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CRYPTATES: INCLUSION COMPLEXES OF MACROPOLYCYCLIC RECEPTOR MOLECULES

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Abstract. Molecular receptors use intermolecular interactions for the selective binding of substrates. Macropolycyclic molecules containing appropriate binding sites and cavities of suitable size and shape, may be designed so as to display molecular recognition in the formation of selective inclusion complexes, cryptates, with metal cations, anions and molecules. Macrocyclic receptors which form stable and selective complexes with primary ammonium and guanidinium groups are discussed; they display central and lateral discrimination. Enhanced rates of intramolecular thiolysis and hydrogen transfer have been observed when suitable reactive groups are attached to the receptor. Macrobicyclic ligands form very stable and selective cryptates with alkali and alkaline-earth cations; they may be modified so as to selectively complex toxic heavy metal cations. Binuclear cryptates of two types have been synthesized: macrobicyclic complexes of an ellipsoidal Bis-Tren ligand and cylindrical macrotricyclic complexes. They display interesting properties (like cation-cation interactions, copper protein type spectral parameters etc.) and are suitable for formation of "cascade complexes" by interaction of substrates with the bound cations. Spherical macrotricyclic receptors form cryptates with cations, anions and small inorganic species. They display tetrahedral recognition and may be considered as topologically optimal receptors for the ammonium ion, the water molecule, the halide ions, with which they form cryptates where the substrate is held in the intramolecular cavity by a tetrahedral array of hydrogen bonds.

Finally, the macrobicyclic Bis-Tren system in its protonated form, complexes triatomic species like the azide anion. It represents a further step in the design of abiotic molecular receptors for polyatomic molecules or ions. The main lines of further developments in the chemistry of macropolycycles comprise

the design of receptors for other important groups (carboxylate, phosphate), of polynuclear complexes and cascade complexes of potential use in polynuclear catalysis, of molecular catalysts as enzyme models and new chemical reagents.

INTRODUCTION

Just as there is a field of *molecular chemistry* based on the covalent bond, there is a field of *supramolecular chemistry*, the chemistry of molecular assemblies and of the intermolecular bond. *Molecular receptors* are organic structures, held by covalent bonds, which are able to complex selectively ions or molecules. Substrate binding makes use of various intermolecular interactions (electrostatic interactions, hydrogen bonding, Van der Waals forces, short range repulsions etc.) and leads to an assembly of two or more molecules, a *supermolecule*. The design of the receptor determines which substrate is bound. The substrate-specific "synthesis" of a supermolecule thus involves organic (regioselectivity; stereospecific) synthesis of a receptor by formation of covalent bonds, followed by one or several binding steps using intermolecular bonds in an arrangement predetermined in the design of the receptor. In addition to binding sites, the receptor may bear reactive sites or lipophilic groups for dissolution in a membrane so that its *functions* include molecular recognition, molecular catalysis and transport. These general considerations are summarized in Figure 1.

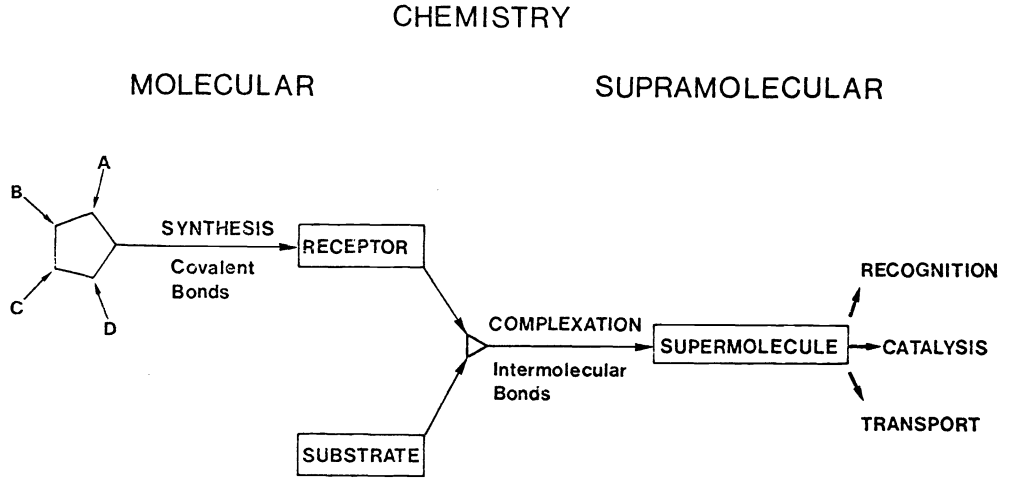


Fig. 1 From molecular to supramolecular chemistry.

Figure 2 presents a schematic representation of a receptor as a cavity bearing a combination of several receptor sites, each of which may involve several binding sites; both topology and binding show receptor-substrate *complementarity* (Ref. 1)

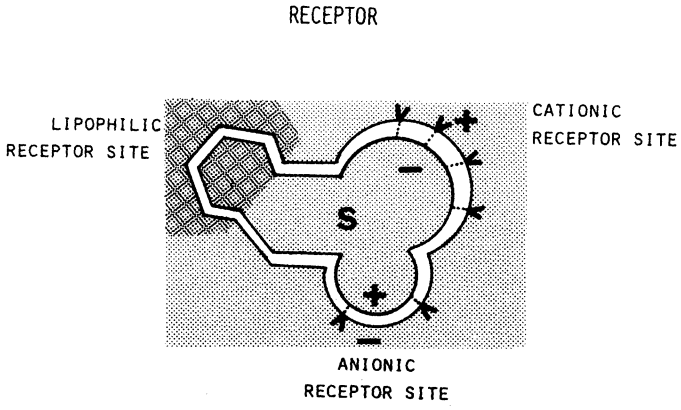


Fig. 2 Schematic representation of a molecular receptor. S is the bound substrate

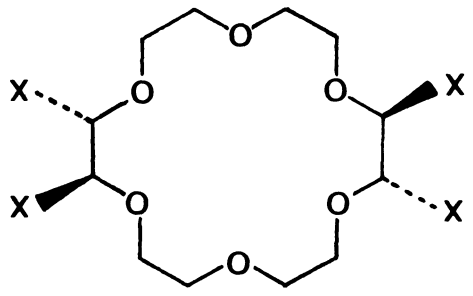
A further step, sequential complexation and selection, leads to *cascade complexes* where one or more substrates initially bound by the receptor serve as binding sites for a new substrate. The formation of such cascade complexes opens the way to even a higher form of organization: *regulation*.

Macropolycyclic mesomolecules (Ref. 2) contain intramolecular cavities, clefts and pockets delineated by molecular segments which may bear various sites for binding substrates and for performing reactions on bound molecules. By their architecture they provide means for the designed arrangement in space of binding sites, reactive groups and bound substrates. They may be either *biomimetic* or *abiotic* receptors , carriers and catalysts insofar as they may i) serve as models of biological systems and processes, ii) provide access to non-biological systems, processes or functions displaying biological-like efficiency and selectivity. The binding of a substrate by a macropolycyclic receptor forms a *cryptate* , an inclusion complex in which the substrate is contained inside the molecular cavity (or *crypt*) of the ligand (or *cryptand*).

We have studied several classes of macropolycycles: macrocycles, macrobicycles, cylindrical and spherical macrotricycles (for representations see Ref. 1,2). The molecular architecture, held by various structuration units, defines the topology of the receptor cavity. The nature, number, arrangement of the binding sites determine the energetic (stability) and recognition (selectivity) characteristics of the receptor-substrate interaction (Ref. 1). We have previously reviewed various aspects of the chemistry of cryptates (Ref. 1,2). We shall center the present report on other developments of our work and only briefly mention the earlier results when necessary for the sake of completness of the discussion.

MACROCYCLIC RECEPTORS

Macrocyclic polyethers of the "crown" type have attracted much interest by their property to complex various metal cations which are included in the central, circular cavity of the ring (Ref. 4). Among their most interesting features is the ability of 18-crown-6 1, to bind primary ammonium salts by inclusion of the anchor group $-NH_3^+$ into the macrocyclic cavity (Ref. 4). This property has been used successfully to effect the resolution of racemic ammonium salts (Ref. 5,6) especially by means of chiral crown ethers containing the binaphtyl group as chiral unit inserted in the ring (Ref. 5). However, this group, while possessing interesting structural features, has been shown to cause a large decrease in association constant with respect to the parent macrocycle 1 (Ref. 7). Our own efforts in the field of ammonium complexation were directed towards the synthesis of a chiral, polyfunctional macrocycle where the functionalities would be attached directly to the aliphatic carbons of 18-crown-6, 1, so as to retain the features of this structure. This has been realized by the one-step synthesis of the tetrafunctional and chiral macrocyclic cryptand 2 from the bis(N,N-dimethyl) amide of L-(+)-tartaric acid (Ref. 8). The amide groups in 2 may be used for the attachment of various structural units X which line the periphery of the central cavity. With such derivatives it should be possible: (i) to influence complexation stability and selectivity via "lateral recognition" between the bound ammonium salt and the residues X whose choice will determine the nature of the interactions (electrostatic, hydrogen bonding, hydrophobic etc.); (ii) to perform molecular polyfunctional *catalysis* if the X units incorporate catalytic groups. A prerequisite for such studies is also that the complexes formed be stable enough for performing tasks (i) and (ii) even in water.



1 X=H

2 X=$CONMe_2$

3 X=$COO^-NMe_4^+$

4 X=L-CONH-CH(CH_2-(3-indole))-$COO^-NMe_4^+$

5 X=$CONH-CH_2-COO^-NMe_4^+$

6 X=L-CONH-CH(CH_2-SH)-CO_2Me

Receptor Properties of Macrocycles of Type 2.

The attachment of amino-acid side chains to 2 via a peptide bond yields "parallel" peptides (as compared to linear oligopeptides), compounds 4, 5, 6. The complexation properties of macrocycles 1-5 are very instructive. Various structural effects may be discerned (Ref. 9).

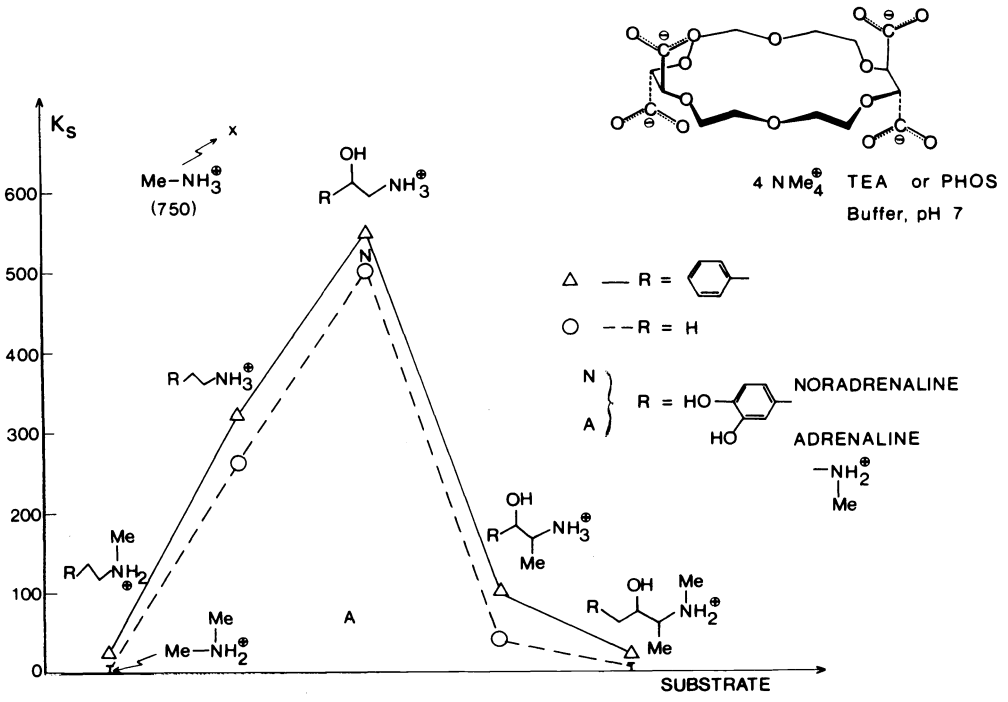


Fig. 3 Structural effects on complexation selectivities of ammonium salts by the macrocyclic tetracarboxylate receptor 3.

Central discrimination between primary ammonium groups R-NH_3^+ and more highly substituted ammonium salts, is very marked. The -NH_3^+ serves as anchoring group by penetrating into the macrocyclic cavity; this becomes sterically more and more difficult as the degree of substitution increases. Thus, primary ammonium salts are much more strongly complexed than secondary ones, as is clearly apparent from the results presented in Figure 3 (Ref. 10). Strong discrimination is observed within the pairs $CH_3NH_3^+/(CH_3)_2NH_2^+$, noradrenaline/adrenaline, norephedrine/ephedrine. This selectivity is of special interest in the latter two cases in view of the physiological activities of these substrates.

Lateral discrimination is obtained by changing side groups. Figure 4 shows the structural effects on complexation of the K^+ cation. Additional data are found in Figure 3 and in Ref. 9. Electrostatic, hydrophobic and charge transfer effects are observed. The tetracide 3 forms by far the most stable K^+ and R-NH_3^+ complexes reported to date for a macrocyclic polyether, emphasizing the primordial role of electrostatic interactions. Comparing the compounds containing tryptophanate, 4, and glycinate, 5, residues the much higher stabilities observed for both K^+ and R-NH_3^+ may be attributed to the effect of the lipophilic indole groups which shield the carboxylates from solvation and increase the contribution of ion-pairing interaction with the bond ammonium group. Diammonium salts bind especially strongly. These effects are all illustrated by the stable complex 7 of a

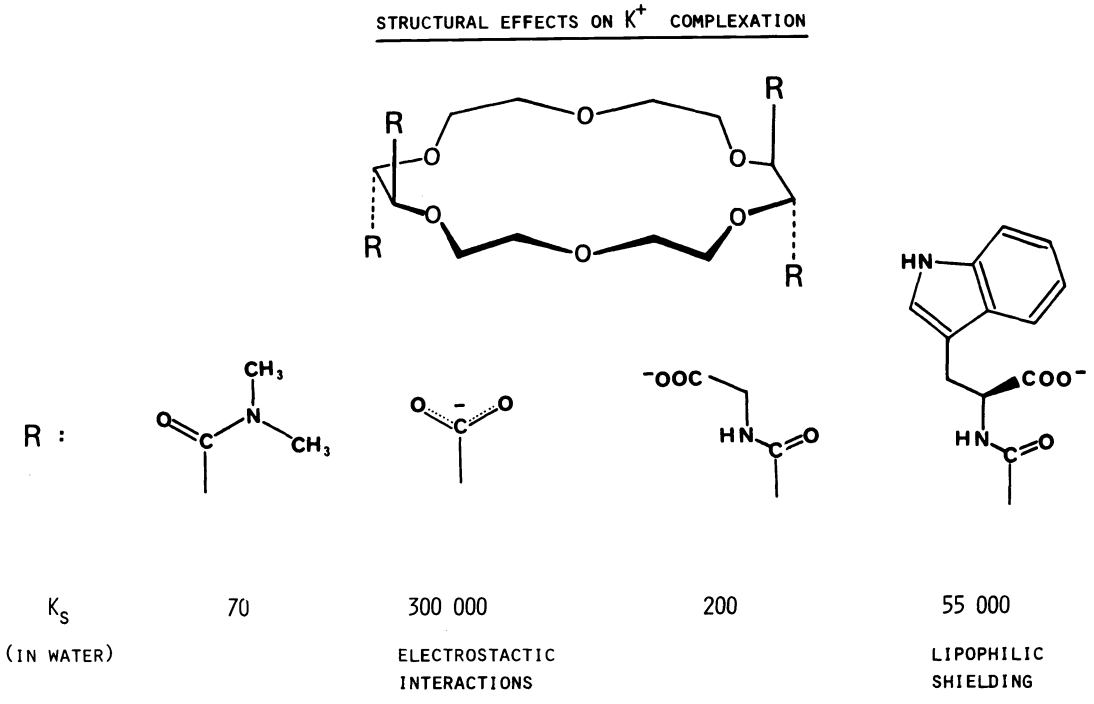
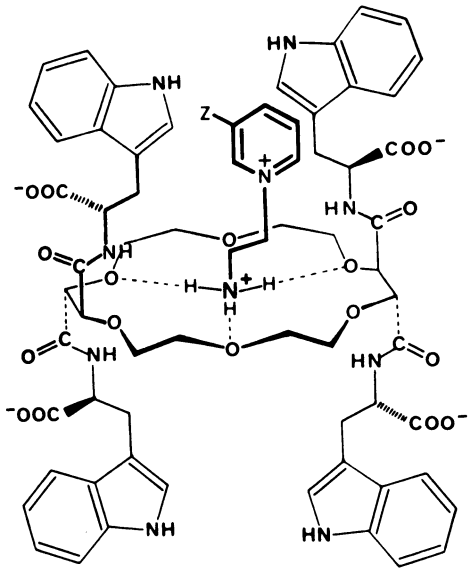


Fig. 4 Structural effects on the complexation of the potassium cation by the macrocyclic receptors 2-5.

nicotinamide derivative with 4: anchoring of NH_3^+ into the ring, electrostatic interactions between the carboxylate groups and the two ammonium sites, lipophilic enhancement of the electrostatic interaction by the indole residues, donor-acceptor interaction between the indole and pyridinium groups as shown by a charge-transfer band in the electronic spectrum (Ref. 9).

A Guanidinium Receptor.

A hexacarboxamide 27-crown-9 is obtained in small quantity in the preparation of 2 (Ref. 11). Such a ring system has been shown to complex guanidinium salts (Ref. 12) but again the carboxylate groups very markedly enhance the complexation properties yielding a very stable guanidinium complex 8 (stability constant about 6500 in water). Central discrimination is also observed: the stability constants decrease markedly for monosubstituted guanidinium groups and become very weak for instance with tetramethylguanidinium. These substituent effects confirm that guanidinium is bound inside the macrocycle in a array of hydrogen bonds and electrostatic interactions represented schematically in structure 8.



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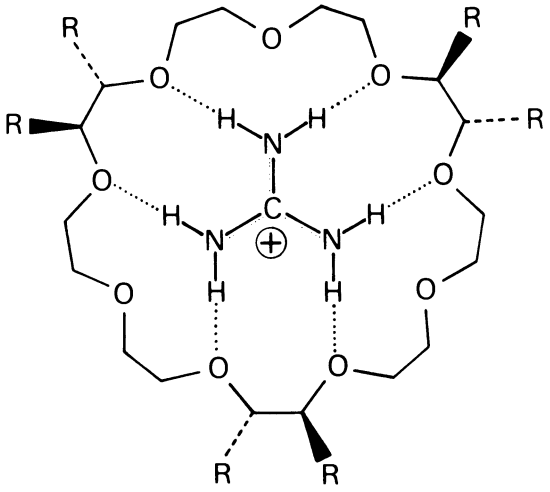


8 R=$COO^{-}NMe_4^{+}$

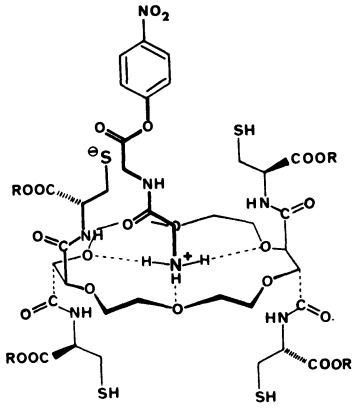
Since the guanidinium group of arginine still forms a sufficiently stable complex, the ligand in 8 may be expected to display interesting binding properties towards the arginine rich peptides and proteins associated with the nucleic acids (protamines, nucleohistones).

The high stabilities of the complexes of the macrocyclic polycarboxylates 3 and 8 and the strong destabilizing effects of substituents confirm that the largest contribution to stability arises from electrostatic cation-anion interaction, whereas the selectivity is due to binding of the primary ammonium and guanidinium groups inside the circular cavity of the macrocycle.

Molecular Catalysis: Enhanced Rates of Hydrogen Transfer and of Deacylation in Molecular Complexes.

Synthetic molecular catalysts which provide both a receptor site for substrate binding and a reactive site for transformation of the bound substrate are of interest as enzyme models or as new types of efficient and selective chemical reagents. Utilisation of the substrate binding properties of cyclodextrins lead to derivatives displaying rate enhancement (Ref. 13) and stereospecificity (Ref. 14). Macrocyclic compounds containing a hydrophobic cavity (Ref. 15) and a reactive site have been synthesized. Recently functionalized macrocyclic polyethers have been shown to display substantially enhanced rates of thiolysis of amino-ester salts (Ref. 16) and of hydrogen transfer from a 1,4-dihydropyridine to a sulfonium salt (Ref. 17).

We have observed accelerated (factor ∿ 150) rates of thiolysis for the reaction of the cysteinyl-crown catalyst 6 with complexed diglycine p-nitrophenyl hydrobromide (see structure 9). The intracomplex reaction is inhibited by addition of potassium cation and shows substrate and chiroselectivity: dipeptide esters react faster than aminoacid esters and glycyl-L-phenylalanine ester reacts faster (factor ∿ 6) than its antipode (Ref. 18).



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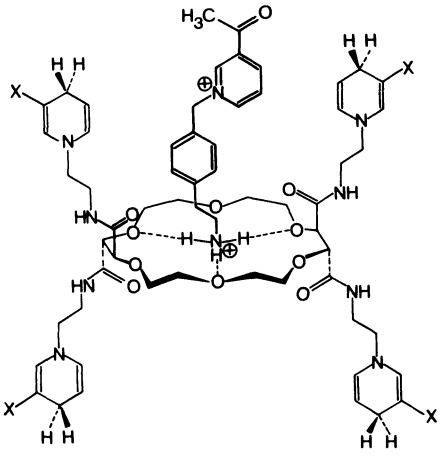


10 X=CONHBu

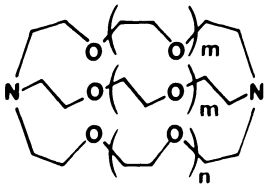
When 1,4-dihydropyridyl side-chains are attached to the macrocyclic ammonium receptor 2, enhanced rates of hydrogen transfer to bound pyridinium salt substrates are observed. Structure 10 represents one of the receptor-substrate complexes studied. The intracomplex 1,4- dihydropyridine to pyridinium hydrogen transfer is inhibited by addition of a complexable cation which displaces the substrate (Ref. 19).

Systems like 9, 10 and those described by other groups (Ref. 16 and 17) diplay some of the features which molecular catalysts should possess. Larger acceleration factors and higher specificities should be obtained with more rigid receptors (of higher cyclic order) containing properly oriented reactive sites and transition state binding sites, held in position by additional bridges. They should also provide means of studying the mechanism and stereochemistry of the reactions involved.

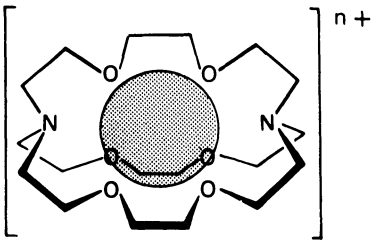
MACROBICYCLIC CRYPTATES

Macrobicyclic ligands in their *in-in* conformation contain an internal cavity of about spherical shape well suited for the *recognition of spherical cations*, the alkali and alkaline-earth cations (AC's and AEC's). Indeed macrobicyclic molecules like 11-13 (Ref. 20) form, with many metal cations, inclusion complexes (Ref. 21), *cryptates*, in which the cation is contained in the center of the molecular cavity of the macrobicycle

in the *in-in* form (see 14).



11 [2.1.1] m=0, n=1
12 [2.2.1] m=1, n=0
13 [2.2.2] m=n=1



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The *stabilities* of the complexes with suitable AC's and AEC's, are several orders of magnitude higher (Ref. 22) than those of natural (Ref. 23) or synthetic macrocyclic ligands (Ref. 4). Cryptands 11-13 thus function as *receptors* for spherical cations. The importance of the bicyclic topology is shown by a very large *macrobicyclic cryptate effect* on stabilities: the stability of the $[K^+ \subset 2.2.2]$ cryptate is higher by a factor of about 10^5 than the stability of the K^+ complex of a comparable monocyclic ligand (Ref. 22). A similar effect is found for AEC's (e.g. $[Ba^{2+} \subset 2.2.2]$) which also form very stable cryptates.

The AC and AEC cryptates display *cavity selectivity*, the preferred cation being that whose size fits the cavity. Lengthening of the bridges of the macrobicycle causes a gradual increase in cavity size, the cryptands [2.1.1], [2.2.1] and [2.2.2] complex preferentially Li^+, Na^+ and K^+ respectively. They present peak selectivity, whereas larger systems of this type display plateau selectivity (Ref. 22). Control over the M^{2+}/M^+ selectivity between AEC's and AC's has also been achieved by suitable structural modifications (Ref. 24).

The special complexation properties of the macrobicyclic ligands, define a *cryptate effect* characterized by a *high stability*, a *high selectivity* of complexation and efficient *shielding* of the complexed cation from the environment.

Effect of Binding Sites.

The replacement of oxygen binding in cryptands 11-13 by nitrogen or sulfur leads to a decrease in stability and selectivity of the AC and AEC complexes. However new interesting complexation properties are found with other cations. Only two examples will be mentioned here.

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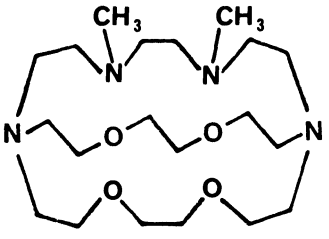

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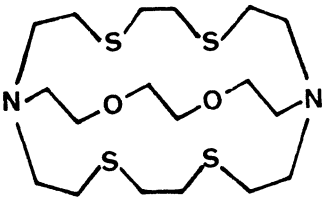
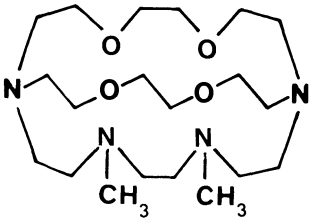


Cryptand 15 shows a very high selectivity for Cd^{2+}, Hg^{2+}, Pb^{2+} while complexing the biologically important cations Zn^{2+} and Ca^{2+} much less strongly (Ref. 25). Figure 5 illustrates the case of Cd^{2+} and shows that this selectivity is due to a double parameter discrimination: the nitrogen binding sites of 15 favour Cd^{2+} and Zn^{2+} over Ca^{2+} whereas its cavity fits better Cd^{2+} and Ca^{2+} than the small Zn^{2+} cation. The selectivities are even higher for Pb^{2+} with respect to Zn^{2+} and Ca^{2+}. Thus, cryptands like 15 or derivatives using similar principles, may represent important assets in the control of *toxic heavy metal cations* in the environment or in organisms. Cryptand [2.2.2] has been used for the decorporation of radioactive strontium from contamined organisms (Ref. 26).

	Cd^{++}	Zn^{++}	Ca^{++}
IONIC RADIUS Å	1.03	0.83	1.06
BINDING SITES PREFERENCE	O<N	O<N	N<O



CAVITY RADIUS 1.4 Å

LOG K_S (WATER; 25°)		
12.0	6.0	4.3

SELECTIVITIES	Cd/Zn	Cd/Ca
	10^6	$5x10^7$

Fig. 5 Selective complexation of cadmium versus zinc and calcium by cryptand 15. Double parameter discrimination: ionic radius and binding site preference.

The sulfur containing cryptand 16 (Ref. 27) markedly stabilizes the Cu(I) oxidation state. A solution of the green cryptate $[Cu^{2+} \subset$ 16] becomes colourless in the presence of an alcohol for instance; the Cu(I) cryptate formed is stable in air. Thus cryptates may stabilize uncommon oxidation states. Another example is provided by the stabilization of Eu(II) in its cryptate with [2.2.2] (Ref. 28).

The numerous utilizations of macrobicyclic cryptates in organic and inorganic chemistry have been reviewed recently (Ref. 2) and will not be mentioned here.

BINUCLEAR CRYPTATES

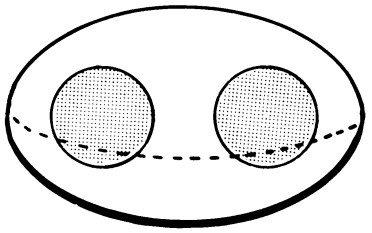
Macrobicyclic ligands incorporating two or more separate receptor sites for metal cations may form binuclear or polynuclear inclusion complexes, *polynuclear cryptates*, in which the distance and arrangement of the cations, held inside the molecular cavity, may be regulated via ligand design. They provide a novel entry into the study of cation-cation interactions at short distances. At larger intercationic separation, inclusion of a substrate bound between the cation leads to *cascade complexes* via a sequential, double selection process: selection of the cations by the ligand receptor sites, selection of the substrate controlled by the nature and arrangement of the complexed cations. Cascade complexes may allow selective fixation and transport of a substrate as well as the development of new bi-(or poly-) nuclear catalysts for multicenter-multielectronic processes (condensation of two or more included substrates held in proximity, O_2 and N_2 reduction, water splitting, etc.). In addition, the polynuclear cryptates may also serve as bioinorganic models for metalloproteins (hemocyanin, hemerythrin, copper proteins, oxidases etc.).

We have studied two types of systems using two different structural units as basic building blocks for the controlled organization of cations in space, the tripod and the macrocyclic subunits:

(i) coaxial arrangement of two tripod subunits linked by three bridges leads to macrobicyclic Bis-Tripod systems;

(ii) face-to-face linkage of two macrocycles forms *cylindrical macrotricyclic cryptands*.

In these systems, each subunit is a receptor site for a metal cation, forming *binuclear cryptates*. The distance of the cations depends on the length of the bridges linking the subunits. In both cases a central cavity may be available for substrate inclusion. These two types of binuclear cryptates are schematically represented by structure 17 and 18.



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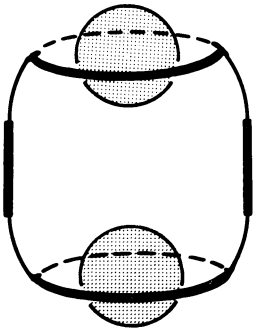

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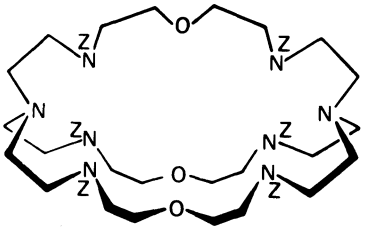
MACROBICYCLIC BINUCLEAR CRYPTATES - THE BIS-TREN SYSTEM

Since the Tren ligand $N(CH_2CH_2NH_2)_3$ displays remarkable complexation properties toward transition metal cations (Ref. 29), we decided to incorporate such units at the two poles of a macrobicyclic system. The synthetic strategy followed that developed earlier for the macrobicycles 11-13 (Ref. 20). Using $CH_2CH_2OCH_2CH_2$ segments as bridges linking the two Tren subunits, the Bis-Tren macrobicycle 19 has been obtained (Ref. 30).



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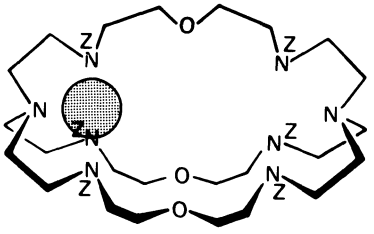

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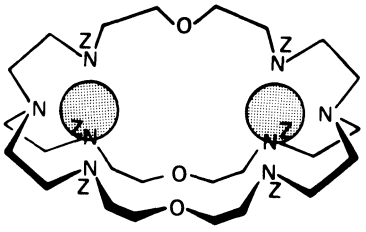

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The *in-in* form 19 is suited for complexation of two cations, one at each end of the ellipsoidal cavity. Binuclear cryptates $[2M^{n+} \subset 19]$ have been prepared for Zn(II), Cu(II), Co(II) cations. The intercationic distance may be grossly estimated at about 5 Å . The stability constants have not yet been determined but should lie in the range of above those of Tren itself (Ref. 29). A proton NMR study of the complexation of Zn(II) shows the successive formation of the mononuclear, 20, and binuclear, 21, complexes. Both intramolecular (left to right) and intermolecular cation exchange is slow in 20.

The powder ESR spectrum of the $[2Cu^{2+} \subset 19]$ complex is in agreement with an environment of axial symmetry for the copper cations; the presence of a weak signal at half field indicates cation-cation interaction .

Some indication about the interaction of 21 with substrates has been obtained; changes in the EPR and/or UV spectra are observed on addition of H_2O, CN^- and N_3^- to acetonitrile solutions of the bis-Cu(II) complex. Further studies about the formation, isolation and properties of cascade complexes are in progress.

BINUCLEAR CRYPTATES OF CYLINDRICAL MACROTRICYCLIC LIGANDS

Cylindrical macrotricyclic ligands are formed by two macrocycles linked by two bridges. 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 the lateral and central cavities. Among the various synthetic strategies (Ref. 1) which lead to such systems, the two paths A and B represented in Figure 6 have

been used at present. Scheme A allows the introduction of different bridges, while path B may yield macrotricycles incorporating two different macrocyclic subunits.

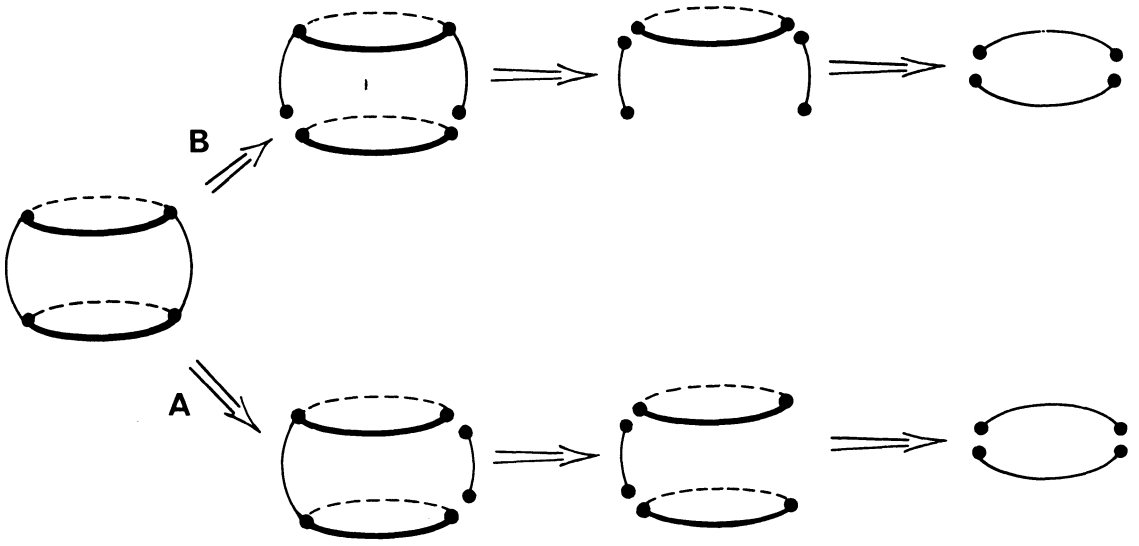
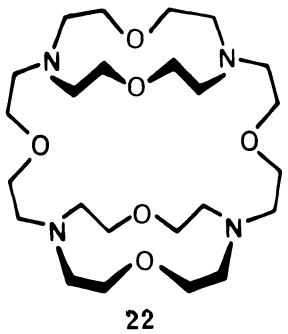


Fig.6 Two different synthetic strategies for the construction of cylindrical macrotricyclic systems.

Cryptates of Polyoxa Macrotricycles.

The first cylindrical macrotricycles to be described, compounds 22-24 and analogs, contain oxygen and nitrogen binding sites (Ref. 31-33). The smaller ligand 22 gives a binuclear complex $[2Ag^{+} \subset 22]\ Ag(NO_3)_3^{2-}$ (Ref. 31) whose crystal structure shows that the two silver cations are located inside the central cavity, each on top of one of the rings and at a distance of 3.88 Å (Ref. 34).



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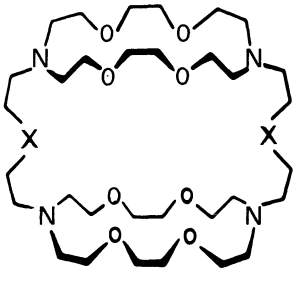
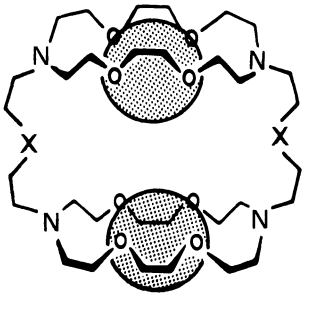


23 X=O

24 X=CH_2



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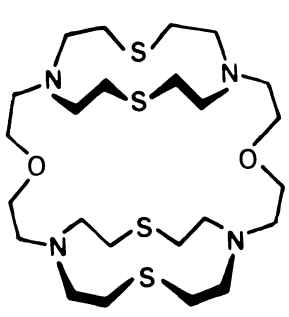
Ligands 23 and 24 have been obtained following scheme A in Figure 6 (Ref. 32). They form binuclear cryptates 25 with several AC's and AEC's as well as with Ag^+ and Pb^{2+}; a heteronuclear complex $[Ag^+Pb^{2+} \subset 23]$ has also been observed (Ref. 33). The crystal structure of $[2Na^+ \subset 23]\ 2I^-$ shows that the Na^+ cations penetrate partially the top and bottom macrocyclic cavities and are located 6.40 Å apart (Ref. 35). The binuclear AC and AEC cryptates of 23 and 24 have appreciable stability, even highly charged species like $[2Ba^{2+} \subset 23]$; the results show that the larger macrotricycles like 23 and 24 contain two almost independent macrocyclic units (Ref. 33). The mononuclear AEC complexes of 22 display intra-molecular cation exchange (Ref. 36); the same process is probably present in the complexes of 23 and 24 (Ref. 33).

Binuclear Transition Metal Cryptates of Polythia Macrotricyclic Ligands.

Binuclear cryptates of transition metals, of special interest for the reasons outlined above, require the introduction of suitable binding sites in the ligand.

We have developed a general synthetic strategy which allows the introduction of different macrocyclic subunits following path B of Figure 6. It involves: a) attachment of two appendages at diagonally opposed positions of a suitable macrocycle; b) activation of the free termini of these appendages; c) condensation with the second macrocycle. Such systems may complex two different cations and/or stabilize different oxidation states.



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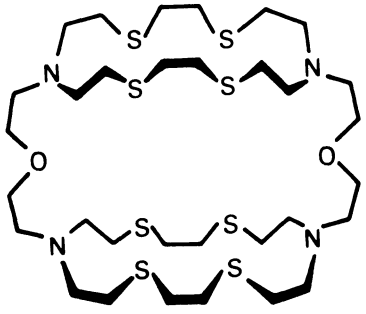

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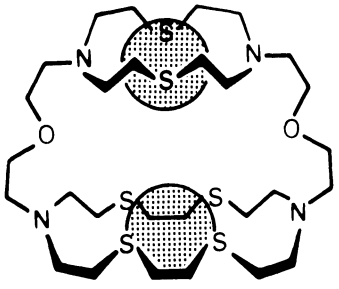


29

Three polythia cylindrical macrotricycles containing twelve membered $-N_2S_2$ and eighteen-membered-N_2S_4 units have been obtained at present: [12]-[12] 26, [18]-[18] 27, and [12]-[18] 28 (Ref. 37). The synthetic sequence is represented in Figure 7 for the dissymmetric macrotricycle 28. All three ligands 26-28 form *binuclear cryptates* by complexation of two transition metal cations, one on each macrocyclic subunit (see for instance 29).

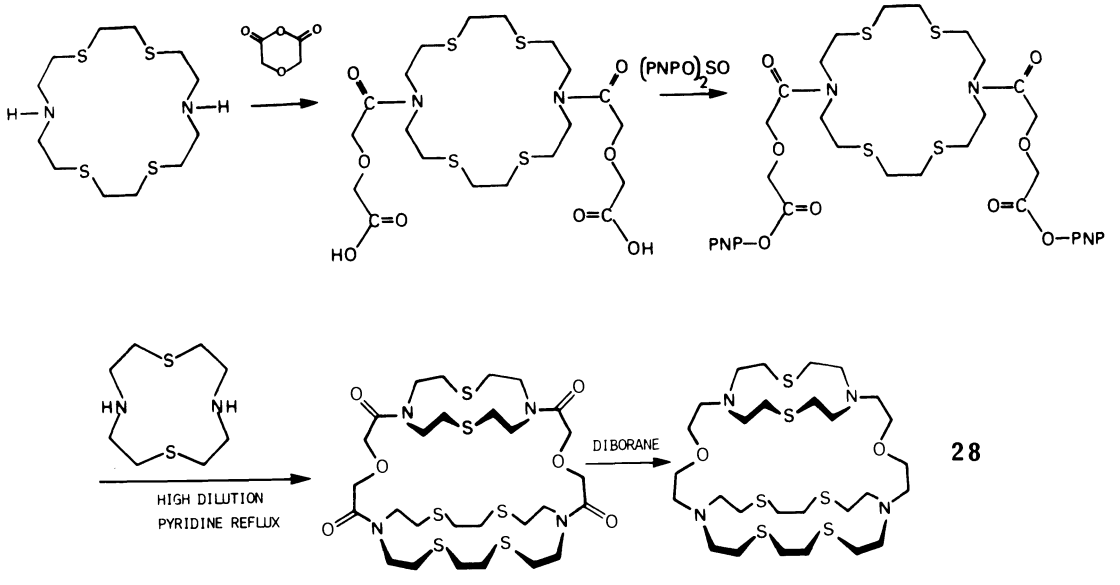


Fig. 7 Synthetic sequence for the preparation of the dissymmetric ligand 28.

For the moment most of our work has been concerned with the Cu(II) and Cu(I) complexes (Ref. 37). Bis-Cu(II) and Bis-Cu(I) complexes of ligands 26-28 have been obtained. Ligand 28 forms a mixed complex 29 in which the Cu(I) and Cu(II) cations are probably located in the 18- and 12-membered rings respectively. The electronic absorption spectra, the EPR properties and the redox potentials of the bis-Cu(II) complexes present interesting features and ressemble those of polythia-macrocycles (Ref. 38) and of copper proteins (Ref. 39). An intense absorption band is present in the visible region around 600 nm. Electrochemical reduction of [2Cu(II) ⊂ 26] 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 and (Ref. 38) of copper proteins (Ref. 39).

The difference between mononuclear and binuclear species is clearly apparent in the EPR powder spectra shown in Figure 8. Both spectra are of the axial type, but the monocyclic Cu(II) complex has $g_{//} < g_{\perp}$ whereas the reverse holds for the binuclear species [2Cu(II) ⊂ 26]; the value of the parameter $G < 4.0$ is indication for Cu-Cu exchange coupling. Furthermore, in the frozen solution EPR spectra the same monocyclic complex shows a normal $A_{//}$ hyperfine splitting (0.015 cm^{-1}) whereas the binuclear species displays a small $A_{//}$ splitting ($\sim$ 0.008 cm^{-1}) similar to the values found in copper proteins (Ref. 39).

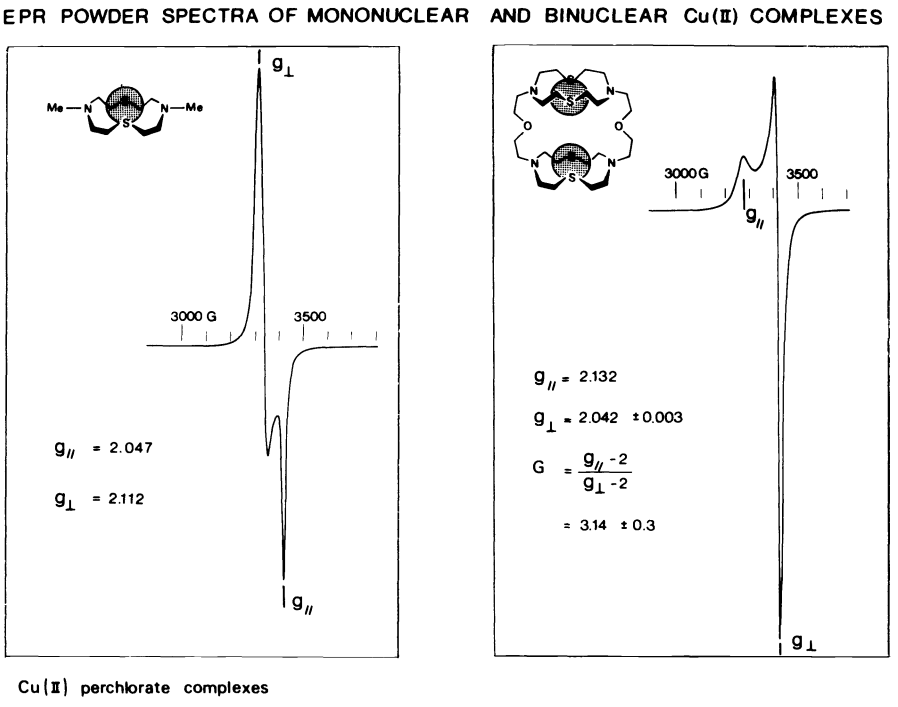


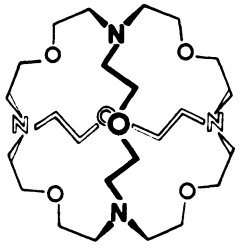
Fig. 8 EPR powder spectra of the binuclear bis-Cu(II) complex of ligand 26 and of the corresponding mononuclear macrocyclic complex (left).

The intercationic distances in the binuclear complexes of 26, 27 and 28 may be estimated to be about 5, 6 and 7 Å respectively. The crystal structure of [2Cu(II) ⊂ 26] confirms the binding of a Cu(II) cation to each macrocycle and gives a Cu-Cu distance of 5.6 Å (Ref. 40). Thus, there is space between the two cations for inclusion of a substrate of compatible size and of suitable binding properties. No definitive evidence for such processes has yet been obtained but spectral changes due to reaction of [2Cu(II) ⊂ 26] with potassium superoxide and of [2Cu(I) ⊂ 26] with oxygen have been observed. They might involve binuclear processes. Further work is in progress.

SPHERICAL MACROTRICYCLIC RECEPTORS AND THEIR CRYPTATES

The first spherical macrotricycles to be synthesized, cryptand 30, contain four nitrogen sites and six oxygen sites located respectively at the corners of a tetrahedron and an octahedron (Ref. 41). In its i_4 form, 30 contains a spherical cavity which should be ideal

for *spherical recognition*. The earlier studies on the properties of spherical cryptands have been reviewed (Ref. 2); we shall only briefly recall the major results and mention some new data.



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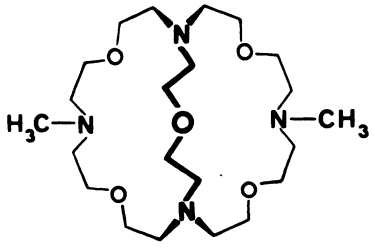


31

Cation and Molecule Cryptates.

Ligand 30 forms stable cryptates with the spherical AC's and AEC's (Ref. 41).

Molecule cryptates are formed with small inorganic polyatomic species. The tetrahedral arrangement of the nitrogen sites makes ligand 30 the topologically *optimal receptor for the ammonium ion* : $[NH_4^+ \subset 30]$ (Ref. 42). The NH_4^+ cation is held in a tetrahedral array of N^+—H....N hydrogen bonds; the six oxygen sites bring further stabilization by two combined effects: six electrostatic $O \rightarrow N^+$ interactions and twelve bent hydrogen bonds N^+—H....O (Fig. 9). The structure has been confirmed by crystallographic analysis (Ref. 43). Preliminary measurements show that the $[NH_4^+ \subset 30]$ cryptate is indeed very stable (in the 10^5-10^6 range). Exchange of the cation is very slow. Furthermore the *effective* pK_a of NH_4^+ in the complex is close to 14; in other words the strong binding of NH_4^+ leads to an increase in pK_a of 4-5 powers of ten! (Ref. 43). This effect has relevance to pK_a changes in enzyme active sites and biological receptor sites; it clearly illustrates the very large changes which may occur on binding of a substrate.

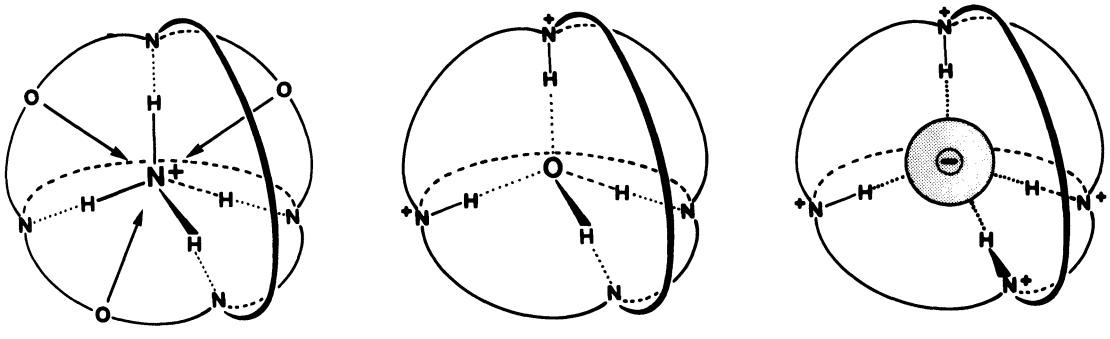


Fig. 9 Tetrahedral binding of NH_4^+ (left), H_2O (center) and Cl^- (right) by the spheroïdal macrotricyclic ligand 24 (left), its diprotonated form (center) and its tetraprotonated form (right). For the NH_4^+ complex (left) only four of the six possible electrostatic $O \rightarrow N^+$ interactions are shown.

Cryptand $\underline{\underline{30}}$ has also interesting acid-base properties: (i) the second protonation is as easy as the first one ($pK_1 \sim pK_2 \sim 10.5$) whereas the third one is much more difficult ($pK_3 \sim 5.3$); (ii) proton exchange between the diprotonated and unprotonated species is very slow even at pH 10.7 ($< 20\ sec^{-1}$ at 25°C); (iii) for comparison, the macrobicycle $\underline{\underline{31}}$ displays normal decreasing pK_a's and fast proton exchange. These results agree with the formulation of the diprotonated species as a *water cryptate* , $[H_2O \subset \underline{\underline{31}}\text{-}H_2^{2+}]$ (Fig. 9). The water molecule is held in an ideal tetrahedral array of hydrogen bonds; it accepts two $N\text{-}H^+ \ldots O$ bonds from the protonated nitrogen sites and donates two O-H...N hydrogen bonds to the unprotonated nitrogen sites, the whole system undergoing fast, synchronous, proton exchange: $\overset{+}{N}\text{—}H \ldots O\text{—}H \ldots N \rightleftharpoons N \ldots H\text{—}O \ldots H\text{—}\overset{+}{N}$. The high pK_2 of cryptand $\underline{\underline{30}}$ may be considered as a *positive cooperativity* effect mediated by the effector molecule, H_2O; it is due to the special stabilization of the diprotonated species by the complexed water molecule. Since on exchange of H_2O, the NH^+ protons would probably also exchange the results indicate that the complexed water molecule undergoes slow exchange; this point is being studied using oxygen-17 NMR spectroscopy in ^{17}O-enriched water. The two cryptates $[NH_4^+ \subset \underline{\underline{30}}]$ and $[H_2O \subset \underline{\underline{30}}\text{-}H_2^{2+}]$ indicate that the spherical macrotricycle $\underline{\underline{30}}$ is a *molecule receptor* displaying *tetrahedral recognition*.

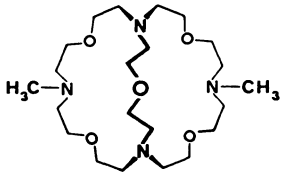
Spherical Anion Cryptates.

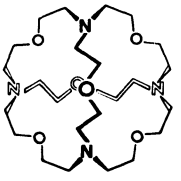
In their tetraprotonated form the spherical macrotricycles become *receptors for spherical anions* of suitable size. They form macrotricyclic anion cryptates $[X^- \subset LH_4^{4+}]$ with halide anions held in a tetrahedral array of $N^+\text{—}H \ldots X^-$ hydrogen bonds inside the cavity of the tetraprotonated ligand in its i_4 form as confirmed by the crystal structure of $[Cl^- \subset \underline{\underline{30}}\text{-}H_4^{4+}]\ 3Cl^-,\ 7\ H_2O$ (Ref. 43). The stability constants of the anion cryptates of ligands $\underline{\underline{30}}$-$\underline{\underline{32}}$ are listed in Figure 10. The unique very high stability and selectivity of the $[Cl^- \subset \underline{\underline{30}}\text{-}H_4^{4+}]$ cryptate is evidence for a marked *macrotricyclic effect*: the presence of closed and rigid cavity of suitable size holding a stereochemically optimal array of hydrogen bonding sites. The macrobicyclic analog $\underline{\underline{31}}$ forms anion complexes with much lower stability and selectivity. The same holds for the halide katapinates and diprotonated macrobicyclic diamines (Ref. 45).

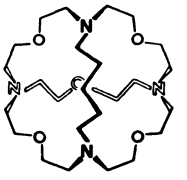
ANION CRYPTATES

STABILITIES/SELECTIVITIES/ [3]-CRYPTATE EFFECT

Log K_S







32

ANION				
Cl^-	W	1.7	⩾4.0	⩾4.5
	M/W	3.1	-	-
Br^-	W	<1.0	<1.0	1.55
	M/W	1.7	1.75	3.2

METHOD : ANION SELECTIVE ELECTRODES

PH : 1.50 W ; 1.30 M/W 9/1

Fig. 10 Stability constants (log K_S) of the halide ion cryptates with the spherical macrotricycles 30, 32 and the macrobicycle 31 (in aqueous, W, or methanol/water 9/1 solution) (Ref. 44).

Recently, interesting results about quaternary ammonium salts of 30 and of larger ligands (obtained by the same synthetic scheme as 30) have been described; they also form macrotricyclic anion cryptates (Ref. 46). The lower stabilities and selectivities found emphasize the role of a suitably designed array of ionic hydrogen bonds in achieving high stabilities and selectivities.

It is clear that elongation of the bridges of the macrotricycle 30 increases cavity size and should allow complexation of larger anions, in a manner similar to the changes in cavity size and cation complexation properties of the macrobicyclic cryptands 11-13 (Ref. 22). Thus it should be possible to produce a range of anion complexation stabilities and selectivities by designed structural modification of the basis spherical structure 30.

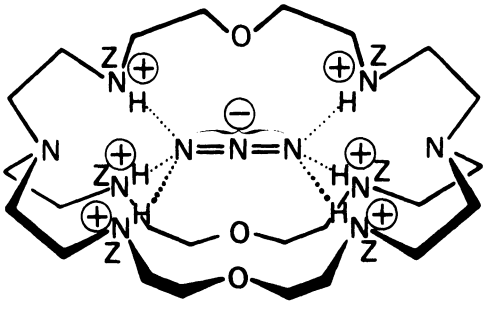
MACROBICYCLIC RECEPTORS FOR TRIATOMIC SPECIES

Like there is a coordination chemistry for cations, the development of a *coordination chemistry for anions* appears feasible. The major task of ligand design consists in providing a cavity of suitable shape and size holding a topologically suitable array of ionic hydrogen bonds while hindering as much as possible the solvation of the

hydrogen bond donor sites. The stereochemical requirements of intermolecular hydrogen bonding being softer than those associated with covalent bonds, receptor-substrate complementarity is less stringent in terms of angular orientation than of spatial location of the hydrogen bonds.

The spherical anion cryptates mentioned above represent a first set of systems. As a further step the binding of triatomic anions or anionic groups was investigated. Inversion of the binding properties of the Bis-Tren ligand 19 by protonation of the six nitrogen sites in the bridges should afford an ellipsoïdal cavity lined with three $\overset{+}{N}$—H hydrogen bond donor sites around each pole. The size of the cavity also appears to be suitable for triatomic species ABC where A,B,C are atoms of the first row.

It has been found that addition of sodium azide to an aqueous solution of cryptand 19 at pH 5 yields marked changes in the carbon-13 NMR spectrum. Analysis of the data indicates the formation of a complex of 1/1 stoichiometry and high stability. The results agree with the formulation of this species as an *azide cryptate* $[N_3^- \subset 19\text{-}H_6^{6+}]$ in which the linear N_3^- anion is held in the molecular cavity by six hydrogen bonds, three of them surrounding each terminal nitrogen of the anion, as schematically represented in structure 33 (Ref. 47). The hexaprotonated ligand ($19\text{-}H_6^{6+}$) is thus a *receptor for triatomic species* . Preliminary measurements indicate that other anions are less well complexed. The carboxylate $R\text{-}CO_2^-$ group is locally triatomic but non-linear; its binding is being investigated.



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It may be noted that in the vast majority of cases, biological systems make use of charged receptors and charged substrates for efficient binding and recognition, the most important anionic sites being carboxylate and phosphate. The development of abiotic receptors and carriers for these groups is in progress. Since anions are expected to bind more strongly than neutral molecules because of larger electrostatic interactions, the design of ligands for anions also opens the way to the binding of neutral molecules. A most interesting case would be the complexation (and activation) by ($19\text{-}H_6^{6+}$) of the CO_2 (and N_2O) molecule whose size and shape are close to those of N_3^-.

PROSPECTS

The prospects for the chemistry of macropolycyclic systems and their cryptates have been considered earlier (Ref. 1 & 2). It suffices to note here that the development of abiotic macropolycyclic receptors, carriers and catalysts for cationic, anionic or neutral substrates should have broad impact in various fields of organic, inorganic and biological chemistry, and span wide areas from building a body of chemistry of the intermolecular bond to activation of bound species, via ammonium binding, phosphate transport, polynuclear metal cation catalysis, bioorganic modelling, environment protection etc.

ACKNOWLEDGEMENTS

I wish to express my gratitude to the coworkers whose skill and dedication allowed to realize the work described above. Their names appear in the references listed. The expenses incurred were borne by grants from the Centre National de la Recherche Scientifique and the Délégation Générale à la Recherche Scientifique et Technique.

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