Macrocyclic Carbonyl Compounds as Structural Models of Natural Ion Carriers

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The observation that many naturally occurring organic compounds, the macrocycles in particular, selectively bind metal ions and charged molecules stimulated extensive interest in this family of compounds, commonly referred to as ionophores.[1-3] Ionophores form metal ion complexes that are lipid soluble and thereby effect ion transport through lipid membranes. Due to these properties, ionophores play an important role in biological systems, in which they control the balance of the essential metal ions such as potassium, calcium, and iron. The basic function of this family of compounds in biological systems offers many possibilities for their use in biochemical research and pharmacology.[4] In addition, their selective binding and transport properties encourage their application in chemical analysis, separation, and catalysis.[5,6]

Natural ionophores are complex systems and are relatively rare. They occur in minute amounts in natural sources, and their synthesis, if possible at all, requires tedious multistep procedures with low overall yields.[1-4] Extensive research has therefore been devoted to the design of synthetic compounds that have comparable binding properties. These efforts led to the introduction of crown ethers,[7] of cryptands,[8] and lately also of spherands.[9] Remarkable selectivity has been achieved with some of these synthetic compounds. However, they usually lacked the subtle balance between binding, transport, and release properties that make the natural systems unique.

Natural ionophores and the ionophores thus far prepared synthetically often make use of different functional groups. While the former may contain amide and lactone groups, synthetic macrocycles have largely been based on ether and aza ring systems. When the ether groups in the latter are successively replaced by lactones, the resulting ring systems show reduced binding affinity.[10] These differences between the natural and the synthetic ion carriers attracted our attention and led us to examine their origin by examining the structural regularities of synthetic model compounds varying in the nature and number of functional groups, in ring size, and in ring symmetry. It was hoped that this structural approach would provide a tool for the systematic preparation of synthetic macrocyclic compounds that mimic the conformation of the natural ionophores, and thereby enable future preparation of artificial ionophores. The rationale behind this approach was that the potential of a macrocyclic compound to serve as ion carrier may be estimated, in a first approximation, from its conformation in the noncomplexed state. In addition, this structural work was anticipated to provide an insight into the design of the natural systems and to help to understand how and why they acquire their ionophoric properties.

This study required several series of novel macrocyclic carbonyl compounds and necessitated the development of appropriate synthetic methods for their preparation. In this Account we describe the development of these synthetic methods and the structural regularities of the synthesized compounds, as determined by X-ray analyses. The conformations of these compounds will be compared with those of the natural ionophores, in an attempt to derive preliminary guidelines for the design of synthetic carbonyl (amide and lactone) compounds that mimic the arrangement of naturally occurring ionophores.

Synthesis of Macrocyclic Polycarbonyl Compounds

The preparation of macrocyclic compounds is a challenging synthetic problem since it requires the cy-

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(8) B. Dietrich, J. M. Lehn, and J. Simon, *Angew. Chem. Int., Ed. Engl.*, **13**, 406 (1974); J. M. Lehn, *Acc. Chem. Res.*, **11**, 49 (1978); J. M. Lehn, *Struct. Bonding (Berlin)*, **16**, 1 (1973).

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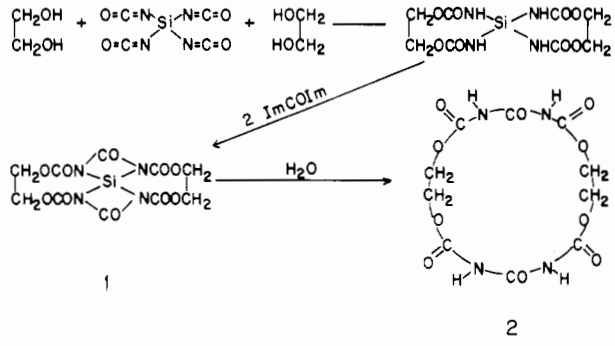
Scheme I



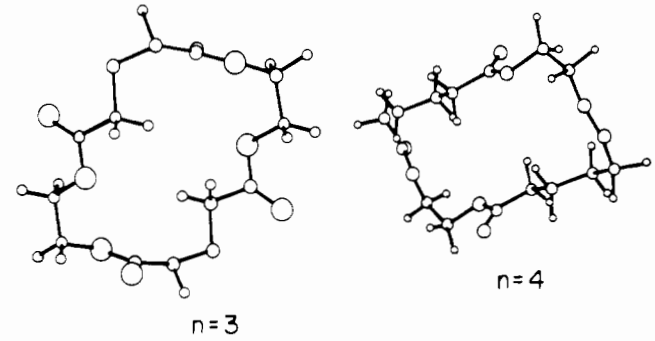


Figure 1. Crystal structures of tetralactones 6.

clization of acyclic substrates, rather than their condensation to polymeric products. Extensive research efforts were devoted to the development of such cyclization procedures. In the past, high dilution techniques were introduced in order to prepare cyclic perfume ingredients such as civetone or muscone.[11] Macrolide antibiotics, on the other hand, were prepared by a variety of double activation techniques[12] and the use of mercury salts as catalysts.[13] A different family of compounds, the aza compounds related to porphyrin, were prepared by using metal ions as templates,[14] and access to the corrin family was through a remarkable, symmetry-allowed, photochemically induced antarafacial 1,16-hydrogen transfer and an antarafacial 1,5-π,-σ-isomerization.[15] Further, specific methods, such as "zipper type" ring enlargements, were developed for the preparation of spermine and sperimidine alkaloid macrocycles.[16] Although the value of these methods is apparent from the successful syntheses of a large variety of natural products, they are rather inapplicable for the systematic synthesis of polyfunctional carbonyl compounds composed of several identical subunits. In an attempt to synthesize such compounds, we developed a novel method based on the use of silicon and tin derivatives as *covalent templates*.[17-23] The method involves binding difunctional substates around a silicon or tin derivative, which serves as a template for intramolecular condensation. Finally the metalloid element is expelled.

The selection of the metalloid elements silicon and tin for this purpose was based on their unique chemical properties, which derive from their intermediate position between transition metals and non-metals. Metalloids form covalent bonds with many heteroatoms such as oxygen, nitrogen, or sulfur[24,25] and, unlike carbon, can accommodate up to four heteroatoms around a single atom. Moreover, metalloid–heteroatom bonds are highly reactive and undergo substitution with electrophiles, such as activated carbonyl compounds, and insertion with isocyanates or ketenes. On the other hand, metalloid–heteroatom bonds are susceptible to hydrolysis under extremely mild conditions. The combination of these two properties, chemical versatility toward organic substrates and easy removal by mild hydrolysis, makes the metalloids versatile tools for the synthesis of macrocyclic products.

In an exploratory experiment, silicon tetraisocyanate, $Si(NCO)_4$, was used as a template as shown in Scheme I. Ethylene glycol was attached to the silicon template by reaction with silicon tetraisocyanate to give a spirane-type intermediate. Condensation of the latter with carbonyldiimidazole (ImCOIm) provided the polycyclic product **1**, containing silicon. The silicon–nitrogen was easily cleaved by addition of a few drops of water to give the macrocyclic biuret **2**.[17]

The formation of the intermediate **1** and its efficient conversion to the macrocyclic product **2** demonstrated the feasibility of our approach by establishing the role of the metalloid element as template. However this example suffers from several shortcomings. The first step leads to competitive polymerization resulting in low overall yields, and the reaction scheme is restricted to the preparation of urea and carbamate products. In an attempt to overcome these limitations, other metalloid derivatives were screened as possible templates. After a series of trial reactions, silicon–nitrogen compounds emerged as the materials of choice for the preparation of nitrogen containing macrocycles, and tin–oxygen compounds for the preparation of oxygen-containing macrocycles. With these metalloid derivatives, a series of macrocyclic lactones and amides varying in the number and the location of the functional groups and in the ring size and ring symmetry were prepared.

Macrocyclic Compounds with Mirror Symmetry

One of the most versatile compounds for the template preparation of macrocyclic oxygen compounds proved

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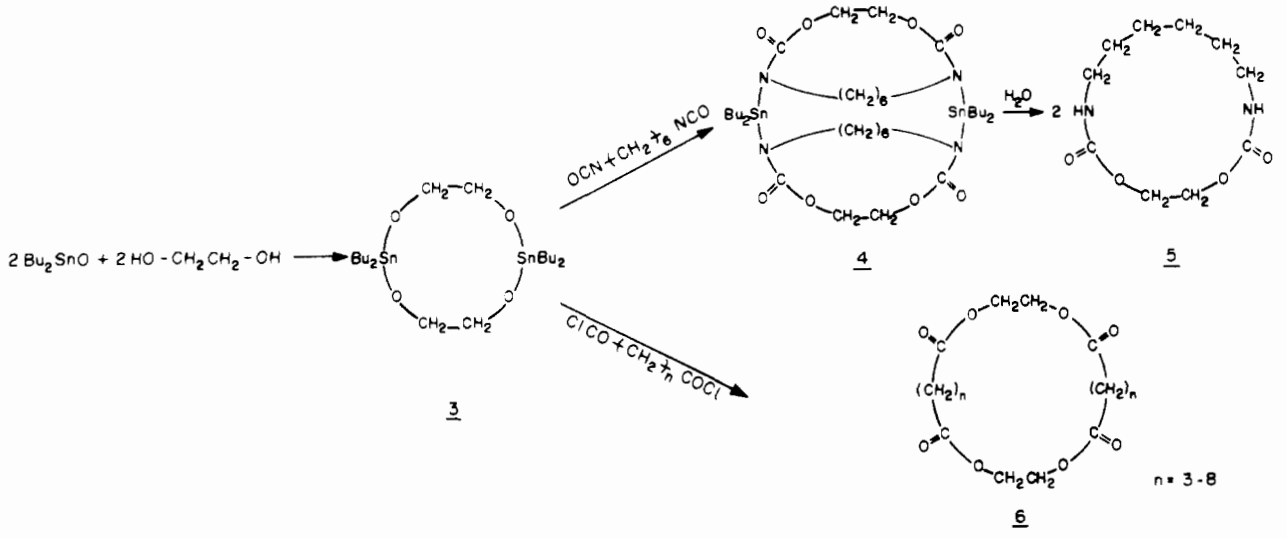
Scheme II



to be the distannoxane **3**. This distannoxane was used for the preparation of both difunctional and tetrafunctional macrocyclic compounds.

Reaction of **3** with 1,6-diisocyanatohexane resulted in insertion of the azomethine bond between the tin–oxygen bond, providing the polycyclic intermediate **4**. Hydrolysis of the latter gave the macrocyclic dicarbamate **5**[18] (Scheme II). Whereas reaction of distannoxane **3** with a diisocyanate provided a difunctional macrocyclic compound as the only ring product, condensation of distannoxane **3** with other carbonyl compounds gave tetrafunctional macrocycles. Specifically, diacyl dihalides reacted with **3** to provide macrocyclic tetralactones **6** as the sole cyclic products, as shown in Scheme II.[19] The yields varied with the chain length of the acid derivative, being between 40 and 70%.

Structural analyses of these systems, by X-ray diffraction, enabled us to distinguish between two families of compounds, namely those with acyl residues containing *even*-numbered and *odd*-numbered methylene chains (Figure 1). In the "even" tetralactones (e.g., n = 4) one pair of adjacent carbonyl groups (belonging to the same acyl residue) was found to point below the plane of the ring, the other pair above the plane of the ring. In the "odd" tetralactones (e.g., n = 3 or 7) one pair of carbonyl groups (belonging to the same acyl residue) was found to point above and outside the surface of the ring, the other pair below and outside the surface of the ring. However, none of these systems defined an internal space by virtue of its carbonyl groups, as would be required for ion binding.

The dependence of the carbonyl orientation on the interlinking chain appears to be a general phenomenon. Alterations of physical constants such as melting point, solubility, and dipole moment with chain length have been observed in macrocyclic diketones,[26] diamides, and dilactams[27] as well as in diesters and dilactones.[28] These alterations have been attributed to changes in the relative orientation of the carbonyl groups, as being either "syn" or "anti" to each other.[26-28] The configurations of the lactone groups have all been found to be transoid, in agreement with earlier observations on

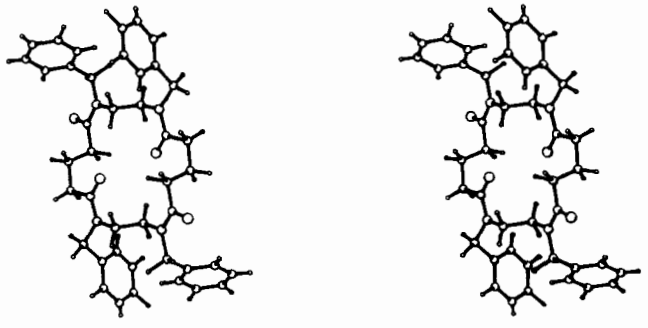


Figure 2. Stereoscopic view of crystal structure of tetraamide **9** (n = 3).

cyclic lactones with rings containing more than nine members.[29]

Tin compounds proved to be useful templates for the preparation of carbamates and lactones, but do not appear appropriate for the preparation of the corresponding nitrogen analogues, ureas and amides. This is because the preparation of the latter requires metalloid–nitrogen compounds. Tin–nitrogen compounds are extremely sensitive to moisture and often difficult to prepare.[30] Silicon derivatives were therefore selected as templates for the preparation of nitrogen-bearing macrocycles, since silicon–nitrogen compounds are sufficiently reactive.[31]

Cyclic silazanes **7**, prepared from dimethylbis(diethylamino)silane and diamines, were used for the preparation of difunctional and tetrafunctional macrocycles. Specifically, condensation of silazane **7** with diisocyanates was found to give the corresponding macrocyclic diurea **8**[17] (Scheme III). None of the corresponding macrocyclic tetraurea was formed.

The reaction of cyclic silazanes **7** with diacyl dihalides followed a different pattern. Macrocyclic diamides **9a** or tetramides **9** were obtained, depending on the nature of the diamine and diacyl reactants.[20] Diamines with even-numbered methylene chains formed macrocyclic diamides with even diacyl dihalides and macrocyclic tetramides **9** with odd diacyl dihalides. On the other

(26) G. Borgen and J. Dale, *Acta Chem. Scand.*, **26**, 1799 (1972).
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(28) J. Dale, *J. Chem. Soc.*, 72 (1965).
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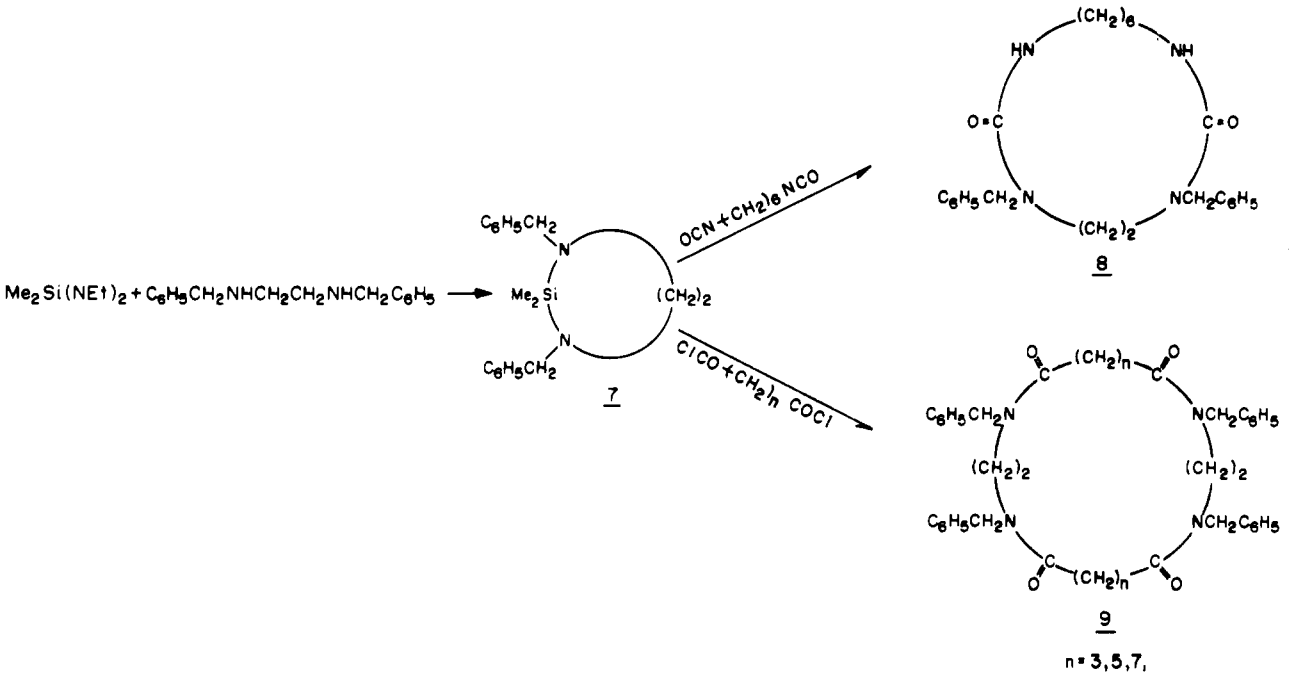
(30) K. Jones and M. F. Lappert in "Organotin Compounds", Vol. 2, A. K. Sawyer, Ed., Marcel Dekker, New York, 1971, p 509.
(31) U. Wannegat, *Adv. Inorg. Chem. Radiochem.*, **6**, 225 (1964); R. Fessenden, *Chem. Rev.*, **61**, 361 (1961).

Scheme III



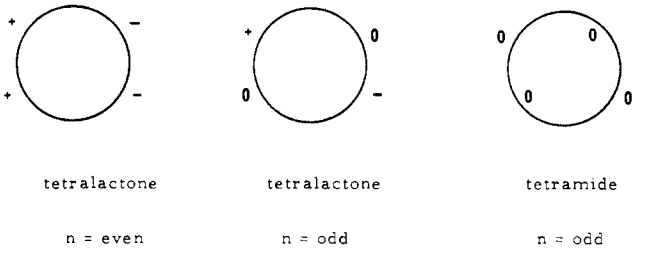


Figure 3.

hand, diamines with odd-membered methylene chains gave macrocyclic tetramides **9** with even diacyl dihalides. This product selection is believed to reflect the preference of even-membered over odd-membered macrocyclic ring systems.

The crystal structure of the tetramide **9** (Figure 2) showed that its amide bonds assume alternating cisoid and transoid configurations. This is different from the arrangement observed in the corresponding tetralactones but analogous to that found in cyclic tetrapeptides and sarcosides.[32] The carbonyl groups of the cisoid amide bond were found to point outside the plane of the ring, while those of the transoid bonds point toward the interior of the ring.

The tetrafunctional macrocyclic compounds described so far are all characterized by "head-to-head" arrangements of the ester carbonyl groups ($-OCO(CH_2)_nCOO-$) In these arrangements the molecules assume one of the conformations schematically illustrated in Figure 3. A plus sign indicates that the carbonyl group points above the plane, a minus sign that it points below the plane, and a zero sign that it is within the plane of the ring (Figure 3).

The carbonyl groups in these systems, independent of the length of the interlinking chains (even or odd), do not define an internal cavity in the uncomplexed molecules, since only two of the four carbonyl oxygens are available for binding. It occurred to us, however,

(32) J. Dale and K. Titlestad, *Acta Chem. Scand., Ser. B*, **B29**, 353 (1975).

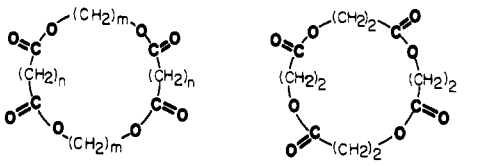


Figure 4.

Figure 5.

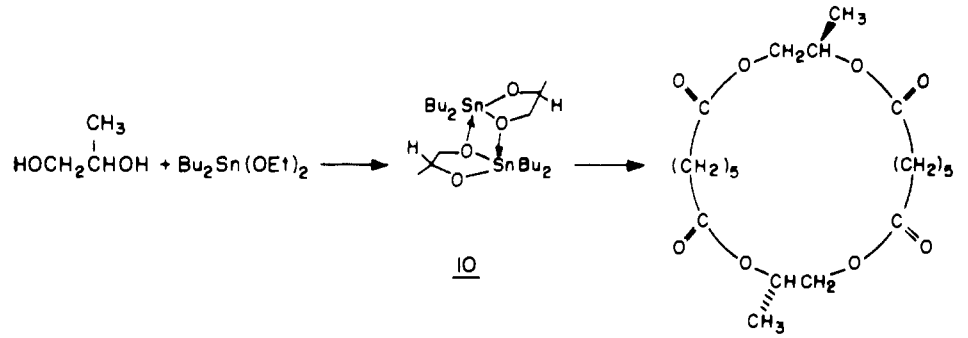
that for tetrafunctional carbonyl compounds to form a binding cavity the mirror symmetry has to be disturbed. A priori this may be achieved in either of two ways: (i) by introduction of substituents or (ii) by arranging the lactone (or amide) groups in a "head-to-tail" ($-OCO(CH_2)_nOCO-$) sequence as commonly observed in naturally occuring ionophores of the peptide and depsipeptide families, instead of "head-to-head" ($-OCO(CH_2)_nCOO-$) sequence (Figure 4).

Macrocyclic Tetralactones with Side Chains

In systems with two side chains, two possible structures are envisioned, those with substituents in a "syn" configuration (structure A), and those with substituents in an "anti" configuration (structure B) (Figure 5). The synthesis of such compounds requires the stereospecific introduction of two chiral residues into the ring system. Two chiral residues of identical configuration lead to one of the two possible diastereoisomers, while two chiral residues of opposite configuration lead to the other diastereomer.

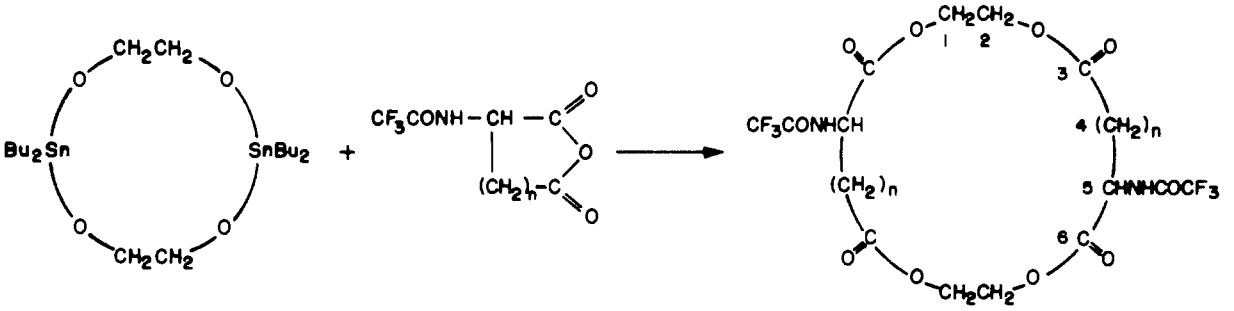
We found that such compounds may indeed be synthesized stereospecifically from chiral diol or chiral acid residues using tin–oxygen compounds as templates, as described above. For example, the dimethylated macrocyclic pimelate **11** was obtained as the sole ring

Scheme IV



10 11

Scheme V



12 n=1 a. L-isomer 14 n=1
13 n=2 b. D-isomer 15 n=2
ab. LD mixture

product upon reaction of stannoxane **10** with pimeloyl chloride (Scheme IV).[21]

The sterespecificity observed in this reaction may be rationalized by the presence of dimeric complexes of stannoxane **10** with the methyl groups at the most distant positions from each other (Scheme IV). The association of both acyclic and cyclic tin–oxygen compounds has been found to be a general phenomenon in solution. This has been demonstrated by ebullioscopic and cryoscopic methods[34] and by tin-119 NMR analysis.[35] The extent of association has been shown to be greatly dependent on stereochemical factors, a fact that suggests the structures outlined in Scheme IV. Reaction of such complexes with diacyl dihalides may occur from each of the two faces of the complex, yielding the isolated product **11**.

Crystal structure determination of the dimethylated macrocycle **11** showed that this compound assumes the same conformation as the corresponding nonsubstituted tetralactones with acyl residues of an odd number of methylene groups. The carbonyl groups adjacent to the substituents were found to point in opposite directions, above and below the plane of the ring, and the carbonyl groups further from the substituents to point outside the plane of the ring.

Although the pimelate ring system **11** does not have an internal cavity, it occurred to us that tetralactones of this kind might prove to have complexing properties if they contain two additional binding sites through functionalized (ligating) side chains. The two possible diastereoisomers (structures A and B) would be expected to exhibit different binding properties. In the "syn" isomer (A) one coordination site of the guest ion would remain unsaturated. Such systems could provide model structures for the design of catalysts, mimicking the active sites of metalloenzymes.[33] In the "anti" isomer (B), on the other hand, the coordinated ion could be embedded into a closed shell by the opposing side chains. Such systems might be useful as ion carriers.

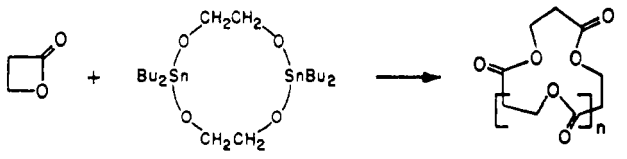
The preparation of such compounds with ligating side chains was achieved by using acidic amino acids, such as aspartic acid and glutamic acid anhydrides. Condensation of the anhydrides **12a** (or **12b**) and **13a** (or **13b**) with stannoxane **3** provided a single macrocyclic tetralactone **14aa** (70%) and **15aa** (50%), respectively, and in better than 99% optical purity[21,22] (Scheme V).

In this reaction the regiospecific formation of the antiparallel (rather than the parallel) arrangement in the products may be attributed to attack of the anhydride molecules on the stannoxane at the positions most distant from each other (Scheme V).

These chiral products are representatives of general structure A with "syn" configuration (Figure 5). The preparation of the corresponding diastereoisomer with "anti" configuration was achieved by successive treatment of stannoxane **3** with 1 equiv each of D-*N*-(trifluoroacetyl)glutamic anhydride (**13b**) and L-*N*-(trifluoroacetyl)glutamic anhydride (**13a**). The isolated "meso" macrocycle **15ab** appeared indistinguishable from the chiral macrocycle **15aa** in its spectroscopic

(33) J. F. Ricordan and B. L. Vallee, *Adv. Exp. Med. Biol.*, 48, 33 (1974).
(34) P. J. Smith and A. P. Typciauskas, *Annu. Rep. NMR Spectrosc.*, 8, 1291 (1978).
(35) P. J. Smith, R. F. M. White, and L. Smith, *J. Organomet. Chem.*, 40, 341 (1972).

Scheme VI



n = 1-6
16, n = 1
17, n = 2

properties. However, the different arrangement of its functional side chains was indicated by its binding affinity toward europium ions. NMR studies showed that the "anti" isomer binds europium 50% more efficiently than does the "syn" isomer, demonstrating the different topologies of these two systems and the contribution of the side chains to the binding process. Synthetic macrocyclic peptides,[36] crown ethers,[37] and aza compounds[38,39] with ligating side chains have been described earlier and are often found to possess improved binding efficiencies. However, no comparison between compounds of different configuration ("syn" vs. "trans") has to the best of our knowledge so far been put forward.

It is also interesting to compare the synthetic macrocycles with ligating side chains to some of the natural ion carriers such as enterobactin and dimerum acid.[3,40] The synthetic complexing agents were designed to span a cavity by virtue of both side chains and ring backbone, whereas the above two natural siderophores span octahedral or tetrahedral cavities with the side chains only.

As indicated above, macrocyclic carbonyl compounds with a "head-to-head" arrangement of the carbonyl groups may not form internal cavities suitable for binding, even if they contain substituents that interrupt the mirror plane symmetry as in the pimelate **11**. Inspection of naturally occurring ionophores of the peptide and depsipeptide families led us to believe that a "head-to-tail" arrangement of amide or lactone groups is necessary for a ring compound to define an internal cavity suitable for binding. Attempts were therefore made to provide access to macrocyclic ring compounds with rotational rather than reflection symmetry.

Macrocyclic Polylactones with Rotational Symmetry

With propiolactone as monomer and cyclic distannoxane **3** as template and catalyst, a series of macrocyclic polylactones with a "head-to-tail" arrangement of the lactone groups were prepared in an overall yield approaching 80% (Scheme VI, Figure 6).[23]

This cyclic oligomerization represents a new method for the preparation of macrocyclic compounds. The mechanism may involve multiple insertion of propiolactone into the tin–oxygen bond and subsequent expulsion of the macrocyclic products. The established

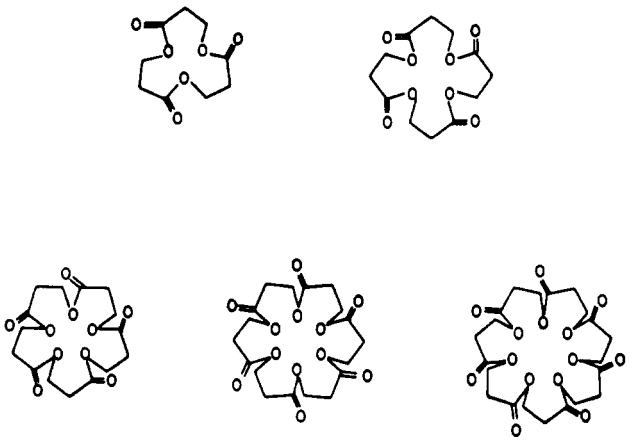


Figure 6.

reversibility of propiolactone insertion into tin–oxygen bonds and the possibility of multiple insertions support such a pathway.[41]

The crystal structures of the trilactone **16** and tetralactone **17** were determined in order to compare the arrangement of these synthetic systems with those of the natural ionophores having a "head-to-tail" orientation of their functional groups. The structure of the trilactone **16** is given in Figure 7. It is seen that the backbone of the trilactone **16** adopts a crown conformation with all carbonyl groups on one side of the plane of the ring. The all-syn arrangement of the carbonyl groups found in this compound is analogous to that observed in many synthetic and natural macrocyclic polycarbonyl compounds. Tri-*o*-thymotide, for instance, a trilactone that forms clathrate inclusion complexes with many guest molecules, assumes a similar conformation[42] as do many cyclic tripeptides, both in the solid state and in solution[43]

Of particular interest is, however, the iron carrier enterobactin,[3] the cyclic backbone of which is identical with that of the synthetic trilactone **16**. Enterobactin is used by microorganisms for the transport of iron from the medium into the cell. Its efficiency is believed to be due to its high complexing power ($K = 10^{+52}$) and to the fact that it is metabolized after absorption by the cell, preventing the diffusion of iron back to the medium. Although no crystal structure studies of enterobactin or its iron complex have been reported, NMR studies of this compound in solution indicate a propeller-like conformation of the aromatic residues, with the ring carbonyl groups pointing down from the cyclic backbone.[3] (Figure 7). The trilactone skeleton in this molecule probably plays a major role in directing all the functionalized side chains to point to the same face of the ring and thereby to span the desired octahedral cavity.

The tetralactone **17**, on the other hand, was found to assume a different conformation, with the carbonyl groups pointing alternatingly above and below the plane of the ring (Figure 8). In this arrangement the carbonyl groups span an internal cavity of tetrahedral geometry.

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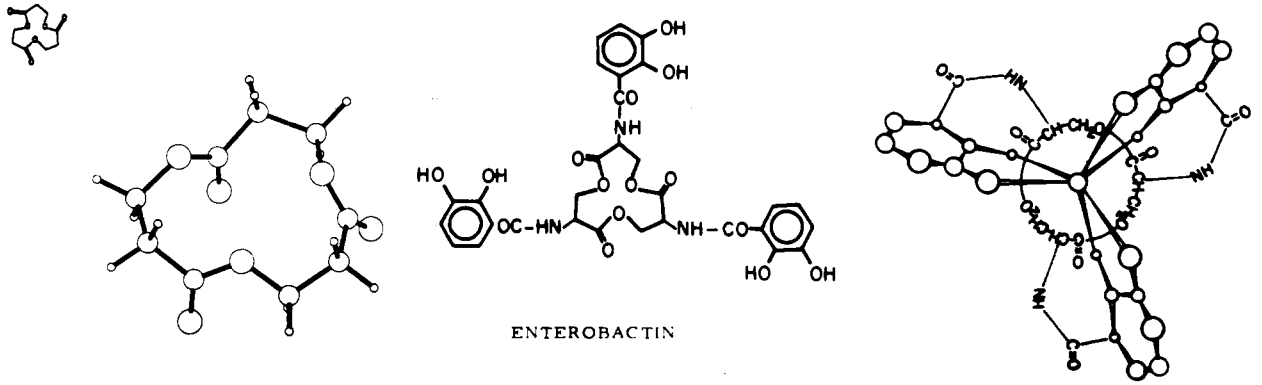

Figure 7. Crystal structure of trilactone **16** and solution conformation of enterobactin.[3b]

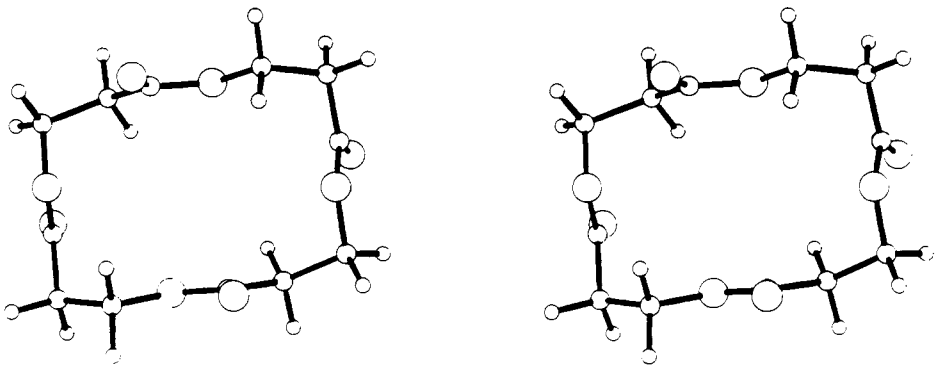

Figure 8. Stereoscopic view of crystal structure of tetralactone **17**.

This alternating orientation of the carbonyl groups is analogous to that observed in many natural products such as the actin ionophores. The potassium carrier nonactin,[44] for example, is characterized by a 4-fold rotational symmetry axis with alternating ether and lactone groups around the ring. The carbonyl groups alternate above and below the ring plane, forming an internal tetrahedral cavity (Figure 9). It may therefore be concluded that for a macrocyclic tetracarbonyl compound to form an internal cavity the presence of a 4-fold rotational symmetry axis is essential.

It is also significant that in both the synthetic tetralactone **17** and the natural ionophore nonactin the chains between the carbonyl groups contain an odd number of atoms (three and seven, respectively). This seems to be essential for such tetralactones to define an internal tetrahedral cavity and is supported by the fact that a tetralactone recently described by Okada[45] containing an even number of atoms (four) between the carbonyl groups fails to form an internal cavity (crystal structure). The influence of chain length on the orientation of carbonyl groups is also indicated by the behavior of difunctional macrocyclic carbonyl compounds. In these compounds, the orientation of the carbonyl groups assumes alternatingly a "syn" or "anti" orientation with chain lengths alternating between "odd" and "even".[26-28]

Concluding Remarks

In an attempt to gain insight into the characteristics of naturally occurring carbonyl-containing ionophores, we have examined the structural regularities of synthetic model compounds varying in the number of functional groups, in ring size, and in symmetry. These studies led to the formulation of preliminary *guidelines as to the design of internal cavities* and revealed the importance of ring *symmetry* ("head-to-tail" vs. "head-to-head" arrangement of functional groups) *and of ring size* (*length of chains between functional groups*). It appears that a "head-to-tail" arrangement of binding sites (*rotational symmetry*) and *odd-membered interlinking chains* are necessary for a system to form an internal cavity and thereby to serve as ion carrier. Macrocyclic lactones and amides proved to be particularly useful model compounds for deducing such guidelines, since the directional properties of carbonyl groups add a third dimension to these ring systems and thereby provide sensitive probes to trace geometrical features.

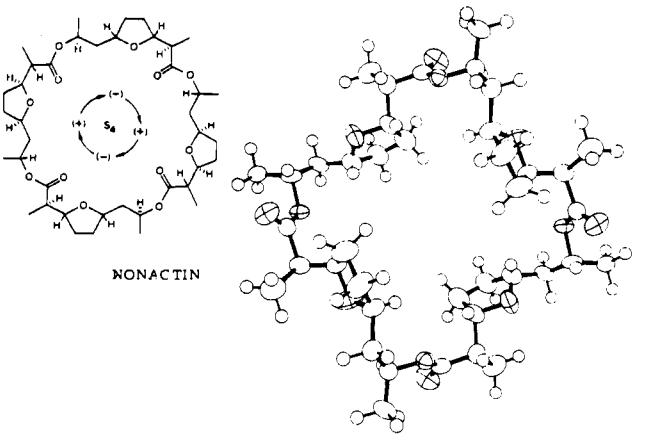

Figure 9. Crystal structure of nonactin.[44]

The neccessity of geometrically well-defined internal cavities for ion binding to occur has earlier been advo-

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cated on the grounds of kinetic, thermodynamic, and structural studies on both natural[1,2,3,46,47] and synthetic ion carriers.[8,9,48] The rules represented here may thereby be regarded but as preliminary structural guidelines toward the attainment of the desired internal cavities. We are currently engaged in further experimental and theoretical studies to validate these rules, as we believe that they may assist in the understanding of natural systems and in the design of new synthetic analogues.

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Chemistry of Triosmium Carbonyl Cluster Compounds and Its Implications for Catalysis

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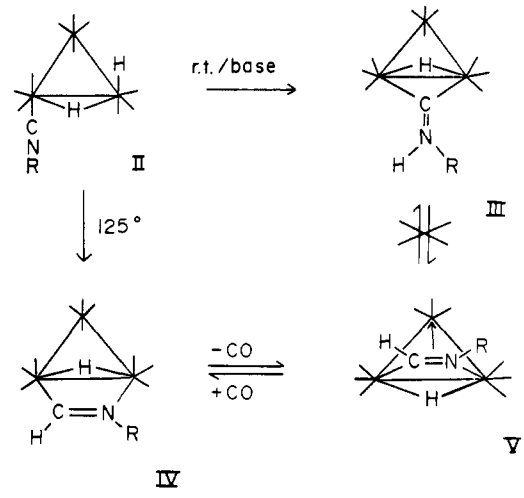
The subject of catalysis as mediated by transition-metal agents can be separated into two fairly distinct areas known as heterogeneous catalysis and homogeneous catalysis. Heterogeneous catalysis typically takes place under multiphase conditions, and in many systems the chemical transformations occur at exposed metal atoms on the surface of a solid.[1-3] Homogeneous catalysis, on the other hand, takes place in a single phase (usually solution), and in most cases the chemical transformations occur on a single metal atom in a molecular complex.[4,5] Because of these basic physical and chemical differences, the chemistry in these areas has been developed fairly independently. Recently it has been speculated that polynuclear metal complexes containing metal–metal bonds (commonly referred to as cluster compounds)[6] might serve as models for surfaces and that the study of them might help to bring the research in these two areas closer together.[7-9] However, it is also probable that these cluster complexes will prove to have chemical and physical properties that are unique unto themselves, and thus may provide the basis for the development of a new class of transition-metal catalysts.[10,11] For these reasons we have undertaken a study of the chemistry of a series of triosmium carbonyl cluster complexes formed by the addition of a variety of small heteronuclear unsaturated molecules to the cluster complex $H_2Os_3(CO)_{10}$.

The molecule $H_2Os_3(CO)_{10}$ (I) has been shown to contain a triangular cluster of 3 osmium atoms with 10 linear terminal carbonyl ligands.[12] The two hydride ligands bridge one unusually short osmium–osmium internuclear separation. Electronically, the cluster contains 46 electrons, which is 2 fewer than the 48-electron closed-shell configurations characteristic of triangular clusters. Various theories have been advanced to rationalize the bonding in I,[12a,13] but its most important feature is that it does behave chemically as if it were electron deficient. For example, it readily adds donors, L (e.g., CO, phosphines, phosphites, isocyanides, etc.) (eq 1) to form 1:1 adducts that contain the closed-shell 48-electron configuration.[14]

Scheme I



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