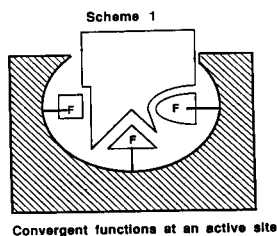


Julius Rebek, Jr.

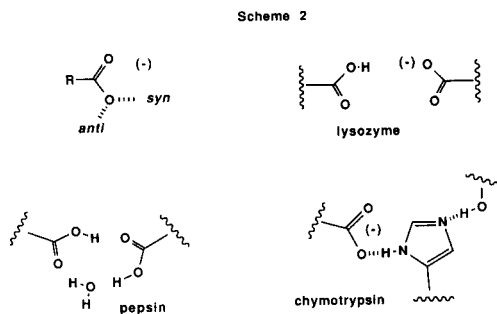
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*J. Heterocyclic Chem.*, **27**, 111 (1990).

Like many people working in molecular recognition today, I look to Nature for inspiration. One of the things I see is depicted schematically below. Most biological macromolecules present convergent functionality towards the small molecules that they act upon. These concave shapes, whether they be grooves on a double stranded nucleic acid or the active site of an enzyme, present a surface lined with functional groups of the proper size, shape and electronics for complementarity to the smaller, convex substrates.

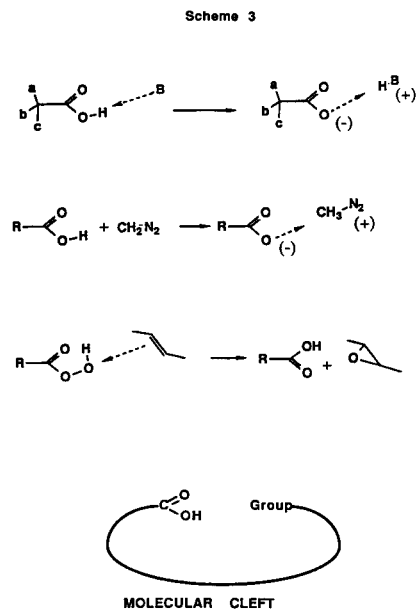


The convergence of functionality has more than mere aesthetic appeal. In the case of the carboxyl function, stereoelectronic considerations suggest most effective catalysis can be obtained by a convergent arrangement. As Gandour [1] pointed out nearly ten years ago, when the carboxyl group appears at the active site of an enzyme, the more basic *syn* lone pairs are inevitably directed toward the substrate. This is evident in the sketches below of the active site of lysozyme, aspartic proteinases, and even the serine proteinases, where the more basic lone pair is directed toward the proton relay apparatus of the catalytic triad.



There are expressions of these stereoelectronic effects at carboxyl oxygen in more familiar, organic chemical settings. For example, the rather low efficiency of asymmetric protonation by conventional carboxylic acids reflects the great distance between the basic site as it approaches and the asymmetric center at the  $\alpha$  carbon on the other side of the molecule. Another reaction which also shows no steric components is the esterification of carboxylic

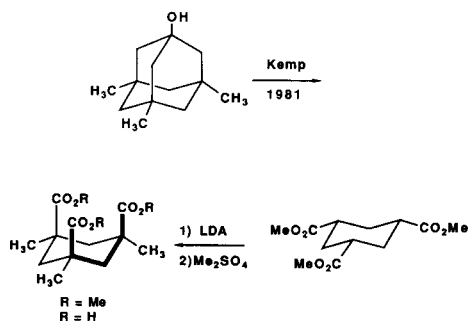
acids with diazomethane. After the initial proton transfer, the displacement takes place along the line defined by the *syn* lone pair; there is little opportunity for groups on the diazo compound and the  $\alpha$  carbon to interact. In an effort to engineer steric effects into reactions of this sort, and those involved in the Prilashajev reaction [2], we set out to make molecules in the general shape of clefts, that is, lined with carboxyl functions in such a way that the microenvironment near the OH bond of the carboxyl acid could be altered at will. Since the first bond away from the carboxyl is pointing in precisely the wrong direction, it is clear that a U-turn has to be built in into such structure, that is, the molecule must fold back upon itself if the microenvironment near the OH bond is to be tailored to specific needs.



After many false starts with seemingly promising scaffolds, we were rescued by Dan Kemp who, in 1981, described [3] the synthesis of a very unusual tricarboxylic acid, an oxidative degradation product of trimethyl adamantanol. In this molecule, the three carboxyl groups are forced into a triaxial arrangement by the equatorial methyl groups. As a result, a U-shaped relationship exists between any two carboxyl functions and it is this U-shape that allows us to build molecules that fold back upon themselves. This module is used repeatedly in our work, not only as the triacid but in various other oxidation levels. We developed a more efficient synthesis [4] from trimelic acid: hydrogenation, then treatment with strong base and dimethyl sulfate give us good yields of the *cis*,

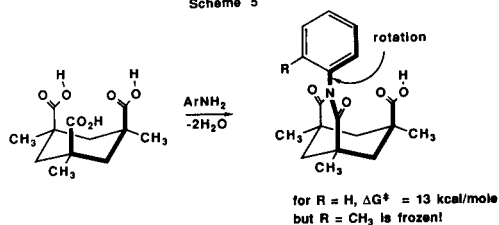
*cis* isomer. As a consequence, earlier this year, the Kemp triacid has become commercially [5] available.

Scheme 4



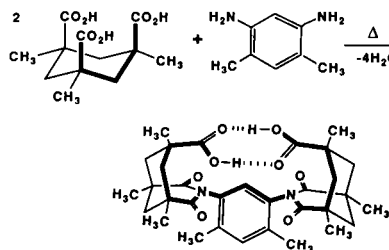
We found that condensation of the Kemp triacid or its derivatives with aniline led to imides. These imides show slow rotation about the *C*-aryl and *N*-imide bond that lead to dynamic NMR effects. However, *ortho* substituted imides such as that derived from *ortho* toluidine proved quite rigid, that is, the seemingly passive methyl groups of the molecule act to restrict its rotational and other conformational freedom [6]. The resulting structure is an advantageous one for our purposes: groups *meta* to the original nitrogen are suspended in space above the OH bond of the acid, that is, in the right region of space for control of these stereoelectronic effects.

Scheme 5



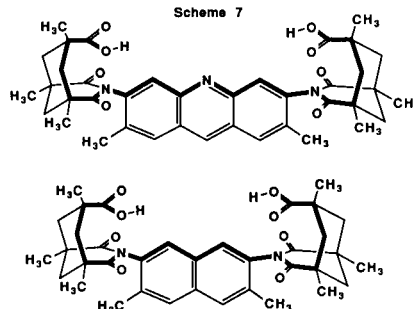
Even so, it took us a long time to do the right experiment which was, of course, to condense two equivalents of the Kemp triacid with an appropriate diamine such as meta xylydine diamine [7]. In this structure, the two carboxyl groups show the spectroscopic earmarks of a hydrogen bonded dimer, but the methyl groups prevent any escape of the two carboxyl functions from one another. Epimerizations and rotations are prevented, a situation that leads to quite unusual acid base characteristics of these dicarboxylic acids.

Scheme 6



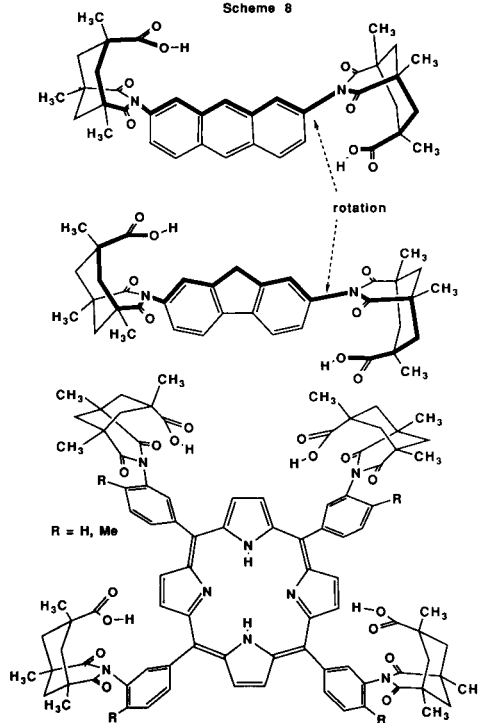
We will not dwell here on those characteristics as they are published elsewhere [8], but point out that a number of diamines from simple aromatic and heterocyclic spacers are readily available in this series. They lead to dicarboxylic acids with unusual affinities for metal ions, about which more later. For the moment, we note that the architectural cliché can be repeated with a variety of rigid aromatic spacer units. For example, acridine yellow presents all of the functional groups necessary and even gives an additional one: the acridine nuclear nitrogen. It leads to a structure with 8 or so Å between opposing carboxyl oxygens and it is made in high yield by mere fusion of the two components. If this be the "stretch limousine" version, an intermediate "midsized" version is represented by the naphthalene derivative. In this structure about 5 1/2 Å separate the two opposing carboxyl oxygens.

Scheme 7



While these two structures present well defined molecular clefts, it would be desirable to have intermediate spacers. Some of these could be envisioned such as a biphenylene derivative, but the synthetic investment involved in their preparation seems rather high. Of course, a num-

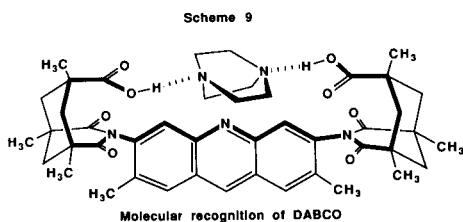
Scheme 8



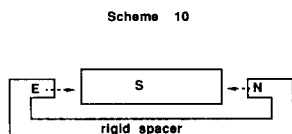
ber of flexible spacers represented by  $\alpha$ ,  $\omega$  diamino alkanes is also available and we have prepared a number of these. But a real continuity of series would be desirable with more than a few points; a series of structures in which a carboxyl function moves apart by, say,  $1/2 \text{ \AA}$  increments could lead to some better measure of these stereoelectronic effects. There are a number of other spacers. For example, the fluorene derivative shown presents carboxyls at a greater distance in somewhat different "pitch" with respect to one another [9]. An acridine derivative without the methyl groups presents an opportunity to test issues of preorganization in a setting where the two functional groups are not in direct contact, that is, they do not suffer some enthalpic destabilization in the organized ground state, but rather, they are at the mercy of purely entropic considerations.

A very large spacer indeed is presented by the tetraarylporphyrin derivative shown. It is easily woven together by a much improved synthesis due to Jon Lindsey [10]. In such a structure up to four carboxyl groups can converge on the center of the molecule.

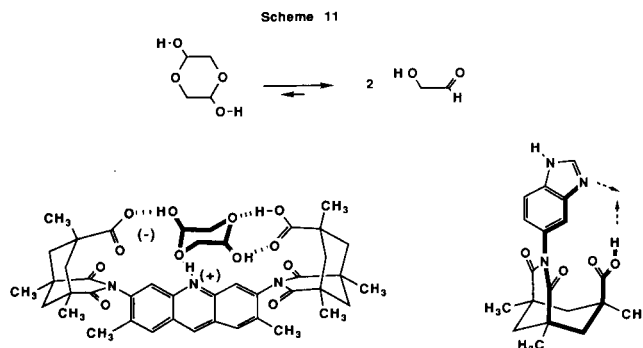
In any of these structures the convergence of acidity at certain distances that are well defined suggested that complementary molecules with divergent basicity would be complexed. Indeed, structures such as DABCO and other heterocycles have been examined with a number of these systems. For example, the tetra-aryl porphyrin complexes two equivalents of 4,4 bipyridine [11] and, at appropriate pH, one might expect paraquat and its derivatives would also be bound.



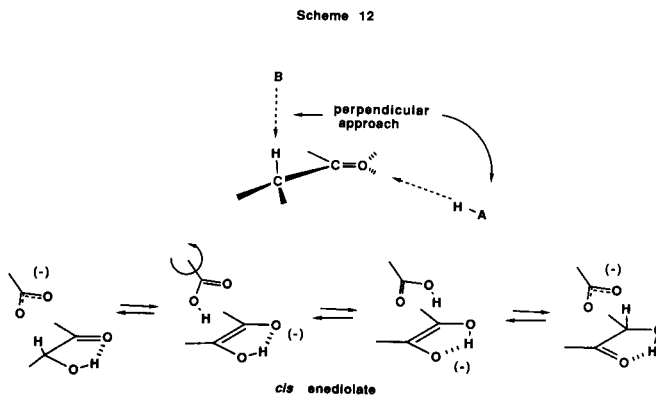
Many of our complexation studies have been reported in detail, and here we are concerned more with the application of these materials as possible catalysts in a more dynamic setting. Again, the principal advantage here seems to be convergence. The sketch below shows a nucleophile N and electrophile E pair (or an acid and base, for that matter) could act simultaneously on a substrate S in a concerted or "push-pull" manner with structures offering a rigid spacer between the two functions. If the spacer is flexible, the two functions will collapse upon one another, and catalytic functions will disappear. Even if the functions diverge it is possible to envision polymeric structures in which intermolecular annihilation of functionality takes place. Thus, a combination of a concave surface with convergent functionalities presents a special advantage.



Our most successful case in a catalytic setting involves the cleavage of the hemiacetal shown below. The acridine diacid is an extraordinarily effective catalyst for this presumably because complexation leads to a functional arrangement poised for catalysis [12]. There is high specificity for this substrate and rate enhancements of  $10^4$  are observed over conventional catalysts for hemiacetal cleavage such as 2-pyridone. The identity of the functional groups involved in the proton transfer reactions remains shrouded in mystery. Conventional cleavage, in which acid and base components approach in a parallel manner [13] or more unconventional forms such as antiperiplanar presentation of the acid base pair are possible. We are currently evaluating molecules such as the benzimidazole shown which limit the number of approaches and may help us find some of these answers.

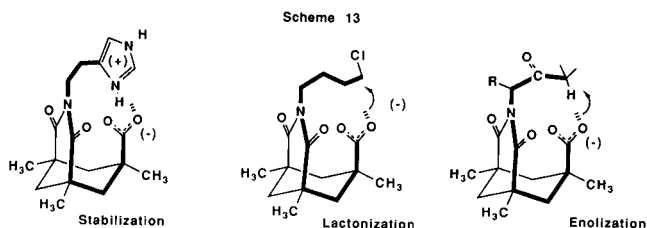


A perpendicular approach of acid and base is also indicated for push-pull or concerted enolization reactions. The basic component must come in along a line that leads to a resonance-stabilized enolate as anticipated by Corey and Sneen [14] whereas recent NMR experiments [15] suggest protonation of the *syn* lone pair of the enolate leads to the more stable form of the enol. It may be significant that isomerases of nature also proceed via *cis* enediolates [16] wherein intramolecular proton transfer might be achieved.



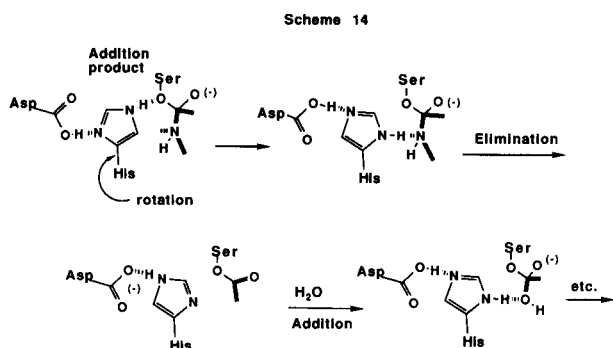
At any rate, we are working to build molecules that can complex an enolizable ketone then lead to concerted catalysis. We are approaching this in a number of contexts, but mostly in those intended to evaluate some stereoelec-

tronic components. Intramolecular general-base catalysis by carboxylate in the past has invariably involved the less basic *anti* lone pairs [17]. We have devised a system in which the more basic *syn* lone pairs are presented toward an enolizable hydrogen. This is the condensation product of an amino ketone with a Kemp triacid derivative. In these systems, a modest enhancement is observed [18] that can be attributed to the *syn* lone pair and we are pursuing these observations in lactonization reactions [19] such as that shown below.



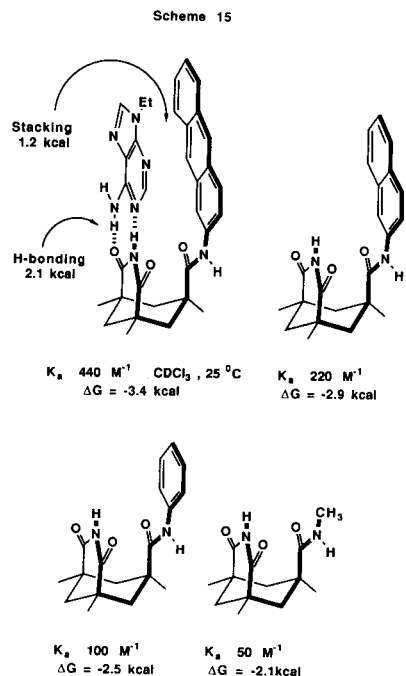
We have also examined the stereoelctronic issue in the context of a carboxylate-imidazolium pair. This is readily available from histamine and the Kemp triacid; enhancement of the basicity of the histamine moiety can be observed [20] when in contract with the more basic *syn* lone pair.

There may be even more special consequences of these two functions when they appear in esterases and proteases. A special interplay may lead to translocation of protons by rotation around the bond which anchors the heterocycle. Breaking and reformation of hydrogen bonds to the carboxyl could be accomplished in a variety of directions. One possibility is shown below. The implication is that the shape of histidine may be as important as its  $pK_a$  for its function at the active sites of enzymes [21].



A second area in which we've been able to take complexation ability and use it to drive the chemical reactions has been in our study of adenine recognition [22]. Base pairing is one of the more classical forms of molecular recognition and we have used the U-turn in the Kemp triacid to separate base pairing and stacking effects in a number of related molecules. For example, the imide presents a hydrogen bonding surface that imitates thymine, whereas virtually any aromatic "shelf" can be appended to the structure to provide a polarizable stacking surface. One series is shown below from the anthryl to the methyl

group; a monotonic decrease is observed in the stacking efficiencies [23]. Nearly in order of magnitude in binding affinities can be had from a large polarizable surface in the relatively non-competing solvent,  $CDCl_3$ . The advantage of using this solvent which is, of course, somewhere between aqueous solution and the gas phase, is that hydrogen bonding effects are magnified in the solvent and association constants are of the magnitude that are easily studied by NMR titrations.

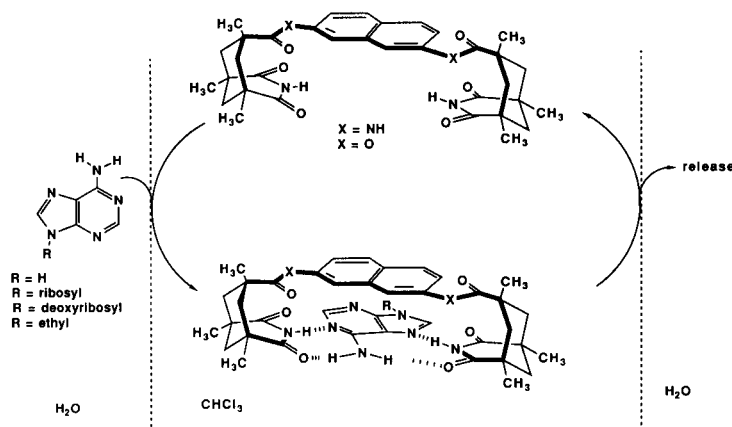


By placing two imides on a single aromatic surface at the right distance such as that represented by the naphthalene, an enormous affinity for adenine can be observed. For example, this material presents not only Watson-Crick, but simultaneous Hoogsteen base-pairing as a possibility. The affinity is so high that such structures can extract not only adenine but even adenosine derivatives from aqueous solution into chloroform and transport [24] them across simple liquid membranes.

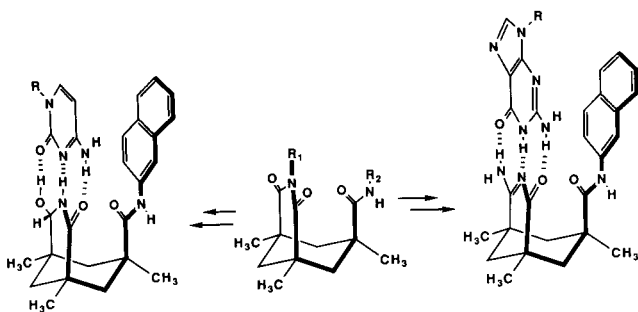
Remote steric effects can also be engineered into this system. For example, the *t*-butyl derivative permits stacking and base pairing only in the Hoogsteen sense [25]. The Watson-Crick sense forces the side chain groups too close to each other in the two components.

The hydrogen bonding edges can be altered. Mere reduction of the imide leads to a hydroxy lactam and high affinity and selectivity for cystosine derivatives can be observed over adenine derivatives [26]. More recently, we have taken the imide nitriles and rearranged them with amide anions to give acylated amidines. These now base-pair nicely to guanosone derivatives [27].

Scheme 16

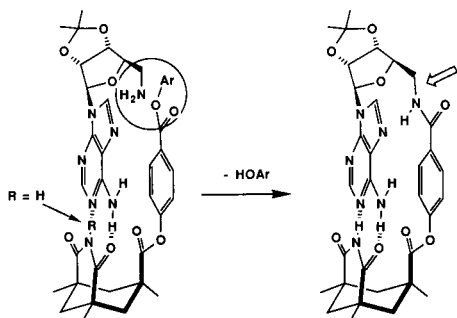


Scheme 17



The use of base pairing as a template to drive reactions such as acyl transfer reactions was examined. In general, attaching an adenine covalently to a receptor for adenine would lead to a molecule that is, at the very least, self-complementary. Depending on the orientation of the recognition surfaces with respect to one another, the system could oligomerise, it could dimerize or it could fold shut in an intramolecular sense. We have observed these behaviors [28].

Scheme 18

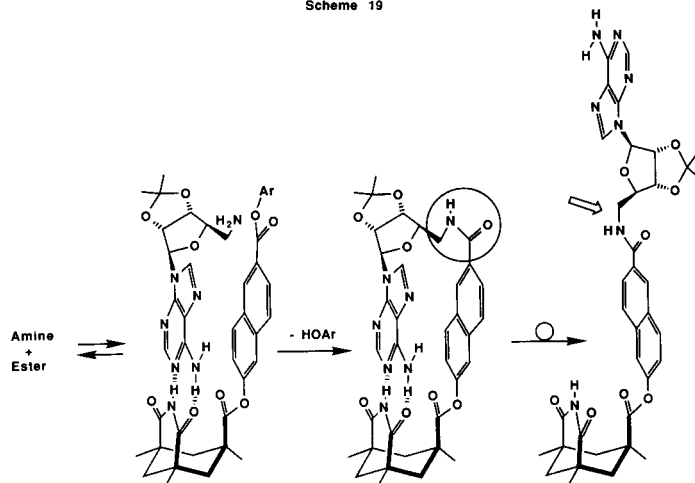


For example, with the phenyl spacer it can be shown that base pairing precedes acyl transfer in the system shown. Here the electrophile is pentafluorophenyl ester or acylimidazole. The nucleophile is the aminoadenosine derivative shown. The acyl transfer occurs several times more rapidly with the NH than with N-methyl substituted

imide. Such a result can hardly be attributed to classic steric effects. However, on completion of acyl transfer, the system remains folded in the Watson-Crick sense shown because a *trans* amide can be accommodated by this short aromatic spacer.

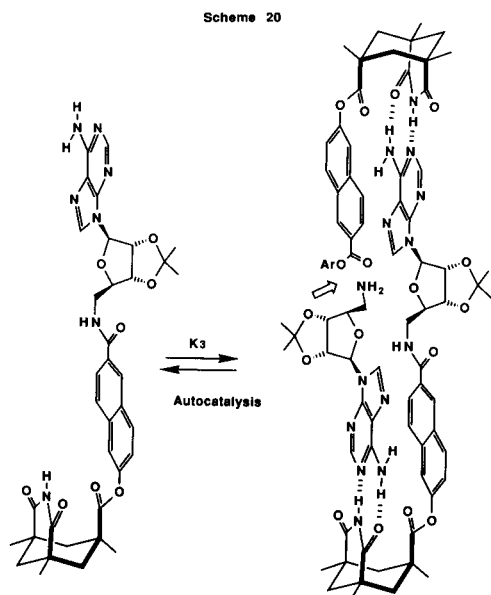
With a naphthalene spacer, a much more intriguing result obtained. Again, it was shown that base-pairing enhances the acyl transfer and that competitive inhibition with diacyl amino pyridine can be observed. However, now the acyl transfer product leads to a *cis* amide and the *cis-trans* isomerization "jackknives" open the molecule to expose complementary hydrogen bonding and stacking surfaces.

Scheme 19

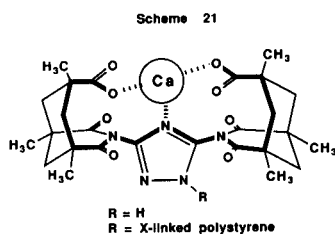


At high concentrations, dimerization of this material is observed, but even so, the substance acts as a template for its own synthesis, that is, autocatalysis can be observed. Merely adding the product to a coupling reaction mixture enhances the initial rate several fold. Presumably, another form of intramolecular reaction can take place such as depicted in the termolecular complex shown. Here, the system gathers the electrophile and nucleophile components in such a way that acyl transfer is facilitated. The initial

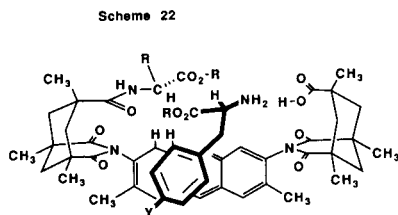
product is the dimer which can dissociate at the appropriate dilutions. At any rate, for the first time, this primitive sign of life, self-replication with autocatalysis, can be observed in a model system.



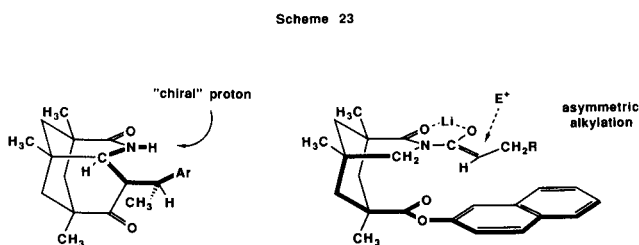
A somewhat more practical application can be observed for the high affinity that the simplest diacids show toward alkali metal ions [29]. For example, the triazole derivative depicted can be attached to calcium not only through the carboxylate functions but also through the heterocyclic nitrogen. We anticipate that other metal ions, when forced into a ligand with *trans* contacts will show different reaction selectivities than those in more conventional contexts and we are exploring these possibilities.



Applications in asymmetric processes have also shown some success, for example, the acridine derivative shown discriminates between enantiomeric forms of phenylalanine derivatives [30]. Acid base reactions gather the two components, then aromatic stacking interactions help pin the partners together in such a way that asymmetric centers can sense each other effectively.



We have also developed certain asymmetric proton sources for use with prochiral enolates [31]. The system initially examined by Hunig [32] has been studied with a number of lactams as proton sources. Extraordinary enantioselectivities have been observed. More recently, the application of these structures to cycloadditions and enolate alkylations has been achieved. We will report on these in due course [33].



Acknowledgements.

I am grateful to the superb assistance of my coworkers; their names appear on the publications cited. The NIH, NSF and Year Laboratories provided financial support of this research.

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