

DINUCLEAR CRYPTATES: DIMETALLIC MACROPOLYCYCLIC INCLUSION COMPLEXES
CONCEPTS - DESIGN - PROSPECTS

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ABSTRACT - Macropolycyclic structures possessing receptor sites for several substrates may present a variety of new properties compared to single site receptors. Inclusion of two metal cations yields dinuclear cryptates in which the geometrical arrangement and the properties of the cations depend on the features of the ligand: the nature of the binding sites, of the subunits by which the cations are complexed, of the framework which connects the subunits. Three main classes of macropolycycles are considered: bis-chelating macrocycles, macrobicycles of either axial bis-tripodal or lateral chelating-macrocyclic type, cylindrical macrotricycles. The design of these structures is analyzed with respect to the choice and effect of binding sites, subunits and framework, on the properties of the cryptates formed: complexation and redox features, cation-cation interaction at short distances, formation of cascade complexes by fixation of substrates on the bound cations. Dinuclear cryptates of each type have been obtained, as well as several bridged species. Their structural, physical and chemical properties are discussed. The prospects of these type of complexes are outlined especially with respect to the design of polynuclear cryptates, catalysis of multicenter-multielectronic processes, biomimesis of metalloproteins and of biological redox processes.

Macropolycyclic structures are able to provide suitable frameworks for the arrangement in space of several receptor sites, allowing the binding of several substrates or the multiple binding of a single polyfunctional substrate. They delineate molecular cavities into which the substrates penetrate, forming inclusion complexes, *cryptates*, whose geometry may be regulated via ligand design (1). In addition to the functions displayed by single site (*monotopic*) molecular receptors (1) (recognition, catalysis, transport), the simultaneous or successive participation of several sites to substrate binding by multisite (*polytopic*) receptors provides an entry into higher forms of molecular behaviour, *cooperativity*, *allostery* and *regulation*. Such *co-systems* may display successive binding of different substrates yielding "*cascade*" complexes (2-5).

Polytopic receptors may be symmetric or dissymmetric, contain equivalent or non-equivalent binding subunits; they may complex identical (homonuclear complexes) or different (heteronuclear complexes) substrates, inorganic metal cations, organic or biological molecular cations, inorganic or organic molecular anions as well as neutral molecules.

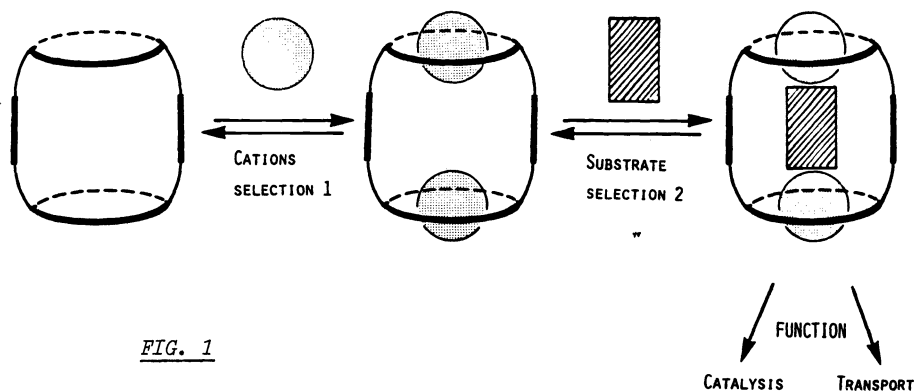
Among the great variety of species which can be imagined, we shall limit our present discussion to dinuclear complexes formed by inclusion of two metal cations into a macropolycyclic ligand containing two binding subunits, i.e. the topic will be concerned with our work on *dinuclear cryptates of metal cations*.

In these complexes, the distance and arrangement of the cations may be monitored via the design of the ligand. They provide a novel approach to the study of *cation-cation*

interactions at short intercationic distances (magnetic coupling, electron transfer, modified redox properties). At larger separation, *inclusion of substrates* bound to the cations leads to cascade complexes via a sequential, double selection process: selection of the cations by the ligand binding sub-units, selection of the substrates controlled by the nature and arrangement of the complexed cations. Cascade complexes may display several exciting properties:

- selective fixation and transport of substrates (for instance gases);
- catalysis of multicenter-multielectronic processes;
- activation of the fixed substrates;
- condensation or cross-reaction (thermal or photochemical) of different substrates brought together and held in proximity.

Figure 1 illustrates schematically the formation of a cascade complex in the case of a macrotricyclic dinucleating cryptand (see below).



In addition, di- and polynuclear cryptates may also serve as bioinorganic models for metalloproteins (copper proteins, hemocyanin, hemerythrin, oxidases, etc.).

The design of suitable macropolycyclic ligands capable of forming polynuclear cryptates implies three main levels of structural analysis concerning:

- the nature of the *coordination sites*, (N,O,P,S etc.) on which depend the selection of the complexed cations, their redox and substrate binding properties, etc.;
- the properties of the *binding subunits* chosen for incorporation into the macropolycyclic structure: nature and geometry (chelating, tripodal, cyclic); number and arrangement of coordination sites which determine the coordinative saturation and the geometry of the coordination shell of the cations; conformational and stereochemical features; *toposelectivity*, i.e. orientational selectivity for cation localization determining whether or not the cation will be bound inside or outside the molecular cavity;
- the *macropolycyclic architecture* which defines the framework holding the structure and establishes how the subunits are built into the final structure: geometry; cyclic order; number and arrangement (distance, orientation) of the binding subunits; internal dynamics (flexibility versus rigidity) of the polycyclic system; nature, number and flexibility of the connective branches linking the subunits; accessibility of the bound cations to interactions with the environment, etc.

Depending on the nature of the subunits used as building blocks and on the number of connecting bridges used for their construction, a variety of macropolycyclic structures may be envisaged. Our work has been, at present, mainly concerned with the four types of ligands and of derived dinuclear cryptates represented in *Figure 2*:

- connection of two *chelate* subunits leads to *macrocylic* dinuclear cryptates;
- coaxial arrangement of two *tripodal* subunits linked by three bridges yields *axial macrobicyclic* (bis-tripodal) systems;
- bridging of a chelate unit over a macrocycle gives *lateral macrobicyclic* cryptates;
- face-to-face linkage of two *macrocycles* forms *cylindrical macrotricyclic* cryptands and cryptates .

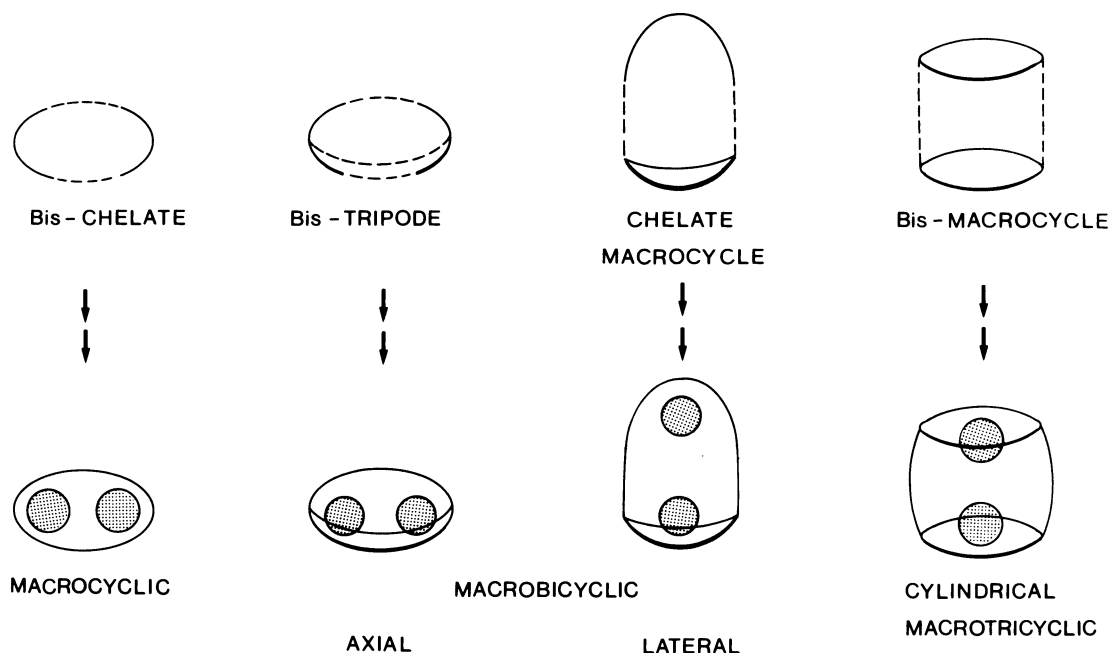


FIG. 2. Macropolycyclic cryptands and dinuclear cryptates resulting from connection of chelating, tripodal and macrocyclic subunits.

In these systems, the choice of the subunit determines the number and direction of the free coordination sites on the complexed cations while the length and geometry of the bridges defines the relative positions of the complexed cations. The possibility to achieve control over these fundamental properties is a particularly attractive feature of macropolycyclic ligands. Another type of structure, *bis-macrocycles*, based on the linkage of two macrocycles by a single bridge will also be considered below.

MACROCYCLIC DINUCLEAR CRYPTATES

Bis-chelating macrocyclic ligands may encircle two metal cations, holding them in the interior of the molecular cavity, thus forming macrocyclic dinuclear cryptates. When the two chelating units are of different nature, heteronuclear complexes may form. If the distances are suitable, bridging of the two cations by a substrate molecule may occur, forming a cascade type complex. These processes are illustrated schematically in *Figure 3*.

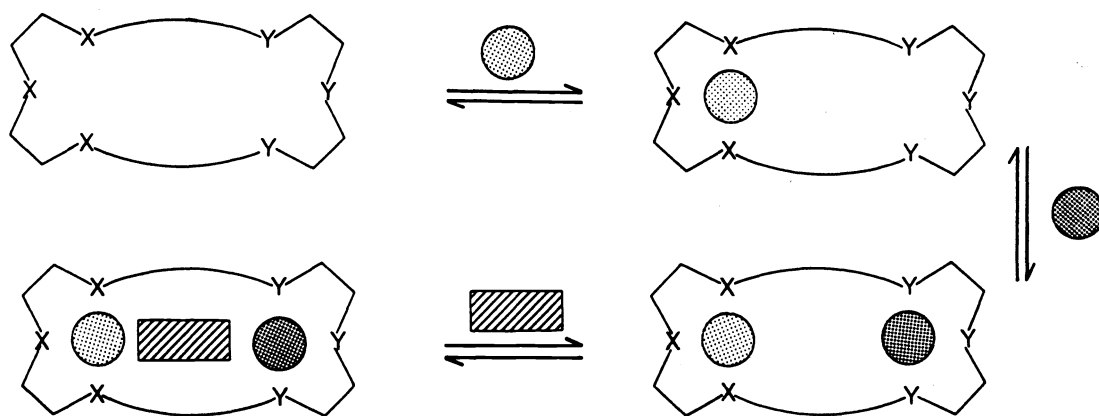
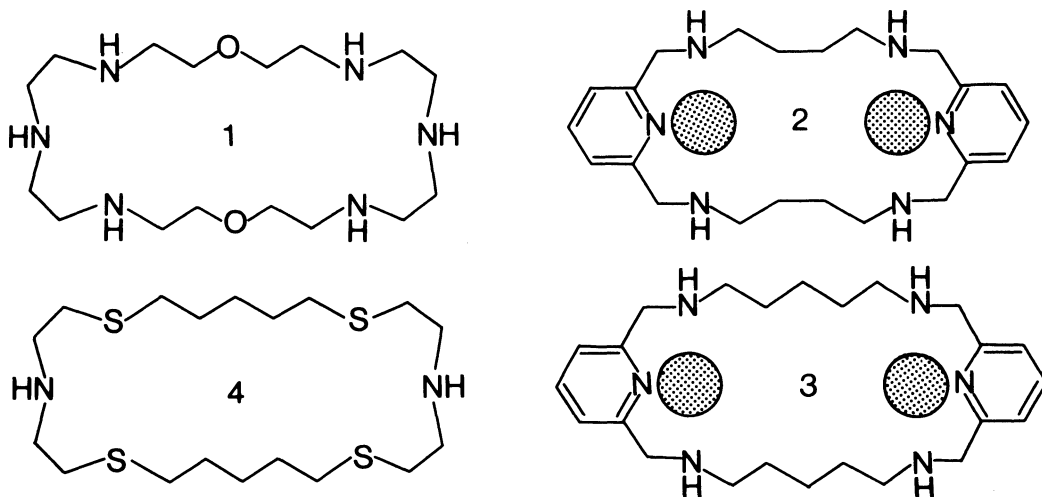


FIG. 3. Sequential formation of a cascade complex, involving complexation of two different metal cations by a dissymmetric macrocyclic ligand to give a heterometallic dinuclear cryptate, followed by binding of a substrate across the two cations.

In 1970, independent reports described the first examples of dinuclear complexes in which the metal cations were enclosed in a macrocyclic ligand: a bis-Ni(II) complex of an octathia-24-membered ring [24]-S₈ (6), a bis-Cu(II) complex of a hexaaza-18-membered ring (7) and the dinuclear complexes of a tetraaza, dioxo-20-membered macrocycle (8). The latter type of complexes contain bridging coordination sites; a number of analogous "compartmental" ligands have been prepared, yielding both homo- and hetero-dinuclear complexes (9,10). Dirhodium and dirhenium complexes of tetraazaannulene macrocycles have been reported recently (11,12). Most of these complexes are formed by Schiff base condensation reactions in presence of the cation to be complexed acting as template; the cation-free ligands are usually not obtained. Dinuclear complexes of alkali cations (Na⁺, K⁺) have been described for large macrocyclic polyethers (13,14).

Our own work on dinuclear macrocyclic cryptates has been concerned mainly with ligands containing two chelating subunits of the diethylene triamine type: the hexaaza-dioxo-compound [24]-N₆O₂, **1**, and the two macrocycles bearing two diagonally disposed pyridine groups [22]-N₄Py₂, **2**, and [24]-N₄Py₂, **3**. All three compounds have been synthesized by a route leading to the cation free ligands.



A precursor of macrocycle 1 had been described earlier (15); another route has now also been developed (16). The synthetic scheme leading to compound 2 is shown in *Figure 4*; a similar path has been used for compound 3 (17). They do not represent the most straightforward routes to the desired compounds, but make use of intermediate materials which may also serve for the synthesis of other types of ligands .

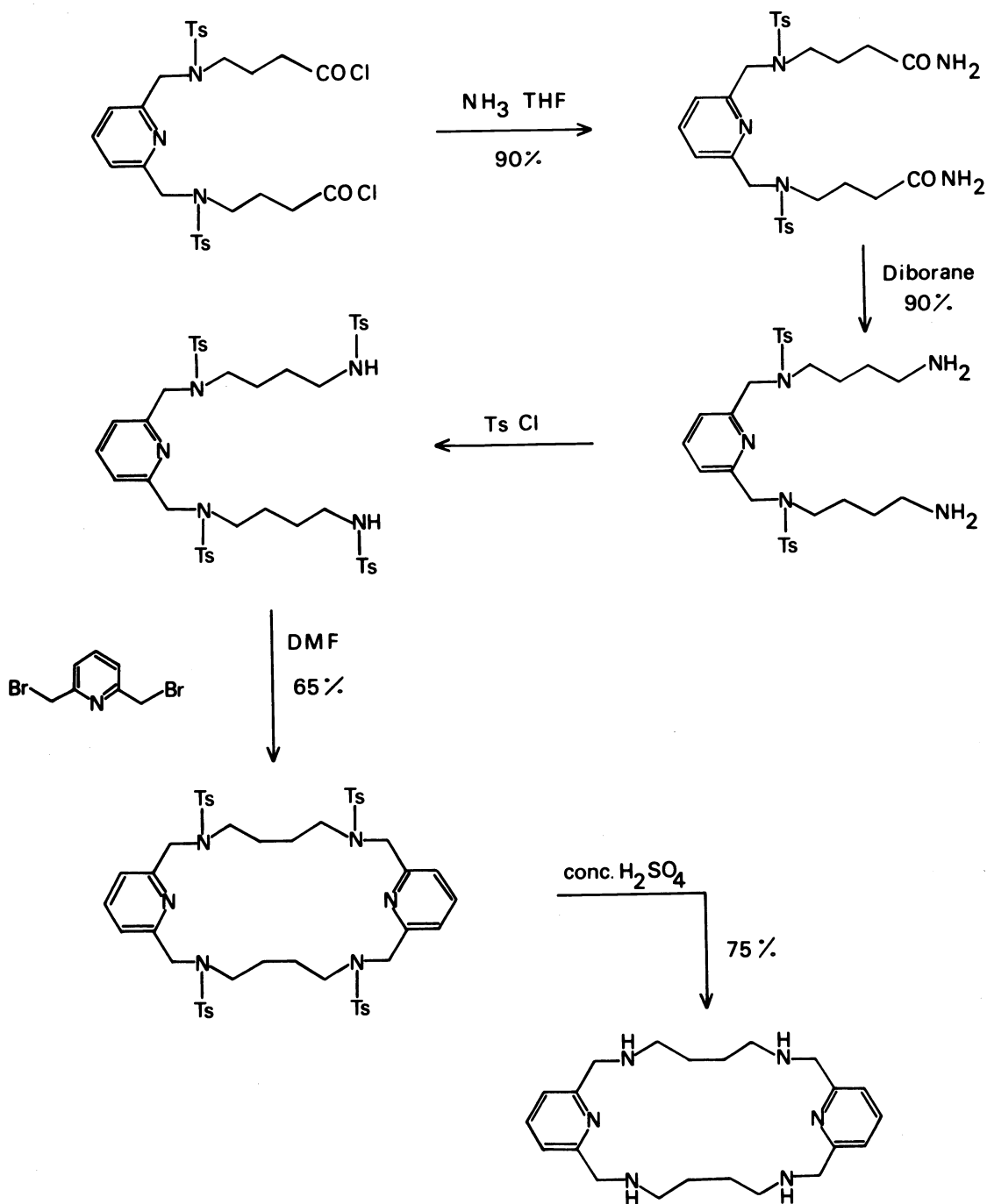


FIG. 4. Reaction sequence for the synthesis of the macrocyclic ligand 2.

All three ligands form dinuclear Cu(II) complexes in which both cations are expected to be contained inside the macrocyclic cavity. Indeed, in presence of azide ion, macrocycles 1 and 2 yield the inclusion complexes $[2 \text{ Cu}(\text{N}_3)_2 \subset \text{L}]$ (using a formalism proposed earlier (1); $\text{L} = \underline{1}$ or $\underline{2}$) in which each Cu(II) is bound to the three nitrogen sites on one side of the ring and to two N_3^- ions, as shown by crystal structure determination (18); the Cu(II)-Cu(II) distances are 5.98 and 4.79 Å in the complexes $\text{L} = \underline{1}$ and $\underline{2}$ respectively. The magnetic properties of these species indicate isolated, uncoupled Cu(II) sites (19). A dinuclear Pb(II) complex of a related ligand has been obtained by template Schiff base condensation (20).

A particularly interesting property of dinucleating ligands, is that they may dispose the complexed cations in an arrangement suitable for bridging by a substrate, thus forming a cascade complex (Figure 3). The imidazolite group is an especially attractive unit, since such bridges are known or proposed to occur in dimetallic centers of certain metalloproteins. A species of this type could indeed be obtained from the bis-Cu(II) complex of macrocycle 1 on addition of sodium imidazolite. The crystal structure of the compound isolated indicates that a $\text{Cu}_2(\text{im})^{3+}$ ion is incorporated into the macrocycle 1; each Cu(II) cation is held by one of the diethylenetriamine subunits, and the imidazolite anion bridges the two cations; the coordination shell is completed by a neutral imidazole ligand on each metal centre (Figure 5) (21). The magnetic properties of this compound should be of interest and are being studied.

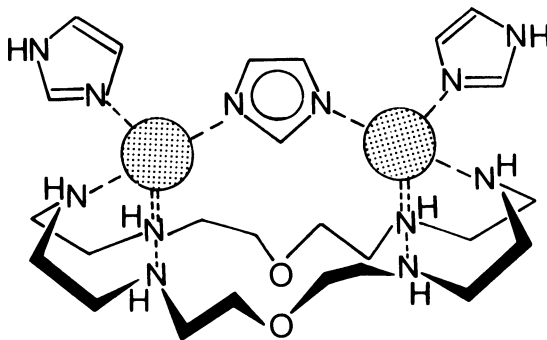


FIG. 5. Representation of the structure of the bridged dinuclear cryptate $[\text{Cu}_2(\text{imH})_2(\text{im}) \subset \underline{1}]^{3+}$ (20).

Two other bridged dinuclear macrocyclic complexes have been reported recently. A 24-membered ring 4 containing two SNS chelating units linked by $-(\text{CH}_2)_5-$ bridges has been shown to yield a dinuclear Cu(II) complex in which the cations are located inside the macrocyclic ligand, and coordinated each to a NS_2 chelate unit, to one nitrogen of an end-on azide ion and to two nitrogens of two di- $\mu(1,3)$ -azido end-to-end bridging azide ions. This complex possesses the remarkable property of being completely diamagnetic despite the rather long intercationic distance of 5.145 Å (22).

In two binuclear Cu(II) complexes of a 30-membered Schiff base macrocyclic ligand, the cations are bridged by a small ligand (N_3^- or OH^- respectively); while the azide bridged complex is only weakly antiferromagnetically coupled, the hydroxide bridged species shows stronger coupling (23).

The results already obtained show that dinucleating macrocyclic ligands present a number of interesting properties, especially when subsequent binding of other substrates and

bridging occurs to the coordination sites which are still available on the complexed cations. They are therefore particularly well suited for studying cascade complexation, the bringing together of small molecules, catalysis. Further flexibility in ligand modification results from the possibility of attaching *lateral branches* to sites like trivalent N, as is for instance the case with ligands $\underline{1-4}$ where H on N may be replaced by chains like $\text{CH}_2\text{CH}_2\text{X}$ (X=SR, NR₂, Pyridyl, PR₂ etc.).

Taking these considerations into account, three types of coordination sites may be distinguished in the design of macrocyclic dinucleating (or polynucleating) ligands, depending on the utilization of the coordination positions available around a given cation:

- *fixation sites*, which serve to strongly bind the cations to the macrocyclic structure and hold them in place; if maximum use is to be made of the sites available around a certain cation, the ligand should only provide the minimum number of binding sites compatible with the requirement of stability of the complex in the conditions of the experiment; two or three sites in a chelating unit (for instance an $\alpha\alpha'$ -bipyridyl site) may be sufficient for devising such a "*minimal ligand*";
- *modulation sites*, which may serve to bind monodentate ligands (like PPh₃ for instance) intended at modifying the properties of the cations;
- the remaining *catalysis sites*, would allow to bind substrates and to perform reactions on them.

A given system may for instance involve 2 or 3 fixation sites; 1 or 2 modulation sites and 1 or 2 catalytic sites per metal cation centre of a di- (or poly-) nuclear macrocyclic complex. Of course, these considerations also apply to the macropolycyclic ligands discussed below, although they allow probably less flexibility in coordination site utilization, since they usually provide more fixation sites and more geometrical constraint (which may be advantageous for certain goals) than the bis- (or poly-) chelating macrocycles.

A further variation of interest, is the synthesis of *dissymmetric* ligands containing for instance two different chelating subunits (see *Figure 3*); they may form heterodinuclear complexes, or homonuclear ones in which the cations have different properties. The combination of a redox site (like Cu²⁺) with a Lewis acid site (like Zn²⁺) may be envisaged. Such studies are underway.

MACROBICYCLIC DINUCLEAR CRYPTATES

AXIAL MACROBICYCLIC SYSTEMS

The tripodal ligand, tren N(CH₂CH₂NH₂)₃, is known to display remarkable complexing properties towards transition metal cations. It thus is a suitable building block for incorporation into dinucleating macropolycyclic ligands. Linking two tren units by three bridges of equal length, yields a Bis-Tren ligand which belongs to the class of macrobicyclic cryptands (1), and in which the two tripodal subunits are arranged in a coaxial fashion. It should be able to complex two metal cations each held by one tren group, forming a dinuclear cryptate of the *axial* macrobicyclic type (*Figure 2*).

The synthesis of the Bis-Tren ligand $\underline{5}$ has been realized via a path involving a selectively protected macrocycle of type $\underline{1}$ as intermediate (15). An analogous macrobicyclic cryptand [3.3.3], containing two triethanolamine N(CH₂CH₂OH)₃ subunits, had been obtained earlier (1, 24)), and the sulfur containing analog has been reported recently (22).

Structure $\underline{5}$ represents the Bis-Tren molecule in its in-in form. It contains an ellipsoidal cavity which should be able to take up two cations, one at each pole. Indeed dinuclear complexes are formed with two Ag^+ , Zn^{2+} , Cu^{2+} , Co^{2+} cations. The structure of these complexes may be schematically represented by $\underline{5-M}_2$, the intercationic distance being roughly estimated to about $4.5 \pm 0.5 \text{ \AA}$. They are dinuclear cryptates $[2M \subset \underline{5}]^{n+}$.

An NMR study indicated that the dinuclear complex is formed via the unsymmetric mononuclear species $\underline{5-M}$ in which both side to side cation exchange inside the cavity and cation exchange outside the cavity are slow. The stability constants K_{S1} and K_{S2} (Figure 6) of the mononuclear and dinuclear complexes have been obtained by pH metric titration for Zn^{2+} , Cu^{2+} , Co^{2+} , Ni^+ cations (25). For Cu^{2+} $\log K_{S1}$ and $\log K_{S2}$ are respectively 16.6 and 11.8.

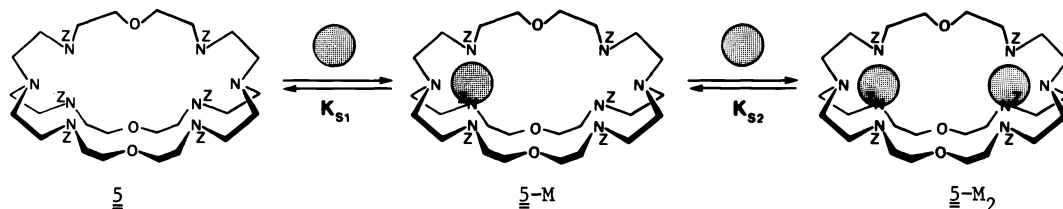
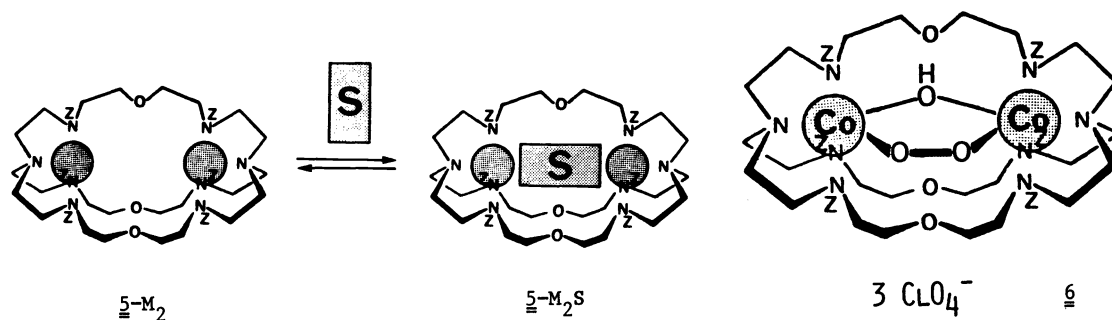


FIG. 6. Schematic representation of the formation of mononuclear and dinuclear cryptate complexes of the Bis-Tren ligand $\underline{5}$.

The powder ESR spectrum of the blue $[2 \text{Cu}^{2+} \subset \underline{5}]$ complex contains a weak signal at half-field indicating some coupling between the two ions. Formation of cascade species $\underline{5-M}_2S$

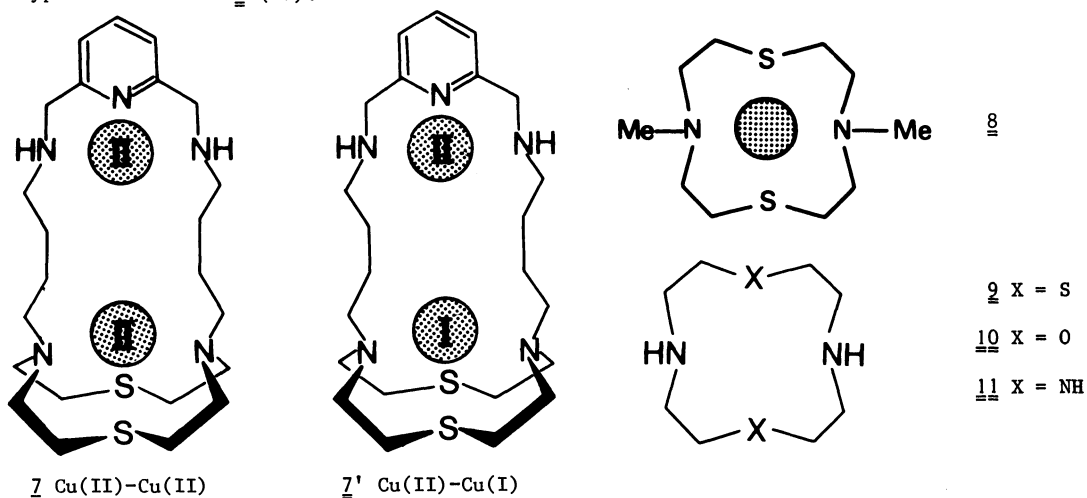


involves insertion of a substrate between the two cations. Evidence that such a process may occur has been obtained from the changes in the electronic spectrum of $[2 \text{Cu}^{2+} \subset \underline{5}]$ on addition of H_2O , CN^- , N_3^- (15). Oxidation of the bis- Co^{2+} complex yields the bridged μ -peroxo, μ -hydroxo species $[\text{Co}(\text{O}_2, \text{OH})\text{Co} \subset \underline{5}]^{3+}$ as indicated by isolation, spectral (26) and titration (25) data. The structure of this complex is schematically represented by $\underline{6}$. The crystal structure of the analogous species formed by tren itself $[(\text{tren})\text{Co}(\text{O}_2, \text{OH})\text{Co}(\text{tren})]^{3+}$ has been determined (27). The binding of O_2 is found to be weaker in $\underline{6}$ than in the tren complex (25). Evidence for the formation of a bridged species with cyanide ion has been obtained for the bis- Cu^{2+} , Ni^{2+} and Co^{2+} complexes from spectral data. More accurate structural data are not available at present for these complexes of the Bis-Tren cryptand, since it has not yet been possible to grow crystals suitable for X-Rays crystallography.

LATERAL MACROBICYCLIC SYSTEMS

When a chelating subunit is bridged over a macrocycle, a macrobicyclic molecule is obtained which may complex two cations, one in the macrocycle and the second one chelated on the side of the ligand. The intercationic axis is not anymore in the direction of the bridgeheads of the bicyclic system as with the axial type complexes considered previously, but rather oriented perpendicular to it. The resulting complexes may be described as *lateral* macrobicyclic dinuclear cryptates.

A molecule of this type has been synthesized by linking the 2,6-bis(aminomethyl)pyridine chelating unit present in the macrocycles 2 and 3, to a diaza-dithia-12-membered macrocycle [12]-N₂S₂ 9 by two -(CH₂)₄- bridges. A complex of this ligand with two Cu²⁺ ions has been obtained; it may be schematically represented by the lateral dinuclear cryptate structure 7 (17).



The two copper ions in 7 are expected to have markedly different redox properties since the bis-Cu²⁺ complex of the macrocycle 2 is reduced at a potential about 500 mV less positive than the Cu²⁺ complex 8 of the N,N-dimethyl-[12]-N₂S₂ macrocycle. Indeed, the dinuclear bis-Cu²⁺ cryptate 7 undergoes monoelectronic reduction at about +550 mV (versus NHE in propylene carbonate); the second Cu²⁺ ion has a much less positive redox potential (+ 70 mV) (28). The first reduction must occur at the Cu²⁺ ion complexed by the [12]-N₂S₂ subunit, allowing the facile formation of a mixed valence Cu(I)-Cu(II) dinuclear cryptate 7'. The structural and spectral properties of this interesting species are being studied in more detail. It should be possible to obtain heterometallic dinuclear complexes of type 7. Finally, substrate fixation on such type of complexes is also of interest. Another system belonging to this general lateral macrobicyclic class, would be the dinucleating ligands obtained by diagonally bridging a porphyrin macrocycle with chains containing a chelating unit. Heterometallic dinuclear complexes of such ligands might be interesting bioinorganic models of metalloproteins like superoxide dismutase.

DINUCLEAR CRYPTATES OF CYLINDRICAL MACROTRICYCLIC LIGANDS

GENERAL CONSIDERATIONS

Face to face linkage of two macrocycles by two bridges yields macrotricyclic molecules of the cylindrical type (*Figure 2*). They define *three cavities*: two lateral circular cavities inside the macrocycles and a central cavity. Modifying the size of the macrocycles and the length of the bridges changes the sizes of these cavities and affects the distance and the coordination arrangement of complexed cations. In addition to the obvious role of the *binding sites* (nature, number) on cation selection (*Figure 2*) and on properties of the complexed cations, the *nature of the macrocycles* will affect the position of the bound cations, the stereochemistry, redox and magnetic properties of the complexes (see also ref. 29).

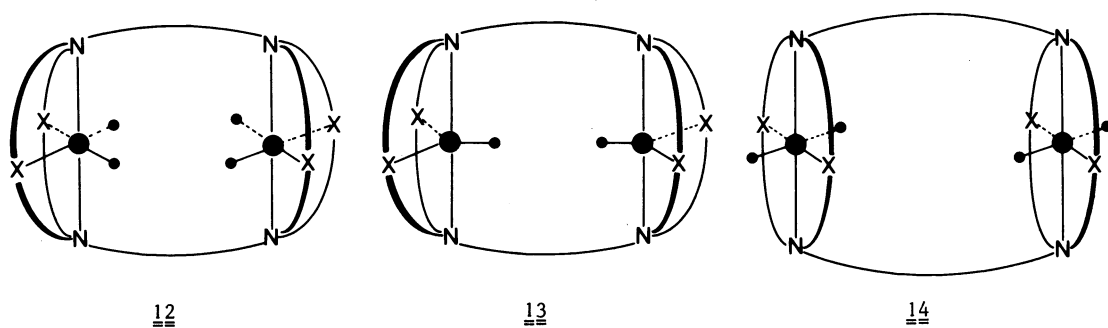
Ring size plays an important role. The cavity of a [12]-membered cyclic ligand, like [12]-N₂S₂ 9 or its analogs [12]-N₂O₂ 10 and [12]-N₄ 11, is too small for cation inclusion; the bound cation is expected to sit on top of the ring, out of the plane of the donor atoms, and appears held in a cup with a *cis*-coordination arrangement. A *cis*-octahedral geometry is, for example, present in [12]-N₄ macrocyclic complexes as indicated by spectral, magnetic (30,31) and crystal structure (32) results. With larger tetradentate macrocycles, like 16- and 18-membered rings, the cation may penetrate more or less into the cavity and a *trans*-octahedral geometry is obtained. Rings of intermediate size (e.g. 14-membered ones) have the possibility to present either arrangement (33-35).

Consequently, with [12]-[12] macrotricyclic ligands build on two 12-membered rings, the two bound cations are expected to be held preferentially *inside* the central cavity (*topo-selectivity*) by virtue of the bridges and the stereochemistry at the bridgeheads, and displaced towards each other. Furthermore, the remaining free coordination sites are directed *into* the central cavity more or less towards each other. With *cis*-octahedral or trigonal-bipyramidal geometry on each lateral macrocycle, there will be respectively four (*s*₄) or two (*s*₂) syn oriented free coordination sites, as represented schematically by structures 12 and 13.

When the macrocycles are of larger size, the macrotricyclic complexes of cations with octahedral coordination may for instance present two inside (syn) and two outside (anti) oriented free coordination sites (*s*₂*a*₂) (see structure 14).

The *nature of the bridges* linking the macrocycles, their length, their conformational properties, affects the intercationic distance, allowing or hindering cation-cation interaction at short distances or inclusion of a given substrate (substrate selection, *Figure 1*) at larger separations.

Thus, by a judicious choice of suitable structural fragments (binding sites, macrocycles, bridges) it should in principle be possible to closely monitor the properties of the dinuclear complexes of cylindrical macrotricyclic ligands. The number and orientation of free coordination sites on the complexed cations are of special importance for *catalysis*, potentially allowing to bring into proximity and activating two or more reactant substrates.



SYNTHETIC STRATEGIES

Various synthetic plans may be followed for constructing the cylindrical macrotricyclic architecture (36). The two paths A and B represented in *Figure 7* have been used at present. Scheme A allows the introduction of different bridges, while path B may yield macrotricycles incorporating two different macrocyclic subunits.

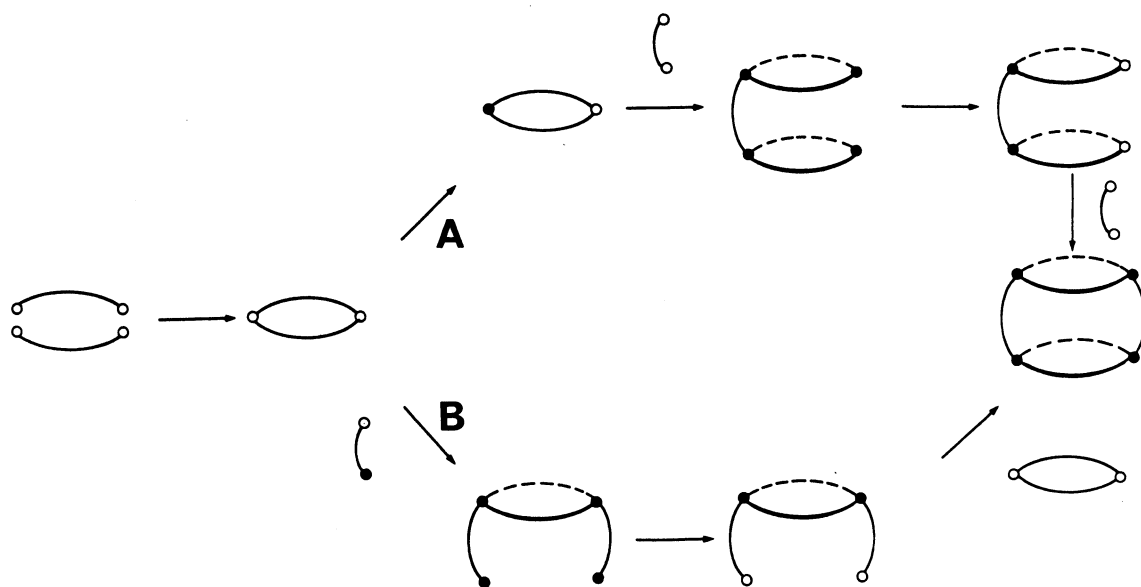
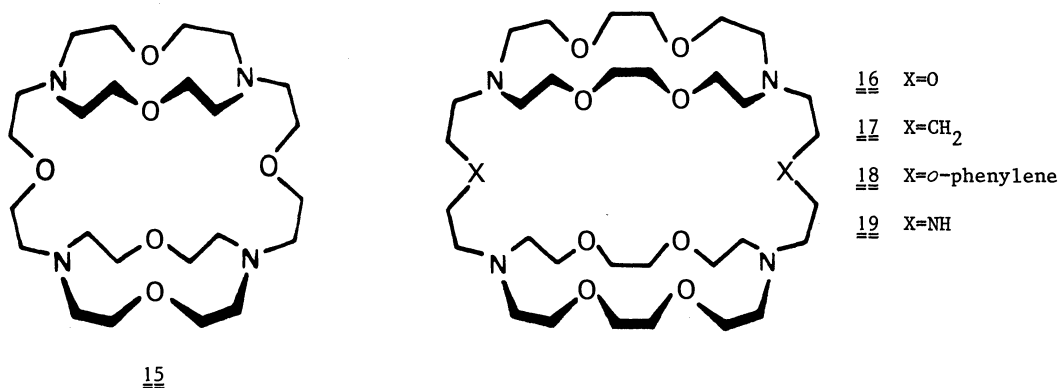


FIG. 7. Two synthetic strategies for the construction of cylindrical macrotricyclic systems (open and closed circles represent respectively reactive and protected or unreactive functions).

DINUCLLEAR CRYPTATES OF POLYOXA-MACROTRICYCLES

The first cylindrical macrotricyclic ligands described were compounds 15-19, which bear oxygen and nitrogen sites.



The macrotricyclic 15 (37,38) which contains the [12]-N₂O₂ subunit 10, yields a very stable, slowly exchanging dinuclear cryptate [2 Ag⁺ ⊂ 15] (37), whose crystal structure shows that the two silver cations are located inside the central cavity, each on top of one of the twelve-membered rings (see above) and at a distance of 3.88 Å (39). It also forms a crystalline bis-Cu(II) complex [2 Cu²⁺ ⊂ 15] (17), in which the cations do not appear to be significantly coupled (19). Electrochemical reduction of this complex to the bis-Cu(I) species occurs in two successive mono-electronic steps at markedly positive potentials (+0.56 and +0.49 vs. NHE in propylene carbonate) comparable to the redox potential found for the sulfur analog discussed below (28). Ligand 15 also gives complexes with alkali cations (37), as well as with alkaline-earth and lanthanum cations (40).

The symmetrical macrotricyclics 16-19, which contain the [18]-N₂O₄ macrocyclic subunits, have been synthesized following path A of *Figure 7* (41). They form dinuclear complexes with alkali, alkaline-earth, Ag⁺, Pb²⁺ cations (42,43). The 18-membered rings are large enough for cations of size smaller or equal to that of K⁺ or Rb⁺, to penetrate more or less deeply into their cavity. Consequently, the cations of dinuclear complexes are further apart. Indeed, the crystal structure of [2 Na⁺ ⊂ 16] 2 I⁻ shows that the two cations are located in each macrocycle and are 6.40 Å apart (44). This is a much larger distance than that of the two Ag⁺ cations in [2 Ag⁺ ⊂ 15] despite the identity of the bridges linking the rings in 15 and 16; it results from partial penetration of the Na⁺ cations into the macrocyclic cavities.

On the basis of these structural data and of NMR results (43), the mononuclear complexes of the tricyclic cryptands are non-symmetrical with the cation located on one side of the central cavity, while the dinuclear cryptates are expected to be symmetrical (*Figure 8*). The formation of *heteronuclear* dimetallic cryptates has also been observed in the case of [Ag⁺Pb²⁺ ⊂ 16], in equilibrium with the corresponding two homo-dinuclear species (43). Ligands 15-19 should be able to form other dinuclear cryptates; of special interest would be those involving transition metal and lanthanide cations.

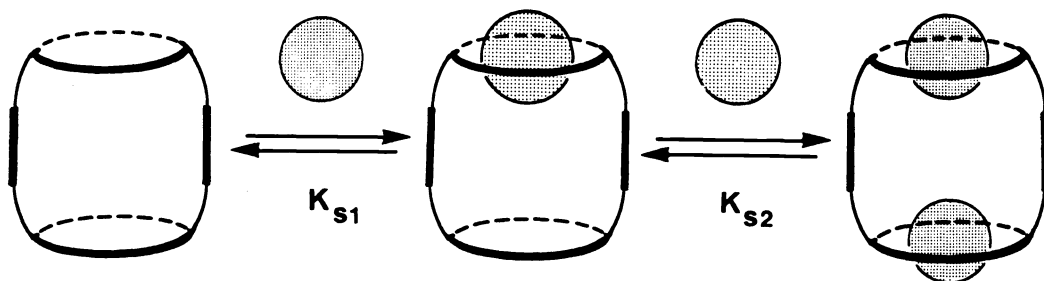
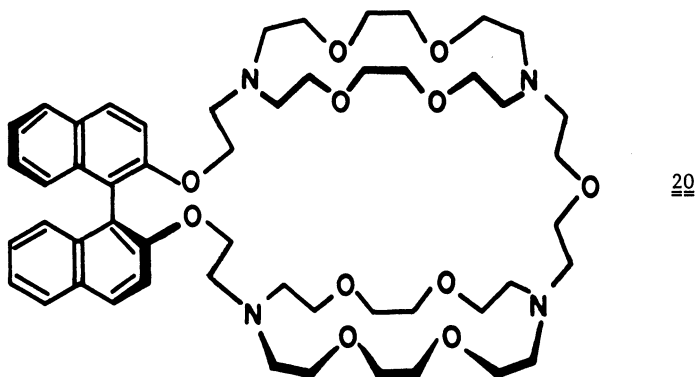


FIG. 8. Schematic representation of the successive formation of mononuclear and dinuclear cryptates with cylindrical macrotricyclic ligands.

Cryptands of type 16-19 where the two $[18]-N_2O_4$ subunits are further apart have been synthesized; they contain naphthyl, biphenyl or other groups in the bridges and yield ammonium as well as metal cation cryptates (see ref. 5 and references therein).

Unsymmetrical macrotricycles, containing two identical macrocycles but two different bridges, may be obtained following scheme A of *Figure 8*, as pointed out above. Such a structure, 20, incorporating a chiral binaphthyl bridge, has been synthesized and shown to bind metal cations, as well as to complex and transport chiral molecular cations and anions with weak chiral discrimination (4,45). The latter process may be considered as a *metallo-receptor* model system, where binding of an anionic substrate is dependent on prior binding of a metal cation.



Stability Constants and Kinetic Processes

The stability constants of the 1/1 and 2/1 complexes of the cylindrical macrotricyclic ligands correspond to the equilibria shown in *Figure 8*. Ligand 15 forms 1/1 alkali complexes with stabilities comparable to those of macrocyclic ligands, except for the larger cations Rb^+ and Cs^+ which probably fit better into the cavity; the alkaline-earth cations form remarkably stable complexes ($\log K_g$ of the order of 7 in water (40)). The alkali and alkaline-earth cryptates of the larger macrotricycles 16-18 show two main features (43):

- the stabilities K_{s1} and selectivities of the 1/1 complexes are similar to those of the model macrocycle N,N' -dimethyl- $[18]-N_2O_4$;
- the stabilities and selectivities of the binuclear complexes (K_{s2} , see *Figure 8*) are

similar to those of the 1/1 complexes; it is especially remarkable that K_{s2} for the formation of $[2 \text{ Ba}^{2+} \subset \underline{16}]$ is as high as K_{s1} for $[\text{Ba}^{2+} \subset \underline{16}]$.

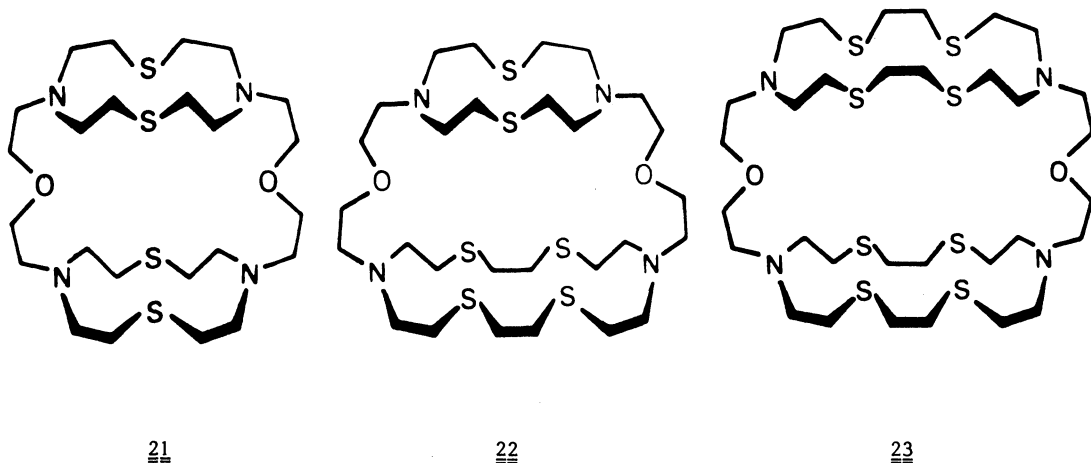
Both results lead to the conclusion that the larger macrotricycles contain two almost independent macrocyclic units.

Kinetic processes have been observed in several cases. Temperature dependent ^{13}C -NMR measurements allowed to detect an *intra-molecular cation exchange* process in the 1/1 Ca^{2+} , Sr^{2+} and Ba^{2+} complexes of ligand 15. The spectral changes observed agree with an internal cation exchange between the two macrocycles. Intermolecular exchange occurs also, but at much slower rate than the internal fluxional process (40). It is probable that the same internal process takes place in the alkali complexes of 15 and in the non-symmetrical 1/1 complexes of 16-18 (43) but at much faster rates. These interesting dynamic features of macrotricyclic complexes also bear relation to the elementary jump process between binding sites which may occur in cation channels.

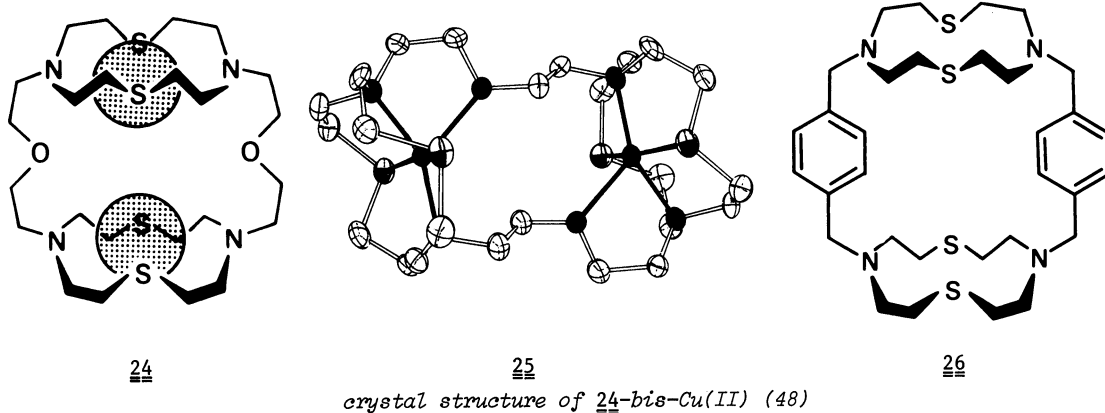
DINUCLLEAR CRYPTATES OF POLYTHIA-MACROTRICYCLES

In order to combine the rich chemistry of transition metal cations with the fascinating set of polymorphic macrotricyclic structures, the introduction of other binding sites than oxygen, like nitrogen or sulfur, was sought. To this end we have synthesized a series of polythia-macrotricyclic cryptands, and we have developed a general synthetic strategy which allows the introduction of two different macrocyclic subunits along path B of *Figure 7*. It involves: a) attachment of two appendages at diagonally situated positions of a suitable macrocycle; b) activation of the free termini of these appendages; c) condensation with the second macrocycle in high dilution conditions.

Three polythia macrotricycles containing 12-membered, $[12]\text{-N}_2\text{S}_2$, 9, and 18-membered, $[18]\text{-N}_2\text{S}_4$, macrocyclic subunits have been obtained at present: the $[12]\text{-}[12]$ 21, $[12]\text{-}[18]$ 22 and $[18]\text{-}[18]$ 23 cryptands (46). Most studies have been performed with these substances. Two other macrotricycles of $[15]\text{-}[15]$ and $[16]\text{-}[16]$ type, based on $[15]\text{-N}_2\text{S}_3$ and $[16]\text{-N}_2\text{S}_2$ (with three CH_2 groups between two heteroatoms) macrocycles, have also been synthesized (47). The synthetic sequence has been reported earlier (see ref. 46 and *Figure 7* in ref. 2). All three ligands 21-23 from *dinuclear cryptates* by complexation of two transition metal cations, one on each macrocyclic subunit (see for instance structure 24).



Bis-Cu(II) and bis-Cu(I) complexes of ligands 21-23 have been obtained (see for example structure 24). With the dissymmetric cryptand 22 a mixed Cu(II)-Cu(I) complex is formed, in which the Cu(I) and Cu(II) cations are probably located in the 18- and 12-membered rings respectively. The distance of the two cations is expected to increase gradually along the series of dinuclear complexes of ligands 21, 22, 23. The crystal structure of the violet [2 Cu(II) C 21] species 25 confirms that the two copper cations are bound inside the macrotricyclic cavity each on the macrocycle, and gives a Cu-Cu distance of 5.62 Å (48). The coordination polyhedron of each copper cation is a somewhat distorted tetragonal pyramid in which the metal ion lies ~ 0.34 Å out of the N_2S_2 plane, towards the axial oxygen atom.



The electronic absorption spectra, the EPR properties and the redox potentials of the bis-Cu(II) cryptates display interesting features, which present analogies with those of polythia macrocycles (49) and of copper proteins (50).

Most studies have at present been concerned with the bis-copper complexes of cryptand 21. pH-Metric titration yielded stability constants $\log K_{s1} \sim 10.9$ and $\log K_{s2} \sim 9.0$ (aqueous solution) for the formation of the mono- and dinuclear Cu(II) cryptates respectively (Figure 8) (51). The electronic spectrum of the bis-Cu(II) complex contains an intense absorption band in the visible region around 560 nm. The corresponding bis-Cu(I) species shows a characteristic absorption around 355 nm (46).

Electrochemical reduction of [2 Cu(II) C 21] indicates reversible transfer of two electrons at a markedly positive potential (+445 mV), which falls in the domain of those found for Cu(II) complexes of polythia macrocycles (49) and of copper proteins (50). The results are consistent with the reduction of the two Cu(II) ions in two mono-electronic steps, each involving a copper centre, with little interaction between the two centres (see also below) (52). Thus, the dinuclear [2 Cu(II) C 21] cryptate may be considered as a *dielectronic receptor* unit, which might be able to exchange two electrons in a single encounter. It represents a prototype for the study of cooperativity between two (or more) sites in electron transfer processes and for catalysis of reactions requiring the transfer of several electrons.

The EPR powder spectrum of [2 Cu(II) C 21] is of axial type and has $g_{\parallel} > g$, whereas the reverse holds for the mononuclear model species, the [12]- N_2S_2 macrocyclic Cu(II) complex 8 (see Figure 8 in ref. 2). In frozen solution, the EPR spectrum of this monocyclic complex shows a hyperfine splitting A_{\parallel} of usual value (0.015 cm^{-1}), whereas the dinuclear species displays a small A_{\parallel} splitting ($\sim 0.008 \text{ cm}^{-1}$), similar to the values found for *single* copper sites in copper proteins (50). This property results probably from the coordination at each

individual copper site in 24, since the two sites are only weakly coupled.

Variable temperature magnetic susceptibility measurements indicate that the two Cu(II) cations are coupled antiferromagnetically with an exchange term $J = -54.5 \text{ cm}^{-1}$, despite the absence of any bridging species between the two cations (53); furthermore a study of the temperature dependence revealed an interesting phenomenon of "magnetic plasticity" (53). A lower exchange interaction $J \sim -10 \text{ cm}^{-1}$ (53) is found for the bis Cu(II) complex of the macrotricyclic 26, in which the two [12]-N₂S₂ macrocycles are linked by two *para*-xylylene bridges (54); the two cations are therefore expected to be farther apart than in the complex 24.

In the dinuclear complexes discussed here the two cations are separated from each other by a distance depending on the ligand. There is space between the two ions for inclusion of a substrate of compatible size and suitable binding properties. No definitive evidence for such processes has yet been obtained, although a number of observations have been made which indicate that they might be occurring (46).

FURTHER TYPES OF MACROTRICYCLIC SYSTEMS

The macrotricyclic systems described above make use of saturated macrocyclic subunits. Incorporation of one or two unsaturated macrocycles (e.g. porphyrins) leads to two new types of molecules. Thus, by combination of saturated and unsaturated rings three subclasses of macrotricycles may be distinguished as represented schematically in *Figure 9*.

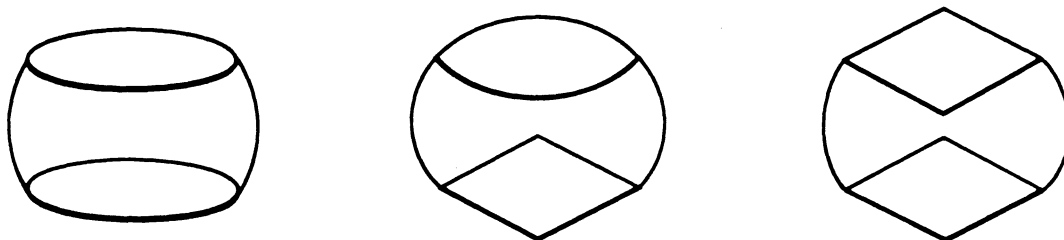


FIG. 9. Schematic representation of the three subclasses of macrotricyclic structures obtained by combining saturated macrobicyclic ligands (represented by a circle) and unsaturated ones (represented by a square) into two homotopic systems (left and right) and a heterotopic one (centre).

The macrotricycles described here belong to one such subclass (*Figure 9, left*). Porphyrins represent a particularly interesting subunit of the unsaturated macrocyclic type. Combination of the [18]-N₂O₄ ring with a porphyrin yields a "crowned" porphyrin (55,56), which belongs to the second subclass (*Figure 9, middle*). Connecting two porphyrins gives face-to-face porphyrins (57-60) which are members of the third subclass (*Figure 9, right*). Such species may have interesting new properties as compared to those of the isolated single macrocycles, such as bridging by bound substrates (like superoxide anion, ref 61) or catalysis (e.g. catalysis of oxygen electroreduction, ref. 62).

BIS-MACROCYCLES

Linking two macrocycles by a *single* bridge leads to *bis-macrocycles*. Several such ligand molecules have been obtained; they are an intermediate step along path A (*Figure 7*)

of macrotricyclic synthesis (41) or have been obtained for their own purpose (63,64). They may form mono- or dinuclear complexes; in the latter the relative position of the cations is less well defined than in macrotricyclics, since the two subunits may take up any orientation between the two extreme *syn* and *anti* arrangements (*Figure 10*).

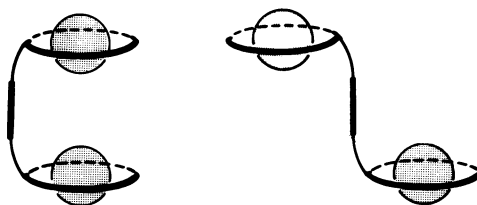


FIG. 10. Syn and anti orientations of bis-macrocylic complexes.

This greater flexibility may however also be advantageous, since it allows easier adaptation when repositioning of the cationic sites is required in the course of a given process, like substrate binding. Reversible CO and O₂ fixation has been reported for a bis-Cu(I) complex of this type (63).

PROSPECTS

The dinucleating macropolycyclic ligands discussed above represent a first step in the construction of multisite molecular receptors, whose architecture allows to arrange receptor sites in space in such a way as to bring together several substrates at a given position and in a desired orientation. Cooperation between the sites brings a new dimension to the properties of such co-systems (5). Dinuclear and polynuclear cryptates are not limited to metal cations. Using other receptor sites may allow binding anions or neutral species as well, be they organic or inorganic. Metallo-receptor type function may be provided by the coexistence of binding sites for a metal cation and for an organic molecule (4,42).

Even in the simplest case of dinuclear species, much work remains to be done and numerous properties may be imagined. On the physical side for instance, lanthanide cations like europium or neodymium (used in lasers) might form dinuclear cryptates with ligands 15-18 or their analogs (5); in the resulting cryptates the cations will be held at various distances allowing a study of their optical interactions. On the chemical side, still much too little is known about the catalytic functions which substrate fixation may allow; in this respect, polynuclear complexes of 2nd and 3rd row transition metal cations would be of much interest.

An intriguing type of polynucleating ligands would be those capable of forming *cluster cryptates*. One approach for complexing metal clusters is to maintain them *externally* by complexation of multidentate ligands on their faces, a *capping* process, as is the case with the tripodal tris-phosphine HC(Pφ₂)₃ and analogs (65). Another approach is to construct a cryptand with a cavity large enough for *inclusion* of the whole cluster, holding it by suitable binding sites incorporated in the walls of the cavity or borne by side chains.

In the field of catalysis, multicenter-multielectronic processes represent a particularly fascinating area, both for its fundamental and its practical importance. Oxygen, nitrogen and carbon dioxide reduction, water reduction and oxidation, are all reactions which proceed most easily via di-, tetra- or hexaelectronic reaction paths. The chemistry of (H₂ + CO) might also find great advantage in the development of polynuclear catalysis containing prearranged metal cations.

This rapid sketch of some aspects of the chemical panorama of polynucleating ligands in general and of polynuclear inclusion complexes, cryptates, in particular, will have achieved its objective if it has succeeded in showing how promising the future of the chemistry of these systems appears and how much it gives room to the creative imagination and experimental skill of the chemist.

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