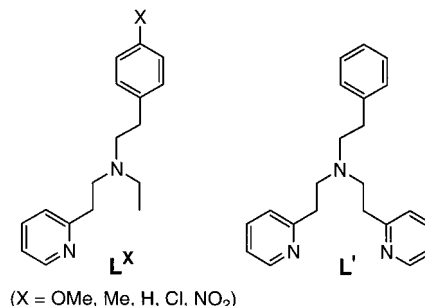
Understanding how metal–dioxygen adducts react in biochemical and synthetic transformations of organic substrates is an important research objective.^[1] Significant progress toward this goal has been made through the detailed characterization of complexes derived from the reaction of dioxygen with Cu^{I} precursors.^[2] Of the adducts characterized by X-ray crystallography to date^[3–5] the (μ - η^2 : η^2 -peroxo)- and

bis(μ -oxo)dicopper units **A** and **B**, respectively, have drawn particular attention as a consequence of their known or potential relevance



to intermediates in hydroxylation reactions performed by copper oxygenases such as tyrosinase and particularly methane monooxygenase (pMMO).^[6] Although **B** has yet to be observed in an enzyme system, the possibility that **A** (identified as an intermediate in tyrosinase and catechol oxidase) may convert into **B** prior to activation of the substrate C–H bond is supported by the observed reactivity of synthetic examples of these cores.^[5, 7, 8] Evidence in support of the ability of core **B** to hydroxylate arene rings,^[9] to abstract H atoms from the weak C–H bonds of dihydroanthracene,^[10] and to oxidatively N-dealkylate ligand substituents has been uncovered.^[5, 11] Mechanistic studies of the latter reaction implicate an initial hydroxylation at the activated position α to the N donor by a rate-controlling C–H bond scission to yield a presumed carbinolamine intermediate, which then decays to the product aldehyde and secondary amine.^[11] However, direct observation of the hydroxylation of aliphatic C–H bonds by **B**, a reaction relevant to the function of monooxygenase (for example, pMMO), has remained elusive.^[12]

Herein we describe a new set of bis(μ -oxo)dicopper complexes with ligand L^{X} (L^{X} = *p*-substituted *N*-ethyl-*N*-[2-(2-pyridyl)ethyl]-2-phenylethylamine; X = OMe, Me, H, Cl, NO₂) that decompose to a product in which the ligand is



hydroxylated at its benzylic position. Detailed characterization of this newly discovered aliphatic C–H bond activation reaction by core **B** reveals important information on the fundamental chemistry underlying copper monooxygenase reactivity.

Figure 1 shows the spectral changes observed upon introduction of O₂ into a solution of $[\text{Cu}^{\text{I}}(\text{L}^{\text{H}})(\text{CH}_3\text{CN})]\text{PF}_6$ in acetone at -90°C .^[13] An absorption band at 402 nm ($\epsilon = 17700\text{ M}^{-1}\text{ cm}^{-1}$)^[14] similar to those of the bis(μ -oxo)dicopper(III) complexes reported previously^[5] appears gradually. Also similar to other complexes with core **B** is that the solution is ESR silent. Furthermore, the resonance Raman spectrum ($\lambda_{\text{ex}} = 457.9\text{ nm}$) of a frozen $[\text{D}_6]\text{acetone}$ solution of the intermediate generated using $[\text{Cu}^{\text{I}}(\text{L}^{\text{H}})(\text{CH}_3\text{CN})]\text{PF}_6$ ($[\text{D}_4]\text{L}^{\text{H}}$: *N*-ethyl-*N*-[2-(2-pyridyl)ethyl]-1,1,2,2-tetradeuterio-2-phenylethylamine) has an intense peak at 607 cm^{-1} that shifts to 578 cm^{-1} upon isotopic substitution with $^{18}\text{O}_2$ (see inset of Figure 1). This frequency and isotopic shift ($\Delta\tilde{\nu} = 29\text{ cm}^{-1}$) are very close to those reported for bis(μ -oxo)di-

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[**] The present study was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Area (Molecular Biometallics: 10129218; Electrochemistry of Ordered Interface: 10131242) from the Ministry of Education, Science, Culture, and Sports of Japan and the National Institutes of Health of the USA (postdoctoral fellowship to P.L.H., grant GM47365 for W.B.T., and grant GM33162 to L.Q.).

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

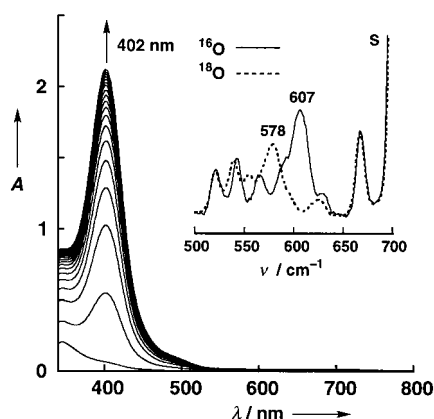


Figure 1. Changes in the UV/Vis spectrum observed at 5 s intervals upon introduction of O_2 gas into an acetone solution of $[Cu^I(L^H)(CH_3CN)]PF_6$ (2.5×10^{-4} M) at $-90^\circ C$ in a UV cell (path length: 1 cm). Inset: resonance Raman spectra of frozen solutions of $[Cu^{II}(D_4L^H)_2(\mu-^{16}O_2)](PF_6)_2$ (—) and $[Cu^{II}(D_4L^H)_2(\mu-^{18}O_2)](PF_6)_2$ (---) in $[D_6]$ acetone; “s” denotes a solvent absorption band.

copper(III) complexes.^[5, 15] These spectral features firmly demonstrate that the oxygenated intermediate formed in the present system has a bis(μ -oxo)dicopper(III) core. The rate of formation of the bis(μ -oxo)dicopper(III) complex is second order with respect to the concentration of the starting Cu^I complex ($\Delta H^\ddagger = 25.3 \pm 1.1$ kJ mol $^{-1}$ and $\Delta S^\ddagger = -22.8 \pm 6.0$ J K $^{-1}$ mol $^{-1}$), which suggests that the bimolecular reaction between an initially formed monomeric superoxocopper(II) complex, $[Cu^{II}(L^X)O_2]^{+}$, and another Cu^I starting compound is rate-determining and that the resulting (μ -peroxo)-dicopper(II) intermediate, $[Cu_2^{II}(L^X)_2(\mu-O_2)]^{2+}$, rapidly converts into the bis(μ -oxo)dicopper(III) species.

When the bis(μ -oxo)dicopper(III) intermediate derived from oxygenation of $[Cu^I(L^H)(CH_3CN)]PF_6$ in acetone at $-78^\circ C$ was warmed and allowed to stand at $25^\circ C$ for 20 h under an atmosphere of O_2 , benzylic hydroxylation of the ligand side arm (phenethyl group) occurred in 46% yield (theoretical maximum is 50%). This result parallels that found previously for the reaction of $[Cu^I(L')PF_6]$ ($L' = N,N$ -bis[2-(2-pyridyl)ethyl]-2-phenylethylamine) with O_2 , although the intermediacy of a bis(μ -oxo)dicopper(III) species was not detected directly in this case.^[7] The mass spectrum of the modified ligand obtained in the reaction of complexes with L^H using $^{18}O_2$ (96% labeled) clearly showed that the origin of the oxygen atom of the OH group was molecular oxygen (peak height: $M^+:(M^++2) = 4.2:100$). In addition, the stoichiometric ratio $O_2:Cu$ for the hydroxylation reaction was determined to be 1:2 by manometry.

Kinetic studies of the ligand hydroxylation revealed it to be a first-order process, presumably involving the intramolecular decay of the bis(μ -oxo)dicopper(III) intermediate. The activation parameters were determined to be $\Delta H^\ddagger_H = 39.1 \pm 0.4$ kJ mol $^{-1}$ and $\Delta S^\ddagger_H = -72.6 \pm 1.9$ J K $^{-1}$ mol $^{-1}$ (Figure 2, ○). An Eyring plot for the ligand hydroxylation reaction for the complexes with $[D_4]L^H$ yielded $\Delta H^\ddagger_D = 52.8 \pm 0.5$ kJ mol $^{-1}$ and $\Delta S^\ddagger_D = -31.1 \pm 2.3$ J K $^{-1}$ mol $^{-1}$; the observed kinetic deuterium isotope effect (KIE) was 35.4 at $-80^\circ C$. The effects of *p*-substituents on the hydroxylation process were also examined using L^X ($X = OMe, Me, H, Cl, NO_2$) and the Hammett plot of

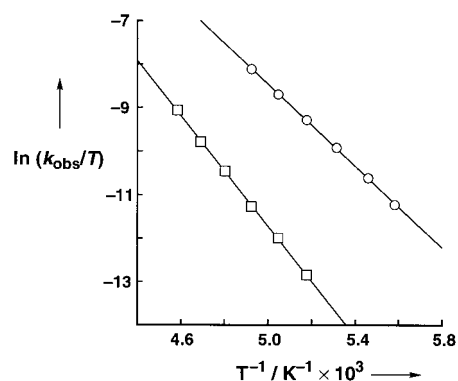
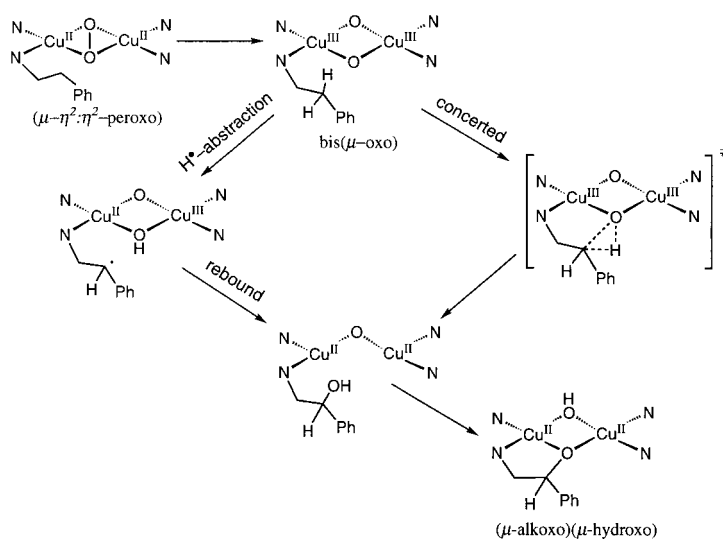


Figure 2. Eyring plots for the ligand hydroxylation of $[Cu^{II}(L^H)_2(\mu-O_2)](PF_6)_2$ (○) and $[Cu^{II}(D_4L^H)_2(\mu-O_2)](PF_6)_2$ (□) in acetone.

the first-order rate constant k_{obs} versus σ^+ ^[16] gave $\rho = -1.48$ ($R = 0.99$).^[17] Overall, the activation parameters, KIE, and ρ value for the ligand hydroxylation are similar to those measured previously for the oxidative N-dealkylation reaction of $[(L^{IPr_3}Cu)_2(\mu-O_2)](ClO_4)_2$ ($L^{IPr_3} = 1,4,7$ -triisopropyl-1,4,7-triazacyclononane); ($\Delta H^\ddagger_H = 55.2 \pm 2.1$ kJ mol $^{-1}$, $\Delta S^\ddagger_H = -59 \pm 8$ J K $^{-1}$ mol $^{-1}$, $\Delta H^\ddagger_D = 62.7 \pm 2.1$ kJ mol $^{-1}$, $\Delta S^\ddagger_D = -50 \pm 8$ J K $^{-1}$ mol $^{-1}$; KIE = 26 at $-40^\circ C$ in THF; $\rho = -0.8$).^[11] Thus, we propose a mechanism for the benzylic hydroxylation that is similar to that suggested for the N-dealkylation reaction, involving either abstraction of a hydrogen atom by core **B** followed by rebinding of a hydroxyl group or a concerted variant (Scheme 1).^[11]



Scheme 1. Mechanism for the hydroxylation of the ligand.

In conclusion, by using the supporting ligand L^X we have observed the clean generation of core **B** followed by aliphatic hydroxylation at the ligand benzylic position through a rate-controlling activation of a C–H bond by the bis(μ -oxo)dicopper unit. A similar hydroxylation occurs in the system supported by L' ,^[7] but the kinetic data show that the intramolecular peroxo $\rightarrow$ bis(μ -oxo) isomerization instead of C–H bond breaking is rate-controlling. Thus, a simple change in the denticity of the supporting ligand results in an important shift

in the relative rates of O–O and C–H bond scission in these dicopper compounds. These results suggest the possible importance of similar ligand effects on related pathways traversed during aliphatic hydroxylations by copper-containing enzymes and other synthetic systems.

Experimental Section

Product analysis and stoichiometry: $[\text{Cu}^{\text{I}}(\text{L}^{\text{H}})(\text{CH}_3\text{CN})]\text{PF}_6$ (0.3 mmol) was dissolved in deaerated acetone (10 mL) under anaerobic conditions, and the solution was cooled down to -78°C using a dry ice/acetone bath. The solution was then exposed to O_2 gas for 1 h at this temperature, and the mixture was further stirred for 20 h at 25°C . An ordinary work-up treatment of the reaction mixture with aqueous NH_4OH followed by extraction with CH_2Cl_2 and evaporation gave a mixture of organic products (the ^1H NMR yield was determined at this point as described below), from which the hydroxylated ligand *N*-ethyl-*N*-[2-(2-pyridyl)ethyl]-2-hydroxy-2-phenylethylamine ($\text{L}^{\text{H}}_{\text{OH}}$) was isolated by flash column chromatography (SiO_2 , $\text{CHCl}_3/\text{CH}_3\text{OH}$, 100/15). ^1H NMR (400 MHz, CDCl_3): δ = 0.99 (t, $^3J(\text{H,H})$ = 7.2 Hz, 3 H; CH_3), 2.48–2.79 (m, 4 H; CH_2), 2.88–3.10 (m, 4 H; CH_2), 4.62 (dd, $^3J(\text{H,H})$ = 3.4, 10.2 Hz, 1 H; CH), 7.13 (ddd, $^3J(\text{H,H})$ = 4.8, 7.8 Hz, $^4J(\text{H,H})$ = 0.8 Hz, 1 H; Py- H_3), 7.18 (d, $^3J(\text{H,H})$ = 7.8 Hz, 1 H; Py- H_3), 7.26 (dd, $^4J(\text{H,H})$ = 1.6, $^3J(\text{H,H})$ = 4.8 Hz, 1 H; *p*-Ph), 7.31–7.38 (m, 4 H; *o*- and *m*-Ph), 7.61 (dt, $^4J(\text{H,H})$ = 1.6, $^3J(\text{H,H})$ = 7.8 Hz, 1 H; py-H4), 8.55 (ddd, $^5J(\text{H,H})$ = 0.8, $^4J(\text{H,H})$ = 1.6, $^3J(\text{H,H})$ = 4.8 Hz, 1 H; py-H6); FT-IR (neat): $\tilde{\nu}$ = 3340 (OH), 1060 cm^{-1} (C–O); MS (positive ion CI): m/z : 271 [$\text{M}^+ + 1$].

The yield of the hydroxylated product $\text{L}^{\text{H}}_{\text{OH}}$ was determined as 46% by using an integral ratio in the ^1H NMR spectrum between the methine proton (CHOH) at δ = 4.62 of $\text{L}^{\text{H}}_{\text{OH}}$ and the pyridine protons at the 6-position (Py- H_6 , δ = 8.55) from both L^{H} and $\text{L}^{\text{H}}_{\text{OH}}$ (Py- H_6 signals of L^{H} and $\text{L}^{\text{H}}_{\text{OH}}$ are overlapped); (CHOH):(Py- H_6) = 0.46:2.00.

The O_2 -uptake measurement was carried out on the reaction of $[\text{Cu}^{\text{I}}(\text{L}^{\text{H}})(\text{CH}_3\text{CN})]\text{PF}_6$ (148.2 mg, 0.294 mmol) in acetone (10 mL) at -78°C . The volume of O_2 consumed during the oxygenation reaction was determined to be 3.51 mL from the difference in the O_2 consumption between the ligand hydroxylation reaction and the blank solution without the reactants under exactly the same conditions using a manometer designed for the small-scale reaction. Thus, the stoichiometry of O_2 :Cu was calculated to be 1:2.03.

Kinetic measurements: The reactions of the copper(II) complexes and O_2 were performed in a 1 cm path length UV/Vis cell that was held in a thermostated cell holder designed for low temperature experiments (Unisoku, fixed within $\pm 0.5^\circ\text{C}$). After the deaerated solution of the copper(II) complex ($2.5 \times 10^{-4}\text{M}$) in the cell had been kept at the desired temperature for several minutes, dry dioxygen gas (25 mL) was bubbled through over 5 s by injection from a 25 mL syringe. The formation of the bis(μ -oxo)dicopper(III) intermediate and the subsequent ligand hydroxylation process were followed by monitoring the absorption band at 402 nm.

Received: May 3, 1999 [Z13358]

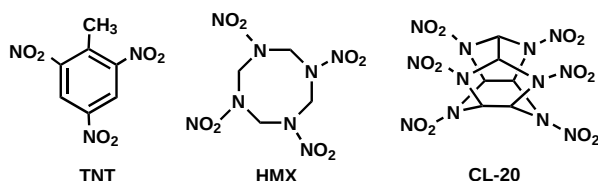
- [1] a) *Active Oxygen in Biochemistry* (Eds.: J. S. Valentine, C. S. Foote, A. Greenberg, J. F. Liebman), Chapman & Hall, London, **1995**; b) *Active Oxygen in Chemistry* (Eds.: C. S. Foote, J. S. Valentine, A. Greenberg, J. F. Liebman), Chapman & Hall, London, **1995**.
- [2] a) K. D. Karlin, Z. Tyeklár, *Adv. Inorg. Biochem.* **1994**, *9*, 123–172; b) K. D. Karlin, S. Kaderki, A. D. Zuberbühler, *Acc. Res. Chem.* **1997**, *30*, 139–147; c) N. Kitajima, *Adv. Inorg. Chem.* **1992**, *39*, 1–77; d) N. Kitajima, Y. Moro-oka, *Chem. Rev.* **1994**, *94*, 737–757; e) W. B. Tolman, *Acc. Chem. Res.* **1997**, *30*, 227–237.
- [3] a) R. R. Jacobsen, Z. Tyeklár, A. Farooq, K. D. Karlin, S. Liu, J. Zubieta, *J. Am. Chem. Soc.* **1988**, *110*, 3690–3692; b) Z. Tyeklár, R. R. Jacobsen, N. Wei, N. N. Murthy, J. Zubieta, K. D. Karlin, *J. Am. Chem. Soc.* **1993**, *115*, 2677–2689.
- [4] a) N. Kitajima, K. Fujisawa, Y. Moro-oka, K. Toriumi, *J. Am. Chem. Soc.* **1989**, *111*, 8975–8976; b) N. Kitajima, K. Fujisawa, C. Fujimoto,

- Y. Moro-oka, S. Hashimoto, T. Kitagawa, K. Toriumi, K. Tatsumi, A. Nakamura, *J. Am. Chem. Soc.* **1992**, *114*, 1277–1291.
- [5] a) J. A. Halfen, S. Mahapatra, E. C. Wilkinson, S. Kaderli, V. G. Young, Jr., L. Que, Jr., A. D. Zuberbühler, W. B. Tolman, *Science* **1996**, *271*, 1397–1400; b) S. Mahapatra, J. A. Halfen, E. C. Wilkinson, G. Pan, X. Wang, V. G. Young, Jr., C. J. Cramer, L. Que, Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11555–11574; c) S. Mahapatra, V. G. Young, Jr., S. Kaderli, A. D. Zuberbühler, W. B. Tolman, *Angew. Chem.* **1997**, *109*, 125–127; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 130–133; d) V. Mahadevan, Z. Hou, A. P. Cole, D. E. Root, T. K. Lal, E. I. Solomon, T. D. P. Stack, *J. Am. Chem. Soc.* **1997**, *119*, 11996–11997; e) E. Pidcock, S. DeBeer, H. V. Obias, B. Hedman, K. O. Hodgson, K. D. Karlin, E. I. Solomon, *J. Am. Chem. Soc.* **1999**, *121*, 1870–1878.
- [6] a) E. I. Solomon, U. M. Sundaram, T. E. Machonkin, *Chem. Rev.* **1996**, *96*, 2563–2605; b) A. Sánchez-Ferrer, J. N. Rodríguez-López, F. García-Cánovas, F. García-Carmona, *Biochim. Biophys. Acta* **1995**, *1247*, 1–11; c) H.-H. T. Nguyen, S. J. Elliot, J. H.-K. Yip, S. I. Chan, *J. Biol. Chem.* **1998**, *273*, 7957–7966, and references therein.
- [7] a) S. Itoh, T. Kondo, M. Komatsu, Y. Ohshiro, C. Li, N. Kanehisa, Y. Kai, S. Fukuzumi, *J. Am. Chem. Soc.* **1995**, *117*, 4714–4715; b) S. Itoh, H. Nakao, L. M. Berreau, T. Kondo, M. Komatsu, S. Fukuzumi, *J. Am. Chem. Soc.* **1998**, *120*, 2890–2899.
- [8] J. Cahoy, P. L. Holland, W. B. Tolman, *Inorg. Chem.* **1999**, *38*, 2161–2168.
- [9] P. L. Holland, K. R. Rodgers, W. B. Tolman, *Angew. Chem.* **1999**, *111*, 1210–1213; *Angew. Chem. Int. Ed.* **1999**, *38*, 1139–1142.
- [10] H. V. Obias, Y. Lin, N. N. Murthy, E. Pidcock, E. I. Solomon, M. Ralle, N. J. Blackburn, Y. M. Neubold, A. D. Zuberbühler, K. D. Karlin, *J. Am. Chem. Soc.* **1998**, *120*, 12960–12961.
- [11] S. Mahapatra, J. A. Halfen, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 11575–11586.
- [12] For aliphatic hydroxylation by a $[\text{Fe}^{\text{III}}(\mu\text{-O})_2\text{Fe}^{\text{IV}}]$ species, see C. Kim, Y. Dong, L. Que, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 3635–3636.
- [13] Analytical data for $[\text{Cu}^{\text{I}}(\text{L}^{\text{H}})(\text{CH}_3\text{CN})]\text{PF}_6$: ^1H NMR (400 MHz, CD_2Cl_2): δ = 1.21 (t, $^3J(\text{H,H})$ = 7.2 Hz, 3 H; CH_2CH_3), 2.17 (s, 3 H; coordinated CH_3CN), 2.82–3.17 (m, 10 H; CH_2), 7.20 (d, $^3J(\text{H,H})$ = 7.4 Hz, 1 H; Py- H_3), 7.32–7.41 (m, 6 H; Ph and py-H5), 7.84 (dt, $^4J(\text{H,H})$ = 2.0, $^3J(\text{H,H})$ = 7.4 Hz, 1 H; py-H4), 8.13 (dd, $^3J(\text{H,H})$ = 5.2, $^4J(\text{H,H})$ = 2.0 Hz, 1 H; py-H6); FT-IR (KBr): $\tilde{\nu}$ = 837 cm^{-1} (PF_6^-); Elemental analysis calcd for $[\text{Cu}^{\text{I}}(\text{L}^{\text{H}})(\text{CH}_3\text{CN})]\text{PF}_6 \cdot 0.5\text{H}_2\text{O}$ ($\text{C}_{19}\text{H}_{26}\text{N}_5\text{O}_5\text{CuPF}_6$): C 44.49, H 5.11, N 8.19; found: C 44.46, H 4.91, N 8.08.
- [14] The molar absorption coefficient (ϵ) at 402 nm was determined by using the deuterated ligand $[\text{D}_4]\text{L}^{\text{H}}$ because the subsequent ligand hydroxylation reaction was much slower than for the case of ligand L^{H} itself, which enabled the value to be determined accurately.
- [15] The isotope-sensitive features in Figure 1 are attributable to Cu_2O_2 core vibrations, and show a striking resemblance to those in a bis(μ -oxo)dicopper complex of another bidentate pyridine/amine ligand.^[9] The presence of multiple Cu_2O_2 core vibrations is a result of the lowered core symmetry in these complexes: P. L. Holland, C. J. Cramer, K. R. Rodgers, E. C. Wilkinson, S. Mahapatra, S. Itoh, M. Taki, S. Fukuzumi, L. Que, Jr., W. B. Tolman, unpublished results.
- [16] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
- [17] The *p*-substitution (L^{X}) and the ligand deuteration ($[\text{D}_4]\text{L}^{\text{H}}$) hardly affect the absorption maximum λ_{max} of the intermediates (402 nm).

Hepta- and Octanitrocubanes**

Mao-Xi Zhang, Philip E. Eaton,* and Richard Gilardi

Highly nitrated cubanes are predicted to be shock-insensitive, very dense, high-energy compounds with great potential as explosives and propellants.^[1] Application of the Kamlett–Jacobs equations^[2] to octanitrocubane using predicted values for density (1.9–2.2 g cm^{−3})^[3] and ΔH_f (81–144 kcal mol^{−1})^[4] leads to calculated detonation velocities and pressures much higher than that of the classic C-nitro explosive TNT, 15–30% greater than that of the N-nitro compound HMX, presently the most energetic of standard military explosives, and perhaps even better than that of the experimental polycyclic nitramine CL-20, arguably the most powerful nonnuclear explosive known.^[5]

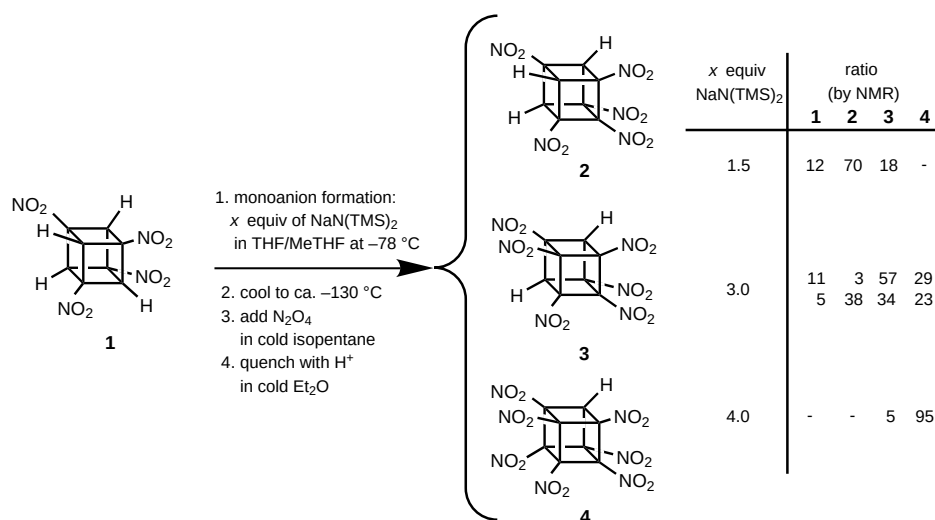


Successful methodology for the synthesis of highly nitrated cubanes is far less predictable. Although nitration is one of the oldest reactions in organic chemistry, it is little understood outside classical electrophilic nitration of π systems. Systematic polynitration of saturated systems is generally unknown. Indeed, generally speaking, systematic substitution of any kind on strained systems like cubane and cyclopropanes is difficult. It is primarily for these reasons that we undertook the challenge of developing a rational synthesis for octanitrocubane. In the process, we were rewarded by many discoveries of new chemistry including ortho-magnesiation, $\Delta^{1,9}$ -ho-

mocubenes, cubene, cubyl carbanyl radical, cubyl cation, cubanediyl, and the $[n]$ cubyls.^[6]

As we have reported previously,^[7] 1,3,5,7-tetranitrocubane (**1**) can be made by dimethyldioxirane oxidation of the tetraamine derived from Curtius-type transformations of the corresponding tetraacid, itself made either from ortho-metalation of amide-activated cubanes^[7a] or from photochlorocarbonylation of cubane monoacid.^[7b, 8] More highly nitrated cubanes cannot be made similarly from more highly carboxylated cubanes, as the conversion would proceed through intermediates that contain an electron-donating group vicinal to a group that is electron-withdrawing; this situation results unavoidably in cleavage of the highly strained cubane cage.^[7b]

As shown earlier,^[7b, 9] **1** is quite acidic ($pK_a \approx 21$). Nitration of its anion (e.g., as the sodium salt) at the melting (approx. -105°C) interface between frozen THF and N_2O_4 gave 1,2,3,5,7-pentanitrocubane (**2**), the first nitrocubane with adjacent nitro groups. Similarly, “interfacial nitration”^[10] of the salt of this even more acidic nitrocubane gave 1,2,3,4,5,7-hexanitrocubane (**3**). As expected the anion of hexanitrocubane is readily formed, but the use of different experimental methodology, as indicated in Scheme 1, proved to be essential



Scheme 1. Sequential nitration of polynitrocubyl anions, and product distribution as a function of the molar ratio of **1** to $\text{NaN}(\text{TMS})_2$.

for its successful conversion into heptanitrocubane (**4**), and this provided as well for better yield, more reproducible, larger scale preparations of **2** and **3**.

1,3,5,7-Tetranitrocubane (**1**) was treated with 1.5 equiv of $\text{NaN}(\text{TMS})_2$ (TMS = trimethylsilyl) at -78°C in tetrahydrofuran/ α -methyltetrahydrofuran (1/1). After the monoanion had formed, the solution was cooled to between -125 and -130°C , giving a clear, but very viscous fluid. This was stirred vigorously as excess N_2O_4 in cold isopentane was added. After one minute nitric acid in cold (-30°C) diethyl ether was added, and then the whole mixture was added to water. Standard workup (CH_2Cl_2 extraction) and NMR analysis showed (for a typical run) that the product mixture contained

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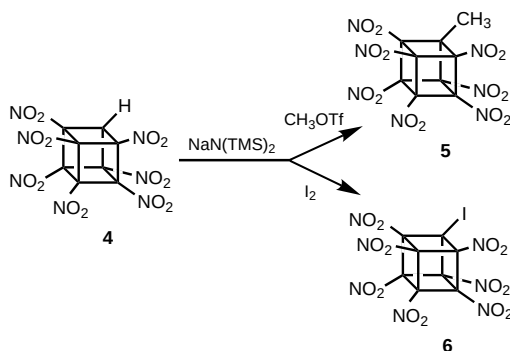
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[**] This work was supported at Chicago by the University of Chicago and by the United States Army Armament Research and Development Center (ARDEC) and at NRL by the Office of Naval Research, Mechanics Division. We are grateful to Nat Gelber of ARDEC for preparing all the tetranitrocubane used in this work and to Art Bates for his advice and assistance with the NMR studies.

principally pentanitrocubane (**2**, 53 % isolated), a little starting material, and some hexanitrocubane (**3**). When the quantity of $\text{NaN}(\text{TMS})_2$ was increased to 3 equiv the distributions of products in seemingly similar runs were quite variable (Scheme 1), but always there was a significant amount of hexanitrocubane formed along with some heptanitrocubane (**4**).^[11] A further increase in base to 4.0 equiv resulted reproducibly in almost complete conversion of **1** (1-gram scale) into heptanitrocubane (95 % by NMR), isolated crystalline in 74 % yield! For this to have happened, many sequential conversions must have occurred very rapidly in the viscous solvent at about -125°C . Nitration of the anion of **1** ($\rightarrow$ **2**), anion formation from **2**, nitration ($\rightarrow$ **3**), anion formation from **3**, and nitration ($\rightarrow$ **4**) are all required. (That all this comes about so quickly is all the more remarkable considering the fact that the first anion, **1**[−], does not form at a useful rate below -78°C .) The sequence ends with formation of the anion of **4** as shown by high-yield production of methylheptanitrocubane (**5**; Scheme 2)^[12] on quenching with methyl triflate rather than acid. Nonetheless, even on addition of excess N_2O_4 , no octanitrocubane was formed.



Scheme 2. Preparation of methyl (**5**) and iodo derivatives (**6**) of heptanitrocubane (**4**). Tf = trifluoromethanesulfonyl.

Heptanitrocubane is easily soluble in polar solvents, for example, acetone, THF, and CH_2Cl_2 . Beautiful, colorless, solvent-free crystals formed when its solution in fuming nitric acid was diluted with sulfuric acid. Single-crystal X-ray analysis confirmed the assigned structure and provided an accurate density at 21°C of 2.028 g cm^{-3} , impressively high for a $\text{C}_8\text{H}_7\text{N}_7\text{O}_{14}$ compound. The crystal structure of **4** shows many intermolecular contacts about each molecule that are shorter than the sum of the van der Waals radii;^[13] 21 between oxygen atoms and 12 between an oxygen and a C, N, or H atom. The latter contacts are electrostatically favorable and help increase the density. The lone hydrogen atom participates in a weak hydrogen bond ($\text{C}-\text{H}\cdots\text{O}$ $2.53\text{ \AA}$, 165.5°) that links molecules in a chain along the *b* axis. The intramolecular bond lengths, angles, and nonbonded contacts are not unusual, resembling those of the lower homologues;^[7] the average C–C cubane-edge distance is $1.561\text{ \AA}$.

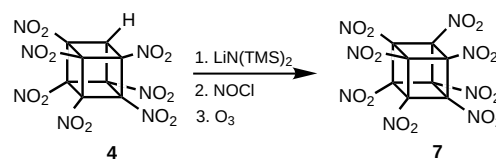
Solutions of **4** in methanol turn yellow ($\lambda_{\text{max}} = 458\text{ nm}$). We suspect this to be the color of the anion. Addition of trifluoroacetic acid decolorized the solution; evaporation of the solvent returned colorless, undecomposed material. If

CD_3OD was used, exchange was quick and deuterioheptanitrocubane was produced. Addition of iodine to the methanol solution gave iodoheptanitrocubane (**6**; Scheme 2);^[14] this formed more rapidly if a little NaF was added as base. Clearly **4** is acidic, reflecting very substantial delocalization of charge in its anion. Heptanitrocubane is sensitive to base. NaF alone in methanol catalyzed its decomposition, as did amines like 2,2,6,6-tetramethylpiperidine. Powerful deflagration occurred when a microdrop of pyridine was added to the dry solid.

Alkali metal salts of **4** were prepared at low temperature in inert solvents by reaction with appropriate bases like $\text{NaN}(\text{TMS})_2$ or $\text{LiN}(\text{TMS})_2$. Such salts in THF decomposed fairly quickly at -100°C , but in CH_2Cl_2 they were relatively stable to about -50°C . Reaction with powerful electrophiles like methyl triflate and iodine gave **5** and **6**, respectively, in high yield (Scheme 2).

Despite the reactivity of heptanitrocubyl anion towards these electrophiles, we could find no indication for any formation of octanitrocubane from reactions of various heptanitrocubane salts with NO_2BF_4 , NO_2PF_6 , acetyl nitrate, methyl nitrate, isoamyl nitrate, $\text{CF}_3\text{CH}_2\text{ONO}_2$, or $\text{CF}_3\text{SO}_2\text{ONO}_2$. Indeed, although it is not well-known, such “obviously electrophilic” reagents are generally useless for nitrations of non-resonance-delocalized anions.^[10] Although N_2O_4 and (to a degree) NO_2Cl do nitrate some nitrocubyl anions,^[7b, 9] both failed to give any octanitrocubane on reaction with salts of **4**. As we have speculated previously,^[7b] nitration with these reagents may proceed by oxidation of the carbanion to the corresponding radical; perhaps the anion of **4** is too stabilized for this to occur.

We now report that addition of excess nitrosyl chloride (NOCl) to a solution of the lithium salt of heptanitrocubane (from **4** and $\text{LiN}(\text{TMS})_2$) in CH_2Cl_2 at -78°C followed by ozonation at -78°C until the solution was blue gave, after standard workup, the long-sought octanitrocubane (**7**; Scheme 3) in 45–55 % yield on millimole scale. The intermediate product prior to oxidation was unstable; we suspect that it might be nitrosoheptanitrocubane.^[15]



Scheme 3. “Nitration” of heptanitrocubane (**4**). Synthesis of octanitrocubane (**7**).

Octanitrocubane (**7**) itself is a stable, white solid,^[16] somewhat soluble in hexane and readily soluble in polar organics. Solvent-free crystals for X-ray analysis were obtained from trifluoroacetic acid, from fuming nitric acid/sulfuric acid, and from scrupulously dried cyclohexane. (Only crystals of a monohydrate formed from numerous other solvents, despite great care to achieve “anhydrous conditions”.) X-ray analyses have been performed on single crystals from most batches grown to date; only one form of the nonhydrated compound has thus far been seen. As with **4**, the intramolecular bond lengths, angles, and nonbonded contacts for **7** are not unusual; the average C–C cubane-edge distance is $1.562\text{ \AA}$. The

molecule displays a close approach to D_4 symmetry, although this is not required by the crystal symmetry. In contrast to the remarkably dense molecular packing in heptanitrocubane crystals, the arrangement in the present crystal form of octanitrocubane does not have a nitro group of one molecule interleaved amongst those of another, and thus no oxygen atom closely approaches the electron-deficient carbons of a cubane face. The 14 close approaches between molecules are all electrostatically repulsive $O \cdots O$ interactions. This correlates with a density (1.979 g cm^{-3}) that, though high, is at the lower end of the original range of predictions.^[3] However, taking into account the available data on polynitrocubane crystal structure, the latest and most sophisticated calculations^[17] still predict a density of $2.135^{[17a]}$ or $2.123 \text{ g cm}^{-3[17b]}$ for the most stable polymorph of octanitrocubane, suggesting the existence of a crystal form much denser than that now in hand. As the detonation pressure at the shock wave front in an explosion is thought to be proportional to the square of the

density of the explosive,^[2] we are of course searching for this denser form of **7**.

If the nitro groups of **7** are spinning freely on the NMR time scale, then the carbon atoms would be magnetically equivalent and, on first thought, only a singlet would be expected in the ^{13}C NMR spectrum. From calculations based on observed chemical shifts (in $[\text{D}_6]\text{acetone}$) in less highly nitrated cubanes,^[7b] this would be near $\delta = 88.2$. In fact, the observed ^{13}C resonance ($\delta = 87.8$) is close to this, but it is split into a triplet (Figure 1 a). This was shown to arise from ^{13}C coupling ($J = 8.8 \text{ Hz}$) to the

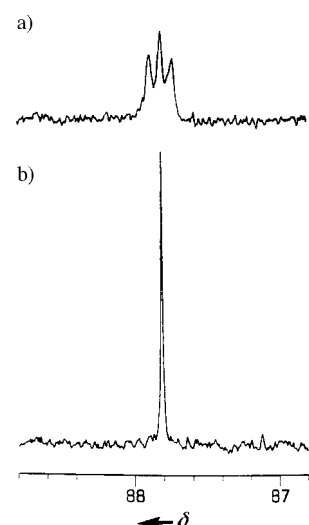


Figure 1. a) The ^{14}N -coupled and b) the ^{14}N -decoupled ^{13}C NMR spectra of octanitrocubane (**7**).

attached ^{14}N nucleus ($I = 1$) of the nitro group; the signal was collapsed to a singlet on decoupling (Figure 1 b). (A specially constructed ^{13}C -observe/ ^{14}N -decouple probe was used.) ^{13}C – ^{14}N coupling is rarely seen,^[18] as quadrupolar relaxation of ^{14}N is effective. However, coupling has been observed in compounds symmetric about the nitrogen nucleus (e.g., quaternary ammonium salts) in which the electric field gradient is near zero. Coburn et al.^[19] have shown that the same pertains when the R group of RNO_2 is very electronegative, as this leads towards charge symmetry about the nitrogen nucleus. In the case at hand, octanitrocubane, R is the strongly electron-withdrawing heptanitrocubyl group.

Received: June 29, 1999 [Z13651]

[1] a) The idea originated with E. E. Gilbert and J. Alster; b) J. Alster, O. Sandus, R. Gentner, N. Slagg, J. P. Ritchie, M. J. S. Dewar, *Calculation of Molecular Properties for Polynitrohedrane Molecules*, Working Group Meeting on High-Energy Compounds, Hilton Head, SC, **1981**.

- [2] M. J. Kamlet, S. J. Jacobs, *J. Chem. Phys.* **1968**, *48*, 23–35. See also: a) L. T. Eremenko, D. A. Nesterenko, *Chem. Phys. Reports* **1997**, *16*, 1675–1683; b) A. M. Astakhov, R. S. Stepanov, A. Yu. Babushkin, *Combustion, Explosion, and Shock Waves* **1998**, *34*, 85–87.
- [3] A variety of methods have been applied: a) A. I. Kitaigorodsky, *Molecular Crystals and Molecules*, Academic Press, New York, **1973**; b) A. Immirzi, B. Perini, *Acta Crystallogr. Sect. A* **1977**, *33*, 216–218; c) H. H. Cady, *Estimation of the Density of Organic Explosives from Their Structural Formulas*, Report #LA-7760-MS, Los Alamos National Laboratory, Los Alamos, NM, **1979**; d) D. A. Cichra, J. R. Holden, C. Dickinson, *Estimation of "Normal" Densities of Organic Explosives from Empirical Atomic Volumes*, Report #NSWC-TR-79-273, Naval Surface Warfare Center (White Oak), Silver Spring, MD, **1980**; e) J. R. Stine, *Prediction of Crystal Densities of Organic Explosives by Group Additivity*, Report #LA-8920, Los Alamos National Laboratory, Los Alamos, NM, **1981**; f) J. Alster, S. Iyer, O. Sandus in *Chemistry and Physics of Energetic Materials* (Ed.: S. N. Bulusu), Kluwer, Dordrecht, **1990**, chap. 28; g) J. R. Holden, Z. Du, H. L. Ammon, *J. Comput. Chem.* **1993**, *13*, 422–437; h) K. Jayasuriya, *Computational Investigation of New Potential Explosive and Propellant Molecules*, Fourteenth Annual Working Group Institute on High-Energy Density Materials, Kiamesha Lake, NY, **1995**, pp. 2943–2963; i) J. S. Murray, T. Brinck, P. Politzer, *Chem. Phys.* **1996**, *204*, 289–299.
- [4] A variety of methods have been applied: a) L. C. Allen, *Estimates for the Thermodynamic Stability of Cubane and its Nitro Derivatives*, Eight Annual Working Group Institute on High-Energy Density Materials, Kiamesha Lake, NY, **1989**, pp. 44–63; b) S. Bourasseau, *J. Energ. Mater.* **1990**, *8*, 378–391; c) P. Politzer, J. S. Murray, M. E. Grice in *Decomposition, Combustion, and Detonation Chemistry of Energetic Materials* (Eds.: T. B. Brill, T. P. Russell, W. C. Tao, R. B. Wardle), Materials Research Society, Pittsburgh, PA, **1996**, 418, pp. 55–66; d) R. J. Spear, I. J. Dagley in *Organic Energetic Compounds* (Ed.: P. L. Marinkas), Nova, Commack, NY, **1996**, chap. 2.
- [5] R. L. Simpson, P. A. Urtiew, D. L. Ornellas, G. L. Moody, K. J. Scribner, D. M. Hoffman, *Propellants Explos. Pyrotech.* **1997**, *22*, 249–255.
- [6] a) Review: P. E. Eaton, *Angew. Chem.* **1992**, *104*, 1447–1462; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1421–1436, and references therein; b) P. E. Eaton, K. Pramod, T. Emrick, R. Gilardi, *J. Am. Chem. Soc.* **1999**, *121*, 4111–4123.
- [7] a) P. E. Eaton, Y. Xiong, R. Gilardi, *J. Am. Chem. Soc.* **1993**, *115*, 10195–10202; b) K. A. Lukin, J. Li, P. E. Eaton, N. Kanomata, J. Hain, E. Punzalan, R. Gilardi, *J. Am. Chem. Soc.* **1997**, *119*, 9591–9602.
- [8] a) A. Bashir-Hashemi, *Angew. Chem.* **1993**, *105*, 585–586; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 612–613; b) A. Bashir-Hashemi, J. Li, N. Gelber, H. Ammon, *J. Org. Chem.* **1995**, *60*, 698–702.
- [9] K. A. Lukin, J. Li, R. Gilardi, P. E. Eaton, *Angew. Chem.* **1996**, *108*, 938–940; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 864–866.
- [10] K. Tani, K. Lukin, P. E. Eaton, *J. Am. Chem. Soc.* **1997**, *119*, 1476–1477.
- [11] a) **4**: ^1H NMR ($[\text{D}_6]\text{acetone}$): $\delta = 7.11$; ^{13}C NMR ($[\text{D}_6]\text{acetone}$): $\delta = 89.3$ (3 C), 86.3 (1 C), 83.9 (3 C), 62.7 (1 C, CH); predicted:^[7b] $\delta = 90.1$, 87.5, 83.3, 62.2; b) crystal data for **4** ($\text{C}_8\text{H}_7\text{N}_7\text{O}_{14}$):^[20] $M_r = 419.16$, orthorhombic, space group $Pbcn$; $a = 23.5942(13)$, $b = 8.1735(7)$, $c = 14.2642(5) \text{ \AA}$, $V = 2750.8(3) \text{ \AA}^3$, $Z = 8$, and ρ (X-ray) = 2.028 mg mm^{-3} (average of 2.024 and 2.032 mg mm^{-3} from two separate crystals); 2243 data measured to a 2θ max. of 115° ; $R = 0.0471$, $wR2 = 0.1141$ for all 1881 unique reflections.
- [12] a) **5**: ^1H NMR (CD_3NO_2): $\delta = 2.36$; ^{13}C NMR (CD_3NO_2): $\delta = 87.0$ (3 C), 84.9 (1 C), 84.6 (3 C), 74.4 (1 C), 7.15 (CH_3); b) crystal data for **5** ($\text{C}_9\text{H}_3\text{N}_7\text{O}_{14}$):^[20] $M_r = 433.18$, monoclinic, space group $P2(1)/m$; $a = 7.8254(4)$, $b = 11.2796(5)$, $c = 9.3736(4) \text{ \AA}$, $\beta = 107.153(5)^\circ$, $V = 790.58(6) \text{ \AA}^3$, $Z = 2$, and ρ (X-ray) = 1.820 mg mm^{-3} ; 2345 data measured to a 2θ max. of 113.5° ; $R = 0.0579$, $wR2 = 0.1339$ for all 1115 unique reflections.
- [13] R. S. Rowland, R. Taylor, *J. Phys. Chem.* **1996**, *100*, 7384–7391.
- [14] a) **6**: ^{13}C NMR (CD_3CN): $\delta = 88.3$ (3 C), 85.9 (1 C), 82.9 (3 C), 36.7 (C–I); b) crystal data for **6** ($\text{C}_8\text{IN}_7\text{O}_{14}$):^[20] $M_r = 545.05$, monoclinic, space group $C2/c$; $a = 13.0713(7)$, $b = 8.7215(4)$, $c = 13.8894(12) \text{ \AA}$, $\beta = 95.386(7)^\circ$, $V = 1576.4(2) \text{ \AA}^3$, $Z = 4$, and ρ (X-ray) = 2.297 mg mm^{-3} .

mm⁻³; 1175 data measured to a 2 θ max. of 115°; $R=0.0412$, $wR2=0.1077$ for all 1079 unique reflections.

- [15] See a) W. Hanefeld, *Methoden Org. Chem. (Houben-Weyl) 4th ed.* 1990, Vol 16/2a, pp. 950–979; b) J. M. Kauffman, J. Green, M. S. Cohen, M. M. Fein, E. L. Cottrill, *J. Am. Chem. Soc.* **1964**, 86, 4210–4211; c) E. Müller, H. Metzger, *Chem. Ber.* **1956**, 89, 396–406.
- [16] a) Crystal data for **7** (C₈N₈O₁₆):^[20] $M_r=464.16$, monoclinic, space group $C2/c$; $a=12.7852(8)$, $b=8.8395(3)$, $c=13.9239(8)$ Å, $\beta=98.031(6)^\circ$, $V=1558.17(14)$ Å³, $Z=4$, and ρ (X-ray)=1.979 mg mm⁻³; 2241 data measured to a 2 θ max. of 116°; $R=0.0389$, $wR2=0.0962$ for all 1076 unique reflections.
- [17] a) H. Ammon, private communication, see ref. [3g]; b) Using: W. R. Busing, *WMIN—A Computer Program to Model Molecules and Crystals in Terms of Potential Energy Functions*, Report #ORNL-5747, Oak Ridge National Laboratory, Oak Ridge, TN, **1981**; c) using: D. J. Willock, S. L. Price, M. Leslie, C. R. A. Catlow, *J. Comput. Chem.* **1995**, 16, 628–647.
- [18] J. M. Lehn, J. P. Kintzinger in *Nitrogen NMR* (Eds.: M. Witanowski, G. A. Webb), Plenum, London, **1973**, pp. 79–161.
- [19] M. D. Coburn, C. B. Storm, D. W. Moore, T. G. Archibald, *Magn. Reson. Chem.* **1990**, 28, 16–20.
- [20] X-ray intensity data for **4–7** were measured on a Bruker diffractometer with Cu α radiation ($\lambda=1.54178$ Å) at $T=293$ K. Structures were solved by direct methods, aided by program XS, and refined with the full-matrix least-squares program XL, from SHELXTL (G. Sheldrick, SHELXTL96, *Acta Crystallogr. Sect. A* **1990**, 46, 467). The XL program minimizes F^2 differences, and uses all data; that is, weak data are not considered “unobserved”, and are included in the R -factors reported. Crystallographic data (excluding structural factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-127760 (**4**), -127761 (**5**), -127762 (**6**), and -127763 (**7**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk)

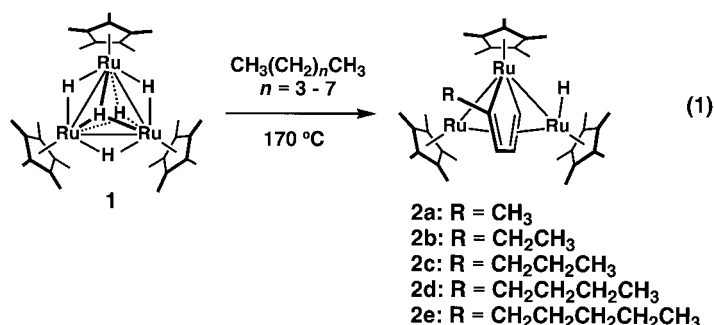
Intermolecular Activation of *n*-Alkanes by a Trinuclear Ruthenium Pentahydride Complex—Formation of *closo*-Ruthenacyclopentadiene Complexes**

Akiko Inagaki, Toshifumi Takemori, Masako Tanaka, and Hiroharu Suzuki*

Activation of the carbon–hydrogen bonds of alkanes is of special importance because of its potential applicability to the functionalization of alkanes. The selective activation of alkane C–H bonds under mild conditions has, therefore, been one of the most challenging targets in recent organometallic

chemistry and has been intensively studied using mononuclear hydride and carbonyl complexes as precursors to the active species.^[1] Over the past ten years we have tackled the activation of organic substrates on multimetallic sites and demonstrated that a metal–polyhydride cluster effectively activates an organic substrate in a unique manner as a result of the cooperative action of the metal centers.^[2] We report herein an unprecedented successive activation of alkane C–H bonds that is mediated by a trinuclear pentahydride complex of ruthenium [$\{(\text{C}_5\text{Me}_5)\text{Ru}\}_3(\mu\text{-H})_3(\mu_3\text{-H})_2$] (**1**).

This novel reaction was discovered during the course of a study on the stability of **1** in solution at high temperature. We have already confirmed that complex **1** is thermally stable for 14 days at 200 °C in a sterically bulky solvent such as 1,3,5-trimethylcyclohexane, and does not decompose into mono- or bimetallic fragments. Heating a solution of **1** in hexane at 170 °C for 120 h resulted in the formation of a novel trinuclear *closo*-ruthenacyclopentadiene complex **2b** ($\text{R}=\text{C}_2\text{H}_5$) in a reasonable yield [Eq. (1)].



Complex **1** reacts with *n*-alkanes such as pentane, heptane, octane, and nonane in a similar manner and leads to the formation of **2a** ($\text{R}=\text{CH}_3$), **2c** ($\text{R}=\text{CH}_2\text{CH}_2\text{CH}_3$), **2d** ($\text{R}=\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), and **2e** ($\text{R}=\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), respectively, in good yields.^[3] The structure of these compounds was inferred from spectroscopic data and then confirmed by an X-ray diffraction study on a single crystal of **2b** (Figure 1).

The most informative data regarding the structure of these complexes comes from the NMR study.^[4] Whereas resonance signals for the triply bridging carbons in the ruthenacycle, C1 and C4, appear at $\delta=118.0$ (d, $J_{\text{CH}}=156$ Hz) and 144.5 (s), respectively, those for the doubly bridging carbon atoms, C2 and C3, are observed at the relatively high-field values of $\delta=66.3$ (d, $J_{\text{CH}}=178$ Hz) and 62.7 (d, $J_{\text{CH}}=174$ Hz) in the ¹³C NMR spectrum. The ¹H NMR spectrum of **2b** reveals, discounting the signals for the C₅Me₅ and R group, three resonances at $\delta=4.35$ (d, $J=4.4$ Hz, H1), 4.30 (dd, $J=4.4$, 1.6 Hz, H2), and 3.88 (br, $w_{1/2}=3.3$ Hz, H3) that are assignable to hydrogen atoms directly bonded to the ruthenacyclopentadiene framework. The ¹H–¹³C COSY spectrum shows these ¹H resonances consistently correlate with the ¹³C signals for the ring carbon atoms of the ruthenacyclopentadiene moiety. The signals of the C₅Me₅ groups appear to be inequivalent in both the ¹H and ¹³C NMR spectra. The inequivalency of the chemical shifts of the resonances for the three C₅Me₅ groups suggests that a hydride ligand does not lie on the pseudosymmetry plane that is coplanar to the ruthenacycle. These resonances are characteristic of the *closo*-

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[**] This research was partly supported by a Fellowship of the Japan Society for the Promotion of Science for Japanese Junior Scientists. The authors are also grateful to Kanto Chemical Co. Inc. for a generous gift of pentamethylcyclopentadiene.

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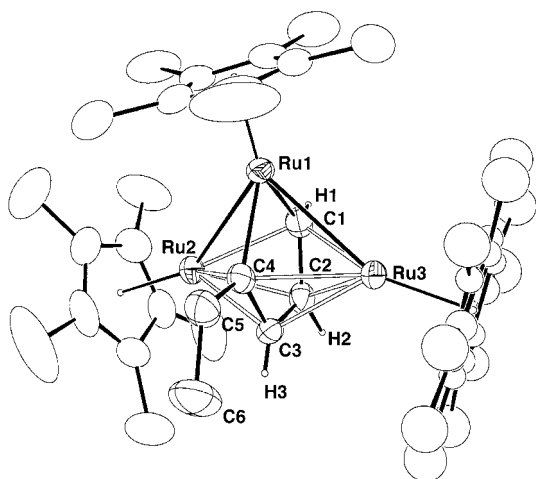


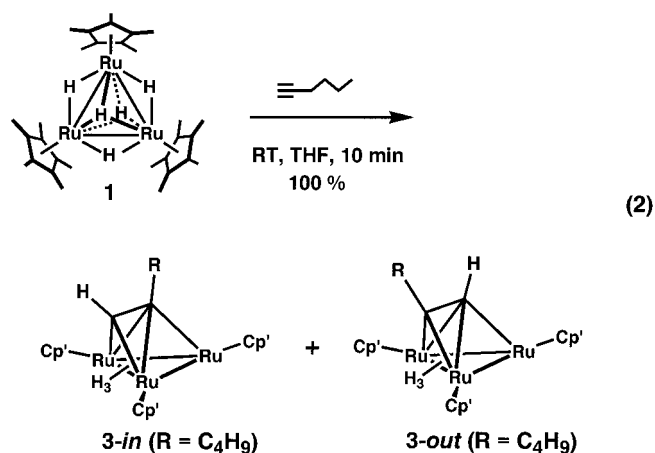
Figure 1. Molecular structure of **2b** (thermal ellipsoids at the 30% probability level). Selected bond lengths [Å] and angles [°]: Ru(1)-Ru(2) 2.7878(10), Ru(1)-Ru(3) 2.7741(10), Ru(1)-C(1) 2.062(9), Ru(1)-C(4) 2.057(7), Ru(2)-C(1) 2.249(8), Ru(2)-C(2) 2.148(7), Ru(2)-C(3) 2.135(7), Ru(2)-C(4) 2.283(7), Ru(3)-C(1) 2.349(8), Ru(3)-C(2) 2.169(8), Ru(3)-C(3) 2.198(7), Ru(3)-C(4) 2.408(7), C(1)-C(2) 1.442(11), C(2)-C(3) 1.449(12), C(3)-C(4) 1.455(11), C(4)-C(5) 1.514(12), C(5)-C(6) 1.492(12); Ru(2)-Ru(1)-Ru(3) 83.72(3), C(1)-Ru(1)-C(4) 78.9(3), Ru(2)-Ru(1)-C(1) 52.7(2), Ru(2)-Ru(1)-C(4) 53.7(2), Ru(3)-Ru(1)-C(1) 55.8(2), Ru(3)-Ru(1)-C(4) 57.5(2), Ru(1)-C(1)-C(2) 117.4(6), C(1)-C(2)-C(3) 112.5(7), C(2)-C(3)-C(4) 115.1(6), C(3)-C(4)-Ru(1) 115.7(6), C(3)-C(4)-C(5) 119.4(7), C(4)-C(5)-C(6) 120.1(9).

ruthenacyclopentadienes **2a–2e**. On the basis of the similarity of the ^1H and ^{13}C chemical shifts and the coupling pattern, complexes **2a**, **2c**, **2d**, and **2e** were unambiguously identified as the analogous *closo*-ruthenacyclopentadienes.

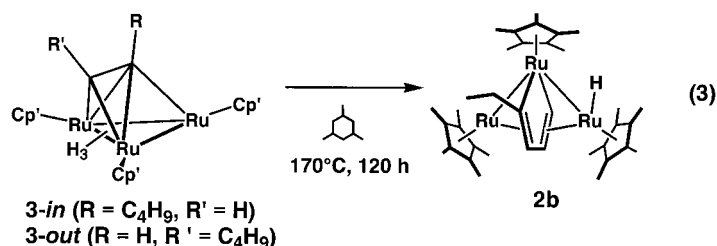
Definitive proof for the proposed structure was provided by an X-ray study on the single crystal of **2b**.^[5] Figure 1 clearly establishes the structural identity of **2b** as a trinuclear *closo*-ruthenacyclopentadiene in which the ruthenacycle bisects the Ru2-Ru3 vector.^[6] The Ru1-Ru2 and Ru1-Ru3 distances are almost identical and the values of 2.7878(10) and 2.7741(10) Å, respectively, lies within the range of those observed for a Ru-Ru single bond. The Ru-Ru bond lengths indicate that the hydride in **2b** is not a bridging one but a terminal one. The hydride is most likely to be located in a space between two C_5Me_5 ligands bound to Ru1 and Ru3, although the position of a hydrogen atom bonded to a ruthenium atom could not be determined by the difference Fourier synthesis. The Ru1-C1 and Ru1-C4 bond lengths of 2.062(9) and 2.057(7), respectively, correspond to the Ru-C σ -bond. The four-carbon fragment from C1 to C4 is π -bonded to Ru2. On the opposite side of the RuC_4 plane, Ru3 is π -bonded to C2 and C3. The values of 2.349(8) and 2.408(7) Å for Ru3-C1 and Ru3-C4, respectively, are significantly longer than that of the Ru-C π -bond.

It is clear that the carbon framework of 2-alkylruthenacyclopentadiene in **2** originates from the *n*-alkane used as the solvent. In this reaction, six C-H bonds of the alkanes are successively cleaved on the trimetallic site, and these results strongly suggest the applicability of transition metal cluster complexes, especially polyhydridometal clusters, to the functionalization of alkanes.

Signals for some of the intermediates were observed by monitoring the reaction by ^1H NMR spectroscopy, and these intermediates finally converged into thermodynamically stable products **2a–2e**. When the reaction of **1** with hexane was monitored at 170 °C by means of ^1H NMR spectroscopy an equilibrated mixture of μ_3 -($\perp$)-hexyne complexes, $\{(\text{C}_5\text{Me}_5)_3\text{Ru}\}_3(\mu\text{-H})_3[\mu_3\text{-}(\perp)\text{-HCCCC}_4\text{H}_9]$ (**3-in**), and $\{(\text{C}_5\text{Me}_5)_3\text{Ru}\}_3(\mu\text{-H})_3[\mu_3\text{-}(\perp)\text{-C}_4\text{H}_9\text{CCH}]$ (**3-out**), were detected in a complex mixture of intermediates.^[7] An attempt to isolate the equilibrated mixture of **3** (**3-in** + **3-out**) from the reaction mixture was unsuccessful, and so we could not get direct evidence that compound **3** was converted into **2b**. We, therefore, confirmed the intermediacy of **3** using an authentic complex independently synthesized by treatment of **1** with 1-hexyne [Eq. (2)].^[8] We employed 1,3,5-trimethylcyclohexane as the solvent in the thermolysis of **3** since it was inactive toward the ruthenium



clusters noted in this manuscript, probably as a result of its bulkiness. As anticipated, thermolysis of **3** in 1,3,5-trimethylcyclohexane at 170 °C led to the formation of **2b** [65% yield; Eq. (3)]. Thermolysis of the authentic μ_3 -($\perp$)-pentyne, μ_3 -



($\perp$)-heptyne, and μ_3 -($\perp$)-octyne complexes $\{[(\text{C}_5\text{Me}_5)_3\text{Ru}(\mu\text{-H})_3\{\mu_3\text{-}(\perp)\text{-HCCR}\}]\}$ and $\{[(\text{C}_5\text{Me}_5)_3\text{Ru}(\mu\text{-H})_3\{\mu_3\text{-}(\perp)\text{-RCCH}\}]\}$ ($\text{R} = \text{C}_3\text{H}_7$, C_5H_{11} , C_6H_{13}), also led to the formation of **2** ($\text{R} = \text{C}_3\text{H}_7$: 67%, $\text{R} = \text{C}_5\text{H}_{11}$: 53%, $\text{R} = \text{C}_6\text{H}_{13}$: 73%).

Although the reaction mechanism of successive C-H bond activation still remains unclear, we believe that alkane C-H bond activation on multimetallic sites is one of the promising approaches to the functionalization of alkanes.

Received: May 3, 1999 [Z13361]

- [1] a) A. H. Janowicz, R. G. Bergman, *J. Am. Chem. Soc.* **1982**, *104*, 352; b) J. K. Hoyano, W. A. G. J. Graham, *J. Am. Chem. Soc.* **1982**, *104*, 3723; c) A. H. Janowicz, R. G. Bergman, *J. Am. Chem. Soc.* **1983**, *105*, 3929; d) P. L. Watson, *J. Am. Chem. Soc.* **1983**, *105*, 6491; e) W. D. Jones, F. J. Feher, *Organometallics* **1983**, *2*, 562; f) C. M. Fendrick, T. J. Marks, *J. Am. Chem. Soc.* **1984**, *106*, 2214; g) R. G. Bergman, *Science* **1984**, *223*, 902; h) R. H. Crabtree, *Chem. Rev.* **1985**, *85*, 245; i) B. A. Arndtsen, R. G. Bergman, *Science* **1995**, *270*, 1970.
- [2] a) H. Suzuki, H. Omori, D. H. Lee, Y. Yoshida, Y. Moro-oka, *Organometallics* **1988**, *7*, 2243; b) H. Suzuki, H. Omori, Y. Moro-oka, *Organometallics* **1988**, *7*, 2579; c) H. Omori, H. Suzuki, Y. Moro-oka, *Organometallics* **1989**, *8*, 1576; d) H. Omori, H. Suzuki, Y. Moro-oka, *Organometallics* **1989**, *8*, 2270; e) H. Suzuki, T. Kakigano, M. Igarashi, M. Tanaka, Y. Moro-oka, *J. Chem. Soc. Chem. Commun.* **1991**, 283; f) H. Omori, H. Suzuki, T. Kakigano, Y. Moro-oka, *Organometallics* **1992**, *11*, 989; g) H. Suzuki, T. Takao, M. Tanaka, Y. Moro-oka, *J. Chem. Soc. Chem. Commun.* **1992**, 476; h) H. Suzuki, H. Omori, D. H. Lee, Y. Yoshida, M. Fukushima, M. Tanaka, Y. Moro-oka, *Organometallics* **1994**, *13*, 1129; i) T. Takao, H. Suzuki, M. Tanaka, *Organometallics* **1994**, *13*, 2554; j) H. Suzuki, Y. Takaya, T. Takemori, M. Tanaka, *J. Am. Chem. Soc.* **1994**, *116*, 10779; k) T. Takao, S. Yoshida, H. Suzuki, M. Tanaka, *Organometallics* **1995**, *14*, 3855; l) K. Tada, M. Oishi, H. Suzuki, M. Tanaka, *Organometallics* **1996**, *15*, 2422; m) T. Takemori, M. Tanaka, H. Suzuki, *Organometallics* **1996**, *15*, 4346; n) A. Inagaki, Y. Takakya, T. Takemori, M. Tanaka, M. Haga, H. Suzuki, *J. Am. Chem. Soc.* **1997**, *119*, 625; o) K. Matsubara, R. Okamura, M. Tanaka, H. Suzuki, *J. Am. Chem. Soc.* **1998**, *120*, 1108.
- [3] Heptane (5 mL) and **1** (59.6 mg, 0.083 mmol) were added to a 50-mL glass autoclave. The reaction mixture was heated at 170 °C for 154 h, during which time the solution changed from reddish brown to purplish brown. Removal of the solvent under reduced pressure afforded crude product **2c** as a brown solid (ca. 70 % purity based on ¹H NMR). The solid was dissolved in toluene and the product purified by column chromatography on neutral alumina. Removal of solvent under reduced pressure afforded 45.3 mg of **2c** as a brown solid (68 % yield).
- [4] **2b**: ¹H NMR (400 MHz, C₆D₆, 23 °C, TMS): δ = 4.35 (d, *J* = 4.4 Hz, 1H; C1-H), 4.30 (dd, *J* = 4.4, 1.6 Hz, 1H; C2-H), 3.88 (brs, *w*_{1/2} = 3.3 Hz, 1H; C3-H), 2.23 (s, 15H; C₅Me₃), 1.85 (q, *J* = 7.2 Hz, 2H; C5-H), 1.82 (s, 15H; C₅Me₃), 1.65 (s, 15H; C₅Me₃), 0.71 (t, *J* = 7.2 Hz, 3H; C6-H), –10.50 (s, 1H; Ru-H); ¹³C NMR (100 MHz, C₆D₆, 23 °C, TMS): δ = 144.5 (s, C4), 118.0 (d, *J*(C,H) = 156 Hz; C1), 90.6 (s; C₅Me₃), 83.0 (s; C₅Me₃), 82.7 (s; C₅Me₃), 66.3 (d, *J*(C,H) = 178 Hz; C2), 62.7 (d, *J*(C,H) = 174 Hz; C2), 36.9 (t, *J*(C,H) = 125 Hz; C5), 19.2 (q, *J*(C,H) = 128 Hz; C6), 13.3 (q, *J*(C,H) = 125 Hz; C₅Me₃), 12.2 (q, *J*(C,H) = 125 Hz; C₅Me₃), 11.7 (q, *J*(C,H) = 126 Hz; C₅Me₃).
- [5] X-ray structural determination of **2b**: Data were collected at 23 °C on a Rigaku AFC5R diffractometer with graphite monochromated MoK_α radiation (ω scan $2\theta_{\max}$ = 50.0°). Laue symmetry revealed a monoclinic crystal system with the dimensions: *a* = 38.477(8), *b* = 8.635(2), *c* = 20.712(4) Å, β = 94.86(2)°, and *V* = 6856(2) Å³. ρ_{calc} = 1.53 g cm^{–3}, *Z* = 8, *M_r* = 790.03; space group *P*2₁/*n* (No. 14). Of the 13326 reflections that were collected, 12946 were unique (*R*_{int} = 0.048). μ = 13.3 cm^{–1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. The structure was solved by the Patterson method (DIRDIF 94 PATTY) and non-hydrogen atoms other than disordered C₅Me₃ groups were refined on *F*² using the SHELXL-97 program systems. The unit cell contains two molecules and one of the C₅Me₃ groups in each molecule is thermally disordered (occupancy: 51.14:48.86 and 51.23:48.77, respectively). Hydrogen atoms H1–3 and H39–41 were located by sequential difference Fourier synthesis and the remaining hydrogen atoms were included in geometric positions. All hydrogen atoms and disordered carbon atoms of C₅Me₃ groups were refined with isotropic thermal parameters. The final structure for **2b** was refined to *R* = 0.0545 for 8447 observed reflections (*F*_o > 4σ(*F*_o)) and *wR*₂ = 0.1615 for 12006 data and 590 parameters. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-118781. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [6] Thus far, a large number of *closo*-metallacyclopentadiene complexes have been known. For example, see a) E. Sappa, A. M. M. Landfredi, A. Tiripicchio, *Inorg. Chim. Acta* **1980**, *42*, 255; b) E. Rosenberg, S. Aime, L. Milone, E. Sappa, A. Tiripicchio, A. M. M. Landfredi, *J. Chem. Soc. Dalton Trans.* **1981**, 2023; c) D. Nuel, F. Dahan, R. Mathieu, *J. Am. Chem. Soc.* **1985**, *107*, 1658; d) E. Cabrera, J. C. Daran, Y. Jeannin, O. Kristiansson, *J. Organomet. Chem.* **1986**, *310*, 367; e) J. C. Daran, E. Gilbert, M. Gouygou, S. Halut, B. Heim, Y. Jeannin, *J. Cluster Sci.* **1994**, *5*, 373; f) D. Lentz, H. Michael-Schultz, M. Reuter, *Organometallics* **1992**, *11*, 2916; g) B. Heim, J. C. Daran, Y. Jeannin, B. Eber, G. Huttner, W. Imhof, *J. Organomet. Chem.* **1992**, *441*, 81; h) G. Gervasio, R. Giordano, E. Sappa, M. Costa, G. Predieri, A. Tiripicchio, *J. Cluster Sci.* **1993**, *4*, 33; i) M. V. Capparelli, Y. D. Sanctis, A. J. Arce, *Acta Crystallogr. Sect. C* **1995**, *51*, 1819; j) K. J. Adams, J. J. Barker, S. A. R. Knox, A. G. Orpen, *J. Chem. Soc. Dalton Trans.* **1996**, 975.
- [7] The reaction of **1** with *n*-hexane was monitored as follows: A 50-mL autoclave was charged with **1** (111.5 mg, 0.156 mmol) and *n*-hexane (10 mL) and the reaction mixture heated at 170 °C for 12 h. The reaction mixture was then cooled down to room temperature. After a portion (0.5 mL) of the reaction mixture had been evaporated, C₆D₆ (0.5 mL) was added to the residue and the ¹H NMR spectrum recorded. The rest of the reaction mixture was again heated at 170 °C. The ¹H NMR spectra of the reaction mixture were measured at intervals of 12 h.
- [8] An equilibrium mixture of regioisomers **3-in** and **3-out** is obtained quantitatively in the reaction of **1** with 1-hexyne. **3-in**: ¹H NMR (400 MHz, [D₈]THF, –80 °C, TMS): δ = 10.22 (s, 1H; Ru-CH), 1.854 (s, 30H; C₅Me₃), 1.845 (s, 15H; C₅Me₃), 1.38 (m, 2H; CH₂), 1.00 (m, 2H; CH₂), 0.74 (t, *J* = 8.0 Hz, 3H; CH₃), 0.40 (m, 2H; CH₂), –6.95 (brs, *w*_{1/2} = 11.0 Hz, 2H; Ru-H), –25.03 (t, *J* = 3.2 Hz, 1H; Ru-H); ¹³C NMR (100 MHz, [D₈]THF, –80 °C, TMS): δ = 180.7 (d, *J*(C, H) = 177 Hz; Ru-CH), 90.7 (s; C₅Me₃), 85.4 (s; C₅Me₃), 67.2 (s; Ru-C), 37.8 (t, *J*(C,H) = 125 Hz; CH₂), 34.9 (t, *J*(C,H) = 125 Hz; CH₂), 25.1 (t, *J*(C,H) = 124 Hz; CH₂), 16.2 (q, *J*(C,H) = 128 Hz; CH₃), 13.7 (q, *J*(C,H) = 125 Hz; C₅Me₃), 13.6 (q, *J*(C,H) = 125 Hz; C₅Me₃); **3-out**: ¹H NMR (400 MHz, [D₈]THF, –80 °C, TMS): δ = 3.84 (m, 2H; CH₂), 1.89 (s, 15H; C₅Me₃), 1.77 (s, 30H; C₅Me₃), 1.63 (m, 2H; CH₂), 1.62 (m, 2H; CH₂), 1.00 (t, *J* = 6.2 Hz, 3H; CH₃), –0.38 (brs, *w*_{1/2} = 7.0 Hz, 1H; Ru-CH), –11.78 (d, *J* = 4.4 Hz, 2H; Ru-H), –25.96 (dt, *J* = 4.4, 3.6 Hz, 1H; Ru-H); ¹³C NMR (100 MHz, [D₈]THF, –80 °C, TMS): δ = 188.7 (s, Ru-C), 91.9 (s; C₅Me₃), 85.8 (s; C₅Me₃), 64.6 (d, *J*(C, H) = 156 Hz; Ru-CH), 43.6 (t, *J*(C,H) = 125 Hz; CH₂), 37.0 (t, *J*(C,H) = 122 Hz; CH₂), 25.8 (CH₂; confirmed by ¹³C-¹H HSC and ¹H-¹H COSY spectra), 16.2 (q, *J*(C,H) = 128 Hz; CH₃), 14.7 (q, *J*(C,H) = 125 Hz; C₅Me₃), 13.0 (q, *J*(C,H) = 126 Hz; C₅Me₃).

Two New Carbaalanes: Compounds with an Al₇C₅ and a [B₁₁H₁₁]^{2–} Analogous Al₇C₄ Cluster**

Werner Uhl,* Frank Breher, Arne Lützen, and Wolfgang Saak

Some polyhedral borane or carborane cluster compounds are known from literature, which contain single aluminum atoms located on positions of high connectivity.^[1]

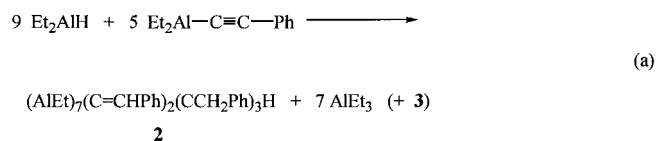
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[**] We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous financial support.

However, the first synthesis of a carborane analogous carbaalane [(AlMe)₈(CCH₂Ph)₅H] (**1**), which has a cluster exclusively formed by aluminum and carbon atoms, was achieved only recently in our group by the treatment of Me₂Al-C≡C-Ph with Me₂AlH.^[2] According to the Wade rules,^[3] **1** may be described as an *arachno* compound, but its molecular core comprises more atoms than usually observed for the corresponding boron compounds. At present, we are much interested in synthesizing further derivatives with different cluster sizes and structures by the systematic variation of the steric demand of their substituents, and we wish to report here on the results obtained with ethyl groups.

Similar to the synthesis of **1**, we dissolved diethylaluminum phenylethinide in a slight excess of diethylaluminum hydride without a further solvent and heated the mixture to 50 °C for 12 h. Triethylalane was formed [Eq. (a)], which was distilled



off in vacuo at the same temperature. Although the residue contained compound **2** owing to the NMR spectroscopic characterization in a high concentration, the crystallization succeeded only with difficulty, and bright orange crystals of **2** were isolated only in a moderate yield of 36 %. The crystal structure determination of **2** (Figure 1)^[4] verified the formation of a new carbaalane with a cluster comprising seven Al and five C atoms. Its structure may be derived from that of **1**, if one vertex of the Al₈ cube remains unoccupied. The cluster has three Al₄ faces, which are bridged by carbon-benzyl units similar as in **1**, and further three Al₃ triangles with an open edge, which are capped by the hydrogen atom H1 and two alkenylidene groups C=C(H)-Ph (C3, C3'), respectively.

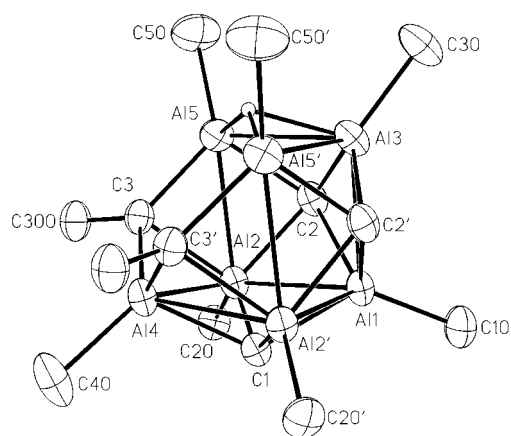
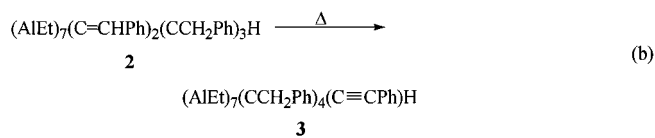


Figure 1. Molecular structure of **2**; the benzyl groups at C1, C2 and C3, the phenyl groups at C300 and the methyl groups of the ethyl substituents are omitted for clarity; bridging hydrogen atom H1 with arbitrary radius. Important bond lengths [pm]: Al1-Al2 260.0(1), Al1-Al3 256.9(2), Al2-Al4 268.5(1), Al2-Al5 267.8(1), Al3-Al5 270.7(1), Al3-H1 185(4), Al5-H1 198(1), Al1-C1 205.7(3), Al1-C2 213.9(3), Al2-C1 203.6(2), Al2-C2 206.1(3), Al2-C3 214.4(3), Al3-C2 202.7(3), Al4-C1 215.0(4), Al4-C3 204.2(3), Al5-C2 205.4(3), Al5-C3 200.3(3), Al1-C10 196.6(4), Al2-C20 195.9(3), Al3-C30 195.6(4), Al4-C40 198.2(5), Al5-C50 194.8(3), C3-C300 136.0(4).

Thus, just one hydroalumination step with EtAlH₂ is missing to generate an ethyl compound analogous to **1**. Short Al-Al distances of 260.0 (Al1-Al2) and 256.9 pm (Al1-Al3) are observed to Al1, which is part of all three Al₄ faces, while larger separations occur in the C and H bridged Al₃ triangles (268.2 and 270.7 pm, respectively). All values are similar to Al-Al distances published for (AlMe₃)₂ (261 pm) showing a 3c-2e bond or for organoelement compounds having Al-Al single bonds (R₂Al-AlR₂; 265 to 266 pm).^[5, 6] The Al-C separations in the cluster (200 to 215 pm) are lengthened compared to those observed to the terminal ethyl groups (196.2 pm). They strongly depend on the coordination sphere of the Al atoms. The C=C double bonds (136.0 pm) have such an orientation, that the π orbitals are perpendicular to the plane Al4-C3-Al5. They overlap partially with the open face of the cluster. Including the π-electrons, a total number of 16 electron pairs was calculated for the cluster, which has 12 vertices and for which a *hypho* configuration may thus be discussed. Indeed, the cluster of **2** can be derived from that of *closo*-[B₁₅H₁₅]²⁻,^[7] which owing to quantum chemical calculations adopts a structure with a tricapped hexagonal antiprism. In **2**, three vertices remain unoccupied. However, this hypothesis must be verified by quantum chemical calculations, which are in progress.

The molecular structure of **2** comprises five chemical different types of ethyl groups, two kinds of nonequivalent benzyl substituents and the ethenylidene groups. Thus, very complicated NMR spectra resulted. Their interpretation showed, that similar as in **1** the C atoms of the cluster have an unusual chemical shift to low field [δ = 31.6 (C1), 25.7 (C2) and 156.9 (alkene C atom C3)], while the α C atoms of the ethyl groups attached to aluminum resonate in the expected range of δ = +1 on average. The hydrogen atoms of the alkenylidene groups are observed at δ = 9.33.

Following the isolation of **2**, evaporation of the mother liquor and recrystallization of the residue from toluene, we obtained a further, yellow compound (**3**) in a low yield. **2** was transformed completely into compound **3**, when a solution in benzene was stored for several days at a temperature of 60 °C (estimated from NMR data: first-order reaction, $k \approx 4 \times 10^{-5} \text{ sec}^{-1}$, $\Delta G \approx 110 \text{ kJ mol}^{-1}$). A faster rearrangement was achieved, when the rough product out of the synthesis of **2** was heated to 110 °C for one hour without a solvent [Eq. (b)]. **3** is isomeric to **2**, but quite another, remarkable molecular



structure was observed possessing a cluster of seven Al and four C atoms (Figure 2).^[4] The atoms of the cluster bear terminal ethyl and benzyl groups, respectively. One edge of the cluster (Al3-Al6) is bridged by a hydrogen atom, the opposite one (Al2-Al5) by an ethynide ligand; both bridging atoms are neighbored to Al7 at the top of the cluster, but very long distances (Al7-H1 226, Al7-C5 255.2 pm) indicate only weak interactions. A number of twelve electron pairs was calculated for the Al₇C₄ molecular center, which according to

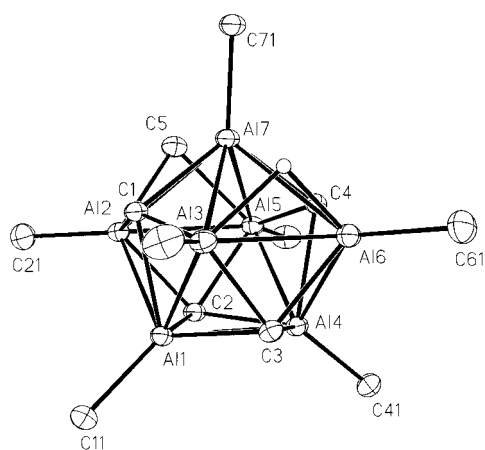


Figure 2. Molecular structure of **3**; the benzyl groups at C1 to C4 and the methyl groups of the ethyl substituents are omitted for clarity; only the first, anionic carbon atom of the ethynide group (C5) above the edge Al2–Al5 was drawn; bridging hydrogen atom H1 with artificial radius. Important bond lengths [pm]: Al1–Al2 259.42(8), Al1–Al3 258.77(8), Al1–Al4 258.65(8), Al2–Al5 267.47(8), Al2–Al7 292.12(9), Al3–Al6 261.23(9), Al3–Al7 281.75(8), Al4–Al5 258.13(8), Al4–Al6 258.91(8), Al5–Al7 290.00(8), Al6–Al7 285.91(8), Al3–H1 178(2), Al6–H1 180(2), Al1–C1 219.6(2), Al1–C2 207.0(2), Al1–C3 209.8(2), Al2–C1 203.5(2), Al2–C2 204.6(2), Al2–C5 211.8(2), Al3–C1 202.5(2), Al3–C3 206.1(2), Al4–C2 208.5(2), Al4–C3 207.2(2), Al4–C4 221.2(2), Al5–C2 206.8(2), Al5–C4 202.3(2), Al5–C5 210.3(2), Al6–C3 204.8(2), Al6–C4 202.6(2), Al7–C1 209.5(2), Al7–C4 209.0(2), Al1–C11 197.7(2), Al2–C21 196.5(2), Al3–C31 195.8(2), Al4–C41 197.5(2), Al5–C51 195.6(2), Al6–C61 195.5(2), Al7–C71 197.1(2).

the Wade rules give a *closo* configuration. Indeed, the arrangement of the atoms in the cluster corresponds to that of *closo*-[B₁₁H₁₁]^{2–} with the very characteristic structural element of a six-membered ring in a boat conformation bridged by a high-connectivity atom (Al7 in **3**). Also, a nice similarity exists concerning the inner cluster atomic separations. With the exception of Al7, short distances (258.1 to 259.4 pm, 261.2 and 267.5 pm) are observed between the Al atoms similar to those of the other carbaalanes, of which the larger ones are detected for the bridged edges. Longer Al–Al distances of 281.8 to 292.1 pm result to the atom Al7 above the boat-shaped six-membered heterocycle, which in contrast to the remaining metal atoms has contact to four Al atoms. The Al–C distances are similar to those observed for the other cluster compounds **1** and **2**. In comparison with [B₁₁H₁₁]^{2–}, **3** has, however, a deviating connectivity of the C and Al atoms at the bottom of the cluster, which may be caused by the strongly differing atomic radii of carbon and aluminum. The chemical shifts of the cluster atoms in the very complicated NMR spectra are similar to those of compound **2**.

As reported here, two novel members (**2** and **3**) of the new class of carbaalanes have been synthesized and characterized. Owing to their structures and number of cluster electrons, the derivatives **1** and **3** can be attributed to the *arachno* and *closo* type compounds, respectively, and may thus be described as analogues of polyhedral boranes or carbaboranes. Only the classification of the structure of **2** remains doubtful, because of the questionable contribution of the π electrons to the bonding in the cluster. Thus, in a short time the carbaalanes have set up as a new class of compounds with a remarkable variety of structures.^[9]

Experimental Section

n-Pentane and cyclopentane were dried over LiAlH₄. Et₂Al–C≡C–Ph was synthesized according to the corresponding dimethyl compound;^[2] it was isolated as highly viscous fluid, which could not be obtained in a crystalline form and decomposed upon an attempt of distillation. Therefore, it was used without further purification [¹H NMR (C₆D₆): δ = 1.46 (t, CH₃), 0.59 (q, AlCH₂); ¹³C (C₆D₆): δ = 120.1 and 93.0 (C≡C), 9.7 (CH₃), 3.2 (AlCH₂)].

2 and **3**: A mixture of 4.04 g (5 mL, 46.9 mmol) Et₂AlH^[10] and 2.90 g (15.6 mmol) Et₂Al–C≡C–Ph without a further solvent was heated to 50 °C under argon for 12 h. All volatile components were distilled off at this temperature in vacuo. A higher temperature led to the complete rearrangement to compound **3**. The residue was dissolved in *n*-pentane. Orange-red, air-sensitive crystals of **2** precipitated upon cooling of the solution to –70 °C (1.02 g, 36 %). The mother liquor was evaporated. The residue was dissolved in toluene. Yellow, air-sensitive crystals of compound **3** were obtained after storing the solution at –30 °C for several weeks (0.255 g, 9 %). **3** was completely formed, if after the separation of the volatile components the rough product of the reaction was heated to 110 °C for 1 h. The product was recrystallized several times from *n*-pentane (yield 42 %). The NMR data were assigned on the basis of ¹H, ¹³C, H,H-COSY, HMQC and HMBC NMR spectra. Only essential resonances are given here; the complete data are available as electronic background information. Characterization of **2**: Decomposition (argon, sealed capillary): 146 °C. ¹H NMR (500 MHz, [D₈]toluene, 275 K): δ = 9.33 (s, 2H, C = CH300), 4.77 (s, 1H, AlH), 3.67 (s, 2H, CH₂ at C1), 3.58 and 3.45 (each 2H, d, ²J_{HH} = –13.8 Hz, CH₂ at C2, diastereotopic). ¹³C NMR (125.8 MHz, [D₈]toluene, 275 K): δ = 34.91 (CH₂ at C1), 31.55 (C1), 33.85 (CH₂ at C2), 25.71 (C2), 183.51 (CH at C3), 156.87 (C3), ethyl groups: 1.05 (Al1–C), 9.75 (C11), 2.44 (Al2–C), 8.86 (C21), Al3–Et and Al4–Et: –0.38 (Al–C), 10.36 (Me), –1.00 (Al–C), 9.82 (Me), 3.44 (Al5–C), 9.98 (C51). IR (paraffin, CsBr plates): $\tilde{\nu}$ [cm^{–1}] = 1945 vw, 1802 vw (Ph); 1647 (br) $\tilde{\nu}$ AlH; 1598 w (Ph); 1578 w $\tilde{\nu}$ C≡C; 1506 m δ CH; 1462 vs (paraffin); 1406 w δ CH₃; 1377 vs (paraffin); 1343 m, 1294 w, 1226 vw, 1198 vw, 1154 w δ CH, $\tilde{\nu}$ CC; 1073 w, 1030 vw $\tilde{\nu}$ CC; 985 m, 957 m, 921 m, 906 m, 832 m (Ph); 748 vs, 703 vs, 689 s, 655 vs, 616 s δ Ph, δ AlH, $\tilde{\nu}$ AlC; 556 m, 456 m, 434 m $\tilde{\nu}$ AlC. UV/Vis (cyclopentane): λ_{max} [nm] (log ϵ): 250 (4.4, sh), 310 (4.7). *M_r* (in benzene by cryoscopy): found 878; calcd 907.0. Characterization of **3**: Decomposition (argon, sealed capillary): 262 °C. ¹H NMR (500 MHz, [D₈]toluene, 275 K): δ = 4.89 (s, 1H, AlH), 3.68 and 3.63 (each 2H, d, ²J_{HH} = –14.9 Hz, CH₂ at C1 and C4, diastereotopic), 3.47 (s, 2H, CH₂ at C2), 3.34 (s, 2H, CH₂ at C3). ¹³C NMR (125.8 MHz, [D₈]toluene, 275 K): δ = 118.89 (PhC≡CAl₂), 86.95 (PhC≡CAl₂), 35.26 (CH₂ at C1 and C4), 34.76 (CH₂ at C2), 34.24 (CH₂ at C3), 19.57 (C1 and C4), 28.56 (C2), 20.78 (C3), Al1–Et and Al4–Et: 2.57 (Al–CH₂) and 9.91 (Me), Al2–Et and Al5–Et: 2.18 (Al–CH₂) and 10.08 (Me), Al3–Et and Al6–Et: –2.01 (Al–CH₂) and 10.19 (Me), Al7–Et: 0.76 (Al–CH₂) and 13.06 (Me). IR (paraffin, CsBr plates): $\tilde{\nu}$ [cm^{–1}] = 2044 m $\tilde{\nu}$ C≡C, 1937 vw, 1800 vw, 1599 m, 1582 w (Ph); 1509 w, 1491 m δ CH₃; 1460 vs (paraffin); 1403 m δ CH₃; 1377 vs (paraffin); 1297 m, 1226 m, 1201 m (br), 1177 m $\tilde{\nu}$ AlH, δ CH, $\tilde{\nu}$ CC; 1074 w, 1028 w $\tilde{\nu}$ CC; 986 s, 955 m, 927 m, 897 m, 823 m (Ph); 790 m (br.) δ AlH; 747 vs, 700 vs, 684 vs, 665 vs (br) δ Ph, $\tilde{\nu}$ AlC; 554 m, 484 w, 455 w, 427 w $\tilde{\nu}$ AlC. UV/Vis (cyclopentane): λ_{max} [nm] (log ϵ): 225 (4.0), 250 (4.1), 290 (4.1). *M_r* (in benzene by cryoscopy): found 887; calcd 907.0.

Received: June 24, 1999 [Z 13619]

- [1] D. M. Schubert, M. A. Bandman, W. S. Rees, Jr., C. B. Knobler, P. Lu, W. Nam, M. F. Hawthorne, *Organometallics* **1990**, *9*, 2046; C. A. Morrison, B. A. Smart, P. T. Brain, D. W. H. Rankin, A. J. Downs, *J. Chem. Soc. Dalton Trans.* **1998**, 2155.
- [2] W. Uhl, F. Breher, *Angew. Chem.* **1999**, *111*, 1578; *Angew. Chem. Int. Ed.* **1999**, *38*, 1477. Polyboranes by hydroboration: B. Wrackmeyer, H. J. Schanz, M. Hofmann, P. von R. Schleyer, R. Boese, *Eur. J. Inorg. Chem.* **1999**, 533; B. Wrackmeyer, H. J. Schanz, M. Hofmann, P. von R. Schleyer, *Eur. J. Inorg. Chem.* **1998**, 633; R. Köster, G. Seidel, B. Wrackmeyer, *Angew. Chem.* **1994**, *106*, 2380; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2294.
- [3] K. Wade, *Adv. Inorg. Chem. Radiochem.* **1976**, *18*, 1.

- [4] Crystal structure of **2**: Crystals from cyclopentane by slow concentration at room temperature over a period of some days; $C_{54}H_{69}Al_7$, orthorhombic, $Pnma$; $a = 2028.45(11)$, $b = 1713.07(6)$, $c = 1490.23(6)$ pm, $V = 5178.4(4)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.163$ g cm⁻³, crystal dimensions: $0.75 \times 0.46 \times 0.34$ mm, diffractometer Stoe IPDS, MoK_{α} radiation, 193 K, measurement range: $4.2 < 2\theta < 52.0^\circ$, 168 exposures, $\Delta\varphi = 1.1^\circ$, 5221 independent reflections, 3512 reflections $F > 4\sigma(F)$, $\mu = 0.175$ mm⁻¹, programs SHELXTL PLUS REL 4.1 and SHELXL-93, 307 parameters, $R1 = 0.052$ and $wR2$ (all data) = 0.156, max/min residual electron density: $0.77/-0.37 \times 10^{30}$ e m⁻³. Crystal structure of **3**: Crystals from toluene; $C_{54}H_{69}Al_7$, triclinic, $P1$, $a = 1082.39(7)$, $b = 1440.15(12)$, $c = 1648.2(2)$ pm, $\alpha = 80.516(11)$, $\beta = 89.883(11)$, $\gamma = 81.348(9)^\circ$, $V = 2504.6(4)$ Å³, $Z = 2$, $d_{\text{calc}} = 1.203$ g cm⁻³, crystal dimensions: $0.80 \times 0.39 \times 0.26$ mm, diffractometer Stoe IPDS, MoK_{α} radiation, 193 K, measurement range $4.2 < 2\theta < 51.8^\circ$, 282 exposures, $\Delta\varphi = 1.1^\circ$, 9016 independent reflections, 6515 reflections $F > 4\sigma(F)$, $\mu = 0.181$ mm⁻¹, 561 parameters, $R1 = 0.035$ and $wR2$ (all data) = 0.107; max/min residual electron density: $0.30/-0.31 \times 10^{30}$ e m⁻³. The positions of the hydrogen atoms H1 were obtained from a difference Fourier synthesis, they were refined isotropically. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 127469 (**2**) and CCDC 127470 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [5] R. G. Vranka, E. L. Amma, *J. Am. Chem. Soc.* **1967**, *89*, 3121; J. C. Huffman, W. E. Streib, *J. Chem. Soc. Chem. Commun.* **1971**, 911.
- [6] W. Uhl, *Z. Naturforsch. B* **1988**, *43*, 1113; R. J. Wehmschulte, K. Ruhlandt-Senge, M. M. Olmstead, H. Hope, B. E. Sturgeon, P. P. Power, *Inorg. Chem.* **1993**, *32*, 2983.
- [7] J. Bicerano, D. S. Marynick, W. N. Lipscomb, *Inorg. Chem.* **1978**, *17*, 3443; M. Gielen, *Polyhedron* **1988**, *7*, 363; P. von Ragué Schleyer, K. Najafian, A. M. Mebel, *Inorg. Chem.* **1998**, *37*, 6765.
- [8] E. H. Wong, L. Prasad, E. J. Gabe, M. G. Gatter, *Inorg. Chem.* **1983**, *22*, 1143; O. Volkov, W. Dirk, U. Englert, P. Paetzold, *Z. Anorg. Allg. Chem.* **1999**, *625*, 1193.
- [9] A review about carbaalanes and other cluster compounds containing aluminium atoms on high-connectivity sites in: W. Uhl, F. Breher, *Eur. J. Inorg. Chem.* **2000**, 1.
- [10] H. Lehmkuhl, K. Ziegler, *Methoden Org. Chem. (Houben-Weyl)* 4th ed. **1952**, Vol. XIII/4, p 58.

Tandem Intermolecular–Intramolecular Carbolithiation: A Versatile Method for Synthesis of Cyclopentanes**

Xudong Wei and Richard J. K. Taylor*

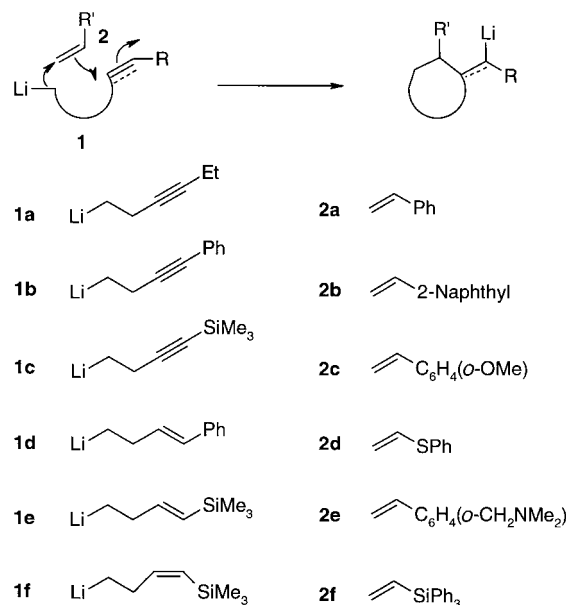
The carbolithiation of alkenes and alkynes is a particularly useful synthetic transformation in that the generation of a new carbon–carbon bond is accompanied by the formation of an organolithium species which can be elaborated directly or after transmetalation.^[1–4] To date, this chemistry has been largely confined to alkenes and alkynes activated by conjugation to carbonyl and related electron-withdrawing groups,

but within this sub-group a rich diversity of examples have been described. However, in recent years, the development of improved procedures for the generation of organolithium reagents^[5] has meant that major advances have been made in the carbolithiation of unactivated alkenes and alkynes.^[2–4] Intramolecular variants have attracted particular attention and a range of synthetically useful 4-, 5-, and 6-*exo* carbolithiation procedures have been reported.^[2f–2n] In addition, the groups of Bailey and Krief have extended this research to develop tandem intramolecular carbolithiation procedures (Scheme 1).^[3]



Scheme 1. The principle of tandem intramolecular carbolithiations.

Encouraged by our research in the intermolecular carbolithiation area^[4] we designed a tandem intermolecular–intramolecular carbolithiation sequence (Scheme 2). This procedure employs organolithium reagents as difunctional, conjunctive reagents and represents a versatile anionic [3+2] approach to substituted cyclopentanes.^[6] This convergent



Scheme 2. Tandem intermolecular–intramolecular carbolithiation.

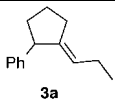
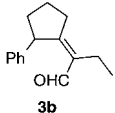
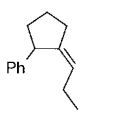
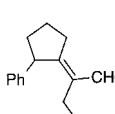
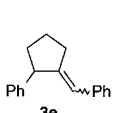
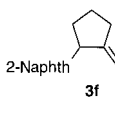
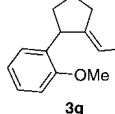
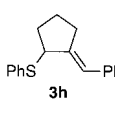
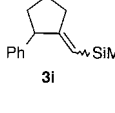
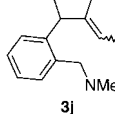
sequence is especially attractive as, in contrast to many tandem processes, the precursors are readily available. After the completion of our studies, we discovered that one isolated example of this procedure had been described: Krief and Barbeaux trapped a homoallylic lithium reagent with ethene, with the resulting organolithium intermediate undergoing cyclization followed by protonation to give a methylcyclopentane.^[3b] Our plan was to establish a general and versatile method for the preparation of complex cyclopentanes with a high level of functionality in a stereocontrolled manner from functionalized organolithium reagents and alkenes. Herein we report the successful realization of this plan.

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[**] We thank the EPSRC for a research fellowship (X.W.).

Several design features were incorporated to facilitate the desired process: 1) homoallylic and homopropargylic systems were chosen to preclude cyclization of the initial organolithium reagents **1**; 2) "activated" alkenes **2** (R = Ar, Ph₃Si, PhS) were employed to facilitate the initial intermolecular carbolithiation and ensure regioselectivity; 3) alkenes **2** were added by syringe-pump over extended times to minimize polymerization processes. The successful reactions are summarized in Table 1 and Table 2. All new compounds were fully

Table 1. Tandem intermolecular–intramolecular carbolithiation processes with the lithiated alkynes **1a–c**.

Entry	1	2	Solvent	Electrophile	Product	Yield [%] (<i>E:Z</i>)
1	1a	2a	diethyl ether	MeOH		61 (97:3)
2	1a	2a	diethyl ether	DMF/H ₃ O ⁺		48 (97:3)
3	1a	2a	diethyl ether:THF (3:1)	MeOH		50 (2:98)
4	1a	2a	diethyl ether:THF (3:1)	DMF/H ₃ O ⁺		43 (2:98)
5	1b	2a	diethyl ether	MeOH		53 (70:30)
6	1b	2b	diethyl ether	MeOH		62 (56:44)
7	1b	2c	diethyl ether	MeOH		60 (100:0)
8	1b	2d	diethyl ether	MeOH		62 ^[a] (100:0)
9	1c	2a	diethyl ether	MeOH		82 (76:24)
10	1c	2e	diethyl ether	MeOH		56 (85:15)

[a] Yield based on recovered starting material.

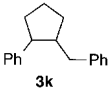
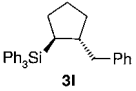
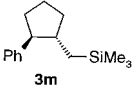
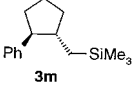
characterized by high-field ¹H and ¹³C NMR spectroscopy and by elemental analysis or high-resolution mass spectrometry. Reactions of the acetylenic reagents **1a–c**,^[7] generated by lithium–iodine exchange using *tert*-butyllithium at –78 °C,^[5] were studied first (Table 1). Alkenes **2a–d** were slowly (0.5–1.5 h) added to the organolithium reagents and we were delighted to observe that, after protonation, the anticipated tandem sequence to give cyclopentanes **3a, c, e–j** proceeded in reasonable to high yields (50–82 %), often with excellent stereocontrol. Thus treatment of styrene with hexynyllithium **1a** (entry 1) gave cyclopentane **3a** in 61 % yield (*E:Z* = 97:3). The preponderance of the *E*-alkene is consistent with the accepted *syn*-carbolithiation mechanism.^[2h] However, when a diethyl ether/THF (3/1) solvent system was employed the corresponding *Z*-isomer **3c** was obtained as the major product (entry 3: *E:Z* = 2:98; structures confirmed by NOE studies). Similar results were obtained when DMF was employed as the electrophilic trapping agent (entries 2 and 4): **3b** was obtained in diethyl ether, **3d** in diethyl ether/THF. We are currently carrying out further reactions to rationalize this unprecedented result, although we assume that the effective size of the lithium substituent is increased in THF and that this leads to vinyl inversion.

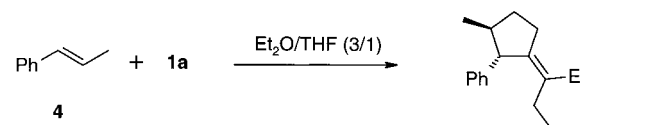
The remaining reactions in Tables 1 and 2 were all carried out in diethyl ether. The reactions of the lithiated alkynes **1b** and **1c** with styrene (entries 5 and 9, respectively) gave the corresponding cyclopentanes **3e** and **3i** as *E/Z* mixtures, presumably as a consequence of fast isomerization of phenyl- and trimethylsilyl-stabilized vinyl anions.^[2h] Other alkene acceptors were also employed. Thus, 2-vinylnaphthalene (**2b**), *ortho*-methoxystyrene (**2c**), phenylthioethene (**2d**), and *ortho*-(dimethylaminomethyl)styrene (**2e**) were all converted into the corresponding cyclopentanes (entries 6–8 and 10). The stereoselective formation of **3g** and **3h** presumably reflects intramolecular coordination of the intermediate vinyl lithium to oxygen and sulfur, respectively, and demonstrates that stereocontrol can be achieved even with phenyl-stabilized vinyl anions.

The reactions of the lithiated alkenes **1d–f**^[7] (Table 2) to give the cyclopentanes **3k–3m** proceeded in reasonable yield, and, in reactions 2–4, excellent stereocontrol. At first sight, the low stereoselectivity observed in the reaction of styrene and **1d** (entry 1) is surprising: we ascribe this to a π -stacking effect, which provides added stabilization for *cis*-**3k**.

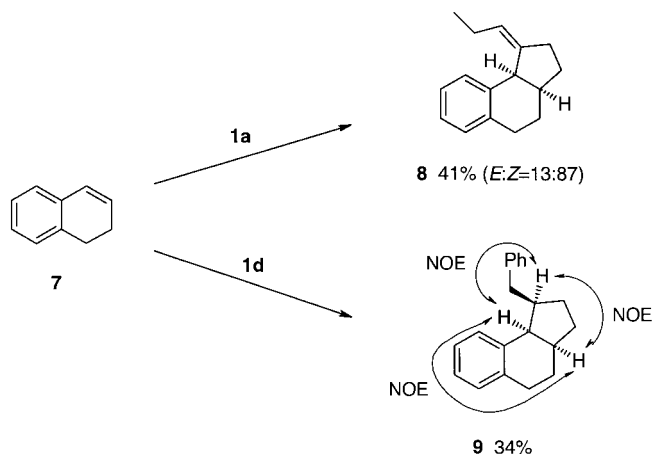
These reactions can also be carried out on disubstituted alkenes (Scheme 3). Thus, reaction of alkynyllithium reagent **1a** with (*E*)-1-phenylpropene (**4**) in diethyl ether/THF followed by protonation produced cyclized adduct **5** in 50 % yield. The corresponding carboxylic acid **6** was obtained when the intermediate vinyl lithium was trapped with carbon dioxide. In a similar manner, reaction of alkynyllithium reagent **1a** with 1,2-dihydronaphthalene (**7**) in diethyl ether/THF produced a single adduct **8** in 41 % yield with the expected predominance of the *Z*-alkene. The corresponding reaction using lithiated alkene **1d** produced tricycle **9** as the only isolable product (although minor diastereomeric impurities were visible in the ¹H NMR spectrum of the crude product). The *cis,cis* stereochemistry of **9**, which was assigned using NOE experiments, presumably reflects the π -stacking

Table 2. Tandem intermolecular–intramolecular carbolithiation processes with lithiated alkenes **1d–f**.

Entry	1	2	Solvent	Electrophile	Product	Yield [%] (<i>cis:trans</i>)
1	1d	2a	diethyl ether	MeOH		52 (50:50)
2	1d	2f	diethyl ether	MeOH		45 (100:0)
3	1e	2a	diethyl ether	MeOH		52 (100:0)
4	1f	2a	diethyl ether	MeOH		45 (100:0)



- 5** E = H, 50% (*E:Z* = 6:94)
6 E = CO₂H, 40% (*E:Z* = 94:6)



Scheme 3. Tandem intermolecular–intramolecular carbolithiation of disubstituted alkenes.

effect observed earlier. Although optimization studies have to be carried out, these results illustrate the potential of this new methodology for the synthesis of polysubstituted cyclopentanes and related annelated systems.

In summary we have demonstrated that tandem intermolecular–intramolecular carbolithiations provide an extremely convenient and versatile route to substituted cyclopentanes from readily available starting materials. In many cases

excellent stereocontrol can be achieved by solvent chelation, intramolecular coordination, or π -stacking effects. Studies to develop asymmetric variants^[1h, 2l–m, 4c, 8] of this methodology and to apply it to natural product synthesis are in progress.

Experimental Section

tert-Butyllithium (1.24 mL, 1.7 M solution in hexanes, 2.1 mmol) was added dropwise to a stirred solution of the corresponding iodoalkene or -alkyne (1.0 mmol) in diethyl ether (9 mL) at -78°C and under an inert atmosphere. The cooling bath was removed after 15 min and the solution of organolithium reagent **1** was allowed to warm up to room temperature. A solution of alkene **2** (0.50 mmol) in diethyl ether (3 mL; or THF in those cases specified in the table) was added slowly with a syringe pump over 1 h at room temperature. Upon completion, the reaction mixture was stirred for another 5 min and quenched with the specified electrophilic reagent. The reaction mixture was diluted to 70 mL with diethyl ether and was washed with water (15 mL), brine (15 mL), and the organic layer was dried over sodium sulfate. After evaporation of the solvent and column chromatography (silica gel) the cyclized product **3** was obtained, for example, **3g** as a white solid (60%, *E:Z*, 100:0): m.p. $69.5\text{--}70.5^{\circ}\text{C}$; thin-layer chromatography R_f = 0.29 (petrol ether $40\text{--}60^{\circ}\text{C}$); ¹H NMR (270 MHz, CDCl₃, 25 $^{\circ}\text{C}$, TMS): δ = 1.67–1.83 (m, 2H), 1.90–2.03 (m, 1H), 2.03–2.19 (m, 1H), 2.70–2.90 (m, 2H), 3.83 (s, 3H), 4.17 (t, ³*J* (H,H) = 8 Hz, 1H), 5.99 (m, 1H), 6.87–6.94 (m, 2H), 7.10–7.30 (m, 7H); ¹³C NMR (67.9 MHz, CDCl₃): δ = 25.7, 32.3, 34.2, 46.6, 55.5, 110.7, 120.6, 122.4, 125.6, 127.1, 128.06, 128.10, 129.1, 133.7, 138.9, 150.0, 157.5; IR (film): $\tilde{\nu}_{\text{max}}$ = 2954, 2866, 1597, 1585, 1491, 1241, 1029, 753 cm^{−1}; MS (EI) *m/z*: 264, [*M*⁺], 173, 91; HR-MS (EI): *m/z*: 264.1518 (calcd for C₁₉H₂₀O: 264.1514, error -1.5×10^{-6}); elemental analysis calcd for C₁₉H₂₀O: C 86.32, H 7.63; found: C 85.96, H 7.78.

Received: June 7, 1999 [Z13525]

- Intermolecular carbolithiation: a) L. F. Cason, H. G. Brooks, *J. Org. Chem.* **1954**, *19*, 1278–1282; b) D. J. Peterson, *J. Org. Chem.* **1966**, *31*, 950–954; c) H. Felkin, G. Swierczewski, A. Tambute, *Tetrahedron Lett.* **1969**, 707–710; d) G. Köbrich, I. Stöber, *Chem. Ber.* **1970**, *103*, 2744–2753; e) J. K. Crandall, A. C. Clark, *J. Org. Chem.* **1972**, *37*, 4236–4242; f) B. Harichian, P. Magnus, *J. Chem. Soc. Chem. Commun.* **1977**, 522–523; g) S. Raucher, G. A. Koolpe, *J. Org. Chem.* **1978**, *43*, 4252–4253; h) S. Klein, I. Marek, J.-F. Normant, *J. Org. Chem.* **1994**, *59*, 2925–2926; S. Norsikian, I. Marek, J.-F. Normant, *Tetrahedron Lett.* **1997**, *38*, 7523–7526, and references therein.
- Intramolecular carbolithiation: a) V. N. Drozd, Yu. A. Ustyniuk, M. A. Tsel'eva, L. B. Dmitriev, *J. Gen. Chem. USSR* **1969**, *39*, 1991–1996; b) J. St. Denis, T. Dolzine, J. P. Oliver, *J. Am. Chem. Soc.* **1972**, *94*, 8260–8261; c) M. J. Smith, S. E. Wilson, *Tetrahedron Lett.* **1981**, *22*, 4615–4168; d) A. Krief, P. Barbeaux, *J. Chem. Soc. Chem. Commun.* **1987**, 1214–1215; e) A. Krief, B. Kenda, B. Remacle, *Tetrahedron* **1996**, *52*, 7435–7463, and references therein; f) A. R. Chamberlin, S. H. Bloom, L. A. Cervini, C. H. Fotsch, *J. Am. Chem. Soc.* **1988**, *110*, 4788–4796; g) W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel, K. B. Wiberg, *J. Am. Chem. Soc.* **1991**, *113*, 5720–5727, and references therein; h) W. F. Bailey, T. V. Ovaska, *J. Am. Chem. Soc.* **1993**, *115*, 3080–3090; i) T. V. Ovaska, R. R. Warren, C. E. Lewis, N. Wachter-Jurcsak, W. F. Bailey, *J. Org. Chem.* **1994**, *59*, 5868–5870; j) W. F. Bailey, M. W. Carson, *J. Org. Chem.* **1998**, *63*, 9960–9967, and references therein; k) E. Lorthois, I. Marek, J.-F. Normant, *Tetrahedron Lett.* **1996**, *37*, 6693–6694; l) I. Coldham, R. Hufton, D. J. Snowden, *J. Am. Chem. Soc.* **1996**, *118*, 5322–5323; I. Coldham, M. M. S. Lang-Anderson, R. E. Rathmell, D. J. Snowden, *Tetrahedron Lett.* **1997**, *38*, 7621–7624, and references therein; m) M. J. Woltering, R. Frölich, D. Hoppe, *Angew. Chem.* **1997**, *109*, 1804–1805; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1764–1766; M. Oestreich, D. Hoppe, *Tetrahedron Lett.* **1999**, *40*, 1881–1884, and references therein.
- Tandem intramolecular carbolithiation: a) W. F. Bailey, K. Rossi, *J. Am. Chem. Soc.* **1989**, *111*, 765–766; b) A. Krief, P. Barbeaux, *Tetrahedron Lett.* **1991**, *32*, 417–420; c) W. F. Bailey, A. D. Khanolkar,

- K. Gavaskar, *J. Am. Chem. Soc.* **1992**, *114*, 8053–8060; d) W. F. Bailey, T. V. Ovaska, *Chem. Lett.* **1993**, 819–820.
- [4] a) X. Wei, R. J. K. Taylor, *Chem. Commun.* **1996**, 187–188; b) X. Wei, R. J. K. Taylor, *Tetrahedron Lett.* **1996**, *37*, 4209–4210; c) X. Wei, R. J. K. Taylor, *Tetrahedron: Asymmetry* **1997**, *8*, 665–668; d) X. Wei, R. J. K. Taylor, *Tetrahedron Lett.* **1997**, *38*, 6467–6470.
- [5] a) W. F. Bailey, E. R. Punzalan, *J. Org. Chem.* **1990**, *55*, 5404–5406; b) E. I. Negishi, D. R. Swanson, C. J. Rousset, *J. Org. Chem.* **1990**, *55*, 5406–5409, and references therein; c) A. Krief, A. Nazih, M. Hobe, *Tetrahedron Lett.* **1995**, *36*, 8111–8114, and references therein.
- [6] For lead references, see T. Hudlicky, J. D. Price, *Chem. Rev.* **1989**, *89*, 1467–1486; F. Neumann, C. Lambert, P. von R. Schleyer, *J. Am. Chem. Soc.* **1998**, *120*, 3357–3370. For a review of tandem processes, see L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163.
- [7] Synthesis of 1-iodo-4-phenyl-3-butene: J. P. McCormick, A. S. Fitterman, D. L. Barton, *J. Org. Chem.* **1981**, *46*, 4708–4712. The other iodide precursors were obtained from the corresponding alcohols by the method of G. L. Lange, C. Gottardo, *Synth. Commun.* **1990**, *20*, 1473–1479.
- [8] For a recent review of enantioselective carbometalations of unactivated olefins, see I. Marek, *J. Chem. Soc. Perkin Trans. 1* **1999**, 535–544.

Ca₁₁N₆(CN)₂ and Ca₄N₂(CN)₂: The True Nature of an “Unusual Binary Nitride” Is Finally Revealed**

Olaf Reckeweg and Francis J. DiSalvo*

The compound reported in the literature as the “electron deficient, binary nitride Ca₁₁N₈” has been an object of discussion for many years.^[1] Both its electronic and crystal structure are not yet fully understood. The only reported structure determination of “Ca₁₁N₈” is based solely on X-ray crystallographic methods.^[1] Because of their similar X-ray scattering factors, boron, carbon, nitrogen, and oxygen are often hard to distinguish with X-ray methods. It has been suggested^[2] an oxygen contamination during the reaction led to the ionic compound (Ca²⁺)₁₁(N³⁻)₆(O²⁻)₂ and the net electrical neutrality simplifies the electronic situation. However, this model requires an unusual coordination sphere for one of the nitrogen atoms. The average Ca–N interatomic distance in “Ca₁₁N₈” is 248 pm for N1 (numbering after ref. [1]) and 242 pm for N2 (both in a distorted octahedral environment), but 263 pm (two 250 pm bonds and one 290 pm bond) for N3 (247 pm with coordination number six in Ca₃N₂^[3]). For this unusual nitrogen (or oxygen) coordination

sphere, or for the even more exceptional electron-deficient binary nitride, no satisfying explanation had been found yet.

While we were pursuing research in the ternary system Ca–Cu–N, a reaction of Ca₃N₂, Cu₃N, and NaN₃ in a stainless steel ampoule yielded metallic copper and two different kinds of crystals. Both crystals appeared as very fine needles, one being a yellow-green color and transparent, the other being dark red, nearly black, but also transparent if intensely illuminated. Both crystals are air and moisture sensitive.

Single crystal X-ray structure analysis showed surprising results.^[4] The crystal structure of the dark-red crystals has a striking resemblance to the one reported for “Ca₁₁N₈”. The crystallographic data (*P*4₂*nm* (No. 102), *a* = 1445(2) pm, and *c* = 360(1) pm for “Ca₁₁N₈”, compared to *P*4₂*mm* (No. 136), *a* = 1452.3(2) pm, and *c* = 360.83(4) pm for the dark-red crystals) and the coordinates of almost all atoms of “Ca₁₁N₈” and our compound are closely related to each other (see Figure 1). The only difference (except the missing mirror plane ⊥ *c* in “Ca₁₁N₈”) is, instead of the single (and already under doubt) nitrogen atom on the N3 position of “Ca₁₁N₈”, our data showed a triatomic unit with three crystallographically independent sites. Refinements with nitrogen atoms on all three sites showed a very large atomic displacement factor for the middle nitrogen atom. Refining a carbon atom for this position instead of a nitrogen atom decreased both *R* values

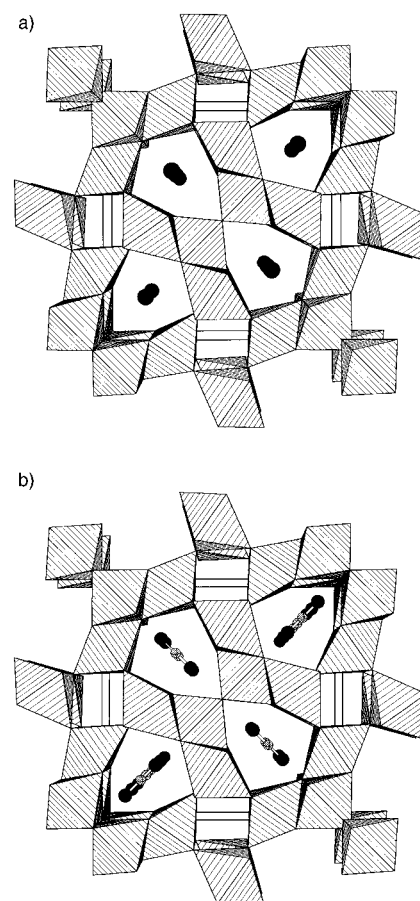


Figure 1. Comparison of the structures of a) “Ca₁₁N₈” and b) **1**. The views parallel to the *c* axes are shown. The distorted Ca₆N octahedra are displayed as hatched polyhedra, nitrogen atoms as black circles, carbon atoms as gray spheres.

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[**] We would like to thank Dipl.-Phys. Sylvia Smolorz for the Raman measurements and Mr. Christopher B. Hoffmann (both Cornell University) for the IR measurements. Financial support by the NSF grant DMR-9805719 and by the NEDO Foundation is gratefully acknowledged.

significantly ($\approx 0.5\%$), the thermal displacement factors became reasonable, and the bond angle and the bond distances were in a range known for cyanamide ions (Table 1). Instead of “ Ca_{11}N_8 ”, we found the red crystals to be $\text{Ca}_{11}\text{N}_6(\text{CN}_2)_2$ (**1**).

Table 1. Spectroscopic^[a, b] and X-ray data of alkaline earth cyanamides.

Compound	$\tilde{\nu}_s$ [cm ⁻¹]	$\tilde{\nu}_{as}$ [cm ⁻¹]	δ [cm ⁻¹]	$d(\text{C}=\text{N})$ [pm]	$\angle$ [°]	Ref.
MgCN ₂	1301	2114	681	124.8(2)	180.00(8)	[5]
CaCN ₂	—	—	—	122.4(16)	180	[6]
SrCN ₂	1251	1989	663	122.8(10)	178.8(9)	[5]
		2023	677	122.2(11)		
BaCN ₂	1238	1947	662	119.2(11)	177.2(18)	[5]
			673			
CaCN ₂ ^[c]	1271	2033	670	—	—	
1 , $\text{Ca}_{11}\text{N}_6(\text{CN}_2)_2$	1263	2008	652	119.3(24)	180.0(14)	own data
			646	123.8(24)		
2 , $\text{Ca}_4\text{N}_2(\text{CN}_2)_2$	1228	1988	672	121.9(12)	179.7(10)	
			647	124.1(13)		

[a] Raman measurements were performed on powdered samples (CaCN_2 and **2**) and on selected crystals (**1**) with a Dilor spectrometer (Aerotech, HeNe laser of $\lambda = 632.8$ nm). All samples sealed airtight in thin-walled glass capillaries. [b] IR measurements were performed with a Mattson Polaris FT-IR spectrometer (KBr pellets). [c] CaCN_2 has been prepared by the reaction of Ca_3N_2 , C, and NaN_3 in silica-jacketed niobium ampoules at 1200 K (1 d.). The X-ray powder diagram could be indexed on the base of the reported^[6] rhombohedral structure (hexagonal, $a = 369.5(1)$ and $c = 1476.7(5)$ pm).

The yellow-green crystals turned out to be the structurally related compound $\text{Ca}_4\text{N}_2(\text{CN}_2)_2$ (**2**, Figure 2), in which a slightly different combination of the same structural elements

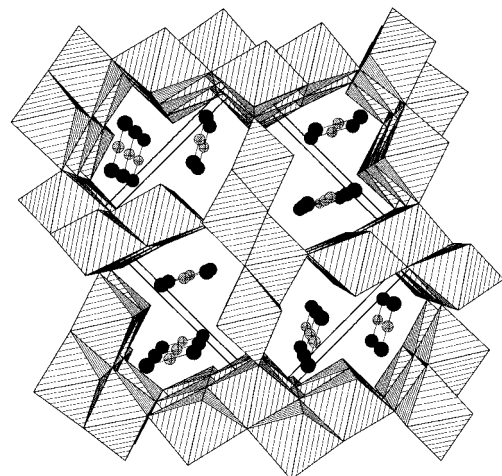


Figure 2. The structure of **2**. A view parallel to the b axis is shown. The distorted Ca_4N octahedra are displayed as hatched polyhedra, nitrogen atoms are displayed as black circles, carbon atoms as gray spheres.

occur as in **1**. Both compounds can be described as open three-dimensional frameworks formed by linking distorted NCa_6 octahedra through shared edges and corners. The CN_2^{2-} guest species are hosted in channels along $[001]$ in **1** and along $[010]$ in **2**.

To confirm the structures obtained by X-ray crystallographic methods, we pursued further experiments. Syntheses

repeated with carbon (as graphite) added in stoichiometric amounts led to high yields ($> 90\%$) of both compounds. With samples obtained this way we confirmed the single crystal data (through single crystal X-ray structure analysis), the unit cell dimensions (by means of indexing the X-ray powder patterns), and the nature of the triatomic unit (through Raman and IR measurements, Table 1). Compounds **1** and **2** can be considered as ionic compounds formulated as $(\text{Ca}^{2+})_{11}(\text{N}^{3-})_6(\text{CN}_2^{2-})_2$ and $(\text{Ca}^{2+})_4(\text{N}^{3-})_2(\text{CN}_2^{2-})$, respectively, as indicated by the bonding distances and angles of their CN_2^{2-} ions.

Some questions remain. One question asks how did we (or Laurent et al.^[1]) incorporate the carbon into the reactions that first yielded the compounds? The most probable explanation is that carbon leached out of the reaction container. Repeated reactions in niobium (instead of stainless steel) ampoules with the same batch of starting materials did not produce either of the two compounds described above. Another question concerns the nature of “ Ca_{11}N_8 ”. The most simple explanation is very often the best, and sometimes even the correct explanation. We feel confident that the most simple explanation, backed up by X-ray and spectroscopic data, is that “ Ca_{11}N_8 ” really is $\text{Ca}_{11}\text{N}_6(\text{CN}_2)_2$.^[7]

Experimental Section

All reagents and reaction containers were handled in a glove box under dry Ar. All reactions were performed with about 0.5 g educt mass, and all syntheses took place at 1300 K (2 d) and the heating and cooling rates were 100 K h^{-1} .

Single crystals of both compounds have first been obtained by the reaction of equimolar amounts of Ca_3N_2 (Ca: Strem, 99.99%, crystalline, dendritic; treated with dry, flowing N_2 at 1300 K for 8 h; product purity checked by its X-ray powder pattern), Cu_3N (Alfa, 99.5%), and NaN_3 (Aldrich, 99%; kept for two days at 400 K before use) in a silica jacketed, cleaned stainless steel ampoule.

Bulk material and single crystals suitable for X-ray analysis were obtained by the reaction of appropriate amounts of Ca_3N_2 , C (Strem, 99.999%, graphite powder; degassed for one day at 700 K under dynamic vacuum) and NaN_3 in cleaned, arc-welded silica-jacketed Nb container (Plansee, Germany, 99.99%). The excess sodium can be removed by vacuum sublimation at 600 K or by washing with liquid, anhydrous ammonia. Microcrystalline materials were also obtained by the reaction of appropriate amounts of Ca_3N_2 and C in alumina boats under a flow of dry N_2 .

Samples of **1** always contained traces of **2**, and vice versa for samples of **2**. Additionally some Ca_3N_2 was identified as an impurity (the impurities were identified by their X-ray powder patterns or by their Raman or IR spectra).

Ca and C were found by microprobe analysis (JEOL 8900, standardless, qualitative mode) of single crystals and of bulk material of both compounds.

On all samples of **2**, Raman and IR spectroscopy confirmed the presence of CN_2^{2-} . IR spectra of **1** are easily observed, but the Raman measurements worked only moderately well, probably due to the strong absorbance of the material, as indicated by its dark red color.

Received: August 23, 1999 [Z13909]

- [1] Y. Laurent, J. Lang, M. Th. Le Bihan, *Acta Crystallogr. B* **1969**, 25, 199–203.
- [2] a) N. E. Brese, M. O’Keeffe, *Struct. Bonding (Berlin)* **1992**, 79, 309–378; b) H.-J. Meyer in *Moderne Anorganische Chemie* (Ed.: E. Riedel), de Gruyter, Berlin–New York, **1999**, p. 433.
- [3] Y. Laurent, J. Lang, M. Th. Le Bihan, *Acta Crystallogr. B* **1968**, 24, 494–499.

[4] Crystal structure analysis data: **1**: Dark red needles; $0.01 \times 0.01 \times 0.15$ mm³; tetragonal; $P4_2/mmm$ (No. 136); $Z=2$; $T=293(2)$ K; $a=1452.32(16)$, $c=360.83(6)$ pm (powder data: $a=1452.9(2)$, $c=360.9(1)$ pm); $V=761.1 \times 10^6$ pm³; $2\theta_{\max}=44^\circ$, $\text{MoK}\alpha$ ($\lambda=71.073$ pm); graphite monochromator, Bruker Smart CCD (ω -scan); 1777 measured reflections, 292 reflections unique; $R_{\text{int}}=0.099$; LP correction; no other absorption correction applied; SHELXTL-5.03 (structure solution: direct methods; structure refinement: full-matrix least-squares on $|F^2|$); 39 parameters (all atoms refined anisotropically except N4 and C); max./min. residual electron density: $0.77/-0.73$ e Å⁻³; $R1=0.061/0.088$, $wR2=0.123/0.136$, $\text{GooF}=1.21/1.16$ (for $233 F_o > 4\sigma(F_o)$ /all 292 unique reflections). **2**: Yellow-green transparent needles; $0.03 \times 0.03 \times 0.15$ mm³; orthorhombic; $Pnma$ (No. 62); $Z=4$; $T=293(2)$ K; $a=1143.9(2)$, $b=357.72(7)$, $c=1384.4(3)$ pm (powder data: $a=1145.8(2)$, $b=358.5(1)$, $c=1386.4(3)$ pm); $V=566.5 \times 10^6$ pm³; $2\theta_{\max}=46.7^\circ$, $\text{MoK}\alpha$ ($\lambda=71.073$ pm); graphite monochromator, Bruker Smart CCD (ω -scan); 2271 measured reflections, 478 unique reflections; $R_{\text{int}}=0.085$; LP correction; no other absorption correction applied; SHELXTL-5.03 (structure solution: direct methods; structure refinement: full-matrix least-squares on F^2); 47 parameters (all atoms except C refined anisotropically); max./min. residual electron density: $0.88/-0.72$ e Å⁻³, $R1=0.056/0.085$, $wR2=0.115/0.126$, $\text{GooF}=1.23/1.12$ (for $344 F_o > 4\sigma(F_o)$ /all 478 unique reflections). Further details of the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49)7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository numbers CSD-410825 (Ca₄N₂(CN₂)) and CSD-410862 (Ca₁₁N₆(CN₂)).

[5] U. Berger, W. Schnick, *J. Alloys Compd.* **1994**, *206*, 179–184.

[6] N.-G. Vannerberg, *Acta Chem. Scand.* **1962**, *16*, 2263–2266.

[7] While preparing the revised version of this text, we were informed of work by P. Hoehn, R. Niewa, M. Ludwig and R. Kniep. Their research on Ca₄N₂(CN₂) and some other phases was presented as Poster P148 at the 7th European Conference on Solid State Chemistry (ECSSC'99), Sept. 15–18, 1999, Universidad Complutense, Madrid (Spain).

“Amphiphilic” Cleavage of γ -Stannyl Ketones with ATPH/RLi: Application to Enone Fragmentation by the Conjugate Addition–Cleavage Sequence**

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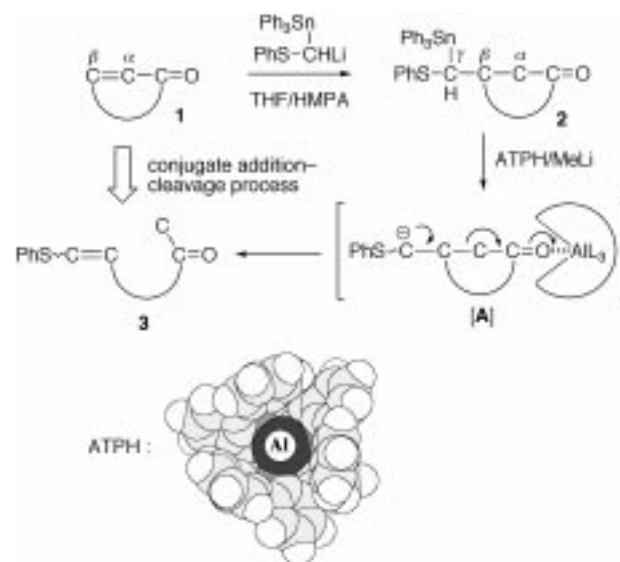
Despite the availability of many carbon–carbon bond forming reactions, including ring closures in organic synthesis, less attention has been paid so far to the corresponding reverse processes, that is, the selective ring cleavage of carbon–carbon bonds.^[1,2] Although it is not of synthetic importance, the McLafferty rearrangement of the C_α – C_β bond of aliphatic carbonyl compounds, as determined by mass spectrometry, is a typical example of such a reaction.^[3]

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[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

The previously known ring-cleavage reactions can be divided into two classes depending on the mode of activation.^[1] Most involve base- or acid-promoted fragmentation by activating either electrofugal or nucleofugal moieties, respectively.^[4] The other, less general type of fragmentation is realized by the intramolecular push–pull effect of the electrofugal and nucleofugal parts,^[2c] as exemplified by retro-aldol reactions.

Here we report a conceptually new, “amphiphilic” cleavage reaction of the C_α – C_β bonds of γ -stannyl ketones **2**, leading to compounds of type **3** (Scheme 1). In combination with the

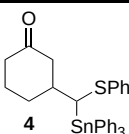
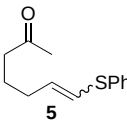
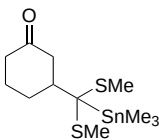
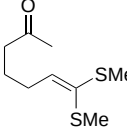
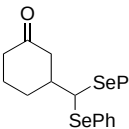
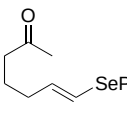
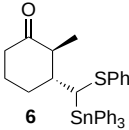
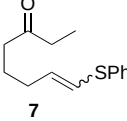
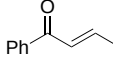
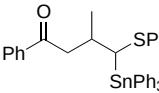
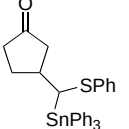
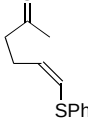
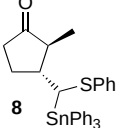
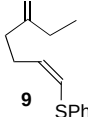
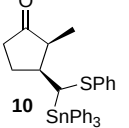
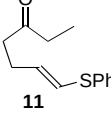
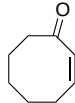
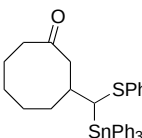
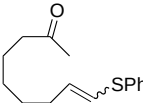


Scheme 1. Conjugate addition and amphiphilic cleavage of enone **1** with ATPH/MeLi leading to ketone **3**. L = 2,6-diphenylphenoxy.

conjugate addition of α -stannyl carbanion to enone **1**, this approach constitutes a novel two-step conjugate addition–cleavage sequence. The new fragmentation is interpretable as the nucleophilic attack of the electrofugal carbanion part to an electrophilically activated carbonyl moiety (in this respect, “amphiphilic” means electrophilically activated nucleophilic), and it should be categorized into a third, yet unexplored class of fragmentation. The success of this amphiphilic cleavage highly relies on the effective use of a combined Lewis acid/base system consisting of aluminum tris(2,6-diphenylphenoxy) (ATPH) and MeLi,^[5] thereby allowing the appropriate push–pull relay of the electrofugal and nucleofugal moieties in the key intermediate [A].

The requisite conjugate adduct, 3-[triphenylstannyl(phenylsulfanyl)methyl]cyclohexanone (**4**) can be readily prepared by treatment of cyclohexenone with triphenylstannyl(phenylsulfanyl)methyl lithium—generated from triphenylstannyl(phenylsulfanyl)methane with lithium diisopropylamide (LDA) in THF^[6]—in the presence of hexamethyl phosphoramide (HMPA) at -78°C . Complexation of **4** with ATPH (1.1 equiv) in toluene/diethyl ether at -78°C and subsequent addition of MeLi (3 equiv) afforded cleanly 7-phenylsulfanyl-6-hepten-2-one (**5**) as a product of C_α – C_β bond cleavage in 96% yield ($Z:E=1.3:1$; Table 1, entry 1). The push–pull effect of γ -lithio ketones by complexation with Lewis acidic ATPH is crucial for effecting the smooth C_α – C_β

Table 1. Selected results of the conjugate addition–cleavage sequence of enones.^[a] See the Experimental Section for details.

Entry	Enone	Reagent	Solvent	Conjugate adduct	yield [%] ^[b,c]	Reagent	Solvent	Cleavage product	yield [%] ^[b] (ratio) ^[d]
1		Ph ₃ Sn PhS-CHLi	HMPA/THF	 4	93	ATPH/MeLi	PhMe/Et ₂ O	 5	96 (1.3:1)
2		Me ₃ Sn (MeS) ₂ -CLi	HMPA/THF		77	ATPH/MeLi	PhMe/THF		85
3		PhSe PhSe-CHLi	ATPH/THF		73	ATPH/BuLi	PhMe/THF		63
4		Ph ₃ Sn PhS-CHLi	HMPA/THF, then MeI	 6	77	ATPH/MeLi	PhMe/Et ₂ O	 7	76 (6:1)
5		Ph ₃ Sn PhS-CHLi	HMPA/THF		64	ATPH/MeLi	PhMe/Et ₂ O		92
6		Ph ₃ Sn PhS-CHLi	HMPA/THF		93	ATPH/MeLi	PhMe/Et ₂ O		56
7		Ph ₃ Sn PhS-CHLi	HMPA/THF, then MeI	 8	83	ATPH/MeLi	PhMe/Et ₂ O	 9	87
8		Ph ₃ Sn PhS-CHLi	HMPA/THF	 10	82	ATPH/MeLi	PhMe/Et ₂ O	 11	89
9		Ph ₃ Sn PhS-CHLi	ATPH/THF		57	ATPH/MeLi	PhMe/THF		85 (1.2:1)

[a] The reaction was carried out with ATPH (1.1 equiv) and RLi (3 equiv; R = Me or Bu) in toluene/diethyl ether at -20°C or toluene/THF (1/1) at -78°C for 20 min. [b] Yield of isolated compound. [c] The diastereomeric ratio of the newly created C–C bond is $\approx 1:1$ (entries 1, 4–9). [d] The *Z:E* ratios of the cleavage products were determined by ^1H NMR analysis.

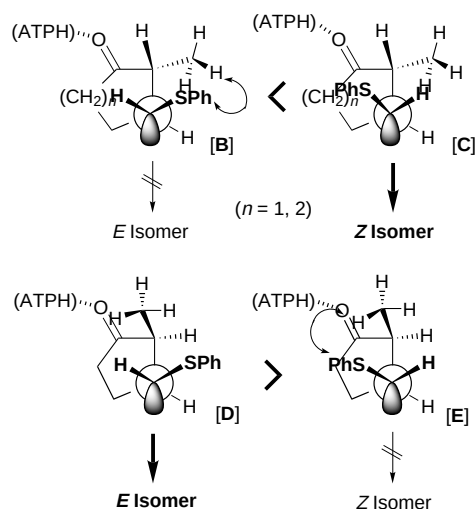
bond cleavage reaction. Indeed, without ATPH, treatment of **4** with MeLi gave deteriorated reaction products without formation of the desired **5**. Use of ordinary Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$ and TiCl_4 in place of ATPH gave unsatisfactory results, mainly due to the facile attack of MeLi on the Lewis acids.

Other selected examples (Table 1) concerning the novel conjugate addition/fragmentation reaction of enones clearly indicate the effectiveness of our approach. In addition to

triphenylstannyl(phenylsulfanyl)methyl lithium, bis(methylsulfanyl)(trimethylstannyl)methyl lithium and bis(phenylselenanyl)methyl lithium are also employable as conjugate addition agents (entries 2 and 3), thereby enhancing the synthetic potential for further manipulation of the cleavage products. The conjugate addition/alkylation sequence further expands the synthetic utility of our approach.

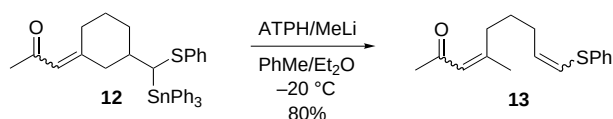
The stereochemical outcome of the newly formed double bonds in the present amphiphilic cleavage is worthy of

comment. The *trans*-conjugate adducts **6** and **8** afforded cleavage products **7** and **9**, respectively, with high *Z* selectivity (Table 1, entries 4 and 7). Since the diastereomeric ratio of the newly created C–C bond in the conjugate adducts **6** and **8** is about 1:1, the conformations of intermediate carbanions should be responsible for the stereochemistry of the cleavage process. The conformer [C] (Scheme 2, *n* = 1, 2) is preferred over [B] (*n* = 1, 2) due to the steric repulsion between the PhS and CH₃ groups. Such a steric effect is also predominant in the amphiphilic cleavage of *cis*-conjugate adduct **10**, giving the *E* isomer **11** (Table 1, entry 8) by way of the preferred conformer [D] rather than [E] (Scheme 2).



Scheme 2. The stereochemical outcome of the amphiphilic cleavage of ketones **6**, **8**, and **10** with ATPH/MeLi, leading to ketones **7**, **9**, and **11**, respectively.

The new amphiphilic cleavage of γ -stannyl enones described herein serves as a highly efficient and general route to functionalized ketones from commercially available enones, and therefore should find considerable utility in selective organic synthesis. Furthermore, this process has been extended to the selective C _{γ} –C _{δ} bond cleavage of $\alpha\beta$ -enone **12** (*E*:*Z* $\approx$ 1:1), giving $\alpha\beta$ -enone **13** in 80% yield (Scheme 3, (3*E*,8*E*):(3*E*,8*Z*):(3*Z*,8*E*):(3*Z*,8*Z*) = 45:30:15:10).



Scheme 3. Selective C _{γ} –C _{δ} bond cleavage of enone **12**.

Experimental Section

The conjugate addition/cleavage sequence of cyclohexenone (Table 1, entry 1): To a solution of LDA—prepared by treatment of diisopropylamine (231 μ L, 1.65 mmol) with BuLi (1.6 M solution in hexane, 0.94 mL, 1.5 mmol) in THF at 0 °C for 30 min—was added a solution of phenylsulfanyl(triphenylstannyl)methane (710 mg, 1.5 mmol) in THF at –78 °C. The mixture was allowed to warm to –20 °C, and then stirred for 30 min to

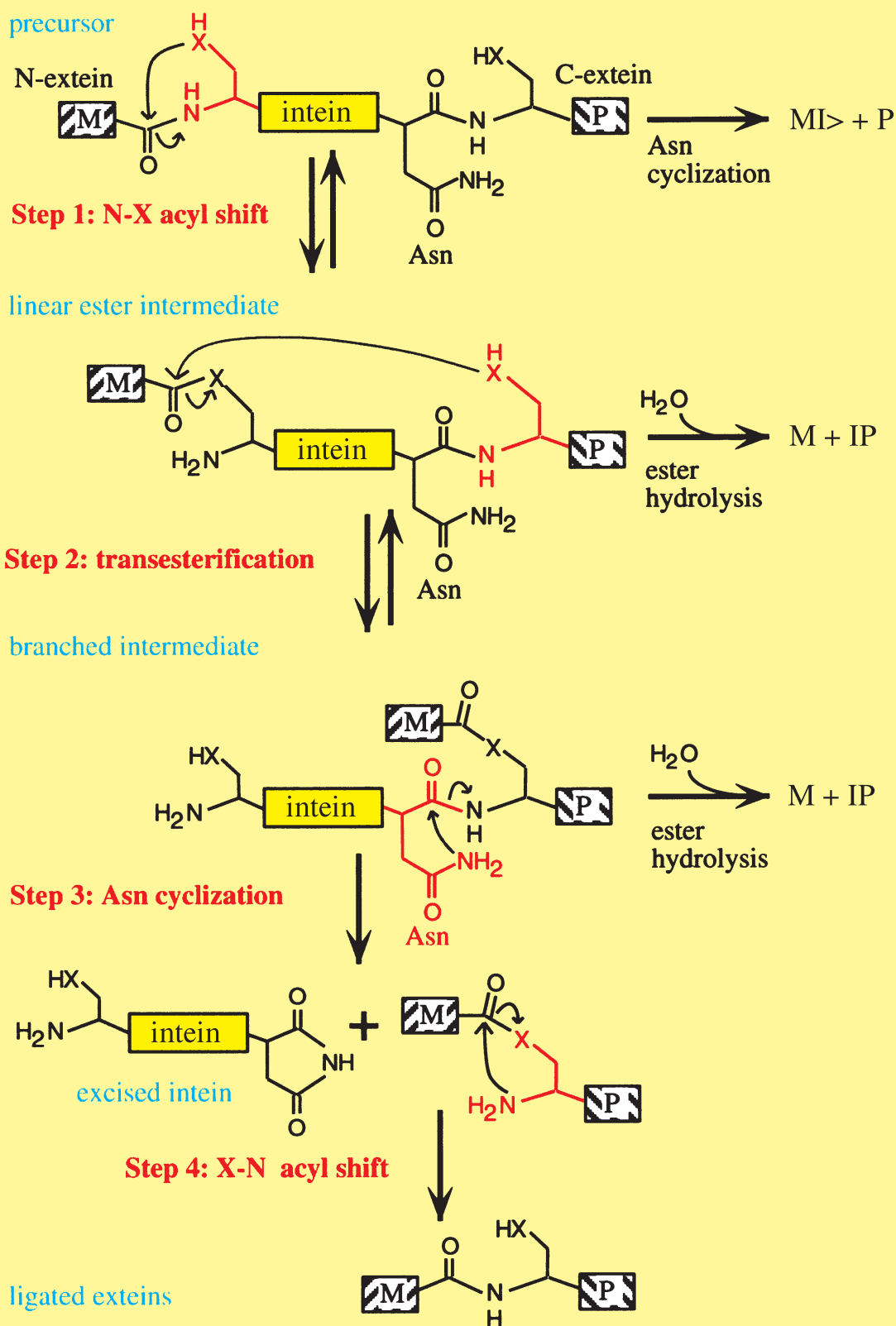
furnish a pale yellow solution. After the mixture was recooled to –78 °C, HMPA (287 μ L, 1.65 mmol) and 2-cyclohexen-1-one (96 μ L, 1 mmol) were added. The solution was stirred at –78 °C for 1 h and poured into water. After extraction with diethyl ether, the organic extracts were dried over Na₂SO₄. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ethyl acetate/hexane (1/4) as eluant) gave **4** as a white solid (529 mg, 0.93 mmol; 93% yield): ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 7.16–7.77 (m, 20H; Ph), 3.72 (d, ³J(H,H) = 2.4 Hz, 1H for a diastereomer; CH(SPh)(SnPh₃)), 3.67 (d, ³J(H,H) = 1.8 Hz, 1H for a diastereomer; CH(SPh)(SnPh₃)), 1.43–2.50 (m, 9H; COCH₂, CH₂, and CH).

A solution of 2,6-diphenylphenol (406 mg, 1.65 mmol) in toluene (4.5 mL) was carefully degassed, and Me₃Al (1.0 M solution in hexane, 0.55 mL, 0.55 mmol) was added at room temperature under argon. Methane gas evolved immediately. The resulting yellow solution was stirred for 30 min and used without purification. After the addition of **4** (285 mg, 0.5 mmol) in toluene (0.5 mL) and diethyl ether (5 mL) at –78 °C, the solution was allowed to warm to –20 °C, and MeLi (1.0 M solution in diethyl ether, 1.5 mL, 1.5 mmol) was added dropwise. The solution was stirred at –20 °C for 20 min and then poured into 1 N HCl. The mixture was extracted with diethyl ether, and the organic extracts were dried over Na₂SO₄. Evaporation of solvents and purification of the residue by column chromatography on silica gel (dichloromethane/hexane (1/3) to ethyl acetate/hexane (1/9) as eluant) gave **5** as a colorless oil (106 mg, 0.479 mmol; 96% yield). The *Z*:*E* ratio of **5** was determined to be 1.3:1 by ¹H NMR spectroscopy: *Z* isomer: ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 7.17–7.42 (m, 5H; Ph), 6.25 (dt, ³J(H,H) = 9.4, 1.3 Hz, 1H; C = CHSPh), 5.78 (dt, ³J(H,H) = 9.4, 7.2 Hz, 1H; CH = C), 2.49 (t, ³J(H,H) = 7.3 Hz, 2H; COCH₂), 2.27 (dq, ³J(H,H) = 7.3, 1.3 Hz, 2H; CH₂C = C), 2.15 (s, 3H; COCH₃), 1.74 (quint, ³J(H,H) = 7.3 Hz, 2H; CH₂); *E* isomer: ¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 7.17–7.42 (m, 5H; Ph), 6.17 (dt, ³J(H,H) = 15.0, 1.3 Hz, 1H; C = CHSPh), 5.91 (dt, ³J(H,H) = 9.4, 15.0 Hz, 1H; CH = C), 2.47 (t, ³J(H,H) = 7.3 Hz, 2H; COCH₂), 2.18 (dq, ³J(H,H) = 7.3, 1.3 Hz, 2H; CH₂C = C), 2.15 (s, 3H; COCH₃), 1.72 (quint, ³J(H,H) = 7.3 Hz, 2H; CH₂).

Received: June 9, 1999 [Z13540]

- Reviews: a) *Comprehensive Organic Synthesis*, Vol 6 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 1041; b) C. A. Grob, P. W. Schiess, *Angew. Chem.* **1967**, 79, 1; *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 1.
- For recent examples of cleavage of C–C bonds within a ring, see a) J. Grimshaw, R. J. Haslett, *J. Chem. Soc. Chem. Commun.* **1974**, 174; b) M. Takayanagi, N. Umamori, K. Tanino, I. Kuwajima, *J. Am. Chem. Soc.* **1993**, 115, 12635; c) H. Harayama, T. Kuroki, M. Kimura, S. Tanaka, Y. Tamaru, *Angew. Chem.* **1997**, 109, 2449; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2352.
- Mass Spectrometry of Organic Ions* (Ed.: F. W. McLafferty), Academic Press, New York, **1963**.
- A similar type of fragmentation was reported by Hamon et al.: D. P. G. Hamon, G. F. Taylor, R. N. Young, *Synthesis* **1975**, 428; however, such a fragmentation has not been developed to a synthetically useful level.
- ATPH can be prepared by treating 2,6-diphenylphenol (3 equiv) in toluene with Me₃Al at room temperature for 30 min. For other synthetic applications, see a) K. Maruoka, H. Imoto, S. Saito, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, 116, 4131; b) K. Maruoka, I. Shimada, H. Imoto, H. Yamamoto, *Synlett* **1994**, 519; c) K. Maruoka, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, 117, 9091; d) S. Saito, H. Yamamoto, *J. Org. Chem.* **1996**, 61, 2928; e) T. Ooi, Y. Hokke, K. Maruoka, *Angew. Chem.* **1997**, 109, 1230; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1181; f) T. Ooi, Y. Kondo, K. Maruoka, *Angew. Chem.* **1997**, 109, 1231; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1183; g) S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, 120, 813; h) S. Saito, H. Yamamoto, *Chem. Eur. J.* **1999**, 5, 1959, and references therein.
- T. Kauffmann, R. Kriesegmann, A. Hamsen, *Chem. Ber.* **1982**, 115, 1818.

The Currently Accepted Mechanism of Protein Splicing



Dissecting the Chemistry of Protein Splicing and Its Applications

Christopher J. Noren, Jimin Wang, and Francine B. Perler*

In memory of Holger W. Jannasch

Inteins are internal polypeptide sequences that are posttranslationally excised from a protein precursor by a self-catalyzed protein-splicing reaction. The protein splicing domain (≈ 150 amino acids) activates cleavage of the peptide bonds at the N- and C-terminal splice junctions, with concomitant formation of a new peptide bond between the flanking polypeptides (exteins). The intein plus a single C-extein amino acid can break two peptide bonds, form a new peptide bond, cleave DNA, and initiate mobility of the intein gene. Nearly 100 inteins have been identified with Ser or Cys at the intein N terminus and the triad, His-(Asn/Gln)-(Ser/Thr/Cys), at the C-terminal splice junction. These conserved residues are known to par-

ticipate in well-studied chemical reactions in other enzymes, which led to a flurry of proposed splicing mechanisms. This review focuses on the three-year period during which a combination of experimental approaches revealed the steps of the protein-splicing pathway, disproving many proposed mechanisms while supporting others. The protein-splicing mechanism involves four coupled nucleophilic displacements: 1) an N $\rightarrow$ O(S) acyl shift of Ser/Cys at the intein N terminus; 2) a transesterification reaction to form a branched intermediate with two N termini; 3) cyclization of the intein C-terminal Asn/Gln to release the intein; and 4) an O(S) $\rightarrow$ N acyl shift of Ser/Thr/Cys to form a native peptide bond between the exteins.

How the intein facilitates these reactions at the molecular level is only beginning to be elucidated. Understanding the mechanism of protein splicing has resulted in the development of a variety of intein-mediated protein-engineering applications, such as protein purification, addition of fluorescent biosensors, expression of cytotoxic proteins, protein semisynthesis, and segmental labeling of proteins for NMR analysis. Inteins in pathogenic microorganisms provide new targets for drug discovery.

Keywords: autocatalysis • bioorganic chemistry • peptides • protein splicing • transesterifications

1. Introduction

Protein biosynthesis was initially thought to be a simple process in which the genetic information in DNA was directly copied into messenger RNA (transcription), which in turn directed the biosynthesis of protein (translation). There are, however, many genes that encode intervening or terminal amino acids (aa) that are absent in the mature protein. When these sequences are removed from RNA prior to translation of the mature messenger RNA, the process is called RNA splicing and the intervening sequences are termed introns

(Scheme 1B). Posttranslational removal of polypeptide segments can occur by protein splicing, autoprocessing, or proteolytic cleavage. In protein splicing, a specific type of intervening sequence, termed an intein,^[1] is excised from an internal site in a precursor protein and the surrounding polypeptides (the exteins) are ligated to form the mature protein (Scheme 1A). Protein splicing yields two stable protein products from a single gene, the excised intein and the ligated exteins, and is directly analogous to RNA splicing of introns.

Inteins are members of a growing family of autocatalytic enzyme-like proteins that perform chemical reactions using the same strategies as enzymes, but do not act on multiple substrates. Other examples of autoprocessing include autocleavage of N-terminal nucleophile amidohydrolase precursors (glycosylasparaginase, penicillin acylase, proteasome, etc.), formation of pyruvoyl enzymes, processing of Hedgehog embryonic signaling proteins, RecA-assisted autocleavage of LexA or lambda repressor, and activation of plasma proteins.^[2, 3] All of these processes, including protein splicing, are initiated by a nucleophilic attack by the activated side-chain

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thiol or hydroxyl group of Cys, Ser, or Thr at an amide bond. Protein splicing is more complicated than these other autocatalytic reactions since it requires rapid sequential and spatial coupling of four distinct nucleophilic displacements.

Protein splicing proceeds by an intramolecular pathway requiring no exogenous cofactors.^[4, 5] All of the information necessary for splicing resides within the intein polypeptide plus the first extein amino acid at the C-terminal splice junction.^[4–10] A given intein can excise from a variety of flanking peptide sequence contexts provided that it precedes its cognate C-extein residue, albeit with varying efficiencies.^[4–10] To avoid confusion,^[11] the term “protein-splicing element” has been used when referring to the splicing-competent intein plus the C-extein Ser, Thr, or Cys residue, as the intein alone cannot mediate protein splicing.

A number of applications have been developed which take advantage of context-independent intein excision, including splicing-dependent protein synthesis,^[12, 13] self-cleaving affinity tags for protein purification,^[7, 14–16] a novel polypeptide ligation system for protein semisynthesis,^[15, 17–20] segmental labeling of proteins for NMR analysis,^[12, 20, 21] and addition of fluorescent biosensors.^[17, 22] Development of these systems involved genetic and biochemical manipulation of protein-splicing elements, guided by the known mechanism of protein splicing. This review will focus on the stepwise elucidation of the protein-splicing mechanism and modulation of the splicing reaction to create these novel applications. Additionally, we will relate recent structural information to the known

mechanistic data in an attempt to dissect the functional requirements for each step in the splicing pathway.

1.1. Inteins Splice as Proteins, Not as RNA

In 1990 two groups independently observed that the open reading frame of the gene for *Saccharomyces cerevisiae* vacuolar ATPase (Sce VMA) was almost twice as large as that of the observed protein product and included 454 aa that had no similarity to other vacuolar ATPases.^[23, 24] It seemed unlikely that this intervening sequence was an intron because it had no similarity to known introns, and because it was in-frame with the predicted mature protein—a condition unnecessary for RNA splicing. By 1993 five more in-frame insertions were found in other genes.^[4, 25–27] The rapid processing of these native precursors in their natural hosts or in *Escherichia coli* left only indirect methods to prove that intein excision was at the protein level. Modifying the “central dogma” of gene expression demanded direct evidence. Several experimental approaches failed to detect spliced RNA.^[10, 23, 24, 27, 28] Silent substitutions that change putative essential intron sequences, but not protein sequence, had no effect on splicing,^[26] whereas disrupting the intein reading frame blocked splicing.^[10, 26, 27] The breakthrough came in 1993 when scientists at New England BioLabs established the first in vitro splicing system. This allowed purification of an active protein splicing precursor and demonstration of its subsequent splicing in the absence of other proteins or cofactors.^[4]

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with Dr. Argiris Efstratiadis. Since 1980 she has been a Senior Research Scientist at New England BioLabs, where she studied the molecular biology of filarial parasites and enzymes from extreme thermophiles, especially Vent DNA polymerase. In 1989 she began studying protein splicing, which is now her major focus.



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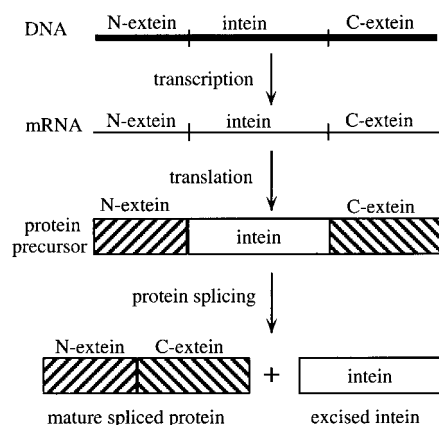


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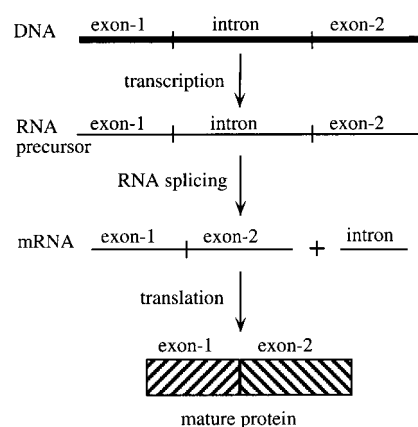
Christopher J. Noren, a native of Manasquan, New Jersey, received his BS in chemistry at the Massachusetts Institute of Technology in 1984. He received his PhD in chemistry from the University of California, Berkeley in 1990, where he codeveloped the unnatural amino acid mutagenesis method in the laboratory of Peter Schultz. He has been at New England BioLabs since 1990, and has been a Senior Scientist since 1993. His efforts at BioLabs have included work on the initial mechanistic studies of protein splicing, as well as developing a series of innovative phage display library technologies.

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A) Protein Splicing:



B) RNA Splicing:



Scheme 1. A comparison of protein splicing of inteins (A) and RNA splicing of introns (B).

1.2. Intein Mobility and Homing Endonuclease Activity

Similar intein alleles have been found in the same position in homologous genes from closely related and highly divergent organisms,^[8, 29–32, 34] although intein distribution is sporadic amongst species. The DNA G + C content and codon usage indicate that some intein genes have recently been transmitted between organisms,^[33, 34] and mobility of an intein gene has been experimentally demonstrated in *S. cerevisiae*.^[37]

Several types of introns are also mobile genetic elements. An intron encoded homing endonuclease^[38] initiates mobility by making a double-stranded break which starts a gene conversion pathway.^[13, 30, 35] Homing endonucleases are a class of sequence-specific double-stranded endonucleases that recognize and cleave DNA at or near the intron or intein insertion site in homologous genes lacking the element.^[35, 38] Many inteins are bifunctional proteins that also exhibit homing endonuclease activity (see Section 1.3).^[26, 28, 37, 38, 41, 43, 44] If an intein-containing allele enters a cell by sexual reproduction, infection, conjugation, transduction, etc., it expresses the intein. The intein endonuclease activity cleaves the intein-minus copy of the gene at or near the intein insertion site (“home”). Since the homing endonuclease recognition site is

interrupted by the intein, the intein-plus gene is the only intact copy of the allele available to repair the cleaved intein-minus gene. Repair of the cleaved intein-minus allele using the intact intein-plus allele as the template results in unidirectional gene conversion into an intein-containing allele. In a similar fashion, intein-minus homologues present on phage, viruses, plasmids or other episomal elements can pick up an intein when they pass through a cell containing an intein-plus homologue.

There are four families of homing endonucleases based on the conserved signature motifs that give each family its name.^[38] Sequence comparisons indicate that most inteins harbor dodecapeptide motif (DOD) family homing endonucleases, although one intein carries an H-N-H family homing endonuclease (Figure 1 and Section 1.3).^[1, 26, 29–31, 35–41] The intein DOD homing endonuclease region is identified by the presence of characteristic motifs, termed intein blocks C, D, E, and H.^[29–32, 38, 40] Several lines of evidence suggest that homing endonuclease genes invaded both intron and intein genes during evolution.

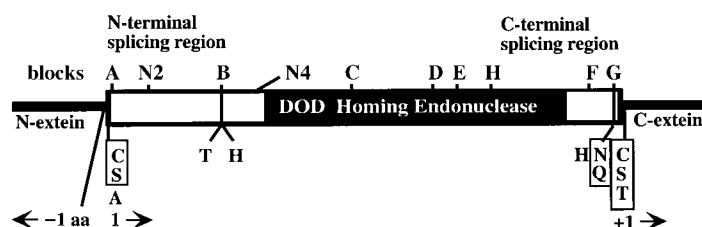


Figure 1. Conserved intein characteristics. A protein-splicing precursor containing an intein with a DOD-type homing endonuclease is depicted with conserved motifs listed above and conserved residues involved in catalysis shown below. Nucleophiles are boxed. Note that some inteins begin with Ala. Intein splicing regions (white boxes) are separated by either an endonuclease domain as depicted or a short linker. By convention, the numbering of amino acids in protein-splicing precursors is as follows: Intein amino acids are numbered from the intein N terminus to its C terminus starting with 1. N-extein amino acids are denoted as negative numbers starting with -1 at the N-terminal splice junction and counting back towards the N terminus of the precursor. The amino acids in the C-extein are numbered from its N terminus (the C-terminal splice junction) to the C terminus of the precursor, beginning with +1 and including a plus sign to denote the C-extein. Arrows indicate the direction of sequential numbering of residues.

1.3. Intein Distribution and Conserved Characteristics

Protein splicing is ubiquitous in nature, with 97 inteins discovered as of July 4, 1999 in unicellular organisms from all three domains of life (eubacteria, archaea, and eucarya) as well as in a virus and a prophage.^[29–32, 40] For more up to date information about inteins, see InBase, the intein registry at <http://www.neb.com/neb/inteins.html>.^[29]

A protein is considered to be interrupted by an intein if:

- 1) extein homologues lack the intervening sequence,
- 2) the intervening sequence is over 100 aa,
- 3) the intervening sequence contains intein motifs,
- 4) the observed protein product is the same size as the predicted open reading frame minus the intein.

The numbering of amino acids in protein splicing precursors is shown in Figure 1.

Inteins range in size from 134 to 600 aa.^[29] Some of the larger inteins are bifunctional proteins with endonuclease activity. Ten conserved sequence motifs are present in most inteins (Figure 1).^[29–31, 40] In a typical protein splicing precursor, the central intein region (encoding a linker or a homing endonuclease domain) is flanked by the N-terminal splicing region (blocks A, N2, B, N4) and the C-terminal splicing region (blocks F and G), which are in turn flanked, respectively, by the N-extein and the C-extein (block G).^[42] Thus, the precursor has a organization like that of Russian nesting dolls (Figure 1). In the Sce VMA intein, part of the homing endonuclease has been transposed into the N-terminal splicing region;^[43–45] comparative sequence analysis suggests that this organization may be rare among known inteins.^[31, 32, 39, 42] Approximately 10% of inteins have a small linker in place of the homing endonuclease domain.^[29]

The intein splicing domain includes blocks A, N2, B, N4, F, and G (Figure 1). No single amino acid is conserved in all inteins. Instead, intein blocks contain related amino acids even in the most conserved positions. All known inteins have a Ser, Thr, or Cys residue on the C-terminal side of both splice junctions, except for two intein families which have Ala at the N-terminal splice junction (Figure 1). N-terminal Edman degradation revealed that the free Tli Pol-2 intein begins with Ser, indicating that the conserved Ser or Cys at the upstream splice junction is the first residue of the intein.^[26] All known inteins end in Asn, except two that end in Gln. Block B contains a Thr-(2 aa)-His motif which is also found in serine proteases, where the His is part of the serine protease catalytic triad.^[46] A second conserved His is present in block G as the penultimate residue in about 90% of inteins.^[29] There is no consensus residue preceding the intein at the C terminus of the N-extein. Since related, but not identical, amino acids are present in conserved motifs, different amino acids act as nucleophiles and assisting residues in each intein. However, conservative substitution of splice junction Ser, Thr, or Cys residues often impairs or inhibits splicing. Therefore, subtle differences in pK_a , nucleophilicity, and conformational properties amongst various inteins potentially increase the complexity of any unified protein-splicing mechanism.

Almost all combinations of splice-junction Ser, Thr, and Cys residues have been observed, except for the presence of Thr at the intein N terminus.^[29] This absence of Thr1 may be due to sample size, since mutation of the Tli Pol-2 intein N-terminal Ser1 to Thr permitted efficient splicing.^[28] If the multiple intein alleles are counted as one intein family, there is little preference for thiol–thiol (36%), hydroxyl–hydroxyl (18%), or thiol–hydroxyl combinations (46%). However, with the presently available set of 39 different intein alleles with Ser, Thr, or Cys at both splice junctions, there is a bias for Cys at the N-terminal splice junction (82%) and against Cys at the C-terminal splice junction (36%).

1.4. Inteins and Hedgehog Protein Autoprocessing Domains

Although protein splicing has yet to be observed in a multicellular organism, the Hedgehog family of embryonic signaling proteins has an autoprocessing domain which most

likely shares a common ancestor with inteins.^[42, 45, 48] The Hedgehog autoprocessing domain and the splicing domain of inteins have a common fold (the HINT module),^[45] share two motifs (blocks A and B),^[46, 47] and perform similar chemical reactions (see Section 2.6).^[42, 45, 46, 48] The Hedgehog precursor is cleaved between the N-terminal signaling domain and the C-terminal processing domain. At the same time, cholesterol is attached to the C terminus of the signaling domain, anchoring it to the cell surface where it mediates pattern formation during embryogenesis. Similar autoprocessing domains have been found in several different nematode genes of unknown function.^[45, 48, 49]

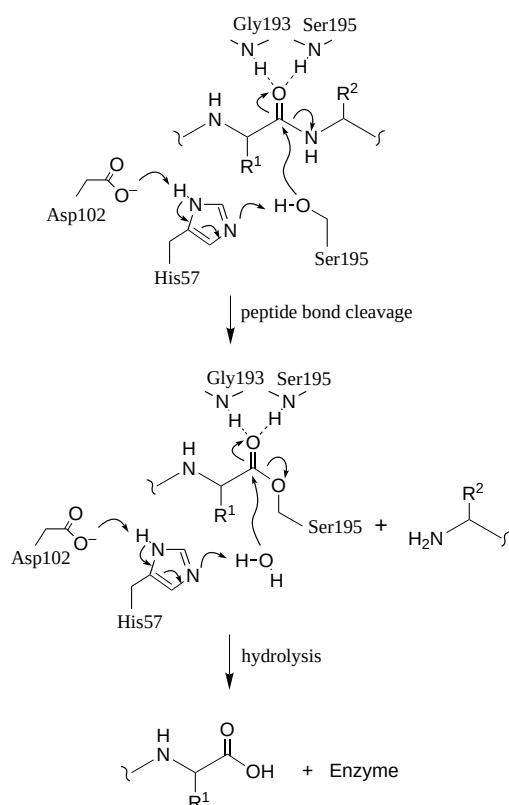
2. Elucidation of the Mechanism of Protein Splicing

Protein splicing results in formation of a native peptide bond in the ligated exteins.^[9] The splicing process can be broken down into three distinct, but coupled chemical reactions: two protein cleavage events followed by a peptide ligation event. Many protein-splicing mechanisms have been proposed, based on the known chemical behavior of the conserved residues at the splice junction.

2.1. Similarity with Serine and Cysteine Proteases

In the serine and cysteine classes of proteases,^[50] the nucleophilic hydroxyl or thiol side chain of the respective active-site serine or cysteine residue attacks the peptide bond of the substrate at the main chain carbonyl carbon (Scheme 2). This results in cleavage of the scissile peptide bond, with release of the C-terminal cleavage product and formation of an acyl-enzyme intermediate comprising the N-terminal product covalently attached to the enzyme as a (thio)ester. Hydrolysis of the (thio)ester linkage releases the N-terminal polypeptide and regenerates the active protease. The protease reaction is driven to completion by hydrolysis of the acyl-enzyme intermediate. As a result, serine and cysteine proteases can be converted into peptide ligases if water is excluded from the reaction^[51] or if the active-site nucleophile is mutagenized into a poor leaving group in the acyl-enzyme hydrolytic step.^[52, 53]

Catalysis of the initial nucleophilic attack on the peptide bond is enhanced by increasing both the electrophilicity of the substrate carbonyl group (by interaction of the carbonyl oxygen atom with adjacent positively charged groups, the “oxyanion hole”, in the transition state) and the nucleophilicity of the attacking hydroxyl or thiol group.^[50] The latter is accomplished by a charge-relay system in which the proton of the attacking species is transferred in the transition state to an adjacent histidine residue, which in turn has its pK_a (and thus basicity) raised by interaction with an adjacent aspartate (in serine proteases) or asparagine residue (in cysteine proteases).^[54, 55] This “catalytic triad” of Asp-His-Ser or Asn-His-Cys is the hallmark of all serine or cysteine proteases. The conserved His, Asn/Gln, and Ser/Thr/Cys residues in inteins (Figure 1 and Section 1.3) are reminiscent of protease catalytic triads, which led us to postulate similar functional roles for these residues in protein splicing.^[26, 28]



Scheme 2. The serine protease mechanism. The active-site catalytic triad residues (Asp102, His57, and Ser195) of chymotrypsin are shown, along with a hypothetical substrate polypeptide in which the scissile bond is between residue R¹ and residue R². Nucleophilic attack by the active-site serine residue is mediated by simultaneous deprotonation by the adjacent His57, which in turn is more basic by interaction with the adjacent negatively charged Asp102. The developing negative charge on the carbonyl oxygen atom is stabilized by interaction with the main-chain protons of Gly193 and Ser195 (the "oxyanion hole"). Tetrahedral intermediates are omitted for clarity.

2.2. An In Vitro Splicing System Leads to the Discovery of a Branched Protein Intermediate

Further elucidation of the splicing mechanism was greatly facilitated by the development of an in vitro splicing system, which allowed time-resolved studies of splicing of a purified precursor protein (Figure 2).^[4] This construct consists of the Psp-GBD Pol intein from the Deep Vent DNA polymerase, flanked on the N-terminal side by the *E. coli* maltose binding protein (MBP) and on the C-terminal side by a 29-kDa fragment of *Dirofilaria immitis* paramyosin (P). The Psp-GBD Pol intein has serine residues at both splice junctions. This three-part fusion, MIP (for MBP intein paramyosin), facilitated affinity purification of unspliced precursor on amylose resin, as well as rapid identification of splicing intermediates and products by either SDS-PAGE or Western blot. The MIP context was permissive for splicing, but not optimal. Splicing was very slow at 12–20 °C, but more rapid above 30 °C. This temperature sensitivity was not due to the isolation of the Psp-GBD Pol intein from an extreme thermophile, since splicing of the native DNA polymerase precursor in *E. coli* was too fast to isolate precursor at

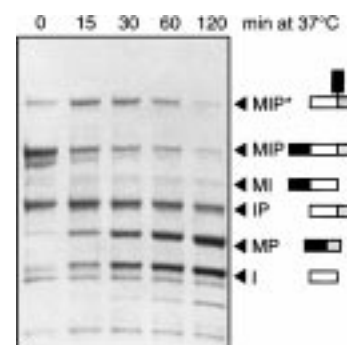


Figure 2. Time-resolved in vitro splicing of purified MIP precursor. MIP, a fusion of MBP, the Psp-GBD Pol intein, and paramyosin, was expressed under nonpermissive splicing conditions and isolated by affinity chromatography on amylose resin.^[4] The initial sample contained the MIP precursor (132 kDa), a small amount of a slowly migrating MIP precursor (MIP*), and spliced MP plus free intein (I), and single splice junction cleavage products (M, IP, MI). Time-resolved splicing of the MIP precursor in the absence of added cofactors was observed in SDS-PAGE stained with Coomassie blue. Black box: M (the N-extein); white box: I (the intein); gray box: P (the C-extein).

20 °C. Temperature-dependent splicing due to nonnative exteins turned out to be rather common.^[4, 8, 13] Splicing of MIP was pH-dependent, with an optimum at pH 4.5–6.5 and a steady decrease in the rate of splicing up to pH 10, at which point splicing was essentially blocked.^[4]

The MIP system allowed identification of a crucial reaction intermediate by sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE). MIP samples yielded spliced products, MP (MBP paramyosin) and the free intein (I), plus products of single splice junction cleavage (see Section 2.8). N-terminal splice junction cleavage yielded the N-extein plus the intein/C-extein (M + IP), and C-terminal splice junction cleavage yielded the N-extein/intein plus the C-extein (MI + P). In addition to the expected splicing and cleavage products, a slowly migrating species appeared early in the course of the reaction and slowly disappeared as precursor was depleted and product was formed (Figure 2). These kinetics are characteristic of an intermediate and the slow SDS-PAGE migration relative to precursor suggested that the splicing reaction goes through either a covalently multimerized or a branched intermediate. Sequencing of the slowly migrating species by N-terminal Edman degradation revealed two overlapping sequences corresponding to the N termini of the N-extein (MBP) and the intein.^[4] Formation and stability of the branched intermediate were pH-dependent: The branched intermediate reverted to precursor at pH 10 and 37 °C, implying that the branch linkage is an ester, since the ester–amide equilibrium would favor the amide at high pH.^[56–58] The existence of this branched intermediate implies that the precursor undergoes a rearrangement in which cleavage of the N-terminal splice junction is coupled to acyl migration of the N-extein to the side chain of a residue in the vicinity of the C-terminal splice junction. This branched intermediate structure ruled out a mechanism which predicted that splicing was initiated by Asn cyclization.^[59]

Mutagenesis of the Ser, Thr, or Cys nucleophile at either splice junction to Ala abolished branch formation, whereas mutagenesis of the intein C-terminal His or Asn had little

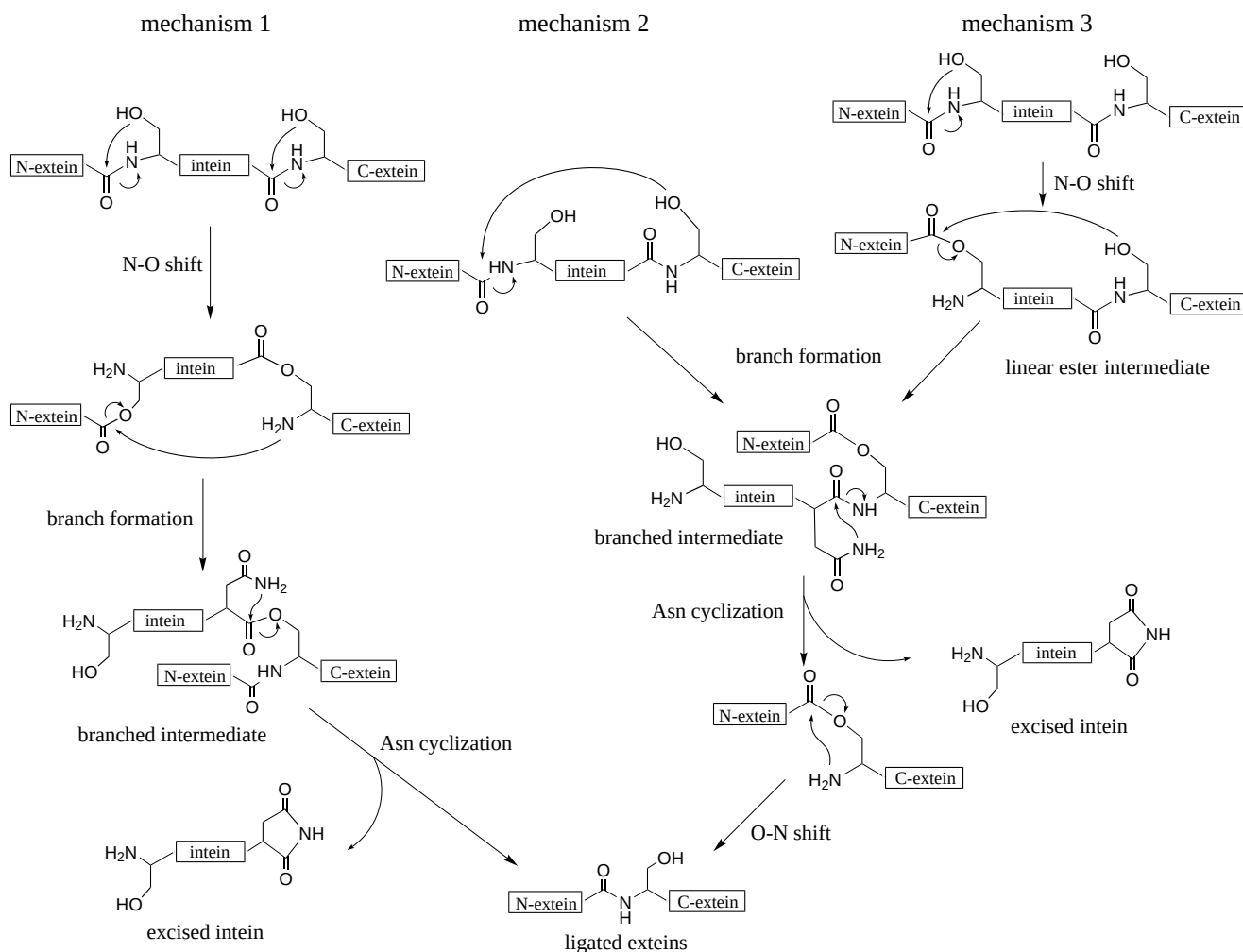
effect on branch formation.^[60] This result immediately ruled out a hypothetical mechanism in which the C-terminal Asn residue is the attacking nucleophile in branch formation.^[61]

2.3. Three Proposed Mechanisms Based on a Branched Protein Intermediate

Three more mechanisms were proposed to explain formation and resolution of the branched intermediate in the context of the known mutagenesis data. In mechanism 1 (Scheme 3), independently proposed by Paulus (personal communication in ref. [4]) and Wallace,^[62] both splice junctions undergo an N→O(S) acyl migration in which the nucleophilic hydroxyl or thiol group of the conserved Ser/Thr/Cys residues at both splice junctions attack the backbone carbonyl group of the preceding residue, resulting in chemically labile (thio)ester linkages at both ends of the intein. The downstream N→O(S) acyl shift produces a free α -amino group on the first residue of the C-extein, which in turn attacks the labile (thio)ester linkage at the N-terminal splice

junction. This reaction breaks the connectivity between the intein and N-extein, and converts the linear (thio)ester intermediate into a branched (thio)ester intermediate in which the intein is joined by an ester linkage to the ligated exteins at the C-terminal splice junction by a peptide bond. The branched intermediate is then resolved by cyclization of the intein C-terminal Asn residue to form a succinimide ring, thereby cleaving the (thio)ester linkage between the intein and the C-extein, liberating both the intein and the ligated extein polypeptides.

In mechanism 2^[63] (Scheme 3) the initial acyl migration is distal, rather than proximal. The nucleophilic hydroxyl or thiol side chain of the C-extein + 1 residue attacks the peptide bond at the N-terminal splice junction, which leads directly to a branched intermediate in which the N-extein is joined to the C-extein by a (thio)ester linkage. This reaction is the intramolecular analogue of the initial step in the serine/cysteine protease mechanism, with the branched intermediate equivalent to the protease acyl-enzyme intermediate. In contrast to mechanism 1, the N-extein, rather than the intein, is joined by an ester linkage to the C-terminal splice junction in the branched intermediate. The branched intermediate is re-



Scheme 3. Three proposed protein-splicing mechanisms. All three mechanisms are shown for a hypothetical intein with Ser at both splice junctions, although the overall mechanism is the same if Cys or Thr is substituted at either or both splice junctions. All tetrahedral intermediates and proton transfer steps are omitted for clarity. See text for details.

solved by cyclization of the intein C-terminal Asn residue, releasing the exteins joined by a (thio)ester linkage. In the absence of the stabilizing environment of the intein active site, a spontaneous $O(S) \rightarrow N$ acyl shift generates the thermodynamically more stable amide linkage between the exteins.^[56, 57, 64, 65]

In mechanism 3^[63] (Scheme 3) an $N \rightarrow O(S)$ acyl shift occurs at the N-terminal splice junction, similar to the first step of mechanism 1. The downstream Ser/Thr/Cys nucleophile then attacks the resulting (thio)ester linkage, rather than the amide linkage as proposed in mechanism 2. The remaining steps of mechanisms 2 and 3 are the same.

The characteristics of the branched intermediate were central in eliminating mechanism 1, which predicts that the exteins are joined by an amide linkage and the intein is linked to the C-extein by a (thio)ester bond. In mechanisms 2 and 3, the intein and C-extein are connected in the branched intermediate by an amide and the N-extein by a (thio)ester linkage. Using the MIP system, it was possible to differentiate between these mechanisms by taking advantage of the lability of ester linkages at high pH.^[63] The fully denatured MIP branched intermediate decayed to M and IP at 65 °C and pH 9, indicating an alkali-labile ester linkage between the N-extein (M) and the intein/C-extein (IP).^[63] This result ruled out mechanism 1, while supporting mechanisms 2 and 3. A similar branched intermediate structure was later shown to exist during splicing of the Sce VMA intein, but was only observed when Cys + 1 was mutated to Ser.^[66]

2.4. Resolution of the Branched Intermediate.

In all three mechanisms (Scheme 3), the branched intermediate is resolved by Asn cyclization to cleave the adjacent C-terminal splice junction. Asn cyclization during protein splicing was demonstrated by introducing a methionine five residues upstream from the C-terminal splice junction of MIP, and treating the purified excised intein with the methionine-specific cleavage reagent cyanogen bromide to release the intein C-terminal tetrapeptide.^[63] HPLC revealed approximately equal amounts of two peptides, both with the expected composition for the intein C-terminal tetrapeptide. Mass spectrometry showed that the two peptides differed in molecular mass by 18 (a water equivalent), as expected for the hydrolyzed and intact forms of a peptide with a C-terminal succinimide moiety. The succinimide ring was relatively stable in vivo and in vitro.^[63] The presence of a succinimide moiety was confirmed using synthetic model peptides, mass spectroscopy, and a colorimetric assay in the Psp-GBD Pol intein^[67] and by mass spectrometry of peptides from the Sce VMA intein.^[66]

Analogous peptide bond cleavage and formation of a C-terminal succinimide by Asn cyclization occurs in peptides at pH 7.4^[68] and during the aging of proteins, such as bovine α -crystallin.^[69] Succinimides are also intermediates in the more common spontaneous deamidation and isomerization of internal Asn residues in proteins and peptides.^[68, 70–73] Unlike protein splicing and α -crystallin aging, the succinimide in these latter reactions is formed by attack of the main-chain

amide nitrogen atom on the side-chain carbonyl group. Hydrolysis of the resultant succinimide at the side-chain or main-chain carbonyl group then produces an internal aspartate or isoaspartate residue, respectively. In peptides, there is a competition between attack by the side-chain amide nitrogen atom on the main-chain carbonyl group versus attack by the main-chain nitrogen atom on the side-chain carbonyl group; in most peptides the former reaction predominates, but the latter reaction is enhanced if Pro, Ser, or His follow Asn in the peptide.^[68, 72] Succinimide formation is thought to be limited by the ability to deprotonate the main-chain nitrogen atom, increasing its nucleophilicity.^[72] Asn cyclization is also limited in proteins by conformational constraints, since structural information suggests that succinimide formation requires a dihedral φ angle of -120° and χ angle of 120° .^[72] Gln isomerizes to form a six-membered ring structure about ten times more slowly than Asn forms a five-membered ring structure due to entropic effects.^[72] Splicing of inteins is orders of magnitude more rapid than cleavage of peptides by Asn or Gln (where the half-life is measured in days, not seconds), suggesting that the splicing element must resemble an enzyme in facilitating this reaction under physiological conditions (see Section 2.1).

2.5. Formation of a Peptide Bond between the Ligated Exteins

Following Asn cyclization and intein excision, the exteins remain joined by a (thio)ester linkage between the carbonyl carbon atom of the N-extein – 1 residue and the hydroxyl or thiol side chain of the C-extein + 1 residue. In the absence of the stabilizing effect of the intein, a spontaneous $O(S) \rightarrow N$ shift occurs, resulting in a thermodynamically more stable amide linkage between the exteins. Model peptides containing internal oxygen ester or thioester linkages at Ser or Cys residues, respectively, rapidly isomerize to the amide form.^[64, 65]

2.6. Activation of the N-Terminal Splice Junction for Cleavage

The final piece of the puzzle concerned the conserved nucleophilic Ser1 or Cys1 at the N-terminal splice junction. Unlike mechanism 3, mechanism 2 (Scheme 3) does not postulate a direct catalytic role for this residue. One possibility is that the hydroxyl or thiol side chain forms an essential hydrogen bond, perhaps to the adjacent carbonyl oxygen atom, which would catalyze the nucleophilic attack by the C-extein + 1 residue by stabilizing the developing negative charge in the transition state for the initial tetrahedral intermediate. Substitution of Ser1 with Cys in the Tli Pol-2 and Psp-GBD Pol inteins reduced the rate of splicing and the amount of spliced product after overnight culture,^[28, 60] while substitution of Cys1 with Ser abolished splicing of the Sce VMA intein^[9, 66, 74] and substitution of Ser1 or Cys1 with Ala blocked splicing in all three inteins. However, N-terminal

splice junction cleavage still occurred after mutation of all three conserved C-terminal splice-junction residues (His-Asn-Ser) to Ala.^[60] These data are more consistent with Ser1 and Cys1 playing a direct nucleophilic role, as in mechanism 3.

Mechanism 3 postulates that Ser1 or Cys1 can undergo an N→O(S) acyl rearrangement; the downstream nucleophile then attacks the resulting (thio)ester linkage, rather than the amide linkage proposed in mechanism 2. Similar N→O(S) acyl rearrangements which lead to cleavage of the resultant (thio)ester bonds are observed in other autocatalytic protein-processing reactions, including pyruvoyl formation, processing of the Hedgehog proteins, and N-terminal nucleophile amidohydrolases.^[2, 3] Pyruvoyl formation in prohistidine decarboxylase is initiated by an N→O acyl shift of Ser82. Mutation of Ser82 to Cys greatly diminished the rate of pyruvoyl formation, which reflects the less than optimal match between the nucleophile and the surrounding electronic environment of the enzyme active site.^[75] A similar phenomenon was seen when conservative substitutions of intein splice junction Ser, Thr, or Cys residues were made,^[6, 9, 28, 60, 66, 74, 76, 77] when the active-site nucleophile of serine or cysteine proteases was changed to cysteine and serine, respectively,^[78] or when the autoprocessing active-site Thr of *Flavobacterium glycosylasparaginase* was mutated to Cys.^[79]

Hydroxylamine cleavage was used to confirm the acyl shift in a Ser82Cys mutant of prohistidine decarboxylase.^[75] In proteins at neutral pH, internal thioester linkages are much more sensitive to cleavage with hydroxylamine than amide and oxygen ester linkages.^[58] The Ser82Cys mutant of prohistidine decarboxylase, unlike the wild-type enzyme, was sensitive to hydroxylamine cleavage. Internal thioesters in proteins can also be displaced by small thiol reagents, resulting in protein cleavage. A similar strategy was used to detect thioester intermediates in processing of the Hedgehog protein and the *Flavobacterium glycosylasparaginase*.^[48, 60, 79, 80] Mutation of the Psp-GBD Pol intein Ser1 to Cys reduced both splicing and branched intermediate formation, but prolonged incubation in the presence of hydroxylamine, free Cys, or thiol reagents resulted in increased levels of N-terminal splice junction cleavage relative to wild-type precursor, diagnostic of the presence of a thioester linkage at the N-terminal splice junction.^[60, 80] In the MIP system, hydroxylamine cleavage at Cys1 also occurs in the presence of additional mutations that block branch formation, indicating that the linear (thio)ester precedes the branched (thio)ester in the splicing pathway.^[60] The position of hydroxylamine cleavage was confirmed by mass spectrometry and HPLC analysis of a C-terminal cyanogen bromide fragment derived from the cleaved N-extein with comparison to a model peptide containing the expected C-terminal hydroxamate moiety.^[80] Similar results were later obtained with the Sce VMA intein.^[66]

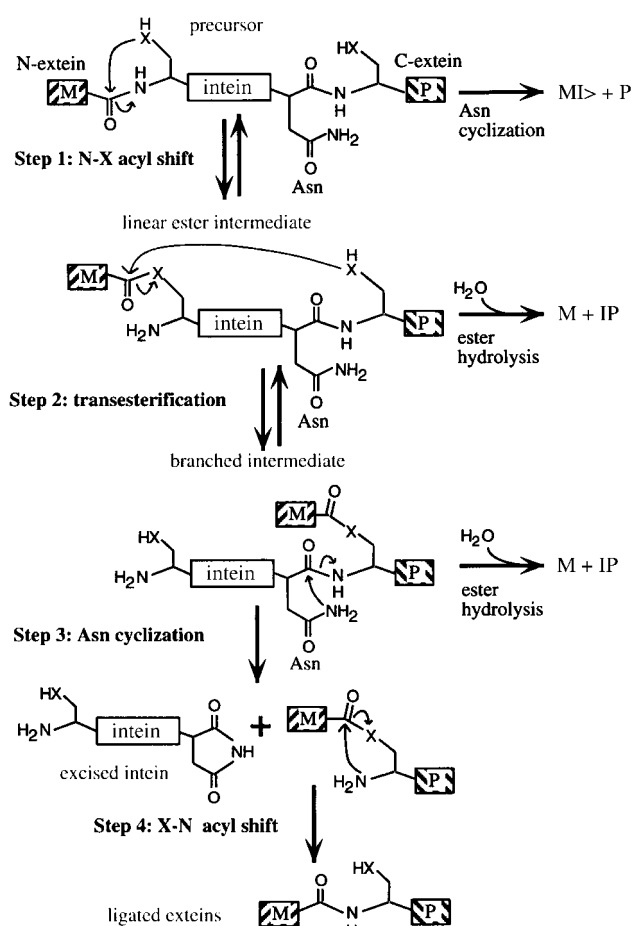
Taken together, these data strongly implicate an N→O(S) acyl shift at the upstream splice junction as the initial step of protein splicing according to mechanism 3. However, two families of putative inteins have an N-terminal Ala residue (see Section 1.3). Preliminary evidence indicates that at least one of these inteins is capable of splicing.^[81] We propose that these Ala1-containing inteins have evolved to splice using mechanism 2, since all other intein motifs are intact.

2.7. The Protein-Splicing Mechanism

The widely accepted mechanism for protein splicing of most inteins is shown in Scheme 4 and consists of four steps:

- 1) attack by the side chain of the first intein residue (Ser, Thr, or Cys) on the preceding carbonyl group, resulting in an acyl shift of the N-extein to the side chain of the first intein residue;
- 2) a transesterification reaction in which the hydroxyl or thiol group on the first C-extein residue (Ser, Thr, or Cys) attacks the (thio)ester linkage, resulting in transfer of the N-extein to the C-terminal splice junction;
- 3) cleavage of the amide linkage at the intein C terminus by Asn or Gln cyclization to release the free intein; and
- 4) spontaneous rearrangement of the (thio)ester linkage between the ligated exteins to the more stable peptide bond amide linkage.

Processing of the Hedgehog protein provides an interesting variation of the intein-mediated transesterification reaction.^[48] In the Hedgehog system, nucleophilic displacement



Scheme 4. The currently accepted mechanism of protein splicing and single splice junction cleavage. X represents either the oxygen present in the side chain of Ser or Thr or the sulfur present in Cys. In some inteins, Asn is replaced by Gln. Inteins with Ala1 probably splice using mechanism 2 (Scheme 3). All tetrahedral intermediates and proton transfer steps are omitted for clarity. Points in the pathway where single splice junction cleavage can occur are also indicated. See text for details. “M” represents the N-extein, and “P” the C-extein. The presence of a C-terminal succinimide is indicated by “>”.

of the thioester linkage between the signaling and autoprocessing domains occurs when the hydroxyl group of cholesterol attacks the thioester. This results in the covalent linkage of cholesterol to the C terminus of the signaling domain, which serves to anchor the signaling domain on the surface of the cell where it controls important aspects of embryonic development.^[48]

2.8. Side Reactions

In addition to the expected excised intein and ligated extein products, protein splicing typically yields products from side reactions, especially when splicing precursors are expressed in heterologous hosts, or when inteins are cloned between foreign exteins. These products arise from cleavage at either or both splice junctions without concomitant ligation and are clear extensions of the mechanism (Scheme 4). Cleavage at the N-terminal splice junction arises from competing hydrolysis of the linear (thio)ester intermediate versus transesterification or by hydrolysis of the (thio)ester in the branched intermediate prior to Asn or Gln cyclization. Cleavage at the C-terminal splice junction arises by Asn or Gln cyclization in the absence of N-extein transfer. Mutating catalytic residues at one splice junction generally increases the cleavage side reaction at the other junction.^[6, 9, 14, 60, 66, 74] For example, replacement of the intein N-terminal residue with Ala results exclusively in cleavage at the C-terminal splice junction, while replacement of the intein C-terminal Asn with Ala results in cleavage at the N-terminal junction.

2.9. The Role of Proximal Extein Amino Acids

Splicing of chimeric precursors is usually slower than in the native precursor, with more abortive single splice junction cleavage products.^[4–10] In our experience, splicing is successful in less than 25 % of chimeric precursors. Moreover, it is often temperature-dependent, suggesting that folding of the intein is impaired.^[4, 8, 13] Since all three nucleophiles in the protein-splicing pathway are splice-junction residues, suboptimal proximal extein sequences are likely to inhibit splicing by destabilizing the active site either chemically or by sterically interfering with packing at the active site.

Although the –1 residue at the N-terminal splice junction does not actively participate in the splicing reaction as a nucleophile or assisting group, its carbonyl carbon atom is the target of three of the four nucleophilic displacements. Several studies have shown that N-extein proximal residues can inhibit or block splicing or rescue splicing defective mutants.^[6, 8, 14, 76, 77] Two systematic studies have demonstrated that some –1 substitutions can block splicing of the Sce VMA and *Mycobacterium xenopi* gyrase A (Mxe GyrA) inteins, although residues that block splicing of one intein may have negligible effect on the other intein.^[6, 14] Amino acids that are most similar to the cognate –1 residue worked best in these studies. Certain amino acids at the –1 position can either reduce the rate of the initial acyl shift or block transesterification.^[14] These observations imply that inteins have

coevolved with their extein sequences to maximize splicing efficiency and that it is best to choose intein insertion sites that are similar to the native insertion site.

2.10. Facilitators of Catalysis and Intein Structure

As discussed in Section 2.1, serine and cysteine proteases facilitate catalysis using an oxyanion hole to increase the electrophilicity of the substrate carbonyl and a charge relay system to increase the nucleophilicity of the attacking hydroxyl or thiol group.^[50] Inteins probably use similar strategies. Mutagenesis studies indicate that the conserved His in block B assists in reactions at the intein N terminus^[77] and in the Hedgehog protein,^[46, 82] but fail to conclusively establish the role of the intein penultimate His residue of block G.

The penultimate His residue is required for splicing and C-terminal splice-junction cleavage of the Psp-GBD Pol intein.^[60] However, the His residue of block G does not appear to be universally required for splicing, although mutation of this residue generally inhibits splicing to varying degrees depending on the intein, the extein, and the substituted amino acid.^[6, 9, 60] Moreover, about 10 % of inteins naturally have a residue other than His at this position, suggesting that when a mutation naturally occurs, the intein can evolve to splice in the absence of a penultimate His.^[29] When four inteins which naturally have Ser, Ala, Phe, or Gly as penultimate residues were tested for their ability to splice in *E. coli*, only the *Chlamydomonas* ClpP intein failed to splice.^[81, 83–85] Mutation of the penultimate Gly residue of *Chlamydomonas* ClpP intein to His^[83] and of the penultimate Phe residue of *M. jannaschii* phosphoenolpyruvate synthase intein to His^[85] significantly improved splicing. On the other hand, mutation of the penultimate Gly residue of *Methanococcus jannaschii* RNA polymerase A' intein to His significantly inhibited splicing, resulting in accumulation of the branched intermediate.^[85] Thus, splicing in *E. coli* of inteins naturally containing penultimate amino acids other than His may improve or worsen when “reverted” to His, depending on the intein. These conflicting results may reflect inteins at different stages of evolution after mutation of their penultimate His residue. Taken together, these data suggest that the intein penultimate His may facilitate splicing and branch resolution by Asn cyclization.

Structural data support the role of both conserved His residues in facilitating protein splicing. The crystal structures of two inteins and part of a Hedgehog autoprocessing domain have been determined.^[45, 86, 87] The Sce VMA intein and the N-terminal portion of the *Drosophila* Hedgehog protein autoprocessing domain were both crystallized after excision from the precursor, while the Mxe GyrA intein was crystallized with a single N-extein residue (Ala –1) and Cys1 mutated to Ser. The *Ca* trace of all three proteins can be superimposed over much of the splicing domain^[42, 45, 48, 86, 87] and form a conserved fold termed a HINT (*Hedgehog intein*) module.^[45] The HINT module consists of two structural subdomains with superimposable *Ca* traces that are related by a pseudotwofold axis of symmetry and have a single

hydrophobic core.^[45] The N and C termini are brought into proximity upon folding of the HINT module, which is composed entirely of β strands and loops.

Unfortunately, the C-extein nucleophile and the scissile bonds are absent from these structures, except for the N-terminal splice junction in the Mxe GyrA intein. In the Mxe GyrA intein structure, Ala-1 and Ser1 are in a *cis* conformation, which may provide part of the driving force for protein splicing.^[87, 88] However, Ala at the -1 position inhibits splicing by 90% and decreases the initial rate of thiol-induced N-terminal cleavage fivefold when the Mxe GyrA intein is in the MIP context.^[14] The positions of Ala-1 and the C-terminal Asn in this structure may be different than in a larger precursor due to interaction between the charged N-terminal α -amino group of Ala-1 and the C-terminal Asn198 carboxylate group (Figure 3).

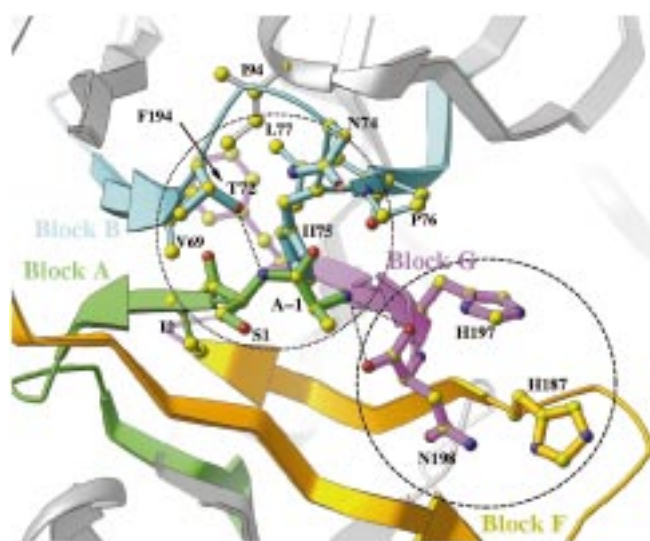


Figure 3. The structure of the Mxe GyrA intein active site. Amino acids present at the Mxe GyrA intein active site and the conserved motifs are depicted based on the Mxe GyrA intein crystal structure.^[87] Two potential oxyanion holes are indicated by the dashed circles. A pair of dashed lines indicates a potential hydrogen-bond interaction between the free amino and carboxy groups of the protein, which may distort the position of these groups in this protein relative to their position in a precursor with larger exteins. A third dashed line indicates a potential hydrogen bond between the hydroxyl group of Thr72 in block B and the nitrogen atom of Ser1 at the scissile bond.

The crystal structures nonetheless provide insight into some of the groups assisting in splicing reactions. The structures reveal an intein with a preorganized active site including two potential oxyanion holes. In all three structures, several block B residues are within hydrogen-bonding distance of the N terminus of the HINT module, potentially interacting in the precursor with either the N-terminal carbonyl oxygen atom at the scissile bond or the amine leaving group, forming an oxyanion hole reminiscent of serine and cysteine proteases (see Section 2.1). These include, but are not limited to, the conserved His and Thr residues (Asn in the Sce VMA intein) in block B (Figure 1 and Section 1.3). In the Mxe GyrA intein structure, His75 of block B is within hydrogen-bonding distance to the Ala-1 carbonyl oxygen atom, and Thr72

and Asn74 of block B are within hydrogen-bonding distance to the main chain nitrogen leaving group (Figure 3).^[87]

Several residues could potentially form a second oxyanion hole to facilitate Asn cyclization (Figure 3). In both inteins, the penultimate His residue is positioned to form a hydrogen bond with the C-terminal carboxylate group, and not the Asn side-chain nitrogen nucleophile. These data suggest that the His residue acts by either stabilizing the developing negative charge on the tetrahedral intermediate of the Asn cyclization reaction or by making the main-chain amine a better leaving group, but not by increasing the nucleophilicity of the attacking side-chain nitrogen atom.^[45, 86, 87]

No amino acid is interacting with the side-chain hydroxyl or thiol group at the N-terminal splice junction to increase its nucleophilicity.^[45, 86, 87] All three structures are of elements with an N-terminal Cys residue. It would be interesting to see the structure of an intein with an N-terminal Ser residue, since such inteins would probably require assistance to increase the nucleophilicity of Ser1, due to its high pK_a .

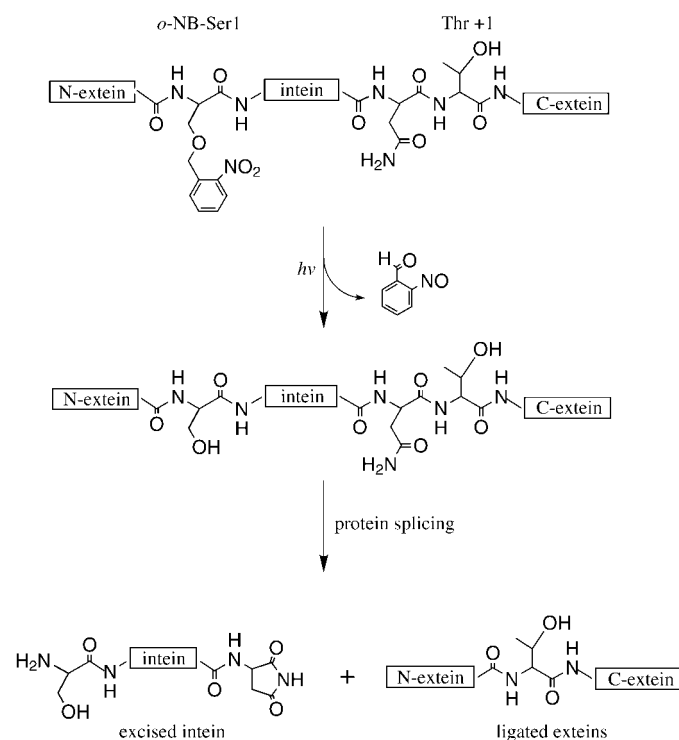
More questions about protein-splicing catalysis remain than have been answered. Which steps in the pathway does the oxyanion hole at the N-terminal splice junction assist, and is there a second oxyanion hole present at the C-terminal splice junction? What type of conformational changes, if any, are required to achieve the four coupled nucleophilic displacements, given that three of them attack the same carbonyl carbon atom? Must side chains move to allow each new nucleophilic group to attack? What residues help align the attacking nucleophile with the electrophilic center? Why do conservative substitutions of Ser, Thr, and Cys usually inhibit splicing? Is the unusual *cis* conformation at the Mxe GyrA intein N-terminal splice junction present in the native precursor, and if so do the resulting steric constraints limit the allowable amino acids at the -1 position? A thorough understanding of the protein-splicing mechanism awaits the determination of the structure of precursors and intermediates from inteins with both Cys and Ser splice-junction residues.

3. Applications

3.1. Control of Splicing

Applications involving control of splicing fall into two categories: pharmaceutical “switches” and tools for protein engineering. Inteins are present in essential genes of human pathogens such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and *Candida tropicalis*. Since intein-containing precursors are inactive, chemical reagents that block splicing would have significant pharmacological value. Controllable inteins inserted into foreign contexts provide a method for activating an enzyme on command, allowing biosynthesis of cytotoxic proteins or controllable gene knockouts. Splicing was first controlled by insertion of the intein into a suboptimal extein context or by intein mutation, such that precursor biosynthesis and splicing occur at different temperatures.^[4, 8, 13, 60]

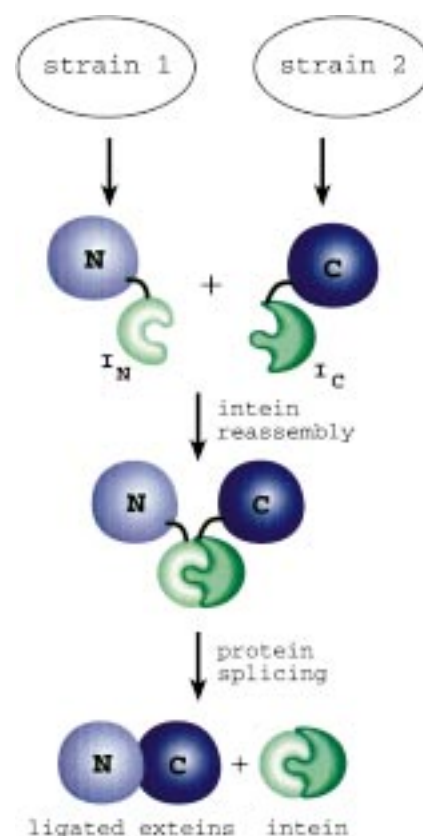
Protein splicing has also been controlled by a novel use of photochemistry and site-directed mutagenesis (Scheme 5).^[89] With a chemically aminoacylated suppressor tRNA and an in



Scheme 5. Control of splicing using photoactive groups. Protein splicing of the Tli Pol-2 intein with a caged photoreactive group is initiated by photolysis of the 2-nitrobenzyl ether of Ser1. *o*-NB denotes the *o*-nitrobenzyl protecting group.^[89]

vitro translation system,^[90] *O*-(2-nitrobenzyl)serine was incorporated in place of Ser1 in the Tli Pol-2 intein. The “caged” protecting group can be released from the precursor by brief irradiation with visible light, initiating splicing by restoring Ser1. Photochemically activated protein splicing should allow a range of time-resolved studies relevant to the mechanism of protein splicing.

Trans-splicing in vitro is another method of controlling splicing by splitting the precursor gene into two fragments which are separately expressed in different cultures (Scheme 6).^[12, 21, 91, 92] After purification, the precursor fragments are mixed under native or denaturing conditions, depending on solubility and reassociation requirements. Reassembly activates the splicing element, resulting in ligation of the exteins and release of the intein fragments. In all cases to date, the precursor has been split in the dispensable endonuclease domain of the intein. Two out of three split sites led to functional trans-splicing in the Psp-GBD Pol intein, and the released split intein complex retained homing endonuclease activity.^[12] Trans-splicing allows the expression of extremely cytotoxic proteins as well as segmental protein modification or labeling. Trans-splicing may also provide a new tool to study protein folding. In another example of nature mimicking biotechnology (or vice versa), the catalytic subunit of the replicative DNA polymerase of *Synechocystis* sp. has been split within its intein by a



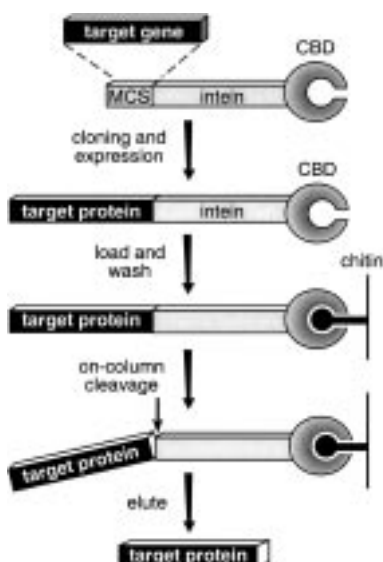
Scheme 6. Trans-splicing: control of splicing by precursor fragmentation. The precursor gene can be split within the intein and each fragment expressed in separate cultures. Reassembly occurs in vitro. The intein fragments (I_N + I_C) reconstitute an active splicing element that then mediates ligation of the extein fragments (N, C).

genome inversion, but trans-splicing in vivo restores DNA polymerase activity to maintain viability of this organism.^[84]

3.2. Protein Purification Vectors

Understanding the mechanism of protein splicing has allowed the conversion of an intein into the more common type of autocleavage element, an autoprotease that cuts a single adjacent peptide bond. Cleavage at only the N-terminal splice junction is achieved by mutating one or more C-terminal splice-junction residues to prevent Asn cyclization while allowing thioester formation.^[14, 16, 60] The thioester linkage can then be cleaved with thiol-specific reagents, including free cysteine, or by nitrogen nucleophiles such as hydroxylamine. Several methods have been used to specifically activate the intein C-terminal splice junction, including mutation of the Sce VMA intein penultimate His^[7] and mutation of the –1 aa in a temperature-controllable Mxe GyrA intein.^[14]

Converting a modified intein, which can only cleave one splice junction, into a purification vector is achieved by 1) introducing a multiple cloning site adjacent to the active splice junction for cloning of the target gene and 2) cloning the gene for an affinity purification tag within the intein or adjacent to the inactive splice junction (Scheme 7). Precursors can be expressed in any eucaryotic or procaryotic host. Intein cleavage is directly activated on the affinity purification



Scheme 7. Intein purification vectors. Purification of target proteins can be achieved by cloning the target protein in-frame with the single active N- or C-terminal splice junction of the modified intein using the multiple cloning site (MCS).^[7, 14–16] After expression under nonpermissive autocleavage conditions, the fusion protein is isolated on a chitin affinity column using the chitin binding domain (CBD) affinity tag that is adjacent to the inactive splice junction. Cleavage is then induced on the column by various methods including thiol reagents or temperature shift, followed by elution of the free target protein.

column, resulting in elution of the target protein while the remainder of the fusion is retained. Two purification vectors are commercially available (New England BioLabs, Inc.) in which the C terminus of the target protein is fused to the active N terminus of the intein, and a 5 kDa bacterial chitin binding domain affinity tag is fused to the inactive C terminus of the intein. The IMPACT system (intein-mediated purification with an affinity chitin-binding tag) employs a modified 454 aa Sce VMA intein,^[16] while a second vector employs a modified 198 aa Mxe GyrA intein.^[14, 15] In a third commercially available purification vector which is also part of the IMPACT system (New England BioLabs, Inc.), a multiple cloning site for the target protein is adjacent to the C terminus of a modified Sce VMA intein in which the central endonuclease domain has been replaced by the 5-kDa chitin binding domain and ten codons are in-frame with the N-terminal splice junction.^[7] In this mutated intein, Asn cyclization is activated by thiol-induced cleavage of the peptide at the intein N terminus.

Intein-mediated protein purification has several advantages over other purification methods. No expensive protease is necessary, and cleavage occurs only at the splice junction and not at protease-sensitive sites in the target protein. Furthermore, purification of a target protein free of vector-derived amino acids can be accomplished in one step, since purification and cleavage occur on the same column.

3.3. Intein-Mediated Polypeptide Ligation and Related Techniques

1998 saw the convergence of two previously unrelated fields, protein splicing and protein semisynthesis, resulting in

generation of a new protein engineering technique termed either “expressed protein ligation” (EPL)^[17, 19, 20, 22] or “intein-mediated protein ligation” (IPL).^[15, 18] The elucidation of the protein-splicing mechanism occurred simultaneously with the development of a procedure for protein semisynthesis, termed “native chemical ligation”.^[65] In native chemical ligation, a synthetic peptide with a C-terminal α -thioester moiety is mixed with a second peptide or protein with an N-terminal cysteine (Scheme 8A). A highly efficient and chemoselective intermolecular reaction takes place, forming a thioester-linked intermediate which spontaneously rearranges by an S $\rightarrow$ N acyl rearrangement to form a peptide bond between the ligated peptides. Thus, native chemical ligation follows all the steps in the protein-splicing pathway except for the Asn cyclization reaction which releases the intein from the ligated exteins (Scheme 4). Native chemical ligation is limited by the ability to make large peptides by solid-phase peptide synthesis and the inability to express a polypeptide with a C-terminal α -thioester or to selectively generate a C-terminal α -thioester in an unprotected polypeptide.

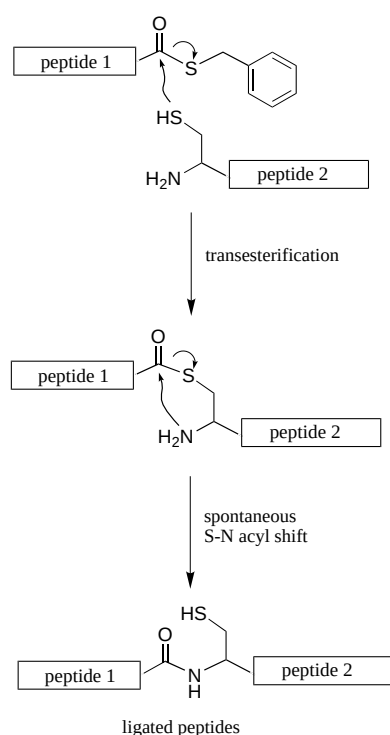
IMPACT and similar intein vectors (see Section 3.2) provide unique tools for biosynthesis of an α -thioester at the C terminus of a target protein, which can then be utilized in various types of chemoselective condensation reactions, including modified native chemical ligation. Other intein vectors yield a polypeptide with an N-terminal Cys residue after cleavage at the intein C-terminal splice junction.^[14, 15] Alternatively, protease digestion can generate an N-terminal Cys residue in a biologically synthesized polypeptide.^[20, 22] To date, the Mxe GyrA intein,^[14, 18] the Sce VMA intein,^[16–20, 22] and the *Methanobacterium thermoautotrophicum* ribonucleoside–diphosphate reductase (Mth RIR1) intein^[15] have been used to express polypeptides with a C-terminal α -thioester.

Initial studies involved condensation of synthetic peptides with intein-derived, biologically expressed proteins containing an α -thioester between the C terminus of the target protein and the N terminus of the intein (Scheme 8B) to express cytotoxic enzymes,^[18] to test the effect of phosphorylation on kinase activity and conformation,^[17] and to examine protein–protein interactions.^[19] Semisynthesis was achieved by:

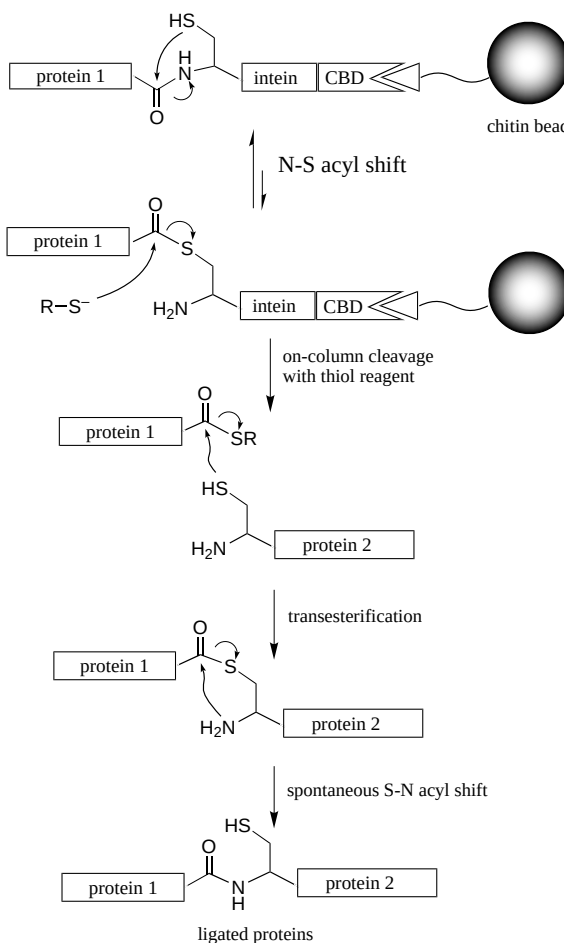
- 1) truncating the target gene immediately prior to the last cysteine codon or at a nonconserved point near the C terminus;
- 2) expressing the truncated enzyme fused to the N terminus of a modified intein;
- 3) purifying the truncated enzyme by affinity chromatography; and
- 4) mixing the truncated enzyme with a synthetic peptide comprising the remainder of the enzyme with an N-terminal Cys, and condensing in the presence of a thiol reagent, such as 2-mercaptoethanesulfonic acid (MESNA) or thiophenol. Alternatively, the thiol reagent can be added first to cleave the truncated protein from the column as an α -thioester, followed by addition of the synthetic peptide (Scheme 8B).

Ligated RNase A required refolding for activity, but the HpaI restriction enzyme did not.^[18] The C-terminal Src kinase (Csk) proteins (50 kDa) catalyze the phosphorylation of a

A) native chemical ligation



B) intein-mediated protein ligation



Scheme 8. Comparison of native chemical ligation and intein-mediated protein ligation. A) Native chemical ligation^[65] involves the coupling of two synthetic peptides, the N-terminal peptide having a C-terminal thioester linkage and the C-terminal peptide (or protein) having an N-terminal cysteine residue. Mixing results in transesterification to yield a ligation product in which the two peptides are joined by a thioester linkage with an adjacent free α -amine. The thioester linkage spontaneously rearranges to the more stable amide linkage. B) Intein-mediated expressed protein ligation^[15, 17–20, 22] utilizes identical coupling chemistry as native chemical ligation, but the α -thioester on the N-terminal segment is generated by on-column cleavage of a recombinant protein fused to a cleavage-competent intein. This circumvents the length requirements imposed by synthetic peptide chemistry. CBD refers to the chitin binding domain, which is used to immobilize the intein, and the triangle represents a chitin moiety attached to a bead. All tetrahedral intermediates and proton transfer steps are omitted for clarity.

conserved tyrosine within the C-terminal tail of Src kinase family members (SH2 domain).^[17] Using a similar synthetic approach with an IMPACT vector (Sce VMA intein) and thiophenol, either a phosphorylated or unphosphorylated synthetic peptide was condensed with the truncated human Csk. The resultant kinase was significantly more active when the phosphorylated peptide was ligated, confirming the role of phosphotyrosine for activity. A fluorescent tag was included in each peptide, allowing analysis of the conformation by limiting proteolysis, which indicated that phosphotyrosine induced a change in Csk conformation. In the third example, a C-terminal peptide was ligated to a truncated σ^{70} subunit of *E. coli* RNA polymerase to demonstrate that this region of the protein is involved in protein–protein interaction in the holoenzyme and in promoter recognition.^[19]

The second generation of IPL utilizes a biologically expressed polypeptide with an N-terminal Cys in place of a synthetic peptide. The N-terminal Cys residue can be generated with two intein vectors in which the N terminus

of the target protein is fused to the intein C terminus,^[14, 15] but not with the commercial IMPACT Sce VMA intein C-terminal splice-junction cleavage system^[7] (see Section 3.2). Alternatively, an N-terminal Cys residue can be generated by protease digestion of an expressed polypeptide^[20, 22] In each example, two large polypeptides were solubly expressed in bacteria and condensed without the need for denaturation or renaturation.^[15, 20, 22]

These same techniques can be used to specifically label the N or C terminus of a protein with any type of tag, which can either be incorporated into a peptide or displace the intein from the α -thioester intermediate. For example, the Hedgehog autoprocessing domain generates a similar thioester linkage which allows attachment of cholesterol to the C terminus of the released signaling domain by a transesterification reaction involving the hydroxyl group of cholesterol.^[46, 48]

A major breakthrough in NMR spectroscopy for protein structure determination was achieved with IPL.^[20] NMR

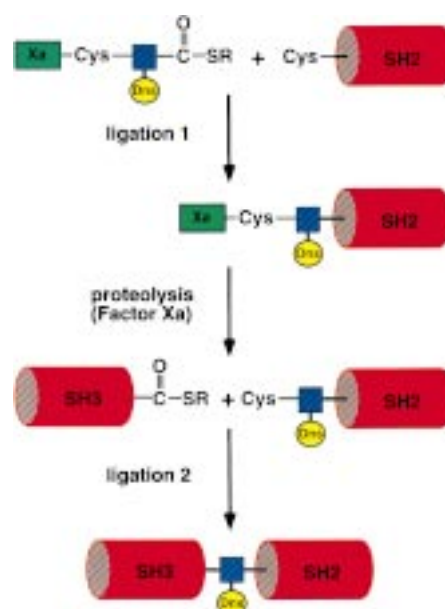
analysis is limited by the loss of resolution with increasing number of amino acids. Segmentally labeling a protein reduces the spectral complexity and has been used to study large proteins whose solution structures were previously unsolvable by NMR spectroscopy. With IPL, a segment or domain of a large protein is isotopically labeled in bacteria with ^{13}C or ^{15}N and then ligated to the remaining unlabeled segment or domain of the protein, also expressed in bacteria. In a series of separate experiments, different parts of the protein are labeled prior to ligation by IPL, allowing the structure of the labeled region to be determined in the context of the entire folded protein. This technique also provides a method of studying the effect of ligand binding or domain interactions by chemical shift perturbation to elucidate structure–activity relationships by NMR spectroscopy. Similar strategies of segmental labeling are possible by trans-splicing^[12] (Section 3.1) and NMR analysis of a small polypeptide has been reported after trans-splicing.^[21] Although both trans-splicing and IPL achieve the same result, trans-splicing is limited by the difficulties of identifying appropriate sites for intein insertion, the need to reconstitute an active intein, and the potential need to denature the precursor fragments prior to reassembly (see Section 3.1).

In another elegant set of experiments, Muir and co-workers have used intein-mediated expressed protein ligation to introduce a protein biosensor between the Src homology 3 (SH3) and Src homology 2 domains (SH2) of the Abelson nonreceptor protein tyrosine kinase (Abl).^[22] A synthetic peptide containing an environmentally sensitive 5-(dimethyl-amino)naphthalene-1-sulfonamide (Dns) fluorophore was sequentially ligated to the Abl-SH2 domain at its C terminus and the Abl-SH3 domain at its N terminus using IPL and native chemical ligation strategies (Scheme 9). The resultant semisynthetic protein has an environmentally sensitive dansyl group in the linker between the SH2 and SH3 domains which was able to report conformational changes upon ligand binding. This protein engineering strategy is generally applicable to the insertion of any type of tag, fluorophore, or unnatural amino acid into a protein of any size or sequence without the limitations of methods involving chemically misacylated suppressor tRNA's^[90] or solid-phase peptide synthesis.

Recently, inteins have also been used to generate cyclized proteins^[93] and proteins with a C-terminal thiocarboxylate for protein semisynthesis.^[94] The C-terminal thiocarboxylate was generated using a 66 aa ThiS peptide, which functions as a sulfur donor for the biosynthesis of the thiazole moiety of thiamin. This was fused to the N terminus of the Sce VMA intein in the IMPACT-CN vector, and the resultant thioester was cleaved with ammonium sulfide. Five milligrams of ThiS-COSH peptide were purified per liter of culture.^[94]

4. Summary and Outlook

In less than ten years, protein splicing has shifted from being a biological oddity to a well-understood, widely observed process that has generated multiple protein-engineering applications. However, we are still unsure of the



Scheme 9. Sequential condensation of protein fragments and the incorporation of a protein biosensor. Sequential condensation of synthetic peptides or biologically expressed polypeptides using a combination of intein-mediated expressed protein ligation and native peptide ligation allows incorporation of a Dns biosensor between the Abl kinase domains SH2 and SH3.^[22] After condensation of the synthetic peptide with the C-terminal polypeptide, the fusion is treated with Factor Xa protease to generate a new N-terminal Cys. The fusion is then allowed to react with the N-terminal polypeptide to generate the mature protein product. The same technique can be used to introduce any unnatural amino acid or chemical reagent at any desired location in a protein. Xa: peptide with Factor Xa cleavage site.

biological function of inteins. Some suggest that intein genes are selfish DNA elements that invade other genes with little penalty after splicing.^[13, 35, 37, 48, 95] It has also been suggested that inteins control expression of the genes in which they reside.^[11, 13, 48, 84, 95] However, the self-processing protein-splicing mechanism seems to leave little room for control, especially since splicing is rapid under physiological conditions. Natural precursors have not been detected in the native host, and no growth conditions have been found that modulate this process in the native organism. It has also been suggested that inteins may have played an important role in early evolution.^[95] Trans-splicing and intein-mediated protein ligation suggest that inteins could have provided a means of trial-and-error domain shuffling to generate improved enzymes at the protein level, especially prior to the development of sophisticated DNA recombination pathways. Once DNA recombination becomes facile, intein genes could provide islands of homology for recombination between genes encoding smaller protein modules.

Although a general mechanism of protein splicing has been elucidated (Scheme 4), exceptions to this mechanism exist in nature. The largest void in our understanding of protein splicing is how the intein facilitates the four nucleophilic displacements. Creative approaches to determining the structure of precursors and intermediates are needed to solve this problem. For example, how do inteins enhance attack of the backbone carbonyl group by the Asn side-chain nitrogen atom, rather than the more common attack of the Asn side-

chain carbonyl group by the main-chain nitrogen atom? Since well-known chemical reactions make up the protein-splicing pathway, the development of applications utilizing inteins has been rapid. Although intein purification vectors were the first intein-derived application, intein-mediated expressed protein ligation and its related applications may prove to be the most important and widely used intein-derived techniques. The ability of intein vectors to chemoselectively generate large polypeptides of any sequence with α -thioesters or N-terminal cysteines circumvents the limits of solid-phase peptide synthesis. Inteins also provide a new target for drug discovery for several diseases. The last year has seen the development of many new protein-engineering applications which utilize IPL to synthesize cytotoxic proteins, add fluorescent tags to proteins, segmentally label proteins for NMR analysis, cyclize proteins, generate C-terminal thiocarboxylates, or introduce fluorophores into proteins. The list of intein-related applications will continue to expand as more chemists become aware of intein-derived tools.

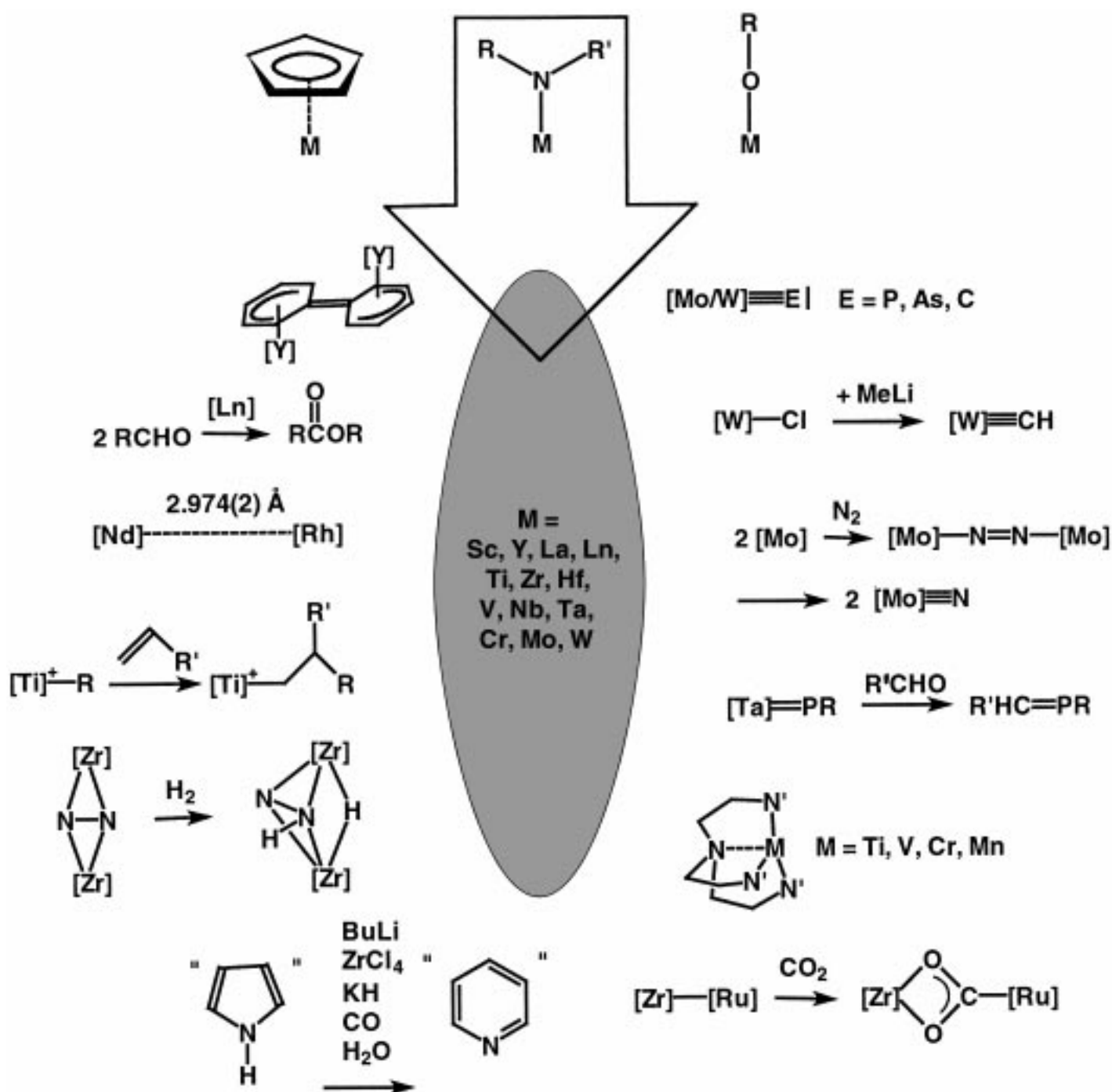
We dedicate this review to the memory of Prof. Holger W. Jannasch (1927–1998) of the Woods Hole Oceanographic Institute, whose exploration of extreme environments led to the characterization of many microbes, including Thermococcus litoralis and Pyrococcus sp. GB-D, from which were cloned intein-containing genes that allowed us to define the protein-splicing mechanism. We thank our colleagues at New England BioLabs, Virginia Cornish and Tom Muir for valuable discussions, Karen Sandman, Karen Noren, Tom Evans, and Maurice Southworth for reading the manuscript, and Tom Muir for preparing Scheme 9.

Received: March 10, 1999 [A331]

- [1] F. B. Perler, E. O. Davis, G. E. Dean, F. S. Gimble, W. E. Jack, N. Neff, C. J. Noren, J. Thorner, M. Belfort, *Nucleic Acids Res.* **1994**, 22, 1125–1127.
- [2] F. B. Perler, M. Q. Xu, H. Paulus, *Curr. Opin. Chem. Biol.* **1997**, 1, 292–299, and references therein.
- [3] F. B. Perler, *Nat. Struct. Biol.* **1998**, 5, 249–52, and references therein.
- [4] M. Xu, M. W. Southworth, F. B. Mersha, L. J. Hornstra, F. B. Perler, *Cell* **1993**, 75, 1371–1377.
- [5] M. Kawasaki, Y. Satow, Y. Anraku, *FEBS Lett.* **1997**, 412, 518–520.
- [6] S. Chong, K. S. Williams, C. Wotkowicz, M. Q. Xu, *J. Biol. Chem.* **1998**, 273, 10567–10577.
- [7] S. Chong, G. E. Montello, A. Zhang, E. J. Cantor, W. Liao, M. Q. Xu, J. Benner, *Nucleic Acids Res.* **1998**, 26, 5109–5115.
- [8] A. Telenti, M. Southworth, F. Alcaide, S. Daugelat, W. R. Jacobs, Jr., F. B. Perler, *J. Bacteriol.* **1997**, 179, 6378–6382.
- [9] A. A. Cooper, Y. Chen, M. A. Lindorfer, T. H. Stevens, *EMBO J.* **1993**, 12, 2575–2583.
- [10] E. O. Davis, P. J. Jenner, P. C. Brooks, M. J. Colston, S. G. Sedgwick, *Cell* **1992**, 71, 201–210.
- [11] H. Paulus, *Chem. Soc. Rev.* **1998**, 27, 375–386.
- [12] M. W. Southworth, E. Adam, D. Panne, R. Byer, R. Kautz, F. B. Perler, *EMBO J.* **1998**, 17, 918–926.
- [13] V. Derbyshire, D. W. Wood, W. Wu, J. T. Dansereau, J. Z. Dalggaard, M. Belfort, *Proc. Natl. Acad. Sci. USA* **1997**, 94, 11466–11471.
- [14] M. W. Southworth, K. Amaya, T. C. Evans, M. Xu, F. B. Perler, *BioTechniques* **1999**, 27, 110–120.
- [15] T. C. Evans, J. Benner, M. Q. Xu, *J. Biol. Chem.* **1999**, 274, 3923–3926.
- [16] S. Chong, F. B. Mersha, D. G. Comb, M. E. Scott, D. Landry, L. M. Vence, F. B. Perler, J. Benner, R. B. Kucera, C. A. Hirvonen, J. J. Pelletier, H. Paulus, M. Q. Xu, *Gene* **1997**, 192, 271–281.
- [17] T. W. Muir, D. Sondhi, P. A. Cole, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 6705–6710.
- [18] T. C. Evans, J. Benner, M. Q. Xu, *Protein Sci.* **1998**, 7, 2256–2264.
- [19] K. Severinov, T. W. Muir, *J. Biol. Chem.* **1998**, 273, 16205–16209.
- [20] R. Xu, B. Ayers, D. Dowburn, T. W. Muir, *Proc. Natl. Acad. Sci. USA* **1999**, 96, 388–393.
- [21] T. Yamazaki, T. Otomo, N. Oda, Y. Kyogoku, K. Uegaki, N. Ito, Y. Ishino, H. Nakamura, *J. Am. Chem. Soc.* **1998**, 120, 5591–5592.
- [22] G. J. Cotton, B. Ayers, R. Xu, T. W. Muir, *J. Am. Chem. Soc.* **1999**, 121, 1100–1101.
- [23] P. M. Kane, C. T. Yamashiro, D. F. Wolczyk, N. Neff, M. Goebel, T. H. Stevens, *Science* **1990**, 250, 651–657.
- [24] R. Hirata, Y. Ohsumi, A. Nakano, H. Kawasaki, K. Suzuki, Y. Anraku, *J. Biol. Chem.* **1990**, 265, 6726–6733.
- [25] E. O. Davis, S. G. Sedgwick, M. J. Colston, *J. Bacteriol.* **1991**, 173, 5653–5662.
- [26] F. B. Perler, D. G. Comb, W. E. Jack, L. S. Moran, B. Qiang, R. B. Kucera, J. Benner, B. E. Slatko, D. O. Nwankwo, S. K. Hempstead, C. K. S. Carlow, H. Jannasch, *Proc. Natl. Acad. Sci. USA* **1992**, 89, 5577–5581.
- [27] H. H. Gu, J. Xu, M. Gallagher, G. E. Dean, *J. Biol. Chem.* **1993**, 268, 7372–7381.
- [28] R. A. Hodges, F. B. Perler, C. J. Noren, W. E. Jack, *Nucleic Acids Res.* **1992**, 20, 6153–6157.
- [29] F. B. Perler, *Nucleic Acids Res.* **1999**, 27, 346–347.
- [30] F. B. Perler, G. J. Olsen, E. Adam, *Nucleic Acids Res.* **1997**, 25, 1087–1093.
- [31] S. Pietrokovski, *Protein Sci.* **1998**, 7, 64–71.
- [32] J. Z. Dalggaard, M. J. Moser, R. Hughey, I. S. Mian, *J. Comput. Biol.* **1997**, 4, 193–214.
- [33] X. Q. Liu, Z. Hu, *Proc. Natl. Acad. Sci. USA* **1997**, 94, 7851–7816.
- [34] H. Fsihi, V. Vincent, S. T. Cole, *Proc. Natl. Acad. Sci. USA* **1996**, 93, 3410–3415.
- [35] M. Belfort, P. S. Perlman, *J. Biol. Chem.* **1995**, 270, 30237–30240.
- [36] A. E. Gorbalenya, *Nucleic Acids Res.* **1998**, 26, 1741–1748.
- [37] F. S. Gimble, J. Thorner, *Nature* **1992**, 357, 301–306.
- [38] M. Belfort, R. J. Roberts, *Nucleic Acids Res.* **1997**, 25, 3379–3388, and references therein.
- [39] J. Z. Dalggaard, A. J. Klar, M. J. Moser, W. R. Holley, A. Chatterjee, I. S. Mian, *Nucleic Acids Res.* **1997**, 25, 4626–4638.
- [40] S. Pietrokovski, *Protein Sci.* **1994**, 3, 2340–2350.
- [41] M. Nishioka, S. Fujiwara, M. Takagi, T. Imanaka, *Nucleic Acids Res.* **1998**, 26, 4409–4412.
- [42] F. B. Perler, *Cell* **1998**, 92, 1–4, and references therein.
- [43] W. Grindl, W. Wende, V. Pingoud, A. Pingoud, *Nucleic Acids Res.* **1998**, 26, 1857–1862.
- [44] Z. He, M. Crist, H. Yen, X. Duan, F. A. Quirocho, F. S. Gimble, *J. Biol. Chem.* **1998**, 273, 4607–4615.
- [45] T. M. Hall, J. A. Porter, K. E. Young, E. V. Koonin, P. A. Beachy, D. J. Leahy, *Cell* **1997**, 91, 85–97.
- [46] J. J. Lee, S. C. Ekker, D. P. von Kessler, J. A. Porter, B. I. Sun, P. A. Beachy, *Science* **1994**, 266, 1528–1537.
- [47] E. V. Koonin, *Trends Biochem. Sci.* **1995**, 20, 141–142.
- [48] a) J. A. Porter, S. C. Ekker, W. J. Park, D. P. von Kessler, K. E. Young, C. H. Chen, Y. Ma, A. S. Woods, R. J. Cotter, E. V. Koonin, P. A. Beachy, *Cell* **1996**, 86, 21–34; b) P. A. Beachy, M. K. Cooper, K. E. Young, D. P. von Kessler, W. Park, T. M. T. Hall, D. J. Leahy, J. A. Porter, *Cold Spring Harbor Symp. Quant. Biol.* **1997**, 62, 191–204.
- [49] T. R. Burglin, *Curr. Biol.* **1996**, 6, 1047–1050, and references therein.
- [50] A. R. Fersht, *Enzyme Structure and Mechanism*, W. H. Freeman, Reading, **1977**.
- [51] C. F. Barbas III, J. R. Matos, J. B. West, C. H. Wong, *J. Am. Chem. Soc.* **1988**, 110, 5162–5166.
- [52] T. Nakatsuka, T. Sasaki, E. T. Kaiser, *J. Am. Chem. Soc.* **1987**, 109, 3808–3810.
- [53] L. Abrahmsen, J. Tom, J. Burnier, K. A. Butcher, A. Kossiakoff, J. A. Wells, *Biochemistry* **1991**, 30, 4151–4159.
- [54] A. Warshel, G. Naray-Szabo, F. Sussman, J. K. Hwang, *Biochemistry* **1989**, 28, 3629–3637.
- [55] D. R. Corey, C. S. Craik, *J. Am. Chem. Soc.* **1992**, 114, 1784–1790.
- [56] K. Iwai, T. Ando, *Methods Enzymol.* **1967**, 11, 262–282.

- [57] T. C. Bruice, S. J. Benkovic in *Bioorganic Mechanisms, Vol. 1* (Eds.: R. Breslow, M. Karplus), W. A. Benjamin, New York, **1966**, pp. 266–297.
- [58] W. P. Jencks, S. Cordes, J. Carriulo, *J. Biol. Chem.* **1960**, 235, 3608–3614.
- [59] A. A. Cooper, T. H. Stevens, *BioEssays* **1993**, 15, 667–673.
- [60] M. Xu, F. B. Perler, *EMBO J.* **1996**, 15, 5146–5153.
- [61] N. D. Clarke, *Proc. Natl. Acad. Sci. USA* **1994**, 91, 11084–11088.
- [62] C. J. Wallace, *Protein Sci.* **1993**, 2, 697–705.
- [63] M. Xu, D. G. Comb, H. Paulus, C. J. Noren, Y. Shao, F. B. Perler, *EMBO J.* **1994**, 13, 5517–5522.
- [64] Y. Shao, H. Paulus, *J. Pept. Res.* **1997**, 50, 193–198.
- [65] P. E. Dawson, T. W. Muir, I. Clark-Lewis, S. B. Kent, *Science* **1994**, 266, 776–779.
- [66] S. Chong, Y. Shao, H. Paulus, J. Benner, F. B. Perler, M. Q. Xu, *J. Biol. Chem.* **1996**, 271, 22159–22168.
- [67] Y. Shao, M. Q. Xu, H. Paulus, *Biochemistry* **1995**, 34, 10844–10850.
- [68] T. V. Brennan, S. Clarke, *Int. J. Pept. Protein Res.* **1995**, 45, 547–553, and references therein.
- [69] C. E. Voorter, W. A. de Haard-Koekman, P. J. van den Oetelaar, H. Bloemendal, W. W. de Jong, *J. Biol. Chem.* **1988**, 263, 19020–19023.
- [70] A. V. Klotz, *Bioorg. Chem.* **1993**, 21, 83–94.
- [71] T. Geiger, S. Clarke, *J. Biol. Chem.* **1987**, 262, 785–794.
- [72] S. Clarke, R. C. Stephenson, J. D. Lowenson in *Stability of Protein Pharmaceuticals, Part A* (Eds.: T. J. Ahern, M. C. Manning), Plenum, New York, **1992**, pp. 1–29, and references therein.
- [73] R. C. Stephenson, S. Clarke, *J. Biol. Chem.* **1989**, 264, 6164–6170.
- [74] R. Hirata, Y. Anraku, *Biochem. Biophys. Res. Commun.* **1992**, 188, 40–47.
- [75] P. Vanderslice, W. C. Copeland, J. D. Robertus, *J. Biol. Chem.* **1988**, 263, 10583–10586.
- [76] S. Nogami, Y. Satow, Y. Ohya, Y. Anraku, *Genetics* **1997**, 147, 73–85.
- [77] M. Kawasaki, S. Nogami, Y. Satow, Y. Ohya, Y. Anraku, *J. Biol. Chem.* **1997**, 272, 15668–15674.
- [78] J. N. Higaki, L. B. Evnin, C. S. Craik, *Biochemistry* **1989**, 28, 9256–9263.
- [79] C. Guan, T. Cui, V. Rao, W. Liao, J. Benner, C. L. Lin, D. Comb, *J. Biol. Chem.* **1996**, 271, 1732–1737.
- [80] Y. Shao, M. Q. Xu, H. Paulus, *Biochemistry* **1996**, 35, 3810–3815.
- [81] M. W. Southworth, F. B. Perler, unpublished results.
- [82] J. A. Porter, D. P. von Kessler, S. C. Ekker, K. E. Young, J. J. Lee, K. Moses, P. A. Beachy, *Nature* **1995**, 374, 363–366.
- [83] C. Huang, S. Wang, L. Chen, C. Lemieux, C. Otis, M. Turmel, X. Q. Liu, *Mol. Gen. Genet.* **1994**, 244, 151–159.
- [84] H. Wu, Z. Hu, X. Q. Liu, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 9226–9231.
- [85] L. Chen, F. B. Perler, unpublished results.
- [86] X. Duan, F. S. Gimble, F. A. Quijcho, *Cell* **1997**, 89, 555–564.
- [87] T. Klabunde, S. Sharma, A. Telenti, W. R. Jacobs, Jr., J. C. Sacchettini, *Nat. Struct. Biol.* **1998**, 5, 31–36.
- [88] B. L. Stoddard, S. Pietrokovski, *Nat. Struct. Biol.* **1998**, 5, 3–5.
- [89] S. N. Cook, W. E. Jack, X. Xiong, L. E. Danley, J. A. Ellman, P. G. Schultz, C. J. Noren, *Angew. Chem.* **1995**, 107, 1736–1737; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1629–1630.
- [90] C. J. Noren, S. J. Anthony-Cahill, M. C. Griffith, P. G. Schultz, *Science* **1989**, 244, 182–188.
- [91] K. V. Mills, B. M. Lew, S. Jiang, H. Paulus, *Proc. Natl. Acad. Sci. USA* **1998**, 95, 3543–3548.
- [92] B. M. Lew, K. V. Mills, H. Paulus, *J. Biol. Chem.* **1998**, 273, 15887–15890.
- [93] a) T. C. Evans, Jr., J. Benner, M. Q. Xu, *J. Biol. Chem.* **1999**, 274, 18359–18363; b) J. A. Camarero, T. W. Muir, *J. Am. Chem. Soc.* **1999**, 121, 5597–5598.
- [94] C. Kinsland, S. V. Taylor, N. L. Kelleher, F. W. McLafferty, T. P. Begley, *Protein Sci.* **1998**, 7, 1839–1842.
- [95] F. B. Perler, *Trends Biochem. Sci.* **1999**, 24, 209–210, and references therein.

Amidometal Chemistry Today



Highlights in the Renaissance of Amidometal Chemistry

Rhett Kempe*

Dedicated to Professor Dirk Walther on the occasion of his 60th birthday

More than 30 years ago intensive work began on the reactivity of the amidometal bond, mainly as a comparison to the metal–carbon bond. The results of these investigations were rather sobering. The amidometal bond in the complexes of early transition metals is kinetically inert, thermodynamically more stable, and thus synthetically far less interesting than the corresponding metal–carbon bond. “Today” amidometal chemistry has come to mean the utilization of the presumed disadvantage of a stable amidometal bond to produce well-defined reaction centers in transition metal complexes. In this way the reactivity of the resulting compounds can be specifically tailored

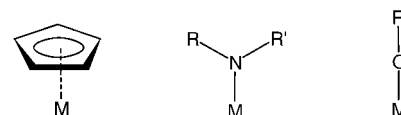
to allow applications in areas such as the activation of small, poorly reactive molecules, homogeneous catalysis, or organic synthesis. Insights into the mechanisms of elementary reactions such as C–H activation, α -H elimination, the cleavage of N–N triple bonds, reactions of N₂ with H₂ within the coordination sphere of transition metals, new routes for the synthesis of macrocycles, polar metal–metal bonds, and complexes with unusual terminal ligands such as phosphorus, arsenic, or carbon are, in addition to interesting transfer or polymerization reactions, just a few selected examples which illustrate what has become possible by the use of amido ligands. Thus,

in addition to the cyclopentadienyl fragment, which as a “directing ligand” has dominated the chemistry of the early transition metals for decades, alternatives are now available for targeted studies. What amido ligands have brought us in new information over the last 5–10 years can be called the renaissance of amidometal chemistry, or the beginning of a “postmetallocene era”.

Keywords: metal–metal interactions • N ligands • nitrogen fixation • nitrogen heterocycles • polymerizations

1. Introduction

In organometallic chemistry considerable effort is being expended on modifying the reactivity of metal–carbon bonds with coligands. The information thus obtained is being extensively used, for example in homogeneous catalysis.^[1] In the choice of such coligands, the cyclopentadienyl (Cp) fragment and phosphanes have hitherto played the decisive role as anionic and neutral donor functions, respectively.^[2] In addition to these classical possibilities for the control of reactivity of complexes, since the beginning of the 1990s exhaustive efforts have been devoted to the development of novel ligands.^[3] As well as the Cp ligand (Scheme 1, left), alkoxy (Scheme 1, right) and amido ligands^[4] (Scheme 1, center) have proved to be suitable for the stabilization of early, electron-poor transition metals in medium to high oxidation states. Of these two alternatives, the amido ligand is



Scheme 1. The three most important ligand types for the stabilization of early transition metals in middle to high oxidation states (R = alkyl, aryl, silyl).

especially interesting since it offers the greater potential in ligand and complex design because of the potential for double substitution at the donor atom.

The foundations of amidometal chemistry were laid in the 1960s and 1970s and are associated with names such as Bürger, Wannagat, Bradley, and Lappert. The motivation for the investigations was mainly the exploration of the reactivity of amidometal bonds in comparison to the metal–carbon bond.^[4] From the middle of the 1970s to the end of the 1980s interest in amidometal complexes stagnated as greater effort was devoted to the metallocenes. Compounds with essentially η^5 -bound Cp ligands have been extensively investigated since their discovery,^[5, 7] with special interest being devoted from the middle of the 1970s to complexes with metals of Group 4.

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This was brought about by the discovery of their high alkene polymerization activities in combination with methylaluminoxane (MAO),^[8, 9] the stability of the ligand–metal bond, and the frontier orbitals set up for the activation of small molecules. The renaissance of amidometal chemistry from the end of the 1980s to the middle of the 1990s is characterized mainly by the search for analogies between Cp and amido ligands. This search was later discontinued, and the actual advantages of amido ligands, that is the many uses in the construction of novel complex compounds with defined reactive centers, were exploited. Until now there has been little interest in the amido complexes of late transition metals. The chemistry of these compounds differs drastically from that of the early transition metals because of the energetically unfavorable combination of “soft” metals with “hard” amido ligands.^[10]

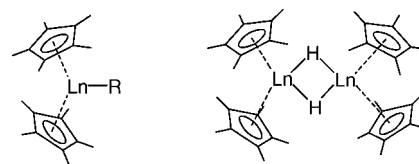
Reviews on the chemistry of the amido complexes of early transition metals may be divided into two categories. On the one hand, there are the “cross-sectional works”, publications in which different amido ligands are described;^[4] on the other, there are the “amido ligand orientated” publications in which the chemistry of only a specific ligand type is described. A comprehensive presentation of amidometal chemistry up to 1981 was both useful and realizable.^[4] Since 1990 this has been restricted to individual ligand types.^[11–23] The plethora of the amido ligands used makes an exhaustive “cross-sectional discussion” difficult since not all compounds can be discussed. However, such scrutiny is desirable as a counterpart to the “ligand-orientated” reviews and in order to stress the significance of amidometal chemistry. A restriction to highlights appears appropriate since in this way trend-setting work can be discussed and the review held within discernible limits.

2. Scandium, Yttrium, and Lanthanoids

2.1. Cp-Free Organolanthanoid Chemistry

Amido chemistry of the Ln metals is greatly influenced by the analogy to metallocene chemistry. The fascination with

lanthanoid complexes stabilized with Cp ligands comes from the opportunities for homogeneous catalytic processes for the formation of C–H, C–C, and C–X bonds.^[24] Here, highly reactive alkyl and hydride species are used as precatalysts or as stoichiometric reagents (Scheme 2).



Scheme 2. Lanthocene catalysts for C–C, C–H, and C–X couplings (R = alkyl, X = heteroatom).

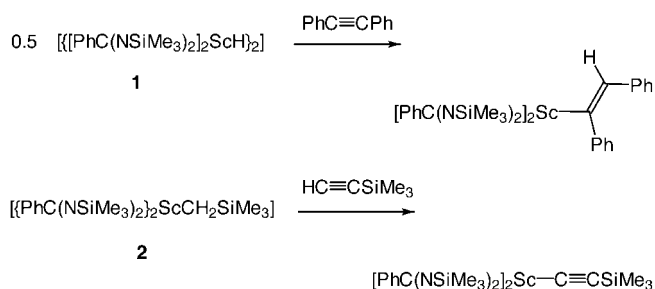
Typical examples of catalytic uses are polymerization,^[25, 26] hydrogenation,^[26, 27] hydroboration,^[28] hydrosilylation,^[29] and hydroamination/cyclization^[30] of olefins. Analogous catalyses have also been described for alkynes (oligomerization,^[31, 32] hydrogenation,^[32] and hydroamination/cyclization^[33]). With the aim of developing new and possibly more active catalysts, Cp-free ligand systems have become popular. Exchanging the Cp ligand for alkoxy or amido functionalities should lead, for example, to improved olefin polymerization catalysts. Chain termination by β -hydrogen transfer can be effectively suppressed at more electron-deficient metal centers because these alkyl complexes are thermodynamically more stable.^[34] In addition to alkoxy ligands, amido ligands are especially good since they fulfill the requirement for effective steric shielding. Examples are the silyl-substituted benzamidinato ligands first described by Dehnicke et al.^[35] and Roesky et al.^[36] The foundations of lanthanoid chemistry were developed mainly by Edelmann et al.^[13, 37] During these investigations it was demonstrated that in the case of central f element ions such ligands represent a steric equivalent to Cp ligands.^[13, 38] Comprehensive spectroscopic measurements on tris(benzamidinato)- and tris(cyclopentadienyl)lanthanoid complexes also confirm an electronic equivalence if the central Ln atom possesses a low electron affinity.^[39] On this basis, and because of the easy accessibility of silyl-substituted

Rhett Kempe was born in Dresden in 1964. He studied chemistry at the Universität Leipzig and received his Diplom under the supervision of Professor J. Sieler in 1989. A subsequent research studentship allowed him to work at the Max-Planck-Institut für Festkörperforschung with Professor H.-G. von Schnering and at the Friedrich-Schiller-Universität in Jena with Professor D. Walther. He received his doctorate from the Universität Leipzig in 1992 for work on the mechanisms of nickel complex catalyzed reactions. During a DAAD postdoctoral research fellowship at the Massachusetts Institute of Technology (1992/93) with Professor R. R. Schrock he became interested in N_2 activation. Then after a period at the Max-Planck-Institut für Kohlenforschung (1993/94) with Professor C. Krüger he began to study for his habilitation at the Max-Planck-Gesellschaft in the group “Complex Catalysis” led by Professor U. Rosenthal in 1994. Habilitation on aminopyridinato ligands, complexes of early transition metals and their use in homogeneous catalysis followed at the Universität Rostock in 1998. He is currently a group leader at the Institut für Organische Katalyseforschung in Rostock. His research interests include the development of novel catalysts and he is working at the interface between coordination chemistry and homogeneous catalysis. He is the author of more than 140 publications and in 1998 he was awarded the Karl-Winnacker-Stipendium.



benzamidinato ligands, the alkyl and hydride species, known to be highly reactive from metallocene chemistry, were synthesized. The preparative methodology is borrowed from metallocene chemistry^[24] and was used successfully for the first time by Teuben et al. for yttrium complexes.^[40] Corresponding scandium complexes are accessible as shown on Scheme 3 and have been described by Arnold et al.^[41]

Compound **1** does not react with ethylene or propylene at room temperature. At 60°C ethylene is only poorly polymerized. The reaction of **1** with internal alkynes such as PhC≡CPh gives the monoinsertion product (Scheme 4). Compound **2** reacts with terminal alkynes under σ-bond metathesis to give the σ-alkynyl complex.^[41]

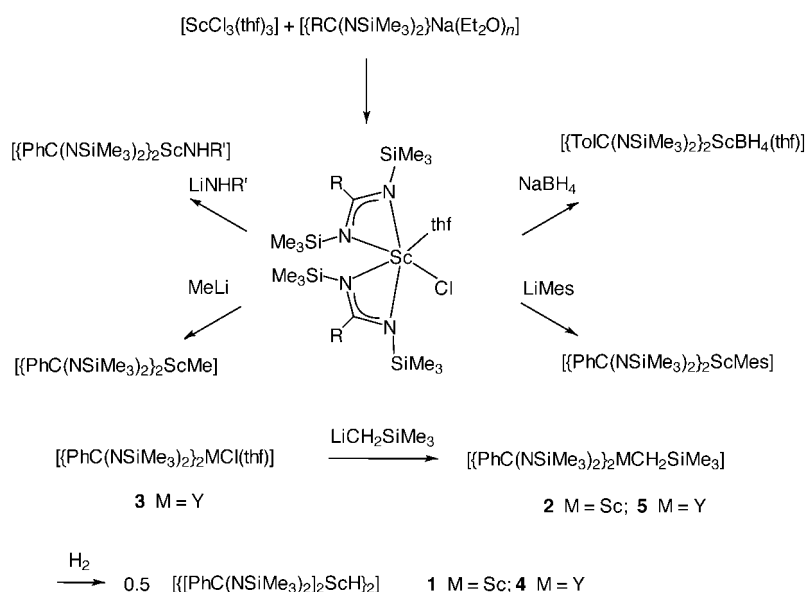


Scheme 4. Reactions of benzamidinatoscandium complexes with terminal alkynes.

Cp* = C₅Me₅), but are higher than that of [Cp₂*YCH₂SiMe₃].^[44] Catalyst deactivation by reaction with the catecholborane is considered to be the reason. If **4** is exposed to an excess of terminal alkyne, selective dimerization occurs in the case of HC≡CR (R = *t*Bu, Ph) with the formation of the head-to-tail coupled product H₂C=C(R)C≡CR with a turnover frequency (TOF) of 35 h⁻¹.^[40] In the case of HC≡CSiMe₃ the head-to-head product is formed exclusively. In contrast, the compounds [Cp₂*YR] (R = H, CH₂SiMe₃) do not form head-to-head or head-to-tail products selectively but instead show greater activity.

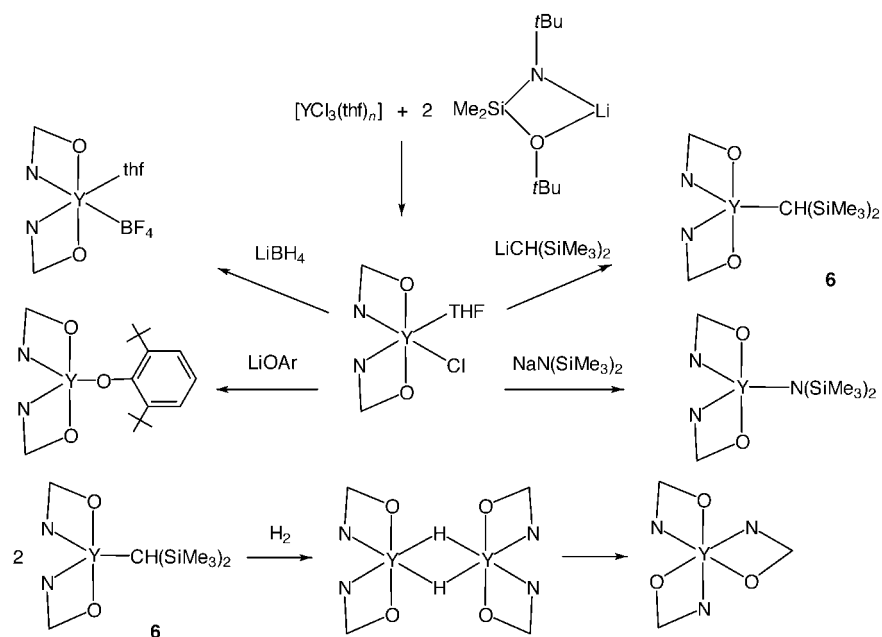
A similar alternative to Cp ligands are alkoxy-silylamido ligands such as *N,O*-bis(*tert*-butyl)-(alkoxydimethylsilyl)amide (Scheme 5).^[45]

In addition to an alkyl complex, alkoxy, hydroboro and amido compounds may be prepared in good yields. The isolation of a hydrido complex is not possible since ligand redistribution occurs and a tris(alkoxysilylamido) complex is formed (Scheme 5, bottom). The steric demand of the *tert*-butyl-substituted ligand is not



Scheme 3. Benzamidinatoscandium complexes (R = Ph, Tol (H₃CC₆H₄); R' = C₆H₃-2,6-*i*Pr₂; Mes = 2,4,6-(H₃C)₃C₆H₂).

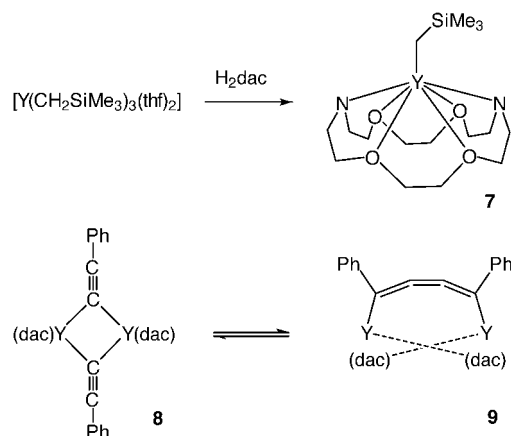
More extensive studies on the reactivity of **3**^[42] confirm the analogy to the chemistry of scandium (Scheme 3). The reaction of **3** with LiAlH₄ is surprising. There is no formation of an aluminum complex, but ligand transfer occurs from the yttrium center to the aluminum center. The activity of **4** during ethylene polymerization is to be classified as low.^[84] At 55°C only 4 kg_{PE} mol_{cat}⁻¹ h⁻¹ is produced. Compound **4** does not react with propylene and 1-hexene.^[43] One reason considered for the low polymerization activities is the strong ionic character of the central atom of the benzamidinatoyttrium complex. Compounds **4** and **5** catalyze the hydroboration of olefins in the presence of catecholborane. The activities are only about 5–10% relative to the activity of [Cp₂*LaCH(SiMe₃)₂] (the best lanthanoid catalyst^[28]



Scheme 5. Alkoxy-silylamido yttrium complexes.

large enough to inhibit a hydrido-alkoxysilylamide exchange. Stoichiometric reactions of **6** with pyridine derivatives lead to η^2 -pyridyl and η^2 - α -picolyl complexes.^[46] It was also demonstrated that the reactivity of these compounds corresponds to the analogous permethylated ytrocenes.

Reactive neutral monoalkyl complexes of the lanthanoids can also be stabilized by doubly deprotonated 4,13-diaza-[18]crown-6 (Scheme 6, top).^[47] Compound **7** is stable as a

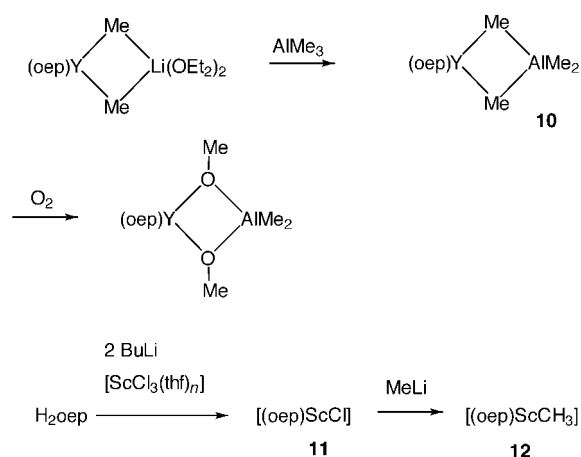


Scheme 6. Alkane elimination in the synthesis of dac-yttrium complexes (top) and in the phenylacetylene complexes existing in equilibrium (bottom).

solid, but decomposes in solution at room temperature.^[48] The reaction of **7** with phenylacetylene (Scheme 6, bottom) is unusual since a color change to dark blue occurs. NMR investigations demonstrated an equilibrium between two compounds, **8** (colorless) and **9** (blue-violet). The equilibrium and hence the color can be reversibly displaced by change in temperature.^[49] The bridging function of the 4,13-diaza-[18]crown-6 dianion (dac) ligand appears to play no role in the stabilization of **9** as analogous reversible coupling reactions have also been described for metallocenes.^[31b, 50] Bisalkyl complexes can be stabilized by corresponding monoaza crown ethers (aza-[18]crown-6).^[51]

Reports on metalloporphyrins of lanthanoids were first published at the beginning of the 1970s by Buchler et al.^[52] and Horrocks et al.^[53] The entry into organometallic chemistry occurred 20 years later. Thus, for example, metalloorganyls MR_3 ($R = CH(SiMe_3)_2$, $M = Y, Lu$) react with octaethylporphyrin (H2oep) to form monoalkyl compounds by alkane elimination. Protonolysis with sterically demanding alcohols, terminal alkynes, or water leads to the formation of monomeric alkoxy complexes, dimeric alkynyl or hydroxy complexes, respectively.^[54]

The reaction of yttrium alkoxy compounds with MeLi gives a dimethylttrate complex (Scheme 7, top) which reacts with $AlMe_3$ to form **10**. This compound shows an interesting selective reaction with one equivalent of O_2 with the formation of a bisalkoxy complex. Compound **11** can be isolated in over 90% yield by salt metathesis, and the chloro ligand is efficiently substituted by reaction with lithium alkyls, amides, and alkoxy compounds (Scheme 7, bottom). The CH_3 resonance signal in the ^1H NMR spectrum of **12** is shifted



Scheme 7. Selective O_2 insertion in **10** and formation of **12**.

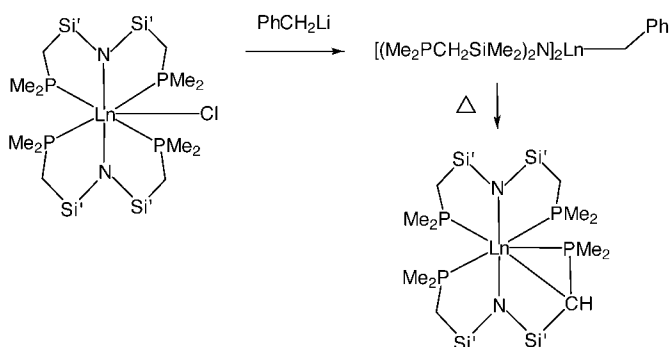
markedly to high field (-5 ppm). Compound **12** reacts with CO_2 or acetone with the insertion of a carbonyl function into the $Sc-C$ (methyl) bond.^[55]

A comparison of the reactivity of the amidolanthanoid complexes with each other is complicated since there have been only individual reports on comparable reactions. Few ligands at all allow the synthesis of stable hydrido complexes. Hitherto, the most extensively investigated were the silyl-substituted benzamidates, which, however, compare poorly with the corresponding metallocenes during catalytic use.

2.2. Lanthanoid-Phosphane Complexes

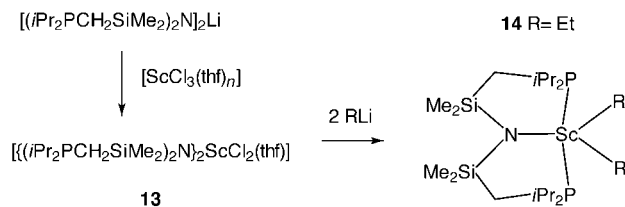
The synthesis of lanthanoid amidophosphane complexes is possible with the amidophosphane hybrid ligands developed by Fryzuk et al.^[11, 12] Biligand complexes are accessible, depending upon the lanthanoid ion, by reaction of the lithiated ligand precursor or potassium salt with $LnCl_3$.^[56] Alkylations with $LiCH_2Ph$ lead to unstable complexes which eliminate toluene at $50^\circ C$ (Scheme 8). In this way cyclometalation of the ligand occurs.^[57]

Monoligand complexes are particularly interesting since now principally two chloro ligands are available for functionalization. Such compounds have been described for yttrium^[58] and scandium.^[59] Mono(amidophosphane)scandium complexes have been extensively studied, and *i*Pr substituents



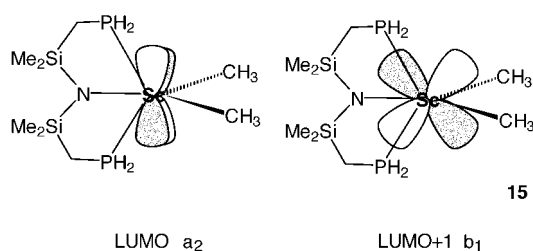
Scheme 8. Cyclometalation of amidophosphane ligands ($Ln = Y, La, Ce, Lu$).

on the phosphorus atom have been useful.^[59] The reaction of $(i\text{Pr}_2\text{PCH}_2\text{SiMe}_2)_2\text{NLi}$ ($(\text{P}_2\text{N})\text{Li}$) with $[\text{ScCl}_3(\text{thf})_3]$ leads to **13** in high yield (Scheme 9). The use of toluene as the solvent is essential. Compound **13** reacts with alkyllithium compounds (RLi , $\text{R} = \text{Me}$, Et , CH_2SiMe_3) to form the corresponding bisalkyl complexes.



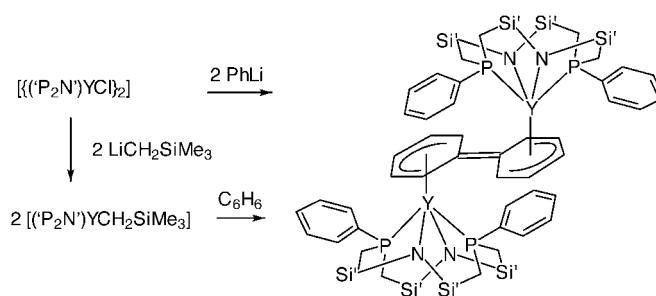
Scheme 9. Bisalkylscandium complexes stabilized by amidophosphane ligands ($\text{R} = \text{Me}$, Et , CH_2SiMe_3).

Analogous reactions with organozinc compounds or Grignard reagents fail. Salt-free bisalkyl complexes have thus far only been obtained by the use of sterically demanding substituents.^[60] Comprehensive NMR investigations and X-ray crystallographic analysis suggested no agostic interactions with the extremely electron-deficient scandium ion. These can be regarded formally as 12e^- complexes. It is also noteworthy that the bisalkyl compounds do not exist as “ate” complexes. The reactions of **14** with H_2 , ethylene, CO , and CO_2 with ligand expulsion are rather sobering. Ethylene is slowly polymerized, whereas the reactions with H_2 , CO , and CO_2 lead to indefinite products with ligand expulsion. That no agostic interactions and no stable products were observed in the reactions with H_2 , CO , and CO_2 can be explained by the electronic structure of **15**. The LUMO and the LUMO + 1 are d orbitals with π symmetry (a_2 and b_1) which are incapable of accommodating the electron densities of molecules like CO (Scheme 10). In contrast, the LUMOs of $[\text{Cp}_2^*\text{ScCH}_3]$ ($1a_1$ and b_2) offer ideal conditions for interactions with electron-rich ligands or ligand fragments.^[61]



Scheme 10. LUMOs of $[(\text{H}_2\text{PCH}_2\text{SiMe}_2)_2\text{N}]_2\text{ScMe}_2$ (a_2 and b_1).

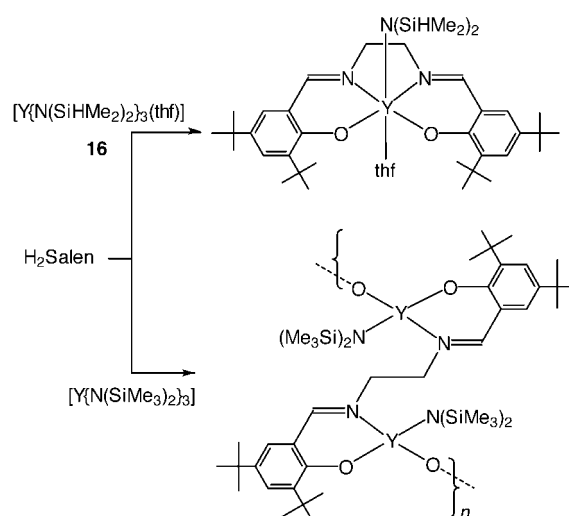
Compounds with diamidodiphosphane ligands possess totally different frontier orbitals.^[102] The reactivity of such alkylyttrium complexes towards benzene is noteworthy for it leads to C–C bond formation and the formation of intensely colored (dark blue) arene complexes (Scheme 11).^[62] Such arene complexes are untypical for yttrium, mainly σ -aryl complexes are known.^[24] A comparison with arenachromium complexes, which are familiar as products of the Hein reaction, is obvious.^[63]



Scheme 11. Areneyttrium complexes by phenyl coupling ($\text{Si}' = \text{Me}_2\text{Si}$).

2.3. New Applications of the Classical Amine Elimination Reaction

Since the beginning of amidometal chemistry amine elimination reactions have been known to be an elegant synthesis variant for the preparation of compounds of Group 4 metals.^[4] Particularly useful starting materials are mixed dimethylamidochloro complexes of the metals of this triad.^[64] Comparable alkylamides of Group 3 metals or the lanthanoids do not exist.^[65] Interesting prospects arise for these metals from the use of silyl amides. The key step here appears to be the choice of a suitable starting complex. Thus the reaction of **16** with bis(salicylidene)ethylenediamine (H_2Salen)^[66] leads to a mononuclear complex which is very soluble in hexane. If $[\text{Y}(\text{N}(\text{SiMe}_3)_2)_3]$ is used, oligomers insoluble in THF are formed (Scheme 12).^[67]



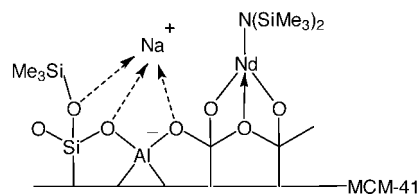
Scheme 12. Amine elimination for the preparation of salenyttrium complexes.

An efficient preparation of *ansa*-yttrocene complexes^[68] and sulfonamide complexes^[69] is similarly possible. Here too the formation of oligomers is observed with **16**.

Homoleptic, trivalent selenates and tellurates of lanthanum and cerium are also preparatively readily accessible by amine elimination.^[70] These compounds exist in toluene or hexane as triply coordinated mononuclear complexes, which was confirmed by the results of multidimensional $^{77}\text{Se}\{^1\text{H}\}$ NMR spectroscopy. Such chalcogenates are significant as precursors

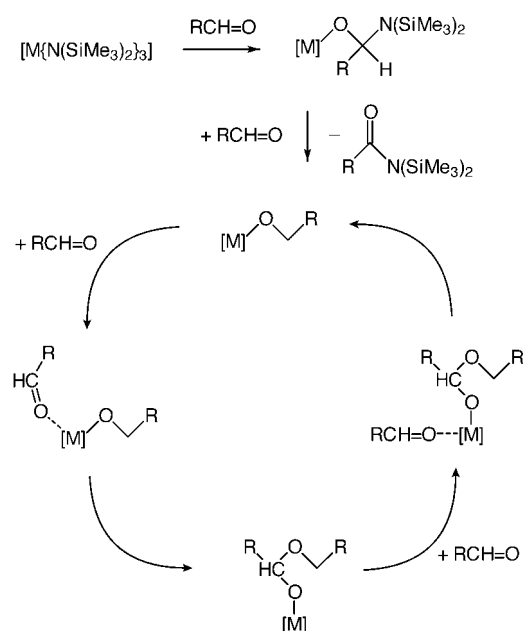
for the preparation of semiconductor materials with a lanthanoid–chalcogenide basis.^[71]

Interesting applications in catalysis are promised by immobilizing amidolanthanide complexes on surfaces of mesoporous silicates.^[72] Amine elimination reactions of silyl amides of lanthanoids with dehydrated MCM-41^[73] led to immobilized lanthanoid complexes (Scheme 13). These are remarkable precatalysts in Danishefsky hetero-Diels–Alder reactions.^[74]



Scheme 13. Immobilization of lanthanoid complexes by amine elimination on MCM-41.

The facile elimination of an amine is also responsible for the extremely high catalytic activity of $[M\{N(SiMe_3)_2\}_3]$ ($M = Sc, Y,$ and Ln) in the Tischenko reaction (or Claisen–Tischenko reaction).^[76] Alkoxy complexes are thought to be the intrinsically active species which are formed from catalyst precursors by amine elimination reactions (Scheme 14). If alkoxy lanthanoid complexes or the corresponding aluminum compounds are used as precatalysts, very little or no activity is observed.^[75]



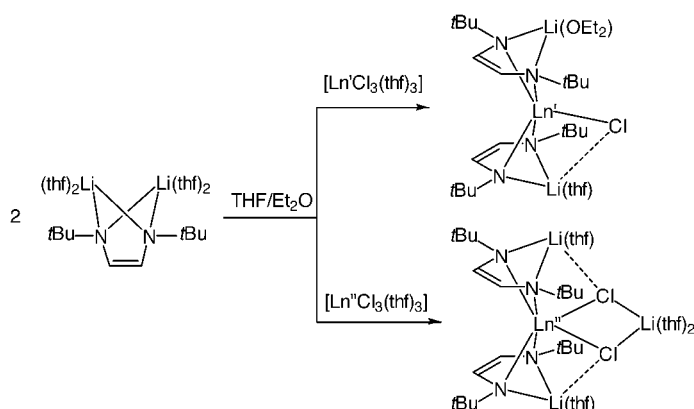
Scheme 14. Suggested mechanism for the lanthanide complex catalyzed Tischenko reaction.

2.4. Structure and Reactivity of “ate” Complexes

Most often sterically demanding, anionic ligands are used in the organometallic chemistry of the lanthanoids to accommodate the requirements of these large, electropositive metals.^[24] Complex chemistry with ligands of low spatial requirement is underdeveloped because compounds with salt

coordination, or “ate” complexes are formed preferentially.^[65] That “ate” complexes are not to be regarded as useless by-products, but have interesting properties in, for example, enantioselective catalysis was recently demonstrated with the alkoxy complexes developed by Shibasaki et al.^[77]

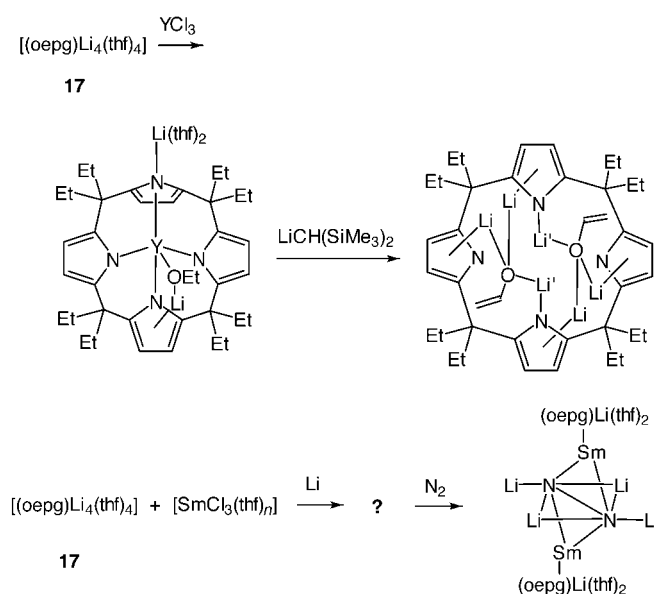
The reaction of doubly lithiated diazadienes with lanthanoid trichlorides leads to “ate” complexes with chemically interesting structures (Scheme 15).^[78] The synthetic potential



Scheme 15. Lanthanoid “ate” complexes with diazadiene ligands ($Ln' = Y, Lu; Ln'' = Sm$).

of such compounds appears to be great since the halogen atoms are apparently readily substituted by organic moieties. The preparation of novel multimetal complexes could be achieved by the exchange of lithium for other metals. Reactions of “ate” complexes with $[CpZrCl_3]$ and $[Cp_2ZrCl_2]$ are noteworthy. In these cases mixed Cp–diazadiene–zirconium complexes are readily formed by ligand transfer.^[78]

Lanthanoid complexes with macrocyclic porphyrinogen ligands^[15, 16] show remarkable reaction behavior as well as interesting structural chemistry. For example, **17** reacts with YCl_3 in THF to form a yttrate–lithium ethanolate complex (Scheme 16, top) in which the ethanolate is formed from



Scheme 16. Lanthanoid “ate” complexes with oepg ligands ($Li' = Li(thf)$).

THF.^[79] The addition of alkyllithium compounds leads to fragmentation of a further THF molecule and the formation of a dilithiated bisenolate salt with “loss” of the central yttrium ion. The reaction of **17** with $[\text{SmCl}_3(\text{thf})_3]$ in THF leads to a golden-yellow solution which becomes deep green on the addition of elemental lithium (Scheme 16, bottom). A green, crystalline compound, which is extremely air-sensitive and readily loses solvent, can be isolated. Reaction of the “green complex” with N_2 leads to an interesting dinitrogen compound.^[80] The N–N distance of the complexed nitrogen is 1.525(4) Å, which is in agreement with an N–N single bond. This means that a four-electron reduction has taken place. Samarium is formally present as Sm^{III} since the magnetic moment of the whole complex is $2.72 \mu_{\text{B}}$.

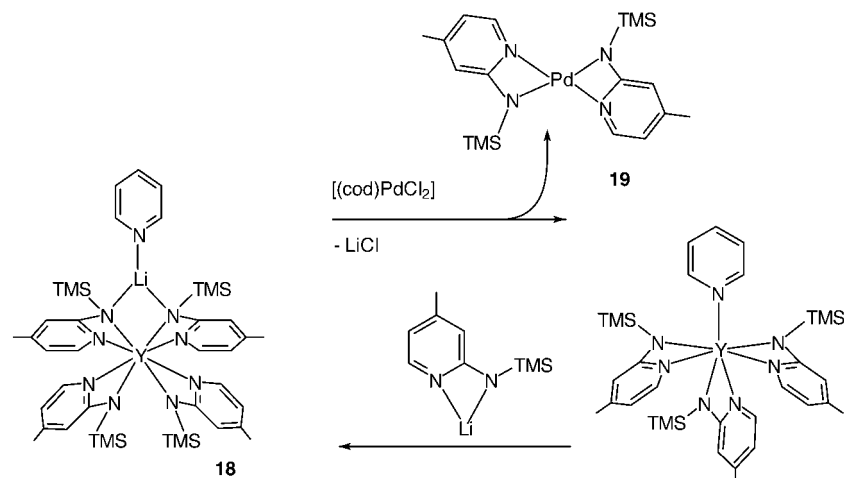
Reactions of lithiated, silyl-substituted aminopyridines with YCl_3 also lead to “ate” complexes such as **18** (Scheme 17). Such compounds are reactive enough to react with the halogenides of late transition metals by salt elimination. In this way, ligand transfers also allowed the synthesis of the first homoleptic amidopalladium complex **19**.^[81] The increase in the efficiency with a cyclic or catalytic reaction procedure in hexane is of interest (Scheme 17). The synthetic principle cited here is a new variant for the preparation of amido complexes of late transition metals where heterodinuclear compounds can be regarded as intermediates of ligand transfer reactions. Ligand transfer can be prevented by the use of bisaminopyridinato ligands, and new dinuclear complexes are accessible by this procedure (Scheme 18).^[82]

In this way the spatial requirements for a metal–metal communication between lanthanoid and metals of the platinum group can be acquired.

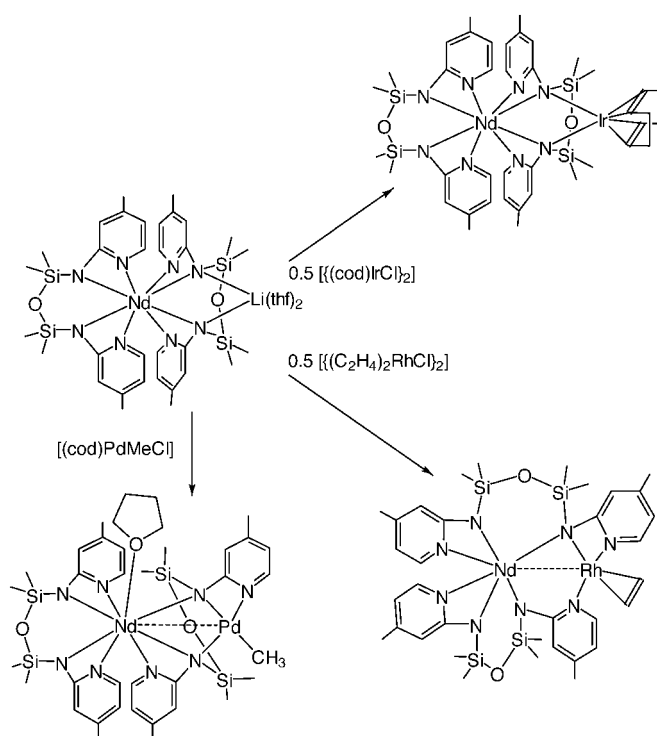
3. Titanium, Zirconium, and Hafnium

3.1. “Living” Olefin Polymerization

In contrast to the amido chemistry of the lanthanoids, in the chemistry of Group 4 metals emphasis is not placed upon the analogy to metallocenes, but may be derived successfully from it, as, for example, in the development of olefin poly-

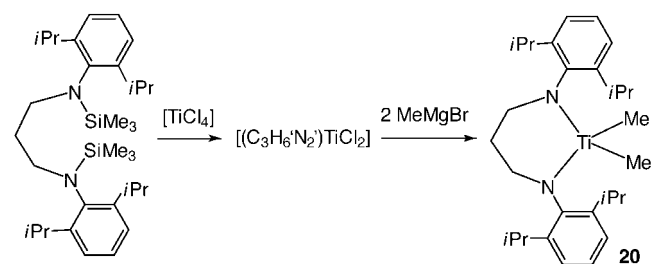


Scheme 17. Yttrate-mediated aminopyridine ligand transfer. cod = 1,5-cyclooctadiene; TMS = Me_3Si .



Scheme 18. Heterobinuclear complexes with bisaminopyridinato ligands.

merization catalysts based on amido complexes. Sterically demanding bis(amido) chelate ligands, whose dichlorotitanium complexes are accessible in good yields by Me_3SiCl elimination (Scheme 19), show very high activities in the



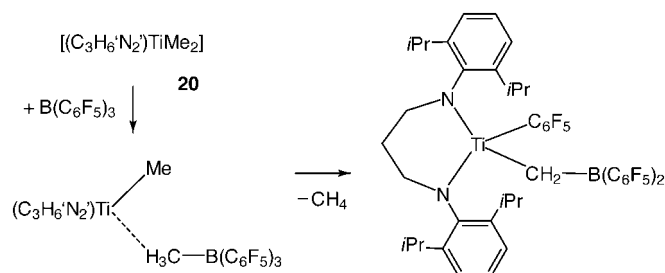
Scheme 19. Bis(amido) complexes with sterically demanding 2,6-diisopropylaryl substituents.

polymerization of 1-hexene if they are activated by Lewis acid cocatalysts.^[83]

The activity of **20** after activation with MAO at 68 °C in pure hexene (polymerization time 0.5 min) also appears extraordinary in comparison to previously described Cp-free, homogeneous catalyst systems with metals of this triad.^[84, 85] However, the activity is significantly lower when carried out at room temperature. If the polymerization is carried out in toluene as solvent the activity falls dramatically, which is explained by π coordination with the solvent.^[85] The narrow molecular weight distribution suggests the presence of a uniformly active catalyst species. Particularly interesting is the observation that olefinic resonances in the NMR

spectra of polymers have not been discovered. This means that chain transfer to aluminum is the dominant chain termination, not β -hydrogen transfer. If alkylaluminum cocatalysts are omitted chain termination can be prevented, which leads to “living” olefin polymerization. Such polymerizations are of special interest for they allow the synthesis of polymers with defined block structures.^[86] There have been only isolated reports of catalyst systems which promote “living” olefin polymerization.^[25g, 87, 88]

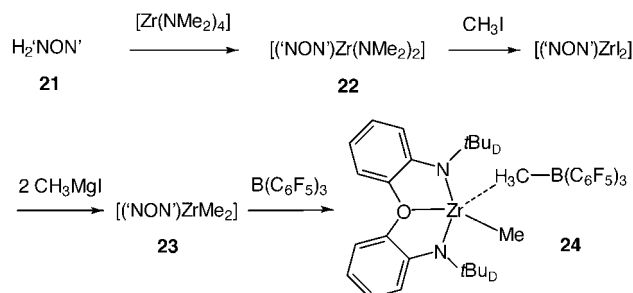
An equimolar ratio of **20** and $\text{B}(\text{C}_6\text{F}_5)_3$ catalyses the “living”, aspecific polymerization of α -olefins at room temperature, which has been confirmed by a linear relationship between the molecular weight M_n and time.^[89] If **20** is allowed to react stoichiometrically with $\text{B}(\text{C}_6\text{F}_5)_3$ in pentane (Scheme 20) methane elimination occurs with the formation



Scheme 20. Catalyst deactivation steps in the $[(\text{C}_3\text{H}_6\text{N}_2)\text{TiMe}_2]$ and $\text{B}(\text{C}_6\text{F}_5)_3$ system.

of an aryl complex inactive in polymerizations, which is indicative of possible catalyst deactivation steps.^[90] Studies on the mechanism of α -olefin insertion (1,2- or 2,1-insertion) with **20** ($\text{Me} = {}^{13}\text{CH}_3$), $\text{B}(\text{C}_6\text{F}_5)_3$, and 10 equivalents of 1-hexene as well as quenching of the unlabeled system with I_2 suggested a preferred 1,2-insertion. The resulting polymers were compared with model compounds such as 3-methylhexane and 2-iodobutane or 1-iodo-2-methylpropane by ${}^1\text{H}$ and ${}^{13}\text{C}$ NMR spectroscopy.^[91]

The work of Schrock et al.^[92] confirms that not only the system developed by McConville et al.^[89] induced the “living” polymerization of higher olefins. The reaction of the tridentate diamido ligand precursor **21** with $[\text{Zr}(\text{NMe}_2)_4]$ leads to **22** by amine elimination (Scheme 21). Subsequent “iodination” can be carried out with CH_3I , and alkylation by reaction with two equivalents of CH_3MgI . If **23** is allowed to react with $\text{B}(\text{C}_6\text{F}_5)_3$ a cationic zirconium complex **24** is formed which



Scheme 21. Partial abstraction of a methyl group by $\text{B}(\text{C}_6\text{H}_5)_3$ in $[(\text{NON}')\text{Zr}]$ complexes.

polymerizes ethylene. The X-ray structure analysis of **24** shows an anion–cation separation of $2.487(12)$ Å. This distance is approximately 0.1 Å shorter than in structures of comparable metallocene compounds.

A possible cause could be the lower spatial shielding of the “NON” ligand ($(\text{NON}') = \text{O}[2\text{-C}_6\text{H}_4\text{N}[\text{C}(\text{CH}_3)(\text{CD}_3)_2]_2$ dianion; $\text{tBuD} = \text{C}(\text{CH}_3)(\text{CD}_3)_2$). The reaction of **23** with $[\text{PhNMe}_2\text{H}][\text{B}(\text{C}_6\text{F}_5)_4]$ leads to a cationic zirconium complex which polymerizes 1-hexene as well as ethylene. A linear relationship between the catalyst/1-hexene ratio and the mean molecular weight ($M_w/M_n < 1/1$) confirms the “living” character of the 1-hexene polymerization. NMR studies showed a preferred 1,2-insertion for the $[(\text{NON}')\text{ZrR}]^+$ ion.^[93]

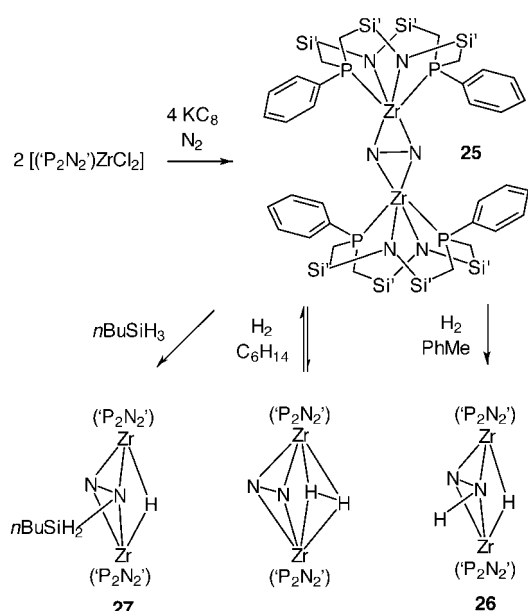
Unlike the metallocenes of Group 4, the amido ligands appear to suppress β -elimination as the chain termination step more effectively. In this way alkene polymerization can be “living” and efficient. With the extensive choice of available amido ligands, in addition to polymer modification, as is realizable with metallocenes,^[94] it is also possible to synthesize different polymer blocks of defined length. Amidometal complexes which could polymerize α -olefins living and isotactically have not yet been described, although a rich selection of diamines with a C_2 -symmetrical backbone are commercially available.

3.2. Reactions of Complexed Dinitrogen with Hydrogen

“The fixation of dinitrogen is one of the great discoveries awaiting the ingenuity of chemists.” This statement by William Crookes (1898)^[95] underlines the significance of the Haber–Bosch process for the manufacture of ammonia from N_2 and H_2 discovered shortly thereafter. Whereas the coordination chemistry of the chemically unreactive dinitrogen has been extensively investigated,^[96] little is known about the reaction of both molecules (N_2 and H_2) with each other within the coordination sphere of a metal complex.

The use of macrocyclic diamidodiphosphane ligands allows a detailed investigation of reactions of complexed dinitrogen with hydrogen.^[97] Hitherto, replacement of the bound nitrogen molecule has been mainly observed in the reactions of N_2 complexes with hydrogen.^[98–100] For example, $[(\text{Cp}_2^*\text{ZrN}_2)(\mu\text{-N}_2)]$ reacts irreversibly with H_2 to form $[\text{Cp}_2^*\text{ZrH}_2]$.^[100] Amidophosphane-stabilized^[14] zirconium complexes are highly suitable for the activation of nitrogen. The unusual characteristic here is the $\mu\text{-}\eta^2$ bonding mode of the N_2 ligand (*side-on* coordination).^[101] Analogously, the use of macrocyclic diamidodiphosphane ligands^[102] also leads to a *side-on* bound dinitrogen zirconium complex **25** (Scheme 22).

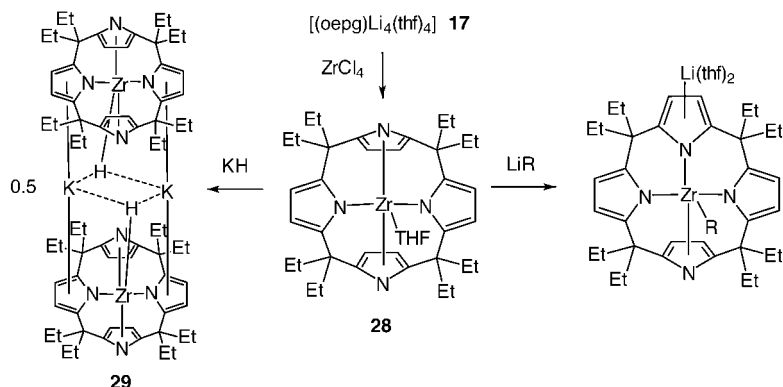
The X-ray structural analysis of **25** shows a N–N distance of $1.43(1)$ Å, similar to that of hydrazine (1.47 Å).^[103] The presence of a fourfold deprotonated hydrazine ligand is also in agreement with the four-electron reduction which accompanied the formation of **25**. If the dark blue complex **25** is allowed to react with H_2 in toluene a color change to yellow-orange takes place. According to extensive NMR spectroscopic investigations a solution of **26** is formed. Recrystallization of **26** from hexane gave a compound whose structure does not agree with these NMR data, but is a $(\mu\text{-}\eta^2\text{-N}_2)$ -

Scheme 22. Reactions of complexed N_2 with H_2 ($Si' = Me_2Si$).

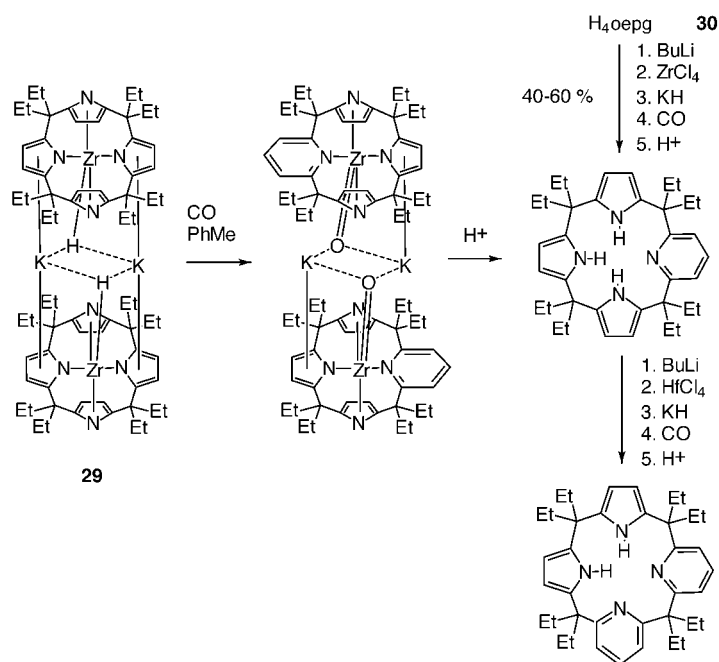
($\mu-\eta-H_2$) complex according to X-ray structural analysis (Scheme 22). The reaction of **25** with *n*-butylsilane leads to **27**, a compound analogous to that of complex **26** detected in solution. The similarity of the reaction behavior of the H–H and Si–H bond could be helpful in the explanation of this analogy.^[104]

3.3. Modification at and with Porphyrinogen Ligands

Chemical modifications of porphyrinogens by the combined use of metals of Group 4 and the alkali metals are interesting. In this way novel macrocycles whose preparation was hitherto not possible by classical organic methods are now efficiently accessible preparatively. Porphyrinogens are starting materials or intermediates in the chemical and biochemical synthesis of porphyrins, as they are spontaneously oxidized to the corresponding porphyrin with the elimination of H_2 when H atoms are present as substituents in the *meso* positions.^[105] Stable porphyrinogens are obtained by dialkyl substitution, as was demonstrated by Baeyer in 1886.^[106] The reaction of **17** with $ZrCl_4$ leads to **28** (Scheme 23).^[107]

Scheme 23. Activation of KH and alkyl lithium complexes at $[(oepg)Zr]$ complexes ($R =$ alkyl, aryl, and allyl substituents).

The ($\sigma,\sigma,\eta^5\eta^5$) bonding mode of the oepg ligands (oepg = octaethylporphyrinogen tetraanion) is in the case of zirconium only slightly energetically more favorable relative to the ($\sigma,\sigma,\sigma,\sigma$) bond isomer.^[108] Compound **28** appears to be an unreactive compound since it is coordinatively and electronically saturated. In reactions with ketones, however, zirconium-supported cleavage of the porphyrinogen framework takes place.^[109] If **28** is allowed to react with LiR ($R =$ alkyl, aryl, allyl) or KH , highly reactive bimetallic alkyl or hydrido complexes are formed (Scheme 23). The reactivity of this class of compounds is demonstrated by the insertion reactions into the bimetallically activated alkyl or hydrido functions (Scheme 24). Thus, for example, terminal olefins, isocyanides,



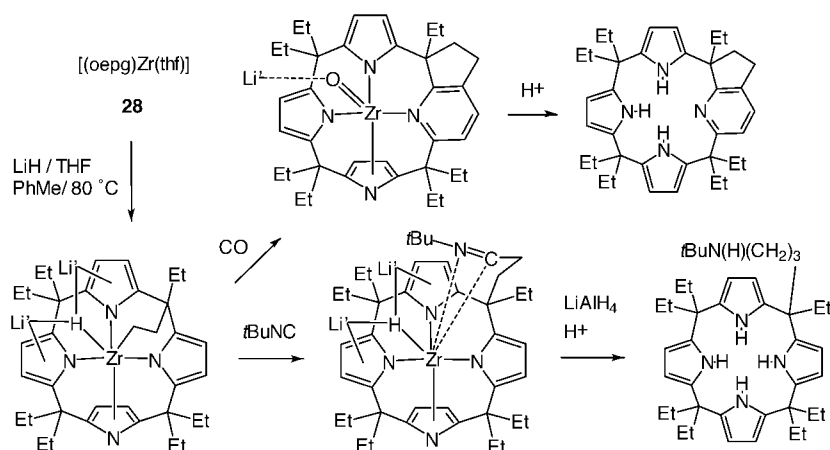
Scheme 24. Selective and sequential ring modifications at oepg ligands.

and alkynes are inserted.^[110] Particularly interesting is the reaction of **29** with carbon monoxide, the CO insertion reaction.^[111] This is formally a conversion of a pyrrole ring of the oepg ligand into the pyridine fragment and thus the formation of the next highest homologue.^[112] At the end, the modified ligand can be cleaved by hydrolysis. If **30** is allowed to react in an analogous sequence with four equivalents of $BuLi$, $ZrCl_4$, KH , CO , the simple pyridine-modified, protonated oepg ligand is obtained after hydrolytic workup. The total reaction yield is 40–60%. A subsequent, analogous transformation ($BuLi$, $HfCl_4$, KH , hydrolysis) leads to the doubly pyridine-modified, protonated oepg ligand (Scheme 24).

These modifications of the porphyrinogenic skeleton are not only a chemical curiosity, they are also suitable for the efficient preparation of novel, macrocyclic compounds and open up the way to artificial porphyrins. In addition to the modification of the ring system of the oepg ligands, the ligand periphery, in effect an ethyl substituent,

can also be modified selectively. A combined transformation rearranges the ring system and the ligand periphery.^[113] The reaction of **28** with LiH in the presence of one equivalent of THF in toluene at 80 °C leads, in analogy to **29**, to the formation of a zirconium–lithium hydrido complex, which by H₂ elimination and C–H activation coordinates an ethyl group of the oepg ligand periphery (Scheme 25).

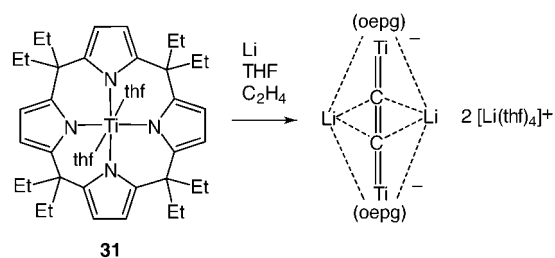
Functionalization of the ligand periphery is carried out by isocyanide insertion. The thus formed imine coordinates at zirconium and can be reduced to the amine with LiAlH₄. Following hydrolytic workup, a macrocycle modified at an ethyl substituent is then formed. A combined transformation of the ligand environment and the heterocyclic system occurs analogously by CO insertion and subsequent hydrolytic workup (Scheme 25). The success of the unusual transforma-



Scheme 25. Modifications at the ring system and/or the oepg ligand periphery (Li' = Li(thf)).

tion is determined by two important properties of the oepg complexes. First, such compounds can coordinate cations in the electron-rich ligand periphery and thus act as carriers of reactive organometallic functionality. Here the considerable difference in the π -bond strength of the pyrrole units in porphyrinogens and in the less basic porphyrins, for which π complexation of alkali metal ions is untypical, must be stressed. Second, the oepg ligands are very flexible and consequently permit C–H bond activation of the ligand periphery.

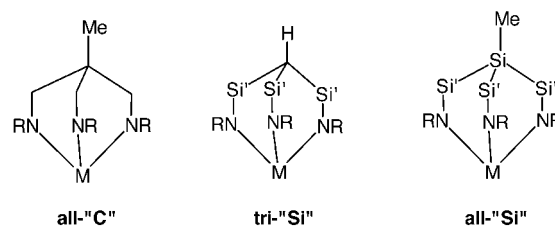
In addition to modifications of the ligands of the oepg complexes, such zirconium compounds can also act as an inert organic matrix. Thus the incorporation of Li₄H₄ and Li₂O by π -pyrrole complexation of the lithium ions through [(oepg)Zr] fragments is possible. In this way remarkable sandwich structures are formed.^[114] The zirconium complex thus facilitates the “solubility” of the ionic compounds in a nonpolar organic phase. One interesting olefin activation reaction is the reduction of **31** with lithium in the presence of ethylene. (Scheme 26).^[115] It appears remarkable that the oepg ligand is inert in spite of the drastic conditions. Unlike **28**, **31** exists as a ($\sigma,\sigma,\sigma,\sigma$) complex and is saturated coordinatively by two additional THF ligands. The reduction product is a dimetallacumulene.^[116] Examples of metal-carbide systems with a C₂ bridge are rare and were hitherto mainly synthesized from alkynes.^[117]



Scheme 26. A dititanacumulene from ethylene.

3.4. Polar Metal–Metal Bonds

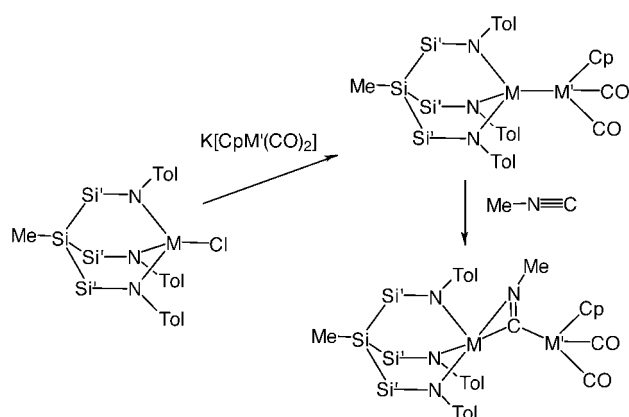
Systematic investigations into the reactivity of polar metal–metal bonds between metals of Group 4 and late transition metals were for a long time limited by the intrinsic instability of such compounds.^[118] Moreover, the large number of different ligands bound to early transition metals made a comparison of the reactivity of such systems impossible.^[119] As a consequence of this the work of Gade et al. was aimed at the development of a ligand system which prevented the self-destruction of the dinuclear compounds.^[120] In this way the metal–metal bond can be kinetically stabilized so that its reactivity towards a large number of substrates can be specifically investigated. The key step is the use of a new class of tripodal, trianionic ligands (Scheme 27). The stability of these ligand–metal bonds and the steric protection of the reaction centers can be modified by variation of the substituent R. The variable geometry of the ligand backbone, all-“C”,^[120, 121] tri-“Si”,^[122, 123] and all-“Si”,^[123, 124] allows the reaction to be optimized to the different size of the metals of the titanium triad.



Scheme 27. Tripodal trisamido ligands with variable backbone (M = metal of Group 4; R = silyl, aryl or alkyl; Si' = Me₂Si).

The reactions of monochloro complexes of titanium, zirconium, and hafnium stabilized by such tripod ligands with K[(C₅H₅)M'(CO)₂] (M' = Fe, Ru) gave heterodinuclear complexes with unbridged metal–metal bonds (Scheme 28).^[125] These dinuclear compounds react with, for example, methylisocyanide with insertion and are examples of a bimetallic variant of α -addition.^[126]

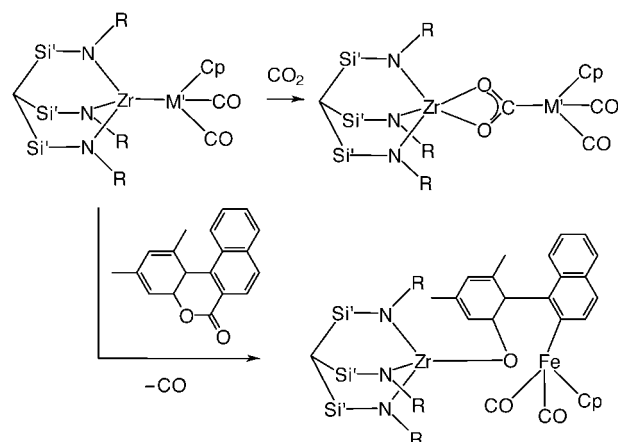
The general applicability of the concept of stabilization of bonds between metals of Group 4 and late transition metals by the use of multidentate amido ligands has also been



Scheme 28. Insertion of methyl isocyanide into polar metal-metal bonds ($M = \text{Ti, Zr, Hf}$; $M' = \text{Fe, Ru}$; $\text{Si}' = \text{Me}_2\text{Si}$).

demonstrated by the synthesis of stable Ti-Co complexes.^[127] The nature of the metal-metal bond between metals of the titanium triad and the late transition metals is to be regarded primarily as a classical σ bond. However, Fenske-Hall calculations on the system $[\text{HC}(\text{CH}_2\text{NH})_3\text{Ti}-\text{Fe}(\text{CO})_2\text{Cp}]$ also confirm π -donor-acceptor interactions which contribute to the stabilization of the metal-metal bond.^[128] This partial multiple bond character is stronger than in the corresponding Sn-Fe bonds and is favored by the energetically low-lying π -acceptor orbitals on the titanium center. Additional π -bond contributions are in agreement with a restricted rotation of both complex fragments around the vector of the metal-metal bond.^[125] Rotation barriers, however, can also be dictated by the steric interactions of the ligand peripheries. A good qualitative description of the bond polarity in unbridged Ti-Co or Zr-Co bimetal complexes^[129] is also possible by Bader analysis of the electron density (Baders AIM)^[130] and electron localization functions (ELF).^[131] The high partial charges of the complex fragments emphasize the strong polar character of the Ti-Co bond. With polycyclic amido ligands the bimetal complexes are not only kinetically inert, but are also thermodynamically more stable.

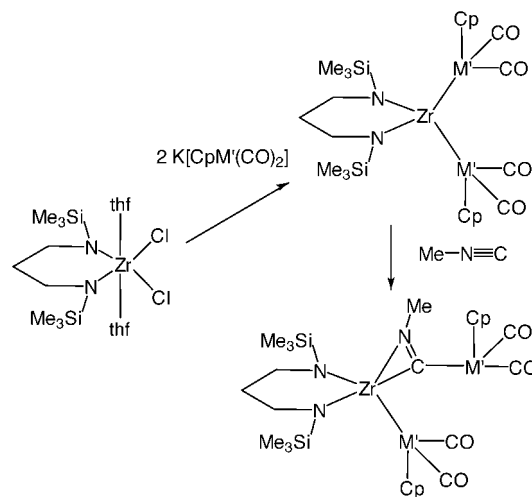
An interesting bimetallic activation of poorly reactive molecules occurs in the reaction of Zr-M' bimetal complexes ($M' = \text{Fe, Ru}$) with heteroallenes such as carbon dioxide (Scheme 29, top).^[132] Both the bonding mode and the



Scheme 29. Cooperative reactivity of heterobimetallic complexes ($M' = \text{Fe, Ru}$; $R = \text{C}_6\text{H}_4\text{F}$; $\text{Si}' = \text{Me}_2\text{Si}$).

bimetallic activation are unusual for carbon dioxide.^[133] The reaction of Zr-Fe bimetal complexes with lactones leads to ring opening with subsequent decarbonylation in which the lactone is simultaneously and thus cooperatively activated by both metal centers (Scheme 29, bottom).^[134]

If bis(amido) chelate ligands are used in place of the tripod ligands there is the possibility to use both remaining chloro ligands for the preparation of trinuclear complexes (Scheme 30).^[135] Analogous examples of metallocene-stabilized compounds^[119b,c] show an extreme instability, and



Scheme 30. Heterobimetallic complexes and selective insertion of methyl isocyanide ($M' = \text{Fe, Ru}$).

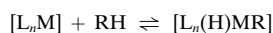
reactions with the Cp ligands of the zirconium fragment were observed. The introduction of the two $[\text{M}'(\text{C}_5\text{H}_5)(\text{CO})]$ units ($M' = \text{Fe, Ru}$) can be carried out sequentially. It is not possible in this way, however, to prepare mixed Zr-Fe-Ru complexes with different potassium salts. A selective reaction with one equivalent of methyl isocyanide is possible.

Unbridged polar metal-metal bonds may be kinetically and thermodynamically stabilized with suitable amido ligands and thus allow insights into details of the reactivity of such compounds and into cooperative activation steps.

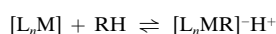
3.5. C-H Activation at d^0 Metal Centers

C-H activation at d^0 metal centers can be investigated very effectively with complexes of the type $[(t\text{Bu}_3\text{SiNH})_3\text{MR}]$ ($M = \text{Ti, Zr}$; $R = \text{alkyl, aryl}$) since these complex compounds eliminate hydrocarbons reversibly.^[136] The C-H activation mediated by transition metal complexes is one of the most fascinating sectors of organometallic chemistry.^[137, 138] Numerous electronically unsaturated metal complexes can activate the C-H bond in different ways:

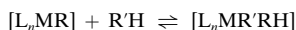
1) oxidative addition of a late transition metal^[139, 140]



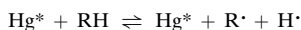
2) heterolytic activation by late transition metals in polar media^[141-143]



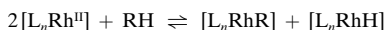
- 3) σ -bond metathesis (early ^[25a, 144, 145] and late transition metal complexes^[146])



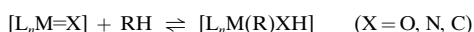
- 4) homolytic cleavage by UV-excited mercury atoms (Hg^*)^[147]



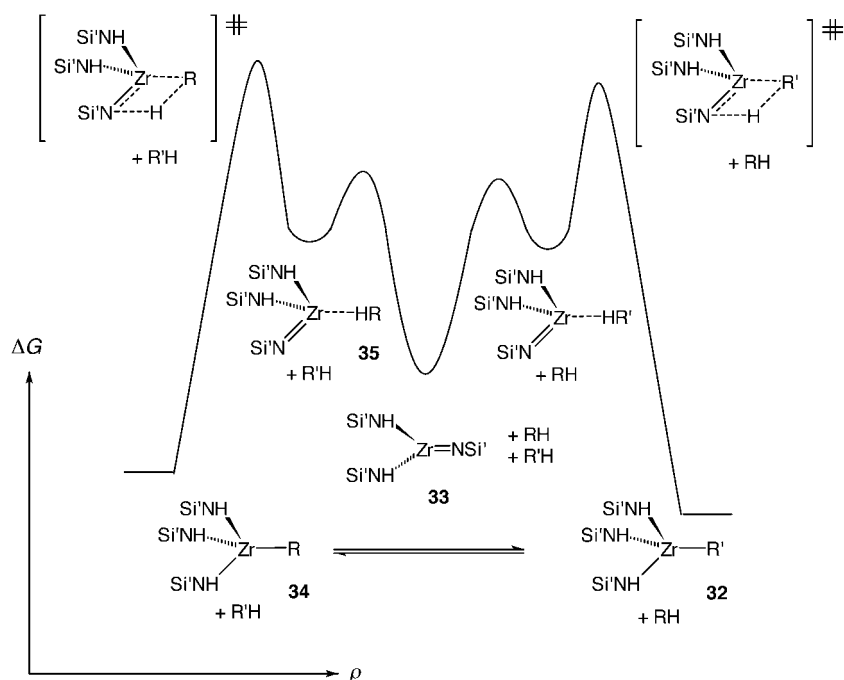
- 5) activation at porphyrin–Rh^{II} complexes^[148]



- 6) 1,2-additions at M=X systems ($X=O$,^[149] NR' ,^[150, 136] and CRR')^[151]



The possibilities for C–H activation listed here can be divided still further in principal into radical mechanisms without intermediate R–H bond interaction and concerted processes which involve such an interaction. The activation of C–H bonds at d⁰ metal imido complexes belong to the latter category (Scheme 31).^[152] Compounds of type **34** can be



Scheme 31. C–H activation by reversible 1,2-R–H elimination starting from $[(tBu_3SiNH)_3ZrR]$ ($Si' = tBu_3Si$; R = alkyl substituent).

prepared by three synthetic routes: salt elimination reactions with alkyllithium or Grignard reagents, the addition of unsaturated substrates to the metal hydride, and C–H bond activation. In the case of C–H activation the intermediate **33** is generated from **32** by thermal 1,2-R'–H elimination, and the subsequent 1,2-R–H addition gives **34**. Kinetic investigations on 1,2-R–H elimination and addition give insights into the mechanism of this C–H activation (Scheme 31). The isolation and characterization of the THF complex of **33** confirms the

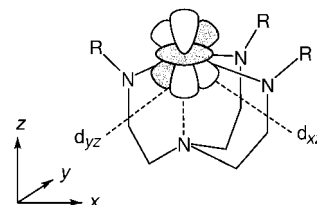
existence of such an intermediate. Studies with deuterated compounds (primary kinetic isotope effect) gave ratios of rate constants of 1,2-R–H and 1,2-R–D elimination which comply with an almost linear H atom transfer^[153] including a concerted C–H bond formation/N–H bond cleavage process with formation of a four-membered transition state. The existence of a four-membered transition state with a slightly deformed methyl group is confirmed by measurement of a secondary kinetic isotope effect. A linear relationship between $\Delta G^\ddagger$ of the 1,2-RH elimination step and the RH proton affinities verifies the existence of **35** as intermediate in the elimination and activation steps. If the bonding of an alkane or arene to a d⁰ center is considered in analogy to the deprotonation of an RH unit, then such a correlation should arise. The calculation of the total energy of the hypothetical molecule $[(H_2N)_2HN=Zr(\eta^2-CH_4)]$ relative to $[(H_2N)_2Zr=NH] + CH_4$ confirms a considerable energy gain by methane coordination.^[154] Also of interest is the comparison with d⁸ systems, where alkane complexes are considered intermediates in the activation of C–H bonds.^[155] Recently, such an intermediate could be directly established.^[156] The course of the 1,2-RH elimination and activation is summarized in Scheme 31. Current investigations of C–H bond activation in homogeneous systems are highly diverse.^[157] To

allow technical application of C–H bond activation, catalytic process management must be coupled with the functionalization of substrates. The radical oxidation of hydrocarbons is the most important application, where selective transformations represent a problem. The results published by Wolczanski et al.^[152] give an insight into the mechanistic details. Investigations on the selectivity of C–H activation at titanium d⁰ complexes have been reported recently, where alkoxy ligands were used to stabilize the high oxidation states.^[158]

4. Vanadium, Niobium, and Tantalum

4.1. Substrate Activation at “Half-Naked” Complexes

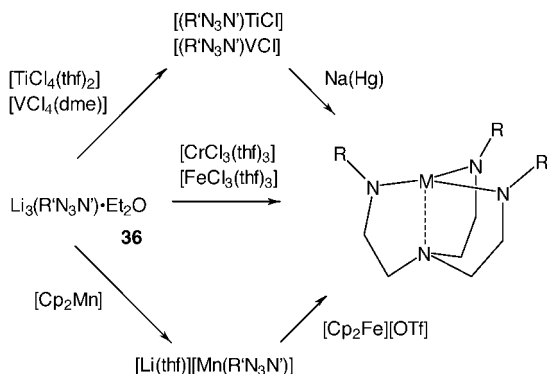
Trisamido amine ligands^[17, 18] coordinate transition metals in a tetradentate manner such that a sterically shielded C₃-symmetric reaction center is formed in which principally three orbitals are concentrated for substrate activation (Scheme 32). Two of



Scheme 32. Orbital relationships of the trisamidoamine complex fragment.

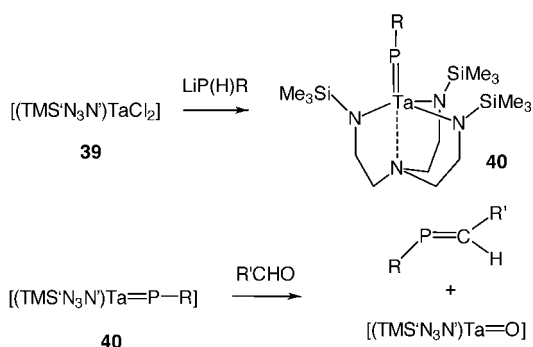
these can be regarded as π -type orbitals ($\approx d_{xz}$ and d_{yz}) and one as a σ -type orbital (d_{z^2}).^[18]

In trigonal-monopyramidal M^{III} complexes of the type $[(tBu(Me)_2Si^+N_3N^-)M]$ ($M = Ti, V, Cr, Mn, Fe$; $tBu(Me)_2Si^+N_3N^- = [(H_3C)_3C](H_3C)_2SiN(CH_2)_3N^-$ trianion), which can be synthesized as illustrated in Scheme 33, this “reactive pocket” is empty, and in this way “half-naked” transition



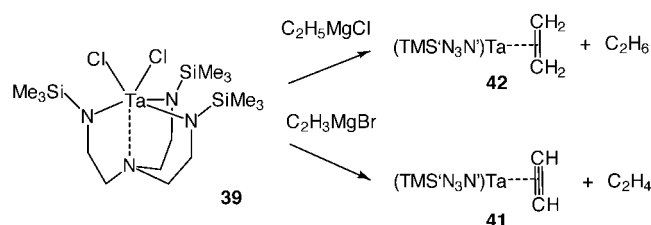
Scheme 33. Synthesis of “half-naked” transition metal complexes ($R = tBu(Me)_2Si$, $M = Ti$ (**37**), V, Cr, Mn ; $R = Me_3Si$, $M = V$ (**38**)). $R'_3N_3N^- = [RN(CH_2)_3N^-]$ trianion; $dme = 1,2$ -dimethoxyethane; $Tf = F_3CSO_2$.

metal complexes can be stabilized.^[159] Of interest is the observation that the direct salt metathesis reaction between **36** and VCl_3 or $TiCl_3$ adducts does not lead to the desired end product. The titanium complex **37** binds CO reversibly, which is unusual for d^1 complexes.^[160] The reactive pocket of the related **38** is set up for the oxidative addition of substrates. Thus, **38** reacts with aziridines, imines, or azides to form imido complexes, with propylene oxide, elemental selenium or sulfur, and $TePMe_3$ to form the corresponding chalcogenide complexes $[(TMS^+N_3N^-)V=X]$ ($TMS^+N_3N^- = [(H_3C)_3SiN(CH_2)_2]_3$ trianion; $X = O, S, Se, Te$).^[161] Analogous tantalum compounds may be obtained by the reactions of **39** with one equivalent of $[(Me_3Si)_3SiELi(thf)_2]$ ($E = Se, Te$) (Scheme 34).^[162] There is currently considerable interest in terminal chalcogenides, particularly the higher homologues, with regard to the synthesis of semiconductors.^[163] The reaction of **39** with $LiPHR$ affords phosphanidenetantalum(v) complexes such as **40** ($R = Ph, Cy$, and tBu), which react smoothly with aldehydes with the formation of phosphalkenes (Scheme 34).



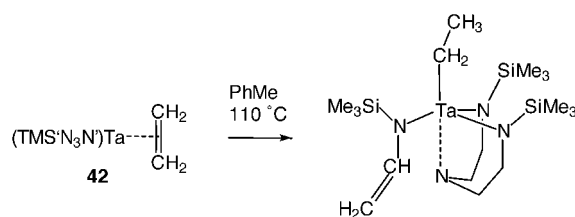
Scheme 34. Phosphinidenetantalum(v) complexes as phospho-Wittig reagents ($R = Ph, tBu$; $R' = tBu$).

Phosphaalkenes^[164] which are stabilized by conjugation^[165] or by sterically demanding substituents^[166] can be prepared by silyl migration^[165] or dehalogenation.^[166] Phosphaalkenes bound to a complex fragment are accessible by phospho-Wittig reactions.^[167] Scheme 34 outlines a new route for the preparation of phosphaalkenes. Of interest is the possibility to modify substituent R .^[168] In the first step “ $[(TMS^+N_3N^-)Ta=PLi]$ ” is generated in the presence of an excess of lithium and is then allowed to react selectively at low temperatures with $R'X$ ($X = Cl, Br$; $R' = Me, nBu, SiMe_3, SiMe_3Ph$). The reactions of **39** with alkyllithium or Grignard reagents are unusual.^[169] In the case of $MeLi$ a bisalkyl complex can be isolated, and the reaction with $C_6H_5CH_2MgCl$ affords an alkylidene complex by α -elimination.^[170] Analogously, lithium amides react smoothly to form the corresponding imido complex. Ethyl or vinyl Grignard reagents react with **39** to form the ethylene or acetylene complex, respectively (Scheme 35). Ethane or ethylene are eliminated simultaneously.



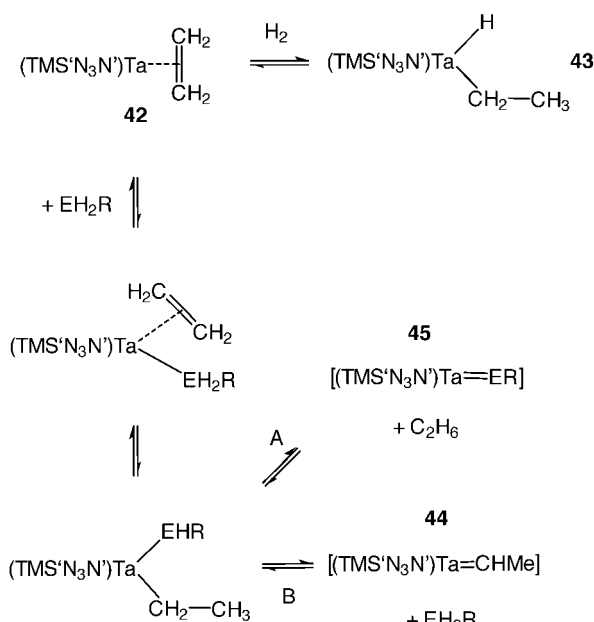
Scheme 35. Ethylene- and acetylenetantalum complexes by ethylene or acetylene elimination.

Unlike **41**, which is very stable and unreactive, **42** decomposes in solution (toluene) at room temperature by ligand decomposition in a first-order reaction (Scheme 36). Remarkably, there is no Si–N bond cleavage. Compound **42** is an



Scheme 36. Possible decomposition processes of triamidoamine ligands.

excellent starting material for the preparation of a reactive $[(TMS^+N_3N^-)Ta]$ complex fragment and reacts reversibly, for example, with hydrogen to form **43**. A catalytic amount of phenylphosphane converts **42** into **44** (Scheme 37), a stoichiometric amount of aniline gives the corresponding imido complex, and trimethylsilylarsane an unstable arsinidene complex analogous to **45**. The mechanism of the reaction of **42** with amines, phosphanes, and arsanes is summarized in Scheme 37. Reaction path A is not observed for $E = P$, and a catalytic amount of phosphane suffices to give a carbene complex selectively. Reaction path A is preferred if $E = N$ or As .



Scheme 37. Suggested mechanism for the reaction of $[(\text{TMS}'\text{N}_3\text{N}')\text{Ta}(\text{C}_2\text{H}_4)]$ with EH_2R ($\text{E} = \text{N}, \text{P}, \text{As}$).

Similar imido, phosphinidene and arsinidene complexes were published recently by Wolczanski et al. with the use of the tri(silyloxy)tantalum complex core.^[171]

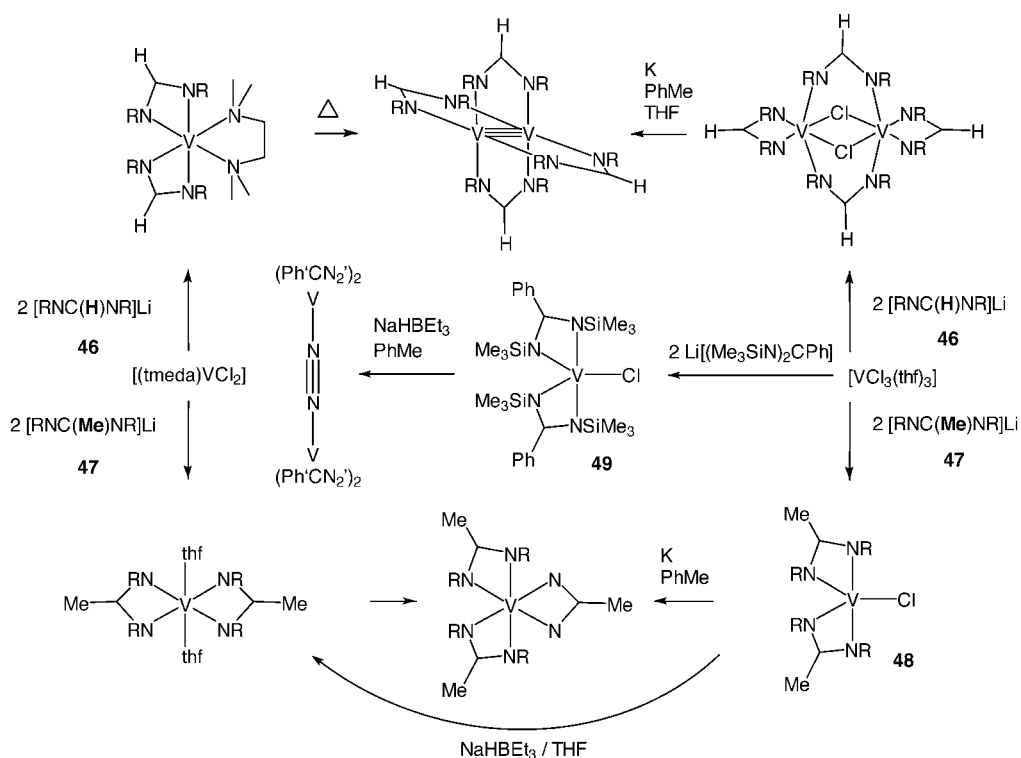
4.2. The Chemistry of Low-Valent Vanadium Complexes

Disproportionation and electron transfer reactions are the most frequently observed reaction pathways when complex compounds whose metals are in an unstable oxidation state decompose. A possible strategy to prevent undesired disproportionation reactions is to embed the metal center into an inert organic matrix. Few possibilities then exist for the molecular ensemble to rearrange and thus modify the oxidation state. This procedure is based on biochemical systems, and was used in the past to isolate transition metal complexes in unusual oxidation states.^[172] Sterically demanding, monodentate silyl or alkyl-amides or bidentate ligands such as amidinates are suitable for the stabilization of low-valent vanadium complexes. The reactivity of vanadium(II) amidinato complexes is only poorly understood since even the smallest change in the steric demand of this ligand

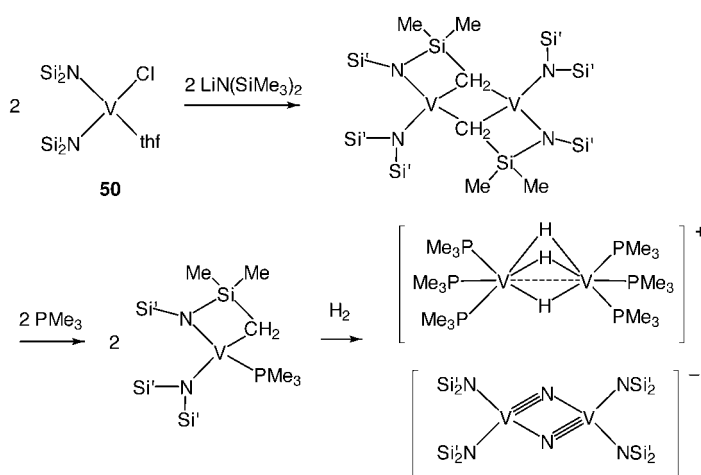
results in the preference for different reaction channels. One fascinating area is the chemistry of vanadium(II) complexes since such compounds can fix N_2 ^[173] and produce short V–V triple bonds.^[174] Vanadium complexes are also interesting as olefin polymerization catalysts.^[84] The products of the reactions of **46** and **47** with $[(\text{tmeda})\text{VCl}_2]$ or $[\text{VCl}_3(\text{thf})_3]$ differ drastically from each other, although the steric differences between the ligands are slight (Scheme 38).^[175]

If instead of **48** the analogous complex **49** is reduced with NaHBET_3 in toluene a dinitrogen complex is formed (Scheme 38).^[176] Alkyl- and allylvanadium(III) complexes may be obtained in good yields by the reaction of **49** with alkyl or allyl Grignard reagents.^[177] These compounds thus are characterized by an exceptionally high thermal stability.

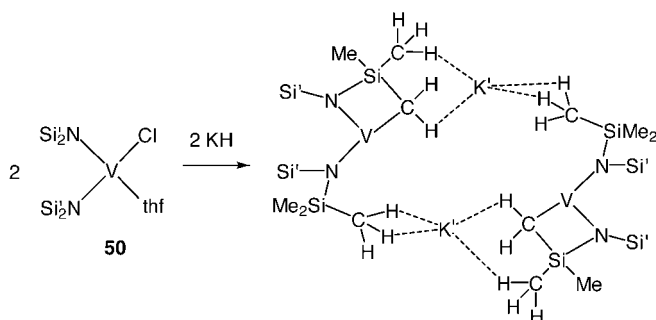
The classical bis(trimethylsilyl)amido ligand, which was introduced into vanadium chemistry by Bradley et al.,^[178] is not inert and tends towards σ -bond metathesis with the formation of a vanadacyclobutane ring (Scheme 39, top).^[179] The V–C bond formed is very reactive.^[180] Thus, for example, isocyanides,^[181] CO, and alkynes are activated or inserted,^[179, 182] and pyridine is partially hydrogenated.^[182] Particularly noteworthy is the reaction of the vanadacyclobutane with H_2 in the presence of PMe_3 (Scheme 39, below).^[183] The hydrido unit is probably formed by hydrogenolysis of both the V–CH₂ and the V–N(SiMe₃)₂ bonds. The formation of $(\text{Me}_3\text{Si})_2\text{NH}$ as by-product supports this. Silane is not found, which supports the supposition that the nitrido ligand of the anion originates from molecular nitrogen which is present during the hydrogenation. Attempts at the isolation of a dinitrogen intermediate have been unsuccessful. Analogous experiments without nitrogen gave only pyrophoric oils whose characterization was difficult due to paramagnetism. The corresponding alkyl complex may be synthesized from



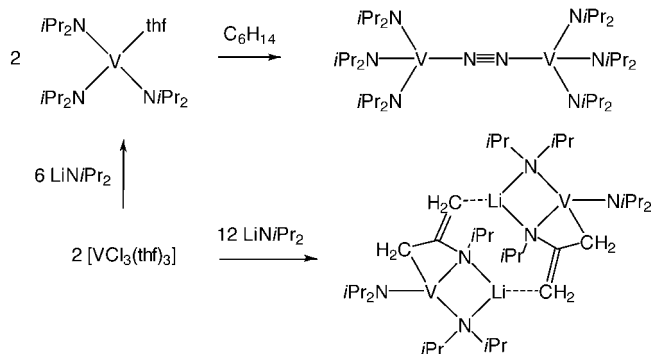
Scheme 38. Reactivity of amidinatovanadium complexes in relationship to the smallest ligand variations.

Scheme 39. Reactivity of silylamidovanadium(III) complexes ($\text{Si}' = \text{SiMe}_3$).

50^[184] by reaction with MgMe_2 .^[185] The reactivity of this compound has been systematically and thoroughly investigated.^[185, 186] The reaction of **50** with KH is interesting because supramolecular organization occurs through agostic $\text{C-H}\cdots$ potassium interactions with the formation of a V_2K_2 ensemble (Scheme 40).^[187]

Scheme 40. Supramolecular organization by agostic $\text{C-H}\cdots$ potassium interactions ($\text{Si}' = \text{SiMe}_3$; $\text{K}' = \text{K}(\text{thf})_2$).

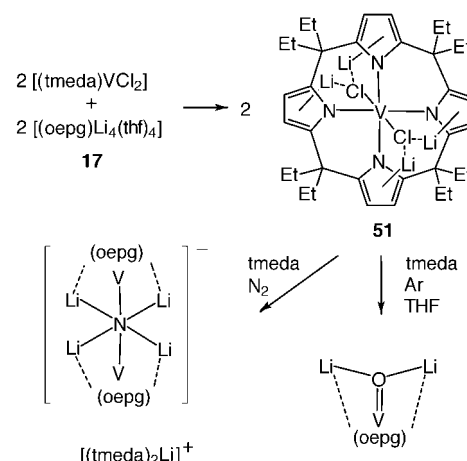
When aryl- and alkylamido ligands are used in place of the $(\text{Me}_3\text{Si})_2\text{N}$ anion a vanadium– N_2 complex is isolated (Scheme 41).^[188] An isostructural Nb–dinitrogen complex



Scheme 41. Reactivity of alkylamidovanadium(III) complexes.

can be stabilized by Cy_2N ligands.^[189] If an excess of lithiated amine (six equivalents) is used in the reaction of $[\text{VCl}_3(\text{thf})_3]$ with $\text{LiN}i\text{Pr}_2$ C–H activation of the amido ligand and generation of a vanadate complex occurs (Scheme 41).

In the reaction of **17** with $[\text{VCl}_3(\text{thf})_3]$ in toluene (room temperature) an inolate complex is formed and THF fragments together with C_2H_6 are eliminated.^[190] The reaction of **17** with $[(\text{tmeda})\text{VCl}_2]$ gives the highly reactive complex **51** (Scheme 42)^[191] in which the vanadium is surrounded octahe-



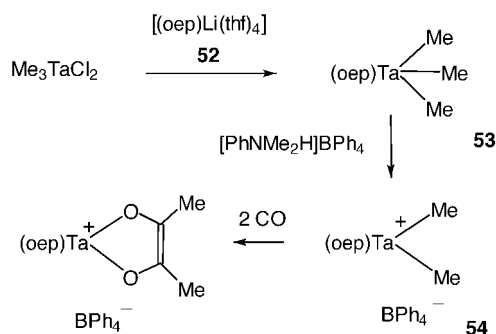
Scheme 42. Reactivity of oepg–vanadium complexes.

drally by four N atoms and two Cl atoms. Complex **51** reacts with N_2 in the presence of tmeda to afford nitrido clusters, and with THF in the absence of dinitrogen to give the terminal oxo complex.

It can be generally said that amido complexes of low-valent vanadium are very reactive, amido ligands rarely behave inertly, and the numerous activation reactions are currently poorly understood. One of the main problems appears to be the frequent paramagnetism which makes targeted investigations of the compounds in solution complicated.

4.3. Compounds with Metals in the High Oxidation State and the Analogy to Group 4

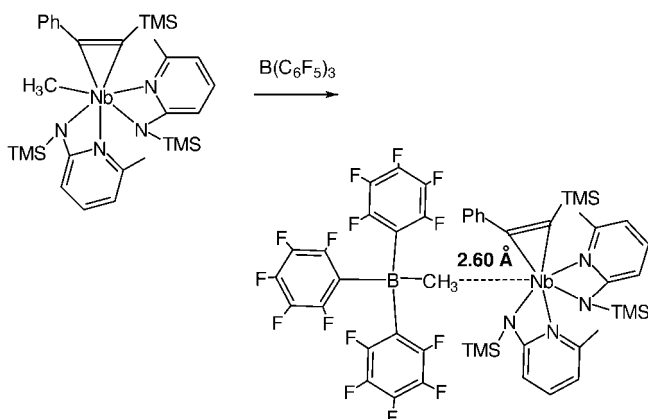
In contrast to vanadium, in the higher homologues of this triad, a tendency towards stabilization of the high oxidation state is observed. Niobium and tantalum compounds, unlike metal complexes of Group 4, have a shadowy existence. Noteworthy is the first ditantalum complex with a Ta–Ta bond which is not stabilized by further bridging ligands.^[192] A homobimetal complex with an unbridged Ta–Ta bond is formed in the reaction of TaCl_5 with four equivalents of LiNCy_2 . The metal–metal distance is 2.8484(7) Å. An efficient entry into tantalum–porphyrin chemistry is made possible with Me_3TaCl_2 , which reacts with **52** to form **53** (Scheme 43).^[193] In contrast, salt elimination routes with TaCl_5 fail. By reaction with $[\text{PhMeNH}]\text{BPh}_4$ **53** can be converted into **54**, which may be regarded to be a porphyrin analogue of



Scheme 43. CO insertion and coupling at cationic tantalum complexes.

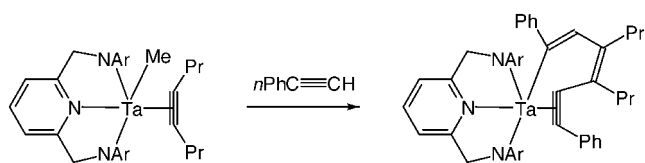
Schrock's dimethyltantallocene cation.^[194] Compound **54** does not react with ethylene, acetone, or CO₂, but reacts smoothly with CO to form the enediolate complex. Benzamidinato complexes of tantalum are accessible by analogous routes.^[195] The starting material of choice is again Me₃TaCl₂.

Reactions of olefins or even their polymerization are unsuccessful in spite of an analogy to cationic metallocenes of Group 4. The partial abstraction of a methyl group appears to be essential, and succeeds with aminopyridinato and niobium alkyne complexes (Scheme 44).^[196] Such compounds polymerize ethylene as "one-component system" and dimerize higher alkenes selectively, for example 1-butene to 2-ethylhexene in the presence of MAO.

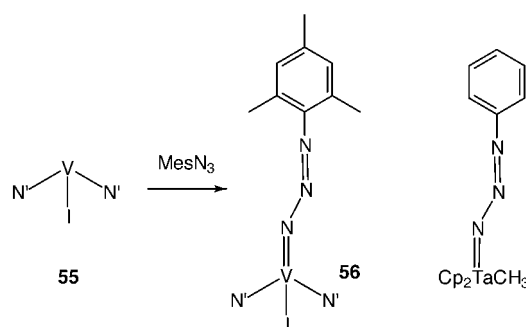


Scheme 44. Partial abstraction of a methyl group in aminopyridine(TMS-Ap)-alkyne complexes of niobium for the generation of active ethylene polymerization systems.

Alkynetantalum complexes with pyridine diamido ligands are suitable model systems to investigate the mechanism of the coordination polymerization of alkynes because successive alkyne insertion and coupling within the coordination sphere of tantalum occurs (Scheme 45).^[197]

Scheme 45. Sequential alkyne insertion and coupling (Ar = 2,6-*i*Pr₂C₆H₃).

A standard reaction for the preparation of imido complexes is the reaction of an organic azide with a metal complex which is capable of two-electron oxidation.^[198] Although organo-azide complexes have been assumed to be intermediates in such reactions, until now none has been completely characterized.^[199] The isolation of such a compound (**56**) has been achieved with the vanadium-amido-iodide complex **55** and mesityl azide at low temperatures (Scheme 46).^[200] The thuscomplexed MesN₃ can be regarded as a diazaenylimido ligand (Scheme 46, left). Compound **56** eliminates N₂ at temperatures above 50 °C and is converted into the corresponding mesitylimido complex. The stabilization of such an intermediate with the [Cp₂TaCH₃] complex fragment was also published (Scheme 46, right).^[201]

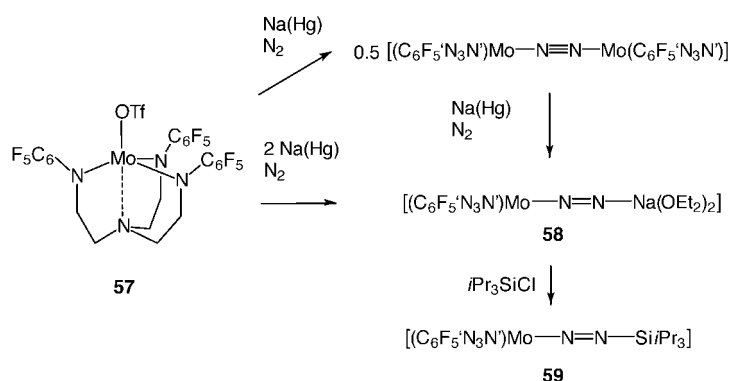
Scheme 46. Diazaenylimido complexes (N' = N[C(CD₃)₂CH₃][3,5-(F,Me)C₆H₃]).

Numerous mixed chalcogenide-chalcogenolate compounds of vanadium have been prepared and comprehensively characterized by Arnold et al. Of note is the systematics of the chemical shifts in the ⁵¹V NMR spectra of such amido complexes,^[202] which, for example, allow a quantification of electronic differences between terminal oxo, seleno, and telluro ligands.

5. Chromium, Molybdenum, and Tungsten

5.1. Cleavage of the Nitrogen–Nitrogen Triple Bond

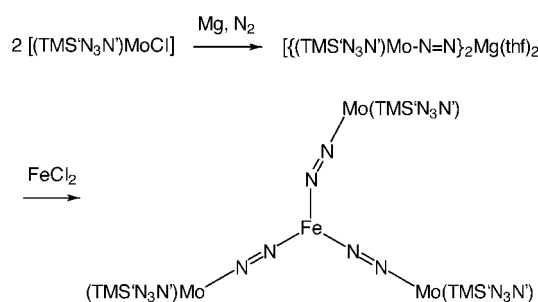
Trisamidoamine complexes of the type [(C₆F₅'N₃N')MCl] (M = Mo, W; C₆F₅'N₃N' = [C₆F₅N(CH₂)₂]₃N trianion) may be obtained in good yields by salt elimination reactions in which Et₃N acts as a base.^[203] The reaction of the respective molybdenum complex with TMSOTf gives **57**, the reduction of which with one or two equivalents of Na(Hg) in the presence of N₂ leads to dinitrogen complexes (Scheme 47). Of note here is that N₂ can be activated stepwise and then partially reduced. Similarly, partially reduced dinitrogen ligands have already been described for vanadium complexes.^[204] The reaction of **58** with *i*Pr₃SiCl gives **59** and underlines the nucleophilic character of the β-nitrogen atom of **58** as well as the stability of the [(C₆F₅'N₃N')Mo(N₂)] fragment. A comparison with the nitrogenase center of *Azotobacter vinelandii* is interesting in this respect. Its X-ray structure analysis^[205] allowed for the first time a detailed insight into the structure of such enzymes, and posed the



Scheme 47. Binuclear and partially reduced dinitrogen complexes.

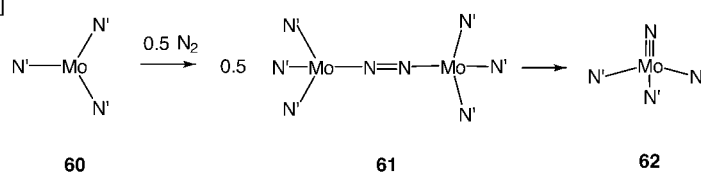
question whether dinitrogen activation takes place at the Fe or the Mo center.^[206] Here, molybdenum is coordinated with three sulfur atoms, a nitrogen donor, a histidine moiety, and homocitrate. A principle argument proposed against activation at the octahedrally coordinated Mo center is its coordination saturation. However, ligand cleavage, for example by protonation or electron transfer processes, must be considered. If the immediate environment of the molybdenum in the nitrogenase center is regarded as a combination of three anionic sulfide functions and a nitrogen donor. Parallels can be drawn with the [(C₆F₅'N₃N')Mo] fragment, which is stabilized by three anionic amido functions and one nitrogen donor function. This infers that the ["S₃N"]Mo^{III} unit of the enzyme could activate N₂ by homocitrate cleavage, analogous to the [(C₆F₅'N₃N')Mo] fragment. In the latter case it is not homocitrate that is expelled, but the anionic triflate ligand is reductively removed. The question whether N₂ in the [(C₆F₅'N₃N')Mo] system is fixed by a d³ or d⁴ center cannot be answered with certainty. However, activation at the molybdenum(III) fragment appears plausible since a dinitrogen complex is formed in the reaction of [MoCl₃(thf)₃] with "Li₃(*t*BuMe₂SiNCH₂CH₂)₃N" in the presence of N₂.^[207] Equally interesting in respect to analogies with Fe–Mo nitrogenase centers are the heterodinuclear complexes with a dinitrogen ligand as bridge between the iron and the molybdenum center. A structurally interesting compound of this type is formed by an unusual salt elimination reaction (Scheme 48).^[208] Furthermore, the synthesis and structure of a uranium–molybdenum–dinitrogen complex has been recently reported.^[209]

The activation and partial reduction of N₂ at the [(C₆F₅'N₃N')Mo] fragment can be carried out, but not, however, cleavage of the N–N triple bond.^[210] Compound **60**



Scheme 48. An unusual Fe–Mo–dinitrogen complex.

is suitable for this purpose (Scheme 49).^[211] If **60** is exposed to an N₂ atmosphere at –35 °C the violet dinitrogen complex **61** is formed, which with a half-life of 35 min at 30 °C rearranges into two equivalents of the nitrido complex **62**.^[212] The same reaction in an ¹⁵N₂ atmosphere give the isotopically labeled

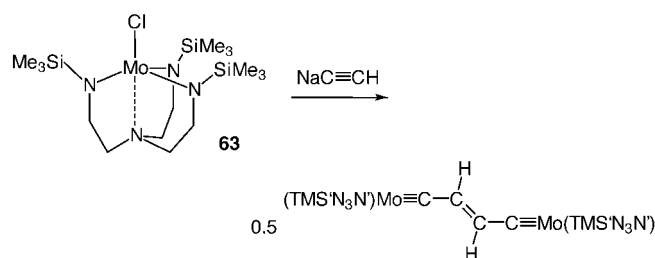
Scheme 49. The cleavage of the N–N triple bond by Mo^{III} complexes (N' = Ar(*t*Bu₃)N).

62, which confirms the source of the nitrido ligand. The thermodynamic driving force of dinitrogen cleavage is the formation of a nitrido complex, as the metal–nitrogen triple bond is the most stable of all metal–ligand bonds.^[213] A comprehensive structural characterization of the violet, paramagnetic intermediate **61** or its analogous ¹⁵N₂ complex by EXAFS^[214] and Raman spectroscopy together with kinetic data on the conversion to the corresponding nitrido complex gave a detailed insight into the course of the N– bond cleavage.^[215] The conversion of **61** into two equivalents of **62** takes place by a first-order reaction. The data of the kinetic isotope effect of the bond cleavage, Mo₂N₂ versus Mo₂¹⁵N₂, confirm that the N–N cleavage is the rate-determining step. Raman spectroscopic studies showed a bond order of two for the N₂ ligand in **61**, and EXAFS measurements showed a linear Mo–N=N–Mo arrangement. Amidomolybdenum complexes are suitable systems to model elemental steps of biological nitrogen activation at a molecular level. It was possible to demonstrate that the N–N bond cleavage need not take place via N–H compounds as intermediates.

5.2. Spontaneous α -Elimination in the Formation of Carbyne Complexes

The classical decomposition reaction of a kinetically labile metal–carbon bond is β -H elimination with the formation of a hydrido complex and release of the corresponding olefin. There may also be parallel α -H elimination with the formation of carbene or carbyne complexes, familiar from the chemistry of the metals of Groups 5 and 6. Both α - and β -elimination has been observed with alkylmolybdenum complexes stabilized by TMS'N₃N' ligands.^[216]

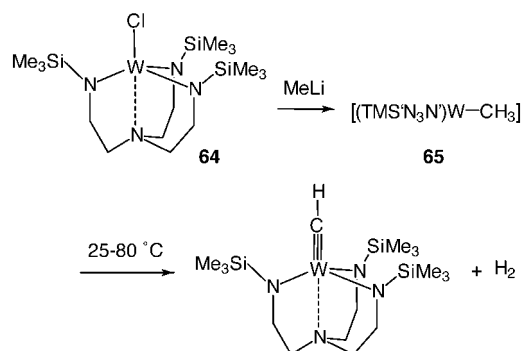
The reactions of **63** with MeLi or LiC≡CR (R = Me, Ph, SiMe₃) give paramagnetic d²-molybdenum methyl or alkynyl complexes, but the reaction with NaC≡CH leads to a diamagnetic d⁰-molybdenum acetylene coupling product (Scheme 50).^[207] Such a coupling can be compared with acetonitrile couplings to d²-tantalum and -niobium centers.^[217] It confirms the high oxidation tendency of the [(TMS'N₃N')Mo]⁺ fragment. Paramagnetic molybdenum complexes of the type [(TMS'N₃N')MoR] (R = alkyl substituent) are capable of both α - and β -eliminations if the corresponding H atoms are present. Where R = cyclopentyl β -



Scheme 50. Alkyne coupling by the formation of carbyne complexes.

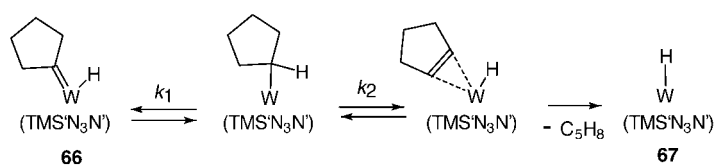
elimination leads to the formation of the hydridocyclopentene complex and the hydridocyclopentylidene complex is formed by α -elimination. The former process occurs more than six orders of magnitude more slowly than the formation of the carbene complex.^[216]

The corresponding tungsten complexes are significantly more capable of α -elimination than alkylmolybdenum complexes. Thus carbyne complexes are formed by α,α -eliminations.^[218] Compound **64** reacts with MeLi to form the alkyl complex **65** which in the temperature range of 25–80 °C is transformed into the corresponding methylidyne complex with loss of H₂ (Scheme 51).^[219] Analogously the reaction of

Scheme 51. Spontaneous α,α -elimination.

64 with LiCH₂R gives carbyne complexes of the type [(TMS'N₃N')W≡CR] (R = Me, Pr, CMe₃, SiMe₃). Because of the steric shielding of the three Me₃Si groups a unimolecular process which occurs via a carbenehydrido complex intermediate is assumed to take place here. In general, the formation of the catalytically active species in classical alkene or alkyne metathesis systems can be explained by such dehydrogenation reactions of alkyl ligands. Analogous to the reaction described in Scheme 51 is the reaction of [(PMe₃)₄WCl₂] with AlMe₃, which leads to *trans*-[Cl(PMe₃)₄W≡CH].^[220]

The transformations of a polyhydridorhenium complex^[221] and an alkylmolybdenum compound^[222] show only a distant relationship. If **64** is allowed to react with cyclopentylolithium α,α -elimination is blocked and the reaction remains at the stage of the carbene–hydrido complex **66** (Scheme 52).^[223] Product **66** is unstable and changes into the paramagnetic compound **67** with the loss of cyclopentene. The reaction of **64** with α -D-cyclopentylolithium at low temperatures gives the kinetically preferred intermediate **66** with “deuterido ligand”, which confirms that in this system α -cleavage occurs faster

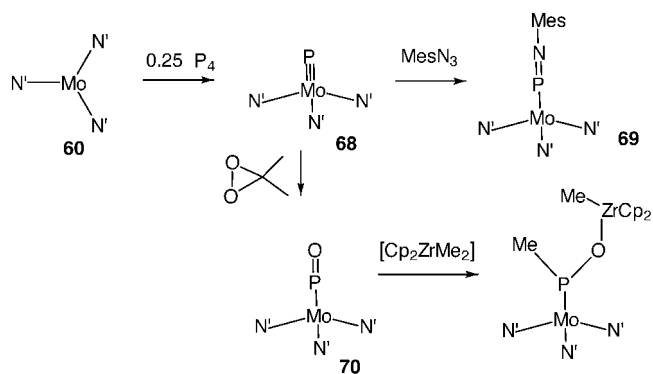
Scheme 52. α - versus β -elimination.

than β -elimination under the given conditions.^[224] At temperatures above 0 °C the D atom wanders to the cyclopentylidene ligand, first to the β -position, then to the γ -position. After cyclopentene cleavage and the formation of the thermodynamically stable final product **67**, statistical deuteration of the cyclopentene is found. Scheme 52 summarizes the equilibrium where $k_1 > k_2$. The preference of α -elimination^[225] over β -H atom cleavage appears to occur more frequently than is assumed but is difficult to confirm.

5.3. Complexes with Phosphorus and Arsenic as Terminal Ligands

Doubly or triply bridged P₁ ligands in binuclear or trinuclear metal complexes are well known.^[226] An unbridged, terminal P₁ ligand (phosphido ligand) was first published simultaneously by Cummins et al.^[227] and Schrock et al.^[228] in 1995.^[229] Ten years before the existence of the M≡P species had already been discussed.^[230] The tendency of compound **60** to react with N₂^[212] or N₂O^[211] by N–N bond cleavage to form the nitrido complex and the affinity of the [(TMS'N₃N')W] fragment for the spontaneous formation of metal–carbon triple bonds^[223, 219] suggest that both systems are set up for the stabilization of a terminal P₁ ligand.

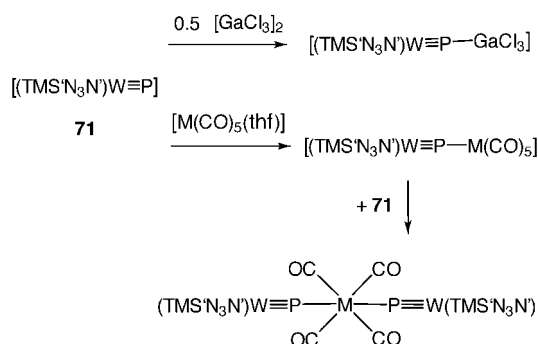
In analogy to dinitrogen cleavage, **60** reacts smoothly with 0.25 equivalents P₄ to form **68** (Scheme 53). The Mo–P distance is 2.119 (4) Å. The derivatization of **68** with mesityl

Scheme 53. Preparation and reactivity of phosphidomolybdenum complexes (N' = Ar(*t*Bu_D)N).

azide leads to the diamagnetic complex **69** (Scheme 53). If **68** is reacted with elemental sulfur a phosphorus monosulfide complex can be isolated. Analogous to this is the reaction with dimethyldioxirane, which gives the corresponding phosphorus monooxide complex. Compound **70** reacts with Cp₂ZrMe₂ to afford the zircon oxane by methyl transfer (Scheme 53). The

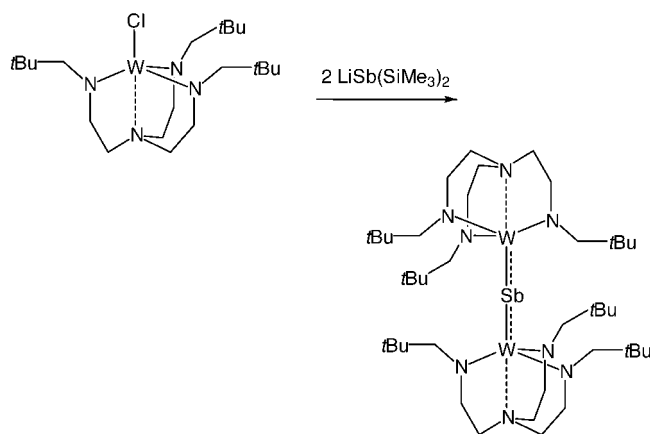
metal–phosphorus triple bond is also stabilized on the $[(\text{TMS}'\text{N}_3\text{N}')\text{M}]$ fragment.^[228] Thus **60** and **64** react with one equivalent of $\text{LiPPh}(\text{H})$ to give the intermediate $[(\text{TMS}'\text{N}_3\text{N}')\text{M}-\text{PPh}(\text{H})]$ ($\text{M} = \text{W}, \text{Mo}$), and with a second equivalent to give $[(\text{TMS}'\text{N}_3\text{N}')\text{M}=\text{P}]$ ($\text{W}-\text{P}$ bond length 2.162(4) Å). The reaction proceeds significantly faster with the tungsten complex.^[231]

The reaction of **71** with $[\text{M}'(\text{CO})_5(\text{thf})]$ ($\text{M}' = \text{Cr}, \text{W}$) leads to structurally interesting homo- and heterobimetal complexes^[232] and with $[\text{GaCl}_3]_2$ to form a $\text{Ga}-\text{P}$ adduct^[233] (Scheme 54). With $\text{LiAsPh}(\text{H})$ a compound of the type



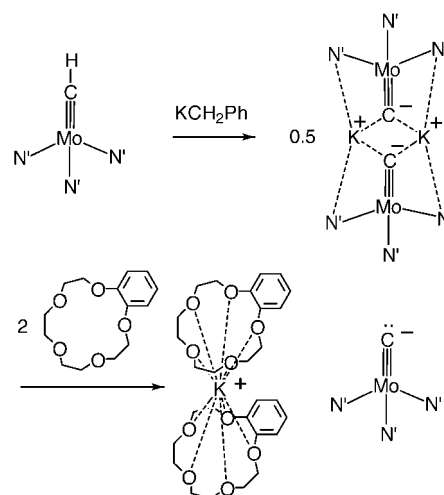
Scheme 54. Phosphido complexes as “neutral ligands” ($\text{M} = \text{Cr}, \text{W}$).

$[(\text{TMS}'\text{N}_3\text{N}')\text{M}=\text{As}]$ ($\text{M} = \text{Mo}, \text{W}$) is obtained.^[232, 234] The $\text{W}-\text{As}$ distance is 2.2903 (11) Å. The $[(\text{TMS}'\text{N}_3\text{N}')\text{W}]$ fragment cannot be used for the preparation of an antimonido or bismuthido complex since the steric demand of the $\text{TMS}'\text{N}_3\text{N}'$ ligand is too large to enable a substitution of the chloro ligand. If a $\text{R}'\text{N}_3\text{N}'$ anion ($\text{R} = \text{neopentyl}$) is used as ligand a compound is isolated in which the antimony atom acts as a symmetrical bridge between two tungsten centers (Scheme 55).^[235]



Scheme 55. Antimony as a bridging ligand.

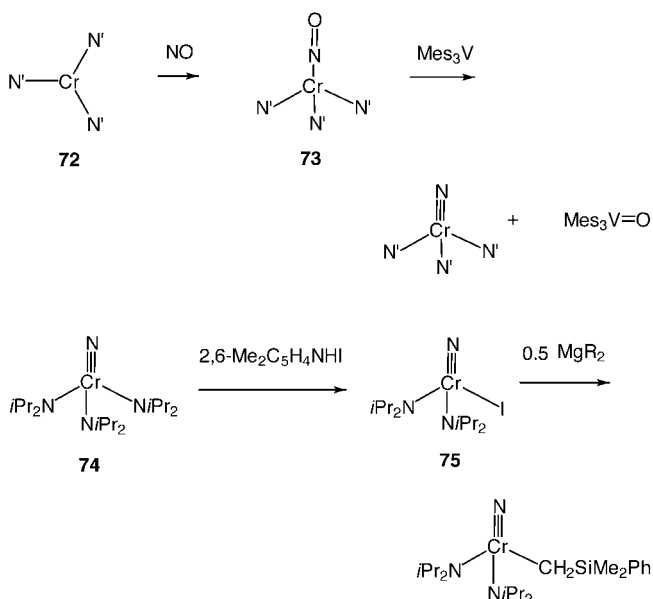
The use of multidentate amido ligands allowed the synthesis of stable phosphido and arsenido complexes for the first time. Not only metals of Group 15 can be terminal ligands, but also carbon. This leads to terminal carbides.^[236] *tert*-Butylamido ligands such as the $\text{Ar}(\text{tBu}_D)\text{N}$ anion ($\text{Ar}(\text{tBu}_D)\text{N} = [3,5-(\text{CH}_3)_2\text{C}_6\text{H}_3]$ [$(\text{H}_3\text{C})(\text{D}_3\text{C})_2\text{C}]$ anion; $\text{tBu}_D = \text{C}(\text{CH}_3)(\text{CD}_3)_2$) are suitable for the synthesis of such species (Scheme 56).



Scheme 56. Carbon as terminal ligand ($\text{N}' = \text{Ar}(\text{tBu}_D)\text{N}$).

5.4. Unusual Transfer Reactions between Metal Complexes

Intermetallic atom transfer reactions have until now been extensively investigated with the example of the nitrogen atom.^[237] The synthetic potential of such reactions appears large if the parallel to organic chemistry is considered. Atom transfer reactions between different metal complexes is an excellent method for the preparation of chromium–nitrido complexes.^[238] The reaction of, for example, **72** with NO leads to **73** (Scheme 57, top), a compound which then is transformed with Mes_3V into the nitrido complex by oxygen transfer when $[\text{Mes}_3\text{V}=\text{O}]$ is formed. An intermetallic $\text{N}-\text{O}$ bond cleavage is unusual^[239] and must be regarded as the inversion of the oxidation of a terminal nitrido complex to a nitrosyl compound.^[240] Compound **74** is formed analogously and reacts with 2,6-lutidinum iodide to form **75**, which can be



Scheme 57. $\text{N}-\text{O}$ bond cleavage by two metal centers ($\text{N}' = \text{Ar}(\text{tBu}_D)\text{N}$, $i\text{Pr}_2\text{N}$; $\text{R} = \text{CH}_2\text{SiMe}_2\text{Ph}$).

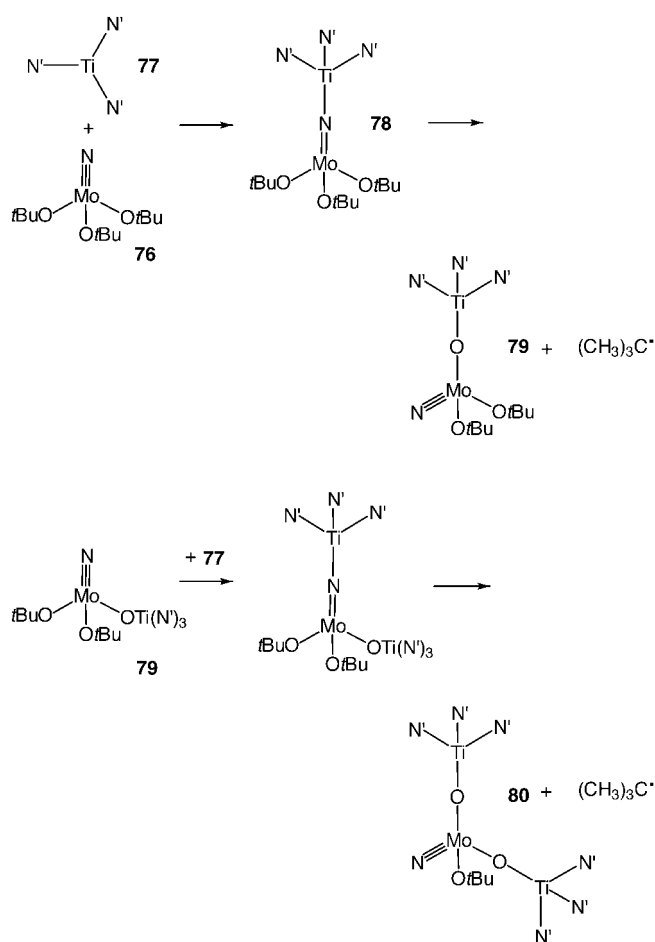
alkylated with 0.5 equivalents of $\text{Mg}(\text{CH}_2\text{SiMe}_2\text{Ph})_2$ (Scheme 57, bottom).^[241]

A nitrogen atom transfer and the cleavage of the dinitrogen triple bond is observed in the system $[\text{N}'_3\text{Mo}]/[\text{O}'_3\text{Mo}]/\text{N}_2$ ($\text{N}' = \text{Ar}(t\text{Bu}_D)\text{N}$, $\text{O}' = t\text{BuO}$).^[242] The reaction of $[\text{O}'_3\text{Mo}=\text{N}]$ with $[\text{N}'_3\text{Mo}]$ in a N_2 -free atmosphere affords $[\text{O}'_3\text{Mo}=\text{MoO}'_3]$ and $[\text{N}'_3\text{Mo}=\text{N}]$ quantitatively. This shows that the nitrido ligand transfer from alkoxy to the amido system is irreversible. The analogous reaction in a $^{15}\text{N}_2$ atmosphere leads quantitatively to a 1:1 mixture of $[\text{N}'_3\text{Mo}=\text{N}]$ and $[\text{O}'_3\text{Mo}=\text{N}]$ with the enrichment of both $^{15}\text{N}_2$ isotopomers being about 40%. That means that in this system, the $[\text{O}'_3\text{Mo}]$ fragment is involved in the N_2 activation and cleavage of the N–N bond with formation of an nitrido complex. Since the nitrido ligand is transferred irreversibly from the alkoxy complex to $[\text{N}'_3\text{Mo}]$, the isotopomer $[\text{O}'_3\text{Mo}=\text{N}]$ can only be formed by $^{15}\text{N}_2$ activation. Since the reaction of $[\text{MoCl}_3(\text{thf})_3]$ with three equivalents of LiOtBu in the presence of N_2 gives $[\text{O}'_3\text{Mo}=\text{MoO}'_3]$ quantitatively, the “[$\text{O}'_3\text{Mo}$]” system alone is not capable of activating N_2 . An intermediate $[\text{N}'_3\text{Mo}-\text{N}=\text{N}-\text{MoO}'_3]$ must be invoked. This decomposes into $[\text{O}'_3\text{Mo}=\text{N}]$ and $[\text{N}'_3\text{Mo}=\text{N}]$, when finally $[\text{O}'_3\text{Mo}=\text{N}]$ transfers the nitrido ligand to $[\text{N}'_3\text{Mo}]$. Model compounds for such N and P atom transfer reactions have been described.^[243] A novel transfer reaction is the constructional reaction of $\text{Mo}-\text{Ti}-\mu\text{-oxo}$ complexes by radical, homolytic C–O bond cleavage in alkoxy ligands. Formally, an alkyl radical in the periphery of a $[\text{Mo}=\text{O}]$ or a $[\text{Mo}=\text{N}]$ fragment, for example a $t\text{Bu}$ radical, is substituted by a titanium complex radical (Scheme 58).^[244]

The reaction of **76** with **77** leads in the first step to the μ -nitrido complex **78**, which is stable at temperatures below -30°C and which isomerizes to **79** with the release of a $t\text{Bu}$ radical in a first-order reaction (Scheme 58). The addition of further **77** leads to **80** and decomposition products of the $t\text{Bu}$ radical where again a $\mu\text{-N}$ intermediate can be observed. The addition of a further equivalent of **77** does not result in further substitution since the system is sterically “overloaded”. A comparable reaction sequence is observed when instead of **76** the compound $[(t\text{BuO})_2\text{Mo}(\text{O})_2]$ is used. Analogous reactions between $[(i\text{PrO})_3\text{V}=\text{O}]$ and **77** stop at the $\mu\text{-oxo}$ complex stage.^[245]

6. Conclusions

Over the last few years especially, amido ligands have greatly enriched the chemistry of the early transition metals and have thus ended the fixation with cyclopentadienyl ligands as control units for the reactivity of such complexes. The real advantages of amido ligands lie in the wide scope of possibilities for the construction of complex compounds with well-defined reaction centers. Focusing on the construction of a Cp equivalent brought only little impetus. In addition to investigations of reaction mechanisms, the most significant advances of amidometal chemistry have been made in the activation and stabilization of unusual species and molecules. The question of consecutive stoichiometric reactions or even catalytic use is a topic for the future.



Scheme 58. $\text{Mo}-\text{Ti}-\mu\text{-oxo}$ complexes by radical C–O bond cleavage.

Little attention has hitherto been paid to the amido complexes of the later transition metals. The “hard” amido ligand is not adapted to the “soft” metals of these triads, which is why there are so few compounds of that type. The reactivity of the M–N bond of these metals should differ substantially from those of the early transition metals. Inert complex fragments probably cannot therefore be generated, although “reactive amido ligands”, capable of inserting unsaturated substrates, remain a possibility. C–N couplings are amongst the most important of reactions.

Multidentate ligands play an important role in supramolecular chemistry. Hitherto little has been reported on the use of amido ligands. Can the many possibilities for the construction of polyfunctional ligands not also be used here, for example in the preparation of microporous metalloorganic materials and zeolite analogues (zeotypes)? Anionic ligands should stabilize structural frameworks more effectively than neutral donor functionalities.

7. Alphabetical List of the Abbreviations of the Amido Ligands Used

Abbreviation	Meaning
$\text{Ar}(t\text{Bu}_D)\text{N}$	$[3,5-(\text{CH}_3)_2\text{C}_6\text{H}_3][(\text{H}_3\text{C})(\text{D}_3\text{C})_2\text{C}]\text{N}$ anion
$t\text{BuMe}_2\text{Si}^-\text{N}_3\text{N}'$	$[(\text{H}_3\text{C})_3\text{C}](\text{H}_3\text{C})_2\text{SiN}(\text{CH}_2)_3\text{N}$ trianion

$C_3H_6N_2^+$	$CH_2(CH_2N-2,6-iPr_2C_6H_3)_2$ dianion
$C_6F_5N_3N^+$	$[F_5C_6N(CH_2)_2]_3N$ trianion
dac	4,13-diaza-[18]crown-6-dianion
'NO'	<i>N,O</i> -bis(<i>tert</i> -butyl)(alkoxydimethylsilyl)amide
'NON'	$O[2-\{C(CH_3)(CD_3)_2NC_6H_4\}_2]$ dianion
oep	octaethylphorphyrin dianion
oepg	octaethylphorphyrinogen tetraanion
$Ph^+CN_2^+$	bis(trimethylsilyl)benzamidonato anion
'P ₂ N'	(<i>i</i> Pr ₂ PCH ₂ SiMe ₂) ₂ N anion
'P ₂ N ₂ '	PhP[CH ₂ Si(CH ₃) ₂ NSi(CH ₃) ₂ CH ₂] ₂ PPh dianion
TMS-Ap	deprotonated <i>N</i> -trimethylsilyl-4-methyl-2-aminopyridine
TMS'N ₃ N'	$[(H_3C)_3SiN(CH_2)_2]_3N$ trianion

I thank Prof. Uwe Rosenthal, the Max-Planck-Gesellschaft, the Fonds der Chemischen Industrie, the Karl-Winnacker-Stiftung, and Bayer AG for their support of our work.

Received: April 19, 1999 [A338]

- [1] B. Cornils, W. A. Herrmann, *Applied Homogenous Catalysis with Organometallic Compounds*, VCH, Weinheim, **1996**.
- [2] C. Elschenbroich, A. Salzer, *Organometallchemie*, Teubner, Stuttgart, **1993**; C. Elschenbroich, A. Salzer, *Organometallics: A Concise Introduction*, 2nd ed., VCH, Weinheim, **1992**.
- [3] A. Togni, L. M. Venanzi, *Angew. Chem.* **1994**, 106, 517–547; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 497–527.
- [4] M. F. Lappert, P. P. Power, A. R. Sanger, R. C. Srivastava, *Metal and Metalloid Amides*, Ellis Norwood, Chichester, UK, **1980**.
- [5] T. J. Kealy, P. L. Pauson, *Nature* **1951**, 168, 1039.
- [6] G. Wilkinson, M. Rosenblum, M. C. Whiting, R. B. Woodward, *J. Am. Chem. Soc.* **1952**, 74, 2125–2126.
- [7] E. O. Fischer, W. Pfab, *Z. Naturforsch. B* **1952**, 7, 377–379.
- [8] A. Andersen, H.-G. Cordes, J. Herwig, W. Kaminsky, A. Merck, R. Mottweiler, J. Pein, H. Sinn, H.-J. Vollmer, *Angew. Chem.* **1976**, 88, 689–690; *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 630–631.
- [9] H. Sinn, W. Kaminsky, H.-J. Vollmer, R. Woldt, *Angew. Chem.* **1980**, 92, 396–402; *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 390–396.
- [10] a) R. G. Pearson, *J. Am. Chem. Soc.* **1963**, 85, 3533–3539; b) R. G. Pearson, *J. Chem. Educ.* **1968**, 45, 581–586; c) R. G. Pearson, *J. Chem. Educ.* **1968**, 45, 643–648.
- [11] M. D. Fryzuk, T. S. Haddad, D. J. Berg, S. J. Rettig, *Pure Appl. Chem.* **1991**, 63, 845–850.
- [12] M. D. Fryzuk, *Can. J. Chem.* **1992**, 70, 2839–2845.
- [13] F. T. Edelmann, *Coord. Chem. Rev.* **1994**, 137, 403–481.
- [14] H. Brand, J. Arnold, *Coord. Chem. Rev.* **1995**, 140, 137–168.
- [15] C. Floriani, *Chem. Commun.* **1996**, 1257–1263.
- [16] C. Floriani, *Pure Appl. Chem.* **1996**, 68, 1–8.
- [17] J. G. Verkade, *Acc. Chem. Res.* **1993**, 26, 483–489.
- [18] R. R. Schrock, *Acc. Chem. Res.* **1997**, 30, 9–16.
- [19] R. R. Schrock, *Pure Appl. Chem.* **1997**, 69, 2197–2203.
- [20] C. C. Cummins, *Chem. Commun.* **1998**, 1777–1786.
- [21] C. C. Cummins, *Prog. Inorg. Chem.* **1998**, 47, 685–836.
- [22] K. Dehnicke, *Chem. Ztg.* **1990**, 114, 295–304.
- [23] J. Barker, M. Killner, *Coord. Chem. Rev.* **1994**, 133, 219–300.
- [24] a) H. Schumann, *Angew. Chem.* **1984**, 96, 475–493; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 474–492; b) W. J. Evans, *Adv. Organomet. Chem.* **1985**, 24, 131–177; c) W. J. Evans, *Polyhedron* **1987**, 6, 803–835; d) R. D. Köhn, G. Kociok-Köhn, H. Schumann in *Encyclopedia of Inorganic Chemistry* (Ed.: R. B. King), Wiley, New York, **1994**; e) C. J. Schaverien, *Adv. Organomet. Chem.* **1994**, 36, 283–362; f) H. Schumann, J. A. Meese-Marktscheffel, L. Esser, *Chem. Rev.* **1995**, 95, 865–986.
- [25] a) M. E. Thompson, S. M. Baxter, A. R. Bulls, B. J. Burger, M. C. Nolan, B. D. Santarsiero, W. P. Schaefer, J. E. Bercaw, *J. Am. Chem. Soc.* **1987**, 109, 203–219; b) K. H. Den Haan, Y. Wielstra, J. H. Teuben, *Organometallics* **1987**, 6, 2053–2059; c) H. J. Heeres, J. Renkema, M. Booi, A. Meetsma, J. H. Teuben, *Organometallics* **1988**, 7, 2495–2502; d) W. J. Evans, L. R. Chamberlain, T. A. Ulibarri, J. W. Ziller, *J. Am. Chem. Soc.* **1988**, 110, 6423–6432; e) P. L. Watson, *J. Chem. Soc. Chem. Commun.* **1983**, 276–277; f) P. L. Watson, *J. Am. Chem. Soc.* **1983**, 105, 6491–6493; g) B. J. Burger, M. E. Thompson, W. D. Cotter, J. E. Bercaw, *J. Am. Chem. Soc.* **1990**, 112, 1566–1577.
- [26] G. Jeske, H. Lauke, H. Mauermann, H. Schumann, T. J. Marks, *J. Am. Chem. Soc.* **1985**, 107, 8111–8118.
- [27] G. A. Molander, J. O. Hoberg, *J. Org. Chem.* **1992**, 57, 3266–3268.
- [28] K. N. Harrison, T. J. Marks, *J. Am. Chem. Soc.* **1992**, 114, 9220–9221.
- [29] T. Sakakura, H.-J. Lautenschlager, M. Tanaka, *J. Chem. Soc. Chem. Commun.* **1991**, 40–42.
- [30] M. R. Gagne, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, 114, 275–294.
- [31] a) H. J. Heeres, A. Heeres, J. H. Teuben, *Organometallics* **1990**, 9, 1508–1509; b) H. J. Heeres, J. H. Teuben, *Organometallics* **1991**, 10, 1980–1986.
- [32] M. St. Clair, W. P. Schaefer, J. E. Bercaw, *Organometallics* **1991**, 10, 525–527.
- [33] Y. Li, P.-F. Fu, T. J. Marks, *Organometallics* **1994**, 13, 439–440.
- [34] a) J. W. Bruno, H. A. Stecher, L. R. Morss, D. C. Sonnenberger, T. J. Marks, *J. Am. Chem. Soc.* **1986**, 108, 7275–7280; b) J. A. Labinger, J. E. Bercaw, *Organometallics* **1988**, 7, 926–928.
- [35] D. Fenske, E. Hartmann, K. Dehnicke, *Z. Naturforsch. B* **1988**, 43, 1611–1615.
- [36] H. W. Roesky, B. Meller, M. Noltemeyer, H.-G. Schmidt, U. Scholz, G. M. Sheldrick, *Chem. Ber.* **1988**, 121, 1403–1406.
- [37] a) F. T. Edelmann, *Angew. Chem.* **1995**, 107, 2647–2669; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2466–2488; b) F. T. Edelmann, *J. Alloys Compd.* **1994**, 207/208, 182–188.
- [38] a) M. Wedler, H. W. Roesky, F. T. Edelmann, *J. Organomet. Chem.* **1988**, 345, C1–C3; b) M. Wedler, M. Noltemeyer, U. Pieper, H. G. Schmidt, D. Stalke, F. T. Edelmann, *Angew. Chem.* **1990**, 102, 941–943; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 894–896; c) M. Wedler, F. Knösel, M. Noltemeyer, F. T. Edelmann, U. Behrens, *J. Organomet. Chem.* **1990**, 388, 21–45; d) M. Wedler, F. Knösel, U. Pieper, D. Stalke, F. T. Edelmann, H.-D. Amberger, *Chem. Ber.* **1992**, 125, 2171–2181.
- [39] C. Hagen, H. Reddmann, H.-D. Amberger, F. T. Edelmann, U. Pegelow, G. V. Shalimoff, N. M. Edelstein, *J. Organomet. Chem.* **1993**, 462, 69–78.
- [40] R. Duchateau, C. T. van Wee, A. Meetsma, J. H. Teuben, *J. Am. Chem. Soc.* **1993**, 115, 4931–4932.
- [41] J. R. Hagadorn, J. Arnold, *Organometallics* **1996**, 15, 984–991.
- [42] R. Duchateau, C. T. van Wee, A. Meetsma, P. T. van Duijnen, J. H. Teuben, *Organometallics* **1996**, 15, 2279–2290.
- [43] R. Duchateau, C. T. van Wee, J. H. Teuben, *Organometallics* **1996**, 15, 2291–2302.
- [44] E. A. Bijpost, R. Duchateau, J. H. Teuben, *J. Mol. Catal. A* **1995**, 95, 121–128.
- [45] R. Duchateau, T. Tuinstra, E. A. C. Brussee, A. Meetsma, P. T. van Duijnen, J. H. Teuben, *Organometallics* **1997**, 16, 3511–3522.
- [46] R. Duchateau, E. A. C. Brussee, A. Meetsma, J. H. Teuben, *Organometallics* **1997**, 16, 5506–5516.
- [47] L. Lee, D. J. Berg, G. W. Bushnell, *Inorg. Chem.* **1994**, 33, 5302–5308.
- [48] L. Lee, D. J. Berg, G. W. Bushnell, *Organometallics* **1995**, 14, 8–10.
- [49] L. Lee, D. J. Berg, G. W. Bushnell, *Organometallics* **1995**, 14, 5021–5023.
- [50] H. J. Heeres, J. Nijhoff, J. H. Teuben, R. D. Rogers, *Organometallics* **1993**, 12, 2609–2617.
- [51] L. Lee, D. J. Berg, F. W. Einstein, R. J. Batchelor, *Organometallics* **1997**, 16, 1819–1821.
- [52] J. W. Buchler, G. Eikermann, L. Puppe, K. Rohbock, H. H. Schneehage, D. Weck, *Liebigs Ann. Chem.* **1971**, 745, 135–151.
- [53] C.-P. Wong, W. D. Horrocks, *Tetrahedron Lett.* **1975**, 2637–2640.
- [54] a) C. J. Schaverien, *J. Chem. Soc. Chem. Commun.* **1991**, 458–460; b) C. J. Schaverien, A. G. Orpen, *Inorg. Chem.* **1991**, 30, 4968–4978.

- [55] a) J. Arnold, C. G. Hoffman, *J. Am. Chem. Soc.* **1990**, *112*, 8620–8621; b) J. Arnold, C. G. Hoffman, D. Y. Dawson, F. J. Hollander, *Organometallics* **1993**, *12*, 3645–3654.
- [56] a) M. D. Fryzuk, T. S. Haddad, *J. Am. Chem. Soc.* **1988**, *110*, 8263–8265; b) M. D. Fryzuk, T. S. Haddad, *J. Chem. Soc. Chem. Commun.* **1990**, 1088–1090.
- [57] M. D. Fryzuk, T. S. Haddad, S. J. Rettig, *Organometallics* **1991**, *10*, 2026–2036.
- [58] M. D. Fryzuk, T. S. Haddad, S. J. Rettig, *Organometallics* **1992**, *11*, 2967–2969.
- [59] M. D. Fryzuk, G. Giesbrecht, S. J. Rettig, *Organometallics* **1996**, *15*, 3329–3336.
- [60] H. van der Heijden, C. J. Schaverien, A. G. Orpen, *Organometallics* **1989**, *8*, 255–258.
- [61] T. A. Albright, J. K. Burdett, M. H. Whangbo, *Orbital Interactions in Chemistry*, Wiley, New York, **1985**.
- [62] M. D. Fryzuk, J. B. Love, S. J. Rettig, *J. Am. Chem. Soc.* **1997**, *119*, 9071–9072.
- [63] H. Zeiss, *Organometallic Chemistry*, ACS Monograph Series, American Chemical Society, Washington DC, USA, **1960**.
- [64] a) E. Benzing, W. Kornicker, *Chem. Ber.* **1961**, *94*, 2263–2267; b) S. Brenner, R. Kempe, P. Arndt, *Z. Anorg. Allg. Chem.* **1995**, *621*, 2021–2024.
- [65] W. J. Evans, R. Anwender, R. J. Doendens, J. W. Ziller, *Angew. Chem.* **1994**, *106*, 1725–1728; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1641–1643.
- [66] E. N. Jacobsen, *Comprehensive Organometallic Chemistry II*, Pergamon, Oxford, **1995**.
- [67] O. Runte, T. Priermeier, R. Anwender, *Chem. Commun.* **1996**, 1385–1386.
- [68] W. A. Herrmann, J. Eppinger, M. Spiegler, O. Runte, R. Anwender, *Organometallics* **1997**, *16*, 1813–1815.
- [69] H. W. Görlitz, M. Spiegler, R. Anwender, *Eur. J. Inorg. Chem.* **1998**, 1009–1014.
- [70] a) D. R. Cary, J. Arnold, *J. Am. Chem. Soc.* **1993**, *115*, 2520–2521; b) D. R. Cary, G. E. Ball, J. Arnold, *J. Am. Chem. Soc.* **1995**, *117*, 3492–3501.
- [71] *Handbook of the Physics and Chemistry of Rare Earths* (Eds.: K. A. Gschneider, L. Eyring), North-Holland, Amsterdam, **1978**.
- [72] a) R. Anwender, R. Roesky, *J. Chem. Soc. Dalton Trans.* **1997**, 137–138; b) R. Anwender, O. Runte, J. Eppinger, G. Gerstenberger, E. Herdtweck, M. Spiegler, *J. Chem. Soc. Dalton Trans.* **1998**, 847–858.
- [73] a) C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710–712; b) J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T.-W. Chu, D. H. Olson, E. W. Sheppard, S. B. McCullen, J. B. Higgins, J. L. Schlenker, *J. Am. Chem. Soc.* **1992**, *114*, 10834–10843; c) J. Y. Ying, C. P. Mehnert, M. S. Wong, *Angew. Chem.* **1999**, *111*, 59–82; *Angew. Chem. Int. Ed.* **1999**, *38*, 56–77.
- [74] G. Gerstenberger, C. Palm, R. Anwender, *Chem. Eur. J.* **1999**, *5*, 997–1005.
- [75] H. Berberich, P. W. Roesky, *Angew. Chem.* **1998**, *110*, 1618–1620; *Angew. Chem. Int. Ed.* **1998**, *37*, 1569–1571.
- [76] a) L. Claisen, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 646–650; b) W. Tschitschenko, *Chem. Zentralbl.* **1906**, 77(I), 1309.
- [77] a) H. Sasai, T. Arai, Y. Satow, K. N. Houk, M. Shibasaki, *J. Am. Chem. Soc.* **1995**, *117*, 6194–6198; b) T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1369–1372.
- [78] H. Görls, B. Neumüller, A. Scholz, J. Scholz, *Angew. Chem.* **1995**, *107*, 732–735; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 673–676.
- [79] J. Jubb, S. Gambarotta, R. Duchateau, J. H. Teuben, *J. Chem. Soc. Chem. Commun.* **1994**, 2641–2642.
- [80] J. Jubb, S. Gambarotta, *J. Am. Chem. Soc.* **1994**, *116*, 4477–4478.
- [81] A. Spannenberg, P. Arndt, R. Kempe, *Angew. Chem.* **1998**, *110*, 824–827; *Angew. Chem. Int. Ed.* **1998**, *37*, 832–835.
- [82] A. Spannenberg, M. Oberthür, H. Noss, A. Tillack, P. Arndt, R. Kempe, *Angew. Chem.* **1998**, *110*, 2190–2192; *Angew. Chem. Int. Ed.* **1998**, *37*, 2079–2082.
- [83] J. D. Scollard, D. H. McConville, N. C. Payne, J. J. Vittal, *Macromolecules* **1996**, *29*, 5241–5242.
- [84] G. J. P. Britovsek, V. C. Gibson, D. F. Wass, *Angew. Chem.* **1999**, *111*, 448–468; *Angew. Chem. Int. Ed.* **1999**, *38*, 428–447.
- [85] a) A. D. Horton, J. Dewith, *Chem. Commun.* **1996**, 1375–1376; b) A. D. Horton, J. Dewith, A. J. van der Linden, H. van de Weg, *Organometallics* **1996**, *15*, 2672–2674.
- [86] G. Odian, *Principles of Polymerization*, Wiley, New York, **1981**.
- [87] a) Y. Doi, S. Ueki, T. Keij, *Macromolecules* **1979**, *12*, 814–819; b) G. Jeske, H. Lauke, H. Mauermann, P. N. Swepson, H. Schuhmann, T. J. Marks, *J. Am. Chem. Soc.* **1985**, *107*, 8091–8103; c) L. Wang, R. S. Lu, R. Bau, T. C. Flood, *J. Am. Chem. Soc.* **1993**, *115*, 6999–7000; d) K. Mashima, S. Fujikawa, Y. Tanaka, H. Urata, T. Oshiki, E. Tanaka, A. Nakamura, *Organometallics* **1995**, *14*, 2633–2640; e) G. Bhandari, Y. Kim, J. M. McFarland, A. L. Rheingold, K. H. Theopold, *Organometallics* **1995**, *14*, 738–745.
- [88] C. M. Killian, D. J. Tempel, L. K. Johnson, M. Brookhart, *J. Am. Chem. Soc.* **1996**, *118*, 11664–11665; M. Brookhart, J. M. Desimone, B. E. Grant, M. J. Tanner, *Macromolecules* **1995**, *28*, 5378–5380.
- [89] J. D. Scollard, D. H. McConville, *J. Am. Chem. Soc.* **1996**, *118*, 10008–10009.
- [90] J. D. Scollard, D. H. McConville, S. J. Rettig, *Organometallics* **1997**, *16*, 1810–1812.
- [91] J. D. Scollard, D. H. McConville, J. J. Vittal, N. C. Payne, *J. Mol. Catal. A* **1998**, *128*, 201–214.
- [92] R. Baumann, D. William, R. R. Schrock, *J. Am. Chem. Soc.* **1997**, *119*, 3830–3831.
- [93] R. Baumann, R. R. Schrock, *J. Organomet. Chem.* **1998**, *557*, 69–75.
- [94] a) H.-H. Brintzinger, D. Fischer, R. Mülhaupt, B. Rieger, R. Waymouth, *Angew. Chem.* **1995**, *107*, 1255–1282; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1143–1170; b) M. Aulbach, F. Küber, *Chem. Unserer Zeit* **1994**, *28*, 197–208; c) P. C. Möhring, N. J. Coville, *J. Organomet. Chem.* **1994**, *479*, 1–29.
- [95] W. Crookes, *The Report of the 68th Meeting of the British Association for the Advancement of Science (Bristol)*, John Murray, London, **1898**.
- [96] a) J. Chatt, J. R. Dilworth, R. L. Richards, *Chem. Rev.* **1978**, *78*, 589–625; b) P. Pelikan, R. Boca, *Coord. Chem. Rev.* **1984**, *55*, 55–112; c) G. J. Leigh, *Acc. Chem. Res.* **1992**, *25*, 177–182; d) M. Hidai, Y. Mizobe, *Chem. Rev.* **1995**, *95*, 1115–1133.
- [97] M. D. Fryzuk, J. B. Love, S. J. Rettig, V. G. Young, *Science* **1997**, *275*, 1445–1447.
- [98] a) M. Hidai, K. Tominari, Y. Uchida, *J. Am. Chem. Soc.* **1972**, *94*, 110–114; b) T. A. George, R. C. Tisdale, *Inorg. Chem.* **1988**, *27*, 2909–2912.
- [99] A mixed dinitrogen-hydrido-tantalum complex has been described: M. D. Fryzuk, S. A. Johnson, S. J. Rettig, *J. Am. Chem. Soc.* **1998**, *120*, 11024–11025.
- [100] J. M. Manriquez, D. R. McAlister, R. D. Sanner, J. E. Bercaw, *J. Am. Chem. Soc.* **1978**, *100*, 2716–2724.
- [101] a) M. D. Fryzuk, M. Mylvaganam, J. D. Cohen, T. M. Loehr, *J. Am. Chem. Soc.* **1994**, *116*, 9529–9534; b) M. D. Fryzuk, T. S. Haddad, M. Mylvaganam, D. H. McConville, S. J. Rettig, *J. Am. Chem. Soc.* **1993**, *115*, 2782–2792; c) J. D. Cohen, M. D. Fryzuk, T. M. Loehr, M. Mylvaganam, S. Rettig, *Inorg. Chem.* **1998**, *37*, 112–119.
- [102] a) M. D. Fryzuk, J. B. Love, S. J. Rettig, *Chem. Commun.* **1996**, 2783–2784; b) M. D. Fryzuk, J. B. Love, S. J. Rettig, *Organometallics* **1998**, *17*, 846–853.
- [103] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkins Trans. 2* **1987**, S1–S19.
- [104] a) X.-L. Luo, G. J. Kubas, J. C. Bryan, C. J. Burns, C. J. Unkefer, *J. Am. Chem. Soc.* **1994**, *116*, 10312–10313; b) X.-L. Luo, G. J. Kubas, C. J. Burns, J. C. Bryan, C. J. Unkefer, *J. Am. Chem. Soc.* **1995**, *117*, 1159–1160; c) J. J. Schneider, *Angew. Chem.* **1996**, *108*, 1133–1139; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1068–1076.
- [105] T. Mashiko, D. Dolphin in *Comprehensive Coordination Chemistry* (Eds.: G. Wilkinson, R. D. Gillard, J. A. McCleverty), Pergamon, Oxford, **1987**.
- [106] A. Baeyer, *Chem. Ber.* **1886**, *19*, 2184–2185.
- [107] D. Jacoby, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Chem. Soc. Chem. Commun.* **1991**, 790–792.
- [108] A. Rosa, G. Ricciardi, M. Rosi, A. Sgamellotti, C. Floriani, *J. Chem. Soc. Dalton Trans.* **1993**, 3759–3766.
- [109] G. Solari, E. Solari, G. Lemerrier, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Inorg. Chem.* **1997**, *36*, 2691–2695.

- [110] a) D. Jacoby, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1993**, *115*, 7025–7026; b) D. Jacoby, S. Isoz, C. Floriani, K. Schenk, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1995**, *14*, 4816–4824.
- [111] a) D. Jacoby, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1993**, *115*, 3595–3802; b) D. Jacoby, S. Isoz, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1995**, *117*, 2793–2804.
- [112] a) L. D. Durfee, I. P. Rothwell, *Chem. Rev.* **1988**, *88*, 1059–1079; b) P. T. Wolczanski, J. E. Bercaw, *Acc. Chem. Res.* **1980**, *13*, 121–127; c) C. E. L. Headford, W. R. Roper in *Reaction of Coordinated Ligands* (Ed.: P. S. Braterman), Plenum, New York, **1986**.
- [113] D. Jacoby, S. Isoz, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Am. Chem. Soc.* **1995**, *117*, 2805–2816.
- [114] C. Floriani, E. Solari, G. Solari, A. Chiesi-Villa, C. Rizzoli, *Angew. Chem.* **1998**, *110*, 2367–2369; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2245–2248.
- [115] S. De Angelis, E. Solari, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Angew. Chem.* **1995**, *107*, 1200–1202; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1092–1094.
- [116] P. Binger, P. Müller, P. Philipps, B. Gabor, R. Mynott, A. T. Herrman, F. Langhauser, C. Krüger, *Chem. Ber.* **1992**, *125*, 2209–2212.
- [117] a) M. Appel, J. Heidrich, W. Beck, *Chem. Ber.* **1987**, *120*, 1087–1089; b) J. Heidrich, M. Steimann, W. Beck, J. R. Phillips, W. C. Troglor, *Organometallics* **1990**, *9*, 1296–1300; c) M. Akita, M. Terada, S. Oyama, Y. Moro-oka, *Organometallics* **1990**, *9*, 816–825; d) K. G. Frank, J. P. Selegue, *J. Am. Chem. Soc.* **1990**, *112*, 6414–6416; e) H. Owaga, K. Onitsuka, T. Joh, S. Takahashi, Y. Yamamoto, H. Yamazaki, *Organometallics* **1988**, *7*, 2257–2260; f) J. A. Davies, M. El-Ghanam, A. A. Pinkerton, D. A. Smith, *J. Organomet. Chem.* **1991**, *409*, 367–376.
- [118] D. W. Stephan, *Coord. Chem. Rev.* **1989**, *95*, 41–107.
- [119] a) C. P. Casey, R. F. Jordan, A. L. Rheingold, *J. Am. Chem. Soc.* **1983**, *105*, 665–667; b) C. P. Casey, R. F. Jordan, A. L. Rheingold, *Organometallics* **1984**, *3*, 504–506; c) C. P. Casey, *J. Organomet. Chem.* **1990**, *400*, 205–221; d) W. S. Sartin, J. P. Selegue, *J. Am. Chem. Soc.* **1985**, *107*, 5818–5820; e) W. S. Sartin, J. P. Selegue, *Organometallics* **1987**, *6*, 1812–1815; f) W. S. Sartin, J. P. Selegue, *Organometallics* **1989**, *8*, 2153–2158; g) D. Selent, R. Beckhaus, J. Pickardt, *Organometallics* **1993**, *12*, 2857–2860.
- [120] L. H. Gade, N. Mahr, *J. Chem. Soc. Dalton Trans.* **1993**, 489–494.
- [121] S. Friedrich, L. H. Gade, A. J. Edwards, M. McPartlin, *Chem. Ber.* **1993**, *126*, 1797–1805.
- [122] H. Memmler, L. H. Gade, J. W. Lauher, *Inorg. Chem.* **1994**, *33*, 3064–3071.
- [123] B. Findeis, M. Schubart, L. H. Gade, F. Möller, I. Scowen, M. McPartlin, *J. Chem. Soc. Dalton Trans.* **1995**, 125–132.
- [124] M. Schubart, B. Findeis, L. H. Gade, W.-S. Li, M. McPartlin, *Chem. Ber.* **1995**, *128*, 329–334.
- [125] B. Findeis, M. Schubart, C. Platzek, L. H. Gade, I. Scowen, M. McPartlin, *Chem. Commun.* **1996**, 219–220.
- [126] a) T. Saegusa, Y. Ito in *Organic Chemistry* (Ed.: I. Ugi), Academic Press, New York, **1971**; b) M. F. Lappert, N. T. Luong-Thi, C. R. C. Milne, *J. Organomet. Chem.* **1979**, *174*, C35–C37; c) L. D. Durfee, I. P. Rothwell, *Chem. Rev.* **1988**, *88*, 1059–1079; d) W. A. Herrmann, T. Cuenca, B. Menjon, E. Herdtweck, *Angew. Chem.* **1987**, *99*, 687–688; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 697–699.
- [127] S. Friedrich, H. Memmler, L. H. Gade, W.-S. Li, M. McPartlin, *Angew. Chem.* **1994**, *106*, 705–708; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 676–679.
- [128] S. Friedrich, H. Memmler, L. H. Gade, W.-S. Li, I. Scowen, M. McPartlin, C. E. Housecroft, *Inorg. Chem.* **1996**, *35*, 2433–2441.
- [129] G. Jansen, M. Schubart, B. Findeis, L. H. Gade, I. J. Scowen, M. McPartlin, *J. Am. Chem. Soc.* **1998**, *120*, 7239–7251.
- [130] R. F. W. Bader, P. L. A. Popelier, T. A. Keith, *Angew. Chem.* **1994**, *106*, 647–659; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 620–632.
- [131] A. Savin, R. Nesper, S. Wengert, T. F. Fässler, *Angew. Chem.* **1997**, *109*, 1893–1918; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1808–1833.
- [132] H. Memmler, U. Kauper, L. H. Gade, I. Scowen, M. McPartlin, *Chem. Commun.* **1996**, 1751–1752.
- [133] a) W. Leitner, *Coord. Chem. Rev.* **1996**, *153*, 257–284; b) W. Leitner, *Angew. Chem.* **1995**, *107*, 2391–2405; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2207–2221; c) P. Braunstein, D. Matt, O. Nobel, *Chem. Rev.* **1988**, *88*, 747–764; d) A. Behr, *Angew. Chem.* **1988**, *100*, 681–698; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 661–678; e) D. Walther, *Coord. Chem. Rev.* **1988**, *79*, 135–174; f) D. A. Palmer, R. van Eldik, *Chem. Rev.* **1983**, *83*, 651–731.
- [134] A. Schneider, L. H. Gade, M. Breuning, G. Bringmann, I. J. Scowen, M. McPartlin, *Organometallics* **1998**, *17*, 1643–1645.
- [135] S. Friedrich, L. H. Gade, I. Scowen, M. McPartlin, *Angew. Chem.* **1996**, *108*, 1440–1443; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1338–1341.
- [136] a) C. C. Cummins, S. M. Baxter, P. T. Wolczanski, *J. Am. Chem. Soc.* **1988**, *110*, 8731–8733; b) C. C. Cummins, C. P. Schaller, G. D. van Duyne, P. T. Wolczanski, A. W. E. Chan, R. Hoffmann, *J. Am. Chem. Soc.* **1991**, *113*, 2985–2994; c) C. P. Schaller, P. T. Wolczanski, *Inorg. Chem.* **1993**, *32*, 131–144.
- [137] a) *Activation and Functionalisation of Alkanes* (Ed.: C. Hill), Wiley, New York, **1989**; b) *Selective Hydrocarbon Activation* (Ed.: P. L. Watson), VCH, Toledo, **1989**; c) A. E. Shilov, *Activation of Saturated Hydrocarbons by Transition Metal Complexes* Reidel, Boston, **1984**.
- [138] a) R. H. Crabtree, *Chem. Rev.* **1985**, *85*, 245–269; b) R. G. Bergman, *Science* **1984**, *223*, 902–908; c) W. A. G. Graham, *J. Organomet. Chem.* **1986**, *300*, 81–91; d) M. L. H. Green, D. O'Hare, *Pure Appl. Chem.* **1985**, *57*, 1897–1910; e) J. Halpern, *Inorg. Chim. Acta* **1985**, *100*, 41–48; f) R. H. Crabtree, D. G. Hamilton, *Adv. Organomet. Chem.* **1988**, *28*, 299–338; g) W. D. Jones, F. J. Feher, *Acc. Chem. Res.* **1989**, *22*, 91–100.
- [139] W. D. Jones, E. T. Hessell, *J. Am. Chem. Soc.* **1993**, *115*, 554–562.
- [140] C. Wang, J. W. Ziller, T. C. Flood, *J. Am. Chem. Soc.* **1995**, *117*, 1647–1648.
- [141] a) M. Lin, A. Sen, *Nature* **1994**, *368*, 613–615; b) L.-C. Kao, A. C. Hutson, A. Sen, *J. Am. Chem. Soc.* **1991**, *113*, 700–701; c) A. Sen, E. Gretz, T. F. Oliver, Z. Jiang, *New J. Chem.* **1989**, *13*, 755–760; d) A. Sen, *Acc. Chem. Res.* **1988**, *21*, 421–428.
- [142] a) G. A. Luinstra, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **1993**, *115*, 3004–3005; b) J. A. Labinger, A. M. Herring, D. K. Lyon, G. A. Luinstra, J. E. Bercaw, I. T. Horvath, K. Eller, *Organometallics* **1993**, *12*, 895–905.
- [143] R. A. Periana, D. J. Taube, E. R. Evitt, D. G. Löffler, P. R. Wentrcek, G. Voss, T. Masuda, *Science* **1993**, *259*, 340–343.
- [144] A. S. Guram, R. F. Jordan, D. F. Taylor, *J. Am. Chem. Soc.* **1991**, *113*, 1833–1835.
- [145] a) P. L. Watson, G. W. Parshall, *Acc. Chem. Res.* **1985**, *18*, 51; b) C. M. Fendrick, T. J. Marks, *J. Am. Chem. Soc.* **1986**, *108*, 425–437.
- [146] P. Burger, R. G. Bergman, *J. Am. Chem. Soc.* **1993**, *115*, 10462–10463.
- [147] C. A. Muedas, R. R. Ferguson, S. H. Brown, R. H. Crabtree, *J. Am. Chem. Soc.* **1991**, *113*, 2233–2243.
- [148] a) B. B. Wayland, S. Ba, A. E. Sherry, *J. Am. Chem. Soc.* **1991**, *113*, 5305–5311; b) X.-X. Zhang, B. B. Wayland, *J. Am. Chem. Soc.* **1994**, *116*, 7897–7898.
- [149] a) S. N. Brown, J. M. Mayer, *J. Am. Chem. Soc.* **1994**, *116*, 2219–2220; b) G. K. Cook, J. M. Mayer, *J. Am. Chem. Soc.* **1994**, *116*, 1855–1868; c) R. A. Sheldon, J. K. Kochi, *Metal Catalyzed Oxidations of Organic Compounds*, Academic Press, New York, **1981**.
- [150] a) W. A. Howard, M. Waters, G. Parkin, *J. Am. Chem. Soc.* **1993**, *115*, 4917–4918; b) J. de With, A. D. Horton, *Angew. Chem.* **1993**, *105*, 958–960; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 903–905; c) P. J. Walsh, F. J. Hollander, R. G. Bergman, *Organometallics* **1993**, *12*, 3705–3723; d) S. Y. Lee, R. G. Bergman, *J. Am. Chem. Soc.* **1995**, *117*, 5877–5878.
- [151] a) C. McDade, J. C. Green, J. E. Bercaw, *Organometallics* **1982**, *1*, 1629–1634; b) L. R. Chamberlain, I. P. Rothwell, J. C. Huffmann, *J. Am. Chem. Soc.* **1986**, *108*, 1502–1509; c) J.-L. Couturier, C. Paillet, M. Leconte, J. M. Basset, K. Weiss, *Angew. Chem.* **1992**, *104*, 622–624; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 628–630; d) H. van der Heijden, B. Hessen, *J. Chem. Soc. Chem. Commun.* **1995**, 145–146.
- [152] a) C. P. Schaller, J. B. Bonanno, P. T. Wolczanski, *J. Am. Chem. Soc.* **1994**, *116*, 4133–4134; b) C. P. Schaller, C. C. Cummins, P. T. Wolczanski, *J. Am. Chem. Soc.* **1996**, *118*, 591–611.
- [153] a) B. K. Carpenter, *Determination of Reaction Mechanisms* Wiley-Interscience, New York, **1984**; b) T. H. Lowry, K. S. Richardson,

- Mechanism and Theory in Organic Chemistry*, Harper and Row, New York, **1987**.
- [154] T. R. Cundari, *Organometallics* **1993**, *12*, 1998–2000.
- [155] a) E. P. Wasserman, C. B. Moore, R. G. Bergman, *Science* **1992**, *255*, 315–318; b) B. H. Weiller, E. P. Wasserman, R. G. Bergman, C. B. Moore, G. C. Pimentel, *J. Am. Chem. Soc.* **1989**, *111*, 8288–8290; c) R. H. Schultz, A. A. Bengali, M. J. Tauber, B. H. Weiller, E. P. Wasserman, K. R. Kyle, C. B. Moore, R. G. Bergman, *J. Am. Chem. Soc.* **1994**, *116*, 7369–7377; d) A. A. Bengali, R. H. Schultz, C. B. Moore, R. G. Bergman, *J. Am. Chem. Soc.* **1994**, *116*, 9585–9589; e) R. A. Periana, R. G. Bergman, *J. Am. Chem. Soc.* **1986**, *108*, 7332–7346; f) J. M. Buchanan, J. M. Stryker, R. G. Bergman, *J. Am. Chem. Soc.* **1986**, *108*, 1537–1550; g) P. E. Bloyce, A. J. Rest, I. Whitwell, *J. Chem. Soc. Dalton Trans.* **1990**, 813–821.
- [156] S. E. Bromberg, H. Yang, M. C. Asplund, T. Lian, B. D. McNamara, K. T. Kotz, J. S. Yeston, M. Wilken, H. Frei, R. G. Bergmann, C. B. Harris, *Science* **1997**, *278*, 260–263.
- [157] B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, *28*, 154–162.
- [158] J. L. Bennett, P. T. Wolczanski, *J. Am. Chem. Soc.* **1997**, *119*, 10696–10719.
- [159] C. C. Cummins, J. Lee, R. R. Schrock, W. M. Davis, *Angew. Chem.* **1992**, *104*, 1510–1512; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1501–1503.
- [160] J. G. Brennan, R. A. Andersen, J. L. Robbins, *J. Am. Chem. Soc.* **1986**, *108*, 335–336.
- [161] C. C. Cummins, R. R. Schrock, W. M. Davis, *Inorg. Chem.* **1994**, *33*, 1448–1457.
- [162] V. Christou, J. Arnold, *Angew. Chem.* **1993**, *105*, 1551–1553; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1450–1452.
- [163] P. O'Brien, *Chemironics* **1991**, *5*, 61–70.
- [164] a) R. Appel in *Multiple Bonds and Low Coordination in Phosphorus Chemistry* (Eds.: M. Regitz, O. J. Scherer), Thieme, Stuttgart, **1990**; b) R. Appel, F. Knoll, I. Ruppert, *Angew. Chem.* **1981**, *93*, 771–784; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 731–744.
- [165] G. Becker, *Z. Anorg. Allg. Chem.* **1976**, *423*, 242–254.
- [166] T. A. van der Knaap, T. C. Klebach, F. Visser, F. Bickelhaupt, *Tetrahedron* **1984**, *40*, 765–776.
- [167] F. Mathey, *Acc. Chem. Res.* **1992**, *25*, 90–96.
- [168] J. S. Freundlich, R. R. Schrock, W. M. Davis, *J. Am. Chem. Soc.* **1996**, *118*, 3643–3655.
- [169] J. S. Freundlich, R. R. Schrock, C. C. Cummins, W. M. Davis, *J. Am. Chem. Soc.* **1994**, *116*, 6476–6477.
- [170] a) R. R. Schrock in *Reactions of Coordinated Ligands* (Ed.: P. S. Braterman), Plenum, New York, **1986**; b) R. R. Schrock, *Acc. Chem. Res.* **1979**, *12*, 98–104.
- [171] a) J. B. Bonanno, P. T. Wolczanski, E. B. Lobkovsky, *J. Am. Chem. Soc.* **1994**, *116*, 11159–11160; b) P. T. Wolczanski, *Polyhedron* **1995**, *14*, 3335–3362.
- [172] a) P. B. Hitchcock, M. F. Lappert, G. A. Lawless, H. Olivier, E. J. Ryan, *J. Chem. Soc. Chem. Commun.* **1992**, 474–476; b) I. F. Urazowski, V. I. Ponomarev, I. E. Nifant'ev, D. A. Leminovskii, *J. Organomet. Chem.* **1989**, *368*, 287–294; c) W. J. Evans, J. W. Grate, R. J. Doedens, *J. Am. Chem. Soc.* **1985**, *107*, 1671–1679; d) L. D. Durfee, P. E. Fanwick, I. P. Rothwell, K. Folting, J. C. Huffmann, *J. Am. Chem. Soc.* **1987**, *109*, 4720–4722; e) S. Gambarotta, M. Chiang, *J. Chem. Soc. Chem. Commun.* **1987**, 698–699.
- [173] a) D. L. Hughes, U. Kleikes, G. J. Leigh, M. Maiwald, J. R. Sanders, C. Sudbrake, J. Weisner, *J. Chem. Soc. Dalton Trans.* **1993**, 3093–3096; b) M. T. Haward, M. W. George, S. M. Howdle, M. Poliakoff, *J. Chem. Soc. Chem. Commun.* **1990**, 913–915; c) R. B. Hita, A. J. Rest, *Organometallics* **1989**, *8*, 1598–1604; d) G. N. Schrauzer, N. Strampach, L. A. Huges, *Inorg. Chem.* **1982**, *21*, 2184–2188; e) A. Yamamoto, S. Go, M. Ookawa, M. Takahashi, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3110–3117; f) J. J. H. Edema, W. Stauthamer, S. Gambarotta, A. Meetsma, F. Bolhuis, *Inorg. Chem.* **1990**, *29*, 1302–1306; g) J. J. H. Edema, A. Meetsma, S. Gambarotta, *J. Am. Chem. Soc.* **1989**, *111*, 6878–6880.
- [174] a) W. Seidel, G. Kreisel, H. Mennega, *Z. Chem.* **1976**, *16*, 492–493; b) F. A. Cotton, M. Millar, *J. Am. Chem. Soc.* **1977**, *99*, 7886–7891; c) F. A. Cotton, G. E. Lewis, G. M. Mott, *Inorg. Chem.* **1983**, *22*, 560–561; d) F. A. Cotton, M. P. Diebold, J. Shim, *Inorg. Chem.* **1985**, *24*, 1510–1516; e) F. A. Cotton, L. M. Daniels, C. A. Murillo, *Angew. Chem.* **1992**, *104*, 795–796; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 737–728; f) F. A. Cotton, L. M. Daniels, C. A. Murillo, *Inorg. Chem.* **1993**, *32*, 2881–2885.
- [175] S. Hao, P. Berno, R. K. Minhas, S. Gambarotta, *Inorg. Chim. Acta* **1996**, *244*, 37–49.
- [176] P. Berno, J.-I. Song, R. Minhas, S. Gambarotta, *J. Am. Chem. Soc.* **1994**, *116*, 7417–7418.
- [177] E. A. C. Brussee, A. Meetsma, B. Hessen, J. H. Teuben, *Organometallics* **1998**, *17*, 4090–4095.
- [178] a) D. C. Bradley, R. G. Copperthwaite, *Chem. Commun.* **1971**, 764–765; b) E. C. Alyea, D. C. Bradley, R. G. Copperthwaite, *J. Chem. Soc. Dalton Trans.* **1972**, 1580–1584.
- [179] P. Berno, R. Minhas, S. Hao, S. Gambarotta, *Organometallics* **1994**, *13*, 1052–1054.
- [180] M. Moore, S. Gambarotta, G. Yap, L. M. Liable-Sands, A. L. Rheingold, *Chem. Commun.* **1997**, 643–644.
- [181] P. Berno, S. Gambarotta, *J. Chem. Soc. Chem. Commun.* **1994**, 2419–2421.
- [182] P. Berno, S. Gambarotta, *Organometallics* **1994**, *13*, 2569–2571.
- [183] P. Berno, S. Gambarotta, *Angew. Chem.* **1995**, *107*, 871–873; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 822–824.
- [184] P. Berno, M. Moore, R. Minhas, S. Gambarotta, *Can. J. Chem.* **1996**, *74*, 1930–1935.
- [185] C. P. Gerlach, J. Arnold, *Organometallics* **1996**, *15*, 5260–5262.
- [186] a) C. P. Gerlach, J. Arnold, *Organometallics* **1997**, *16*, 5148–5157; b) C. P. Gerlach, J. Arnold, *J. Chem. Soc. Dalton. Trans.* **1997**, 4795–4805.
- [187] M. Moore, S. Gambarotta, C. Bensimon, *Organometallics* **1997**, *16*, 1086–1088.
- [188] J.-I. Song, P. Berno, S. Gambarotta, *J. Am. Chem. Soc.* **1994**, *116*, 6927–6928.
- [189] P. Berno, S. Gambarotta, *Organometallics* **1995**, *14*, 2159–2161.
- [190] J. Jupp, S. Gambarotta, *J. Am. Chem. Soc.* **1993**, *115*, 10410–10411.
- [191] J. Jupp, L. Scoles, H. Jenkins, S. Gambarotta, *Chem. Eur. J.* **1996**, *2*, 767–771.
- [192] L. Scoles, K. B. P. Rupp, S. Gambarotta, *J. Am. Chem. Soc.* **1996**, *118*, 2529–2530.
- [193] D. Y. Dawson, H. Brand, J. Arnold, *J. Am. Chem. Soc.* **1994**, *116*, 9797–9798.
- [194] R. R. Schrock, P. R. Sharp, *J. Am. Chem. Soc.* **1978**, *100*, 2389–2399.
- [195] D. Y. Dawson, J. Arnold, *Organometallics* **1997**, *16*, 1111–1113.
- [196] A. Spannenberg, H. Fuhrmann, P. Arndt, W. Baumann, R. Kempe, *Angew. Chem.* **1998**, *110*, 3565–3567; *Angew. Chem. Int. Ed.* **1998**, *37*, 3363–3365.
- [197] a) F. Guerin, D. H. McConville, J. J. Vittal, *Organometallics* **1995**, *15*, 3154–3156; b) F. Guerin, D. H. McConville, J. J. Vittal, G. A. P. Yap, *Organometallics* **1998**, *17*, 1290–1296.
- [198] D. E. Wigley, *Prog. Inorg. Chem.* **1994**, *42*, 239–482.
- [199] a) G. L. Hillhouse, B. L. Haymore, *J. Am. Chem. Soc.* **1982**, *104*, 1537–1548; b) S. Gambarotta, A. Chiesi-Villa, C. Guastini, *J. Organomet. Chem.* **1984**, *270*, C49–C51; c) J. H. Osborne, A. L. Rheingold, W. C. Troglor, *J. Am. Chem. Soc.* **1985**, *107*, 7945–7952; d) D. M. Antonelli, W. P. Schaefer, G. Parkin, J. E. Bercaw, *J. Organomet. Chem.* **1993**, *462*, 213–220.
- [200] M. G. Fickes, W. M. Davis, C. C. Cummins, *J. Am. Chem. Soc.* **1995**, *117*, 6384–6385.
- [201] G. Proulx, R. G. Bergman, *J. Am. Chem. Soc.* **1995**, *117*, 6382–6383.
- [202] C. P. Gerlach, J. Arnold, *Inorg. Chem.* **1996**, *35*, 5770–5780.
- [203] M. Kol, R. R. Schrock, R. Kempe, W. M. Davis, *J. Am. Chem. Soc.* **1994**, *116*, 4382–4390.
- [204] a) C. Woitha, D. Rehder, *Angew. Chem.* **1990**, *102*, 1495–1497; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1438–1440; b) D. Rehder, C. Woitha, W. Priesch, H. Gailus, *J. Chem. Soc. Chem. Commun.* **1992**, 364–365.
- [205] a) J. Kim, D. C. Rees, *Nature* **1992**, *360*, 553–560; b) M. K. Chan, J. S. Kim, D. C. Rees, *Science* **1993**, *260*, 792–794.
- [206] a) D. Sellmann, *Angew. Chem.* **1993**, *105*, 67–70; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 64–66; b) W. H. Orme-Johnson, *Science* **1992**, *257*, 1639–1640; c) H. Deng, R. Hoffmann, *Angew. Chem.* **1993**, *105*, 1125–1128; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1062–1065.

- [207] K.-Y. Shih, R. R. Schrock, R. Kempe, *J. Am. Chem. Soc.* **1994**, *116*, 8804–8805.
- [208] M. B. O'Donoghue, N. C. Zanetti, W. M. Davis, R. R. Schrock, *J. Am. Chem. Soc.* **1997**, *119*, 2753–2754.
- [209] A. L. Odom, P. L. Arnold, C. C. Cummins, *J. Am. Chem. Soc.* **1998**, *120*, 5836–5837.
- [210] M. B. O'Donoghue, W. M. Davis, R. R. Schrock, *Inorg. Chem.* **1998**, *37*, 5149–5158.
- [211] C. E. Laplaza, A. L. Odom, W. M. Davis, C. C. Cummins, *J. Am. Chem. Soc.* **1995**, *117*, 4999–5000.
- [212] C. E. Laplaza, C. C. Cummins, *Science* **1995**, *268*, 861–863.
- [213] W. A. Nugent, J. M. Mayer, *Metal Ligand Multiple Bonds*, Wiley, New York, **1988**.
- [214] S. P. Cramer, K. O. Hodgson, *Prog. Inorg. Chem.* **1979**, *25*, 1–39.
- [215] C. E. Laplaza, M. J. A. Johnson, J. C. Peters, A. L. Odom, E. Kim, C. C. Cummins, G. N. George, I. J. Pickering, *J. Am. Chem. Soc.* **1996**, *118*, 8623–8638.
- [216] R. R. Schrock, S. W. Seidel, N. C. Mösch-Zanetti, K.-Y. Shih, M. B. O'Donoghue, W. M. Davis, W. M. Reiff, *J. Am. Chem. Soc.* **1997**, *119*, 11876–11893.
- [217] a) P. A. Finn, M. S. King, P. A. Kilty, R. E. McCarley, *J. Am. Chem. Soc.* **1975**, *97*, 220–221; b) F. A. Cotton, W. T. Hall, *Inorg. Chem.* **1978**, *17*, 3525–3528.
- [218] S. W. Seidel, R. R. Schrock, W. M. Davis, *Organometallics* **1998**, *17*, 1058–1068.
- [219] K.-Y. Shih, K. Totland, S. W. Seidel, R. R. Schrock, *J. Am. Chem. Soc.* **1994**, *116*, 12103–12104.
- [220] a) P. R. Sharp, S. J. Holmes, R. R. Schrock, M. R. Churchill, H. J. Wasserman, *J. Am. Chem. Soc.* **1981**, *103*, 965–966; b) S. J. Holmes, D. N. Clark, H. W. Turner, R. R. Schrock, *J. Am. Chem. Soc.* **1982**, *104*, 6322–6329.
- [221] M. Leeaphon, P. E. Fanwick, R. A. Walton, *J. Am. Chem. Soc.* **1992**, *114*, 1890–1892.
- [222] K. E. Oglieve, R. A. Henderson, *J. Chem. Soc. Chem. Commun.* **1994**, 377–379.
- [223] R. R. Schrock, K.-Y. Shih, D. A. Dobbs, W. M. Davis, *J. Am. Chem. Soc.* **1995**, *117*, 6609–6610.
- [224] R. R. Schrock, S. W. Seidel, N. C. Mösch-Zanetti, D. A. Dobbs, K.-Y. Shih, W. M. Davis, *Organometallics* **1997**, *16*, 5195–5208.
- [225] a) N. J. Cooper, M. L. H. Green, *J. Chem. Soc. Dalton Trans.* **1979**, 1121–1127; b) N. J. Cooper, M. L. H. Green, *J. Chem. Soc. Chem. Commun.* **1974**, 761–762; c) N. J. Cooper, M. L. H. Green, *J. Chem. Soc. Chem. Commun.* **1974**, 208–209.
- [226] a) O. J. Scherer, *Angew. Chem.* **1990**, *102*, 1137–1155; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1104–1122; b) W. A. Herrmann, *Angew. Chem.* **1986**, *98*, 57–77; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 56–76; c) M. C. Fermin, J. W. Ho, D. W. Stephan, *J. Am. Chem. Soc.* **1994**, *116*, 6033–6034; d) M. H. Chisholm, J. C. Huffman, J. W. Pasterczyk, *Inorg. Chim. Acta* **1987**, *133*, 17–18; e) M. H. Chisholm, K. Foltling, J. W. Pasterczyk, *Inorg. Chem.* **1988**, *27*, 3057–3058.
- [227] C. E. Laplaza, W. M. Davis, C. C. Cummins, *Angew. Chem.* **1995**, *107*, 2181–2183; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2042–2044.
- [228] N. C. Zanetti, R. R. Schrock, W. M. Davis, *Angew. Chem.* **1995**, *107*, 2184–2186; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2044–2046.
- [229] M. Scheer, *Angew. Chem.* **1995**, *107*, 2151–2153; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1997–1999.
- [230] M. Scheer, *Coord. Chem. Rev.* **1997**, *163*, 271–286.
- [231] N. C. Mösch-Zanetti, R. R. Schrock, W. M. Davis, K. Wanninger, S. W. Seidel, M. B. O'Donoghue, *J. Am. Chem. Soc.* **1997**, *119*, 11037–11048.
- [232] M. Scheer, J. Müller, M. Häser, *Angew. Chem.* **1996**, *108*, 2637–2641; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2492–2496.
- [233] M. Scheer, J. Müller, G. Baum, M. Häser, *Chem. Commun.* **1998**, 1051–1052.
- [234] J. A. Johnson-Carr, N. C. Zanetti, R. R. Schrock, M. D. Hopkins, *J. Am. Chem. Soc.* **1996**, *118*, 11305–11306.
- [235] M. Scheer, J. Müller, G. Baum, M. Häser, *Chem. Commun.* **1998**, 2505–2506.
- [236] J. C. Peters, A. L. Odom, C. C. Cummins, *Chem. Commun.* **1997**, 1995–1996.
- [237] a) L. K. Woo, *Chem. Rev.* **1993**, *93*, 1125–1136; b) L. K. Woo, J. G. Goll, D. J. Czaplá, J. A. Hays, *J. Am. Chem. Soc.* **1991**, *113*, 8478–8484; c) F. L. Neely, L. A. Bottomley, *Inorg. Chim. Acta* **1992**, *192*, 147–149; d) L. A. Bottomley, F. L. Neely, *J. Am. Chem. Soc.* **1989**, *111*, 5955–5957; e) M. Bakir, P. S. Withe, A. Dovletoglou, T. J. Meyer, *Inorg. Chem.* **1991**, *30*, 2835–2836.
- [238] A. L. Odom, C. C. Cummins, J. D. Protasiewicz, *J. Am. Chem. Soc.* **1995**, *117*, 6613–6614.
- [239] a) J. D. Debad, P. Legzdins, R. Reina, M. A. Young, R. J. Batchelor, F. W. B. Einstein, *Organometallics* **1994**, *13*, 4315–4321; b) E. B. Brouwer, P. Legzdins, S. J. Rettig, K. J. Ross, *Organometallics* **1994**, *13*, 2088–2091; c) W. L. Gladfelter, *Adv. Organomet. Chem.* **1985**, *24*, 41–86.
- [240] D. S. Williams, T. J. Meyer, P. S. White, *J. Am. Chem. Soc.* **1995**, *117*, 823–824.
- [241] A. L. Odom, C. C. Cummins, *Organometallics* **1996**, *15*, 898–900.
- [242] C. E. Laplaza, A. R. Johnson, C. C. Cummins, *J. Am. Chem. Soc.* **1996**, *118*, 709–710.
- [243] M. J. A. Johnson, P. M. Lee, A. L. Odom, W. M. Davis, C. C. Cummins, *Angew. Chem.* **1997**, *109*, 110–113; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 87–91.
- [244] J. C. Peters, A. R. Johnson, A. L. Odom, P. W. Wanandi, W. M. Davis, C. C. Cummins, *J. Am. Chem. Soc.* **1996**, *118*, 10175–10188.
- [245] P. W. Wanandi, W. M. Davis, C. C. Cummins, M. A. Russell, D. E. Wilcox, *J. Am. Chem. Soc.* **1995**, *117*, 2110–2111.

How Long Have Nonlinear Effects Been Known in the Field of Catalysis?*

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Dedicated to Henri B. Kagan

A widespread belief in chemistry is that racemates and their constituent enantiomers do not differ in their scalar physical properties, such as boiling point. However, there is a series of examples which proves that this is not always the case. A particularly spectacular example is the boiling point of isopropyl trifluorolactate: Under normal pressure the (*S*)-enantiomer has a boiling point approximately 43 °C higher than that of the racemate.^[1] This difference in boiling point allows the separation of a nonracemic mixture of this compound by fractional distillation! These differences in physical properties are due to the formation of diastereomeric aggregations which result from interactions between the two enantiomers. These interactions are also known to be the cause of unexpected sublimation phenomena^[2] and NMR spectra.^[3] At the beginning of the 1970s Horeau et al.^[4] reported the first examples of the nonlinear relationship between optical purity and enantiomeric excess caused by diastereomeric aggregations. Further unusual results which were explained on the basis of enantiomeric interactions have been compiled by Noyori et al.^[5]

The question as to what extent such a nonideal relationship effects chemical reactions goes back to Wynberg and Feringa.^[6] Their well-known work led to the following proposition: "When a chiral substance undergoes a reaction, the reaction rate and the product ratio will depend—inter alia—upon the enantiomeric excess present in the starting material."^[6a]

A logical continuation of this idea has recently led to nonlinear effects in asymmetric catalysis, first described

quantitatively by Kagan and Agami et al. in 1986,^[7] and these effects^[8] are proving to be fruitful in asymmetric synthesis. A recent review on the subject contains not only the results obtained up to the present but also briefly discusses some possible future developments.^[9]

The quantitative inclusion of the activity^[10] in addition to the almost exclusively observed selectivity leads to a considerably better model and almost certainly to a better interpretation of the experimental results. The same treatment is also valid for product selectivity as a function of conversion.^[11]

Until the appearance of the article by Kagan and Agami et al.,^[7] it was generally accepted that the maximum *ee* value obtainable in an asymmetric synthesis was equal to the maximum *ee* value of the chiral auxiliary or chiral catalyst employed in the reaction [Eq. (1)].

$$ee_{\text{prod.}} = ee_0 ee_{\text{aux.}} \quad (1)$$

Here *ee*_{prod} corresponds to the experimentally obtainable enantiomeric excess of the product, *ee*₀ is the value when the auxiliary or catalyst employed is optically pure, and *ee*_{aux} represents the enantiomeric excess of the auxiliary or catalyst. Practical experiments, however, have shown that there are deviations from the linear behavior: These deviations from linearity are designated as either positive or negative nonlinear effects.

Reactions with a positive nonlinear effect are particularly attractive. Starting from an optically impure catalyst in a reaction displaying a positive nonlinear effect, it is possible to obtain reaction products with a higher enantiomeric excess than is expected from the catalyst's optical purity. Essentially this represents an amplification of the chirality.

The model systems developed to explore this effect generally contain a variable number of rapidly exchanging chiral ligands (in the simplest case two, corresponding to the "ML₂ model") surrounding a reaction center. Under stationary conditions there are homo- and heterochiral complexes which lead to enantiomeric and racemic^[12] products, respectively. Analogues of Equation (1) containing correction factors have been derived to give a quantitative description of these cases. The correction factors contain terms representing both the relative reactivities and the ratio between the hetero- and homochiral complexes, and it is these terms which cause

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[**] We would like to thank the Deutsche Forschungsgemeinschaft as well as the Fonds der Chemischen Industrie for their generous support of this work. We are also indebted to the following colleagues for many helpful and productive discussions: Prof. Dr. H. B. Kagan, Prof. Dr. H. Brunner, Prof. Dr. C. Bolm, Prof. Dr. U. Rosenthal, Priv.-Doz. Dr. A. Börner, Priv.-Doz. Dr. M. Michalik.

the nonlinearity in the relationship between the experimentally obtained *ee* values of the product and the *ee* value of the starting material.

An impressive example of a positive nonlinear effect is the alkylation of benzaldehyde with diethylzinc in the presence of a catalytic amount of a chiral amino alcohol, such as 3-*exo*-dimethylaminoisoborneol.^[5, 13] Even the addition of an amino alcohol with only a 15% enantiomeric excess (an optically very impure catalyst) leads catalytically to a product with a optical purity of about 95%—an incredible amplification of chirality!

The basic condition for the appearance of nonlinear effects in stereoselective reactions has been summarized by Kagan as follows: “The generation of diastereomeric species is the key feature that gives deviation from linearity”.^[9]

In connection with this a résumé published by Langenbeck^[14] in 1936 appears astoundingly far-sighted: “It must be possible using a highly stereochemically specific catalyst, and where an equilibrium is formed with the substrate, to realize an increase in the optical purity when one allows an optically impure catalyst to catalyze a reaction starting with an optically impure substrate”.^[15]

The expression that Langenbeck first coined “Reinheitszunahme” (increase in optical purity) corresponds exactly in its content to what we understand nowadays in asymmetric synthesis as a “positive nonlinear effect”.

The following quotations come from Langenbeck’s work entitled “Theory of the Conservation and Origin of Optical Activity in Nature”: “With every synthesis of an optically active compound from inactive starting materials, a degradation in optical purity takes place; that is, the newly formed compound is less optically active than the compound from which the optical activity was derived.” The author continues:

“If an enzyme is synthesized using another optically active enzyme, the newly formed product cannot be optically pure. The infinite repetition of these processes over a geological time period would have led to a complete loss of optical activity in enzymes (and therefore of all naturally occurring compounds) if the degradation in optical purity were not compensated for by an increase in optical purity in different processes.”^[15]

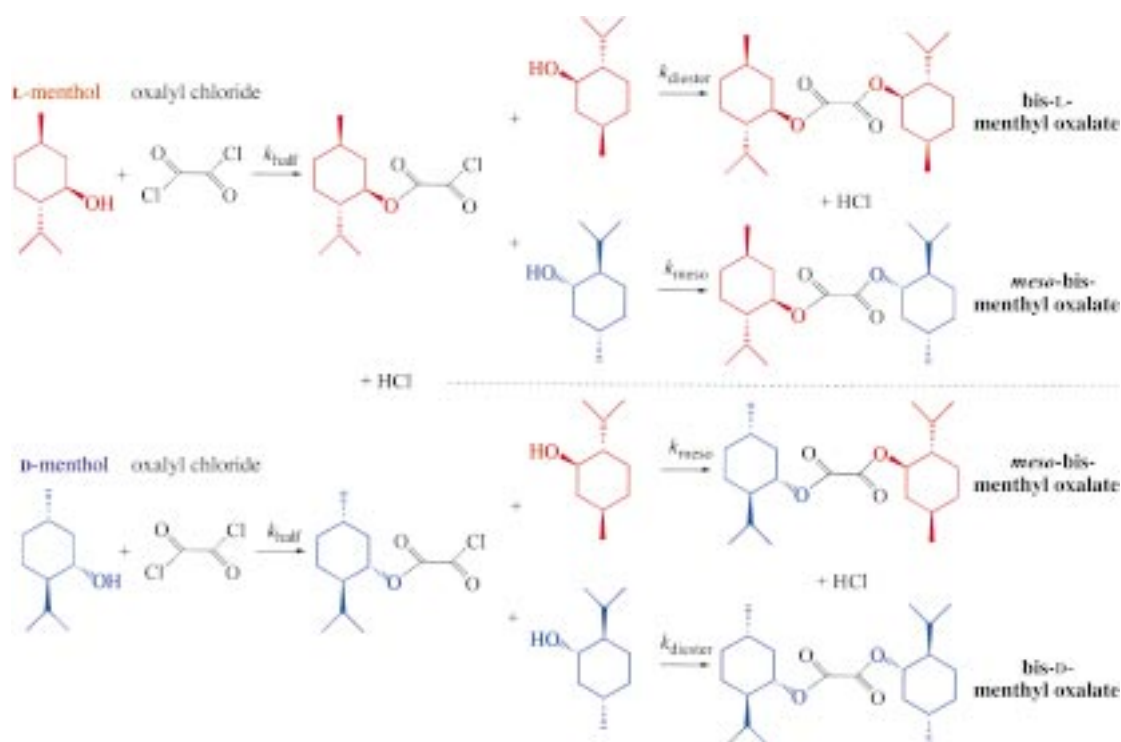
The reaction between L-menthol and oxalyl chloride was used as a simple model system for the experimental investigation of this postulated increase in optical purity (Scheme 1).

The results of the polarimetric determination of the angle of rotation of the product mixture, consisting of the optically active ester as well as the *meso* ester, are shown in Figure 1 (curve I). The optical purity of L-menthol used as the starting material was varied from racemic to optically pure.

Curve II in Figure 1 shows the optical rotation of the product diester, bis-L-menthyl oxalate, as a function of optical purity, thus providing a reference for curve I. Figure 2 shows the same experiment reevaluated using modern chromatographic techniques (HPLC) instead of the original polarimetric measurements.^[16]

Although Langenbeck had no suitable analytical method for determining the proportion of *meso* ester present, he nevertheless correctly predicted the result: “If it were possible to separate the *meso* ester quantitatively, then it would be expected that even with use of L-menthol with a low *ee* value, an increase in the optical purity of the product would be observed”.^[15]

The results obtained with use of racemic menthol (0% *ee*) and optically pure L-menthol (100% *ee*) characterize the limiting values for a linear relationship in a graph of the *ee*



Scheme 1. Reaction sequence for the conversion of oxalyl chloride with optically enriched L-menthol.

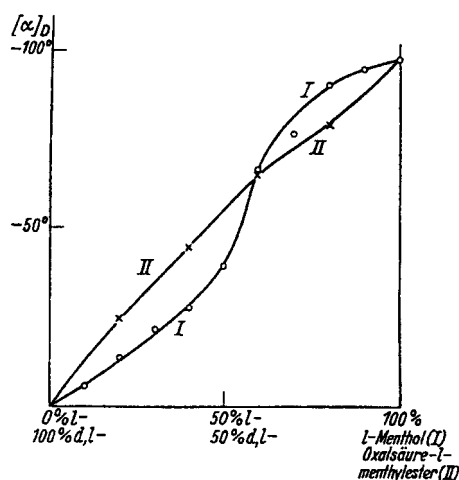


Figure 1. The increase in optical purity for the model reaction of L-menthol with oxalyl chloride reported by Langenbeck.^[15] (The original figure is reproduced here with permission from Oldenbourg Wissenschaftsverlag GmbH. L-Menthol = L-menthol, Oxalsäure-L-menthyl-ester = L-menthyl oxalate.)

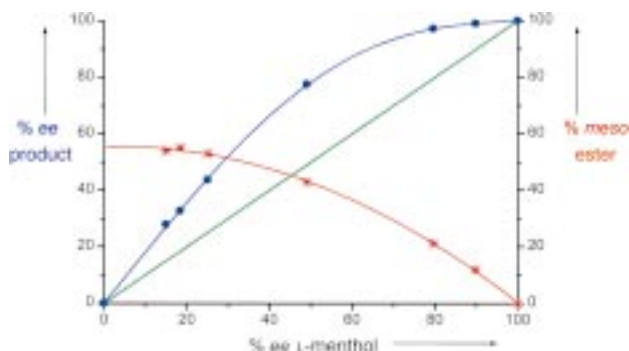


Figure 2. Plot of the enantiomeric excess (%) of the product as well as the percentage of *meso*-bis-menthyl oxalate as a function of the *ee* value (%) of the starting material. (A total of 5 g of the menthol mixture was treated with 50 % of the stoichiometric amount of oxalyl chloride and worked up as described in ref. ^[15]. The resultant ester mixture was analyzed by HPLC.^[16])

values of the product plotted against the *ee* values of the starting material. A positive deviation from this zero point line has been seen for all other *ee* values of menthol, corresponding to a positive nonlinear effect. The fundamental cause of this characteristic deviation is that the addition of optically impure as well as nonracemic menthol leads to the formation of the *meso* ester. The stoichiometry of the *meso* compound dictates that equal quantities of the two enantiomers of menthol are required for its formation. Hence, we always observe a larger *ee* value than expected for the optically active diester, in comparison to the *ee* value of the menthol used.^[17] Consequently this reasoning forbids the existence of negative nonlinear effects. It is important to note that a linear relationship between the *ee* value of the starting material and the *ee* value of the product should always be observed in the case of complete turnover without formation of the *meso* compound.

The cause of the nonlinear effects discussed in Kagen's review^[9] is the formation of an "intermediate" diastereomeric species. In contrast, the cause of the positive nonlinear effects

described by Langenbeck is the formation of a diastereomeric product species.

There is not much literature about positive nonlinear chirality transfer or the practical applications of this effect for reactions which are neither catalytic reactions nor asymmetric syntheses.^[18] Horeau et al. have described a variety of reaction variants.^[19] By removal of the *meso* product and recovery of the starting material, the optical purity of the starting material can be increased. After several repetitions of this procedure it was possible to achieve optical purities of over 95 % in many cases—starting from about 50 %—in accordance with the quantitative equations on the basis of the statistical product distribution. Further examples of this "purification by duplication" are to be found in ref. ^[20]. The amplification effect observed by Langenbeck (Figure 2) itself does not represent a focal point of interest in all examples discussed so far, but has always been viewed as an intermediating effect.

The NMR spectroscopic determination of enantiomeric excess, for example in the case of alcohols, is an interesting application of the "*meso* effect". According to the principle which goes back to Feringa et al.^[21] optically active compounds can be transformed with an achiral reagent such as PCl_3 . Under the condition of a statistical product distribution, it is then easily possible from the NMR spectrum to determine the relationship of the sum of each of the newly formed hetero- and homochiral compounds and therefore the enantiomeric excess of the optically active starting material. The amplification of the enantiomeric excess in the product is meaningless. Analogous approaches can be found in the literature.^[22]

The mechanism for the formation of the bis-menthyl oxalate from the corresponding monoester is shown in Scheme 1. For simplicity the individual steps are assumed to be irreversible. The monoester is able to react to give the optically pure diester or the *meso* form. For these steps the rate constants (k_{diester} and k_{meso}) are, in principle, not equal. The resulting set of differential equations can be solved numerically.^[23] When values are entered for the rate constants and starting concentrations of menthol and oxalyl chloride, the simulation provides the result presented in Figure 3; the reaction was followed to completion.

The simulations carried out can be summarized in the following way: A positive nonlinear effect is always observed for the product selectivity if nonracemic or optically impure

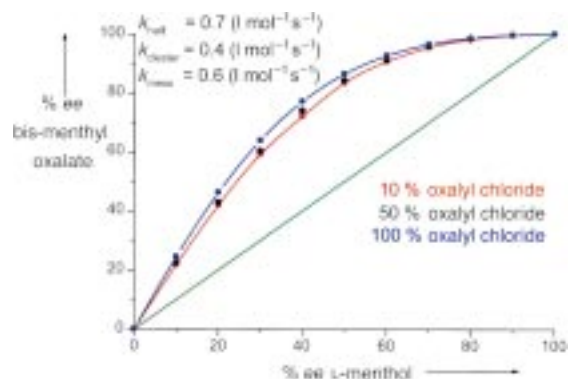


Figure 3. Calculated positive nonlinear effects for the reaction described in Scheme 1. Different starting values for oxalyl chloride were entered; 100 % corresponds to the stoichiometric amount.

(scalemic) starting material is used, since the formation of the *meso* species is a necessary and sufficient condition for amplification of chirality. Even if the rate constants of the *meso* product formation are equal (i.e., a statistical distribution) or smaller than the rate constants of the diester formation, a positive nonlinear effect results. It is easy to understand that with more pronounced formation of the *meso* ester the positive nonlinear deviations also become larger, but at the cost of the yield of the optically enhanced product.

Reactions which are not pure dimerizations of the chiral starting material—in the diester formation shown in Scheme 1 the enantiomeric starting material is coupled through an oxalic acid unit—offer still another interesting aspect, namely, the variation of this component.

The simulation of various starting material concentrations of oxalyl chloride (from sub- to stoichiometric amounts) provide another degree of freedom, which leads to the following results: When $k_{\text{meso}} > k_{\text{diester}}$ (see Figure 3), the positive nonlinear effect with stoichiometric amounts of oxalyl chloride (100%) is larger than for substoichiometric amounts of oxalyl chloride. For the case where $k_{\text{meso}} < k_{\text{diester}}$ this is reversed, the largest positive nonlinear effects being observed when the quantity of oxalyl chloride used is far below the stoichiometric amount.

In connection with the variation of the amount of oxalyl chloride used, a possibly interesting parallel can be found to what has been described in the review^[9] about nonlinear effects in asymmetric catalysis and stereoselective synthesis. What happens when the concentration of the chiral ligand is larger than is necessary for the formation of the homo- and heterochiral complexes? Under certain conditions a further amplification of chirality is to be expected.

The application of this “*meso* effect” is also conceivable for reactions which only work in the presence of a catalyst. An amplification of chirality is to be expected for a variant of the photocatalytic heterocyclization^[24] of C_2 -symmetric chiral alkynes with nitriles to give pyridines. It is possible that this type of amplification phenomenon, whether catalytic or stoichiometric, plays a role in the formation of the homochirality seen in nature.^[25]

Wolfgang Langenbeck's visionary prediction made 60 years ago about an “increase in optical purity” in catalytic asymmetric synthesis is a current area of modern chemistry that is very closely connected with Kagan's work.

The formation of diastereomeric species is the prime and—in the usual case of nonequal reactivity of the hetero- and homochiral catalysts—a sufficient requirement for a nonlinear chirality transfer to be observed. If the diastereomeric interactions take place in the catalyst, the result is a nonlinear effect in asymmetric synthesis and stereoselective reactions.

For the chiral amplification accompanying the formation of a diester from the reaction with a chiral alcohol, first described by Langenbeck, the diastereomeric interactions are transferred from the level of the intermediates to the level of the products. This means that these interactions do not play a role in the catalyst or auxiliary, but only in product formation. The consequences are differences in the reaction type as well as in the requirements of the starting material.

The resulting reaction sequence is not an asymmetric synthesis or stereoselective reaction, but involves the use of a chirally enhanced starting material. A disadvantage is the unproductive formation of the *meso* compound, whereby the starting material can usually be recovered, however, only in racemic form. It would be possible to overcome this disadvantage by either manual methods or by a kinetic resolution followed by renewed use of the starting material. However, the long-known and also indirectly used approach represents an interesting variant of chirality amplification as only positive nonlinear effects can, in principle, occur and applications in catalytic reactions seem possible.

Received: August 25, 1999 [C20027]

- [1] T. Katagiri, C. Yoda, K. Furuhashi, K. Ueki, T. Kubota, *Chem. Lett.* **1996**, 115–116.
- [2] H. Kwart, D. P. Hoster, *J. Org. Chem.* **1967**, 32, 1867–1870.
- [3] T. Williams, R. G. Pitcher, P. Bommer, J. Gutzwiller, M. Uskovic, *J. Am. Chem. Soc.* **1969**, 91, 1871–1872.
- [4] a) A. Horeau, *Tetrahedron Lett.* **1969**, 36, 3121–3124; b) A. Horeau, J. P. Guette, *Tetrahedron* **1974**, 30, 1923–1931.
- [5] R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, 103, 34–55; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 49–69.
- [6] a) H. Wynberg, B. Feringa, *Tetrahedron* **1976**, 32, 2831–2834; b) H. Wynberg, *Chimia* **1976**, 30, 445–451.
- [7] C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, 108, 2353–2357.
- [8] The term “nonlinear effect” is somewhat unfortunate, as other correlations such as the product selectivity as a function of the optical purity of a catalyst are also nonlinear. An example is the dependence of the logarithmic product ratio of selective reactions as a function of the reciprocal temperature (isoinversion principle): a) H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem.* **1991**, 103, 480–515; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 477–515. b) D. Heller, H. Buschmann, *Top. Catal.* **1998**, 5, 159–176. This nonlinear temperature dependence—the first work was carried out by Pracejus (H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, 634, 9–22)—should be typical for all reactions displaying nonlinear effects in the “Kaganian” sense. The product enantiomers result from various reaction pathways.
- [9] C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, 110, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, 37, 2923–3127.
- [10] D. G. Blackmond, *J. Am. Chem. Soc.* **1997**, 119, 12934–12939.
- [11] a) D. G. Blackmond, *J. Am. Chem. Soc.* **1998**, 120, 13349–13353; b) D. G. Blackmond, T. Rosner, T. Neugebauer, M. T. Reetz, *Angew. Chem.* **1999**, 111, 2333–2335; *Angew. Chem. Int. Ed.* **1999**, 38, 2196–2199.
- [12] For an uneven number of ligands, such as in the ML_3 model, the heterochiral species is not a *meso* compound, and this has a corresponding effect on product formation.
- [13] M. Kitamura, S. Okada, S. Suga, R. Noyori, *J. Am. Chem. Soc.* **1989**, 111, 4028–4036.
- [14] W. Langenbeck (1899–1967) together with G. Rienäcker founded the “Institut für Katalyseforschung der Akademie der Wissenschaften” in Rostock, Germany in 1951. This was the first institute for catalysis research in Europe. He is famous above all for his work on enzyme models as well as his text book of organic chemistry. For a detailed summary of Langenbeck's work, see A. Schellenberger, *Chem. Ber.* **1990**, 123, I–XV. A symposium of the German Chemical Society (GDCh) was held in Rostock/Warnemünde on June 21 and 22, 1999 on the occasion of Langenbeck's 100th birthday.
- [15] W. Langenbeck, G. Triem, *Z. Phys. Chem. A* **1936**, 177, 401–408.
- [16] The HPLC measurements were conducted using a Liquid Chromatograph 1090 from Hewlett Packard, equipped with a diode-array detector. The enantiomeric diester was separated from the *meso* form of the bis-menthyl oxalate on an achiral stationary phase Nucleosil NH_2 with 0.015% ethanol in hexane as the eluent. The separation of bis-D-menthyl oxalate from bis-L-menthyl oxalate and the *meso* form

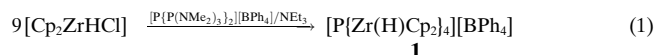
- was successful on a stationary phase Chiralcel OD-H (Daicel) with hexane as the eluent. Area factors between the optically pure diesters and the *meso* compound were disregarded, as these did not change the qualitative results.
- [17] Amplification effects for a reaction of second or higher order that did not proceed with full conversion to products and which are not reducible to diastereomeric units were not investigated further due to the complexity of the problem. For example, if a nonracemic enantiomeric mixture reacted exclusively to give a homodimer product ($2A \rightarrow AA$ or $2B \rightarrow BB$) and if the conversion is less than 100%, the enantiomeric excess of the product is always larger than that of the starting material. Many examples of this type of amplification are discussed by a variety of authors in "Origins of Chiral Homogeneity in Nature": W. A. Bonner in *Topics in Stereochemistry*, Vol. 18 (Eds.: E. L. Eliel, S. H. Wilen), Wiley, New York, **1988**, pp. 1–96.
- [18] a) "Kinetic Resolution": H. B. Kagan, J. C. Fiaud in *Topics in Stereochemistry*, Vol. 18 (Eds.: E. L. Eliel, S. H. Wilen), Wiley, New York, **1988**, pp. 249–330; b) V. Rautenstrauch, P. Megard, B. Bourdin, A. Furrer, *J. Am. Chem. Soc.* **1992**, *114*, 1418–1428.
- [19] J. P. Vigneron, M. Dhaenens, A. Horeau, *Tetrahedron* **1973**, *29*, 1055–1059.
- [20] a) J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, **1981**; b) A. Shanzer, J. Libman, H. E. Gottlieb, *J. Org. Chem.* **1983**, *48*, 4612–4617; c) I. Fleming, S. K. Ghosh, *J. Chem. Soc. Chem. Commun.* **1994**, 99–100.
- [21] B. L. Feringa, A. Smaardijk, H. Wynberg, *J. Am. Chem. Soc.* **1985**, *107*, 4798–4799.
- [22] a) J. Leitich, *Tetrahedron Lett.* **1969**, *38*, 3589–3592; b) M. L. Pasquier, W. Marty, *Angew. Chem.* **1985**, *97*, 328–329; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 315–316; c) W. Marty, M. L. Pasquier, H. Gampp, *Helv. Chim. Acta* **1987**, *70*, 1774–1785.
- [23] Program MATHCAD, version 8 professional (MathSoft, Inc., Copyright **1991–1998**).
- [24] a) B. Heller, G. Oehme, *J. Chem. Soc. Chem. Commun.* **1995**, 179–180. b) B. Heller, D. Heller, G. Oehme, *Eur. Photochem. Accoc. Newsletter* **1998**, *62*, 37–50. c) B. Heller, *Nachr. Chem. Tech. Lab.* **1999**, *47*, 9–14.
- [25] B. L. Feringa, R. A. van Delden, *Angew. Chem.* **1999**, *111*, 3624–3645; *Angew. Chem. Int. Ed.* **1999**, *38*, 3418–3438.

“Breaking the Rules”: A Planar Phosphonium Cation

Douglas W. Stephan*

One hundred and twenty five years ago van't Hoff and Le Bel proposed tetrahedral coordination of carbon atoms.^[1–3] This notion, derived from an examination of physical models, was initially conceived to explain the existence of optical and other isomers. Despite the fact that this concept was vehemently attacked at the time, the implications of the three-dimensional arrangement of atoms in molecules soon precipitated work that formed the basic precepts of what was to become the fields of stereochemistry and conformational analysis. The subsequent developments of the Lewis bonding models and classical molecular orbital theory provided a theoretical grounding for the van't Hoff–Le Bel hypothesis. During the intervening century, this fundamental contribution, made in 1874, was accepted as one of the guiding principles of chemistry. Despite the widespread application of this doctrine in organic and main group chemistry, theoretical predictions in the 1970s suggested the synthesis of planar methane or silane derivatives or their isoelectronic quaternary ammonium or phosphonium analogues might be possible by employing bulky organic or organometallic substituents. While these predictions countered the culture of the day, they threw down a challenging gauntlet to synthetic chemists. Now, almost 30 years after these predictions, Driess and co-workers^[4] have achieved the synthesis and characterization of the first planar tetra-substituted phosphonium salt.

Driess and his colleagues have uncovered that reaction of Schwartz's reagent $[\text{Cp}_2\text{ZrHCl}]$ and the triphosphenium salt $[\text{P}(\text{P}(\text{NMe}_2)_3)_2][\text{BPh}_4]$ in a 9:1 ratio and in the presence of base results in the formation of the green crystalline product $[\text{P}(\text{Zr}(\text{H})\text{Cp}_2)_4][\text{BPh}_4]$ (**1**) in 11 % yield [Eq. (1)].



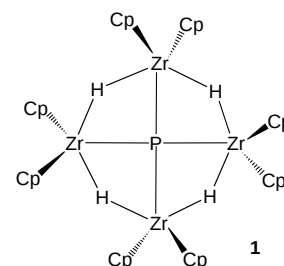
X-ray crystallographic characterization of **1** confirmed the formulation as the phosphonium salt **1**. Moreover, the data establishes the almost ideal square-planar coordination sphere about the central phosphorus atom with Zr–P–Zr

angles very close to 90°. Hydrides bridge adjacent Zr atoms forming a nearly planar eight-membered ring that encircles the central P atom.

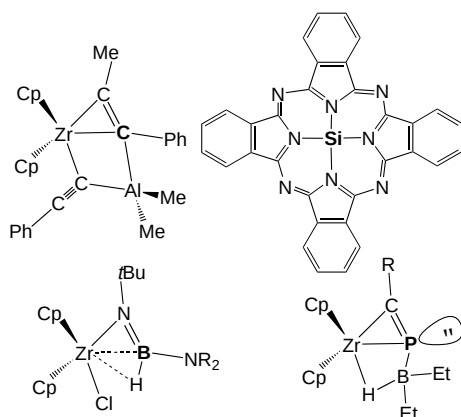
Compound **1** represents an unprecedented example of a square-planar phosphonium salt. Use of the highly electro-positive metal centers as substituents in **1** are thought to provide the π -acceptor capabilities necessary for delocalization of the π electrons on the phosphorus atom. Zirconium–phosphorus π bonding is known to stabilize unusual geometries, for example, the phosphide complex $[(\text{Cp}_2\text{Zr})_2(\mu_2\text{-Cl})(\mu_3\text{-P})(\text{ClZrCp}_2)]$ is trigonal planar at phosphorus.^[5] However, compound **1** represents the first case where such Zr–P interactions have been employed to achieve stabilization of an “anti van't Hoff–Le Bel” configuration. Ab initio calculations support the view that it is electronic factors rather than the steric influence of ancillary ligands that favor the planar phosphorus geometry in **1**.

Previous work by Schmidbaur et al. had described the related per-metalated species $[\text{N}\{\text{Au}(\text{PPh}_3)_4\}_4]^+$ and $[\text{As}\{\text{Au}(\text{PPh}_3)_4\}_4]^+$.^[6] However, these species do not exhibit an “anti van't Hoff–Le Bel” configuration, rather they adopt classical tetrahedral or square-base pyramidal geometries. This is attributable to the poorer π -acceptor properties of the gold fragments and favorable Au...Au interactions. The analogous P-based species is not known although computations also predict a square-pyramidal geometry.^[7]

Other compounds adopting an “anti van't Hoff–Le Bel” configuration, have drawn some recent attention (Scheme 1). Erker and Röttger^[8] have recently reviewed such compounds with a particular emphasis on species containing planar-tetracoordinate carbon centers. In a number of these species, the geometry about the carbon center is also stabilized by the presence of electropositive metal centers (e.g. Ti, Zr, Al). Examples of heteroatom “anti van't Hoff–Le Bel” compounds are less abundant. Several examples of planar tetracoordination exist for boron, while crystals of a phthalocyanine derivative have been found to include a planar silicon atom with a 17% occupancy.^[8] Several compounds have been described in which four metal atoms yield a planar oxygen coordination sphere, although no such species have



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Scheme 1. Selected examples of compounds with atoms in “anti van’t Hoff–Le Bel” configurations.

been reported for nitrogen or phosphorus.^[8] However, if one considers a lone pair of electrons replacing a fourth substituent, then the phosphalkyne complex adduct $[\text{Cp}_2\text{Zr}(\text{RCP})(\text{HBEt}_2)]$ reported by Binger et al.^[9] can be considered to contain a phosphorus atom in an “anti van’t Hoff–Le Bel” configuration.

The strategy employed by Driess et al.^[4] in the isolation of **1** may well have broad implications. Theoretical computations suggest that analogous “anti van’t Hoff–Le Bel” geometries for SiR_4 and $[\text{AlR}_4]^-$ ($\text{R} = \text{Zr}(\text{H})\text{Cl}_2$) may well be accessible. Similar calculations for ER_4 ($\text{E} = \text{B}^-, \text{C}, \text{N}^+$) infer a preference for a distorted tetrahedral geometry. However, it may be that

other electropositive organometallic fragments will provide the requisite π -delocalization permitting access to a broader variety of compounds in “anti van’t Hoff–Le Bel” configurations. While the preparative routes to other compounds containing these unusual geometries remains a synthetic challenge, this breakthrough prompts new and important fundamental questions regarding the effect of distorted geometries on the reactivity and reaction pathways. The discovery of this class of planar-tetracoordinate compounds does not supplant the 125-year-old notions of van’t Hoff and Le Bel, rather, it describes exceptions to the “rules”, broadening our understanding of molecular structure. Perhaps more importantly, these efforts demonstrate that even long-standing tenets of a discipline must be questioned in an effort to more fully understand the fundamentals of the science.

- [1] J. H. van’t Hoff, *Arch. Neerl. Sci. Exactes Nat.* **1874**, 9, 445.
- [2] J. A. Le-Bel, *Bull. Soc. Chim. Fr.* **1874**, 22, 337.
- [3] M. Rouhi, *Chem. Eng. News* **1999**, 77, 28.
- [4] M. Driess, J. Aust, K. Merz, C. van Wüllen, *Angew. Chem.* **1999**, 111, 3967; *Angew. Chem. Int. Ed.* **1999**, 38, 3677.
- [5] J. Ho, R. Rousseau, D. W. Stephan, *Organometallics* **1994**, 12, 1918.
- [6] E. Zeller, H. Beruda, A. Kolb, P. Bissinger, J. Reide, H. Schmidbaur, *Nature* **1991**, 352, 141.
- [7] J. Li, P. Pykkö, *Inorg. Chem.* **1993**, 32, 2630.
- [8] D. Röttger, G. Erker, *Angew. Chem.* **1997**, 109, 840; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 812.
- [9] P. Binger, F. Sandmeyer, C. Krüger, J. Kuhnigk, R. Goddard, G. Erker, *Angew. Chem.* **1994**, 106, 213; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 197.

How Many Networks Can Be Made from Four-Coordinate Atoms?

Ulrich Müller*

In diamonds tetrahedrally coordinated atoms form a recurring, three-dimensional network. The same kind of network is found in cristobalite, with Si–O–Si groups taking the place of C–C bonds. A large number of other networks which consist of similarly joined tetrahedral building units are known among the polymorphs of SiO_2 and H_2O and especially among the zeolites.^[1] In the network we can discern knots (Si atoms), edges (Si–O–Si bonds), and enclosed voids. The voids can be treated as tiles; a zeolite structure is then a three-dimensional recurring tiling. The tiles can have different shapes. For example, cubes, hexagonal prisms, β -cages (octahedra with cut vertices), and several others occur in zeolites. Every knot is joined with four other knots in a first sphere; in

a second (and third, etc.) sphere, there may be different numbers of knots and they can be connected in different ways. For this reason, different kinds of knots can exist. Depending on the number of different kinds of knots the network is called uninodal, binodal, etc.

In two dimensions, there exist eleven different uninodal tilings, which already have been described by Johannes Kepler,^[2] and 508 binodal tilings.^[3] A procedure to calculate the numbers of possible tilings has been developed by the mathematician Dress and co-workers.^[4, 5] Thus, the number of 508 was confirmed^[6] and the number of possible trinodal two-dimensional tilings was calculated to be 16774.^[7] Now the same research group has extended the procedure to three-dimensional tilings,^[8] a fact that was even acknowledged in the daily newspapers. An essential part of the calculations deals with “Delaney symbols”. These allow the neighborhood of a tile to be designated in a concise way. The numbering of all recurring tiling amounts to the numbering of Delaney symbols.

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First results have been presented for networks having four-connected knots. In their consideration, “simple” and “quasi-simple” tilings are distinguished. This is a distinction that is somewhat contrary to the intuition of chemists. In a “simple” tiling every edge is common to exactly three tiles and at every vertex exactly three faces of a tile meet. The pattern is considered to be “simple” even if there are different kinds of tiles. Tiles for example can be cubes, tetrahedra, or prisms, but not octahedra. However, a packing of cubes, which a chemist would consider to be simple, is not “simple” (because an edge is common to four cubes).

For “simple” uninodal tilings there exist nine tilings, six of which correspond to known zeolite types and the other three have been described by O’Keeffe and Hyde.^[9] Diamond, lonsdaleite (hexagonal diamond), cristobalite, gmelinite, cancrinite and further uninodal silicates belong to the 285 possibilities calculated for “quasi-simple” tilings with four-connected networks. Some structures, which from the mathematical point of view, are more complicated (neither “simple” nor “quasi-simple”), such as quartz, are not included in these numbers. The numbers of “simple” binodal und trinodal tilings were calculated to be 117 and 926, respectively; most of these do not correspond to a known structure. Two of them are shown in Figure 1. On the other hand, zeolites are known with up to 12 different kinds of knots.

The different views of what is taken to be “simple”, depend on the starting point. For Dress et al. the tiles are the primary pieces, whereas chemists look essentially at the network of chemical bonds, at knots (atoms), and at coordination polyhedra (which are not tiles). For chemists (and crystallographers), the mathematical problem is not yet solved. Mathematicians can calculate exactly how many tilings are possible. However, the same network can result from some different tilings. The calculated 294 (9 + 285) “simple” and “quasi-simple” uninodal tilings correspond to only 154 or so four-connected networks. The exact number of networks can not yet be calculated; the research group of Dress is still trying hard to solve this. Furthermore, the procedure does not include crystal structures in which two separate networks of the same kind are interwoven, such as in Cu_2O .

The results contradict earlier calculations. Using graphs and “simulated annealing”, Treacy et al.^[10] found 6471 uninodal four-connected networks. However, they admit certain shortcomings in their procedure and state that their list is not complete. Unfortunately, Dress et al.^[8] do not comment on this; they also do not cite the numerous earlier papers dealing with the systematic classification and numbering of structural possibilities of zeolites (and other networks), for example by Smith^[11] or by Bosmans and Andries^[12] (see refs. [10] and [12] for many other citations).

In a uninodal network the knots could be marked by different colors or be occupied by atoms of different elements, without changing the network itself. Thus far, the tilings have not been distinguished by such kinds of marking. Diamond, zinc blende, and chalcopyrite (CuFeS_2) have the same tiling and network, and are not distinguished. In crystal chemistry how many ways a network can be marked, that is how many crystal structure types can result from substitution, is indeed an important question. The numbering of possible substitu-

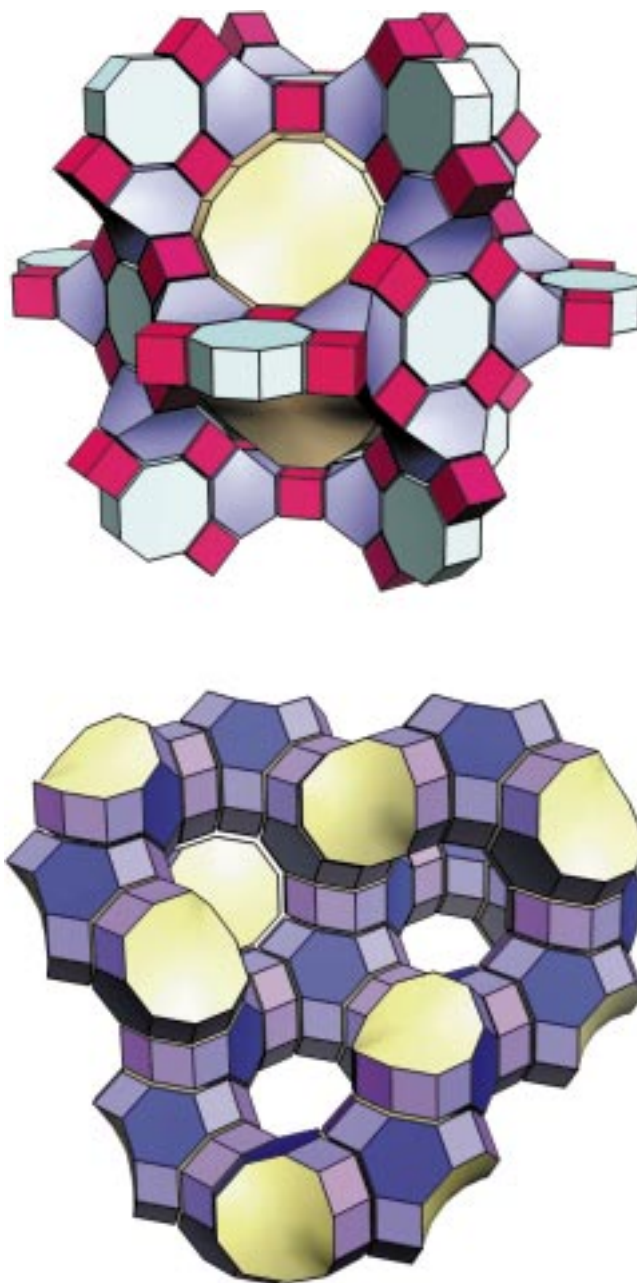


Figure 1. Two examples of the 285 possible binodal tilings (image by Delgado, reproduced with permission from ref. [8]; © 1999, McMillan Magazines).

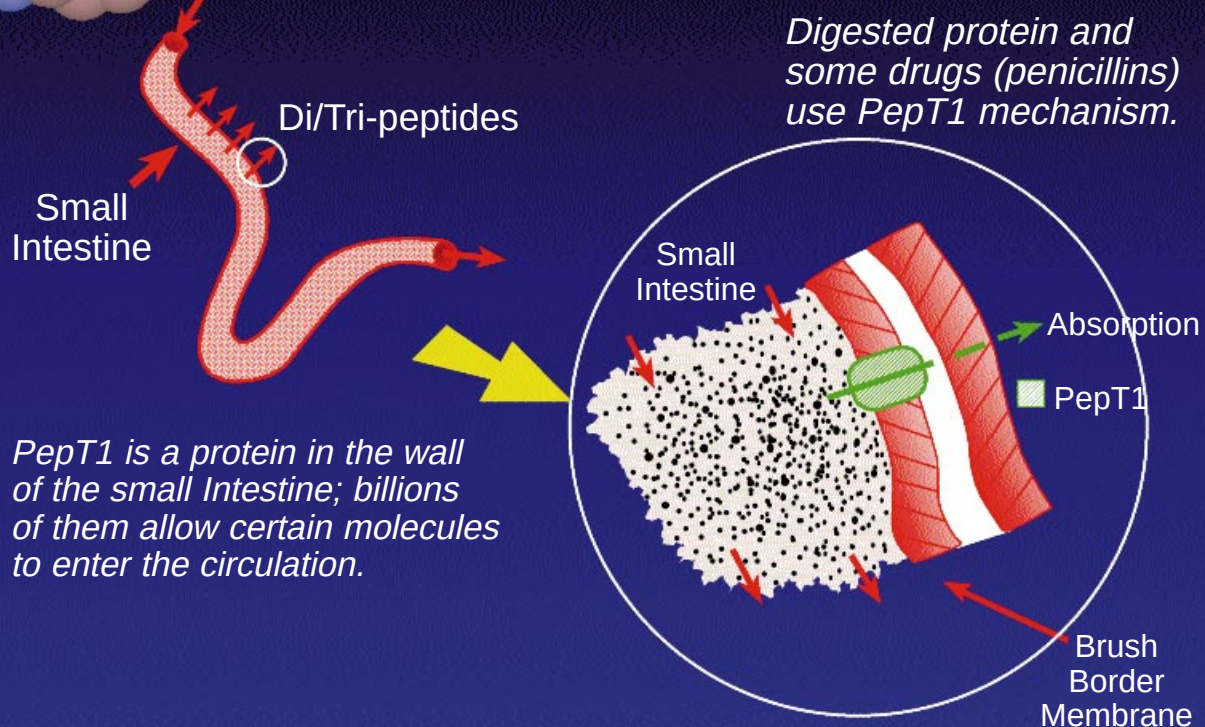
tion derivatives can be achieved with the aid of group theory and combinatorics, as has been known since 1974.

Fortunately, the mathematical papers by White^[13], hardly understandable for chemists, were translated into the language of crystallographers by McLarnan and are, thus, more easily accessible to our community. He also showed the application for sheet silicates, the stacking sequences for the closest packings of spheres, and the substitution derivatives of the wurtzite type;^[14] for further details see ref. [15]. The starting point is the space group of the unsubstituted crystal structure (called aristo type). Substitutions involve symmetry reductions, resulting in subgroups of this space group. The subgroups which may occur can be derived by setting up a

Bärnighausen family tree of group–subgroup relations.^[16] By using matrix algebra and some combinatoric rules with respect to the crystallographic positions of every space group, the numbers of possible structure types for each space group of the family tree can be calculated. The occupation of voids in atomic packing, as well as the production of vacancies, can be treated as a substitution of atoms for voids or vice versa; therefore, the method is not restricted to real substitution derivatives.

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- [1] W. M. Meier, D. H. Olson, C. Baerlocher, *Atlas of Zeolite Structure Types*, Elsevier, London, **1996**.
- [2] J. Kepler, *Harmonice Mundi Libri II*, pp. 31–36; J. Plank, Linz **1619**. German translation: M. Caspar, *Weltharmonik II*, Oldenbourg, München, **1939**, pp. 67–72.
- [3] B. Grünbaum, H. D. Löckenhoff, G. C. Shephard, A. Temsvári, *Geometriae Dedicata* **1985**, *19*, 109.
- [4] A. W. M. Dress, R. Scharlau, *Mitt. Mathem. Seminar Gießen* **1984**, *164*, 83.
- [5] A. W. M. Dress, *Adv. Math.* **1987**, *63*, 196.
- [6] A. W. M. Dress, D. Huson, *Geometriae Dedicata* **1987**, *24*, 295.
- [7] D. H. Huson, *Geometriae Dedicata* **1993**, *47*, 269.
- [8] O. Delgado Friedrichs, A. W. M. Dress, D. H. Huson, K. Klinowski, A. L. Mackay, *Nature* **1999**, *400*, 644.
- [9] M. O’Keeffe, B. Hyde, *Crystal Structures I: Patterns and Symmetry*, Monograph, Mineralogical Association of America, Washington, **1996**.
- [10] M. M. J. Treacy, K. H. Randall, S. Rao, J. A. Perry, D. J. Chadi, *Z. Kristallogr.* **1997**, *212*, 768.
- [11] J. V. Smith, *Am. Mineral.* **1977**, *62*, 703; J. V. Smith, *Am. Mineral.* **1978**, *63*, 960; J. V. Smith, *Am. Mineral.* **1979**, *64*, 551; J. V. Smith, *Am. Mineral.* **1981**, *66*, 777; J. V. Smith, *Am. Mineral.* **1984**, *69*, 104; J. V. Smith, *Towards a comprehensive mathematical theory for the topology and geometry of microporous materials in Zeolites; Facts, Figures, Future Vol. 49A* (Eds.: P. A. Jacobs, R. A. V. Santen), Elsevier, Amsterdam, **1989**, p. 29.
- [12] H. J. Bosmans, K. J. Andries, *Acta Crystallogr. Sect. A* **1990**, *46*, 832; K. J. Andries, H. J. Bosmans, *Acta Crystallogr. Sect. A* **1990**, *46*, 847; K. J. Andries, H. J. Bosmans, *Acta Crystallogr. Sect. A* **1990**, *46*, 855.
- [13] D. White, *Proc. Am. Math. Soc.* **1974**, *47*, 41; D. White, *Discrete Math.* **1975**, *13*, 277.
- [14] T. J. McLarnan, *Z. Kristallogr.* **1981**, *155*, 227; T. J. McLarnan, *Z. Kristallogr.* **1981**, *155*, 247; T. J. McLarnan, *Z. Kristallogr.* **1981**, *155*, 269; T. J. McLarnan, W. H. Baur, *J. Solid State Chem.* **1982**, *42*, 283.
- [15] U. Müller, *Acta Crystallogr. Sect. B* **1992**, *48*, 172; U. Müller, *Z. Anorg. Allg. Chem.* **1998**, *624*, 529.
- [16] H. Bärnighausen, *MATCH Commun. Math. Chem.* **1980**, *9*, 139.
-

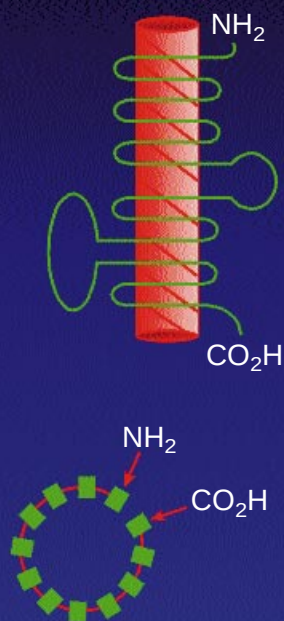
PepT1 Transporter



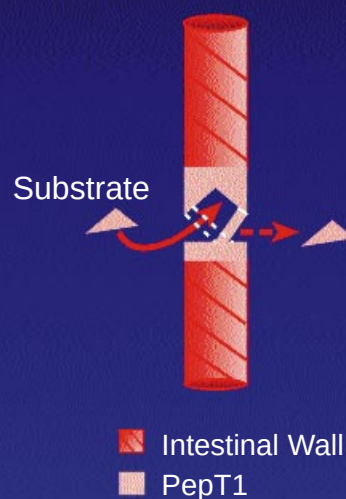
How Does PepT1 Work?

PepT1

- Long protein (707AAS)
- Crosses membrane 12 times
- 12 trans-membrane domain channel
- Di-/tri-peptides transported
- Analogues.....?



Cattle-gate mechanism



Find out more on the following pages.

How to Make Drugs Orally Active: A Substrate Template for Peptide Transporter PepT1**

Patrick D. Bailey,* C. A. Richard Boyd,
J. Ramsey Bronk, Ian D. Collier, David Meredith,
Keith M. Morgan, and Catherine S. Temple

PepT1 is an essential mammalian protein that actively transports small peptides.^[1] It is found in the wall of the small intestine of mammals, and provides the main pathway for the absorption of dietary nitrogen.^[2] Of particular importance medicinally is the ability of PepT1 to transport certain drugs into the circulatory system,^[3–5] which allows them to be taken orally instead of by injection.

Although PepT1 is generally accepted to be a trans-membrane (TM) protein possessing 12 TM domains,^[6] its 3-D structure is still not known. Nevertheless, data on several hundred PepT1 substrates have now been published, and some features for efficient transport have been put forward within certain sub-classes of substrates.^[7] However, no general model for the affinity/transport of substrates by PepT1 has been proposed.

In order to try to generate a template for substrate specificity we have considered the binding and transport properties of virtually all of the published PepT1 substrates. We have also carried out *in vitro* binding and transport studies on around 100 substrates ourselves, initially using brush border membrane vesicles (BBMV),^[8] and more recently using *Xenopus* oocytes in which PepT1 expression has been induced by injection with cRNA;^[9] our work has also included *in vivo* experiments with intact rat jejunum (part of the small intestine), which allowed us to confirm that an excellent correlation exists between the *in vitro* and real-life situations.^[10]

By considering different combinations of potential binding features in 3-D space we have been able to identify a template for PepT1 substrates (Figure 1). This simple model would appear to account for all of the substrate specificities relating to PepT1, and provides an indication of whether substrates will be transported with high, medium, or low efficiency.

The template has the following features, illustrated in Figure 1, and is described below from the N- to the C-terminus: 1) a strong binding site for an N-terminal NH₃⁺ group; 2) preference for the stereochemistry shown (usually L) to accommodate R¹; 3) an extended planar backbone from the N-terminal C_α atom to R²; 4) a hydrogen bond to the carbonyl group of the first peptide bond; 5) alkylation of N² is

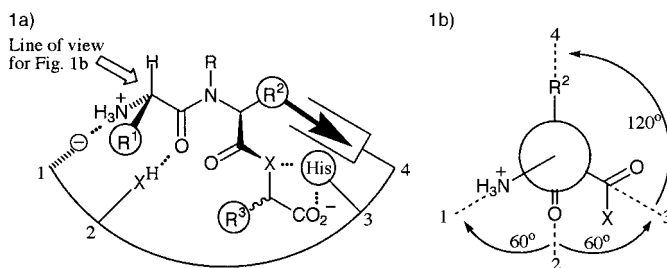


Figure 1. a) Substrate template for binding to PepT1. Free dipeptides terminate with O[−] at X, whilst tripeptides are extended by X=NH; possible complementarity to PepT1 is indicated for the 4 main binding features; plain bonds (—) lie close to the plane of the paper. b) The orientation of the four main binding features, viewed as indicated in Figure 1a.

permitted; 6) specific orientation of three groups at the second residue (usually L); 7) a hydrophobic pocket, which possesses a strong directional vector as indicated; 8) a carboxylate binding site; 9) available space for the side-chain R³; 10) a second carboxylate binding site, with stereochemical consequences on the adjacent chiral center (usually L).

This model effectively identifies four key binding sites (1, 4, 7, and 8/10), whilst the 3-D layout of the template is defined by the other stereochemical and conformational features. Thus, high-affinity substrates can generally adopt the correct 3-D conformation without paying a high energetic price. It is the aggregate effect of all of these factors that governs whether substrates have high, medium, or low affinity for PepT1.

The strong structure–activity correlation is emphasized by looking at eight diverse classes of compound, for which selected data are provided in Table 1: a) amino acid derivatives (entries 1–2); b) dipeptides (entries 3–16); c) β -amino acid dipeptides (entries 17–18); d) peptide space mimics (entries 19–25); e) alanyl anilides (entries 26–29); f) tripeptides (entries 30–33); g) β -lactams (entries 34–36); h) other drugs (entries 37–42).

Particularly notable is the affinity of PepT1 for molecules possessing amino and carboxylic acid groups separated by about 6 Å (see **1**, **2**, and **3** in Figure 2), even in non-peptidic substrates, whereas poor binding is observed for β -Ala-Gly and D-Phe-L-Pro (**4** and **5**), which cannot readily adopt appropriate conformations. The template successfully predicts the stereochemical and side-chain selectivity of PepT1 for dipeptides (**6**); the previously unexplained high affinity of 4-substituted alanyl anilides (**7** and Figure 3) is also consistent with the template, as is the observed low affinity of alanyl benzylamide (**8**). The template explains the selectivity in the binding of tripeptides (**9**) and, remarkably, how β -lactam antibiotics (**10**) can also bind with high affinity; for the latter, the amide group of the β -lactam does not follow the template backbone, but the C–N bond must instead be rotated by 180° (**11** and Figure 3), which leads to the D-stereochemistry of the penicillins/cephalosporins matching the L-stereochemistry of tripeptides.

In conclusion, the template described here provides a model for the orientation of the key binding features of substrates for PepT1. We can therefore, for the first time, predict whether substrates will have high, medium, or low affinity for PepT1, and the template can be used to place a set

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[**] We thank Dr. Andy Vinter for providing the XED98 software and computational advice, and The Wellcome Trust for generous funding.

Table 1. Predicted and observed affinity of selected substrates for PepT1.

Entry	Substrate	Key site ^[a]	Predic- tion ^[b]	K_i [mM] ^[c]	Method ^[d]
1	Phe	N ¹	L	> 50	B, [12]
2	Ac-Phe	C ²	M +	2	B, [12]
3	Phe-Tyr	N ¹	H +	0.1	B, [12]
4	Ac-Phe-Tyr	C ³	M	8.5	B, [12]
5	L-Ala-Gly	N ¹	H	0.027	[11]
6	D-Ala-Gly	N ¹	H –	1.9	[11]
7	Gly-L-Ala	N ¹	H	0.032	[11]
8	Gly-D-Ala	N ¹	M	12	[11]
9	Gly-Asp	N ¹	H –	0.15	[11]
10	Gly-Lys	N ¹	H –	0.15	[11]
11	Gly-Phe	N ¹	H +	0.019	[11]
12	Gly-Sar	N ¹	H	0.37	[11]
13	Pro-Gly	N ¹	M	6.0	[11]
14	Gly-Pro	N ¹	H	0.38	[11]
15	Ala(<i>trans</i> - ψ S)-Pro	N ¹	H	0.3	[13]
16	D-Phe-Pro	N ¹	L	21	B
17	Gly- β -Ala	N ¹	H –	1.3	[11]
18	β -Ala-Gly	N ¹	M	5.2	[11]
19	H ₂ N-(CH ₂) ₃ -CO ₂ H	N ¹	L	> 50	[15]
20	H ₂ N-(CH ₂) ₄ -CO ₂ H	N ¹	M	1.14	[15]
21	H ₂ NCH ₂ C(=O)(CH ₂) ₂ CO ₂ H	N ¹	M +	0.4	[16]
22	4-H ₂ N-C ₆ H ₄ -CO ₂ H	N ¹	M –	11	A
23	3-H ₂ N-C ₆ H ₄ -CH ₂ CO ₂ H	N ¹	M	6	A
24	4-H ₂ N-C ₆ H ₄ -CH ₂ CO ₂ H	N ¹	M	6.5	A, [14]
25	4-H ₂ NCH ₂ -C ₆ H ₄ -CO ₂ H	N ¹	H –	1.4 ($\pm$ 0.4)	A, [9]
26	Ala-NH-Ph	N ¹	M +	2.9	[17], B
27	Ala-NH-C ₆ H ₄ (4-Me)	N ¹	H –	0.34	[17], B
28	Ala-NH-C ₆ H ₄ (4-Ph)	N ¹	H +	0.03	[17]
29	Ala-NH-CH ₂ -Ph	N ¹	M –	14	[17]
30	Ala-Ala-Ala	N ¹	H	0.54	B
31	D-Ala-Ala-Ala	N ¹	M –	15	B
32	Ala-D-Ala-Ala	N ¹	L	16	B
33	Ala-Ala-D-Ala	N ¹	M	4.1	B
34	amoxycillin (a penicillin)	N ¹	H –	2	[18]*
35	cefadroxil (a cephalosporin)	N ¹	H –	0.6	A
36	lorabarbef (a carba-ceph.)	N ¹	H –	1.8	[18]
37	captopril	C ²	M	5	A
38	enalapril	C ²	H	1	A
39	acyclovir	?	L	> 50	[4]*
40	Val-acyclovir	N ¹	M	4.1	[5]
41	L-dopa	N ¹	L	> 50	[5]*
42	L-dopa-Phe	N ¹	H	0.03	[5]*

[a] The key site identifies the key locating feature for the substrate on the template; N¹ = NH₃⁺ site, C² = dipeptide carboxylate site, C³ = tripeptide carboxylate site, ? = no identifiable match. [b] Predicted binding, see text for further information. [c] K_i values were obtained by us (see Experimental Section for A/B) or by others (ref. given in parenthesis; * indicates K_i was estimated from the data).

of related substrates in order of increasing affinity. The template should be of immediate value in designing and improving medicinally important compounds by increasing their oral bioavailability through the PepT1 transport mechanism.

Experimental Section

For all data used in this analysis, representative examples of substrate K_i s determined by other groups were also analyzed under our experimental conditions (see A and B below) at an external pH value of 5.5 to ensure comparability of data. New data reported herein use either A) inhibition of ³H-labeled D-Phe-L-Gln (10 mM) uptake in rat BBMV at pH 5.5^[8] or B) Michaelis–Menten analysis of the inhibition of ³H-labeled D-Phe-L-Gln uptake at pH 5.5 into *Xenopus laevis* oocytes expressing PepT1 from microinjected cRNA.^[9]

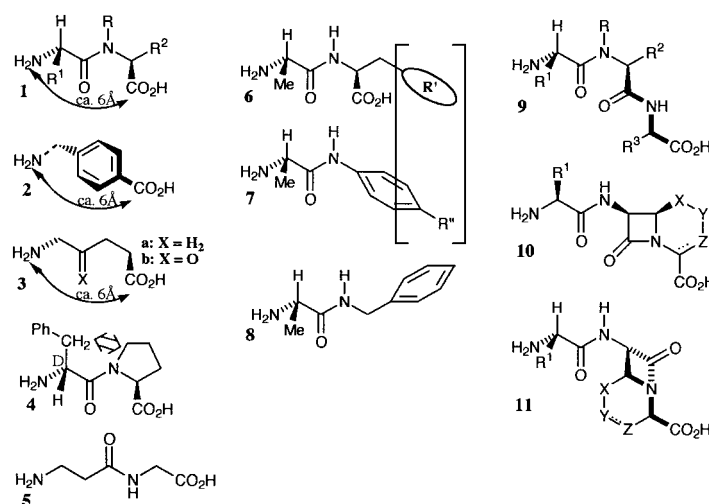


Figure 2. Structures 1–5: Dipeptide analogues showing: the standard L-L dipeptide (1) in the template conformation; space mimics 4-(aminomethyl)benzoic acid (2), 5-aminopentanoic acid (3a), and laevulinic acid (3b), all of which show expected medium/high affinity for PepT1; D-Phe-L-Pro (4) with the steric clash identified; β -Ala-Gly (5) with the template mismatch apparent. Structures 6–8: Dipeptide analogues showing: standard L-L dipeptide (6), emphasising the location of the hydrophobic part (R') of side-chain R²; the high-affinity alanyl anilides (7), showing R'' in the hydrophobic pocket; low-affinity alanyl benzylamide (8). Structures 9–11: Tripeptide analogues showing: standard L-L-L tripeptide (9) in the template conformation; the general structure of L- α -amino penicillin/cephalosporin β -lactam antibiotics (10); 10 presented in the template conformation 11 to explain the medium/high affinity for PepT1 of the orally active β -lactam substrates. (X = S or CH₂ (carba-analogues); Y = nothing and Z = CMe₂ (penicillins); Y = CH and Z = CMe (cephalosporins)).

The predicted affinity was determined by assuming an overlay onto the template (examples shown in Figure 3). Structures were produced in XED98 using extended electron distribution molecular mechanics,^[19] and the default dielectric constant of 4. For template structures, rotations of less than 10° were permitted about the angles identified in Figure 1, and acceptable conformations were required to be within 10 kcal mol^{–1} of the global minima, which were determined by the rigorous fast dynamics/Monte Carlo conformational search routine within XED98.^[20] All of the ten factors identified in the template were given a weighting, and hydrophobicity and entropy factors were also included. This process allowed semi-quantitative assignment of high (H, < 1 mM), medium (M, 1–20 mM), or low (L, > 20 mM) affinity, although this is usually clear by simple inspection; the relative affinity could also be predicted within a group of related substrates (designated by + for higher affinity, and – for lower affinity, in Table 1).

Received: September 6, 1999 [Z13974]

- [1] D. Meredith, C. A. R. Boyd, *J. Membrane Biol.* **1995**, 145, 1.
- [2] a) D. M. Matthews, *Protein Absorption: Development and Present State of the Subject*, Wiley-Liss, New York, **1991**; b) V. Ganapathy, M. Brandsch, F. H. Leibach in *Physiology of the Gastro-intestinal Tract*, 3rd ed. (Ed.: L. R. Johnson), Raven, New York, **1994**, pp. 1773–1794.
- [3] G. L. Amidon, H. J. Lee, *Ann. Rev. Pharmacol. Toxicol.* **1994**, 34, 321.
- [4] P. V. Balimane, I. Tamai, A. Guo, T. Nakanishi, H. Kitada, F. H. Leibach, A. Tsuji, P. J. Sinko, *Biochem. Biophys. Res. Commun.* **1998**, 250, 246.
- [5] I. Tamai, T. Nakanishi, H. Nakahara, Y. Sai, V. Ganapathy, F. H. Leibach, A. Tsuji, *J. Pharm. Sci.* **1998**, 87, 1542.
- [6] Y.-J. Fei, Y. Kanai, S. Nussberger, V. Ganapathy, F. H. Leibach, M. F. Romero, S. K. Singh, W. F. Boron, M. A. Hediger, *Nature* **1994**, 368, 563.

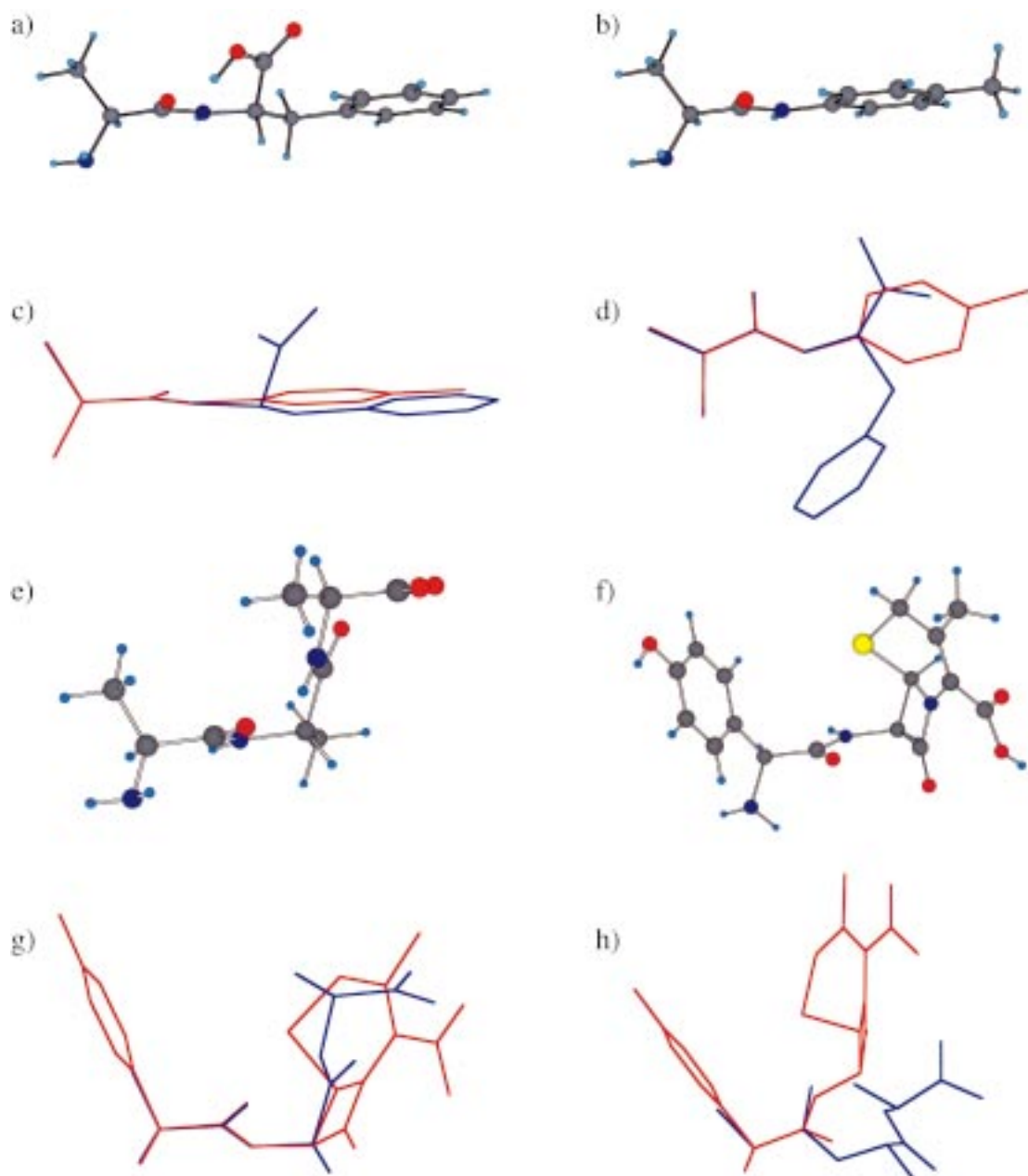


Figure 3. a) L-Ala-L-Phe and b) alanyl (4-methyl)anilide (see structures 6 and 7), in their template conformations; c) overlay of the backbones from (a) and (b), showing good overlap; d) overlay of global minima conformations for (a) and (b), demonstrating poor overlap; e) L-Ala-L-Ala-L-Ala and f) L-cefadroxil (see structures 9 and 11), both in their template conformations; g) overlay of the backbones from (e) and (f), showing good overlap; h) overlay of global minima conformations for (e) and (f), demonstrating poor overlap.

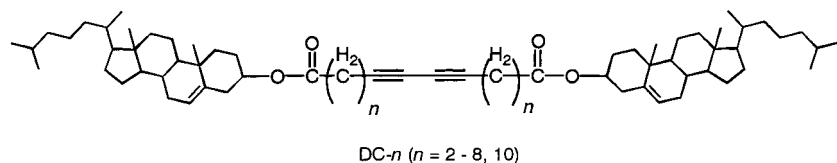
- [7] a) J. B. Li, I. J. Hidalgo, *J. Drug Targeting* **1996**, 4, 9; b) P. W. Swaan, J. J. Tukker, *J. Pharm. Sci.* **1997**, 86, 596.
- [8] C. S. Temple, P. D. Bailey, J. R. Bronk, C. A. R. Boyd, *J. Physiol. (London)* **1996**, 494, 795.
- [9] D. Meredith, C. A. R. Boyd, J. R. Bronk, P. D. Bailey, K. M. Morgan, I. D. Collier, C. S. Temple, *J. Physiol. (London)* **1998**, 512, 629.
- [10] N. Lister, A. P. Sykes, P. D. Bailey, C. A. R. Boyd, J. R. Bronk, *J. Physiol. (London)* **1995**, 484, 173.
- [11] H. Daniel, E. L. Morse, S. A. Adibi, *J. Biol. Chem.* **1992**, 267, 9565.
- [12] N. Guha, C. A. R. Boyd, D. Meredith, *J. Physiol. (London)* **1999**, 517P, 57.
- [13] M. Brandsch, F. Thuncke, G. Kullertz, M. Schutkowski, G. Fischer, K. Neubert, *J. Biol. Chem.* **1998**, 273, 3861.
- [14] C. S. Temple, A. K. Stewart, D. Meredith, N. A. Lister, K. M. Morgan, I. D. Collier, R. D. Vaughan-Jones, C. A. R. Boyd, P. D. Bailey, J. R. Bronk, *J. Biol. Chem.* **1998**, 273, 20.
- [15] F. Döring, J. Walter, J. Will, M. Föcking, M. Boll, S. Amasheh, W. Clauss, H. Daniel, *J. Clin. Invest.* **1998**, 101, 2761.
- [16] F. Döring, J. Will, S. Amasheh, W. Clauss, H. Ahlbrecht, H. Daniel, *J. Biol. Chem.* **1998**, 273, 23211.
- [17] V. Börner, Y.-J. Fei, B. Hartrodt, V. Ganapathy, F. H. Leibach, K. Neubert, M. Brandsch, *Eur. J. Biochem.* **1998**, 255, 698.
- [18] U. Wenzel, D. T. Thwaites, H. Daniel, *Br. J. Pharmacol.* **1995**, 116, 3021.
- [19] J. G. Vinter, *J. Comput. Aided Mol. Des.* **1996**, 10, 417.
- [20] S. D. Morley, D. E. Jackson, M. R. Sanders, J. G. Vinter, *J. Comput. Chem.* **1992**, 13, 693.

Cholesteric Solid Films Formed by Spin-Coating Solutions of Dicholesteryl Esters

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A main topic in supramolecular chemistry is the establishment of well-defined, organized, solid molecular assemblies with more than a single molecular layer.^[1] The lyotropic liquid crystalline property of various compounds has been utilized for such self-assembly with formation of solid films^[2] or fibers.^[3] Upon removal of solvent, lyotropic polymers in solution turn into solids with retention of liquid crystalline molecular ordering. Liquid crystals with low molecular weight, on the other hand, tend to form crystals upon evaporation of solvent if the melting point of the compound is above room temperature. This is because low molecular weight compounds crystallize faster than polymers with high molecular weight and broad molecular weight distribution. Here we report that several dicholesteryl esters of diacetylene dicarboxylic acids with molecular weights higher than 1000 show surface-directed self-assembly, and form an optically reflecting solid film on spin-coating from solutions. It is verified that the reflection of the light is based on a stable helical molecular ordering in the solid film.

Dicholesteryl esters containing a diacetylene unit (DC-*n*; *n* = 2–8, 10) have a relatively high molecular weight, among the highest known for low molecular weight cholesteryl esters.



The diyne unit is introduced as a connector to form the symmetric molecular structure with a long hydrocarbon chain. These compounds form white crystals upon recrystallization from hexane/CH₂Cl₂ or upon removal of solvent from a solution in CH₂Cl₂. Except for DC-3, each crystal shows a clear melting point above 105 °C, no *meso* phases on heating, and a thermotropic cholesteric phase above 80 °C on cooling. All the DC-*n* esters show high solubility in, for example, benzene, halogenated solvents, and tetrahydrofuran.

If a 15 wt% solution in CH₂Cl₂ is spin-coated at 7000 rpm on to a glass plate at 22–23 °C, DC-8 forms a red solid film (Figure 1, right-hand side). The color is temperature-independent below 75 °C and changes into white above this temperature. Colored solid films are obtained from DC-6, DC-7, DC-8, and DC-10, but not from DC-2, DC-3, DC-4, and DC-5; the latter just forms white crystals. Some compounds containing diyne units are known to polymerize topochemi-

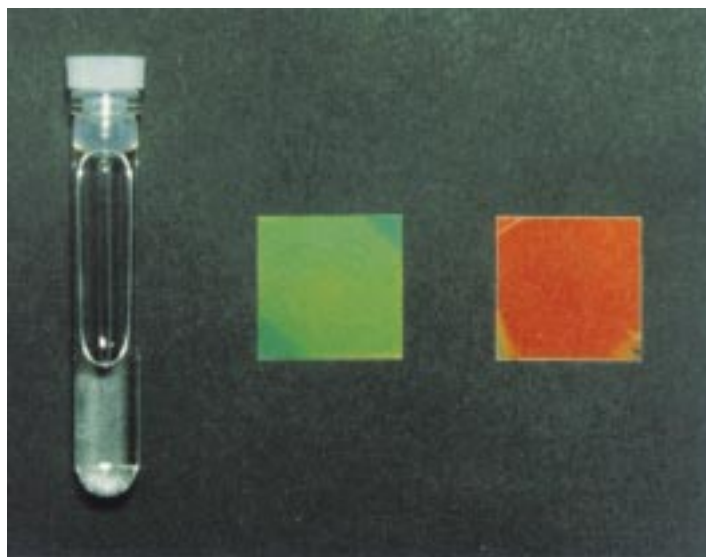


Figure 1. A photograph (taken at room temperature) of iridescent green and red solid films on glass plates obtained by spin-coating solutions of DC-8 in CH₂Cl₂ at 38–40 and 22–23 °C, respectively. A sample of the transparent, colorless solution of DC-8 is shown for comparison. The size and the thickness of the glass plates are 18 × 18 mm and 0.15 mm, respectively. The thickness of the colored solid films is around 1.8 μm.

cally in the crystalline state to provide colored conjugated polymers.^[4] However, all of the DC-*n* esters are chemically quite stable even under UV light, and the color disappeared when the solid film obtained after spin-coating was redissolved in solvent. Therefore the color observed after spin-coating is not due to polymerization of the diyne unit.

The red film obtained with DC-8 shows a reflection band with a peak at 618 nm (width at half-height 80 nm; Figure 2), a large optical rotation dispersion in the positive sense (1.0 deg m^{−1} at maximum), and a large circular dichroism (0.9 deg m^{−1}) centered at the reflection band (Figure 3). The reflectance increases from 1 to 22 % with increasing film thickness; the film thickness could be con-

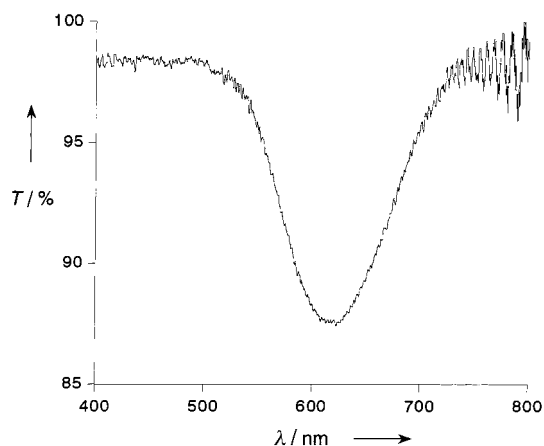


Figure 2. Transmission spectrum of the red solid film shown in Figure 1. A negative peak in the measurement of transmission is not due to absorption of the film but reflection, which is verified by the coincidence of the positions of peaks in separate measurements of reflection and circular dichroism spectra.

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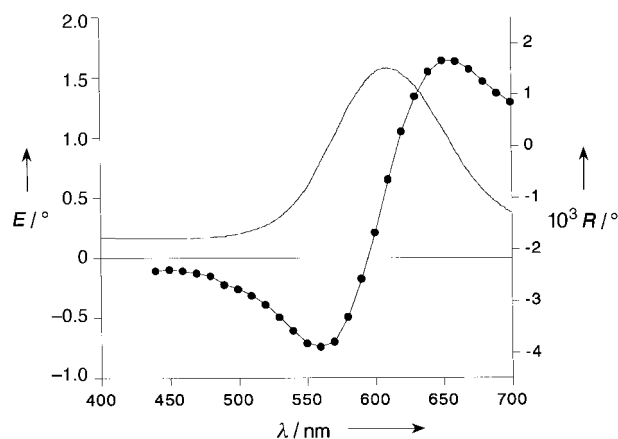


Figure 3. Optical rotation dispersion (---) and circular dichroism spectrum (—) of the red solid film shown in Figure 1.

trolled between 0.5 and 2.0 μm by changing the initial concentration of the solution and the spin speed on coating. These optical features of the solid films are explained by alignment of the molecules into helices, the axes of which are perpendicular to the surface, like for molecules in a known cholesteric liquid crystalline phase.^[5] The X-ray diffraction pattern of the film shows just one broad band in the wide-angle region, which is typical for cholesteric liquid crystals. We concluded that a cholesteric molecular ordering was formed and fixed during spin-coating. Although similar solid films with helical ordering have already been obtained by slow evaporation of solvent from a solution of lyotropic poly(γ -methyl glutamate)^[2b, 6] or poly(γ -benzyl L-glutamate),^[2a, 6] no examples for nonpolymeric compounds have been reported.

Changing the temperature of the substrate allows control of the fixed color. The two samples of DC-8 with different colors in Figure 1 were obtained by tuning the temperature. Figure 4

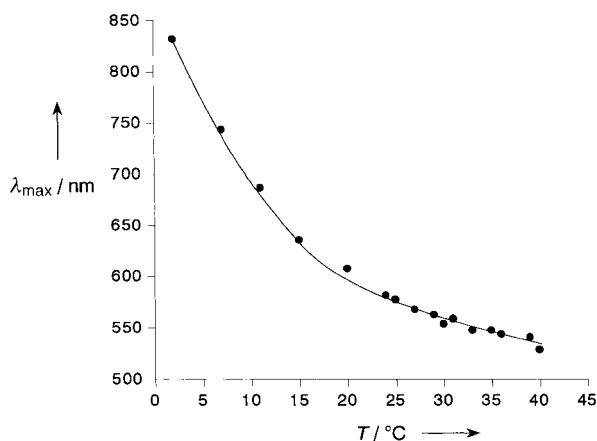


Figure 4. Relationship between the surface temperatures of the substrate and the wavelength of the transmission band for the colored solid films obtained from DC-8. The temperature was controlled and measured with a hot stage (Iuchi Thermo Plate TP-80).

shows the relationship between the temperature of the substrate during coating and the wavelength of the reflection band for the colored solid films obtained (coating by the bar-coater method, see the Experimental Section). The peak shifts

toward longer wavelengths (530 to 832 nm) as the substrate is cooled from 40 to 2 °C, that is, in a temperature region substantially lower than that of the thermotropic cholesteric phase of the compound. If the temperature of the substrate is set above 40 °C, DC-8 does not form the colored solid films; instead, just white crystals appear. The color also depends on the structure of the dicholesteryl compounds and the solvents used (Table 1).

Table 1. Wavelength of the peak observed in transmission spectra of colored solid films formed from DC-8 dissolved in various solvents at 25 °C.

Solvent	λ_{max} [nm]
dichloromethane	585
1,2-dichloroethane	660
chloroform	692
tetrahydrofuran	636
benzene	597

If the spinning speed is under 2000 rpm and the concentration of the solution in CH_2Cl_2 is higher than 15 wt %, or if the spinning speed is 7000 rpm and the concentration of the solution in CH_2Cl_2 is higher than 30 wt %, DC-8 forms white crystals rather than the colored film. It is impossible to obtain colored films thicker than 3 μm . This means that the molecular alignment in a helical mode is surface-directed. On a flat surface the helical axes are uniformly arranged perpendicular to the surface—the effect of the surface extends only about 3 μm . This length is far shorter than the thickness with which a uniform Grandjean texture is attainable for thermotropic cholesteric liquid crystals between a pair of glass plates. This is the reason why evaporation of a solution containing a large amount of DC-*n* in CH_2Cl_2 just resulted in white crystals.

To explain how solid films with a cholesteric molecular ordering are formed, it is reasonable to assume that dicholesteryl esters that are known to be thermotropic liquid crystals with a cholesteric phase above 80 °C show a cholesteric phase at room temperature in the presence of solvents. If the solution shows a cholesteric phase in a certain concentration range at room temperature, the mixture should change from an isotropic solution into a colored cholesteric state above a critical concentration on drying. Then the ordering of molecules can be frozen in the solid upon further drying, keeping the spatially periodic structure.

To see if the assumption is valid or not, we investigated mixtures of DC-8 and 1,2-dichloroethane in different ratios with differential scanning calorimetry (Figure 5). Pure DC-8 shows two exotherm peaks, between which a cholesteric phase is observed. Upon addition of 1,2-dichloroethane, both transitions shift toward lower temperature, and the temperature region in which the mixture shows a cholesteric phase narrows. At 81 wt % DC-8 two peaks merge into one exotherm at 47 °C. At this concentration the mixture is an isotropic solution (above 47 °C) or a crystal with a separated solvent (below 47 °C). The merged transition shifts to lower temperature as the concentration is lowered. These results indicate that mixtures of DC-8 and 1,2-dichloroethane in different ratios do not show a liquid crystalline phase at 47 °C or lower; at this temperature, coating from the solution

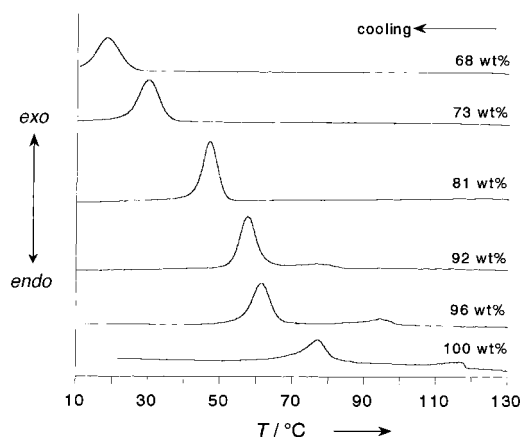


Figure 5. Differential scanning calorimetry thermograms for mixtures of DC-8 and 1,2-dichloroethane in different ratios (cooling rate $2^{\circ}\text{C min}^{-1}$). The concentration of DC-8 is noted above each line.

afforded a cholesteric solid film. Although it is not clear how the solid film is constructed, it is likely that a nonequilibrated change in the concentration of the DC-8 solution on coating shifts the temperature region for the cholesteric phase to lower than that for the static thermotropic phase.

Experimental Section

Dicholesteryl esters DC- n ($n = 2-8, 10$) were synthesized by condensation of cholesterol and the corresponding diacids or by oxidative coupling of the corresponding acetylene derivatives as reported.^[7] MIKASA 1H-DX was used for spin-coating. The surface temperature of the substrate was controlled and monitored by a drier and an infrared thermometer (TASCO THI-400S), respectively. For bar coating, a wire bar (Tester Sangyo Co., Ltd.; no. 12) was used on a temperature-controlled stage (Iuchi THERMO PLATE TP-80).

Received: October 4, 1999 [Z14100]

- [1] Recent reviews: a) M. Muthukumar, O. K. Ober, I. L. Thomas, *Science* **1997**, 277, 1225–1232; b) G. Decher, *Science* **1997**, 277, 1232–1237.
- [2] a) E. T. Samulski, A. V. Tobolsky, *Nature* **1967**, 216, 997; b) T. Tachibana, E. Oda, *Bull. Chem. Soc. Jpn.* **1973**, 46, 2583–2584; c) J. Watanabe, S. Sasaki, I. Uematsu, *Polym. J.* **1977**, 9(3), 337–340; d) G. Charlet, D. G. Gray, *Macromolecules* **1987**, 20, 33–38; e) S. Shimamoto, D. G. Gray, *Chem. Mater.* **1998**, 10, 1720–1726; f) W. Zhao, A. Kloczkowski, J. E. Mark, B. Erman, I. Bahar, *Macromolecules* **1996**, 29, 2805–2812.
- [3] S. Kwolek (du Pont), DE-B 1810426, **1970** [*Chem. Abstr.* **1970**, 72, 112676t].
- [4] Z. Wegner, *Z. Naturforsch. B* **1969**, 24, 824–832.
- [5] H. de Vries, *Acta Crystallogr.* **1951**, 4, 219–226.
- [6] I. Uematsu, Y. Uematsu in *Liquid Crystal Polymers I, Advances in Polymer Science* 59 (Ed.: M. Gordon), Springer, Berlin, **1984**, pp. 37–73.
- [7] N. Tamaoki, G. Kruk, H. Matsuda, *J. Mater. Chem.* **1999**, 9, 2381–2384.

Al₃₀: A Giant Aluminum Polycation

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Aluminum hydrolysis plays a key role in strategic fields like catalysis, the Bayer process for aluminum production, geochemistry, soil science, water treatment, and material sciences. However, elucidation of all hydrolyzed aluminum species in solution has not yet been achieved.^[1–8] Beyond the monomers $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$ and $[\text{Al}(\text{OH})_4]^-$, only the Keggin polycation $[\text{Al}_{12}(\text{AlO}_4)(\text{OH})_{24}(\text{H}_2\text{O})_{12}]^{7+}$ ($\epsilon\text{-Al}_{13}$) has been identified by X-ray diffraction (XRD)^[9–10] and characterized in solution by ^{27}Al NMR. Several other species with hitherto unidentified ^{27}Al NMR signals at $\delta = 4, 64.5, 70$, and 76 were observed, along with broad signals in the 5–12 ppm range. Despite the numerous aforementioned studies, no new assignment has been established. In this in situ ^{27}Al NMR study, thermal treatment of a $\epsilon\text{-Al}_{13}$ solution evolves the new polycation $[\text{Al}_{30}\text{O}_8(\text{OH})_{56}(\text{H}_2\text{O})_{24}]^{18+}$ (Al_{30}). The $\delta = 70$ and 7–12 NMR signals are now definitely assigned to this species. The Al_{30} precipitated as a sulfate and its established structure consists of two $\delta\text{-Al}_{13}$ Keggin units linked by four AlO_6 octahedra. Although polyanions reach considerably larger sizes,^[11] Al_{30} is unique by its size. It is the biggest polycation ever characterized, and the $\delta\text{-Al}_{13}$ units have never before been observed, neither in polycation nor polyanion chemistry.

Polycations are usually based on Keggin structures and described in polyoxometalate chemistry.^[12–15] Keggin ions isomerize under five forms, $\alpha, \beta, \gamma, \delta$, and ϵ , shown in Figure 1 a.

Tungstate and molybdate polyanions usually exhibit α - and β -Keggin structures (with or without cation vacancies) and can lead to pseudo-Keggin dimers by condensation.^[12–15] Dimerisation has never been observed for aluminum polycations, but two polycationic Al_{13} Keggin isomers are known: $\alpha\text{-Al}_{13}$ in the mineral zunyite^[16] and $\epsilon\text{-Al}_{13}$.^[9, 10, 17] The $\epsilon\text{-Al}_{13}$ polycation is obtained from hydrolysis of an aqueous AlCl_3 solution by NaOH at 95°C with a hydrolysis ratio $m_h = [\text{OH}]/[\text{Al}]$ between 1.5 and 2.5. It has a central AlO_4 tetrahedron (narrow ^{27}Al NMR signal at $\delta = 63$), surrounded by twelve corner- and edge-sharing AlO_6 octahedra (very broad NMR signal around $\delta = 12$). The 1:12 $\text{Al}^{\text{IV}}:\text{Al}^{\text{VI}}$ ratio between peaks at $\delta = 63$ and 12 confirms the polycation structure. The $\alpha\text{-Al}_{13}$ cation in zunyite^[16, 18] (synthesized from aluminum hydroxide and silica under hydrothermal treatment at 300°C) has

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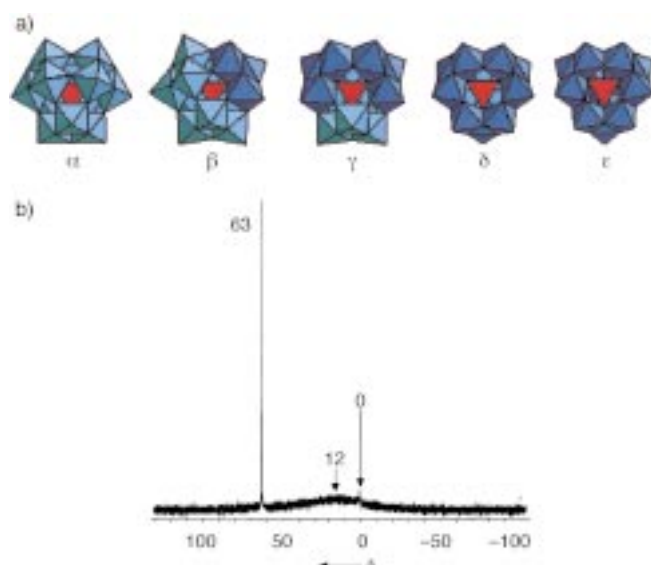


Figure 1. a) Keggin isomers after Baker and Figgis, showing AlO_4 tetrahedra (red) and AlO_6 octahedra (blue).^[12] Isomeric differences (light blue/dark blue octahedra) arise from rotation of three adjacent AlO_6 octahedra through 60° . b) ^{27}Al NMR spectrum of aqueous $\epsilon\text{-Al}_{13}$. The narrow peak at $\delta = 63$ corresponds to AlO_4 sites and the broad region around $\delta = 12$ corresponds to AlO_6 sites.

its AlO_4 signal at $\delta = 72$ ^[19] (observed by solid state MAS ^{27}Al NMR) and a broad, unresolved ensemble of signals between 7 and 12 ppm, corresponding to the shell of AlO_6 octahedra.

Preliminary NMR experiments on the hydrolysis of AlCl_3 solutions at 95°C agree with reported gel-permeation chromatography (GPC) results of Nazar et al.^[8] and indicate that different species, not always assigned to known species, develop as a function of time. We therefore initiated in situ NMR studies of $\epsilon\text{-Al}_{13}$ solutions to observe signal evolution versus time at 95 or 127°C . The results presented here only concern the 127°C case, since an increase of temperature affects the rate of evolution but not the species formed.

In the first stage, conditions were established for obtaining clear solutions with exclusively the $\epsilon\text{-Al}_{13}$ polycation (solution A; see *Experimental Section*). The existence of $\epsilon\text{-Al}_{13}$ was confirmed by both liquid state ^{27}Al NMR (Figure 1b) and by powder X-ray diffraction after room temperature precipitation of the very insoluble $\epsilon\text{-Al}_{13}$ sulfate. A similar NMR examination of the species in solution and sulfate crystallization was the strategy used to characterize Al_{30} .

Evolution of ^{27}Al NMR signals from solution A at 127°C (Figure 2) shows that thermal treatment causes $\epsilon\text{-Al}_{13}$ transformation into species containing aluminum in both tetrahedral and octahedral configurations. At $\delta = 70$ a signal increases at the expense of the $\delta = 63$ signal and becomes dominant after around 5 h at 127°C (48 h at 95°C). NMR signals at $\delta = 64.5$ and 76 appear during thermal treatment. The very weak $\delta = 64.5$ signal disappears when the $\delta = 70$ signal reaches its maximum. At this point, a $\delta = 76$ signal emerges. The signals of the octahedra at 5–12 ppm remain unresolved. Signals around $\delta = 0$ and in the 5–12 ppm region do not undergo any chemical exchange. At room temperature, monomeric $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$ appears at $\delta = 0$ (Figure 1b). At $\delta =$

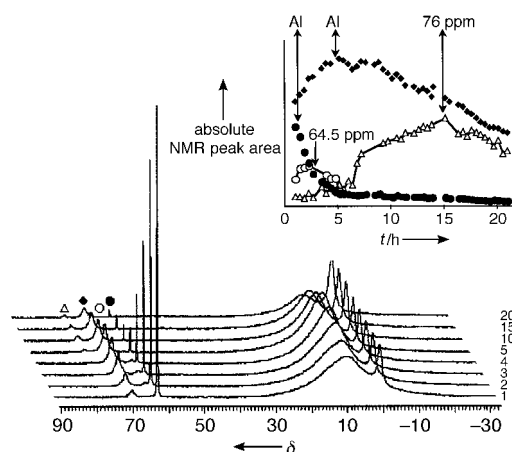


Figure 2. ^{27}Al NMR spectra of solution A over 20 h of thermal treatment at 127°C . Inset: peak areas of the evolving signals of $\epsilon\text{-Al}_{13}$ at $\delta = 63$ (●), of $\delta = 64.5$ (○), of Al_{30} at $\delta = 70$ (◆), and of $\delta = 76$ (△). Scales for ○ and △ series have been multiplied sixfold for clarity.

4 a signal is usually observed, this is still ambiguously assigned but most probably represents edge-sharing $[\text{AlO}_6]$ octahedra. Beyond 70°C these two lines coalesce near $\delta = 0$ due to the large concentration of monomers. No chemical exchange takes place between signals in the 5–12 ppm and in the 0–4 ppm ranges. Signals for $[\text{AlO}_6]$ in the 5–12 ppm range are assigned to polycationic, external Keggin shells. This allows selective crystallization of the latter species.

After 5 h of heating at 127°C (or 48 h at 95°C), the solution (solution B) is brought back to room temperature; the ^{27}Al signals are considerably broader than in the 95 or 127°C solutions. Some amounts of $\epsilon\text{-Al}_{13}$ are still present, but the spectrum is dominated by $\delta = 70$ and 10 components (Figure 3a).

To optimize crystallization, the influence of the sulfate-to-aluminum ratio y was investigated. According to its value, three new morphologies were obtained. Very small platelet- and ovoid-shaped crystals appear for high y values. Their structure determination is currently in progress. For $y = 0.3$, the large crystals corresponding to Al_{30} have a rhombohedral shape and were used for crystal structure determination (see *Experimental Section*).

After crystallization, an ^{27}Al NMR spectrum of the solution (Figure 3b) shows that most of the $\delta = 70$ and 10 signals have disappeared and the existence of almost only $[\text{Al}(\text{H}_2\text{O})_6]^{3+}$ monomers ($\delta = 0$) in the remaining solution. Several rhombohedral crystals were collected and redissolved in water. The resulting solution exhibits a ^{27}Al NMR spectrum (Figure 3c) dominated by $\delta = 70$ and 10 signals, with two more signals at $\delta = 63$ and 0, from additional free $\epsilon\text{-Al}_{13}$ and from some monomers, respectively. Despite the presence of the latter signals, probably coming from intruding $\epsilon\text{-Al}_{13}$ crystals included during the selection of the rhombohedral ones or from some dissociation of Al_{30} , this result proves that $\delta = 70$ and 10 signals are indeed a signature of Al_{30} .

The crystal structure (see *Experimental Section*) reveals a new aluminum polycation with a formula $[\text{Al}_{30}\text{O}_8(\text{OH})_{56}(\text{H}_2\text{O})_{24}]^{18+}$ compensated by nine sulfate ions. The polycation (Figure 3d) results from the combination of two $\delta\text{-Al}_{13}$ units

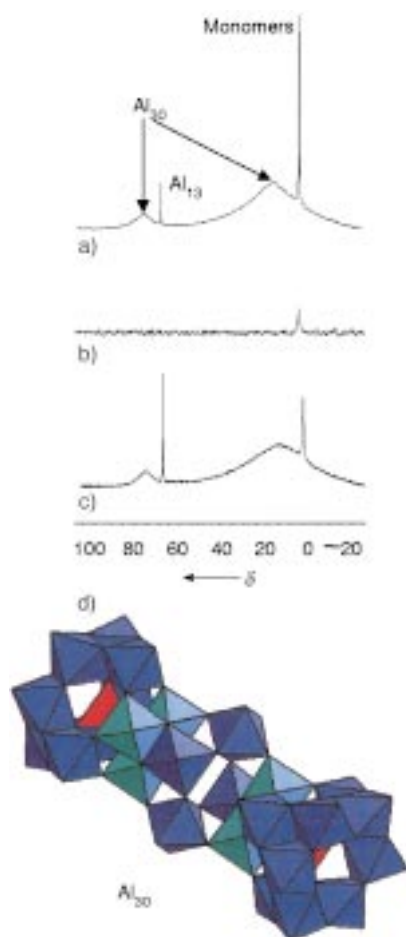


Figure 3. a) ^{27}Al NMR spectrum of solution B at room temperature. b) ^{27}Al NMR spectrum of solution B after precipitation of rhombohedral crystals. c) ^{27}Al NMR spectrum of the redissolved rhombohedral crystals in water. d) Polyhedral representation of $[(\delta\text{-Al}_{13})_2[\text{Al}_4(\text{OH})_8(\text{H}_2\text{O})_6]^{18+}]$. Red = AlO_4 , blue = AlO_6 , the different shades represent the different Keggin configuration.

connected by a crown of four $[\text{AlO}_6]$ octahedra. The formula of the solid is therefore rewritten $[(\delta\text{-Al}_{13})_2\{\text{Al}_4(\text{OH})_8(\text{H}_2\text{O})_6\}](\text{SO}_4)_9$.

From the structural study, Al_{30} formation may be described as follows. During the thermal treatment of $\epsilon\text{-Al}_{13}$, some dissociate into AlO_6 monomers that subsequently add to undissociated $\epsilon\text{-Al}_{13}$. These $\epsilon\text{-Al}_{13}$ species with one to three attached AlO_6 units (capped $\epsilon\text{-Al}_{13+1}$, $\epsilon\text{-Al}_{13+2}$, or $\epsilon\text{-Al}_{13+3}$) are prone to isomerization into the respective δ forms. Once the isomerization is complete, the species may well be sufficiently stable to dimerize.

A correlation between the ^{27}Al NMR chemical shift of the tetrahedral aluminum and the average Al–O bond length in AlO_4 can be made. The chemical shifts of AlO_4 in ϵ -, δ -, and $\alpha\text{-Al}_{13}$ are $\delta = 63$, 70, and 72, respectively, whereas the corresponding mean Al–O distances decrease from 1.821 Å to 1.807 Å and 1.796 Å. This fits well to a linear relation: $d_{\text{Al-O}} = 1.98 - 0.0026 \times \delta$ (Å). The weak variation from $\delta = 63$ to 64.5, which may be commensurate with a variation in $d_{\text{Al-O}}$ of 0.004 Å, is too small to be attributed to an isomerization process. It is probably reasonable to assign that signal to the capped $\epsilon\text{-Al}_{13+1}$, $\epsilon\text{-Al}_{13+2}$, or $\epsilon\text{-Al}_{13+3}$ species. Isomerization of

the latter species into the δ forms will lead to the $\delta = 70$ signal indistinguishable from that of the Al_{30} . Further thermal treatment may lead to a different isomer with a signal at $\delta = 76$. Zuniyte, as we have already quoted, is synthesized at 300 °C. Its isomerization activation energy is probably higher. Thermal treatment at an increased temperature might lead to the formation of $\alpha\text{-Al}_{13}$ isomer, if concomitant stabilization by a proper anion occurs.

Nazar et al.^[8] already observed the different tetrahedral species identified in this work. GPC allowed them to separate the aluminum species. It is worth noting that this elution sequence of the aluminium species is the same as the transformation sequence during the thermal treatment ($\delta = 63$, 70, then 76; see Figure 2 inset). GPC ranks, therefore, the eluted species by their size for a given charge, providing a qualitative charge-to-mass (z/m) ratio selection. In this instance, charge-to-mass order parallels thermal stability. Species Al_{13}^{7+} and Al_{30}^{18+} exhibit a z/m ratio of 10.5×10^{-3} and $7.04 \times 10^{-3} \text{ e g}^{-1}$, respectively. If the NMR signal at $\delta = 76$ would be assigned to $\alpha\text{-Al}_{13}$ isomer, known by GPC to have a smaller size than Al_{30} (but identical to that of $\epsilon\text{-Al}_{13}$), it would imply for this species a charge of 4+ at most, and a z/m ratio smaller than $7.04 \times 10^{-3} \text{ e g}^{-1}$. Conversely, the $\delta = 76$ signal might correspond to a larger polycation of proportionally greater charge. Further work on crystallization and structure determination of the $\delta = 76$ signal is needed to definitely solve the NMR assignments.

In situ ^{27}Al NMR and XRD have allowed us to see that a thermal treatment of an $\epsilon\text{-Al}_{13}$ solution produces a new aluminum cluster Al_{30} , which consists of two $\delta\text{-Al}_{13}$ Keggin units connected by a ring of four octahedral $[\text{AlO}_6]$ units. The highly charged Al_{30} forms from hydrothermal treatment and appears as the second step of aluminum hydrolysis, after formation of $\epsilon\text{-Al}_{13}$. It is the first time that a $\delta\text{-Al}_{13}$ unit, formed from the isomerization of $\epsilon\text{-Al}_{13}$, is characterized. The heretofore unassigned ^{27}Al NMR signals at $\delta = 70$ and 10 were attributed to Al_{30} . Since Al_{30} is more temperature resistant and less sensitive to pH variations than $\epsilon\text{-Al}_{13}$, this compound will certainly open new developments for elucidating the different species and the mechanisms involved in aluminum hydrolysis.^[23]

Experimental Section

Synthesis: NaOH (2 M) was added dropwise to an AlCl_3 solution (0.3 M) maintained at 95 °C under fast stirring. The hydrolysis ratio was $m_h = 2.46$. The solution obtained (solution A) was cooled. The white precipitate, which formed when a drop of base was introduced into the AlCl_3 solution, redissolved immediately under stirring. At the end of the reaction, the solution was clear and contained only $\epsilon\text{-Al}_{13}$ (Figure 1b) and a few $[\text{AlO}_6]$ monomers. Solution A was heated and stirred over 48 h at 95 °C or 5 h at 127 °C to form solution B. Solution B was stable for more than 6 months at room temperature. Crystallization was induced by addition of K_2SO_4 (0.5 M) to 5 mL of B up to a $[\text{SO}_4]:[\text{Al}]$ ratio $y = 0.33$. After one week at room temperature, rhombohedral crystals appeared with millimeter dimensions.

NMR: ^{27}Al NMR has been run on a Bruker DSX-500 spectrometer at room temperature and on a Bruker AMX-400 spectrometer at 127 °C, with 130 and 104 MHz ^{27}Al resonating frequencies, respectively. A Bruker liquid probe BBO-10 mm, designed for a very low aluminum background signal, was used. At room temperature an NMR quartz tube is used. Above 100 °C,

a "hydrothermal NMR tube"^[20] is used instead. The reference $\delta = 0$ was to an external aqueous solution of $\text{Al}(\text{NO}_3)_3$ (1M).

X-ray crystal structure analysis: A crystal fragment was placed into a capillary Lindemann glass to prevent dehydration. Intensities were recorded on a Bruker SMART CCD diffractometer ($\text{MoK}\alpha$ radiation $\lambda = 0.71073 \text{ \AA}$, graphite monochromator) at 300 K. An empirical absorption correction was applied using the SADABS program.^[21] 45 869 unique reflections ($R_{\text{int}} = 0.0746$) were used ($1.31^\circ < \theta < 29.83^\circ$). The structure was solved and refined using the program package SHELXTL 5.03.^[22] The examination of the systematic absences is consistent with the space groups $C2/c$ (No. 15) or Cc (No. 9). The structure was first solved in the space group $C2/c$. Five sulfate groups were located from the observing successive Fourier map analyses. One SO_4^{2-} ion is placed nearby on the 2 axis (at 0, y, $\frac{1}{4}$), which induces a short S–S distance of 1.45 Å. A statistical disorder must occur for this SO_4^{2-} ion and the occupancy factor was refined to 50 %; it corresponds to 4.5 SO_4^{2-} ions for 15 Al atoms (or nine SO_4^{2-} ions per Al_{30}). At this stage, some SO_4^{2-} groups were refined with geometrical restraints and water molecules were located approximately due to their very diffuse average electronic density. The sulfate counterions may not all be accurately positioned. With such a strategy the structure can be described as follows: $\text{Al}_{30}\text{O}_8(\text{OH})_{56}(\text{H}_2\text{O})_{24}(\text{SO}_4)_9 \cdot x\text{H}_2\text{O}$ ($x > 35$), monoclinic, space group Cc (No. 9), $a = 28.0259(5)$, $b = 19.4890(3)$, $c = 28.9883(5) \text{ \AA}$, $\beta = 112.514(1)^\circ$, $V = 14626.6(4) \text{ \AA}^3$, $Z = 4$, $\rho_{\text{calc}} = 1.588 \text{ g cm}^{-3}$, $\mu = 0.452 \text{ mm}^{-1}$, crystal size $0.38 \times 0.26 \times 0.12 \text{ mm}^3$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Fachinformationszentrum Karlsruhe. Further details may be obtained from FIZ, 76344 Eggenstein-Leopoldshafen, Germany (fax: (+49) 7247-808-666; e-mail: crysdata @fiz-karlsruhe.de) on quoting the depository number CSD-410995.

Received: October 7, 1999 [Z14125]

- [1] a) J. W. Akitt, J. M. Elders, X. L. R. Fontaine, A. K. Kundu, *J. Chem. Soc. Dalton Trans.* **1989**, 1889–1895; b) J. W. Akitt, J. M. Elders, X. L. R. Fontaine, A. K. Kundu, *J. Chem. Soc. Dalton Trans.* **1989**, 1897–1901.
- [2] J. P. Jolivet in *De la Solution à l'Oxyde* (Eds.: M. Henry, J. Livage), CNRS, Paris, **1994**.
- [3] J. Y. Bottero, D. Tchoubar, J. M. Cases, F. Flessinger, *J. Phys. Chem.* **1982**, 86, 3667–3673.
- [4] a) D. R. Parker, P. M. Bertsch, *Environ. Sci. Technol.* **1992**, 26, 908–914; b) D. R. Parker, P. M. Bertsch, *Environ. Sci. Technol.* **1992**, 26, 914–921.
- [5] P. H. Hsu, *Clays Clay Miner.* **1997**, 45, 286–289.
- [6] R. C. Turner, *Can. J. Chem.* **1976**, 54, 1910–1915.
- [7] a) J. T. Klopogge, D. Seykens, J. W. Geus, J. B. H. Jansen, *J. Non-Cryst. Solids* **1992**, 142, 87–93; b) J. T. Klopogge, D. Seykens, J. W. Geus, J. B. H. Jansen, *J. Non-Cryst. Solids* **1992**, 142, 94–102.
- [8] L. F. Nazar, G. Fu, A. D. Bain, *Chem. Mater.* **1991**, 3, 602–610.
- [9] G. Johansson, *Acta Chem. Scand.* **1960**, 14, 771–773.
- [10] G. Johansson, G. Lundgren, L. G. Sillen, R. Söderquist, *Acta Chem. Scand.* **1960**, 14, 769–771.
- [11] A. Müller, S. Q. N. Shah, H. Bogge, M. Schmidtman, *Nature* **1999**, 397, 48–50.
- [12] L. C. W. Baker, J. S. Figgis, *J. Am. Chem. Soc.* **1970**, 92, 3794–3797.
- [13] M. T. Pope, A. Müller in *Polyoxometalates: From Platonic Solids to Anti-Retroviral Activity*, Kluwer Academic, Dordrecht, **1994**.
- [14] C. L. Hill, *Chem. Rev.* **1998**, 98, 1–390.
- [15] K. Wassermann, R. Knut, H. J. Lunk, J. Fuchs, N. Steinfeld, R. Stösser, *Inorg. Chem.* **1995**, 34, 5029–5036.
- [16] L. Z. Pauling, *Kristalloghim. Miner.* **1933**, 84, 442.
- [17] W. O'Neil Parker, R. Millini, I. Kiricsi, *Inorg. Chem.* **1997**, 36, 571–575.
- [18] G. Turco, PhD thesis, Université de Nice (France), **1962**.
- [19] A. C. Kunwar, A. R. Thompson, H. S. Gutowsky, E. Oldfield, *J. Magn. Reson.* **1984**, 60, 467–472.
- [20] C. Gerardin, M. In, F. Taulelle, *J. Chim. Phys. Phys. Chim. Biol.* **1995**, 92, 1877.

- [21] G. M. Sheldrick, SADABS (the Siemens Area Detector ABSorption correction), University of Göttingen, **1996**.
- [22] G. M. Sheldrick, SHELXTL 5.03, Bruker Analytical X-ray Systems, Madison, WI, **1994**.
- [23] During submission of this contribution L. F. Nazar, Waterloo University, Canada mentioned her findings of an isolated Al_{13} δ -Keggin isomer and of an Al_{30} cluster.

The Vibrational Inelastic Neutron Scattering Spectrum of Dodecahedrane: Experiment and DFT Simulation**

Bruce S. Hudson,* Dale A. Braden, Stewart F. Parker, and Horst Prinzbach

Because of its high symmetry (I_h) the hydrocarbon dodecahedrane ($\text{C}_{20}\text{H}_{20}$)^[1–4] provides a classic case for vibrational analysis and, as a result, a rigorous test of the methods of ab initio or density functional normal-mode analysis. Under the I_h point group the 114 normal modes of vibration are classified into $2A_g + 1T_{1g} + 2T_{2g} + 4G_g + 6H_g + 3T_{1u} + 4T_{2u} + 4G_u + 4H_u$ symmetry types. There are only 30 discrete vibrational frequencies due to the high average degeneracy. Of these only the 3 T_{1u} modes are active in the IR spectrum and only the 2 A_g and 6 H_g modes are active in the Raman spectrum. Thus 19 of the 30 modes of vibration are unobservable by these optical methods so long as this molecule retains its high symmetry.

Inelastic neutron scattering (INS) spectroscopy is not subject to the restrictions of optical selection rules. This permits all modes to be observed in proportion to the extent to which hydrogen-atom motions contribute to that mode. From a set of calculated normal-mode eigenvectors and

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[**] The Rutherford Appleton Laboratory is thanked for access to neutron beam facilities at ISIS. This work was partially supported by the US National Science Foundation (grant CHE9803058) and utilized the computer systems Exemplar and SGI PCarray at the National Center for Supercomputing Applications, University of Illinois at Urbana-Champaign. We thank Chris Middleton of Syracuse University for development of the program used to plot neutron spectra.

eigenvalues, it is a straightforward matter to calculate the neutron scattering vibrational intensities for a hydrogen-containing species for direct comparison with experiment. This reduces the ambiguity in spectral assignment and provides an additional comparison between the results of calculation and experiment. Recent advances in density functional theory (DFT) for large molecules permit reliable normal-mode calculations. Recent progress in the methods of inelastic neutron scattering spectroscopy allow use of relatively small samples and provide improved resolution. Here we show how these developments fit together. Dodecahedrane is a particularly nice case for a neutron scattering study because its large mass combined with its high symmetry results in a well-resolved spectrum.

The major results of this study are presented in Table 1 and Figure 1 (a broad, complex phonon peak centered at 50 cm^{-1} and extending from 25 to 75 cm^{-1} is not shown). The first point to note is that all of the optical (mostly Raman) frequencies are in good agreement with observed neutron scattering features. This permits identification of these features as due to A_g or H_g (or T_{1u}) symmetry modes. Many other strong features not seen in the optical spectra are observed as expected, illustrating the utility of inelastic neutron scattering.

The degree of agreement between the calculated and observed spectra provides confidence that at least in the frequency region shown the observed transitions can be

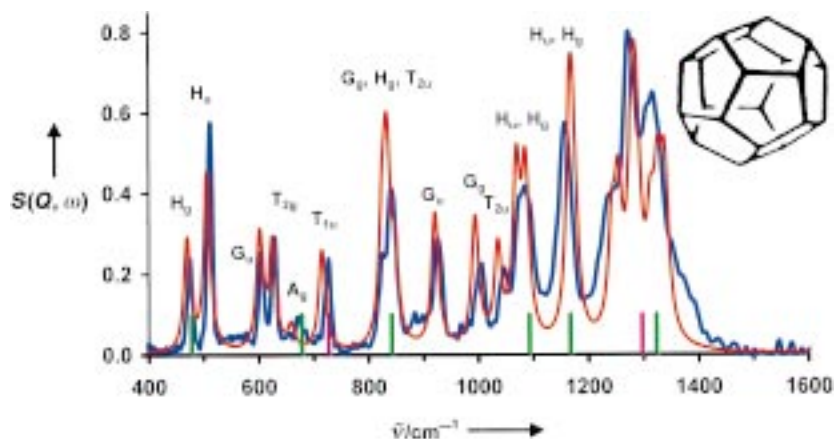


Figure 1. The inelastic neutron scattering spectrum of dodecahedrane (obtained at ISIS with TOSCA, see the Experimental Section). The sample is at a temperature of 15 K. The experimental spectrum is shown in blue. The results of the DFT calculation are shown in red (the calculated frequencies have been multiplied by a factor of 0.99 to improve agreement with experiment). The vertical green lines indicate the reported positions of the Raman-active H_g and A_g transitions, and the vertical pink lines indicate the reported positions of the IR-active T_{1u} transitions (see Table 1).^[3–5] The symmetry labels are from the DFT calculation.

identified with certainty. Some of the bands at higher frequency are composite and await improvements in resolution for their separation. In all cases the calculation produces features with the correct symmetry to account for the Raman and IR features. In the region below 1200 cm^{-1} the features are mostly distinct except for the overlapping bands near 850 cm^{-1} and the two pairs at 1100 and 1180 cm^{-1} . All vibrations give rise to observed features (subject to overlap)—there are no “silent” modes in the INS spectrum. The origin of the activity of these skeletal modes with a technique that depends on the motion of hydrogen atoms is that the rigid attachment of the hydrogen atoms to their respective carbon atoms causes them to follow the carbon-atom motions.

The lowest wavenumber features observed at 477 and 514 cm^{-1} are the H_g and H_u transitions. The relatively high intensity of these signals may be ascribed to the fivefold degeneracy. The calculation predicts that these two transitions should have more equal intensities than is observed (see below).

No splitting is seen at this resolution for these or any other isolated transitions. The neutron spectrum is consistent with I_h symmetry.^[6] The next four transitions are also resolved features with degeneracies of 4, 3, 1, and 3, respectively. These are followed by an overlapping triplet with the appropriate total intensity and then by three more isolated transitions with degeneracies of 4, 4, and 3, respectively. The intensities are roughly proportional to the degeneracies, but the calculations show that over this spectral region there is a variation in intrinsic intensity (i.e., a fractional contribution of hydrogen-atom motion to the total motion of a particular vibrational normal coordinate) by almost a factor of 2.

These individual transitions are followed by two pairs of H_u and H_g transitions. The H_g frequency is above that of the H_u values in each case, as indicated by the fact that the Raman-active H_g transition is seen on the high side of each of the composite neutron bands. This is consistent with the calculation. Also, the predicted H_u/H_g separations of 17 and 6 cm^{-1} appear to be appropriate to the observations.

Table 1. Vibrations of dodecahedrane.

Symmetry ^[a]	Calcd [cm^{-1}] ^[b]	Reported [cm^{-1}]	INS [cm^{-1}] ^[c]
H_g	481	479, ^[d] 480 ^[e]	477
H_u	518		514
G_u	615		607
T_{2g}	639		632
A_g	673	679, ^[d] 676 ^[e]	675
T_{1u}	731	728 ^[f]	727
G_g	843		(845)
H_g	852	843, ^[d] 840 ^[e]	(845)
T_{2u}	866		(845)
G_u	941		930
G_g	1016		1007
T_{2u}	1058		1050
H_u	1093		(1089)
H_g	1191	1094, ^[d] 1092 ^[e]	(1089)
H_u	1192		(1164)
H_g	1198	1168, ^[d] 1164 ^[e]	(1164)
T_{2u}	1269		1270 sh
G_g	1282		1282
T_{1g}	1305		
T_{2g}	1309		1310
H_u	1316		1320
T_{1u}	1341	1298 ^[f]	
G_u	1354		1380 sh
H_g	1367	1324 ^[e]	

[a] In point group I_h . [b] DFT/b3lyp/6-31G**. [c] Values from the inelastic neutron scattering spectrum. Numbers in parentheses indicate that all peaks so marked overlap nearby peaks. [d] Raman data from ref. [5]. [e] Raman data from refs. [3, 4]. [f] IR data from refs. [34].

In the region from 1200–1400 cm⁻¹ a total of eight transitions are expected with symmetries of T_{2u}, G_g, T_{1g}, T_{2g}, H_u, T_{1u}, G_u, H_g (in order of increasing frequency). This order is consistent with the observation of the H_g Raman band on the high-frequency side of the composite band and the appearance of the IR line due to the T_{1u} transition at a frequency lower than the Raman line. There are clearly additional transitions in the INS spectrum at frequencies lower than the observed IR line, also in agreement with the calculated state ordering.

This spectrum illustrates the power of INS in the determination of vibrational transitions that are forbidden by optical spectroscopies. The spectrum of dodecahedrane is notable for the absence of phonon side bands, which are usually increasingly important features at higher frequency. This is in contrast, for example, to the similar molecule adamantane,^[7] where clear phonon wings are observed on all transitions. This difference is probably associated with the smaller amplitude of motion of each atom in the larger dodecahedrane species. The absence of phonon side bands greatly simplifies the interpretation of the spectrum.

This preliminary comparison also demonstrates the utility of INS spectroscopy as a method of testing ab initio/DFT or empirical normal-mode calculations, at least in so far as they provide an adequate description of the participation of hydrogen-atom motions in a normal mode of motion. The new frequencies provided can of course be used for direct comparison with frequencies calculated using other methods. In this way a previous empirical normal-mode calculation of dodecahedrane^[8] is seen to be rather inaccurate. Simulations of the spectral intensity permit added confidence in spectral assignments, even when there is considerable overlap of transitions.

The major residual difference between the calculated and observed INS spectrum is the relative intensity between the first two peaks (H_g and H_u symmetry). Another point is that, in contrast to recent studies of the longitudinal acoustic modes of *n*-alkanes,^[9] we find that for dodecahedrane a slight shift of the spectral scale is needed to match the spectral features. For the related molecule adamantane this effect is considerably larger than for dodecahedrane. For the out-of-plane bending modes of the *n*-alkanes there is a considerable shift of the frequencies to higher values relative to those from DFT calculations that correctly predict the longitudinal acoustic modes.^[9] It is clear in this last case that this is due to intermolecular interactions. It is suspected that intermolecular interactions are the origin of the small shift and intensity effects for dodecahedrane, but this conclusion is complicated by the observation that for adamantane an MP-2 calculation appears to provide much better agreement for frequencies than does the DFT result. This may be due to compensation of effects. More work is required to resolve these issues.

Experimental Section

Inelastic neutron scattering experiments were carried out at the ISIS spallation pulsed neutron source of the Rutherford Appleton Laboratory using the spectrometer TOSCA,^[10] which had a current configuration of ten backscattering banks and was located at 12 m from the moderator. The resolution at this stage is about 2% Δ*E*/*E* full width at half height through

the energy range presented in this study. The synthesis and characterization of the dodecahedrane have been discussed.^[1,2] The sample was 260 mg of high-purity solid dodecahedrane in an aluminum foil sachet contained in an aluminum cell for protection. The cell was mounted in a cryostat held at 15 K. Data were collected for 20 h with ISIS operating at about 180 μA of proton current. The raw data was converted into the dimensionless *S*(*Q*,*ω*) using the standard analysis program GENIE. The spectral data were collected from 16 to 4000 cm⁻¹. The region above 1600 cm⁻¹ was devoid of recognizable features (as expected) except for a broad CH stretch band.

The optimized geometry and normal modes of vibration of dodecahedrane were calculated using Gaussian98.^[11] The B3LYP density functional was used with a 6-31G** basis. The neutron scattering spectral calculations were performed by computing the sum of the squares of the amplitudes of the hydrogen-atom motion for each normal mode.^[9,12,13] This is the amplitude of a Lorentzian peak at the normal-mode frequency for each vibration. The width of the Lorentzian lines was chosen to match the observed spectrum. This width is a linearly increasing function of frequency, as suggested by experimental design and calibration experiments.

Received: August 31, 1999 [Z13947]

- [1] M. Bertau, F. Wahl, A. Weiler, K. Scheumann, J. Wörth, M. Keller, H. Prinzbach, *Tetrahedron* **1997**, 53, 10029.
- [2] M. Bertau, J. Leonhardt, A. Weiler, K. Weber, H. Prinzbach, *Chem. Eur. J.* **1996**, 2, 570.
- [3] L. A. Paquette, R. J. Ternansky, D. W. Balogh, G. Kentgen, *J. Am. Chem. Soc.* **1983**, 105, 5446.
- [4] R. J. Ternansky, D. W. Balogh, L. A. Paquette, *J. Am. Chem. Soc.* **1982**, 104, 4503.
- [5] S. H. Bertz, G. A. Kourouklis, A. Jayaraman, G. Lannoye, J. M. Cook, *Can. J. Chem.* **1993**, 71, 352.
- [6] The IR spectrum of this sample clearly indicates weak features at spectral positions that, on the basis of the neutron scattering and DFT results, we can identify as ungerade vibrations (T_{2u}, G_u, and H_u). This weak activity is consistent with the T_h site group symmetry reported for the crystal.^[1] This spectrum and the corresponding lattice-induced Raman spectrum will be discussed in a later paper.
- [7] <http://www.isis.rl.ac.uk/insdata/>.
- [8] C. Coulombeau, A. Rassat, *J. Chim. Phys.* **1988**, 85, 369.
- [9] S. F. Parker, D. A. Braden, J. A. Tomkinson, B. S. Hudson, *J. Phys. Chem. B* **1998**, 102, 5955; D. A. Braden, S. F. Parker, J. Tomkinson, B. S. Hudson, *J. Chem. Phys.* **1999**, 111, 429.
- [10] S. F. Parker, C. J. Carlile, T. Pike, J. Tomkinson, R. J. Newport, C. Andreani, F. P. Ricci, F. Sachetti, M. Zoppi, *Physica B* **1998**, 154, 241–243.
- [11] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *Gaussian 98*, Revision A.5, Gaussian, Inc., Pittsburgh PA, **1998**.
- [12] B. S. Hudson, A. Warshel, R. G. Gordon, *J. Chem. Phys.* **1974**, 61, 2929.
- [13] A. C. Zemach, R. J. Glauber, *Phys. Rev.* **1956**, 101, 118; A. C. Zemach, R. J. Glauber, *Phys. Rev.* **1956**, 101, 129.

Supramolecular Materials with Electroactive Chemical Functions**

Gregory N. Tew, Martin U. Pralle, and Samuel I. Stupp*

Discovering and understanding the important forces in molecular self-assembly continues to be an area of great interest in materials science. Many groups are working in this field and perhaps just as many different strategies are employed to control the organization of molecules.^[1, 2] In recent years, our laboratory has reported on a class of supramolecular materials formed by molecules with triblock architecture, termed rodcoil molecules, that self-organize into discrete mushroom-shaped nanostructures. To date all systems studied consist of a diblock coil of oligostyrene and oligoisoprene or oligobutadiene covalently attached to a rigid block made up of biphenyls linked through ester bonds.^[3–5] A more recent report described a set of triblock molecules based on styrene and isoprene but rod segments containing phenylene vinylene (PV) sequences in addition to biphenyl esters.^[6, 7]

The study of these materials enabled us to gain an understanding of the important factors leading to the formation of nanostructured supramolecular materials.^[5, 7] One important factor in these systems is the architectural design, where a large, bulky amorphous coil is attached to a rigid, well-defined rod compound by a flexible, amorphous segment with smaller cross-section. Also, the diblock coil to rigid rod volume fraction was proposed to have a large impact on the ability of the systems to self-organize into discrete nanostructures. Perhaps the best test for these principles is the design of systems with very different chemistries that retain the architectural requirements of rodcoil **2** (see Scheme 2). The chemical structure shown in Scheme 2 as molecule **1** was chosen to test our hypothesis and the general applicability of the triblock architecture to order into discrete nanostructures. These molecules contain a diblock coil of oligo-4-diphenylaminostyryl-ethylene oxide and an oligomer of phenylene vinylene.

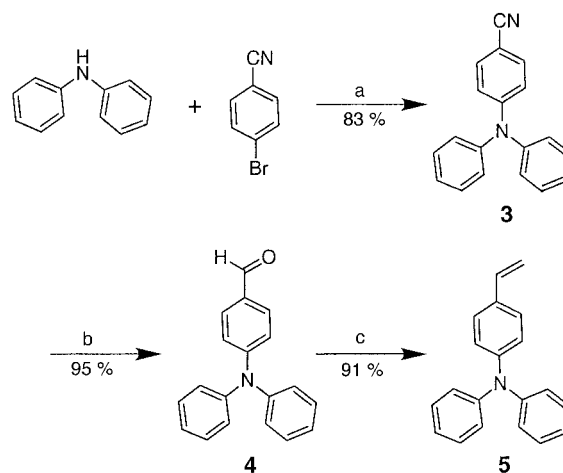
Triphenylamines (TPAs) are currently of interest as hole transport layers in light-emitting devices and are used extensively in the photocopying and laser-printing industry.^[8] Incorporating this functionality into the rodcoil architecture could potentially lead to unique nanostructured optoelectronic devices. This inspired the development of monomer **5** (see Scheme 1). In addition to these photonic properties, this segment must have a structure mimicking styrene within the

triblock architecture, where the block is amorphous and sterically larger than either of the other two blocks.

The second block of the coil is ethylene oxide and represents a drastic change in chemical properties from isoprene or butadiene but is architecturally very similar. Chemically, these dienes are highly diverse with roughly a 50:50 ratio of 1,4- and 1,2-addition products plus a great range of stereochemical diads along the backbone.^[9] By contrast, polymerized ethylene oxide does not produce any of these diversities. Furthermore, ethylene oxide is hydrophilic while the dienes are hydrophobic. Although ethylene oxide differs greatly in a chemical context from the dienes, architecturally they are quite similar because both have a very small cross-section and are highly flexible linear coils.

A rigid rod block of pentameric PV represents the third block of the triblock architecture in **1** and replaces the biphenyl segments found in the original triblock molecule **2**. Again, while PV is different chemically, it has the same architectural features as the biphenyl esters and provides similar driving forces for self-organization. Here we report the synthesis and characterization of supramolecular films composed of **1**.

Traditionally the synthesis of TPA derivatives involved exceedingly harsh conditions, generally leading to low yields for sensitive molecules.^[10] However, this situation changed greatly in the last few years due to seminal work by Hartwig^[11] and Buchwald et al.^[12] on the chemistry of aromatic aminations.^[13] Ligand choice was shown to greatly affect the yield of the reaction, and 1,1'-bis(diphenylphosphanyl)ferrocene (dppf) is best for synthesizing TPA derivatives.^[14] Aromatic amination using diphenylamine and 4-bromobenzonitrile produced **3** in 83 % yield (Scheme 1). The cyano group was then reduced and the product **4** under Wittig-type conditions transformed to **5**.^[15]

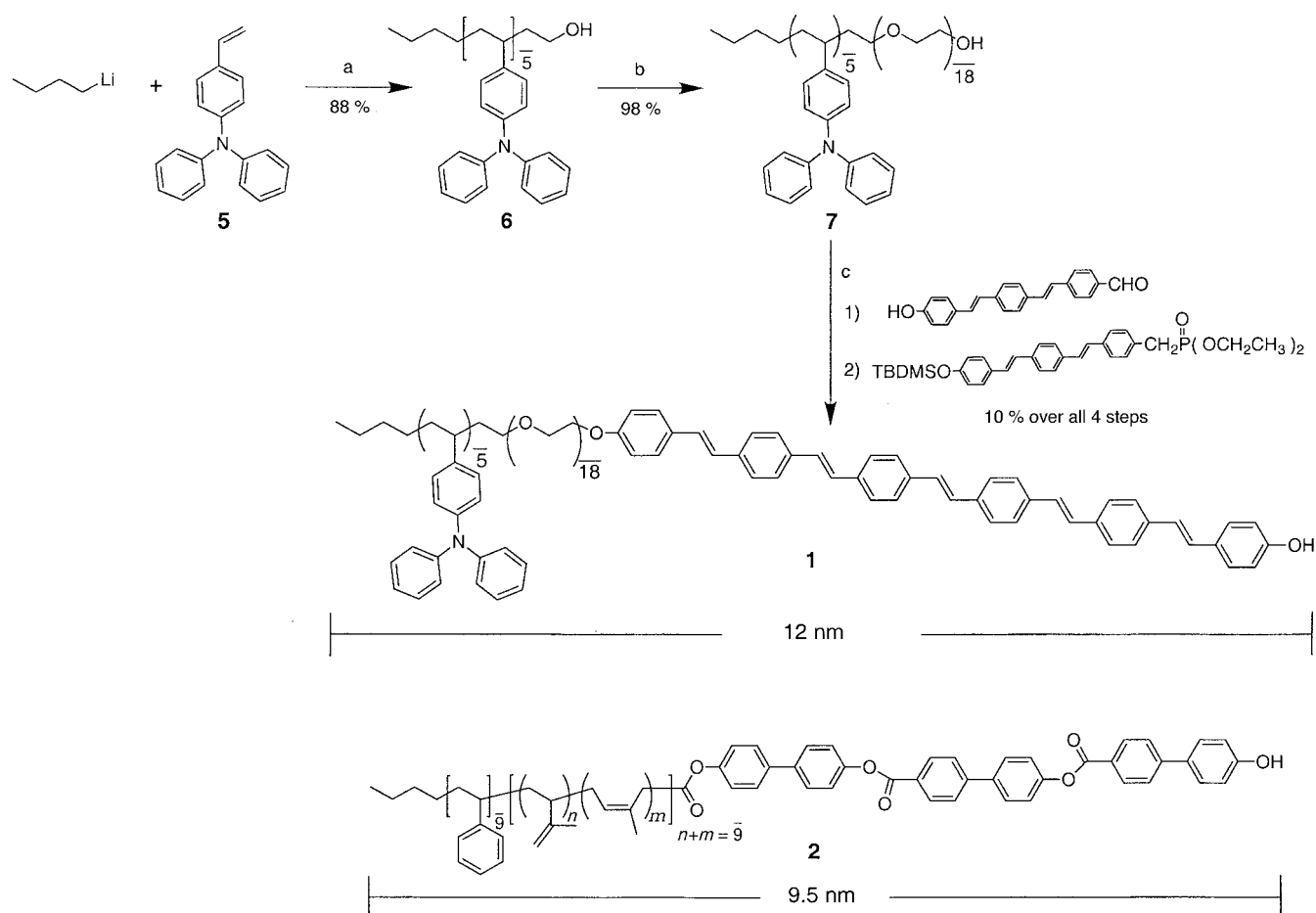


Scheme 1. Reagents: a) $[Pd_2(dba)_3]$ (2 mol %), dppf (3 mol %), sodium *tert*-butoxide, dry toluene, 70 °C, 8 h; b) DIBALH, THF, –78 to –20 °C, 7 h; c) methyltriphenylphosphonium bromide, LDA, THF, 0 °C to RT. dba = dibenzylideneacetone, DIBALH = diisobutylaluminum hydride, LDA = lithium diisopropylamide, RT = room temperature.

Typical anionic living polymerization conditions followed by quenching of the reaction with ethylene oxide as gas yielded the oligomer **6** of TPA in 88 % yield (Scheme 2).^[9]

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[**] This work was performed at the University of Illinois at Urbana-Champaign and supported by grants from the Army Research Office (DAAH04-96-1-0450) and the Office of Naval Research (N00014-96-1-0515). G.N.T. wishes to thank the Beckman Institute for Advanced Science and Technology at the University of Illinois for a research assistantship (1997–1998) and the ACS Division of Organic Chemistry for a fellowship (1998–1999).



Scheme 2. Reagents: a) 1. Benzene/THF (10/1), RT, 30 min; 2. ethylene oxide (gas), RT, 30 min; 3. MeOH; b) 1. potassium dihydronaphthylide, THF, RT; 2. ethylene oxide, 45 °C, 24 h; c) 1. methyl sulfonic anhydride, pyridine, CH₂Cl₂, 0 °C, 48 h; 2. Cs₂CO₃, tetrabutylammonium bromide, THF, 70 °C, 48 h; 3. LDA, THF, –78 to –20 °C; 4. 0 °C to RT; 5. tetrabutylammonium fluoride, THF, –78 °C, 4 h (TBDMS = *tert*-butyldimethylsilyl).

Oligomer **6** has a polydispersity index (PDI) of 1.09 by gas-phase chromatography (GPC) and 1.08 by MALDI mass spectrometry. The MALDI mass spectrum of **6** displays a classic Poisson distribution (Figure 1). Other work has been reported on a very different synthetic route to monomer **5**.^[16, 17] Polymerization of ethylene oxide used modified procedures reported by Hillmyer and Bates^[18] with a simpler reaction setup. These polymerization conditions afforded the diblock oligomer **7** (PDI = 1.10 by GPC). The synthesis of the all-*trans* PV rod and its covalent grafting to the coil has been reported previously.^[7]

Polarized optical microscopy (POM) investigations showed **1** to be a thermotropic liquid crystalline material with birefringence from room temperature to 300 °C, where the material becomes isotropic. Small-angle X-ray scattering (SAXS) reflections (Figure 2) indicate a *d*-spacing of 9.2 nm. This spacing is consistent with a monolayer-type packing because the spacing is slightly less than the fully extended length of the molecule. However, a definite assignment of the reflection as the (001) *d*-spacing cannot be made unequivocally in the absence of higher order reflections. Nonetheless several previously characterized triblock systems show *d*-spacings with higher order reflections that confirm the presence of a monolayered material.^[7] These previous systems

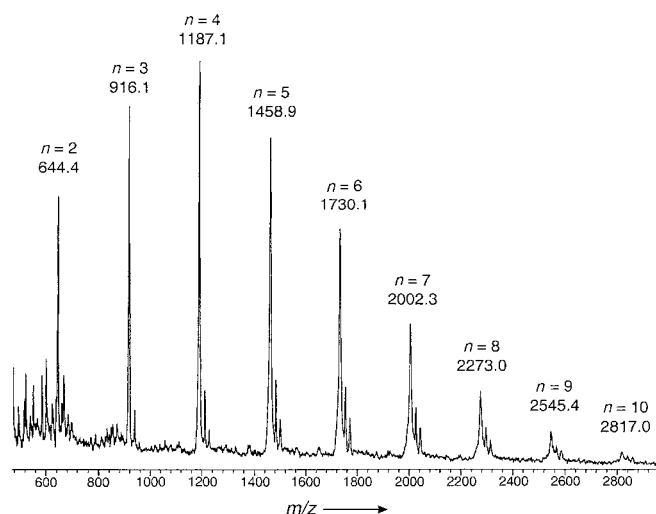


Figure 1. MALDI mass spectrum of **6** showing the peaks associated with different chain lengths, the narrow polydispersity, and the Poisson distribution of the oligomeric segments of TPA.

display similar primary spacings as found for **1**, suggesting this material may also be layered. Furthermore, the electron micrograph discussed below is not consistent with hexagonal or cubic symmetry.

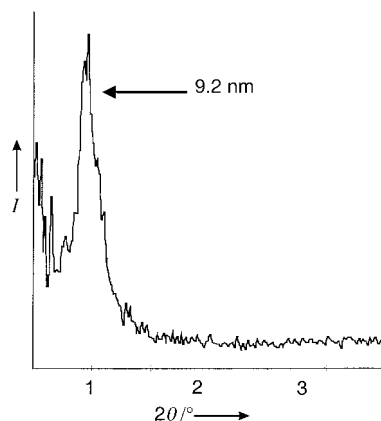


Figure 2. SAXS curve of **1** indicating a layer spacing of 9.2 nm, which suggests monolayer and not bilayer formation.

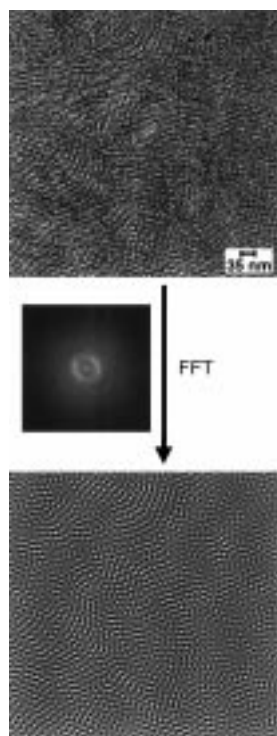


Figure 3. TEM micrograph (top), Fourier filter FFT (middle), and transformed image of **1** (bottom). Micrographs characterize the aggregates as circular with center-to-center distances of 12 nm. The nanostructures are positioned on a pseudo-hexagonal lattice with $a = b = 12$ nm, and an angle of 68° .

When thin films of **1** were characterized by transmission electron microscopy (TEM), we found that indeed nanophase segregation into discrete objects occurs in this particular system. A typical TEM micrograph is shown in Figure 3 along with its Fourier-filtered image, which reveals clearly the dark–light contrast expected in these nanostructured systems. Electron diffraction (ED) indicates this material contains crystalline domains, which is a characteristic of our other self-organized triblock systems. Therefore in the image, contrast between light and dark regions arises from strong diffraction scattering in the rod domains versus weak scattering in the amorphous coils. Upon use of an objective aperture these scattering events were removed from the image, generating the observed contrast. For this reason, the dark areas should contain the rod segments of **1** while the lighter regions must be composed of amorphous domains of coil segments, presumably the TPA and ethylene oxide segments. Figure 3 shows the nanostructures formed by **1** are arranged in an

oblique two-dimensional superlattice with an angle of 68° and dimensions of $a = 12$ nm and $b = 12$ nm. These nanostructures are larger than the nanostructures formed by **2**, as expected based on the fact that molecule **1** is longer than **2**.

Interestingly, the ED pattern in Figure 4 top suggests rod segments in **1** are oriented perpendicular to the plane of the film, and the crystal structure is identical to that found in a

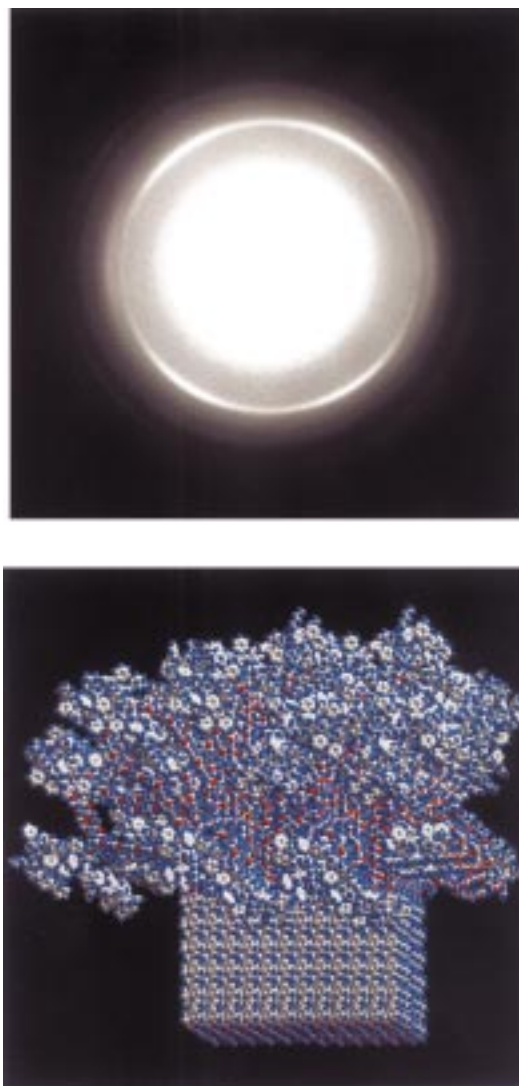


Figure 4. The ED pattern (top) shows films of **1** to contain crystalline domains. The rods crystallize into a unit cell very similar to that of poly(*p*-phenylene vinylene). Based on the ED pattern, TEM image, and SAXS curve, the supramolecular aggregate should be composed of approximately 144 molecules as is shown at the bottom.

previously investigated rodcoil material containing oligostyrene, oligoisoprene, and the same rod segments.^[7] Also, this crystal structure is essentially identical to that observed in poly(*p*-phenylene vinylene) when viewed down the *c* axis, as the rod segments within the nanostructure pack in a herringbone fashion with unit cell dimensions of $a = 7.95$ Å and $b = 5.15$ Å.^[19] However, this is a two-dimensional lattice where *c*-direction order is interrupted by alternating layers of amorphous coil blocks and crystallized rod segments. The ED pattern shows arcs that have been previously observed in rodcoil systems and indicate orientation between objects.^[3, 7] In the ED pattern, reflections corresponding to crystallization of the ethylene oxide coil are not observed, suggesting that both ethylene oxide segments and TPA segments are contained in amorphous domains. The lack of crystallinity in the ethylene oxide segments is probably due to confinement between TPA and rod segments. Figure 4bottom shows a schematic drawing of the supramolecular aggregate.

Figure 5a shows emission spectra from **1** and **6** when the excitation wavelength is 302 nm. This excitation wavelength is λ_{max} for TPA chromophores and is almost transparent for

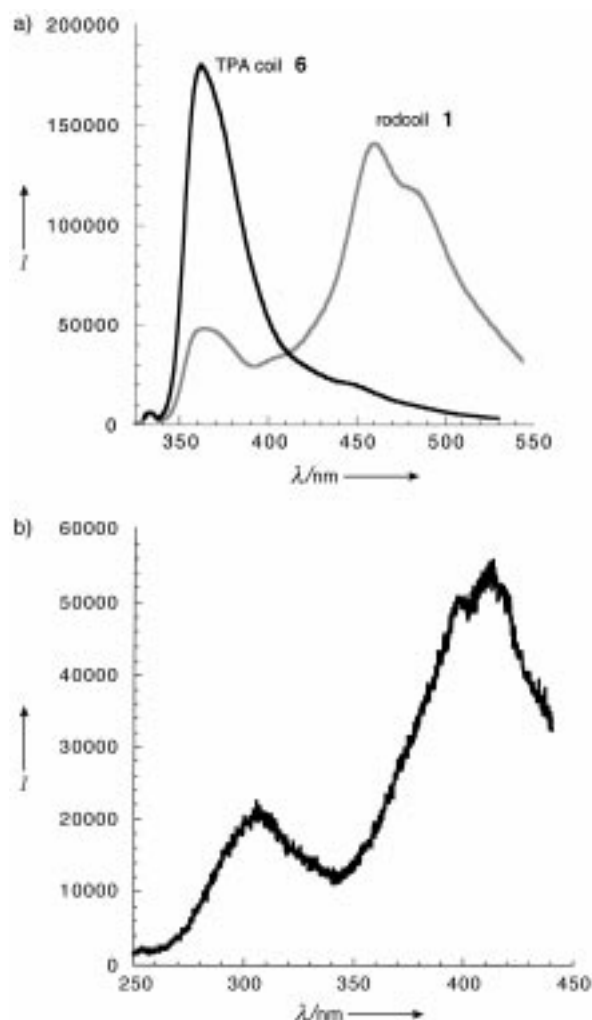


Figure 5. a) Emission spectra from **6** and **1** at the same optical density using 302 nm as the excitation wavelength. The emission spectra suggest energy transfer between the coil and the rod segments. b) An excitation spectrum of **1** with monitoring at 460 nm indicates emission for the coil. This strongly supports energy transfer between coil and rod segments.

structural units in the PV rod segments. The emission curve containing only one peak is from **6** and characterizes the oligo-TPA segments as having an emission with a maximum at 368 nm. Interestingly, the emission of **1** when excited with light at 302 nm shows substantial emission from PV segments. Additional experiments^[20] on quantum efficiency, solvent dielectric measurements, and the excitation scan shown in Figure 5b suggest that energy transfer is occurring between the coil-like TPA and rod-like PV segments of these molecules. Although there is some absorption and emission from rod blocks at 302 nm, the evidence of energy transfer from molecular coil to molecular rod is strong. The observation of energy transfer has been reported within block copolymers;^[21, 22] however, the design of nanostructured systems with luminescent properties is of current interest. An interesting possibility for this system would be the stacking

of the interactive functions into contact as a result of the three-dimensional arrangement of supramolecular nanostructures.

The formation of highly monodisperse and ordered supramolecular nanostructures by design has been demonstrated using the rules of sterically frustrated crystallization. The chemical design of the molecules studied incorporated functions of electronic and photonic interest in their primary sequence. This fact suggests that a broad range of functional chemistries could be used to design nanostructured organic materials.

Experimental Section

SAXS studies were carried out on a Siemens Anton Paar High-Resolution Small Angle Camera equipped with a Hi-Star area detector and Siemens SAXS software mounted on an M18X-HF22 SRA rotating anode generator. Powder diffraction rings were integrated over 360° to yield the diffraction patterns, and the system was calibrated using a silver behenate standard. TEM studies were performed on a Phillips CM 200 TEM operating at 120 keV accelerating voltage.

3: Diphenylamine (4.48 g), 4-bromobenzonitrile (4.38 g), $[\text{Pd}_2(\text{dba})_3]$ (0.44 g), dppf (0.40 g), sodium *tert*-butoxide (3.24 g), and dry toluene (200 mL, ca. 0.1 M based on amine) were heated to 70 °C for 8 h. Upon cooling to room temperature, the reaction mixture was filtered and concentrated by rotatory evaporation. The material was purified by column chromatography (CH_2Cl_2 /hexane 40/60) to give **3** as a white solid (5.39 g, 78 % yield). ^1H NMR (500 MHz, CDCl_3): δ = 7.41 (d, J = 9.0 Hz, 2H), 7.33 (t, J = 7.9 Hz, 4H), 7.16 (m, 6H), 6.96 (d, J = 8.8 Hz, 2H).

4: Compound **3** (5.0 g) was dissolved in Et_2O (185 mL) and the solution cooled to –78 °C. Subsequently DIBALH (28 mL, 1.0 M in hexane) was added. The reaction was stirred overnight at –20 °C, and then the mixture was transferred by cannula onto 10 % AcOH/ice. The Et_2O layer that separated was collected. Column chromatography in CH_2Cl_2 gave **4** as a yellow solid (4.83 g, 95 % yield). ^1H NMR (500 MHz, CDCl_3): δ = 9.81 (s, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.34 (t, J = 8.2 Hz, 4H), 7.17 (m, 6H), 7.01 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3 , attached proton test (APT)): δ = 90.5 (CHO), 153.4 (C_{ar}), 146.2 (C_{ar}), 131.4 (C_{ar}), 129.8 (C_{ar}), 129.2 (C_{ar}), 126.4 (C_{ar}), 125.2 (C_{ar}), 119.4 (C_{ar}); FAB-MS: m/z : 273 [M^+].

5: Methyltriphenylphosphonium bromide (7.20 g) was treated with freshly prepared LDA (2 equiv.) in THF (180 mL) at –78 °C. This mixture was allowed to warm to 0 °C, and then a solution of **4** (2.50 g in 30 mL THF) was added by cannula. The reaction mixture was stirred at room temperature overnight after which it was poured into $\text{H}_2\text{O}/\text{Et}_2\text{O}$ and the organic layer was washed with H_2O and saturated aq. NaCl. The organic layer was collected, dried, filtered, and concentrated by rotatory evaporation to give a crude white solid, which was purified by column chromatography (CH_2Cl_2 /hexane 1/99, a small amount of toluene helps dissolve the crude solid) to afford **5** as a white solid (2.26 g, 91 % yield). ^1H NMR (500 MHz, CDCl_3): δ = 7.29 (d, J = 8.4 Hz, 2H), 7.25 (m, 4H), 7.09 (d, J = 7.5 Hz, 4H), 7.02 (m, 4H), 6.66 (dd, J = 17.6, 10.6 Hz, 1H), 5.64 (dd, J = 17.6, 0.9 Hz, 1H), 5.16 (dd, J = 10.6, 0.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3 , APT): δ = 47.8 (C_{ar}), 147.7 (C_{ar}), 136.4 (C_{vinyl}), 132.1 (C_{ar}), 129.5 (C_{ar}), 127.3 (C_{ar}), 124.6 (C_{ar}), 123.8 (C_{ar}), 123.1 (C_{ar}), 112.4 (C_{vinyl}); EI-MS: m/z : 271 [M^+].

6: Benzene (100 mL) and THF (15 mL) were placed in a flask, and *n*BuLi (2.11 mL) was added. A solution of **5** (3.40 g) in benzene (20 mL) and THF (7.5 mL) was added by cannula. The reaction mixture was stirred for 30 min and then quenched by bubbling dry ethylene oxide through the solution. The solvent was evaporated by rotatory evaporation, and the crude material was purified by chromatography on silica gel (CH_2Cl_2 /hexane 20/80) to provide **6** (3.15 g, 88 % yield). ^1H NMR (500 MHz, CD_2Cl_2): δ = 6.95 (brm, 77H), 3.38 (brm, 2H), 2.24 (brm, 8H), 1.05 (brm, 13H), 0.87 (m, 3H); GPC (254 nm, THF): PDI = 1.09, M_n = 1236; FD-MS: PDI = 1.08, M_n = 1902; MALDI-MS: PDI = 1.14, M_n = 1957.

7: Compound **6** (0.50 g) was dissolved in THF/DMSO (10/1), and potassium dihydronaphthylide was titrated into the reaction mixture until a slight

green color persisted for more than 20 min. Ethylene oxide was condensed to a liquid (0.21 mL) and added to the reaction mixture. The flask was sealed and heated at 45 °C for 8 h. After cooling to room temperature, the THF was removed by rotatory evaporation. Filtration through a plug of silica gel removed DMSO and naphthalene by-products (**7**: 0.61 g, 98 % yield). ¹H NMR (500 MHz, CD₂Cl₂): δ = 6.95 (brm, 73H), 3.57 (brm, 72H), 3.17 (brm, 2H), 2.24 (brm, 8H), 1.05 (brm, 13H), 0.85 (m, 3H); GPC (254 nm, THF): PDI = 1.13, *M_n* = 1489.

1: ¹H NMR (500 MHz, CD₂Cl₂): δ = 6.95 (brm, 120H), 3.57 (brm, 80H), 2.24 (brm, 8H), 1.05 (brm, 13H), 0.85 (m, 3H); GPC (254 nm, THF): PDI = 1.15, *M_n* = 2277.

Received: August 26, 1999 [Z13928]

- [1] J. M. Lehn, *Supramolecular Chemistry*, VCH, New York, **1995**.
- [2] *Comprehensive Supramolecular Chemistry*, Vol. 11 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle), Pergamon, New York, **1996**.
- [3] S. I. Stupp, V. LeBonheur, K. Walker, L. S. Li, K. Huggins, M. Keser, A. Amstutz, *Science* **1997**, 276, 384–389.
- [4] E. R. Zubarev, M. U. Pralle, L. M. Li, S. I. Stupp, *Science* **1999**, 283, 523–526.
- [5] M. U. Pralle, C. M. Whitaker, P. V. Braun, S. I. Stupp, unpublished results.
- [6] G. N. Tew, L. M. Li, S. I. Stupp, *J. Am. Chem. Soc.* **1998**, 120, 5601–5602.
- [7] G. N. Tew, M. U. Pralle, S. I. Stupp, *J. Am. Chem. Soc.* **1999**, in press.
- [8] *Polymers for Light Wave and Integrated Optics* (Ed.: L. A. Hornak), Marcel Dekker, New York, **1992**.
- [9] M. Morton, *Anionic Polymerization: Principles and Practice*, Academic Press, New York, **1983**.
- [10] J. Lindsey, *Tetrahedron* **1984**, 40, 1433–1456.
- [11] J. F. Hartwig, *Angew. Chem.* **1998**, 110, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, 37, 2047–2067.
- [12] J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, 118, 7215–7216.
- [13] M. Kosugi, M. Kameyama, T. Magita, *Chem. Lett.* **1983**, 927–930.
- [14] S. Thayumanavan, S. Barlow, S. R. Marder, *Chem. Mater.* **1997**, 9, 3231–3235.
- [15] G. N. Tew, L. M. Li, M. U. Pralle, S. I. Stupp, *Abstr. Pap. MRS* (Boston, MA) **1997**, p. J3.35.
- [16] W. J. Feast, R. J. Peace, I. A. Sage, E. L. Wood, *Polym. Bull.* **1999**, 42, 167–174.
- [17] R. G. Compton, M. E. Laing, A. Ledwith, I. Abu-Abdoun, *J. Appl. Electrochem.* **1988**, 18, 431–440.
- [18] M. A. Hillmyer, F. S. Bates, *Macromolecules* **1996**, 29, 6194–7002.
- [19] T. Granier, E. L. Thomas, D. R. Gagnon, F. E. Karasz, R. W. Lenz, *J. Polym. Sci. B* **1986**, 24, 2793–2804.
- [20] The fact that the TPA and PV chromophores both have absorbance at 302 nm makes the interpretation of energy transfer more difficult. To determine if indeed energy transfer is occurring several experiments were performed. The absorption and emission spectra were measured in six different dielectric solvents to rule out electron transfer; the solvents, in order of decreasing dielectric constant, were acetonitrile, tetrahydrofuran, chloroform, diethyl ether, benzene, and cyclohexane. There was no observable shift in λ_{max} for absorption or emission. A series of different concentrations was investigated with UV/Vis spectroscopy to ensure no molecular aggregation was occurring in solution. The concentration was varied from optical density of 0.1 to 1.1 absorbance units. Finally, quantum efficiencies (ϕ) were determined to be $\phi = 0.07$ for **6** and $\phi = 0.04$ for **1**.
- [21] D. M. Watkins, M. A. Fox, *J. Am. Chem. Soc.* **1996**, 118, 4344–4353.
- [22] S. E. Webber, *Chem. Rev.* **1990**, 90, 1469–1482.

Kinetic Footprinting of an RNA-Folding Pathway Using Peroxynitrous Acid**

Steven G. Chaulk and Andrew M. MacMillan*

Complex RNA molecules are at the heart of a number of fundamental biological processes, including translation, tRNA maturation, and RNA splicing.^[1] The unique three-dimensional structures adopted by these molecules determine their activity and in some cases, such as the assembly of the spliceosome, a dynamic series of rearrangements of the RNA structure is required to assemble an active catalytic complex. Considerable progress has been made, using phylogenetic, X-ray, NMR, and chemical probing techniques, towards understanding the two- and three-dimensional structures adopted by large RNAs.^[2–8] The mechanisms and pathways by which large RNAs fold into these structures are obviously of interest, and there is a need for novel approaches to study these processes.

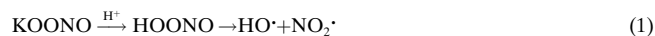
One of the most powerful techniques for probing nucleic acid structure is chemical footprinting. Diffusible hydroxyl radicals produced from Fe-ethylenediaminetetraacetate (EDTA) or Cu-phenanthroline complexes effect cleavage of the phosphodiester backbone of both DNA and RNA; cleavage of radio-labeled molecules can be easily analyzed on high-resolution polyacrylamide gels.^[9, 10] Protection against such cleavage through binding of a protein or formation of a higher order structure is detected as an area of reduced cleavage or footprint. These commonly used footprinting techniques may be regarded as *thermodynamic* since the radicals are typically generated over a 10–60 minute time period and thus are useful for examining a system at equilibrium. Elegant *kinetic* footprinting studies were performed by Chance, Brenowitz, Woodson, and co-workers to elucidate the folding pathway of the Group I ribozyme—radicals were produced on a 50–100 ms timescale by synchrotron X-ray irradiation of folding reactions and allowed the visualization of discrete intermediates on the folding pathway.^[11] Our interest in the dynamics of RNA structure has prompted us to explore the application of other readily available chemical footprinting reagents to kinetic studies of RNA folding. Here we describe the first use of such a reagent, peroxynitrous acid, as a tool for examining the folding pathway of a complex RNA: the *Tetrahymena* ribozyme.

Peroxynitrous acid (HOONO) is unstable in aqueous solution, undergoing homolytic cleavage to generate hydroxyl radical and nitrogen dioxide,^[12, 13] and has been employed in

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[**] A.M.M. acknowledges support from the Natural Sciences and Engineering Research Council of Canada. The authors are grateful to Vernon Anderson for calling their attention to peroxynitrous acid as a footprinting reagent. We thank Martha Rook and Jamie Williamson for providing plasmid pT7L-21 and we are grateful to Vanita Sood and Rick Collins for helpful discussions.

footprinting studies of tRNA and of a *lac* repressor/DNA complex.^[14, 15] The reagent is conveniently stored as the stable potassium salt in basic solution, and radical formation may be initiated by dilution into a neutral buffered reaction [Eq. (1)].



The half-life of the decomposition process is between one and two seconds at neutral pH;^[16] the observation that many RNA folding events occur on a timescale of minutes^[17] immediately suggests the potential of HOONO as a kinetic footprinting reagent in such systems.

We chose the L-21 *Tetrahymena* ribozyme, a 385 nucleotide sequence-specific endoribonuclease derived from a self-splicing Group I intron, as a model system for our studies because it has been exceptionally well characterized biochemically and because the structures of several large fragments have been determined by X-ray crystallography.^[3, 4] Phylogenetic comparisons^[2] were originally used to predict a number of conserved paired regions (P) and provided a two-dimensional map of the ribozyme structure (Figure 1 a)—the folding of the RNA into its active three-dimensional structure is a magnesium-dependent process which produces a compact structure of tightly packed helical regions.^[3, 4] Equilibrium footprinting of the *Tetrahymena* ribozyme with Fe-EDTA showed a strong,

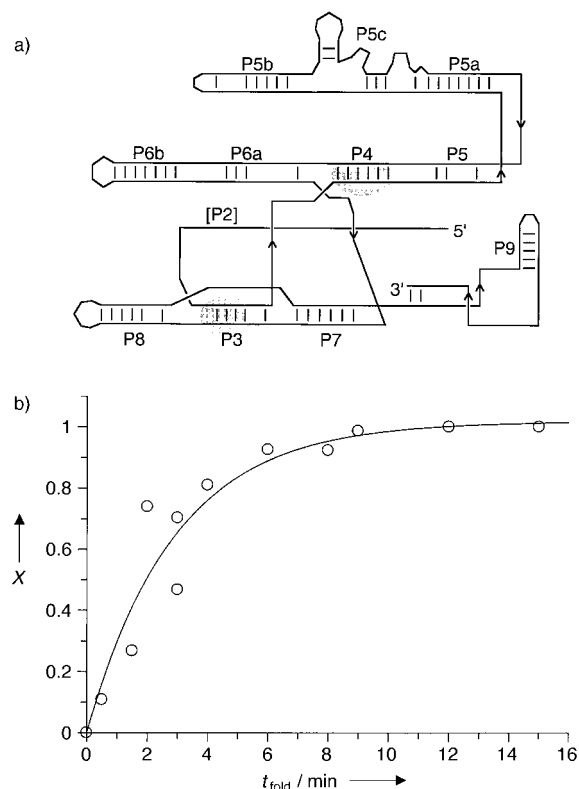


Figure 1. a) Schematic representation of the secondary structure of the *Tetrahymena* L-21 *ScaI* ribozyme showing base-paired (P) regions. The P3 and P4 regions, which are strongly protected from radical-induced cleavage in the folded RNA molecule,^[9] are shaded; b) folding of the ribozyme, assayed through analysis of endoribonuclease activity following addition of Mg^{2+} . X represents the fraction of RNA cleaved at a particular folding time, normalized to the final observed cleavage. Cleavage reactions were carried out with excess ribozyme for 50 s. The first-order rate constant for the overall folding process k_{fold} is $\sim 0.4 \text{ min}^{-1}$.

magnesium-dependent protection of the P3 and P4 regions (highlighted in Figure 1 a).^[9]

We synthesized the ribozyme by T7 run-off transcription from the plasmid pT7L-21 and assayed it for activity in the cleavage of a ^{32}P -labeled 11 nucleotide RNA substrate.^[17] By using this activity as an assay for magnesium-dependent folding of the ribozyme^[17] we were able to observe a folding process taking place over several minutes with an observed rate k_{fold} of 0.4 min^{-1} (Figure 1 b).

We carried out the kinetic footprinting studies by the addition of freshly prepared potassium peroxyntirite to folding reactions containing ^{32}P -end-labeled RNA at various time points following the addition of magnesium chloride. Reactions were desalted by precipitation and analyzed by denaturing gel electrophoresis (Figure 2 a). Control cleavages

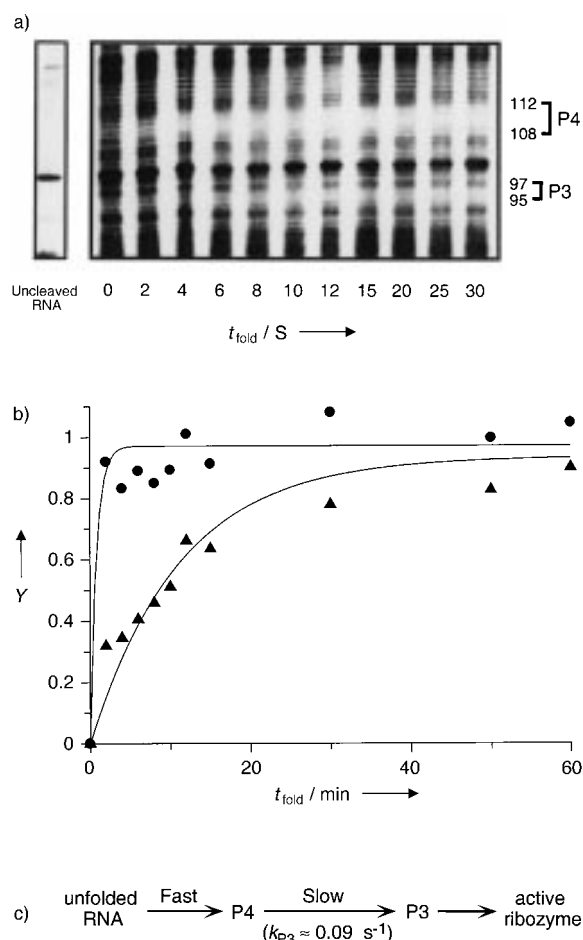


Figure 2. Peroxynitrous acid footprinting of the ribozyme during folding. a) Lower portion of a gel showing cleavage of the ribozyme at indicated times following addition of Mg^{2+} . The position of cleavage is shown by reference to paired regions described in Figure 1 a; b) relative protection of the P3 (▲) and P4 (●) regions of the ribozyme as a function of folding time. Y represents the fraction of RNA protected from cleavage, relative to unfolded RNA, at a given folding time; c) partial hierarchy of the folding pathway of the *Tetrahymena* ribozyme.

with RNase T1 were carried out to create a G ladder and thus allow mapping of cleavage sites to specific regions of the ribozyme sequence. It is apparent that the addition of Mg^{2+} results in significant protection of portions of the ribozyme

from radical-induced cleavage. In order to assess the time and domain dependence of such cleavage, we quantified cleavages over specific regions and plotted these as a fraction of relative protection versus time (Figure 2b). This analysis suggests that individual domains of the ribozyme assemble at different rates (Figure 2c) and is consistent with the results of both synchrotron X-ray footprinting^[11] and an oligonucleotide hybridization/cleavage assay,^[17] two other methods that have been used to analyze the folding pathway of the *Tetrahymena* ribozyme. The P4-P6 region is protected very quickly during the folding process and has been proposed as a scaffold around which other folding events take place.^[18] Assembly of the P3 helix at the core of the catalytic domain is a late-occurring event and may be reflective of kinetic traps along the folding pathway.^[19]

The formation of the P4 helix clearly occurs too fast to be measured with the peroxynitrous acid reagent—analysis of events such as these requires the more rapid radical generation available through synchrotron irradiation. However, formation of the P3 helix is significantly slower. This event takes place with a first-order rate constant (k_{p3} 0.09 s⁻¹); the half-time for protection is roughly eight seconds. A comparison with the overall rate of folding (Figure 1b) indicates that P3 formation is not the rate determining step—we are carrying out additional investigations, including an analysis of the rates of folding of other regions of the ribozyme.

Our results with the *Tetrahymena* system validate the use of peroxynitrous acid as a kinetic footprinting tool; this easily used methodology should prove valuable in the elucidation of many relatively slow RNA folding pathways and the examination of RNA dynamics in complex systems.

Experimental Section

Potassium peroxynitrite synthesis: HCl (0.5 M, 5 mL) was added to a stirred ice-cooled aqueous solution (10 mL) containing NaNO₂ (0.6 M, 0.41 g) and H₂O₂ (3 %). A solution (5 mL) containing diethylenetriaminepentaacetic acid (400 μM, 3.3 mg) and KOH (1.6 M) was added immediately afterwards. The resulting mixture was stirred for 5 minutes then MnO₂ (100 mg) was added and stirring continued for 20 minutes. Excess MnO₂ was removed by gravity filtration (performed at 4 °C). Typical yields of potassium peroxynitrite were 80–130 mM measured by UV absorbance at 302 nm (ϵ = 1670 M⁻¹ cm⁻¹). Even a slight delay in the addition of the KOH/diethylenetriaminepentaacetic acid solution resulted in significantly lower yields of potassium peroxynitrite. The potassium peroxynitrite solution was stored at –78 °C with no decrease in concentration after 10 weeks.

Peroxyntous acid footprinting: L-21 Group I ribozyme folding was initiated by the addition of MgCl₂ (final concentration 10 mM) to a solution (final volume 20 μL) containing final concentrations of NaCl (80 mM), NaH₂PO₄/Na₂HPO₄ (50 mM, pH 7), 5'-end labeled ribozyme (50 nM, 3 × 10⁶ cpm) at 22 °C. Footprinting was then effected by the addition of potassium peroxynitrite (1 μL, 130 mM) at the indicated times (see Figure 2). Footprinting reactions were allowed to proceed for 20 seconds before freezing on dry ice, followed by ethanol precipitation. Reactions (1 × 10⁶ cpm) were then subjected to denaturing polyacrylamide gel electrophoresis (PAGE, 6%, 19:1) for 2.3 hours at 85 W. Dried gels were exposed to a molecular dynamics phosphor screen, which was then scanned on a Molecular Dynamics Storm 860 Phosphorimager. To calculate the fractional peroxynitrous acid protection (footprint), the background intensity (ImageQuant 5.0) was first subtracted and a correction for differences in lane loading was applied. The intensity of a region at a given time was divided by the intensity of the same region at time zero. The resulting fractional intensities were normalized from 0 to 1. Plots of normalized fractional protection versus folding time were fitted to a first-

order exponential (GraFit 3.00) using data averaged from five separate experiments.

Received: July 26, 1999 [Z13782]

- [1] See *The RNA world*, 2nd ed. (Eds.: R. F. Gesteland, T. R. Cech, J. F. Atkins), Cold Spring Harbor Laboratory, Cold Spring Harbor, **1999**.
- [2] F. Michel, E. Westhof, *J. Mol. Biol.* **1990**, *216*, 585–610.
- [3] J. H. Cate, A. R. Gooding, E. R. Podell, K. Zhou, B. L. Golden, C. E. Kundrot, T. R. Cech, J. A. Doudna, *Science* **1996**, *273*, 1678–1685.
- [4] B. L. Golden, A. R. Gooding, E. R. Podell, T. R. Cech, *Science* **1998**, *282*, 259–264.
- [5] W. G. Scott, *Curr. Opin. Struct. Biol.* **1998**, *8*, 720–726.
- [6] M. Wu, I. Tinoco, Jr., *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 11555–11560.
- [7] A. A. Szewczak, L. Ortoleva-Donnelly, S. P. Ryder, E. Moncoeur, S. A. Strobel, *Nat. Struct. Biol.* **1998**, *5*, 1037–1042.
- [8] R. T. Batey, R. P. Rambo, J. A. Doudna, *Angew. Chem.* **1999**, *111*, 2472–2491; *Angew. Chem. Int. Ed.* **1999**, *38*, 2326–2343.
- [9] J. A. Latham, T. R. Cech, *Science* **1989**, *245*, 276–282.
- [10] C.-H. B. Chen, D. S. Sigman, *J. Am. Chem. Soc.* **1988**, *110*, 6570–6572.
- [11] a) B. Sclavi, S. A. Woodson, M. Sullivan, M. R. Chance, M. Brenowitz, *J. Mol. Biol.* **1997**, *266*, 144–159; b) B. Sclavi, M. Sullivan, M. R. Chance, M. Brenowitz, S. A. Woodson, *Science* **1998**, *279*, 1940–1943.
- [12] C. E. Richeson, P. Mulder, V. W. Bowry, K. U. Ingold, *J. Am. Chem. Soc.* **1998**, *120*, 7211–7219.
- [13] P. A. King, V. E. Anderson, J. O. Edwards, G. Gustafson, R. C. Plumb, J. W. Suggs, *J. Am. Chem. Soc.* **1992**, *114*, 5430–5432.
- [14] P. A. King, E. Jamison, D. Strahs, V. E. Anderson, M. Brenowitz, *Nucleic Acids Res.* **1993**, *21*, 2473–2478.
- [15] M. Götte, R. Marquet, C. Isel, V. E. Anderson, G. Keith, H. J. Gross, B. Ehresmann, H. Heumann, *FEBS Lett.* **1996**, *390*, 226–228.
- [16] J. S. Beckman, T. W. Beckman, J. Chen, P. A. Marshall, B. A. Freeman, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 1620–1624.
- [17] P. P. Zarrinkar, J. R. Williamson, *Science* **1994**, *265*, 918–924.
- [18] E. A. Doherty, J. A. Doudna, *Biochemistry* **1997**, *36*, 3159–3169.
- [19] M. S. Rook, D. K. Treiber, J. R. Williamson, *J. Mol. Biol.* **1998**, *281*, 609–620.

Solvation of the Carbonyl Compound as a Predominant Factor in the Diastereofacial Selectivity of Nucleophilic Addition**

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Discussions of factors controlling stereoselectivity commonly focus on steric and/or electronic features of the catalyst and/or the substrate.^[1] However, selectivity is a kinetic

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[**] This work was supported by MURST and the University of Bologna (Fund for Selected Topics). We thank Andrea Garelli for assistance with the NMR spectroscopy.

phenomenon governed by the ratio of the rate of formation for one stereoisomer with respect to that of the other. The stereoselectivity can be influenced not only by varying the reactants but also by changing the reaction conditions. In this perspective, reaction temperature and solvent are readily available parameters for controlling selectivity.

Solvents play a critical role in chemical processes: both equilibrium constants and reaction rates may change drastically in different solvents.^[2] There are examples of the effect of solvent on face selectivity in which a variation of the diastereomeric excess is observed and others in which a complete reversal of diastereoselectivity occurs because of a change in the reaction solvent.^[3] We believe that the influence of solvent on diastereomeric excess can be considered a macroscopic effect arising from molecular, microscopic solute–solvent interactions which differently affect the two reaction paths leading to the diastereomers. The description, from a microscopic point of view, of solvation processes and of their effects on the energetics and dynamics of chemical reactions constitutes a general topic of main relevance, but research in this field is still only at the beginning.^[4]

The effect of temperature on diastereoselectivity has long been observed and its influence is not uniform: on increasing the reaction temperature the diastereoselectivity may decline, but it may be constant or even increase. Analysis of the logarithmic values of the isomer ratio (*S*) as a function of the reciprocal temperature results in the linear relationship shown in Equation (1), where $S = k/k' = I/I'$, k , k' are the overall rate constants, and I , I' are the relative amounts of the *anti* and the *syn* isomer, respectively.

$$\ln S = -(\Delta\Delta H^\ddagger/RT) + (\Delta\Delta S^\ddagger/R) \quad (1)$$

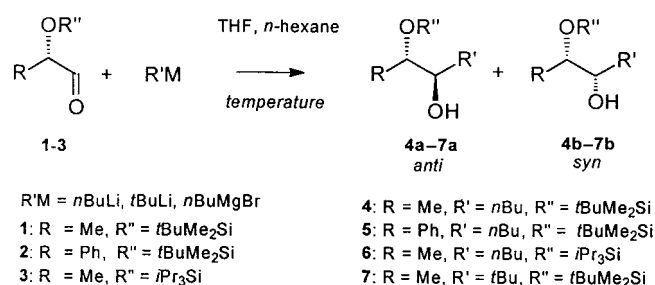
According to Eyring's theory,^[5] when this relationship is plotted, the slope corresponds to the difference in the overall activation enthalpies and the intercept represents the difference in the overall activation entropies. However, for some reactions a nonlinear plot is obtained. In these cases, the corresponding Eyring plots generally consist of two linear regions intersecting at a so-called inversion temperature (T_{inv}). This phenomenon was reviewed in 1991 by Scharf et al.,^[6] and in the meantime other processes with a nonlinear relationship between stereoselectivity and reaction temperature have been described.^[7]

In recent papers we have formulated the idea that a sort of phase modification occurs at T_{inv} .^[8] In our hypothesis the inversion temperature could constitute a transition between two different solvation states that could be described as two different solute–solvent clusters with a different order.^[9] These supramolecular structures behave like different molecules and produce a measurable change in thermodynamic properties and therefore in diastereoselectivity. In this hypothesis T_{inv} represents the interconversion temperature between two supramolecules, and it does not imply any change either in the rate-determining step or in the reaction mechanism.

In the present investigation we report preliminary results that strengthen our proposal on the solvation of carbonyl compounds as the predominant factor in the nonlinear effect

of temperature on diastereofacial selectivity. In fact, we report evidence that T_{inv} does not depend on nucleophiles, and that its value can be obtained from a ^{13}C NMR experiment in which the change in the $\text{C}=\text{O}$ chemical shift versus temperature is recorded.

(2*S*)-*O*-(*tert*-Butyldimethylsilyl)lactic aldehyde (**1**), (2*S*)-*O*-(*tert*-butyldimethylsilyl)mandelic aldehyde (**2**), and (2*S*)-*O*-(triisopropylsilyl)lactic aldehyde (**3**) were allowed to react with *tert*-butyllithium and *n*-butyllithium in THF and *n*-hexane, and with *n*-butylmagnesium bromide in THF to give the corresponding *anti* and *syn* monoprotected diols (Scheme 1). The addition reactions were performed by adding



Scheme 1. Formation of the *anti* and *syn* monoprotected diols.

a stoichiometric amount of the organometallic reagent dropwise to a solution of the pure aldehyde in dry THF or *n*-hexane. The reaction was conducted at temperatures ranging over 150 °C. The diastereomeric excess of the products was determined by GC analysis.^[10] The results were elaborated in the corresponding Eyring plots. The data have been treated by the least-squares method to obtain linear relationships. Each aldehyde–solvent combination gave plots with two linear regions in the temperature range explored, and in all cases we determined the characteristic T_{inv} value (Table 1).

Table 1. Inversion temperatures (T_{inv}) for the addition of *n*BuLi, *t*BuLi, and *n*BuMgBr to aldehydes **1–3** in *n*-hexane and THF as well as the ^{13}C NMR break temperatures (T_{NMR}) in the linear variation of $\delta(^{13}\text{C}=\text{O})$ versus temperature.

Aldehyde/RM'	Solvent	T_{inv} [°C]	Aldehyde	Solvent	T_{NMR} [°C]
1 / <i>n</i> BuLi	<i>n</i> -hexane	−83	1	$[\text{D}_{14}]n\text{-hexane}$	−68
1 / <i>t</i> BuLi	<i>n</i> -hexane	−81			
1 / <i>n</i> BuLi	THF	−12	1	$[\text{D}_8]\text{THF}$	0
1 / <i>n</i> BuMgBr	THF	+1			
1 / <i>t</i> BuLi	THF	−13			
2 / <i>n</i> BuLi	THF	−63	2	$[\text{D}_8]\text{THF}$	−47
2 / <i>n</i> BuMgBr	THF	−65			
3 / <i>n</i> BuLi	THF	−46	3	$[\text{D}_8]\text{THF}$	−42

The diastereofacial selectivity of *n*BuLi addition to lactic aldehyde **1** in *n*-hexane is only slightly temperature sensitive. Nevertheless, T_{inv} is quite evident at −83 °C (Figure 1a). With *t*BuLi the selectivity is notably affected and increases with reducing temperature. Interestingly, both plots exhibit quite similar inversion temperatures.

The reactions with *t*BuLi and *n*BuLi in THF at low temperature give divergent plots on account of the opposite temperature effect on the selectivity (Figure 1b). The diastereofacial selectivity in the addition of *n*BuMgBr to **1** is less

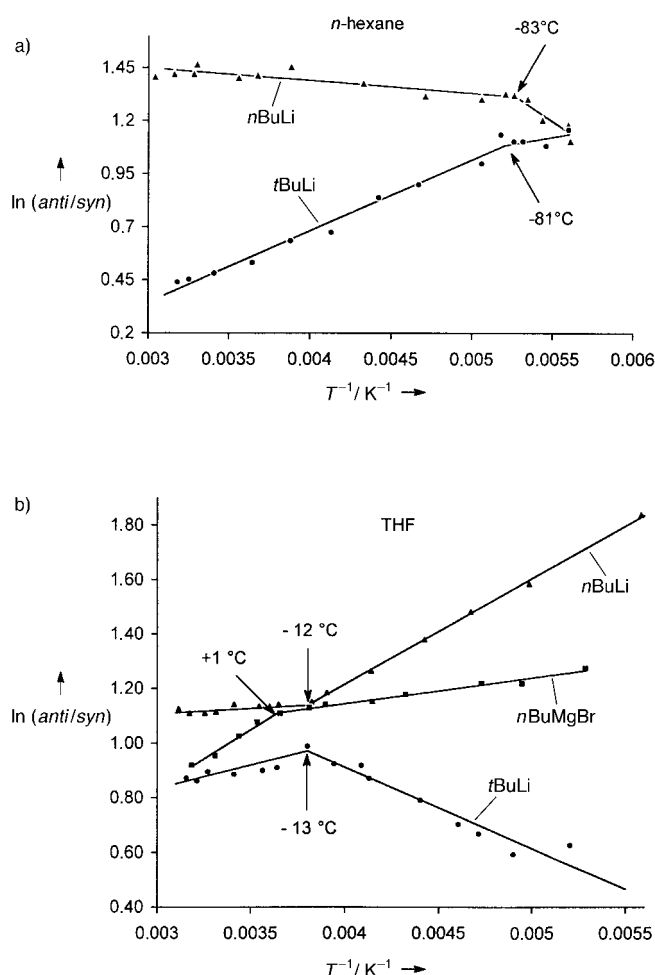


Figure 1. Eyring plots for the *anti/syn* ratio of the diastereomers formed from the nucleophilic addition of *n*-butyllithium ($\blacktriangle$), *tert*-butyllithium ($\bullet$), and *n*-butylmagnesium bromide ($\blacksquare$) to **1** at various temperatures in *n*-hexane (a) and THF (b).

affected by temperature than the organolithium reactions. In this case T_{inv} is $+1^\circ\text{C}$. The plots are more differentiated at low temperature with *t*BuLi, *n*BuLi, and *n*BuMgBr. Remarkably, all three plots in Figure 1 show T_{inv} values in a narrow temperature range.

In the next set of experiments *n*BuMgBr and *n*BuLi were added to mandelic aldehyde **2** (Figure 2). Both plots reach negative values of $\ln(\text{anti/syn})$; thus, it is possible to invert the diastereofacial selectivity by means of reaction temperature. Despite the slight change in selectivity with temperature, these two plots have a very similar T_{inv} value (-65 and -63°C , respectively).

In nucleophilic addition reactions of this type, temperature and solvent effects on the diastereomeric excess might be ascribed to the presence of different organometallic species in solution.^[11] However, the dynamic process that involves the aggregation state of the organometallic reagent acts before the reacting event (C–C bond formation) so that the corresponding rate constants are identical for the reaction paths that lead to both *syn* and *anti* diastereomers. Thus, a mere ground-state effect would be irrelevant. The tendency of organometallic species to aggregate may to some extent influence the structure of the transition states. Moreover, we

found that different organometallic reagents with different molecular structures in solution have similar inversion temperatures. Thus, the influence of aggregation and solvation of the organometallic compound on stereoselectivity is limited by the kinetic expression of selectivity ($S = k/k'$),^[12] where in the ratio of overall kinetic constants all the equal terms vanish. All the above results clearly show that T_{inv} is greatly dependent on the aldehyde–solvent combination and less on the nucleophile. This fact emphasizes our idea that the solvation of the starting carbonyl compound accounts for the T_{inv} value.

NMR techniques provide a powerful method for investigating the local electronic environment of the molecular structure, and nuclear shielding is a sensitive probe of intermolecular interactions and solvent effects.^[13] In this study we conducted a series of ^{13}C NMR experiments in deuterated THF and *n*-hexane with aldehydes **1–3** to determine whether the chemical shift is temperature dependent. Figure 3a displays the change in the C=O ^{13}C chemical shift as a function of temperature in $[\text{D}_4]n$ -hexane for aldehyde **1**. This result can be directly compared with the Eyring plot for the reaction of same aldehyde with *n*BuLi in THF (Figure 1).

The ^{13}C chemical shift of C=O in aldehyde **1** decreased on warming. This effect could be the result of a loss of electron density near the observed nucleus. On further checking the experimental data points we recognized a break in the linear variation of chemical shift versus temperature. We applied the least median squares (LMS) regression to determine the T value of these breaks more precisely.^[14] Use of the LMS regression improves the reliability and the ability to objectively define the segments of the straight line given by experimental data. Table 1 lists the break temperatures for the substrates studied. These temperature values change with the solvent and the substrate and, surprisingly, they correspond or are fairly close to the inversion temperatures obtained with the same substrate–solvent combination in the nucleophilic addition reaction.

This result reinforces our hypothesis that T_{inv} corresponds to a transition between two differently ordered solvation states. As we stated earlier the inversion temperature reflects

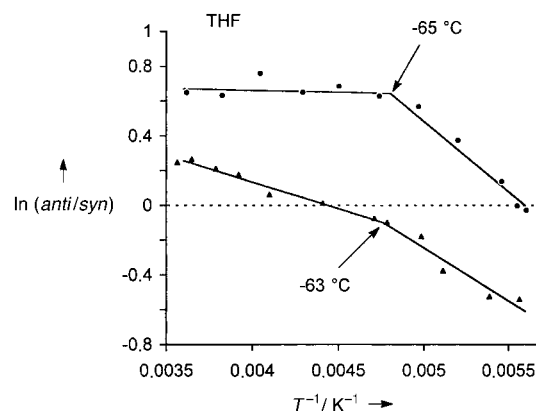


Figure 2. Eyring plots for the *anti/syn* ratio of the diastereomers formed from the nucleophilic addition of *n*-butyllithium ($\blacktriangle$) and *n*-butylmagnesium bromide ($\bullet$) to **2** at various temperatures in THF.

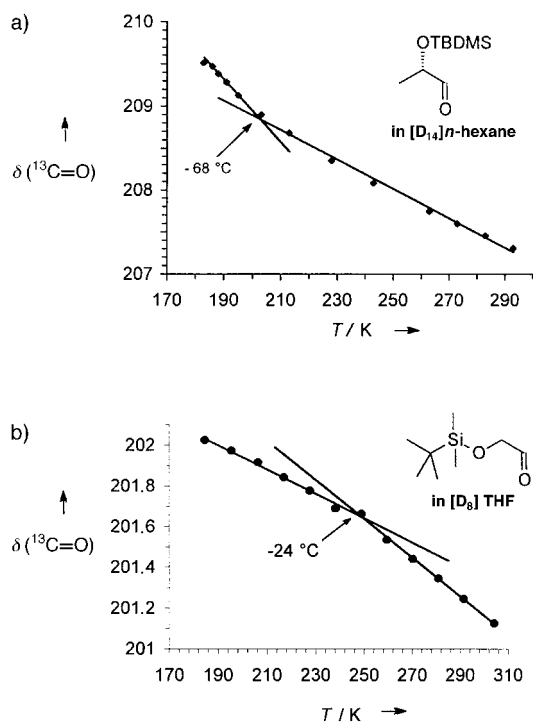


Figure 3. Plots of $\delta(^{13}\text{C}=\text{O})$ versus temperature for **1** in deuterated *n*-hexane (a) and for 2-(*tert*-butyldimethylsilyloxy)ethanal in deuterated THF (b). Solid lines are the fitting results. See text for details on the line fitting. TBDMS = *tert*-butyldimethylsilyl.

the solvation state of the carbonyl compound. Changes in the solvation state with the temperature can be not continuous, and it makes an abrupt change corresponding to the T_{inv} value. Because of its very nature this phenomenon should not be tied to the presence of a stereocenter in the carbonyl compound. In fact, the plot in Figure 3b shows the change in the ^{13}C chemical shift of $\text{C}=\text{O}$ for 2-(*tert*-butyldimethylsilyloxy)ethanal in deuterated THF, and it shows a break at $T = -24^\circ\text{C}$. This achiral aldehyde has a change in its solvation shell that could affect its reactivity simply because two different solvation clusters exist in the two temperature regions and act as two different molecules. This result challenges us to find a reaction that will show nonlinear selectivity with temperature and a T_{inv} value close to the break temperature revealed in the ^{13}C NMR experiment.

We have demonstrated that the inversion temperature observed in Eyring plots obtained for diastereoselective nucleophilic additions to α -chiral aldehydes does not depend on nucleophiles. The ^{13}C NMR results clearly connect the phenomenon of T_{inv} with the solvation of the starting carbonyl compound, and they shed light on nonlinear temperature effects on stereoselectivity. This confirms our earlier hypothesis of the solvent-dependent nature of T_{inv} .

Experimental Section

The ^{13}C chemical shift measurements were made with a Varian Gemini 300 instrument operating at 75.5 MHz using a 5-mm probe. All chemical shifts are quoted relative to signals of the deuterated solvent. The temperature was controlled by a variable-temperature unit using the flow of temperature-regulated nitrogen gas. The temperature was calibrated from differences in the chemical shift of a methanol sample.^[15] The *anti/syn* ratios and

the *de* values were obtained from GC analysis of the crude products or of the corresponding *O*-trimethylsilyl-derivatives. The average standard deviation for the *de* measurements was less than 1%.

In a typical experiment, the aldehyde (1 mmol) was dissolved in anhydrous solvent (20 mL) under an inert atmosphere, and the solution was cooled or warmed to the desired temperature. Then *n*-butyllithium, *tert*-butyllithium, or *n*-butylmagnesium bromide (1.2 mmol) was added. After the starting aldehyde had disappeared (GC monitoring), the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 ($3 \times 50\text{ mL}$), and the extracts were dried with Na_2SO_4 and concentrated to dryness. Chromatography of the residue on a silica gel column gave a mixture of alcohols **4a–7a** and **4b–7b**. The calculated chemical yields ranged from 80 to 90%. After removal of the *t*BuMe₂Si group by means of Bu_4NF in THF, the configuration of the 1,2-diol was determined by comparison with reported data.^[16]

Received: June 9, 1999 [Z13537]

- [1] For a review on classical conformational models, see E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 875; R. E. Gawley, J. Aubé, *Principles of Asymmetric Synthesis*, Pergamon, Oxford, **1996**.
- [2] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, Weinheim, **1990**.
- [3] See for example: N. Hoffmann, H. Buschmann, G. Raabe, H.-D. Scharf, *Tetrahedron* **1994**, *50*, 11167; G. Cainelli, D. Giacomini, F. Perciaccante, *Tetrahedron: Asymmetry* **1994**, *5*, 1913; Y. Inoue, N. Yamasaki, T. Yokoyama, A. Tai, *J. Org. Chem.* **1992**, *57*, 1332; D. Awandi, F. Henin, J. Muzart, J.-P. Pete, *Tetrahedron: Asymmetry* **1991**, *2*, 1101.
- [4] D. J. Giesen, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem.* **1995**, *99*, 7137; G. D. Hawkins, D. A. Liotard, C. J. Cramer, D. G. Truhlar, *J. Org. Chem.* **1998**, *63*, 4305; M. F. Ruiz-Lopez, X. Assfeld, J. I. Garcia, J. A. Mayoral, L. Salvatella, *J. Am. Chem. Soc.* **1993**, *115*, 8780; M. Sola, A. Lledos, M. Duran, J. Bertran, J.-L. M. Abboud, *J. Am. Chem. Soc.* **1991**, *113*, 2873.
- [5] H. Eyring, *J. Phys. Chem.* **1935**, *3*, 107; S. Glasstone, K. J. Laidler, H. Eyring, *The Theory of Rate Processes*, McGraw-Hill, New York, **1941**, Chap. 4.
- [6] H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem.* **1991**, *103*, 480; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 477.
- [7] For recent papers, see K. J. Hale, J. H. Ridd, *J. Chem. Soc. Perkin Trans. 2* **1995**, 1601; J. Muzart, F. Hénin, S. J. Aboulhoda, *Tetrahedron: Asymmetry* **1997**, *8*, 381; M. Palucki, P. J. Pospisil, W. Zhang, E. N. Jacobsen, *J. Am. Chem. Soc.* **1994**, *116*, 9333; J. Brunne, N. Hoffmann, H.-D. Scharf, *Tetrahedron* **1994**, *50*, 6819; T. Göbel, K. B. Sharpless, *Angew. Chem.* **1993**, *105*, 1417; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1329; J. Muzart, F. Hénin, J.-P. Pête, A. M'boungou-M'Passi, *Tetrahedron: Asymmetry* **1993**, *4*, 2531; I. Tóth, I. Guo, B. E. Hanson, *Organometallics* **1993**, *12*, 477.
- [8] G. Cainelli, D. Giacomini, P. Galletti, A. Marini, *Angew. Chem.* **1996**, *108*, 3016; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2849; G. Cainelli, D. Giacomini, P. Galletti, *Eur. J. Org. Chem.* **1999**, *61*; G. Cainelli, D. Giacomini, P. Galletti, *Chem. Commun.* **1999**, 567.
- [9] Partial ordering of molecules is possible in solution, and a temperature-dependent change in this order is already manifested in the nonlinearity of some spectroscopic properties. See for instance: J. B. Robert, *Mol. Phys.* **1997**, *90*, 399; M. A. Wendt, J. Meiler, F. Weinhold, T. C. Farrar, *Mol. Phys.* **1998**, *93*, 145.
- [10] GC analyses were carried out on a HRGC 5300 Carlo Erba instrument using a OV 1701 (25 m) column with a chiral phase.
- [11] J. F. McGarrity, C. A. Ogle, *J. Am. Chem. Soc.* **1984**, *107*, 1805; J. F. McGarrity, C. A. Ogle, Z. Brich, H.-R. Loosli, *J. Am. Chem. Soc.* **1984**, *107*, 1810.
- [12] D. Heller, H. Buschmann, *Top. Catal.* **1998**, *5*, 159.
- [13] For solvent effects on chemical shift see for instance: T. Helgaker, M. Jaszunski, K. Ruud, *Chem. Rev.* **1999**, *99*, 293; E. Y. Lau, J. T. Gerig, *J. Am. Chem. Soc.* **1996**, *118*, 1194; E. Y. Lau, J. T. Gerig, *J. Chem. Phys.* **1995**, *103*, 3341, and references therein.

- [14] P. J. Rousseeuw, *J. Am. Stat. Ass.* **1984**, 79, 871; M. Ortiz, A. Herrero-Gutierrez, *Chemom. Intell. Lab. Syst.* **1995**, 27, 231.
 [15] H. Friebolin, G. Schilling, L. Pohl, *Org. Magn. Reson.* **1979**, 12, 569.
 [16] J. A. Katzenellenbogen, S. B. Bowlus, *J. Org. Chem.* **1973**, 38, 627; W. Kroutil, M. Mischitz, K. Faber, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3629; C. Chiappe, A. Cordoni, G. Lo Moro, C. D. Palese, *Tetrahedron: Asymmetry* **1998**, 8, 341.

Novel Single- and Double-Layer and Three-Dimensional Structures of Rare-Earth Metal Coordination Polymers: The Effect of Lanthanide Contraction and Acidity Control in Crystal Structure Formation**

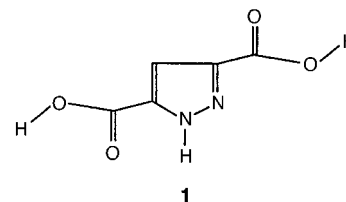
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The concept of rational design of micro- and mesoporous and other functional materials has attracted much attention because of the potential of these materials in various applications, such as molecular magnets, nonlinear optical devices, catalysts, molecular sieves, and sensors.^[1] The construction of coordination networks possessing zeolite- or clay-like structures offers great challenges and opportunities in terms of controlling their shape and size for selective adsorption. Much of the work has so far been focused on coordination polymers containing transition metal (Groups 8 to 10) and post-transition metal (Groups 11 and 12) elements including Fe, Co, Ni, Cu, Ag, Zn, Cd, and Hg. Rare-earth metal compounds have seldom been investigated.^[2] To date, no systematic investigation across the lanthanide series with a single ligand has been carried out. Due to their high coordination number and special magnetic and fluorescence properties, the lanthanide series is likely to provide new materials that possess specific properties and desired features. In this communication, we report the hydrothermal synthesis, structures, and properties of six novel lanthanide coordination polymers and the investigation of the effects of lanthanide contraction and solution pH on the crystal structures of these compounds.

Hydrothermal synthesis^[3] is an effective and promising method for growing crystals of numerous inorganic compounds. Recently, we and others have successfully grown

single crystals of a variety of transition metal coordination polymers using this approach.^[4, 5] Our exploratory studies also show that the hydrothermal environment is suitable for preparation of lanthanide compounds.

In this work, we have chosen a single, multifunctional ligand, 3,5-pyrazoledicarboxylic acid (H₃pdc, **1**), based on the following considerations: a) it has multiple coordination sites



that allow structures of higher dimensions; b) it has an asymmetric geometry that may lead to acentric crystal structures; and c) it has abstractable protons that allow various, acidity-dependant coordination modes. In general, the lanthanide series can be divided into three groups according to their masses: the lighter La–Pm (Group 1), the intermediate Sm–Dy (Group 2), and the heavier Ho–Lu (Group 3). Representative metals from each Group were selected and investigated.

In a typical reaction 0.25 mmol of rare-earth metal(III) nitrate and 0.25 mmol of **1** in 10 mL H₂O was used. The mixture was placed into a 23 mL acid-digestion bomb lined with Teflon and heated at 150 °C for 3 days. Reactions with Group 1 lanthanide nitrates Ln(NO₃)₃ (Ln = La, Ce) generated [Ln₂(Hpdc)₃(H₂O)₄] · 2 H₂O, Ln = La (**2**), Ln = Ce (**3**). Group 2 nitrate Eu(NO₃)₃ produced [Eu₂(Hpdc)₃(H₂O)₆] (**4**) and a minor product [Eu₂(Hpdc)₃(H₂O)₄] · 2 H₂O that is isostructural to **2** and **3**, while Group 3 nitrates Ln(NO₃)₃ (Ln = Er, Lu) yielded [Er₂(Hpdc)₃(H₂O)₆] (**5**), and [Ln(Hpdc)(H₂pdc)(H₂O)₂], Ln = Er (**6**), Ln = Lu (**7**).

Single-phase polycrystalline samples of both **2** and **3** were obtained with 68% and 71% yields, respectively. Both compounds are stable in air and are not soluble in any common solvents. Single crystal X-ray diffraction analyses were performed on selected crystals of both compounds. Their crystal structures^[6] are isotypic with a three-dimensional framework (see Figure 1a) containing nine-coordinate lanthanide metal centers. There are two types of metal environments in this structure. As shown in Figure 1b, three Hpdc²⁻ ligands chelate to Ln1 through a carboxylate oxygen and adjacent nitrogen atoms (O3/N2, O5/N3, O9/N5), occupying six coordination sites of Ln1. The remaining three coordination sites of Ln1 are taken by another three Hpdc²⁻ ligands, each through a single carboxylate oxygen atom (O2, O7, O12). The second metal environment has Ln2 bonding to a chelated carboxylate group of a Hpdc²⁻ ligand (O1, O2) and to three carboxylate groups of three additional Hpdc²⁻ ligands (O5, O9, O11). The remaining four coordination sites are occupied by the oxygen atoms of four water molecules (O13, O14, O15, O16). There are three crystallographically independent Hpdc²⁻ molecules in the structure, each having a different coordination mode. The highly unsymmetric coordination pattern of the metal and the ligand led to a crystal structure

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[**] This work was supported by the National Science Foundation (DMR-9553066).

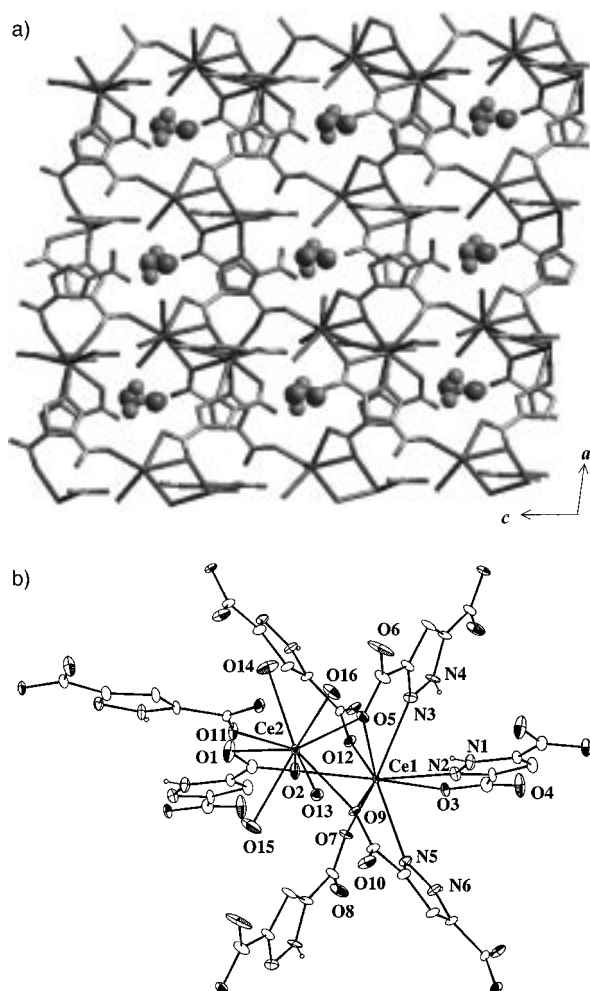


Figure 1. a) View of $[\text{Ln}_2(\text{Hpdc})_3(\text{H}_2\text{O})_4] \cdot 2 \text{H}_2\text{O}$, $\text{Ln} = \text{La}$ (**2**), $\text{Ln} = \text{Ce}$ (**3**), along the b axis. Large and small solid spheres represent O and H atoms of the uncoordinated water molecules. b) ORTEP drawing of **3**. Both Ce1 and Ce2 atoms are nine coordinate. Selected distances [Å]: Ce1–Ce2 4.0381(12), Ce1–O7 2.427(5), Ce1–O3 2.456(5), Ce1–O12 2.458(5), Ce1–O2 2.469(5), Ce1–O5 2.610(5), Ce1–O9 2.616(4), Ce1–N5 2.628(6), Ce1–N3 2.632(7), Ce1–N2 2.654(6), Ce2–O16 2.413(5), Ce2–O11 2.427(5), Ce2–O13 2.530(5), Ce2–O15 2.541(6), Ce2–O5 2.547(5), Ce2–O1 2.589(5), Ce2–O9 2.595(4), Ce2–O14 2.596(6), Ce2–O2 2.668(5).

belonging to an acentric space group.^[6] The resultant three-dimensional structure contains open channels along the b axis that are occupied by two noncoordinating water molecules. The approximate dimensions of these channels are 3.5×4.5 Å (Figure 1 a).

Europium was chosen as a representative metal from the Group 2 lanthanides, and compound **4** was synthesized under similar experimental conditions. A minor europium compound, isostructural with **2** and **3**, was also found in the reaction mixture. The crystal structure of **4** (Figure 2 a)^[7] is a claylike double layer that is rare for coordination polymers.^[8] As illustrated in Figure 2b, the coordination polyhedron around each europium atom is a square antiprism with three sites occupied by oxygen atoms from three coordinated water molecules (O7, O8, O9) and the other three sites by carboxylate groups from three Hpdc²⁻ ligands (O2, O3, O5). In the remaining two sites are a chelated carboxylate oxygen and adjacent nitrogen atom from the fourth Hpdc²⁻ ligand

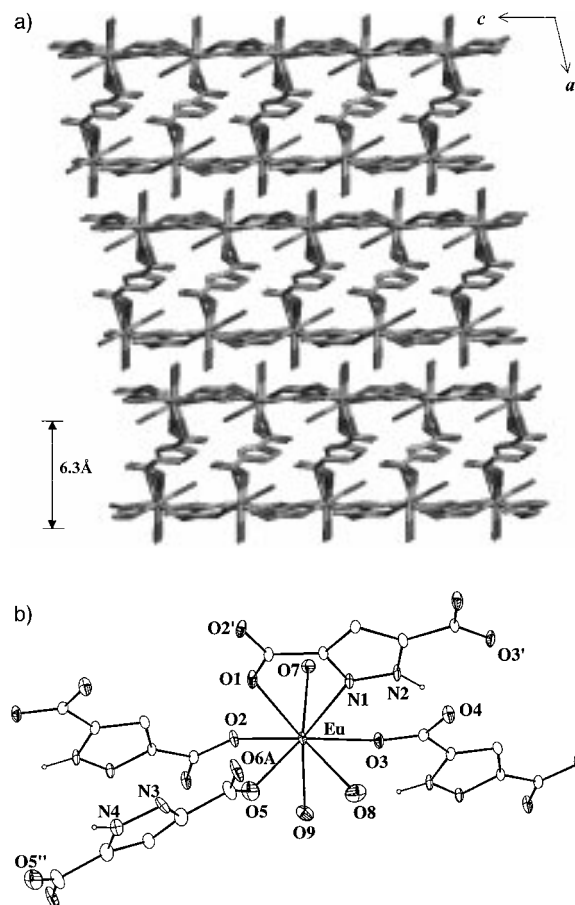


Figure 2. a) View of $[\text{Eu}_2(\text{Hpdc})_3(\text{H}_2\text{O})_6]$ (**4**) along the b axis. The interlayer interactions between the double layers are through hydrogen bonds ($\text{O4} \cdots \text{O7} = 2.767(4)$ Å, $\text{O2} \cdots \text{O7} = 2.785(4)$ Å, not shown). b) ORTEP drawing of **4**. Each Eu atom is eight coordinate. Selected bond lengths [Å]: Eu–O5 2.336(3), Eu–O7 2.375(3), Eu–O3 2.379(3), Eu–O2 2.416(3), Eu–O8 2.438(3), Eu–O9 2.441(3), Eu–O1 2.451(3), Eu–N1 2.523(3).

(O1/N1). There are two types of Hpdc²⁻ ligands in this structure: one type within the metal layer bonds to three Eu^{III} atoms through its O2', O3', and O1/N1; the other type lies between the two metal layers and connects them via two oxygen atoms from two different carboxylate groups (O5, O5''). This results in a unique double-layer structure with a distance of 6.3 Å between the two single layers (Figure 2 a). The double layers are connected through hydrogen bonding interactions. Worth mentioning here is that such a double-layer structure can be regarded as a unique molecular “floor” directly linked by pillars (Hpdc²⁻) through covalent bonds.^[9]

Two elements from Group 3, erbium and lutetium, were investigated. The double-layer structure was obtained for erbium (**5**)^[7] and a new single-layered structure, $[\text{Ln}(\text{Hpdc})(\text{H}_2\text{pdc})(\text{H}_2\text{O})_2]$, was obtained for both Er (**6**) and Lu (**7**).^[10] Figure 3 a gives a view of this structure along the a axis. All metal atoms are eight coordinate. Each metal is coordinated by two Hpdc²⁻ ligands (one through a chelating O1 and N1, and the other through a carboxylate oxygen O3), two H₂pdc⁻ ligands (one through a chelating O5 and N3, and the other through a carboxylate oxygen O6), and by two water molecules (O9, O10). This results in a single-layer structure

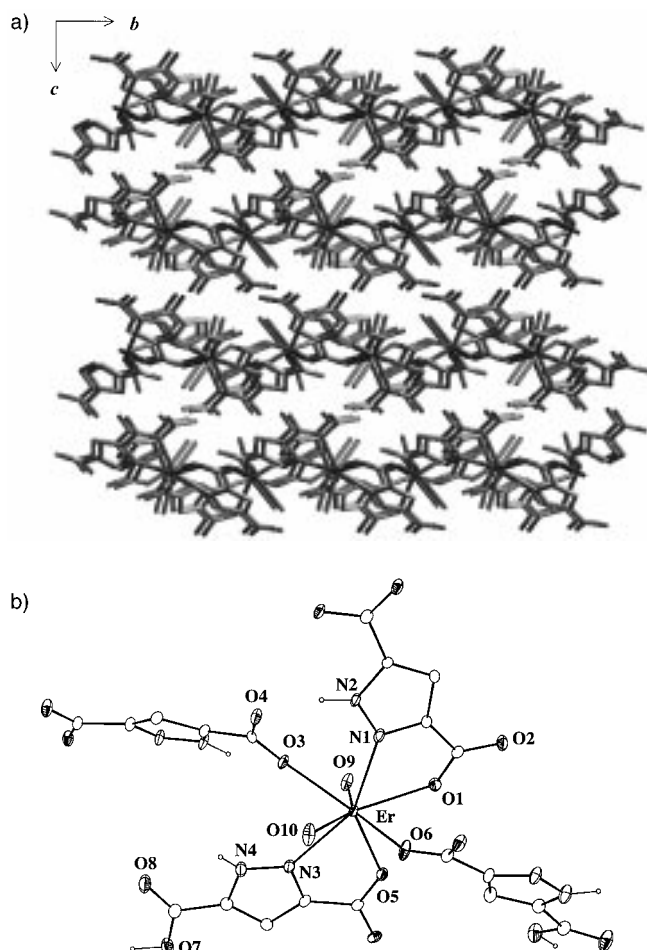


Figure 3. a) View of $[\text{Ln}(\text{Hpdc})(\text{H}_2\text{pdc})(\text{H}_2\text{O})_2]$, $\text{Ln} = \text{Er}$ (6), $\text{Ln} = \text{Lu}$ (7), along the a axis. The interlayer interactions are through hydrogen bonds (not shown). b) ORTEP drawing of 6. Er atoms are eight coordinate. Selected bond lengths [Å]: Er-O1 2.437(4), Er-O3 2.345(4), Er-O5 2.302(4), Er-O6 2.287(4), Er-O9 2.304(4), Er-O10 2.318(4), Er-N1 2.395(4), Er-N3 2.486(5).

$[\text{Ln}(\text{Hpdc})(\text{H}_2\text{pdc})(\text{H}_2\text{O})_2]$. Both Hpdc^{2-} and H_2pdc^- bond to two metal centers but with different coordination modes. The former uses two whereas the latter uses only one carboxylate group in bonding. The weak interactions between the layers are through hydrogen bonding.

It is interesting to observe the effect of lanthanide contraction through the structure formation of the title compounds. While Group 1 elements La and Ce form only the three-dimensional structures (2, 3, nine-coordinate metal centers), the Group 2 element Eu gives rise to both double-layer (4, eight-coordinate metal centers) and three-dimensional structures. The analogous three-dimensional structures for Group 3 Er and Lu, however, have never been observed because of the considerably smaller atomic sizes of these elements. While the metal is eight-coordinate in both double- and single-layer structures, the size of the coordination sphere of the metal is larger in the former than in the latter due to the different number of coordinated water molecules. This is consistent with the observation that Er crystallizes in both structures (5 and 6) while smaller Lu only forms a single-layer structure (7).

The products of hydrothermal synthesis are often affected by the acidity of the reactions. In this study, it is clear that the pH of the reactions played a crucial role in the formation of the single- and double-layer structures. The coordination of ligand 1 can be controlled by the amount of H^+ in a reaction mixture: $\text{H}_3\text{pdc} \leftrightarrow \text{H}_2\text{pdc}^- + \text{H}^+ \leftrightarrow \text{Hpdc}^{2-} + 2\text{H}^+$. In Hpdc^{2-} both carboxylate groups are available for coordination, while only one is in H_2pdc^- . In the single-layer structures (6, 7), one half of the pyrazoledicarboxylate ligands participate in bonding as H_2pdc^- and the other half as Hpdc^{2-} , whereas in the double-layer structures (4, 5) all ligands bond to metal centers as Hpdc^{2-} . By adjusting the pH value, we successfully isolated a single-phase, double-layer erbium structure (5) at pH 5, and its single-layer structure (6) at pH 1, respectively. That adjusting the pH value gives no effect in separating $[\text{Eu}_2(\text{Hpdc})_3(\text{H}_2\text{O})_6]$ (4, the double-layer structure) from $[\text{Eu}_2(\text{Hpdc})_3(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$ (the three-dimensional structure) is obvious, since both compounds contain the same number of Hpdc^{2-} as the only ligand.

Thermogravimetric analysis (TGA) of the new compounds also revealed some interesting features. Compounds with both single- and double-layer structures cannot be recovered after loss of the water molecules through heating, whereas the crystal structure of the three-dimensional lanthanum and cerium compounds (2, 3) are recoverable to a large degree during a heating-cooling and dehydration-hydration cycle. Figure 4 gives the PXRD patterns taken on lanthanum

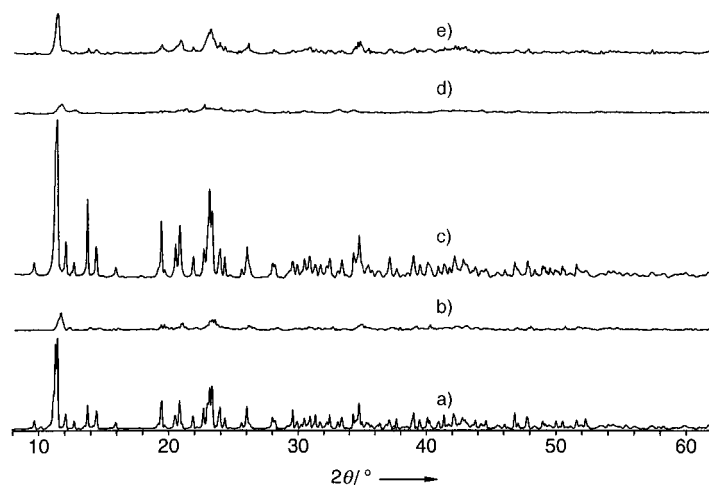


Figure 4. PXRD patterns for 2, a) taken at room temperature, b) after heating to 125 °C, c) after rehydration for 30 min, d) after reheating to 220 °C, e) after rehydration for 36 h.

samples. The details of the characteristic peaks of the crystal structure began to disappear after the sample was heated to 125 °C, at which time two noncoordinated water molecules evolved from the sample (Figure 4b). The structure recovered almost completely when this sample was exposed to water for a short period of time, observed by comparing the PXRD pattern, taken after rehydrating the heated sample (Figure 4c), to the original powder pattern (Figure 4a). Figure 4d shows when the sample was heated to 220 °C, both noncoordinated as well as coordinated water molecules in 2 evolved from the sample. The crystal structure collapsed

almost completely. After 36 hours in water, the structure began to recover and the major features reappeared in the powder pattern (Figure 4e). This remarkable phenomenon has also been observed, even more profoundly, in a number of transition metal 3,5-pyrazoledicarboxylate polymers.^[11]

In summary, we have synthesized six novel lanthanide metal coordination polymers (**2–7**) via hydrothermal reactions. These compounds crystallize in three new structural types with the metal coordination number steadily decreasing from nine only (La, Ce) to nine and eight (Eu) to eight only (Er, Lu) as a result of lanthanide contraction. By controlling the reaction pH values, we have successfully and selectively isolated single-phase erbium compounds in different structures (**5, 6**). The formation of a crystal structure in an acentric space group for compounds **2** and **3** shows it is possible to synthesize new materials for NLO devices using lanthanide metals in combination with asymmetric ligands. Furthermore, the structure recovery process that was observed in compounds **2** and **3** reveals an interesting phenomenon whose nature and possible applications deserve further investigation.

Experimental Section

Synthesis of 2, 3, 4, 7: Reactions of $\text{Ln}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (La 0.105 g; Ce 0.108 g; Eu 0.112 g; Lu 0.118 g), **1** (0.043 g) and H_2O (10 mL) in the mole ratio of 1:1:2222 were conducted in a 23 mL acid digestion bomb at 150 °C for 3 days (pH 2–3). The products were collected after washing by H_2O (2 × 5 mL) and acetone (2 × 5 mL). La compound **2**: 0.048 g, 68%; Ce compound **3**: 0.049 g, 71%; Eu compound **4**: 0.038 g, which also contained $[\text{Eu}_2(\text{Hpdc})_3(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$ as a minor component; Lu compound **7**: 0.042 g, 63%.

Synthesis of 5: Hydrated $\text{Er}(\text{NO}_3)_3$ (0.176 g), **1** (0.085 g), Et_3N (0.014 mL) and H_2O (10 mL) in the mole ratio of 1:1:2:1111 reacted in a 23 mL acid digestion bomb at 150 °C for 3 days (pH 5). The washing procedure described above was applied to the product. Compound **5** was collected in quantitative yield.

Synthesis of 6: Hydrated $\text{Er}(\text{NO}_3)_3$ (0.176 g), **1** (0.085 g), HNO_3 (0.033 mL) and H_2O (10 mL) in the mole ratio of 1:1:1:1111 reacted in a 23 mL acid digestion bomb at 150 °C for 3 days (pH 1). The product was washed and collected as single-phase **6** in low yield.

Received: July 12, 1999 [Z13715]

- [1] a) O. Sato, T. Iyoda, A. Fujishima, K. Hashimoto, *Science* **1996**, 271, 49–51; b) O. R. Evans, R. Xiong, Z. Wang, G. K. Wong, W. Lin, *Angew. Chem.* **1999**, 111, 557–559; *Angew. Chem. Int. Ed.* **1999**, 38, 536–538; c) T. Bein, *Supramolecular Architecture*, Am. Chem. Soc., Washington, DC, **1992**; d) M. Fujita, Y. J. Kwon, S. Washizu, K. Ogura, *J. Am. Chem. Soc.* **1994**, 116, 1151–1152; e) O. M. Yaghi, US-A 5648 508 **1997**; f) M. Munakata, L. P. Wu, T. Kuroda-Sowa, M. Maekawa, Y. Suenaga, K. Furuichi, *J. Am. Chem. Soc.* **1996**, 118, 3305–3306.
- [2] a) D. M. L. Goodgame, S. Menzer, A. T. Ross, D. J. Williams, *J. Chem. Soc. Chem. Commun.* **1994**, 2605–2606; b) D. M. L. Goodgame, S. P. W. Hill, D. J. Williams, *Inorg. Chim. Acta* **1998**, 272, 131–140; c) V. Kirtsis, A. Michaelides, S. Skoulouli, S. Golhen, L. Ouahab, *Inorg. Chem.* **1998**, 37, 3407–3410; d) C. V. K. Sharma, R. D. Rogers, *Chem. Commun.* **1999**, 83–84; e) T. M. Reineke, M. Eddaoudi, M. Fehr, D. Kelley, O. M. Yaghi, *J. Am. Chem. Soc.* **1999**, 121, 1651–1657.
- [3] a) R. A. Ludise, *Progress in Inorganic Chemistry*, Vol. 3, Interscience, New York, **1962**; b) A. Rabenau, *Angew. Chem.* **1985**, 97, 1017; *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 1026; c) R. A. Ludise, *Chem. Eng. News* **1987**, 56, 30.

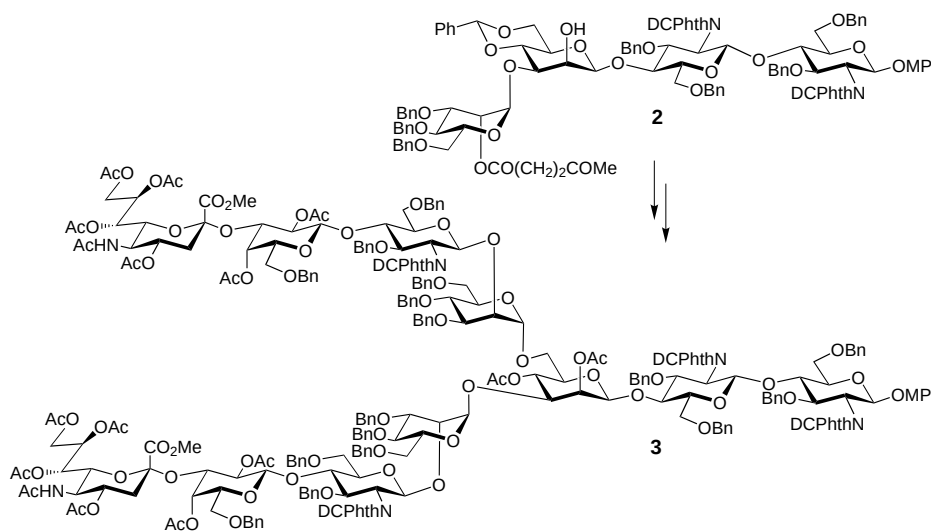
- [4] a) J. Y. Lu, B. R. Cabrera, R. J. Wang, J. Li, *Inorg. Chem.* **1998**, 37, 4480–4481; b) J. Y. Lu, M. A. Lawandy, J. Li, T. Yuen, C. L. Lin, *Inorg. Chem.* **1999**, 38, 2695–2704; c) B. R. Cabrera, R. J. Wang, J. Li, T. Yuen, *Solid State Chemistry of Inorganic Materials II*, Vol. 453 (Eds.: P. K. Davies, A. J. Jacobson, C. C. Torardi, T. A. Vanderah), Mater. Res. Soc., Pittsburgh, **1999**, pp. 493–498; d) M. A. Lawandy, X. Y. Huang, J. Y. Lu, J. Li, T. Yuen, C. L. Lin, *Inorg. Chem.*, in press; e) J. Y. Lu, B. R. Cabrera, R. J. Wang, J. Li, *Inorg. Chem.*, in press.
- [5] a) O. M. Yaghi, H. Li, *J. Am. Chem. Soc.* **1996**, 118, 295–296; b) O. M. Yaghi, H. Li, T. L. Groy, *J. Am. Chem. Soc.* **1996**, 118, 9096–9101; c) S. O. H. Gutschke, M. Molinier, A. K. Powell, E. P. Winpenny, P. T. Wood, *Chem. Commun.* **1996**, 823; d) P. Feng, X. Bu, G. D. Stucky, *Nature* **1997**, 338, 735–741; e) D. Hargman, R. P. Hammond, R. Haushalter, J. Zubieta, *Chem. Mater.* **1998**, 10, 2091–2100; f) D. J. Chesnut, A. Kusnetzow, R. R. Birge, J. Zubieta, *Inorg. Chem.* **1999**, 38, 2663–2671.
- [6] a) Compound **2**: $0.22 \times 0.10 \times 0.02$ mm, monoclinic, space group *Cc*, $a = 15.797(3)$, $b = 8.881(2)$, $c = 18.411(4)$ Å, $\beta = 98.37(3)^\circ$, $V = 2555.4(9)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.205$ Mg m⁻³, $\mu(\text{MoK}\alpha) = 3.395$ mm⁻¹, $F(000) = 1632$, ω -2 θ scans, max./min. transmission 1.000/0.940, 6135 unique reflections ($\theta_{\text{max}} = 28^\circ$), 4638 observed ($I > 2\sigma(I)$), 368 parameters, $R = 0.0573$, $R_w = 0.1183$, residual electron density max./min. $2.20/-2.24$ e Å⁻³. Compound **3**: $0.11 \times 0.08 \times 0.01$ mm, monoclinic, space group *Cc*, $a = 15.724(3)$, $b = 8.849(2)$, $c = 18.354(4)$ Å, $\beta = 98.40(3)^\circ$, $V = 2526.4(9)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.236$ Mg m⁻³, $\mu(\text{MoK}\alpha) = 3.655$ mm⁻¹, $F(000) = 1640$, ω -2 θ scans, max./min. transmission 1.000/0.766, 4919 unique reflections ($\theta_{\text{max}} = 26^\circ$), 4802 observed ($I > 2\sigma(I)$), 371 parameters, $R = 0.0316$, $R_w = 0.0804$, residual electron density max./min. $1.61/-1.38$ e Å⁻³. b) X-ray diffraction studies were performed on single crystals using $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å) with an Enraf-Nonius CAD4 diffractometer at 293 K. Lorentz, polarization, and empirical absorption corrections were applied for all compounds. Direct phase determination yielded the position of the heavy atoms. The remaining non-hydrogen atoms were located from the subsequent difference Fourier synthesis. Most of the hydrogen atoms were located from difference Fourier maps while the rest were placed on calculated positions. Hydrogen atoms were not refined and their isotropic thermal parameters were set to $1.2 \times U_{\text{eq}}$ of the parent non-hydrogen atoms. A full-matrix least-squares refinement on F^2 reached final convergence. All computations were performed using the SHELX-97 program package (G. Sheldrick, University of Göttingen). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-129657–129661. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [7] Compound **4**: $0.15 \times 0.06 \times 0.06$ mm, monoclinic, space group $P2_1/c$, $a = 10.985(2)$, $b = 10.187(2)$, $c = 10.462(2)$ Å, $\beta = 100.11(3)^\circ$, $V = 1162.3(4)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 2.498$ Mg m⁻³, $\mu(\text{MoK}\alpha) = 5.453$ mm⁻¹, $F(000) = 840$, ω -2 θ scans, max./min. transmission 0.999/0.807, 2272 unique reflections ($\theta_{\text{max}} = 26^\circ$), 2040 observed ($I > 2\sigma(I)$), 206 parameters, $R = 0.0239$, $R_w = 0.0646$, residual electron density max./min. $0.87/-0.80$ e Å⁻³. [6b] Compound **5**: $0.60 \times 0.28 \times 0.22$ mm, monoclinic, space group $P2_1/c$, $a = 10.915(1)$, $b = 10.113(1)$, $c = 10.462(1)$ Å, $\beta = 100.475(9)^\circ$, $V = 1135.58(19)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 2.646$ Mg m⁻³, $\mu(\text{MoK}\alpha) = 7.447$ mm⁻¹, $F(000) = 860$, ω -2 θ scans, max./min. transmission 1.000/0.637, 2220 unique reflections ($\theta_{\text{max}} = 26^\circ$), 2091 observed ($I > 2\sigma(I)$), 206 parameters, $R = 0.0212$, $R_w = 0.0575$, residual electron density max./min. $1.10/-0.72$ e Å⁻³. [6b]
- [8] a) S. C. Zimmerman, *Science* **1997**, 276, 543–544; b) V. A. Russell, C. C. Evans, W. Li, M. D. Ward, *Science* **1997**, 276, 575–579.
- [9] J. A. Swift, A. M. Pivovar, A. M. Reynolds, M. D. Ward, *J. Am. Chem. Soc.* **1998**, 120, 5887–5894.
- [10] Compound **6**: $0.28 \times 0.22 \times 0.10$ mm, monoclinic, space group $P2_1/n$, $a = 10.822(2)$, $b = 9.216(2)$, $c = 14.228(3)$ Å, $\beta = 104.79(3)^\circ$, $V = 1372.0(5)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 2.481$ Mg m⁻³, $\mu(\text{MoK}\alpha) = 6.188$ mm⁻¹, $F(000) = 980$, ω -2 θ scans, max./min. transmission 0.999/0.527, 2691 unique reflections ($\theta_{\text{max}} = 26^\circ$), 2326 observed ($I > 2\sigma(I)$), 227 parameters, $R = 0.0302$, $R_w = 0.0808$, residual electron density max./min. $1.74/-2.19$ e Å⁻³. [6b]
- [11] L. Pan, X. Y. Huang, J. Li, *Chem. Commun.*, submitted.

Synthesis of an α -(2,3)-Sialylated, Complex-Type Undecasaccharide**

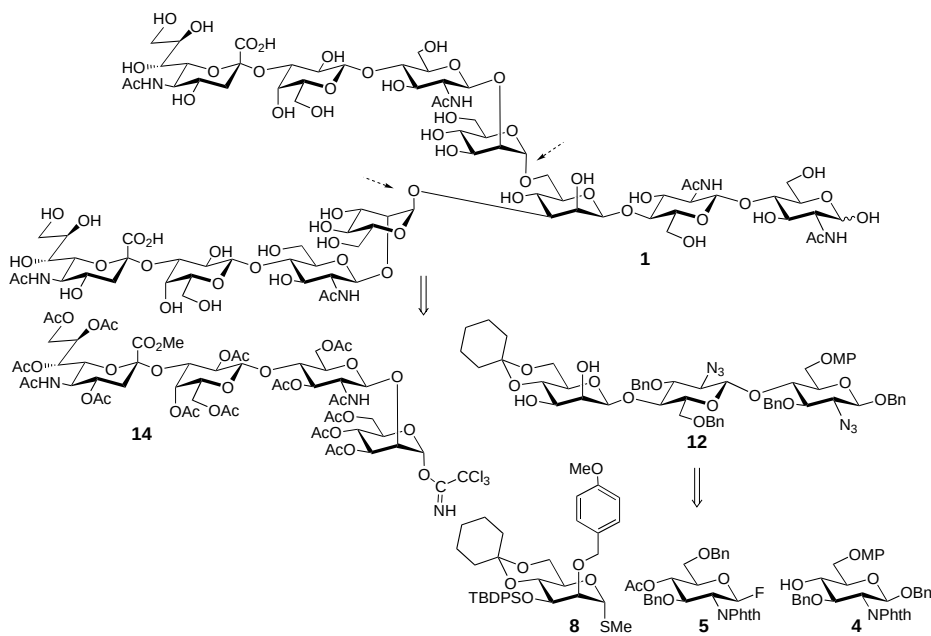
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N-Glycosylation is a widespread posttranslational modification of eukaryotic proteins. N-Glycans are functional constituents of glycoproteins and serve to control the intra- and intercellular distribution and three-dimensional structure of glycoproteins and also protect them against degradation. Furthermore, N-glycans are involved in important biological processes including cell differentiation, cell adhesion, and malignant transformation.^[1] Here we report the synthesis of undecasaccharide **1** (see Scheme 2), one of the prototypical structures of complex-type N-glycans of mammalian origin.^[2] This represents the first purely chemical synthesis of **1** achieved with strict stereochemical control.^[3]

With the aim of constructing this complex molecule in a stereocontrolled fashion, our initial investigation centered around the use of tetrasaccharide **2**^[4a] (Scheme 1), obtainable by *p*-methoxybenzyl-assisted intramolecular aglycon delivery (IAD), as the key intermediate, which was eventually transformed into the fully protected undecasaccharide **3**. However, deprotection of **3** turned out to be highly challenging, mainly due to the difficulty of manipulating sialic acid methyl ester in the presence of a 4,5-dichlorophthaloyl (DCPhth) group, and vice versa.



Scheme 1. The tetrasaccharide **2** served as a template for the formation of undecasaccharide **3**. The deprotection of **3** failed. Bn = benzyl, DCPhth = 4,5-dichlorophthaloyl, MP = *p*-methoxyphenyl.



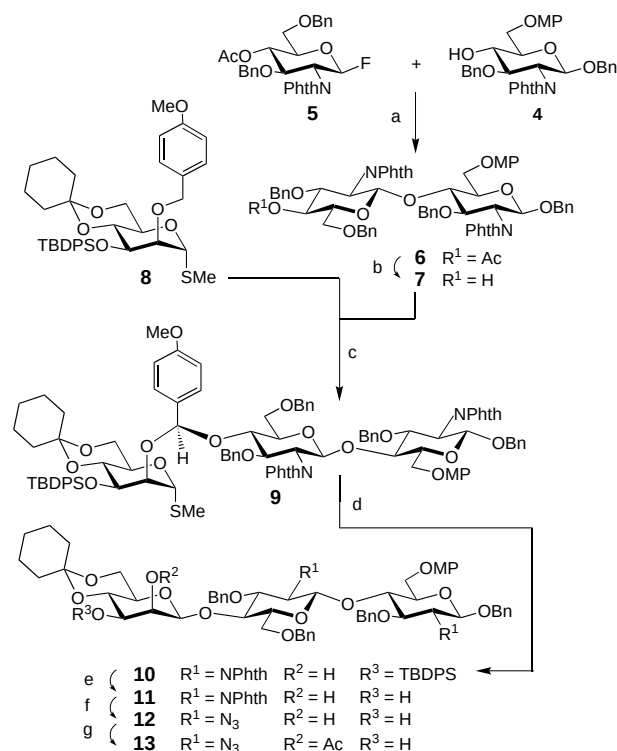
Scheme 2. The undecasaccharide **1** was constructed from the β -mannosidic trisaccharide **12** and trichloroacetimidate **14**^[11] as key building blocks. Compound **12** was prepared from the monosaccharides **4**,^[5b,c] **5**^[5d] and **8**.^[5a] Phth = phthaloyl, TBDPS = *tert*-butyldiphenylsilyl.

In our revised synthetic plan (Scheme 2), the core trisaccharide **12** was designed as the key intermediate on the basis of the following considerations: First, acetamido groups were masked as azides in the hope that problems associated with the potential nucleophilicity of acetamido groups and/or the base lability of phthalimide (or DCPhth) can be largely eliminated at the stage of critical glycoside bond forming reactions and/or manipulation of the protecting groups. Additionally, to maximize the efficiency of β -mannosylation, cyclohexylidene-protected **8**^[5a] was adopted as the mannosyl donor; it has proved to be the most suitable glycosyl donor for such purposes.

In practice, preparation of trisaccharide **12** was executed with monosaccharide components **4**,^[5b,c] **5**,^[5d] and **8**^[5a] (Scheme 3) and commenced with the high-yield preparation

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[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture. Additional financial support (J.S., M.L.) from the STA fellowship of the Japanese government and the Feodor-Lynen fellowship are acknowledged. We are grateful to Ms. Tamiko Chijimatsu for the NMR and Dr. Sadamu Kurono for the ESI-MS measurements. We thank Dr. Tomoya Ogawa for his encouragement throughout this work and Ms. Akeni for technical assistance.



Scheme 3. a) $[\text{Cp}_2\text{HfCl}_2]$, AgOTf, molecular sieves (4 Å), CH_2Cl_2 , -30°C ; b) NaOMe, MeOH (75%, 2 steps); c) DDQ (1.5 equiv) molecular sieves (4 Å), CH_2Cl_2 , 2 h; d) MeOTf (3.4 equiv), DBMP (3.8 equiv), molecular sieves (4 Å), $\text{ClCH}_2\text{CH}_2\text{Cl}$, 45°C , 36 h (78%); e) TBAF, HOAc, THF (78%); f) 1. ethylenediamine, *n*-BuOH, 100°C , 24 h, 2. Ti-N_3 , DMAP, CH_3CN , CH_2Cl_2 , 5 h (84%); g) 1. $\text{CH}_3\text{C}(\text{OEt})_3$, *p*-Tos-OH/ OH_2 , C_6H_6 , 1 h, 2. 80% HOAc, 5 min (92%). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DBMP = 2,6-di-*tert*-butyl-4-methylpyridine, DMAP = 4-dimethylaminopyridine, OTf = trifluoromethanesulfonate, TBAF = tetrabutylammonium fluoride, *p*-Tos-OH/ OH_2 = *p*-toluenesulfonic acid monohydrate, Ti-N_3 = trifluoromethanesulfonyl azide.

of chitobiose derivative **6** under Suzuki conditions.^[6] Subsequent deacetylation gave **7**, which in turn was subjected to β -mannosylation. Coupling with methylthio mannoside **8** according to our two-step protocol for IAD^[4, 5a] effected clean formation of β -mannoside **10** via mixed acetal **9** in 78% yield. The $^1\text{J}(\text{C}, \text{H})$ coupling constant of C-1³ (161.7 Hz, Table 1) confirmed the configuration of the newly generated β -mannosidic linkage.^[7] Reaction of **10** with tetrabutylammonium fluoride (TBAF) led to the diol **11**. Subsequent removal of the phthaloyl group^[8] followed by a diazo transfer reaction^[9] afforded bisazido compound **12** in 84% yield. Regioselective acetylation at position C-2³ was performed under Lemieux conditions^[10] to furnish **13** in high yield.

Trichloroacetimidate **14** (Scheme 2), which corresponds to symmetric branches linked to mannose,^[3] was prepared as described previously.^[11] The glycosylation of 2³-O-acetylated **13** with **14** (1.9 equiv) provided **16** in 69% yield (Scheme 4). Alternatively, a similar reaction with diol **12** gave 3-O-glycosylated **15** as the sole isolable coupling product in 61% yield, which was acetylated to **16**. Removal of the cyclohexylidene group to give diol **17** was followed by further glycosylation to undecasaccharide, again with trichloroacetimidate **14** as glycosyl donor. This reaction gave the undeca-

Table 1. Selected physical data of **1**, **10**, **15**, **16**, **18**, and **19**

1: $[\alpha]_D^{20} = -2.1$ ($c = 0.33$ in H_2O); ^1H NMR (500 MHz, D_2O , 25°C , *t*BuOH): $\delta = 5.19$ (d, $^3\text{J}(1,2) = 2.7$ Hz, 0.67H; H-1^{1a}), 5.11 (d, $^3\text{J}(1,2) < 1.0$ Hz, 1H; H-1^{1b}), 4.92 (d, $^3\text{J}(1,2) < 1.0$ Hz, 1H; H-1⁴), 4.75 (d, $^3\text{J}(1,2) < 1.0$ Hz, 1H; H-1³), 4.69 (d, $^3\text{J}(1,2) = 7.8$ Hz, 0.33H; H-1^{1b}), 4.61 (d, $^3\text{J}(1,2) = 7.8$ Hz, 0.67H; H-1^{2b}, α form), 4.60 (d, $^3\text{J}(1,2) = 7.6$ Hz, 0.33H; H-1^{2b}, β form), 4.57 (d, $^3\text{J}(1,2) = 8.0$ Hz, 2H; H-1^{5/5}), 4.55 (d, $^3\text{J}(1,2) = 7.8$ Hz, 1H; H-1^{6b}), 4.54 (d, $^3\text{J}(1,2) = 7.8$ Hz, 1H; H-1^{6b}), 4.24 (dd, $^3\text{J}(2,3) = 2.4$ Hz, 1H; H-2³), 4.19 (dd, $^3\text{J}(2,3) = 3.0$ Hz, 1H; H-2⁴), 4.13–4.10 (m, 3H; H-2⁴, H-3^{6/6}), 2.75 (dd, $^3\text{J}(3,4) = 4.3$ Hz, $^2\text{J}_{\text{gem}} = 12.3$ Hz, 2H; H-3eq^{NN}), 2.08–2.03 (6s, 18H; NAc), 1.80 (t, $^3\text{J}(3,4) \approx ^2\text{J}_{\text{gem}} = 12.0$ Hz, 2H; H-3ax^{NN}); ^{13}C NMR (125 MHz, D_2O , 25°C , *t*BuOH): $\delta = 175.71$ – 174.53 (C=O), 103.34 (C-1⁶), 103.30 (C-1⁶), 102.06 (C-1²), 101.08 (C-1³), 100.52 (C-2^{NN}), 100.23 (C-1⁴, C-1⁵), 100.17 (C-1⁵), 97.77 (C-1⁴), 95.50 (C-1^{1b}), 91.12 (C-1^{1a}), 40.33 (C-3^{NN}), 23.03–22.57 (NAc); ESI-MS (neg. mode, MeOH/ $\text{H}_2\text{O} = 1/1$): m/z : 1110.7 $[(M^- - 2\text{H})/2]$; calcd for $\text{C}_{84}\text{H}_{136}\text{N}_6\text{O}_{62}/2$ $[(M^- - 2\text{H})/2]$: 1110.9

10: $[\alpha]_D^{20} = 19.9$ ($c = 2.67$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3 , 25°C , TMS): $\delta = 5.17$ (d, $^3\text{J}(1,2) = 8.2$ Hz, 1H; H-1^{1b}), 4.96 (d, $^3\text{J}(1,2) = 8.1$ Hz, 1H; H-1^{2b}), 4.33 (d, $^3\text{J}(1,2) < 1.5$ Hz, 1H; H-1³), 1.08 (s, 9H; CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 25°C , TMS): $\delta = 100.04$ (C-1³, $^1\text{J}(\text{C}, \text{H}) = 161.7$ Hz), 99.70 (cyclohexylidene), 97.07 (C-1¹), 96.87 (C-1²), 26.96 (C(CH_3)₃), 19.39 (C(CH_3)₃)

15: $[\alpha]_D^{20} = -14.9$ ($c = 0.5$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 4.99$ (d, $^3\text{J}(1,2) = 2.1$ Hz, 1H; H-1¹), 4.68 (d, $^3\text{J}(1,2) = 8.1$ Hz, 1H; H-1^{6b}), 4.50 (d, $^3\text{J}(1,2) < 1.5$ Hz, 1H; H-1³), 4.43 (m, 1H; H-1⁵), 4.35 (m, 1H; H-1¹), 4.28 (m, 1H; H-1²), 3.91 (m, 1H; H-2³); ^{13}C NMR (125 MHz, CDCl_3 , 25°C , TMS): $\delta = 101.08$ (C-1¹), 101.01 (C-1⁶), 100.45 (C-1²), 100.20 (cyclohexylidene), 99.97 (C-1⁵), 99.32 (C-1³, $^1\text{J}(\text{C}, \text{H}) = 162.2$ Hz), 98.78 (C-1⁴, $^1\text{J}(\text{C}, \text{H}) = 172.8$ Hz), 96.80 (C-2^N), 70.76 (C-2³); FAB-MS (pos. mode, NBA^[a]): m/z : 2461.0 $[M^+ + \text{H} + \text{Na}]$; calcd for $\text{C}_{115}\text{H}_{145}\text{N}_8\text{NaO}_{50}$ $[M^+ + \text{H} + \text{Na}]$: 2460.9

16: ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 5.10$ (m, 1H; H-2³)

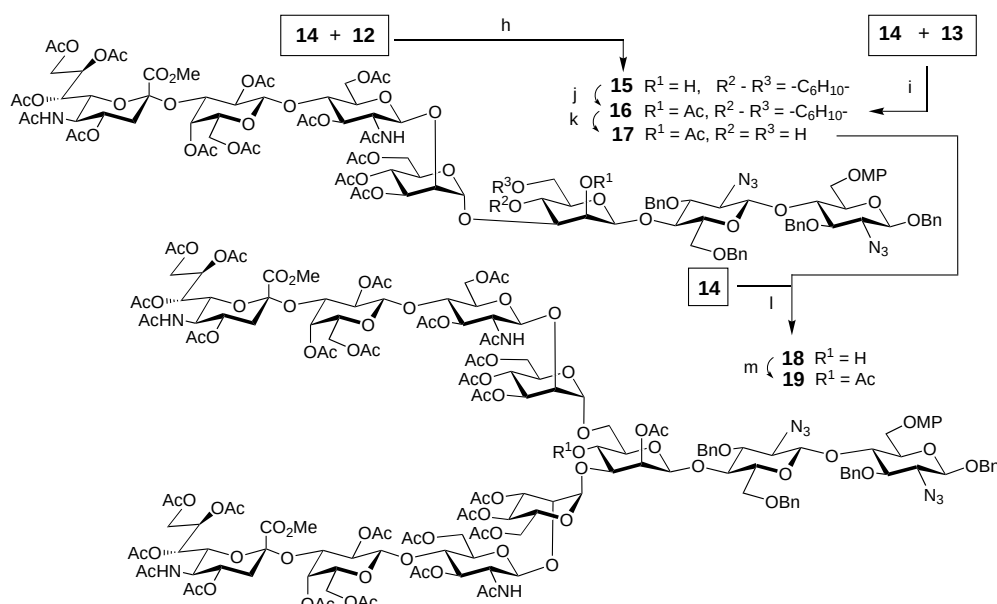
18: $[\alpha]_D^{20} = -9.8$ ($c = 1.0$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 5.10$, 4.64, 4.63, 4.59, 4.56, 4.43, 4.34, 4.30, 4.24 (H-1¹–H-1⁶ and H-1⁴–H-1⁶, not assigned), 3.74 (m, 1H; H-4³); ^{13}C NMR (125 MHz, CDCl_3 , 25°C , TMS): $\delta = 101.17$, 100.88, 100.69, 100.47, 100.32, 99.95, 99.65 ($^1\text{J}(\text{C}, \text{H}) = 177.3$ Hz), 97.96, 97.79 ($^1\text{J}(\text{C}, \text{H}) = 170.8$ Hz), (C-1¹–C-1⁶ and C-1⁴–C-1⁶, not assigned), 96.74 (C-2^{NN}), 68.61 (C-4³); FAB-MS (pos. mode, NBA^[a]): m/z : 3759.8 $[M^+ + \text{H} + \text{Na}]$, calcd for $\text{C}_{167}\text{H}_{215}\text{N}_{10}\text{NaO}_{86}$ $[M^+ + \text{H} + \text{Na}]$: 3759.3

19: ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 5.03$ (dd, $^3\text{J}(3,4) \approx ^3\text{J}(4,5) = 8.8$ Hz, 1H; H-4³)

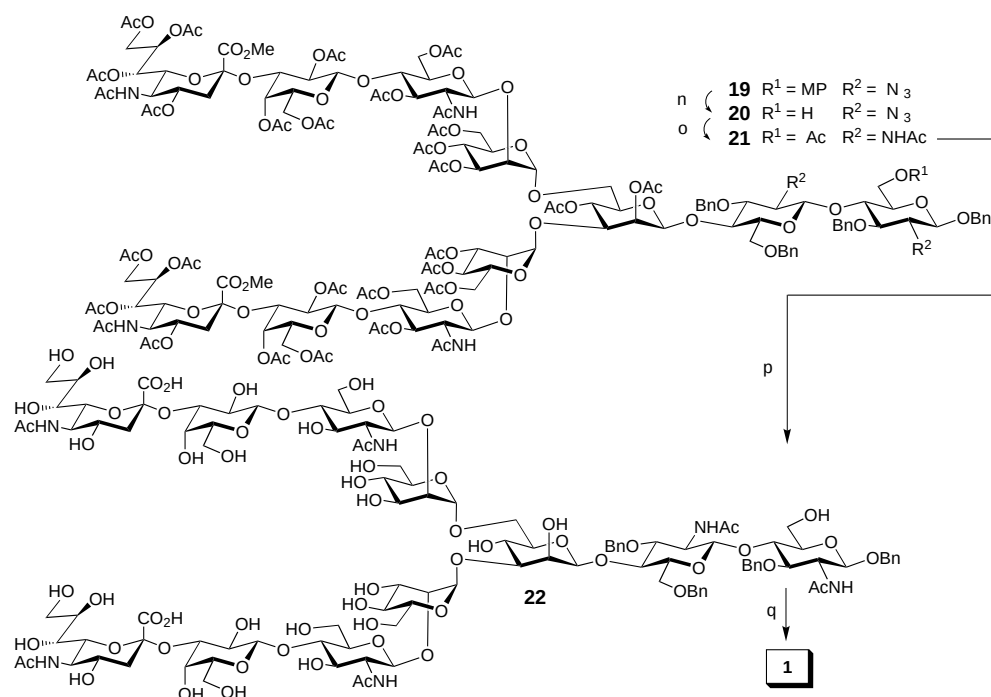
[a] NBA = *m*-nitrobenzyl alcohol. [b] $\delta(^1\text{H})$ was determined from a $^1\text{H}/^{13}\text{C}$ HMQC-COSY spectrum.

saccharide **18** in 50% yield, which was counterbalanced by recovered **17**. Acetylation of **18** gave **19**, detailed ^1H NMR analysis of which fully supported its regio- and stereochemical integrity (Table 1).

Having obtained the full backbone structure of the target undecasaccharide, we executed complete deprotection of **19** (Scheme 5). First, the *p*-methoxyphenyl group at the reducing end GlcNAc residue was removed with ammonium cerium(IV) nitrate^[12] to afford **20**. Azido groups were converted into acetamides by a two-step procedure to give **21** in 82% yield.^[13] Cleavage of the methyl ester and *O*-acetyl groups was performed under alkaline conditions to give **22**, which was finally subjected to hydrogenation over 10% Pd/C. After purification by size exclusion chromatography (Biogel P-2, H_2O), the target molecule was isolated in 98% yield. The ^1H NMR spectrum (500 MHz, Table 1) revealed that all chemical shifts of synthetic **1** are essentially identical with those reported for the reference compound **1** isolated from human chorionic gonadotropin.^[2a]



Scheme 4. h) TMS-OTf (0.2 equiv), molecular sieves (4 Å), CH₂Cl₂, -20 °C (61 %); i) BF₃/OEt₂ (1.5 equiv), CH₂Cl₂, molecular sieves (4 Å), -15 °C (69 %); j) Ac₂O, pyridine, DMAP (quantitative); k) *p*-Tos-OH/OH₂ (2.7 equiv), CH₃CN (92 %); l) BF₃/OEt₂ (2 equiv), molecular sieves (4 Å, AW 300), CH₂Cl₂, -20 °C (50 %); m) Ac₂O, pyridine, DMAP (92 %). TMS-OTf = trimethylsilyl trifluoromethanesulfonate.



Scheme 5. Deprotection of undecasaccharide **19** gives the target compound **1**. n) (NH₄)₂Ce(NO₃)₆, CH₃CN/toluene/H₂O (8/7/7), 0 °C, 15 h (80 %); o) 1. 1,3-propanedithiol, DIEA, pyridine/H₂O (7/3), 2. Ac₂O/pyridine (82 %); p) 1. NaOMe/MeOH, 12 h, 2. H₂O, 50 °C, 1 h; q) Pd/C (10 % Pd), H₂, MeOH/H₂O/HOAc (4/2/2), 5 h (98 %). DIEA = *N,N*-diisopropylethylamine.

In summary, we have achieved the convergent and stereocontrolled synthesis of the diantennary complex-type N-glycan **1**, which consists of eleven sugar residues and includes synthetically challenging sequences such as α -linked sialic acids and β -linked mannose. Our basic strategy may well be flexible enough to provide access to other decorated structures. Since undecasaccharide intermediates **18** and **20** have hydroxy groups that can be specifically liberated, synthetic

routes to bisecting GlcNAc- and 6-*O*-Fuc- containing structures can be readily conceived.

Received: August 20, 1999 [Z13906]

- [1] a) A. Varki, *Glycobiology* **1993**, 3, 97–130; b) R. Dwek, *Chem. Rev.* **1996**, 96, 683–720.
- [2] a) J. B. L. Damm, J. P. Kamerling, G. W. K. van Dedem, J. F. G. Vliegthart, *Glycoconjugate J.* **1987**, 129–144; b) K. Hard, A. Mekking, J. B. L. Damm, J. P. Kamerling, W. DeBoer, R. A. Wijnants, J. F. G. Vliegthart, *Eur. J. Biochem.* **1990**, 193, 263–271.
- [3] For a combined chemical and enzymatic approach to complex-type N-glycans, including a successful synthesis of **1** linked to Asn, see a) C. Unverzagt, *Angew. Chem.* **1996**, 108, 2507–2510; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2350–2353; b) J. Seifert, C. Unverzagt, *Tetrahedron Lett.* **1997**, 38, 7857–7860.
- [4] a) M. Lergenmüller, T. Nakada, K. Kuramochi, A. Dan, T. Ogawa, Y. Ito, *Eur. J. Org. Chem.* **1999**, 1367–1376; b) Y. Ito, T. Ogawa, *Angew. Chem.* **1994**, 106, 1843–1845; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1765–1767; c) A. Dan, M. Lergenmüller, M. Amano, Y. Nakahara, T. Ogawa, Y. Ito, *Chem. Eur. J.* **1998**, 4, 2182–2190.
- [5] a) Y. Ito, Y. Ohnishi, T. Ogawa, Y. Nakahara, *Synlett* **1998**, 1102–1104; b) W. Günther, H. Kunz, *Carbohydr. Res.* **1992**, 228, 217–241; c) compound **4** was synthesized from ethyl 4,6-*O*-benzylidene-2-*O*-benzyl-2-deoxy-2-phthalimido- β -D-glucopyranoside^[5b] in three steps: 1. BnOH, *N*-iodosuccinimide (NIS), TfOH, CH₃CN, molecular sieves (3 Å), -40 °C (82 %); 2. *p*-Tos-OH/OH₂ (5 equiv), CH₃CN (85 %); 3. *p*-methoxyphenol, (C₆H₅)₃P, diethylazodicarboxylate (DEAD), CH₂Cl₂ (85 %); d) C. Unverzagt, *Angew. Chem.* **1994**, 106, 1170–1172; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 1102–1104.
- [6] K. Suzuki, T. Maeta, T. Suzuki, T. Matsumoto, *Tetrahedron Lett.* **1989**, 30, 6879–6882.
- [7] a) K. Bock, C. Pedersen, *J. Chem. Soc. Perkin Trans. 2* **1974**, 293–297; b) S. Wolfe, B. M. Pinto, V. Varma, R. Y. N. Leung, *Can. J. Chem.* **1990**, 68, 1051–1062.
- [8] O. Kanie, S. C. Crawley, M. M. Palcic, O. Hindsgaul, *Carbohydr. Res.* **1993**, 243, 139–164.

- [9] a) C. J. Cavender, V. J. Shiner, *J. Org. Chem.* **1972**, *37*, 3567–3679;
b) A. Vasella, C. Witzig, J. L. Chiara, M. Martin-Lomas, *Helv. Chim. Acta* **1991**, *74*, 2073–2077.
[10] R. U. Lemieux, H. Driguez, *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075.
[11] J. Seifert, T. Ogawa, Y. Ito, *Tetrahedron Lett.* **1999**, *40*, 6803–6807.
[12] T. Fukuyama, A. A. Laird, L. M. Hotchkiss, *Tetrahedron Lett.* **1985**, *26*, 6291–6292.
[13] H. Baylay, D. N. Standring, J. R. Knowles, *Tetrahedron Lett.* **1978**, *19*, 3633–3634.

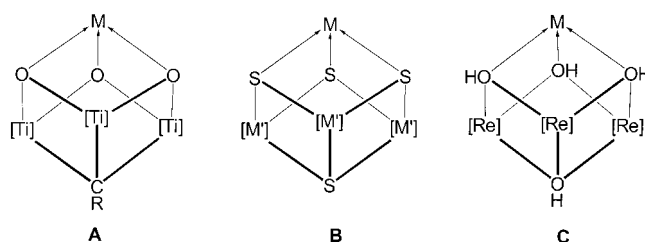
Construction of Heterometallic Cubanes

**$[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-CR})\}(\mu_3\text{-O})_3\{\text{Mo}(\text{CO})_3\}]$
($\text{R} = \text{H, Me}$; $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) and
 $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-N})\}(\mu_3\text{-NH})_3\{\text{M}(\text{CO})_3\}]$
($\text{M} = \text{Cr, Mo, W}$); Crystal Structure of
 $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-CMe})\}(\mu_3\text{-O})_3\{\text{Mo}(\text{CO})_3\}]^{**}$**

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*Dedicated to Alexander von Humboldt
on the occasion of his commemorative year 1999*

Until now we have focused on the rich chemistry of alkylidyne groups on a trinuclear support without metal–metal bonds $[\{\text{TiCp}^*(\mu\text{-O})\}_3(\mu_3\text{-CR})]$ ($\text{R} = \text{H}$ (**1**), Me (**2**); $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$). We showed that metal carbonyl hydrides and unsaturated molecules such as carbon monoxide, isocyanides, and ketones are incorporated into the Ti_3O_3 core with direct participation of the alkylidyne units.^[1] In the course of our studies, we discovered that these complexes can also act as macrocyclic, tridentate six-electron donor ligands (Scheme 1, **A**) and thus provide an effective route to heterocubanes with $\text{MTi}_3(\mu_3\text{-CR})(\mu\text{-O})_3$ cores. To our knowledge, the only comparable behavior is the incorporation of metal ions by the

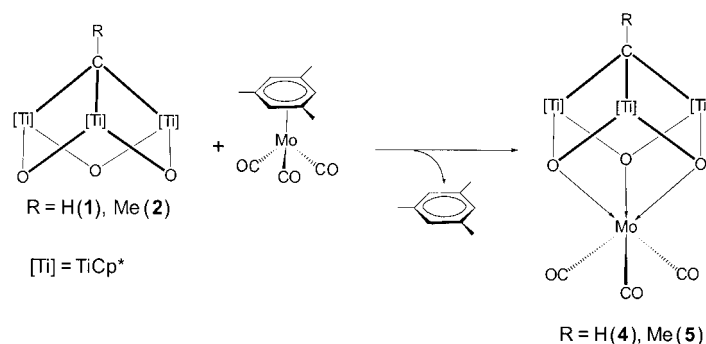


Scheme 1. Precubane systems as tripodal ligands.

$\text{M}'_3\text{S}_4$ ($\text{M}' = \text{Fe, Mo}$) precubane clusters (Scheme 1, **B**), which leads to heterometallic cubane-type $\text{MM}'_3\text{S}_4$ cores,^[2] and the hydroxymetalate complex $[\text{Re}_3(\text{CO})_9(\mu\text{-OH})_3(\mu_3\text{-OH})]$, which acts as a tripodal ligand (Scheme 1, **C**) to form “double-cubane” structures.^[3] Furthermore, the $(\mu_3\text{-CR})\text{Ti}_3(\mu_3\text{-O})_3\text{Mo}(\text{CO})_3$ cores described here could be invaluable as discrete and ideal models of oxide-supported metal carbonyl complexes for studying the catalyst–support interaction.^[4]

Here we report the formation of the heterometallic cubanes $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-CR})\}(\mu_3\text{-O})_3\{\text{Mo}(\text{CO})_3\}]$ ($\text{R} = \text{H}$ (**4**), Me (**5**)) and $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-N})\}(\mu_3\text{-NH})_3\{\text{Mo}(\text{CO})_3\}]$ (**6**) from $[\text{Mo}(\text{CO})_3(1,3,5\text{-Me}_3\text{C}_6\text{H}_3)]$ and the alkylidyne complexes **1** and **2** and the isoelectronic $[\{\text{TiCp}^*(\mu\text{-NH})\}_3(\mu_3\text{-N})]$ (**3**), respectively. Treatment of **3** with the hexacarbonyl complexes $[\text{M}(\text{CO})_6]$ ($\text{M} = \text{Cr, Mo, W}$) also leads to **6** and the analogous heterocubane derivatives $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-N})\}(\mu_3\text{-NH})_3\{\text{M}(\text{CO})_3\}]$ ($\text{M} = \text{W}$ (**7**), Cr (**8**)).

Reaction of the trimetallic starting materials **1** and **2** with one equivalent of $[\text{Mo}(\text{CO})_3(1,3,5\text{-Me}_3\text{C}_6\text{H}_3)]$ ^[5] in hexane at 80 °C for four days led to displacement of the mesitylene ligand from molybdenum to afford in good yield the dark green crystalline heterocubanes **4** and **5**, respectively (Scheme 2). The solid compounds are stable under argon at room temperature but decompose slowly (months) in $[\text{D}_6]\text{benzene}$ with formation of **1** or **2**.^[6]



Scheme 2. Synthesis of the heterometallic cubane complexes **4** and **5**.

The ^{13}C NMR spectra of both complexes show one signal at $\delta \approx 227$ for the three equivalent terminal carbonyl groups and exhibit a downfield shift of the alkylidyne carbon signals ($\delta(\mu_3\text{-CR}) = 410.3$ (**4**), 434.8 (**5**) relative to **1** ($\delta(\mu_3\text{-CH}) = 383.2$) and **2** ($\delta(\mu_3\text{-CMe}) = 401.7$). In the IR spectra of these compounds, the three terminal CO groups give rise to two strong bands between 1915 and 1815 cm^{-1} , as expected for complexes containing a *fac*- $\text{Mo}(\text{CO})_3$ group.^[7]

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[**] The authors are grateful for financial support from the DGES (PB96-0672) and the Universidad de Alcalá. C.S. also thanks the DGES for a Predoctoral Fellowship.

Supporting information for this article is available on the WWW under
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The molecular structure of **5** was determined by X-ray diffraction (Figure 1)^[8, 9] and revealed a heterometallic cubane in which the molybdenum tricarbonyl moiety is linked to the ethylidyne complex **2** through the three bridging oxygen atoms. The bond lengths and angles of **5** are quite similar to

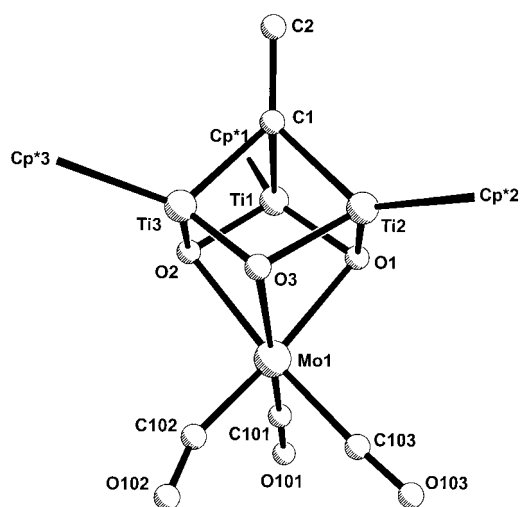
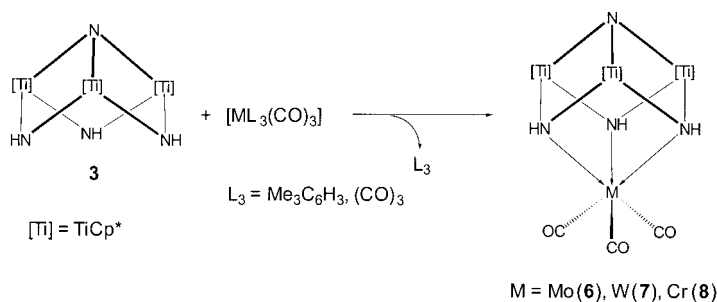


Figure 1. Simplified view of the molecular structure of complex **5**. Selected average bond lengths [Å] and angles [°]: Mo–O 2.308(15), Mo–C 1.92(4), Mo...Ti 2.998(4), Ti–Cp* 2.090, Ti...Ti 2.856(5); Cp*–Ti–C1 125.3, C1–Ti–O 86.8(8), Ti–O–Ti 100.4(7), O–Ti–O 99.0(7), Ti–O–Mo 91.4(7), O–Mo–O 75.4(5). Cp* = η^5 -C₅Me₅. Cp* groups are omitted for clarity.

those of the parent compound **2** (see Supporting Information),^[10] with the exception of the O–Ti–O angles, which are approximately 4° smaller in **5**. This similarity is also exhibited by the complexes [Fe₃S₄S₃]^[11] (S^γ refers to the sequence position of the cysteine residue) and [NEt₄]₃[[Fe₃(SET)₃](μ₃-S)₃Mo(CO)₃]^[12] a precubane behavior of the former was invoked.^[28] Thus, the alkylidyne complex **2** acts like a preorganized ligand^[13] that donates electron density to the molybdenum atom through the three electron-rich bridging oxygen atoms to give a heterometallic (μ₃-CR)Ti₃(μ-O)₃Mo cubane core.

As might be anticipated from its isoelectronic and isostructural relationship to **1** and **2**, the trinuclear nitrido complex **3**^[14] reacts slowly at room temperature with [Mo(CO)₃(1,3,5-Me₃C₆H₃)] or by irradiation with [M(CO)₆] (M = Cr, Mo, W) to give the crystalline heterocubanes **6–8**, analogous to the oxoalkylidynes **4** and **5** (Scheme 3). Complexes **6–8** are thermally stable under argon both in the solid state and in



Scheme 3. Synthesis of the heterometallic cubane complexes **6–8**.

solution. Heating them in solution in [D₆]benzene to 100 °C causes no decomposition.

The IR spectra of **6–8** show a N–H band at about 3360 cm^{−1}, and the carbonyl region is practically identical to those of **4** and **5**. Their ¹³C NMR spectra contain signals attributable to the three equivalent Cp* ligands and the M(CO)₃ fragments. The ¹H NMR spectra of **6–8** and the ¹⁵N NMR spectrum of [[Ti₃Cp₃(μ₃-¹⁵N)](μ₃-¹⁵NH)₃Mo(CO)₃] (¹⁵N**6**) displayed signals at δ(μ₃-NH) = 11.5 (**6**), 11.4 (**7**), 10.9 (**8**), δ(μ₃-¹⁵NH) = −13.7, and δ(μ₃-¹⁵N) = 399.2.

To understand the electronic structures of these heterocubane compounds, their optimal geometries were calculated by density functional theory (DFT) methods on the model compounds [[Ti₃Cp₃(μ₃-CH)](μ₃-O)₃Mo(CO)₃] (**4'**; Cp = η^5 -C₅H₅) and [[Ti₃Cp₃(μ₃-N)](μ₃-NH)₃Mo(CO)₃] (**6'**). The analogous chromium and tungsten clusters were also investigated.^[15–19] The experimental geometry of complex **4** is well reproduced by the DFT calculations. The largest deviation between experimental and theoretical bond lengths is in the Ti...Mo distances; the calculated value is 0.082 Å shorter than the experimental value. The analysis of the orbitals of **4'** indicates that this cluster has six electrons from the metal (Figure 2), four of which are in orbitals of e symmetry and two

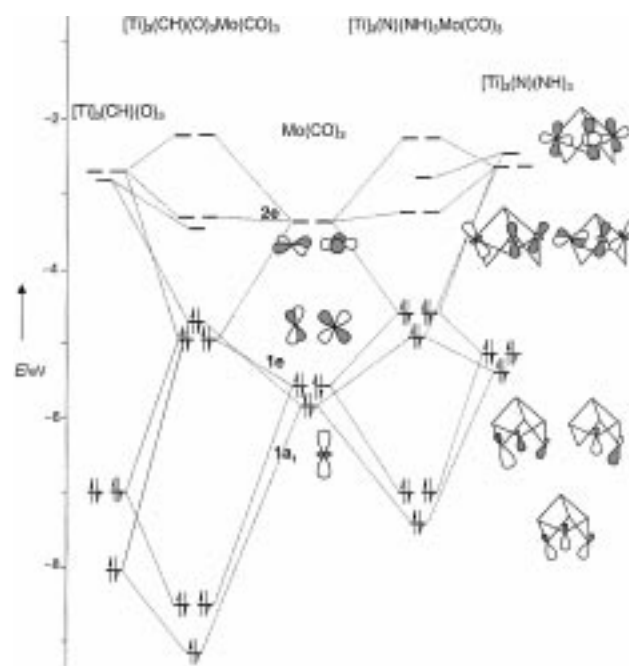


Figure 2. Interaction orbital diagram for the complexes **4'** and **6'**. [Ti] represents TiCp.

in an orbital of a₁ symmetry. The contributions of molybdenum to these orbitals are about 84 and 88% (Mulliken), respectively. The LUMO has a₁ symmetry and is a bonding combination of titanium d orbitals. These results clearly confirm that the formation of the cluster is not accompanied by oxidation of the molybdenum center and, as in the precubane precursor, the oxidation state of the titanium atom is still +4. Although the oxidation state of molybdenum should be regarded as zero, the Mo atom shares electron

density by means of metal–metal coupling with the Ti_3 unit, mainly through molybdenum orbitals of e symmetry. The elongation of the $\text{Mo}\cdots\text{Ti}$ distances by 0.1 Å when one electron is removed from the doubly degenerate metal orbitals reveals the presence of a positive metal–metal interaction. Harris et al.^[20] reported similar charge delocalization in the cubane-type clusters $[\text{MMo}_3\text{S}_4]$ (M = Ni, Pd, Co).

The energy of dissociation of **4'** to give the fragments $[\{\text{Ti}_3\text{Cp}_3(\mu_3\text{-CH})\}(\mu\text{-O})_3]$ and $[\text{Mo}(\text{CO})_3]$ was calculated to be +216.7 kJ mol^{−1}. The equivalent process for **6'** requires 134 kJ mol^{−1} more. We can rationalize this major energy difference by means of the orbital interaction diagram given in Figure 2. The higher energy of the NH lone pairs (−5.10 and −5.39 eV) relative to oxygen (−6.96 and −8.08 eV) favors σ donation from the ligand to the molybdenum fragment and therefore stabilization of the ligand lone pairs. In turn, the energy of the 1e orbitals of the molybdenum fragment increases, and this favors its interaction with the unoccupied titanium orbitals of the trinuclear ligand.

When chromium or tungsten replaced molybdenum in **4'**, the behavior was similar, but the dissociation energies were somewhat higher. The calculated values were 249.4 kJ mol^{−1} for the chromium and 287.5 kJ mol^{−1} for the tungsten complex. The same trend was observed when this substitution was made in complex **6'**, for which the bonding energies were 375.7 and 444.8 kJ mol^{−1}, respectively. There is a relationship between the bonding energy and the sharing of the electrons on the metal by Mo– Ti_3 coupling. The greatest delocalization occurs in $[\{\text{Ti}_3\text{Cp}_3(\mu_3\text{-N})\}(\mu_3\text{-NH})_3\{\text{W}(\text{CO})_3\}]$, in which 0.86 e are transferred from the tungsten center to the Ti_3 core, 0.72 e through the degenerate orbitals on the metal and 0.14 e through the orbital of a_1 symmetry on the metal. The smallest charge transfer occurs in complex **4'**, in which about 0.5 e are transferred from the molybdenum center to the titanium atoms. The electron delocalization in the Ti_3M clusters could be associated with the relatively high wavenumbers of the three terminal CO ligands in these complexes.

The energies of the reactions in Schemes 2 and 3 (M = Mo, $\text{L}_3 = \text{C}_6\text{H}_6$) were also calculated. Whereas for the precubane $[\{\text{Ti}_3\text{Cp}_3(\mu_3\text{-CH})\}(\mu\text{-O})_3]$ the process is exothermic with a relatively small reaction energy of −29.7 kJ mol^{−1}, for the trinuclear nitride $[\{\text{Ti}_3\text{Cp}_3(\mu_3\text{-N})\}(\mu\text{-NH})_3]$ the process is largely exothermic with a reaction energy of −164.4 kJ mol^{−1}. This discrepancy could be the origin of the different stabilities of complexes **4–6**.

To our knowledge, these results represent the first examples of an unprecedented family of cubane clusters containing Ti_3M heterometallic cores. These compounds can be easily synthesized by reaction of the organometallic complexes **1–3** with appropriate metal carbonyl complexes. Calculations showed that although the formation of complexes **4–8** is not accompanied by changes in the oxidation state of the metal centers, the metal carbonyl fragment shares electron density with the titanium atoms by means of metal–metal interactions. We believe that the trinuclear titanium complexes **1–3** offer many possibilities as *fac*-coordinating ligands, and we are now investigating the incorporation of diverse metal complex fragments.

Experimental Section

4: $[\text{Mo}(\text{CO})_3(1,3,5\text{-Me}_3\text{C}_6\text{H}_3)]$ (0.19 g, 0.64 mmol) was added to a solution of **1** (0.40 g, 0.65 mmol) in hexane (50 mL). The reaction mixture was heated at 80 °C for four days to give **4** as black crystals. Yield: 0.25 g (48 %). ¹H NMR (300 MHz, $[\text{D}_2]$ dichloromethane, 20 °C, TMS): δ = 2.01 (s, 45H; C_5Me_3), 13.78 (s, 1H; CH); ¹³C NMR (75 MHz, $[\text{D}_2]$ dichloromethane, 20 °C): δ = 12.3 (q, $J(\text{C},\text{H})$ = 126.2 Hz; C_5Me_3), 124.2 (m; C_5Me_3), 227.5 (s; CO), 410.3 (d, $J(\text{C},\text{H})$ = 136.0 Hz; $\equiv\text{CH}$); IR (KBr): $\tilde{\nu}$ = 2915 (s), 1913 (vs) (CO), 1816 (vs) (CO), 1377 (s), 653 (s), 612 (s), 574 cm^{−1} (s); MS (EI, 70 eV): m/z (%): 791 (1) [M^+], 706 (3) [$M^+ - 3\text{CO}$], 610 (28) [$M^+ - \text{Mo}(\text{CO})_3$].

Compound **5** was prepared analogously to **4** from **2** (0.70 g, 1.12 mmol) and $[\text{Mo}(\text{CO})_3(1,3,5\text{-Me}_3\text{C}_6\text{H}_3)]$ (0.33 g, 1.11 mmol). Yield: 0.42 g (66 %). ¹H NMR (300 MHz, $[\text{D}_2]$ dichloromethane, 20 °C, TMS): δ = 2.00 (s, 45H; C_5Me_3), 2.08 (s, 1H; CH); ¹³C NMR (75 MHz, $[\text{D}_2]$ dichloromethane, 20 °C): δ = 11.9 (q, $J(\text{C},\text{H})$ = 125.5 Hz; C_5Me_3), 42.5 (q, $J(\text{C},\text{H})$ = 125.5 Hz; $\equiv\text{CMe}$), 124.2 (m; C_5Me_3), 226.8 (s; CO), 434.8 (s; $\equiv\text{CMe}$); IR (KBr): $\tilde{\nu}$ = 2915 (s), 1911 (vs) (CO), 1818 (vs) (CO), 1376 (s), 632 (s), 614 (s), 583 cm^{−1} (vs); MS (EI, 70 eV): m/z (%): 704 (10) [$M^+ - 3\text{CO} - \text{CH}_4$], 624 (20) [$M^+ - \text{Mo}(\text{CO})_3$]; elemental analysis (%) calcd for $\text{C}_{35}\text{H}_{48}\text{MoO}_6\text{Ti}_3$ (804.40): C 52.26, H 6.02; found: C 52.71, H 6.14.

6: Method A: $[\text{Mo}(\text{CO})_3(1,3,5\text{-Me}_3\text{C}_6\text{H}_3)]$ (0.30 g, 0.99 mmol) and **3** (0.60 g, 0.99 mmol) were dissolved in toluene (30 mL). The reaction mixture was stirred at room temperature for three days. Black crystals of **6** were obtained (0.55 g, 70 %). [¹⁵N]**6** was prepared by a similar method from $[\{\text{TiCp}^*(\mu\text{-}^{15}\text{NH})\}_3(\mu_3\text{-}^{15}\text{N})]$ ([¹⁵N]**3**). Method B: Compound **6** was prepared on an NMR-tube scale from **3** and $[\text{Mo}(\text{CO})_6]$ by using the same procedure as for **7**. ¹H NMR (300 MHz, C_6D_6 , 20 °C, TMS): δ = 1.86 (s, 45H; C_5Me_3), 11.50 (br.s, 3H; NH); ¹³C{¹H} NMR (75 MHz, C_6D_6 , 20 °C): δ = 11.8 (C_5Me_3), 118.9 (C_5Me_3), 230.7 (CO); ¹⁵N NMR (50.7 MHz, $\text{C}_6\text{D}_6/\text{CDCl}_3$, 20 °C):^[21] δ = −13.7 (d, $J(\text{N},\text{H})$ = 70.2 Hz; $\mu_3\text{-NH}$), 399.2 (s; $\mu_3\text{-N}$); IR (KBr): $\tilde{\nu}$ = 3361 (m) (NH), 2914 (s), 1915 (vs) (CO), 1822 (s) (CO), 1378 (s), 723 (s), 618 cm^{−1} (vs); MS (EI, 70 eV): m/z (%): 704 (41) [$M^+ - 3\text{CO}$]; elemental analysis (%) calcd for $\text{C}_{33}\text{H}_{48}\text{MoN}_4\text{O}_3\text{Ti}_3$ (788.4072): C 50.27, H 6.14, N 7.11; found: C 50.69, H 6.11, N 7.28.

7: Compound **3** (0.30 g, 0.49 mmol) and $[\text{W}(\text{CO})_6]$ (0.17 g, 0.49 mmol) were dissolved in toluene (60 mL) and irradiated with UV light for 4 h. The solution was concentrated and cooled to about −40 °C, and **7** was obtained as a reddish crystalline solid (0.18 g, 42 %). ¹H NMR (300 MHz, C_6D_6 , 20 °C, TMS): δ = 1.84 (s, 45H; C_5Me_3), 11.39 (br.s, 3H; NH); ¹³C{¹H} NMR (75 MHz, C_6D_6 , 20 °C): δ = 11.8 (C_5Me_3), 119.2 (C_5Me_3), 225.6 (CO); IR (KBr): $\tilde{\nu}$ = 3360 (m) (NH), 2914 (s), 1914 (s) (CO), 1832 (s) (CO), 1378 (s), 724 (s), 616 cm^{−1} (s).

Compound **8** was prepared similarly to **7** from **3** (0.3 g, 0.49 mmol) and $[\text{Cr}(\text{CO})_6]$ (0.11 g, 0.49 mmol) with UV irradiation for 5 h. Yield: Black, crystalline **8** (0.21 g, 57 %). ¹H NMR (300 MHz, C_6D_6 , 20 °C, TMS): δ = 1.87 (s, 45H; C_5Me_3), 10.90 (br.s, 3H; NH); ¹³C{¹H} NMR (75 MHz, C_6D_6 , 20 °C): δ = 11.8 (C_5Me_3), 118.3 (C_5Me_3), 243.9 (CO); IR (KBr): $\tilde{\nu}$ = 3363 (m) (NH), 2912 (s), 1911 (vs) (CO), 1829 (vs) (CO), 1377 (s), 719 (s), 630 (s), 620 cm^{−1} (s).

Received: September 10, 1999 [Z14001]

- [1] a) R. Andrés, M. Galakhov, A. Martín, M. Mena, C. Santamaría, *J. Chem. Soc. Chem. Commun.* **1995**, 551–552; b) M. Galakhov, M. Mena, C. Santamaría, *Chem. Commun.* **1998**, 691–692; c) R. Andrés, M. Galakhov, M. Pilar Gómez-Sal, A. Martín, M. Mena, C. Santamaría, *Chem. Eur. J.* **1998**, *4*, 1206–1213.
- [2] Some examples: a) J. N. Butt, F. A. Armstrong, J. Breton, S. J. George, A. J. Thomson, E. C. Hatchikian, *J. Am. Chem. Soc.* **1991**, *113*, 6663–6670; b) J. N. Butt, A. Sucheta, F. A. Armstrong, J. Breton, A. J. Thomson, E. C. Hatchikian, *J. Am. Chem. Soc.* **1991**, *113*, 8948–8950; c) K. K. P. Srivastava, K. K. Surerus, R. C. Conover, M. K. Johnson, J. B. Park, M. W. W. Adams, E. Münck, *Inorg. Chem.* **1993**, *32*, 927–936; d) W. Cen, S. C. Lee, J. Li, F. M. MacDonnell, R. H. Holm, *J. Am. Chem. Soc.* **1993**, *115*, 9515–9523; e) W. Fu, J. Telsner, B. M. Hoffman, E. T. Smith, M. W. W. Adams, M. G. Finnegan, R. C. Conover, M. K.

- Johnson, *J. Am. Chem. Soc.* **1994**, *116*, 5722–5729; f) M. G. Finnegan, R. C. Conover, J.-B. Park, Z. H. Zou, M. W. W. Adams, M. K. Johnson, *Inorg. Chem.* **1995**, *34*, 5358–5369; g) J. Zhou, J. W. Raebiger, C. A. Crawford, R. H. Holm, *J. Am. Chem. Soc.* **1997**, *119*, 6242–6250; h) G. Sakane, K. Hashimoto, M. Takahashi, M. Takeda, T. Shibahara, *Inorg. Chem.* **1998**, *37*, 4231–4234; i) R. Hernandez-Molina, V. P. Fedin, M. N. Sokolov, D. M. Saysell, A. G. Sykes, *Inorg. Chem.* **1998**, *37*, 4328–4334; j) B. Rink, M. Brorson, I. J. Scowen, *Organometallics* **1999**, *18*, 2309–2313.
- [3] W. A. Herrmann, A. Egli, E. Herdtweck, R. Alberto, F. Baumgärtner, *Angew. Chem.* **1996**, *108*, 486–489; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 432–434.
- [4] See, for example, a) B. C. Gates, *Chem. Rev.* **1995**, *95*, 511–522; b) K. I. Hadjiivanov, D. G. Klissurski, *Chem. Soc. Rev.* **1996**, 61–69; c) J. Evans, *Chem. Soc. Rev.* **1997**, 11–19; d) A. Hu, K. M. Neyman, M. Stauffer, T. Belling, B. C. Gates, N. Rösch, *J. Am. Chem. Soc.* **1999**, *121*, 4522–4523.
- [5] R. J. Angelici, *Synthesis and Technique in Inorganic Chemistry*, 2nd ed., Saunders, Philadelphia, **1977**, 132–133.
- [6] However, this process is accelerated by heating; for example **4** is 50% transformed into **1** after 12 h at about 80 °C.
- [7] a) C. Elschenbroich, A. Salzer, *Organometallics: A Concise Introduction*, 2nd ed., VCH, Weinheim, **1992**, p. 230; b) N. L. Armanasco, M. V. Baker, M. R. North, B. W. Skelton, A. H. White, *J. Chem. Soc. Dalton Trans.* **1998**, 1145–1149.
- [8] X-ray structure determination of **5**: Dark green crystals of **5** were obtained by slow crystallization from a saturated solution in hexane. The data were collected on an Enraf Nonius CAD4 diffractometer at room temperature. Intensity measurements were performed by $\omega/2\theta$ scans in the range $3^\circ < \theta < 27^\circ$ on a crystal of dimensions $0.35 \times 0.28 \times 0.23$ mm. Of the 4409 measured reflections, 4193 were independent; largest minimum and maximum in the final difference Fourier synthesis: -1.063 and $1.621 \text{ e } \text{\AA}^{-3}$, $R1 = 0.107$ and $wR2 = 0.296$ (for 2496 reflections with $F > 4\sigma(F)$). The values of $R1$ and $wR2$ are defined as $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$; $wR2 = \{[\sum w(F_o^2 - F_c^2)^2] / [\sum w(F_o^2)^2]\}^{1/2}$. The structure was solved by direct methods (SHELXS-97) and refined by least-squares against F^2 (SHELXL-97).^[9] Space groups $P2_1$ and $P2_1/m$ were used to solve and refine the structure, but only the former gave a sensible chemical structure due to disorder in the pentamethylcyclopentadienyl rings and the poor quality of the crystal (unfortunately, data could not be obtained at low temperature). However, this disorder did not affect the location of the core of the molecule. The hydrogen atoms were positioned geometrically and refined by using a riding model. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134178. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [9] G. M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, Universität Göttingen, Germany, **1997**.
- [10] R. Andrés, M. Galakhov, A. Martín, M. Mena, C. Santamaría, *Organometallics* **1994**, *13*, 2159–2163.
- [11] C. R. Kissinger, E. T. Adman, L. C. Sieker, L. H. Jensen, *J. Am. Chem. Soc.* **1988**, *110*, 8721–8723.
- [12] D. Coucouvanis, S. Al-Ahmad, A. Salifoglou, W. R. Dunham, R. H. Sands, *Angew. Chem.* **1988**, *100*, 1404; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1353–1355.
- [13] K. J. Haack, R. Goddard, K. R. Pörschke, *J. Am. Chem. Soc.* **1997**, *119*, 7992–7999.
- [14] H. W. Roesky, Y. Bai, M. Noltemeyer, *Angew. Chem.* **1989**, *101*, 788; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 754–755.
- [15] All DFT calculations were carried out with the ADF program^[16] by using triple- ζ and polarization Slater basis sets to describe the valence electrons of C, N, and O. For titanium, a frozen core composed of the 1s, 2s, and 2p orbitals was described by double- ζ Slater functions, the 3d and 4s orbitals by triple- ζ functions, and the 4p orbital by a single orbital. Basis sets of the same quality were used for Cr, Mo, and W. Hydrogen atoms were described by triple- ζ and polarization functions. The geometries and binding energies were calculated with gradient corrections. We used the local spin density approximation, characterized by the electron gas exchange ($X\alpha$ with $\alpha = 2/3$) together with Vosko–Wilk–Nusair parametrization^[17] for correlation. Becke's nonlocal corrections^[18] to the exchange energy and Perdew's nonlocal corrections^[19] to the correlation energy were added. Quasirelativistic corrections were employed by using the Pauli formalism with corrected core potentials. The quasirelativistic frozen core shells were generated with the auxiliary program DIRAC.^[16] In the DFT calculations on complexes **4**–**8**, the methyl groups were replaced by hydrogen atoms.
- [16] a) ADF2.3, Department of Theoretical Chemistry, Vrije Universiteit, Amsterdam; b) E. J. Baerends, D. E. Ellis, P. Ros, *Chem. Phys.* **1973**, *2*, 41–51; c) G. te Velde, E. J. Baerends, *J. Comput. Phys.* **1992**, *99*, 84–98.
- [17] S. H. Vosko, L. Wilk, M. Nusair, *Can. J. Phys.* **1980**, *58*, 1200–1211.
- [18] a) A. D. Becke, *J. Chem. Phys.* **1986**, *84*, 4524–4529; b) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098–3100.
- [19] a) J. P. Perdew, *Phys. Rev. B* **1986**, *33*, 7406–7406; b) J. P. Perdew, *Phys. Rev. B* **1986**, *34*, 8822–8824.
- [20] C. S. Bahn, A. Tan, S. Harris, *Inorg. Chem.* **1998**, *37*, 2770–2778.
- [21] The ^{15}N NMR spectrum was referenced to external CH_3NO_2 ($\delta = 0.00$).

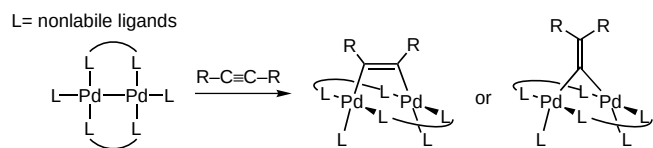
Coupling of Alkynes on a Pd–Pd Bond to Generate an Electrophilic μ -Butenediylidene Moiety**

Tetsuro Murahashi, Toshiaki Otani, Taketoshi Okuno, and Hideo Kurosawa*

In spite of its potential relevance to new palladium-catalyzed reactions, dipalladium(II)-mediated C–C bond-forming reactions have rarely been achieved in a well-defined manner.^[1] This seems curious since the Pd^I–Pd^I complexes are readily accessible and the Pd^{II} and Pd⁰ oxidation states also exist.^[2] One reason could be that relatively nonlabile auxiliary ligands are used to support the Pd–Pd bond (for example, $\text{Ph}_2\text{PCH}_2\text{PPh}_2$, RNC)^[2] so that only a single molecule of unsaturated compounds such as alkynes can be bound (Scheme 1).^[3] We sought Pd–Pd complexes that can provide multiple coordination sites for substrate molecules. We report here a facile, regioselective coupling of a terminal alkyne onto the Pd–Pd bond of $[\text{Pd}_2(\text{PPh}_3)_2(\text{CH}_3\text{CN})_4](\text{PF}_6)_2$ (**1**),^[4] a dipalladium complex with more labile ligands, to generate an electrophilic μ -1 κ C1,4:2 κ C1,4-butenediylidene framework.

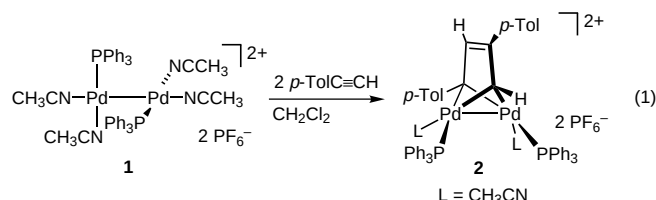
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[**] We thank Prof. Y. Kai and E. Mochizuki (Osaka University) for use of X-ray crystallographic analysis facilities and collection of the data for **2** and **3**. Partial support of this work through Grant-in-Aid for Scientific Research, Ministry of Education, Science and Culture, and CREST of Japan Science and Technology Corporation is gratefully acknowledged. T.M. acknowledges the JSPS research fellowships for young scientists. Thanks are also due to the Analytical Center, Faculty of Engineering, Osaka University for the use of NMR facilities.



Scheme 1. The known reaction patterns of Pd–Pd complexes with alkynes.

The dipalladium(II) complex **1** reacted with two equivalents of *p*-tolylacetylene (*p*-TolC≡CH) immediately at 0 °C in CH₂Cl₂ to give a single product **2** as red crystals in 60% yield after recrystallization from CH₂Cl₂/*n*-hexane [Eq. (1)]. The



reaction was quantitative according to ¹H and ³¹P NMR spectroscopic analysis. The solid-state structure of **2** was determined by X-ray structure analysis (Figure 1) and showed

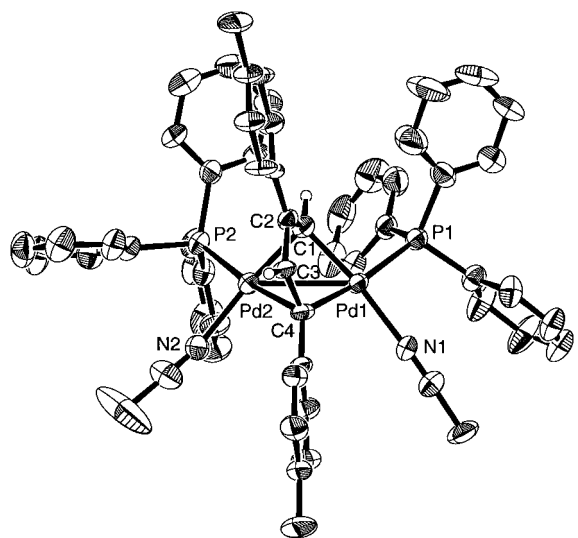
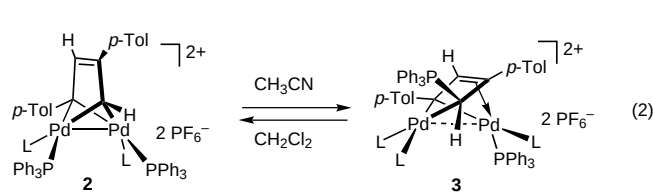


Figure 1. ORTEP plot of **2** (counteranions omitted for clarity). Selected bond lengths [Å] and angles [°]: Pd1–Pd2 2.798(1), Pd1–C1 2.01(1), Pd1–C4 2.06(1), Pd2–C1 2.02(1), Pd2–C4 2.18(1), C1–C2 1.40(2), C2–C3 1.43(2), C3–C4 1.38(2); Pd1–C1–Pd2 87.9(5), C1–C2–C3 109(1), C2–C3–C4 115(1), Pd1–C4–Pd2 82.4(4).

that *p*-tolylacetylene was dimerized in a head-to-tail manner to form a slightly tilted^[5] CHC(Tol)CHC(Tol) bridge across the Pd–Pd bond. The solution ³¹P NMR spectrum of **2** showed only one sharp singlet at δ = 24.96, even at –90 °C, which is consistent with the essentially symmetric bridge structure. Although a number of μ-1κC1,4:2κC1,2,3,4 and μ-1κC1,2,3,4:2κC1,2,3,4 bridging structures of similar C₄ units have been constructed on M–M bonds, the structural characteristics of **2** are rare^[6] and may reflect the carbene-like nature of two terminal carbon atoms coordinated to a 4e acceptor [L₂Pd–PdL₂]²⁺, as in [Pd₂Cl₄(μ-CO)₂]^{2–},^[7] rather than

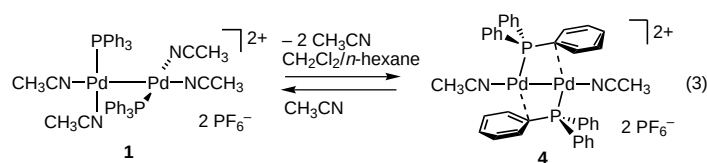
a butadienediyl structure coordinated to a 6e acceptor without a Pd–Pd bond [L₂PdPdL₂]²⁺.^[8] The reaction shown in Equation (1) is in contrast to the oxidative coupling of alkynes to mononuclear Pd⁰ to give palladacyclopentadienes, which is limited to disubstituted activated alkynes such as dimethylacetylene dicarboxylate (DMAD).^[9] Moreover, terminal acetylenes usually undergo oxidative addition of an acetylenic C–H bond to Pd⁰ to give a transient alkynyl palladium hydride complex.^[10]

When **2** was dissolved in CD₃CN the new product **3** was immediately generated quantitatively [Eq. (2)]. A single crystal of **3** suitable for X-ray diffraction analysis was obtained



from CH₃CN/Et₂O. One PPh₃ ligand of **2** migrated to the H-bearing bridging C atom to generate a phosphane ylide complex containing a palladacyclopentenyl moiety.^[11] The ³¹P NMR spectrum of **3** in CD₃CN at –45 °C showed two sets of pairs of doublets with a ratio of 2:1.^[12] Both isomers of **3** were readily converted into **2** in CH₂Cl₂ by loss of a CH₃CN ligand, which means that formation of the ylide is reversible. To our knowledge, such nucleophilic addition at C4 of dinuclear μ-C₄R₄ complexes has not been reported so far in a well-defined manner.

This unique dimerization of an acetylene system may be attributable to the ability of **1** to generate at least two vacant sites on Pd–Pd in solution. This proposal is supported by the facile dissociation of acetonitrile from **1** to give the orange-yellow dipalladium complex **4**, which was isolated in 87% yield on precipitation from a solution of **1** in CH₂Cl₂ [Eq. (3)]. The reverse reaction proceeded in CH₃CN solution.



The X-ray crystal structure of **4** (Figure 2) showed that the two vacant sites generated by loss of two CH₃CN ligands were occupied by η¹-bound^[13] *ipso*-carbon atoms of the PPh₃ phenyl rings (Pd–C_{ipso} 2.336(4) Å).^[14] The distances between Pd1 and the *ortho*-C atoms adjacent to C1 (2.703(4), 2.974(4) Å) are outside the range for Pd–C interaction. No significant structural perturbation of the geometry at the η¹-phenyl or at the phosphorus atom was induced by the μ-1κP:2κC1 coordination,^[15] except that the P–C bond of the coordinated phenyl group (P1–C1 1.832(4) Å) was somewhat longer than those of the uncoordinated phenyl groups (1.801(4), 1.806(4) Å). While triphenylphosphane is one of the most versatile ligands for Pd catalysts, there is no precedent in

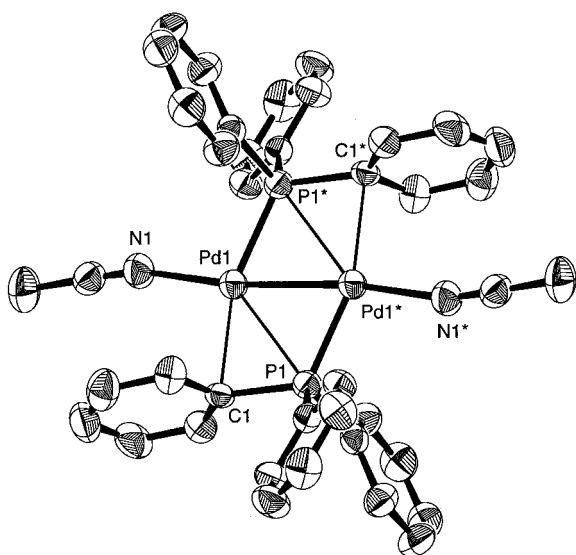
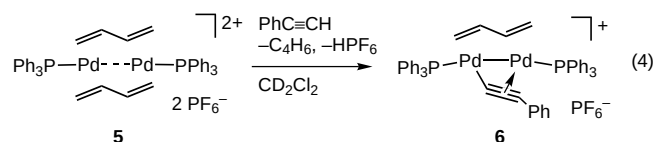


Figure 2. ORTEP plot of **4** (counteranions omitted for clarity). Selected bond lengths [Å] and angles [°]: Pd1–Pd1* 2.5833(7), Pd1*–P1 2.213(1), Pd1–P1 2.753(1), Pd1–C1 2.336(4), P1–C1 1.832(4); Pd1–Pd1*–P1 69.56(3), Pd1*–Pd1–P1 48.87(2), Pd1–P1–C1 57.1(1), P1–C1–Pd1 81.7(1).

which it bridges two Pd centers.^[16] The lability of the PPh₃ bridge of **4** in solution was confirmed by variable-temperature NMR studies. A single set of phenyl carbon signals of the PPh₃ ligands at 23 °C split into two sets with relative intensities of 1:2 at –90 °C, consistent with the coordination and decoordination of the phenyl groups. The fluxional behavior at room temperature could arise from dissociation of *ipso*-C atoms from Pd followed by rotation about the P–Pd bond. Note that **4** reacted with two equivalents of tolylacetylene in CH₂Cl₂ to give **2** in 74% yield after recrystallization; this represents a simple alkyne coupling on the metal–metal bond without any loss of the auxiliary ligands.

Finally, we also examined the reaction of phenylacetylene with another Pd–Pd complex containing labile bridging ligands, namely, [(μ-1,3-butadiene)₂Pd₂(PPh₃)₂](PF₆)₂ (**5**).^[4] However, instead of an alkyne coupling taking place the quantitative formation of complex **6**, presumably having a μ-1κC1:2κC1,2-alkynyl ligand, occurred in CD₂Cl₂ after 30 min at room temperature with dissociation of one of the 1,3-butadiene ligands [Eq. (4)]. Presumably, the remaining μ-1,3-diene ligand, which would become rather tightly bound^[17]



after the initial exchange between acetylene and the other butadiene ligand of **5**, prohibits either insertion of alkyne into the Pd–Pd bond,^[3] which may represent the initial step of the alkyne coupling in Equation (1), or the coordination of a second molecule of the alkyne.

In summary, alkyne coupling on a Pd–Pd bond yielded an electrophilic butenediylidene species with complete regiose-

lectivity (head-to-tail).^[18] However, the presence of bridging ligands such as 1,3-butadiene prevented dimerization and allowed the formation of a μ-alkynyl ligand.

Experimental Section

2: To an orange solution of **4** (400.0 mg, 0.361 mmol) in CH₂Cl₂ (30 mL) was added dropwise a solution of *p*-tolylacetylene (100.4 μL, 0.721 mmol) in CH₂Cl₂ (5 mL) at 0 °C. After stirring the mixture for 20 min, the resultant red solution was poured into *n*-hexane. Red crystals of **2** (358.1 mg, 74% yield) were obtained after recrystallization from CH₂Cl₂/*n*-hexane. ¹H NMR (270 MHz, CD₂Cl₂, 25 °C): δ = 8.75 (d, *J* = 3.5 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.6–7.2 (m, PPh₃, 30H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.61 (dt, *J* = 7.80 Hz, *J* = 3.5 Hz, 1H), 2.42 (s, Me, 3H), 2.38 (s, Me, 3H), 1.74 (brs, CH₃CN, 6H); ¹³C NMR (100 MHz, CD₂Cl₂, –60 °C, CH COSY): δ = 196.99 (t, *J* = 60 Hz, C(Tol)-CHC(Tol)CH), 172.84 (s, C(Tol)CHC(Tol)CH), 147.40 (s, C(Tol)-CHC(Tol)CH), 146.06 (s, *p*-Tol), 144.12 (s, *p*-Tol), 139.38 (s, *ipso*-Tol), 133.39 (d, *J* = 13.5 Hz, PPh₃), 131.60 (s, PPh₃), 130.39 (s, C(Tol)-CHC(Tol)CH), 130.10 (s, *m*-Tol), 129.86 (s, *o*-Tol), 129.04 (d, *J* = 10.1 Hz, PPh₃, *m*-Tol), 128.40 (s, *o*-Tol), 127.69 (d, *J* = 47.2 Hz, PPh₃), 126.88 (s, *ipso*-Tol), 123.17 (s, C≡N), 21.67 (s, Me), 21.62 (s, Me), 2.44 (CH₃CN); ³¹P NMR (109 MHz, CD₂Cl₂, 25 °C): δ = 24.76 (s); elemental analysis calcd for C₃₈H₅₂N₂P₄F₁₂Pd₂: C 51.92, H 3.91, N 2.09; found: C 51.71, H 3.84, N 2.12. Crystal data for **2**·2CH₂Cl₂·2H₂O:^[19] C₆₀H₆₀N₂P₄O₂Cl₄F₁₂Pd₂, *M_r* = 1547.68, space group *P* $\bar{1}$ (no. 2), *a* = 14.458(4), *b* = 20.078(4), *c* = 13.703(5) Å, α = 106.49(2), β = 108.28(3), γ = 70.73(2)°, *V* = 3492.58 Å³, *Z* = 2, *F*(000) = 1548, ρ_{calcd} = 1.468 g cm^{–3}, μ(MoKα) = 8.31 cm^{–1}. The data were collected at 223 K on a Rigaku RAXIS CS imaging plate area detector up to 2θ_{max} = 60.0°. The structure was solved by direct methods; 775 variables were refined with 9167 reflections (*I* > 3σ(*I*)) by full-matrix least-squares methods to *R*1 = 0.095 and GOF = 2.32.

3: Orange crystals of **3** were obtained in 87% yield by crystallization from a solution of **2** in CH₃CN/Et₂O. At ambient temperature all NMR signals were broadened, probably as a result of the interconversion between the isomers on the NMR timescale. Major isomer: ¹H NMR (270 MHz, CD₃CN, –45 °C): δ = 7.9–7.2 (m, PPh₃, 30H), 7.04 (d, *J* = 4.86 Hz, 2H), 6.75 (d, *J* = 7.83 Hz, 2H), 6.51 (d, *J* = 7.83 Hz, 2H), 6.28 (brdd, 1H), 4.54 (d, *J* = 3.51 Hz, 1H); ³¹P NMR (109 MHz, CD₃CN, –45 °C): δ = 31.39 (d, *J* = 25 Hz), 26.37 (d, *J* = 25 Hz). Minor isomer: ¹H NMR (CD₃CN, –45 °C): δ = 3.45 (s, 1H), other signals could not be assigned; ³¹P NMR (CD₃CN, –45 °C): δ = 24.19 (d, *J* = 22 Hz), 20.41 (d, *J* = 22 Hz); elemental analysis calcd for C₆₀H₅₅N₃P₄F₁₂Pd₂: C 52.11, H 4.01, N 3.04; found: C 51.89, H 4.00, N 2.71. Crystal data for **3**·2Et₂O:^[19] C₆₈H₇₅N₃O₂P₄F₁₂Pd₂, *M_r* = 1531.08, space group *P* $\bar{1}$ (no. 2), *a* = 18.72(3), *b* = 18.723(7), *c* = 10.580(4) Å, α = 96.43(3), β = 105.51(6), γ = 90.39(8)°, *V* = 3548(4) Å³, *Z* = 2, *F*(000) = 1560, ρ_{calcd} = 1.433 g cm^{–3}, μ(MoKα) = 6.73 cm^{–1}. The data were collected at 223 K on a Rigaku RAXIS CS imaging plate area detector up to 2θ_{max} = 60.4°. The structure was solved by direct methods; 865 variables were refined with 12340 reflections (*I* > 3σ(*I*)) by full-matrix least-squares methods to *R*1 = 0.104 and GOF = 5.19. The Pd–Pd distance was 2.811(4) Å.

4: Compound **1** (1.300 g, 1.09 mmol) was dissolved in CH₂Cl₂, and the solution poured into *n*-hexane to give orange crystals of **4** (1.052 g, 87% yield). ¹³C NMR (150 MHz, CD₂Cl₂, 23 °C): δ = 134.98 (s, *p*-Ph), 133.08 (d, *J* = 12.6 Hz, *o*-Ph), 131.44 (d, *J* = 11.6 Hz, *m*-Ph), 119.90 (s, C≡N), 116.29 (brs, *ipso*-Ph), 2.96 (s, Me); ³¹P NMR (162 MHz, CD₂Cl₂, 25 °C): δ = 23.13 (s); elemental analysis calcd for C₄₀H₃₆N₂P₄F₁₂Pd₂: C 43.30, H 3.27, N 2.52; found: C 43.15, H 3.28, N 2.43; ESI-MS for C₄₀H₃₆N₂P₄F₆Pd₂: calcd: 964.49, found: 964.5; ¹³C NMR (162 MHz, CD₂Cl₂, –90 °C, Ph* indicates coordinated Ph): δ = 136.83 (s, *p*-Ph*), 133.90 (d, *J* = 12.6 Hz, *o*-Ph), 133.50 (s, *m*-Ph*), 132.83 (s, *p*-Ph), 129.04 (d, *J* = 11.5 Hz, *m*-Ph), 127.31 (s, *o*-Ph*), 126.02 (d, *J* = 55.3 Hz, *ipso*-Ph), 118.31 (s, C≡N), 92.11 (d, *J* = 49.5 Hz, *ipso*-Ph*), 2.94 (s, Me). Crystal data for **4**:^[19] C₄₀H₃₆N₂P₄F₁₂Pd₂, *M_r* = 1109.41, space group *P* $\bar{1}$ (no. 2), *a* = 11.045(2), *b* = 12.434(2), *c* = 8.354(2) Å, α = 90.92(2), β = 92.94(2), γ = 110.95(1)°, *V* = 1069.3(4) Å³, *Z* = 1, *F*(000) = 550, ρ_{calcd} = 1.723 g cm^{–3}, μ(MoKα) = 10.60 cm^{–1}. The data were collected at 296 K on a Rigaku AFC5R diffractometer up to 2θ_{max} = 55.1°. The structure was solved by Patterson methods; 271 variables were

refined with 4171 reflections ($I > 3\sigma(I)$) by full-matrix least-squares methods to $R1 = 0.049$, $R_w = 0.036$ and $GOF = 3.03$.

6: Phenylacetylene (14.5 μL , 0.132 mmol) was added to a yellow suspension of **5** (100.0 mg, 0.0881 mmol) in benzene and the solution stirred for 5 min at room temperature. Then pyridine (7.1 μL , 0.0881 mmol) was added, and the mixture was stirred for 10 min. The resultant orange solution was filtered, and the filtrate was poured into *n*-hexane to afford **6** as a yellow powder (63.7 mg, 70% yield). The NMR spectra of the reaction mixture in CD_2Cl_2 confirmed quantitative formation of **6** without addition of pyridine. ^1H NMR (400 MHz, CD_2Cl_2 , 25 °C): $\delta = 7.6\text{--}7.4$ (m, PPh₃, 30H), 7.00 (t, $J = 7.6$ Hz, 1H), 6.80 (t, $J = 7.6$ Hz, 2H), 6.59 (d, $J = 7.6$ Hz, 2H), 3.67 (brs, 2H), 3.02 (brs, 2H), 2.79 (brd, 2H); ^{31}P NMR (162 MHz, CD_2Cl_2 , 25 °C): $\delta = 33.8$ (s); elemental analysis calcd for $\text{C}_{48}\text{H}_{41}\text{P}_3\text{F}_6\text{Pd}_2$: C 55.56, H 3.98; found: C 55.35, H 4.03; Raman (solid): $\tilde{\nu}_{\text{C}\equiv\text{C}} = 2008, 1975\text{ cm}^{-1}$; the fluxional nature of **6** at 25 °C was confirmed by variable-temperature NMR analyses; ^1H NMR (400 MHz, CD_2Cl_2 , -80°C): $\delta = 7.6\text{--}7.4$ (m, 30H), 6.94 (t, 1H), 6.75 (t, 2H), 6.48 (d, 2H), 4.14 (brd, 1H), 3.71 (brm, 1H), 3.19 (brd, 1H), 3.05 (brs, 1H), 2.22 (brm, 2H); ^{31}P NMR (162 MHz, CD_2Cl_2 , -80°C): $\delta = 35.2$ (d, $J = 51.8$ Hz), 32.7 (d, $J = 51.8$ Hz).

Received: June 2, 1999 [Z13510]

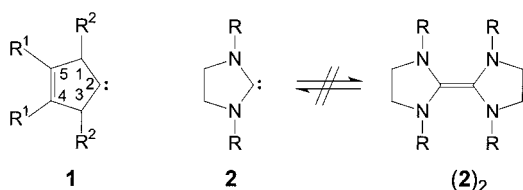
- [1] S. J. Young, B. Kellenberger, J. H. Reibenspies, S. E. Himmel, M. Manning, O. P. Anderson, J. K. Stille, *J. Am. Chem. Soc.* **1988**, *110*, 5744, and references therein.
- [2] P. M. Maitlis, P. Espinet, M. J. H. Russel in *Comprehensive Organometallic Chemistry*, Vol. 6 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, **1982**, chap. 38.3.
- [3] a) C.-H. Lee, C. T. Hunt, A. L. Balch, *Inorg. Chem.* **1981**, *20*, 2498; b) H. Werner, P. Thometzek, K. Zenkert, R. Goddard, H.-J. Kraus, *Chem. Ber.* **1987**, *120*, 365; c) S. J. Higgins, B. L. Shaw, *J. Chem. Soc. Dalton Trans.* **1988**, 457; d) J. A. Davies, K. Kirshbaum, C. Kluwe, *Organometallics* **1994**, *13*, 3664; e) T. R. Jack, C. J. May, J. Powell, *J. Am. Chem. Soc.* **1977**, *99*, 4707.
- [4] T. Murahashi, T. Otani, E. Mochizuki, Y. Kai, H. Kurosawa, S. Sakaki, *J. Am. Chem. Soc.* **1998**, *120*, 4536. We also found that **1** can be easily prepared from $[\text{Pd}(\text{PPh}_3)_2(\text{CH}_3\text{CN})_2](\text{PF}_6)_2$ and 0.5 equiv of $[\text{Pd}_2(\text{dba})_3]$ (dba = *trans,trans*-dibenzylideneacetone) in $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ in 70% yield of isolated product.
- [5] The slight tilting of the C_4 framework results in an angle of 74.5° between the C1-C2-C3-C4 mean plane and the Pd1-Pd2 vector.
- [6] Acetylene coupling on metal-metal bonds of middle transition metals has been reported; $\mu\text{-}1\kappa\text{C1,2,3,4:}2\kappa\text{C1,2,3,4}$ type: a) Q. Feng, M. L. H. Green, P. Mountford, *J. Chem. Soc. Dalton Trans.* **1992**, 2171; $\mu\text{-}1\kappa\text{C1,4:}2\kappa\text{C1,2,3,4}$ -type: b) S. A. R. Knox, R. F. D. Stansfield, F. G. A. Stone, M. J. Winter, P. Woodward, *J. Chem. Soc. Dalton Trans.* **1982**, 173; c) M. H. Chisholm, K. Folting, J. C. Huffman, I. P. Rothwell, *J. Am. Chem. Soc.* **1982**, *104*, 4389, and references therein; d) Review: W. P. Fehlhammer, H. Stolzenberg in *Comprehensive Organometallic Chemistry*, Vol. 4 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, **1982**, chap. 31.4; A similar complex $[(\mu\text{-}1\kappa\text{C1,4:}2\kappa\text{C1,4-CHC(Ph)C(Ph)CH)Ni}_2(\text{depe})_2](\text{PF}_6)_2$ (depe = 1,2-bis(diethylphosphanyl)ethane) was derived from a butadienediyl Ni^{II} complex without any evidence of acetylene coupling on the Ni-Ni bond: e) C. J. Lawrie, H. E. Dankosh, B. K. Carpenter, *J. Organomet. Chem.* **1991**, *411*, C7; $[(\mu\text{-}1\kappa\text{C1,4:}2\kappa\text{C1,4-CHC(CH}_2\text{OH)C(CH}_2\text{OH)-CH)Ni}_2(\text{diimine})_2]$, which has a different formal valency of the metal centers from **3**, has also been structurally characterized: f) R. Diercks, L. Stamp, J. Kopf, H. tom Dieck, *Angew. Chem.* **1984**, *96*, 891; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 893.
- [7] N. M. Kostić, R. F. Fenske, *Inorg. Chem.* **1983**, *22*, 666.
- [8] According to a calculation $\mu\text{-}1\kappa\text{C1,4:}2\kappa\text{C1,2,3,4}$ -bridging bonding is more stable than $\mu\text{-}1\kappa\text{C1,4:}2\kappa\text{C1,4}$ bonding to the 6e acceptor $\text{Fe}_2(\text{CO})_6$; D. L. Thorn, R. Hoffmann, *Inorg. Chem.* **1978**, *17*, 127.
- [9] a) K. Moseley, P. M. Maitlis, *J. Chem. Soc. Dalton Trans.* **1974**, 169; b) R. van Belzen, R. A. Klein, H. Kooijman, N. Veldman, A. L. Spek, C. J. Elsevier, *Organometallics* **1998**, *17*, 1812.
- [10] a) G. A. Chukhadzhyan, Z. K. Evoyan, L. N. Melkonyan, *Zh. Obshch. Khim.* **1975**, *45*, 1114; b) F. Schager, W. Bonrath, K.-R. Pörschke, M. Kessler, C. Kürger, K. Seevogel, *Organometallics* **1997**, *16*, 4276, and references therein.
- [11] Metallocyclopentenyl complexes derived from acetylenes are very rare: H. Yamazaki, K. Yasufuku, Y. Wakatsuki, *Organometallics* **1983**, *2*, 726.
- [12] The exact structure of the minor isomer was not identified. It may arise from exchange of PPh_3 ligand with one of the three acetonitrile ligands of the major isomer; the two isomers interconvert rapidly at room temperature (see Experimental Section).
- [13] A limited number of η^1 -benzene complexes have been reported: a) R. A. Bartlett, H. Chen, P. P. Power, *Angew. Chem.* **1989**, *101*, 325; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 316; b) L. R. Falvello, J. Fornies, R. Navarro, V. Sicilia, M. Tomás, *Angew. Chem.* **1990**, *102*, 952; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 891; c) L. R. Falvello, J. Fornies, R. Navarro, V. Sicilia, M. Tomás, *J. Chem. Soc. Dalton Trans.* **1994**, 3143; d) P. Braunstein, U. Englert, G. E. Herberich, M. Neuschütz, *Angew. Chem.* **1995**, *107*, 1090; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1010.
- [14] $[\text{Pd}_2(\text{dppp})_2]^{2+}$ (dppp = 1,3-bis(diphenylphosphanyl)propane) has a similar *ipso*-phenyl coordination structure: P. H. M. Budzelaar, P. W. N. M. van Leeuwen, C. F. Roobeek, A. G. Orpen, *Organometallics* **1992**, *11*, 23.
- [15] For example, the η^1 -coordinated phenyl ring maintained its aromaticity ($\text{C-C } 1.361(7)\text{--}1.398(5)\text{ \AA}$) and planarity, whereby P1 also lies on the same plane. The C1-P1-Pd1 angle of $118.5(1)^\circ$ is in the usual range for coordinated phosphane ligands.
- [16] The only example of a triphenylphosphane bridge across trinuclear Pd-Pd-Pd was recently found in $[\text{Pd}_3(\mu_3\text{-}1\kappa\text{P:}2\kappa\text{C1,2:}3\kappa\text{C3,4-PPh}_3)_2(\text{PPh}_3)_2]^{2+}$: a) S. Kannan, A. J. James, P. R. Sharp, *J. Am. Chem. Soc.* **1998**, *120*, 215; $\mu\text{-}1\kappa\text{P:}\eta^1\text{-PPh}_3$ ($x = 2,4,6$) coordination was observed with other transition metals: b) G. B. Robertson, P. O. Whimp, *J. Organomet. Chem.* **1973**, *60*, C11; c) R. Luck, R. H. Morris, J. F. Sawyer, *Organometallics* **1984**, *3*, 1009; d) H.-F. Hsu, S. R. Wilson, J. R. Shapley, *Organometallics* **1997**, *16*, 4937; e) I. Ara, L. R. Falvello, J. Fornies, E. Lalinde, A. Martín, F. Martínez, M. T. Moreno, *Organometallics* **1997**, *16*, 5392.
- [17] The μ -butadiene ligand in the monobutadiene complex $[\text{Pd}_2(\mu\text{-}1,3\text{-butadiene})(\mu\text{-Cl})(\text{PPh}_3)_2]^{+4}$ is much less labile than that of **5**.
- [18] Products analogous to **2** were obtained when $p\text{-X-C}_6\text{H}_4\text{C}\equiv\text{CH}$ ($\text{X} = \text{H}, \text{Cl}$) were used (36–56% yield according to NMR spectroscopy; relatively low yields were partly a result of decomposition of the products). Inner alkynes such as $\text{PhC}\equiv\text{CPh}$ and $\text{PhC}\equiv\text{CMe}$ also reacted with **1** or **4**, but more complicated results were obtained under the reaction conditions of Equation (1).
- [19] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-124471 (**2**), -124472 (**3**), and -124473 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Evidence for an Equilibrium between an N-heterocyclic Carbene and Its Dimer in Solution**

F. Ekkehardt Hahn,* Lars Wittenbecher, Duc Le Van, and Roland Fröhlich

Dedicated to Professor Wolf-Peter Fehlhammer on the occasion of his 60th birthday

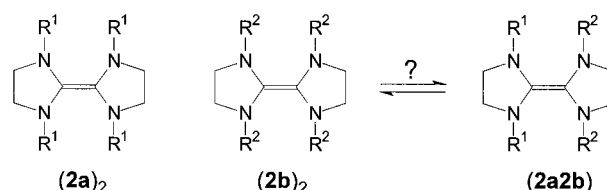
Shortly after the isolation of the first stable N-heterocyclic carbene **1** (derived from imidazole),^[1] the synthesis and characterization of saturated carbenes **2** (derived from imidazoline and postulated by Wanzlick more than 40 years ago^[2]) was successfully carried out.^[3] However, carbenes of type **2** were not prepared by the dissociation of electron-rich enetetramines (**2**)₂ as suggested by Wanzlick (Scheme 1); they were obtained by deprotonation of imidazolium salts^[3a] or by reduction of imidazoline-2-thiones.^[3b]



Scheme 1.

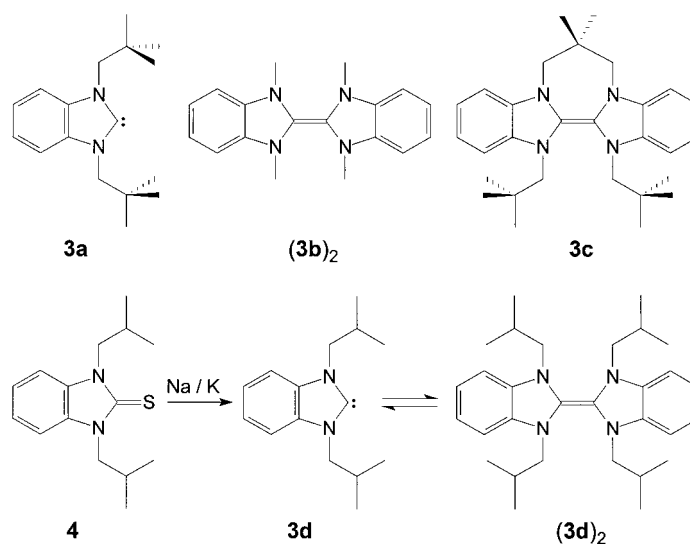
Numerous carbene complexes **2**=ML_n have been prepared by the reaction of enetetramines (**2**)₂ with coordinatively unsaturated transition metal complexes by cleavage of the C–C double bond.^[4] However, no evidence for the formation of free carbene intermediates **2** has been observed in these reactions.

On the contrary, investigations of the metathesis reaction between cyclic and acyclic enetetramines by Winberg et al.^[5] did not lead to the corresponding cross products. Lemal and co-workers^[6] showed that the metathesis reaction between (**2a**)₂ and (**2b**)₂ leading to mixed olefins **2a2b** (Scheme 2) only proceeds in the presence of electrophiles. On the basis of these findings the existence of the free carbenes and the equilibrium between **2** and (**2**)₂ postulated by Wanzlick was excluded. In addition, subsequent investigations by Lappert et al. led to the same result.^[7] In contrast to this, Denk et al. recently showed by NMR spectroscopy that metathesis products of type **2a2b** can be obtained from two different enetetramines at elevated temperatures.^[8]



Scheme 2. Metathesis experiment using two different enetetramines.

While the detection of these metathesis products indicates the existence of the “Wanzlick-equilibrium” between enetetramine and carbene, it can not be regarded as proof of such. Denk et al. have already pointed out that the formation of the metathesis product **2a2b** from (**2a**)₂ and (**2b**)₂ can also be explained by a [2+2] cycloaddition/cycloreversal.^[8] Only the detection of **2** and (**2**)₂ at the same time in the absence of any electrophile can be regarded as unequivocal proof for an equilibrium between carbene and enetetramine. In this paper we describe dibenzotetraazafulvalene (**3d**)₂ which at ambient temperature is already in equilibrium with the corresponding annelated N-heterocyclic carbene **3d**. In addition, we present the opening of the bridged compound **3c** to form a molybdenum dicarbene complex (Scheme 3).



Scheme 3.

We recently described the first stable annelated N-heterocyclic carbene **3a**.^[9] Despite the unsaturated nature of the N-heterocyclic ring, this carbene shows structural and spectroscopic properties which are typical for saturated carbenes of type **2**. In addition, the fast dimerization of the N-methylated derivative, which is sterically less crowded, to form (**3b**)₂^[9, 10] is characteristic for saturated N-heterocyclic carbenes. Unsaturated derivatives of type **1** seldom form enetetramines,^[1b] or only after suitable double bridging.^[11] Since derivatives of type **3** are stable as either N-heterocyclic carbenes, such as **3a**, or as enetetramines, such as (**3b**)₂, due to the bulky substituents at the nitrogen atoms,^[12] we felt this was a chance to find evidence of the sought-after equilibrium between carbene and enetetramine, by adaptation of the N substituents.

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[**] This project was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

The first clues towards a carbene/enetetramine equilibrium were provided by the reduction of a C₃-linked dithione to give the enetetramine **3c** (Scheme 3). Despite considerable steric bulk at the N-substituents the bridge leads to the immediate formation of the enetetramine **3c**. The analogous dimerization was not observed for **3a** or for a number of single-bridged imidazoline-2-ylidenes by Chen et al.^[11] The formation of enetetramine **3c** in solution was established by ¹³C NMR spectroscopy ($\delta(\text{C}2) = 119.5$) and in the solid state by X-ray diffraction analysis (Figure 1).^[19a] In the crystal the ene-

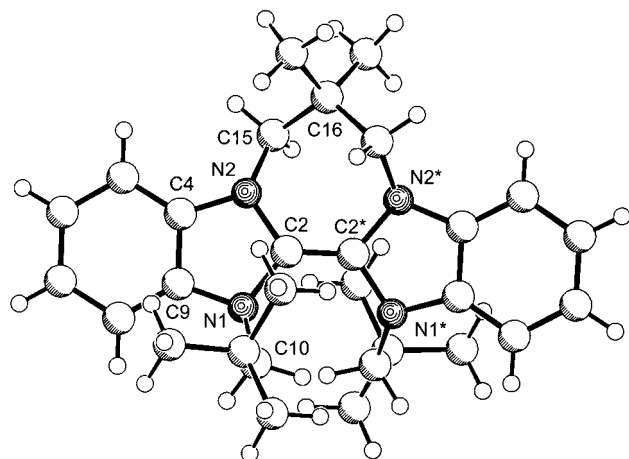


Figure 1. Molecular structure of **3c** in the crystal (SCHAKAL-depiction). Selected bond lengths [Å] and angles [°]: N1-C2 1.4212(11), N1-C9 1.3992(12), N1-C10 1.4640(12), N2-C2 1.4214(11), N2-C4 1.3981(12), C2-C2* 1.345(2), C4-C9 1.4001(14); C2-N1-C9 107.13(7), C2-N1-C10 121.40(8), C9-N1-C10 121.43(8), C2-N2-C4 107.17(7), N1-C2-N2 107.64(8), N1-C2-C2* 125.81(5), N2-C2-C2* 125.94(5). Symmetry (*) 1 - x, y, 1/2 - z.

tetramine **3c** is twisted along the C2-C2* axis. However, the N-C=C-N torsion angles differ, most likely due to the C₃ bridge (N2-C2-C2*-N2* 21.6(1)°, N1-C2-C2*-N1* 1.4(1)°). A similar twist of the double bond was found in the enetetramine (**3b**)₂, although the twist angles were nearly identical (16.8(1)° and 14.4(1)°, respectively).^[10] On the other hand, both molecules show a regular length for the double bond (**3c**: 1.345(2); (**3b**)₂ 1.344(4) Å). NMR spectroscopic studies did not indicate the dissociation of **3c** into two bridged N-heterocyclic carbenes.

The decrease of steric bulk at the N substituents leads to the formation of enetetramines after reduction of the corresponding thiones, even without a bridge. Such behavior has never previously been observed for unbridged Arduengo-type carbenes.^[11] The enetetramine (**3d**)₂ was obtained in 50% yield by reduction of the diisobutyl-substituted thione **4** with Na/K alloy in toluene. After workup (careful separation of K₂S), compound (**3d**)₂ can be collected from the solution as yellow crystals. The X-ray diffraction analysis^[19b] (Figure 2) again showed a twisted olefin (torsion angle N1-C2-C12-N2 15.7(2)°) with a regular C=C bond length of 1.332(5) Å.

While crystallization experiments with **3d** always resulted in the isolation of the enetetramine (**3d**)₂, ¹³C NMR spectroscopic investigations of the reaction mixture indicated the presence of both the carbene **3d** ($\delta(\text{C}2) = 227.8$, compare to **3a**^[9] $\delta(\text{C}2) = 231.5$) and the entetetramine (**3d**)₂ ($\delta(\text{C}2) = 119.0$,

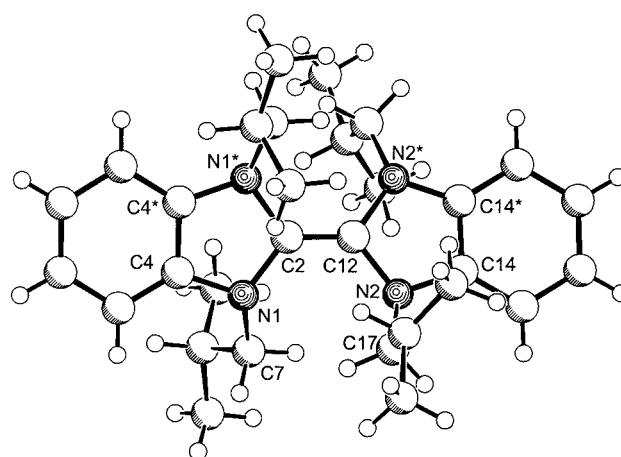


Figure 2. Molecular structure of (**3d**)₂ in the crystal (SCHAKAL-depiction). Selected bond lengths [Å] and angles [°]: N1-C2 1.439(3), N1-C4 1.405(4), N1-C7 1.476(4), N2-C12 1.432(3), N2-C14 1.384(4), N2-C17 1.480(4), C2-C12 1.332(5), C4-C4* 1.389(6), C14-C14* 1.393(6); C2-N1-C4 107.3(2), C2-N1-C7 122.2(2), C4-N1-C7 118.4(2), C12-N2-C14 108.0(2), C12-N2-C17 121.7(2), C14-N2-C17 118.3(2), N1-C2-N1* 107.0(3), N1-C2-C12 126.51(15), N2-C12-N2* 106.2(3), N2-C12-C2 126.9(2). Symmetry (*) y, x, -z.

compare to (**3b**)₂^[10] $\delta(\text{C}2) = 121.0$). This surprising result prompted us to start detailed NMR spectroscopic studies. Crystalline enetetramine (**3d**)₂ was dissolved in dry, deoxygenated [D₈]toluene and ¹H NMR spectra were recorded at intervals of one hour. The use of crystalline (**3d**)₂ and carefully purified toluene makes the presence of the electrophile (K₂S) very unlikely. The first spectrum (Figure 3), which

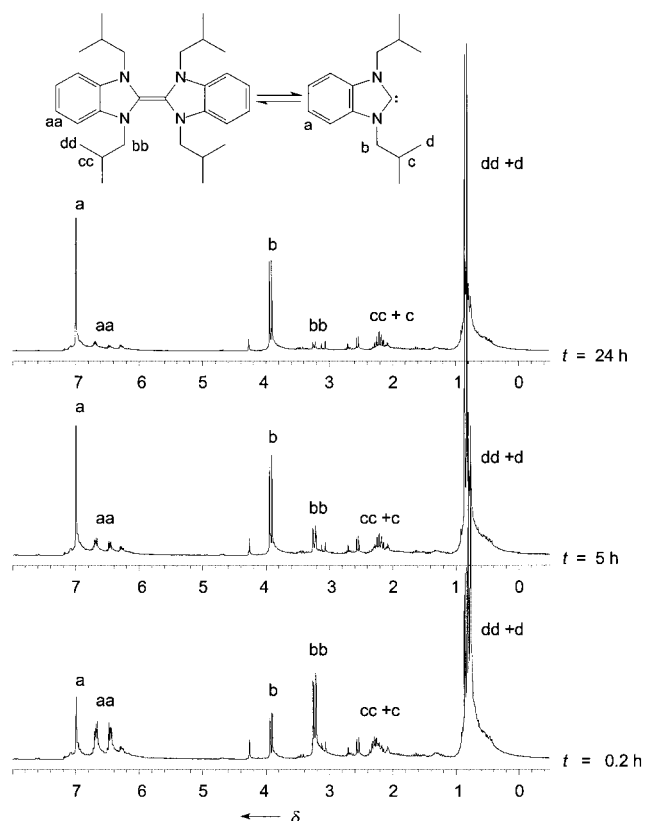


Figure 3. Time-resolved ¹H NMR spectra (200 MHz, [D₈]toluene) of (**3d**)₂ at 298 K.

is still dominated by resonance signals of the enetetramine (**3d**)₂ (bb: $\delta(\text{NCH}_2) = 3.23$, aa: $\delta(\text{Ar-H}) = 6.66$ and 6.48), already indicates the formation of carbene **3d** (b: $\delta(\text{NCH}_2) = 3.92$, a: $\delta(\text{Ar-H}) = 7.08$). The appearance of signals for **3d** in the first spectrum is attributed to the time elapsed between the preparation of the sample and the first data being acquired (0.2 h). With time, the intensities of the **3d** resonance signals increase and the intensities of (**3d**)₂ resonance signals decrease. After 24 h no more changes can be detected and the system equilibrates at a ratio of 90% **3d** and 10% (**3d**)₂. When the starting concentration of (**3d**)₂ is higher, the equilibrium establishes at a ratio of 85:15. Identical results were obtained from ¹³C NMR spectroscopy by the disappearance of the C2 resonance signal of the enetetramine at $\delta = 119.0$ and by the increase of the carbene C2 resonance signal at $\delta = 227.8$. However, the signal intensities in ¹³C NMR spectra did not allow a quantitative estimation of the equilibrium.

The simultaneous detection of **3d** and (**3d**)₂ by NMR spectroscopy in a solution prepared from pure (**3d**)₂ constituted evidence of the equilibrium between the N-heterocyclic carbene and the corresponding enetetramine as well as the dissociation of the enetetramine into two carbenes in a direct route, rather than the indirect route via the metathesis products. We are convinced that catalytically active electrophiles were absent under the reaction conditions specified.

The dissociation of the double bond in (**3d**)₂ at ambient temperature can be rationalized in terms of the binding model developed by Carter, Goddard, Malrieu, and Trinquier (CGMT Model^[13a]), which was also used by Chen^[13b] to discuss the weakness of the double bond in electron-rich olefins. In formal dimers of singlet carbenes **1–3** the strength of the C–C double bond can be approximated by the bond strength of a regular double bond (usually the (sp²–sp²) σ /(p–p) π -double bond of ethylene of $172 \text{ kcal mol}^{-1}$ ^[14]) minus the sum of the singlet–triplet energy gap for both carbene parts. The singlet–triplet energy gap amounts to approximately 85 kcal mol^{-1} ^[15] per “Arduengo” carbene of type **1**, which has been used to explain the weakness of the C=C bond in molecules of type (**1**)₂ and the difficulties in their preparation. The singlet–triplet gap is smaller for carbenes of type **2** due to the saturation of the N-heterocyclic ring; the enetetramines (**2**)₂ are readily formed but difficult to dissociate into carbenes.^[13b] Annulated N-heterocyclic carbenes of type **3** obviously have an intermediate singlet–triplet energy gap; the formation and dissociation of dibenzotetraazafulvalenes (**3**)₂ are primarily determined by the steric bulk of the N substituents. This behavior emphasizes the unusual properties of the carbenes of type **3**, which have the topology of unsaturated N-heterocyclic carbenes (type **1**) but show the reactivity of saturated derivatives (type **2**). However, the energy gap between the singlet and triplet states must also be considerable for carbenes of type **3**, as can be seen from the strong twist of the C–C double bond (N–C=C–N torsion angle $15.7(2)^\circ$; relative to torsion angles of $16.8(1)$ and $14.3(1)^\circ$ in (**3b**)₂^[10] and 6 and 8° in N-methylated (**2**)₂.^[3b]

Even so, **3c** is more sterically hindered than (**3d**)₂; opening of the C–C double bond in **3c** can not be observed under regular conditions, which we have attributed to the C₃ bridge.

However, in analogy to reactions already reported,^[4, 16] the dibenzotetraazafulvalene can be opened by coordinatively unsaturated transition metal complexes (acting as Lewis acids) to form a dicarbene complex. Treatment of **3c** with [Mo(nor)(CO)₄] (nor = norbornadiene) yields the dicarbene complex **5** after 1 h. The X-ray diffraction analysis^[19c] of **5** (Figure 4) shows an approximately octahedral complex. The

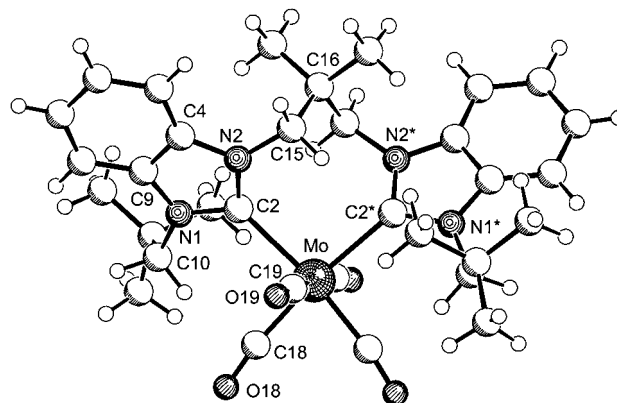


Figure 4. Molecular structure of **5** in the crystal (SCHAKAL depiction). Selected bond lengths [Å] and angles [°]: Mo–C2 2.234(3), Mo–C18 1.963(3), Mo–C19 2.035(3), N1–C2 1.385(4), N1–C9 1.387(4), N1–C10 1.452(4), N2–C2 1.367(4), N2–C4 1.392(3), N2–C15 1.462(3), C4–C9 1.372(5), C18–O18 1.160(3), C19–O19 1.135(4); C2–Mo–C2*, $95.77(14)$, C2–Mo–C18 $92.03(10)$, C2–Mo–C18* $170.98(10)$, C2–Mo–C19 $99.77(12)$, C2–Mo–C19* $82.51(12)$, C18–Mo–C18* $80.57(15)$, C18–Mo–C19 $91.72(12)$, C18–Mo–C19* $85.71(12)$, C18*–Mo–C19 $85.71(12)$, C18*–Mo–C19* $91.72(12)$, C19–Mo–C19* $176.6(2)$, C2–N1–C9 $111.4(3)$, C2–N1–C10 $124.7(3)$, C9–N1–C10 $123.8(3)$, C2–N2–C4 $112.3(2)$, C2–N2–C15 $124.7(2)$, C4–N2–C15 $122.4(2)$, N1–C2–N2 $103.3(2)$, Mo–C18–O18 $173.1(2)$, Mo–C9–O19 $174.1(3)$. Symmetry (*) $1/2 - y, 1/2 - x, 1/2 - z$.

Mo–C(carbene) bond length ($2.324(3) \text{ Å}$) is, within experimental error, the same as the equivalent bond length in *fac*-[Mo(Im)₃(CO)₃] (Im = *N,N'*-dimethylimidazolin-2-ylidene).^[17] The C₃ bridge between the two carbene donors in **5** allows a C(carbene)–Mo–C(carbene) bond angle of $95.77(14)^\circ$ in the octahedral complex **5**, whereas the C₁ bridge between two benzimidazolin-2-ylidene groups, at least in the PdI₂ complex, leads to an acute C–Pd–C-angle of $83.7(3)^\circ$.^[18] The excellent donor ability of the carbene groups in **5** is also illustrated by the different Mo–CO bond lengths for the CO ligands which are *cis* and *trans* to the carbene ligands ($2.035(3)$ and $1.963(3) \text{ Å}$).^[20]

Experimental Section

All work was performed in an atmosphere of dry argon with thoroughly dried reagents and solvents. All of the carbenes and dibenzotetraazafulvalenes were obtained by reduction of the corresponding benzimidazole-2-thiones^[9] with Na/K alloy in toluene. ¹H and ¹³C NMR spectra were obtained at 200 or 50.3 MHz, respectively.

4: yellow oil. ¹H NMR ([D₈]THF): $\delta = 6.98$ (m, 4H; Ar–H), 3.88 (d, 4H; NCH₂), 2.26 (m, 2H; CHMe₂), 0.73 (d, 12H; CH₃); ¹³C NMR ([D₈]THF): $\delta = 169.3$ (C=S), 131.6 , 121.8 , 108.6 (Ar–C), 51.1 (NCH₂), 27.0 (CHMe₂), 19.5 (CH₃).

Mixture of **3d** and (**3d**)₂: solid yellow crystals of (**3d**)₂ (m.p. 32°C); ¹H NMR ([D₈]toluene): $\delta = 7.08$ (m, 4H; Ar–H **3d**), 6.66 (m, 4H; Ar–H (**3d**)₂), 6.48 (m, 4H; Ar–H (**3d**)₂), 3.92 (d, 4H; NCH₂ **3d**), 3.23 (d, 8H; NCH₂ (**3d**)₂), 2.33 (m, 2H; CHMe₂ **3d**), 2.36 (m, 4H; CHMe₂ (**3d**)₂), 0.80

(d, 12H; CH₃ **3d**), 0.89 (d, 24H; CH₃ (**3d**)₂); ¹³C NMR ([D₈]toluene): δ = 227.8 (carbene-C **3d**), 119.0 (N₂C=CN₂ (**3d**)₂), 135.8, 121.2, 110.3 (Ar-C **3d**), 142.3, 120.2, 110.1 (Ar-C (**3d**)₂), 55.6 (NCH₂ **3d**), 55.8 (NCH₂ (**3d**)₂), 29.4 (CHMe₂ **3d**), 26.1 (CHMe₂ **3d** = **3d**), 20.5 (CH₃ **3d**), 20.9 (CH₃ (**3d**)₂).

3c: Yellow crystals (m.p. 37 °C); ¹H NMR (C₆D₆): δ = 7.18 (m, 4H; Ar-H), 6.08 (m, 4H; Ar-H), 4.52 (s, br, 4H; NCH₂), 4.11 (s, 4H; NCH₂), 0.97 (s, 18H; C(CH₃)₃), 0.81 (s, 6H; C(CH₃)₂); ¹³C NMR (C₆D₆): δ = 119.5 (N₂C=CN₂), 141.9, 141.8, 120.1, 119.4, 108.8, 105.8 (Ar-C), 58.6 (NCH₂), 22.4 (NCH₂), 36.7 (CMe₃), 33.6 (CMe₂), 29.4 (C(CH₃)₃), 25.0 (C(CH₃)₂).

5: A solution of [Mo(nor)(CO)₄] (300 mg, 1.0 mmol) was added dropwise to a solution of **3c** (336 mg, 0.80 mmol) in THF (30 mL) under argon. The yellow reaction solution was stirred for 12 h at ambient temperature. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (3 mL). This solution was purified by chromatography (SiO₂, hexane/ethyl acetate 5/1) and the product solution was reduced in volume, yielding yellow crystals of **5**. Yield 402 mg (80 %). ¹H NMR (CDCl₃): δ = 7.53–7.22 (m, 8H; Ar-H), 5.55, 4.93, 4.32, 3.91 (d, 2H; NCH₂), 1.10 (s, 18H; C(CH₃)₃), 0.88 (s, 6; C(CH₃)₂); ¹³C NMR (CDCl₃): δ = 219.9 (*trans*-CO), 210.0 (*cis*-CO), 208.2 (carbene-C), 136.4, 135.9, 122.6, 122.2, 113.2, 110.8 (Ar-C), 59.1, 52.4 (NCH₂), 41.0 (CMe₂), 35.0 (CMe₃), 29.6 (C(CH₃)₃), 24.8 (C(CH₃)₂).

Received: June 7, 1999

Revised: August 18, 1999 [Z13519]

- [1] a) A. J. Arduengo, III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361; b) review: W. A. Herrmann, C. Köcher, *Angew. Chem.* **1997**, *109*, 2256; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162.
- [2] H.-W. Wanzlick, *Angew. Chem.* **1962**, *74*, 129; *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 75.
- [3] a) A. J. Arduengo, III, J. R. Goerlich, W. J. Marshall, *J. Am. Chem. Soc.* **1995**, *117*, 11027; b) M. K. Denk, A. Thadani, K. Hatano, A. J. Lough, *Angew. Chem.* **1997**, *109*, 2719; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2607.
- [4] M. F. Lappert, *J. Organomet. Chem.* **1988**, *358*, 185, and references therein.
- [5] H. E. Winberg, J. E. Carnahan, D. D. Coffman, M. Brown, *J. Am. Chem. Soc.* **1965**, *87*, 2055.
- [6] D. M. Lemal, R. A. Lovald, K. I. Kawano, *J. Am. Chem. Soc.* **1964**, *86*, 2518.
- [7] D. J. Cardin, M. J. Doyle, M. F. Lappert, *J. Chem. Soc. Chem. Commun.* **1972**, 927.
- [8] M. K. Denk, K. Hatano, M. Ma, *Tetrahedron Lett.* **1999**, *40*, 2057.
- [9] F. E. Hahn, L. Wittenbecher, R. Boese, D. Bläser, *Chem. Eur. J.* **1999**, *5*, 1931.
- [10] E. Cetinkaya, P. B. Hitchcock, H. Küçükbay, M. F. Lappert, S. Al-Juaid, *J. Organomet. Chem.* **1994**, *481*, 89.
- [11] a) T. A. Taton, P. Chen, *Angew. Chem.* **1996**, *108*, 1098; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1011; b) Z. Shi, R. P. Thummel, *J. Org. Chem.* **1995**, *60*, 5935.
- [12] Imidazole-based carbenes with sterically demanding N-substituents are also stable as monomers, whereas sterically less-demanding N-substituents lead to enetetramines.^[3b]
- [13] a) M. Driess, H. Grützmacher, *Angew. Chem.* **1996**, *108*, 908; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 828; b) P. Chen, *Adv. Carbene Chem.* **1998**, *2*, 45.
- [14] S. I. Miller, *J. Chem. Educ.* **1978**, *55*, 778.
- [15] C. Heinemann, W. Thiel, *Chem. Phys. Lett.* **1994**, *217*, 11; D. A. Dixon, A. J. Arduengo, III, *J. Chem. Phys.* **1991**, *95*, 4180.
- [16] Z. Shi, R. P. Thummel, *Tetrahedron Lett.* **1995**, *36*, 2741.
- [17] K. Öfele, W. A. Herrmann, D. Mihailos, M. Elison, E. Herdtweck, T. Priemer, P. Kiprof, *J. Organomet. Chem.* **1995**, *498*, 1.
- [18] F. E. Hahn, M. Foth, *J. Organomet. Chem.* **1999**, *585*, 241.
- [19] X-ray structure analysis: All data sets were collected on a Enraf-Nonius CAD4 or a Nonius Kappa-CCD diffractometer with a rotating anode FR591 (Nonius) used as a radiation source. The following programs were used: EXPRESS and COLLECT for data collection; MolEN and Denzo-SMN for data reduction; SORTAV for absorption correction of CCD-Data; SHELXS-97 for structure solution; SHELXL-97 for structure refinement; and SCHAKAL-92 for molecular graphics. Crystallographic data (excluding structure fac-

tors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-124994 (**3c**), -124995 (**3d**)₂ and -124996 (**5**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033, e-mail: deposit@ccdc.cam.ac.uk). a) **3c** (C₂₉H₄₀N₄): *M*_r = 444.65, colorless crystals 0.30 × 0.30 × 0.15 mm, *a* = 19.155(1), *b* = 0.534(1), *c* = 15.439(1) Å, β = 123.92(1)°, *V* = 1585.1(3) Å³, ρ_{calcd} = 1.142 g cm⁻³, μ = 0.68 cm⁻¹, empirical absorption correction (0.980 ≤ *T* ≤ 0.990), *Z* = 4 (C16 and midpoint of the C2–C2* bond on a twofold axis), monoclinic, space group *C2/c* (No. 15), λ = 0.71073 Å, *T* = 198 K, ω and φ scans, 9982 measured reflections (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.71 Å⁻¹, 3884 unique and 3070 observed reflections [*I* ≥ 2σ(*I*)], 184 refined parameters, *R* = 0.047, *wR*² = 0.117, max. (min.) residual electron density 0.28 (–0.17) e Å⁻³, positional disorder of the bridging atoms C15, C16 and C17, hydrogen atoms calculated and refined as riding atoms. b) **3d** (C₃₀H₄₄N₄): *M*_r = 460.69, yellow crystals, 0.30 × 0.20 × 0.10 mm, *a* = 10.558(3), *c* = 24.577(7) Å, *V* = 2739.6(13) Å³, ρ_{calcd} = 1.117 g cm⁻³, μ = 4.99 cm⁻¹, no absorption correction (0.865 ≤ *T* ≤ 0.952), *Z* = 4 (C2–C12 bond on twofold axis), tetragonal, space group *P4₂/2₁2* (No. 96), λ = 1.54178 Å, *T* = 223 K, ω/2θ scans, 3162 measured reflections (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.62 Å⁻¹, 2802 unique and 1953 observed reflections [*I* ≥ 2σ(*I*)], 160 refined parameters, *R* = 0.060, *wR*² = 0.160, max. (min.) residual electron density 0.32 (–0.27) e Å⁻³, Flack parameter 0.0(11), hydrogen atoms calculated and refined as riding atoms. c) **5** (C₃₃H₄₀N₄O₄Mo): *M*_r = 652.63, yellow crystals, 0.35 × 0.30 × 0.25 mm, *a* = 17.637(1), *c* = 20.517(1) Å, *V* = 6382.1(6) Å³, ρ_{calcd} = 1.358 g cm⁻³, μ = 4.53 cm⁻¹, empirical absorption correction (0.858 ≤ *T* ≤ 0.895), *Z* = 8 (C16 and Mo on a twofold axis), tetragonal, space group *P4₂/nbc* (No. 133), λ = 0.71073 Å, *T* = 198 K, ω and φ-scans, 17302 measured reflections (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.71 Å⁻¹, 4888 unique and 3515 observed reflections [*I* ≥ 2σ(*I*)], 195 refined parameters, *R* = 0.055, *wR*² = 0.126, max. (min.) residual electron density 0.50 (–0.76) e Å⁻³, hydrogen atom positions calculated and refined as riding atoms.

- [20] Note added in proof (December 21, 1999): The thermal dissociation of sterically less-demanding dibenzotetraazafulvalenes was recently demonstrated by Lemal et al. on the basis of NMR data. See Y. Liu, P. E. Linder, D. M. Lemal, *J. Am. Chem. Soc.* **1999**, *121*, 10626.

Chromophore Alignment in a Chiral Host Provides a Sensitive Test for the Orientation – Intensity Rule of Induced Circular Dichroism**

Xiangyang Zhang and Werner M. Nau*

Circular dichroism is an essential spectral property for probing chirality.^[1,2] An interesting effect arises when an achiral guest chromophore is complexed in a chiral host. The guest becomes optically active, a phenomenon referred to as “induced” circular dichroism (ICD).^[3–5] The spectroscopic information resulting from this interaction is unique, since sign and magnitude of the ICD signal depend on the relative orientation of the chromophore in the host. Harata et al. have

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[**] This work was supported by the Swiss National Science Foundation and the Fonds der Chemischen Industrie. We thank Dr. G. Scherer, Institute of Organic Chemistry, as well as A. Merz and T. Schultheiss, Institute of Biophysical Chemistry, for assistance with the NMR-ROESY and ICD measurements.

developed a rule for the inclusion complexes of cone-shaped chiral hosts like cyclodextrins (CDs).^[6] According to this rule, a positive ICD signal arises when the electric transition dipole moment is aligned parallel to the axis of the host, but the signal is negative and half as strong when it is oriented in a perpendicular manner (Figure 1).^[2, 5] More recently, a similar

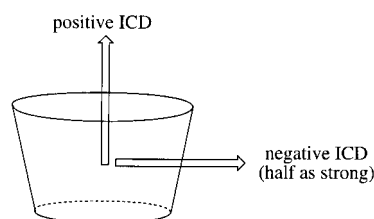
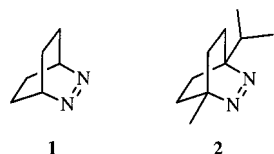


Figure 1. Dependence of the sign and intensity of the induced circular dichroism (ICD) effect on the direction of the electric transition dipole moment of the guest in CD inclusion complexes.

rule has also been developed for ICD effects outside the host cavity,^[7] where the sign of the ICD signal is opposite to that arising inside the host cavity, and a refined computational treatment for ICD effects has been introduced.^[8, 9]

Knowledge of the relative orientation of the guest in host–guest complexes, in particular when weak van der Waals interactions operate,^[4] is important for the development of functional supramolecular materials, such as those for catalytic or analytical purposes. Crystal structure determination may provide accurate data for CD complexes in the solid state.^[10, 11] Structural information for host–guest complexes in solution, however, is accessible only in limiting cases. Although recent advances in the interpretation of NMR data open new opportunities along this line,^[12] relative orientations of host–guest complexes have often been assigned by ICD effects.^[5] Harata's rule, which provides a qualitative basis for structural interpretations of ICD effects, has been examined by shifting the electronic transitions in benzene and naphthalene through substituents^[6, 13–16] while maintaining the (axial) orientation of the guest. These sophisticated “photo-physical tests” have provided strong support for the rule.

The simplest and perhaps most intuitive test of Harata's rule would involve a flip of a chromophore within the chiral CD cavity. Such a change of the alignment of the same chromophore within the same host from parallel to perpendicular should not only invert the sign of the ICD signal, but also provide a promising test for the predicted strength of the



ICD effect (see Figure 1). This “structural test” has not been performed to our knowledge. Hence, our present finding of a weaker and inverted ICD effect upon going from the β -CD complex of azoalkane **1** to that of the sterically modified derivative **2** should be of interest. Variations in the sign of the ICD effect have been previously observed by using different hosts, for example, β -CD and γ -CD.^[17, 18] However, the required deep inclusion, shown by Figure 1,^[6, 7] has not been experimentally established in these studies. For azoalkanes **1** and **2**, complete immersion in the CD cavity can be proven by NMR measurements.

Initial evidence for 1:1 complexation of azoalkane **1** by β -CD was obtained in the course of a recent fluorescence study.^[19] Azoalkane **1** and the derivative **2** exhibit high binding constants with β -CD in water (both ca. 1000 M^{-1}).^[20] The mode of association has now been established by means of NMR 2D-ROESY spectra. These revealed selective NOE enhancements between both the inner CD protons (H-3 and H-5) and all the protons of azoalkanes **1** and **2**. This provides evidence for the formation of a deep inclusion complex. The protons which displayed intermolecular cross peaks in the ROESY spectra were also the ones which exhibited chemically induced NMR shifts (CIS). Interestingly, the CIS values of the guest molecules provided a first indication for different modes of inclusion of azoalkanes **1** and **2**. Namely, the CIS values for the comparable *syn* and *anti* protons of azoalkane **2** were significantly smaller than those for **1** and, strikingly, those for the *syn* protons had opposite signs (Figure 2).

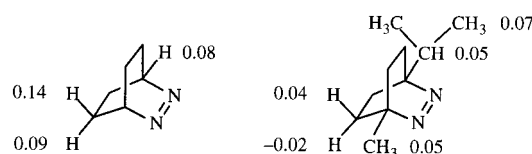


Figure 2. CIS values for inclusion of azoalkanes **1** and **2** into β -CD.

Further insight into the specific modes of inclusion in β -CD was obtained by force-field calculations.^[21] Azoalkane **1** has a nearly spherical shape of about $5\text{ \AA}$ diameter, which renders several modes of inclusion in the β -CD cavity (diameter range $6\text{--}6.5\text{ \AA}$) feasible. AMBER calculations produced four principal conformations for azoalkane **1** in β -CD, which can be referred to as lateral, frontal, apical, and basal inclusions (Figure 3a). The apical inclusion had the lowest potential energy, but the energetic difference to the lateral and basal conformation was small (within 1.5 kcal mol^{-1}). Only the frontal inclusion appeared to be significantly disfavored by 3.1 kcal mol^{-1} . Simulations using molecular dynamics^[21] retained the four principal conformations. In contrast, the selection of MM+ as an alternative force field caused the energy minima of the basal and frontal inclusions to disappear, leaving only the apical and lateral conformations as viable geometries, with the latter only 1.0 kcal mol^{-1} higher in energy.

The dimension of azoalkane **2** along its long axis (about $8\text{ \AA}$) exceeds the cavity diameter of β -CD significantly. This renders only the frontal mode of inclusion feasible for **2**, and accordingly a strong preference for this conformation ($>10\text{ kcal mol}^{-1}$) was obtained by the AMBER calculations. A marginal preference (0.6 kcal mol^{-1}) for the conformation with the larger isopropyl group penetrating into the cavity was found (Figure 3b).

More definitive evidence for the inclusion geometries was obtained from the ICD signals of the characteristic $\text{azo } n \rightarrow \pi^*$ absorption in the near UV. Although azoalkanes **1** and **2** showed very similar absorption maxima (ca. 375 nm) and extinction coefficients (ca. $55\text{ M}^{-1}\text{ cm}^{-1}$) in their β -CD complexes, they gave rise to opposite ICD effects, namely positive

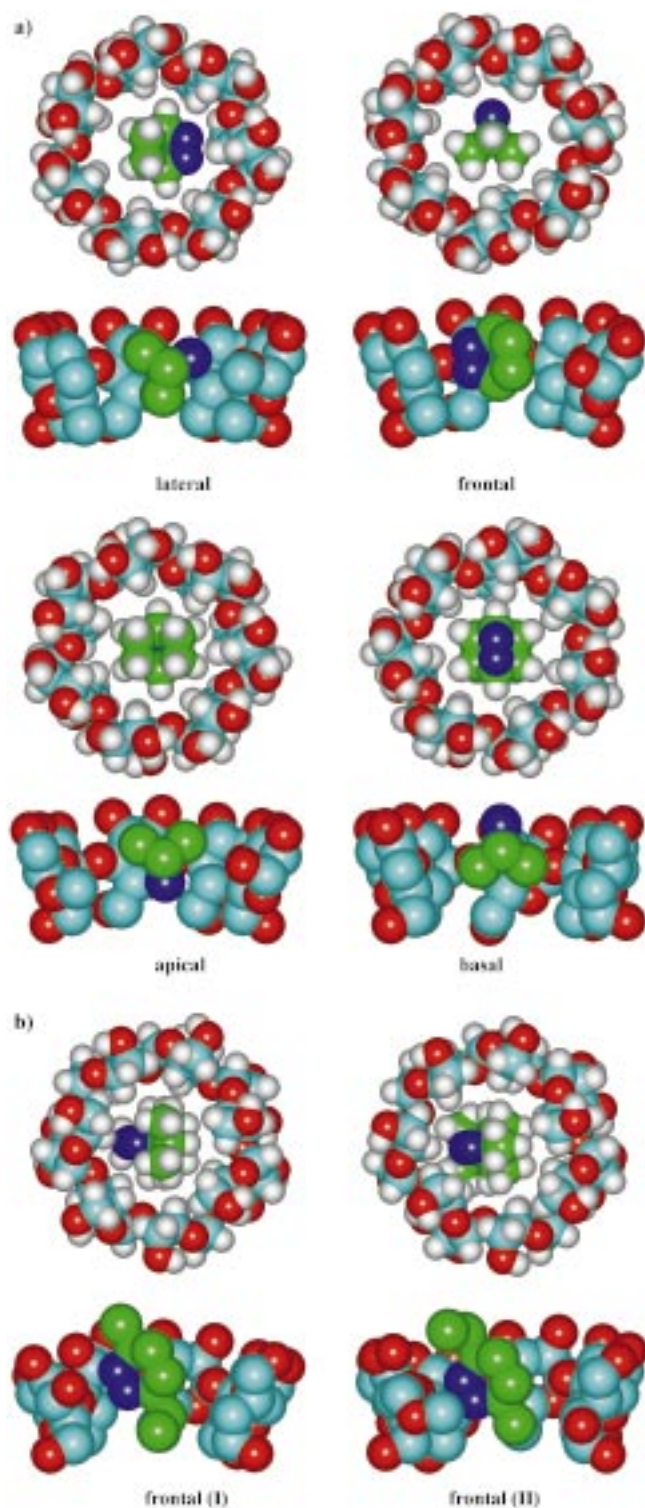


Figure 3. AMBER-optimized β -CD inclusion complexes. a) Azoalkane **1**: Upper views are from the wider rim, and the lower views are intersections from the side (hydrogen atoms removed for clarity); b) azoalkane **2**: Upper views are from the narrower rim, and the lower views are intersections from the side (hydrogen atoms removed for clarity). Shown for (b) are the two frontal modes of inclusion with the isopropyl (I) and the methyl group (II) entering the cavity.

for **1** and negative as well as significantly weaker for **2** (Figure 4). Since both azoalkanes display similar binding constants and form deep inclusion complexes, as corroborated

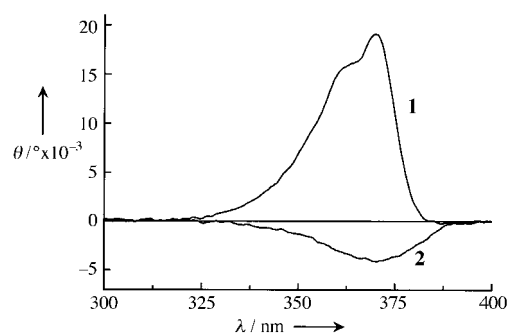


Figure 4. ICD spectra for azoalkanes **1** and **2** (4.0 mM) in the presence of β -CD (12.0 mM) in D_2O .

by the ROESY spectra, this marked variation can only be interpreted in terms of different modes of inclusion. This interpretation is supported by the results from molecular modeling (Figure 3) and the observed CIS values (Figure 2).

According to Harata's rule, a positive ICD effect is expected for a parallel alignment of the electric transition dipole moment relative to the CD axis, while a negative effect should result from a perpendicular alignment (Figure 1). The $n \rightarrow \pi^*$ transition moment of *cis*-azoalkanes points along the p orbitals of the azo π -system. This direction can be readily determined by simple multiplication of the relevant signs of the lobes of the pertinent n_- and π^* orbitals as illustrated in Figure 5. Consequently, one expects a negative ICD effect for

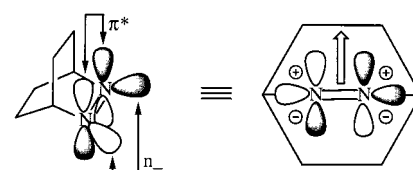


Figure 5. Determination of the electric transition dipole moment for the lowest $n \rightarrow \pi^*$ electronic transition of azoalkanes **1** and **2** by formal multiplication of the orbital lobes of the involved n_- and π^* orbitals. The vector pointing from the resulting region of electron deficiency $\ominus$ to that of electron excess $\oplus$ provides the direction of the electric transition dipole moment.

the apical, basal, as well as the frontal inclusion modes (Figure 1) due to the perpendicular alignment of the transition moment. The negative ICD signal for azoalkane **2** is, thus, in agreement with the frontal inclusion, which is the only sterically feasible one. The positive ICD signal for azoalkane **1** must arise from the lateral conformation, which is the only one to ensure a nearly parallel orientation of the transition moment. Also noteworthy is that the intensity of the ICD signal for azoalkane **1** is significantly stronger than that for **2**, as expected from Harata's rule. However, although the chromophore characteristics remain the same, the experimental effect is more pronounced than that predicted by theory (a factor of four to five versus two).

In summary, this work provides an example for a conformational assignment of host–guest complexes in solution. The ICD effects predicted by Harata's rule are actually observed for azoalkanes **1** and **2**, for which two different modes of inclusion in a CD apply. We consider these results as a

sensitive test case of Harata's rule, since the transition moment of the localized azo chromophore is insensitive to the alkyl substitution pattern. The present "structural test" is distinct, compared to earlier studies,^[6, 13–16] since a whole chromophore is actually flipped around in the chiral cavity. Most importantly and in contrast to related studies,^[17, 18] different orientations of the same chromophore (–N=N–) could be explored within the same host (β -CD).

Experimental Section

β -CD (Fluka) and >99.8% D₂O (Glaser AG, Basel, Switzerland) were used as received. All experiments were performed at ambient temperature in D₂O for consistency with the NMR measurements. The azoalkane **2** was synthesized by cycloaddition of α -terpinene with *N*-methyltriazolinedione (both from Aldrich), subsequent hydrogenation, hydrolysis, and oxidation, in analogy to literature methods for the known azoalkane **1**.^[22]

2: M.p. 34–35 °C; UV (D₂O): $\lambda_{\text{max}} = 373 \text{ nm}$ ($\epsilon = 54 \text{ cm}^{-1}\text{M}^{-1}$); ¹H NMR (300 MHz, D₂O): $\delta = 2.43$ (sept, 1 H, $J = 6.9 \text{ Hz}$), 1.74 (s, 3 H), 1.54–1.51 (m, 4 H, *anti*), 1.24 (d, 6 H, 6.9 Hz), 1.11–1.08 (m, 4 H, *syn*); ¹³C NMR (75 MHz, D₂O): $\delta = 69.03, 63.75, 34.50, 28.74, 25.33, 23.70, 17.81$; GC–MS [column SE-30, 70 °C (for 10 min)–10 K min^{–1}–270 °C (for 10 min)]: 13.82 min; MS: 166.16 (M^+), 138 ($M^+ - N_2$), 123 (138 – CH₃), 109, 95 (138 – iC₃H₇), 81, 67, 55, 41; elemental analysis calcd for C₁₀H₁₈N₂ (%): C 72.24, H 10.91, N 16.85; found: C 72.13, H 10.68, N 17.08.

ICD spectra were recorded with a Jasco J-720 circular dichrograph (0.2 nm resolution, 25 accumulations, 1 cm cell). Blank measurements of D₂O and solutions of β -CD, **1**, and **2** provided no ICD effects in the region examined. The ¹H NMR (300 MHz) CIS values were determined under conditions of nearly quantitative (> 90%) complexation (2.5 mM azoalkane, 8.8 mM β -CD). 2D-ROESY spectra (600 MHz) were obtained for solutions of 9.6 mM azoalkane and 4.6 mM β -CD in D₂O.

Received: July 30, 1999 [Z13807]

- [1] K. Nakanishi, N. Berova, R. W. Woody, *Circular Dichroism: Principles and Applications*, VCH, New York, **1994**.
- [2] A. Rodger, B. Nordén, *Circular Dichroism and Linear Dichroism*, Oxford University Press, New York, **1997**.
- [3] K. A. Connors, *Chem. Rev.* **1997**, 97, 1325–1357.
- [4] M. V. Rekharsky, Y. Inoue, *Chem. Rev.* **1998**, 98, 1875–1917.
- [5] Y. A. Zhdanov, Y. E. Alekseev, E. V. Kompantseva, E. N. Vergeichik, *Russ. Chem. Rev.* **1992**, 61, 563–575.
- [6] K. Harata, H. Uedaira, *Bull. Chem. Soc. Jpn.* **1975**, 48, 375–378.
- [7] M. Kodaka, *J. Am. Chem. Soc.* **1993**, 115, 3702–3705.
- [8] G. Marconi, S. Monti, B. Mayer, G. Köhler, *J. Phys. Chem.* **1995**, 99, 3943–3950.
- [9] R. S. Murphy, T. C. Barros, J. Barnes, B. Mayer, G. Marconi, C. Bohne, *J. Phys. Chem. A* **1999**, 103, 137–146.
- [10] K. Harata, *Chem. Rev.* **1998**, 98, 1803–1827.
- [11] W. Saenger, *Inclusion Compounds*, Vol. 2 (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol), Academic Press, London, **1984**.
- [12] H.-J. Schneider, F. Hacket, V. Rüdiger, *Chem. Rev.* **1998**, 98, 1755–1785.
- [13] H. Shimizu, A. Kaito, M. Hatano, *Bull. Chem. Soc. Jpn.* **1979**, 52, 2678–2684.
- [14] H. Shimizu, A. Kaito, M. Hatano, *Bull. Chem. Soc. Jpn.* **1981**, 54, 513–519.
- [15] M. Kamiya, S. Mitsuhashi, M. Makino, H. Yoshioka, *J. Phys. Chem.* **1992**, 96, 95–99.
- [16] M. Kodaka, *J. Phys. Chem. A* **1998**, 102, 8101–8103.
- [17] D. Krois, U. H. Brinker, *J. Am. Chem. Soc.* **1998**, 120, 11627–11632.
- [18] N. Kobayashi, M. Opallo, *J. Chem. Soc. Chem. Commun.* **1990**, 477–479.
- [19] W. M. Nau, X. Zhang, *J. Am. Chem. Soc.* **1999**, 121, 8022–8032.
- [20] The presence of a fluorescent chromophore in azoalkanes **1** and **2** and their water solubility allow the determination of binding constants (unit M^{–1}) with β -CD by several independent techniques. Values of

1100 ± 300, 900 ± 100, 700 ± 300 (ref. [19]), and 920 ± 100 (this work) for azoalkane **1**, and 900 ± 150, 1070 ± 60, 750 ± 200, and 830 ± 150 (all this work) for azoalkane **2** were determined from NMR, UV, fluorescence, and ICD spectroscopy, respectively. The quantitative analysis of these data corroborates the formation of 1:1 complexes.

- [21] Calculations were carried out with HyperChem 5.0 (Hypercube Inc.). The AMBER-S parameterization for saccharides was employed, see: S. W. Homans, *Biochemistry* **1990**, 29, 9110–9118. The rigid azoalkanes **1** and **2** were kept frozen in the AM1-optimized geometries. Molecular dynamics calculations were performed according to an established protocol for simulated annealing, see: G. Fronza, A. Mele, E. Redenti, P. Ventura, *J. Org. Chem.* **1996**, 61, 909–914.
- [22] P. S. Engel, D. E. Keys, A. Kitamura, *J. Am. Chem. Soc.* **1985**, 107, 4964–4975.

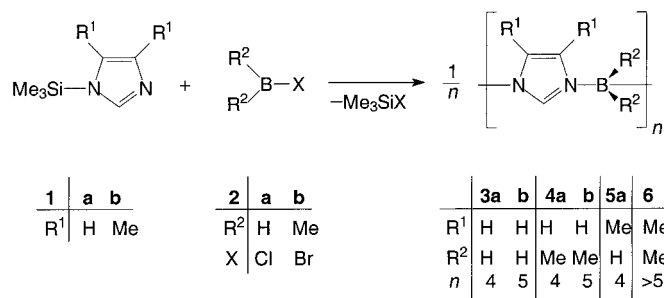
Macrocyclic Imidazolyboranes**

Andre Weiss, Hans Pritzkow, and Walter Siebert*

Dedicated to Professor Gerhard Fritz
on the occasion of his 80th birthday

Polymeric structures have been described for 1-imidazolyldiethylborane^[1a] and 1-imidazolyldiphenylborane,^[1b] in which a chainlike arrangement results from intermolecular N→B donor/acceptor interactions. An analogous behavior is observed in the cyanoborane (NC–BH₂)_n synthesized from NaBH₃CN and HCl.^[2] Besides polymeric compounds cyclic cyanoboranes were found consisting of four to ten monomers and showing a maximum of product distribution at $n = 5$. In the following we report on macrocyclic imidazolyboranes.

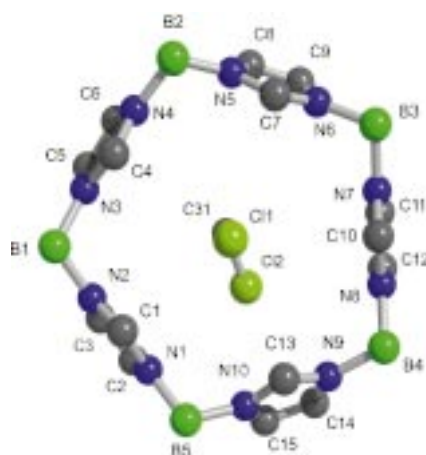
Initial evidence for the formation of macrocyclic imidazolyboranes occurred in an attempt to prepare bis(3-borane-imidazoly)boranes from 1-trimethylsilyl-3-borane-imidazole and RBCl₂ (R = *NiPr*₂, C₆H₅). Astonishingly, the mass spectra of the products contained a signal group around m/z 319 and indicated tetrameric imidazolyborane **3a**. Therefore we allowed 1-trimethylsilylimidazole (**1a**) to react with the chloroborane **2a** under high dilution and obtained a mixture of oligomeric imidazolyboranes.



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**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 247).

The mass spectrum of the reaction product shows the molecular ions from the monomer to the pentamer, and the GC-MS analysis confirms the formation of tetrameric **3a** and pentameric **3b** in a ratio of 2.3:1 and excludes the appearance of the units from $n = 1-3$; the corresponding signals in the mass spectrum indicate the fragment ions of higher membered species. After separation of the two macrocycles by column chromatography we obtained crystals of **3b** suitable for X-ray structure analysis^[3] from a saturated solution in CH_2Cl_2 . Compound **3b** displays a funnellike conformation (Figure 1).



173 (58) $[\text{C}_6\text{H}_{12}\text{B}_3\text{N}_4]^+$, 93 (90) $[\text{C}_3\text{H}_7\text{B}_2\text{N}_2]^+$; ^1H NMR (200 MHz, CD_2Cl_2): $\delta = 6.95$ (s, 2 H, 4,5-H), 7.56 (s, 1 H, 2-H); ^{13}C NMR (50 MHz, CD_2Cl_2): $\delta = 124.6$ (s, C-4,5), 140.0 (s, C-2); ^{11}B NMR (64 MHz, CD_2Cl_2): $\delta = -9.5$ (s).

Tetrameric 1-imidazolylmethylborane **4a**: The reaction was analogous to that of **3a**, **b**, but with CH_2Cl_2 instead of THF. Yield: 97% (contains 5% **4b**).

Tetrameric 1-(4,5-dimethylimidazolyl)borane **5a**: A BH_3Cl solution (40 mL of a 0.45 M solution in THF) was added dropwise to a stirred solution of **1b** (3.02 g, 17.9 mmol) in THF (150 mL) over 4 h at 0°C . The workup procedure was analogous to that of **3a**, **b** and gave colorless **5a** (1.65 g, 85%). EI-MS: m/z (%): 431 (55) $[\text{M}_4 - \text{H}]^+$, 337 (8) $[\text{C}_{15}\text{H}_{20}\text{B}_4\text{N}_6]^+$, 229 (60) $[\text{C}_{10}\text{H}_{20}\text{B}_3\text{N}_4]^+$, 216 (28) $[\text{M}_2]^+$, 203 (12) $[\text{C}_{10}\text{H}_{16}\text{BN}_4]^+$, 121 (100) $[\text{C}_5\text{H}_{11}\text{B}_2\text{N}_2]^+$, 108 (29) $[\text{M}]^+$; ^1H NMR (200 MHz, CD_2Cl_2): $\delta = 2.12$ (s, 6 H, CH_3), 6.64 (s, 1 H, 2-H); ^{13}C NMR (50 MHz, CD_2Cl_2): $\delta = 8.2$ (s, CH_3), 128.1 (s, C-4,5), 135.3 (s, C-2); ^{11}B NMR (64 MHz, CD_2Cl_2): $\delta = -11.8$ (s, br.).

Received: August 16, 1999 [Z13879]

- [1] a) K.-D. Müller, L. Komorowski, K. Niedenzu, *Syn. React. Inorg. Chem.* **1978**, 149–154; b) I. A. Boenig, W. R. Conway, K. Niedenzu, *Syn. React. Inorg. Chem.* **1975**, 5, 1–5.
- [2] B. F. Spielvogel, R. F. Bratton, C. G. Moreland, *J. Am. Chem. Soc.* **1972**, 94, 8997–8598.
- [3] Structural data of **3b**: monoclinic $P2_1/a$, $a = 18.315(9)$, $b = 16.547(8)$, $c = 20.456(10)$ Å, $\beta = 115.84(2)^\circ$, $V = 5580(5)$ Å³, $Z = 8$. A total of 7769 independent reflections (4227 observed, $I > 2\sigma(I)$), the measurement was carried out on a four-circle diffractometer (MoK_α radiation, ω scan, $T = -60^\circ\text{C}$) $R1 = 0.0842$, $wR2 = 0.2150$. Structural data of **5a**: monoclinic $P2_1/c$, $a = 12.5847(2)$, $b = 17.7859(3)$, $c = 11.4299(2)$ Å, $\beta = 106.3090(10)^\circ$, $V = 2455.41(7)$ Å³, $Z = 4$. A total of 5999 independent reflections (4691 observed, $I > 2\sigma(I)$), $R1 = 0.0552$, $wR2 = 0.1254$. The measurement was carried out on a Bruker AXS diffractometer (MoK_α radiation, ω scan, $T = -100^\circ\text{C}$). The structures were solved with direct methods (SHELXS86) and refined with all measured reflections against F^2 (SHELXL97).^[8] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133110 (**3b**) and CCDC-133111 (**5a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [4] A. J. Arduengo, J. R. Göhrlich, W. J. Marshall, *J. Am. Chem. Soc.* **1995**, 117, 11027–11028, and references therein.
- [5] W. A. Herrmann, C. Köcher, *Angew. Chem.* **1997**, 109, 2256–2282; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2162–2187, and references therein.
- [6] U. Kernbach, M. Ramm, P. Luger, W. P. Fehlhammer, *Angew. Chem.* **1996**, 108, 333–335; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 310–312.
- [7] a) A. Wacker, H. Pritzkow, W. Siebert, *Eur. J. Inorg. Chem.* **1998**, 843–849; b) A. Wacker, PhD thesis, Universität Heidelberg, Germany, **1999**.
- [8] G. M. Sheldrick, SHELXS86, Universität Göttingen, **1986**, G. M. Sheldrick, SHELXL97, Universität Göttingen, **1997**.

Nitrophenolate as a Building Block for Lanthanide Chains and Clusters**

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Inorganic clusters continue to attract considerable attention because they represent the bridge linking molecular and solid state chemistry and because they are useful tools for understanding the size-dependent physical properties of electronic material.^[1] While the cluster chemistry of the transition metals is now firmly established and huge clusters have been isolated—especially clusters of molybdenum,^[2] copper,^[3] and silver^[4]—the analogous chemistry of the lanthanides is virtually undeveloped.^[5] Whereas systematic studies on the lanthanide clusters of sulfur, selenium, and tellurium have recently been reported,^[6] most of the lanthanide–oxygen clusters have been obtained by unexpected synthetic routes such as the decomposition of ether solvents,^[7] the decomposition of grease,^[8] or the reaction with traces of water in the mixture.^[9] While we were preparing this paper, a systematic synthesis of pentadecanuclear lanthanide–tyrosine clusters from water was discovered by Zheng et al.^[10]

We report here on the systematic preparation of lanthanide–oxygen clusters by partial hydrolysis of a water-sensitive reaction mixture. To reach this synthetic goal we were most interested in using a ligand which features different coordination modes. During our investigations it turned out that this is ideally achieved by using *o*-nitrophenolate. Transmetalation of potassium *o*-nitrophenolate with anhydrous yttrium or lutetium trichloride in THF with rigorous exclusion of air followed by crystallization from THF/pentane (1/4) leads to infinite chains of **1a** ($\text{Ln} = \text{Y}$) and **1b** ($\text{Ln} = \text{Lu}$). The



new complexes have been characterized by standard spectroscopic techniques, and the solid-state structures of **1a** and **1b** (Figure 1a) were established by single-crystal X-ray diffraction.^[11] Compounds **1a** and **1b** are isostructural. Each lanthanide ion of **1** is surrounded by four *o*-nitrophenolate anions which act as bidentate ligands. Thus, each lanthanide ion is eightfold coordinated. Nevertheless, two different coordination modes of the *o*-nitrophenolate are realized in **1**; the nitro group may either point to the left side or to the right side of the chain. Thus, the dissimilarities in the coordination spheres of the lanthanide ions in **1** is caused by different orientations of the ligands around the metal center. The Ln–O bond lengths for Ln–OR are: 221.1(8)–231.8(9) (**1a**) and 219.5(12)–232.4(11) pm (**1b**); and for Ln–ONO are: 231.5(8)–249.7(8) (**1a**) and 234.7(11)–250.4(9) pm (**1b**). The potassium cations are located in between the

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Additional generous support from Prof. Dr. D. Fenske is gratefully acknowledged.

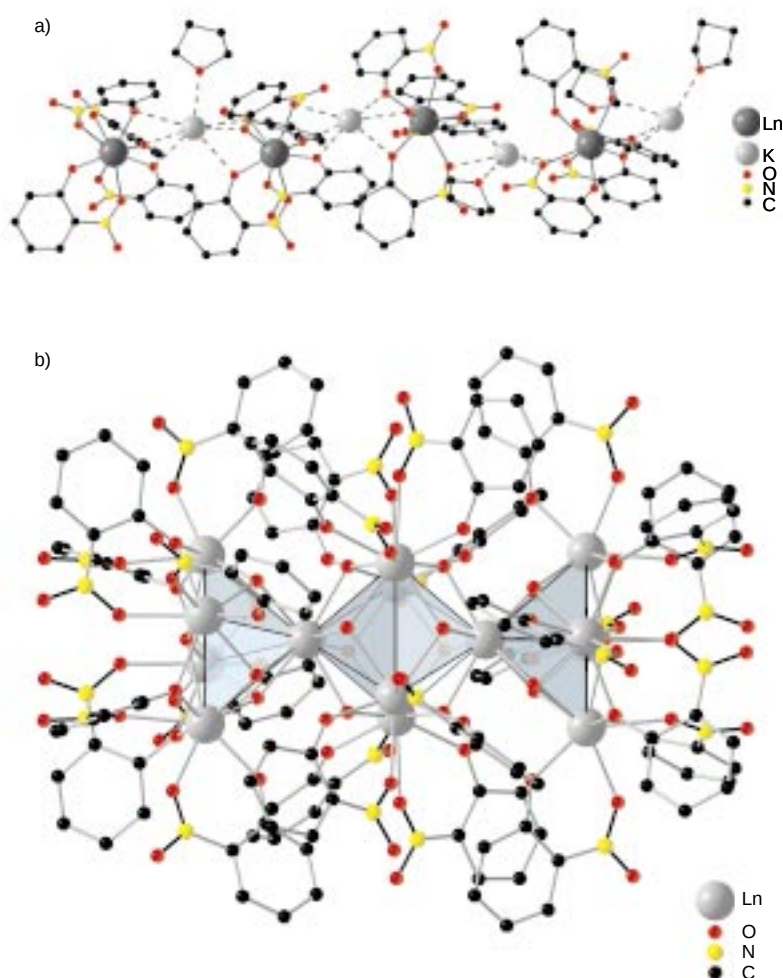
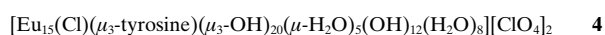
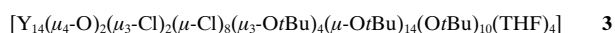
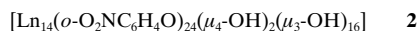


Figure 1. a) Solid-state structure of **1** (Ln = Y or Lu). One unit from an infinite chain is shown with hydrogen atoms omitted for clarity; b) solid-state structure of **2** (Ln = Er or Yb) with hydrogen atoms omitted for clarity.

$[(o\text{-O}_2\text{NC}_6\text{H}_4\text{O})_4\text{Ln}]^-$ anions. Each potassium ion is coordinated by four to six nitro groups.^[12] Additionally, one equivalent of THF is coordinated to three of the four potassium cations; the fourth equivalent of THF does not coordinate to a metal ion.

When the above reaction conditions were used with anhydrous erbium or ytterbium trichloride and the crystallization was performed in the presence of air, tetradecanuclear clusters of **2a** (Ln = Er) or **2b** (Ln = Yb) were obtained as orange crystals (Figure 1 b). For both compounds the solid-state structures were established by single-crystal X-ray diffraction.^[13] We believe they are the largest lanthanide structures known,^[5] besides **3**^[14] and **4**.^[10]



Cluster **2** is a highly symmetrical molecule which features a crystallographic D_4 symmetry. The Ln_{14} core of **2** can be described as a chain of three corner-sharing Ln octahedra,

with a corner missing from the two outer octahedra (Figure 1 b). The octahedra are twisted at 45° to each other. Each triangular face of these octahedra is capped by one μ_3 -OH group, which means the two corner-sharing Ln ions are each surrounded by eight μ_3 -OH groups in a square-antiprismatic fashion. In contrast to the well-known $[\text{M}_6\text{X}_8]^{n+}$ clusters such as $[\text{Mo}_6\text{Cl}_8]^{4+}$ ^[15] no metal–metal bonding is observed in **2**. One oxygen atom is attached to the four lanthanide ions on the cut-off face of the outer octahedra. These μ_4 -bonded oxygen atoms are shifted 52 pm out of the Ln_4 square plane. The Ln–O bond distances to these oxygen atoms are: 250.9(3) (**2a**) and 247.5(3) pm (**2b**).^[16] Each of the twelve Ln ions which are non-corner-sharing is coordinated by two *o*-nitrophenolate ligands. The different coordination modes which are observed in **2** (Figure 1 b) demonstrate the flexibility of the *o*-nitrophenolate ligand. Although no structural investigations on lanthanide *o*-nitrophenols are known, there are a number of publications dealing with lanthanide picrates.^[17] Most of these compounds are mono- or dinuclear complexes which were prepared in water.

Whereas most lanthanide oxide clusters seem to be formed by a partial hydrolysis of the reaction mixture and the syntheses are hard to reproduce, we were able to synthesize **2** several times, even when using different batches of solvent and starting material.^[18] Both **1** and **2** could only be obtained by the reaction of potassium *o*-nitrophenolate with the chlorides of the heavier lanthanides or yttrium. No reaction was observed upon mixing potassium *o*-nitrophenolate and LaCl_3 in THF. Since LaCl_3 is less soluble in THF

than the heavier lanthanide trichlorides, this observation is not surprising.

In summary, the reaction of potassium *o*-nitrophenolate with anhydrous yttrium and some of the lanthanide trichlorides gives unusual products. In the absence of air infinite chains were obtained, whereas crystallization in air leads to tetradecanuclear lanthanide clusters. To the best of our knowledge the setup of these clusters is unique in coordination chemistry.

Experimental Section

1 and 2: Under a nitrogen atmosphere THF (25 mL) was added to a mixture of LnCl_3 (2.0 mmol) and potassium *o*-nitrophenolate (1.063 g, 6 mmol) at room temperature. The mixture was stirred for 16 h at room temperature and then the solution was filtered and concentrated.

1: Pentane was layered on top of the recrystallization solution (THF/pentane, 1/4). Orange crystals were obtained after one day. **1a:** Yield 410 mg (37 %); ^1H NMR ($[\text{D}_8]\text{THF}$, 250 MHz, 25°C): δ = 1.72–1.79 (m; THF), 3.57–3.66 (m; THF), 6.36 (t, 1 H; Ph), 6.66 (d, 1 H; Ph), 7.15 (t, 1 H; Ph), 7.73 (d, 1 H; Ph); IR (KBr disk): $\tilde{\nu}$ = 1598 (s; C=C), 1537 (s; C–NO₂), 1485 (s), 1426 (s), 1319 (s), 1252 (s; C–O), 1140 (s), 1081 (s), 1019 (m), 745 (s) cm^{-1} ; elemental analysis calcd. for $\text{C}_{112}\text{H}_{96}\text{K}_4\text{N}_{16}\text{O}_{52}\text{Y}_4$ (3010.09): C 44.69, H 3.21, N 7.45; found: C 44.22, H 3.55, N 7.69. **1b:** Yield 344 mg (28 %); ^1H NMR ($[\text{D}_8]\text{THF}$, 250 MHz, 25°C): δ = 1.72–1.79 (m; THF),

3.57–3.66 (m; THF), 6.49 (t, 1H; Ph), 6.70 (d, 1H; Ph), 7.32 (t, 1H; Ph), 7.89 (d, 1H; Ph); IR (KBr disk): $\tilde{\nu}$ = 1599 (s; C=C), 1540 (s; C–NO₂), 1502 (s), 1427 (s), 1324 (s), 1255 (s; C–O), 1135 (s), 1083 (s), 1018 (s), 799 (s), 746 (s) cm⁻¹; elemental analysis calcd. for C₁₁₂H₉₆K₄Lu₄N₁₆O₅₂ (3354.33): C 40.10, H 2.88, N 6.68; found: C 39.22, H 2.98, N 6.11.

2: In the presence of air hexane was layered on top of the recrystallization solution (THF/hexane, 1/4), and then the reaction vessel was closed. Orange crystals were obtained after 12 h. **2a**: Yield 110 mg (12%); IR (KBr disk): $\tilde{\nu}$ = 3526 (w; OH), 3106 (w), 1604 (vs; C=C), 1541 (m; C–NO₂), 1503 (vs), 1463 (s), 1324 (vs), 1249 (vs; C–O), 1137 (vs), 1083 (s), 799 (s) 745 (s) cm⁻¹; elemental analysis calcd. for C₁₇₆H₁₇₈Er₁₄N₂₄O₉₈ (6539.06): C 32.72, H 2.39, N 5.24; found: C 32.85, H 2.99, N 5.98. **2b**: Yield 130 mg (14%); IR (KBr disk): 3520 (w; OH), 3100 (w), 1604 (vs; C=C), 1557 (s; C–NO₂), 1541 (s), 1505 (vs), 1468 (s), 1324 (vs), 1258 (vs; C–O), 1136 (vs), 1086 (vs), 801 (s) 744 (s) cm⁻¹; elemental analysis calcd. for C₁₇₆H₁₇₈N₂₄O₉₈Yb₁₄ (6619.98): C 31.93, H 2.71, N 5.08; found: C 31.87, H 2.64, N 5.57.

Received: September 13, 1999 [Z14004]

- [1] a) *Clusters and Colloids: From Theory to Applications* (Ed.: G. Schmidt), VCH, Weinheim, **1994**; b) *Physics and Chemistry of Metal Cluster Compounds* (Ed.: L. J. de Jongh), Kluwer, Dordrecht, **1994**.
- [2] A. Müller, E. Krickmeyer, H. Bögge, M. Schmidtman, F. Peters, *Angew. Chem.* **1998**, *110*, 3567–3571; *Angew. Chem. Int. Ed.* **1998**, *37*, 3360–3363.
- [3] H. Krautscheid, D. Fenske, G. Baum, M. Semmelmann, *Angew. Chem.* **1993**, *105*, 1364–1367; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1303–1306.
- [4] D. Fenske, N. Zhu, T. Langetepe, *Angew. Chem.* **1998**, *110*, 2784–2788; *Angew. Chem. Int. Ed.* **1998**, *37*, 2640–2644.
- [5] R. Anwender, *Angew. Chem.* **1998**, *110*, 619–622; *Angew. Chem. Int. Ed.* **1998**, *37*, 599–602.
- [6] a) D. Freedman, T. J. Emge, J. G. Brennan, *J. Am. Chem. Soc.* **1997**, *119*, 11112–11113; b) D. Freedman, J. H. Melman, T. J. Emge, J. G. Brennan, *Inorg. Chem.* **1998**, *37*, 4162–4163.
- [7] H. C. Aspinall, M. R. Tillotson, *Inorg. Chem.* **1996**, *35*, 2163–2164.
- [8] S. Kraut, J. Magull, U. Schaller, M. Karl, K. Harms, K. Dehnicke, *Z. Anorg. Allg. Chem.* **1998**, *624*, 1193–1201.
- [9] R. Anwender, F. C. Munck, T. Priemeier, W. Scherer, O. Runte, W. A. Herrmann, *Inorg. Chem.* **1997**, *36*, 3545–3552.
- [10] R. Wang, Z. Zheng, T. Jin, R. J. Staples, *Angew. Chem.* **1999**, *111*, 1929–1931; *Angew. Chem. Int. Ed.* **1999**, *38*, 1813–1815.
- [11] Single-crystal X-ray diffraction data:^[19] **1a** (C₁₁₂H₉₆K₄N₁₆O₅₂Y₄, M_r = 3010.09): space group $P\bar{1}$ (no. 2), a = 1213.0(2), b = 2063.2(4), c = 2597.4(5) pm, α = 102.96(3), β = 94.34(3), γ = 94.77(3)° at 203 K, Z = 2, V = 6283(2) 10⁶ pm³, ρ = 1.591 g cm⁻³, $2\theta_{\max}$ = 48°, 36557 reflections collected, 18671 independent reflections (R_{int} = 0.1304), 8511 refined reflections with $I > 2\sigma(I)$ to R^1 = 0.0859 and wR^2 = 0.1853. **1b** (C₁₁₂H₉₆K₄Lu₄N₁₆O₅₂, M_r = 3354.33): space group $P\bar{1}$ (no. 2), a = 1210.6(2), b = 2037.2(4), c = 2591.9(5) pm, α = 103.00(3), β = 93.91(3), γ = 94.92(3)° at 203 K, Z = 2, V = 6180(2) 10⁶ pm³, ρ = 1.802 g cm⁻³, $2\theta_{\max}$ = 50°, 42925 reflections collected, 20437 independent reflections (R_{int} = 0.1010), 16256 refined reflections with $I > 2\sigma(I)$ to R_1 = 0.0774 and wR_2 = 0.2224.
- [12] We consider a K–O interaction to be a coordinating interaction if the K–O distance is significantly shorter than 300 pm.
- [13] Single crystal X-ray diffraction data:^[19] **2a** × 8 THF (C₁₇₆H₁₇₈Er₁₄N₂₄O₉₈, M_r = 6539.06): space group $P4/nnc$ (no. 126), a = 1927.0(9), c = 3381.0(7) pm at 203 K, Z = 2, V = 12555(4) 10⁶ pm³, ρ = 1.730 g cm⁻³, $2\theta_{\max}$ = 45°, 19412 reflections collected, 4059 independent reflections (R_{int} = 0.0744), 2940 refined reflections with $I > 2\sigma(I)$ to R_1 = 0.0481 and wR_2 = 0.1477. **2b** × 8 THF (C₁₇₆H₁₇₈N₂₄O₉₈Yb₁₄, M_r = 6619.98): space group $P4/nnc$ (no. 126), a = 1919.7(3), c = 3465.6(7) pm at 203 K, Z = 2, V = 12403(4) 10⁶ pm³, ρ = 1.773 g cm⁻³, $2\theta_{\max}$ = 45°, 34864 reflections collected, 4040 independent reflections (R_{int} = 0.0680), 3239 refined reflections with $I > 2\sigma(I)$ to R_1 = 0.0506 and wR_2 = 0.1524. In both structures the H atoms could not be refined.
- [14] W. J. Evans, M. S. Sollberger, *Inorg. Chem.* **1988**, *27*, 4417–4423.
- [15] R. G. Woolley, *Inorg. Chem.* **1985**, *24*, 3519–3525.
- [16] P. F. Kruger, V. McKee, *Chem. Commun.* **1997**, 1341–1342.

- [17] a) J. D. Ayala, L. B. Zinner, G. Vicentini, A. Del Pra, G. Bomberieri, *Inorg. Chim. Acta* **1993**, *211*, 161–166; b) J. M. Harrowfield, L. Weimin, B. W. Skelton, A. H. White, *Aust. J. Chem.* **1994**, *47*, 321–337.
- [18] Compound **2a** was made four times and **2b** twice. The lattice constants of the obtained crystals were determined by single-crystal X-ray diffraction each time and found to be the same.
- [19] X-ray structure analyses: General: All data sets were collected by STOE-IPDS. The structure was solved by Patterson methods (SHELXS-86 and SHELXL-93) and refined by full-matrix least-square techniques. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-134394 (**1a**), -134395 (**1b**), -136363 (**2a**), and -134397 (**2b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; email: deposit@ccdc.cam.ac.uk).

Molecular Recognition of Carbohydrates by Artificial Polypyridine and Polypyrimidine Receptors**

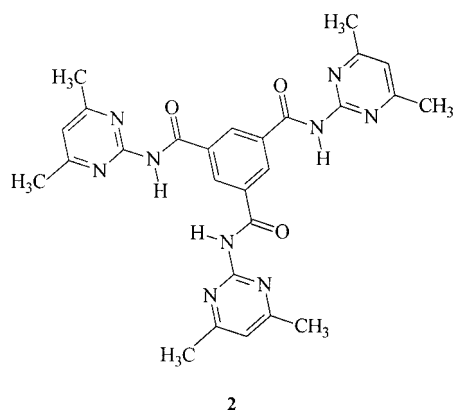
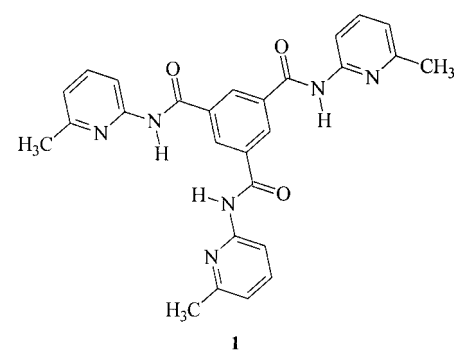
Monika Mazik,* Heinz Bandmann, and Willi Sicking

The molecular recognition of carbohydrates is one of the challenging goals of supramolecular chemistry.^[1a] This is due to the three-dimensional complexity of sugar structures and to the key roles which carbohydrates play in a wide range of biological processes.^[1b] The analysis of the X-ray crystallographic structures of sugar–protein complexes reveals that hydrogen bonds between hydroxy groups as well as between ring oxygens of the sugar molecule and polar residues of the protein are the main factors in conferring specificity and affinity to protein–carbohydrate interactions.^[2] Furthermore, stacking of sugar CH moieties with aromatic amino acid side chains, such as the indole and phenol rings of Trp and Tyr, respectively, modulates the stability of protein–carbohydrate complexes.

Mimicking these binding strategies may lead to effective, artificial systems as a key for developing new types of biorelevant materials. Systematic biomimetic studies with synthetic receptors should lead to better understanding of carbohydrate recognition in biological processes. Despite intense current interest in the development of artificial carbohydrate receptors,^[3–5] only a few effective hydrogen-bonding host molecules can be found in the literature for sugars in organic solvents. The described carbohydrate receptors mostly possess macrocyclic structures, are accessible only by multistep syntheses, and, although multidentate, are often essentially two-dimensional.^[6]

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** A Lise–Meitner stipend to M.M. from the Fonds zur Förderung des Wissenschaftlichen Nachwuchses is gratefully acknowledged. We thank the Deutsche Forschungsgemeinschaft for financial support (SFB 452).



We describe here the recognition and binding of monosaccharides to simple, acyclic saccharide receptors, **1** and **2**, which incorporate three pyridine–amide or pyrimidine–amide moieties interconnected by a phenyl spacer. Although these host molecules possess an acyclic structure, they are able to bind effectively to monosaccharides. These types of host molecules provide both hydrogen bonding sites and π -bonds for facilitating stacking interactions and should thus be able to participate in three-dimensional recognition of sugars.

As a starting point for the design of monosaccharide receptors, we examined the adaptability of the polypyridine **1** and polypyrimidine **2** receptors for the recognition of glucopyranosides. Additionally, comparative complexation studies with hosts **3** and **4** were carried out. To evaluate the recognition capabilities of the receptors for glucopyranoside in aprotic solvents such as chloroform, the octyl derivatives **5** and **6** were selected.

Compounds **1–3** were synthesized from benzene-1,3,5-tricarbonyl chloride (trimesic chloride) and 2-amino-6-methylpyridine,^[7] 2-amino-4,6-dimethylpyrimidine or *p*-toluidine, respectively. Compound **4** was prepared by reaction of isophthaloyl dichloride with 2-amino-6-methylpyridine.^[8,9]

The interactions between hosts **1–4** and glucopyranosides were investigated by ¹H NMR spectroscopy. The complexation of glucopyranosides through receptors **1** and **2** (selected data is shown in Table 1) was shown in the NMR spectrum of the complex by the significant downfield shifts of the signals for the receptor amide protons ($\Delta\delta = 0.7$) and the upfield shifted resonance signals for the aromatic protons of the receptor. The former downfield shift of signals reflects the formation of a hydrogen-bonded complex, and the latter may be attributed to the stacking interactions between aromatic groups of the receptors and the glucopyranoside ring.

The formation of a complex between **5** and **1** is also visible during the addition of powdered *n*-octyl- β -D-glucopyranoside to a suspension of receptor **1** in CDCl₃, which leads to facile dissolution and formation of a clear solution. The binding constants were determined in chloroform at 25 °C by NMR titration experiments; the titration data were analysed by nonlinear regression analysis using the Hostest 5.6 program.^[10] For all binding experiments the ratio method indicates a 1:1 stoichiometry.^[11] In contrast to β -glucopyranoside **5**, the α -anomer **6** showed lower affinity for **1**.

Molecular modeling revealed a possible structure for the complex of **1** and **5**, which suggests the formation of six hydrogen bonds (three amide-NH...OH and three pyr-N...HO bonds) and stacking interactions of the pyranoside ring with the central phenyl ring. All the OH groups of **5** participate in hydrogen bonding; the CH₂OH group participates in cooperative hydrogen bonds (Figure 1).

The existence of these hydrogen-bonding and stacking interactions is also indicated by the NMR data (downfield

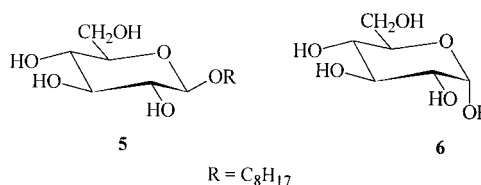
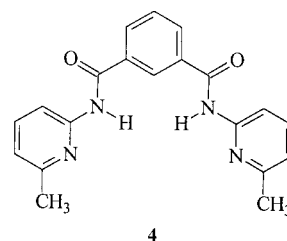
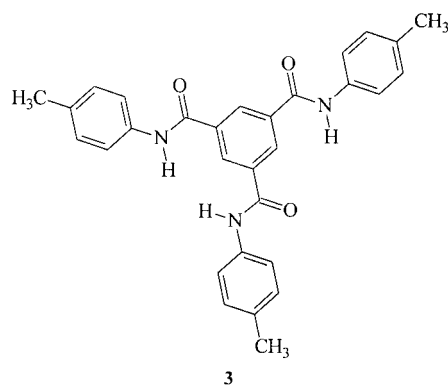


Table 1. Selected physical and spectroscopic data of compounds **1** and **2**.

1 : M. p. 253 °C; ¹ H NMR (500 MHz, CDCl ₃): δ = 2.48 (s, 9H; 3 $\times$ CH ₃), 6.95 (d, J = 7.5 Hz; 3H _{arom}), 7.66 (m; 3H _{arom}), 8.17 (d, J = 7.9 Hz; 3H _{arom}), 8.73 (s; 3H _{arom}), 8.91 (s, 3H; 3 $\times$ NH); ¹³ C NMR (125 MHz): 163.36 (C=O), 157.07, 150.39, 138.87, 135.69, 129.24, 119.84, 111.09, 23.97 (CH ₃); HR-MS, calcd for C ₂₇ H ₂₄ N ₆ O ₃ : 480.1910; found: 480.1903
2 : M. p. 188 °C; ¹ H NMR (500 MHz, CDCl ₃): δ = 2.40 (s, 18H; 6 $\times$ CH ₃), 6.76 (s; 3H _{arom}), 8.75 (s; 3H _{arom}), 9.34 (s 3H; 3 $\times$ NH); ¹³ C NMR (125 MHz): 168.41 (C=O), 163.72, 157.10, 135.55, 130.22, 116.37, 23.87 (CH ₃); HR-MS, calcd for C ₂₇ H ₂₄ N ₆ O ₃ : 525.2237; found: 525.2229

shifts of NH signals, upfield shifts of the signals for aromatic protons of the receptor). The binding constant of *n*-octyl- β -glucopyranoside (**5**) and receptor **1** was found to be 8700 M^{-1} ($-\Delta G_{298} = 22.47\text{ kJ mol}^{-1}$), and for *n*-octyl- α -glucopyranoside (**6**) and **1**, the binding constant amounts to 4000 M^{-1} ($-\Delta G_{298} = 22.47\text{ kJ mol}^{-1}$), and for *n*-octyl- α -glucopyranoside (**6**) and **1**, the binding constant amounts to 4000 M^{-1} ($-\Delta G_{298} = 20.54\text{ kJ mol}^{-1}$). Replacement of the pyridine

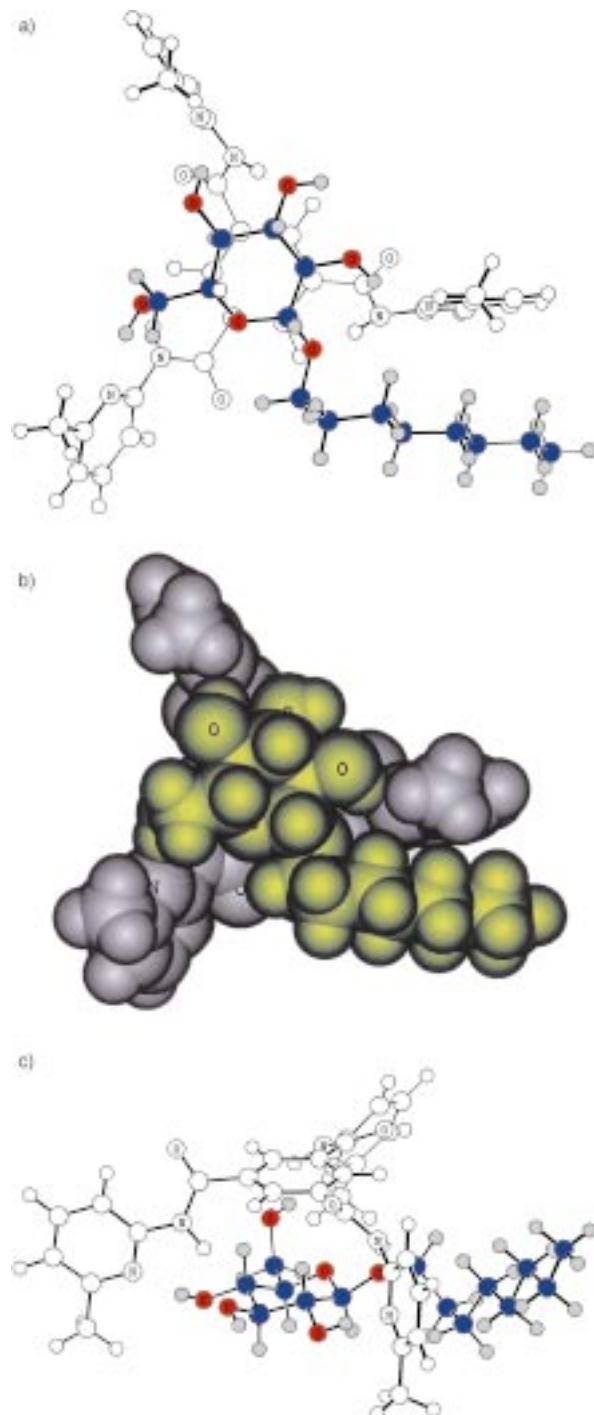


Figure 1. The energy-minimized structure of the complex formed between receptor **1** and octyl β -D-glucopyranoside (**5**) (Molecular modeling with MacroModel 5.0, Amber* force field). The intermolecular amide-NH...OH and pyr-N...HO hydrogen bonds ($1.87\text{--}1.94\text{ \AA}$) and the stacking interactions in the complex are shown. a) top view, b) CPK model (top view), c) side view.

groups by pyrimidine groups in the receptor structure leads to larger binding constants for both the β - and the α -anomer and also a similar affinity of host **2** to both anomers. The receptor **2** revealed K_a values of 13700 M^{-1} ($-\Delta G_{298} = 23.60\text{ kJ mol}^{-1}$) and 12500 M^{-1} ($-\Delta G_{298} = 23.37\text{ kJ mol}^{-1}$) for **5** and **6**, respectively.

In order to test the importance of the presence of the pyridine nitrogen atoms in the receptor structure, compound **3** was synthesized. Contrary to **1**, compound **3** is poorly soluble in chloroform and could not be solubilized in this solvent even at high concentrations of octyl glucopyranoside, which indicates a weak binding between **5** and **3**. These results indicate that the nitrogen atoms in the structure of **1** are of great importance for the binding affinity and hydrogen bonding between amide-NH/pyridine-N or pyrimidine-N of the receptors and the OH groups of **5** or **6** is primarily responsible for the complexation in chloroform. As the positions of the ^1H NMR signals for the methyl protons of **1** and **2** and the octyl protons of **5** and **6** are virtually unaffected, it is highly unlikely that these subunits contribute significantly to the stabilisation of the resulting complex.

In order to prove how important the presence of the three pyridine-amide subunits in the receptor structure is, compound **4** was prepared and its complexation affinity was determined. In CDCl_3 receptor **4** forms 1:1 complexes with octyl glucopyranosides, as determined by the ratio method. The complexation of **4** with **5** or **6** can also be followed by ^1H NMR spectroscopy. The signals for the amide-NH protons undergo downfield shifts upon binding of guests **5** or **6**. The binding constants amount to 1100 and 460 M^{-1} ($-\Delta G_{298} = 17.35\text{ kJ mol}^{-1}$ and $-\Delta G_{298} = 15.19\text{ kJ mol}^{-1}$) for **5** and **6**, respectively. This shows that the hydrogen-bonding interactions with host **4**, which has a multiple but essentially two-dimensional binding site, are less favorable than with host **1**. Receptor **1** being a superior receptor to the bipyridyl receptor **4** for glucopyranoside in chloroform is also supported by the pronounced downfield shift of the signals for the key amide protons in **1** on complexation with pyranoside ($\Delta\delta = 0.7$ compared to 0.2 in the complex with **4**). The smaller binding constants and the shifts of the ^1H NMR signals for **4** reflect the importance of three-dimensional recognition.

In summary, the hydrogen-bonding receptors presented here were found to be effective for the recognition of pyranosides. The results demonstrate the adjustability of the amido-pyridine and amido-pyrimidine arrangement as hydrogen-bonding motifs for monosaccharides. The advantages of these systems are a) a simple and quick synthesis of small subunits (unsuccessful macrocyclisations are not necessary), b) the possible variation of the structure (variation of the spacer and the heteroaromatic moieties in order to modulate the selectivity of the receptors), c) the easy construction of water soluble host molecules (suitable substituents in spacer or in aromatic subunits), and d) the capability for three-dimensional recognition of guest molecules.

Received: September 15, 1999 [Z14016]

- [1] a) A. P. Davis, R. S. Wareham, *Angew. Chem.* **1999**, *111*, 3160–3179; *Angew. Chem. Int. Ed.* **1999**, *38*, 2978–2996; b) N. Sharon, H. Lis, *Science* **1989**, *246*, 227–234; N. Sharon, H. Lis, *Sci. Am.* **1993**, *268*(1), 74–81.

- [2] R. U. Lemieux, *Chem. Soc. Rev.* **1989**, 18, 347–374; F. A. Quiocho, *Pure. Appl. Chem.* **1989**, 61, 1293–1306; W. I. Weiss, K. Drickamer, *Annu. Rev. Biochem.* **1996**, 65, 441–473.
- [3] a) Y. Aoyama, Y. Tanaka, S. Sugara, *J. Am. Chem. Soc.* **1989**, 111, 5397–5404; b) K. Kobayashi, Y. Asakawa, Y. Kato, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, 114, 10307–10313; c) Y. Kikuchi, K. Kobayashi, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, 114, 1351–1358; d) Y. Aoyama, Y. Tanaka, H. Toi, H. Ogoshi, *J. Am. Chem. Soc.* **1988**, 110, 634–635; e) R. Yanagihara, Y. Aoyama, *Tetrahedron Lett.* **1994**, 35, 9725–9728; f) M. Inouye, T. Miyake, M. Furusyo, H. Nakazumi, *J. Am. Chem. Soc.* **1995**, 117, 12416–12425; g) M. Inouye, K. Takahashi, H. Nakazumi, *J. Am. Chem. Soc.* **1999**, 121, 341–345; h) R. P. Bonar-Law, A. P. Davis, B. A. Murray, *Angew. Chem.* **1990**, 102, 1497–1499; *Angew. Chem. Int. Ed. Engl.* **1990**, 30, 1407–1409; i) A. P. Davis, R. S. Wareham, *Angew. Chem.* **1998**, 110, 2397–2400; *Angew. Chem. Int. Ed.* **1998**, 37, 2270–2273; j) J. Cuntze, L. Owens, V. Alcazar, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1995**, 78, 367–390; k) A. Bähr, A. S. Droz, M. Püntener, U. Neidlein, S. Anderson, P. Seiler, F. Diederich, *Helv. Chim. Acta* **1998**, 81, 1931–1963; l) J. C. Morales, S. Penades, *Angew. Chem.* **1998**, 110, 673–676; *Angew. Chem. Int. Ed.* **1998**, 37, 654–657; m) G. Das, A. D. Hamilton, *Tetrahedron Lett.* **1997**, 38, 3675–3678; n) R. Liu, W. C. Still, *Tetrahedron Lett.* **1993**, 34, 2573–2576; k) R. P. Bonar-Law, J. K. M. Sanders, *J. Am. Chem. Soc.* **1995**, 117, 259.
- [4] T. D. James, K. Sandanayake, S. Shinkai, *Angew. Chem.* **1996**, 108, 2039–2050; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1910–1922, and references therein
- [5] Y. Aoyama in *Comprehensive Supramolecular Chemistry*, Vol. 2 (Eds.: J. L. Atwood, J. E. D. Davis, D. D. MacNicol, F. Vögtle), Pergamon, Oxford, **1996**, pp. 279–307.
- [6] Examples of receptors which are able participate in three-dimensional recognition of sugars are described in refs. [3i, n, k].
- [7] B. König, O. Möller, P. Bubenitschek, P. G. Jones, *J. Org. Chem.* **1995**, 60, 4291–4293.
- [8] J. Yang, E. Fan, S. J. Geib, A. D. Hamilton, *J. Am. Chem. Soc.* **1993**, 115, 5314–5315; S. J. Geib, C. Vicent, E. Fan, A. D. Hamilton, *Angew. Chem.* **1993**, 105, 83–85; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 119–121.
- [9] M. Mazik, D. Bläser, R. Boese, *Tetrahedron* **1999**, 55, 12771–12782.
- [10] C. S. Wilcox, N. M. Glagovich, Program HOSTEST 5.6, University of Pittsburgh. We thank Professor C. S. Wilcox for giving access to his HOSTEST program.
- [11] H. Tsukube, H. Furuta, A. Odani, Y. Takeda, Y. Kudo, Y. Inoue, Y. Liu, H. Sakamoto, K. Kimura in *Comprehensive Supramolecular Chemistry*, Vol. 2 (Eds.: J. L. Atwood, J. E. D. Davis, D. D. MacNicol, F. Vögtle), Pergamon, Oxford, **1996**, pp. 425–482.

Sequential Nucleophilic Substitution: A Powerful Strategy for the Solid-Phase Production of Diverse Compound Libraries

Florencio Zaragoza* and Henrik Stephensen

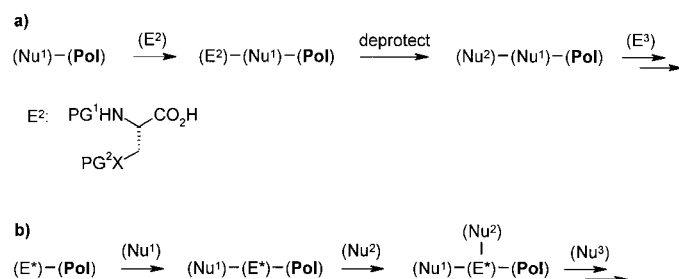
Solid-phase synthesis enables automated multistep syntheses to be performed in parallel and, therefore, plays an outstanding role in the quest for new candidates for development in the pharmaceutical industry.^[1] We report here a new synthetic strategy which is rapid, because a new element of

diversity is introduced in each step, and which enables the direct use of unprotected, polyfunctional reagents.

Solid-phase synthetic sequences suitable for library production must be based on reagents available in large number and with a broad variety of additional structural elements. For drug discovery it is important to include structural elements relevant for protein binding (e.g. hydrogen-bond donors and acceptors, cationic, anionic, aromatic, or lipophilic groups).^[2] The efficient development of synthetic sequences must be initiated by an evaluation of commercially available reagents and of reactions which can be conducted on insoluble supports. Such an analysis reveals that only a few types of reagent are available in a wide variety for the preparation of diverse compound libraries. The most suitable of these are amines, alcohols, carboxylic acids, and thiols. Reagents with two required reactive groups (amino acids, amino alcohols, haloketones, anthranilic acids, 2-iodophenols, etc.), on the other hand, are not available in large numbers and are, therefore, less suitable for library production.

The evaluation of reactions shows that acylations and other electrophilic transformations of support-bound intermediates will severely limit the choice of additional functional groups present in the final product. Hydrogen-bond donors, for instance, must generally be protected to prevent them from being acylated as well (Scheme 1), but monoprotected bifunctional reagents are expensive and not readily available. On the other hand, nucleophilic transformations of support-bound intermediates do not usually require protection of the additional functional groups, which enables the direct use of unprotected, polyfunctional reagents. Moreover, most of our preferred reagents (see above) are nucleophiles, and we conclude that, for the production of large and diverse arrays of potential drug candidates, nucleophilic substitutions must play a central role. Syntheses which enable repetitive nucleophilic substitutions to be carried out with a support-bound polyelectrophile (Scheme 1) will be most useful.^[3]

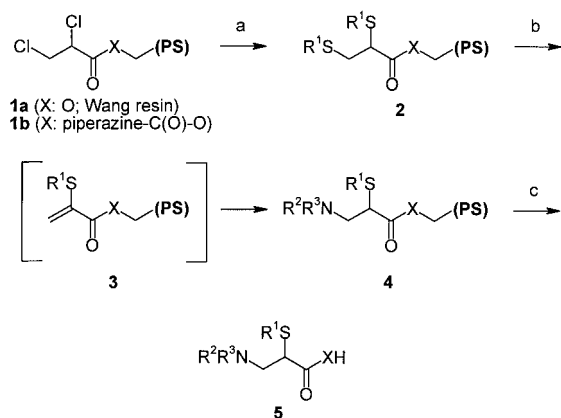
As an illustrative example of sequential nucleophilic substitution, we present here a solid-phase synthesis of substituted 2-thio-3-aminopropionic acid derivatives (Scheme 2). We used 2,3-dichloropropionic acid as a polyelectrophile, either esterified with Wang resin (**1a**) or linked to a support-bound amine (**1b**).^[4] Treatment of **1** with excess thiol R¹SH in the presence of DIPEA led to a clean, double nucleophilic substitution, yielding the resin-bound 2,3-dithio-



Scheme 1. a) Traditional oligomer (e.g. peptide) synthesis by sequential acylations/deprotections. Side-chain protection is required; few building blocks are available. b) Sequential nucleophilic substitutions on a support-bound polyelectrophile. No side-chain protection is required; many building blocks are available. Nu: nucleophile, E: electrophile, E*: polyelectrophile, Pol: polymeric support, PG: protective group.

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propionic acid derivative **2**.^[5] Further treatment of **2** with an amine in the presence of DBU led to β -elimination of one thiol and incorporation of the amine by a Michael addition.^[6]

This new reaction sequence proceeds well with aromatic and aliphatic thiols, although when using aliphatic thiols in combination with the support-bound amide **1b**, heating is generally required to achieve complete incorporation of the amine R²R³NH. We have used primary and secondary aliphatic amines, α -amino acid esters, and aniline with success. Both the thiols and the amines can be polyfunctional (e.g. **5f**, **5g**, **5j**; Table 1), making this synthetic sequence suitable for the production of highly functionalized compounds, without the need for protecting groups.

In conclusion, sequential nucleophilic substitution is a fast and efficient tool for the production of highly diverse compound libraries. Other polyelectrophiles, such as polyhalogenated arenes, have also proved suitable for sequential nucleophilic substitution on solid-phase supports and these results will be reported in due course.

Experimental Section

Synthesis of 5a-TFA. DIPEA (0.9 mL, 5.17 mmol, 8.6 equiv), and thio-phenol (0.6 mL, 5.84 mmol, 10 equiv) were added, in the order given, to a suspension of **1a** (0.60 g, ca. 0.6 mmol) in NMP (9.0 mL). The mixture was shaken at 20 °C for 22 h, filtered, and the resin was washed with NMP (3 $\times$ 6 mL). The resin was suspended in NMP (9 mL), and piperidine (0.6 mL, 6.07 mmol, 10 equiv) and DBU (0.9 mL, 6.02 mmol, 10 equiv) were added. The mixture was shaken at 20 °C for 22 h, filtered, and extensively washed with NMP, CH₂Cl₂, and methanol. Cleavage from the support was effected by treatment of the resin with TFA/CH₂Cl₂ (1/1, 9 mL, 20 °C, 0.5 h). Filtration, and concentration of the filtrate yielded crude **5a** (306 mg, 99% pure by evaporative light scattering) as an oil. Crystallization from AcOEt/heptane at –20 °C yielded the title compound (144 mg, 63%) as a colorless solid; m.p. 81–83 °C; LCMS: *m/z*: 266 [MH⁺]; ¹H NMR (400 MHz, [D₆]DMSO) δ = 1.51 (br.s, 2H), 1.72 (br.s, 4H), 2.98–3.29 (m, 4H), 3.34 (dd, *J* = 13.5 Hz, 1H), 3.53 (dd, *J* = 13.8 Hz, 1H), 4.29 (dd, *J* = 5.8 Hz, 1H), 7.38–7.43 (m, 3H), 7.50–7.55 (m, 2H); ¹³C NMR (100 MHz, [D₆]DMSO) δ = 20.48 (t), 21.82 (t), 43.41 (d), 52.40 (t), 56.26 (t), 128.21 (d), 128.81 (d), 130.35 (s), 132.45 (d), 170.08 (s); elemental analysis calcd for C₁₄H₁₉NO₂S·C₂H₅F₃O₂ (379.40): C 50.65, H 5.31, N 3.69; found: C 50.94, H 5.38, N 3.63.

Received: August 19, 1999 [Z13901]

Table 1. Yields and purities of crude 3-amino-2-thiopropionic acid derivatives **5**

Compound	Product ^[a]	Purity [%] ^[b] (214 nm/254 nm)	Yield [%] ^[c]
5a		90/100	75
5b		73/85 ^[d]	49
5c		85/– ^[e]	75
5d		90/95	95
5e		68/75 ^[d,f]	73
5f		82/86	79
5g		72/– ^[e]	31
5h		50/64	74
5i		61/86 ^[d,f]	90
5j		91/87	94

[a] All products are TFA salts. [b] The wavelength numbers refer to the HPLC UV detector. [c] Determined by ¹H NMR spectroscopy using [D₆]DMSO as an internal standard and calculated on the basis of a loading of 1.00 mmol g^{–1} in resin **1a** and a loading of 0.68 mmol g^{–1} in resin **1b**.^[7] [d] ¹H NMR spectrum is available as Supporting Information on the WWW or from the author. [e] The product showed no significant absorption at 254 nm. [f] The second nucleophilic substitution was conducted at 80 °C.

- [1] E. M. Gordon, M. A. Gallop, D. V. Patel, *Acc. Chem. Res.* **1996**, 29, 144–154; X. Williard, I. Pop, L. Bourel, D. Horvath, R. Baudelle, P. Melnyk, B. Deprez, A. Tartar, *Eur. J. Med. Chem.* **1996**, 31, 87–98; N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki, J. Steele, *Tetrahedron* **1995**, 51, 8135–8173; E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor, M. A. Gallop, *J. Med. Chem.* **1994**, 37, 1385–1401.
- [2] A. M. Davis, S. J. Teague, *Angew. Chem.* **1999**, 111, 778–792; *Angew. Chem. Int. Ed.* **1999**, 38, 736–749.
- [3] The highest possible number of sequential nucleophilic substitutions will depend on the structure of the polyelectrophile chosen. Two or three sequential substitutions with typical nucleophiles will lead to products reaching the highest recommended molecular weight for an orally available drug (ca. 500–600 g mol^{–1}).
- [4] As a model amine we used piperazine bound to the Wang resin as a carbamate: F. Zaragoza, S. V. Petersen, *Tetrahedron* **1996**, 52, 10823–10826. Primary amines bound to polystyrene through backbone amide linkages can also be used, which expands the scope of this synthesis significantly.

- [5] The structure of resin **2** was confirmed by acidolytic cleavage from the support and analysis of the crude product by HPLC and LCMS.
 [6] B. L. Mylari, T. A. Beyer, T. W. Siegel, *J. Med. Chem.* **1991**, *34*, 1011–1018; J. F. Harris, *J. Org. Chem.* **1972**, *37*, 1340–1346.
 [7] The loading of resin **1a** was as indicated by the manufacturer. The loading of resin **1b** was determined by acylation with 4-fluoro-3-nitrobenzoic acid, cleavage from the support, and yield determination of the monoacylated piperazine by ^1H NMR spectroscopy.

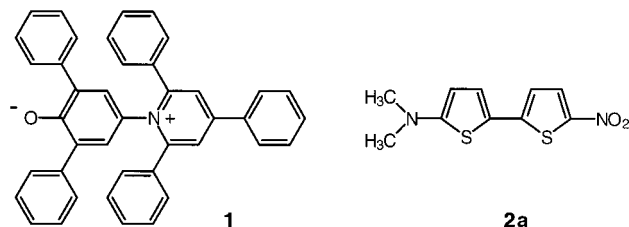
New Solvatochromic Dyes of the 5-Dimethylamino-5'-nitro-2,2'-bithiophene Type**

Horst Hartmann,* Katrin Eckert, and Anke Schröder

Dedicated to Professor Christian Reichardt on the occasion of his 65th birthday

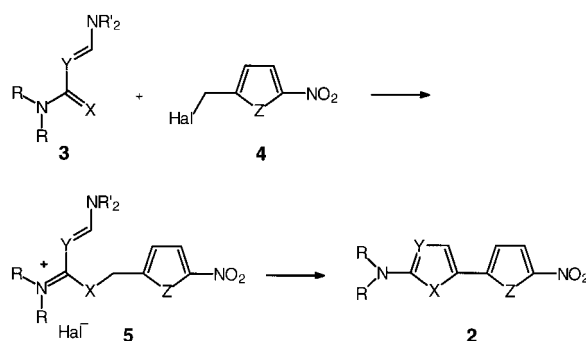
Solvatochromic dyes are suitable as probes for the determination of solvent polarity.^[1] Pyridinium betaines **1**, whose long-wavelength absorption is shifted towards shorter wavelengths by more than 9700 cm^{-1} (negative solvatochromism) on changing from a nonpolar to a polar solvent, have proved to be particularly suitable for this purpose.^[2] However, probe dyes **1** suffer from the defect that in acidic solvents they can lose their solvent sensitivity in part or totally by protonation. This disadvantage is not displayed by the positive solvatochromic 2,2'-bithiophene dye **2a** described recently by Effenberger and Würthner.^[3] It can therefore also be used to advantage for the determination of the solvent polarity of protic solvents. More recently the polarity of solid surfaces was also determined with this dye.^[4] However, in comparison to **1**, **2a** exhibits a significantly lower solvent sensitivity of about 4700 cm^{-1} , which is only about half the value for the pyridinium betaine dye.

In the synthesis of 5-dimethylamino-5'-nitro-substituted 2,2'-bithiophene **2a**, use was made of a heteroaryl–heteroaryl coupling mediated by organometallic intermediates. This method is also suitable for the preparation of other 5-donor-5'-acceptor-substituted 2,2'-bithiophenes.^[3] Until now, however, it has not been suitable for the synthesis of compounds of analogous structure in which, for example the thiophene fragment is replaced by ring systems with equal numbers of π electrons. Consequently, nothing is known of the suitability of such compounds for the determination of solvent polarity.



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[**] This work was supported by the Deutsche Forschungsgemeinschaft.
 Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



We describe now an alternative route for the preparation of **2a** that is also suitable for the synthesis of other compounds of structure **2** in which the dimethylamino and the nitro groups may be replaced by other substituents with electron-donor or electron-acceptor properties and the thiophene rings may be replaced by other ring systems of similar electronic structure. The principle features of this route were developed initially by Rajappa in the 1970s^[5] and later expanded by, in particular, Liebscher and ourselves.^[6] It consists of the reaction of a compound of the general formula **3**^[7,8] with a halomethyl compound **4** with formation of iminium salts of type **5**. These are then transformed into the respective target compounds of type **2** by treatment with a suitable auxiliary base.

Table 1 illustrates a number of the compounds of the general type **2** which we have been prepared. Their structures were confirmed by elemental analysis and by spectrographic methods.^[9] Characteristic compound data are summarized in Table 2.

The compounds described are highly crystalline, air-stable but light-sensitive solids. Their color is highly dependent upon

Table 1. Selected compound data of compounds of type **2**.^[a,b]

2b : M.p. 160–162 °C; ^1H NMR (CDCl_3): $\delta = 3.23$ (t, 4H, NCH_2), 3.74 (t, 4H, OCH_2), 6.28 (d, 1H, CH), 7.09 (d, 1H, CH), 7.45 (d, 1H, CH), 7.97 (d, 1H, CH)
2c : M.p. 142–143 °C; ^1H NMR (CDCl_3): $\delta = 6.51$ (d, 1H, CH), 6.85 (d, 1H, CH), 7.12–7.17 (m, 3H, CH), 7.20–7.23 (m, 4H, CH), 7.30–7.36 (m, 4H, CH), 7.78 (d, 1H, CH)
2e : M.p. 233–234 °C; ^1H NMR (CDCl_3): $\delta = 3.51$ (t, 4H, NCH_2), 3.79 (t, 4H, OCH_2), 7.18 (d, 1H, CH), 7.85 (s, 1H, CH), 8.02 (d, 1H, CH)
2g : M.p. 206–207 °C; ^1H NMR (CDCl_3): $\delta = 3.04$ (s, 3H, CH_3), 5.79 (d, 1H, CH), 6.66 (d, 1H, CH), 7.32 (d, 1H, CH), 7.76 (d, 1H, CH)
2h : M.p. 210–212 °C; ^1H NMR (CDCl_3): $\delta = 3.20$ (m, 4H, NCH_2), 3.85 (m, 4H, OCH_2), 6.08 (d, 1H, CH), 6.74 (d, 1H, CH), 7.30 (d, 1H, CH), 7.78 (d, 1H, CH)
2i : M.p. 220–221 °C; ^1H NMR (CDCl_3): $\delta = 3.04$ (s, 6H, CH_3), 5.86 (d, 1H, CH), 7.38 (d, 1H, CH), 7.43 (d, 2H, CH), 8.10 (d, 2H, CH)
2j : M.p. 200–201 °C; ^1H NMR (CDCl_3): $\delta = 3.21$ (m, 4H, NCH_2), 3.85 (m, 4H, OCH_2), 6.16 (d, 1H, CH), 7.40 (d, 1H, CH), 7.48 (d, 2H, CH), 8.14 (d, 2H, CH)
2k : M.p. 260–262 °C; ^1H NMR (CDCl_3): $\delta = 3.54$ (m, 4H, NCH_2), 3.82 (m, 4H, OCH_2), 6.79 (d, 1H, CH), 7.44 (s, 1H, CH), 7.79 (d, 1H, CH)
2l : M.p. 226–228 °C; ^1H NMR (CDCl_3): $\delta = 3.83$ (m, 4H, NCH_2), 3.81 (m, 4H, OCH_2), 7.43 (d, 2H, CH), 7.51 (s, 1H, CH), 8.15 (d, 2H, CH)
2m : M.p. 122–125 °C; ^1H NMR ($[\text{D}_6]\text{DMSO}$): $\delta = 2.95$ (s, 6H, CH_3), 5.92 (d, 1H, CH), 7.04 (d, 1H, CH), 7.21 (d, 1H, CH), 7.74 (d, 1H, CH)
2n : M.p. 147–148 °C; ^1H NMR ($[\text{D}_6]\text{DMSO}$): $\delta = 3.17$ (t, 4H, NCH_2), 3.74 (t, 4H, OCH_2), 6.20 (d, 1H, CH), 7.12 (d, 1H, CH), 7.24 (d, 1H, CH), 7.77 (d, 1H, CH)

[a] For the substitution pattern, see Table 2. [b] **2a**: ref. [3], **2d**: ref. [6d], **2f** and **2o**: ref. [6e], **2p** and **2q**: ref. [11b].

Table 2. Absorption and solvatochromism data for 5-donor–5'-acceptor-substituted 2,2'-bithiophenes of type **2**.

Compd	R ₂ N	X	Y	Z	Acceptor	$\lambda_{\max}$ (lg ϵ) ^[a]	<i>a</i>	<i>b</i>	<i>r</i>
2a	Me ₂ N	S	CH	S	NO ₂	537 (4.36)	21.150	–3.33	–0.9906
2b	morpholino	S	CH	S	NO ₂	501 (4.31)	22.246	–3.13	–0.9945
2c	(C ₆ H ₅) ₂ N	S	CH	S	NO ₂	507 (4.28)	21.399	–2.08	–0.9831
2d	morpholino	S	CH	CH=CH	NO ₂	437 (4.36)	24.480	–2.26	–0.9907
2e	morpholino	S	N	S	NO ₂	456 (4.30)	23.453	–2.19	–0.9673
2f	morpholino	S	N	CH=CH	NO ₂	406 (4.30)	25.716	–1.55	–0.9851
2g	Me ₂ N	Se	CH	S	NO ₂	544 (4.26)	20.918	–3.47	–0.9868
2h	morpholino	Se	CH	S	NO ₂	505 (4.19)	21.876	–3.06	–0.9798
2i	Me ₂ N	Se	CH	CH=CH	NO ₂	474 (4.30)	22.956	–2.53	–0.9898
2j	morpholino	Se	CH	CH=CH	NO ₂	445 (4.23)	24.059	–2.26	–0.9806
2k	morpholino	Se	N	S	NO ₂	462 (4.22)	23.332	–2.40	–0.9798
2l	morpholino	Se	N	CH=CH	NO ₂	409 (4.18)	25.516	–1.56	–0.9045
2m	Me ₂ N	S	CH	S	CN	417 (4.34)	25.124	–1.59	–0.9857
2n	morpholino	S	CH	S	CN	397 (4.41)	26.041	–1.33	–0.9783
2o	morpholino	S	CH	CH=CH	CN	378 (4.41)	27.186	–1.18	–0.9650
2p	morpholino	S	CH	S	CH=C(CN) ₂	536 (4.54)	19.866	–1.65	–0.9883
2q	morpholino	S	CH	S	C(CN)=C(CN) ₂	681 (4.69)	16.826	–2.61	–0.9229

[a] In [nm], measured in dichloromethane.

the acceptor substituent, but less so upon the ring substituents X, Y, and Z. Whereas the cyano-substituted compounds **2m–2o** are yellow, the nitro-substituted derivatives **2a–2l** are mostly dark red. The dicyanovinyl-substituted compound **2p** is violet, and the tricyanovinyl compound **2q** deep blue.

To determine the suitability of the described dyes for the determination of solvent polarity their absorption spectra were measured in a range of solvents of different polarity. The most intense long-wave absorption maxima were compared with the solvent specific π^* values introduced by Kamlet and Taft^[10] and modified by Effenberger, Würthener, and Steybe with polarization terms^[3b] (Figure 1). The correlation parameters *a*, *b*, and *r* obtained with Equation (1) for all compounds investigated are shown in Table 2.

$$1/\lambda_{\max} = a + b\pi^* \quad (1)$$

Whereas parameter *r* is a measure of the quality of the relevant correlation, parameter *b* reflects the solvent sensitivity of the respective dye. Its negative sign indicates a positive solvatochromism. Parameter *a* shows the absorption wavelength in units of 10^{–5} cm of the respective dye in a nonpolar solvent of polarity index $\pi^* = 0$.

As can be seen, the donor–acceptor-substituted 2,2'-bithiophene dye **2a** exhibits almost the greatest solvent dependency of its long-wavelength absorption band. Neither the replacement of the dimethylamino group by other donor groups (for example, by a morpholino group or diphenylamino group) nor the replacement of the nitro group by another acceptor group (for example, a dicyano- or tricyanovinyl group) nor the exchange of one of the two thiophene rings by other ring systems (for example, by a thiazole, selenazole, or phenyl moiety) leads to a marked increase in the solvent sensitivity of the relevant absorption band of the respective compound. However, a slight increase in solvent dependency was measured with **2g**, in which the dimethylamino-substi-

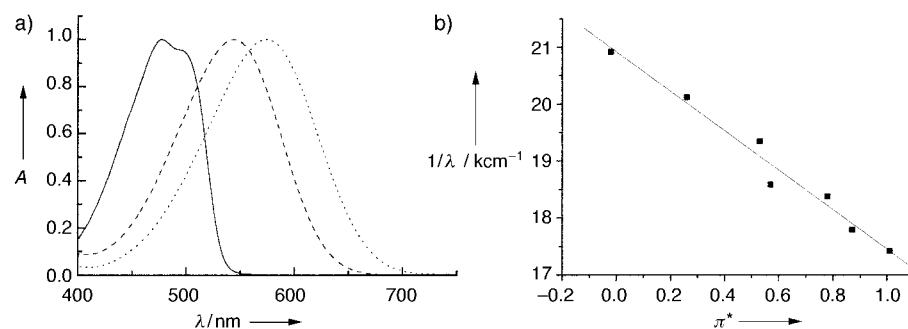


Figure 1. a) Normalized absorption spectra of **2g** in cyclohexane (—), dichloromethane (---), and DMSO (····); b) correlation of the measured $\lambda_{\max}$ values of **2g** with the π^* values of different solvents calculated with Equation (1).

tuted thiophene ring was replaced by a selenophene ring. With a *b* value of –3.47 this compound exhibits the greatest solvent dependency yet measured for a compound of structure **2**, and thus for a positive solvatochromic compound. To illustrate this fact the corresponding spectroscopic data and the correlation data determined for **2g** are shown graphically in Figure 1.

The statements expressed here remain valid, in principle, if other solvent parameters are used for a quantitative description of the solvent dependency of the absorption spectra of the compounds investigated, or if the range of solvents used is significantly extended (see the Supporting Information).

Because of the structural similarity of all the compounds investigated, it would be reasonable to expect that in each case the difference in dipole moment between the ground state and the first excited state would be responsible for the solvent dependency of the absorption bands.^[15] That would mean that this difference is particularly large in **2g**, followed by the difference in **2a**. However, attempts to support this suggestion by appropriate MO calculations, for example in the framework of the known PPP formalism with optimized molecular geometry, have been unsuccessful until now. Thus, within the investigated series of compounds **2** no proportionality between measured solvent sensitivity, quantified by the corresponding *b* value, and calculated dipole moment change could be established.

Experimental Section

The starting materials **3** and **4** used in the preparation of compounds of type **2** were known or could be prepared by literature methods.^[7, 8, 11] Previously unknown sulfur- or selenium-containing reagents of type **3** with X = S or Se and Y = CH were obtained by reaction of the corresponding 3-chloro-3-dialkylaminopropeniminium salts^[12] with sodium sulfide or selenide^[13] in ethanol.^[14]

3-Chloro-3-morpholinopropenylidene dimethyliminium perchlorate was prepared according to the literature method.^[12a] M.p. 177–180 °C; ¹H NMR (CDCl₃): δ = 3.20 (s, 3H, NCH₃), 3.41 (s, 3H, NCH₃), 3.75 (m, 4H, NCH₂), 3.91 (m, 4H, OCH₂), 5.84 (d, 1H, CH), 8.23 (d, 1H, CH).

General method for the preparation of **2**: Equivalent amounts of **3** and **4** (each 0.01 mol) were dissolved in methanol (50 mL) or acetonitrile (50 mL) and then heated to boiling for a short time. After the reaction solution had cooled, it was treated with either triethylamine (25 mL) or a 25 % sodium methylate solution (50 mL) and then briefly warmed again. After the reaction mixture had once more cooled, it was treated with water (10 mL) and the precipitated solid was filtered off.

In this way, for example, **2a** (m.p. 174–176 °C; 176–177 °C^[3a]) was formed from 1,3-bis(dimethylamino)propene-3-thione **3** (X = S, Y = CH, R₂N = NR₂' = (CH₃)₂N) and 5-chloromethyl-2-nitrothiophene^[11c] in 93 % yield, and **2g** (m.p. 206–207 °C) was prepared from 1,3-bis(dimethylamino)propene-3-selenone **3** (X = Se, Y = CH, R₂N = NR₂' = (CH₃)₂N) and 5-chloromethyl-2-nitrothiophene in 75 % yield.

Received: July 20, 1999 [Z13749]

- [1] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, Weinheim, **1988**.
- [2] C. Reichardt, *Chem. Rev.* **1994**, *94*, 2319–2358.
- [3] a) F. Effenberger, F. Würthner, *Angew. Chem.*, **1993**, *105*, 742–744; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 719–721; b) F. Effenberger, F. Würthner, F. Steybe, *J. Org. Chem.* **1995**, *60*, 2082–2091.
- [4] S. Spange, A. Reuter, E. Vilsmeier, *Colloid Polym. Sci.* **1996**, *274*, 59–69.
- [5] a) S. Rajappa, B. G. Advani, *Tetrahedron Lett.* **1969**, 5067–5068; b) S. Rajappa, B. G. Advani, *Indian J. Chem. B* **1971**, *9*, 759–760; c) S. Rajappa, B. G. Advani, *Indian J. Chem. B* **1971**, *9*, 761–762; d) S. Rajappa, B. G. Advani, *Indian J. Chem.* **1974**, *12*, 1; e) S. Rajappa, B. G. Advani, R. Sreenivasan, *Synthesis* **1974**, 656–657.
- [6] a) J. Liebscher, H. Hartmann, *J. Prakt. Chem.* **1976**, *318*, 731–744; b) J. Liebscher, H. Hartmann, *Synthesis* **1979**, 241–264; c) J. Liebscher, B. Abegaz, H. Hartmann, *DD-Patent* 201306, **1983** [*Chem. Abstr.* **1984**, *100*, 51590]; d) J. Liebscher, B. Abegaz, A. Areda, *J. Prakt. Chem.* **1983**, *325*, 168–172; e) J. Liebscher, K. Feist, *Synthesis* **1985**, 412–414; f) J. Liebscher, A. Knoll, B. Abegaz, P. Czerney, *Bull. Chem. Soc. Ethiop.* **1987**, *1*, 29–31; g) J. Liebscher, *Z. Chem.* **1988**, *28*, 291–292.
- [7] J. Liebscher, A. Knoll, B. Abegaz, *Z. Chem.* **1987**, *27*, 8–15, and references therein.
- [8] W. Kantlehner, M. Hauber, M. Vettel, *J. Prakt. Chem.* **1996**, *338*, 403–413.
- [9] The ¹H NMR spectra were measured with a Varian 300 MHz spectrometer and the UV/Vis spectra with a Perkin-Elmer Lambda-900 spectrometer in the following solvents (π* values in parentheses): cyclohexane (–0.02), tetrachloromethane (+0.26), toluene (+0.53), ethanol (+0.57), dichloromethane (+0.78), DMF (+0.87), DMSO (+1.01).
- [10] a) J. Kamlet, J. L. M. Abboud, M. H. Abraham, R. W. Taft, *J. Org. Chem.* **1983**, *48*, 2877–2887; b) M. J. Kamlet, J. L. M. Abboud, R. W. Taft, *J. Am. Chem. Soc.* **1977**, *99*, 6027–6038; c) R. W. Taft, M. J. Kamlet, *J. Am. Chem. Soc.* **1976**, *96*, 2886–2894; d) R. W. Taft, M. J. Kamlet, *J. Chem. Soc. Perkin Trans. 2* **1979**, 1723–1729.
- [11] Compounds of type **4** were prepared according to a) H. G. O. Becker, *Organikum*, 19th ed., Johann Ambrosius Barth, Leipzig, **1988**; b) K. Eckert, A. Schröder, H. Hartmann, *Eur. J. Org. Chem.*, in press; c) P. J. Newcombe, R. K. Norris, *Aust. J. Chem.* **1979**, *32*, 2647–2658.
- [12] a) Z. Arnold, *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051–3057; b) W. Schroth, U. Jahn, D. Ströhl, *Chem. Ber.* **1994**, *127*, 2013–2022.

- [13] D. L. Klayman, T. S. Griffins, *J. Am. Chem. Soc.* **1973**, *95*, 197–199.
- [14] 1,3-Bis(dimethylamino)propene-3-selenone **3** (X = Se, Y = CH, R₂N = NR₂' = (CH₃)₂N) was obtained from [3-chloro-3-dimethylaminopropenylidene]dimethyliminium perchlorate^[12a] and Na₂Se: M.p. 120–122 °C, ¹H NMR (CDCl₃): δ = 3.06 (s, 3H, NCH₃), 3.16 (s, 3H, NCH₃), 3.29 (s, 3H, NCH₃), 3.50 (s, 3H, NCH₃), 8.77 (s, 1H, CH); 1-dimethylamino-3-morpholinopropene-3-selenone **3** (X = Se, Y = CH, R₂N = morpholino, NR₂' = (CH₃)₂N) was prepared from (3-chloro-3-morpholinopropenylidene)dimethyliminium perchlorate and Na₂Se in a similar way: M.p. 123–125 °C; ¹H NMR (CDCl₃): δ = 2.96 (s, 4H, NCH₂), 4.11 (s, 4H, OCH₂), 5.28 (d, 1H, CH), 8.37 (d, 1H, CH).
- [15] a) E. Lippert, *Z. Elektrochem.* **1957**, *61*, 962–975; b) W. Liptay, *Z. Naturforsch. A* **1965**, *20*, 1441–1471; c) D. R. Kanis, M. A. Ratner, T. J. Marks, *Chem. Rev.* **1994**, *94*, 195–242.

Doubly *meso*-β-Linked Diporphyrins from Oxidation of 5,10,15-Triaryl-Substituted Ni^{II}- and Pd^{II}-Porphyrins*

Akihiko Tsuda, Aiko Nakano, Hiroyuki Furuta, Hideki Yamochi, and Atsuhiko Osuka*

In recent years there has been a considerable upsurge in the synthesis of covalently linked multiporphyrin arrays. These compounds are interesting in light of their unique photo-electronic properties and potential applications as mimics of light-harvesting systems in photosynthesis, and as electron-energy transfer moieties in molecular wires.^[1] Among these, fused oligoporphyrins sharing a common extended π-electron network are of particular interest because of their remarkable red-shifted absorption bands as well as their extremely enhanced electronic communications that are favorable for molecular wires.^[2, 3] Indeed, several fused diporphyrins and oligoporphyrins exhibit significantly red-shifted Soret bands and intense Q-bands,^[2, 3] which demonstrates the promising potential of fused multiporphyrins. Here we report a facile synthesis of other fused diporphyrins that contain two *meso*-β direct linkages.

Recently we found that the one-electron oxidation of 5,15-diaryl-substituted metalloporphyrins bearing sterically uncongested *meso*-positions led to the formation of directly linked porphyrin dimers. The Zn^{II} complex gave a *meso*-*meso*-linked diporphyrin by oxidation with a Ag^I salt or by

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[**] This work was supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan and by CREST (Core Research for Evolutional Science and Technology) of Japan Science and Technology Corporation (JST). A. T. thanks JSPS Research Fellowship for Young Scientists. We thank Prof. G. Saito and Mr. T. Aoki for their help in recording the single-crystal X-ray structure data.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

electrochemical oxidation,^[4,5] while the electrochemical oxidation of the Ni^{II} and Pd^{II} complexes gave a *meso*- β -linked diporphyrin.^[6] With regard to the reaction mechanism, which involves the reaction of a radical cation with a neutral metalloporphyrin, the different regioselectivity observed may be explained in terms of different HOMO orbitals between Zn^{II}-porphyrin and Ni^{II}- and Pd^{II}-porphyrins. Probably the former favors the A_{2u} HOMO, which exhibits large electron density at the *meso*-carbon atoms, whereas the latter favor the A_{1u} HOMO, which exhibits significant density at β -pyrrole carbon atoms.^[7]

We then examined oxidation reactions of metalloporphyrins with a strong oxidant which facilitated the instantaneous generation of a porphyrin radical cation. Initially 5,15-diaryl-Ni^{II}-porphyrin **1** was treated with an equivalent amount of tris(4-bromophenyl)aminium hexachloroantimonate (BAHA), a typical one-electron oxidizing agent, in CHCl₃ for 12 h. Separation by preparative size-exclusion (SEC) chromatography and the analysis by MALDI-TOF mass spectrometry revealed the formation of dimeric, trimeric, and tetrameric porphyrins. Diporphyrin **2**, which was isolated in a pure form from the diporphyrin fraction by flash silica gel column chromatography, was characterized by FAB mass spectrometry (m/z 1550.0 [$M+1$]; calcd for C₉₆H₉₈N₈Cl₂-Ni₂=1548.6) and ¹H NMR spectroscopy (no *meso*-proton, three sets of mutually coupled doublets for β -protons at δ =9.42 and 9.11, 9.08 and 8.74, and 8.46 and 8.41, and a singlet for the β -proton (H_a) at δ =8.98). In addition, a 2D-ROESY NMR measurement of **2** revealed distinct ROESY effects between protons H^a and H^b, indicating their close proximity. In the reaction of **3** with BAHA the diporphyrin **2** was also obtained in 68% yield together with *meso*-*meso*-linked diporphyrin **4** (10% yield). Noteworthy is that singly *meso*- β -linked diporphyrin **5**^[6] was quantitatively converted into

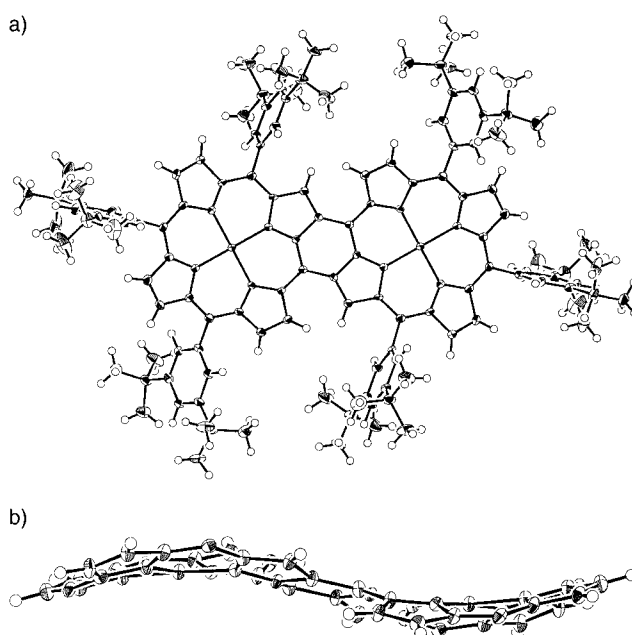
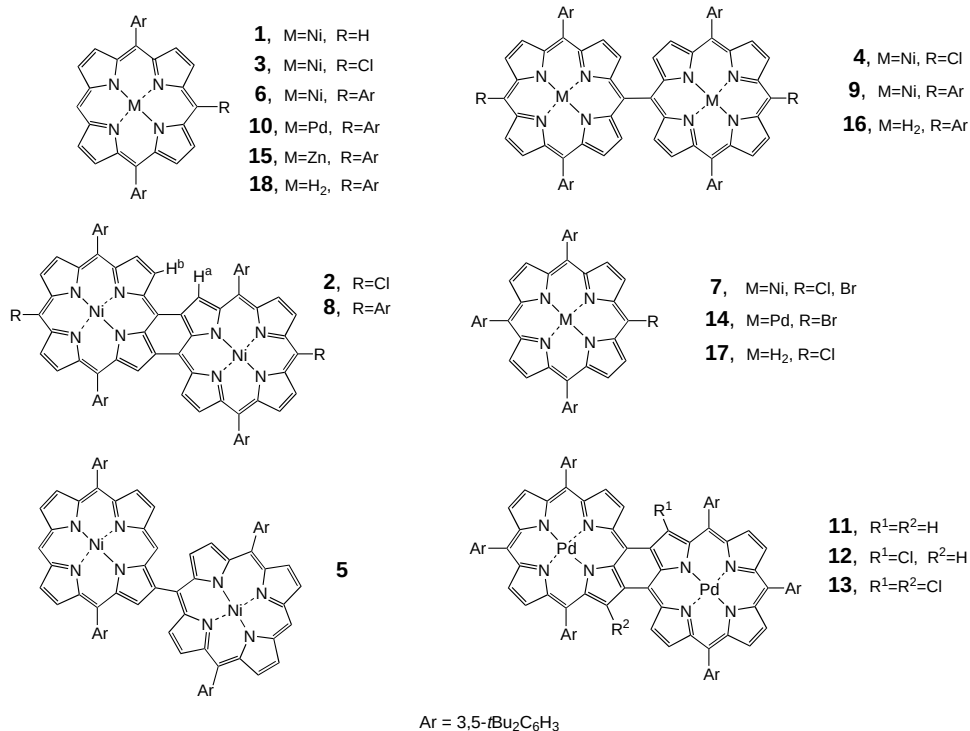


Figure 1. Molecular structure of **8**. a) Top view, b) side view.

doubly *meso*- β -linked diporphyrin **2** upon treatment with BAHA, presumably through oxidative ring closure between another *meso*- β position and *meso*-chlorination. The triporphyrin and tetraporphyrin fractions obtained from the reaction of **1** with BAHA are complicated mixtures and their further characterization is in progress.^[8]

In the search for a route that avoids these complicated higher order coupling reactions, we next examined the reaction of 5,10,15-triaryl-Ni^{II}-porphyrin **6**.^[9] In addition to *meso*-halogenated products **7**^[10] (29%), doubly *meso*- β -linked diporphyrin **8** was obtained in 53% yield along with *meso*-*meso*-linked diporphyrin **9**^[9] (10%). The molecular structure of **8** was confirmed by X-ray crystallography (Figure 1).^[11] The two porphyrin rings are almost coplanar, but adopt a ruffled conformation; the mean deviation of the 24 core atoms above or below the mean plane is 0.82 Å. The two newly formed *meso*- β bonds are 1.45 Å long, and are similar in length to the C₂-C₃ bond (1.48 Å) of 1,3-butadiene; the Ni-Ni distance is 8.61 Å.

Similar doubly *meso*- β -linked diporphyrin products **11**–**13** were obtained in the reaction of Pd^{II}-porphyrin **10** with 1.2 equivalents of BAHA in 20, 18, and 19% yields, respectively. The product ratio of **11**–**13** depends on the reaction time and the amount of BAHA used. Thus, use of three



equivalents of BAHA led to the formation of the dichlorinated diporphyrin **13** in 49% yield as a sole doubly *meso*- β -linked diporphyrin product along with the *meso*-brominated product **14**.^[12] The regioselectivity of the chlorination as judged by the ¹H NMR data is interestingly quite high only at the β -position next to the fused ring. The reaction of 5,10,15-triaryl- Zn^{II} -porphyrin **15** with BAHA gave the *meso*-*meso*-linked diporphyrin **16** (31%) as a single diporphyrin product along with the *meso*-chlorinated porphyrin **17** (31%). The analogous oxidation of the free porphyrin base **18** gave the *meso*-*meso*-linked dimer **16** in 41% yield with the recovery of **18** (38%). Therefore, it might be concluded that in the reaction with BAHA Ni^{II} - and Pd^{II} -porphyrins with a A_{1u} HOMO orbital afford a doubly *meso*- β -linked diporphyrin as a main product, while the Zn^{II} -porphyrin and a free porphyrin base with a A_{2u} HOMO orbital gives a *meso*-*meso*-linked diporphyrin.

The absorption spectra of **5**, **6**, **8**, and **9** are shown in Figure 2 for comparison. In contrast to the normal absorption spectrum of **6** with a sharp Soret band at 412 nm, singly *meso*- β and *meso*-*meso*-linked dimers **5** and **9** exhibit broadened

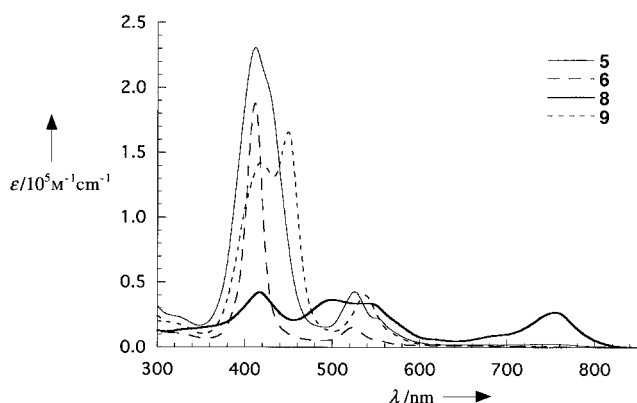


Figure 2. Absorption spectra of **5**, **6**, **8**, and **9** in CHCl_3 .

and split Soret bands, respectively. The absorption spectrum of the doubly *meso*- β -linked diporphyrin **8** has an entirely different spectral shape with four bands at 417, 501, 538, and 756 nm with similar intensities. The most notable feature is a red-shifted, intense Q-band. Other doubly *meso*- β -linked diporphyrins **2**, **11**–**13** exhibit similar absorption spectra with a red-shifted Q-band at 756, 748, 747, and 734 nm, respectively, suggesting that these broad absorption spectra with a red-shifted, intense Q-band are common for this doubly *meso*- β -linked diporphyrin structure. These features, which are similar but much stronger than those in a 1,4,5,8-tetraaza-anthracene-bridged diporphyrin^[2] and a directly β -fused diporphyrin^[3], are indicative of extensively delocalized π -electron systems. Thus these new diporphyrins are interesting with regard to nonlinear optical susceptibilities^[8, 13] and application as conducting “molecular wires”.^[14]

The electrochemical properties of doubly *meso*- β -linked diporphyrins are also interesting, since the one-electron oxidation potentials of the Ni^{II} -porphyrin monomers, 0.87 V^[15] in **3** and 0.76 V in **6**, drop to 0.63 and 0.52 V in the doubly *meso*- β -linked diporphyrins **2** and **8**, respectively.

Similar trends are also observed for Pd^{II} -porphyrins: the one-electron oxidation potentials of **11**–**13** are 0.57, 0.59, and 0.62 V, respectively, and are thus significantly lower than that of **10** (0.82 V).

The oxidation of 5,10-diaryl- and 5,10,15-triaryl- Ni^{II} - and Pd^{II} -porphyrins with BAHA constitutes a new, facile synthetic route to doubly *meso*- β -linked diporphyrins that exhibit unique optical and electrochemical properties stemming from their full π -conjugation.^[16] The lower oxidation potentials of the doubly *meso*- β -linked diporphyrins than that of the starting metalloporphyrin suggest an extension of this synthetic strategy to higher oligoporphyrins.

Experimental Section

A 50-mL round-bottomed flask was charged with a solution of **6** (30 mg, 32 mmol) in CHCl_3 (20 mL). The reaction vessel was covered with foil. BAHA (32 mg, 39 mmol) was added in one portion. After the mixture had been stirred for 12 h at room temperature, the mixture was diluted with water. The organic layer was separated off, washed with water, and dried over anhydrous MgSO_4 . The product was initially separated by preparative size-exclusion column chromatography (BioRad Bio-Beads SX-1 packed in CHCl_3 in a 4.5×95 cm gravity flow column; flow rate 3.8 mL min^{-1}). Elution with CHCl_3 yielded a fast-eluting diporphyrin fraction and a slow-eluting monoporphyryr fraction. The latter was identified as **7** (9 mg, 28%), an approximate 1:1 mixture of *meso*-chlorinated and *meso*-brominated porphyrins. The former was separated by flash chromatography over a silica gel (Wakogel FC-40) column. Elution with hexane/ CH_2Cl_2 (95:5) gave **8** as the first fraction and **9** as the second fraction. Some of **8**, which remained on the silica gel, was eluted with CH_2Cl_2 . Yields: **8** (16 mg, 53%); **9** (3 mg, 10%).

8 ¹H NMR (500 MHz, CDCl_3 , 25 °C, TMS): δ = 1.45 (s, 36 H; *t*Bu), 1.51 (s, 36 H; *t*Bu), 1.54 (s, 36 H; *t*Bu), 7.67 (t, J = 1.8 Hz, 2 H; Ar-H), 7.72 (t, J = 1.8 Hz, 2 H; Ar-H), 7.75 (t, J = 1.8 Hz, 2 H; Ar-H), 7.79 (d, J = 1.8 Hz, 4 H; Ar-H), 7.84 (d, J = 1.8 Hz, 4 H; Ar-H), 7.96 (d, J = 1.8 Hz, 4 H; Ar-H), 8.37 (d, J = 4.9 Hz, 2 H; Por- β), 8.40 (s, 4 H, 8.46; Por- β), 8.45 (d, J = 4.9 Hz, 2 H; Por- β), 8.77 (d, J = 4.9 Hz, 2 H; Por- β), 9.05 (s, 2 H; Por- β), 9.49 (d, J = 4.9 Hz, 2 H; Por- β); FAB-MS: m/z (%): 1858, calcd for $\text{C}_{124}\text{H}_{140}\text{N}_8\text{Ni}_2$; 1857; UV/Vis (CHCl_3): λ_{max} = 417 (Soret), 501, 538, and 756 nm.

9 ¹H NMR (500 MHz, CDCl_3 , 25 °C, TMS): δ = 1.40 (s, 72 H; *t*Bu), 1.48 (s, 36 H; *t*Bu), 7.64 (t, J = 1.8 Hz, 4 H; Ar-H), 7.74 (t, J = 1.8 Hz, 2 H; Ar-H), 7.87 (d, J = 1.8 Hz, 8 H; Ar-H), 7.94 (d, J = 1.8 Hz, 4 H; Ar-H), 8.09 (d, J = 4.9 Hz, 4 H; Por- β), 8.58 (d, J = 4.9 Hz, 4 H; Por- β), 8.81 (d, J = 4.9 Hz, 4 H; Por- β), 8.86 (d, J = 4.9 Hz, 4 H; Por- β); FAB-MS: m/z (%): 1861.9, calcd for $\text{C}_{124}\text{H}_{142}\text{N}_8\text{Ni}_2$; 1859.0; UV/Vis (CHCl_3): λ_{max} = 419 (Soret), 450 (Soret), and 538 nm.

Received: June 14, 1999 [Z13549]

- [1] a) M. R. Wasielewski, *Chem. Rev. Jpn.* **1992**, 92, 435; b) D. P. Arnold, G. A. Hearsh, *J. Am. Chem. Soc.* **1993**, 115, 12197; c) V. V. Borovkov, G. V. Ponomarev, A. Ishida, T. Kaneda, Y. Sakata, *Chem. Lett.* **1993**, 1409; d) V. S. Y. Lin, S. G. DiMaggio, M. J. Therien, *Science* **1994**, 264, 1105; e) R. W. Wagner, J. S. Lindsey, *J. Am. Chem. Soc.* **1994**, 116, 9759; f) B. Jiang, S. W. Yang, D. C. Barbini, W. E. Jones, Jr., *Chem. Commun.* **1998**, 213; g) D. A. Shultz, H. Lee, K. P. Gwaltney, *J. Org. Chem.* **1998**, 63, 7584; h) P. N. Taylor, J. Huuskonen, G. Rumbles, R. T. Aplin, E. Williams, H. L. Anderson, *Chem. Commun.* **1998**, 909; i) J. Wytko, V. Berl, M. McLaughlin, R. R. Tykwinski, M. Schreiber, F. Diederich, C. Boudon, J. P. Gisselbrecht, M. Gross, *Helv. Chim. Acta* **1998**, 81, 1964; j) K. Susumu, T. Shimidzu, K. Tanaka, H. Segawa, *Tetrahedron Lett.* **1996**, 37, 8399; k) R. G. Khoury, L. Jaquinod, K. M. Smith, *Chem. Commun.* **1997**, 1057; l) L. Ruhlmann, S. Lobstein, M. Gross, A. Giraudeau, *J. Org. Chem.* **1999**, 64, 1352; m) O. Mongin, A. Gossauer, *Tetrahedron* **1997**, 53, 6835; n) M. O. Senge, X. Feng, *Tetrahedron Lett.* **1999**, 40, 4165.

- [2] a) M. J. Crossley, P. L. Burn, *J. Chem. Soc. Chem. Commun.* **1987**, 39; b) M. J. Crossley, P. L. Burn, *Chem. Commun.* **1991**, 1569; c) M. J. Crossley, L. J. Govenlock, J. K. Prasker, *Chem. Commun.* **1995**, 2379.
- [3] a) L. Jaquinod, O. Siri, R. G. Khoury, K. M. Smith, *Chem. Commun.* **1998**, 1261; b) M. G. H. Vicente, M. T. Cancilla, C. B. Lebrilla, K. M. Smith, *Chem. Commun.* **1998**, 2355.
- [4] A. Osuka, H. Shimidzu, *Angew. Chem.* **1997**, 109, 93; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 135.
- [5] T. Ogawa, Y. Nishimoto, N. Yoshida, N. Ono, A. Osuka, *Chem. Commun.* **1998**, 337.
- [6] T. Ogawa, Y. Nishimoto, N. Yoshida, N. Ono, A. Osuka, *Angew. Chem.* **1999**, 111, 140; *Angew. Chem. Int. Ed.* **1999**, 38, 176.
- [7] P. J. Spellane, M. Gouterman, A. Antipas, S. Kim, Y. C. Liu, *Inorg. Chem.* **1980**, 19, 386.
- [8] MALDI-TOF MS analysis revealed the molecular weights of 2260 (monochlorinated triporphyrins) and 2295 (dichlorinated triporphyrins) for the triporphyrin fraction, and those of 2970 (tetraporphyrins), 3000 (monochlorinated tetraporphyrins), and 3032 (dichlorinated tetraporphyrins) for the tetraporphyrin fraction. The triporphyrin and tetraporphyrin fractions show the absorption bands at 405, 555, 765, and 899 nm and 407, 559, 776, and 910 nm, respectively.
- [9] N. Yoshida, H. Shimidzu, A. Osuka, *Chem. Lett.* **1998**, 55.
- [10] Mixture of *meso*-chlorinated and -brominated porphyrins in a ratio of 1:1.
- [11] Data of the crystal structure of $8 \cdot 2C_6H_{14}$: $C_{124}H_{140}N_8Ni_2 \cdot 4C_6H_{14}$, $M_r = 2204.63$, crystal from $CHCl_3/C_6H_{14}$, crystal dimensions $0.2 \times 0.3 \times 0.25$ mm, space group $P\bar{1}$, $a = 14.807(1)$, $b = 15.293(1)$, $c = 16.595(1)$ Å, $\alpha = 68.256(4)$, $\beta = 77.287(5)$, $\gamma = 75.368(5)^\circ$, $V = 3344$ Å³, $Z = 1$, $\rho_{\text{calc}} = 1.09$ g cm⁻³; $\mu_{\text{Mo}} = 3.23$ cm⁻¹; $\theta_{\text{max}} = 27.5^\circ$. For 11 968 reflections measured; $R_1 = 0.093$ for 8446 data [$I > 3\sigma(I)$], $wR_2 = 0.114$ for all measured data. Diffraction data were collected on a Mac Science DIP-2020K imaging plate system diffractometer (105 K, Mo α radiation $\lambda = 0.71069$ Å). The structure was solved by direct methods and refined by F^2 with all observed reflections. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were added to calculated positions. Programs used: structure determination with SIR92 and refined with teXane for Windows. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133210. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [12] In this case, *meso*-chlorinated product was not obtained. A possible mechanism for the *meso*-bromination may be bromine-atom abstraction by a metalloporphyrin *meso*-radical, since the only available bromine source is BAHA.
- [13] M. Terazima, H. Shimidzu, A. Osuka, *J. Appl. Phys.* **1997**, 81, 2946.
- [14] J. R. Reimers, T. X. Lü, M. J. Crossley, N. S. Hush, *Chem. Phys. Lett.* **1996**, 256, 353.
- [15] Redox potentials versus $AgClO_4/Ag$ were measured by cyclic voltammetry in $CHCl_3$.
- [16] After submission of this paper, we became aware that the analogous doubly *meso*- β -linked diporphyrin without chlorine substitution at *meso*-position was formed in the reaction of **1** with $TeCl_4$: K. Sugiura, T. Matsumoto, S. Ohkouchi, Y. Naitoh, T. Kawai, Y. Takai, K. Ushiroda, Y. Sakata, *Chem. Commun.* **1999**, 1957.

[Ni(NHPnPr₃)(S₃)]⁺, the First Nickel Thiolate Complex Modeling the Nickel Cysteinate Site and Reactivity of [NiFe] Hydrogenase**

Dieter Sellmann,* Franz Geipel, and Matthias Moll

Dedicated to Professor Gerhard Fritz
on the occasion of his 80th birthday

Hydrogenases assume a central role in the natural hydrogen and energy metabolism by catalyzing the reaction (1a). The characteristic feature of H₂ activation by hydrogenases is the heterolytic H₂ cleavage according to Equation (1b). It is established by the H₂/D⁺ exchange [Eq. (1c)], and serves as test reaction for hydrogenase activity.^[1]



The molecular structures of a [NiFe]^[2] and recently also that of a [FeFe] hydrogenase^[3] have been determined by X-ray crystallography. However, the mechanisms of reactions (1a)–(1c) remained discussed controversially, in particular with regard to the role and oxidation states of the metals in the active centers.^[4] Figure 1 schematically depicts the active center of the [NiFe] hydrogenase from *D. Gigas* in the oxidized (inactive) form.

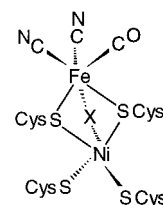


Figure 1. Schematic drawing of the active center of [NiFe] hydrogenase from *D. Gigas* in the oxidized form ("X" = O²⁻, OH⁻, H₂O).^[2a]

Since the discovery of nickel as essential metal of [NiFe] hydrogenases,^[5] the nickel sulfur entity of their active centers has attracted particular attention. Redox titrations, EPR, IR, and EXAFS results indicated it as the H₂ activation site. The redox processes of [NiFe] hydrogenases were interpreted either as nickel-centered comprising oxidation states ranging from Ni^{III} to Ni⁰,^[1] or as nickel thiolate centered yielding nickel thiyl species.^[6] Alternatively, it was recently postulated that the redox processes are centered at the iron atom which is electronically coupled to nickel in the oxidation state Ni^I.^[4a, 7]

Nickel complexes with hydrogenase activity are extremely rare. So far, catalysis of a H₂/D⁺ exchange could be observed only with the thiosemicarbazone complex [NiL₂]Cl₂ (L = *o*-C₆H₄(OH)-CH=N-NHCSNH₂).^[8] Model complexes with nickel thiolate cores and catalysis activity for the H₂

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[**] Transition Metal Complexes with Sulfur Ligands, Part 141. We gratefully acknowledge support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 140: Ref. [10].

heterolysis have remained unknown inspite of intensive research.^[9] Such complexes could solve the important question, which requirements must be met in order to achieve a heterolytic H₂ activation.

The reactions of [Ni(NHPnPr₃)(‘S₃’)] (**1a**) [‘S₃’²⁻ = bis(2-sulfanyphenyl)sulfide(2-)]^[10] yielded answers to this question. Complex **1a** is diamagnetic in the solid state and in solution, has a four-coordinate Ni^{II} center surrounded by one N, one thioether, and two thiolate donors, and exhibits a strongly flattened tetrahedral coordination geometry. Figure 2 depicts the molecular structure determined by X-ray crystallography.^[10]

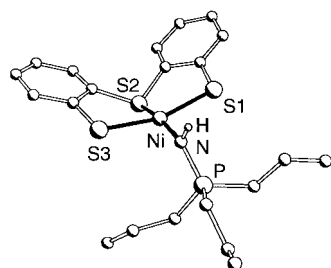
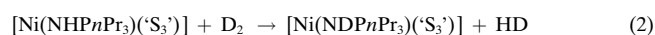


Figure 2. Molecular structure of **1a** (C-bonded H atoms omitted).

When treated with D₂ at slightly elevated pressure (10 bar), complex **1a** gave the DNPnPr₃ complex **1b** and HD [Eq. (2)].



The reaction is slow and could be monitored by ¹H/²H NMR spectroscopy. The ²H NMR spectrum of the reaction solution (CH₂Cl₂) showed the ND signal of **1b** at δ = −1.85 after 96 h. Running the reaction (2) under 30 bar D₂ in a high-pressure NMR tube allowed the observation of the second product HD, which gives rise to a 1:1:1 triplet in the ¹H NMR spectrum (Figure 3).

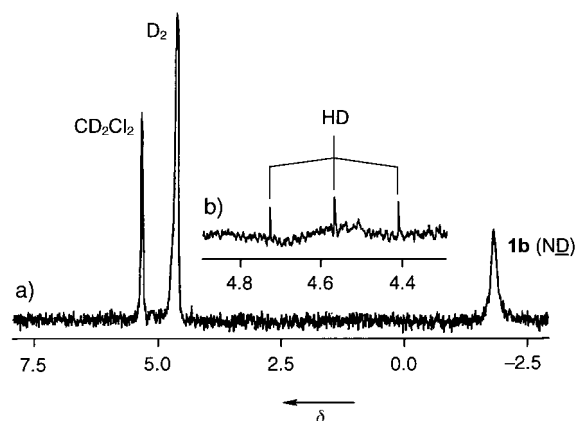


Figure 3. a) ²H NMR spectrum of the solution of **1a** in CH₂Cl₂ under D₂ (10 bar), recorded at standard pressure after 96 h. b) HD region of the CD₂Cl₂ reaction solution when **1a** had been treated with D₂ at 30 bar for 96 h.

Removal of all volatiles yielded solid **1b**. Its IR spectrum (KBr) exhibited a ν(ND) band at 2427 cm^{−1} that could be assigned through comparison with the ν(NH) band of **1a** at 3273 cm^{−1} (ν(NH): ν(ND) = 1.35).

The NH proton of **1a** is weakly acidic, as demonstrated by the H⁺/D⁺ exchange according to Equation (3).

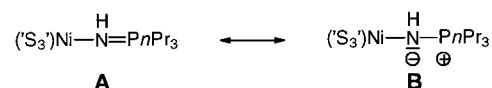


Preliminary experiments showed that the homologous [M(NHPnPr₃)(‘S₃’)] complexes with M = Pd^{II}, Pt^{II} undergo identical reactions [Eq. (2) and (3)], but are more active giving rise to shorter reaction times.

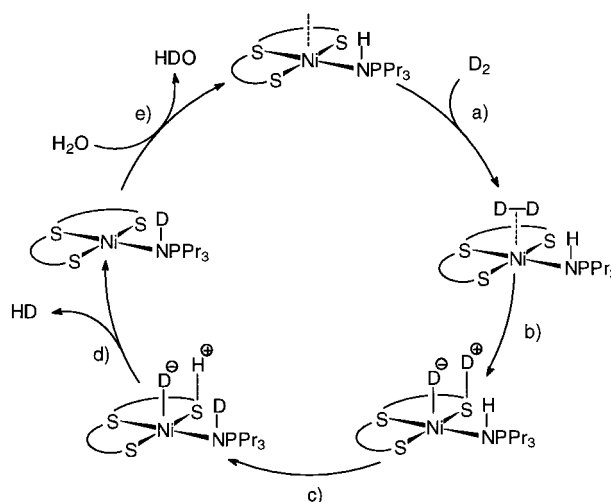
The Equations (2) and (3) demonstrate that **1a** is able to exchange NH protons with molecular D₂ and (subsequently) with H⁺ or D⁺. Substitution of D₂ for H₂ and combination of Equations (2) and (3) sums up to give Equation (4), which demonstrates that **1a** catalyzes the hydrogenase reaction (1c) and the heterolytic cleavage of H₂ (D₂).



Complex **1a** contains a four-coordinate Ni^{II} center, which potentially can add one or two more ligands. In addition, complex **1a** has two built-in Brønsted basic sites represented by the thiolate-donor lone pairs. A third Brønsted basic site potentially is the N donor of the HNPnPr₃ ligand when it assumes the phosphonium imine structure **B**.^[10]



These considerations, supported by previous results on the H₂ activation at transition metal thiolate sites,^[11] suggest the mechanism outlined in Scheme 1 for the D₂ heterolysis catalyzed by **1a**.



Scheme 1. Mechanism of the [Ni(NHPnPr₃)(‘S₃’)] catalyzed D₂/H⁺ exchange according to Equation (1c).

D₂ adds to the nickel center (step a) and is heterolytically cleaved by the concerted action of the Lewis acidic nickel center and one Brønsted basic thiolate donor (step b). The resulting acidic thiol deuteron scrambles with the acidic phosphorane imine proton (step c). The thiol proton and nickel deuteride ligand combine to give HD, which is released (step d as reversal of steps a and b). The resulting DNPnPr₃ complex **1b** can exchange with H₂O to give back the starting catalyst **1a** (step e).

The results reported here allow a series of conclusions:

- 1) Identification and isolation of *both* the reaction products **1b** and HD enabled the unambiguous proof of the D₂ heterolysis by complex **1a**. Therefore, the HNPnPr₃ ligand of **1a** becomes an important probe for the reaction mechanism. Furthermore, H₂/D₂ exchange reactions catalyzed homolytically by metal traces, reaction flask walls, etc. can be excluded.
- 2) The H₂ heterolysis catalyzed by [NiFe] hydrogenases can take place at a Ni^{II} center coordinated by cysteinyl ligands. It does *not* require a Ni^{II} → Ni^I reduction. It requires only the removal of the “X” ligand (“X” = O²⁻, OH⁻, or H₂O) when the inactive oxidized form of [NiFe] hydrogenase is (reductively) converted into the active form.
- 3) The [NiS₄] geometry in Figure 1 is neither tetrahedral nor planar, but strongly distorted. The same holds true for the [NiNS₃] geometry of **1a**. The symmetry of four-coordinate Ni^{II} complexes, however, strongly influences the relative energies of nickel acceptor and donor orbitals that must interact with the σ and σ* orbitals of H₂.^[12] Thus it could be the asymmetry of the nickel sites in [NiFe] hydrogenase and **1a** that favors their interaction with H₂.

Experimental Section

All manipulations were carried out under exclusion of air.

D₂/NH exchange of **1a** with D₂ and identification of **1b**: In a NMR tube, a purple solution of **1a** (45 mg, 0.1 mmol) in CH₂Cl₂ (2 mL) was treated with D₂ (10 bar) in an autoclave. ²H NMR spectra were recorded after 48 and 96 h at standard pressure. After removal of all volatiles, the purple residue was identified as **1b** by IR spectroscopy.

D₂/NH exchange of **1a** with D₂ and identification of HD: The reaction of **1a** with D₂ under 30 bar was carried out in CD₂Cl₂ in a high-pressure NMR tube (Fa. Wilmad, 528-PV-1, inner diameter 2.2 mm) and monitored by ¹H NMR spectroscopy after 48 h and 96 h.

D⁺/NH exchange of **1a** with D₂O and identification of **1b**: To a saturated solution of **1a** in CD₂Cl₂, a 50-fold excess of D₂O was added. The reaction was monitored by ¹H NMR spectroscopy by the decrease of the νNH signal of **1a**. The resulting **1b** was precipitated from the solution by addition of *n*-hexane and identified by its IR spectrum in KBr.

1a: ¹H NMR (269.6 MHz, CD₂Cl₂): δ = 7.50 (d, 2H; C₆H₄), 7.28 (d, 2H; C₆H₄), 7.06 (m, 2H; C₆H₄), 6.92 (m, 2H; C₆H₄), 1.94 (m, 6H; PCH₂), 1.69 (m, 6H; CH₂), 1.05 (t, 9H; CH₃), -1.85 (s, br, 1H; NH); IR (KBr): ν(NH) = 3273 cm⁻¹. **1b**: ²H NMR (61.25 MHz, CH₂Cl₂): δ = -1.85 (s, br, 1D; ND); IR (KBr): ν(ND) = 2427 cm⁻¹.

Received: August 11, 1999 [Z13862]

- [1] a) S. P. Albracht, *Biochem. Biophys. Acta* **1994**, *1188*, 167–204; b) A. F. Kolodziej, *Progr. Inorg. Chem.* **1994**, *41*, 493–598; c) M. W. W. Adams, *Biochem. Biophys. Acta* **1990**, *1020*, 115–145; d) R. Cammack, V. M. Fernandez, K. Schneider in *Bioinorganic Chemistry of Nickel* (Ed.: J. R. Lancaster, Jr.), VCH, Weinheim, **1988**, pp. 167–190; e) R. Cammack in *Bioinorganic Catalysis* (Ed.: J. Reedijk), Marcel Dekker, New York, **1993**, pp. 189–226.
- [2] a) A. Volbeda, M. H. Charon, C. Piras, E. C. Hatchikian, M. Frey, J. C. Fontecilla-Camps, *Nature* **1995**, *373*, 580–587; b) M. A. Halcrow, *Angew. Chem.* **1995**, *107*, 1307–1310; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1193–1196; c) A. Volbeda, E. Garcin, C. Piras, A. L. de Lacey, V. M. Fernandez, E. C. Hatchikian, M. Frey, J. C. Fontecilla-Camps, *J. Am. Chem. Soc.* **1996**, *118*, 12989–12996.

- [3] a) J. W. Peters, W. N. Lanzilotta, B. J. Lemon, L. C. Seefeldt, *Science* **1998**, *282*, 1853–1858; b) Y. Nicolet, C. Piras, P. Legrand, E. C. Hatchikian, J. C. Fontecilla-Camps, *Structure* **1999**, *7*, 13–23.
- [4] a) J. C. Fontecilla-Camps, *Struct. Bonding (Berlin)* **1998**, *91*, 1–29; b) M. Frey, *Struct. Bonding (Berlin)* **1998**, *90*, 97–126; c) M. J. Maroney, G. Davidson, C. B. Allan, J. Figlar, *Struct. Bonding (Berlin)* **1998**, *92*, 2–65.
- [5] E. G. Graf, R. K. Thauer, *FEBS Lett.* **1981**, *136*, 165–169.
- [6] M. J. Maroney, M. A. Pressler, S. A. Mirza, J. P. Whitehead, R. J. Gurbiel, B. M. Hoffmann, *Adv. Chem. Ser.* **1995**, *246*, 21–60.
- [7] a) A. L. de Lacey, E. C. Hatchikian, A. Volbeda, M. Frey, J. C. Fontecilla-Camps, V. M. Fernandez, *J. Am. Chem. Soc.* **1997**, *119*, 7181–7189; b) C.-H. Lai, W.-Z. Lee, M. L. Miller, J. H. Reibenspies, D. J. Darensbourg, M. Y. Darensbourg, *J. Am. Chem. Soc.* **1998**, *120*, 10103–10114.
- [8] M. Zimmer, G. Schulte, X.-L. Luo, R. H. Crabtree, *Angew. Chem.* **1991**, *103*, 205–207; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 193–195.
- [9] a) M. A. Halcrow, G. Christou, *Chem. Rev.* **1994**, *94*, 2421–2481; b) D. Sellmann, S. Fünfgelder, G. Pöhlmann, F. Knoch, M. Moll, *Inorg. Chem.* **1990**, *29*, 4772–4778; c) H. J. Krüger, G. Peng, R. H. Holm, *Inorg. Chem.* **1991**, *30*, 734–742; d) S. Fox, Y. Wang, A. Silver, M. Millar, *J. Am. Chem. Soc.* **1990**, *112*, 3218–3220; e) C. A. Grapperhaus, M. Y. Darensbourg, *Acc. Chem. Res.* **1998**, *31*, 451–459; f) M. Kumar, G. J. Colpas, R. O. Day, M. J. Maroney, *J. Am. Chem. Soc.* **1989**, *111*, 8323–8325; g) S. A. Mirza, R. O. Day, M. J. Maroney, *Inorg. Chem.* **1996**, *35*, 1992–1995; h) G. Musie, P. J. Farmer, T. Tuntulani, J. H. Reibenspies, M. Y. Darensbourg, *Inorg. Chem.* **1996**, *35*, 2176–2183; i) G. J. Colpas, R. O. Day, M. J. Maroney, *Inorg. Chem.* **1992**, *31*, 5053–5055; j) F. Osterloh, W. Saak, D. Haase, S. Pohl, *Chem. Commun.* **1996**, 777–778; k) F. Osterloh, W. Saak, D. Haase, S. Pohl, *Chem. Commun.* **1997**, 979–980; l) C.-H. Lai, J. H. Reibenspies, M. Y. Darensbourg, *Angew. Chem.* **1996**, *108*, 2551–2553; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2390–2392; m) D. K. Mills, Y. M. Hsiao, P. J. Farmer, E. V. Atnip, J. H. Reibenspies, M. Y. Darensbourg, *J. Am. Chem. Soc.* **1991**, *113*, 1421–1423; n) E. Bouwman, R. K. Henderson, A. L. Spek, J. Reedijk, *Eur. J. Inorg. Chem.* **1999**, *4*, 217–219; o) Th. L. James, L. Cai, M. C. Muetterties, R. H. Holm, *Inorg. Chem.* **1996**, *35*, 4148–4161.
- [10] D. Sellmann, F. Geipel, F. W. Heinemann, *Eur. J. Inorg. Chem.* in press.
- [11] a) D. Sellmann, G. H. Rackelmann, F. W. Heinemann, *Chem. Eur. J.* **1997**, *3*, 2071–2080; b) D. Sellmann, T. Gottschalk-Gaudig, F. W. Heinemann, *Inorg. Chem.* **1998**, *37*, 3982–3988; c) D. Sellmann, J. Sutter, *Acc. Chem. Res.* **1997**, *30*, 460–469.
- [12] T. A. Albright, J. K. Burdett, M. H. Whangbo in *Orbital Interactions in Chemistry*, Wiley, New York, **1985**, pp. 295–309.

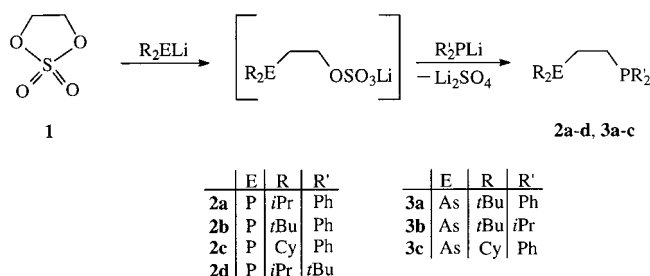
A New Synthetic Route to Unsymmetrical 1,2-Bis(phosphanyl)ethanes and 1,2-Arsanyl(phosphanyl)ethanes with and without a Stereogenic Center**

Guido Fries, Justin Wolf, Matthias Pfeiffer, Dietmar Stalke, and Helmut Werner*

Dedicated to Professor Egon Uhlig on the occasion of his 70th birthday

Bistertiary phosphanes of the general composition 1,2- $C_2H_4(PR_2)_2$ are among the widest used chelating ligands in coordination chemistry.^[1] The most well-known derivatives of this type, 1,2-bis(diphenylphosphanyl)ethane (dppe) and 1,2-bis(dimethylphosphanyl)ethane (dmpe), are commonly prepared either from 1,2- $C_2H_4Cl_2$ and $NaPPh_2$,^[2] from 1,2- $C_2H_4Br_2$, $HPPh_2$, and $NaOH$,^[3] or from 1,2- $C_2H_4(PCl_2)_2$ and excess CH_3MgI .^[4] Corresponding 1,2-bis(phosphanyl)ethanes bearing *different* substituents at the phosphorus centers such as $Me_2PCH_2CH_2PPh_2$, $Me_2PCH_2CH_2P(CH_2CMe_3)_2$, or $Ph_2PCH_2CH_2PnBu_2$, are accessible upon stepwise addition of dimethylvinylthiophosphorane to HPR'_2 and $LiAlH_4$ ^[5] or by reaction of $Ph_2P(CH=CH_2)$ with $LiPRR'$ and subsequent hydrolysis.^[6] The yields are in most cases moderate (exception: $Me_2PCH_2CH_2PPh_2$), reaching rarely more than 50 %.

In the search for reactive, coordinatively unsaturated rhodium and ruthenium complexes, which possibly could be used for metal-catalyzed C–C coupling reactions,^[7] we recently became interested in the ligating properties of unsymmetrical 1,2-bis(phosphanyl)ethanes and report here a simple and fairly general one-pot synthesis for these compounds. The starting material for **2a–d** is the cyclic sulfate **1** (Scheme 1),



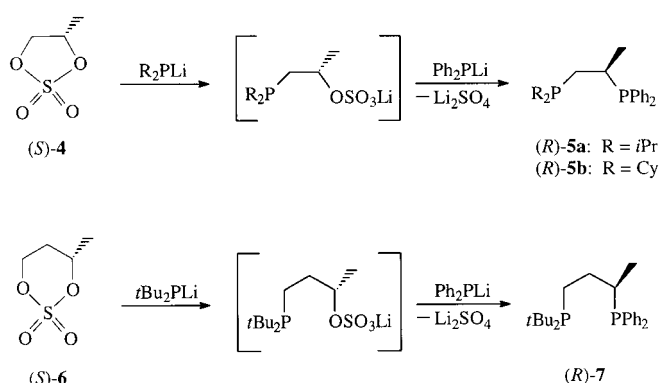
Scheme 1. Synthesis of **2a–d** and **3a–c**. Cy = cyclohexyl.

which is obtained upon treatment of 1,2-ethanediol with $SOCl_2$ followed by catalytic oxidation with $NaIO_4$.^[8,9] The cleavage of one of the C–O bonds in **1** and the concomitant opening of the five-membered ring occurs rapidly and

quantitatively by addition of the lithium phosphide $LiPR_2$ to a solution of **1** in THF at $-70^\circ C$. After warming the solution to room temperature and renewed cooling to $-70^\circ C$, the addition of the second P-nucleophile $LiPR'_2$ leads to the substitution of the sulfate group by the PR'_2 unit. Subsequent hydrolysis affords an oily residue, which can be eventually distilled by using a Kugelrohr at 2.5 mbar. Compounds **2a**, **2b**, and **2d** are isolated as highly viscous liquids, while **2c**, after crystallization from methanol, is obtained as a colorless crystalline solid. The yields range from 30 % for **2d** to 65–75 % for **2a–c**.

This one-pot procedure for the new unsymmetrical 1,2-bis(phosphanyl)ethanes **2a–d** is remarkable because of its easy synthetic approach, short reaction times, and high efficiency (except for **2d**). Moreover, the synthetic strategy can be extended to related 1,2-arsanyl(phosphanyl)ethanes (Scheme 1). Up to now, only two examples of compounds of the general composition $R_2AsCH_2CH_2PR'_2$, namely $Ph_2AsCH_2CH_2PPh_2$ ^[10] and $Me_2AsCH_2CH_2PPh_2$,^[11] were known; however, for the latter of those no detailed preparative procedure and analytical data were given. The new synthetic method described herein furnishes the chelating systems **3a–c** in good yields. For the preparation of **2a–c** as well as of **3a** and **3c** it is only important to note that the stronger nucleophile (for example, $LiPr_2$ for **2a** or $LiAs/tBu_2$ for **3a**) is added first and the weaker nucleophile ($LiPPh_2$ for **2a** and **3a**) second. If this order is reversed, mixtures of products are obtained.

The results presently known led us to suggest that for the 1,2-bis(phosphanyl)ethanes as well as for the As,P-analogues a wide range of substituents R and R' at the two donor atoms can be employed. With regard to possible applications in catalysis,^[12] it is equally important that the new synthetic method is also suitable for the preparation of chiral unsymmetrical chelating ligands of the type $R_2PCH(R'')CH_2PR'_2$. In Scheme 2 two examples are shown. In a test experiment we



Scheme 2. Synthesis of **5a**, **5b** and **7**.

initially treated the racemic mixture of the cyclic sulfate **4** stepwise with R_2PLi (R = *i*Pr, Cy) and Ph_2PLi and isolated the corresponding product in an analogous way to that described for **2a–d**. By using the *S* enantiomer of **4**, the *R* enantiomers **5a** and **5b** are obtained in a completely regioselective fashion by inversion of configuration at the stereogenic center. Although the yields of **5a** and **5b** (about 40 %) are moderate, they are similar to those reported for **PROPHOS**^[13] and

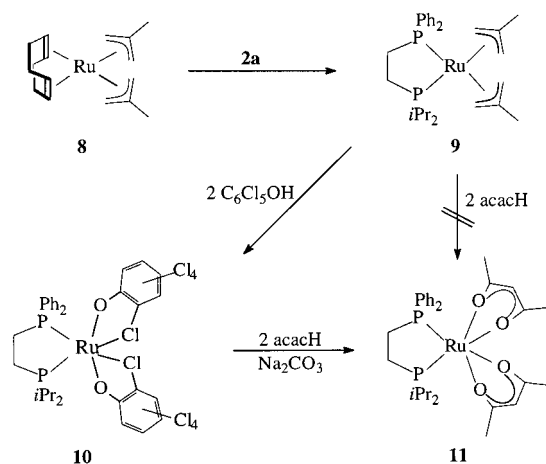
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[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 347), the Fonds der Chemischen Industrie, and from the BASF AG.

CYCPHOS^[14] (these compounds were prepared from the corresponding chiral bis(tosylate) and two equivalents of LiPPh₂). The optical rotation $[\alpha]_D^{20}$ of **5a** and **5b** (+201° and +167° in CH₂Cl₂, respectively) is comparable to that of PROPHOS ($[\alpha]_D^{20}$ = +186°).^[13]

To explore the application of the new synthetic methodology further, we also prepared the chiral unsymmetrical 1,3-bis(phosphanyl)propane (*R*)-**7** (Scheme 2), which displayed an optical rotation of $[\alpha]_D^{20}$ = +39° (in CH₂Cl₂). Recently, Huttner and co-workers reported the synthesis of related enantiopure 1,3-bis(phosphanyl)propanes of the general composition R₂PCH₂CH(X)CH₂PR₂ (where X is an OH or OR functionality) from epichlorohydrins and attempted to use the corresponding cationic rhodium complexes [C₈H₁₂Rh{R₂PCH₂CH(X)CH₂PR₂}]⁺ as precatalysts for the enantioselective hydrogenation of (*Z*)-acetamidocinnamic acid.^[15] Moreover, Gulyas, Arva, and Bakos prepared the chiral sulfate Ph₂PCH(Me)CH₂CH(Me)OSO₃Li, which is soluble in water and has been employed as cocatalyst in a biphasic reaction for the rhodium-catalyzed hydroformylation of 1-octene.^[16] The composition of this chiral sulfate is related to that of the (not isolated) intermediate which is formed upon treatment of (*S*)-**6** with *t*Bu₂PLi. The compound (*R*)-**7**, the bis(phosphanyl)ethanes **2a–d** and (*R*)-**5a, b**, and the arsanyl(phosphanyl)ethanes **3a–c** were characterized by elemental analysis, mass spectra (sometimes as the oxides), and NMR techniques.

In order to test the ligating properties of the unsymmetrical 1,2-bis(phosphanyl)ethanes, we treated, in analogy to work done by Jolly^[17] and Leitner^[18], the 1,5-cyclooctadieneruthenium complex **8**^[19] with **2a** in hexane (4 h, reflux temperature). The substitution product **9** was isolated as a yellow, slightly air-sensitive solid in 72 % yield (Scheme 3).



Scheme 3. Synthesis of **9–11**. acacH = acetylacetone.

While even at elevated temperatures **9** is inert toward acetylacetone, it affords complex **10** almost quantitatively upon treatment with two equivalents of pentachlorophenol. The interesting feature is that the ¹³C NMR spectrum of **10** (in [D₈]toluene) displays only one signal for the *ortho*- and *meta*-carbon atoms of the OC₆Cl₅ units both at 295 K and 188 K. This observation indicates that in solution a dynamic process takes place, which involves (on the NMR time scale) a rapid

coordination/decoordination of the *ortho*-chlorine atoms of the six-membered ring to the metal center. The crystal structure of **10**^[20] (Figure 1) confirms the existence of weak Ru–Cl interactions comparable to those between transition

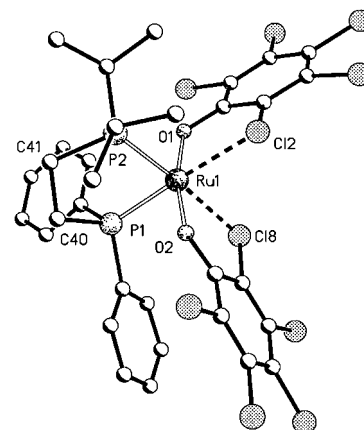


Figure 1. Molecular structure of **10** in the crystal. Selected bond lengths [Å] and bond angles [°]: Ru–P1 2.2341(13), Ru–P2 2.2578(13), Ru–O1 2.088(3), Ru–O2 2.078(3), Ru–Cl2 2.5240(13), Ru–Cl8 2.4978(13); P1–Ru–P2 84.32(5), P1–Ru–O1 99.45(9), P1–Ru–O2 89.24(9), P1–Ru–Cl2 176.70(4), P1–Ru–Cl8 94.03(5), P2–Ru–O1 94.51(9), P2–Ru–O2 93.00(8), P2–Ru–Cl2 98.90(5), P2–Ru–Cl8 174.32(4), O1–Ru–O2 169.03(11), O1–Ru–Cl2 79.60(9), O1–Ru–Cl8 91.12(9), O2–Ru–Cl2 91.34(9), O2–Ru–Cl8 81.53(8), Cl2–Ru–Cl8 82.85(4). The noncoordinated THF molecule is omitted for clarity.

metals and other C–Cl bonds.^[21] The Ru–Cl distances of 2.498(1) Å and 2.524(1) Å in **10** are significantly longer than in *trans*-[RuCl₂(dppe)₂] (2.4325(12) Å)^[22] and *trans*-[RuCl₂(dppm)₂] (2.426(1) Å)^[23], where “normal” covalent Ru–Cl bonds are present (dppm = bis(diphenylphosphanyl)methane).

In contrast to **9**, compound **10** reacts with acetylacetone and Na₂CO₃ to give the chelate complex **11** which was isolated as an air-stable yellow solid in 89 % yield. This result illustrates that **10** could be considered as a masked 14-electron species in which the additional interaction between the *ortho*-chlorine atoms of the C₆Cl₅ units and the metal prevents a subsequent oligomerization or decomposition process. Recent work by Baratta et al.^[24] has demonstrated a second example of a ruthenium(II) complex with a formal 14-electron configuration; in this case two strong agostic Ru⋯CH interactions relieve part of the electronic unsaturation at the metal center.

Experimental Section

All reactions were carried out under an argon atmosphere. ³¹P NMR: 81.0 MHz, CDCl₃; MS: CI, isobutane, 150 eV.

2a: A 1.76 M solution of *n*BuLi in hexane (8.1 mL, 14.24 mmol) was added to a solution of *i*Pr₂PH (1.68 g, 14.24 mmol) in THF (25 mL) at –70 °C. The resulting reaction mixture was slowly allowed to warm to 25 °C and stirred for 30 min at this temperature. It was then again cooled to –70 °C and added dropwise to a solution of **1** (1.77 g, 14.24 mmol) in THF (45 mL) at –70 °C. After the reaction was complete, the colorless solution was allowed to thaw, stirred for 30 min at room temperature, and subsequently cooled to –70 °C. The solution was then treated with a solution of Ph₂PLi in THF (prepared from Ph₂PH (2.63 g, 14.11 mmol) in THF (20 mL) and a 1.76 M solution of *n*BuLi in hexane (8.0 mL, 14.11 mmol)). After the reaction mixture had been allowed to thaw, it was heated for 3 h at 60 °C. The

volatiles were removed in vacuo, the residue was dissolved in diethyl ether (50 mL), and the solution was hydrolyzed with water (20 mL). The organic phase was separated, washed twice with water (10 mL), dried over Na_2SO_4 , and filtered. After the solvent was removed, the remaining oily residue was distilled in a Kugelrohr at 200 °C/2.5 mbar. A colorless, highly viscous, air-sensitive liquid was obtained. Yield: 3.55 g (76 %); b.p. 200 °C (2.5 mbar); ^1H NMR (200 MHz, CDCl_3): δ = 7.41 (m, 10H; C_6H_5), 2.20 (m, 2H; $\text{PCH}_2\text{CH}_2\text{P}$), 1.73 (m, 2H; PCHCH_3), 1.48 (m, 2H; $\text{PCH}_2\text{CH}_2\text{P}$), 1.08 (dd, $J(\text{P,H})$ = 11.7, $J(\text{H,H})$ = 6.9 Hz, 6H; PCHCH_3), 1.02 (dd, $J(\text{P,H})$ = 9.0, $J(\text{H,H})$ = 7.1 Hz, 6H; PCHCH_3); ^{13}C NMR (50.3 MHz, CDCl_3): δ = 138.2 (d, $J(\text{P,C})$ = 13.9 Hz; *ipso*-C of C_6H_5), 132.5 (d, $J(\text{P,C})$ = 18.5 Hz; *ortho*-C of C_6H_5), 128.1 (s; *para*-C of C_6H_5), 128.0 (d, $J(\text{P,C})$ = 12.0 Hz; *meta*-C of C_6H_5), 26.3 (dd, $J(\text{P}^1\text{C})$ = 20.4, $J(\text{P}^2\text{C})$ = 12.9 Hz; $\text{PCH}_2\text{CH}_2\text{P}$), 23.0 (d, $J(\text{P,C})$ = 12.9 Hz; PCHCH_3), 19.8 (d, $J(\text{P,C})$ = 14.8 Hz; PCHCH_3), 18.7 (d, $J(\text{P,C})$ = 10.2 Hz; PCHCH_3), 17.2 (dd, $J(\text{P}^1\text{C})$ = 19.4, $J(\text{P}^2\text{C})$ = 15.7 Hz; $\text{PCH}_2\text{CH}_2\text{P}$); ^{31}P NMR: δ = 10.3 (d, $J(\text{P,P})$ = 33.0 Hz; $i\text{Pr}_2\text{P}$), -11.9 (d, $J(\text{P,P})$ = 33.0 Hz; Ph_2P); MS: m/z (%): 331 (5.3) $[\text{M}+1]^+$, 187 (14.3) $[\text{Ph}_2\text{P}+1]^+$, 119 (9.0) $[\text{iPr}_2\text{P}+1]^+$. Compounds **2b–d** were prepared as described for **2a**; **2c** was obtained after recrystallization from methanol as a colorless, air-sensitive, crystalline solid; **2b** and **2d** are colorless, highly viscous, air-sensitive liquids; yield 70 % (**2b**), 65 % (**2c**), 30 % (**2d**). Characteristic data for **2b**: b.p. 190 °C (2.5 mbar) ^{31}P NMR: δ = 36.4 (d, $J(\text{P,P})$ = 34.3 Hz; $i\text{Bu}_2\text{P}$), -12.3 (d, $J(\text{P,P})$ = 34.3 Hz; Ph_2P); MS: m/z (%): 359 (22.9) $[\text{M}+1]^+$, 187 (4.4) $[\text{Ph}_2\text{P}+1]^+$, 147 (3.2) $[\text{iBu}_2\text{P}+1]^+$; **2c**: m.p. 54 °C; ^{31}P NMR: δ = 2.3 (d, $J(\text{P,P})$ = 30.5 Hz; Cy_2P), -11.9 (d, $J(\text{P,P})$ = 30.5 Hz; Ph_2P); MS: m/z (%): 411 (4.5) $[\text{M}+1]^+$, 199 (19.7) $[\text{Cy}_2\text{P}+1]^+$, 187 (28.9) $[\text{Ph}_2\text{P}+1]^+$; **2d**: ^{31}P NMR: δ = 36.9 (d, $J(\text{P,P})$ = 30.5 Hz; $i\text{Bu}_2\text{P}$), 10.7 (d, $J(\text{P,P})$ = 30.5 Hz; $i\text{Pr}_2\text{P}$); MS: m/z (%): 323 (13.8) $[\text{iPr}_2\text{P}(\text{O})\text{CH}_2\text{CH}_2\text{P}(\text{O})\text{iBu}_2+1]^+$.

3a: Preparation analogous to **2a**, from $i\text{Bu}_2\text{AsH}$ (2.70 g, 14.18 mmol), a 1.77 M solution of $n\text{BuLi}$ (8.00 mL, 14.18 mmol), **1** (1.76 g, 14.18 mmol), and Ph_2PLi (prepared from Ph_2PH (2.61 g, 14.02 mmol) and a 1.77 M solution of $n\text{BuLi}$ in hexane (7.92 mL, 14.02 mmol)). Compounds **3b** and **3c** were prepared similarly; like **3a** they are colorless, highly viscous, air-sensitive liquids; yield 54 % (**3a**), 62 % (**3b**), 56 % (**3c**). Characteristic data for **3a**: b.p. 210 °C (2.5 mbar); ^{31}P NMR: δ = -11.7 (s); MS: m/z (%): 403 (26.9) $[\text{M}+1]^+$, 191 (10.9) $[\text{iBu}_2\text{As}+1]^+$, 187 (17.4) $[\text{Ph}_2\text{P}+1]^+$; **3b**: Sdp. 140 °C (2.5 mbar); MS: m/z (%): 351 (7.3) $[\text{iPr}_2\text{P}(\text{O})\text{CH}_2\text{CH}_2\text{As}i\text{Bu}_2+1]^+$; **3c**: b.p. 245 °C (2.5 mbar); ^{31}P NMR: δ = -11.6 (s); MS: m/z (%): 455 (10.6) $[\text{M}+1]^+$, 243 (19.1) $[\text{Cy}_2\text{As}+1]^+$, 187 (30.5) $[\text{Ph}_2\text{P}+1]^+$.

(*R*)-**5a**: Preparation analogous to **2a**, from $i\text{Pr}_2\text{PH}$ (735 mg, 6.22 mmol), a 1.74 M solution of $n\text{BuLi}$ (3.6 mL, 6.22 mmol), (*S*)-**4** (842 mg, 6.22 mmol), and Ph_2PLi (prepared from Ph_2PH (1.56 g, 6.22 mmol) and a 1.74 M solution of $n\text{BuLi}$ in hexane (3.6 mL, 6.22 mmol)). Compound (*R*)-**5b** was obtained similarly; like (*R*)-**5a** it is a colorless, highly viscous, air-sensitive liquid; yield 37 % [(*R*)-**5a**], 36 % [(*R*)-**5b**]. Characteristic data for (*R*)-**5a**: b.p. 200 °C (2.5 mbar); optical rotation $[\alpha]_D^{20}$ = +201° (c = 0.73, CH_2Cl_2); ^{31}P NMR: δ = 1.9 (d, $J(\text{P,P})$ = 19.1 Hz; $i\text{Pr}_2\text{P}$), 0.2 (d, $J(\text{P,P})$ = 19.1 Hz; Ph_2P); MS: m/z (%): 345 (28.8) $[\text{M}+1]^+$, 187 (9.7) $[\text{Ph}_2\text{P}+1]^+$, 119 (8.9) $[\text{iPr}_2\text{P}+1]^+$; (*R*)-**5b**: b.p. 235 °C (2.5 mbar); $[\alpha]_D^{20}$ = +167° (c = 0.73, CH_2Cl_2); ^{31}P NMR: δ = 1.2 (d, $J(\text{P,P})$ = 19.1 Hz; Cy_2P), -8.2 (d, $J(\text{P,P})$ = 19.1 Hz; Ph_2P); MS: m/z (%): 426 (6.2) $[\text{M}+1]^+$, 199 (21.6) $[\text{Cy}_2\text{P}+1]^+$, 187 (27.6) $[\text{Ph}_2\text{P}+1]^+$.

(*R*)-**7**: Preparation analogous to **2a**, from $i\text{Bu}_2\text{PH}$ (2.19 g, 14.96 mmol), a 1.76 M solution of $n\text{BuLi}$ (8.50 mL, 14.96 mmol), (*S*)-**6** (2.28 g, 14.96 mmol), and Ph_2PLi (prepared from Ph_2PH (2.79 g, 14.96 mmol) and a 1.76 M solution of $n\text{BuLi}$ in hexane (8.50 mL, 14.96 mmol)). (*R*)-**7** was obtained as a colorless, highly viscous, air-sensitive liquid; yield 3.06 g (53 %); b.p. 200 °C (2.5 mbar); optical rotation $[\alpha]_D^{20}$ = +39° (c = 0.86, CH_2Cl_2); ^{31}P NMR: δ = 28.3 (s; $i\text{Bu}_2\text{P}$), -2.4 (s; Ph_2P); MS: m/z (%): 387 (100) $[\text{M}+1]^+$.

Received: August 9, 1999 [Z13844]

- [1] a) G. M. Kosolapoff, L. Maier, *Organic Phosphorus Compounds*, Vol. 1, Wiley, New York, **1972**, pp. 289–545; b) O. Stelzer, K.-P. Langhans, *The Chemistry of Organophosphorus Compounds*, Vol. 1 (Ed.: F. R. Hartley), Wiley, New York, **1990**, pp. 191–254.
- [2] K. Issleib, D. W. Müller, *Chem. Ber.* **1959**, 92, 3175–3182.
- [3] K. Issleib, K. Krech, K. Gruber, *Chem. Ber.* **1963**, 96, 2186–2192.
- [4] R. J. Burt, J. Chatt, W. Hussain, G. J. Leigh, *J. Organomet. Chem.* **1979**, 182, 203–206.

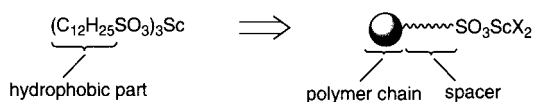
- [5] a) R. B. King, J. C. Cloyd, Jr., *J. Am. Chem. Soc.* **1975**, 97, 53–60; b) R. B. King, J. C. Cloyd, Jr., R. H. Reimann, *J. Org. Chem.* **1976**, 41, 972–977.
- [6] S. O. Grim, J. Del Gaudio, R. P. Molenda, C. A. Tolman, J. P. Jesson, *J. Am. Chem. Soc.* **1974**, 96, 3416–3422.
- [7] Reviews: H. Werner, *Nachr. Chem. Tech.* **1992**, 40, 435–444; H. Werner, *J. Organomet. Chem.* **1994**, 475, 45–55; H. Werner, *Chem. Commun.* **1997**, 903–910.
- [8] G. Caron, G. W.-M. Tseng, R. J. Kaslauskas, *Tetrahedron: Asymmetry* **1994**, 5, 83–92.
- [9] Similar cyclic sulfates, but with four C atoms in the bridge, were used by Burk et al. for the synthesis of 1,2-bis(phospholano)benzene derivatives (DUPHOS): M. J. Burk, *J. Am. Chem. Soc.* **1991**, 113, 8518–8519; M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, 115, 10125–10138.
- [10] W. Levason, C. A. McAuliffe, *Inorg. Synth.* **1976**, 16, 188–192.
- [11] L. S. Chia, W. R. Cullen, J. R. Sams, J. C. Scott, *Can. J. Chem.* **1976**, 54, 3185–3191.
- [12] a) H. Brunner, *Chem. Unserer Zeit* **1980**, 14, 177–183; b) H. Brunner, *Handbook of Enantioselective Catalysis with Transition Metal Compounds*, VCH, Weinheim, **1993**.
- [13] M. D. Fryzuk, B. Bosnich, *J. Am. Chem. Soc.* **1978**, 100, 5491–5494.
- [14] D. P. Riley, R. E. Shumate, *J. Org. Chem.* **1980**, 45, 5187–5193.
- [15] J. Karas, G. Huttner, K. Heinze, P. Rutsch, L. Zsolnai, *Eur. J. Inorg. Chem.* **1999**, 405–420.
- [16] H. Gulyas, P. Arva, J. Bakos, *Chem. Commun.* **1997**, 2385–2386.
- [17] S. Holle, P. W. Jolly, J. Kuhnigk, *J. Organomet. Chem.* **1997**, 543, 255–258.
- [18] W. Leitner, C. Six, *Chem. Ber.* **1997**, 130, 555–558.
- [19] M. O. Albers, E. Singleton, Y. E. Yates, *Inorg. Synth.* **1989**, 26, 253–254.
- [20] Crystal data of **10** · $\text{C}_4\text{H}_8\text{O}$: $\text{C}_{36}\text{H}_{36}\text{Cl}_{10}\text{O}_3\text{P}_2\text{Ru}$, M_r = 1034.16, triclinic, space group $P\bar{1}$, a = 12.381(4), b = 13.088(2), c = 14.374(4) Å, α = 66.69(2), β = 80.19(2), γ = 71.57(2)°, V = 2026.7(7) Å³, Z = 2, ρ_{calc} = 1.695 Mg m⁻³, $F(000)$ = 1040, λ = 0.71073 Å, T = 193(2) K, μ = 1.162 mm⁻¹. The data were collected on an Enraf-Nonius-CAD4-diffractometer. The intensity measurements were carried out on a shock-cooled crystal (0.5 × 0.4 × 0.2 mm) in an oil drop^[25] according to the $2\theta/\omega$ scan method in the range 6° < 2θ < 45°. Of a total of 7185 reflections collected, 5269 were independent (R_{int} = 0.0245) and were used for the refinement of 481 parameters. Max/min residual electron density: 507/569 e nm⁻³, $R1(F > 2\sigma(F))$ = 0.035 and $wR2$ = 0.083 (all data) with $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$ and $wR2 = (\sum w(F_o^2 - F_c^2)^2 / \sum w(F_c^2)^2)^{0.5}$. The structure was solved by Patterson methods (SHELXS-97)^[26] and refined with full-matrix least-squares on F^2 (SHELXL-97).^[27] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133284. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [21] a) M. A. Tena, O. Nürnberg, H. Werner, *Chem. Ber.* **1993**, 126, 1597–1602; b) M. F. Richardson, G. Wulfsberg, R. Marlow, S. Zaghonni, D. McCorkle, K. Shadid, J. Gagliardi, Jr., B. Farris, *Inorg. Chem.* **1993**, 32, 1913–1919; c) W. Beck, K. Schlöter, *Z. Naturforsch. B* **1978**, 33, 1214–1222; d) R. J. Kulawiec, R. H. Crabtree, *Coord. Chem. Rev.* **1990**, 99, 89–115.
- [22] C.-W. Chang, P.-C. Ting, Y.-C. Lin, G.-H. Lee, Y. Wang, *J. Organomet. Chem.* **1998**, 553, 417–425.
- [23] A. R. Chakravarty, F. A. Cotton, W. Schwotzer, *Inorg. Chim. Acta* **1984**, 84, 179–185.
- [24] W. Baratta, E. Herdtweck, P. Rigo, *Angew. Chem.* **1999**, 111, 1733–1735; *Angew. Chem. Int. Ed.* **1999**, 38, 1629–1631.
- [25] a) T. Kottke, D. Stalke, *J. Appl. Crystallogr.* **1993**, 26, 615–619; b) T. Kottke, R. J. Lagow, D. Stalke, *J. Appl. Crystallogr.* **1996**, 29, 465–468; c) D. Stalke, *Chem. Soc. Rev.* **1998**, 27, 171–178.
- [26] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, 46, 467–470.
- [27] G. M. Sheldrick, SHELXL-97, program for structure refinement, **1997**, Universität Göttingen.

A Novel Polymer-Supported Scandium Catalyst Which Shows High Activity in Water**

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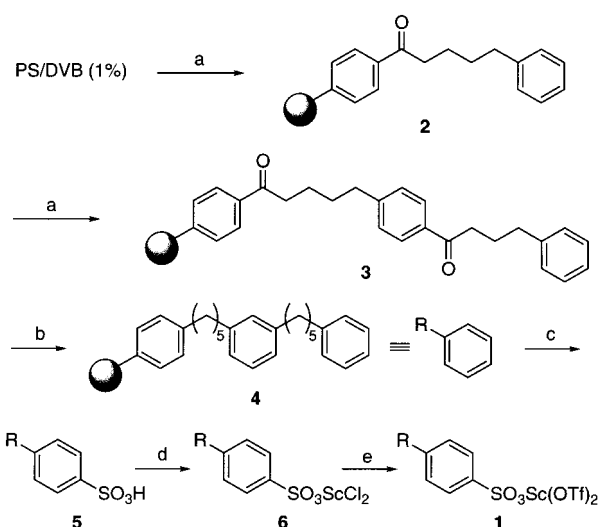
Organic reactions in water without the use of any harmful organic solvents are now of great interest in organic synthesis.^[1] While several useful synthetic reactions in an aqueous media containing an amount of organic co-solvent have been reported,^[1, 2] many of these reactions proceed sluggishly in pure water, probably because most of the organic reagents are not completely dissolved.^[3] To address this issue, we have recently developed Lewis acid–surfactant combined catalysts (LASCs) such as scandium tris(dodecyl sulfate) and scandium tris(dodecanesulfonate).^[4, 5] In the presence of a catalytic amount of a LASC, organic materials rapidly formed a dispersed colloidal system in water, and aldol reactions of silyl enol ethers with aldehydes proceeded smoothly without the use of organic solvents. While this is the first example of Lewis acid catalysis in pure water, a disadvantage is that rather tedious procedures are needed to recover the catalyst. In this paper, we report a solution of this problem: a novel polymer-supported scandium-based Lewis acid which shows high activity in water and can be easily recovered and reused.

The utility of polymer-supported catalysts in preparative procedures, such as simplification of product work-up, and the easy separation, isolation, and reuse of the catalysts is well-recognized.^[6] Our idea was to change the hydrophobic part of a LASC to polymer chains having “spacers” composed of alkylaromatic moieties and to develop a novel polymer-supported catalyst that can be used in water (Scheme 1).



Scheme 1. Abstract representation of the Lewis acid catalysts reported here. Left: example LASC. Right: the scandium-based active site is separated by an alkylaromatic “spacer” moiety from polymeric support.

Preparation of the polymer-supported scandium catalyst **1** was performed according to Scheme 2.^[7, 8] Polystyrene (PS), cross-linked with divinylbenzene (DVB, 1 %), was treated with 5-phenylvaleryl chloride in carbon disulfide in the presence of aluminum trichloride at room temperature for 24 h.^[9] After quenching and washing with aqueous and organic solvents, the resulting resin **2** was treated with 5-phenylvaleryl chloride once again to afford ketone resin **3**. The carbonyl groups of **3**



Scheme 2. Preparation of **1**. a) AlCl_3 , $\text{Ph}(\text{CH}_2)_4\text{COCl}/\text{CS}_2$; b) AlCl_3 , $\text{LiAlH}_4/\text{Et}_2\text{O}$; c) $\text{ClSO}_3\text{H}/\text{CH}_2\text{Cl}_2$, $\text{CH}_3\text{CO}_2\text{H}$; d) $\text{ScCl}_3/\text{CH}_3\text{CN}$; e) $\text{TfOH}/\text{CH}_2\text{Cl}_2$.

were reduced using aluminum trichloride–lithium aluminum hydride^[10] in diethylether to afford “double spacer” resin **4**. After sulfonation (chlorosulfonic acid/acetic acid), resin **5** was treated with scandium(III) chloride in acetonitrile at room temperature for 24 h to give the polymer-supported scandium chloride **6**. Finally, **6** was treated with trifluoromethanesulfonic acid (TfOH) to afford **1**.^[11]

The catalytic activity of **1** was first tested in the allylation reactions of carbonyl compounds with tetraallyltin, which are among the most fundamental and important carbon–carbon bond-forming reactions in organic synthesis.^[12] We chose the reaction of 4-phenyl-2-butanone with tetraallyltin as a model [Eq. (1)]. It was found that the reaction proceeded smoothly in the presence of 3.2 mol % of **1** in water at room temperature for 12 h, to afford the corresponding homoallylic alcohol in 92 % yield.^[13] It is noted that even less reactive ketone reacted smoothly under these conditions. Moreover, **1** was easily recovered after the reaction was completed by simple filtration and reused (Table 1, entry 1). The recovery was quantitative in each case and no loss of activity was observed for the recovered catalyst. While 95 % yield was attained

Table 1. Examination of reaction conditions [Eq. (1)].^[a]

Entry	Solvent	Catalyst ^[b] [mol %]	Yield [%]
1	H_2O	3.2	92 (93, ^[c] 90 ^[d])
2	H_2O	1.6	95 (90, ^[e] 92 ^[f])
3	H_2O	0.8	84
4	CH_2Cl_2	3.2	38
5	CH_3CN	3.2	15
6	benzene	3.2	28
7	EtOH	3.2	20
8	DMF	3.2	trace

[a] 1.29 mmol g^{-1} of **5** was used unless otherwise noted. [b] Determined by elemental analysis of Sc in **1**. [c] 2nd use. [d] 3rd use. [e] 0.52 mmol g^{-1} of **5** was used. [f] 2.46 mmol g^{-1} of **5** was used.

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** This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. S.N. thanks the JSPS fellowship for Japanese Junior Scientists.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

using 1.6 mol % of **1**, a slight decrease in the yield was observed when 0.8 mol % of **1** was employed under the same reaction conditions (RT, 12 h). As for the loading levels of **5**, similar results were obtained at the loading between 0.52–2.46 mmol g⁻¹ (entry 2). We also examined the effect of solvents (entries 1, 4–8). While excellent yield was obtained in water, much lower yields were observed in the other solvents (dichloromethane, acetonitrile, benzene, ethanol, DMF). In all cases, the reaction mixture was clean as only the starting materials and the product were observed by thin-layer chromatography during the reaction. This meant that the reaction rate was much faster in water than in organic solvents and that use of water as the solvent was essential in this allylation reaction using **1** as a catalyst.

Several examples of the **1**-catalyzed allylation reactions in water [Eq. (2)] are shown in Table 2. Aromatic, aliphatic, as

Table 2. Allylation reactions catalyzed by **1** as shown by Equation (2)

Entry	R ¹	R ²	Yield [%]
1	Ph	H	82
2	Ph(CH ₂) ₂	H	quant.
3	cyclo-C ₆ H ₁₁	H	72
4	(<i>E</i>)-PhCH=CH	H	99
5	2-pyridyl	H	83
6	PhCO	H ^[a]	90 ^[b]
7	Ph(CH ₂) ₂	Me	quant.
8	(<i>E</i>)-PhCH=CH	Me	91
9	Ph	CO ₂ Et	90

[a] Monohydrate. [b] Diallylated adduct was obtained.

well as heterocyclic aldehydes worked well to give the corresponding homoallylic alcohols in high yields. In the reaction of an α,β -unsaturated aldehyde, only 1,2-addition occurred. When phenylglyoxal monohydrate was treated with tetraallyltin under the reaction conditions, the diallylated adduct was obtained in 90% yield. We also tested other ketones and the desired 1,2-addition adducts were obtained in high yields. No 1,4-addition took place when an α,β -unsaturated ketone was employed. It is noted that the catalyst was recovered quantitatively after the reactions and reused in all cases.

A preliminary kinetic study was performed in the allylation reaction of 4-phenyl-2-butanone with tetraallyltin (Figure 1). We have already reported that scandium triflate (Sc(OTf)₃) catalyzed allylation reactions of carbonyl compounds with tetraallyltin in aqueous media (H₂O/THF, H₂O/CH₃CN, H₂O/EtOH/toluene) and organic solvents.^[14] It was found that the Sc(OTf)₃-catalyzed reaction in H₂O/THF (1/9, (e)) or H₂O/EtOH/toluene (1/7/4, (d)) proceeded much slower than the **1**-catalyzed reaction in water (a). Although the initial rate of the Sc(OTf)₃-catalyzed reaction in dichloromethane (c) was comparable to the **1**-catalyzed reaction in water, the former stopped after 2 h when the yield reached around 50%. It should be noted that the **1**-catalyzed reaction was faster than the example LASC-catalysed reaction (catalyst: scandium tris(dodecanesulfonate), STDS) in water (b).^[15]

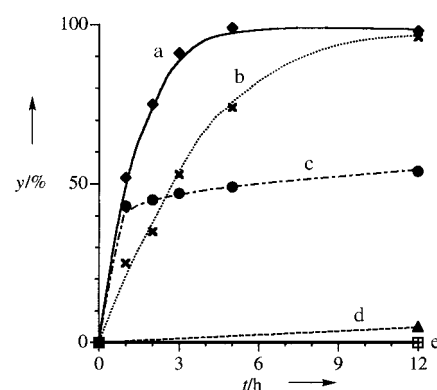
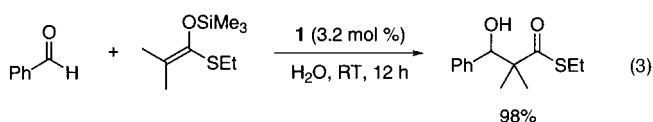
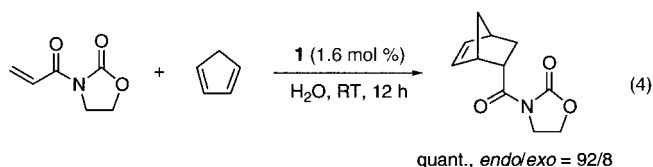


Figure 1. Kinetic studies in the reaction of 4-phenyl-2-butanone with tetraallyltin. a) **1** in water; b) STDS in water; c) Sc(OTf)₃ in CH₂Cl₂; d) Sc(OTf)₃ in H₂O/EtOH/toluene; e) Sc(OTf)₃ in H₂O/THF. All reactions were carried out using 3.2 mol % of the catalysts.

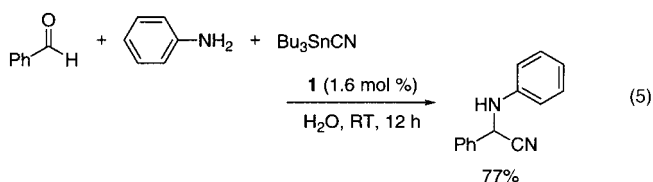
Finally, use of **1** in other synthetic reactions was briefly surveyed. In the presence of 3.2 mol % of **1**, benzaldehyde reacted with 1-ethylthio-1-trimethylsiloxy-2-methyl-1-propene at room temperature for 12 h in water [Eq. (3)] to



afford the corresponding aldol-type product in 98% yield (77% yield using 1.6 mol % of **1**). The Diels–Alder reaction of 3-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene also proceeded smoothly in the presence of 1.6 mol % of **1** in water [Eq. (4)] to afford the corresponding adduct quantitatively



(RT, 12 h, *endo/exo* = 92/8). Moreover, the Strecker-type reaction of benzaldehyde, aniline, and tributyltin cyanide was performed.^[16] The reaction proceeded cleanly in the presence of 1.6 mol % of **1** in water [Eq. (5)] to afford the



corresponding α -amino nitrile derivative in 77% yield (RT, 12 h). These results indicated that **1** was an excellent Lewis acid catalyst for several useful carbon–carbon bond-forming reactions in water.

In summary, we have developed a novel polymer-supported scandium catalyst. The catalyst has polymer chains and spacers which would help to form hydrophobic reaction fields in water. Several useful carbon–carbon bond-forming reac-

tions proceeded smoothly in the presence of a catalytic amount of **1** in water without using any organic co-solvents. To the best of our knowledge, this is the first example of the polymer-supported Lewis acid catalyst that can be used in this manner. It is noted that the reactions proceeded much faster in water than in other media including organic solvents. The simple procedures, easy recovery, reusable catalyst, and the use of water as a solvent are expected to contribute to development of benign chemical processes.

Experimental Section

A typical experimental procedure is described for the allylation reaction of 4-phenyl-2-butanone with tetraallyltin. 4-Phenyl-2-butanone (0.4 mmol), tetraallyltin (0.2 mmol), and **1** (0.0064 mmol, 1.6 mol %) were combined in water (3 mL). The mixture was stirred for 12 h at RT. Catalyst **1** was filtered and washed with ethyl acetate. The filtrate was extracted with ethyl acetate, and the combined organic layers were dried (Na₂SO₄). After filtration and concentration, the residue passed through a column packed with silica gel to afford the allylated adduct in 95 % yield. The recovered **1** was reused several times without loss of activity.

Received: September 20, 1999 [Z14035]

- [1] a) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie A&P, London, **1998**; b) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, **1997**; c) A. Lubineau, J. Augé, Y. Queneau, *Synthesis* **1994**, 741–760; d) C.-J. Li, *Chem. Rev.* **1993**, 93, 2023–2035; e) H.-U. Reissig in *Organic Synthesis Highlights* (Ed.: H. Waldmann), VCH, Weinheim, **1991**, pp. 71–76; f) C. Einhorn, J. Einhorn, J. Luche, *Synthesis* **1989**, 787–813.
- [2] a) S. Kobayashi, *Synlett* **1994**, 689–701; b) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15–27.
- [3] S. Kobayashi, T. Wakabayashi, S. Nagayama, H. Oyamada, *Tetrahedron Lett.* **1997**, 38, 4559–4562.
- [4] S. Kobayashi, T. Wakabayashi, *Tetrahedron Lett.* **1998**, 39, 5389–5392.
- [5] While most Lewis acids were believed to be unstable in water, water-tolerant Lewis acids are now known: a) S. Kobayashi, *Chem. Lett.* **1991**, 2187–2190; b) S. Kobayashi, S. Nagayama, T. Busujima, *J. Am. Chem. Soc.* **1998**, 120, 8287–8288; c) J. B. F. N. Engberts, B. L. Feringa, E. Keller, S. Otto, *Recl. Trav. Chim. Pays-Bas* **1996**, 115, 457–464. See also Ref. [2].
- [6] For leading references on polymer catalysts, see: a) S. J. Shuttleworth, P. K. Sharma, *Synthesis* **1997**, 1217–1239; b) D. C. Bailey, S. H. Langer, *Chem. Rev.* **1981**, 81, 109–148; c) A. Akelah, D. C. Sherrington, *Chem. Rev.* **1981**, 81, 557–587; d) J. M. J. Frechet, *Tetrahedron* **1981**, 37, 663–683. For recent works, see: e) D. A. Annis, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, 121, 4147–4154, and references therein.
- [7] Details are described in Supporting Information.
- [8] While we have previously developed polymer-supported scandium catalysts, most of them work well in organic solvents but reactions proceed sluggishly in water without organic co-solvents. a) S. Kobayashi, S. Nagayama, *J. Org. Chem.* **1996**, 61, 2256–2257; b) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1996**, 118, 8977–8978; c) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1998**, 120, 2985–2986.
- [9] a) J. M. Frechet, L. Nuyens, *Can. J. Chem.* **1976**, 54, 926–934; b) S. Kobayashi, M. Moriwaki, *Tetrahedron Lett.* **1997**, 38, 4251–4254.
- [10] a) J. H. Brewster, H. O. Bayer, S. F. Osman, *J. Org. Chem.* **1964**, 29, 110–115; b) R. F. Nystrom, C. R. A. Berger, *J. Am. Chem. Soc.* **1958**, 80, 2896–2898.
- [11] While the structures of **2–4** were confirmed using SR–MAS NMR,^[17] the degree of sulfonation of **5** was determined by titration. The scandium loading of **1** was determined by elemental analysis. All details are given in the Supporting Information.
- [12] Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, 93, 2207–2293.
- [13] No reaction occurred without **1**. The reaction proceeded in lower yield using a polymer-supported scandium catalyst without the spacer moiety.

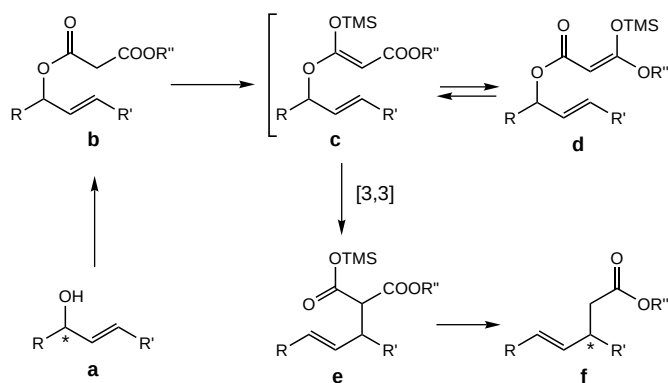
- [14] I. Hachiya, S. Kobayashi, *J. Org. Chem.* **1993**, 58, 6958–6960.
- [15] S. Kobayashi, T. Wakabayashi, H. Oyamada, *Chem. Lett.* **1997**, 831–832.
- [16] S. Kobayashi, T. Busujima, S. Nagayama, *Chem. Commun.* **1998**, 981–982.
- [17] S. Kobayashi, R. Akiyama, T. Furuta, M. Moriaaki, *Molecules online*, **1998**, 2, 35–39.

A New Variant of the Claisen Rearrangement from Malonate-Derived Allylic Trimethylsilyl Ketene Acetals: Efficient, Highly Enantio- and Diastereoselective Syntheses of (+)-Methyl Dihydroepijasmonate and (+)-Methyl Epijasmonate**

Charles Fehr* and José Galindo

Among the large variety of [3,3] sigmatropic rearrangements,^[1] the Johnson ortho ester Claisen rearrangement^[2] has proven to be particularly useful, owing to its facile and broad applicability. Nonetheless, it also suffers from some limitations: trimethyl orthoacetate is impractical, because the reaction temperature is limited by its low boiling point (105–110 °C) and therefore, triethyl orthoacetate (b.p. 142–145 °C) is commonly used. As the Johnson Claisen rearrangement requires excess ortho ester, its industrial application is unattractive in those cases that require ulterior transesterification (e.g. for the synthesis of methyl esters).

We now report an alternative methodology, which is based on the Claisen rearrangement of trimethylsilyl(TMS)-ketene acetals of type **c** (presumably in equilibrium with **d**) derived from malonates **b**, followed by desilylation/decarboxylation of malonates **e** to esters **f** (Scheme 1). The synthetic concept



Scheme 1. Claisen rearrangement from malonate-derived TMS ketene acetals.

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[**] O. Etter is thanked for his skilful experimental work and Dr. E. Ohleyer is acknowledged for his contribution to the enzymatic part of the project.

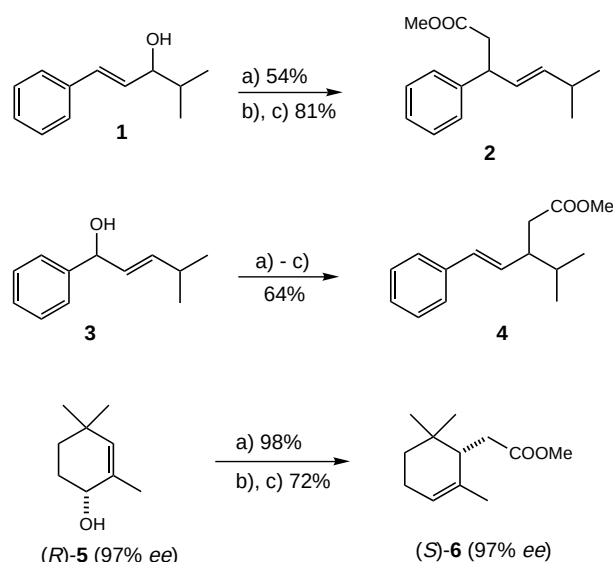
consists of linking any desired ester functionality (CO₂Me in this case) to the Claisen system, and then to discarding, after rearrangement, the ester unit that is involved in the rearrangement by desilylation/decarboxylation. Compared to an alkyl group, the TMS group allows the rearrangement to occur at lower temperature,^[3] and following rearrangement, a selective desilylation/decarboxylation of the malonates **e** to the esters **f** is facilitated by the differentiated functionalities of the ester groups in **e** (Scheme 1). This new variant thus allows a perfect chirality transfer from **a** to **f** in both cyclic and acyclic systems.

Two literature precedents for rearrangements of allyl malonates should be mentioned: transesterification/rearrangement of an allylic alcohol and diethyl isopropyl malonate in the presence of Ti(OEt)₄ at 160–190 °C,^[4] and the rearrangement of ethyl ketene acetals derived from allylic alcohols and ethyl β,β-diethoxyacrylate at 150–200 °C.^[5] The first procedure turned out to be unsuitable for substrates that are prone to dehydration, and the second protocol, which also requires high reaction temperatures, additionally suffers from the difficulty of preparing ethyl β,β-diethoxyacrylates.

To demonstrate the feasibility of this new methodology, the two regioisomeric and relatively sensitive racemic allylic alcohols **1** and **3** were chosen as substrates. The corresponding allyl methyl malonates (Scheme 1: type **b**) were prepared from the alcohols and methyl malonyl chloride, and used without purification. Deprotonation (NaH (or KH)/THF) and silylation (TMSCl) afforded the labile silyl ketene acetals of type **c** (or **d**)^[6] which, when heated in THF at 50–65 °C for 3 h, underwent smooth rearrangement to the rearranged malonates of type **e**.^[7] These were desilylated and decarboxylated (*N*-methylpyrrolidone (NMP), H₂O, NaCl, 140 °C)^[8] to afford the methyl esters **2** and **4**, respectively, in high yield (Scheme 2). Neither **2** nor **4** were contaminated with their regioisomeric esters (**4** and **2**, respectively), and no traces of isomeric (*Z*)-enoates could be detected, thus indicating that the reaction proceeds via a highly ordered transition state. As a consequence, this malonate rearrangement should be ideal for the transfer of chirality in nonracemic cyclic and acyclic systems.^[9]

Indeed, as a test substrate, the known allylic alcohol (*R*)-**5**^[10] was rearranged into the sterically constrained ester (*S*)-**6**^[11] in 70 % yield and without any loss in enantiomeric purity (GC: Megadex 5: peak 1).

In the context of our planned syntheses of (+)-methyl dihydroepijasmonate ((+)-**16a**) and (+)-methyl epijasmonate ((+)-**16b**), we next chose allylic alcohols (*R*)-**8a** and (*R*)-**8b** as substrates, whose conversion into the rearranged esters (*R*)-**10a** and (*R*)-**10b** (GC: Megadex 5: peak 1), respectively, also proceeded in good yield and without any racemization (Scheme 3). Allylic alcohols (*R*)-**8a** (93 % *ee*, [α]_D²⁰ = +28 (*c* = 2.7 in CHCl₃)) and (*R*)-**8b** (92 % *ee*; ([α]_D²⁰ = +58 (*c* = 3.5 in CHCl₃)) were prepared by oxazaborolidine-catalyzed highly enantioselective BH₃·SMe₂ reduction^[12] of the readily accessible parent enones **7a** and **7b**.^[13] The only moderate

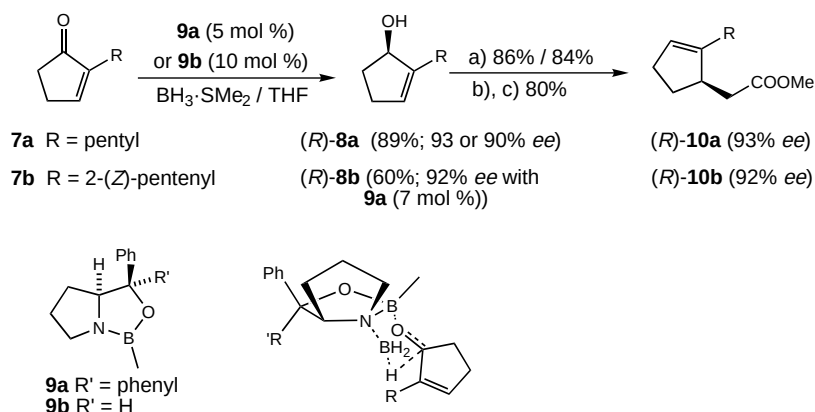


Scheme 2. Regiocontrol and chirality transfer in the Claisen rearrangement of malonate-derived TMS ketene acetals: a) methyl malonyl chloride (1.2 equiv), NEt₃ (1.3 equiv), CH₂Cl₂, 2–5 °C, 30 min; b) NaH (1.25 equiv), THF or DME, 55 °C, 1 h, then TMSCl (2.0 equiv), 50–65 °C, 3 h or DME, 85 °C, 8 h (for (*S*)-**6**); c) NMP, H₂O (1.8 equiv), NaCl (1.3 equiv), 140 °C, 30 min.

yield obtained in the reduction of **7b** to (*R*)-**8b** (60 %) is due to competing hydroboration of the 2-(*Z*)-pentenyl double bond.

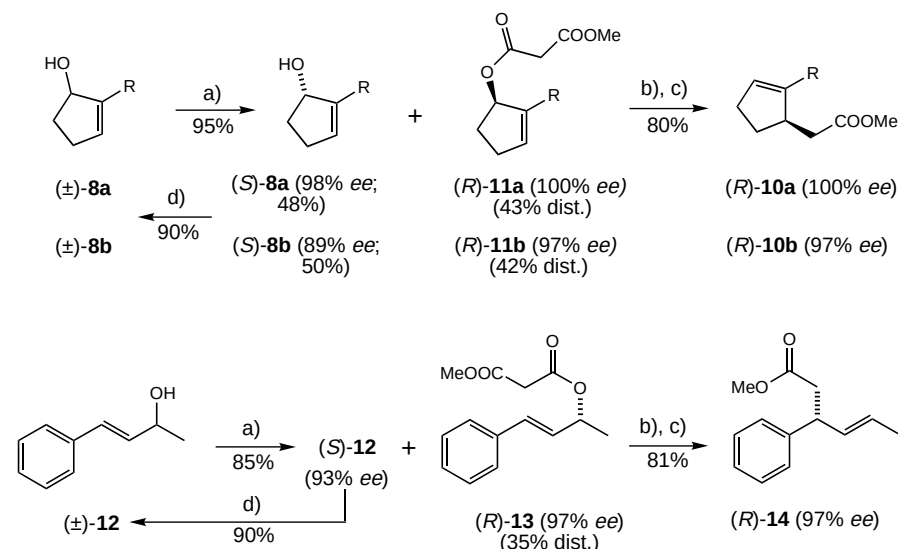
The diphenyl prolinol derived oxazaborolidine **9a** is thought to bind substrate and borane as shown in Scheme 3.^[12] However, as the contribution of the α-phenyl group is not evident, we also examined the reduction of **7a** with the hitherto unknown monophenyl prolinol^[14] derived oxazaborolidine **9b**. Its efficiency turned out to be slightly inferior to **9a**: whereas 5 mol % of **9a** affords (*R*)-**8a** of 93 % *ee*, **9b** (5 or 10 mol %) gives rise to 86 or 90 % *ee*.

As an alternative to this enantioselective reduction/esterification protocol for access to the enantiopure malonate intermediates, we have now developed a new procedure involving enzymatic kinetic resolution. This method achieves highly selective mono-transesterification of dimethyl malonate with one enantiomer of a racemic allylic alcohol substrate.^[15] Thus, treatment of (±)-**8a** or (±)-**8b**^[16] and



Scheme 3. Preparation of (*R*)-**10a** and (*R*)-**10b** by enantioselective reduction/Claisen rearrangement: a)–c) see Scheme 2.

dimethyl malonate at 40 °C and reduced pressure with catalytic amounts of Novozym 435 (immobilized *Candida antarctica* from Novo Nordisk) in the presence of KHCO_3 (5 mol %)^[17] affords the corresponding malonates (*R*)-**11a** or (*R*)-**11b** with excellent enantioselectivity (97–100 % *ee*) and almost 50 % conversion (Scheme 4). Conversion to the



Scheme 4. Enzymatic transesterification of dimethyl malonate and allylic alcohols, followed by Claisen rearrangement of the malonate-derived TMS ketene acetals: a) dimethyl malonate (1.15 molar equivalents), KHCO_3 (0.05 equivalents), Novozym 435 (10 wt %), 40 °C, 8 Torr, 80 min; b) and c) see Scheme 2; d) aqueous H_2SO_4 , THF, 20 °C, 24 h.

rearranged methyl esters (*R*)-**10a** and (*R*)-**10b** was subsequently effected as described above.^[18] The unconverted alcohols, (*S*)-**8a** and (*S*)-**8b**, could be racemized under acidic conditions and recycled, thus further improving the efficiency of this process.

Another example, the transformation of (±)-**12** to (*R*)-**14** (97 % *ee*) demonstrates the superiority of this methodology in comparison with the related Pd-catalyzed malonate allylation reaction, where, starting from (*S*)-**12** (39 % *ee*), ester (*S*)-**14** (30 % *ee*) is obtained only as a very minor regioisomer (8 % of mixture).^[19]

With (*R*)-**10a** and (*R*)-**10b** in hand, we were now ready to accomplish very efficient syntheses of (+)-methyl dihydroepijasmone ((+)-**16a**) and (+)-methyl epijasmone ((+)-**16b**).

Ever since the isolation of (–)-methyl jasmonate ((–)-**15b**), which possesses an elegant jasmine odor, from *Jasmine oil* in 1962,^[20] racemic methyl jasmonate ((±)-**15b**) has engendered intense research activity culminating in two industrial syn-

theses of (±)-**15b**.^[21] Later on, isolation of the enantiomers of **15b**, as well as those of its diastereomer **16b**, revealed that solely (1*R*,2*S*)-(+)-**16b**, the primary product of biosynthesis, was organoleptically active.^[22] Thus, although all stereoisomers of **15b** may exert synergic effects or improve a perfume composition as fixatives or enhancers, under equilibrating

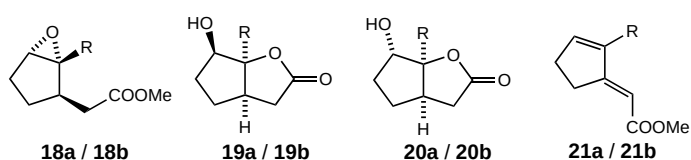
conditions racemic **15b** contains as little as 3 % of the olfactively active (+)-methyl epijasmone ((+)-**16b**). In addition, (+)-**16b** displays several other biological activities such as regulation of plant growth^[23] and plant defense,^[24] as well as signal transmission in interplant communication.^[25] Therefore, renewed recent synthetic activity has centered around methyl epijasmone (**16b**) in its racemic^[26, 27] or nonracemic form.^[26, 28]

In close analogy, (+)-methyl dihydroepijasmone ((+)-**16a**)^[29] represents the organoleptically active stereoisomer of methyl dihydrojasmonate (Hedione: ((±)-**15a** (93 %) + (±)-**16a** (7 %)).

The major synthetic challenge comprises the elaboration of the *cis*-relationship in these *cis*-2,3-disubstituted cyclopentanones which are known to readily undergo epimerization. Indeed, all reported syntheses pass through the corresponding secondary

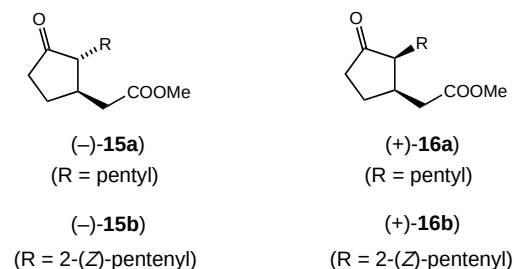
alcohol and necessitate a careful oxidation in the final step.^[26] Based on our recent findings^[30] that the preference for peracid attack on the more electron-rich π -face of a C–C double bond is increased by the use of strong peracids (electrostatic interactions), we envisaged the diastereoselective epoxidation of **10a** and **10b**. *syn*-Epoxides **17a** and **17b** would then be expected to undergo a Lewis acid catalyzed stereocontrolled suprafacial 1,2-H migration^[31] leading to the *cis*-jasmonates **16a** and **16b** (Scheme 5).

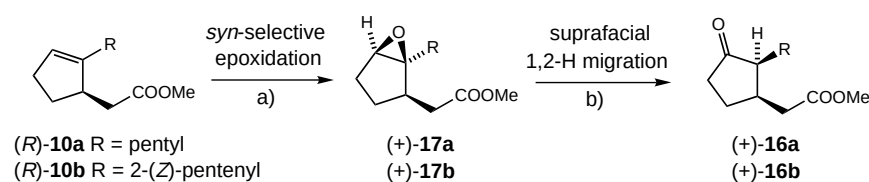
Indeed, epoxidation of (*R*)-**10a** with the strongest commonly used peracid, trifluoroperacetic acid, afforded the *syn*-epoxide **17a** with an excellent 99:1 diastereoselectivity.^[32] Permaleic acid and *m*-chloroperbenzoic acid (*m*CPBA)



showed decreased *syn/anti* selectivities of 89:11 and 86:14 and afforded lactones **19a** and **20a** in trace amounts.^[33]

The rearrangement of epoxide **17a** could be effected with a variety of Lewis acids, but in addition to **16a**, variable amounts of lactone **19a** and diene ester **21a** were produced. For instance, both LiClO_4 in diethyl ether,^[31b] often used for acid-sensitive substrates, and trimethylsilyl triflate^[31c] afford-





Scheme 5. Synthesis of (+)-methyl dihydroepijasmonate and (+)-methyl epijasmonate. a) $(\text{CF}_3\text{CO})_2\text{O}$ (2.0 equiv), H_2O_2 (1.35 equiv), Na_2CO_3 (2.7 equiv), CH_2Cl_2 , -50°C ; b) $\text{BF}_3\cdot\text{OEt}_2$ (0.25–0.32 equiv), CH_2Cl_2 , $2-13^\circ\text{C}$, 30 min.

ed large quantities of **19a** (30%) and **21a** (35 and 48% respectively) and only minor amounts of **16a** (28 and 10%, respectively).

The highest yields and selectivities in favor of **16a** were obtained with catalytic amounts of AlCl_3 (86%; containing 3% of **15a**), $\text{BF}_3\cdot\text{OEt}_2$ [31d] (83%; containing 2% of **15a**), or by using the dried, acidic clay Filtrol G-24 (75%; containing 5% of **15a**). Interestingly, no examples of AlCl_3 -promoted epoxide rearrangements of this type have been reported. [31a]

These conditions were next successfully applied to the synthesis of (+)-methyl epijasmonate ((+)-**16b**). The syn-selective epoxidation of (*R*)-**10b** using trifluoroperacetic acid at -50°C afforded exclusively syn-epoxide (+)-**17b** (83%). Notably, the trisubstituted double bond in **10b** is epoxidized much faster than the disubstituted one; only 5% of di-epoxidation products are generated. Finally, stereocontrolled rearrangement of epoxide (+)-**17b** using catalytic amounts of $\text{BF}_3\cdot\text{OEt}_2$ or AlCl_3 gave (+)-**16b** (97% ee) in 80% yield, accompanied by 6% of (–)-**15b**.

We have developed a concise, highly stereocontrolled synthesis of (+)-methyl dihydroepijasmonate ((+)-**16a**) and (+)-methyl epijasmonate ((+)-**16b**) based on an original methodology, comprising an enzyme-catalyzed enantioselective mono-esterification with dimethyl malonate, a novel Claisen rearrangement of the malonate-derived allylic silyl ketene acetal, and a highly stereoselective epoxidation–rearrangement sequence.

Experimental Section

(*R*)-**11a**: A homogeneous mixture of (±)-**8a** (27.5 g, 181 mmol) and dimethyl malonate (27.5 g, 208 mmol, 2.30 molar equivalents with respect to (*R*)-**8a**) was treated with ground KHCO_3 (0.89 g, 8.9 mmol) and then with Novozym 435 (immobilized *Candida antarctica* from Novo Nordisk, 1.80 g) and gently swirled in a 100-mL flask connected to a Büchi rotavapor at 40°C and 8 Torr. [34] After 80 min, the reaction mixture was filtered and rinsed (Et_2O), washed (saturated NaHCO_3 , saturated NaCl), dried (Na_2SO_4), and concentrated (48.4 g). Distillation under vacuum afforded a fraction (26.5 g; b.p. $35-90^\circ\text{C}/0.8$ Torr) containing (*S*)-**8a** (98% ee), dimethyl malonate, and some (*R*)-**11a** and (*R*)-**11a** (19.95 g; b.p. $93-105^\circ\text{C}$; yield: 43%; 100% ee, as determined by conversion into (*R*)-**10a**). For determining the yield of recovered (*S*)-**8a**, the mixed fractions (26.5 g) were hydrolyzed (KOH , MeOH , H_2O) to afford distilled (*S*)-**8a** (yield: 13.31 g; 48%; 89% ee).

Racemization of (*S*)-**8a**: The above distillation fraction was dissolved in THF (160 mL) and treated with 2% aqueous H_2SO_4 (100 mL). The slightly turbid mixture was stirred at 24°C for 24 h, poured into a stirred 5% aqueous NaOH solution, and extracted twice with Et_2O . The organic phase was washed (H_2O , then saturated NaCl), dried (Na_2SO_4), concentrated, and distilled (bulb-to-bulb) to afford (±)-**8a** (12.2 g; containing 2% of dehydration products; yield: 90%).

(*R*)-**10a**: Malonate (*R*)-**11a** (9.90 g, 39.0 mmol) was added at 55°C within 15 min to a mechanically stirred suspension of washed ($3\times$ pentane) NaH (55% in oil; 2.14 g (1.18 g pure NaH), 49.0 mmol) in THF (100 mL) (350 mL three-necked flask, N_2), whereby immediate gas evolution (H_2) was observed. After 30 min, trimethylchlorosilane (8.50 g (9.80 mL); 78.0 mmol) was added rapidly. After the milky reaction mixture had been heated at 55°C for 3 h, the product mixture containing the desired silyl methyl malonate of type **e** (Scheme 1) was concentrated at reduced pressure, dissolved in

pentane, filtered through Celite, and concentrated (13.81 g; yield: 84% (GC); ^1H NMR (360 MHz, CDCl_3): $\delta = 3.72$ and 3.66 (83:17 (COOMe))). The crude product was dissolved in NMP (30 mL) and added slowly (90 min) to a hot (140°C) mixture of NMP (60 mL (58.1 g)), H_2O (1.2 mL, 67 mmol), and NaCl (2.90 g, 49 mmol). After 15 min, the cooled reaction mixture was poured into water, and the ester was extracted (Et_2O , $2\times$), washed (H_2O , $3\times$, saturated aqueous NaCl), dried (Na_2SO_4), filtered, and concentrated. Bulb-to-bulb distillation of the residue (8.89 g) at $70-80^\circ\text{C}$ (oven temperature)/0.07 Torr afforded ester (*R*)-**10a** (7.10 g, 92% pure (80% yield; 100% ee (Megadex 5; peak 1)). A sample was further purified by chromatography (SiO_2 ; cyclohexane/ AcOEt 98/2): $[\alpha]_D^{20} = +27$ ($c = 2.1$ in CHCl_3).

(+)-**16a** (using AlCl_3): A solution of (+)-**17a** (28.2 g, 124 mmol) in toluene (60 mL) was added between 4 and 7°C (ice bath) in 45 min to a mechanically stirred solution of AlCl_3 (2.50 g, 19.0 mmol) in toluene (800 mL), to which had been added a trace amount of Na_2CO_3 (31 mg). Fifteen minutes after complete addition, the clear reaction mixture was hydrolyzed by adding a saturated NaHCO_3 solution (125 mL) at such a rate that the temperature did not exceed 15°C . After the mixture was stirred for 15 h at room temperature, the organic layer was separated, washed (10% H_2SO_4 , then H_2O , then saturated NaCl), dried (Na_2SO_4), and concentrated. The crude product (29.7 g; **16a/15a** = 97:3) was mixed with Primol 352 (Esso (heavy hydrocarbon), 100 g) and CaCO_3 (820 mg) and distilled at $85-90^\circ\text{C}/0.01$ Torr to afford (+)-**16a** (25.9 g, 93% pure [35] (86%; **16a/15a** = 95:5; 100% ee, as determined by chiral GC (Megadex 5 or CD-Chirasil-DEX CB)).

(+)-**16a** (using $\text{BF}_3\cdot\text{OEt}_2$): Compound (+)-**17a** (100 g, 442 mmol) was added between 2 and 5°C in 35 min to a mechanically stirred solution of $\text{BF}_3\cdot\text{OEt}_2$ (15.7 g, 110 mmol) in CH_2Cl_2 (800 mL). Two minutes after complete addition, the orange-brown reaction mixture was hydrolyzed by adding quickly a saturated NaHCO_3 solution (280 mL) (CO_2 evolution). After the mixture had been stirred for 2 h at room temperature, the organic layer was separated, washed with H_2O (50 mL), and concentrated. Leybold distillation at $82^\circ\text{C}/0.08$ Torr afforded (+)-**16a** (89.5 g, 92% pure [35] (containing **21a** (7%)), 83%; **16a/15a** = 98:2; 100% ee).

(+)-**16b** (using $\text{BF}_3\cdot\text{OEt}_2$): A solution of (+)-**17b** (2.0 g, 94% pure (containing diepoxides (5%)); 8.40 mmol) in CH_2Cl_2 was added between 11 and 13°C in 25 min to a stirred solution of $\text{BF}_3\cdot\text{OEt}_2$ (0.38 g (0.34 mL), 2.68 mmol) in CH_2Cl_2 (20 mL). Two minutes after complete addition, the dark reaction mixture was hydrolyzed and isolated as above. Yield after bulb-to-bulb distillation: 1.65 g (92% pure [35] (containing **21b** (6%)), 80%; **16b/15b** = 94:6; 97% ee, as determined by chiral GC (Megadex 5 or CD-Chirasil-DEX CB)).

Received: September 3, 1999 [Z 13965/13966]

- [1] H. Frauenrath, *Methods of Organic Chemistry (Houben-Weyl) 4th ed.* 1952–, Vol. E 21d, 1995, p. 3301; P. Wipf, *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, 1991, p. 827; F. E. Ziegler, *Chem. Rev.* 1988, 88, 1423; G. W. Daub, J. P. Edwards, C. R. Okada, J. W. Allen, C. T. Maxey, M. S. Wells, A. S. Goldstein, M. J. Dibley, C. J. Wang, D. P. Ostercamp, S. Chung, P. S. Cunningham, M. A. Berliner, *J. Org. Chem.* 1997, 62, 1976; W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* 1970, 92, 741.
- [2] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* 1970, 92, 741.

- [3] R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, 98, 2868; R. E. Ireland, P. Wipf, J. D. Armstrong III, *J. Org. Chem.* **1991**, 56, 650. Review: S. Pereira, M. Srebnik, *Aldrichimica Acta* **1993**, 26, 17. For the Claisen rearrangement of allylic silylketene acetals derived from β -oxoesters, see: J. C. Gilbert, T. A. Kelly, *Tetrahedron* **1988**, 44, 7587.
- [4] P. Herold, R. Duthaler, G. Rihs, C. Angst, *J. Org. Chem.* **1989**, 54, 1178.
- [5] S. Raucher, K.-W. Chi, D. S. Jones, *Tetrahedron Lett.* **1985**, 26, 6261.
- [6] Lithium diisopropylamide (LDA)/TMSCl is ineffective. In one case (**8a** to **10a**), the intermediate ketene acetals were isolated (ca. 35 and 30%, ¹H NMR of OMe singlets at δ = 3.63 and 3.73), but these were accompanied by about 20% of starting malonate (formed by ready hydrolysis) and rearranged malonates (15 and 2–3%, respectively).
- [7] LDA/ZnCl₂, effective in certain chelate–enolate Claisen rearrangements (see U. Kazmaier, *Liebigs Ann. Chem.* **1997**, 285), was tested for the rearrangement of (*R*)-**5** derived malonate, but gave rise to a slow reaction with formation of side products.
- [8] Alternatively, desilylation can be performed in a separate step (5% aqueous HCl, THF).
- [9] For a review on chirality transfer by sigmatropic rearrangements, see: R. K. Hill, *Asymmetric Synthesis*, Vol. 3 (Ed.: J. D. Morrison), Academic Press, Orlando, **1984**, p. 503 and ref. [1].
- [10] K. Mori, *Synlett* **1995**, 1097; K. Mori, M. Amaike, M. Itou, *Tetrahedron* **1993**, 49, 1871; H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, 110, 1792; *Angew. Chem. Int. Ed.* **1998**, 37, 1703.
- [11] M. Ribí, C. J. Eugster, *Helv. Chim. Acta* **1969**, 52, 1732 ($[\alpha]_D^{20}$ = –92 (c = 2.2 in CHCl₃); ref.: (*R*)-**6**: $[\alpha]_D^{24}$ = +69 (CHCl₃)).
- [12] Reviews: E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, 110, 2092; *Angew. Chem. Int. Ed.* **1998**, 37, 1986; V. K. Singh, *Synthesis* **1992**, 605.
- [13] For two industrial syntheses, see F. Näf, R. Decorzant, *Helv. Chim. Acta* **1978**, 61, 2524; H. Kataoka, T. Yamada, K. Goto, J. Tsuji, *Tetrahedron* **1987**, 43, 4107.
- [14] A. Ookawa, K. Soai, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1465 (modified Friedel–Crafts sequence).
- [15] U. T. Strauss, U. Felfer, K. Faber, *Tetrahedron: Asymmetry* **1999**, 10, 107; W. Boland, C. Frössl, M. Lorenz, *Synthesis* **1991**, 1049.
- [16] Enones **7a** and **7b** were reduced to ($\pm$)-**8a** (94%) and ($\pm$)-**8b** (93%) with LiAlH₄ in Et₂O, or more economically with polymethylhydrosiloxane (PMHS) and catalytic amounts of zinc 2-ethylhexanoate and NaBH₄; H. Mimoun, *J. Org. Chem.* **1999**, 64, 2582.
- [17] Under these conditions, the liberated MeOH, a known inhibitor of lipases, is removed by evaporation. Without KHCO₃, the pH of the initial reaction mixture is about 3, and the reaction does not reach completion; in some experiments, partial racemization was noted.
- [18] For Johnson–Claisen rearrangements performed on enantiopure allylic alcohols, which in turn were obtained by enzymatic kinetic resolution, see K. Mori, *Liebigs Ann. Chem.* **1993**, 77; E. Brenna, N. Caraccia, C. Fuganti, D. Fuganti, P. Grasselli, *Tetrahedron: Asymmetry* **1997**, 8, 3801.
- [19] T. Hayashi, A. Yamamoto, T. Hagihara, *J. Org. Chem.* **1986**, 51, 723; I. Stary, P. Kocovsky, *J. Am. Chem. Soc.* **1989**, 111, 4981. However, enantioselective Pd-catalyzed malonate allylations show promise in symmetrical allylic systems. For the enantioselective preparation of cyclopentenyl malonates, see S. R. Gilbertson, D. Xie, *Angew. Chem.* **1999**, 111, 2915; *Angew. Chem. Int. Ed.* **1999**, 38, 2750, and references therein.
- [20] E. Demole, E. Lederer, D. Mercier, *Helv. Chim. Acta* **1962**, 45, 675; E. Demole, M. Stoll, *Helv. Chim. Acta* **1962**, 45, 692.
- [21] See ref. [13].
- [22] R. Nishida, T. E. Acree, H. Fukami, *J. Agric. Food Chem.* **1985**, 33, 425; R. Nishida, T. E. Acree, H. Fukami, *Agric. Biol. Chem.* **1985**, 49, 769; for its isolation: T. C. Baker, R. Nishida, W. L. Roelofs, *Science* **1981**, 214, 1359; R. Nishida, T. E. Acree, *J. Agric. Food Chem.* **1984**, 32, 1001.
- [23] B. Parthier, *Bot. Acta* **1991**, 104, 446.
- [24] a) Reviews: F. Schröder, *Angew. Chem.* **1998**, 110, 1271; *Angew. Chem. Int. Ed.* **1998**, 37, 1213; M. H. Beale, J. L. Ward, *Nat. Prod. Rep.* **1998**, 533; b) W. Boland, J. Hopke, J. Donath, J. Nüske, F. Bublit, *Angew. Chem.* **1995**, 107, 1715; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1600; G. Sembdner, B. Parthier, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **1993**, 44, 569.
- [25] E. F. Farmer, C. A. Ryan, *Proc. Natl. Acad. Sci. USA* **1990**, 87, 7713.
- [26] For a comprehensive review, see: T. K. Sarkar, B. K. Ghorai, *J. Indian Chem. Soc.* **1999**, 76, 693.
- [27] H. Tanaka, S. Torii, *J. Org. Chem.* **1975**, 40, 462; R. V. Stevens, N. Hrib, *Tetrahedron Lett.* **1981**, 22, 4791; T. Kitahara, K. Miura, Y. Warita, Y. Takagi, K. Mori, *Agric. Biol. Chem.* **1987**, 51, 1129; L. Crombie, K. M. Mistry, *J. Chem. Soc. Perkin Trans 1* **1991**, 1981; G. Stork, O. Ouerfelli, *New J. Chem.* **1992**, 16, 95; T. K. Sarkar, B. K. Ghorai, A. Banerji, *Tetrahedron Lett.* **1994**, 35, 6907; T. K. Sarkar, B. K. Ghorai, S. K. Nandy, B. Mukherjee, A. Banerji, *J. Org. Chem.* **1997**, 62, 6006.
- [28] a) G. Helmchen, A. Goeke, G. Lauer, M. Urmann, J. Fries, *Angew. Chem.* **1990**, 102, 1079; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1024; K. Weinges, U. Lernhardt, *Liebigs Ann. Chem.* **1990**, 751; T. Kitahara, T. Nishi, K. Mori, *Tetrahedron* **1991**, 47, 6999; H. Stadtmüller, P. Knochel, *Synlett* **1995**, 463; H. Stadtmüller, A. Vaupel, C. E. Tucker, T. Stüdemann, P. Knochel, *Chem. Eur. J.* **1996**, 2, 1204; G. J. Roth, S. Kirschbaum, H. J. Bestmann, *Synlett* **1997**, 618; J. S. U. H. S. Park, S. Gupta, J. K. Cha, *Synth. Commun.* **1997**, 27, 2931; T. K. Sarkar, B. Mukherjee, S. K. Ghosh, *Tetrahedron* **1998**, 54, 3243; b) see also: F.-P. Montforts, I. Gesing-Zibulak, W. Grammenos, M. Schneider, K. Laumen, *Helv. Chim. Acta* **1989**, 72, 1852; C. Borm, E. Winterfeldt, *Liebigs Ann.* **1996**, 1209, and references therein.
- [29] V. Rautenstrauch, J.-J. Riedhauser (Firmenich), EP-B 715615 **1998** (prior. 23.06.1994).
- [30] C. Fehr, *Angew. Chem.* **1998**, 110, 2509; *Angew. Chem. Int. Ed.* **1998**, 37, 2407.
- [31] a) Review: B. Rickborn, *Comprehensive Organic Synthesis*, Vol. 3 (Eds.: B. M. Trost, I. Fleming), Pergamon, New York, **1991**, p. 733; b) R. Sudha, K. Malola Narasimhan, V. Geetha Saraswathi, S. Sankararaman, *J. Org. Chem.* **1996**, 61, 1877; c) H. Sasai, T. Arai, E. Emori, M. Shibasaki, *J. Org. Chem.* **1995**, 60, 465; d) H. B. Henbest, T. I. Wrigley, *J. Chem. Soc.* **1957**, 4765.
- [32] For the hydroboration of racemic ($\pm$)-**10a**, which is also syn-selective (70:30), leading predominantly to the *trans*-disubstituted system, see: T. Kitahara, K. Hamaguchi, Y. Warita, Y. Takagi, K. Mori, *Agric. Biol. Chem.* **1986**, 50, 1867.
- [33] Alternatively, pure *syn*-epoxide **17a** could also be obtained in 79% yield by permaleic acid epoxidation (maleic anhydride, H₂O₂, CH₂Cl₂, 10°C), as concomitant acid-catalyzed lactonization of the *anti*-epoxide **18a** to **20a** (10% formed) is much faster than that of **17a** to **19a** (1% formed).
- [34] The reaction was followed by quenching samples with NaHCO₃/Et₂O, followed by silylation of the unconverted alcohol with *N,O*-bis(trimethylsilyl)acetamide (BSA) in toluene at 100°C for 5 min and chiral GC analysis (Megadex 5). Normal GC analysis did not always give reproducible results (thermal instability of **11a**).
- [35] The product can be further purified by flash column chromatography (SiO₂ F 60, 35–70 μ), using CH₂Cl₂ as solvent.

Diastereoselective Ce(OiPr)₃-Catalyzed Pinacol Couplings of Aldehydes**

Ulrich Groth* and Mario Jeske

In general, 1,2-diols can be generated by bishydroxylation of olefinic double bonds^[1] or reductive coupling of carbonyl compounds.^[2] The latter method plays an important part in the synthesis of HIV-protease inhibitors^[3] and natural products such as taxol.^[4] The reaction has to be performed in a diastereoselective fashion to synthesize these compounds. Economic and ecological reasons have meant that transition metal catalyzed pinacol couplings are of current interest. The catalytic cycles known so far allow the use of the catalytic low-valent metal species down to 1 mol %.^[5] The formation of the active coupling reagent takes place by in situ reduction using metals such as manganese, magnesium, or zinc. Fürstner^[6] was the first to develop a catalytic reaction by using trimethylsilyl chloride to cleave the metal–oxygen bond in the intermediate formed. The application of this methodology to pinacol couplings allowed disilylated diols to be obtained.^[5, 7]

Gansäuer observed high diastereoselectivities of up to 98.5:1.5 for carbonyl reductions by using catalytic amounts of racemic ethylene-bis-(η^5 -tetrahydroindenyl)titanium dichloride [(ebthiTiCl₂)]^[8] and in situ reduction with zinc.^[9] A big disadvantage of this methodology is the fact that only aromatic and α,β -unsaturated aldehydes can be coupled; aliphatic aldehydes do not react under these reaction conditions.

By using low-valent samarium and vanadium species, respectively, Endo et al.^[7a] and Hirao et al.^[7d] demonstrated that aromatic as well as aliphatic aldehydes can be coupled in a catalytic fashion. In these cases high diastereoselectivities could only be obtained for sterically demanding substrates such as cyclohexylcarbaldehyde. The *rac*:*meso* ratio decreased to 50:50 on coupling aliphatic aldehydes.

Cerium reagents can be used widely in synthetic organic chemistry as a result of their oxophilicity.^[10] Besides the diastereoselective addition of organocerium reagents to carbonyl compounds,^[11] the reduction of α,β -unsaturated ketones to allylic alcohols with NaBH₄ in the presence of cerium trichloride^[12] is of great synthetic interest. However, a catalytic application of cerium compounds has up until now remained unknown.

Herein we report on cerium(III) isopropanolate catalyzed pinacol couplings of carbonyl compounds with diethylzinc as the reductive agent. Instead of the expected addition of an ethyl group to the carbonyl function the reductive coupling of

two aldehydes to 1,2-diols could be observed. To the best of our knowledge this represents the first cerium-catalyzed reaction in organic synthesis. Table 1 shows the influence of the reaction time, reaction temperature, and the amount of catalyst on the yield and diastereoselectivity for the reductive coupling of benzaldehyde. Excellent yields and high diastereoselectivities of disilylated 1,2-diols could be achieved in favor of the *rac*-isomer under noncatalytic conditions (entry 1). Diastereoselectivity and yield did not change remarkably even if only a catalytic amount of cerium reagent was employed. An increase of diastereoselectivity could be achieved by decreasing the reaction temperature, but in this case lower yields were observed (entry 4). The best reaction conditions were observed by adding benzaldehyde over several hours to the reaction mixture. In this case 1,2-bis(trimethylsiloxy)-1,2-diphenylethane could be obtained in a yield of 84 % and a diastereoselectivity of 97:3 in favor of the

Table 1. Pinacol coupling of benzaldehyde (**1**) to give 1,2-bis(trimethylsiloxy)-1,2-diphenylethane (**2**) under various reaction conditions.

Entry	Amount of cat. [mol %]	<i>t</i> [h]	<i>T</i> [°C]	Yield (2) [%]	
				2a	2b
1	100	15	25	90	98:2
2	10	12	25	73	96:4
3	5	12	25	70	95:5
4	5	12	–15	48	98:2
5	3	15 ^[a]	25	84	97:3
6	0	15	25	0	–

[a] Addition of PhCHO over 10 h.

rac-diol (entry 5). A by-product of 1-phenyl-1-propanol was isolated (16 %), which resulted from the addition of an ethyl group from diethylzinc to the carbonyl function over the prolonged reaction time. No reaction to the coupling product could be observed if the cerium catalyst was absent (entry 6).

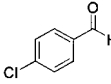
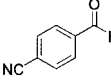
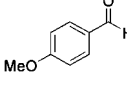
In order to investigate the scope and limitations of this pinacol-type coupling reaction different aldehydes were converted into their corresponding diols under optimized reaction conditions. As shown in Table 2 substituted aromatic aldehydes could be coupled reductively in yields of 73–84 % with diastereoselectivities of up to 98:2. Thereby the mesomeric effects of the substituents in the aromatic aldehydes show only a small influence on the yield and diastereoselectivity (entries 1–4).

In this context it is remarkable that even aliphatic aldehydes could undergo pinacol coupling despite their known very limited tendency to do so. The coupling of secondary and tertiary aldehydes proceeded smoothly in yields of 54–64 % (entries 5–8) and diastereoselectivities of up to 98:2. The comparison of the reductive coupling of isovaleraldehyde (entry 7) and cyclohexylcarbaldehyde (entry 8) shows clearly the steric demand of the six-membered

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[**] Lanthanides in Organic Synthesis, Part 3. This work was supported by the “Fonds der Chemischen Industrie” and by the “EU Commission, Directorate General XII”. We are grateful to the WITCO GmbH, Bergkamen, for the generous support of diethylzinc. M.J. also thanks the “Stiftung Stipendienfonds des Verbandes der Chemischen Industrie” for the award of a promotion stipend. Part 2: ref. [11].

Table 2. Pinacol couplings of aromatic and aliphatic aldehydes under optimal catalytic conditions.

$\text{R}-\text{CHO} \xrightarrow[\text{ZnEt}_2, \text{TMSCl}]{\text{Ce}(\text{O}i\text{Pr})_3 (3 \text{ mol}\%)} \text{R}-\text{CH}(\text{OSiMe}_3)-\text{CH}(\text{OSiMe}_3)-\text{R} + \text{R}-\text{CH}(\text{OSiMe}_3)-\text{CH}(\text{OSiMe}_3)-\text{R}$			
3		4a	4b
Entry	Aldehyde	Yield (4) [%]	4a:4b
1		84	97:3
2		76	98:2
3		74	94:6
4		73	95:5
5		57	90:10
6		54	88:12
7		62	92:8
8		64	98:2
9		71	96:4
10		65	95:5

ring, which enforces an increase in the diastereoselectivity. Moreover, pivalaldehyde, which up until now could not be coupled reductively in a catalytic fashion, was converted into its corresponding disilylated 1,2-diol (entry 9) in a yield of 71%. In this case the presence of a double bond was also tolerated (entry 10). Nevertheless aliphatic aldehydes without any β -substitution such as hexanal cannot be coupled reductively with this catalytic system.

The pinacol coupling presented here also allows preparations on a large scale, which is of great interest for industrial applications. For example, 5.74 g (81%) of 1,2-bis(trimethylsiloxy)-1,2-diphenylethane could be isolated after conversion of 4.24 g (40 mmol) of benzaldehyde. In this procedure the amount of the applied cerium(III) isopropanolate was reduced down to 1 mol%.

The reaction mechanism of this reductive coupling is not yet clear and is therefore the subject of current investigations. The following mechanisms seem to be possible: the zinc hydride that results from disintegration of diethylzinc seems to serve as a reductive agent and reduce cerium(III) isopro-

panolate to cerium(II) isopropanolate, which itself reacts with the carbonyl group to give the ketyl with regeneration of Ce^{III} . On the other hand, one could imagine that the reaction mechanism is dominated by a one-electron transfer of diethylzinc^[14] to the carbonyl group complexed by means of cerium(III) isopropanolate in analogy to the Grignard reaction.^[13] The ethyl radical cannot be attached to the sterically demanding complexed ketyl. The pinacol then develops by recombination of two ketyls.

In summary, the advantage of the presented pinacol coupling can be characterized as follows: besides the high diastereoselective coupling of aromatic aldehydes, even aliphatic aldehydes can be coupled with high diastereoselectivities. According to this method the pinacol coupling of sugar and amino aldehydes to pharmacological interesting diols should also succeed.

Experimental Section

The reactions were carried out in an argon atmosphere using Schlenk techniques. Substances which are sensitive against moisture and air were stored in a glove box. $\text{Ce}(\text{O}i\text{Pr})_3$ was synthesized according to the procedure described in ref. [15].

General procedure: A 1M solution of diethylzinc in hexane (10 mL, 10 mmol) was added to $\text{Ce}(\text{O}i\text{Pr})_3$ (48 mg, 0.15 mmol, 3 mol%) in a Schlenk tube. Subsequently, a 1M solution of cyclohexylcarbaldehyde in THF (5.0 mL, 5.0 mmol) and a 1.5M solution of trimethylsilyl chloride in THF (5.0 mL, 7.5 mmol) were added slowly (5–15 h). After the addition of a saturated aqueous solution of ammonium chloride (20 mL), the reaction mixture was extracted with diethyl ether (50 mL, $\times 3$), the combined organic layers were dried over magnesium sulfate, and the solvent was removed by evaporation. The residue was purified by flash chromatography to yield 0.59 g (64%) of 1,2-bis(trimethylsiloxy)-1,2-dicyclohexylethane (Table 2, entry 8). ^1H NMR (400 MHz, CDCl_3): δ = 0.12 (s, 18H; SiMe_3), 1.11–1.81 (m, 20H; CH_2), 2.18–2.27 (m, 2H; CH), 3.65 (d, J = 6.5 Hz, 2H; CHOSiMe_3); ^{13}C NMR (100.6 MHz, CDCl_3): δ = 1.10 (SiMe_3), 25.76 (C3), 26.57 (C4), 27.14 (C2), 41.96 (C1), 68.46 (COSiMe_3).

Received: December 1, 1998 [Z12732]

- Reviews: a) H. Kropf, J. Thiem, *Methoden Org. Chem. (Houben-Weyl)* 4th ed. 1952–, Vol. 6/1 a/1, **1984**, pp. 592–607; b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, 94, 2483–2547; c) H. Becker, K. B. Sharpless, *Angew. Chem.* **1996**, 108, 447–449; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 448–451.
- Reviews: a) H. Kropf, J. Thiem, *Methoden Org. Chem. (Houben-Weyl)* 4th ed. 1952–, Vol. 6/1 a/2, **1984**, pp. 1485–1508; b) G. M. Robertson, *Comprehensive Organic Synthesis*, Vol. 3 (Ed.: B. M. Trost, I. Fleming, G. Pattenden), Pergamon, Oxford, **1991**, pp. 563–610; c) A. Fürstner, R. Csuk, C. Rohrer, H. Weidmann, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1729–1734; d) A. Fürstner, B. Bogdanovic, *Angew. Chem.* **1996**, 108, 2582–2609; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2442–2469.
- B. Kammermeier, G. Beck, D. Jacobi, H. Jendralla, *Angew. Chem.* **1994**, 106, 719–721; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 685–687.
- a) I. Shiina, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, K. Saitoh, T. Mukaiyama, *Chem. Lett.* **1997**, 419–420; b) K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, E. J. Sorensen, *J. Am. Chem. Soc.* **1995**, 117, 634–644.
- T. Hirao, B. Hatano, M. Asahara, Y. Muguruma, A. Ogawa, *Tetrahedron Lett.* **1998**, 39, 5247–5248.
- Review: A. Fürstner, *Chem. Eur. J.* **1998**, 4, 567–570.

- [7] a) R. Nomura, T. Matsuno, T. Endo, *J. Am. Chem. Soc.* **1996**, *118*, 11666–11667; b) A. Gansäuer, *Chem. Commun.* **1997**, 457–458; c) A. Svatos, W. Boland, *Synlett* **1998**, 549–551; d) T. Hirao, M. Asahara, Y. Muguruma, A. Ogawa, *J. Org. Chem.* **1998**, *63*, 2812–2813.
- [8] F. Wild, L. Zsolnai, G. Huttner, H. H. Brintzinger, *J. Organomet. Chem.* **1982**, *232*, 233–248.
- [9] a) A. Gansäuer, *Synlett* **1997**, 363–364; b) A. Gansäuer, M. Moschioni, D. Bauer, *Eur. J. Org. Chem.* **1998**, 1923–1927.
- [10] Reviews: a) G. A. Molander, *Chem. Rev.* **1992**, *92*, 29–68; b) T. Imamoto, *Comprehensive Organic Synthesis*, Vol. 1 (Ed.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon, Oxford, **1991**, 231–250; c) T. Imamoto, *Lanthanides in Organic Synthesis*, Academic Press, London, **1994**.
- [11] C. Alcaraz, U. Groth, *Angew. Chem.* **1997**, *109*, 2590–2592; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2480–2482.
- [12] A. L. Gemal, J.-L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
- [13] a) E. C. Ashby, J. N. Argyropoulos, G. R. Meyer, A. B. Goel, *J. Am. Chem. Soc.* **1982**, *104*, 6788–6789; b) T. Holm, *Acta Chem. Scand. Ser. B* **1983**, *37*, 567–584.
- [14] W. Kaim, *Nachr. Chem. Tech. Lab.* **1984**, *32*, 436–439.
- [15] P. Eckenberg, U. Groth, T. Köhler, *Liebigs Ann. Chem.* **1994**, 673–677.

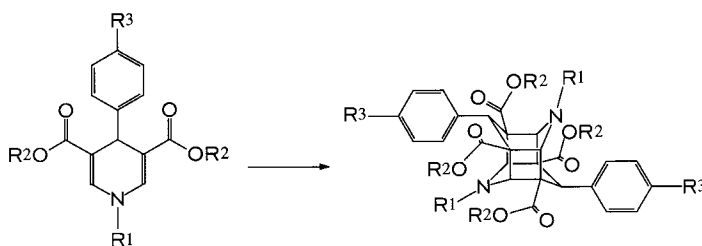
The First Functionalized 6,12-Diazatetrakisomocubanes**

Andreas Hilgeroth* and Ute Baumeister

Despite all efforts, accessibility of cage compounds analogous to cubane is limited. These compounds have presented a constant synthetic challenge since the first cubane compound was obtained.^[1, 2] The limited development of novel functionalization reactions such as photochemical carboxylation^[2, 3] has led to the synthesis of compounds with interesting pharmacological effects: This includes the carcinogenic effect of phenyl-substituted cubanes and substituted bishomocubanes and the recently observed anti-HIV effect of carboxylated cubanes.^[2, 4] Initial efforts in combinatorial chemistry of cubanes have made accelerated discovery of new substances possible.^[5] Since this only involves derivatives and not new basic structures, the challenge of finding alternative possibilities for synthesizing new cage compounds remains.

By the use of topochemically controlled photodimerization of symmetric 4-aryl-1,4-dihydropyridines to form centrosymmetric 3,9-diazatetraasteranes, we were recently able to

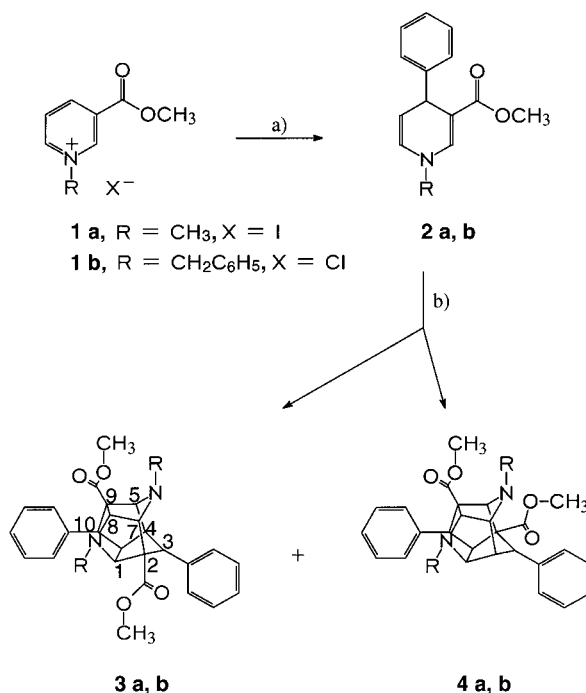
develop a process for synthesizing tetraasteranes that are analogous to aza compounds in almost quantitative yield (Scheme 1).^[6] These cubane analogs currently hold interest as novel HIV-1 protease inhibitors.^[7]



Scheme 1. Formation of 3,9-diazatetraasteranes from 4-aryl-1,4-dihydropyridines.

Here, the first C_2 -symmetric and asymmetric 6,12-diazatetrakisomocubanes are presented. They were obtained, totally unexpectedly, as the main products from the reaction of asymmetric 4-aryl-1,4-dihydropyridines, and enrich the pool of interesting cage compounds.

Starting from N-alkyl-substituted pyridinium compounds **1**,^[8] the 4-aryl-1,4-dihydropyridines **2**^[9] can be obtained in over 90 % yield by regioselective reaction with equimolar amounts of phenylmagnesium chloride in the presence of catalytic amounts of copper(I) iodide^[10] (Scheme 2).



Scheme 2. a) PhMgCl , CuI (cat.), THF, RT; b) $h\nu$, MeOH/THF .

Irradiation of solutions of 4-aryl-1,4-dihydropyridines **2** by Ultra-Vitalux lamps ($\lambda \geq 270 \text{ nm}$), with excitation of the 1,4-dihydropyridine chromophores at $\lambda_{\text{max}} = 348 \text{ nm}$ (**2a**) or 346 nm (**2b**), resulted in the dimerization products **3** and **4** in overall yields of more than 80 %. ^1H NMR spectroscopy showed that the C_2 -symmetric compound **3** is characterized by a simple set of proton signals for the two 1,4-dihydropyridine

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[**] This work was supported by the German Pharmaceutical Society (DPhG) and by the Fonds der Chemischen Industrie.

units,^[11] whereas the asymmetric product **4** reveals a corresponding double set for these two units.^[12] The IR spectrum of **3** contains only one ester carbonyl band,^[11] whereas that of **4** shows two bands.^[12]

X-ray crystal structure analyses of both compounds (Figures 1a and 1b) were undertaken to clarify the configuration, and confirmed the existence of the totally unexpected structures.

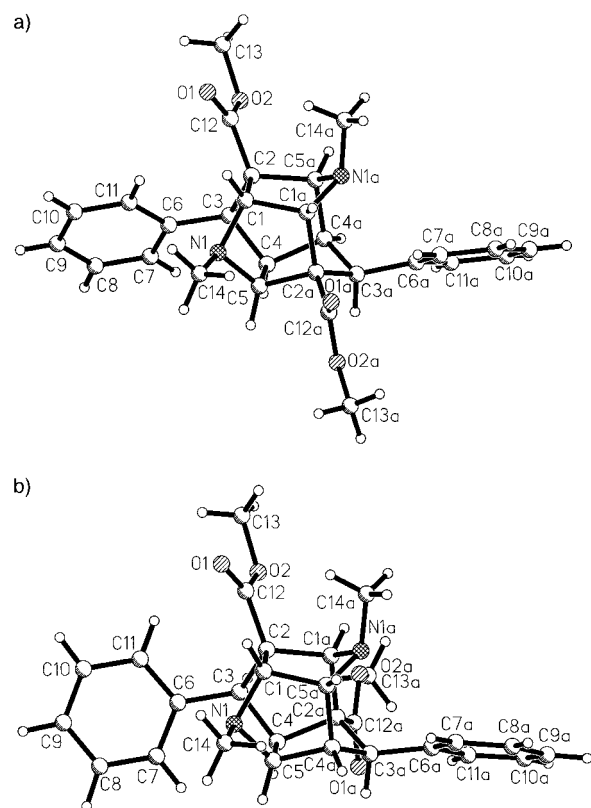
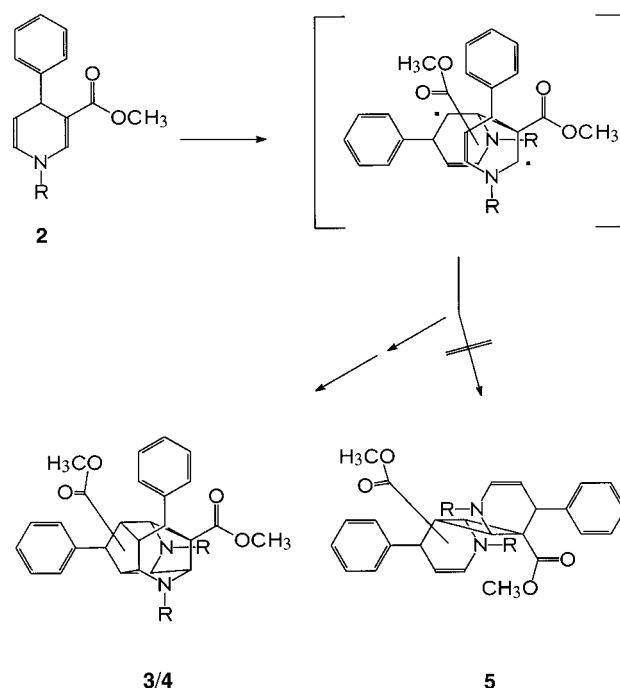


Figure 1. Molecular structures of **3a** (a) and **4a** (b) in the crystal.

In contrast to the previously observed head-to-tail 1,4-dihydropyridine dimers with centrosymmetric cage structures of 3,9-diazatetraasteranes or their C_2 -symmetric, *syn*-dimeric intermediates,^[6, 13] the linkage of the two 1,4-dihydropyridine rings in **3** and **4** are not in a head-to-tail arrangement of 180° to each other, but form an angle of only 90°. Stereochemically **3** is the product of common enantiomeric forms, whereas **4** is made up of different enantiomers. Both compounds can formally be considered as resulting from the attack of one dihydropyridine molecule on the far side of the dihydropyridine ring of the second molecule (i.e., the side that does not face the aryl moiety). Steric reasons are responsible for the axial arrangement of the phenyl rings in this case.

The mechanism of the formation of the adducts **3** and **4** is of great interest. Starting from the formation of the primary diradical according to known photodimerization reactions, a nonconcerted [2+2]cycloaddition with bond rotation^[14]—analogous to the mechanism of a classical [2+2]cycloaddition for the previously observed 1,4-dihydropyridine photodimerization^[6, 13]—should lead to the formation of the *anti*-dimers **5** (Scheme 3). The formation of **3/4** via the hypothetical primary diradical adduct is currently under investigation.



Scheme 3. Formation of **3/4** via a primary diradical.

The synthesis presented here provides easy access to novel functionalized diaza cage compounds by means of an interesting mechanism of formation. Further work with structural variants as starting materials should increase the range of such functionalized cage compounds even further. The solid-state chemistry of asymmetric 4-aryl-1,4-dihydropyridines is also under investigation. The structural similarity of the C_2 -symmetric tetrakisomocubanes **3** to the 3,9-diazatetraasteranes^[15] gives rise to great interest in these compounds in particular as potential inhibitors of C_2 -symmetric HIV-1 protease.

Experimental Section

The pyridinium salts **1a, b** (10 mmol) were suspended in anhydrous THF (100 mL). After addition of copper(I) iodide (0.5 mmol) a 1M solution of phenylmagnesium chloride (10 mL, 10 mmol) was added dropwise to the suspension. After stirring for 2 h, the solution was treated with an aqueous solution of ammonium chloride (60 mL) and then extracted with diethyl ether (150 mL). The ether phase was washed with 20% ammonia/ammonium chloride solution (1/1, 60 mL), water, 10% hydrochloric acid (2 ×), water, and sodium chloride solution, and then dried over sodium sulfate. After filtration, the ether was removed under vacuum and the oily residue was taken up in methanol. Upon cooling, **2a** or **2b** crystallized in 90% yield.

The 4-aryl-1,4-dihydropyridines **2a, b** (2 mmol) were dissolved in methanol/THF (40 mL) under stirring in a quartz glass flask. The solution was then irradiated with a Ultra-Vitalux lamp from a distance of 60 cm for four weeks. Quartz glass flasks were used to ensure that the short wavelengths of the light, which triggered the cyclization of the *syn*-dimers of symmetric 4-aryl-1,4-dihydropyridines to 3,9-diazatetraasteranes, were also able to penetrate.^[6] As soon as no more starting materials could be detected by thin-layer chromatography and product formation without detectable intermediate product formation was shown to be complete, the solvent was removed by evaporation. The adducts **3a, b** and **4a, b** were obtained by fractional crystallization.

X-ray crystal structure analysis of **3a**: One white prism 0.72 × 0.37 × 0.19 mm³ in size was measured at room temperature with a STADIA

diffractometer, Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), and a graphite monochromator. A total of 14022 reflections were measured using a $\omega/2\theta$ scan mode ($3.3^\circ \leq 2\theta \leq 54.0^\circ$). Crystal system: tetragonal, space group $P4_2/n$, $Z = 8$, $a = 24.846(3)$, $b = 24.846(3)$, $c = 7.8219(13) \text{ \AA}$; $V = 4828.6(12) \text{ \AA}^3$; $\rho_{\text{calc}} = 1.262 \text{ g cm}^{-3}$; $\mu = 0.084 \text{ mm}^{-1}$. The structure was solved directly with SHELXS97 with 7011 independent reflections, the structure was refined according to full-matrix least-squares procedures (SHELXL97); $wR^2 = 0.1919$ for 7011 reflections, $R^1 = 0.0986$ for 2706 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 311 refined parameters. The positions of the hydrogen atoms were calculated according to geometric considerations and refined isotropically.

X-ray crystal structure analysis of **4a**: A yellow crystal $0.57 \times 0.48 \times 0.34 \text{ mm}^3$ in size was measured at room temperature with a STADIA diffractometer, Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$), and a graphite monochromator. A total of 13516 reflections were measured using a $\omega/2\theta$ scan mode ($3.3^\circ \leq 2\theta \leq 54.9^\circ$). Crystal system: triclinic, space group $P\bar{1}$, $Z = 2$, $a = 9.6489(3)$, $b = 9.8280(5)$, $c = 13.2209(6) \text{ \AA}$, $\alpha = 82.092(5)$, $\beta = 69.261(5)$, $\gamma = 84.237(4)^\circ$; $V = 1159.53(10) \text{ \AA}^3$; $\rho_{\text{calc}} = 1.313 \text{ g cm}^{-3}$; $\mu = 0.088 \text{ mm}^{-1}$. The structure was solved directly with SHELXS97 using 6758 independent reflections, the structure was refined according to full-matrix least-squares procedures (SHELXL97); $wR^2 = 0.1340$ for 6758 reflections, $R^1 = 0.0477$ for 5035 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 405 refined parameters. The positions of the hydrogen atoms were calculated geometrically and refined isotropically.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133187. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Received September 3, 1999 [Z13960]

- [1] P. E. Eaton, T. W. Cole, *J. Am. Chem. Soc.* **1964**, *86*, 962–964, 3157–3158.
- [2] P. E. Eaton, *Angew. Chem.* **1992**, *104*, 1447–1462; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1421–1436.
- [3] A. Bashir-Hashemi, *Angew. Chem.* **1993**, *105*, 585–586; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 612.
- [4] a) T. Hasegawa, N. Tomohiro, T. Kakita, H. Toyoda, H. Toya, I. Ueda, *Chem. Pharm. Bull.* **1993**, *41*, 1760–1768; b) S. Borman, *Chem. Eng. News* **1994**, 28(11), 34–36.
- [5] a) T. Carell, E. A. Wintner, A. Bashir-Hashemi, J. Rebek, *Angew. Chem.* **1994**, *106*, 2159–2162; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2059–2061; b) T. Carell, E. A. Wintner, J. Rebek, *Angew. Chem.* **1994**, *106*, 2162–2164; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2061–2064.
- [6] A. Hilgeroth, U. Baumeister, F. W. Heinemann, *Eur. J. Org. Chem.* **1998**, 1213–1218.
- [7] A. Hilgeroth, A. Billich, *Arch. Pharm. Pharm. Med. Chem.* **1999**, 332, 3–5.
- [8] a) M. R. Lamborg, R. M. Burton, N. O. Kaplan, *J. Am. Chem. Soc.* **1957**, *79*, 6173–6177; b) A. G. Anderson, G. Berkelhammer, *J. Am. Chem. Soc.* **1958**, *80*, 992–999.
- [9] All new compounds were characterized by IR, ^1H NMR, and ^{13}C NMR spectroscopy and mass spectrometry, solubility permitting, and by elemental analysis. Selected physical data for **2a**: yellow crystals, m.p. 115–120°C; IR (KBr): $\tilde{\nu} = 1682 \text{ cm}^{-1}$ (C=O); ^1H NMR (500 MHz, CD_3OD , 25°C, TMS): $\delta = 3.10$ (s, 3H; NCH_3), 3.53 (s, 3H; COOCH_3), 4.41 (d, $^3J(\text{H,H}) = 4.7 \text{ Hz}$, 1H; 4-H), 4.89 (dd, $^3J(\text{H,H}) = 7.8$, 4.7 Hz, 1H; 5-H), 5.94 (d, $^3J(\text{H,H}) = 7.8 \text{ Hz}$, 1H; 6-H), 7.09–7.87 (m, 6H; aromat. H, 2-H); UV/Vis (methanol): $\lambda_{\text{max}}(\epsilon) = 348$ (4324), 232 (6229); MS (70 eV): m/z (%): 229 (2) [M^+], 212 (9) [M^+], 169 (100) [$M^+ - 60$].
- [10] D. L. Comins, E. D. Stroud, J. J. Herrick, *Heterocycles* **1984**, *22*, 151–157.
- [11] Selected physical data for **3a**: white needles, yield: 39%, m.p. 212–218°C, IR (KBr): $\tilde{\nu} = 1723 \text{ cm}^{-1}$ (C=O); ^1H NMR (500 MHz, CDCl_3 , 25°C, TMS): $\delta = 2.04$ (s, 6H; NCH_3), 3.18 (AA'HH'RR'XX', $^3J(\text{H,H}) = 9.4$, 1.9 Hz, $2 \times ^4J(\text{H,H}) = 1.9 \text{ Hz}$, 2H; 4-, 11-H), 3.37 (d,

$^3J(\text{H,H}) = 1.9 \text{ Hz}$, 2H; 3-, 10-H), 3.69 (s, 6H; COOCH_3), 3.84 (dt, $^3J(\text{H,H}) = 9.4 \text{ Hz}$, $2 \times ^4J(\text{H,H}) = 1.9 \text{ Hz}$, 2H; 1-, 5-H), 4.59 (t, $^4J(\text{H,H}) = 1.9 \text{ Hz}$, 2H; 7-, 8-H), 7.05–7.18 (m, 10H; aromat. H); UV/Vis (chloroform): $\lambda_{\text{max}}(\epsilon) = 250$ (973); MS (70 eV): m/z (%): 458 (3) [M^+], 229 (34) [$M^+/2$], 214 (6) [$M^+/2 - \text{CH}_3$], 152 (100) [$M^+/2 - \text{Ph}$].

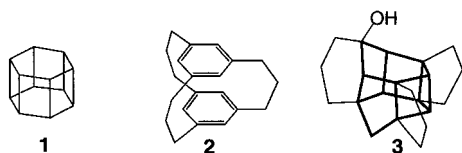
- [12] Selected physical data for **4a**: small yellow spheres, yield: 42%, m.p. 188–191°C, IR (KBr): $\tilde{\nu} = 1725$, 1713 cm^{-1} (C=O); ^1H NMR (500 MHz, CDCl_3 , 25°C, TMS): $\delta = 2.00$, 2.04 ($2 \times$ s, 6H; NCH_3), 3.73, 3.75 ($2 \times$ s, 6H; COOCH_3), 3.25 (dd, $^3J(\text{H,H}) = 8.9$, 3.1 Hz, 1H, 4-H), 3.29 (ddd, $^3J(\text{H,H}) = 8.9$, 4.9, 3.3 Hz, 1H; 9-H), 3.36 (d, $^3J(\text{H,H}) = 3.1 \text{ Hz}$, 1H; 3-H), 3.38 (d, $^3J(\text{H,H}) = 3.3 \text{ Hz}$, 1H; 10-H), 3.51 (ddd, $^3J(\text{H,H}) = 8.9$, 4.5 Hz, $^4J(\text{H,H}) = 2.9 \text{ Hz}$, 1H; 8-H), 3.76 (ddd, $^3J(\text{H,H}) = 8.9$, 4.9 Hz, $^4J(\text{H,H}) = 2.7 \text{ Hz}$, 1H; 5-H), 4.43 (dd, $^3J(\text{H,H}) = 4.5 \text{ Hz}$, $^4J(\text{H,H}) = 2.7 \text{ Hz}$, 1H, 7-H), 4.58 (d, $^4J(\text{H,H}) = 2.9 \text{ Hz}$, 1H; 1-H), 7.03–7.19 (m, 10H; aromat. H); UV/Vis (chloroform): $\lambda_{\text{max}}(\epsilon) = 250$ (2863); MS (70 eV): m/z (%): 458 (15) [M^+], 427 (4) [$M^+ - \text{OCH}_3$], 228 (35) [$M^+/2 - 1$], 214 (6) [$M^+/2 - \text{CH}_3$], 152 (100) [$M^+/2 - \text{Ph}$].
- [13] U. Eisner, J. R. Williams, B. H. Matthews, H. Ziffer, *Tetrahedron* **1970**, *26*, 899–909.
- [14] M. Klessinger, J. Michl, *Excited States and Photochemistry of Organic Molecules*, VCH, Weinheim, **1995**, p. 404.
- [15] A. Hilgeroth, R. Fleischer, M. Wiese, F. W. Heinemann, *J. Comput. Aided Mol. Des.* **1999**, *13*, 233–242.

Formation of a Novel Cage Compound with a Pentacyclo[6.3.0.1^{4,11}.0^{2,6}.0^{5,10}]dodecane Skeleton by Photolysis of [3₄](1,2,4,5)Cyclophane**

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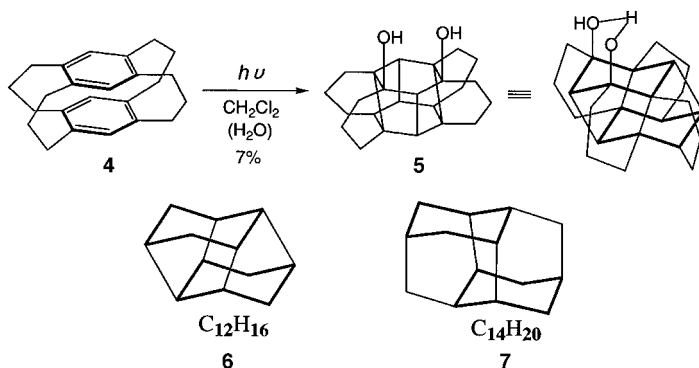
Prismanes constitute a fascinating family of $(\text{CH})_n$ polyhedra,^[1] several members of which, namely, prismane,^[2] cubane,^[3] and pentaprismane,^[4,5] have been successfully synthesized. Recently, attention has focused on the challenging objective of synthesizing the higher prismanes, in particular, hexaprismanes **1**. Despite many efforts, they have so far eluded synthesis, mainly because of the lack of proper synthetic routes and the expected higher strain energies than the lower prismanes. In our approach to construct the hexaprismane skeleton by photolysis of multibridged [3_n]cyclophanes ($n = 3–6$) we first optimized the reaction conditions using the lowest homologue [3₃](1,3,5)cyclophane (**2**),

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- [**] Multibridged [3_n]Cyclophanes. Part 8. For previous papers, see refs. [6 (Part 6) and 8 (Part 7)]. We gratefully acknowledge the financial support by the Grant-in-Aid for the Priority Area (A) of Creation of Delocalized Electronic Systems (no. 11133244) from the Ministry of Education, Science, Sports, and Culture, Japan.



and found that **2** was converted into the bishomopentaprismane skeleton **3** upon irradiation in H_2O -saturated CH_2Cl_2 with a low-pressure Hg lamp.^[6] The photolysis of the next higher homologue of **2**, [3₄](1,2,4,5)cyclophane (**4**),^[7] was studied to obtain the hexaprismane derivatives and further information on the reaction mechanism. Recently, an improved and practical synthetic method has made **4** readily available.^[8]

A solution of **4** in H_2O -saturated CH_2Cl_2 (6.9×10^{-4} mol L^{-1}) was irradiated with a low-pressure Hg lamp for 1.5 h at room temperature under Ar. The reaction was monitored by HPLC and TLC. Separation of the crude product by column chromatography on silica gel with AcOEt/hexane (1/2) afforded the starting material **4** (45 %) and a new cage compound **5** as colorless crystals (7 %; Scheme 1).^[9] The mass



Scheme 1. Photochemical reaction of **4** in H_2O -saturated CH_2Cl_2 by irradiation with a low pressure Hg lamp provided the novel cage compound **5**. The skeleton of **5** (**6**) and diamondane **7** are also shown.

spectrum indicates a molecular formula of $\text{C}_{24}\text{H}_{32}\text{O}_2$ (m/z 352.2) and the base peak (m/z 335.2) arises from the dehydration of M^+ . The hydroxy proton signals appear as a singlet in the ^1H NMR spectrum at $\delta = 4.15$. The proton-decoupled ^{13}C NMR spectrum of **5** shows six signals ($\delta = 17.7, 19.2, 23.0, 25.6, 26.1, 35.8$) for the secondary carbon atoms, five ($\delta = 44.9, 48.1, 52.5, 57.4, 58.3$) for the tertiary carbon atoms, and three ($\delta = 50.6, 54.6, 85.1$) for the quaternary carbon atoms, which suggests a structure with some symmetry. The highly deshielded quaternary carbon signal at $\delta = 85.1$ is assigned to those bearing a hydroxy group. The structure was finally identified as **5** on the basis of an X-ray structural analysis.^[10]

The novel polycyclic compound is composed of six cyclohexane rings in the chair conformation, four of which are transformed from the original trimethylene bridges and the remaining two originate from the benzene rings (Figure 1). To the best of our knowledge the pentacyclo[6.3.0.1^{4,11}.0^{2,6}.0^{5,10}]-dodecane skeleton **6** was designed by Evtushenko et al. as a member of the $\text{C}_{12}\text{H}_{16}$ family,^[11] but its synthesis has not yet

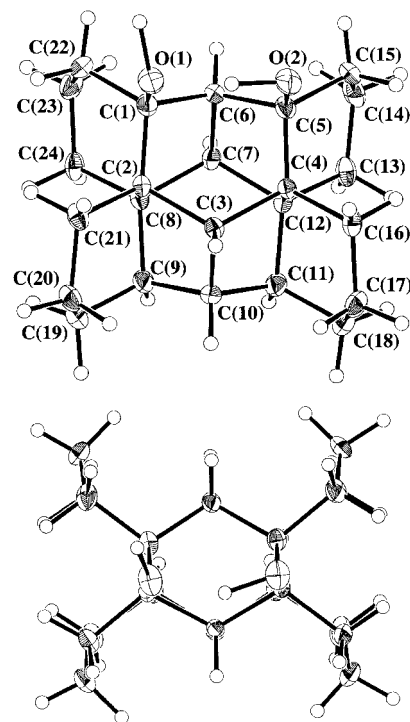


Figure 1. ORTEP drawing of **5** (30 % probability ellipsoids).

been described in the literature. The skeleton **6** resembles diamantane **7** (pentacyclo[7.3.1.1^{4,12}.0^{2,7}.0^{6,11}]tetradeceane), which was first synthesized by Schleyer et al. in 1965 and named “congressane”.^[12] However, the upper and lower cyclohexane rings in the chair conformation are directly connected at four positions (C2–C8, C4–C12, C3–C10, C6–C7) in **5**, whereas the latter two positions are connected with C_1 units in **7**. Structure **5** has C_s symmetry with only one symmetry plane (C3–C6–C7–C10) located between the two hydroxy groups. Although the bond lengths and bond angles of diamantane **7** are normal,^[13] the C3–C10 and C6–C7 bonds of **5**, which are connected to the upper and lower cyclohexane rings in the chair conformation, are abnormally long (1.603(4), 1.610(4) Å) as compared with the RHF/6-31G* optimized C–C bond length (1.552 Å) of a cyclopentane ring. These elongated bond lengths are regenerated within the range of ± 0.003 Å by the RHF/6-31G* level MO calculations. The upper and lower six-membered rings of the skeleton **6** are cyclohexanes with a distorted chair conformation; the dihedral angles of the C1–C2–C4–C5 and C5–C6–C1 planes (104.2°) as well as the C8–C9–C11–C12 and C9–C10–C11 planes (101.9°) are much smaller than those of the C1–C2–C4–C5 and C2–C3–C4 planes (152.8°) as well as the C8–C9–C11–C12 and C8–C7–C12 planes (155.6°; Figure 2). The corresponding value of a cyclohexane ring in the chair conformation as estimated by the RHF/6-31G* level MO calculations is 130.5°. Thus shortening of the C_1 bridges in diamantane **7** to no bridges causes a significant deformation of the chair-cyclohexane rings in **6**, by elongation of the C3–C10 and C6–C7 bond lengths, and a much higher strain energy for **6** than for **7**. According to the MM3 calculations,^[14] the steric energy of **6** is 54.8 kcal mol^{−1} higher than that of **7**.

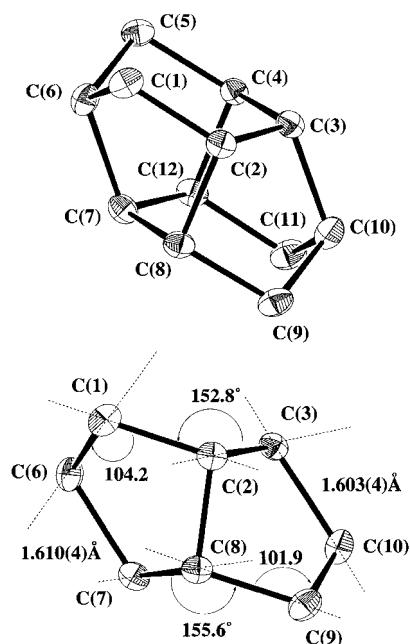


Figure 2. Crystal structure of the skeleton of **5** (6, hydrogen atoms are omitted for clarity). Selected bond lengths [Å] and angles [°]: C(1)–C(2) 1.521(4), C(1)–C(6) 1.546(4), C(2)–C(3) 1.587(4), C(2)–C(8) 1.537(4), C(3)–C(4) 1.588(4), C(3)–C(10) 1.603(4), C(4)–C(5) 1.526(4), C(4)–C(12) 1.536(4), C(5)–C(6) 1.548(4), C(6)–C(7) 1.610(4), C(7)–C(8) 1.578(4), C(7)–C(12) 1.578(4), C(8)–C(9) 1.528(4), C(9)–C(10) 1.531(4), C(10)–C(11) 1.532(4), C(11)–C(12) 1.534(4); C(1)–C(2)–C(3) 115.6(2), C(1)–C(6)–C(7) 103.8(2), C(1)–C(2)–C(8) 100.6(2), C(2)–C(3)–C(4) 116.0(2), C(2)–C(3)–C(10) 102.3(2), C(3)–C(4)–C(5) 115.9(2), C(3)–C(4)–C(12) 97.9(2), C(4)–C(5)–C(6) 99.8(2), C(5)–C(6)–C(1) 111.9(3), C(5)–C(6)–C(7) 103.8(2), C(6)–C(7)–C(8) 103.6(2), C(6)–C(1)–C(2) 100.0(2), C(6)–C(7)–C(12) 103.8(2), C(7)–C(8)–C(9) 115.7(2), C(7)–C(8)–C(2) 97.9(2), C(8)–C(9)–C(10) 100.3(2), C(8)–C(2)–C(3) 98.3(2), C(9)–C(10)–C(11) 106.9(3), C(10)–C(11)–C(12) 99.9(2), C(10)–C(3)–C(4) 102.7(2), C(11)–C(12)–C(7) 115.9(2), C(11)–C(12)–C(4) 100.8(3), C(12)–C(7)–C(8) 114.7(2), C(12)–C(4)–C(5) 100.7(2), C(6)–C(1)–C(5)–C(4) 104.2(2), C(10)–C(11)–C(9)–C(8) 101.9(2), C(3)–C(2)–C(4)–C(5) 152.8(2), C(7)–C(12)–C(8)–C(9) 155.6(2).

Thus a new polycyclic compound **5** having a pentacyclo[6.3.0.1⁴.11.0^{2.6}.0⁵.10]dodecane skeleton was formed by the photolysis of **4** in a H₂O-saturated CH₂Cl₂ solution. The series of reactions involving first the formation of the hexaprismane derivative followed by protonation and equilibration of the resultant carbocations, and interception of the most stable cation with a hydroxide ion are proposed, similar to the photochemical reaction of **2**.^[6]

Received: April 9, 1999

Revised: June 24, 1999 [Z13266]

- [7] T. Shinmyozu, S. Kusumoto, S. Nomura, H. Kawase, T. Inazu, *Chem. Ber.* **1993**, *126*, 1815–1818.
- [8] W. Sentou, T. Satou, M. Yasutake, C. Lim, Y. Sakamoto, T. Itoh, T. Shinmyozu, *Eur. J. Org. Chem.* **1999**, 1223–1231.
- [9] Selected spectroscopic data and elemental analysis for **5**: m.p. 268–270 °C (decomp); ¹H NMR (600 MHz, CDCl₃, TMS): δ = 1.11 (d, *J* = 3.1 Hz, 1H), 1.13 (d, *J* = 3.1 Hz, 1H), 1.23–1.78 (m, 24H), 1.81 (d, *J* = 5.2 Hz, 1H), 1.89 (d, *J* = 2.7 Hz, 2H), 2.23 (d, *J* = 5.2 Hz, 1H), 4.15 (s, 2H, OH); ¹³C NMR (150 MHz, CDCl₃, TMS, DEPT): δ = 17.7 (2 × sec.), 19.2 (2 × sec.), 23.0 (2 × sec.), 25.6 (2 × sec.), 26.1 (2 × sec.), 35.7 (2 × sec.), 44.9 (tert.), 48.0 (tert.), 50.6 (2 × quat.), 52.5 (2 × tert.), 54.6 (2 × quat.), 57.4 (tert.), 58.2 (tert.), 85.2 (2 × quat.); FABMS: *m/z*: 352.2 [*M*⁺]. Elemental analysis calcd for C₂₄H₃₂O₂ · 0.25 H₂O: C 80.74, H 9.17; found: C 80.43, H 9.07.
- [10] The X-ray crystal data for **5**: C₂₄H₃₂O₂, *T* = 23 °C, MoK_α (Rigaku AFC7R diffractometer, λ = 0.71070 Å), crystal dimensions 0.30 × 0.05 × 0.40 mm³ (colorless prism), *a* = 9.219(3), *b* = 14.821(3), *c* = 6.995(2) Å, α = 94.09(2), β = 110.93(2), γ = 82.08(2)°, triclinic, space group *P*1̄ (no. 2), *Z* = 2, μ(Mo) = 0.82 cm^{−1}, *M*_r = 352.52, *V* = 884.0(4) Å³, anode power 45 kV × 250 mA, ρ_{calcd} = 1.324 g cm^{−3}, 2θ_{max} = 55.0°, *F*(000) = 384. 4381 reflections were measured, 1975 observed (*I* < 3σ(*I*)), with 363 parameters. The structure was solved by the direct method and was refined on Sir88.^[11] Data were corrected for Lorentz polarizations. The data/parameter ratio was 5.44. *R* = 0.044, *R*_w = 0.043, GOF = 1.01, max./min. residual density +0.22/−0.22 e Å^{−3}. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-114176. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [11] A. V. Evtushenko, M. S. Malchanova, B. B. Smirnov, V. A. Shlyapochnikov, *Russ. Chem. Bull.* **1996**, *45*, 2302–2308.
- [12] a) C. Cupas, P. von R. Schleyer, D. J. Trecker, *J. Am. Chem. Soc.* **1965**, *87*, 917–918; b) I. L. Karle, J. Karle, *J. Am. Chem. Soc.* **1965**, *87*, 918–919; c) T. M. Grund, E. Osawa, V. Z. Williams, Jr., P. von R. Schleyer, *J. Org. Chem.* **1974**, *39*, 2979–2986; d) T. M. Grund, M. Nomura, P. von R. Schleyer, *J. Org. Chem.* **1974**, *39*, 2987–2994; e) T. M. Grund, P. von R. Schleyer, G. D. Unruh, G. J. Gleicher, *J. Org. Chem.* **1974**, *39*, 2995–3003.
- [13] M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, D. Viterbo, *J. Appl. Crystallogr.* **1989**, *22*, 389–403.
- [14] The computations were performed with MM3-92, graphically facilitated by CAChe from Sony/Tektronics Co. The MM3 program was obtained from the Technical Utilization Corporation. The program was developed by N. L. Allinger and co-workers, University of Georgia. The Gaussian 94 program,^[15] graphically facilitated by Insight II from Ryoka Systems Inc. on Silicon Graphics Octane, was used for ab initio MO calculations.
- [15] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1995**.

[1] For reviews, see a) H. Dodziuk in *Topics in Stereochemistry*, Vol. 21 (Eds.: E. L. Eliel, S. H. Wilen), Wiley, **1994**, p. 351–380; b) M. A. Forman, *Org. Prep. Proced. Int.* **1994**, *26*, 291–320.

[2] T. J. Katz, N. Acton, *J. Am. Chem. Soc.* **1973**, *95*, 2738–2739.

[3] P. E. Eaton, T. W. Cole, *J. Am. Chem. Soc.* **1964**, *86*, 3157–3158.

[4] P. E. Eaton, Y. S. Or, S. J. Branca, *J. Am. Chem. Soc.* **1981**, *103*, 2134–2136.

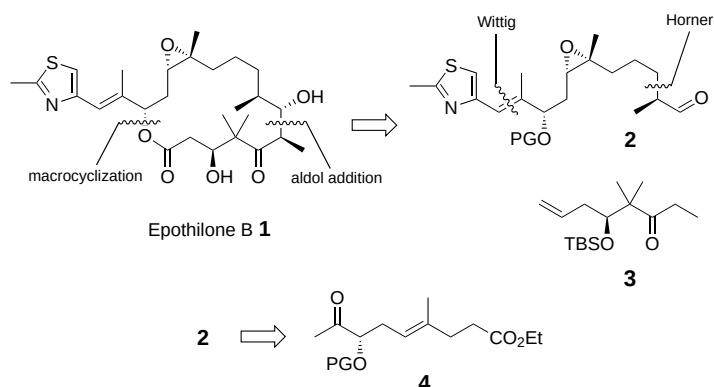
[5] P. E. Eaton, U. R. Chakraborty, *J. Am. Chem. Soc.* **1978**, *100*, 3634–3635.

[6] Y. Sakamoto, T. Kumagai, K. Matohara, C. Lim, T. Shinmyozu, *Tetrahedron Lett.* **1999**, *40*, 919–922.

How Stable Are Epoxides? A Novel Synthesis of Epothilone B**

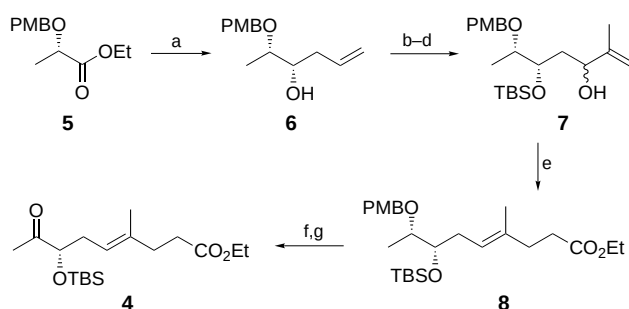
Harry J. Martin, Martina Drescher, and Johann Mulzer*

Epothilone B (**1**), a novel antitumor agent,^[1] features a trisubstituted epoxide as a central structural element, whose precise contribution to the biological activity is not yet clear.^[2] In all syntheses of **1** so far,^[3] the corresponding (*Z*)-olefin (epothilone D) was epoxidized in the last step with diastereoselectivities between 4:1 and 20:1 in favor of the desired β isomer. This strategy has been chosen obviously to avoid undesired additions to a presumably labile epoxide. We wanted to test the alleged lability of the epoxide by a new synthesis in which the epoxide is introduced at a very early stage and then deliberately carried through the hardships of a multistep synthesis. The key step of our synthesis featured an aldol addition of epoxyaldehyde **2** to the known ketone **3**^[3b] (Scheme 1). Fragment **2** was to be obtained from the (*E*)-



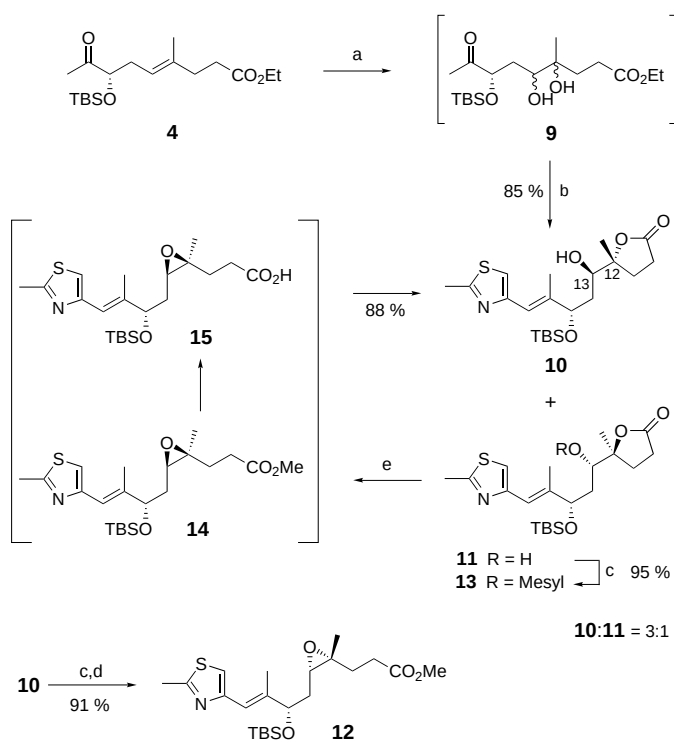
Scheme 1. Retrosynthetic analysis. PG=protective group, TBS=tert-butyldimethylsilyl.

enoate **4** readily available from (*S*)-ethyl lactate **5** (Scheme 2) which was reduced to the aldehyde and submitted to a chelate-controlled allyl addition to give **6**. Chain elongation produced allylic alcohol **7** which was used in a Johnson Claisen rearrangement to furnish (*E*)-olefin **8** as a single stereoisomer. In the conversion of the ester **4** into the key building block **2** it is particularly important to avoid the introduction of O[−] and OH functions in γ -position to one of the epoxide carbon atoms, since, as previous studies have shown, otherwise opening of the epoxide is inevitable. Removal of the *p*-methoxybenzyl (PMB) group and Swern oxidation delivered ketone **4**, which on asymmetric dihydroxylation^[4] furnished diol **9** as an inseparable mixture of isomers. Without purification, this mixture was converted into olefins



Scheme 2. Synthesis of (*E*)-olefin **4**: a) 1 equiv DIBAL, CH₂Cl₂, −78 °C, 2 h, 1 equiv MgBr₂·Et₂O, then 2 equiv Allyl–MgBr, −78 to 20 °C, 12 h, 92 %, diastereoselectivity 9:1; b) 1.4 equiv TBSCl, 4 equiv imidazole, DMF, 22 °C, 24 h, 98 %; c) O₃, CH₂Cl₂/MeOH (15:1) −78 °C, then PPh₃, 96 %; d) isopropenyl–MgBr, THF, −10 °C, 45 min, 89 % as a 1:1 mixture of diastereomers; e) 8 equiv triethylorthoacetate, C₂H₅CO₂H (catalytic amount), xylene, 140 °C, 12 h, 95 %, only *E* isomer; f) 1.1 equiv DDQ, CH₂Cl₂/H₂O (19:1), 0.5 h, 94 %; g) 2.5 equiv (COCl)₂, 4 equiv DMSO, 6 equiv NEt₃, −78 °C, 97 %. DIBAL=diisobutylaluminum hydride; DDQ=2,3-dichloro-5,6-dicyanobenzoquinone; DMSO=dimethyl sulfoxide; PMB=*p*-methoxybenzyl.

10 and **11** by a Wittig reaction. After chromatographic separation, **10** was mesylated and treated with potassium carbonate in methanol to give the desired epoxide **12** (Scheme 3). In contrast to the highly (*E*)-selective (>98:2)



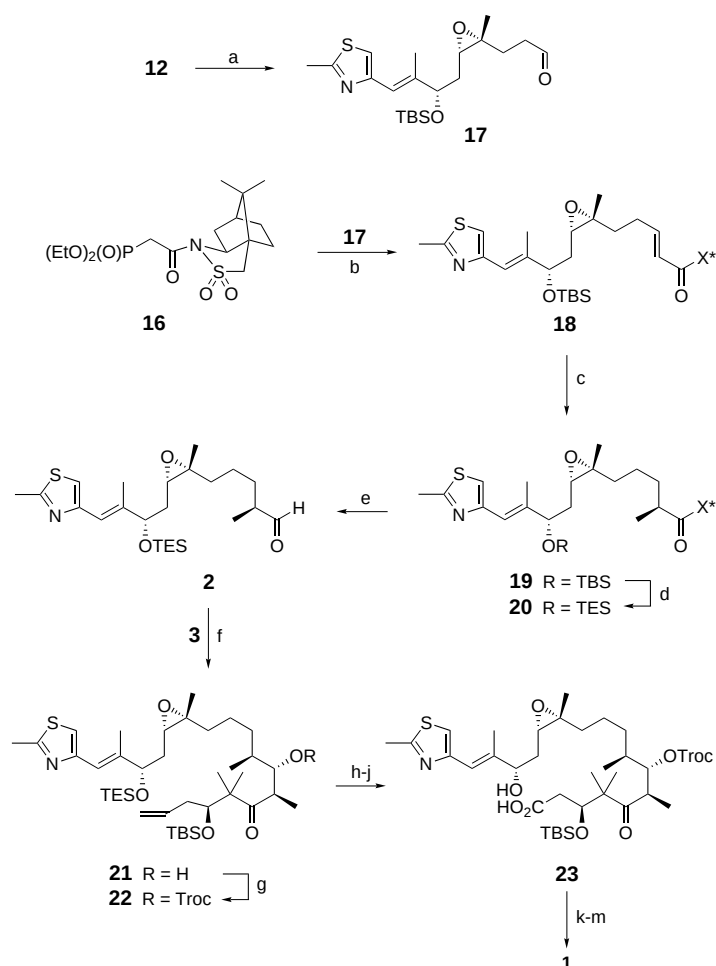
Scheme 3. Synthesis of the *cis*-epoxide **12**: a) AD-mix- β , methanesulfonamide, *t*BuOH/H₂O (1:1), room temperature, 20 h; b) 2.2 equiv (2-methylthiazol-4-ylmethyl)-tributylphosphonium chloride, 2.2 equiv KHMDS, THF, −78 °C, 0.5 h, then **9**, −78 to 35 °C, 5 min, 78–85 % over two steps, **10**:**11** ca. 3:1; c) 2 equiv MsCl, 2.5 equiv NEt₃, CH₂Cl₂, −15 °C, 3 h; d) 2 equiv K₂CO₃, MeOH, 0.75 h, 91 % over two steps; e) 2 equiv K₂CO₃, MeOH, room temperature, 1 h; 2 equiv K₂CO₃, MeOH/H₂O, 36 h; extraction with aqueous HCl (1N)/CH₂Cl₂, then silica gel, CH₂Cl₂, 3 d, 88 %. KHMDS=potassium bis(trimethylsilyl)amide; Ms=mesyl=methanesulfonyl.

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[**] Financial support by the Österreichische Fonds zur Förderung der wissenschaftlichen Forschung and Schering AG Berlin is gratefully acknowledged.

Wittig reaction, the dihydroxylation was much less diastereoselective (3:1). To recover stereochemically misdirected material, **11** was converted into **10** by a double inversion at C12 and C13. Hence, **11** was first converted into the mesylate **13**, which was successively treated with potassium carbonate, water, and 1N HCl (Scheme 3) to give stereoisomerically pure **10** via the nonisolated intermediates **14** and **15**. By this procedure, olefin **4** was converted into the desired (12*R*,13*S*)-epoxide **12** without stereochemical loss. To complete the synthesis of fragment **2**, we used a Horner olefination followed by auxiliary-controlled introduction of the methyl group at C8 (Scheme 4). Thus epoxide **12** was reduced to aldehyde **17**, which was treated with chiral phosphonate **16**^[5] in the presence of lithium hydroxide (prepared in situ from BuLi/THF/H₂O) to give the enolsultam **18** (X* = sulfane residue) in good yield. 1,4-Hydride addition with *L*-selectride furnished the enolate which was trapped with methyl iodide to give **19** with excellent diastereoselectivity ($\geq 99:1$, HPLC analysis).^[6] The proper choice of the protective group (PG) for the 15-OH function was particularly important as this PG had to be stable through all transformations up to the macrolactonization. On the other hand, the PG should be removable in the presence of the epoxide at any stage of the sequence. This requirement was extremely hard to fulfil in view of the imminent formation of a 15,12-oxolane ring. A TBS protective group proved insufficient in this respect as its removal proceeded only with 40% yield. However, after conversion of the 15-OTBS derivative **19** into the 15-OTES analogue **20**, all remaining synthetic steps could be carried out in high yield. Specifically, the reductive removal of the auxiliary with DIBAL furnished aldehyde **2** which was treated with the lithium enolate of ketone **3** to give the aldol adduct **21** with a diastereoselectivity of $>95:5$ (NMR and HPLC analysis). Troc-protection of the 7-OH function gave **22**, which was converted into seco acid **23** by oxidation of the terminal olefin to the aldehyde, followed by 15-O-desilylation and Pinnick oxidation of the aldehyde. Yamaguchi macrolactonization of **23** and removal of the Troc protective group and the 3-OTBS protective group furnished diastereomerically pure **1**.

The epoxide, introduced early into the molecule, has proven its stability under the following conditions: 1) reductive (neutral (DIBAL), ionic (selectride), and metallic (Zn)); 2) oxidative (osmium tetroxide/sodium periodate, sodium chlorite); 3) basic (fluoride in aprotic solvents, DMAP, LDA, enolates). In this respect, it is remarkable that carbon and oxygen anions do not open the epoxide, even when they are generated in a 1,5-relationship to the epoxide; 4) electrophilic (acylation with an acyl chloride in the Yamaguchi reaction). Of all reagents applied, only dilute acid has led to (in this case desired) epoxide opening (**15** $\rightarrow$ **10**). Apart from providing us with the valuable information that epoxides are by no means such highly reactive intermediates as postulated,^[7] the early introduction of the epoxide has been of advantage in the overall synthesis of **1**. For instance, the formation of thiazole-N-oxides previously observed in the *m*-chloroperoxybenzoic acid epoxidation of the C12–C13 double bond^[8] has been avoided as well as the formation of the (12*S*,13*R*)-epoxide which is hard to separate from the correct



Scheme 4. Synthesis of epothilone B (**1**) by aldol addition and macrolactonization: a) 1.1 equiv DIBAL, CH₂Cl₂, –95 to –80 °C, 1 h, 93%; b) 1.1 equiv BuLi, Et₂O, 0 °C, 1.1 equiv H₂O (in THF), then **16**, 5 min, room temperature, then **17**, 30 min, room temperature, 92%; c) 1.4 equiv *L*-selectride, THF, –78 to –60 °C, 0.5 h, 8 equiv HMPA, 12 equiv MeI, –78 to 20 °C, 16 h, 78%; d) 1.) 4 equiv TBAF, THF, room temperature, 3 h; 2.) TESCl, NEt₃, cat. DMAP, room temperature, 1 h, 85% over 2 steps; e) 2 equiv DIBAL, CH₂Cl₂, –95 to –80 °C, 1 h, 93%; f) 1.5 equiv LDA, 1.5 equiv **3**, –78 to –40 °C, –78 °C then **2**, 15 min, 92%, diastereoselectivity 95:5; g) 6 equiv 2,2,2-trichloroethoxy chloroformate (TrocCl), 18 equiv pyridine, CH₂Cl₂, 20 °C, 0.5 h, 94%; h) 1.) 0.05 equiv OsO₄, 1 equiv NMO, THF/*t*BuOH/H₂O (5:5:1), room temperature, 16 h; 2.) 3 equiv NaIO₄, EtOH/H₂O (4:1), 22 °C, 1 h; i) HF·pyridine, pyridine, THF, room temperature, 0.5 h; j) NaClO₂, NaH₂PO₄, *t*BuOH/2,2-dimethyl-2-butene (2:1), room temperature, 1 h, 63% for four steps; k) 2.0 equiv 2,4,6-trichlorobenzoyl chloride, 2.5 equiv NEt₃, room temperature, 1 h, then added slowly (1 h) to a solution of 8 equiv DMAP in toluene (0.002 M in seco acid), 0.5 h room temperature, 65%; l) 80 equiv Zn, 100 equiv NH₄Cl, 80 °C, 20 min; m) HF·pyridine, pyridine, 30 °C, 7 d, 62% for 2 steps. *L*-Selectride = lithium-tri-*sec*-butylboranate; HMPA = hexamethyl phosphoric acid triamide; TBAF = tetrabutylammonium fluoride; TES = triethylsilyl; DMAP = *N,N*-dimethyl-4-aminopyridine; LDA = lithium diisopropylamide; NMO = *N*-methylmorpholine-*N*-oxide.

stereoisomer. Additionally, the diastereocontrol of the aldol addition with the epoxyaldehyde is significantly better than it is with the olefinic aldehyde.^[3b,f,g] The use of ester **4** as an intermediate allows the application of the Claisen rearrangement as an efficient chain-elongation procedure. Also, it is possible to introduce additional double bonds after the epoxide has been generated which may be useful for the

preparation of novel epothilone derivatives. On the other hand, the necessary exchange of the 15-O-silyl protective groups is a clear disadvantage. As to the biological role of the epoxide in epothilone B (**1**), it appears doubtful that it is opened under physiological conditions because of the high stability of the oxirane. Rather, the epoxide may interact with the receptor unchanged or may be used in an intramolecular hydrogen bridge with the 3-OH function to generate a favorable conformation.^[9]

Received: April 27, 1999 [Z13320]

Identification of Toxic 2,4-Decadienal in Oxidized, Low-Density Lipoprotein by Solid-Phase Microextraction

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9-Hydroxy-10,12-octadecadienoic acid (9-HODE) induces the liberation of interleukin-1 β (IL-1 β) together with α,β -unsaturated aldehydes, especially 2,4-decadienal, from macrophages.^[1] IL-1 β in turn stimulates the proliferation of smooth muscle cells.^[2,3] This process is regarded as being connected to atherogenesis,^[1] since particularly high levels of IL-1 β were detected in atherosclerotic plaques.^[4] 2,4-Decadienal was detectable only in trace quantities after copper(II) ion induced air oxidation of low-density lipoprotein (LDL).^[1] In addition, this detection required long separation procedures and preparation of the 2,4-dinitrophenylhydrazone derivative.^[1,5]

A detection method which needs neither sample procession nor derivatization is solid-phase microextraction (SPME).^[6,7] It also avoids the formation of artifacts by handling. Electron impact mass spectrometry (EI-MS) is excellent for the characterization of α,β -unsaturated aldehydes. We used the combination of SPME/EI-MS to obtain insight into the events proceeding in the artificial oxidation of LDL: Blood samples were withdrawn from volunteers and LDL was isolated immediately.^[9] The LDL thus obtained was oxidized by air after addition of catalytic amounts of CuSO₄. Samples were collected in time intervals and analyzed by GC/MS. The measurement of the compounds present is achieved by determining the total ion current. Such a chromatogram is reproduced in Figure 1.

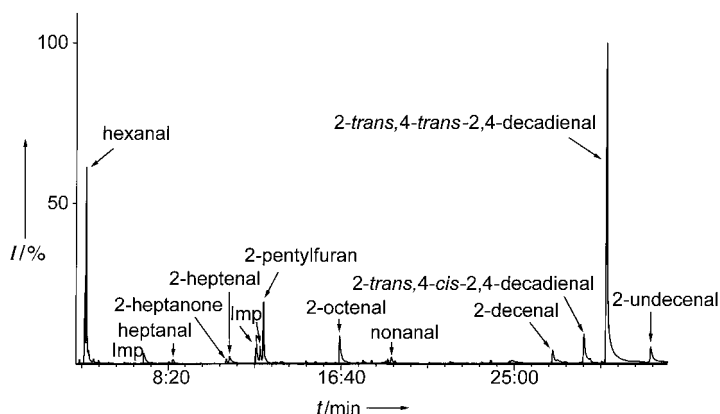
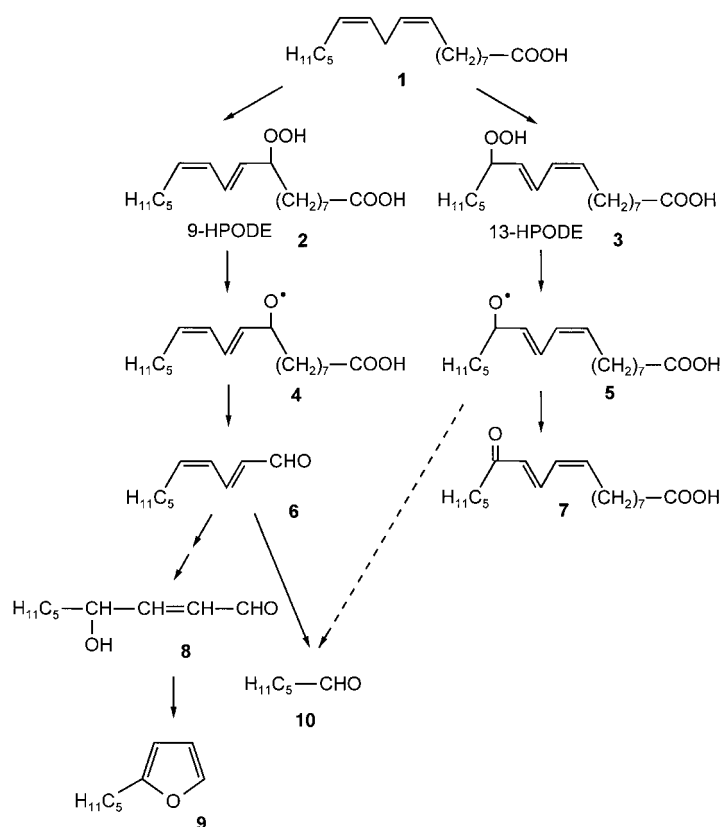


Figure 1. Reconstituted ion current chromatogram (RIC) of a LDL sample after 24 h oxidation with 50 μ M CuSO₄ solution at 37 °C.

LDL contains different amounts of individual antioxidants which are consumed first. Therefore, some time (lag-time) is required before lipid peroxidation starts.^[10] This lag-time also

- [1] a) Isolation of the epothilones: a) G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-B 4138042, **1993** [*Chem. Abstr.* **1993**, 120, 52841]; b) antitumor activity: D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Res.* **1995**, 55, 2325; c) review of the chemistry and biology of the epothilones: K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, 110, 2120; *Angew. Chem. Int. Ed.* **1998**, 37, 2014.
- [2] a) D.-S. Su, A. Balog, D. Meng, P. Bertinato, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, 109, 2178; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2093; b) K. C. Nicolaou, N. Wissinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, 387, 268.
- [3] a) D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y. H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* **1997**, 109, 775; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 757; b) K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc.* **1997**, 119, 7974; c) D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1997**, 119, 10073; d) S. A. May, P. A. Grieco, *Chem. Commun.* **1998**, 1597; e) D. Schinzer, A. Bauer, J. Schieber, *Synlett* **1998**, 861; f) A. Ballog, C. Harris, K. Savin, X.-G. Zhang, T.-C. Chou, S. J. Danishefsky, *Angew. Chem.* **1998**, 110, 2821; *Angew. Chem. Int. Ed.* **1998**, 37, 2675; g) J. Mulzer, A. Mantoulidis, E. Öhler, *Tetrahedron Lett.* **1998**, 39, 8633; h) J. D. White, R. G. Carter, K. F. Sundermann, *J. Org. Chem.* **1999**, 64, 684.
- [4] review: H. C. Kolb, M. S. VanNieuwenzhe, K. B. Sharpless, *Chem. Rev.* **1994**, 94, 2483.
- [5] ent-15: W. Oppolzer, D. Dupuis, G. Poli, T. M. Raynham, G. Bernardinelli, *Tetrahedron Lett.* **1988**, 29, 5885.
- [6] W. Oppolzer, G. Poli, *Tetrahedron Lett.* **1986**, 27, 4717.
- [7] a) Review: J. Gorzynski Smith, *Synthesis* **1983**, 629; epoxides as intermediates in natural product syntheses: b) Monensin: G. Schmid, T. Tukuyama, K. Akasaka, Y. Kishi, *J. Am. Chem. Soc.* **1979**, 101, 259; c) Ionomycin A: D. A. Evans, A. M. Ratz, B. E. Huff, G. S. Sheppard, *J. Am. Chem. Soc.* **1995**, 117, 3448; d) brevetoxin: K. C. Nicolaou, *Angew. Chem.* **1996**, 108, 644; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 589. Regarding the stability of "early" epoxides in total synthesis see: e) E. J. Corey, B. B. Snider, *J. Am. Chem. Soc.* **1972**, 94, 2549; f) E. J. Corey, J. P. Dittami, *J. Am. Chem. Soc.* **1985**, 107, 256; g) D. A. Evans, A. S. Kim, R. Metternich, V. J. Novack, *J. Am. Chem. Soc.* **1998**, 120, 5921.
- [8] G. Höfle, N. Glaser, M. Kiffe, H. J. Hecht, F. Sasse, H. Reichenbach, *Angew. Chem.* **1999**, 111, 2090; *Angew. Chem. Int. Ed.* **1999**, 38, 1971.
- [9] M. Wang, X. Xia, Y. Kim, D. Hwan, J. M. Jansen, M. Botta, D. C. Liotta, J. P. Snyder, *Org. Lett.* **1999**, 1, 43.

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Scheme 1. Processes occurring in the oxidation of linoleic acid (1, from LDL samples) with air/Cu²⁺ ions.

depends on the amount of added copper ions. It amounted in our experiments to 2–5 h. Immediately after the start of oxidation the only main oxidation product is 2-*trans*,4-*cis*-2,4-decadienal (6 in Scheme 1). Additional products, for example, 2-*trans*,4-*trans*-2,4-decadienal, hexanal (10 in Scheme 1, and 2-pentylfuran (9 in scheme 1), are detectable merely in trace amounts at this time. Within 2 h the peak corresponding to 2-*trans*,4-*trans*-2,4-decadienal becomes the main peak, and also the peaks corresponding to hexanal (10) and 2-pentylfuran (9) increase considerably in intensity. After 12 h these peaks are several times larger than that of 2-*trans*,4-*cis*-2,4-decadienal. In addition, small peaks are recognized which correspond to 2-octenal, 2-decenal, and 2-undecenal (the two latter compounds are oxidation products of oleic acid). After 24 h the chromatogram reproduced in Figure 1 was obtained.

After oxidation for 36 h 2-*trans*,4-*trans*-2,4-decadienal was still recognizable as the main peak, nevertheless the amounts of hexanal (10) and 2-pentylfuran (9) had increased further. After five days the product spectrum had changed a great deal: 2-*trans*,4-*trans*-2,4-decadienal was detectable in trace amounts only, the main peaks corresponded to 9 and 10. Many additional peaks were also recognized. Since adsorption of compounds at the SPME fibre is not proportional to the quantity present, the intensity ratio recognized in successive runs do not reflect a quantitative picture of the compounds present. Nevertheless—according to model experiments—half quantitative deductions are possible, which allow insight into the kinetics of lipid peroxidation (LPO). Such measurements have been previously impossible or were at least not

possible in such a mild and simple way with other methods. The observation of 2-*trans*,4-*trans*-2,4-decadienal as the main peak in these experiments suggests that this compound is subjected to a fast degradation or reaction with other compounds present in LDL. In order to confirm this speculation the compounds detected in the chromatograms were subjected to a renewed oxidation in their pure form by air/Cu²⁺ ions.

The degradation of 2-*trans*,4-*trans*-2,4-decadienal, a well known fat aroma product, by air has already been investigated by Schreier et al.^[11] They obtained 2-octenal, hexanal (10), 4-hydroxy-2-nonenal (4-HNE; 8 in Scheme 1), and 2-pentylfuran (9). We detected the same products in the above mentioned oxidation of LDL with Cu²⁺/air, 4-HNE (8) admittedly only in trace quantities. However, 8 was detectable in larger amounts after derivatization with pentafluorobenzylhydroxylamine hydrochloride.^[12] This result can be explained since 4-HNE is relatively polar and polar compounds are much less prone to adsorption than unpolar aldehydes on the SPME fibre used by us. When pure *trans*-4-hydroxy-2-nonenal was stirred in air with copper(II) ions the main peak was found to correspond to 2-pentylfuran (9). In contrast, 4-HNE remained unchanged on stirring for a long time in the absence of bivalent metal ions. This result demonstrates that traces of bivalent metal ions catalyze the transformation of 8 to 9.

A main degradation path of 2-*trans*,4-*cis*-2,4-decadienal (6) leads to hexanal (10). Its generation has been previously deduced by cleavage of 9-*cis*,11-*trans*-13-hydroperoxy-9,11-octadecadienoic acid (13-HPODE; 3 in Scheme 1),^[13] although this process seemed doubtful for energetic reasons.^[14, 15] 10-*trans*,12-*cis*-9-Hydroperoxy-10,12-octadecadienoic acid (9-HPODE; 2 in Scheme 1) and 13-HPODE (3) are generated in comparable amounts by LPO of linoleic acid (1 in Scheme 1). Cleavage of 2 generates 2-*trans*,4-*cis*-2,4-decadienal (6). Thus the enormous prevalence of 6 over hexanal (10) immediately after the start of LPO demonstrates that 10 is generated directly by cleavage of small amounts of 3 only.

In conclusion the following sequence of events is deduced: First linoleic acid (1) is transformed by oxidation to 9-HPODE (2) and 13-HPODE (3; Scheme 1).^[14, 15] Cleavage of the peroxy bond in 2 by copper(II) ions generates the radical 4, which then decomposes to 2-*trans*,4-*cis*-2,4-decadienal (6). In contrast 3 reacts to form radical 5 and further to 9-*cis*,11-*trans*-13-oxo-9,11-tridecadienoic acid (7). The latter (polar compound) is not detectable by the SPME method used by us.

In the presence of peroxy radicals 6 undergoes an analogous Baeyer–Villiger oxidation^[16] and is epoxidized. Opening of the epoxide ring finally generates 4-HNE (8), which is then cyclized to 2-pentylfuran (9). Otherwise 6 is cleaved in the course of a retroaldol reaction after addition of water^[17] to form hexanal (10). The cyclization of 4-HNE (8) to 2-pentylfuran (9) described in Scheme 1 is thus similar to a method used for the synthesis of trisubstituted furans.^[18]

α,β -unsaturated aldehydes are starting materials for Michael reactions. 2-*trans*,4-*trans*-2,4-Decadienal, which has a higher toxicity than 4-HNE (8),^[19] is expected, as a result of

its larger conjugated system, to react faster than **8**. Indeed, 2-*trans*,4-*trans*-2,4-decadienal reacts quickly with glutathione to give a large number of products.^[20] It is, therefore, understandable that this compound so far escaped detection in blood samples of atherosclerotic patients.

LPO processes are increased by tissue injury, for example, in the course of a myocardial infarction.^[21] As a consequence, it is expected that the early oxidation processes described in this paper should also occur in vivo.^[22]

Experimental Section

LDL was isolated according to Leiss et al.,^[9] or was obtained commercially (Fluka). LDL, obtained from 3–5 mL serum, was dissolved in 1 mL of phosphate buffer (0.1 M, pH 7.4) in a GC vial fitted with a stirring bar. 1 mL of a 10 or 100 µM aqueous solution of CuSO₄ was added. The vial was closed with a septum, and the mixture stirred at 37 °C. The septum was penetrated by the SPME device and the 100 µm fibre (polydimethylsiloxane, PDMS) half submerged in the solution. After 2 h, 3 h, 4 h, 5 h, 6 h, 10 h, 12 h, 1 d, 2 d, 4 d, 7 d the fibre was removed from the vial and directly introduced into the inlet of the GC/MS instrument (MAT 95 mass spectrometer (Finnigan), EI ion source, 70 eV, HP 5890 series II gas chromatograph, fused silica gel column from J&W Scientific, DB 05, 30 m × 0.32 mm, carrier gas H₂, splitless, injector temperature 280 °C, temperature program: 5 min isothermic at 40 °C, then 3 °C min⁻¹ up to 300 °C). The usual flushing of the septum by purge gas prevents detection of compounds with high volatility. In order to avoid this, flushing of the septum was shut down for 30 s when the PDMS fibre was introduced. Use of a special, narrow GC liner tube allowed adjustment of the peak form of the chromatograms and resulted in a considerable improvement of the quality of the mass spectra.

Model oxidations with pure 2,4-decadienal and 4-hydroxy-2-nonenal were carried out in a similar manner as those of LDL samples.

Received: May 12, 1999

Revised: September 14, 1999 [Z13410]

- [1] C. E. Thomas, R. L. Jackson, D. F. Ohlweiler, G. Ku, *J. Lipid Res.* **1994**, 35, 417–427.
- [2] E. W. Raines, S. K. Dower, R. Ross, *Science* **1989**, 243, 393–396.
- [3] G. Ku, N. S. Doherty, J. A. Wolos, R. L. Jackson, L. F. Schmidt, D. Hendricks, *Am. J. Cardiol.* **1988**, 62, 77B–81B.
- [4] A. M. Wang, M. V. Doyle, D. Mark, *Proc. Natl. Acad. Sci. USA.* **1989**, 86, 9717–9722.
- [5] H. Esterbauer, K. H. Cheeseman, *Methods Enzymol.* **1990**, 186, 407–421.
- [6] C. L. Arthur, L. M. Killam, K. D. Buchholz, J. Pawliszyn, J. R. Berg, *Anal. Chem.* **1992**, 64, 1960–1966.
- [7] Z. Zhang, J. Pawliszyn, *Anal. Chem.* **1993**, 65, 1843–1845.
- [8] G. Spiteller, W. Kern, P. Spiteller, *J. Chromatogr. A* **1999**, 843, 29–98.
- [9] O. Leiss, U. Murawski, H. Egge, *J. Clin. Chem. Clin. Biochem.* **1979**, 17, 619–625.
- [10] H. Esterbauer, G. Jürgens, O. Quehenberger, E. Koller, *J. Lipid Res.* **1987**, 28, 495–509.
- [11] B. Grein, M. Huffer, G. Scheller, P. Schreier, *J. Agric. Food Chem.* **1993**, 41, 2385–2390.
- [12] F. J. G. M. Van Kuijk, D. W. Thomas, R. J. Stephens, E. A. Dratz, *Biochem. Biophys. Res. Commun.* **1986**, 139, 144–149.
- [13] H. Esterbauer, H. Zollner, R. J. Schaur in *Membrane Lipid Oxidation, Vol. II* (Ed.: C. Vigo-Pelfrey), CRC, Boca Raton, FL, USA, **1991**, Chap. 11, pp. 239–268.
- [14] H. W. Gardner, *Free Radicals Biol. Med.* **1989**, 7, 65–86.
- [15] E. N. Frankel, *Prog. Lipid Res.* **1982**, 22, 1–33.
- [16] W. A. Pryor, N. A. Porter, *Free Radicals Biol. Med.* **1990**, 8, 541–543.
- [17] D. B. Josephson, R. C. Lindsay, *J. Food Sci.* **1987**, 52, 1186–1218.
- [18] P. Lee, H. S. Ho Kim, S. Kim, *Chem. Lett.* **1994**, 12, 2401–2402.

- [19] T. Kaneko, S. Honda, S. I. Nakano, M. Matsuo, *Chem. Biol. Interact.* **1987**, 63, 127–137.
- [20] M. Spiteller, Universität Dortmund, private communication, **1999**.
- [21] A. Dudda, G. Spiteller, F. Kobelt, *Chem. Phys. Lipids* **1996**, 82, 39–51.
- [22] Note added in proof (30. December 1999): Recently A. Miralto et al., reported antiproliferative and apoptotic effects of 2-*trans*, 4-*trans*-2,4-decadienal on human carcinoma cells. (A. Miralto, G. Barone, G. Romano, S. A. Poulet, A. Ianora, G. L. Russo, I. Buttino, G. Mazzarella, M. Laabir, M. Cabrini, M. G. Giacobbe, *Nature* **1999**, 402, 173–176.)

Oxidation of Linoleic Acid in Low-Density Lipoprotein: An Important Event in Atherogenesis**

Dieter Spiteller and Gerhard Spiteller*

Half of all deaths in Germany are caused by vascular diseases,^[1] which are caused in part by deposition of cholesterol-rich plaques in the arteries. Cholesterol, an essential compound in cell membranes, is transferred to the cells by the low-density lipoprotein (LDL). LDL consists of a lipid core composed mainly of cholesterol esters. This core is surrounded by a layer of phospholipids that are wrapped by a protein. Lysyl residues of that protein are recognized by receptors that are arranged in so-called coated pits at the cell surface. The entire coated pit together with receptor-bound LDL molecules is then enclosed by a protein and transported inside the cell where the LDL is separated from the receptor. The liberated LDL is digested: proteins are broken down to amino acids and cholesterol esters and phospholipids are saponified. Depending on the need for cholesterol more or less receptors are generated.^[2, 3]

Oxidatively modified LDL^[4, 5] is no longer recognized by the LDL receptor but is recognized by scavenger receptors of macrophages. LDL is taken up without limitation by macrophages,^[2, 3] which are finally deposited as plaques. LDL is very sensitive to oxidation, which occurs by copper(II) ion catalysis in air^[5, 6] or on its own in three to six months when stored at 0 °C.^[7] Oxidatively modified LDL (oxLDL) is toxic^[4] and the toxic components can be extracted with organic solvents.^[5] Thus it was suspected that the toxic compounds might be the products of lipid peroxidation (LPO) of polyunsaturated fatty acids (PUFAs).^[4] Some of these products were identified,^[8, 9, 10] but most remained unknown until now.

Since LPO products occur in LDL in only trace amounts compared to other compounds their identification requires

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[**] We are indebted to the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for financial support. We are obliged to W. Kern for providing the diazomethane solution.

highly sensitive and specific methods. Substituted fatty acids and products generated therefrom give, after appropriate derivatization, characteristic electron impact mass spectra (EI-MS). We therefore used this method for the identification of LPO products generated by copper ion induced air oxidation of LDL^[5] that are also found after storage of samples of LDL at 0 °C.^[7]

Pure PUFAs were first oxidized in the same way as the LDL samples (Cu²⁺ ion catalyzed air oxidation at 37 °C). The lipid fraction of the reaction products was treated with pentafluorobenzylhydroxylamine-hydrochloride to derivatize the carbonyl groups.^[9] Free acid groups were methylated by a short treatment with diazomethane. Finally the hydroxyl groups were trimethylsilylated with *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA). The mixture of products thus obtained was analyzed by GC/MS through measurement of the total ion current. The compounds generated turned out to be nearly identical to LPO products that had been identified previously by oxidation of PUFAs with other oxidizing reagents (for example, Fe³⁺/air),^[11, 12] although we recognized an increased tendency for the generation of higher oxidized products (for example, transformation of aldehydes into the corresponding acids). The knowledge of the thus obtained spectra facilitated the identification of analogous products after oxidation of the LDL samples in air. Samples withdrawn at time intervals enabled insight into the reaction sequences. Detection of esterified oxidized PUFAs required an additional hydrolysis step. Figures 1–3 show the time-dependent change in the products in one of the LDL samples.

Figure 1 shows a part of the reconstituted ion-current chromatogram (RIC) of a LDL sample before oxidation. The RIC of the same sample after 6 h oxidation is represented in Figure 2 and after 24 h oxidation in Figure 3. The identified products are listed in Table 1.

The RIC of LDL samples of different donors and commercially available LDL samples are not qualitatively different. In contrast the proportion of acids and of their oxidation products is individually different. They also depend strongly on the kind of diet: High levels of linoleic acid in the diet doubles and triples the amount of oxidation products in LDL 12–16 h after intake of a meal rich in linoleic acid.^[13] 9-Hydroxy-10,12-octadecadienoic acid (9-HODE) and 13-hydroxy-9,11-octadecadienoic acid (13-HODE) are already present in trace amounts before oxidation of LDL (Figure 1), which indicates that oxidation of linoleic acid occurs even in healthy persons to a small extent.

Oxidation of LDL does not start immediately as antioxidants present are consumed first.^[8] This lag-time is dependent on the amount of copper ions added, but is different for each individual sample. In the present case oxidation products were first recognized after 6 h incubation with CuSO₄/air (Figure 2) by an increase of HODE derivatives (peak 33). Although 9-HODE and 13-HODE have been detected after copper ion induced LDL oxidation previously^[10] and occur highly enriched in blood samples of patients suffering from atherosclerosis,^[14] epoxyhydroxyoctadecenoic acids (EpHODs, peaks 37 and 38), as well as 9- and 13-oxooctadecadienoic acids (KODEs, peaks 35, 36, and 39) have not been described as oxidation products of LDL. Their presence is remarkable,

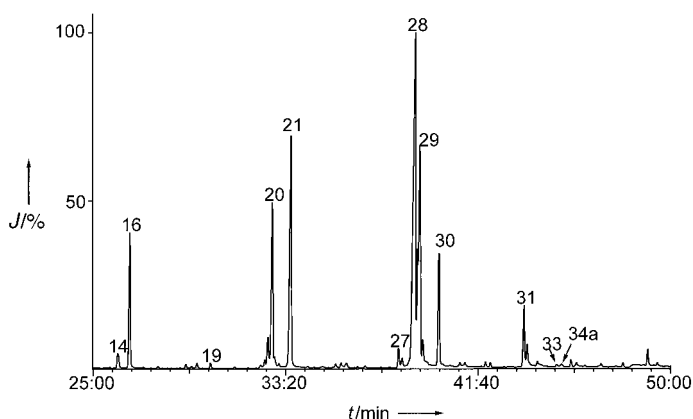


Figure 1. Part of the RIC of a LDL sample before oxidation. The donor was a healthy male aged 67 years (total cholesterol 199 mg dL⁻¹, LDL cholesterol 127 mg dL⁻¹, HDL cholesterol 57 mg dL⁻¹, triglycerides 71 mg dL⁻¹). The numbers above the peaks correspond to the compounds listed in Table 1.

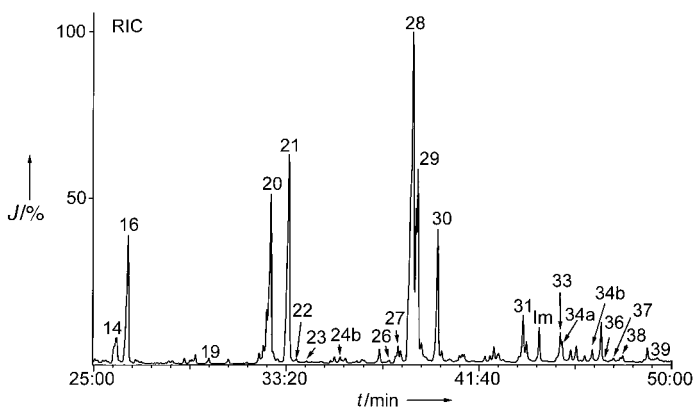


Figure 2. Part of the RIC of the same LDL sample as shown in Figure 1 after 6 h oxidation (5 μM CuSO₄, air, 37 °C). Im = impurity.

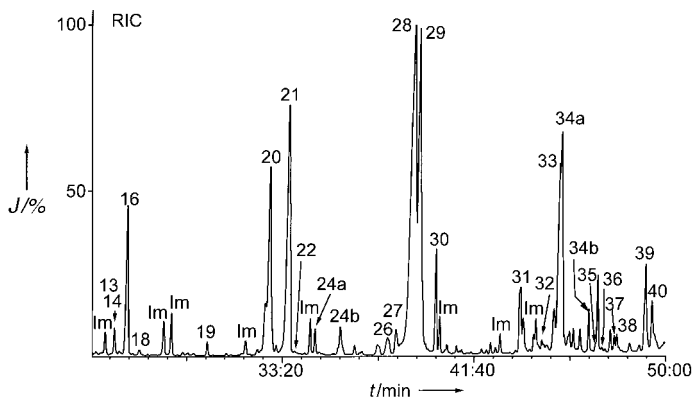
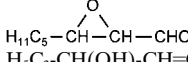
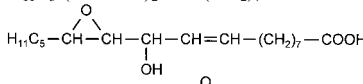
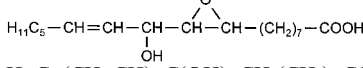


Figure 3. Part of the RIC of the same LDL sample as in Figure 1 after 24 h oxidation. Im = impurity.

since epoxides (by opening of the epoxide ring) and KODEs (in the course of a Michael reaction) react with nucleophiles (especially glutathion) and should develop toxic properties by blocking enzymes containing SH groups.

The product pattern changed considerably within 24 h (Figure 3). The level of acid oxidation products, especially HODEs (peaks 33, 34 a, and 34 b), increased dramatically, but

Table 1. Compounds identified before and after oxidation of LDL samples with CuSO₄/air and of minimally oxidized LDL samples.^[a]

Entry	Origin (point of attack) ^[b]	Product	Derivative detected ^[c]	found ^[d] in				
				LDL ^[e]			MM-LDL	
				0 h	6 h	24 h		
1	LEA (n-3)	H ₅ C ₂ -CHO	PFBO				+	
2	AA (n-6), LA (n-6)	H ₁₁ C ₅ -CH(OH)-COOH	TMS/OMe				+	
3	AA (n-10), LA (n-10),	H ₁₁ C ₅ -(CH=CH) ₂ -CHO					+	
4	AA, LA	OHC-COOH	PFBO/OMe				+	
5	AA, LA	H ₉ C ₄ -CHO	PFBO				+	
6	AA, LA, LEA	OHC-CH ₂ -COOH	PFBO/OMe				+	
7	LA (n-10), LEA (n-10)	HOOC-(CH ₂) ₆ -COOH	OMe/OMe				+	
8	AA (n-6), LA (n-6)	H ₁₁ C ₅ -CHO	PFBO				+	+
9	LEA (n-3)	H ₅ C ₂ -CH(OH)-CHO	TMS/PFBO				+	
10	AA (n-10), LA (n-10)	H ₁₁ C ₅ -CH(OH)-CH=CH-COOH	TMS/OMe				+	
11		CH ₂ (OH)-CH(OH)-CHO	TMS/TMS/PFBO				+	
12	LA (n-10), LEA (n-10)	HOOC-(CH ₂) ₇ -COOH	OMe/OMe				+	
13	AA (n-6), LA (n-6)	H ₁₁ C ₅ -CH(OH)-CHO	TMS/PFBO		+	+		
14		H ₂₅ C ₁₃ -COOH	OMe	+	+	+	+	
15	LA (n-6)	H ₁₁ C ₅ -CO-CH ₂ OH (artifact, rearrangement product of 13)	TMS/PFBO				+	
16		H ₂₇ C ₁₃ -COOH	OMe	+	+	+	+	
17	AA (n-10), LA (n-10)		PFBO				+	
18	LEA (n-10)	H ₅ C ₂ -CH(OH)-CH=CH-CHO	TMS/PFBO				+	
19		H ₂₉ C ₁₄ -COOH	OMe	+	+	+	+	
20		H ₂₉ C ₁₅ -COOH	OMe	+	+	+	+	
21		H ₃₁ C ₁₅ -COOH	OMe	+	+	+	+	
22	AA, LA, LEA	OHC-CHO	PFBO/PFBO				+	+
23	LA (n-10), LEA (n-10)	OHC-(CH ₂) ₆ -COOH	PFBO/OMe				+	+
24	LA (n-10), AA (n-10)	H ₁₁ C ₅ -CH(OH)-CH=CH-CHO	TMS/PFBO		+	+	+	
25	LA (n-10), AA (n-10)	H ₁₁ C ₅ -(CH=CH) ₂ -CHO	PFBO		+	+		
26	LA (n-10), LEA (n-10)	OHC-(CH ₂) ₇ -COOH	PFBO/OMe		+	+	+	
27		H ₃ C-(CH ₂ -CH=CH) ₃ -(CH ₂) ₇ -COOH	OMe	+	+	+	+	
28		H ₃ C-(CH ₂) ₃ -(CH ₂ -CH=CH) ₂ -(CH ₂) ₇ -COOH	OMe	+	+	+	+	
29		H ₁₇ C ₈ -CH=CH-(CH ₂) ₇ -COOH	OMe	+	+	+	+	
30		H ₃₅ C ₁₇ -COOH	OMe	+	+	+	+	
31		H ₉ C ₄ -(CH ₂ -CH=CH) ₄ -(CH ₂) ₃ -COOH	OMe	+	+	+	+	
32	OA (n-9)	H ₁₇ C ₈ -CH=CH-CH(OH)-(CH ₂) ₆ -COOH	TMS/OMe				+	+
	OA (n-10)	H ₁₅ C ₇ -CH=CH-CH(OH)-(CH ₂) ₇ -COOH	TMS/OMe				+	+
	OA (n-9)	H ₁₇ C ₈ -CH(OH)-CH=CH-(CH ₂) ₆ -COOH	TMS/OMe				+	+
	OA (n-10)	H ₁₅ C ₇ -CH(OH)-CH=CH-(CH ₂) ₇ -COOH	TMS/OMe				+	+
33	LA (n-6)	H ₁₁ C ₅ -CH(OH)-(CH=CH) ₂ -(CH ₂) ₇ -COOH	TMS/OMe	+	++	+++	++	
34	LA (n-10)	H ₁₁ C ₅ -(CH=CH) ₂ -CH(OH)-(CH ₂) ₇ -COOH	TMS/OMe	+	++	+++	++	
35	LA (n-6)	H ₁₁ C ₅ -CO-(CH=CH) ₂ -(CH ₂) ₇ -COOH	OMe				+	+
36	LA (n-10)	H ₁₁ C ₅ -(CH=CH) ₂ -CO-(CH ₂) ₇ -COOH	OMe				+	+
37	LA (n-6)		TMS/OMe		+	++	++	
38	LA (n-10)		TMS/OMe		+	++	++	
39	LA (n-6), (n-10)	H ₁₁ C ₅ -(CH=CH) ₂ -C(OH)=CH-(CH ₂) ₆ -COOH	ETMS/OMe				+	
		H ₉ C ₄ -CH=C(OH)-(CH=CH) ₂ -(CH ₂) ₇ -COOH	ETMS/OMe					
40	AA (n-10)	H ₁₁ C ₅ -(CH=CH) ₂ -CH(OH)-(CH ₂ -CH=CH) ₂ -(CH ₂) ₃ -COOH	TMS/OMe				+	+
	AA (n-12)	H ₁₁ C ₅ -(CH=CH-CH ₂) ₂ -CH(OH)-(CH=CH) ₂ -(CH ₂) ₃ -COOH	TMS/OMe				+	+
	AA (n-9)	H ₁₁ C ₅ -CH=CH-CH ₂ -CH(OH)-(CH=CH) ₂ -CH ₂ -CH=CH-(CH ₂) ₃ -COOH	TMS/OMe				+	+
	AA (n-13)	H ₁₁ C ₅ -CH=CH-CH ₂ -(CH=CH) ₂ -CH(OH)-CH ₂ -CH=CH-(CH ₂) ₃ -COOH	TMS/OMe				+	+
41	LA (n-10)	H ₁₁ C ₅ -CH=CH-CH(OH)-CH(OH)-CH(OH)-(CH ₂) ₇ -COOH	TMS/TMS/ TMS/OMe				+	
42	LA (n-6)	H ₁₁ C ₅ -CH(OH)-CH(OH)-CH=CH-CH(OH)-(CH ₂) ₇ -COOH	TMS/TMS/TMS/OMe				+	
43	LA (n-10)	H ₁₁ C ₅ -CH(OH)-CH=CH-CH(OH)-CH(OH)-(CH ₂) ₇ -COOH	TMS/TMS/TMS/OMe				+	
44	LA (n-10), AA (n-10)	H ₁₁ C ₅ -CO-CH=CH-CHO	PFBO/PFBO				+	
45	LA (n-6)	OHC-CH=CH-CH(OH)-(CH ₂) ₇ -COOH	PFBO/TMS/OMe				+	
46	LA (n-6)	H ₁₁ C ₅ -CO-(CH=CH) ₂ -(CH ₂) ₇ -COOH	PFBO/OMe				+	
47	LA (n-10)	H ₁₁ C ₅ -(CH=CH) ₂ -CO-(CH ₂) ₇ -COOH	PFBO/OMe				+	

[a] The compounds are arranged according to increasing elution time from the GC column; the entry number corresponds to the peaks in Figures 1–3. The origin of identified compounds, their structural formulas, and the type of derivative are given in a separate column. [b] AA = arachidonic acid, LA = linoleic acid, LEA = linolenic acid, OA = oleic acid. The point of attack is described by the number of the carbon atom in the starting material by counting from the carbon (n) at the alkyl end of the chain. [c] ETMS = enol trimethylsilyl ester, OMe = methyl ester, PFBO = pentafluorobenzyloxime, TMS = trimethylsilyl ether. [d] The grading of + to +++ represents the relative proportion of product formed. [e] The duration of the oxidation (Cu²⁺/O₂) is given.

also an increased generation of aldehydes was observed, for example, of 4-hydroxy-2-nonenal^[15] (4-HNE; peaks 24a and 24b two isomers) or of 2-hydroxyheptanal (peak 13).

In contrast to the typical linoleic acid oxidation products (HODEs, KODEs, EpHODs) oxidation products of arachidonic acid, for example, hydroxyeicosatetraenoic acids (peak 40, several isomers) were present only in low amounts. This result is somewhat surprising because it was previously assumed^[3] that LPO preferentially affects arachidonic acid. A nearly equal tendency for linoleic and arachidonic acid to be oxidized is also indicated by the nearly equal decrease of the peaks corresponding to these acids (peak 28 and 31) in the oxidized samples).

Oleic acid oxidation products (peak 32) are detectable in small amount after oxidation for 24 h.^[10] This observation demonstrates that oxidative attack is also possible only at monoallylically activated methylene groups in LDL.

In contrast to previous views^[3] the preferential presence of linoleic acid oxidation products can be understood if one considers that radicals, which induce LPO processes, only recognize the $-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-$ group. They therefore attack free PUFAs as well as their esters with comparable probability. LDL consists predominantly of cholesterol linoleate,^[16] while cholesterol arachidonate is present in much less amounts. Furthermore, LPO products of arachidonic acid degrade faster than those of linoleic acid. Thus the observed prevalence of linoleic acid oxidation products is explained.

HODEs, the main products of LPO of LDL, are physiologically highly reactive compounds: In combination with other LPO products, for example, 2,4-decadienal, HODEs effect the release of interleukin-1 β from macrophages,^[17] they activate the peroxisome-proliferator-activated receptor protein (PPAR- γ),^[18] which plays a role in cell differentiation,^[19] they induce inflammation,^[20] and cause swelling of mitochondria.^[21] Toxic properties are ascribed in particular to 4-HNE, which undergoes, like all α,β -unsaturated aldehydes, Michael reactions.^[15, 22, 23] Even more toxic is 2,4-decadienal^[24] because of its higher conjugation and hence higher reactivity. Since the same structural element is present in KODEs, the latter should have analogous toxicity, but this had not been investigated.

Copper-ion induced air oxidation is an unphysiological method. A more physiologically similar mild oxidation of LDL occurs just by storing LDL samples at 0 °C.^[7] This minimally modified LDL (MM-LDL) is still recognized by the LDL cell receptor, but not by the scavenger receptor.^[7] We isolated such a MM-LDL from a serum sample stored for six months at 0 °C. The sample was investigated in exactly the same way as that oxidized with Cu²⁺/air. The chromatogram was similar to that obtained from a LDL sample oxidized for 10 h with Cu²⁺/air. Since this MM-LDL is still recognized by the LDL receptor^[7] it should be transferred into the cell and digested there (see above). Consequently HODEs, KODEs, EpHODs, 4-HNE, and 2,4-decadienal should be introduced into the cell. This sequence might explain why fatty streaks, which are the first signs of a beginning atherosclerosis, develop beneath a structurally intact endothel.^[25] In contrast it was suggested previously that LDL would be oxidized during atherosclerosis by a prolonged stay at the surface of

endothelial cells, which would result in potential oxidation by an unknown manner.^[26]

The increase in HODEs occurs years before the first signs of atherosclerotic changes become evident in the arteries,^[27] and thus also before oxidized LDL is recognized by the scavenger receptor of macrophages. In model experiments we detected that lysine residues of the LDL protein, which are responsible for receptor binding, are much less susceptible to oxidation than PUFAs. Consequently our investigations suggest that atherosclerosis starts with an increased oxidation of the PUFAs in cholesterol esters and phospholipids in LDL. The increase of the cholesterol level in atherosclerotic patients is therefore only a side effect of the much more important oxidation of the fatty acid part. The increase in the oxidation products exceeds that of cholesterol by more than one order of magnitude.^[16]

Experimental Section

LDL was purchased (Fluka AG) or prepared according to Leiss^[28] by fractional precipitation of serum from healthy donors immediately after withdrawal of blood. MM-LDL was obtained by storage of serum samples at 0 °C for 3–6 months.

LDL oxidation: LDL derived from serum (40 mL) was dissolved in phosphate buffer (PBS; 20 mL, 0.1M, pH 7.4), and an aqueous CuSO₄ solution (10 μM , 20 mL) added. The solution was stirred at 37 °C. Samples (10 mL) were withdrawn after 0, 6, 12, and 24 h, and extracted according to the procedure of Bligh and Dyer.^[29] A 0.05 mM methanolic pentafluorobenzylhydroxylamine hydrochloride solution (50 μL) was added. After 10 min the solvent was removed on a rotatory evaporator at room temperature. The residue was dissolved in 0.1M PBS (10 mL, pH 7.4) by ultrasonification, and cholesterol esterase (Fluka AG, 1 mg) was added. The solution was stirred for 1 h at 37 °C. Hydroperoxides were destroyed by addition of P(OCH₃)₃ (20 μL)^[30] (the enzyme is deactivated if P(OCH₃)₃ is added before enzymatic hydrolysis). The solution was brought to pH 2 after hydrolysis and the saponified lipids were extracted according to Bligh and Dyer.^[29] After removal of CHCl₃, the residue was dissolved in MeOH/H₂O (85/15, 5 mL) by ultrasonification and filtered over a previously equilibrated RP-18 cartridge. The methanol was removed, conc. HCl added (pH 2), and the products were extracted with diethyl ether. The diethyl ether was removed by a stream of nitrogen. The residue was treated for 2 min with 5 % solution of diazomethane in diethyl ether (0.5 mL), and the excess CH₂N₂ and solvent were removed under a stream of nitrogen (Caution: if HCl is not removed completely, hydroxy functions are partly transferred to methyl ethers by the subsequent treatment with diazomethane). The residue was treated with MSTFA (10 μL ; 60 min, 40 °C). The samples prepared were then subjected to GC/MS analysis.

The oxidation of linoleic acid and arachidonic acid was performed as described recently,^[31] except that a 5 μM solution of CuSO₄ was used instead of Fe ions.

GC/MS: Finnigan MAT 95, 70 eV, ICIS data system, connected to a HP 5890 Series II gas chromatograph, fused silica gel column coated with DB-05 (J&W Scientific Instruments) i.d. 0.25 mm, 30 m, H₂, injector 280 °C, temperature program: 3 min isothermal at 50 °C, 4 °Cmin⁻¹ to 100 °C, 3 °Cmin⁻¹ to 300 °C, 10 min isothermal at 300 °C, injection volume 0.6–3 μL .

Received: May 21, 1999

Revised: September 16, 1999 [Z13452]

[1] Statistisches Bundesamt, press release July 15, 1996, July 22, 1997 and September 10, 1998 (<http://194.95.119.6/presse/deutsch/monat.htm>).

[2] J. L. Goldstein, M. S. Brown, *Annu. Rev. Biochem.* **1977**, 46, 897–930.

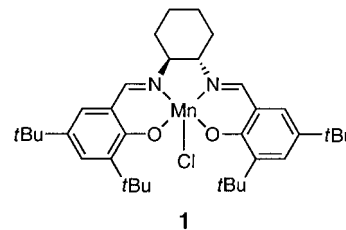
[3] M. S. Brown, J. L. Goldstein, *Annu. Rev. Biochem.* **1983**, 52, 223–261.

- [4] D. W. Morel, J. R. Hessler, G. M. Chisolm, *J. Lipid Res.* **1983**, *24*, 1070–1076.
- [5] U. P. Steinbrecher, S. Parthasarathy, D. S. Leake, J. L. Witztum, D. Steinberg, *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 3883–3887.
- [6] U. P. Steinbrecher, H. Zhang, M. Loughheed, *Free Radicals Biol. Med.* **1990**, *9*, 155–168.
- [7] J. A. Berliner, M. C. Territo, A. Sevanian, R. Soroush, J. A. Kim, B. Bamshad, M. Esterson, A. M. Fogelman, *J. Clin. Invest.* **1990**, *85*, 1260–1266.
- [8] H. Esterbauer, G. Jürgens, O. Quehenberger, E. Koller, *J. Lipid Res.* **1987**, *28*, 495–509.
- [9] F. J. G. M. van Kuijk, A. N. Siakotos, L. G. Fong, R. J. Stephens, D. W. Thomas, *Anal. Biochem.* **1995**, *224*, 420–424.
- [10] T. Wang, W. G. Yu, W. S. Powell, *J. Lipid Res.* **1992**, *33*, 525–537.
- [11] H. W. Gardner, R. Kleiman, D. Weisleder, *Lipids* **1974**, *9*, 696–706.
- [12] E. N. Frankel, *J. Am. Oil Chem. Soc.* **1984**, *61*, 1908–1917.
- [13] C. Schwarz and G. Spiteller, unpublished results.
- [14] W. Jira, G. Spiteller, W. Carson, A. Schramm, *Chem. Phys. Lipids* **1998**, *91*, 1–11.
- [15] H. Esterbauer, R. J. Schaur, H. Zollner, *Free Radicals Biol. Med.* **1991**, *11*, 81–128.
- [16] H. Esterbauer, J. Gebicki, H. Puhl, G. Jürgens, *Free Radicals Biol. Med.* **1992**, *13*, 341–390.
- [17] C. E. Thomas, R. L. Jackson, D. F. Ohlweiler, G. Ku, *J. Lipid Res.* **1994**, *35*, 417–427.
- [18] L. Nagy, P. Tontonoz, J. G. Alvarez, H. Chen, R. M. Evans, *Cell* **1998**, *93*, 229–240.
- [19] A. Chawla, E. J. Schwarz, D. D. Dimaculangan, *Endocrinology* **1994**, *135*, 798–800.
- [20] D. Moch, T. Schewe, H. Kuehn, D. Schmidt, P. Buntrock, *Biomed. Biochim. Acta* **1990**, *49*, 201–207.
- [21] G. A. Blondin, *Ann. N. Y. Acad. Sci. (Carriers Channels Biol. Syst.)* **1975**, *264*, 98–111.
- [22] K. Uchida, S. Toyokuni, K. Nishikawa, S. Kawakishi, H. Oda, H. Hiiai, E. R. Stadtman, *Biochemistry* **1994**, *33*, 12487–12494.
- [23] S. Srivastava, A. Chandra, L.-F. Wang, W. E. Seifert, Jr., B. B. DaGue, N. H. Ansari, S. K. Srivastava, A. Bhatnagar, *J. Biol. Chem.* **1998**, *273*, 10893–10900.
- [24] T. Kaneko, S. Honda, S. I. Nakano, M. Matsuo, *Chem. Biol. Interact.* **1987**, *63*, 127–137.
- [25] D. Steinberg, *Atherosclerosis Reviews 18* (Eds.: J. Stokes, M. Mancini), Raven, New York, **1988**, 1–23.
- [26] D. Steinberg, *J. Biol. Chem.* **1997**, *272*, 20963–20966.
- [27] W. Jira, G. Spiteller, A. Schramm, *Chem. Phys. Lipids* **1996**, *84*, 165–173.
- [28] O. Leiss, U. Murawski, H. Egge, *J. Clin. Chem. Clin. Biochem.* **1979**, *17*, 619–625.
- [29] E. G. Bligh, W. J. Dyer, *Can. J. Biochem. Physiol.* **1959**, *37*, 911–917.
- [30] P. Spiteller, G. Spiteller, *Chem. Phys. Lipids* **1997**, *89*, 131–139.
- [31] P. Spiteller, G. Spiteller, *Biochim. Biophys. Acta* **1998**, *1392*, 23–40.

Radical Intermediates in the Jacobsen – Katsuki Epoxidation**

Luigi Cavallo and Heiko Jacobsen*

The generation of optically active epoxides by oxygen-transfer reactions represents one of the most elegant techniques used in the formation of carbon–oxygen bonds in asymmetric synthesis.^[1] The catalytic protocol developed by Jacobsen and co-workers,^[2] which involves the use of the Mn^{III}–salen complex **1** and derivatives thereof, currently stands as the most powerful method in this field; it has been



proven effective for virtually every class of unfunctionalized, conjugated olefins,^[3] and industrial production of the catalyst on a ton scale has become possible.^[4] Although the importance of steric bulk in the 3,3'-position of the salen ligand and the profound influence of electronic effects due to the substituents in 5,5'-position were recognized early on^[5] and rationalized in model calculations,^[6] the mechanism of the Mn^{III}–salen catalyzed epoxidation is still a matter of controversy. The *cis*–*trans* isomerization observed in the transformation of conjugated alkenes gave rise to several proposed mechanisms. Starting with a Mn^V–oxo–salen complex as the catalytically active species—experimental evidence has recently been provided for this^[7]—the reaction might proceed either by direct substrate attack at the oxo ligand in a concerted or sequential fashion involving radical intermediates, or by substrate attack at both the metal and oxo centers to generate an oxametallacyclic intermediate (Scheme 1, pathways **Ic**, **Is**, and **II**, respectively). New experimental results seem to provide evidence for substrate attack at the oxo ligand only,^[8] as well as for the existence of mangano-oxetanes;^[9] the controversial mechanistic debate has recently been summarized in a highlight.^[10]

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[**] L.C. acknowledges financial assistance from the Ministero della Ricerca Scientifica e Tecnologica. H.J. is indebted to Prof. H. Berke for continued support.



Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

- [7] D. Feichinger, D. A. Plattner, *Angew. Chem.* **1997**, *109*, 1796; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1718.
- [8] N. S. Finnley, P. J. Pospisil, S. Chang, M. Palucki, R. G. Konsler, K. B. Hansen, E. N. Jacobsen, *Angew. Chem.* **1997**, *109*, 1798; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1720.
- [9] C. Linde, M. Arnold, P.-O. Norrby, B. Åkermark, *Angew. Chem.* **1997**, *109*, 1802; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1723.
- [10] T. Linker, *Angew. Chem.* **1997**, *109*, 2150; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2060.
- [11] The self-consistent GGA-BP86 calculations were performed using the ADF program package, version 2.3.^[12] Main group elements were described by a double ζ STO basis including one polarization function, whereas for Mn a triple ζ STO basis with one additional 4p function was used (ADF basis sets III and IV, respectively). Transition states have been characterized by one negative eigenvalue of the approximate Hessian, and by a coordinate-tracing procedure. For more computational details and further references, see ref. [12d].
- [12] a) E. J. Baerends, D. E. Ellis, P. E. Ros, *Chem. Phys.* **1973**, *2*, 41; b) G. teVelde, E. J. Baerends, *J. Comp. Phys.* **1992**, *99*, 84; c) C. Fonseca - Guerra, O. Visser, J. G. Snijders, G. teVelde, E. J. Baerends in *Methods and Techniques in Computational Chemistry: METECC-95* (Eds.: E. Clementi, G. Corongiu) STEF, Cagliari, **1995**, p. 305; d) G. teVelde, *ADF 2.3 User's Guide*, Vrije Universiteit, Amsterdam, **1997**.
- [13] P. J. Pospisil, D. H. Carsten, E. N. Jacobsen, *Chem. Eur. J.* **1996**, *2*, 974.
- [14] Experimental data (F. C. Rix, M. Brookhart, P. S. White, *J. Am. Chem. Soc.* **1996**, *118*, 4746), and theoretical calculations (D. G. Musaev, R. D. J. Froese, M. Svensson, K. Morokuma, *J. Am. Chem. Soc.* **1997**, *119*, 367; P. Margl, L. Deng, T. Ziegler, *Organometallics* **1998**, *17*, 933) suggest that at room temperature the $-T\Delta S$ contribution to the free energy of ethene coordination to transition metal d^0 and d^8 compounds is in the range 40–50 kJ mol⁻¹. It is argued that enthalpies of coordination higher than 50 kJ mol⁻¹ are needed to give rise to stable ethene-coordinated species. A similar $-T\Delta S$ contribution to the free energy of epoxide coordination, and hence similar conclusions, can also be reasonably assumed in the present study.
- [15] C. Linde, B. Åkermark, P.-O. Norrby, M. Svensson, *J. Am. Chem. Soc.* **1999**, *121*, 5083.
- [16] Consult the supporting information for optimized geometries and final energies of all species.
- [17] N. J. Henson, P. J. Hay, A. Redondo, *Inorg. Chem.* **1999**, *38*, 1618.
- [18] For **3** and **4**, besides the *S2* and *S4* cases already discussed, we also located singlet *S0* geometries, within 3 kJ mol⁻¹ of the related triplet species. The formation of *S0-6* and *S0-9** from *S0-4* is, however, endothermic by 33 and 91 kJ mol⁻¹, respectively. Thus, the epoxide formation is not likely to occur on the *S0* surface. For a discussion of the different spin states of Mn^V-oxo complexes, see also ref. [15]. For **2** and **10**, no complexes possessing *S0*-ground states could be localized.

Molecular Design of Liquid-Crystalline Block Molecules: Semifluorinated Pentaerythritol Tetrabenzoates Exhibiting Lamellar, Columnar, and Cubic Mesophases**

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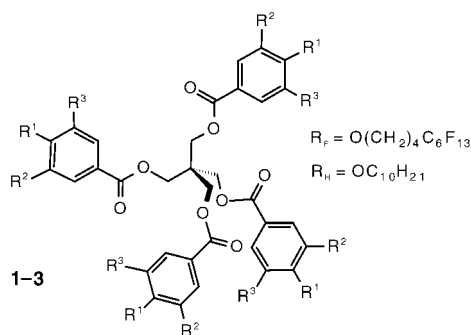
The spontaneous formation of fluid supermolecular assemblies with well-defined morphologies (e.g. layers, interpenetrating networks, columns, and spheroids) is fundamental for structure formation in biological systems as well as for the tailoring of novel materials. Thus, the investigation of the driving forces of this self assembly process and the rational design of molecules which can form specific supermolecular structures on different length scales are contemporary research topics. Molecules, able to self assemble to these well-organized states of soft matter, can be divided into three classes: anisometric molecules (with a rod- or disclike shape), amphiphilic molecules (lipids/surfactants),^[1] and block copolymers.^[2] Applications for rodlike thermotropic liquid crystals include electrooptical devices, the lyotropic mesophases of surfactant/water systems can be utilized as templates for the preparation of mesoporous materials, and the ordered structures of block copolymers are, for example, applied in the preparation of ordered arrays of nanosized noble metal and semiconductor particles.

In low molecular weight systems, such as thermotropic liquid crystals, the molecular shape is a major design consideration to tailor the mesophase type. For example, calamitic molecules favor layers (smectic phases), disclike molecules organize to columns (columnar phases), and tapered or cone-shaped amphiphilic^[3] or dendritic molecules^[4] can form cylindrical or spheroidal aggregates which self assemble into columnar or micellar cubic mesophases. This contrasts with block copolymers, for which no specific molecular shape is necessary to produce a wide range of different morphologies. They can be obtained simply by changing the number and size of the incompatible polymer blocks.^[2] The same diversity of different phases can also be found in lyotropic amphiphile/solvent systems with dependence on solvent content and temperature.^[1]

The question arose if it would be possible to form different supermolecular structures, previously known from block copolymers and lyotropic systems, with low molecular weight molecules, specifically with molecules built up of different building blocks but without a specific anisometric shape or a pronounced amphiphilicity. Indeed, it was recently shown that star-shaped pentaerythritol tetrakis(3,4-dialkoxybenzoates), such as **2H** (Scheme 1)^[5, 6] and related linear compounds,^[5b, 7]

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



Scheme 1. Basic skeleton of all compounds. The **1** compounds have substituents at the R^1 positions only, **2** at R^1 and R^2 , and **3** at all R^1 – R^3 positions. Substituents are summarized in Table 1.

Table 1. Substituents, thermotropic phase transition temperatures, ($T^\circ\text{C}$) and corresponding enthalpy values ($\Delta H/\text{kJ mol}^{-1}$, in square brackets) of compounds **1F**–**3F** and **1H**–**3H**.^[5b]

Compound	R^1	R^2	R^3	Phase transitions ^[a]
1H	R_H	H	H	Cr 42 Iso
1F	R_F	H	H	Cr 59 [30.5] S_A 88° [2.2] Iso
2H	R_H	R_H	H	Cr 54 (Col_{h2} 47°) Iso
2F ^[9]	R_F	R_F	H	Cr 88 [86.5] Col_{h2} 131° [5.6] Iso
3H	R_H	R_H	R_H	Cr 41 (Col_{h2} 8°) Iso
3F	R_F	R_F	R_F	Cr 36 [46.6] Cub_{12} 101° ^[b] [1.8] Iso

[a] Abbreviations: Cr = crystalline phase, Col_{h2} = inverted hexagonal columnar mesophase, Cub_{12} = inverted micellar cubic mesophase, S_A = smectic A phase, Iso = isotropic liquid; values in brackets refer to monotropic (metastable) mesophases. [b] Refers to the heating scan, in the cooling cycle the phase transition occurs at 85 °C.

can form liquid crystalline phases. The occurrence of these phases was explained as a consequence of microsegregation of the more polar central benzoate units from the apolar alkyl chains.^[5,7,8] However, while exclusively columnar mesophases have been realized with the pentaerythritol derivatives, attempts to change the mesophase structure by variation of the number of chains have so far failed. Thus, the columnar phase of **2H** was significantly destabilized on grafting additional alkyl chains (**2H**→**3H**) and it was completely lost on reduction of their number (**2H**→**1H**).^[5b]

Because perfluorinated chains can stabilize mesophases,^[9] we hoped that the analogous compounds **1F** and **3F**, with semifluorinated chains instead of the alkyl chains, could be mesogenic. Indeed, all three molecules **1F**–**3F** exhibit thermodynamically stable, enantiotropic liquid crystalline phases (see Table 1), but most importantly they have completely different mesophases.

By using optical microscopy between crossed polarizers, the formation of a birefringent fanlike texture was observed on cooling compound **1F**, with four semifluorinated chains, to 88 °C. Shearing gave a typical “oily streaks” optical texture with homeotropic regions, which indicates a mesophase with a layer structure (S_A). X-ray scattering has confirmed this phase assignment (one sharp reflex in the small angle region and a diffuse scattering in the wide angle region) with a layer periodicity of $d = 3.2$ nm. This periodicity is in agreement with these molecules arranged in layers consisting of alternating sublayers of the microsegregated semifluorinated chains and sublayers of the polar benzoate units.

As reported earlier, compound **2F** with eight semifluorinated chains has a hexagonal columnar mesophase (Col_{h2} , $a_{\text{hex}} = 3.6$ nm at $T = 80^\circ\text{C}$).^[10] Here the polar regions form cylinders surrounded by the semifluorinated chains.

No birefringence was found on cooling **3F** which has twelve chains. However, a significant increase in viscosity was observed at 85 °C. Calorimetric measurements indicate a phase transition which occurs at 101 °C in the heating scan and at 85 °C in the cooling scan (scan rate 10 K min^{-1}). Obviously, the transition to this isotropic phase can be significantly supercooled and is typical for three-dimensional ordered mesophases. X-ray investigations of this highly viscous (plastic) isotropic phase indicated two independent sharp reflexes in the small angle region and a diffuse scattering in the wide angle region. This, together with the other observations (optical isotropy, viscosity, supercooling) confirm the existence of a cubic mesophase.

The cubic mesophase occurs in a phase sequence $S_A \rightarrow \text{Col}_{h2} \rightarrow \text{Cub}$ on increasing the number of semifluorinated chains and keeping the size of the polar central unit constant. Hence, the polar/apolar interface curvature becomes increasingly negative in the order described above and therefore the cubic 3D lattice of compound **3F** should be built up by discrete spheroidic entities containing the polar parts of the molecules surrounded by a continuum of the nonpolar chains (inverted micellar cubic phases, Cub_{12}). In order to prove this hypothesis, we investigated binary mixtures of different concentration of compounds **1F** and **3F** by optical microscopy. The results are summarized in the phase diagram shown in Figure 1. The most important observation is that

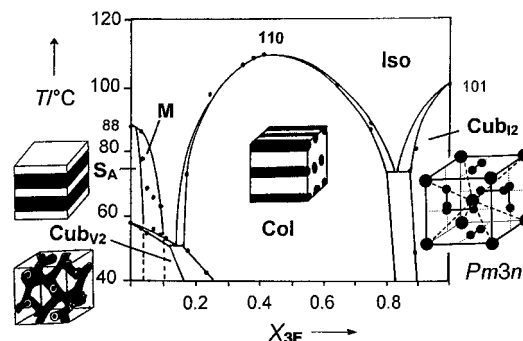


Figure 1. Phase diagram of the binary system **1F/3F** and schematic sketches of the mesophase; crystalline phases are not shown. Abbreviations: M = unknown birefringent mesophase; ^[14,15] Cub_{v2} = inverted bi-continuous cubic mesophase; for the other abbreviations see Table 1. In the sketches of the mesophase structures the black regions represent the polar microsegregated regions. By example for a Cub_{v2} phase a Gyroid labyrinth is shown, but the actual structure could be different. The positions of the micelles in the $Pm3n$ lattice of the Cub_{12} phase are shown as dots (the size of the dots is not related to the micelle size) whereby two micelles of one type are located at the corners and in the center and six micelles of another type are located pairwise at the face bisectors of the cubes, it is possible that these micelles have a nonspherical shape.^[3c, d, 4a, 13]

a broad region ($X_{3F} = 0.15$ – 0.85) of a columnar mesophase, built up from cylindrical aggregates, is induced between the smectic phase of compound **1F** (planar aggregates) and the cubic phase of **3F**. As the polar/apolar interface curvature is reduced on addition of **1F**, the aggregates forming the cubic

phase must be more curved than the cylindrical aggregates in the induced columnar phase. This shows the cubic phase must comprise closed spheroidal aggregates, which additionally confirms the proposed inverted micellar structure of the cubic mesophase of **3F** (Cub₁₂ phase).

For such thermotropic Cub₁₂ phases, *Pm3n* lattices have been found almost exclusively.^[3, 4, 11] Indeed, the relative positions of the small angle reflexes in the cubic phase of **3F** at $\theta = 1.57^\circ$ and 1.73° correspond to the most intensive reflexes found for other inverted micellar cubic mesophases of the *Pm3n* type.^[3] Assuming such a *Pm3n* lattice, the reflexes can be indexed to 200 and 210, and a cubic lattice parameter $a_{\text{cub}} = 5.6$ nm calculated. The number of molecules per unit cell was calculated according to $n = a_{\text{cub}}^3 (N_A/M) \rho$ (N_A = Avogadro constant, M = molecular mass), assuming a density of $\rho = 1.4 \text{ g cm}^{-3}$ ^[12] to give around 28 molecules per unit cell.

Though the precise shape of the micelles in *Pm3n* phases is still under debate, it is now accepted that the unit cells contain eight discrete micellar aggregates of two different types (see Figure 1).^[3c, d, 4a, 13] Two aggregates of one type are located at the corners and in the center of the unit cell, forming a body centered sublattice, and six aggregates of the other type are located pairwise at the face bisectors of the cubes. Hence, the 28 molecules should be shared among eight entities forming the unit cell of the *Pm3n* lattice, and therefore the cubic lattice should be built up of aggregates consisting of three to four **3F** molecules. The aggregates thus represent micelles built up by the assembly of molecules deformed, on average, to a conelike shape.

A closer inspection of the binary phase diagram (Figure 1) indicates in regions with a high concentration of **1F** ($X_{3F} = 0.10$ – 0.15) another optically isotropic region. Below a temperature of about 50°C this isotropic phase is highly viscous and plastic, which again points to a cubic mesophase. As this phase occurs between a smectic and an inverted columnar phase it should be an inverted bicontinuous cubic phase consisting of interpenetrating networks of branched columns formed by the polar regions within the apolar continuum of the semifluorinated chains (Cub_{V2}).^[14]

In regions of very low concentration of **3F** ($X_{3F} = 0.05$ – 0.10), close to conditions for the smectic phase, an additional birefringent mesophase (M) is induced. Shearing a sample of this mesophase shows bright, homogeneous regions by optical microscopy. We assume that this phase could probably be another intermediate phase with a two- or three-dimensional structure.^[15]

These results show that a wide variety of completely different mesophases can be realized by the self assembly of pure samples or binary systems of molecules in which a starlike shape is provided by a tetrahedral central core. Because the flexibility of these molecules allows them to adopt different conformations the actual average conformation changes during the process of self assembly, whereby conformers which fit best with the geometry provided by the interfaces are favored. The interface geometry itself can simply be tailored by changing the space required by the incompatible units. This is a primary difference with classical thermotropic liquid crystals, and with the columnar and cubic mesophases formed by tapered- or cone-shaped amphiphiles

and dendrons. For these molecules, the self assembly is facilitated by a complimentary shape provided by a special molecular architecture.^[3, 4]

The increased mesophase stability of all fluorinated compounds **1F**–**3F** in comparison to the related alkyl compounds **1H**–**3H** should arise largely from an increased intramolecular polarity contrast on replacing alkyl chains by the semifluoroalkyl chains, which favors microsegregation. The larger cross-section^[16] of the fluorinated alkyl chains should be responsible for the transition from a columnar to a micellar cubic phase upon replacing the alkyl chains of **3H** by semifluorinated chains. It should be pointed out that **3F** is the first fluorinated molecule which forms a thermotropic micellar cubic mesophase. Furthermore, the phase sequence $S_A \leftrightarrow (M) \leftrightarrow \text{Cub}_{V2} \leftrightarrow \text{Col}_{h2} \leftrightarrow \text{Cub}_{12}$ represents the whole sequence of inverted, lyotropic phases of surfactant solvent systems, which is realized here for the first time in a binary systems of only two different low molecular weight block molecules in the absence of any solvent. This observation is of fundamental interest, because it shows that it is indeed possible to design all types of mesophases (smectic, columnar, bicontinuous cubic, and micellar cubic) without the classical concepts of rigidity/anisometry and amphiphilicity.^[17] Additionally, these novel compounds represent an interesting borderline case between low molecular weight amphiphiles (surfactants, lipids) and block copolymers.

Experimental Section

For the synthesis of **1F** and **3F** the appropriately substituted benzoic acid (1.2 mmol), *N*-cyclohexyl-*N'*-(2-morpholinoethyl)carbodiimide methyl-*p*-toluene sulfonate (1.4 mmol, 0.61 g), and a catalytic amount of 4-dimethylaminopyridine (10 mg) were added to a suspension of pentaerythritol (0.3 mmol, 41 mg) in a 1:1 mixture of dry CH_2Cl_2 and Freon 113 (40 mL). The reaction mixture was stirred for 72 h at 20°C and afterwards washed once with water. The aqueous phase was extracted with CHCl_3 (20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by preparative centrifugal thin layer chromatography (Chromatotron, Harrison Research) eluted with CHCl_3 .

1F: ^1H NMR (400 MHz, CDCl_3 , 25°C , TMS): $\delta = 1.74$ – 2.25 (m, 24H, CH_2), 4.04 (t, $^3J(\text{H,H}) = 5.7$ Hz, 8H, OCH_2), 4.62 (s, 8H, CCH_2), 6.83 (d, $^3J(\text{H,H}) = 8.9$ Hz, 8H, H_{ar}), 7.92 (d, $^3J(\text{H,H}) = 9.0$ Hz, 8H, H_{ar}); ^{13}C NMR (100 MHz, CDCl_3 , 25°C , TMS): $\delta = 18.14$ (CH_2), 29.46 (CH_2), 31.56 (t, $^2J(\text{C,F}) = 22.4$ Hz, CH_2CF_2), 43.99 (quart. C), 64.41 (CH_2OCO), 68.39 (OCH_2), 115.24 (H_{ar}), 123.08 (H_{ar}), 132.87 (C_{ar}), 164.01 (C_{ar}), 166.94 (C=O); ^{19}F NMR (188 MHz, CDCl_3 , 25°C , CF_3Ph): $\delta = -82.42$ (t, $^3J(\text{F,F}) = 9.1$ Hz, 12F, CF_2), -116.00 (t, $^3J(\text{F,H}) = 14.7$ Hz, 8F, CF_2CH_2), -123.52 (br s, 8F, CF_2), -124.48 (br s, 8F, CF_2), -125.14 (br s, 8F, CF_2), -127.72 (br s, 8F, CF_2); Elemental analysis for $\text{C}_{75}\text{H}_{56}\text{F}_{52}\text{O}_{12}$ (2113): calcd: C 41.49, H 2.67; found: C 41.40, H 2.92.

3F: ^1H NMR (200 MHz, CDCl_3 , 25°C , TMS): $\delta = 1.7$ – 2.3 (m, 72H, CH_2), 3.92–3.99 (m, 24H, OCH_2), 4.64 (s, 8H, CCH_2), 7.17 (s, 8H, H_{ar}); ^{13}C NMR (100 MHz, CDCl_3 , 25°C , TMS): $\delta = 18.12$ (CH_2), 29.64 (CH_2), 30.57 (CH_2), 31.69 (t, $^2J(\text{C,F}) = 22.4$ Hz, CH_2CF_2), 43.99 (quart. C), 65.00 (CH_2OOC), 69.44 (OCH_2), 109.11 (C_{ar}), 125.35 (C_{ar}), 143.57 (C_{ar}), 153.78 (CH_{ar}), 166.69 (C=O); ^{19}F NMR (188 MHz, CDCl_3 , 25°C , CF_3Ph): $\delta = -82.73$ (br s, 36F, CF_3), -116.38 (m, 24F, CH_2CF_2), -123.78 (br s, 24F, CF_2), -124.47 (br s, 24F, CF_2), -125.31 (br s, 24F, CF_2), -128.03 (br s, 24F, CF_2); Elemental analysis for $\text{C}_{153}\text{H}_{112}\text{F}_{156}\text{O}_{20}$ (5234): calcd: C 35.11, H 2.16; found: C 34.91, H 2.23.

Received: March 11, 1999

Revised: September 22, 1999 [Z13145]

- [1] Review: J. M. Seddon, R. H. Templer in *Handbook of Biological Physics, Vol. 1* (Eds.: R. Lipowsky, E. Sackmann), Elsevier, Amsterdam, **1995**, p. 97.
- [2] I. W. Hamley, *The Physics of Block Copolymers*, Oxford University Press, Oxford, **1998**, p. 24.
- [3] a) K. Borisch, S. Diele, P. Göring, C. Tschierske, *J. Chem. Soc. Chem. Commun.* **1996**, 237; b) K. Borisch, S. Diele, P. Göring, H. Müller, C. Tschierske, *Liq. Cryst.* **1997**, 22, 427; c) K. Borisch, S. Diele, P. Göring, H. Kresse, C. Tschierske, *Angew. Chem.* **1997**, 109, 2188; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2087; d) K. Borisch, S. Diele, P. Göring, H. Kresse, C. Tschierske, *J. Mater. Chem.* **1998**, 8, 529.
- [4] a) V. S. K. Balagurusamy, G. Ungar, V. Percec, G. Johansson, *J. Am. Chem. Soc.* **1997**, 119, 1539; b) S. D. Hudson, H.-T. Jung, V. Percec, W.-D. Cho, G. Johansson, G. Ungar, V. S. K. Balagurusamy, *Science* **1997**, 278, 449; c) V. Percec, C.-H. Ahn, W.-D. Cho, A. M. Jamieson, J. Kim, T. Leman, M. Schmidt, M. Gerle, M. Möller, S. A. Prokhorova, S. S. Sheiko, S. Z. D. Cheng, A. Zhang, G. Ungar, D. J. P. Yearley, *J. Am. Chem. Soc.* **1998**, 120, 8619.
- [5] a) A. Pegenau, P. Göring, C. Tschierske, *J. Chem. Soc. Chem. Commun.* **1996**, 2563; b) A. Pegenau, P. Göring, S. Diele, C. Tschierske, *Eur. J. Chem.* **1999**, 5, 1643.
- [6] Other liquid crystalline pentaerythritol derivatives have been reported, but their mesogenity was provided by extended anisometric (calamitic, disclike, or taper-shaped) rigid cores fixed to the pentaerythritol unit; calamitic units: R. Eidenschink, F.-H. Kreuzer, W. H. de Jeu, *Liq. Cryst.* **1990**, 8, 879; K. Zab, D. Joachimi, O. Agert, B. Neumann, C. Tschierske, *Liq. Cryst.* **1995**, 18, 489; J. Andersch, S. Diele, D. Lose, C. Tschierske, *Liq. Cryst.* **1996**, 21, 103; K. Praefcke, P. Psaras, A. Eckert, *Liq. Cryst.* **1993**, 13, 551; disclike units: J. L. Schulte, S. Laschat, V. Vill, E. Nishikawa, H. Finkelmann, M. Nimtz, *Eur. J. Org. Chem.* **1998**, 2499; extended taper-shaped units: J. Malthête, *New J. Chem.* **1996**, 20, 925.
- [7] Linear oligoalkylene amides without the possibility to form hydrogen bonds show columnar or smectic phases: U. Stebani, G. Lattermann, M. Wittenberg, J. H. Wendorff, *J. Mater. Chem.* **1997**, 7, 607.
- [8] C. Tschierske, *J. Mater. Chem.* **1998**, 8, 1485.
- [9] a) C. Viney, R. J. Twieg, T. P. Russell, L. E. Depero, *Liq. Cryst.* **1989**, 5, 1783; b) T. Doi, Y. Sakurai, A. Tamatani, S. Takenaka, S. Kusabashi, Y. Nishihata, H. Terauchi, *J. Mater. Chem.* **1991**, 1, 169; c) H. T. Nguyen, G. Sigaud, M. F. Achard, F. Hardouin, R. J. Twieg, K. Betterton, *Liq. Cryst.* **1991**, 10, 389; d) S. Pensec, F.-G. Tournilhac, P. Bassoul, *J. Phys. II France* **1996**, 6, 1597; e) S. V. Arehart, C. Pugh, *J. Am. Chem. Soc.* **1997**, 119, 3027; f) S. Takenaka, *J. Chem. Soc. Chem. Commun.* **1992**, 1748; g) G. Johansson, V. Percec, G. Ungar, K. Smith, *Chem. Mater.* **1997**, 9, 164; h) U. Dahn, C. Erdelen, H. Ringsdorf, R. Festag, J. H. Wendorff, P. A. Heiney, N. C. Maliszewskyj, *Liq. Cryst.* **1995**, 19, 759; i) V. Percec, D. Schlüter, Y. K. Kwon, J. Blackwell, M. Möller, P. J. Slangen, *Macromolecules* **1995**, 28, 8807; j) V. Percec, G. Johansson, G. Ungar, J. Zhou, *J. Am. Chem. Soc.* **1996**, 118, 9855.
- [10] A. Pegenau, X. H. Cheng, C. Tschierske, P. Göring, S. Diele, *New J. Chem.* **1999**, 23, 465.
- [11] In only one case a transition from a thermotropic $Pm3n$ phase to another micellar cubic phases was mentioned, see ref. [4c].
- [12] Approximately 61 % of the molecular volume of compound **3F** consists of the perfluoroalkyl groups (calculated using volume increments, see: A. Immrizi, B. Perini *Acta Crystallogr. Sect. A* **1977**, 33, 216). For this part of the calculation the density of perfluorohexane ($\rho = 1.682 \text{ g cm}^{-3}$) was assumed. The remaining 39 % was assumed to have a density of 1.0 g cm^{-3} which gave the average value of $\rho = 1.4 \text{ g cm}^{-3}$.
- [13] a) J. Charvolin, J. F. Sadoc, *J. Phys. (Paris)* **1988**, 49, 521; b) K. Fontell, K. K. Fox, E. Hansson, *Mol. Cryst. Liq. Cryst. Lett.* **1985**, 1, 9; c) R. Vargas, P. Mariani, A. Gulik, V. Luzzati, *J. Mol. Biol.* **1992**, 225, 137; d) H. Delacroix, T. Gulik-Krzywicki, P. Mariani, V. Luzzati, *J. Mol. Biol.* **1993**, 229, 526; e) P. Sakya, J. M. Seddon, R. H. Templer, R. J. Mirkin, G. J. T. Tiddy, *Langmuir* **1997**, 13, 3706.
- [14] The formation of the Cub_{V2} phase from the S_{A} phase and from the M phase is kinetically hindered. Therefore the M phase can be cooled down to room temperature and the cubic phase only develops slowly. Once formed it can be heated to $54 - 56^\circ\text{C}$ where the transition to the M phase occurs.
- [15] It could be a 2D-modulated variant of the S_{A} phase (ribbon phase) or a noncubic 3D phase as, for example, a tetragonal phase: A. M. Levelut,

B. Donnio, D. W. Bruce, *Liq. Cryst.* **1997**, 22, 753; M. C. Holmes, *Curr. Opin. Colloid Interface Sci.* **1998**, 3, 485. However, because of the rather low viscosity a ribbon phase seems to be more likely. Here the smectic layers are interrupted in regular intervals with formation of ribbonlike segments. These segments are arranged in a 2D lattice.

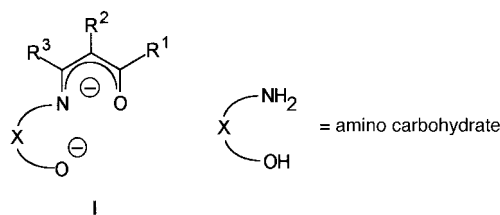
- [16] B. E. Smart in *Organofluorine Chemistry, Principles and Commercial Applications* (Eds.: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum, New York, **1994**, p. 57.
- [17] Compounds **1H-3H** and **1F-3F** are also amphiphilic in a wider sense, because they are built up of two incompatible units, but in contrast to classical amphiphiles, the mesophases of compounds **1F-3F** could not be changed by the addition of protic solvents.

New Building Blocks for the Design of Oligonuclear Copper Complexes Based on Amino Carbohydrates**

Rainer Wegner, Michael Gottschaldt, Helmer Görls, Ernst-G. Jäger,* and Dieter Klemm*

Dedicated to Professor Dirk Walther on the occasion of his 60th birthday

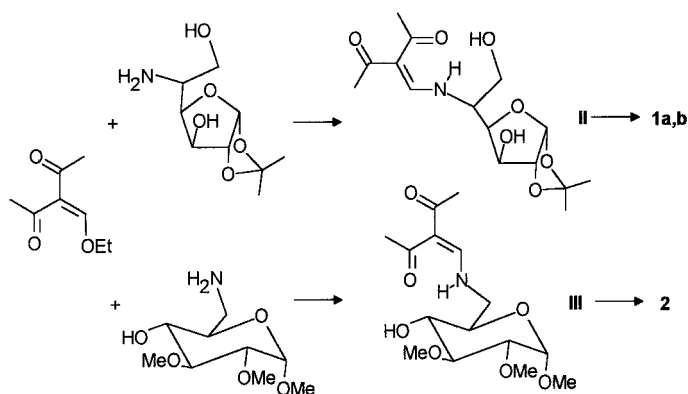
Next to iron, copper is the most important biological element for binding, transport, and activation of molecular oxygen. Copper-containing oxidases for the four-electron reduction of oxygen often display dinuclear (e.g. catechol oxidase)^[1] or oligonuclear active centers (e.g. ascorbate oxidase).^[2] The great biological importance of such copper complexes has induced intensive studies on oligonuclear model compounds.^[3] Our concept for the design of oligonuclear complexes is to use structurally modified amino derivatives of carbohydrates instead of the proteins that are the “backbones” of the natural systems and to bind the metal through tridentate, anionic ligand structures of type **I**.



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- [**] We thank the Deutsche Forschungsgemeinschaft (collaborative research project SFB 436 “metal-mediated reactions modeled after nature”), the Fonds der Chemischen Industrie, and the Thuringian Ministry for Science, Research and Culture for financial support.

The protonated forms of such chelating ligands **I** are easily accessible by condensation of hydroxyalkylamines with 1,3-dicarbonyl compounds. Even with the first prototypes^[4] a high tendency of the metal complexes to reach coordinative saturation by the formation of di- or tetranuclear complexes was found.^[5] Much interest has been shown for the copper complexes^[5–16] because of the ligand-dependant magnetic interaction between the metal centers. The substituents R^1 – R^3 as well as the bridging groups X ^[17] are useful for tuning properties such as redox potential and Lewis acidity of the central atom, which are important for catalytic reactions.

Based on current knowledge, carbohydrates are not typical biological coordination partners for metal atoms. However, as synthetic catalysts they are an interesting alternative to proteins: These chiral, polyfunctional natural substances are accessible in a broad range of molecular sizes, and obey the rules of unit conformation and configuration. They can be functionalized selectively in various ways as mono-, oligo-, or polysaccharides and can be structured supramolecularly (fibers, gels, membranes, mono- and multilayers).^[18–20] Hydrophilic and lipophilic properties as well as biological properties such as biocompatibility and biological decomposition and activity can be directed in a broad range. Investigations in recent years on the metallo-organic^[21] and complex chemistry^[22–27] of N-glycosides, nonmodified carbohydrates, and inositols have shown that carbohydrates have a very interesting potential as complex ligands. We present here the first structurally defined coordination compounds of β -oxoamine ligands on the basis of amino carbohydrates. Compounds **1a**, **1b** (from ligand **II**), and **2** (from ligand **III**) can be crystallized from methanol/water (**1a**), toluene (**1b**), or methanol/diethyl ether (**2**; Scheme 1).^[29] Single-crystal X-ray structures were obtained for **1a** and **2**.



Scheme 1. Synthesis of ligands **II** and **III**.

The asymmetric unit of **1a**^[30] contains two dinuclear complexes, in which the bridging alcoholate oxygen atoms in the 3-position of the ligand build a Cu_2O_2 four-membered ring with the copper atoms (Figure 1). The distances between the copper atoms are 2.977(1) and 3.020(1) Å, respectively. Striking is the low symmetry of the compound, which is also typical for many natural copper centers. One copper atom is coordinated in a distorted square planar fashion, whereas the other copper atom is in a distorted square pyramidal environ-

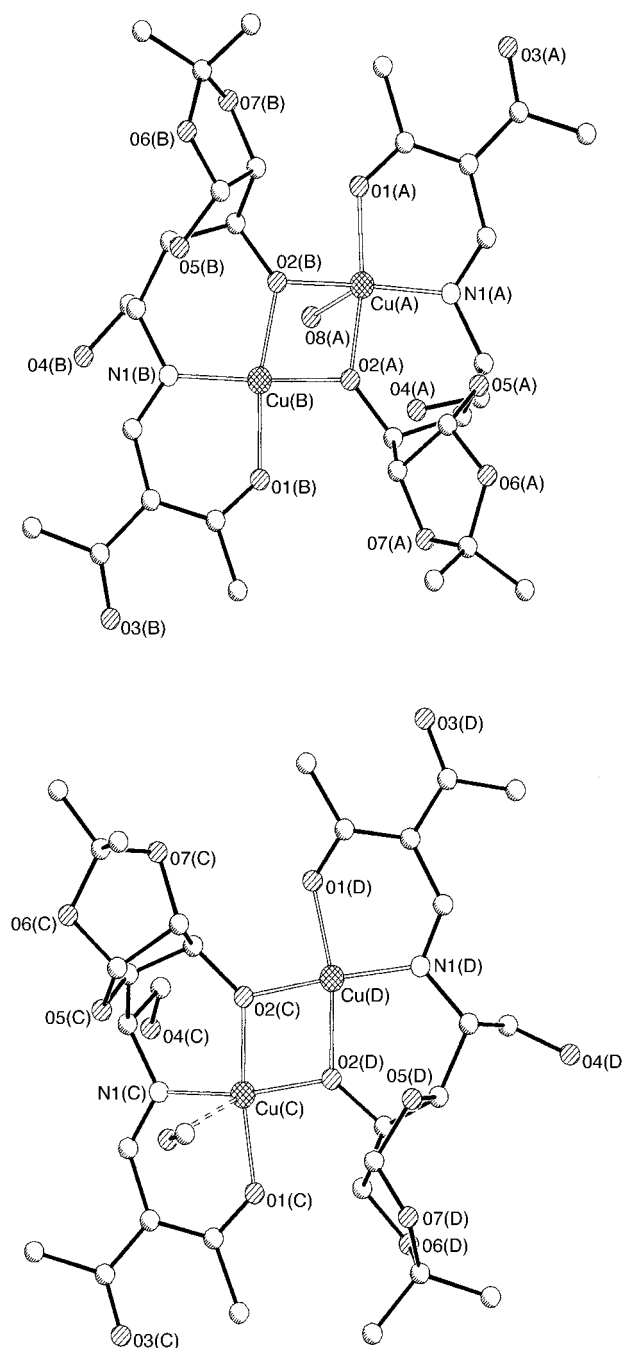


Figure 1. Structure of the two complex molecules in **1a**.

ment by binding of a water or methanol ligand. The bond lengths and angles in the central coordination unit all show values which could be expected for the named geometries. The different coordination of solvent molecules to the two copper atoms gives a hint that possible substrate molecules might be bound to the copper centers in an unsymmetrical way. Crystals of **1b** were obtained from toluene and are of lower quality, so that only the structural motive could be determined. It shows the presence of symmetric dinuclear complexes without axial ligands.

Investigation of the magnetic properties of **1a** shows diamagnetism over the whole temperature region of 4–300 K, caused by a very strong antiferromagnetic coupling.

This coupling is less strong in **1b**. At room temperature the remaining paramagnetism and the diamagnetism of the sample compensate, so that no resulting susceptibility can be measured. Compound **1b** is EPR-silent but, as a result of the remaining paramagnetism, shows no NMR spectrum which can be interpreted, except for the signals of the peripheral methyl groups. Such strong antiferromagnetic coupling is also characteristic of copper complexes of Schiff bases of 3-aminopropanol.^[5–7] This is in contrast to the weak or even lacking coupling in complexes derived from Schiff bases of 2-aminoethanol^[5, 8–16] or 2-aminoglucose.^[28]

Complex **2**^[31] shows a trinuclear structure (Figure 2) which can formally be interpreted by an insertion of a copper acetate monomer in a dinuclear compound similar to **1a**. At a first

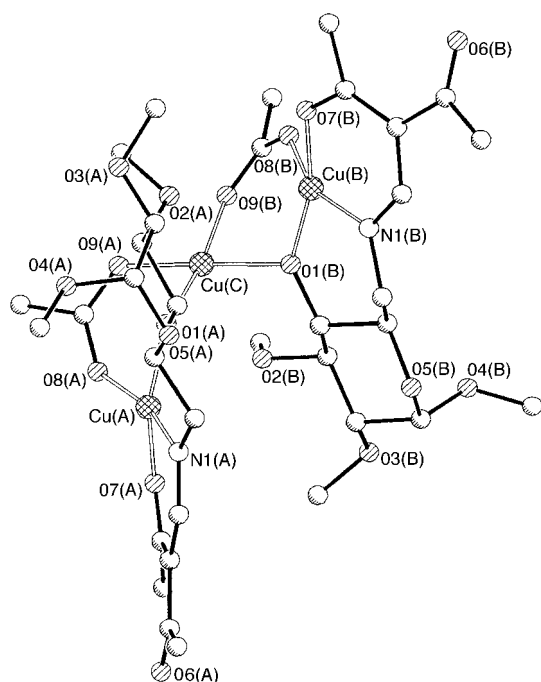


Figure 2. Structure of the copper complex **2**.

glance, a distorted square planar environment is found for all three copper atoms in the trimer. By intermolecular, chain-type binding of the peripheral oxygen atoms of neighboring molecules with Cu(A), a square-pyramidal coordination of Cu(A) results, in which the central atom is moved 0.046(3) Å out of the base plane. At the two other copper atoms the methoxy oxygen atoms in the 3-position of the ligand serve as axial ligands; Cu(B) (with O2(A)) reaches a distorted square pyramidal geometry, and Cu(C) (with O2(A) and O2(B)) a distorted octahedral geometry. The additional donor atoms allow, by addition of a third copper atom to two building blocks of type **1**, a rarely observed trinuclear structure. With all three copper atoms having different axial ligands, **2** shows—like **1a**—a strikingly low symmetry. Even the copper–copper distances between Cu(C) and its neighbors differ significantly (3.248(3) and 3.207(3) Å). Nevertheless, both values are within a range known for such complexes, in which two metal atoms are bridged by a catechol ligand. This is a remarkable parallel to the oxidases named above.

The effective magnetic moment of **2** at room temperature is $2.71 \mu_B$ (Figure 3). The temperature-dependant measurement showed an antiferromagnetic coupling, by which the para-

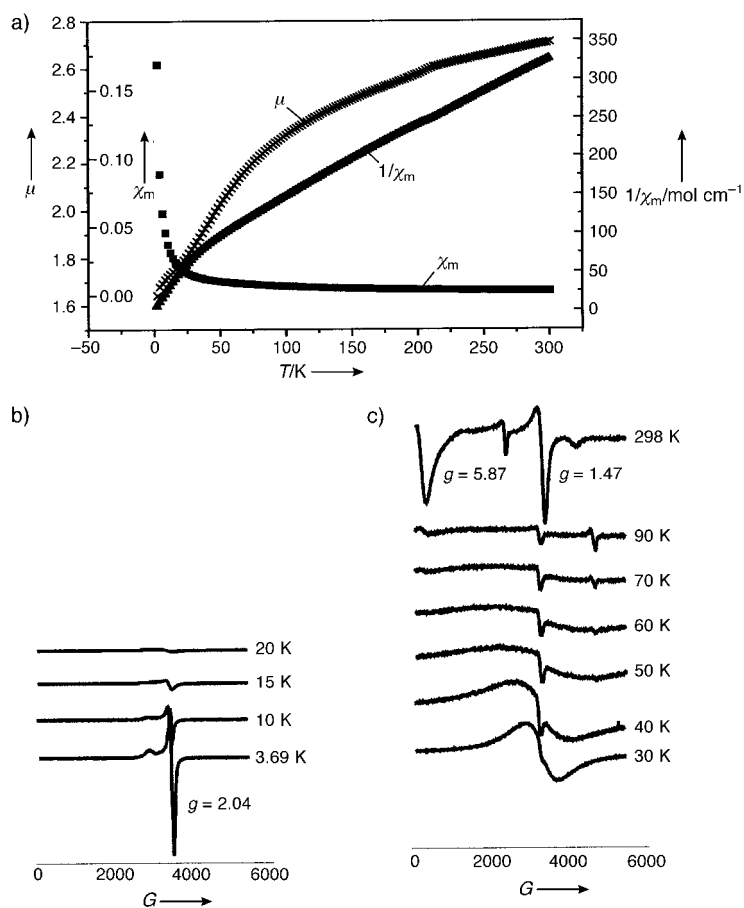


Figure 3. a) Magnetic behavior (χ_m vs. T (■), χ_m^{-1} vs. T (▲), and magnetic moment μ vs. T (x)) and b), c) EPR spectra (right: $\times 20$ for $T > 30$ K) of **2**.

magnetism at 2 K is decreased to $1.64 \mu_B$. This is close to the spin-only value of a $S = \frac{1}{2}$ ground state. The EPR spectrum can be described as a signal for $S = \frac{1}{2}$ at $g = 2.04$ and two signals of a paramagnet with $S = 1$ at $g = 1.47$ and 5.87 . Whereas the latter signals decrease in intensity with decreasing temperature, the signal for the doublet state grows stronger and obeys a Boltzmann distribution. Therefore, it can be assumed that two copper atoms in **2** are coupled antiferromagnetically, while the third one is not involved in coupling interactions. Taking this into regard, fitting of the measured data results in a coupling constant J of -309 cm^{-1} , which underlines the observed strong coupling.^[5–7]

The structures of **1a**, **b** and **2** contain elements which are found in different metalloenzymes, for example the 1,3-bridging of two metal atoms by an acetate and by an alcoholate, as in **2**. The double alcoholate bridge in **1a,b** is reminiscent of catechol oxidase^[1] and other oxidases and oxygenases with copper centers. Owing to their low symmetry, the oligonuclear building blocks in **1a** and **2** might be of some importance for catalytic reactions.

Indeed, both compounds catalyze the oxidation of 3,5-di-*tert*-butylcatechol (dtbc) with oxygen [Eq. (1)].^[32] Figure 4

shows the time-dependent difference spectra for the reaction of a 10^{-4} M solution of **1a** with 50 equivalents of dtbc. The

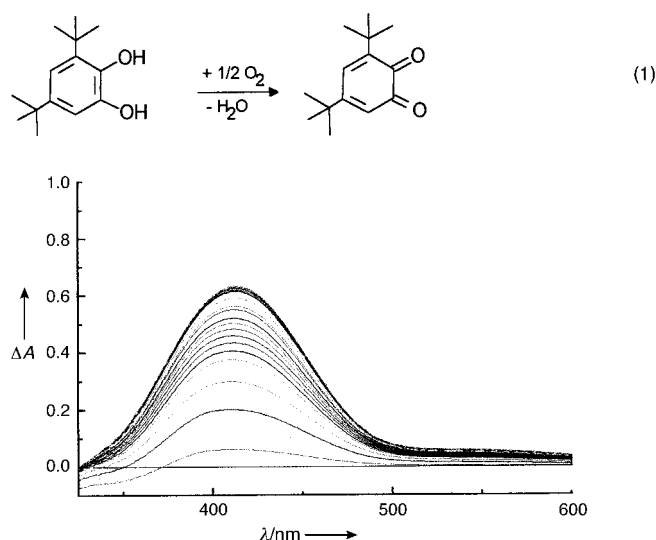


Figure 4. Difference spectrophotometric analysis of the oxidation of dtbc catalyzed by **1a**.

kinetic investigations were carried out as described in the literature.^[32] With regard to the catalyst, a first-order reaction was determined for each reaction; with regard to the substrate, saturation kinetics was observed in both cases. Interpretation of the data with the Michaelis–Menten model leads to rate constants k_{cat} of 2.8(3) and 135(5) h^{-1} for **1a** and **2**, respectively. Therefore, especially **2** is an efficient catalyst.

Experimental Section

General synthesis of bis[1,2-*O*-isopropylidene-5-deoxy-5-*N*-(3-acetylbut-3-en-2-on-4-yl)aminoglucufuranosidato]aquadecopper(II)-bis[1,2-*O*-isopropylidene-5-deoxy-5-*N*-(3-acetylbut-3-en-2-on-4-yl)aminoglucufuranosidato-methanolato]dicopper(II) · 4 H₂O (**1a**), bis[1,2-*O*-isopropylidene-5-deoxy-5-*N*-(3-acetylbut-3-en-2-on-4-yl)aminoglucufuranosidato]dicopper(II) · *n* C₇H₈ (**1b**), and bis[1,2,3-*O*-trimethyl-6-deoxy-6-*N*-(3-acetylbut-3-en-2-on-4-yl)aminoglucosidato]bis(μ-acetato)tricopper(II) (**2**): 5-Amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucufuranoside^[29] or 6-amino-6-deoxy-1,2,3-*O*-trimethyl-α-D-glucopyranoside^[29] (0.5 mmol) was dissolved in methanol (**1a**, **b**: 15 mL; **2**: 10 mL). Triethylamine (202 mg, 2 mmol) and 3-ethoxymethylene-2,4-pentandione (78 mg, 0.5 mmol) were added dropwise. This leads to the ligands **II** and **III**. After the mixture was stirred for 1 h, copper acetate monohydrate (**1a**, **b**: 91 mg, 0.5 mmol; **2**: 136 mg, 0.75 mmol) was added. The reaction mixture was left to stand overnight, and then the solvent was evaporated.

Isolation of **1a**, **b**: The residue was taken up in toluene. Upon slow evaporation of the solvent, crystallization of **1b** occurs. Recrystallization of **1b** from water/methanol (1/1) leads to the precipitation of **1a**.

Isolation of **2**: The residue was taken up in diethyl ether. Upon slow evaporation of the solvent, blue crystals of **2** can be obtained.

Received: July 12, 1999 [Z13708]

- [1] T. Klabunde, C. Eicken, J. C. Sacchetti, B. Krebs, *Nature Struct. Biol.* **1998**, 5, 1084–1090.
- [2] A. Messerschmidt, *Metal Sites Proteins Models* **1998**, 90, 37–68.
- [3] R. Than, A. A. Feldmann, B. Krebs, *Coord. Chem. Rev.* **1999**, 182, 211–241.
- [4] a) E.-G. Jäger, *Z. Chem.* **1966**, 6, 111–112; b) H. Elias, D. Hess, H. Paulus, E.-G. Jäger, F. Gräfe, *Z. Anorg. Allg. Chem.* **1990**, 589, 101–114.

- [5] a) J. J. Bertrand, J. A. Kelley, C. E. Kirkwood, *Chem. Commun.* **1968**, 1329–1331; b) J. A. Bertrand, J. A. Kelley, *Inorg. Chim. Acta* **1970**, 4, 203–209; c) J. A. Bertrand, J. A. Kelley, J. L. Breece, *Inorg. Chim. Acta* **1970**, 4, 247–250; d) J. A. Bertrand, C. Marabella, D. G. Vanderveer, *Inorg. Chim. Acta* **1978**, 26, 113–119.
- [6] a) E. Sinn, *Inorg. Chem.* **1976**, 15, 358–365; b) J. A. Davis, E. Sinn, *J. Chem. Soc. Dalton Trans.* **1976**, 165–170.
- [7] a) N. Matsumoto, T. Tsutsumi, A. Ohyoshi, H. Okawa, *Bull. Chem. Soc. Jpn.* **1983**, 56, 1386–1392; b) N. Matsumoto, I. Ueda, Y. Nishida, S. Kida, *Bull. Chem. Soc. Jpn.* **1976**, 49, 1308–1312; c) N. Matsumoto, T. Kondo, M. Kodera, H. Okawa, S. Kida, *Bull. Chem. Soc. Jpn.* **1989**, 62, 4041–4043.
- [8] F. Wiesemann, B. Krebs, H. Görls, E.-G. Jäger, *Z. Anorg. Allg. Chem.* **1995**, 621, 1883–1892.
- [9] a) W. Haase, *Chem. Ber.* **1973**, 106, 3132–3148; b) L. Merz, W. Haase, *J. Chem. Soc. Dalton Trans.* **1978**, 1594–1598; c) L. Merz, W. Haase, *J. Chem. Soc. Dalton Trans.* **1980**, 875–879; d) R. Mergehenn, L. Merz, W. Haase, *J. Chem. Soc. Dalton Trans.* **1980**, 1703–1709; e) L. Walz, H. Paulus, W. Haase, H. Langhof, F. Nepveu, *J. Chem. Soc. Dalton Trans.* **1983**, 657–664; f) L. Schwabe, W. Haase, *J. Chem. Soc. Dalton Trans.* **1985**, 1909–1913; g) H. Astheimer, F. Nepveu, L. Walz, W. Haase, *J. Chem. Soc. Dalton Trans.* **1985**, 315–320.
- [10] H. Oshio, Y. Saito, T. Ito, *Angew. Chem.* **1997**, 122, 2789–2791; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2673–2675.
- [11] Yu. M. Chumakov, V. N. Biyushkin, T. I. Malinovskii, S. Kulemu, V. I. Tsapkov, M. S. Popov, N. M. Samus, *Koord. Khim.* **1990**, 16, 945–949.
- [12] a) V. Tangoulis, S. Paschalidou, E. G. Bakalbassis, S. P. Perlepes, C. P. Raptopoulou, A. Terzis, *Chem. Commun.* **1996**, 1297–1298; b) V. Tangoulis, C. P. Raptopoulou, A. Terzis, S. Paschalidou, S. P. Perlepes, E. G. Bakalbassis, *Inorg. Chem.* **1997**, 36, 3996–4006.
- [13] G. A. van Albada, J. Reedijk, R. Hamalainen, U. Turpeinen, A. L. Spek, *Inorg. Chim. Acta* **1989**, 163, 213–217.
- [14] P. L. Dedert, T. Sorrell, T. J. Marks, J. A. Ibers, *Inorg. Chem.* **1982**, 21, 3506–3517.
- [15] a) H. Muhonen, *Acta Chem. Scand. Ser. A* **1980**, 34, 79; b) H. Muhonen, W. E. Hatfield, J. H. Helms, *Inorg. Chem.* **1986**, 25, 800–812.
- [16] J. Sassmannshausen, H. F. von Schnering, L. Walz, *Z. Kristallogr.* **1997**, 212, 656–661.
- [17] a) E.-G. Jäger, K. Müller, *Z. Anorg. Allg. Chem.* **1981**, 482, 201–216; b) E.-G. Jäger, K. Schuhmann, H. Görls, *Chem. Ber.* **1997**, 130, 1643–1646.
- [18] D. Klemm, T. Heinze, B. Philipp, W. Wagenknecht, *Acta Polym.* **1977**, 48, 277–297.
- [19] D. Klemm, B. Philipp, T. Heinze, U. Heinze, W. Wagenknecht, *Comprehensive Cellulose Chemistry, Vols. 1 and 2*, Wiley-VCH, Weinheim, **1998**.
- [20] J. Tiller, P. Berlin, D. Klemm, *Macromol. Chem. Phys.* **1999**, 200, 1–9.
- [21] D. N. Williams, U. Piarulli, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *J. Chem. Soc. Dalton Trans.* **1994**, 1243–1250.
- [22] a) P. Klüfers, H. Piotrowski, J. Uhlendorf, *Chem. Eur. J.* **1997**, 3, 601–608; b) H. P. Wu, C. Janiak, P. Klüfers, P. Mayer, *Chem. Commun.* **1998**, 2637–2638; c) P. Mayer, P. Klüfers, *Acta Crystallogr. Sect. C* **1998**, 54, 583–586; d) R. Ahlrichs, B. Ballauf, K. Eichkorn, O. Hanemann, G. Kettenbach, P. Klüfers, *Chem. Eur. J.* **1998**, 4, 835–844; e) A. Geisselmann, P. Klüfers, B. Pilawa, *Angew. Chem.* **1998**, 123, 1181–1184; *Angew. Chem. Int. Ed.* **1998**, 37, 1119–1121; f) J. Bürger, P. Klüfers, *Z. Anorg. Allg. Chem.* **1998**, 624, 359–360.
- [23] a) S. Yano, *Coord. Chem. Rev.* **1988**, 92, 113–156; b) S. Yano, M. Doi, S. Tamakoshi, W. Mori, M. Mikuriya, A. Ichimura, I. Kinoshita, Y. Yamamoto, T. Tanase, *Chem. Commun.* **1997**, 997–998; c) S. Yano, S. Inoue, R. Nouchi, M. Reiko, S. Kaoru, Y. Yoshie, Y. Yasuda, M. Kato, T. Tanase, T. Kakuchi, Y. Mikata, T. Suzuki, Y. Yamamoto, *J. Inorg. Biochem.* **1998**, 69, 15–23; d) T. Tanase, T. Onaka, M. Hakagoshi, I. Kinoshita, S. Shibata, M. Doe, J. Fujii, S. Yano, *Chem. Commun.* **1997**, 2115–2116; e) T. Tsubomura, M. Ogawa, S. Yano, K. Kobayashi, T. Sakurai, S. Yoshikawa, *Inorg. Chem.* **1990**, 29, 2622–2626.
- [24] Y. Zhou, B. Wagner, K. Polborn, K. Sunkel, W. Beck, *Z. Naturforsch. B* **1994**, 49, 1193–1202.
- [25] J. M. Harrowfield, M. Mocerino, B. W. Skelton, W. Wei, A. H. White, *J. Chem. Soc. Dalton Trans.* **1995**, 783–797.
- [26] a) A. Bernalte-Garcia, M. A. Diaz-Diez, F. J. Garcia-Barros, F. J. Higes-Rolando, C. Valenzuela-Calahorra, *Trans. Met. Chem.* **1996**, 21,

Simple Synthesis of a Chlorin–Fullerene Dyad with a Novel Ring-Closure Reaction**

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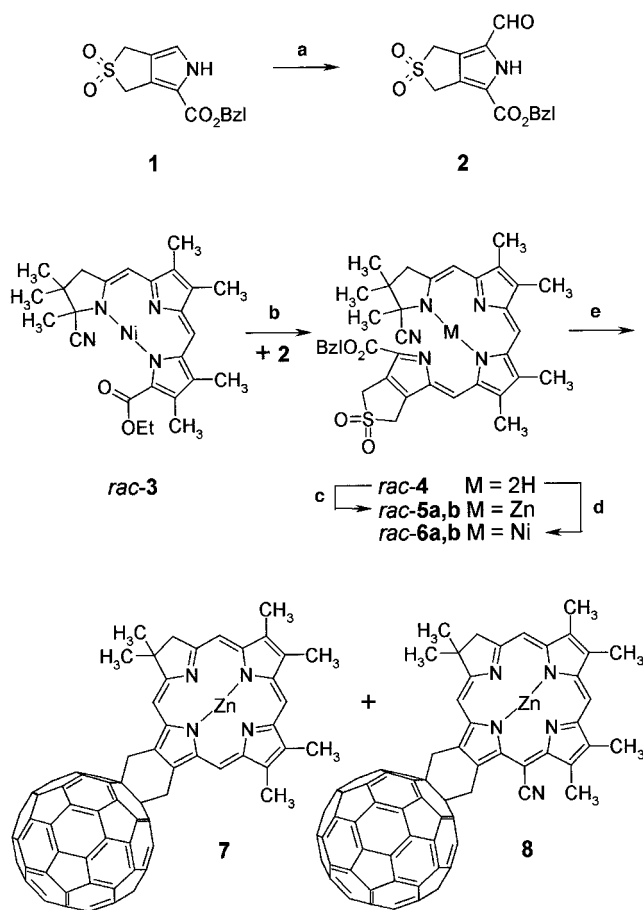
Amongst the covalent functionalizations of buckminster fullerene C₆₀,^[1] the linkage to porphyrins has opened the possibility of constructing artificial photosynthetic systems^[2] in which there is light-induced transfer of electrons or energy from a porphyrin donor to a fullerene acceptor. Apart from one example in which a derivative of naturally occurring chlorophyll was attached to a fullerene by [2+3] cycloaddition,^[3] all known fullerene-based photosynthetic models contain completely unsaturated porphyrins and phthalocyanines as the donor unit;^[4] they are usually linked to C₆₀ by long ether or ester bridges.^[5] We report here on the total synthesis of a dyad that contains fullerene C₆₀ bound to a chlorin by two methylene bridges and thus at a very small distance. The dyad, which is synthesized in an unusual one-pot reaction with concomitant formation of the chlorin macrocycle and linkage to the fullerene, is the first of this type that contains a chlorin moiety which is the chromophore in naturally occurring photosynthetic systems.

The starting point for the synthesis was the tripyrrolenickel complex *rac-3* (Scheme 1); we have already employed this complex in the synthesis of chlorins^[6] and corrins.^[7] After hydrolysis of the ester group in *rac-3*, the pyrrole aldehyde **2** was linked to tricyclic *rac-3* by decarboxylation and decarboxylation. Subsequent recomplexation with zinc(II) or nickel(II) acetate gave the tetrapyrrolemetal complexes *rac-5a, b* and *rac-6a, b*. The robust nickel complex *rac-6a, b* was produced in order to characterize the tetracyclic compound. It was obtained as a separable binary mixture of diastereomers on account of the chiral center at C-1 and because of the helicity of the chromophore in the complex. The labile linear tetrapyrrolezinc complex *rac-5a, b* was cyclized upon heating in the presence of C₆₀ to give the chlorin–fullerene dyad **7** along with the 15-cyano-substituted dyadic system **8** as a side product. This one-pot reaction is a complex cascade of single steps, the exact sequence of which has not yet been determined; however, it involves 1) loss of cyanide and formation of an enamine double bond at C-1, 2) cyclization between C-19 and the enamino double bond under the templating influence of the central zinc ion, 3) decarboxylation, 4) oxidation of the initially formed dihydrochlorin with atmospheric oxygen, 5) extrusion of sulfur dioxide, and finally 6) a Diels–Alder reaction between the diene formed and C₆₀ as the dienophile to yield dyad **7**. The 15-cyano-

- 197–199; b) M. A. Diaz-Diez, F. J. Garcia-Barros, F. J. Higes-Rolando, A. Bernalte-Garcia, C. Valenzuela-Calahorra, *Trans. Met. Chem.* **1995**, *20*, 402–405; c) M. A. Diaz-Diez, F. J. Garcia-Barros, F. J. Higes-Rolando, A. Bernalte-Garcia, C. Valenzuela-Calahorra, *Polyhedron* **1993**, *12*, 2519–2523.
- [27] a) K. Hegetschweiler, M. Weber, V. Huch, R. J. Geue, A. D. Rae, A. C. Willis, A. M. Sargeson, *Inorg. Chem.* **1998**, *37*, 6136–6146; b) G. J. Reiss, W. Frank, K. Hegetschweiler, D. Kuppert, *Acta Crystallogr. Sect. C* **1998**, *54*, 614–616; c) L. Hausherr-Primo, K. Hegetschweiler, H. Ruegger, L. Odier, R. D. Hancock, H. W. Schmalte, V. Gramlich, *J. Chem. Soc. Dalton Trans.* **1994**, 1689–1701.
- [28] E.-G. Jäger, R. Wegner, H. Görls, D. Klemm, M. Gottschaldt, unpublished results.
- [29] Synthesis: K. Dax, B. Gaigg, V. Grassberger, B. Kölbinger, A. E. Stütz, *J. Carbohydr. Chem.* **1990**, *9*, 479–499; B. P. Bashlyk, H. F. Chow, L. E. Fellows, G. W. J. Fleet, *Tetrahedron* **1987**, *43*, 415.
- [30] Crystal data for **1a**: C₃₀H₄₂Cu₂N₂O₁₄·1.75 H₂O·0.5 CH₃OH, *M*_r = 837.79, blue prisms, crystal size 0.28 × 0.24 × 0.20 mm³, monoclinic, space group *P*2₁, *a* = 10.3923(3), *b* = 13.8859(5), *c* = 25.9903(8) Å, β = 101.517(2)°, *V* = 3675.1(2) Å³, *T* = –90 °C, *Z* = 4, ρ_{calcd} = 1.514 g cm^{–3}, μ(MoKα) = 12.33 cm^{–1}, *F*(000) = 1748; a total of 15 126 reflections up to *h*(0/14), *k*(–19/19), *l*(–25/27) in the range 2.30° ≤ θ ≤ 30.52° (completeness of data θ_{max} = 78.2%), of which 14 812 were symmetry-independent (*R*_{int} = 0.0410) and 11 657 observed with *F*_o > 4σ(*F*_o), 933 parameters, 1 restraint, *R*₁_{obs} = 0.081, *wR*₂_{obs} = 0.141, *R*₁_{all} = 0.1106, *wR*₂_{all} = 0.1533, GOF = 1.095, Flack parameter 0.35(1) (racemic twin), max./min. residual electron density 0.646/–0.695 e Å^{–3}. Distances [Å] and angles [°]: Cu(A)···Cu(B) 2.977(1), Cu(A)/Cu(B)–O/N 1.893(5)–1.956(5), Cu(A)–O8(A) 2.382(5); O/N–Cu–O/N 76.1(2)–102.1(2) and 166.6(2)–173.8(2), Cu(C)···Cu(D) 3.020(1), Cu(C)/Cu(D)–O/N 1.918(5), Cu(C)–O(4) 2.674(5), O/N–Cu–O/N 75.9(2)–107.6(2) and 166.7(2)–176.1(2).^[31b]
- [31] a) Crystal data for **2**: C₃₄H₃₂Cu₂N₂O₁₈, *M*_r = 967.40, blue prisms, crystal size 0.32 × 0.30 × 0.20 mm³, monoclinic, space group *P*2₁, *a* = 10.0735(3), *b* = 21.3865(7), *c* = 10.4135(2) Å, β = 110.789(1)°, *V* = 2097.4(1) Å³, *T* = –90 °C, *Z* = 2, ρ_{calcd} = 1.532 g cm^{–3}, μ(MoKα) = 15.82 cm^{–1}, *F*(000) = 1002; a total of 6973 reflections up to *h*(–12/12), *k*(–20/26), *l*(–12/13) in the region 5.19° ≤ θ ≤ 26.37° (completeness of data θ_{max} = 98.7%), of which 6973 were symmetry-independent (*R*_{int} = 0.035) and 6127 observed with *F*_o > 4σ(*F*_o); 514 parameters, 1 restraint, *R*₁_{obs} = 0.039, *wR*₂_{obs} = 0.087, *R*₁_{all} = 0.050, *wR*₂_{all} = 0.094, GOF = 1.029, Flack parameter 0.01(1), max./min. residual electron density 0.257/–0.355 e Å^{–3}. Distances [Å] and angles [°]: Cu(A)···Cu(B) 5.735(3), Cu(A)···Cu(C) 3.248(3), Cu(B)···Cu(C) 3.207(3), Cu–O/N 1.940(4), Cu(A)···O6(B) (symmetry operation for equivalent atoms: –*x*, 0.5 + *y*, –*z*) 2.753(4), Cu(B)···O2(A) 2.898(4), Cu(C)–O2(A) 2.586(4), Cu(C)–O2(B) 2.572(4); O1(A)–Cu(A)–N1(A) 95.6(1), O/N–Cu–O/N 73.6(1)–106.9(1) and 152.0(1)–172.3(1). b) Crystallographic Data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-129253 (**1a**) and -129254 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [32] General remarks on the kinetic investigations: The measurements were carried out as described in J. Reim, B. Krebs, *J. Chem. Soc. Dalton Trans.* **1997**, 3793–3804. For qualitative testing of the catalytic activities, 10^{–4} M solutions of the copper complexes in methanol were mixed with 50 equivalents of dtcb. The reaction with oxygen was monitored by observing the absorption of the quinone at 400 nm against a solution of the pure complex with the same concentration by means of UV/Vis spectroscopy (VARIAN-Spectrophotometer Cary 5). As reference for the catalytic reaction, a 10^{–4} M solution of copper acetate monohydrate was used, which shows a significant lower activity (*k* < 1.5 h^{–1}). The given rate constants are mean values of three measurements with a discrepancy value of the Lineweaver–Burk plot of *r* ≥ 0.992.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds des Verbandes der Chemischen Industrie in the form of a doctoral grant for O.K. We thank Dr. Mayer-Posner, Bruker-Daltonik GmbH, for recording the MALDI-TOF mass spectra and the Hoechst AG for their donation of fullerene.



Scheme 1. Synthesis of the chlorin–fullerene dyad **7**. a) POCl₃, DMF, 90 °C, 1 h (73 %); b) 1.) 5 N KOH, MeOH/H₂O (9/1), THF, reflux, 45 min; 2.) **2** (1.8 equiv), *p*-TsOH, CHCl₃, reflux, 30 min; c) Zn(OAc)₂, NaOAc, room temperature, 20 min, chromatography, *rac*-**5a, b** (74 % based on *rac*-**3**); d) Ni(OAc)₂·4H₂O, NaOAc, room temperature, 20 min, chromatography, *rac*-**6a** (39 % based on *rac*-**3**), *rac*-**6b** (37 % based on *rac*-**3**); e) *rac*-**5a, b**, C₆₀ (2.6 equiv), 1,2,4-trichlorobenzene, 220 °C, 30 min, chromatography, **7** (32 %), **8** (4 %).

substituted side product **8** may be formed by the addition of cyanide to an intermediate dihydrochlorin.

Despite the complex course of reaction and the drastic reaction conditions, the total yield of 32 % is remarkably high. The average yield for the individual steps is 83 %. With regard to the synthesis of different chlorins, the cyclization method described here is considerably simpler than those previously reported.^[6]

The corresponding ethyl ester of pyrrole **1**,^[8] which serves as the starting material for the aldehyde building block **2**, cannot be formulated with a canonical diene structure, in contrast to the macrotetraene after the release of sulfur dioxide. Nevertheless it readily reacts with C₆₀ to give the corresponding Diels–Alder adduct **10**.

The luminescence spectra (Figure 1) of the chlorin–fullerene dyad **7** and the bare chlorin **9** were compared after excitation at the wavelength of the Soret band (401 and 395 nm, respectively). The fullerene acceptor in **7** quenched the luminescence, whereas luminescence was observed for **9**. The quenching of the luminescence was independent of the concentration of dyad **7**, which indicates an intramolecular

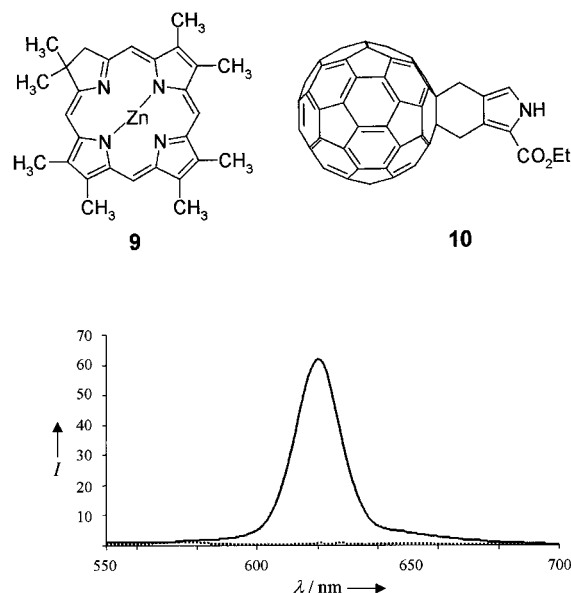


Figure 1. Fluorescence spectra of **7** (•••) and **9** (—) in CHCl₃ (*c* = 10^{−6} M) after excitation at the individual Soret bands (401 and 395 nm, respectively).

transfer of electrons or energy from the chlorin moiety to the fullerene moiety.

Experimental Section

Selected spectroscopic data:

rac-**6a**: ¹H NMR (200 MHz, CDCl₃): δ = 0.59, 0.79, 0.92 (3 s, 3 × 3 H, 3 CH₃ at C-1 and C-2), 2.26 (d, ⁵*J* = 0.77 Hz, 3 H), 2.28 (s, 6 H), 2.40 (d, ⁵*J* = 0.73 Hz, 3 H) (2.26–2.40: 4 CH₃ at C-7, C-8, C-12, and C-13), 2.53, 2.63 (AB system, ²*J*_{AB} = 16.72 Hz, 2 H, 3-CH₂), 4.33, 4.49 (AB system, ²*J*_{AB} = 15.77 Hz, 2 H, CH₂SO₂), 4.39, 4.48 (AB system, ²*J*_{AB} = 14.88 Hz, 2 H, CH₂SO₂), 5.02, 5.27 (AB system, ²*J*_{AB} = 12.37 Hz, 2 H, benzylester CH₂), 6.30, 6.70, 7.08 (3 s, 3 × 1 H, 5-H, 10-H, 15-H), 7.30 (m, 5 H, Ph).

rac-**6b**: ¹H NMR (200 MHz, CDCl₃): δ = 0.56, 1.09, 1.42 (3 s, 3 × 3 H, 3 CH₃ at C-1 and C-2), 2.23 (d, ⁵*J* = 0.85 Hz, 3 H), 2.26 (s, 6 H), 2.35 (d, ⁵*J* = 0.71 Hz, 3 H) (2.23–2.35: 4 CH₃ at C-7, C-8, C-12, and C-13), 2.35, 2.77 (AB system, ²*J*_{AB} = 15.66 Hz, 2 H, 3-CH₂), 4.32, 4.46 (AB system, ²*J*_{AB} = 15.71 Hz, 2 H, CH₂SO₂), 4.39, 4.48 (AB system, ²*J*_{AB} = 14.84 Hz, 2 H, CH₂SO₂), 5.14, 5.26 (AB system, ²*J*_{AB} = 12.44 Hz, 2 H, benzylester-CH₂), 6.18, 6.62, 6.99 (3 s, 3 × 1 H, 5-H, 10-H, 15-H), 7.26–7.30 (m, 5 H, Ph).

7: *rac*-**5a, b** (5.0 mg, 7.0 μmol) and C₆₀ (13.3 mg, 18.46 μmol, 2.63 equiv) were dissolved in 1,2,4-trichlorobenzene (5 mL). The mixture was boiled for 30 min with a bath temperature of 220 °C under argon and the solvent then removed in a bulb tube at 60 °C in a high vacuum. The residue was purified by chromatography on alumina (60 mL, neutral, activity II–III) with toluene to remove the unchanged C₆₀ and then with dichloromethane/ethyl acetate (19/1). Isothermal recrystallization from dichloromethane/*n*-pentane gave **7**. Yield: 2.7 mg (2.24 μmol, 31.92 %). ¹H NMR (200 MHz, CDCl₃): δ = 2.07 (s, 6 H, 2 CH₃ at C-2), 3.25, 3.35, 3.41 (3 s, 12 H, 4 CH₃ at C-7, C-8, C-12, and C-13), 4.57 (m, 2 H, CH₂, C-3), 5.68, 5.74 (2 s, 2 × 2 H, 2 CH₂ at C-17 and C-18), 8.68, 8.83, 9.47, 9.82 (4 s, 4 × 1 H, H-5, H-10, H-15, H-20); UV/Vis (CHCl₃): λ_{max} (lg ε) = 705 (extremely weak), 622 (4.29), 580 (3.90, plateau), 401 (4.69), 304 (4.44, sh), 257 (4.62); MS (MALDI-TOF, 9-nitroanthracene): *m/z* (%): 1204 (35) [*M*⁺], 484 (100) [*M*⁺ − C₆₀].

8: Selected spectroscopic data: UV/Vis (CHCl₃): λ_{max} (lg ε) = 658 (4.20), 620 (3.42, plateau), 521 (3.29), 419 (4.45), 410 (4.41, sh), 311 (4.17, sh), 257 (4.52); MS (MALDI-TOF, 9-nitroanthracene): *m/z* (%): 1229 (22) [*M*⁺], 509 (100) [*M*⁺ − C₆₀].

Received: July 22, 1999 [Z13763]

- [1] A. Hirsch, *The Chemistry of the Fullerenes*, Thieme, Stuttgart, **1994**.
 [2] a) D. Gust, T. A. Moore in *Topics in Current Chemistry*, Vol. 159, *Photoinduced Electron Transfer III* (Ed.: J. Mattay), Springer, Berlin, **1991**, pp. 103–151; b) M. R. Wasielewski, *Chem. Rev.* **1992**, 92, 435–461; c) J. Deisenhofer, J. R. Norris, *The Photosynthetic Reaction Center*, Academic Press, San Diego, **1993**; d) H. Kurreck, M. Huber, *Angew. Chem.* **1995**, 107, 929–947; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 849–867.
 [3] a) J. Helaja, A. Y. Tauber, Y. Abel, N. V. Tkachenko, H. Lemmetyinen, I. Kilpeläinen, P. H. Hynninen, *J. Chem. Soc. Perkin Trans. I* **1999**, 2403–2408; b) N. V. Tkachenko, L. Rantala, A. Y. Tauber, J. Helaja, P. H. Hynninen, H. Lemmetyinen, *J. Am. Chem. Soc.* **1999**, 121, 9378–9387.
 [4] a) T. G. Linssen, K. Dürr, M. Hanack, A. Hirsch, *J. Chem. Soc. Chem. Commun.* **1995**, 103–104; b) T. Drovetskaya, C. A. Reed, P. D. W. Boyd, *Tetrahedron Lett.* **1995**, 36, 7971–7974; c) D. Kuciauskas, S. Lin, G. R. Seely, A. L. Moore, T. A. Moore, D. Gust, T. Drovetskaya, C. A. Reed, P. Boyd, *J. Phys. Chem.* **1996**, 100, 15926–15932; d) E. Dietel, A. Hirsch, E. Eichhorn, A. Rieker, S. Hackbarth, B. Röder, *J. Chem. Soc. Chem. Commun.* **1998**, 1981–1982; e) A. C. Tomé, R. F. Enes, J. P. C. Tomé, J. Rocha, M. G. P. M. S. Neves, J. A. S. Cavaleiro, J. Elguero, *Tetrahedron* **1998**, 54, 11141–11150; f) P. Cheng, S. R. Wilson, D. I. Schuster, *J. Chem. Soc. Chem. Commun.* **1999**, 89–90; g) N. Armaroli, F. Diederich, L. Echegoyen, T. Habicher, L. Flamigni, G. Marconi, J.-F. Nierengarten, *New J. Chem.* **1999**, 77–84.
 [5] a) H. Imahori, Y. Sakata, *Adv. Mater.* **1997**, 9, 537–546; b) D. Gust, T. A. Moore, A. L. Moore, *Res. Chem. Intermed.* **1997**, 23, 621–651; c) N. Martín, L. Sánchez, B. Illescas, I. Pérez, *Chem. Rev.* **1998**, 98, 2527–2547; d) F. Diederich, R. Kessinger, *Acc. Chem. Res.* **1999**, 32, 537–545.
 [6] a) F.-P. Montforts, *Angew. Chem.* **1981**, 93, 795–796; *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 778–779; b) F.-P. Montforts, U. M. Schwartz, *Liebigs Ann. Chem.* **1985**, 1228–1253; c) F.-P. Montforts, B. Gerlach, F. Höper, *Chem. Rev.* **1994**, 94, 327–347; d) F.-P. Montforts, M. Glase-napp-Breiling in *Progress in Heterocyclic Chemistry*, Vol. 10 (Eds.: G. W. Gribble, T. L. Gilchrist), Pergamon, Oxford, **1998**, pp. 1–24.
 [7] a) F.-P. Montforts, *Angew. Chem.* **1982**, 94, 208–209; *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 214–215; *Angew. Chem. Suppl.* **1982**, 499–505; b) F.-P. Montforts, J. W. Bats, *Helv. Chim. Acta* **1987**, 70, 402–411.
 [8] a) Y. Abel, E. Haake, G. Haake, W. Schmidt, D. Struve, A. Walter, F.-P. Montforts, *Helv. Chim. Acta* **1998**, 81, 1978–1996; b) G. Haake, D. Struve, F.-P. Montforts, *Tetrahedron Lett.* **1994**, 35, 9703–9704.

The First Crystal Structure of a Germanium(II) Amide with a Germanium–Lithium Bond and Its Behavior Towards Oxygen and Water**

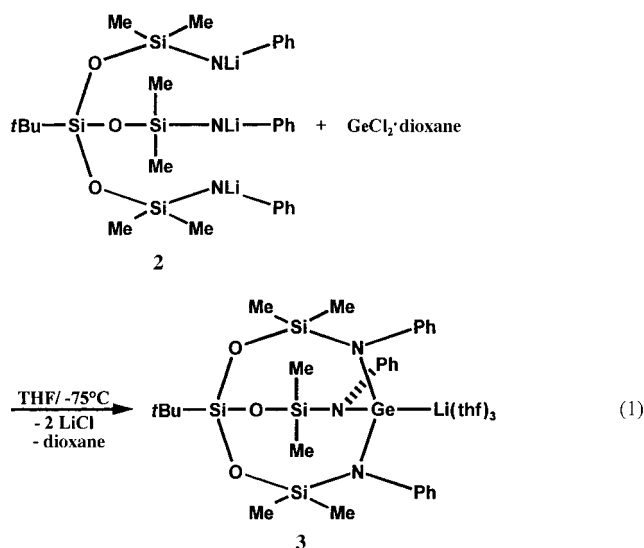
Michael Veith,* Oliver Schütt, and Volker Huch

Dedicated to Professor Gerhard Fritz
on the occasion of his 80th birthday

Amides of Group 4 metals that contain metal–lithium bonds are relatively rare. A few years ago, Gade et al. reported the crystal structure of a tripodal silyl amide with a

tin(II)–lithium bond.^[1] A mixed germanium–lithium amide was also synthesized;^[2] however, the structure of this compound could not be determined by X-ray structure analysis. In recent years only a few compounds containing germanium–lithium bonds have been synthesized and characterized by X-ray crystallography.^[3–5] Very little is known about the chemistry of these compounds. We report here on the synthesis and crystal structure of a tripodal germanium(II) siloxamide with a germanium–lithium bond as well as on the reaction behavior of this bond towards water and oxygen. Interestingly, these reactions led to a simple Li/H exchange and an insertion of an oxygen atom into the germanium–lithium bond, respectively. We were able to isolate the reaction products from the hydrolysis and the oxidation and determine the structure of these compounds by X-ray crystallography.

The ligand system used was the tripodal amine *t*BuSi(Me)₂NHPh (**1**);^[6] its lithium salt **2**^[6] was taken as the starting material for the synthesis of the germanium(II) siloxamide **3**. Compound **2** reacted with an adduct of germanium (II) chloride and dioxane^[7] (equimolar amounts with respect to **2**) in THF at –75 °C to give the heterometallic amide **3** in good yields [Eq. (1)]. The ¹H, ¹³C, ²⁹Si, and ⁷Li NMR spectra of **3** in

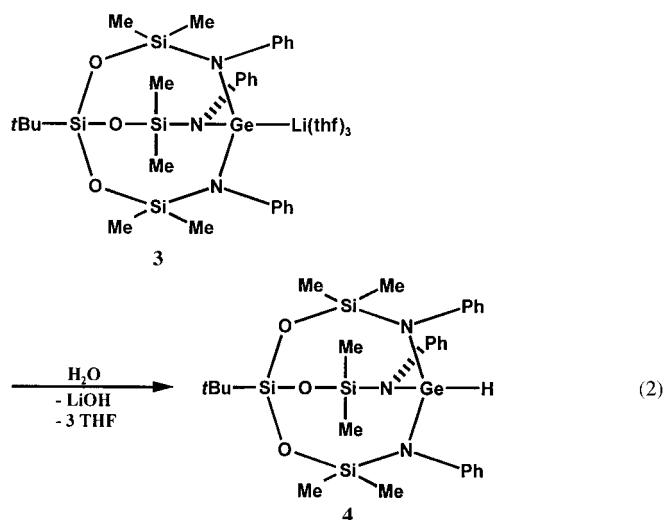


solution showed only one singlet each for the dimethylsilyl groups, for the methyl groups of the *tert*-butyl group, and for the lithium atom. This indicates that in solution **3** should have, at least on a time-average, *C*_{3v} symmetry. The ¹H and ¹³C NMR spectra also contain signals for coordinated THF molecules.

Controlled hydrolysis of **3** in THF gave the solvent-free germanium hydride **4** in 63 % yield [Eq. (2)] along with the soluble side product **1** (20–30 %). The remarkably simple Li/H exchange, for which there are only a few analogies,^[8] can be explained by an attack of the oxygen atom of the water molecule on the Lewis acidic lithium atom of the Ge–Li bond. The proton transfers to the partially negatively charged germanium atom to yield **4** and lithium hydroxide. This corresponds to a change in the partial charge on the germanium atom since the proton is now regarded as a hydride. In the IR spectrum of the product the characteristic

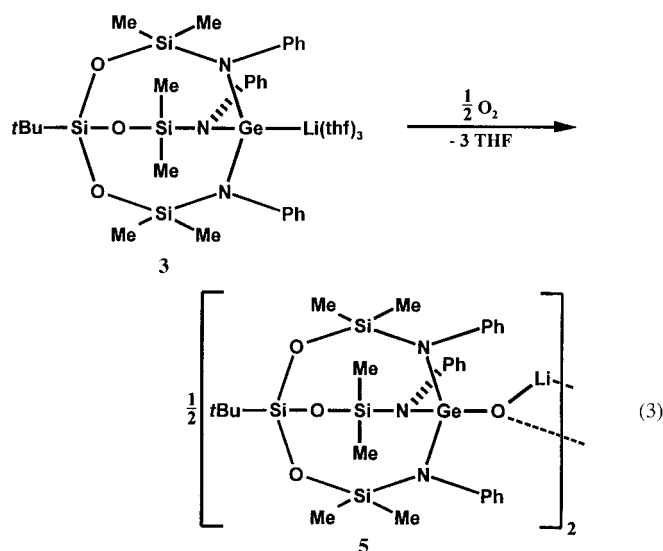
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[**] This work was supported by the Fonds der Chemischen Industrie as part of the DFG project “Spezifische Phänomene in der Siliciumchemie”.



Ge–H vibration at $\tilde{\nu}=2105\text{ cm}^{-1}$ is present, which indicates that **4** has indeed been formed. The IR spectra of other germanium hydrides show bands at similar wavenumbers.^[9–13] The ^1H , ^{13}C , and ^{29}Si NMR spectra of **4** also contain only one singlet each for the dimethylsilyl groups and the methyl groups of the *tert*-butyl group. Therefore, it is assumed that there are C_{3v} -symmetric molecules in solution as well. The ^1H NMR spectrum also contains a singlet for the hydride hydrogen atom at $\delta=5.66$.

When dry oxygen was bubbled through a solution of **3** in benzene for a short time the color lightened from orange to yellow. The reason for the color change is the insertion of an oxygen atom into the germanium–lithium bond. This oxidation of germanium(II) produces a germanium(IV) center in the dimeric, solvent-free lithium germanolate **5** [Eq. (3)]. A



simultaneous hydrolysis, possibly caused by traces of water, to afford the hydroxide $t\text{BuSi}(\text{OSiMe}_2\text{NPh})_3\text{GeOH}$ (**6**) and a subsequent in situ lithiation to the germanolate **5** can be excluded, since in the NMR spectrum of the reaction solution no compounds other than **5** were detected. The soluble germanol **6** was synthesized independently by hydrolysis of **5**

and was completely characterized.^[14] The NMR spectra of **5** in solution are similar to those of **3** and **4**.

An X-ray crystal structure analysis was undertaken for all three germanium compounds,^[15] and the structures obtained are shown in Figures 1–3. The compounds all contain the bicyclic cage $[t\text{BuSi}(\text{OSiMe}_2\text{NPh})_3\text{Ge}]$ and only differ in the functionalization of the tetrahedrally coordinated germanium atom. The SiO_3 and GeN_3 units of the bicycles are twisted relative to one another. The germanium amide **3** and the hydride **4** are almost C_3 -symmetric; however, dimeric **5** has crystallographic C_i symmetry. In **3** the bond length between the germanium and the lithium atom ($2.904(12)\text{ \AA}$) is unusually large (Figure 1); in other compounds with germa-

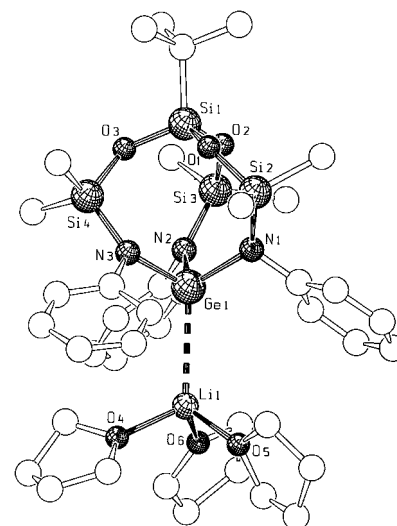


Figure 1. Crystal structure of **3**. Selected bond lengths [$\text{\AA}$] and angles [$^\circ$]: Ge1–N1 1.983(4), Ge1–N2 1.983(4), Ge1–N3 1.979(4), Ge1–Li1 2.904(12), Si2–N1 1.734(5), Si3–N2 1.746(4), Si4–N3 1.740(4); N3–Ge1–N1 101.43(18), N3–Ge1–N2 102.25(18), N1–Ge1–N2 101.55(18), N3–Ge1–Li1 114.0(3), N1–Ge1–Li1 119.3(3), N2–Ge1–Li1 115.8(3). The hydrogen atoms are omitted for clarity. The unlabeled atoms are carbon atoms.

nium–lithium interactions,^[3–5] the bond length is much closer to the sum of the covalent radii ($2.56\text{ \AA}$). The relatively large Ge–N bond lengths (av $1.982(4)\text{ \AA}$) along with the large Ge–Li bond length suggest a germanate which forms a contact ion pair with the lithium atom.

In the germanium hydride **4**,^[15] the length of the Ge–H bond ($1.40(3)\text{ \AA}$, Figure 2) is similar to that found in other germanium hydrides.^[9, 10, 16–20] The formal oxidation of Ge^{II} by the hydrolysis of **3** to give Ge^{IV} in **4** is reflected in the considerably shorter average N–Ge bond length of $1.848(3)\text{ \AA}$ (compared to $1.982(4)\text{ \AA}$ in **3**). In contrast, the average bond angle increases from $101.74(18)^\circ$ in **3** to $111.84(13)^\circ$ in **4**.

Lithium germanolate **5**, which is formed by the insertion of oxygen into the Ge–Li bond, is a dimer as a result of the Lewis acid–Lewis base interactions between the lithium and the oxygen atom to give an approximately rhombic, planar, four-membered Li_2O_2 ring; the inversion center of the dimer lies in the center of this ring (Figure 3). Because of the low coordination numbers, the Li–O bond lengths in **5** are smaller than those of other compounds that contain planar four-membered Li_2O_2 rings.^[21–25] The lithium atoms are not only

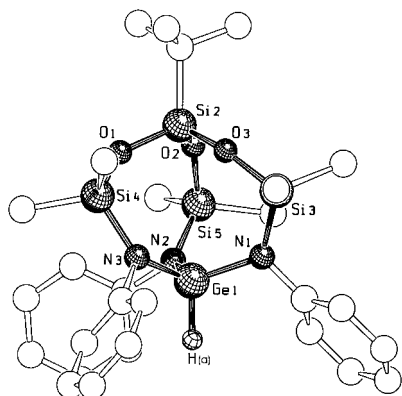


Figure 2. Crystal structure of **4**. Selected bond lengths [Å] and angles [°]: Ge1–N3 1.848(3), Ge1–N2 1.848(3), Ge1–N1 1.849(3), Ge–H(a) 1.40(3), Si3–N1 1.733(3), Si4–N3 1.738(3), Si5–N2 1.749(3); N3–Ge1–N2 110.29(13), N3–Ge1–N1 113.65(13), N2–Ge1–N1 111.59(13), N1–Ge1–H(a) 106.1(12), N2–Ge1–H(a) 109.9(13), N3–Ge1–H(a) 105.0(13). The hydrogen atoms are omitted for clarity. The unlabeled atoms are carbon atoms.

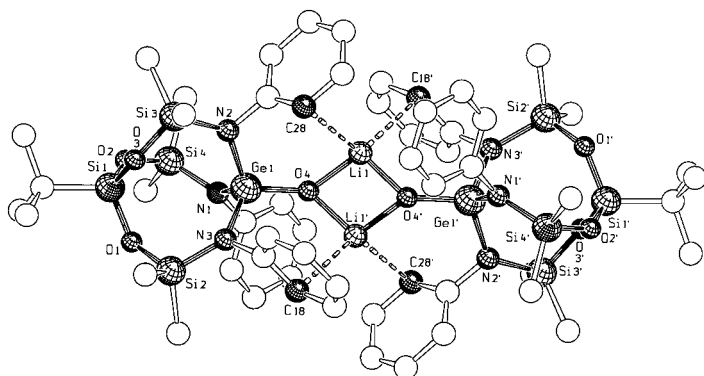


Figure 3. Crystal structure of **5**. Selected bond lengths [Å] and angles [°]: Ge1–N1 1.847(6), Ge1–N3 1.866(5), Ge1–N2 1.866(6), Ge1–O4 1.702(4), Si2–N3 1.725(5), Si3–N2 1.738(6), Si4–N1 1.729(6), Li1–O4' 1.806(15), O4–Li1 1.784(15), Li1–Li1' 2.31(3), C18–Li1' 2.61(2), C28–Li1 2.71(2); N1–Ge1–N3 109.6(2), N1–Ge1–N2 110.0(3), N3–Ge1–N2 109.6(3), Li1–O4–Li1' 80.0(7), O4–Li1–O4' 100.0(7). The hydrogen atoms are omitted for clarity. The unlabeled atoms are carbon atoms.

coordinated to two oxygen atoms, they also weakly interact with the π electrons of the phenyl groups (shortest Li–C bond lengths: 2.61(2), 2.71(2) Å), so that they have distorted tetrahedral coordination. The shortening of the Ge–O bond (1.702(4) Å) is remarkable: This bond is not only 0.25 Å shorter than the sum of the covalent radii of germanium and oxygen, but it is also shorter than typical Ge–O single bonds.^[13, 26–29] This is apparently caused by the high electronegativity of the “charged” oxygen atom. As in **4**, the oxidation state of Ge^{IV} in **5** is responsible for the shorter Ge–N bonds (av 1.860(6) Å) and larger N–Ge–N angles (av 109.73(3)°) than in **3**. Our results are remarkable in that there is a simple change of charge on the germanium atom in **3** as a consequence of the lithium–hydrogen exchange (**4**) and a simple insertion of oxygen into a bond between two electropositive elements (**5**).

Experimental Section

3: To a solution of **2** (0.60 g, 1 mmol) in THF (20 mL) at –75 °C was added GeCl₂·dioxane (0.23 g, 1 mmol) in THF (5 mL). The mixture was stirred

for 2 h at ≈25 °C, concentrated under vacuum, taken up in diethyl ether, and filtered. Slow concentration of the filtrate under reduced pressure resulted in precipitation of colorless prisms of **3**. Yield: 0.70 g (80 %). ¹H NMR (200.13 MHz, C₆D₆): δ = 0.63 (s, 18H; OSi(CH₃)₂N), 1.30 (s, 9H; SiC(CH₃)₃), 1.32 (m, 12H; THF), 3.25 (m, 12H; THF); ¹³C NMR (50.3 MHz, C₆D₆): δ = 3.95 (s, 6C; OSi(CH₃)₂N), 16.96 (s, 1C; SiC(CH₃)₃), 26.65 (s, 3C; SiC(CH₃)₃), 25.51 (s, 6C; THF), 68.35 (s, 6C; THF), 118.48, 126.31, 128.10, 154.65 (4s; arene C); ²⁹Si NMR (39.7 MHz, C₆D₆): δ = –8.96 (s, 3Si; OSi(CH₃)₂N), –56.05 (s, 1Si; SiC(CH₃)₃); ⁷Li NMR (77.7 MHz, C₆D₆): δ = –3.57 (s, 1Li; GeLi); correct elemental analysis; cryoscopy: calcd 876.85, found 890.

4: To **2** (0.65 g, 1.08 mmol) in THF (20 mL) at –75 °C was added dropwise GeCl₂·dioxane (0.25 g, 1.08 mmol) in THF (5 mL). After stirring for 2 h at about 25 °C, the mixture was cooled with ice and a 1M solution of water in dioxane (1 mL) was slowly added. The mixture was stirred for 2 h at about 25 °C. The solvent was evaporated to give a solid residue, which was taken up in hexane (20 mL). The LiCl precipitate was filtered off, and the filtrate was slowly concentrated under reduced pressure until colorless parallelepipeds of **4** began to precipitate. Yield: 0.44 g (63 %). ¹H NMR (200.13 MHz, C₆D₆): δ = 0.40 (s, 18H; OSi(CH₃)₂N), 1.18 (s, 9H; SiC(CH₃)₃), 5.66 (s, 1H; GeH); ¹³C NMR (50.3 MHz, C₆D₆): δ = 2.37 (s, 6C; OSi(CH₃)₂N), 16.59 (s, 1C; SiC(CH₃)₃), 25.92 (s, 3C; SiC(CH₃)₃), 123.86, 128.20, 129.34, 147.34 (4s; arene C); ²⁹Si NMR (39.7 MHz, C₆D₆): δ = –4.64 (s, 3Si; OSi(CH₃)₂N), –56.91 (s, 1Si; SiC(CH₃)₃); IR (NaCl, hexane): $\tilde{\nu}$ = 2105.3 cm^{–1}; correct elemental analysis; cryoscopy: calcd 654.60, found 660.

5: Compound **3** (0.9 g, 1.03 mmol) was dissolved in benzene (20 mL) and dry oxygen was bubbled through the solution for approximately 10 s at about 25 °C. The mixture was stirred for 30 min. The solvent was evaporated to give a yellow solid which was recrystallized from hexane to afford **5** as colorless, cuboid rods with a total yield of 0.51 g (73 %). ¹H NMR (200.13 MHz, C₆D₆): δ = 0.38 (s, 36H; OSi(CH₃)₂N), 1.20 (s, 18H; SiC(CH₃)₃); ¹³C NMR (50.3 MHz, C₆D₆): δ = 2.57 (s, 12C; OSi(CH₃)₂N), 16.65 (s, 2C; SiC(CH₃)₃), 26.04 (s, 6C; SiC(CH₃)₃), 123.31, 128.77, 129.95, 148.26 (4s; arene C); ²⁹Si NMR (39.7 MHz, C₆D₆): δ = –6.37 (s, 6Si; OSi(CH₃)₂N), –55.85 (s, 2Si; SiC(CH₃)₃); ⁷Li NMR (77.71 MHz, C₆D₆): δ = –4.99 (s, 2Li; GeOLi); correct elemental analysis; cryoscopy: calcd 1353.07, found 1340.

Received: July 9, 1999 [Z13699]

- [1] K. W. Hellmann, L. H. Gade, O. Gevert, P. Steinert, *Inorg. Chem.* **1995**, *34*, 4069–4078.
- [2] M. Contel, K. W. Hellmann, L. H. Gade, I. J. Scowen, M. McPartlin, M. Laguna, *Inorg. Chem.* **1996**, *35*, 3713–3715.
- [3] R. West, H. Sohn, D. R. Powell, T. Müller, Y. Apeloig, *Angew. Chem.* **1996**, *108*, 1095; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1002–1004.
- [4] S. Freitag, R. Herbst-Irmer, L. Lameyer, D. Stalke, *Organometallics* **1996**, *15*, 2839–2841.
- [5] J. H. Hong, Y. Pan, P. Boudjouk, *Angew. Chem.* **1996**, *108*, 213–216; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 186–188.
- [6] M. Veith, O. Schütt, V. Huch, *Z. Anorg. Allg. Chem.* **1999**, *625*, 1155–1164.
- [7] T. Fjeldberg, A. Haaland, B. E. R. Schilling, M. F. Lappert, A. J. Thorne, *J. Chem. Soc. Dalton Trans.* **1986**, 1551–1556.
- [8] A. G. Brook, F. Abdesaken, H. Söllradl, *J. Organomet. Chem.* **1986**, *299*, 9–13.
- [9] M. Veith, A. Detemple, V. Huch, *Chem. Ber.* **1991**, *124*, 1135–1141.
- [10] F. Cosledan, A. Castel, P. Rivière, J. Satgé, M. Veith, V. Huch, *Organometallics* **1998**, *17*, 2222–2227.
- [11] H. Schmidbaur, J. Rott, G. Reber, G. Müller, *Z. Naturforsch. B* **1988**, *43*, 727–732.
- [12] K. M. Baines, J. A. Cooke, J. J. Vittal, *J. Chem. Soc. Chem. Commun.* **1992**, 1484–1485.
- [13] M. F. Lappert, S. J. Miles, J. L. Atwood, M. J. Zaworotko, A. J. Carty, *J. Organomet. Chem.* **1981**, *212*, C4–C6.
- [14] O. Schütt, Dissertation, Universität des Saarlandes, **1999**.
- [15] Crystal structure analysis: diffractometer: Stoe IPDS (**3**), Stoe AED 2 (**4**, **5**). **3:** Monoclinic, *C*2/c, *a* = 19.401(4), *b* = 15.434(3), *c* = 34.151(7) Å, β = 98.31(3)°, *V* = 10119(4) Å³, *Z* = 8, 5535 “observed”

reflections, 496 parameters, $R = 0.0633$. **4**: Triclinic, $P\bar{1}$, $a = 10.689(2)$, $b = 11.170(2)$, $c = 15.330(6)$ Å, $\alpha = 84.2(3)$, $\beta = 89.39(3)$, $\gamma = 73.24(3)^\circ$, $V = 1743.3(6)$ Å³, $Z = 2$, 3849 “observed” reflections, 356 parameters, $R = 0.0373$. The hydride hydrogen atom H(a) was localized by differential Fourier synthesis and refined with a free isotropic B value. **5**: Monoclinic, $C2/c$, $a = 25.090(5)$, $b = 10.798(2)$, $c = 30.262(6)$ Å, $\beta = 106.99(3)^\circ$, $V = 7841(3)$ Å³, $Z = 8$, 4103 “observed” reflections, 370 parameters, $R = 0.0598$. Further details of the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany (fax: (+49)7247-808-666; e-mail: crysdata@fiz-karlsruhe.de) on quoting the depository numbers CSD-133780 (**3**), -133781 (**4**), and 133782 (**5**).

- [16] C. Brelière, F. Carré, R. J. P. Corriu, G. Royo, *Organometallics* **1988**, *7*, 1006–1008.
- [17] M. J. Barrow, E. A. V. Ebsworth, M. M. Harding, D. W. H. Rankin, *J. Chem. Soc. Dalton Trans.* **1980**, 603–606.
- [18] M. Lazraq, J. Escudié, C. Couret, J. Satgé, M. Dräger, R. Dammel, *Angew. Chem.* **1988**, *100*, 885–887; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 828–830.
- [19] T. S. Cameron, K. M. Mannan, S. R. Strobert, *Cryst. Struct. Commun.* **1975**, *4*, 601.
- [20] W. P. Freeman, T. D. Tilley, F. P. Arnold, A. L. Rheingold, P. K. Gantzel, *Angew. Chem.* **1995**, *107*, 2029–2031; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1887–1890.
- [21] P. B. Hitchcock, N. H. Buttrus, A. C. Sullivan, *J. Organomet. Chem.* **1986**, *303*, 321–327.
- [22] K. J. Weese, R. A. Bartlett, B. D. Murray, M. M. Olmstead, P. P. Power, *Inorg. Chem.* **1987**, *26*, 2409–2413.
- [23] J. Hvosllef, H. Hope, B. D. Murray, P. P. Power, *J. Chem. Soc. Chem. Commun.* **1983**, 1438–1439.
- [24] B. Bogdanović, C. Krüger, B. Wermeckes, *Angew. Chem.* **1980**, *92*, 844–845; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 817–818.
- [25] M. Motevalli, D. Shah, A. C. Sullivan, *J. Chem. Soc. Dalton Trans.* **1993**, 2849–2855.
- [26] M. Veith, M. Nötzel, L. Stahl, V. Huch, *Z. Anorg. Allg. Chem.* **1994**, *620*, 1264–1270.
- [27] C. Glidewell, M. B. Hursthouse, D. Lloyd, K. W. Lumbard, R. L. Short, *J. Chem. Res. (S)* **1986**, 400–401.
- [28] A. Schäfer, W. Saak, M. Weidenbruch, H. Marsmann, G. Henkel, *Chem. Ber.* **1997**, *130*, 1733–1737.
- [29] M. Veith, S. Becker, V. Huch, *Angew. Chem.* **1989**, *101*, 1287–1288; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1237–1238.

Crystal Design of Barium Sulfate using Double-Hydrophilic Block Copolymers

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The controlled growth of crystals with respect to size, shape, and crystal structure, the so-called “crystal design”, is a preindustrial manufacturing procedure known since the Middle Ages, but has returned as a key aspect of modern materials science. The reasons for this are obvious, since the use of powders as abrasives, fillers, or ceramic precursors

relies on the homogeneity of the powders to certain particle sizes and shapes. Further, the patterns of bioceramic matter such as bone, teeth, or seashells, with their properties superior to current man-made ceramics, show that control of the growth of single nanocrystals as well as their simultaneous alignment in some ordered superstructure is a motive to generate water-borne, environmentally friendly materials.^[1] In this Communication, biological principles to control crystal growth are mimicked with easily synthesized polymers where the growth of BaSO₄ is affected to effect a wide variety of well-defined morphologies.

The morphology of single nanocrystals or colloidal micro-particles is classically controlled by application of low molecular mass additives or salts, hydrothermal hydrolysis of amorphous solids, or special crystallization conditions.^[2] In recent years, biological molecules were isolated from living systems, for example from seashells, and the crystal growth control was repeated in in-vitro experiments.^[3] Recently, a new class of crystal modifiers, the double-hydrophilic block copolymers, was developed^[4a] and found to be very active in the control of the crystal morphologies of calcium carbonate^[4a, 5] and hydroxyapatite.^[6] Those polymers are designed as “molecular tools”, where one block interacts strongly with the mineral surface whereas the other block just keeps the “construction site” in solution. In this work, we report on the control and generation of unconventional crystal superstructures of barite, BaSO₄, using such block copolymers.

We varied the functional polymer block over a broad range, building polymer-bound arrays of carboxylate groups, aspartic acids, sulfonates, and phosphonates. Poly(ethyleneglycol)-*block*-poly(ethyleneimine)-poly(acetic acid) (PEG-*b*-PEIPA, PEG = 5000 g mol⁻¹, PEIPA = 1800 g mol⁻¹) was obtained as described in ref. [4a]. Poly(ethyleneglycol)-*block*-poly(ethyleneimine)-poly(sulfonic acid) (PEG-*b*-PEIPSA, PEG = 5000 g mol⁻¹, PEIPSA = 2360 g mol⁻¹) was prepared similarly by quantitative reaction with 1,3-propanesultone^[4b]. A commercial poly(ethyleneglycol)-*block*-poly(methacrylic acid) (PEG-*b*-PMAA, PEG = 3000 g mol⁻¹, PMAA = 700 g mol⁻¹; Goldschmidt AG) was used as received. PEG-*b*-PMAA-Asp, with amino acid side chains, was prepared by amidation of PEG-*b*-PMAA with aspartic acid (27 %),^[4b] while PEG-*b*-PMAAP was prepared by partially monophosphonating (21 %) the COOH groups of PEG-*b*-PMAA^[5]. All polymers were purified by exhaustive dialysis. Crystal modification data is presented for these five double-hydrophilic block copolymers together with poly(methacrylic acid) (PMAA, as sodium salt; Aldrich, PMMA = 6500 g mol⁻¹).

The “synthesis” of the BaSO₄ particles involves simultaneous addition of 0.5 M Ba(OAc)₂ (Aldrich), 0.5 M (NH₄)₂SO₄ (Aldrich), and a 1 g L⁻¹ aqueous solution of the different polymers (at pH 5 unless otherwise specified) in a double-jet reactor^[4a] maintained at 25 °C. The continuous reactant supply of 0.5 mL h⁻¹, leading to a BaSO₄ formation rate of 1.39×10^{-5} mol L⁻¹ min⁻¹, was stopped when the solution became turbid or crystal formation could be observed. The precipitates were left to stand in their mother solutions for at least 24 h to ensure equilibration.

The resulting BaSO₄ precipitates were characterized by scanning electron microscopy (SEM), and by transmission

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electron microscopy (TEM) (SEM: DSM940 A, TEM: EM912 Omega, Carl Zeiss, Jena). Dry powder samples were used for the measurements of X-ray powder diffraction (XRD) using PDS120 unit and Cu K α radiation (Nonius GmbH, Solingen), and thermogravimetry (TG) on a Netzsch TG 209 unit (Selb, Germany). The obtained XRD patterns were indexed with reference to the unit cell of the barite structure ($a = 8.87$, $b = 5.45$, $c = 7.15$ Å, space group $Pnma$).^[7] The crystallite sizes of the BaSO₄ particles were estimated from the half-height width of the barite-(211) peak according to the Scherrer equation.

The control precipitation experiment, at pH 7 without an additive, yielded rectangular BaSO₄ crystals of about 0.6 μm length with a mean aspect ratio of 1.2 (Figure 1a). Similar

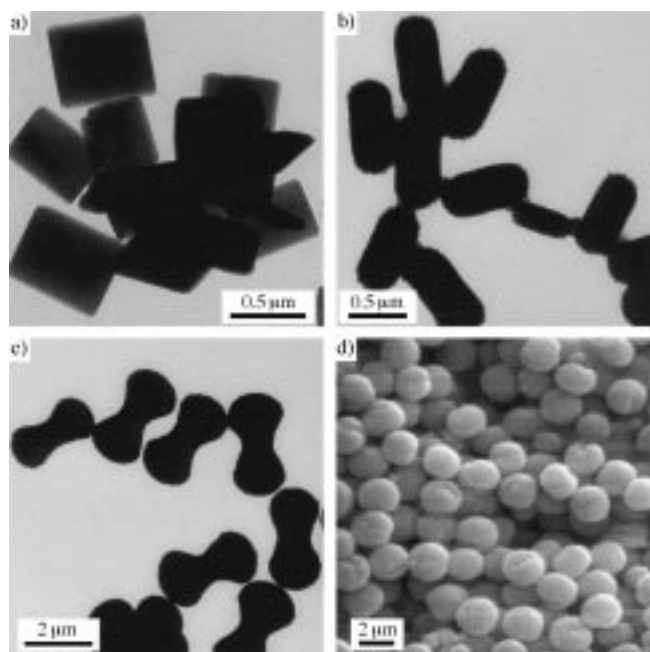


Figure 1. BaSO₄ particles formed in the presence of a) no additives, b) PMAA, c) PEG-*b*-PEIPA, and d) PEG-*b*-PMAA-Asp, observed by TEM (a–c) and SEM (d). BaSO₄ particles show various morphologies such as rectangular tablets (a), rods (b), peanuts (c), and peaches (d).

tablets were obtained at pH 5 and pH 9, although severe aggregation was observed at pH 9. These tablets are similar to those of BaSO₄ crystallized from a supersaturated solution under static growth conditions, each of which was a single crystal elongated along the [001] crystallographic axis.^[8] However, the BaSO₄ tablets obtained here are smaller, presumably because double-jet precipitation results in fast nucleation and many small crystals.

The obtained products precipitated in presence of PMAA at pH 5 are elongated particles with an average length of 0.8 μm and an aspect ratio of about 2.1 (Figure 1b). The rough surface of the rods indicates that they consist of primary crystallites, corresponding to XRD evidence of a mean crystal size of 22 nm. The overall shape implies that the superstructure is composed of rod-like crystallites aligned along the rod axes. This result on the simple polymer suggests a

significant interaction between the polymeric pattern of carboxylic acid groups and the crystallizing BaSO₄, resulting in the considerable influence on both the primary crystallization as well as on the superstructure.

If a similar functional block is connected to an inert, soluble PEG block to form the additive PEG-*b*-PMAA, a new overall morphology is formed. At pH 9, a peanutlike morphology (similar to Figure 1c but only 0.8 μm long) composed of 14 nm primary crystallites (XRD) is found, whereas at pH 5, peachlike, 2 μm sized particles of 18 nm primary crystallites (XRD) were obtained, very similar to those shown in Figure 1d. This result illustrates that incorporation of a solubilizing block into the template structure is also important for the crystal morphology. Obviously, stabilization of the primary crystallites and their subsequent aggregation into a macrostructure are facilitated by the block copolymer structure.

As shown in Figure 1c, well-defined peanutlike particles around 3.0 μm in size are also obtained with PEG-*b*-PEIPA as a modifier at pH 5. Using PEG-*b*-PMAA-Asp at the same pH results again in uniform peachlike particles of an average 2.3 μm size (Figure 1d). In this case, the equatorial depression of the particular superstructure becomes visible. The corresponding XRD results showed that both the peanuts and the peaches consist of barite primary crystallites (27 nm for PEG-*b*-PEIPA and 19 nm for PEG-*b*-PMAA-Asp).

It is interesting to note that similar peanutlike particles of hematite ($\alpha\text{-Fe}_2\text{O}_3$) have been produced by a gel-sol method in the presence of sulfate ions.^[9] It has been reported that sulfate restrained the growth in all directions normal to the c axis of hematite resulting in crystalline rods, whereas the peanut superstructure is the product of the aggregation of these rods directed by specific forces.^[9, 10] In the present case, it is assumed that the COOH groups of both PEG-*b*-PMAA and PEG-*b*-PEIPA play a similar role restricting crystallization of BaSO₄ in all directions but one, where directional aggregation of the rodlike primary crystallites leads to peanutlike particles. Our preliminary TEM studies on thinly cut samples confirmed the presence of nanometer-sized rodlike crystallites in the peanutlike BaSO₄ particles, supporting the proposed building mechanism.

It is further speculated that Figures 1b–d represent different stages of the directed aggregation of BaSO₄ nano-rods in a process which has been described in detail for the formation of fluorapatite superstructures in a gelatin matrix.^[11, 12] In a like manner, the peanut shape is explained by electrical field lines of a primary rodlike crystallite (see Figure 1b) which directs the aggregation of further crystallites. This was again confirmed by TEM of thin cuts of the peanutlike macrostructures which showed the primary crystallites are aligned along field lines (data not shown). Further growth at the caps of the peanut structure yield a sphere with an equatorial depression, such as the peaches, in analogy to similarly composed fluorapatite particles.^[11]

Thermogravimetry has revealed that the final superstructures contain a small, but relevant, amount of polymer (5–12 wt-%) embedded between the primary BaSO₄ crystallites. The fact that the superstructures do not fall apart, even if ultrasound or good solvents for PEG are applied, suggests that the polymer acts as a binder for the different primary

crystallites. This binding appears to be stronger than in the case of calcium minerals, as similar CaCO_3 particles can fall apart into the primary crystallites upon ultrasonication.

Phosphonation of the carboxylic acid groups of PEG-*b*-PMAA leads to a remarkable variation in the morphology of the BaSO_4 particles, namely, large bundles of nanofibers of BaSO_4 are produced. Many bundles of fibers show lengths of some tens of micrometers, most of which exhibit clear starting points. Appearances that include snails, bananas, and cones, can be observed. Figure 2a depicts a SEM image showing a

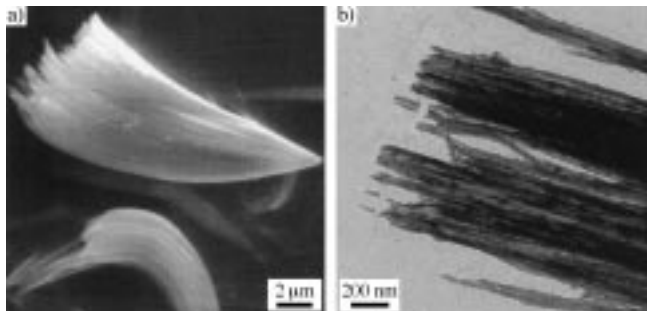


Figure 2. Micrographs of BaSO_4 particles formed in the presence of PEG-*b*-PMAAP observed using a) SEM and b) TEM. The high-magnification images show the structure as bundles of nanofibers.

conelike bundle of BaSO_4 nanofibers. The common starting points of the nanofibers suggest that they could be formed by heterogeneous nucleation from single centers (e. g., on the connection point between the two reactant jets or at the glass wall of the reaction vessel) followed by crystal growth along a single crystal direction. This can again be achieved by selective blocking of the crystal growth of all faces parallel to one axis by polymer adsorption. The corresponding TEM image of a thin slice shown in Figure 2b confirms the presence of bundles of nanofibers and shows that the fibers forming bundles are rather uniform in diameter (20–30 nm). The corresponding XRD pattern of these nanofibers exhibits relatively sharp barite scattering peaks, which gives for the main (211) peak an average crystallite size of about 60 nm, which is close to the resolution of the diffractometer. This result strongly indicates the single crystal structure of each fiber.

A better insight how the polymer interacts with the primary crystallites and how the morphology is controlled is gained by electron diffraction on very thin samples. We were not able to microtome the bigger particles, but microtoming of the nanofibers was possible. Figure 3a presents a TEM image of a thin section of a BaSO_4 nanofiber bundle formed in the presence of PEG-*b*-PMAAP. The section has been cut nearly along the fiber axis, resulting in an area of long continuous nanofibers that are aligned nearly parallel and exhibit rather uniform diameters (20–30 nm). The corresponding electron diffraction pattern (Figure 3b) consists of elongated but individual diffraction spots, most of which can be indexed as the reflections corresponding to the [001] zone of barite. It can be seen that the (210) reflection is located along the direction normal to the fiber axis, suggesting that the fiber axis is along the crystallographic $[1\bar{2}0]$ axis. It is noteworthy that a few

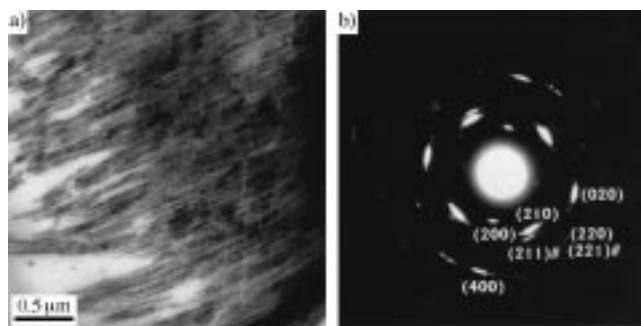


Figure 3. a) TEM micrograph and b) electron diffraction pattern of a thin section of a bundle of BaSO_4 nanofibers, formed in the presence of PEG-*b*-PMAAP, cut nearly along the fiber axis. The diffraction pattern corresponds to the upper-right region of (a), containing continuous, approximately parallel nanofibers. All indexed reflections correspond to the [001] zone of barite except the reflections labeled “#”. The observation that the (210) reflection is located normal to the fiber axis suggests that the fibers are elongated along the $[1\bar{2}0]$ axis.

reflections corresponding to other zones are also present in the whole diffraction pattern due to a degree of rotation of some fibers around their own axes. Specifically, reflections (211) and (221) accompany reflections (210) and (220), respectively. That the (211) reflection is also located normal to the fiber axis confirms that the fibers are elongated along the $[1\bar{2}0]$ axis. The absence of symmetry in the diffraction pattern with respect to the $[1\bar{2}0]$ axis indicates that the individual fibers cannot randomly rotate around their axes. This implies that these nanofibers assembled into a single bundle are vectorially aligned, and either geometric packing or force fields result in a high degree of correlation between the fibers with respect to the crystallographic direction. Further, that the nanofibers are elongated along the $[1\bar{2}0]$ axis indicates that the PEG-*b*-PMAAP copolymer preferentially adsorbs on the faces parallel to the $[1\bar{2}0]$ axis, such as (001), (210), and (211).

This remarkable interaction between PEG-*b*-PMAAP and the growing BaSO_4 particles is attributed to the specific pattern of the phosphonate groups along the polymer backbone. It is well known that (poly)phosphonate-type additives are effective inhibitors for the crystallization of barite.^[13, 14] Indeed the presence of PEG-*b*-PMAAP delayed the precipitation of BaSO_4 significantly. For example, macroscopic crystal formation with PEG-*b*-PMAAP was not observed until 180 min, whereas the same solution with PMAA and the carboxylic acid-containing block copolymers became turbid in less than 50 min. It was also observed that only a small amount of large fibers was formed when the injection of reactants was stopped at 180 min, and the majority of fibers form gradually under static conditions. This finding indicates that a metastable, inhibited BaSO_4 species is kept in solution at rather high concentrations (strong inhibition effect with PEG-*b*-PMAAP), which subsequently slowly recrystallizes to the observed large bundles of BaSO_4 fibers.

It is noteworthy that similar nanofibers of BaSO_4 have also been synthesized in reverse microemulsions, consisting of a continuous oil phase and water droplets stabilized by the surfactant AOT (sodium 5,14-diethyl-8,11-dioxo 7,12-dioxaoctadecane-2-sulfonate).^[15] In this case, the reaction solutions

were also initially transparent and became cloudy over a relatively long period, indicating a similar formation mechanism of the nanofibers.

A striking flowerlike morphology was obtained by the precipitation of BaSO_4 in presence of the sulfonated derivative PEG-*b*-PEIPSA, revealing the remarkable influence of the nature of the functional groups of the double-hydrophilic copolymers. As shown in Figure 4a, the flowerlike particles

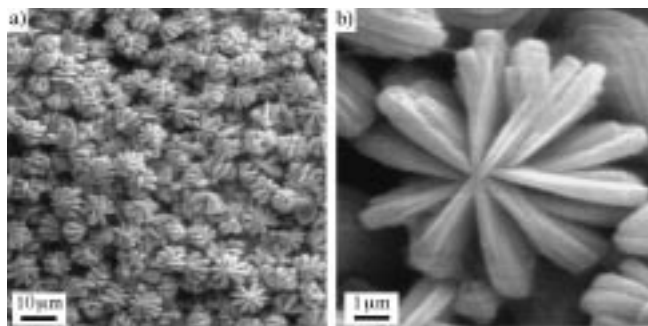


Figure 4. SEM micrographs of BaSO_4 particles, formed in the presence of PEG-*b*-PEIPSA, shows a) flowers with ten petals and b) enlarged to show details of a single flower.

are regular and rather uniform in size and shape, most of which are about 10 μm in size and have ten petals. Figure 4b presents a high-magnification image of a single particle.

It can be seen that the flower shows faceted surfaces, indicating that it is composed of large crystals. This is consistent with the XRD pattern which exhibited sharp barite diffraction peaks. The mechanism of the flower formation can again only be explained by selective adsorption of the polymer. In a first step, it is assumed that a rodlike primary crystal is formed (the axis of the flower). In a second step, these primary crystals nucleate secondary crystals which grow along ten of the directions perpendicular to the rod axis which are only weakly blocked by PEG-*b*-PEIPSA (role of the strength of adsorption). Finally, the sides of the petals are overgrown with secondary crystalline layers.

The role of the polymer on the resulting crystal morphology must be stressed to explain the variations observed for barite crystals. The exposed faces of barite crystals do show different polarity patterns and averaged interface energies, and adsorb the variously modified polymers with different efficiencies. A polymer-modified crystal grows into the direction where the crystallization hindrance is weakest, and fibers are formed when all but two sites are blocked. Peanut- and peachlike morphologies result from the parallel alignment of several crystalline rods to form rodlike particles in the micron range, where aggregation seems inhibited or even vectorially con-

trolled by local electric fields, and the overall morphology is obtained depending on the strength of the dipole contribution. In contrast, stopping the primary growth and having secondary growth exclusively at the sides of the primary rod results in the flowerlike morphology.

In summary, it has been demonstrated that double-hydrophilic block copolymers can direct the room-temperature crystal growth of BaSO_4 into novel morphologies. These BaSO_4 particles are promising candidates for materials science due to the importance of shape and texture in determining properties of materials.^[16] Functionalized polymers extend the possibilities of inorganic morphogenesis,^[17] since polyanionic block copolymers are similar to the proteins that organisms use to exert control over biomineral growth^[18, 19] and synthetic protein mimics.^[20] By varying the binding and solvating blocks in double-hydrophilic block copolymers, more specific templates become available for the formation of complex architectures.

Received: April 27, 1999

Revised: September 13, 1999 [Z13321]

- [1] S. Mann, J. Webb, R. J. P. Williams, *Biomaterialization, Chemical and Biochemical Perspectives*, VCH, Weinheim, **1989**.
- [2] E. Matijevic, *Chem. Mater.* **1993**, *5*, 412–426.
- [3] S. Weiner, L. Addadi, *J. Mater. Chem.* **1997**, *7*, 689–702.
- [4] a) M. Sedlak, M. Antonietti, H. Cölfen, *Macromol. Chem. Phys.* **1998**, *199*, 247–254; b) M. Sedlak, unpublished results.
- [5] H. Cölfen, M. Antonietti, *Langmuir* **1998**, *14*, 582–589.
- [6] M. Antonietti, M. Breulmann, C. Göltner, H. Cölfen, K. K. W. Wong, D. Walsh, S. Mann, *Chem. Eur. J.* **1998**, *4*, 2493–2500.
- [7] C. M. Pina, U. Becker, P. Risthaus, D. Bosbach, A. Putnis, *Nature* **1998**, *395*, 483–486.
- [8] B. R. Heywood, S. Mann, *J. Am. Chem. Soc.* **1992**, *114*, 4681–4686.
- [9] T. Sugimoto, M. M. Khan, A. Muramatsu, H. Itoh, *Colloids Surf. A* **1993**, *79*, 233–247.
- [10] D. Shindo, G.-S. Park, Y. Waseda, T. Sugimoto, *J. Colloid Interface Sci.* **1994**, *168*, 478–484.
- [11] R. Kniep, S. Busch, *Angew. Chem.* **1996**, *108*, 2788–2791; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2624–2626.
- [12] a) S. Busch, Ph.D. thesis, Technische Hochschule Darmstadt, **1998**; S. Busch, H. Dolhaine, A. DuChesne, S. Heinz, O. Hochrein, F. Laen, O. Padebrad, U. Vietze, T. Weiland, R. Kniep, *Eur. J. Inorg. Chem.* **1999**, 1643–1653.
- [13] R. J. Davey, S. N. Black, L. A. Bromley, D. Cottier, B. Dobbs, J. E. Rout, *Nature* **1991**, *353*, 549–550.
- [14] M. C. Leeden, G. M. Rosmalen, *J. Colloid Interface Sci.* **1995**, *171*, 142–149.
- [15] J. D. Hopwood, S. Mann, *Chem. Mater.* **1997**, *9*, 1819–1828.
- [16] S. Mann, G. A. Ozin, *Nature* **1996**, *382*, 313–318.
- [17] H. Yang, N. Coombs, G. A. Ozin, *Nature* **1997**, *386*, 692–695.
- [18] G. Falini, S. Albeck, S. Weiner, L. Addadi, *Science* **1996**, *271*, 67–69.
- [19] A. M. Belcher, X. H. Wu, R. J. Christensen, P. K. Hansma, G. D. Stucky, D. E. Morse, *Nature* **1996**, *381*, 56–58.
- [20] J. P. Garra, C. S. Sikes, *Colloids Surf. A* **1993**, *80*, 103–112.

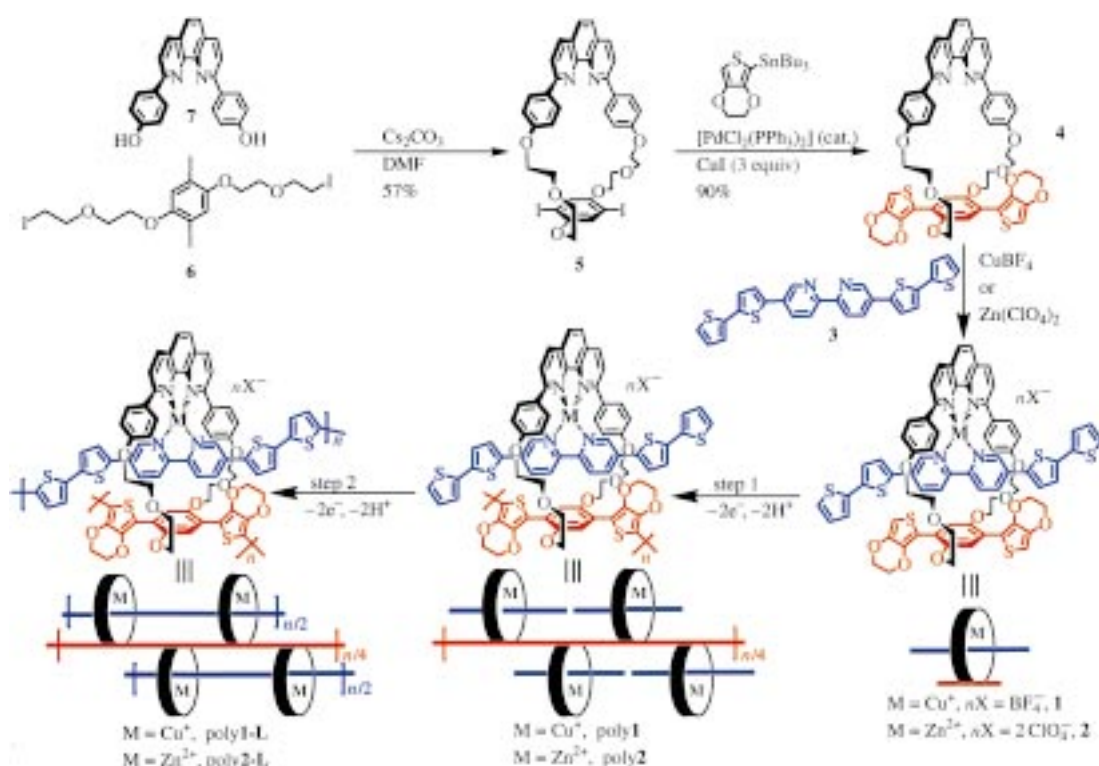
Three-Strand Conducting Ladder Polymers: Two-Step Electropolymerization of Metallorotaxanes**

Julio Buey and Timothy M. Swager*

Semiconductor electronic devices derive their useful electrical characteristics from the interfacing of dissimilar materials.^[1] It stands to reason that the true potential of molecular electronics can only be realized by mastering the assembly of molecular structures with multiple electronic functionalities. Futuristic technologies aside, even present-day molecular or polymer electronic devices require the use of multiple electronic elements. For example, conjugated polymer light-emitting devices are generally constructed from multiple layers of conjugated polymers or specific charge transporters.^[2] However, these devices represent very simple structures compared to what can be envisioned by application of

established supramolecular principles.^[3] Specifically, interlocking or interpenetrating rotaxane structures are powerful tools for the assembly of multiple molecular components.^[4]

We have targeted rotaxane recognition and assembly methods to produce new architectures wherein two different electronic materials with complementary properties can be assembled into a single “super-polymer.” In this effort, we have built upon our previous work on conducting polymetallorotaxanes,^[5] and report herein a new type of metallorotaxane monomer bearing two independently electropolymerizable groups, located both in the threading unit and the macrocycle host. We further report that the controlled assembly and polymerization of these metallorotaxane monomers leads to the formation of novel three-stranded ladder polymers, wherein one of the conjugated chains is sandwiched between two other chains. In this structure the internal polymer behaves as a partially isolated molecular wire when the outer strands are in an insulating state.



Scheme 1. Mixing of **3**, **4**, and Cu^{1+} or Zn^{2+} ions to produce metallorotaxane monomers **1** and **2**, and subsequent polymerization.

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[**] Funding from the Office of Naval Research and the Spanish Ministerio de Educación y Ciencia (fellowship to J.B.) is gratefully acknowledged. This work was supported in part by the MRSEC Program of the National Science Foundation (award number DMR 98-08941). We also thank Mr. Richard Kingsborough for his invaluable help with the electrochemical measurements as well as for helpful discussions, Dr. Robert Deans for providing some tetraethyleneglycol intermediates, and Sarah O'Connor for assisting our computational investigations.

A key design principle is the choice of rotaxane monomers with two moieties having widely separated oxidation potentials that allow for orthogonal electropolymerization (Scheme 1). We have previously reported the 4,4'-bis(dithienyl)-2,2'-bipyridine threading ligand **3**^[6] and its use for the formation of conducting polymetallorotaxanes.^[5, 7] Ligand **3** is electron-poor in nature and requires a more positive oxidation potential to undergo electropolymerization than would be required for an isolated bithiophene. To complement this threading group, we designed and synthesized a new macrocycle, **4** (Scheme 1), bearing an electron-rich 1,4-bis(ethylenedioxythiophene)-2,5-dialkoxybenzene group that is easily oxidatively polymerized at lower potentials.

In accord with methods pioneered by Sauvage and co-workers,^[4b,c] simple mixing of **3**, **4**, and Cu^{1+} or Zn^{2+} ions produces metallorotaxane monomers **1** and **2** (Scheme 1). Controlled oxidation results in the electropolymerization of the macrocycle **4**, while leaving the threading group **3** untouched. Higher potentials can be subsequently applied to polymerize **3**. The detailed procedure is as follows: Microelectrode arrays^[8] were immersed in a solution (0.1M $n\text{Bu}_4\text{NPF}_6$, CH_2Cl_2) of **1**, **2**, or **4** (0.3 mM) and then cycled between -0.5 and 0.55 V versus ferrocene/ferrocenium (Fc/Fc^+). This procedure results in the oxidative electropolymerization of the macrocycle to produce poly**1**, poly**2**, and poly**4**. Consistent with the proposed polymerization, cyclic voltammograms of poly**2** in fresh monomer-free electrolyte gave voltammograms indistinguishable from those obtained from poly**4**. The cyclic voltammogram of poly**1** (Figure 1) is also similar but contains an added $\text{Cu}^{1+}/\text{Cu}^{2+}$ wave centered at 0.11 V vs. Fc/Fc^+ . The UV/Vis spectra also support the selective polymerization of the macrocyclic ligand, and both poly**1** and poly**2** displayed absorption spectra similar to that of poly**4** ($\lambda_{\text{max}} = 503\text{ nm}$) with an additional absorption feature at about 450 nm assigned to the threading ligand **3**.

Subjecting deposited films of poly**1** or poly**2** to higher potentials in monomer-free electrolyte resulted in the polymerization of the 4,4'-bis(dithienyl)-2,2'-bipyridine threading

ligand to form ladder polymers poly**1-L** and poly**2-L**, respectively (Scheme 1). This process is readily apparent from Figure 1, wherein the first sweep to 1 V vs. Fc/Fc^+ results in a large irreversible oxidation current. This irreversible current is expected since oxidation of the threading ligand **3** will produce radical cations that undergo intermolecular coupling with loss of protons to form new thiophene–thiophene linkages (i.e., polymerization). The second sweep over the same expanded potential range lacks this irreversible oxidation and is identical to all subsequent sweeps.

The efficiency of the second polymerization can be deduced from an analysis of the irreversible charge relative to the reversible charge. A key parameter is the mass of the polymer immobilized on the electrodes. Once the mass of the polymer has been determined, the degree of oxidation of the polymer is also known. This analysis was afforded by a comparison of poly**1**, poly**2**, and poly**4**. Due to the fact that the metal ions do not directly interact with the electronic structure of the macrocyclic polymer, poly**2** and poly**4** have nearly identical cyclic voltammograms over the potential region of -0.5 to 0.55 V vs. Fc/Fc^+ , and display the same number of Coulombs per gram of polymer deposited. Polymer poly**1** has an additional one-electron $\text{Cu}^{1+}/\text{Cu}^{2+}$ wave in that potential region, which also serves as an internal standard to establish the moles of polymer repeating units in the film.

We find that poly**1**, poly**2**, and poly**4** are respectively oxidized by 3.2, 2.2, and 2.2 electrons per repeating unit when cycled to 0.55 V vs. Fc/Fc^+ . With regard to the efficiency of the second polymerization of poly**1** and poly**2**, the respective irreversible charge passed was 1.7 and 2.1 electrons per repeating group. A quantitative polymerization results in two electrons per monomer being removed irreversibly. Hence the second polymerization is quantitative for poly**2**, whereas for poly**1** it appears that some loss of the threading ligand **3** and the Cu ion occurs. The lower stability of the Cu complex is not unexpected, since at higher potential the Cu^{2+} ion generated would prefer to be five-coordinate, which is not easily accommodated by the rotaxane structure. After the first sweep to high potential a stable reproducible voltammogram is observed, and with application of 0.98 V vs. Fc/Fc^+ 5.3, 5.4, and 3.3 electrons per repeating unit were removed for poly**1-L**, poly**2-L**, and poly**4**, respectively. For a perfect structure we would expect that poly**1-L**, due to the presence of Cu ion, would be oxidized by one more electron than poly**2-L**. The smaller value for poly**1-L** reflects the concurrent loss of **3** and the Cu ion. The two-electron difference between poly**2-L** and poly**3** is also consistent with our previous investigations that demonstrated the two high potential waves ($+0.6$ and $+0.85\text{ V}$ vs. Fc/Fc^+) are one-electron oxidations of the tetrathienyl segments.^[5, 6, 9]

The linear dimensions of the two polymerizable groups and the structure of the metallorotaxane were chosen to promote the formation of a three-stranded ladder polymer (Scheme 1). Neglecting minor effects arising from conformational issues (there are two enantiomeric conformations of **1** and **2**) the polymer formed from the threading unit is twice as long as the polymer containing the macrocycle. Additionally, computationally optimized structures^[10] of the monomers indicate that the two polymerizable groups are rigidly held in a parallel

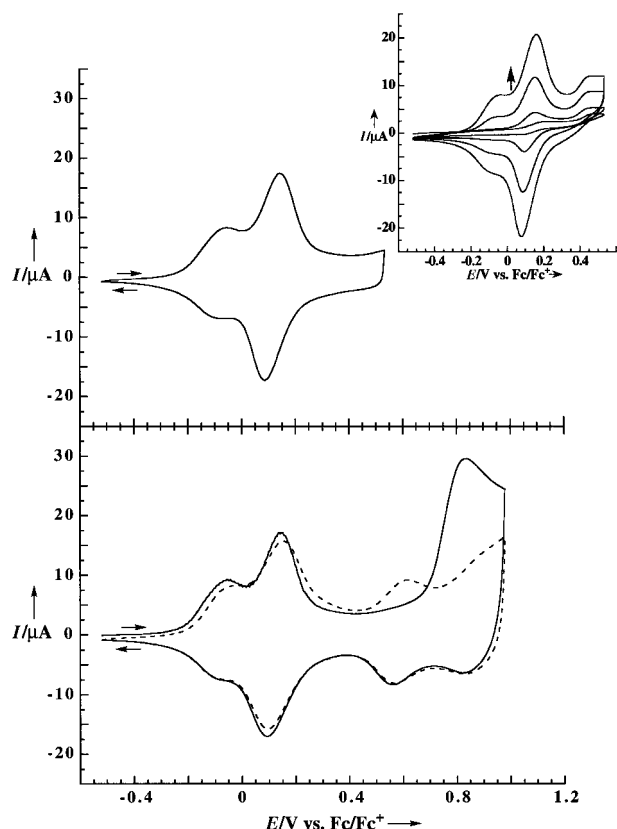


Figure 1. Cyclic voltammograms of **1**, poly**1**, and poly**1-L** on interdigitated microelectrodes with a spacing of $5\text{ }\mu\text{m}$ between adjacent electrodes (0.1M $(n\text{Bu}_4\text{N})\text{PF}_6$ in CH_2Cl_2 at a sweep rate of 100 mV s^{-1}). Top: A film of poly**1** in fresh, monomer-free electrolyte. Inset: The first electropolymerization to grow films of poly**1** after 1, 20, 40, and 60 potential cycles. Bottom: The first scan (solid line) and second scan (dashed line) of the same film when swept to 1.0 V vs. Fc/Fc^+ . The first scan shows the large irreversible oxidation to form poly**1-L**.

orientation. These structural features and the polymerization of the threading ligand require the structure of the polymer to contain a predominance of the three-stranded ladder architecture shown in Scheme 1. The data does not preclude the presence of cross-links, and it is likely that the structure contains defects. This ladder polymer structure is of particular interest due to the fact that the macrocyclic-containing polymer (poly4) is sandwiched between two chains for poly3. In other words, we have in essence assembled a three-stranded molecular wire in which the internal wire is encapsulated between two polymer chains.

To further illustrate the viability of this structure, we have conducted molecular mechanics calculations on oligomers assembled from the computationally optimized monomer.^[10] In these calculations a single enantiomer of **1** was used. As can be seen from the space-filling structure shown in Figure 2, there is a clear match of the polymer lengths, and the chain of poly4 is incarcerated between two strands of poly3. An additional feature revealed by the structure is the steric constraints of the phenanthroline portion of the macrocycle. This unit presents a rigid steric barrier that prevents close contacts between neighboring polymers and thereby promotes intrapolymer coupling in the second polymerization to favor the three-strand ladder structure.

Comparisons of the conductivity and electrochemistry of poly1-L, poly2-L, and poly4 (Figure 3) support our assertion that the internal polymer behaves as a partially isolated wire when the outer two polymer strands are in their insulating (undoped) state. The observed electroactivity results from

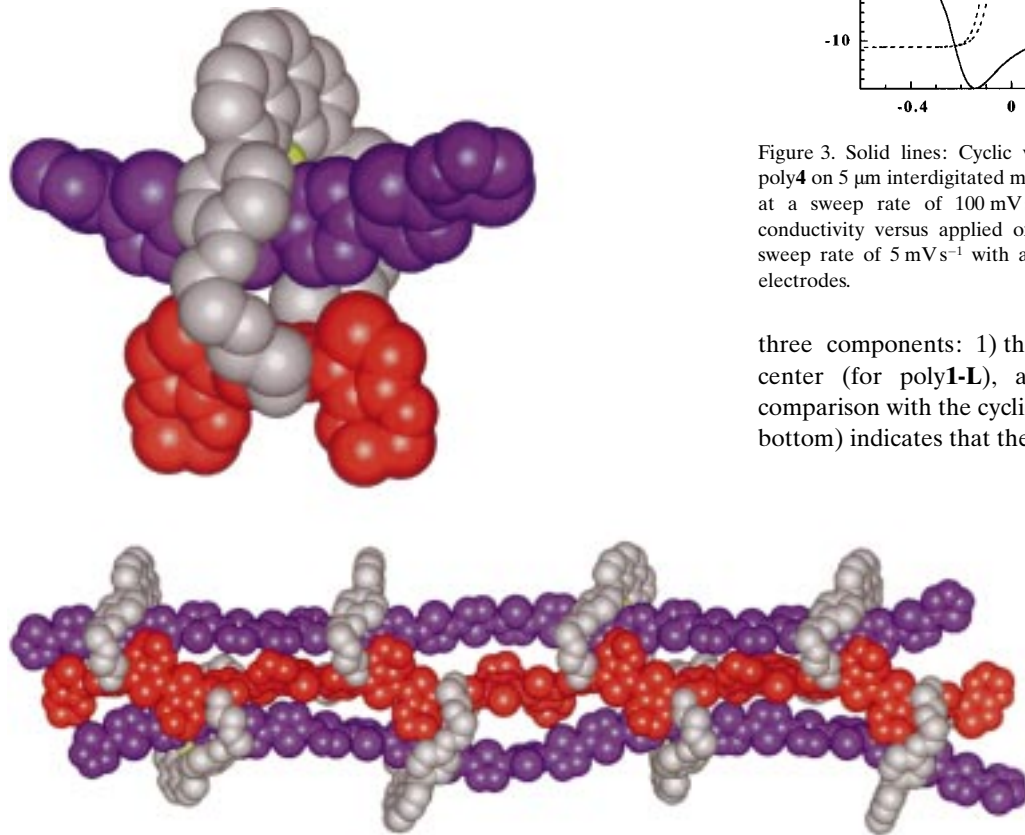


Figure 2. Space-filling model of **1** (top) and an octamer of poly1-L (bottom). The backbone of poly4 is shown in red, the diethylene glycol chains and the phenanthroline portion of the macrocycle are shown in gray, and the poly3 chains are shown in purple.

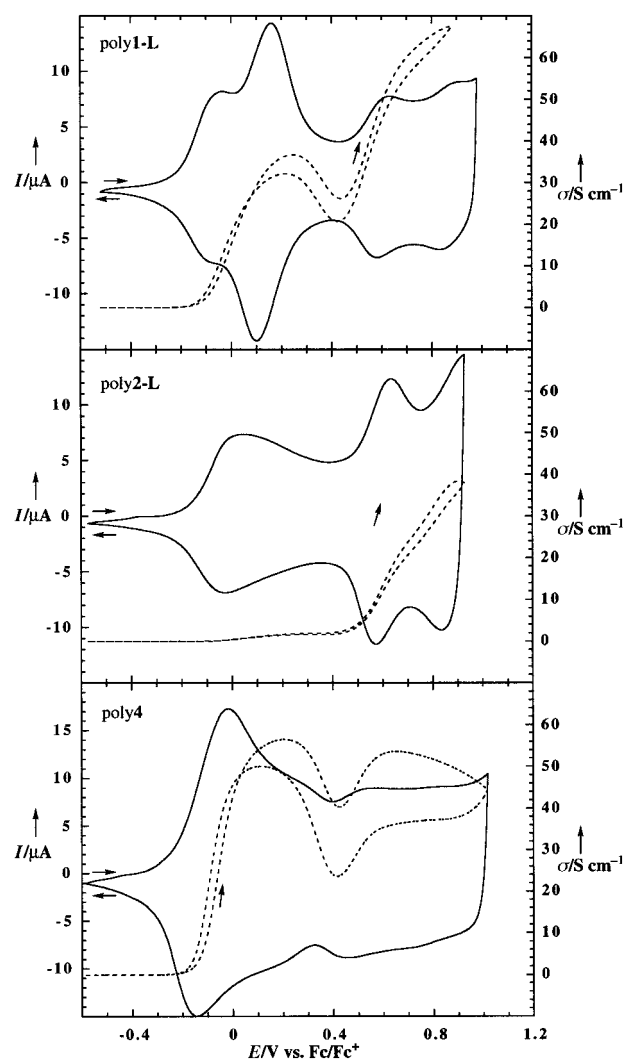
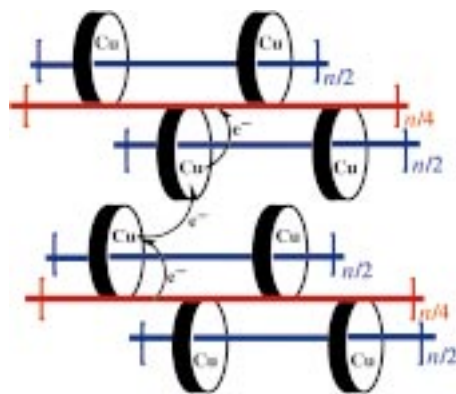


Figure 3. Solid lines: Cyclic voltammograms of poly1-L, poly2-L, and poly4 on 5 μm interdigitated microelectrodes (0.1M $(n\text{Bu}_4\text{N})\text{PF}_6$ in CH_2Cl_2 at a sweep rate of 100 mV s^{-1}). Dashed lines: Plots of the in situ conductivity versus applied oxidation potential of the same films at a sweep rate of 5 mV s^{-1} with a 40 mV offset potential between adjacent electrodes.

three components: 1) the macrocyclic polymer, 2) the Cu center (for poly1-L), and 3) the threading polymer. A comparison with the cyclic voltammogram of poly4 (Figure 3, bottom) indicates that the first wave at about 0.1 V vs. Fc/Fc^+ and a broad featureless wave for electroactivity at more positive potentials than for poly1-L and poly2-L can be assigned to the macrocycle-containing polymer. For poly1-L the $\text{Cu}^{\text{I+}}/\text{Cu}^{\text{2+}}$ wave overlaps the wave for electroactivity of the macrocyclic polymer, which creates an optimal situation for the Cu-centered electroactivity to enhance the conductivity.

The conductivities of rotaxane complexes of poly3 have

been previously determined to be low (ca. 10^{-3} Scm^{-1}), and thus the poly4 backbone is the dominant contributor to the conductivity of the ladder polymers. Simple inspection of Figure 2 reveals that the conductivity of poly1-L^[11] (σ) at 0.25 V vs. Fc/Fc⁺ is 38 Scm^{-1} , approximately 20 times higher than for poly2-L at the same potential ($\sigma = 2 \text{ Scm}^{-1}$); the conductivity of poly4 at the same potential is 66 Scm^{-1} . All three materials poly1-L, poly2-L, and poly4 display comparable (within a factor of 2) conductivities at high potentials ($\approx 0.9 \text{ V}$ vs. Fc/Fc⁺). These comparisons of conductivity demonstrate that the central macrocyclic polymer (poly4) in poly1-L and poly2-L is isolated by the outer polymers (poly3 chains) when they are in their insulating states. When the poly3 chains are insulating, the electroactivity of the Cu ions can assist in interchain transport. We had previously determined that the conductivity of polymers is enhanced when the wave for electroactivity of a metal center overlaps that of the conjugated polymer.^[5b, 12] Based upon these previous studies the redox potential of the Cu ion is optimally positioned to participate in the conduction. This effect, illustrated in Scheme 2, is responsible for the much larger conductivity at



Scheme 2. Schematic representation of the participation of the Cu ion in the conduction.

lower potentials of poly1-L relative to poly2-L. In the absence of a rotaxane structure the polymer chains of poly3 can come in close proximity, and poly4 exhibits a high conductivity without the Cu-centered electroactivity. At higher potentials the poly3 chains are redox-active and mediate interchain conduction. Hence, we have similar conductivities for poly1-L, poly2-L, and poly4.

We have demonstrated a powerful new approach for the assembly of conducting three-strand ladder polymers. By design, we have produced a noncovalent ladder polymer that encloses a central polymer in a sandwich structure between two other polymers. The three-strand structure may be extended to create supramolecular structures wherein a central polymer is protected between two inert insulating polymers. Such an approach may prove important in the quest for insulated metallic molecular wires and also provides a novel mechanism for the formation of high stability conjugated polymers. The dramatic effect of the copper ion on the conductivity also suggests that similar processes may be of use for the design of chemoresistive sensory materials.

Experimental Section

General procedures: Reactions were carried out in oven-dried glassware using standard Schlenk techniques under an inert atmosphere of dry argon. ¹H NMR spectra were recorded with a Bruker AC-250 or Varian Inova-500 MHz spectrometers. Electrochemical measurements were performed in an air-free dry-box using a computer-controlled Autolab Model PGSTAT 20 potentiostat from Eco Chemie. All electrochemical measurements were performed on interdigitated array microelectrodes purchased from AAI-ABTECH with an interelectrode spacing of 5 μm , with a platinum coil counterelectrode and an isolated Ag wire quasi-reference electrode. All potentials are reported versus the Fc/Fc⁺ redox couple. Compound 6 was synthesized from the tosylate^[14] by simple exchange with iodide ion, and 7 was prepared as reported previously.^[15] Macrocycle 5 was produced by straightforward adaptation of conditions used for the synthesis of related macrocycles.^[15]

4: Compound 5 (100 mg, 0.115 mmol), 2-(tributylstannyl)-3,4-ethylene-dioxythiophene (124 mg, 0.288 mmol), CuI (66 mg, 0.346 mmol), and *trans*-[PdCl₂(PPh₃)₂] (4 mg) were dissolved in dry DMF (10 mL), and the mixture was stirred overnight at 80 °C. The DMF was then evaporated, and the residue was extracted with CH₂Cl₂/NH₄OH. The organic phase was dried, and the crude product was precipitated with hexane. Column chromatography (SiO₂, CH₂Cl₂/MeOH 99/1) afforded the desired compound as a yellow solid in 90% yield. ¹H NMR (500 MHz, CDCl₃): δ = 3.98 (m, 4H), 4.02 (m, 4H), 4.11 (m, 4H), 4.23 (m, 8H), 4.31 (m, 4H), 6.40 (s, 2H), 7.07 (d, J = 8.0 Hz, 4H), 7.74 (s, 2H), 7.81 (s, 2H), 8.07 (d, J = 8.2 Hz, 2H), 8.26 (d, J = 8.2 Hz, 2H), 8.39 (d, J = 8.0 Hz, 4H); HR-MS (FAB): calcd for C₅₀H₄₂N₂O₁₀S₂ [M+H]⁺: 895.2359, found: 895.2346.

Monomer 1: A solution of [Cu(MeCN)₄]BF₄ (5.3 mg, 0.017 mmol) in dry deoxygenated MeCN (2 mL) was transferred through a cannula to a solution of 3 (8 mg, 0.017 mmol) and 4 (15 mg, 0.017 mmol) in dry deoxygenated CH₂Cl₂ (10 mL). After 3 h stirring the solvents were evaporated, and the residue was dissolved in acetone and filtered. Concentration and addition of diethyl ether afforded compound 1 as a green powder that was isolated in 60% yield. ¹H NMR (500 MHz, [D₆]acetone): δ = 3.79, 3.9, 4.05, 4.18, 4.29, 4.38, 4.69 (m, 24H), 6.30 (d, J = 8.8 Hz, 4H), 6.61 (s, 2H), 7.14 (dd, J = 5.2, 5.2 Hz, 2H), 7.30 (m, 4H), 7.36 (dd, J = 3.7, 1.2 Hz, 2H), 7.39 (d, J = 4.0 Hz, 2H), 7.51 (dd, J = 5.2, 1.2 Hz, 2H), 7.64 (d, J = 8.5 Hz, 4H), 7.79 (dd, J = 8.5, 2.4 Hz, 2H), 8.18 (s, 2H), 8.26 (d, J = 2.1 Hz, 2H), 8.29 (d, J = 8.2 Hz, 2H), 8.31 (s, 2H), 8.89 (d, J = 8.2 Hz, 2H); HR-MS (FAB): calcd for C₇₆H₅₈N₄O₁₀S₆Cu [M+H]⁺: 1442.1851, found: 1442.1878.

Monomer 2: The synthesis was performed as described for 1, using [Zn(ClO₄)₂]·6H₂O (4.2 mg, 0.01 mmol), 3 (5.4 mg, 0.01 mmol), and 4 (10 mg, 0.01 mmol). The product was isolated in 90% yield as an orange solid. ¹H NMR (500 MHz, [D₆]acetone): δ = 3.70, 3.88, 3.93, 4.04, 4.16, 4.29, 4.40, 4.67 (m, 24H), 6.52 (d, J = 9.0 Hz, 4H), 6.67 (s, 2H), 7.16 (dd, J = 5.0, 5.0 Hz, 2H), 7.33 (d, J = 4.0 Hz, 4H), 7.37 (dd, J = 3.5, 1.2 Hz, 2H), 7.42 (d, J = 4.0 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.56 (dd, J = 5.2, 1.2 Hz, 2H), 7.59 (d, J = 8.5 Hz, 4H), 7.87 (dd, J = 8.5, 2.5 Hz, 2H), 8.15 (s, 2H), 8.39 (m, 2H), 8.44 (d, J = 8.5 Hz, 2H), 8.49 (s, 2H), 9.18 (d, J = 8.5 Hz, 2H); HR-MS (FAB): calcd for C₇₆H₅₈N₄O₁₀S₆Zn [M+H]⁺: 1443.1846, found: 1443.1873.

Received: August 30, 1999 [Z13941]

- [1] S. M. Sze, *The Physics of Semiconductor Devices*, 2nd ed., Wiley, New York, **1981**.
- [2] P. K. H. Ho, D. S. Thomas, R. H. Friend, N. Tessler, *Science* **1999**, 285, 233.
- [3] *Comprehensive Supramolecular Chemistry*, Vols. 1–10 (Eds.: J. L. Atwood, J. D. D. Davies, D. D. MacNicol, F. Vögtle), Pergamon, New York, **1996**.
- [4] a) F. M. Raymo, J. F. Stoddart, *Chem. Rev.* **1999**, 99, 1643; b) J. C. Chambron, J.-P. Sauvage, *Chem. Eur. J.* **1998**, 4, 1362; c) J.-P. Sauvage, *Acc. Chem. Res.* **1998**, 31, 611.
- [5] a) S. S. Zhu, T. M. Swager, *J. Am. Chem. Soc.* **1996**, 118, 8713; b) S. S. Zhu, T. M. Swager, *J. Am. Chem. Soc.* **1997**, 119, 12568.
- [6] S. S. Zhu, T. M. Swager, *Adv. Mater.* **1996**, 8, 497.
- [7] P. L. Vidal, M. Billon, B. Divisia-Blohorn, G. Bidan, J. M. Kern, J.-P. Sauvage, *Chem. Commun.* **1998**, 629.

- [8] a) G. P. Kittleson, H. S. White, M. S. Wrighton, *J. Am. Chem. Soc.* **1984**, *106*, 7389; b) J. W. Thackeray, H. S. White, M. S. Wrighton, *J. Phys. Chem.* **1985**, *89*, 5133.
- [9] S. S. Zhu, R. P. Kingsborough, T. M. Swager, *J. Mater. Chem.* **1999**, *9*, 2123–2134.
- [10] All calculations were performed with the Spartan program (Wavefunction, Inc.). The geometry of **1** was optimized using semiempirical calculations (PM3). The structure of the octamer was minimized by molecular mechanics (MMFF94).
- [11] To obtain conductivities the coverage on the electrodes were determined by profilometry and are related to that of poly(3-methylthiophene), $\sigma = 60 \text{ S cm}^{-1}$ to correct for non-uniform coverage. This method has been established to provide a reliable measurement of a number of electropolymerizable monomers.^[12, 13]
- [12] R. P. Kingsborough, T. M. Swager, *Adv. Mater.* **1998**, *10*, 1100.
- [13] a) G. Zotti, G. Schiavon, *Synth. Met.* **1990**, *39*, 183; b) G. Schiavon, S. Sitran, G. Zotti, *Synth. Met.* **1989**, *32*, 209.
- [14] Q. Zhou, T. M. Swager, *J. Am. Chem. Soc.* **1995**, *117*, 12593.
- [15] C. O. Dietrich-Buchecker, J.-P. Sauvage, *Tetrahedron Lett.* **1983**, *24*, 5091.

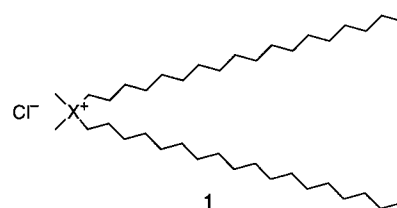
Polar Thin Films Produced by Phosphonium Liquid Crystals: Two-Dimensional Self-Assembled Ionic Layers with Spontaneous Polarization**

Akihiko Kanazawa, Tomiki Ikeda,* and Jiro Abe

The area of thin film assemblies that have layer structures is rapidly developing into a key technology with applications ranging from chemical sensor systems to electronic materials (dielectrics, semiconductors, superconductors, optoelectronics, magnetic substances, and so forth).^[1] The layered thin films are usually prepared from organic or inorganic materials by a variety of physical and chemical techniques (including, among others, laser ablation, evaporation, sputtering, chemical vapor deposition, the Langmuir–Blodgett technique, and sol–gel processing).^[1a,b, 2] For solid-state thin films, however, it is often difficult to control the layer structure and the molecular (or atomic) arrangement. Since crystalline materials are mainly used as sources for the thin film assemblies, the assembly structures are limited by the intrinsic single-crystal structures of these sources. Clearly, the ability to control of organizational structure at the molecular or atomic levels is very important in development of new functionalized materials. Recently, supramolecular assemblies have been regarded as one of the most promising systems for applications in highly functionalized materials.^[3] Liquid-crystalline materials have self-assembly characteristics for forming various phases and

provide additional features such as the ability to respond to applied external fields. The assembly structures are directed by the choice of phase, so that the structurally controlled thin films could be prepared by quenching from the appropriate fluid phase into the solid state.^[4] The incorporation of the liquid-crystalline properties into layered materials may be expected to bring about emergence of more functionalized thin films with characteristic structural features.

Through systematic studies on the applications of ionic amphiphiles to multifunctional materials (for example: antimicrobial agents, surfactants, phase-transfer catalysts, anti-static agents, ion exchangers, curing agents), we found that phosphonium salts, which are composed of an ion pair of positive phosphorus and negative halide atoms as well as two long alkyl segments, **1** ($X = P$), possess a high degree of molecular organization abilities in comparison with the common quaternary ammonium analogs, **1** ($X = N$), with the same structure except for the positively charged heteroatom.^[5]



Even in the bulk state, the phosphonium salts showed an advantageous feature as a thermotropic liquid crystal in spite of being structurally simple amphiphiles.^[5c, 6] These salts formed a multilayer structure based on the bilayer stacking of the smectic A phase, which is built up from alternating layers of ions and alkyl segments. If such ionic liquid crystals are applied to solid-state systems, they may be regarded as a novel class of layered thin films because of the presence of two-dimensional polar layers, which are composed of pairs of positive and negative ions forming an electric dipole, separated by the insulating alkyl layers. Here we present unique feature of self-assembled layered thin films produced by the phosphonium liquid crystals, which was revealed through the evaluation of the second-order nonlinear optical properties (Figure 1).

To determine the spatial arrangement of ions in the layers the second-harmonic generation (SHG) was measured, which is an effective tool for evaluation of dipolar alignment in the molecular organizations. For the SHG measurement, we used the thermotropic liquid-crystalline phosphonium chloride (P-LC) and the quaternary ammonium analog (N-LC) as a reference liquid crystal. Solid-state samples retaining a smectic layer structure were readily prepared by injecting the compounds into a sandwiching cell with a gap of 15 μm in the isotropic phase, followed by rapid cooling to room temperature. These samples were colorless and transparent. Figure 2 shows changes in the SHG intensity observed for the P-LC and the N-LC films. The polarized exciting beam was introduced along the z axis (Figure 1b). Second-harmonic generating signals were clearly observed for P-LC (Figure 2a). On the other hand, N-LC with the same hydrophobic structure was SHG-inactive (Figure 2b). These results indicate that the second-order nonlinear optical response of the

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[**] We thank Makoto Ogura and Atsuya Takahashi of Fujitsu, Ltd., and Azuma Matsuura and Tomoaki Hayano of Fujitsu Laboratories, Ltd., for the use of the latest version of the ANCHOR II system.^[14]

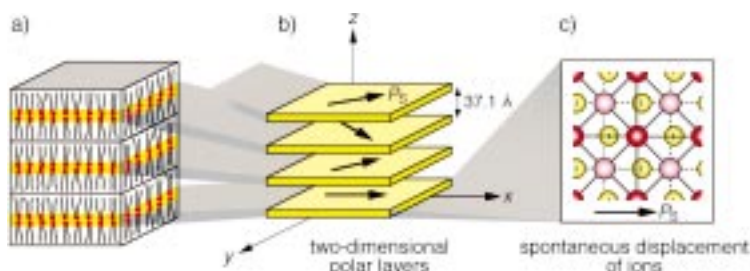


Figure 1. Schematic illustration of the self-organized layered thin film of the phosphonium liquid crystal (P-LC). a) Molecular alignment in the solid-state P-LC sample retains a bilayer structure, which was evaluated by the X-ray diffraction analysis using thin film methods. The diffraction patterns gave several higher-order Bragg reflections and the layer spacing (37.1 Å) is equal to twice the 18.5 Å molecular length. b) Two-dimensional polar layers, as an SHG-active site comprising the self-assembled phosphonium molecules, are aligned parallel to the glass substrates (x,y plane). Square plates and arrows correspond to an ionic layer and a spontaneous polarization (P_s), respectively. c) Realized relative arrangement of the phosphonium ions in a layer on the basis of the simplest square-array model with a tetrahedral unit cell. Dark- and light-red circles correspond to the positively charged phosphorus atoms with the long alkyl tails above and below the lattice plane, respectively, located on the corners of the tetrahedral cell. Yellow circles in each unit cell correspond to the chloride anions located in the spaces between the bilayers and are surrounded by four cations.

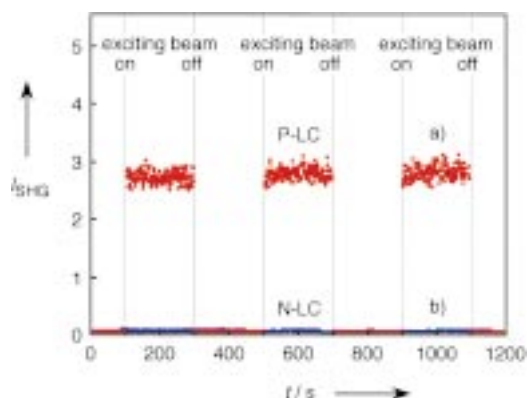


Figure 2. Change in the intensity of SHG signals on irradiation of the layered thin samples with the exciting beam: a) P-LC; b) N-LC. A Q-switched Nd:YAG laser ($\lambda = 1064$ nm, 10 Hz repetition rate, 6 ns pulse duration) was used for the exciting light source. The pulse energy of laser was controlled with neutral-density filters, then passed through a $\frac{1}{4}$ waveplate and a plate polarizer to polarized the beam along the x or y axis (see Figure 1). The sample sandwiched in the cell was placed on a sample stage in the x,y plane. The polarized laser beam passed through a UV-Vis cutoff filter and was focused on the sample along the z axis. After the sample, an IR filter, a polarization analyzer, and interference filter were used to remove all but the SHG signal (532 nm) with the same plane polarization as the fundamental wave. The SHG signal was detected with a photomultiplier and processed with a boxcar integrator interfaced with a computer.

amphiphilic organizations is related to their liquid-crystalline properties and this phenomenon is specific for the phosphonium species.

The phosphonium self-assembly was confirmed to be composed of highly ordered layer structure based on the bilayer stacking even in the solid state (Figure 1a). This implies that the SHG from the P-LC sample is due to the nonlinear polarization in the ionic layer. For SHG, a non-centrosymmetrical molecular or atomic arrangement of the materials is required in the bulk phase. In the phosphonium assembly, if noncentrosymmetrical macroscopic arrangement of

ions in the ionic layer is induced spontaneously, the ionic layer may possess second-order nonlinear optical properties. Many polar crystals with a non-centrosymmetric structure, such as barium titanate and sodium nitrite, are known to show a second-order nonlinear optical response.^[1a,b,7] The spontaneous polarization (P_s) as an overall permanent electric polarization occurs in the absence of an external electric field because of the displacement of ions or because of ordering of the dipole groups.^[1,7,8] We propose herein a possible model for the polar thin film produced by the self-assembly of two-dimensional ionic phosphonium layers (Figure 1b). The P_s occurs by the spontaneous displacement of ions in each layer plane as shown in Figure 1c. This may be due to the collective effect of each ion pair as an electric dipole. It is of interest that the P-LC thin film possesses a macroscopically ordered P_s , even though each ionic layer is separated by insulating glassy alkyl segments. Further, the angular dependence of the polarization of the exciting beam on the SHG activity was observed. When the exciting beam polarized along the x axis was employed, the thin film assembly

was most active in the SHG. In contrast, with the exciting beam polarized along the y axis, the intensity of the SHG signals decreased.

Here we must clarify why the phosphonium thin film shows the P_s resulting from the spontaneous displacement of ions in the layer plane. The phosphorus atom is able to form pentavalent molecules, for example PCl_5 , in which there are more than four electron pairs around the central atom because of the participation of 3d orbitals participating in bonding^[9] or the presence of three-center four-electron bonds.^[10] On the other hand, the nitrogen atom is unable to form such pentavalent compounds. We predict therefore that the P_s of the phosphonium assembly is attributed to the electronic structure of the phosphorus atom. Figure 3 shows the potential energy surfaces of the liquid crystals calculated through the density functional method, in which the chlorine displacement in linear $[\text{XH}_4\text{--Cl--XH}_4]^+$ ($\text{X} = \text{N}, \text{P}$) was varied.^[11] The P-LC sample was found to give a bistable geometry with the noncentrosymmetric atomic arrangement. This result indicates that the phosphonium cation would form a weak P–Cl bond with the chloride anion. In contrast, N-LC showed only the centrosymmetric geometry. These results therefore support our hypothesis that in the two-dimensional noncentrosymmetric polar layers the spontaneous displacement of ions originates from the variety of bonding of the phosphorus atoms. The detailed mechanism of the bond formation between phosphonium and chloride ions, however, is not well understood at the present stage of research.

The phosphonium self-assembly with a polar order essentially differs from the conventional supramolecular systems because the origin of macroscopic polarization is not due to a dipolar alignment in molecule-based organizations,^[3c–1] but due instead to a noncentrosymmetrical atomic arrangement of ion pairs as an electric dipole.^[12]

Received: May 17, 1999 [Z13419]

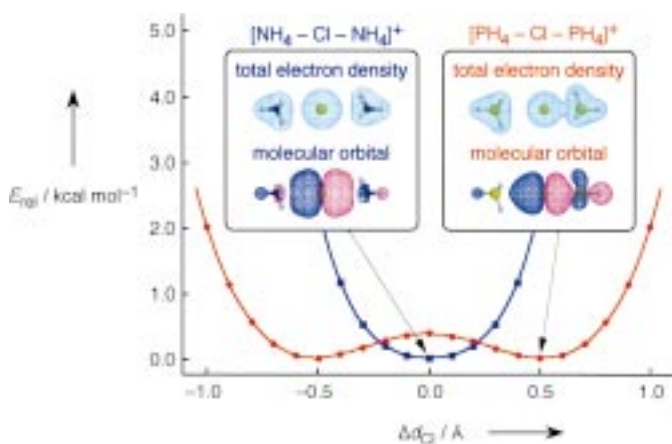


Figure 3. Potential energy surfaces of the LC samples, which were obtained by theoretical calculations on the linear $[\text{XH}_4\text{-Cl-XH}_4]^+$ ($\text{X} = \text{N}, \text{P}$) model. In these molecular models, the distances between the heteroatoms were fixed; 7.0 and 6.6 Å for P-LC and N-LC, respectively, which were estimated by the X-ray measurement. To determine the most stable atomic arrangement the degree of the displacement of the chlorine atom was varied and the molecular structures were fully optimized at the DFT/Beck3LYP level of theory using the 6-31G(d) basis set. The potential energy was calculated simultaneously. Inserted figures show the total electron density and one of the most significant molecular orbital which contributes to the interaction between the chloride atom and heteroatom in each molecular model. The contour level is 0.015 au. The molecular orbitals show that the orbital mixing between nitrogen and chlorine atoms in $[\text{NH}_4\text{-Cl-NH}_4]^+$ occurs out of phase (i.e., antibonding manner), while that between phosphorus and chlorine atoms in $[\text{PH}_4\text{-Cl-PH}_4]^+$ is in phase and indicates bonding.

- [1] a) C.-Y. Li, Y. Xu, *Handbook of Photonics* (Ed.: M. C. Gupta), CRC Press, Boca Raton, FL, **1997**, pp. 87–124; b) *Thin Film Ferroelectric Materials and Devices* (Ed.: R. Ramesh), Kluwer Academic Publishers, Hingham, MA, **1997**; c) R. Schöllhorn, *Angew. Chem.* **1996**, *108*, 933; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 859, and references therein; d) M. T. Weller, *Inorganic Materials Chemistry*, Oxford University Press, New York, NY, **1994**.
- [2] a) A. V. Bune, V. M. Fridkin, S. Ducharme, L. M. Blinov, S. P. Palto, A. V. Sorokin, S. G. Yudin, A. Zlatkin, *Nature* **1998**, *391*, 874; b) C. T. Seip, G. E. Granroth, M. W. Meisel, D. R. Talham, *J. Am. Chem. Soc.* **1997**, *119*, 7084.
- [3] a) J.-M. Lehn, *Angew. Chem.* **1988**, *100*, 91; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89; b) J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, **1995**, pp. 89–138; c) H. Wang, M. Y. Jin, R. C. Jarnagin, T. J. Bunning, W. Adams, B. Cull, Y. Shi, S. Kumar, E. T. Samulski, *Nature* **1996**, *384*, 244; d) G. N. Tew, L. Li, S. I. Stupp, *J. Am. Chem. Soc.* **1998**, *120*, 5601; e) W. M. K. P. Wijekoon, S. K. Wijaya, J. D. Bhawalkar, P. N. Prasad, T. L. Penner, N. J. Armstrong, M. C. Ezenyilimba, D. J. Williams, *J. Am. Chem. Soc.* **1996**, *118*, 4480; f) W. Lin, W. Lin, G. K. Wong, T. J. Marks, *J. Am. Chem. Soc.* **1996**, *118*, 8034; g) X. Yang, D. McBranch, B. Swanson, D.-Q. Li, *Angew. Chem.* **1996**, *108*, 572; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 538; h) M. Kauranen, T. Verbiest, C. Boutton, M. N. Teerenstra, K. Clays, A. J. Schouten, R. J. M. Nolte, A. Persoons, *Science* **1995**, *270*, 966; i) O.-K. Kim, L.-S. Choi, H.-Y. Zhang, X.-H. He, Y.-H. Shih, *J. Am. Chem. Soc.* **1996**, *118*, 12220; j) C. Dhenaut, I. Ledoux, I. D. W. Samuel, J. Zyss, M. Bourgaud, H. L. Bozec, *Nature* **1995**, *374*, 339; k) T. Verbiest, S. V. Elshocht, M. Kauranen, L. Hellemaans, J. Snauwaert, C. Nuckolls, T. J. Katz, A. Persoons, *Science* **1998**, *282*, 913; l) T. J. Marks, M. A. Ratner, *Angew. Chem.* **1995**, *107*, 167; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 155.
- [4] L. Y. Park, J. M. Rowe, *Chem. Mater.* **1998**, *10*, 1069.
- [5] a) A. Kanazawa, T. Ikeda, T. Endo, *Antimicrob. Agents Chemother.* **1994**, *38*, 945; b) A. Kanazawa, T. Ikeda, T. Endo, *J. Appl. Bacteriol.* **1995**, *78*, 55; c) A. Kanazawa, T. Ikeda, *Coord. Chem. Rev.*, in press.

- [6] a) A. Kanazawa, O. Tsutsumi, T. Ikeda, Y. Nagase, *J. Am. Chem. Soc.* **1997**, *119*, 7670; b) A. Kanazawa, T. Ikeda, *Mater. Res. Soc. Symp. Proc.* **1999**, *559*, 201.
- [7] G. A. Smolenskii, V. A. Bokov, V. A. Isupov, N. N. Krainik, R. E. Pasynkov, A. I. Sokolov, *Ferroelectrics and Related Materials* (Ed.: G. W. Taylor), Gordon and Breach, New York, NY, **1984**.
- [8] a) D. F. Shriver, P. W., Atkins, C. H. Langford, *Inorganic Chemistry*, Oxford University Press, Oxford, **1994**, pp. 765–766; b) C. Kittel, *Introduction to Solid State Physics*, 5th ed., John Wiley & Sons, New York, **1976**, pp. 413–417; c) *Solid-State Physics*, 2nd ed. (Eds.: H. Ibach, H. Lüth), Springer, Berlin, **1995**, chap. 11.
- [9] a) K. A. R. Mitchell, *Chem. Rev.* **1969**, *69*, 157; b) A. Rauk, L. C. Allen, K. Mislow, *J. Am. Chem. Soc.* **1972**, *94*, 3035; c) R. Hoffmann, J. M. Howell, E. L. Muetterties, *J. Am. Chem. Soc.* **1972**, *94*, 3047.
- [10] a) J. I. Musher, *Angew. Chem.* **1969**, *81*, 68; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 54; b) C. W. Perkins, J. C. Martin, A. J. Arduengo, W. Lau, A. Alegria, J. K. Kochi, *J. Am. Chem. Soc.* **1980**, *102*, 7753; c) W. Kutzelnigg, *Angew. Chem.* **1984**, *96*, 262; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 272; d) P. A. Cahill, C. E. Dykstra, J. C. Martin, *J. Am. Chem. Soc.* **1985**, *107*, 6359; e) A. E. Reed, P. V. R. Schleyer, *J. Am. Chem. Soc.* **1990**, *112*, 1434; f) R. J. Hach, R. E. Rundle, *J. Am. Chem. Soc.* **1951**, *73*, 4321; g) G. C. Pimentel, *J. Chem. Phys.* **1951**, *19*, 446.
- [11] The ionic layer within the layered self-assembly formed by the samples is electrically neutral. As shown in Figure 1c, the tetrahedral unit cell, consisting of one chloride anion and four cations, exhibits a positive trivalent state, which is significantly different from the ideal electroneutrality model. Thus, the positive univalent $[\text{XH}_4\text{-Cl-XH}_4]^+$ model was used to approximate the ideal model.
- [12] The interaction of the molecule with an electromagnetic field is described as the perturbation Hamiltonian. The interaction Hamiltonian can be written as a multiple expansion by a canonical transformation $\mathcal{H}_1 = -(\mu \times E + m \times H + Q \times \nabla E + \dots)$, where μ , m , and Q correspond to the electric dipole, magnetic dipole, and electric quadrupole moments of the molecules, respectively.^[13a] Within the electric dipole approximation, SHG is allowed in a molecular organization with dipole symmetry (dipolar order) but forbidden in one with quadrupole symmetry (e.g., an antiparallel array of the dipolar molecules). In the latter case, SHG should be dominated by electric quadrupole and magnetic dipole contributions. The conventional cyanobiphenyl-based liquid crystals, possessing dipole moments along the molecular long axis, have been reported to show an SHG activity in the smectic A phase.^[13b] It has been concluded that the nonlinear optical response is due to the antiparallel orientational order of the molecules in each layer, that is, the smectic A films have quadrupole rather than dipole symmetry.^[13b] In the case of molecular assemblies with quadrupole symmetry, the SHG can be observed even in the fluid phase possessing a centrosymmetric macroscopic structure. On the other hand, if an electric dipole process contributes to the SHG, the materials should exhibit no SHG activity in the fluid phase because of the disruption of polar ordering of dipoles (i.e., non-centrosymmetric structure). In the usual polar crystals with a non-centrosymmetric structure, it is known that the macroscopic polarization disappears at a certain (Curie) temperature resulting from the increase of lattice vibration through order–disorder solid–solid phase transition.^[14] A similar phenomenon was observed also for the solid-state P-LC film. We confirmed that P-LC shows no SHG activity in the temperature range of 75–82 °C not only in the smectic A phase but also in the solid phase retaining a smectic layer structure. This indicates disruption of dipolar order in the ionic layers occurs earlier than the solid to liquid-crystalline phase transition. Additionally, if the P-LC film is truly composed of the two-dimensional domains with P_s based on the dipolar order, their P_s directions are assumed to be changed by the external field such as an electric field and a mechanical stress. A lateral electric field was then applied to the sample film along the x axis by using substrates with a pattern of interdigitated electrodes. When the exciting beam polarized along the x axis was employed, the P-LC film was more active in the SHG than that before application of the electric field. In contrast, with irradiation of the exciting beam polarized along the y axis, the intensity of the SHG signals decreased outstandingly. This result implies that the P_s of the ionic layers can be aligned macroscopically by application of the lateral electric field. If the SHG from P-LC is due to the alternate

arrangement of the positive and negative ions in each layer plane (quadrupole symmetry), such modulation of the polar order may not be observed. In fact, the N-LC film, possessing quadrupole symmetry in the ionic layers, was inactive at all for the SHG under the same experimental condition. On the basis of these preliminary results, therefore, we concluded that the SHG from the P-LC film may be governed by the customary electric dipole process rather than the electric quadrupole process.

- [13] a) *Nonlinear Optical Properties of Organic Molecules and Crystals, Vol. 1* (Eds.: D. S. Chemla, J. Zyss), Academic Press, Orlando, FL, 1987, pp. 63–72; b) H. Hsiung, Y. R. Shen, *Phys. Rev. A* **1986**, *34*, 4303.
[14] ANCHOR II V1L5, Fujitsu, Ltd., Kureha Chemical Industry, Co. Ltd., Tokyo, 1995.

Global Chirality in Rigid Decametallic Ruthenium Dendrimers**

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One hallmark of dendrimer chemistry is the ability to construct nanometer-sized assemblies with discrete architectures and defined connectivity.^[1] In many cases, however, the ability to control the primary structure does not translate into the ability to control the global structure with high spatial organization and fidelity. Conformational flexibility within the dendrimer often leads to compact “molten globule” tertiary structures despite the composition. The incorporation of rigid monomers and linkages has led to shape-persistent dendrimers with restricted conformations, however, some rotational motion prevents complete spatial control.^[2] A related, but heretofore elusive, goal is the construction of dendrimers that exhibit a global chiral topology.^[3] Efforts to impart such a “tertiary” structure have focused predominantly on the incorporation of chiral carbon centers (C_1 symmetric) into the “primary” structure of the dendrimer.^[4] While

interesting chiroptic effects are observed in several cases, none show adoption of a preferred global chiral structure.

In contrast, spatially well-defined nanoscopic molecules, such as helicates, rings, squares, and boxes, are readily assembled by using metal-directed self-assembly methods.^[5] Many such structures exhibit macroscopic chirality and several have even been prepared in enantiopure form through the use of chiral ligands.^[6] The self-assembly approach has one drawback, in that the high lability of the metal ions required for such facile assembly typically makes such structures equally susceptible to decomposition or reorganization under conditions far milder than observed for most dendrimers.

We describe herein the synthesis of chiral, conformationally rigid metallodendrimers, which rival organic dendrimers in robustness and self-assembled structures in spatial fidelity. The $[\text{Ru}(\text{diimine})_3]^{2+}$ unit is our basic chiral synthon for supramolecular synthesis. This unit has enjoyed considerable attention as a building block for metallodendrimers largely because of its favorable room-temperature luminescence and redox properties, as well as its excellent chemical stability.^[7] Until recently, however, the lack of stereospecific synthetic methods in the preparation of multimetallic assemblies has meant that such dendrimers are diastereomeric mixtures.^[8] We have developed a stereospecific synthetic strategy for assembling such units into dendritic arrays and now demonstrate the power of this method to direct the tertiary structure of a nanosized molecule.

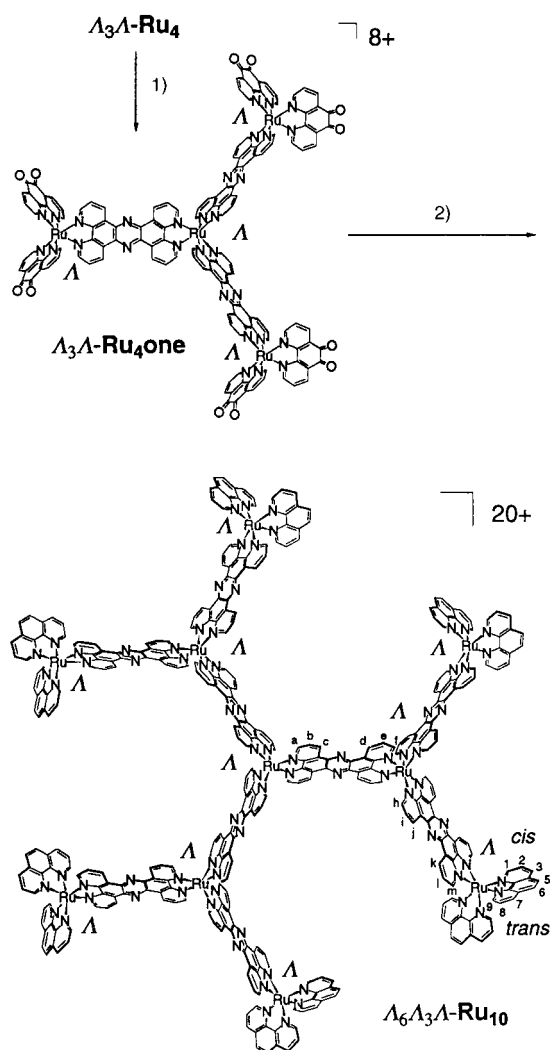
The homochiral decamer $\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10}$ was prepared in enantiopure form following the divergent synthetic route shown in Scheme 1. The notation used, $\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10}$, gives first the stereochemistry of the outermost shell of ruthenium atoms, then the stereochemistry of the next outermost ruthenium sites, and then of the core atom. Central to this strategy is the use of substitutionally inert ruthenium trisdiimine complexes as chiral synthons which are connected by the condensation reaction between quinone and diamine functional groups at the periphery. The ruthenium tetramer $[\Lambda\text{-Ru}\{\Lambda\text{-(tpphz)}\text{Ru}(\text{phen})_2\}_3]^{8+}$ (tpphz = tetrapyrrodo[3,2-*a*:2',3'-*c*:3'',2''-*h*:2''',3'''-*j*]phenazine) ($\Lambda_3\Lambda\text{-Ru}_4$) was prepared by this method^[9] and can act as the core for further dendritic growth after oxidation of the terminal phenanthrolines to the quinone product $\Lambda_3\Lambda\text{-Ru}_4\text{one}$ (Scheme 1). In this manner, the parent hydrocarbon acts as the protected form of the quinone and permits a controlled growth scheme. This reaction gives 67% yield of the desired quinone and proceeds with retention of stereochemistry, despite the harsh reaction conditions, as determined by circular dichroism (CD) and by analogy to a model study of this reaction on mononuclear chiral complexes.^[10] Addition of excess $\Lambda\text{-}[\text{Ru}(\text{phen})_2(\text{phendiamine})]^{2+}$ produces the decamer in $\approx 20\%$ yield after purification by alumina- and gel-packed column chromatography. The diastereomeric decamer $\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10}$ was prepared in a similar manner from $\Lambda_3\Lambda\text{-Ru}_4\text{one}$ and $\Lambda\text{-}[\text{Ru}(\text{phen})_2(\text{phendiamine})]^{2+}$. Both show excellent solubility in acetonitrile or dimethyl sulfoxide as the hexafluorophosphate salt, or in water as the chloride salt. These complexes are robust and show good stability even under harsh conditions (heat, concentrated acids and bases) and are stable to racemization in the absence of intense irradiation.^[11]

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[**] This work was supported by the Robert A. Welch Foundation. We thank Prof. Zoltan Schelly for assistance and discussions in obtaining the electric birefringence data, Prof. Kurt Mislow for helpful discussions on stereochemistry, and Prof. Barton Kaman for use of the mass spectrometry equipment. The authors would also like to thank the North Carolina Supercomputing Center for their partial support of the computational component of this work.



Scheme 1. Synthesis of the dendrimers. 1) H_2SO_4 , HNO_3 , NaBr , 100°C ; 2) 7 equiv $\Lambda\text{-}[\text{Ru}(\text{phen})_2(\text{phen}(\text{diamine}))][\text{PF}_6]_2$, $\text{MeCN}/\text{H}_2\text{O}$, reflux 15 h.

The decamers are composed of 448 non-hydrogen atoms (not including those of the anions), have a net $20+$ charge, and have diameters estimated at >5 nm. The decameric structure of the cations, $[\text{Ru}_{10}\text{C}_{360}\text{H}_{204}\text{N}_{78}]^{20+}$, was confirmed using electrospray-ionization mass spectrometry (ESI-MS). For example, the spectrum of $\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10}$ as a $20[\text{PF}_6]^-$ salt (Figure 1) clearly shows a dominant set of peaks correspond-

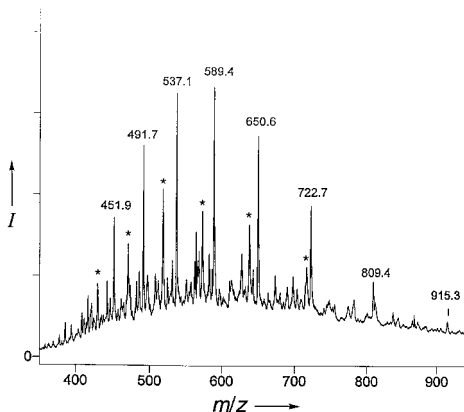


Figure 1. ESI-MS of $(\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10})[\text{PF}_6]_{20}$.

ing to m/z of 915.3 ($\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10} - 9[\text{PF}_6]$) $^{9+}$, 809.4 ($\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10} - 10[\text{PF}_6]$) $^{10+}$, 722.7 ($\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10} - 11[\text{PF}_6]$) $^{11+}$, 650.6 ($\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10} - 12[\text{PF}_6]$) $^{12+}$, 589.4 ($\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10} - 13[\text{PF}_6]$) $^{13+}$, 537.1 ($\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10} - 14[\text{PF}_6]$) $^{14+}$, 491.7 ($\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10} - 15[\text{PF}_6]$) $^{15+}$, and 451.9 ($\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10} - 16[\text{PF}_6]$) $^{16+}$. A second set of much smaller peaks (marked with * in Figure 1) correspond to a defect structure that is missing one peripheral ruthenium complex (" Ru_9 "). This impurity was not removed by chromatography but constitutes a minor component overall as determined by NMR spectroscopy (Figure 2). Previous studies of related metallodendrimers $^{[12]}$ have also shown that the PF_6^- ions can undergo extensive hydrolysis, which may be the source of the smaller baseline peaks.

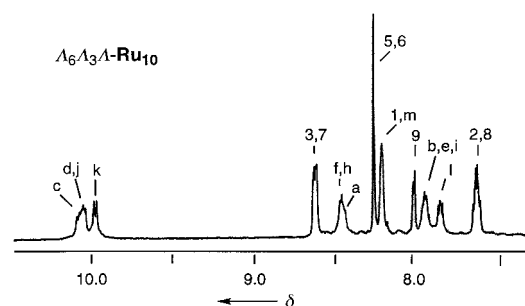


Figure 2. ^1H NMR of $(\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10})[\text{PF}_6]_{20}$ in $[\text{D}_3]\text{MeCN}$ (500 MHz). Proton assignments shown in Scheme 1.

As shown in Figure 2, the D_3 symmetry of $\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10}$ is clearly evident in the simplicity of the ^1H NMR data. However, of the 20 peaks expected from symmetry considerations, only 12 somewhat broad peaks are clearly resolved. COSY data indicate the broadness is largely due to multiple overlapping peaks, which is not too surprising considering the similarity of the microenvironment about the core and intermediate ruthenium centers. Furthermore, we suspect the line broadening is partially an effect of the large size and colloidal behavior (see below) of these complexes in solution which slows molecular tumbling on the NMR time scale. The assignment of peaks in Figure 2 was made on the basis of COSY data, along with comparison to the previously described dimers and tetramers. The spectrum for $\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10}$ is nearly identical to that for $\Lambda_6\Lambda_3\Lambda\text{-Ru}_{10}$, differing significantly only in the location of H_a and H_c which are both shifted upfield by ≈ 0.05 ppm. The small residual peaks along the baseline at $\delta = 8.06$ and 8.33 show a small but detectable amount of the defect structure " Ru_9 " is present.

Space-filling models of the two decamers (Figure 3) demonstrate the tertiary structure of the isomers. The stick-and-ball figures depict the spatial relationship and connectivity of ruthenium centers, and provide a simplified view of the global stereochemistry. Molecular modeling at the semiempirical level (PM3) was used to obtain the $[\text{Ru}(\text{phen})_3]^{2+}$ core. This calculated structure was in excellent agreement with the crystallographic data for the same cation $^{[13]}$ and was used to construct models for the decameric structure (see Experimental Section). Due to the overall conformational rigidity, we believe the modeling provides a substantially accurate picture of the molecular topology.

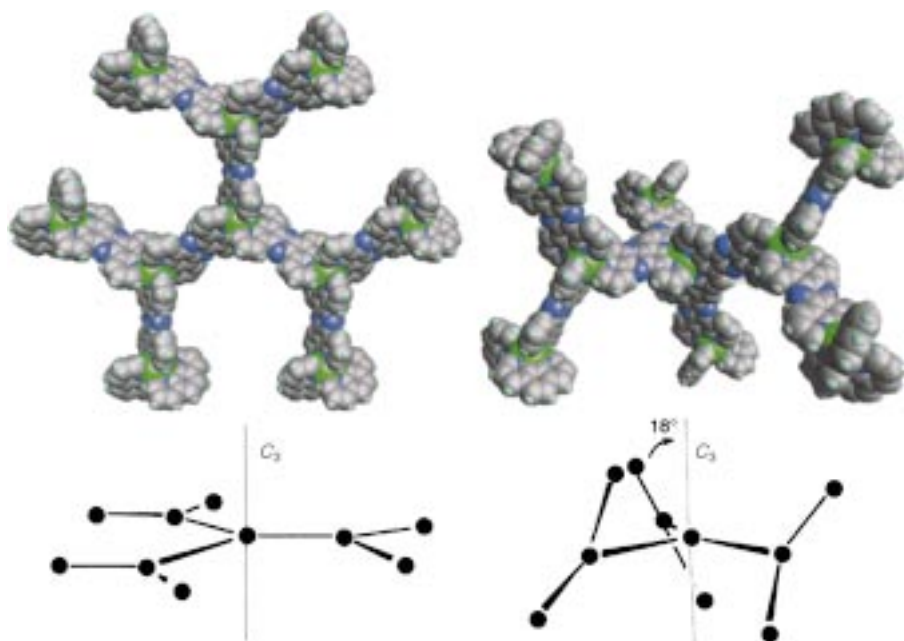


Figure 3. Space-filling models of $(T)-(A_6A_3A-Ru_{10})$ viewed down the molecular C_3 axis (left) and $(P)-(A_6A_3A-Ru_{10})$ viewed perpendicular to the molecular C_3 axis (right). Green represents ruthenium and blue represents nitrogen atoms. Representative ball-and-stick drawings of the ruthenium atom connectivity and topology are shown below.

The two diastereomers differ only in the stereochemistry at three dendritic sites, however, this small change has a dramatic effect on the overall topology. When viewed from the central ruthenium core, each arm consists of a plane of four ruthenium centers. For $A_6A_3A-Ru_{10}$, the pitch angle of this plane relative to the molecular C_3 axis is $\approx 18^\circ$, resulting in a massive *right-handed* propeller structure. For $A_6A_3A-Ru_{10}$, this pitch angle is 90° resulting in a flat disklike structure. The notation *P* (clockwise), *M* (counter-clockwise), and *T* (achiral) are introduced here as global stereochemical descriptors^[14] to indicate the global helicity as depicted in Figure 3. Preparation of $A_6A_3A-Ru_{10}$ would give the *M* isomer. The macroscopic pitch angle is a direct consequence of the local 36° pitch angle relative to the C_3 axis found for the $[Ru(phen)_3]^{2+}$ synthons.^[15] The core and adjacent stereocenter may combine constructively ($90^\circ - [36^\circ(A) + 36^\circ(A)] = 18^\circ$) to give the propeller structure or cancel ($90^\circ - [36^\circ(A) - 36^\circ(A)] = 90^\circ$) to give the planar structure.

Surprisingly, despite these large differences in the global structure we do not observe any readily discernable features in the CD results that unambiguously can be attributed to either diastereomer. As observed in the diastereomeric dimers and tetramers,^[13] the magnitude of the CD signal in the metal-to-ligand charge-transfer region (MLCT, 420–480 nm) is approximately proportional to the number of individual metal chromophores in enantiomeric excess (*ee*) within each structure. For the homochiral $(P)-(A_6A_3A-Ru_{10})$ an intense molar CD of +178 (477 nm, MeCN) is observed, which is roughly a 10-fold increase over $A-[Ru(phen)_3]^{2+}$ (+21, 471 nm, MeCN). Complex $(T)-(A_6A_3A-Ru_{10})$ gives a molar CD of +76 at 464 nm corresponding to approximately four $A-[Ru(phen)_3]^{2+}$ chromophores in enantiomeric excess. The lack of CD features related to the global chirality in $(P)-$

$(A_6A_3A-Ru_{10})$ can be attributed to weak electronic coupling between chromophores.

Significantly, the differing topologies for $(T)-(A_6A_3A-Ru_{10})$ and $(P)-(A_6A_3A-Ru_{10})$ do affect the colloidal properties as measured by electric birefringence. Campagna and co-workers have shown that related metallo-dendrimers are colloidal in dilute acetonitrile.^[16] Dynamic light scattering experiments show that both $(T)-(A_6A_3A-Ru_{10})$ and $(P)-(A_6A_3A-Ru_{10})$ exhibit polydisperse aggregation phenomena in acetonitrile (as PF_6^- salt) and water (as Cl^- salt). While no distinction between diastereomers could be observed in the light scattering experiment, both the amplitude and relaxation time for the forward and backwards birefringence signals (Figure 4) clearly show a distinct difference for the two colloids. For the *T* isomer (Figure 4b), the amplitude of the birefringence is small and the

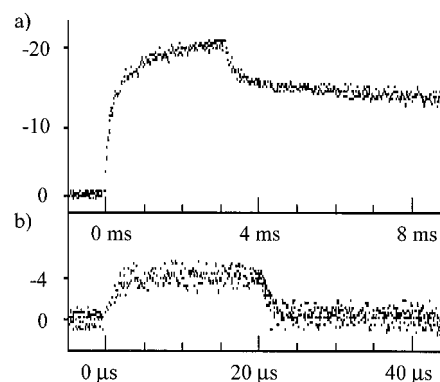


Figure 4. Plot of the electric field induced birefringence signals ($E = 4.8 \text{ kV cm}^{-1}$) of a) $(P)-(A_6A_3A-Ru_{10})$ at $77 \mu M$ as Cl^- salt in water, with pulse length = 3 ms and b) $(T)-(A_6A_3A-Ru_{10})$ at $74 \mu M$ as Cl^- salt in water, with pulse length = 20 μs . The ordinate is proportional to the transmitted light intensity.

corresponding decay signal is fast (in the microsecond range). On the other hand, for the *P* isomer (Figure 4a) the amplitude of the birefringence is much larger and the decay far slower (in the millisecond range) and anomalous (full data is not shown). To confirm that this result is a consequence of differing topology and not simply the diastereotopic nature of the complexes, A_3A-Ru_4 and A_3A-Ru_4 were examined. These two diastereomers have globally similar molecular topologies and also form polydisperse colloids in aqueous solution. In this control experiment, the birefringence signals were indistinguishable (both samples 0.22 mM as Cl^- salt in water). It is apparent that under the influence of an electric field, the isotropic chiral solution of $(P)-(A_6A_3A-Ru_{10})$ becomes optically anisotropic, which is likely due to structural distortion/orientation of the aggregates in the direction of the field, E ,

whereas the rapid evolution of the birefringence for (*T*)-(*A*₆*A*₃*A*-**Ru**₁₀) can be attributed to electronic polarization. These dramatic results show the influence of tertiary structure on the colloidal and macroscopic properties of such systems. Full details of the dynamics of the physical events involved will be discussed in a forthcoming paper.

We believe our method for making enantiomerically pure and rigid metallodendrimers opens a unique passage into the realm of nanochemistry with the ability to synthesize robust, enantiopure, nanoscopic assemblies with precisely tailored structures. These shape-specific metallodendrimers can be compared with many proteins in that they exhibit specific tertiary structures as a consequence of their primary sequence (local stereochemistry, e. g. *A*-*A*-*A* versus *A*-*A*-*A*) and secondary structure (every four adjacent Ru atoms constitute a plane). Ultimately, we aim to use such structures as nanoscopic platforms from which larger nanoscopic or mesoscopic arrays may be constructed.

Experimental Section

The tetramers *A*₃*A*-**Ru**₄[PF₆]₈ and *A*₃*A*-**Ru**₄[PF₆]₈ were synthesized according to literature procedures.^[9]

The isomers of **Ru**₄one[PF₆]₈ were prepared by slow addition of the appropriate isomer of **Ru**₄[PF₆]₈ (0.1 g, 0.03 mmol) to concentrated H₂SO₄ (3 mL) chilled to 0 °C in an ice water bath. NaBr (0.125 g) and HNO₃ (2.5 mL) were added to the resulting solution, which was heated to 100 °C for 20 min, cooled to room temperature and then poured into chilled water (50 mL, 0 °C) containing NaClO₄ (5 g). After the mixture was allowed to stand for 12 h at 0 °C the precipitate was filtered, washed with water (3 mL) then slurried with Dowex 21 K anion exchange resin (Cl⁻ form, 10 g) in water (30 mL) for 30 min which slowly redissolved the product. The resin solution was filtered and addition of excess NH₄PF₆ to the supernatant produced an immediate precipitate which was filtered, washed with water (3 mL), and then extracted with MeCN (10 mL). The MeCN extract was treated with excess water to give a dark brown precipitate which was filtered, washed, and dried in the vacuum oven at 60 °C. Typical yield 0.063 g (60 %). Elemental analysis (%): C₁₄₄H₇₂N₃₀F₄₈P₈Ru₄ · 4H₂O calcd: C 42.70, H 1.99, N 10.37; found: C 42.79, H 1.79, N 10.62; ¹H NMR (500 MHz, [D₃]MeCN, 25 °C, TMS): δ = 10.05 (d, *J* = 10.0 Hz, 6H), 10.03 (d, *J* = 9.1 Hz, 6H), 8.63 (d, *J* = 7.8 Hz, 6H), 8.53 (d, *J* = 7.6 Hz, 6H), 8.48 (d, *J* = 4.7 Hz, 6H), 8.44 (d, *J* = 4.9 Hz, 6H), 8.24 (d, *J* = 4.9 Hz, 6H), 8.07 (dd, *J*₁ = 7.1 Hz, *J*₂ = 5.8 Hz, 6H), 8.02 (d, *J* = 5.1 Hz, 6H), 7.98 (dd, *J*₁ = 7.3 Hz, *J*₂ = 5.7 Hz, 6H), 7.74 (dd, *J*₁ = 7.4 Hz, *J*₂ = 6.1 Hz, 6H), 7.53 (m, 6H); ESI MS: *m/z*: 1182 (**Ru**₄one-3[PF₆])³⁺, 850 (**Ru**₄one-4[PF₆])⁴⁺, 651 (**Ru**₄one-5[PF₆])⁵⁺, 519 (**Ru**₄one-6[PF₆])⁶⁺, 424 (**Ru**₄one-7[PF₆])⁷⁺; IR (KBr): ν̄ = 1699 cm⁻¹ (C=O stretch).

[*A*₆*A*₃*A*-**Ru**₁₀][PF₆]₂₀ and [*A*₆*A*₃*A*-**Ru**₁₀][PF₆]₂₀ were prepared similarly by addition of *A*-[Ru(phen)₂(phenylideneammine)][PF₆]₂^[17] (90 mg, 0.094 mmol, 7.2 equiv) to a solution of *A*₃*A*-**Ru**₄one[PF₆]₈ or *A*₃*A*-**Ru**₄one[PF₆]₈ (50 mg, 0.013 mmol), as appropriate, dissolved in MeCN/H₂O (2/1), and refluxing under N₂ for 15 h. After the mixture was allowed to cool, the product was precipitated by addition of NH₄PF₆ (30 mg) dissolved in water (5 mL) and removal of most of the MeCN by evaporation under vacuum. The reddish brown precipitate was purified by column chromatography packed with neutral Al₂O₃ using 1 % NH₄PF₆ in MeCN (*m/v*) as eluent. The first band collected was then passed through a second column packed with lipophilic sephadex (LH-20) using MeCN/THF (1/1) as eluent. Typical yield 25 mg (21 %). Elemental analysis: C₃₆₀H₂₀₄N₇₈F₁₂₀P₂₀Ru₁₀ calcd: C 45.36, H 2.16, N 11.46; found: C 45.85, H 2.43, N 11.10.

[*A*₆*A*₃*A*-**Ru**₁₀][PF₆]₂₀: ¹H NMR (500 MHz, [D₃]MeCN, 25 °C, TMS): δ = 10.03–10.0 (m, 24H), 9.93 (d, *J* = 7.8 Hz, 12H), 8.62 (d, *J* = 8.1 Hz, 24H), 8.48 (m, 18H), 8.43 (m, 6H), 8.27 (s, 24H), 8.23 (br d, 24H), 8.02 (d, *J* = 4.2 Hz, 12H), 7.96 (m, 24H), 7.87 (m, 12H), 7.65 (dd, *J*₁ = 12.7 Hz, *J*₂ = 5.6 Hz, 24H); UV/Vis (MeCN): λ_{max}(ε) = 441 (225 000), 370 (272 000), 303

(468 000), 280 (707 000), 264 (719 000); CD (MeCN): λ_{min/max}(Δε) = 464 (76), 425 (–49), 270 (1756), 258 (–1261).

[*A*₆*A*₃*A*-**Ru**₁₀][PF₆]₂₀: ¹H NMR (500 MHz, [D₃]MeCN): δ = 10.03–10.0 (m, 24H), 9.95 (d, *J* = 7.5 Hz, 12H), 8.63 (d, *J* = 7.3 Hz, 24H), 8.47 (m, 24H), 8.28 (s, 24H), 8.23 (d, *J* = 8.3 Hz, 24H), 8.04 (d, *J* = 4.7 Hz, 12H), 7.96 (m, 24H), 7.88 (dd, *J*₁ = 8.1 Hz, *J*₂ = 5.6 Hz, 12H), 7.66 (dd, *J*₁ = 13.2 Hz, *J*₂ = 7.8 Hz, 24H); UV/Vis (MeCN): λ_{max}(ε) = 443 (205 000), 371 (252 000), 303 (430 000), 279 (645 000), 264 (657 000); CD (MeCN): λ_{min/max}(Δε) = 477 (178), 421 (–119), 272 (1639), 258 (–1220).

Positive electrospray–ionization mass spectra were obtained on a Jaguar time-of-flight mass spectrometer (Sensar Larson–Davis, Provo, UT). The electrospray interface was heated to 50 °C. The electrospray needle and the sampling cone potentials were 2100 V and 500 V, respectively. The samples were dissolved in MeCN (1–5 × 10⁻⁴ M). Sample solutions were introduced into the mass spectrometer with a microsyringe pump (PHD2000 Harvard Apparatus, South Natick, MA) at a flow rate of 1.5 μL min⁻¹ through PEEK tubing (64 μm i. d., Upchurch Scientific, Oak Harbor, MA). Resolution at *m/z* 800 was approximately 2700.

Electric birefringence measurements were obtained on a locally constructed instrument, described previously.^[18] Computational modeling was carried out using the Spartan suite of programs (Wavefunction Inc., Irving, CA). Semiempirical calculations were performed on Silicon Graphics Indigo2 workstations using PM3(TM) method and parameters. The default optimization criteria for Spartan 5.0.3 were used in all cases. All optimized structures, including those of the tris-ruthenium(II) complexes of bipyridine, 1,10-phenanthroline, and the [(phen)₂Ru(tpphz)Ru(phen)]⁴⁺ dimer, lacked imaginary frequencies. The optimized PM3(TM) structures were then reoptimized by using molecular mechanics and Sybyl parameters. The computed bond lengths and angles in these complexes (both PM3(TM) and Sybyl-optimized structures) compared well with the bond lengths and angles reported from three-dimensional X-ray studies. The building blocks for the more complex structures were constructed by optimizing the [Ru(phen)₂(tpphz)]²⁺ and the [Ru(tpphz)₃]²⁺ complexes and then cleaving the resulting complexes at the dinitrogen bridges. These optimized building blocks were then assembled into the desired tetramers and decamers which were then optimized by using molecular mechanics and the Sybyl parameters. The three-dimensional space-filling molecular ion structures were generated by converting the optimized mechanics structures from Spartan to the UniChem (Ver. 4.1, Oxford Molecular, Oxford, UK) graphical user interface.

Received: May 26, 1999
Revised: September 3, 1999 [Z13466]

- [1] For recent reviews see: a) G. R. Newkome, E. He, C. N. Moorefield, *Chem. Rev.* **1999**, 99, 1689; b) H.-F. Chow, T. K.-K. Mong, M. F. Nongrum, C.-W. Wan, *Tetrahedron* **1998**, 54, 8543; c) D. A. Tomalia, R. Esfand, *Chem. Ind. London* **1997**, 416; d) F. Zheng, S. C. Zimmerman, *Chem. Rev.* **1997**, 97, 1681.
- [2] a) Z. Xu, M. Kahr, K. L. Walker, C. L. Wilkins, J. S. Moore, *J. Am. Chem. Soc.* **1994**, 116, 4537; b) Z. Xu, J. S. Moore, *Angew. Chem.* **1993**, 105, 1394; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1354.
- [3] H. W. I. Peerlings, E. W. Meijer, *Chem. Eur. J.* **1997**, 3, 1563.
- [4] a) J. R. McElhanon, D. V. McGrath, *J. Am. Chem. Soc.* **1998**, 120, 1647; b) P. Murer, D. Seebach, *Angew. Chem.* **1995**, 107, 2297; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 2116; c) D. Seebach, J.-M. Lapierre, K. Skobridis, G. Greiveldinger, *Angew. Chem.* **1994**, 106, 457; *Angew. Chem. Int. Ed. Engl.* **1994**, 33, 440; d) J. F. G. A. Jansen, H. W. I. Peerlings, E. M. M. de Brabander-Van den Berg, E. W. Meijer, *Angew. Chem.* **1995**, 107, 1231; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1206; e) P. R. Ashton, S. E. Boyd, C. L. Brown, N. Jayaraman, S. A. Nepogodiev, J. F. Stoddart, *Chem. Eur. J.* **1996**, 2, 1115.
- [5] For recent reviews on this extensive field see: a) M. Fujita, *Chem. Soc. Rev.* **1998**, 27, 417; b) J.-M. Lehn, *Supramolecular Chemistry, Concepts and Perspectives*, VCH, New York, **1995**.
- [6] For a recent comprehensive review of this topic see: U. Knof, A. von Zelewsky, *Angew. Chem.* **1999**, 111, 312; *Angew. Chem. Int. Ed.* **1999**, 38, 303.
- [7] a) V. Balzani, S. Campagna, G. Denti, A. Juris, S. Serroni, M. Venturi, *Acc. Chem. Res.* **1998**, 31, 26; b) S. Campagna, G. Denti, S. Serroni, A. Juris, M. Venturi, V. Ricevuto, V. Balzani, *Chem. Eur. J.* **1995**, 1, 211.

- [8] Recent reviews of stereospecific syntheses: a) F. M. MacDonnell, M.-J. Kim, S. Bodige, *Coord. Chem. Rev.* **1999**, 185–186, 535; b) F. R. Keene, *Chem. Soc. Rev.* **1998**, 27, 185; c) F. R. Keene, *Coord. Chem. Rev.* **1997**, 166, 121.
- [9] S. Bodige, A. S. Torres, D. J. Maloney, D. Tate, A. Walker, G. Kinsell, F. M. MacDonnell, *J. Am. Chem. Soc.* **1997**, 117, 10364.
- [10] A. S. Torres, D. J. Maloney, D. Tate, Y. Saad, F. M. MacDonnell, *Inorg. Chim. Acta*, in press.
- [11] F. M. MacDonnell, M.-J. Kim, unpublished results.
- [12] C. Moucheron, A. Kirsch-DeMesmaeker, A. Dupont-Gervais, E. Leize, A. Van Dorsselaer, *J. Am. Chem. Soc.* **1996**, 118, 12834.
- [13] D. J. Maloney, F. M. MacDonnell, *Acta Crystallogr. Sect. C* **1997**, 53, 705.
- [14] a) J. H. Brewster, *Top. Curr. Chem.* **1974**, 47, 29; b) K. Mislow in *Topics in Stereochemistry*, Vol 22 (Ed.: S. E. Denmark), Wiley, New York, **1999**, Chap. 1.
- [15] S. Campagna, S. Serroni, S. Bodige, F. M. MacDonnell, *Inorg. Chem.* **1999**, 38, 692.
- [16] S. Campagna, A. Giannetto, S. Serroni, G. Denti, S. Trusso, F. Mallamace, N. Micali, *J. Am. Chem. Soc.* **1995**, 117, 1754.
- [17] S. Bodige, F. M. MacDonnell, *Tetrahedron Lett.* **1997**, 38, 8159.
- [18] N. Asgharian, X. Wu, R. L. Meline, B. Derecskei, H. Cheng, Z. A. Schelly, *J. Mol. Liq.* **1997**, 72, 315.

On the Location of Li⁺ Cations in the Fast Li-Cation Conductor La_{0.5}Li_{0.5}TiO₃ Perovskite**

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Interest in solids which conduct lithium ions has increased considerably in recent years because of the potential application of such solids in rechargeable lithium batteries. The ionic conductivity of La_{2/3-s/3}Li_sTiO₃ perovskites is one of the highest reported values in crystalline lithium cation conductors^[1,2] ($\sigma \approx 10^{-3} \Omega^{-1} \text{cm}^{-1}$ at $T = 300 \text{ K}$), which makes these compounds good candidates for use as solid electrolytes in lithium batteries. The conductivities in the Pr and Nd perovskites are two and three orders of magnitude lower than for their La analogues.^[2]

The perovskite structure (general formula ABO₃) can be regarded as a three-dimensional framework made up of

vertex-sharing BO₆ octahedra with a large A cation in each of the 12-coordinated cavities of the framework. In the solid solution La_{2/3-s/3}Li_sTiO₃ ($0 \leq s \leq 0.5$) Li atoms were thought to replace La atoms at the A sites, which would lead to a progressive reduction of vacancies at these positions. However, the location of the Li atoms in the crystal structures of this family had not previously been possible from X-ray diffraction (XRD) data.

If the radius of the A cation is too small, the void is reduced in size by tilting of the BO₆ octahedra. The effect of tilting, when widely extended, is a predominant feature in the determination of the overall space-group symmetry of a particular perovskite. The precise structure determination of these oxides by XRD is particularly difficult because the superlattice reflections associated with the tilting of the TiO₆ octahedra arise from the oxygen atoms, which are weak scatterers when compared with La and Ti. Hence, neutron powder diffraction (NPD) measurements are more suitable for these investigations.

Following previous work,^[3-5] we report a neutron powder diffraction study of the perovskite with the highest Li-substitution level, La_{0.5}Li_{0.5}TiO₃, in which we have, for the first time, located the Li⁺ cations within the structure and have established the tilting scheme of the TiO₆ octahedra. Moreover, our data demonstrate that the solid solution mentioned does extend up to values of $s = 0.5$, a figure which had been controversial up to this time.

The powder sample of La_{0.5}Li_{0.5}TiO₃ exhibited excellent crystallinity, as shown by the sharpness of the XRD reflections (Figure 1a). The XRD pattern could be indexed in a cubic unit cell with $a = 3.8714(5) \text{ \AA}$, characteristic of a perovskite structure. Nevertheless, the NPD pattern (Figure 1b) clearly showed the presence of superstructure reflections which could not be indexed in the simple cubic unit cell; these reflections arise from the tilting of the TiO₆ octahedra. Therefore, it was necessary to consider a larger unit cell. The reflections of the NPD diagram of La_{0.5}Li_{0.5}TiO₃ were indexed in an hexagonal unit cell with the systematic absences suggesting the space group $R\bar{3}c$ (no. 167). This rhombohedral space group corresponds to one of Glazer's octahedral tilt schemes for perovskite related structures,^[6] which is adopted by a wide number of perovskites when the tilting angle of the octahedra remains small (for instance, LaAlO₃, LaCuO₃, or LaNiO₃).

A first Rietveld refinement was performed on a structural model in which Li atoms were not included; the starting parameters used were those of LaNiO₃^[7] in the hexagonal setting of the space group $R\bar{3}c$ ($Z = 6$) with La placed at 6a (0,0,1/4), Ti at 6b (0,0,0), and oxygen at 18e ($x,0,1/4$) positions; the single x parameter was to be determined during the refinement. Unit cell parameters were $a = 5.4711(4) \text{ \AA}$, $c = 13.404(1) \text{ \AA}$. The refinement of the La occupancy factor (over 6a positions) led to the expected value of 0.5 atoms per formula unit. This result seemed to exclude the possibility that the Li cations are located at A sites of the perovskite, randomly distributed over the 6a positions together with La. This situation would have led to a significantly lower La occupancy factor, since the scattering length of Li is negative (see the Experimental Section). After the Rietveld refinement of this structural model, an R_{Bragg} factor of 0.074 was

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[**] This work was supported financially by Spanish CICYT (Spain, projects PB97-1181 and MAT98-1053-C04-03). The authors acknowledge ILL-Grenoble for making available time on the diffractometer.

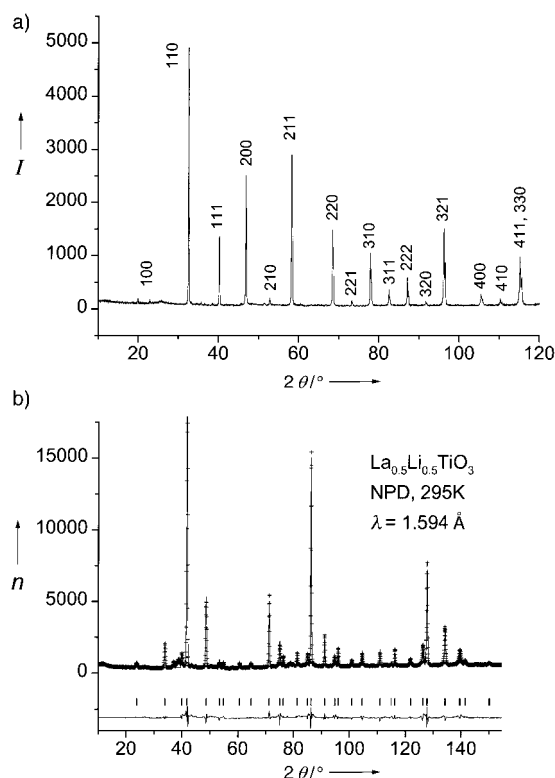


Figure 1. a) XRD diagram for $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$, indexed according to a simple cubic unit cell (subcell of the true structure); b) calculated (full line) and observed (horizontal marks) neutron powder diffraction profiles at 295 K, refined in the rhombohedral $R\bar{3}c$ space group. The difference profile is shown underneath.

reached, including anisotropic refinement of the oxygen thermal motion.

The small discrepancies between the observed and calculated intensities provided information on the remaining scattering density which was not considered in the starting model. A Fourier synthesis, performed over the difference between observed and calculated structural factors, yielded information on the location of the "missing" atoms. A difference Fourier map at this step showed us the unambiguous location of Li atoms at 18d $(1/2, 0, 0)$ positions. As shown in Figure 2, peaks of negative density ($\rho \approx -1.1 \text{ fm } \text{\AA}^{-3}$) are

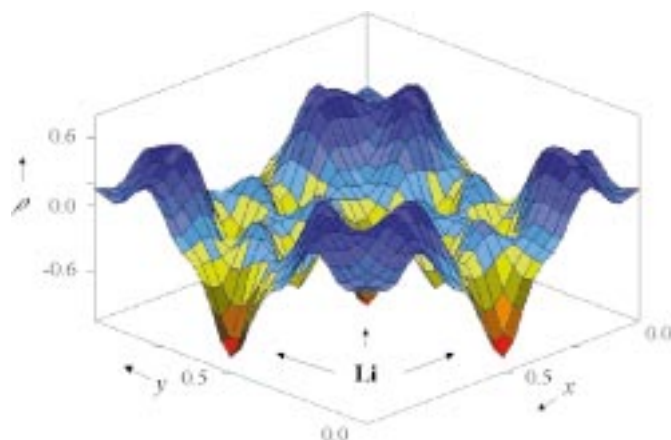


Figure 2. Difference Fourier map for $z=0$ showing the location of Li atoms at $(1/2, 0, 0)$ and equivalent positions. The vertical axis corresponds to the scattering density ρ (in $\text{fm } \text{\AA}^{-3}$), which is negative at the Li positions.

located in the $z=0$ Fourier section at $(1/2, 0, 0)$ and equivalent positions. After the introduction of Li into the structural model, the R_{Bragg} factor dropped to 0.048. The refined occupancy factor was in excellent agreement with the expected Li content of 0.5 atoms per formula unit. The quality of the fit of NPD data after the final refinement is illustrated in Figure 1b. The final atomic coordinates and thermal factors are included in Table 1.^[8] A simplified view of the crystal structure is shown in Figure 3.

Table 1. Atomic coordinates and isotropic thermal factors (B_{iso}) for $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$ after the final NPD refinement.

Atom	Site	x	y	z	f_{occ}	$B_{\text{iso}}[\text{\AA}^2]$
La	6a	0	0	0.25	0.504(9)	0.17(10)
Li	18d	0.5	0	0	0.162(3)	6.7(10)
Ti	6b	0	0	0	1.0	1.17(12)
O ₁	18e	0.5321(6)	0	0.25	1.0	1.75(8) ^[a]

[a] Anisotropic thermal factors: $\beta_{11}=0.024(2)$, $\beta_{22}=0.008(3)$, $\beta_{33}=0.0026(5)$, $\beta_{12}=0.004(3)$, $\beta_{13}=-0.0019(5)$, $\beta_{23}=-0.0037(5)$.



Figure 3. Elementary pseudo-cubic unit cell for $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$ perovskite, which shows the relative location of Li (dark large spheres) and La (light large spheres) atoms. La positions are half-occupied; Li positions are one-sixth occupied.

The structure of $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$ is constituted by a network of TiO_6 octahedra slightly tilted along the pseudocubic rhombohedral axes ($a^-a^-a^-$ in Glazer's nomenclature^[6]) in order to optimize La–O distances. The Ti–O–Ti angle, which describes the tilting of the octahedra, is close to 170° . The bond lengths are all reasonable;^[8] the TiO_6 octahedra are almost perfectly regular (Ti–O 1.943(1) $\text{\AA}$), and La is 12-fold coordinated to oxygen atoms with La–O bond lengths in the range 2.911–2.559 $\text{\AA}$. La positions are half-occupied, leaving 0.5 vacancies per formula unit, distributed at random in the structure. The Li^+ cations are fourfold coordinated to oxygen atoms, in square-planar configuration. This environment for Li is different to the tetrahedral-like coordination found by Skakle et al.^[9] in the Pr and Nd analogues, which show a much lower conductivity. In $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$, the Li cations are placed at the middle of windows formed by four TiO_6 octahedra, with Li–O bond lengths of 1.81 and 2.07 $\text{\AA}$.

The simplified structure illustrated in Figure 3 corresponds to the ABO_3 cubic perovskite structure ($Z=1$), where Ti atoms occupy the corners of a cube, oxygen atoms are at the middle of the edges, and La ions (or La vacancies) are the geometrical center of the cube. The position occupied by Li corresponds to the center of every face. Since there are 0.5 Li atoms per formula unit (i.e., per pseudo-cubic unit cell), the occupancy factor of Li is only $\frac{1}{2}$.

The observed oxygen thermal factors are surprisingly high; $B_{\text{iso}}(\text{O})$ takes a value of $1.75(8) \text{ \AA}^2$. This large value accounts for disorder introduced by Li distribution, leading to small shifts of those O atoms directly linked to Li, which introduces an overall smearing of the O nuclear density. In fact, the oxygen thermal factor is rather anisotropic, described by very flattened ellipsoids. The short axis of the ellipsoid is along the highly covalent Ti–O–Ti bonds.

We suggest a mechanism for Li diffusion across the solid, in which the unoccupied five-sixths of 18d positions and half of the 6a positions (the remaining half being occupied by La atoms) constitute the path for Li hopping. The Li cations reside at 18d positions (where they have been located by diffraction methods), but the conduction mechanism appears to involve A vacancies, which Li^+ ions can hop into, avoiding those perovskite subcells that contain La cations. This model can be used to explain the dependence of Li conductivity (σ_{dc}) on Li content seen by Kawai and Kuwano,^[10] and Inaguma et al.^[11] They observed that the maximum conductivity in $\text{La}_{2/3-s}\text{Li}_s\text{TiO}_3$ is detected at high Li contents ($s \approx 0.35$). This observation could not be interpreted on the basis of a random distribution of Li, La and A vacancies in the A sites of a perovskite, as a strong decrease in σ_{dc} would be predicted for $s \approx 0.5$. However, the huge σ_{dc} for high Li contents can be explained by assuming the existence of a high number of vacant sites (the unoccupied 18d and 6a positions) which participate in the Li motion. The unusual coordination of Li, in the center of the oxygen windows determined by four TiO_6 octahedra, and the existence of a partially unoccupied cation sublattice for Li motion, explains the ion mobility and, therefore, the ionic conductivity and outstanding electrical properties of these promising Li-conducting materials.

Experimental Section

In order to reduce the absorption cross-section of the sample in the neutron experiment, a ^7Li -enriched $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$ sample (4 g) was prepared in polycrystalline form by heating a stoichiometric mixture of high-purity Li_2CO_3 , La_2O_3 , and TiO_2 reagents at 1200°C . The powder obtained from the reaction was pelletized and fired at 1350°C in air for 12 h and then quenched to room temperature. The metal molar ratio was determined by inductively coupled plasma spectroscopy (ICP) using a JY-70 PLUS spectrometer.

The XRD patterns were collected at 295 K with $\text{Cu}_{\text{K}\alpha}$ radiation in a Philips PW1050/25 diffractometer, by step-scanning from 10 to 120° in 2θ , in increments of 0.02° and with a counting time of 5 s for each step. The NPD diagram of $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$ was collected at 295 K in the high-resolution D2B diffractometer at ILL-Grenoble. A wavelength of $1.594 \text{ \AA}$ was selected from a Ge monochromator. The counting time was 4 h, using 4 g of sample contained in a vanadium can. The first 28 peaks of the NPD diagram of $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$ were unambiguously indexed with the TREOR4 program^[12] in an hexagonal unit cell (de Wolff figure of merit $M_{20}=16$).

For the neutron profile refinements (FULLPROF program),^[13] a pseudo-Voigt function was chosen to generate the line shape of the diffraction

peaks. The coherent scattering lengths for La, Li, Ti, and O were 8.24, -1.90 , -3.438 , and 5.803 fm . The Li atoms were located by Fourier synthesis, using the FOURIER and GFOURIER programs.^[14] In the final refinement run, the following parameters were refined: background coefficients, zero-point, half-width, and pseudo-Voigt parameters for the peak shape; scale factor and positional parameter for O; occupancy factors for La and Li; thermal isotropic factors for La, Li, and Ti, and anisotropic factors for O; and unit-cell parameters. Crystallographic data for $\text{La}_{0.5}\text{Li}_{0.5}\text{TiO}_3$: $R\text{-}3c$, hexagonal setting, $a=5.4711(4)$, $c=13.404(1) \text{ \AA}$, $V=347.44(5) \text{ \AA}^3$, $\rho_{\text{calcd}}=4.84 \text{ g cm}^{-3}$, $Z=6$, $R_{\text{wp}}=0.086$, $R_{\text{p}}=0.061$, $R_{\text{exp}}=0.019$, $R_{\text{Bragg}}=0.048$, measurement range $10 \leq 2\theta \leq 155^\circ$, 3190 data points, 84 observed reflections, 23 parameters refined. Further details of the crystal structure investigations can be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, Germany (fax: $+49$) 7247-808-666; e-mail: crysdata@fiz-karlsruhe.de), on quoting the depository number CSD-411039.

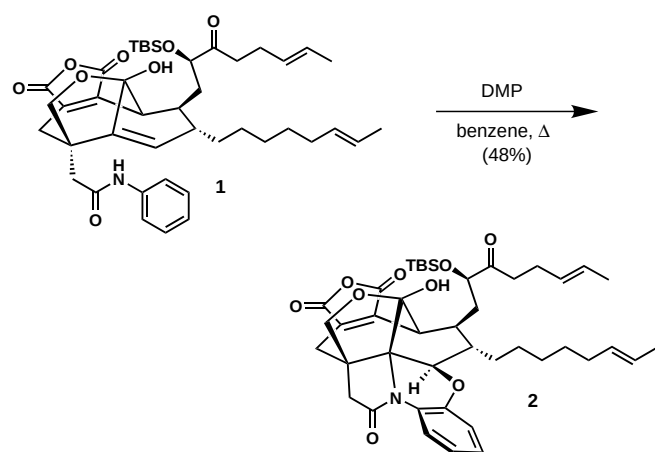
Received: July 5, 1999 [Z13679]

- [1] Y. Inaguma, L. Chen, M. Itoh, T. Nakamura, T. Uchida, M. Ikuta, M. Wakihara, *Solid State Commun.* **1993**, *86*, 689.
- [2] M. Itoh, Y. Inaguma, W. Jung, L. Chen, T. Nakamura, *Solid State Ionics* **1994**, *70/71*, 203.
- [3] C. León, M. L. Lucía, J. Santamaría, M. A. París, J. Sanz, A. Várez, *Phys. Rev. B* **1996**, *54*, 183.
- [4] C. León, J. Santamaría, M. A. París, J. Sanz, J. Ibarra, L. M. Torres, *Phys. Rev. B* **1997**, *56*, 5302.
- [5] C. León, J. Santamaría, M. A. París, J. Sanz, J. Ibarra, A. Várez, *J. Non-Cryst. Solids* **1998**, *235–237*, 753.
- [6] A. M. Glazer, *Acta Crystallogr. B* **1972**, *28*, 3384.
- [7] J. L. García-Muñoz, J. Rodríguez-Carvajal, P. Lacorre, J. B. Torrance, *Phys. Rev. B* **1992**, *46*, 4414.
- [8] Main interatomic distances [$\text{\AA}$] and angles [$^\circ$]: La–O ($\times 3$) 2.559(2), ($\times 3$) 2.911(2), ($\times 6$) 2.742(1), La–O 2.738, Li–O ($\times 2$) 1.811(2), ($\times 2$) 2.0669(2), Ti–O ($\times 6$) 1.943(1), Li–La ($\times 2$) 1.9345(1), Li–Li ($\times 8$) 2.7360(2), Li–Ti ($\times 4$) 2.7360(2); O–Li–O 90.2(1), 180.0, Ti–O–Ti 169.61(2), O–Ti–O 90.24(14).
- [9] J. M. S. Shackle, G. C. Mather, M. Morales, R. I. Smith, A. R. West, *J. Mater. Chem.* **1995**, *5*, 1807.
- [10] H. Kawai, K. Kuwano, *J. Electrochem. Soc.* **1994**, *141*, L78.
- [11] Y. Inaguma, L. Chen, M. Itoh, T. Nakamura, *Solid State Ionics* **1994**, *70/71*, 196.
- [12] P. E. Werner, L. Eriksson, M. Westdahl, *J. Appl. Crystallogr.* **1985**, *16*, 367.
- [13] J. Rodríguez-Carvajal, *Physica (Amsterdam)* **1993**, *192 B*, 55.
- [14] J. González-Platas, J. Rodríguez-Carvajal, unpublished results.

New Synthetic Technology for the Rapid Construction of Novel Heterocycles—Part 1: The Reaction of Dess–Martin Periodinane with Anilides and Related Compounds**

K. C. Nicolaou,* Yong-Li Zhong, and Phil S. Baran

Contemporary organic synthesis is faced with the challenge of developing simple methods for the rapid construction of complex, biologically relevant compounds which rival the complexity and diversity of natural products for combinatorial chemistry, biological screening, and chemical biology studies. Total synthesis endeavors provide novel forums and opportunities for exploration and for the discovery and development of new chemistry to address this formidable task. During the course of our recent total synthesis of the CP molecules^[1] we observed the unexpected conversion of **1** into **2** (Scheme 1), brought about by exposure of **1** to DMP^[2] in



Scheme 1. Serendipitous observation leading to the present methodologies. DMP = Dess–Martin periodinane, TBS = *tert*-butyldimethylsilyl.

refluxing benzene. This serendipitous discovery directly led to the development of a number of new chemical processes for the construction of molecular diversity, while unearthing a new paradigm for periodinane-mediated reactions with ani-

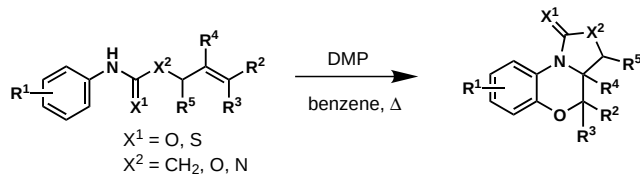
Table 1. DMP-mediated construction of novel polycycles.

Entry	Substrate	Product	Yield [%]
1 2	 	 	15 10
3		 [ca. 1:1]	11
4		 [ca. 2:1]	49
5			40
6			52
7			36
8			38
9		 [ca. 2:1] other regioisomer (–Br)	42
10			37

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[**] We thank Drs. D. H. Huang, G. Siuzdak, and R. Chadha for NMR spectroscopic, mass spectrometric and X-ray crystallographic assistance, respectively, and Professor A. Vavoglīs for helpful discussions. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, a doctoral fellowship from the National Science Foundation (to P.S.B.), and grants from Schering Plough, Pfizer, Glaxo Wellcome, Merck, Hoffmann–La Roche, DuPont, and Abbott Laboratories.

lides and related substrates (Scheme 2). Herein we report an unprecedented cascade reaction for the elaboration of complex natural product-like heterocycles from simple building blocks in only two synthetic operations.



Scheme 2. General construction of complex, natural product-like polycycles from a DMP-mediated cascade reaction.

Our first attempts to establish the generality of this new transformation were disappointing. As seen in entries 1–3 in Table 1^[3], the reactions of very simple anilides bearing a terminal alkene led to low yields of the desired products, presumably due to an excess of conformational freedom enjoyed by these substrates. We then reasoned that embedding a ring into the olefinic segment of the starting material might solve this problem. Indeed, as can be seen from entries 4–10 in Table 1, the chemical yields were considerably improved with this modification to provide a variety of complex polycycles. Notable is the capacity of this process to rapidly generate three stereocenters in a diastereocontrolled manner from simple achiral starting materials. The substrates shown in Table 1 were all easily prepared by the EDC-mediated dehydration of a substituted aniline with the appropriate carboxylic acid. The structure of one of these polycyclic products, compound **7b**, was verified by X-ray crystallographic analysis (Figure 1).^[4]

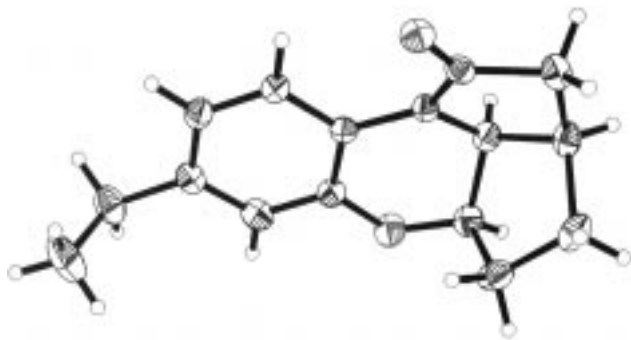
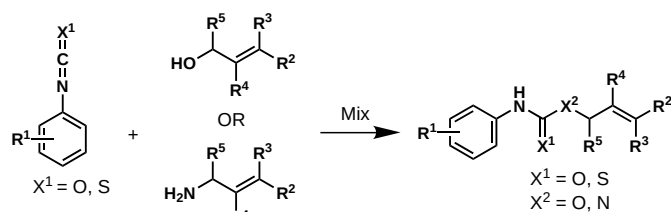


Figure 1. X-ray crystal structure of **7b**.

Recognizing that the scope and versatility of the reaction could be considerably enhanced if the library of starting materials was expanded to other effortlessly available compounds, we considered the nucleophilic attack of allylic alcohols or allylic amines on phenyl isocyanates or phenyl iso(thio)cyanates (Scheme 3).^[5] The resulting substrates would lead to rigid scaffolds capable of projecting a manifold of functional groups in defined, three-dimensional space and they would be available in one step from readily accessible sources. Implementation of this strategy led to the results demonstrated in Table 2. To our delight, carbamates **13a–17a**, thiocarbamate **23a**, and urea **24a** afforded



Scheme 3. Preparation of reaction substrates from phenyl isocyanates or phenyl iso(thio)cyanates and allylic alcohols or allylic amines.

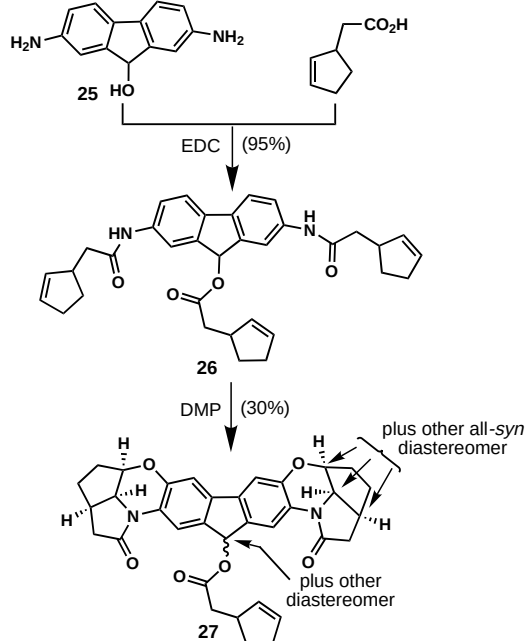
the corresponding polycycles in moderate to good yields (36–56 %, Table 2). Given that hypervalent iodine reagents readily interact with sulfur-containing molecules,^[6] the ease with which the reaction occurs with the thiocarbamate is admirable. In the case of urea **24a** the presumption that restriction of conformational freedom should enhance reactivity (vide supra) is accurately reflected, since simple amides lacking the rigidity incurred by the added nitrogen (see Table 1, entry 1) led to only low yields of polycyclic products. In the carbamate entries of Table 2, the formed products can be easily hydrolyzed (NaOH/EtOH) to provide the corresponding benzomorpholines **18–22** in excellent yields (90–96 %). This DMP-

Table 2. DMP-mediated construction of novel polycycles from carbamates, thiocarbamates, and ureas, and the synthesis of benzomorpholines.

Entry	Substrate	Product	Yield [%]	Benzo-morpholine	Yield [%]
1			50		95
2			42		95
3			40		96
4			38		95
5			36 ^[a]		90
6			42	—	—
7			56	—	—

[a] Ratio of diastereoisomers was about 1.5:1.

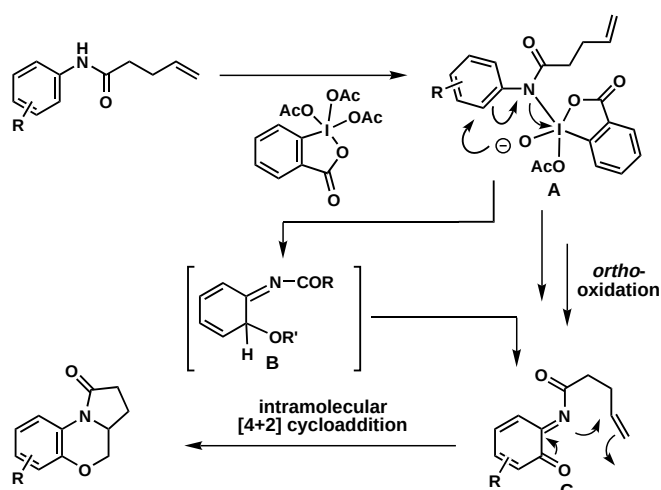
initiated cascade reaction also adds to the armory of reactions which generate quaternary centers in a stereoselective fashion (see Table 1, entries 9 and 10; Table 2, entries 2, 3, and 6). As a further test of the power of this process to deliver complex molecular diversity, we enlisted the diamide **26**, derived from bis-aniline **25**, as a potential substrate (Scheme 4). The reaction furnished the complicated polycycle **27**, harboring no less than ten rings and seven stereocenters (30% yield, mixture of four diastereoisomers).



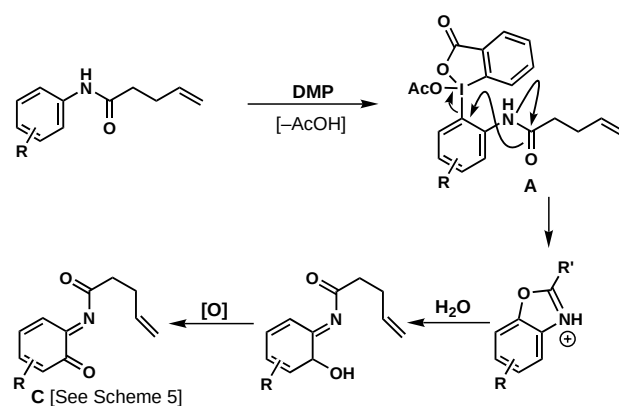
Scheme 4. Facile generation of complex polycycle **27** from simple bis-aniline **25** (mixture of four diastereoisomers). EDC = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide.

Operationally, the reactions are as simple as the DMP-mediated oxidation of alcohols; they can be performed in benzene or benzonitrile (BTF)^[7] under an aerobic atmosphere and are usually complete within 1 h at 80 °C. Standard workup, followed by chromatography, furnishes the products in generally moderate to good yields, which are satisfying due to the high level of complexity attained rapidly in a single step.

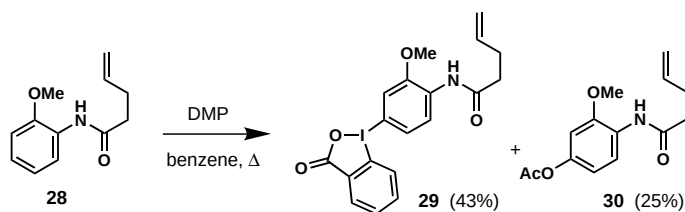
We propose the following tentative mechanism to account for the products arising from this remarkable cascade reaction (Scheme 5). The anilide nitrogen rapidly engages the electrophilic DMP reagent^[8] to provide an intermediate of type **A**. *ortho*-Oxidation then occurs leading to the novel diene **C**,^[9] presumably by a further oxidation of the intermediate **B**. An intramolecular hetero Diels–Alder reaction of **C** completes the tandem sequence. An alternative mechanism which converges at intermediate **C** could also be envisaged (Scheme 6). The isolation of compounds **29** and **30** from the reaction of substrate **28** with DMP (Scheme 8) provides credence for certain facets of the proposed mechanism in Scheme 5. In addition, we found that the interactions of periodinane species with amides is, so far, limited to anilides.^[10] This is also reflected by the ease with which



Scheme 5. Tentative mechanistic proposal for the DMP-mediated cascade reaction of aryl carbamoyl alkenes.



Scheme 6. An alternative mechanistic pathway to explain the formation of intermediate **C**.



Scheme 7. Informative by-products in the reaction of **28** with DMP.

unsymmetricalureas (Table 2, entry 7) reacted. This result coupled with the isolation of aryl acetate **30** and aryl periodinane **29** (Scheme 6) implies that both the amide nitrogen and the phenyl ring are active participants in the reaction.

Notwithstanding the development of a highly useful protocol for the construction of complex, diverse heterocycles, which are relevant to chemical biology and medicinal chemistry, in two synthetic operations from ubiquitous and commercially available materials, we believe that we have uncovered a new class of chemical processes. The following communication^[10] serves to demonstrate that the present reaction is perhaps only a glimpse of the rich heterocyclic chemistry attainable with periodinane-type reagents.

Experimental Section

DMP (2.0 equiv) was added in one portion to a solution of **7a** (0.1 mmol) in benzene (4 mL) or BTF.^[6] The solution was heated at reflux (or at 80–85 °C for the reactions in BTF) for about 30 min at which point TLC indicated complete consumption of starting material. Dilution with EtOAc followed by washing with 5 % aq. NaHCO₃ (2 ×) and brine, drying over MgSO₄, and concentration led to crude **7b**. Pure **7b** was isolated in 40 % yield after column chromatography (silica gel, EtOAc:hexane 1:2) (see Table 3 for selected physical properties).

Received: September 3, 1999 [Z13963]

Table 3. Data for selected compounds.

7b: colorless needles, m.p. 135–136 °C (methanol); R_f = 0.37 [silica, EtOAc:hexane 1:2]; IR (film): $\tilde{\nu}_{\max}$ = 2965, 2922, 1694, 1576, 1512, 1437, 1383, 1302, 1260, 1227, 1163, 1115, 866, 814 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, J = 3.5 Hz, 1H), 6.80–6.71 (m, 2H), 4.77–4.70 (m, 1H), 3.87 (dd, J = 5.5, 1.2 Hz, 1H), 2.96 (dd, J = 17.2, 8.6 Hz, 1H), 2.83–2.73 (m, 1H), 2.58 (q, J = 7.6 Hz, 2H), 2.24 (d, J = 17.3 Hz, 1H), 2.13–1.97 (m, 2H), 1.70–1.50 (m, 2H), 1.95 (t, J = 7.6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 172.6, 144.0, 142.0, 128.0, 120.5, 121.1, 115.7, 78.6, 57.6, 39.7, 32.4, 29.0, 28.5, 15.5; HRMS (MALDI-FTMS), calcd for C₁₅H₁₈NO₂ [(M+H)⁺]: 244.1338, found 244.1332

24b: R_f = 0.65 [silica, EtOAc:hexane 1:1]; IR (film): $\tilde{\nu}_{\max}$ = 2919, 2850, 1709, 1501, 1437, 1260, 753 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.95 (dd, J = 7.0, 2.6 Hz, 1H), 7.00–6.94 (m, 2H), 6.89 (dd, J = 7.4, 2.2 Hz, 1H), 5.83–5.72 (m, 1H), 5.23 (dd, J = 18.3, 1.1 Hz, 1H), 5.22 (d, J = 9.2 Hz, 1H), 4.34 (dd, J = 10.5, 3.3 Hz, 1H), 4.10–4.02 (m, 1H), 3.94–3.88 (m, 2H), 3.79 (t, J = 10.5 Hz, 1H), 3.61 (t, J = 9.4 Hz, 1H), 3.11 (dd, J = 9.4, 5.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 156.8, 144.4, 132.6, 127.8, 123.4, 121.5, 120.6, 118.4, 116.6, 66.9, 47.8, 46.4, 43.6; HRMS (MALDI-FTMS), calcd for C₁₃H₁₅N₂O₂ [(M+H)⁺]: 231.1133, found 231.1128

29: colorless needles, m.p. 108–109 °C (hexane:diethyl ether 2:1); R_f = 0.18 [silica, EtOAc:hexane 1:4]; IR (film): $\tilde{\nu}_{\max}$ = 3296, 3084, 2920, 2850, 1761, 1731, 1679, 1649, 1526, 1461, 1408, 1267, 1238, 1179, 1144, 1079, 1032, 1008, 908, 885 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.44 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 8.02 (dd, J = 7.9, 1.5 Hz, 1H), 7.73 (br s, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.22 (dt, J = 7.9, 1.5 Hz, 1H), 6.84 (dd, J = 8.8, 2.5 Hz, 1H), 6.81 (d, J = 1.5 Hz, 1H), 5.92–5.82 (m, 1H), 5.12 (d, J = 16.9 Hz, 1H), 5.04 (d, J = 10.2, 1H), 3.89 (s, 3H), 2.50 (br s, 4H); ¹³C NMR (125 MHz, CDCl₃): δ = 170.7, 165.4, 148.7, 146.8, 142.1, 137.2, 134.5, 133.7, 132.0, 128.5, 126.2, 120.5, 116.3, 114.0, 104.7, 95.1, 56.4, 37.5, 29.9; HRMS (MALDI-FTMS), calcd for C₁₉H₁₈INO₄Na [M+Na⁺]: 474.0178, found 474.0178

30: colorless needles, m.p. 63–64 °C (hexane:diethyl ether 2:1); R_f = 0.10 [silica, 1:4 ethyl acetate:hexane]; IR (film): $\tilde{\nu}_{\max}$ = 3355, 3073, 2979, 2920, 2850, 1761, 1679, 1602, 1526, 1491, 1408, 1367, 1267, 1202, 1185, 1150, 1114, 1032, 956, 897 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.37 (d, J = 8.8 Hz, 1H), 7.69 (br s, 1H), 6.67 (dd, J = 8.8, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 5.91–5.78 (m, 1H), 5.11 (d, J = 17.6 Hz, 1H), 5.04 (d, J = 10.3 Hz, 1H), 3.85 (s, 3H), 2.48 (br s, 4H), 2.28 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 170.3, 169.7, 148.2, 146.4, 136.8, 125.5, 120.0, 115.8, 113.5, 104.3, 55.8, 37.1, 29.4, 21.1; HRMS (FAB), calcd for C₁₄H₁₇NO₄Na [M+Na⁺]: 286.1055, found 286.1050

- [1] K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, H.-S. Choi, W. H. Yoon, Y. He, K. C. Fong, *Angew. Chem.* **1999**, *111*, 1774–1781; *Angew. Chem. Int. Ed.* **1999**, *38*, 1669–1675; K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, K. C. Fong, Y. He, W. H. Yoon, H.-S. Choi, *Angew. Chem.* **1999**, *111*, 1781–1784; *Angew. Chem. Int. Ed.* **1999**, *38*, 1676–1678.
- [2] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7278; c) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549–7552.
- [3] Compounds **3b** and **4b** are formed as single regioisomers, whereas **5b** and **6b** are mixtures. Efforts to understand this peculiar finding are underway.

- [4] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133866. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [5] S. Patai, *The Chemistry of Cyanates and Their Derivatives*, Wiley, Chichester, **1977**; S. Ozaki, *Chem. Rev.* **1972**, *72*, 457–496.
- [6] a) A. Varvoglis, S. Spyroudis, *Synlett* **1998**, 221–232; b) *Hypervalent Iodine in Organic Synthesis* (Ed.: A. Varvoglis), Academic Press, San Diego, **1996**; c) T. Wirth, U. H. Hirt, *Synthesis* **1999**, 1271–1287; d) A. Varvoglis, *The Organic Chemistry of Polycoordinated Iodine*, VCH, Weinheim, **1992**.
- [7] A. Ogawa, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 450–451.
- [8] Studies to determine whether DMP, its hydrolysis product,^[2c] or both are the active oxidants in this reaction are underway.
- [9] A multistep route to this type of diene is known, however the reaction requires the presence of chlorine substituents on the aryl ring, see: H. W. Heine, B. J. Barchiesi, E. A. Williams, *J. Org. Chem.* **1984**, *49*, 2560–2565.
- [10] K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 1029–1032; *Angew. Chem. Int. Ed.* **2000**, *39*, 1029–1032.

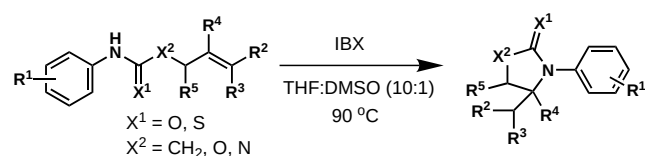
New Synthetic Technology for the Rapid Construction of Novel Heterocycles—Part 2. The Reaction of IBX with Anilides and Related Compounds**

K. C. Nicolaou,* Yong-Li Zhong, and Phil S. Baran

In the preceding communication^[1] we disclosed a new cascade reaction for the preparation of novel heterocycles. The present discovery arose while optimizing that process, namely, the reaction of Dess–Martin periodinane (DMP) with anilides. When we attempted to access the polycycles reported^[1] using IBX^[2] we observed astoundingly efficient cyclization to *N*-phenyl γ -lactams. Herein, we report that the reaction of IBX with anilides leads not only to γ -lactams, but also to a variety of other heterocycles including oxazolidinones, thioxazolidinones, and cyclic ureas in high yields (Scheme 1).

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[**] We thank Drs. D. H. Huang, G. Siuzdak, and R. Chadha for NMR spectroscopic, mass spectrometric and X-ray crystallographic assistance, respectively, and Professor A. Varvoglis for helpful discussions. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, a doctoral fellowship from the National Science Foundation (to P.S.B.), and grants from Schering Plough, Pfizer, GlaxoWellcome, Merck, Hoffmann–La Roche, DuPont, and Abbott Laboratories.



Scheme 1. Synthesis of novel heterocycles by treatment of unsaturated aryl amides, carbamates, thiocarbamates, and ureas with IBX. IBX = *o*-iodoxybenzoic acid; 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide; a precursor to DMP.

This simple reaction represents a fundamentally new strategy for the construction of molecular diversity relevant to biological screening and drug discovery

Specifically, we have found that a plethora of simple as well as complex anilides with an alkene functionality participate in an IBX-mediated cyclization reaction leading to a variety of novel structures (Table 1). Significantly, the reaction is unbiased to substitution on the aryl moiety.^[3] Reactions with substrates which harbor electron-donating groups (e.g. entry 6), electron-withdrawing groups (e.g. entries 4 and 7), halides (e.g. entries 2, 4, 7, 11, 13, 15, 17, and 18), and sterically encumbered groups (e.g., entry 8) situated at the *ortho*, *meta* or *para* positions all proceed smoothly and in high yields. An X-ray crystal structure of one of the obtained products, complex heterocycle **16b**, is shown in Figure 1.^[4]

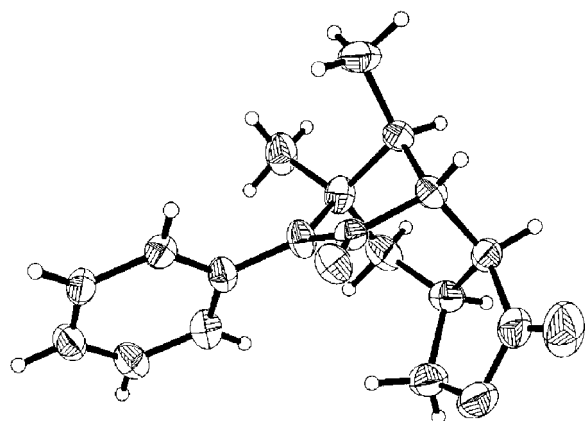


Figure 1. X-ray crystal structure of **16b**.

Considering the plethora of readily available phenyl isocyanates, allylic alcohols, and allylic amines, we recognized the diverse array of building blocks that could potentially be funneled into this new reaction. The generality of this two-step sequence for the construction of molecular diversity is demonstrated in Table 2. Remarkably, oxazolidinones (**19b**–**26b**, entries 1–8), thioxazolidinones (**33b**, entry 9) and cyclic ureas (**34b**, **35b**, entries 10, 11) are readily available from the corresponding carbamates, thiocarbamates and open-chain ureas, respectively, using this straightforward protocol. Hydrolysis of the oxazolidinones (NaOH/EtOH) permits access to *cis*-*N*-phenyl 1,2-amino alcohols (**27**–**32**, Table 2). The challenging task of establishing quaternary centers (e.g. Table 1, entries 16, 17; Table 2, entries 2, 5, 7), including spiro compounds such as **25b**, proceeds smoothly without loss of efficiency. The procedure is operationally extremely simple and involves dissolution of the substrate and IBX in

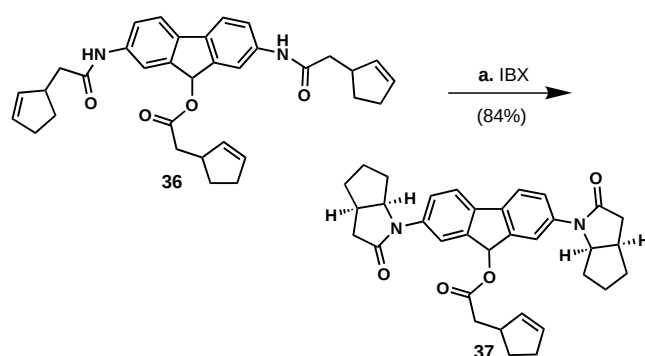
Table 1. IBX-mediated cyclization of aryl carbamoyl alkenes to form heterocycles.

Entry	Substrate	Product	Yield [%]
1 2 3 4	1a: R = H 2a: R = Br 3a: R = Et 4a: R = F	1b: R = H 2b: R = Br 3b: R = Et 4b: R = F	86 79 89 80
5	5a	5b	90
6 7 8	6a: R = OMe 7a: R = F 8a: R = <i>t</i>Bu	6b: R = OMe 7b: R = F 8b: R = <i>t</i>Bu	88 80 70
9	9a	9b [ca. 1:1]	90
10	10a	10b	90
11	11a	11b	86
12 13	12a: R = H 13a: R = Br	12b: R = H 13b: R = Br	90 84
14 15	14a: R = H 15a: R = Br	14b: R = H 15b: R = Br	93 89
16 17	16a: R = H 17a: R = Br	16b: R = H 17b: R = Br	88 86
18	18a	18b	82

Table 2. IBX-mediated cyclization of carbamates, thiocarbamates, and open-chain ureas to form oxazolidinones, thioxazolidinones, and cyclic ureas and synthesis of 1,2-amino alcohols.

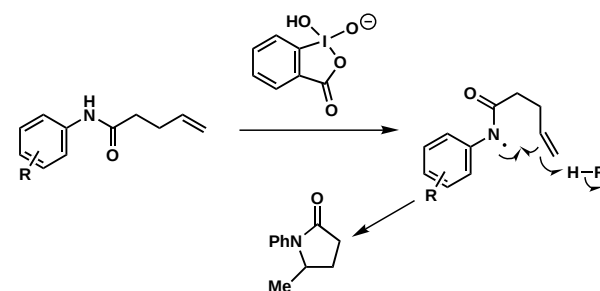
Entry	Substrate	Product	Yield [%]	1,2-amino alcohol	Yield [%]
1			88	—	—
2			90	—	—
3			85		94
4			72		92
5			88		98
6			95		95
7			76		90
8			83		95
9			86	—	—
10			90	—	—
11			70	—	—

THF:DMSO (10:1) in a sealed tube and heating at 90 °C for a number of hours. The reaction is impervious to air or water, producing the desired products even using water as a co-solvent. The high efficiency and reliability of this IBX-mediated reaction was not diminished even in the case of bis-amide **36**, wherein cyclization occurred to furnish the polycycle **37** in 84 % yield (Scheme 2).



Scheme 2. Facile generation of complex polycycle **37** from the simple bis-amide **36**. a) IBX (4.0 equiv), THF:DMSO (10:1), 90 °C, 24 h, 84 %.

Based on preliminary experimental results we choose to depict the IBX-mediated cyclization as proceeding through an amide-centered reactive intermediate, such as a radical (Scheme 3). The precise steps leading to these intermediates cannot be confidently defined at present, nor can the exact nature of this intermediate. IBX may somehow interact with



Scheme 3. Tentative mechanistic proposal of the IBX-mediated cyclization of aryl carbamoyl alkenes.

anilides to produce a species which behaves as an amidyl radical,^[5] thus engaging the proximate olefin in a 5-*exo-trig* fashion followed by hydrogen abstraction, presumably from the solvent. In contrast with mechanistic studies for the reaction of alcohols with IBX,^[6] NMR studies on the present reaction indicate that anilides do not form stable intermediates with this reagent.^[7] The complexes of anilides with IBX might, therefore, be short-lived. Additional evidence for the radicaloid^[8] character of the reaction is seen in Table 1, entry 9 in which case a 1:1 ratio of diastereoisomers was obtained indicating a disordered transition state, as expected from such a pathway.

As with the reaction of DMP with amides, discussed in the preceding communication,^[1] the present process has (so far) only been demonstrated to proceed with anilides, suggesting the requirement for a proper electronic environment surrounding the nitrogen.^[9] Although the reason for this rather peculiar requirement remains unknown, we suspect that the aryl moiety of these systems assumes an active (more than just a stabilizing) role in the reaction, just as it does in the case of DMP.

The structural types produced by the reactions reported in this and the preceding communication^[1] are found in innumerable natural products and medicinally important compounds^[10] and as such these processes may find important applications in organic synthesis. Furthermore, the extraordinary ease with which the starting materials for these reactions can be prepared, coupled with the striking complexity which is attainable in one step, makes this protocol ideal for the generation of manifold libraries of relevant compounds for biological screening and chemical biology purposes. Additional studies to delineate the precise mechanism by which periodinanes interact with anilides, efforts to expand the scope of these reactions to other substrates, and the development of solid-phase strategies incorporating these new reactions are underway. Finally, these disclosures underscore the importance of total synthesis in catalyzing the discovery and development of new and enabling technologies for organic synthesis, biology, and medicine.

Experimental Section

IBX (2.0 equiv) was added to a solution of **16a** (0.1 mmol) in THF:DMSO (10:1, 4 mL total volume). The solution was placed in a sealed tube and heated for 12 h at 90 °C, followed by another addition of IBX (2.0 equiv) and heating for a further 12 h period at the same temperature. The reaction mixture was diluted with EtOAc and washed with 5% aq. NaHCO₃ and brine, dried over MgSO₄, and concentrated. After purification by preparative thin layer chromatography (PTLC, silica, EtOAc:hexane 1:2), compound **16b** was obtained in 88% yield (see Table 3 for selected physical properties).

Received: September 3, 1999 [Z13964]

Table 3. Data for selected compounds.

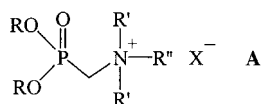
16b: X-ray crystal structure given (see Figure 1). Colorless cubic crystals, m.p. 238–239 °C, (acetone-hexane); R_f = 0.37 [silica, EtOAc:hexane 1:2]; IR (film): $\tilde{\nu}_{\max}$ = 2968, 2865, 1767, 1675, 1589, 1490, 1379, 1169, 1014, 866, 761, 693 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.40–7.33 (m, 2H), 7.27–7.22 (m, 1H), 7.19–7.15 (m, 2H), 4.40 (t, J = 7.2 Hz, 1H), 4.07 (dd, J = 7.2, 5.2 Hz, 1H), 3.12 (m, 1H), 2.93 (dd, J = 8.0, 4.4 Hz, 1H), 2.69 (d, J = 3.6 Hz, 1H), 2.16 (d, J = 12.0 Hz, 1H), 2.00–1.92 (m, 2H), 1.62 (s, 1H), 1.24–1.11 (m, 6H); ¹³C NMR (125 MHz, CDCl₃): δ = 176.0, 173.2, 136.1, 129.2, 129.1, 126.8, 125.2, 123.5, 71.3, 64.9, 64.4, 48.3, 45.7, 40.9, 35.4, 31.8, 20.8, 13.7; HRMS (MALDI-FTMS), calcd for C₁₇H₂₀NO₃ [(M+H)⁺]: 286.1443, found 286.1443 24b: R_f = 0.25 [silica, ethyl acetate:hexane 1:1]; [α]_D²⁵ = –175° (c = 0.04, CHCl₃); IR (film): $\tilde{\nu}_{\max}$ = 2920, 2848, 1736, 1598, 1499, 1401, 1242, 1206, 1164, 1122, 1087, 1011 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.59 (d, J = 7.9 Hz, 1H), 7.47 (dd, J = 7.9, 7.3 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 5.36 (t, J = 4.3 Hz, 1H), 5.24 (t, J = 7.0 Hz, 1H), 5.01 (t, J = 7.0 Hz, 1H), 2.59 (dd, J = 15.9, 2.9 Hz, 1H), 2.35 (dd, J = 15.4, 2.8 Hz, 1H), 2.18 (m, 1H), 2.04 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 171.0, 154.9, 137.7, 129.7 (2C), 125.0, 120.5 (2C), 77.8, 75.4, 61.1, 40.3, 37.4, 21.6; HRMS (MALDI-FTMS), calcd for C₁₄H₁₅NO₄Na [M+Na]⁺: 284.0899, found 284.0910 30: R_f = 0.4 [silica, ethyl acetate:methylene chloride 1:1]; [α]_D²³ = –250° (c = 0.1, CHCl₃); IR (film): $\tilde{\nu}_{\max}$ = 3380, 2361, 1602, 1503, 1432, 1321, 1262, 1099, 751 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.19 (dd, J = 8.7, 7.5 Hz, 2H), 6.67 (t, J = 8.7 Hz, 1H), 6.66 (d, J = 7.5 Hz, 2H), 4.34–4.30 (m, 2H), 4.17 (br s, 1H), 3.68 (ddd, J = 11.5, 7.3, 4.2 Hz, 1H), 2.86 (br s, 1H), 2.60 (ddd, J = 15.2, 9.2, 7.0 Hz, 1H), 2.07 (dq, J = 13.8, 1.6 Hz, 1H), 1.96 (ddd, J = 15.2, 5.7, 4.2 Hz, 1H), 1.65 (ddt, J = 13.8, 7.3, 2.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 146.4, 129.5 (2C), 119.1, 114.3 (2C), 72.4, 72.1, 59.0, 41.9, 41.2; HRMS (MALDI-FTMS), calcd for C₁₁H₁₆NO₂ [(M+H)⁺]: 194.1181, found 194.1183

- [1] K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *Angew. Chem.* **2000**, *112*, 1026–1029; *Angew. Chem. Int. Ed.* **1999**, *38*, **2000**, *112*, 1026–1029.
- [2] First preparation of IBX: C. Hartman, V. Meyer, *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1727; for a superior route to IBX, see: M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537–4538; introduction of the acronym “IBX”: A. R. Katritzky, B. L. Duell, J. K. Gallos, *Org. Magn. Reson.* **1989**, *27*, 1007; use of IBX as a selective oxidant for alcohols: M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019–8022; E. J. Corey, A. Palani, *Tetrahedron Lett.* **1995**, *36*, 3485–3488.
- [3] One exception is the nitro group, in which case the reaction did not proceed under the normal conditions.
- [4] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133867. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- [5] a) A.-C. Callier, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1994**, *35*, 6109–6112; b) A.-C. Callier, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1995**, *36*, 8791–8794; c) M. Newcomb, J. L. Esker, *Tetrahedron Lett.* **1991**, *32*, 1035–1038; d) M. Newcomb, J. L. Esker, *Tetrahedron Lett.* **1993**, *34*, 6877–6880; e) A. J. Clark, J. L. Peacock, *Tetrahedron Lett.* **1998**, *39*, 6029–6032; f) A. J. Clark, R. P. Filik, J. L. Peacock, G. H. Thomas, *Synlett* **1999**, 441–443; g) A. J. Clark, R. J. Deeth, C. J. Samuel, H. Wongtap, *Synlett* **1999**, 444–446.
- [6] S. De Munari, M. Frigerio, M. Santagostino, *J. Org. Chem.* **1996**, *61*, 9272–9279; M. Frigerio, M. Santagostino, S. Sputore, G. Palmisano, *J. Org. Chem.* **1995**, *60*, 7272–7276.
- [7] A 0.05 mmol scale reaction was performed in [D₆]DMSO at varying temperatures (25–110 °C) in an NMR tube. No intermediates could be detected; only product formation and some decomposition of IBX was observed.
- [8] B. B. Snider, *Chem. Rev.* **1996**, *96*, 339–363.
- [9] The DMP cascade reaction^[11] also requires anilides as substrates.
- [10] A literature search using SciFinder (ACS) to probe the popularity of these structural types in natural products and medicinally important compounds led to over 50 000 hits. The potential that these functionalities have for further elaboration to other scaffolds is nearly infinite. The following are some selected examples. Natural products: Yunna-neic acids A-D, uremic toxin-decreasing effects: T. Takashi, A. Nishimura, I. Kouno, G.-I. Nonaka, T.-J. Young, *J. Nat. Prod.* **1996**, *59*, 843–849; isoschizogamine, HIV inhibitor: J. Hajicek, J. Taimr, M. Budesinsky, *Tetrahedron Lett.* **1998**, *39*, 505–508; G. T. Tan, J. M. Pezzuto, A. D. Kinghorn, S. H. Hughes, *J. Nat. Prod.* **1991**, *54*, 143–154. Medicinally important compounds: a) Therapeutic CNS agents: M. Varasi, F. Heidempergher, C. Caccia, P. Salvati (Pharmacia S.p.A., Italy), WO-A 95-EP1650; b) 5-HT₃ antagonists: M. Varasi, F. Heidempergher, C. Arrigoni, C. Caccia (Farmitalia Carlo Erba S.R.L., Italy), WO-A 93-EP1498; c) antihyperlipidemics: S. Yano, T. Ohno, K. Ogawa, H. Yamada, T. Shirasaka, H. Kawamura, S. Watanabe (Taiho Pharmaceutical Co., Ltd., Japan), WO-A 93JP559; d) hypolipemics and hypoglycemics: H. Yanagisawa, K. Fujimoto, T. Fujita, K. Wada, M. Oguchi, T. Yoshioka, T. Fujiwara, H. Horikoshi (Sankyo Co., Japan) JP-A 95-162442; e) monoamine oxidase inhibitors: C. Banzati, A. Della Torre, P. Melloni, D. Pieracciolli, P. Salvadori, *J. Heterocycl. Chem.* **1983**, *20*, 139–140; f) antidepressants: (Erba, Carlo S.p.A., Italy) IT-B 75-30829.

Cationic Phosphonolipids Containing Quaternary Phosphonium and Arsonium Groups for DNA Transfection with Good Efficiency and Low Cellular Toxicity**

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The search for synthetic vectors able to complex DNA, carry the resulting "lipoplex" through cell membranes, and then deliver the DNA in (or close to) the nucleus in order to replace a deficient gene is of current interest. Unlike viral vectors, synthetic vectors do not impose limitations on the size of the encapsulated genetic material and illicit no immunogenic response. Since the pioneering work of Felgner et al.^[1] the most studied vectors are cationic lipids, perhaps because of the basic nature of biological amines. One must note that the cationic or polycationic charge is always carried by nitrogen atoms in these lipids. Thus, quaternary ammonium compounds (DOTMA, DDAB, DOTAP, DORIE, GLB), polyamines (DOGS, DPPES, DOSPA, GL67), and guanidines (BGTC) were synthesized and studied.^[2]



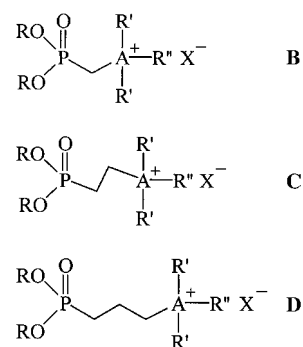
Scheme 1. Previous phosphonolipids with $R = C_{14}H_{29}$, $C_{18}H_{37}$, $C_{18}H_{35}$; R' , $R'' = \text{alkyl}$ and other functional groups; $X = \text{halogen}$.

In continuing our work on phosphonolipids **A**^[3] (Scheme 1), we paid special attention to the results of Stekar's group: the replacement of the quaternary ammonium polar head in edelfosine and miltefosine^[4] (two antineoplastically zwitterionic phospholipids) by a phosphonium or arsonium group resulted in maintained cytostatic activity together with decreased cellular toxicity. It should be noted that unlike arsenic(III) compounds arsonium compounds such as arsenobetaines, which occur abundantly in seafoods, are not cytotoxic for humans.^[5] Since changing a nitrogen atom for a phosphorus or arsenic atom in cationic lipids increases the volume of the cationic head, one can expect a modification of the interactions of the vector with the solvent and DNA. Therefore we explored the effects of such a replacement in lipidic ammonium phosphonates. We examined also the influence of the length of the chain between the cation and the phosphoryl group (Scheme 2).

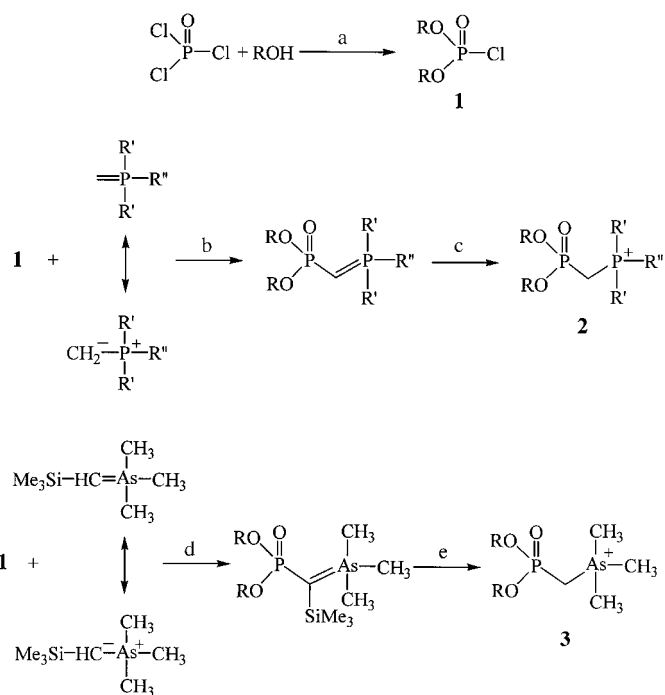
The ammonium phosphonates **A** were easily obtained in two steps from lipidic phosphites by a Mannich reaction

followed by quaternization of the resulting aminophosphonates.^[3a] But the analogues **B–D** in Scheme 2, in which the polar head is replaced and the chain length between the cation and the phosphonate is increased, required other synthetic pathways.

Methylenephosphonium and -arsonium analogues were synthesized according to Scheme 3. Fatty dialkylchlorophosphate **1** (obtained from $POCl_3$, 2 equiv fatty alcohol, and 4 equiv diisopropylethylamine) was treated with phosphorus and arsenic ylides,^[6] which led after acidification to the crude phosphonium and arsonium methylenephosphonates **2** and **3**, respectively, as powders or waxes depending on the R groups. Purification by successive washing with or precipitation from diethyl ether at low temperature afforded pure **2** and **3** (see Tables 1 and 2 for selected NMR data). Trimethylsilyl-stabilized ylides were used for arsonium compounds.^[6] The silyl groups were finally removed with MeOH, Me_3SiOH , or H_2O .



Scheme 2. General formula of the new phosphonolipids ($R = C_{14}H_{29}$, $C_{18}H_{35}$, $C_{18}H_{33}$; R' , $R'' = \text{alkyl}$; $A = N$, P , As ; $X = \text{halogen}$).



Scheme 3. Synthesis of **2** and **3** ($R = C_{14}H_{29}$, $C_{18}H_{35}$; R' , $R'' = \text{alkyl}$). a) Et_2O , NEt_3Pr_2 (4 equiv), 72 h, $20^\circ C$; b) THF, 1 h, $0^\circ C$; c) THF, HX , 1 h, $20^\circ C$; H_2O/NaX , 24 h, $20^\circ C$; d) Et_2O , 1 h, $0^\circ C$; e) Et_2O , HX , 1 h, $20^\circ C$, then Et_2O , Me_3SiOH , MeOH or H_2O/NaX , 24 h, $20^\circ C$ ($X = \text{halide}$).

Ammonium and phosphonium ethylenephosphonates **7** and **8** were obtained in five steps starting from 2-bromoethyldiethylphosphonate (Schemes 4 and 5), which was quantitatively converted into the bis-trimethylsilylated derivative

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[**] We thank the AFLM (Association Française de Lutte contre Pa Mucoviscidose) for financial support.

Table 1. Selected ^{31}P NMR data for compounds **1–12** with $\text{R} = \text{C}_{14}\text{H}_{29}$, $\text{R}' = \text{R}'' = \text{Me}$; $\text{X} = \text{I}$ (121.49 MHz, CDCl_3 , 298 K).

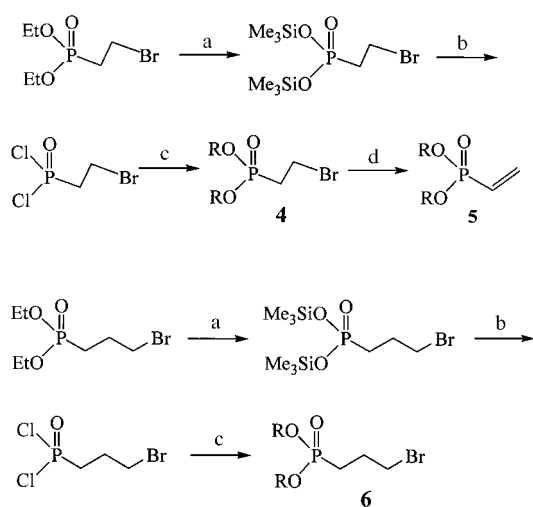
	1 ^[a]	2	3	4	5	6	7	8	9	10	11	12
$\delta(\text{P}=\text{O})$	4.65	16.70	20.38	26.08	17.40	30.84	23.66	27.19	29.11	29.35	27.59	30.24
$\delta(\text{P}^+)$	–	25.71	–	–	–	–	–	29.12	–	–	29.64	–
$J_{\text{P-P}}$ [Hz]	–	12.7	–	–	–	–	–	34.0	–	–	5.4	–

[a] In C_6D_6 .

Table 2. Selected ^{13}C and ^1H NMR data (100 and 400 MHz, CDCl_3 , 298 K, δ , J [Hz]) for compounds **2**, **3**, and **7–12**.

Cmpd	A	H_a	H_b	H_c	C_a	C_b
2	P	3.59 dd $J_{\text{H-P}} = 16.6$ $J_{\text{H-P}^+} = 19.2$	–	–	22.08 dd $J_{\text{C-P}} = 133.1$ $J_{\text{C-P}^+} = 47.5$	–
3	As	3.56 d $J_{\text{H-P}} = 16.4$	–	–	21.47 d $J_{\text{C-P}} = 136.7$	–
7	N	2.38 m	3.77 m	–	21.30 d $J_{\text{C-P}} = 138.6$	61.89 s
8	P	2.17 m	2.84 m	–	18.40 dd $J_{\text{C-P}} = 143.4$ $J_{\text{C-P}^+} = 4.0$	18.50 dd $J_{\text{C-P}^+} = 43.2$ $J_{\text{C-P}} = 4.4$
9	As	2.35 dt $J_{\text{H-H}} = 6.8$ $J_{\text{H-P}} = 17.1$	2.95 dt $J_{\text{H-H}} = 6.9$ $J_{\text{H-P}} = 26.8$	–	19.80 d $J_{\text{C-P}} = 143.4$	20.46 d $J_{\text{C-P}} = 4.0$
10	N	2.10 m	1.87 m	3.86 m	21.51 d $J_{\text{C-P}} = 143.2$	17.13 s
11	P	1.96 m	1.68 m	2.76 m	25.31 dd $J_{\text{C-P}} = 141.7$ $J_{\text{C-P}^+} = 17.1$	24.00 dd $J_{\text{C-P}^+} = 52.1$ $J_{\text{C-P}} = 15.1$
12	As	1.99 m	1.89 m	2.88 m	25.84 d $J_{\text{C-P}} = 141.0$	16.73 d $J_{\text{C-P}} = 4.4$

on treatment with bromotrimethylsilane,^[7] then into the corresponding dichloride according to the method of Bhongle et al.^[8] The fatty bromoethylphosphonate **4** was then easily prepared by reaction of the dichloride with the appropriate alcohol. Elimination of HBr was achieved by treatment with

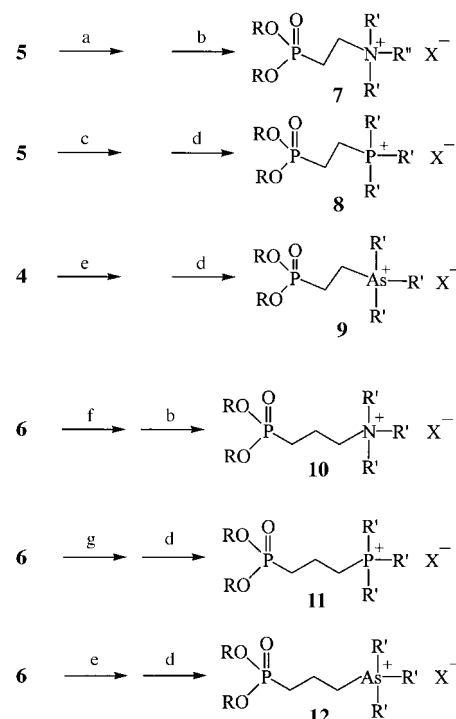


Scheme 4. Synthesis of **4–6** ($\text{R} = \text{C}_{14}\text{H}_{29}$, $\text{C}_{18}\text{H}_{35}$, $\text{C}_{18}\text{H}_{33}$; R' , $\text{R}'' = \text{alkyl}$). a) CH_2Cl_2 , BrSiMe_3 , 24 h, 20°C ; b) CH_2Cl_2 , oxalyl chloride, dimethylformamide (DMF), 2 h, 20°C ; c) Et_2O , ROH , NEt_3 , 24 h, 20°C ; d) THF, NEt_3 , 48 h, reflux.

NEt_3 in refluxing THF. The addition of a secondary amine to vinylic **5**, followed by quaternization with $\text{R}''\text{X}$ led to ammonium phosphonates **7**. Phosphonium phosphonates **8** were obtained by addition of acidic quaternary phosphonium salts. Direct quaternization of AsR_3 by bromophosphonate **4** in a sealed tube led to the corresponding arsonium bromides. Metathesis with NaI converted the bromides into the iodides.

The synthons **6** for propylenephosphonate compounds were synthesized by the same synthetic pathway as that employed for **4** (Scheme 4), then converted into the ammonium phosphonates **10** and to the phosphonium (**11**) and arsonium derivatives (**12**) by direct quaternization with phosphanes or arsanes (sealed tube) (Scheme 5). These syntheses are efficient, with nearly quantitative yields for phosphonates **7** to **12**.

All these onium compounds could be purified by recrystallization from diethyl ether or ethyl acetate at -20°C and were obtained in overall yields higher than 60%. They were fully characterized by ^1H , ^{13}C , and ^{31}P NMR spectroscopy (see Tables 1 and 2 for selected values). Their thermotropic properties were studied by differential



Scheme 5. Synthesis of **7–12** ($\text{R} = \text{C}_{14}\text{H}_{29}$, $\text{C}_{18}\text{H}_{35}$, $\text{C}_{18}\text{H}_{33}$; R' , $\text{R}'' = \text{alkyl}$; $\text{X} = \text{halogen}$, trifluoromethanesulfonate). a) EtOH , HNR'_2 , 96 h, 20°C ; b) Et_2O , $\text{R}''\text{X}$, 24 h, 20°C ; c) DMF, $[\text{HR}''\text{R}'_2\text{P}]^+\text{X}^-$, 48 h, reflux; d) CH_2Cl_2 , $\text{NaX}/\text{H}_2\text{O}$, 48 h, 20°C ; e) sealed tube, AsR_3 , 72 h, 70°C ; f) DMF/ H_2O , HNR'_2 , 2 h, reflux; g) THF, PR'_3 , 24 h, 20°C .

scanning calorimetry. They are air and water stable up to 60 °C. At higher temperatures the phosphonium and arsonium compounds are more stable than the corresponding ammonium compounds. It is worth noting that stable aqueous microemulsions (lasting at least three weeks) with concentrations of up to 10 mg mL⁻¹ were obtained with phosphonium and arsonium compounds. Under the same conditions ammonium compounds underwent hydration to yield unstable suspensions and should thus be prepared immediately before use.

Ammonium, phosphonium, and arsonium fatty phosphonates were simultaneously assessed for transfection of a reporter gene β -galactosidase on two adherent cell lines (CFT1, Hela) and one hematopoietic nonadherent cell line (K562), with lipofectine as reference, consistent with previously described protocols.^[3b] Figure 1 compares the data for

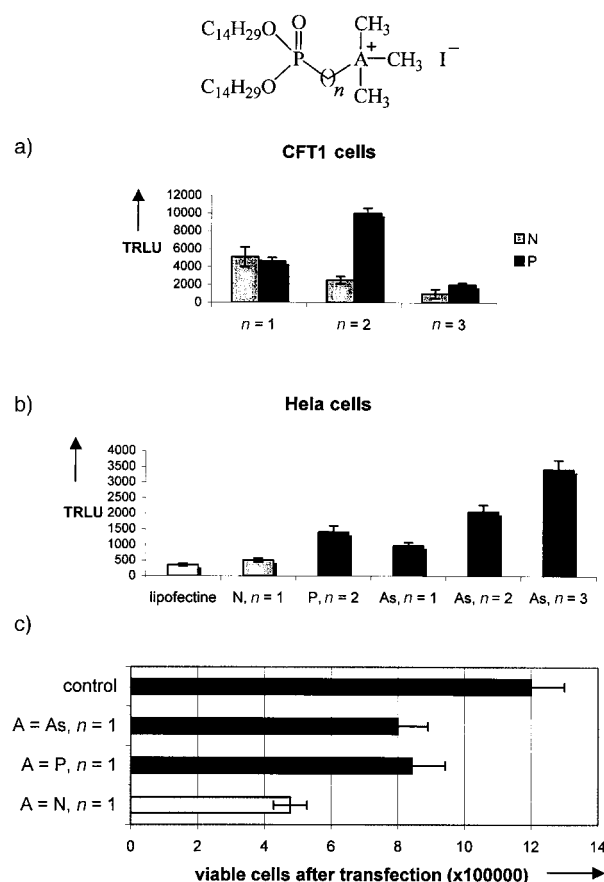
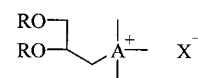


Figure 1. Results of transfection activity on CFT1 (a) and Hela cells (b), and cellular toxicity on K562 cells (c). TRLU = total relative light unit.

oniums (A = N, P, As) in which R = C₁₄H₂₉ and R' = R'' = CH₃. It is clear from the two first histograms that phosphonium and arsonium salts are more efficient than ammonium compounds, especially for transfection into Hela cells. Cellular toxicity was evaluated as the number of cells surviving the transfection experiment using a chemiluminescent assay (Packard);^[9] nontransfected cells served as a control. The third histogram indicates clearly that phosphonium and arsonium compounds are less cytotoxic than the ammonium derivatives, which is consistent with the observations of Stekar et al.^[4]

A more detailed biological study with a complete biological evaluation of efficiency and toxicity will be published soon elsewhere. Moreover, we have continued with this concept of replacing ammonium in the polar head of cationic lipids and have synthesized the phosphonium and arsonium analogues of DOTMA^[1] and DOTAP^[10] (Scheme 6), two well-studied nonviral vectors. These new compounds are currently under biological evaluation.



Scheme 6. Phosphonium and arsonium analogues of DOTAP and DOTMA (A = P, As; X = halogen; R = C₁₈H₃₅, C₁₇H₃₃C(O), C₁₅H₃₁C(O)).

Received: July 12, 1999 [Z13717]

- [1] P. L. Felgner, T. R. Gadek, M. Holm, R. Roman, W. C. Hardy, M. Wenz, J. P. Northrop, G. P. Ringold, M. Danielsen, *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 7413.
- [2] For a recent review, see A. D. Miller, *Angew. Chem.* **1998**, *110*, 1862; *Angew. Chem. Int. Ed.* **1998**, *37*, 1768.
- [3] a) G. Le Bolch, N. Le Bris, J.-J. Yaouanc, J.-C. Clément, H. des Abbayes, M.-P. Audrézet, C. Férec, *Tetrahedron Lett.* **1995**, *36*, 6681; b) V. Floch, G. Le Bolch, C. Guillaume-Gable, N. Le Bris, J.-J. Yaouanc, H. des Abbayes, C. Férec, J.-C. Clément, *Eur. J. Med. Chem.* **1998**, *33*, 12.
- [4] J. Stekar, G. Nössner, B. Kutscher, J. Engel, P. Hilgard, *Angew. Chem.* **1995**, *107*, 195; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 238.
- [5] H. Yamauchi, T. Kaise, Y. Yamamura, *Bull. Environ. Contam. Toxicol.* **1986**, *36*, 350.
- [6] a) H. Schmidbaur, W. Tronich, *Angew. Chem.* **1967**, *79*, 412; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 448; b) H. Schmidbaur, W. Tronich, *Inorg. Chem.* **1968**, *7*, 168–169.
- [7] C. E. McKenna, M. T. Higa, N. H. Cheung, M. C. McKenna, *Tetrahedron. Lett.* **1977**, *2*, 155.
- [8] N. N. Bhongle, R. H. Notter, J. G. Turcotte, *Synth. Commun.* **1987**, *17*, 1071.
- [9] V. Floch, N. Legros, S. Loisel, C. Guillaume, J. Guilbot, T. Benvegnu, V. Ferrieres, D. Plusquellec, C. Férec, *Biochem. Biophys. Res. Commun.* **1998**, *251*, 360.
- [10] L. Stamatou, R. Leventis, N. Zuckerman, *Biochemistry* **1988**, *27*, 3917.

Phosphane Sulfide/Octacarbonyldicobalt-Catalyzed Pauson–Khand Reaction Under an Atmospheric Pressure of Carbon Monoxide

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Dedicated to Professor Jean-Marie Lehn
on the occasion of his 60th birthday

The Pauson–Khand reaction, a method for constructing the cyclopentenone skeleton from an alkene, an alkyne, and carbon monoxide, has found extensive use in synthetic organic

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chemistry, including natural product synthesis.^[1] Recently there have been dramatic developments in catalytic Pauson–Khand-type reactions with various transition metal catalysts.^[2, 3] However, most of these catalytic reactions require drastic conditions such as high pressure, high temperature, and/or irradiation. Only a few catalytic Pauson–Khand reactions under atmospheric pressure are known.^[2e, 2i, 2o, 2p]

We recently demonstrated that phosphane sulfides can be used as ligands in the palladium-catalyzed bis-alkoxycarbonylation of olefins.^[4] The fact that tributylphosphane oxide promotes the stoichiometric cobalt-mediated Pauson–Khand reaction and gives a greatly improved yield^[5] prompted us to attempt the catalytic version of this reaction with a variety of phosphane chalcogenides as ligands. The cobalt-catalyzed reaction proceeded smoothly and in good yield even under an atmospheric pressure of CO, provided that an optimized quantity of a suitable phosphane sulfide was added. Here we report one of the most practical procedures to date for the catalytic Pauson–Khand reaction, achieved by using a phosphane sulfide as an additive.

We first examined the reaction with a catalytic amount of octacarbonyldicobalt in the presence of a variety of phosphane chalcogenides (Table 1). Enyne **1a** was treated with octacarbonyldicobalt (3 mol %) in the presence of a phosphane chalcogenide in benzene at 70 °C for 7 h under a CO atmosphere (1 atm). In the absence of ligand the $[\text{Co}_2(\text{CO})_8]$ catalyst decomposed before completion of the reaction; hence, the yield of product was low (entry 1). Belanger et al. recently reported an 83 % yield for the same reaction under almost identical reaction conditions, except that a very high purity cobalt complex was used to obtain reproducible results.^[2i, 6] Since tributylphosphane oxide is a good promoter

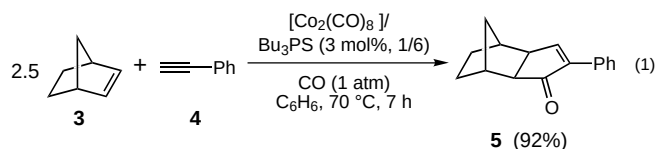
Table 1. Effect of phosphane chalcogenides on the cobalt-catalyzed Pauson–Khand reaction.^[a]

Entry	Additive	Ratio ^[b]	Yield [%] ^[c]
1	none	–	50
2	Ph ₃ PO	4	48
3	Ph ₃ PS	4	55
4	Ph ₃ PSe	4	trace
5	An ₃ PS ^[d]	4	70
6	(Me ₂ N) ₃ PS	2	67
7	(Me ₂ N) ₃ PS	4	79
8	(Me ₂ N) ₃ PS	6	79
9	(Me ₂ N) ₃ PS	8	77
10	Bu ₃ PS	2	74
11	Bu ₃ PS	4	72
12	Bu ₃ PS	6	90 ^[e]
13	Bu ₃ PS	8	75
14	Bu ₃ PS	6	84 ^[f]
15	dppeS ₂ ^[g]	2	34

[a] The reaction was performed in the presence of 3 mol % of $[\text{Co}_2(\text{CO})_8]$ for 7 h in benzene (0.14 M substrate) under 1 atm of CO. [b] Ratio of phosphane sulfide to $[\text{Co}_2(\text{CO})_8]$. [c] Yield of isolated product. [d] An = *p*-anisyl group. [e] The reaction was complete within 5 h. [f] Under the same conditions as entry 12 except for the concentration (0.079 M). [g] dppeS₂ = bis(diphenylthiophosphanyl)ethane.

of the stoichiometric reaction^[5] we tried triphenylphosphane oxide in our catalytic version. However, this resulted in the formation of by-products and no improvement in the yield of the desired compound (entry 2). Only traces of the product were obtained with triphenylphosphane selenide (entry 4) as a result of a rapid decomposition of the cobalt complex. In contrast, the reaction proceeded catalytically under an atmospheric pressure of CO upon addition of a monodentate phosphane sulfide (entries 5–14), and the yield of product was moderately to greatly improved, even with unpurified $[\text{Co}_2(\text{CO})_8]$.^[6] Bidentate diphosphane disulfides such as dppeS₂ slowed the reaction (entry 15), whereas monodentate phosphane sulfides, especially those with electron-donating substituents on the phosphorus atom, effectively promoted the catalytic reaction to afford the product in good yields (entries 5–14). Both the ratio of phosphane sulfide to $[\text{Co}_2(\text{CO})_8]$ and the concentration of the catalyst were critical (entries 6–14), probably because a ligand-exchange equilibrium exists between the phosphane sulfide, CO, and the olefin.^[7] A ratio of six equivalents of tributylphosphane sulfide to cobalt complex gave the best results (entry 12). Careful control of the reaction temperature was essential, as in other similar reactions; the reaction did not proceed below 50 °C, while the catalyst decomposed above 70 °C.^[2i] Although 1,2-dimethoxyethane (DME) is usually used as solvent in the catalytic Pauson–Khand reaction,^[8] phosphane sulfide ligands were more effective in benzene.

The scope of this reaction was then investigated with $[\text{Co}_2(\text{CO})_8]/\text{Bu}_3\text{PS}$ (Table 2). Intramolecular reactions proceeded smoothly to give the corresponding bicyclic cyclopentenones in good yields. A substituent on the alkyne or alkene moiety did not prevent the reaction from proceeding. Although an enyne containing a 1,2-disubstituted alkene group required a longer reaction time, the corresponding cyclopentenone was formed in good yield (entry 2), and the isomer ratio of the substrate (*E/Z* = 90/10) was almost maintained in the product (*trans/cis* = 85/15). Enynes connected by a heteroatom also gave the corresponding cyclopentenones in good yields when increased ratios of catalyst to substrate were used (entries 4, 5).^[9] In many cobalt-catalyzed Pauson–Khand reactions oxaynyne-type substrates, such as allyl propargyl ethers, demonstrate low reactivity. In contrast, **1e** gave a satisfactory result with 10 mol % of catalyst under our conditions. Without phosphane sulfide the reaction stopped at its initial stage to afford **2e** in only 25 % yield. By using the same conditions and the reactive olefin norbornene (**3**) an intermolecular version of the catalytic Pauson–Khand reaction was achieved [Eq. (1)].



Although the role of the phosphane sulfide is still not clear, the following are plausible explanations for its effectiveness: 1) Lewis bases such as amines^[10] and phosphane oxides^[5] are known to promote the stoichiometric Pauson–Khand

Table 2. Catalytic Pauson–Khand reaction in the presence of $[\text{Co}_2(\text{CO})_8]$ /Bu₃PS under an ambient pressure of CO.^[a]

Entry	Substrate ^[b]	Product	Yield ^[c] [%]
1			90 (50)
2			86
3			90
4			87 ^[d]
5			83 ^[e] (25)

[a] The reaction was performed on a 0.4-mmol scale. A mixture of substrate, $[\text{Co}_2(\text{CO})_8]$, and Bu₃PS in benzene (0.14 M substrate) was stirred under CO (1 atm) at 70 °C. [b] E = CO₂Et. [c] Yield of isolated product. The yields in parentheses are those obtained without phosphane sulfide. [d] 5 mol % of the cobalt complex and 30 mol % of the phosphane sulfide were employed, since the reaction was slow when only 3 mol % of the catalyst was used. [e] 10 mol % of the cobalt complex and 40 mol % of the phosphane sulfide were used, since the reaction did not go to completion when only 3–5 mol % of the catalyst was used.

reaction, and since dissociation of coordinated CO must take place before olefin coordination can occur, this effect presumably arises from acceleration of this ligand-exchange reaction. The reaction is faster in the presence of phosphane sulfide and this suggests that the phosphane sulfide may promote the catalytic cycle by means of its favorable basicity and coordinative lability. 2) In the stoichiometric, thermal Pauson–Khand reaction, the $[\text{Co}_2(\text{CO})_8]$ complex is transformed into a $[\text{Co}_4(\text{CO})_{12}]$ cluster, which requires CO pressure for reconversion to the active species $[\text{Co}_2(\text{CO})_8]$.^[2k] In our case, a coordinatively unsaturated species formed by elimination of the product could be trapped as a phosphane sulfide complex before it can decompose; the reaction would then proceed in a catalytic manner under only 1 atm of CO. This mechanism is in accord with the fact that the reaction at a lower concentration required a higher ratio of tributylphosphane sulfide to catalyst; occupation of the vacant ligand site and/or promotion of ligand exchange is suppressed by dilution.

Experimental Section

Typical procedure: A solution of enyne **1a** (99 mg, 0.42 mmol), $[\text{Co}_2(\text{CO})_8]$ (4.3 mg, 0.013 mmol), and tributylphosphane sulfide (17.7 mg, 0.077 mmol) in dry benzene (3 mL, 0.14 M solution of substrate) was vigorously stirred at 70 °C under a CO atmosphere (supplied from a balloon, 1 atm) until the substrate was consumed. When the substrate could no longer be detected by thin-layer chromatography, the reaction mixture was heated under reflux for 20 min to ensure complete reaction. The reaction mixture was then evaporated to dryness, and the residue was purified by preparative TLC on silica gel.

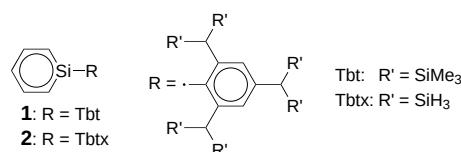
Received: August 25, 1999 [Z13925]

- Recent reviews: a) N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081–1119; b) N. E. Schore, *Org. React.* **1991**, *40*, 1–90; c) N. E. Schore in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 1037–1064; d) N. E. Schore in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Ed.: L. S. Hegehus), Pergamon, Oxford, **1995**, pp. 703–739; e) O. Geis, H. G. Schmalz, *Angew. Chem.* **1998**, *110*, 955–958; *Angew. Chem. Int. Ed.* **1998**, *37*, 911–914; f) N. Jeong in *Transition Metals in Organic Synthesis*, Vol. 1 (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, pp. 560–577.
- For Co-catalyzed reactions, see: a) V. Rautenstrauch, P. Mégard, José Conesa, W. Küster, *Angew. Chem.* **1990**, *102*, 1441–1443; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1413–1416; b) N. Jeong, S. H. Hwang, Y. Lee, *J. Am. Chem. Soc.* **1994**, *116*, 3159–3160; c) B. Y. Lee, Y. K. Chung, *J. Am. Chem. Soc.* **1994**, *116*, 8793–8794; d) N. Y. Lee, Y. K. Chung, *Tetrahedron Lett.* **1996**, *37*, 3145–3148; e) B. L. Pagenkopf, T. Livinghouse, *J. Am. Chem. Soc.* **1996**, *118*, 2285–2286; f) N. Jeong, S. H. Hwang, Y. W. Lee, J. S. Lim, *J. Am. Chem. Soc.* **1997**, *119*, 10549–10550; g) T. Sugihara, M. Yamaguchi, *J. Am. Chem. Soc.* **1998**, *120*, 10782–10783; h) T. Sugihara, M. Yamaguchi, *Synlett* **1998**, 1384–1386; i) D. B. Belanger, D. J. R. O'Mahony, T. Livinghouse, *Tetrahedron Lett.* **1998**, *39*, 7637–7640; j) D. B. Belanger, T. Livinghouse, *Tetrahedron Lett.* **1998**, *39*, 7641–7644; k) J. W. Kim, Y. K. Chung, *Synthesis* **1998**, 142–144. For Ti-catalyzed reactions, see: l) F. A. Hicks, N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 9450–9451; m) F. A. Hicks, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 11688–11689; n) S. C. Berk, R. B. Grossman, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 4912–4913. For Rh-catalyzed reactions, see: o) Y. Koga, T. Kobayashi, K. Narasaka, *Chem. Lett.* **1998**, 249–250; p) N. Jeong, S. Lee, B. K. Sung, *Organometallics* **1998**, *17*, 3642–3644. For Ru-catalyzed reactions, see: q) T. Kondo, N. Suzuki, T. Okada, T. Mitsudo, *J. Am. Chem. Soc.* **1997**, *119*, 6187–6188; r) T. Morimoto, N. Chatani, Y. Fukumoto, S. Murai, *J. Org. Chem.* **1997**, *62*, 3762–3765.
- For a detailed comparison of various Pauson–Khand-type reactions, see F. A. Hicks, N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 5881–5898.
- M. Hayashi, H. Takezaki, Y. Hashimoto, K. Takaoki, K. Saigo, *Tetrahedron Lett.* **1998**, *39*, 7529–7532.
- D. C. Billington, I. M. Helps, P. L. Pauson, W. Thomson, D. Willison, *J. Organomet. Chem.* **1988**, *354*, 233–242.
- We used commercially available octacarbonyldicobalt (Fluka and Kanto Chemicals) without further purification. Both products gave comparable results; in many cases the difference in yield was less than 2 %.
- A similar equilibrium was proposed to account for the acceleration arising from an internal sulfur ligand in an intramolecular Pauson–Khand reaction: M. E. Krafft, I. L. Scott, R. H. Romero, *Tetrahedron Lett.* **1992**, *33*, 3829–3832.
- Cobalt-catalyzed Pauson–Khand reactions are usually performed in DME; see refs. [2b–e, 2h–j].
- In the case of entry 5, reaction with a catalyst to additive ratio of 1:4 gave a better result than with a ratio of 1:6, but the reason for this is unclear.
- T. Sugihara, M. Yamada, H. Ban, M. Yamaguchi, C. Kaneko, *Angew. Chem.* **1997**, *109*, 2884–2886; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2801–2804.

Synthesis and Properties of an Overcrowded Silabenzene Stable at Ambient Temperature**

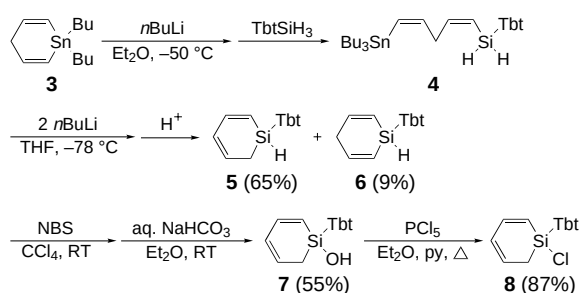
Keiji Wakita, Norihiro Tokitoh,* Renji Okazaki,* and Shigeru Nagase

Benzene, a 6 π -electron ring system, is the simplest and most fundamental example of an aromatic compound.^[1] Because of similarities and differences between carbon and silicon, the chemistry of the silicon-substituted analogues of benzene, the silabenzenes, have been explored extensively.^[2] Although aromatic character of silabenzene has been theoretically predicted and some silabenzenes were observed spectroscopically in the gas phase and in low-temperature matrices,^[3] their high reactivity prevented the syntheses of silabenzenes as stable molecules. Märkl et al.^[4] previously reported the synthesis of 2,6-bis(trimethylsilyl)-1,4-di-*tert*-butylsilabenzene, but it was reported as stable only below -100°C in solution (THF/Et₂O/petroleum ether, 4/1/1) and, judging from its relatively high field ²⁹Si NMR chemical shift ($\delta = 26.8$), stabilized by the coordination of a Lewis-base solvent (see below). In contrast, we have recently succeeded in the synthesis of the first stable silabenzene compound, 2-silabenzene, by protecting its reactive silicon center with an extremely bulky substituent group, 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl ("Tbt"). We report here the synthesis and characterization of the stable silabenzene bearing the Tbt group



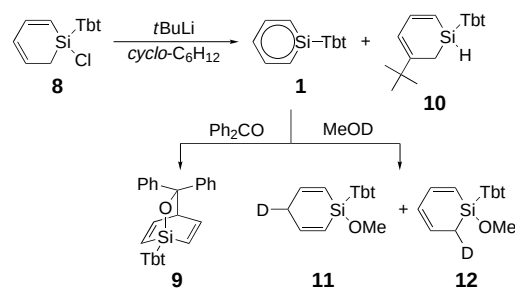
We first tried to synthesize a precursor of **1** by introducing the Tbt group to some silacyclohexadienes, but the substitu-

tions were not favorable.^[6] After examining several routes, we finally succeeded in the synthesis of **8**, which is a suitable precursor of **1**, starting from stannacyclohexadiene **3**^[7] and Tbt-substituted trihydrosilane^[8] (Scheme 1).



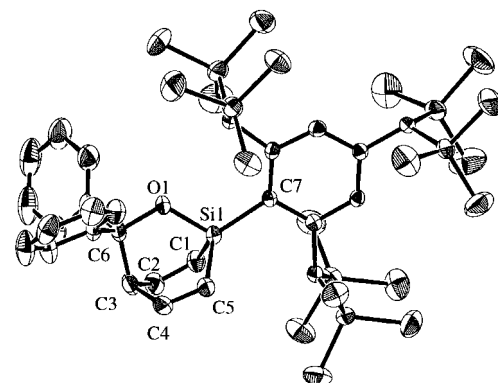
Scheme 1. Synthesis of **8**, a precursor of silabenzene **1**.

Treatment of **8** with one equivalent of *t*BuLi afforded two products. One of them was identified as **1** by its downfield shifted ²⁹Si NMR signal ($\delta = 92.5$, [D₁₂]cyclohexane) and by comparison of the ¹³C and ¹H NMR chemical shifts with calculated values (see below). Silabenzene **1** was trapped with Ph₂CO to afford the [4+2] cycloadduct **9** (Scheme 2), the



Scheme 2. Synthesis of silabenzene **1** from precursor compound **8**, and the treatment of **1** with diphenyl ketone (trapping reaction) and with methan[²H]ol.

structure of which was determined by X-ray crystallographic analysis (Figure 1).^[9] The other product in the reaction with *t*BuLi was **10** which bears a *tert*-butyl group on the ring. The



formation of **10** is most likely interpreted in terms of some radical pathways, although the accurate mechanism is unclear at present. In a separate reaction, **1** treated with MeOD formed adducts **11** and **12** in a 3:2 ratio. These reactions of **1** as a 1,3-diene are clearly different from those of 2(Tbt)-2-silanaphthalene, which reacted only as unconjugated Si-C double bond with several reagents.^[5]

The NMR signals due to the silabenzene ring of **1** were assigned by 2D NMR techniques and the results are shown in Table 1 along with chemical shifts calculated for the model compound **2**. The observed values are in excellent agreement with calculated ones. The ²⁹Si chemical shift of the central silicon atom of **1** ($\delta = 92.5$) is close to that previously reported for 2(Tbt)-2-silanaphthalene ($\delta = 87.3$).^[5]

Table 1. Selected chemical shifts (δ) as observed by ²⁹Si, ¹³C, and ¹H NMR spectroscopy and as calculated^[10, 11] for **1** and **2**.

	Observed ^[a] 1 (R = Tbt)	Calculated ^[b] 2 (R = Tbtx)
Si	92.51	89.88
C2	122.18	126.67
C3	143.38	148.52
C4	116.13	121.50
H2	6.80	6.99
H3	7.80	8.08
H4	6.51	6.78

[a] [D₁₂]Cyclohexane, TMS, room temperature. [b] Carried out at the GIAO-B3LYP/6-311G(d)(6-311G(3d)) on Si//B3LYP/6-31G(d) level.

The ¹J_{Si-C} value for **1** (83 Hz) observed for a Si-C bond in the ring is larger than that of a single bond (for example 50 Hz for Me₄Si)^[12] and lies between the two ¹J_{Si-C} values obtained for 2(Tbt)-silanaphthalene (92 and 76 Hz).^[5] The ¹J_{Si-C} value of **1** is also almost the same as the 84 Hz reported for (Me₃Si)₂Si=C(Ad)OSiMe₃ (Ad = 1-adamantyl),^[13] with a Si-C bond length of 1.764 Å.^[14] These results indicate the delocalized character of **1**, which is supported by the calculated structure of a model compound **2**. The Si-C2 bond length in **2** is 1.777 Å, which is a middle value between Si-C single and double bonds, and is similar to the average value of two Si-C bond lengths of 2-silanaphthalene (calculated to be 1.750 and 1.791 Å).^[5] Other C-C bond lengths in **2** (C2-C3 = 1.401 Å; C3-C4 = 1.402 Å) are found to be almost the same as those of benzene (1.39–1.40 Å).^[1]

No change was observed in its NMR spectrum even after the [D₁₂]cyclohexane solution of **1** was stored for many weeks at room temperature under an inert atmosphere. Removal of the solvent and redissolution in the same solvent did not change the NMR signals either, indicating that **1** is stable in the solid state at ambient temperature. Furthermore, measurement of ²⁹Si NMR in THF/C₆D₆ (6/1) induced no significant change of the chemical shift ($\delta = 93.4$), suggesting that **1** is not coordinated by THF. These stabilities of **1** are clearly different from those Märkl^[4] previously reported for 2,6-bis(trimethylsilyl)-1,4-di-*tert*-butylsilabenzene, demonstrating the excellent steric protection afforded by the Tbt group. Unfortunately, isolation of **1** has not been achieved yet since separation of the mixture of **1** and **10** requires exposure to air.

Experimental Section

A solution of **8** (33.2 mg, 0.0487 mmol) in dry cyclohexane (2 mL) was placed in a glovebox filled with argon and *t*BuLi (0.59 M hexane solution, 0.08 mL, 0.05 mmol) was added. After the solution was transferred into an NMR tube and then degassed, the tube was sealed. After measurement of NMR spectra, the tube was opened in a glovebox and benzophenone (18 mg, 0.010 mmol) was added. Purification by GPLC and FCC afforded **9** (9.1 mg, 27%) and **10** (7.9 mg, 20%). Compounds **9–12**, and **4–7** in the synthesis of **8** showed satisfactory spectroscopic and analytical data, which will be reported elsewhere.

Received: July 26, 1999 [Z13780]

- V. J. Minkin, M. N. Glukhovtsev, Y. B. Simkin, *Aromaticity and Antiaromaticity; Electronic and Structural Aspects*, Wiley, New York, 1994.
- For reviews on sila-aromatic compounds, see: a) G. Raabe, J. Michl, *Chem. Rev.* **1985**, 85, 419; b) G. Raabe, J. Michl in *The Chemistry of Organosilicon Compounds* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1989**, pp. 1102–1108; c) Y. Apeloig in *The Chemistry of Organosilicon Compounds* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1989**, pp. 151–166; d) A. G. Brook, M. A. Brook, *Adv. Organomet. Chem.* **1996**, 39, 71; e) Y. Apeloig, M. Karni in *The Chemistry of Organosilicon Compounds, Part II* (Eds.: Y. Apeloig, Z. Rappoport), Wiley, New York, **1998**, chap. 1.
- a) B. Solouki, P. Rosmus, H. Bock, G. Maier, *Angew. Chem.* **1980**, 92, 56; *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 51; b) G. Maier, G. Mihm, H. P. Reisenauer, *Angew. Chem.* **1980**, 92, 58; *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 52; c) C. L. Kreil, O. L. Chapman, G. T. Burns, T. J. Barton, *J. Am. Chem. Soc.* **1980**, 102, 841; d) G. Maier, G. Mihm, H. P. Reisenauer, *Chem. Ber.* **1982**, 115, 801; e) G. Maier, G. Mihm, R. O. W. Baumgärtner, H. P. Reisenauer, *Chem. Ber.* **1984**, 117, 2337; f) G. Maier, K. Schöttler, H. P. Reisenauer, *Tetrahedron Lett.* **1985**, 26, 4079; g) P. Jutzi, M. Meyer, H. P. Reisenauer, G. Maier, *Chem. Ber.* **1989**, 122, 1227.
- G. Märkl, W. Schlosser, *Angew. Chem.* **1988**, 100, 1009; *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 963.
- N. Tokitoh, K. Wakita, R. Okazaki, S. Nagase, P. von R. Schleyer, H. Jiao, *J. Am. Chem. Soc.* **1997**, 119, 6951.
- K. Wakita, N. Tokitoh, R. Okazaki, *Chem. Lett.* **1998**, 687.
- A. J. Ashe III, W.-T. Chan, *J. Org. Chem.* **1979**, 44, 1409.
- H. Suzuki, N. Tokitoh, R. Okazaki, J. Harada, K. Ogawa, S. Tomoda, M. Goto, *Organometallics* **1995**, 14, 1016.
- Crystal structure data of **9**: Rigaku R-Axis IV imaging plate detector, MoK α radiation, graphite monochromator. The reflections were recorded at 293 K from a colorless prismatic crystal with dimensions 0.4 × 0.3 × 0.1 mm³ to 2 $\theta_{\max}$ = 55°. The structure was solved by direct methods (SHELXS86) and refined by full-matrix least-squares optimization. C₄₅H₇₄OSi₇, *M*_r = 827.68, monoclinic, space group *P*₂₁/*a*, *Z* = 4, *a* = 18.521(4), *b* = 11.189(3), *c* = 26.28(3) Å, β = 107.133(5)°, *V* = 5204(3) Å³, ρ_{calcd} = 1.056 g cm⁻³, μ = 2.12 cm⁻¹; of 8596 measured reflections, 6779 observed for *I* > 3 σ (*I*). Hydrogen atoms were placed in calculated positions and not refined, all other atoms were refined anisotropically. *R* = 0.054, *R*_w = 0.049 for 478 parameters; max./min. residual electron density 0.22/−0.35 e Å⁻³. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-127402. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
- M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. DeFrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, *Gaussian 94*, Gaussian Inc., Pittsburgh, **1995**.

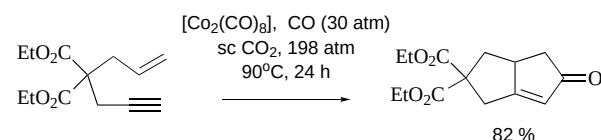
- [11] The shielding constants of TMS at this level are 321.38 (for Si), 183.19 (for C) and 32.16 (for H).
 [12] H.-O. Kalinowski, S. Berger, S. Braun, *Carbon-13 NMR Spectroscopy*, Wiley, New York, **1986**, p. 600.
 [13] A. G. Brook, F. Abdesaken, G. Gutekunst, N. Plavac, *Organometallics* **1982**, *1*, 994.
 [14] A. G. Brook, S. C. Nyburg, F. Abdesaken, B. Gutekunst, G. Gutekunst, R. K. M. R. Kallury, Y. C. Poon, Y. Chang, W. Wong-Ng, *J. Am. Chem. Soc.* **1982**, *104*, 5668.

Catalytic Intermolecular Pauson–Khand Reactions in Supercritical Ethylene**

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Supercritical fluids are rapidly becoming alternative reaction media for conventional organic reactions.^[1] The advantages of reactions in supercritical fluids include the high solubility of gaseous reactants, rapid diffusion of solutes, and weakening of the solvation around the reacting species. In addition, these fluids are easily recycled and allow the separation of the dissolved compounds by selective precipitation, which implicates possibilities in the development of environmentally benign processes. Sequential precipitation of the product and catalyst is possible by a gradual release of pressure.^[2]

Recent progress has shown that supercritical fluids can substitute conventional organic solvents in various transition metal catalyzed transformations.^[3] We demonstrated that catalytic intra- and intermolecular Pauson–Khand reactions could be carried out in supercritical CO₂ with high efficiency (Scheme 1).^[4] We report here a new dimension of this



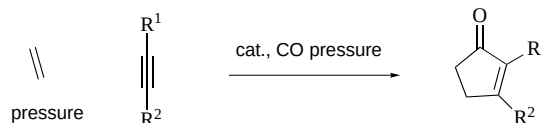
Scheme 1. Example for a Pauson–Khand reaction in supercritical (sc) CO₂.

application, that is, an intermolecular Pauson–Khand reaction in supercritical ethylene. Ethylene is one of the most abundant raw materials in the petrochemical industry. Direct

coupling of ethylene with the proper acetylenes under Pauson–Khand conditions provides an efficient and economical method for preparing synthetically useful cyclopentenones.^[5]

Pauson–Khand reactions of ethylene with stoichiometric amounts of hexacarbonyldicobalt–alkyne complexes have been reported.^[6, 7] Rautenstrauch et al. described the first catalytic Pauson–Khand reaction between heptyne and ethylene in toluene in 1990.^[8] This catalytic reaction showed a high turnover number (220), but it suffered from the harsh reaction conditions and had a low chemical yield (<50%). This might be attributed to the low effective concentration of ethylene in the solvent and the ill-defined, catalytic cobalt–carbonyl species formed under the reaction conditions employed.

Encouraged by our success with CO₂ as a supercritical fluid, we first tried to apply the previously employed conditions for the reaction with ethylene. We ran a series of reactions (48 h at 80 °C) in supercritical CO₂ (*p*_{final} = 200 atm) with phenylacetylene (**1a**) and ethylene (10–45 atm at 34 °C) with various pressures of CO (1–30 atm) and in the presence of a catalytic amount of [Co₂(CO)₈] (**I**). The result was disappointing and the chemical yield of 2-phenylcyclopentenone (**1b**) never exceeded 10%. Therefore, we decided to seek the possibility of a direct coupling reaction in supercritical ethylene (Scheme 2).



Scheme 2. Intermolecular Pauson–Khand reactions between ethylene and alkynes (see Table 1).

Supercritical ethylene can be obtained easily (*T*_c = 9 °C, *p*_c = 34 atm) and has been used for the preparation of the complex [Cr(CO)₅(CH₂CH₂)] and its polymer.^[9, 10] We envisioned that it can also be used for the Pauson–Khand reaction. Under these conditions, a high effective concentration of the rather less reactive ethylene as well as of carbon monoxide would be expected.

The catalysts examined with substrate **1a**, which are all soluble in supercritical ethylene—for example, [Co₂(CO)₈] (**I**), [Co₄(CO)₁₁(P(OPh)₃)] (**II**), or [Co₄(CO)₁₂] (**III**), worked well although the efficiency of each catalyst varied from case to case. On the other hand, [Co₂(CO)₆(P(OPh)₃)₂] (**IV**), which is a reliable catalyst in organic solvents,^[5d] did not work because of its low solubility in supercritical ethylene.

We optimized the reaction conditions with catalysts **II** and **III** in most cases.^[11] Ethylene (110 atm at 34 °C) and CO (5 atm at 34 °C) were charged into a mixture of phenylacetylene (3 mmol) and catalyst **II** (0.09 mmol) in a stainless-steel reactor (80 mL). The reaction mixture was gradually warmed to 85 °C over 6 h, where the pressure in the reactor usually reached 200–210 atm. The reaction mixture was allowed to react at that temperature for 46 h. 2-Phenylcyclopentenone (**1b**) was obtained in 80% yield (Table 1, entry 1). Only 2-substituted cyclopentenone was obtained.

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[**] Part of this work was supported by a grant from the Center for Molecular Design and Synthesis (CMDS) at KAIST.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.

Table 1. Results of intermolecular catalytic Pauson–Khand reactions in supercritical ethylene (Scheme 2).^[a]

Entry	Substrate	R ¹	R ²	Catalyst [mol %]	t[h]	Conversion [%]	Products	Yield [%]
1	1a	Ph	H	II (3)	46	100	1b	80
2	1a	Ph	H	III (3)	24	100	1b	77
3	2a	C ₅ H ₁₁	H	II (3)	42	100	2b	70
4	3a	HO(CH ₂) ₃	H	II (3)	46	100	3b	46
5	4a	Me ₃ SiO(CH ₂) ₃	H	II (3)	64	100	3b	82 ^[b]
6	4a	Me ₃ SiO(CH ₂) ₃	H	I (3)	30	50	3b	40 ^[b]
7	5a	CH ₃ CH(OSiMe ₃)CH ₂	H	II (5)	44	100	5b	74 ^[b]
8	6a	Me ₃ SiOCH ₂	H	II (5)	24	100	6b	30 ^[b]
9	6a	Me ₃ SiOCH ₂	H	III (5)	48	100	6b	23 ^[b]
10	7a	<i>t</i> BuMe ₂ SiOCH ₂	H	II (5)	24	100	6b	41 ^[b]
11	8a	MeO ₂ C(CH ₂) ₂	H	II (5)	30	100	8b	75
12	8a	MeO ₂ C(CH ₂) ₂	H	III (5)	40	100	8b	87

[a] The optimum conditions for each substrate are given. The reactions were carried out in a bomb equipped with a sapphire window at 85 °C for the specified reaction time. The initial pressure of CO was 5 atm and of ethylene was 110 atm at 34 °C. The liquid phase was observed at that temperature. At 85 °C the reaction mixture became one red, homogeneous supercritical phase. It remained as a single phase even after completion of the reaction. [b] Yield of free alcohol isolated after treatment with concentrated HCl.

Complications by alkyne trimerization leading to triphenylbenzenes (1,3,5- or 1,3,4-substituted) were not observed under these reaction conditions. For **1a**, catalyst **III** worked equally well to provide **1b** in 77 % yield. It is noteworthy that catalyst **III** was once considered as thermally inactive for the Pauson–Khand reaction.^[12]

The reaction with aliphatic terminal alkyne **2a** proceeded uneventfully to provide **2b** in 70 % yield (Table 1, entry 3). When alcohols were used as substrate the hydroxyl groups needed to be protected for clean reaction and high chemical yield. For example, alkynol **3a** reacted without protection to give the desired product **3b** (entry 4) together with many unidentified side products in only 46 % yield after column chromatography. Use of the trimethylsilyl-protected substrate **4a** improved the reaction significantly to generate **3b** in 82 % yield after treatment of the resulting Pauson–Khand product with acid (entry 5).

The trimethylsilyl-protected homopropargyl alcohol **5a** underwent the reaction very nicely to give **5b** in 74 % yield (entry 7). However, propargyl alcohol derivatives **6a** and **7a** were inferior to the previous substrates under these conditions (entries 8 to 10). Regardless of the protecting groups and reaction conditions employed, only modest chemical yields were obtained (41 % at best).

ω -Alkynoate **8a** provided the corresponding cyclopentenone **8b** in high yield (up to 87 % with catalyst **III**; entries 11 and 12). [Co₄(CO)₁₂] (**III**) turned out to be the best catalyst for this substrate. However, the limitation of the reaction in supercritical ethylene was also evident. For example, a disubstituted alkyne such as 2-butyne did not react under these reaction conditions. A similar observation is also reported in the literature.^[13] [CpCo(CO)₂]-catalyzed trimerization of alkyne in supercritical H₂O is limited to terminal alkynes. α,ω -Bisalkyne (e.g. 1,7-octadiyne), which is a good substrate in the intermolecular reaction with norbornadiene in supercritical CO₂, was reluctant to undergo the Pauson–Khand reaction.^[4]

In summary we have demonstrated an efficient catalytic Pauson–Khand reaction in supercritical ethylene. Supercritical ethylene can be used not only as a substrate but also as a

solvent. Under these conditions, even a low pressure of CO (5 atm) is sufficient for the reaction to take place.^[14]

Experimental Section

To **1a** (306 mg, 3.0 mmol) in a pressure bomb was added [Co₄(CO)₁₂] (**III**, 54.5 mg, 0.091 mmol), and the bomb (80 mL) was flushed three times with CO and then charged with CO (5 atm, 99.9 %) at 34 °C. Subsequently ethylene (99.5 %) was added and then compressed to 110 atm. The reaction mixture was warmed to 85 °C and allowed to react for 24 h. After that it was cooled to room temperature, and the CO and excess ethylene were released carefully in a well-vented hood. The reaction residue was dissolved in acetone, concentrated in vacuo, and purified by chromatography (SiO₂, *n*-hexane/ethyl acetate 9/1) to give the product **2a** as a colorless oil (366 mg, 2.3 mmol, 77 %).^[14]

Received: September 6, 1999 [Z13975]

- [1] *Chemical Synthesis using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley-VCH, Weinheim, 1999.
- [2] J. F. Brennecke, *Chem. Ind. (London)* **1996**, 831.
- [3] a) P. G. Jessop, T. Ikariya, R. Noyori, *Chem. Rev.* **1999**, 99, 475, and references therein; b) P. G. Jessop, Y. Hsiao, Y. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, 118, 344; c) M. J. Burk, S. G. Feng, M. F. Gross, W. J. Tumas, *J. Am. Chem. Soc.* **1995**, 117, 8277; d) P. G. Jessop, T. Ikariya, R. Noyori, *Nature* **1994**, 368, 231; e) J. W. Rathke, R. J. Klingler, T. R. Krause, *Organometallics* **1991**, 10, 1350; f) S. Kainz, D. Koch, W. Baumann, W. Leitner, *Angew. Chem.* **1997**, 109, 1699; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1628; g) A. Fürstner, D. Koch, K. Langemann, W. Leitner, C. Six, *Angew. Chem.* **1997**, 109, 2562; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2466.
- [4] N. Jeong, S. H. Hwang, Y. W. Lee, J. S. Lim, *J. Am. Chem. Soc.* **1997**, 119, 10549.
- [5] a) P. L. Pauson, I. U. Khand, *Ann. N. Y. Acad. Sci.* **1977**, 295, 2; b) N. E. Schore in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, UK, **1995**, pp. 703–739; c) N. Jeong in *Transition Metals for Organic Synthesis*, Vol. 1 (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, pp. 560–577; for catalytic reactions, see d) N. Jeong, S. H. Hwang, Y. Lee, Y. K. Chung, *J. Am. Chem. Soc.* **1994**, 116, 3159; e) B. Y. Lee, Y. K. Chung, N. Jeong, Y. Lee, S. H. Hwang, *J. Am. Chem. Soc.* **1994**, 116, 8793; f) B. L. Pagenkopf, T. Livinghouse, *J. Am. Chem. Soc.* **1996**, 118, 2285; g) N. Y. Le, Y. K. Chung, *Tetrahedron Lett.* **1996**, 37, 3145.
- [6] a) C. Johnstone, W. J. Kerr, U. Lange, *J. Chem. Soc. Chem. Commun.* **1995**, 459; b) D. C. Billington, I. M. Helps, P. L. Pauson, W. Thomson, D. J. Willison, *J. Organomet. Chem.* **1988**, 354, 233; c) D. C. Billington, W. J. Kerr, P. L. Pauson, *J. Organomet. Chem.* **1988**, 341, 181.

- [7] a) A. R. Gordon, C. Johnstone, W. R. Kerr, *Synlett* **1995**, 1083; b) S. Shambayati, W. E. Crowe, S. L. Schreiber, *Tetrahedron Lett.* **1990**, 31, 5289; c) N. Jeong, Y. K. Chung, B. Y. Lee, S. H. Lee, S. E. Yoo, *Synlett* **1991**, 204.
- [8] V. Rautenstrauch, P. Megard, J. Conesa, W. Kuster, *Angew. Chem.* **1990**, 102, 1441; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1413.
- [9] J. A. Banister, S. M. Howdle, M. Poliakoff, *J. Chem. Soc. Chem. Commun.* **1993**, 1814.
- [10] S. Beuermann, M. Buback, M. Busch in *Chemical Synthesis using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley-VCH, Weinheim, **1999**, pp. 326–350.
- [11] **Caution!** Although no incident occurred during this study, we observed that highly purified $[\text{Co}_2(\text{CO})_8]$ and $[\text{Co}_4(\text{CO})_{12}]$ ignited spontaneously at times upon contact with air. Special precaution should be paid. Therefore, we prefer to use stable $[\text{Co}_4(\text{CO})_{11}\text{-P(OPh)}_3]$ to avoid any potential danger.
- [12] J. W. Kim, Y. K. Chung, *Synthesis* **1998**, 142.
- [13] K. S. Jerome, E. J. Parsons, *Organometallics* **1993**, 12, 2991.
- [14] See ref. [8]. Note that a much higher pressure of CO (100 bar at the inception) was required under their conditions.

The First Red Azo Lake Pigment whose Structure is Characterized by Single Crystal Diffraction**

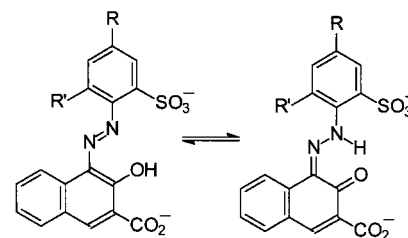
Alan R. Kennedy,* Craig McNair, W. Ewen Smith, Greig Chisholm, and Simon J. Teat

As organic pigments are used in the form of crystals dispersed throughout the media to be colored, their color characteristics depend not only on their molecular structure but also crucially upon their crystal structure. Furthermore, the crystal structure influences the stability of the pigment to solvent, heat, and light and also determines the crystal morphology which is in turn related to color strength, hiding power, stability, flow, and dispersion properties.^[1] As a good pigment is, by design, highly insoluble, it is difficult to grow the large, high-quality crystals needed for conventional diffraction methods and thus little detailed structural information is available. These generalizations are true of the red azo pigments as exemplified by Ca4B toner (the calcium salt of 4-(4-methyl-2-sulfophenyl)azo-3-hydroxy-2-naphthalic acid; also known as CIPR 57:1) which is considered the worldwide standard process red for printing and its continuing industrial importance is attested to by the patent literature.^[2]

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[**] We thank Prof. R. E. Mulvey for valuable discussions and EPSRC for funding.

Previous work on the structure of Ca4B^[3] showed that the classification “azo pigment” is actually a misnomer, as in the solid state the pigment exists largely as the keto-hydrazone tautomer (Scheme 1). Further, deprotonation occurs at the



Scheme 1. Tautomerism in red azo pigments.

sulfonate and carboxy groups but not at the hydroxy/hydrazone group, and there is only one type of calcium binding site. Harris et al.^[3a] suggested from solid-state NMR measurements that the calcium atom is complexed by sulfonate and carboxylate groups from different molecules and thus proposed a simple polymeric structure with azo molecules bridged by Ca^{2+} ions, whereas Fryer and coworkers^[3c] showed evidence from electron microscopy that Ca4B exists as head-to-tail dimers.

We have now succeeded in growing, by slow evaporation of a DMF solution, small crystals of a dichloro analogue of Ca4B (**1**) suitable for characterization by synchrotron radiation.^[4] Compound **1** displays a complex, supramolecular structure of a type not previously suspected for red azo pigments but which we believe to be consistent with the experimental evidence in the published work on Ca4B, and which we propose to be a suitable model structure to relate to the structure of many other red azo pigments.

The structural analysis confirms that the azo dianion is deprotonated at the sulfonate and carboxylate groups. The Ca atoms are eight coordinate through bonding to three sites (carboxylate, keto, and sulfonate) on one azo anion, to two terminal water molecules, and to three oxygen atoms supplied by bridging interactions to the carboxylate groups of neighboring azo anions (Figure 1). That the azo anion acts in such a

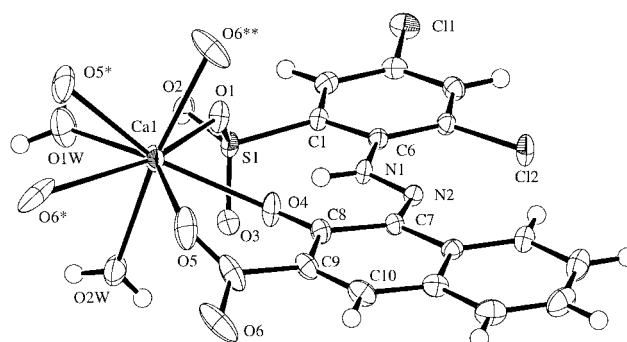


Figure 1. Molecular structure of **1** showing the coordination geometry about Ca1. Selected distances [Å]: Ca1–O1 2.542(2), Ca1–O4 2.394(2), Ca1–O5 2.385(2), Ca1–O1W 2.449(2), Ca1–O2W 2.352(2), Ca1–O5* 2.440(2), Ca1–O6* 2.881(2), Ca1–O6** 2.374(2), N1–N2 1.304(2), N1–C6 1.395(2), N2–C7 1.333(2), C8–O4 1.257(2), C7–C8 1.458(3), C8–C9 1.451(3), C9–C10 1.349(3). Symbols: * = $-x + 1, y + 0.5, -z + 0.5$; ** = $x, y + 1, z$.

terdentate mode with the keto group binding to calcium had not previously been suspected. The Ca–O6* distance of 2.881(2) Å, corresponding to one of the bonds to the bridging, chelated carboxylate group, is considerably longer than the other Ca–O distances (2.352(2)–2.542(2) Å). In contrast to the transition metal chemistry of simple keto-hydrazo dyes, no Ca–N bond is formed.^[5] That the azo ligand exists predominantly in the keto-hydrazo form is shown by the lengthening of the N1–N2, C7–C8, and C8–C9 distances and by the complimentary shortening of the C8–O4, N2–C7, and C9–C10 distances. The ligand is nearly planar (C6–N1–N2–C7, N1–N2–C7–C8, and N2–N1–C6–C1 dihedral angles are 178.4(2)°, 0.1(3)°, and 176.8(2)°, respectively), a conformation which is favored by the internal hydrogen bond between the hydrazo and keto groups. The calcium atom is significantly displaced from this ligand plane as shown in Figure 1. The geometry of the azo ligand is in good agreement with that seen in reference [6] (a sodium salt of an azo dye rotaxane, which is the only previously known structure to show complexation of a main group metal with any type of keto-hydrazo species) and also with the main group salts of orange G^[7] where the hydrated metal cations are not bonded to the dye.

The extended structure of **1** is shown in Figure 2. Its salient feature is the polymeric double-chain of calcium atoms that propagate along the *b* direction by translation and the action of the 2₁ screw axis. This architecture is suggestive of the ring–ladder structures found in certain group I amides and organometallic compounds^[8] and, under that system, would be described as an infinite ladder structure of alternating, fused Ca₂O₂ rhomboids and CaOCO kites.^[9] (Replacing the chelating carboxylate group with a monoatomic bridge species would give a conventional ladder arrangement.) Both ring types are internally folded and, together with an angle of 122° between the two ring types, give the ladder a zig-zag conformation. This double-chain structure is germane to that

of Ca4B. It is proposed from electron microscopy^[3c] that Ca4B has unit cell parameters $a = 8.4$, $b = 5.8$, $c = 18$ Å, $\beta = 92^\circ$, and $Z = 2$. Notice that both *b* and *c* are similar in **1**, indicating some relationship between the two structures, but especially that the *b* distance corresponds to the calcium–calcium separation along the chain. This must indicate that Ca4B has a similar central, polymeric, double-chain structure. Where unit cells can be derived from powder diffraction, this parameter could be used as a diagnostic feature to assign other azo red pigments to this structural type.

The water ligands on one strand of the calcium double chain all lie below the ladder plane whilst those on the other strand lie above, giving an *anti* arrangement. Figure 2 highlights other structural features. The azo ligands are parallel to their companions on the same side of the ladder, but are angled with respect to those on the opposite side. The closest contacts between parallel ligands fall just within the range usually accepted as indicating π -stacking (N1...C10 3.43 and C5...C12 3.46 Å). All the azo ligands in a chain run in the same head-to-tail orientation along the *b* direction and the inter-chain contacts in the *a* and *c* directions are also head-to-tail. The interchain contacts in the *c* direction are dominated by sulfonate–water hydrogen bonding (there is also hydrogen bonding present along the chains) but in the *a* direction the chains are separated by at least van der Waals distances. There are no significant interchain Cl...Cl or Cl...H contacts.

This highly directionalized supramolecular structure, featuring the self assembly motifs of a polydentate chelate, ligands bridging metal atoms, hydrogen bonding, and π -stacking is consistent with the poor and highly anisotropic crystal growth properties of red azo lake pigments. It is also consistent with the previous work on Ca4B, but combines the known data in a previously unsuspected manner to give a new and unsuspected outcome. Further work on a range of derivatives of both **1** and Ca4B is currently underway in an attempt to relate changes in structure to changes in color.

Received: September 8, 1999 [Z13984]

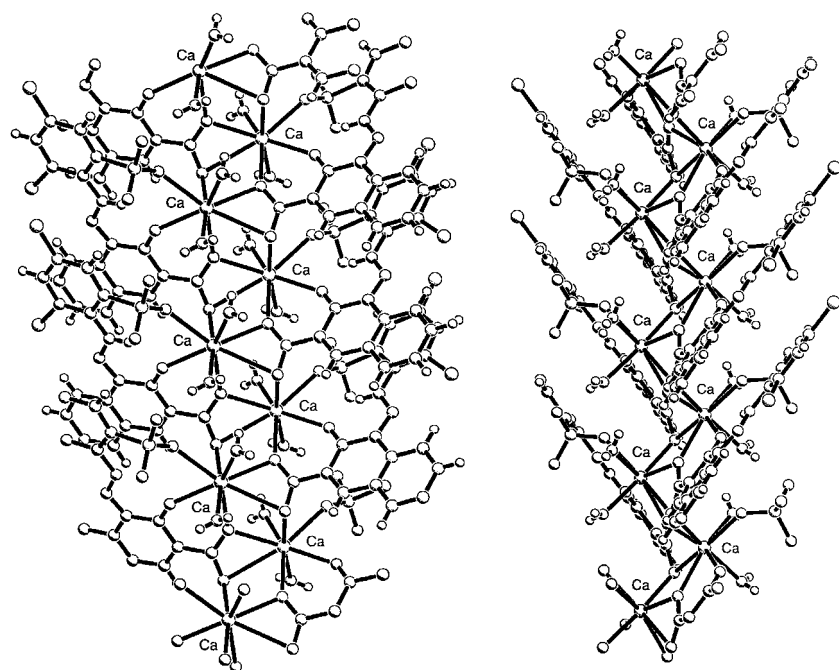


Figure 2. Two views of the polymeric structure of **1** as it extends along the *b* direction.

- [1] Z. Hao, A. Iqbal, *Chem. Soc. Rev.* **1997**, 26, 203.
- [2] For general information on Ca4B, see: a) W. Herbst, K. Hunger, *Industrial Organic Pigments: Production, Properties, Applications*, VCH, New York, **1993**; b) *Pigment Handbook*, 2nd ed., (Ed.: P. A. Lewis), Wiley Interscience, New York, **1988**.
- [3] a) R. K. Harris, P. Jonsen, K. J. Packer, C. D. Campbell, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1383; b) J. Clarkson, D. R. Armstrong, C. H. Munro, W. E. Smith, *J. Raman Spectrosc.* **1998**, 29, 421; c) G. R. Duckett, J. R. Fryer, T. Baird, *Inst. Phys. Conf. Ser.* **1985**, 78, 437.
- [4] a) R. J. Cernik, W. Clegg, C. R. A. Catlow, G. Bushnell Wye, J. V. Flaherty, G. W. Greaves, I. Burrows, D. J. Taylor, S. J. Teat, M. Hamichi, *J. Synchrotron Radiat.* **1997**, 4, 279; b) Crystal structure data for **1**: C₁₇H₁₂CaCl₂N₂O₈S, $M = 515.33$, red needles, $150 \times 20 \times 5 \mu\text{m}$. Si111 monochromated synchrotron radiation from Daresbury Station 9.8 ($\lambda = 0.68910$ Å), $T = 150$ K; monoclinic, space group $P2_1/c$; $a = 19.2996(8)$, $b = 5.6514(2)$, $c = 18.1528(8)$ Å; $\beta = 104.454(2)^\circ$;

$V = 1917.25(13) \text{ \AA}^3$; $Z = 4$; $\mu = 0.768 \text{ mm}^{-1}$; $\rho_{\text{calcd}} = 1.785 \text{ Mg m}^{-3}$; $2\theta_{\text{max}} = 54^\circ$; 11456 reflections collected, 4540 unique used ($R_{\text{int}} = 0.0280$). The structure was solved and refined on F^2 using published programs and techniques [10] to convergence at $R1 = 0.0369$ (for 3848 reflections with $I > 2\sigma(I)$), $wR2 = 0.0904$, and $S = 1.061$ for 300 parameters. Maximum residual electron density $0.43 \text{ e \AA}^{-3}$. The H atoms on N and O were treated isotropically but all other H atoms were placed in calculated positions. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134039. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

- [5] For a representative example, see: S. B. Choudhury, D. Ray, A. Chakravorty, *J. Chem. Soc. Dalton Trans.* **1992**, 107.
- [6] S. Anderson, W. Clegg, H. L. Anderson, *Chem. Commun.* **1998**, 2379.
- [7] W. H. Ojala, L. K. Lu, K. E. Albers, W. B. Gleason, T. I. Richardson, R. E. Lovrien, E. A. Sudbeck, *Acta Crystallogr. Sect. B* **1994**, 50, 684.
- [8] R. E. Mulvey, *Chem. Soc. Rev.* **1998**, 27, 339.
- [9] P. C. Andrews, W. Clegg, R. E. Mulvey, P. A. O'Neil, H. M. M. Wilson, *J. Chem. Soc. Chem. Commun.* **1993**, 1142.
- [10] a) G. M. Sheldrick, SHELXL-97, University of Göttingen, Germany, **1997**; b) W. Clegg, M. R. J. Elsegood, S. J. Teat, C. Redshaw, V. C. Gibson, *J. Chem. Soc. Dalton Trans.* **1998**, 3037.