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Supramolecular Chemistry: Receptors, Catalysts, and Carriers

Jean-Marie Lehn

Summary. Supramolecular chemistry is the study of the structures and functions of the supermolecules that result from binding substrates to molecular receptors. Macropolycyclic receptors and coreceptors have been designed that form cryptate inclusion complexes and display molecular recognition towards spherical, tetrahedral, and linear substrates of various kinds (metal cations, inorganic anions, and organic or biological cations or anions). Anion binding has led to the development of anion coordination chemistry. Metalloreceptors simultaneously bind organic molecules and metal ions; speleands combine polar and nonpolar binding subunits. Receptors bearing reactive functional groups may act as molecular reagents or catalysts, performing a chemical transformation on the bound substrates (by such reactions as hydrogen transfer, ester cleavage, and protoadenosinetriphosphatase and protokinase activities). Receptors fitted with lipophilic groups can operate as molecular carriers, translocating bound species through a membrane; this transport can be coupled to chemical potentials (proton and redox gradients).

Beyond molecular chemistry based on the covalent bond lies supramolecular chemistry based on molecular interactions—the associations of two or more chemical entities and the intermolecular bond (*1–3*).

Molecular interactions are the basis of the highly specific processes that occur in biology, such as a substrate binding to an enzyme or a receptor, the assembling of protein complexes, intermolecular reading of the genetic code, signal induction by neurotransmitters, and cellular recognition. The correct manipulation of the energetic and stereochemical features of the noncovalent, intermolecular forces (electrostatic forces, hydrogen bonding, van der Waals forces, and so forth) within a defined molecular architecture should allow the design of artificial receptor molecules capable of binding substrate species strongly and selectively, forming supramolecular entities, so-called supermolecules, of well-defined structure and function. One might say that supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond (*4*).

In order for the receptor to "recognize" a potential substrate and bind to it, the two species must complement each other both in size and shape (geometry) and binding sites (energy). This extends Emil Fischer's "lock and key" concept from steric fit to other, intermolecular, properties.

Receptor chemistry, therefore, may be considered generalized coordination chemistry. It extends the purpose of designed organic complexing agents from the coordination of transition metal ions, for which they were first used, to the coordination of all kinds of substrates: cationic, anionic, and neutral species of an inorganic, organic, or biological nature.

In addition to binding sites, the receptor may bear reactive sites that transform the bound substrate, which would make the receptor a molecular reagent or catalyst. If it is fitted with lipophilic groups that allow it to dissolve in a membrane, it may act as a molecular carrier. Thus, the functional properties of a supermolecule cover molecular recognition, catalysis (transformation), and transport (translocation) (Fig. 1) (*4*).

Macropolycyclic Receptors

Molecular recognition requires that a receptor and its substrates be in contact over a large area. Thus, artificial receptors must contain intramolecular cavities sufficiently large to allow substrate inclusion as well as structural elements that endow the three-dimensional framework with planned geometric and dynamic features (a balance between flexibility and rigidity). This leads to concave, hollow molecules of defined architecture that can bind substrate species by multiple noncovalent interactions.

Macropolycyclic architectures, in principle, meet the requirements. Being large (macro) and highly connected (polycyclic), they are suitable for the construction of molecules containing the cavities, clefts, and pockets that provide the framework for arrangement of binding sites, reactive groups, and bound species.

The binding of a substrate by a macropolycyclic receptor forms an inclusion complex, a cryptate, in which the substrate is contained inside the molecular cavity (crypt) of the ligand (cryptand). Although we introduced cryptates as a class of cation-inclusion complexes (*5*), they may be considered a general type of compound, independent of the nature of the receptor and substrate. As our work progressed to include several classes of macropolycyclic structures—macrocycles, macrobicycles, and cylindrical and spherical macrotricycles (Fig. 2)—the initial studies of macrobicyclic cationic cryptates expanded into the study of the structures and functions of supermole-

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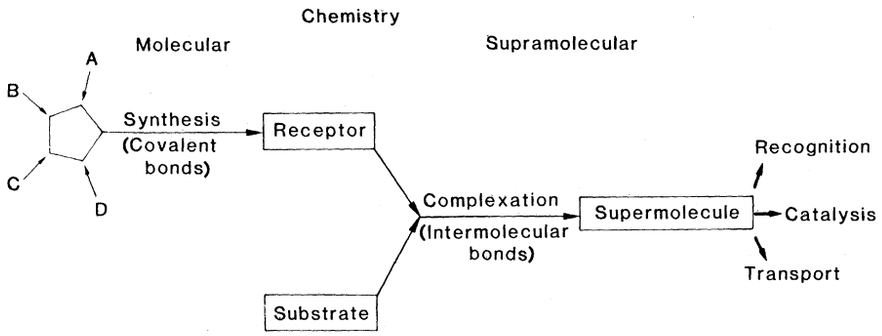


Fig. 1. From molecular to supramolecular chemistry.

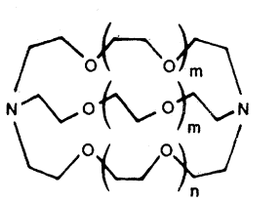
cules, covering the design of artificial molecular receptors, catalysts, and carriers. These species may be either biomimetic or abiotic since they may either serve as models of biological systems and reactions or provide access to nonbiological systems or processes displaying the efficiency and selectivity of biological ones.

This review will mainly cover molecular recognition and the design of molecular receptors, going from monotopic receptors, which possess a single site for substrate complexation, to polytopic receptors, which contain several binding subunits. Some of the results cited will demonstrate the molecular catalysis and transport properties of supermolecules (*6*).

Spherical Recognition: Cationic Cryptates of Macrobicyclic Ligands

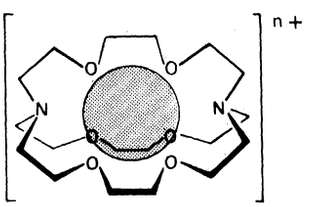
The coordination chemistry of alkali cations developed only about 15 years ago after the discovery that natural (*7*) or synthetic (*8, 9*) macrocycles and macrobicycles (*1, 5, 10, 11*) are powerful ligands. Whereas macrocycles define a two-dimensional, circular hole, macrobicycles define a three-dimensional, spheroidal cavity, particularly well suited for binding the spherical alkali cations (AC) and alkaline-earth cations (AEC).

Indeed, macrobicyclic ligands such as **1** through **3** form cryptates [$M^{n+} \subset$ cryptand], **4**, by inclusion of metal cations inside the molecule. The optimal cryptates of AC and AEC have stabilities



1 m=0, n=1
2 m=1, n=0
3 m=n=1

several orders of magnitude higher than those of either the natural or synthetic macrocyclic ligands. They show pronounced selectivity as a function of the size complementarity between the cation and the intramolecular cavity, a feature termed spherical recognition. As the bridges of the macrobicycle are lengthened from cryptand **1** to **3**, the most strongly bound ion becomes, respectively, Li^+, Na^+, and then K^+. Cryptand **3** also displays a higher selectivity for Sr^{2+} and Ba^{2+} than for Ca^{2+}. Suitable structural modifications can result in a high AC to AEC (M^+ to M^{2+}) selectivity (*1, 5, 10, 11*).



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Cryptands **1** through **3** thus function as receptors for spherical cations. Their special complexation properties result from their macropolycyclic nature and define a cryptate effect characterized by high stability and selectivity, slow exchange rates, and efficient shielding of the bound ion from the environment.

Numerous other macrobicyclic cryptands and cryptates have been obtained. Replacing the oxygen sites in **1** through **3** with sulfur or nitrogen sites yields cryptands that show marked preference for transition metal ions and that allow highly selective complexation of toxic heavy metals such as cadmium, lead, and mercury. Cryptation markedly affects the redox properties of the enclosed metal ion (*12*) and may stabilize uncommon oxidation states such as Eu^{II} (*12a*).

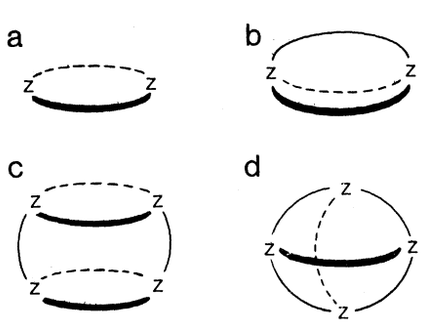
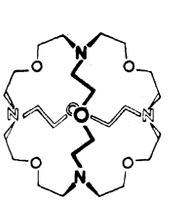


Fig. 2. Some macropolycyclic structures: (a) macrocyclic, (b) macrobicyclic, (c) cylindrical macrotricyclic, and (d) spherical macrotricyclic.

Tetrahedral Recognition by Macrotricyclic Cryptands

Selective binding of a tetrahedral substrate requires the construction of a receptor molecule with a tetrahedral recognition site. This may be achieved by positioning four suitable binding sites at the corners of a tetrahedron and linking them with six bridges. Such a structure, formally a cylindrical macrotricycle, has been realized in the spherical cryptand **5**, which contains four nitrogens located at the corners of a tetrahedron and six oxygens located at the corners of an octahedron, as shown by **6** (*11*).



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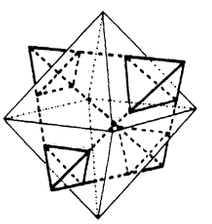

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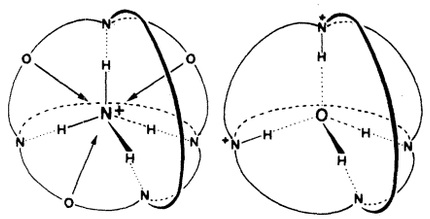
Indeed, **5** binds the tetrahedral NH_4^+ cation exceptionally strongly and selectively (as opposed to K^+) (*13*), forming an ammonium cryptate, designated by [$NH_4^+ \subset$ **5**] and shown as **7**. This complex presents a high degree of structural and binding complementarity between the substrate, NH_4^+, and receptor, **5**. The ammonium ion fits into the cavity of **5**, and it is held by a tetrahedral array of $^+$N–H . . . N hydrogen bonds and by electrostatic interactions with the six oxygens. The strong binding in **7** results in an effective pK_a for the NH_4^+ that is about six units higher than that of free NH_4^+. This illustrates how large may be the changes in substrate properties brought about by binding. Similar changes may take place when substrates bind to enzyme-active sites and to biological receptors.

The remarkable protonation features of **5** led to the formulation of the diprotonated species as the water cryptate, [$H_2O \subset$ **5**–$2H^+$], **8**, in which the water molecule accepts two $^+$N–H . . . O bonds from the protonated nitrogens and donates O–H . . . N bonds to the unpro-

tonated ones (*2, 11*). The second protonation of **5** is facilitated by the substrate; it is considered a "positive cooperativity" effect, which is mediated by H_2O as the effector. When **5** is tetraprotonated, it forms the chloride cryptate [$Cl^- \subset$ **5**–$4H^+$], **9**, in which the included anion is bound by four ^+N–H . . . X^- hydrogen bonds (*2, 11, 14*).

The spherical macrotricycle **5** is thus a receptor molecule possessing a tetrahedral recognition site that binds the substrates in a tetrahedral array of hydrogen bonds, as in **7**, **8**, and **9**. It illustrates the molecular engineering required in abiotic receptor chemistry.



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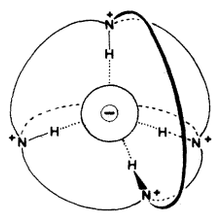

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Chemical Applications of Cryptates

The strong binding of AC's and AEC's by neutral cryptands of types **1** through **3** has led to numerous applications both in pure and applied chemistry. Cryptate formation transforms a small metal cation into a large, spheroidal, organic cation about 10 Å in diameter, a sort of super-heavy AC or AEC. This allows the study of ionic solvation and makes the bound ions more difficult to reduce. The stability of the cryptates and the large distance imposed by the thick organic-ligand shell between the enclosed cation and the environment (both the anion and the solvent) have many physical and chemical consequences (*11, 15–19*).

Cryptate counterions are able to stabilize unusual species such as alkalides, as in ([$Na^+ \subset$ **3**]Na^-) (*17*), electrides, as in ([$M^+ \subset$ cryptand]e^-) (*17*), and anionic clusters of the heavy posttransition metals, as in ([$K^+ \subset$ cryptand]$_2$ Pb_5^{2-}) (*18*).

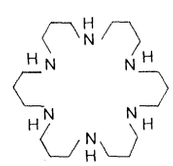
Cryptation promotes the solubilization of salts and dissociation of ion pairs, resulting in strong anion activation. It thus markedly increases the rate of numerous reactions, such as those involving the generation of strong bases, nucleophilic substitutions, carbanion reactions, alkylations, rearrangements, anionic polymerizations, and phase transfer catalyses. It may even change their course. Conversely, cryptate formation inhibits reactions in which cation participation (electrostatic catalysis) plays an important role. Thus, cryptands are powerful tools for studying the mechanism of ionic reactions that involve complexable metal cations. Their effect on a reaction is a criterion for ascertaining the balance between anion activation and cation participation under a given set of conditions (*16*).

Cryptands, either alone or fixed on a polymer support, have been used in many processes, including selective extraction of metal ions, solubilization, isotope separation, decorporation of radioactive or toxic metals, and cation-selective analytical methods (*19*). A number of patents have been granted for such applications.

Anion Receptor Molecules and Anion Coordination Chemistry

In view of the fundamental role played by anions in chemical as well as biological processes, the binding of anions by organic ligands would be expected to provide a multitude of novel structures with properties of wide significance. However, it has received little attention in comparison with cation coordination, which has been the subject of numerous studies. Only in recent years has anion coordination chemistry been developed as a new area of coordination chemistry (*2, 14, 20*). This arose from the design of anion receptor molecules of various types, especially macrocyclic and macropolycyclic polycations capable of forming strong and selective complexes with inorganic anions and with negatively charged functional groups (such as carboxylate and phosphate) of organic or biological substrates. The binding strength and selectivity of the receptors are provided by electron-deficient interaction sites (like the positively charged sites of the polyammonium and polyguanidinium cations, which may establish multiple ^+N–H . . . X^- bonds), suitably arranged around an intramolecular cavity of a shape and size adapted to the anionic substrate to be bound (*14, 20–23*).

Polyammonium macrocycles of various ring sizes (for instance, **10** through **12**) act as anion receptors towards organic polycarboxylates, displaying stabilities and selectivities that result from both electrostatic and structural effects (*21*). The binding of complex anions of transition metals, such as the hexacyanides $M(CN)_6^{n-}$, markedly affects their redox and photochemical properties (*24, 25*). The strong complexation of adenosine mono-, di-, and triphosphates (AMP, ADP, and ATP) is particularly significant in view of their role in bioenergetics. It presents the possibility of devising molecular catalysts and carriers for these substrates. Substances like **10** and **11** are cyclic analogs of biological polyamines and could thus interact with biomolecules; indeed several macrocyclic polyamines induce efficient polymerization of actin.



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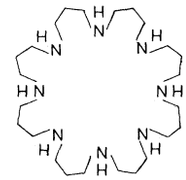

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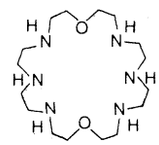

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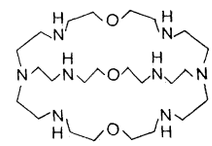

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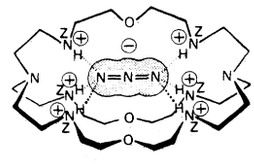
Protonated macrobicyclic diamines form katapinates by inclusion of halide ions (*22*). Tetraprotonated macrotricycles, such as **5**–$4H^+$, are geometrically suitable receptors for spherical anions and form anion cryptates with halides. Thus, **5**–$4H^+$ yields a chloride cryptate [$Cl^- \subset$ **5**–$4H^+$], **9**, of high stability, and it shows a high selectivity for chloride over bromide, but it does not complex other types of anions (*14*).

The hexaprotonated form of the ellipsoidal cryptand Bis-Tren, **13**, binds various monoatomic and polyatomic anions and extends the recognition of anionic substrates beyond the spherical halides (*23*). The strong and selective binding of the linear, triatomic anion N_3^- results from its complementarity to the receptor **13**–$6H^+$. In [$N_3^- \subset$ **13**–$6H^+$], **14**, the substrate is held inside the cavity by two pyramidal arrays of ^+N–H . . . N^- hydrogen bonds, each of which binds one of the two terminal nitrogens of N_3^-.



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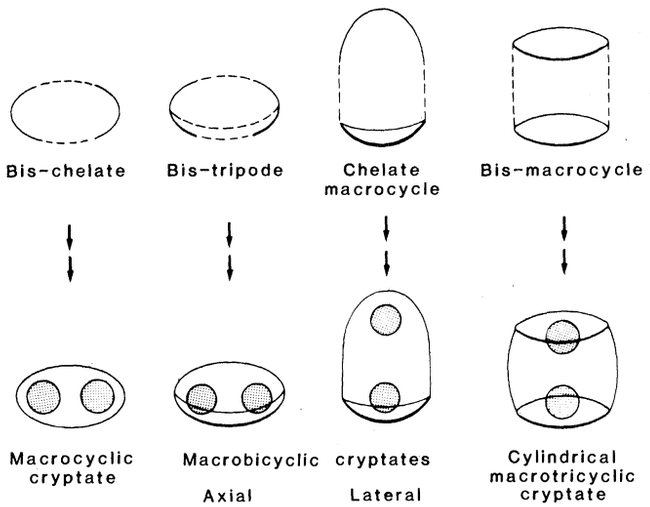
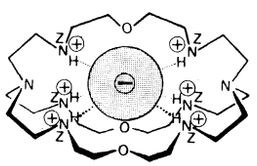


Fig. 3. Some dinuclear cryptates of macropolycyclic cryptands resulting from connection of chelating, tripodal, and macrocyclic subunits.

The noncomplementarity between the ellipsoidal **13**–$6H^+$ and the spherical halides results in much weaker binding and appreciable distortions of the ligand, as seen in the crystal structures of the cryptates **15** where the bound ion is F^-, Cl^-,



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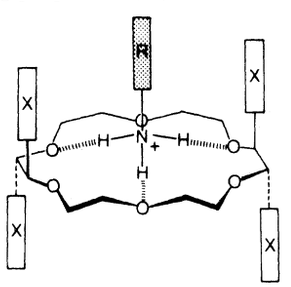
or Br^-. In these compounds, the F^- is bound by a tetrahedral array of hydrogen bonds; and the Cl^- and the Br^-, by an octahedral array. Thus, **13**–$6H^+$ is a molecular receptor for the recognition of linear triatomic species of a size compatible with the size of the molecular cavity.

A cryptate effect is observed for anion complexes as well as cation complexes. In general, an increase in cyclic order from acyclic to macrocyclic to macrobicyclic significantly increases the stability and selectivity of the anion complexes formed by polyammonium ligands.

In addition, in **14**, the receptor is built from two protonated tripodal subunits of the tren type, $N(CH_2CH_2NH_2)_3$, located at each pole of the molecule, which cooperate in substrate binding. This is a feature of coreceptor molecules, which will be discussed below.

Macrocyclic Receptors for Ammonium Ions

Macrocyclic polyethers and aza-polyethers selectively bind primary ammonium ions by anchoring the $-NH_3^+$ into the circular cavity with three $^+N-H \ldots X$ (X = O, N) hydrogen bonds (*2, 6, 8, 26, 27*). In view of the role of such substrates in both chemistry and biology, we sought a derivative that would yield stronger complexes than those of the parent macrocycles and bear functional groups for further modification. Thus, the chiral, tetrafunctional macrocycle in **16** was devised, which, by attachment of lateral substituents to the central core, led to molecular receptors with a variety of binding properties (*27*).



16a $X=CO_2^-$
b X=CONHR
c $X=2 \times CO_2^-$, 2 x CONHR (syn or anti isomer)
d $X=CONMe_2$

The tetracarboxylate, **16a**, forms the strongest metal-ion and ammonium complexes of any crown ether. It displays marked selectivity in favor of primary ammonium ions against more highly substituted ones (central discrimination). Of special interest is its selective binding of biologically active ions such as noradrenaline and norephedrine with respect to their N-methylated derivatives, adrenaline and ephedrine.

Varying the side groups, X, in **16b** affects the interactions (electrostatic, lipophilic, H-bonding, and charge transfer) between the side groups and the R group of the centrally bound substrate. This affects both the stability and selectivity of the complexes, which is called lateral discrimination, and allows the receptor-substrate interactions in biological systems to be modeled, for instance, the interaction between nicotinamide and tryptophane (*28*).

The structural features of **16** and its remarkable binding properties make it an attractive unit for the construction of macropolycyclic multisite receptors, molecular catalysts, and carriers for membrane transport. Such extensions require separate handling of the side groups, as in the face- and side-discriminated derivatives **16c** (*29*).

Coreceptor Molecules

Coreceptors are defined as polytopic receptor molecules combining two or more discrete binding subunits within the same macropolycyclic architecture (*30*). In terms of the general functions of supramolecular systems, recognition, catalysis, and transport, they may act as coreceptors, cocatalysts, or cocarriers whose subunits cooperate for, respectively, the complexation, transformation, or translocation of either several singly bound substrates or a multiply bound, polyfunctional substrate. Depending on the subunits, such coreceptors may bind metal ions, organic molecules, or both. Their ability to perform multiple recognition provides entry into higher forms of molecular behavior, such as cooperativity, allostery, regulation, and communication (signal transfer).

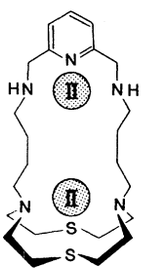
Dinuclear and Polynuclear Metal-Ion Cryptates

Macropolycyclic ligands incorporating two or more binding subunits for metal ions form dinuclear or polynuclear cryptates in which the distance and arrangement of the cations held inside the molecular cavity may be controlled through ligand design. They allow the study of cation-cation interactions (magnetic coupling, electron transfer, redox, and photochemical properties) as well as the inclusion of bridging substrates to yield cascade complexes, which are of interest for bioinorganic modeling and multicenter-multielectron catalysis.

Depending on the nature and number of binding subunits and of connecting bridges used as building blocks, a variety of macropolycyclic structures may be envisioned. Ditopic ligands that contain two units, which may be chelating, tripodal, or macrocyclic, bind two metal ions to form dinuclear cryptates of various types (Fig. 3). Combining three or four such subunits leads to tritopic and tetratopic metal-ion receptors. Dissymetric ligands that contain subunits with

"hard" and "soft" binding sites yield complexes in which the bound ions act as either redox or Lewis-acid centers. Representatives of these types of ligands and complexes have been obtained and studied. Only a few will be illustrated here (*31*).

Dinuclear cooper (II) cryptates of macrocyclic ligands (for example, **12**) or macrobicyclic ligands (for example, **13**) containing bridging groups (imidazolato, hydroxo, or azido) display antiferromagnetic or ferromagnetic coupling between the ions and bear a relation to dinuclear sites of copper proteins. Lateral macrobicycles are dissymetric by design; thus, monoelectronic reduction of the Cu(II) bound to the [12]-N_2S_2 macrocyclic subunit in the bis-Cu(II) cryptate **17**, gives a mixed-valence Cu(I)-Cu(II) complex. Macrotricycle **18** also forms a dinuclear Cu(II) cryptate, which acts as a dielectronic receptor and exchanges two electrons in a single electrochemical wave.



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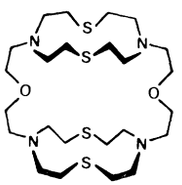

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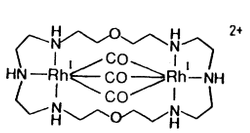
Polytopic receptors have the ability to assemble metal ions and bridging species within their molecular cavity to form "cluster cryptates." The bis-chelating macrocycle **12** gives complex **19** in which a triply bridged $[Rh(CO)_3Rh]^{2+}$ unit is built inside the ligand cavity (*32*). A trinuclear complex **20** containing a [tris-Cu(II), bis-μ_3-hydroxo] group in the cavity is formed by a tritopic, tris-ethylenediamine ligand (*33*). These few examples may at least have shown how rich the field of polynuclear metal cryptates is, both in structures and properties. Their chemical reactivity and use in catalysis have barely been studied up to now.



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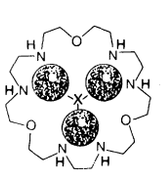

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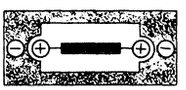
Diammonium Cryptates of Macrotricyclic Coreceptors

When two binding subunits are located at the poles of a coreceptor molecule, the complexation of a difunctional substrate will depend on the complementarity of the distance between the two binding sites in the receptor and the distance between the two corresponding functional groups in the substrate (*30*). Such linear recognition by ditopic coreceptors has been achieved for both dicationic and dianionic substrates, diammonium and dicarboxylate ions, respectively; it corresponds to the binding modes illustrated in **21** and **22**.



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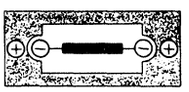
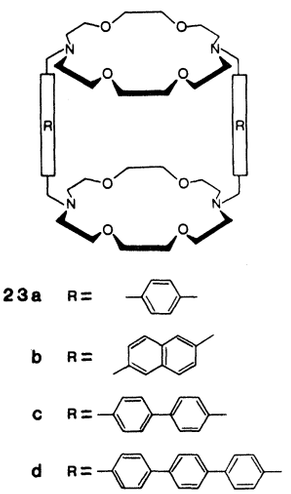


22

The cylindrical macrotricycles **23a** through **23d**, which contain two macrocyclic subunits capable of binding $-NH_3^+$ groups, yield molecular cryptates with diammonium ions. In the supermolecules thus formed, **24**, the substrate is located in the central molecular

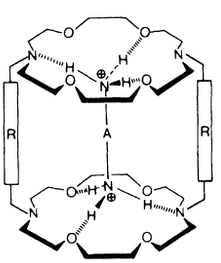


23a R=

b R=

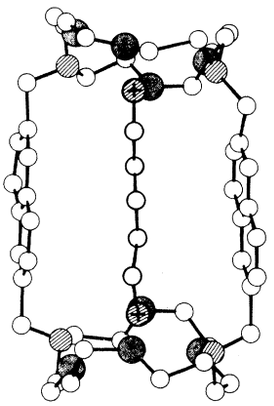
c R=

d R=



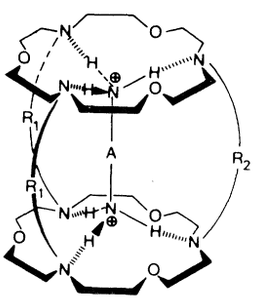
24

cavity of the coreceptor and anchored by each terminal $-NH_3^+$ group to an [18]-N_2O_4 macrocycle with three hydrogen bonds, as confirmed by the crystal structure of $[^+H_3N-(CH_2)_5-NH_3^+ \subset$ **23d**], **25** (*34*).



25

The $^+H_3N-(CH_2)_n-NH_3^+$ substrate that is preferentially bound has a length complementary to the length of the molecular cavity, with n = 4, 5, and 7 for **23a**, **23b**, and **23c**, respectively, Thus, ligand **23b** discriminates between cadaverine (n = 5) and putrescine (n = 4) cations. Similar effects may be expected for polyamines of various chain lengths such as ornithine, lysine, diammonium dipeptides, or spermine. Different selectivity sequences have been obtained with other macrotricycles (*35*), and triply bridged cyclindrical receptors show a high degree of selectivity in forming their diammonium cryptates, **26** (*36*).



26

These results are evidence for structural complementarity of receptors and substrates being the basis for linear molecular recognition.

Carbon-13 nuclear magnetic resonance studies of complexes of the type **24** indicate that complementary receptor-substrate pairs display similar molecular motions, a dynamic fit, in addition to their steric fit. Thus, complementarity between components of a supramolecular species expresses itself in both structural and dynamic properties (*37*).

Ditopic Coreceptors for Dicarboxylate Anions

The two hexaammonium macrocycles **27a** and **27b** possess the features of ditopic coreceptor molecules for dianionic

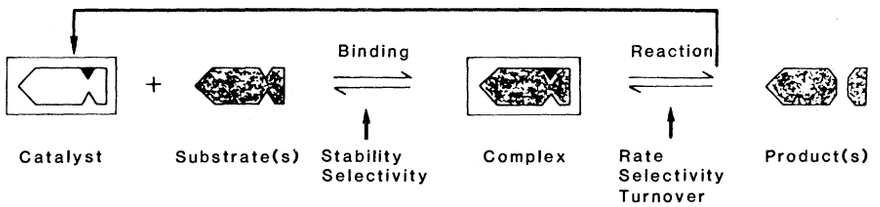
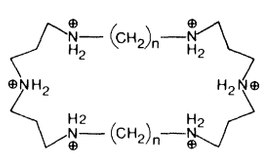


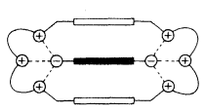
Fig. 4. Schematic representation of the supramolecular catalysis process.

substrates, since they contain two triammonium chelating subunits that may serve as binding sites for a negatively charged group, as shown in **28**. They complex dicarboxylates with a selectivity that depends on the chain length of the substrates, $^{-}O_2C-(CH_2)_m-CO_2^{-}$. The preferential binding of substrates with $m = 2$ and 3 by **27a** and of substrates with $m = 5$ and 6 by **27b** corresponds to an equivalent increase in length of the polymethylene chains separating binding subunits in both the substrates and the receptors. Receptors **27a** and **27b** also bind biological dicarboxylates of compatible chain lengths, respectively, amino acid and dipeptide dicarboxylates (*38*).

As in the binding of diammonium substrates to macrotricyclic coreceptors, this chain length selection describes a linear recognition process, based on structural complementarity in a ditopic binding mode, **20**. In both cases, the receptor acts as a discriminating sensor of molecular length.



27a n=7
b n=10

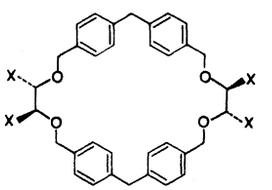


28

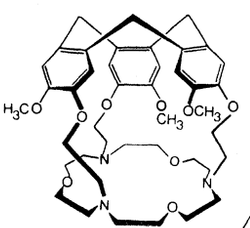
Speleands and Speleates of Molecular Cations

The combination of polar binding subunits with more or less rigid, apolar shaping components provides amphiphilic, macropolycyclic coreceptors of cryptand type, termed speleands, that form speleates by substrate inclusion (*30, 39, 40*).

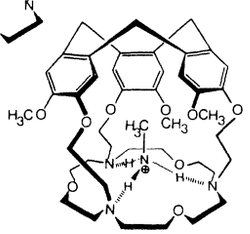
The macrocyclic speleand **29** combines two tartaric acid units with two diphenylmethane groups (*40*). It strongly binds a range of molecular cations by electrostatic and hydrophobic effects. It not only yields, with primary ammonium ions, more stable complexes than the common polyether macrocycles (except **16a**), but also it strongly binds secondary, tertiary, and quaternary ammonium substrates. Among the latter, the complexation of acetylcholine is of special interest: it provides one specific answer to the general question of how acetylcholine can be bound and sheds light on the type of interactions that may play a role in biological acetylcholine receptors.



29 $X=CO_2^-$



30a



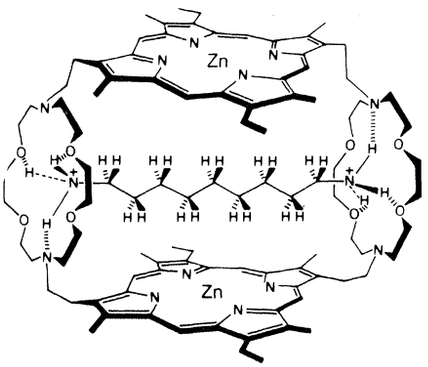
30b

The macropolycyclic speleand **30a** combines an [18]-N_3O_3 macrocyclic binding subunit with a cyclotriveratrylene shaping component (*39*). Its tight intramolecular cavity allows inclusion of the $CH_3-NH_3^+$ ion, which results in the speleate [$CH_3-NH_3^+ \subset$ **30a**], shown as **30b**.

Numerous other combinations of (polar) binding units and (apolar) architectural components may be imagined, making speleands attractive for the design of novel, efficient molecular receptors.

Metalloreceptors and Mixed-Substrate Supermolecules

Metalloreceptors are heterotopic coreceptors that contain substrate-selective binding subunits for the complexation of both metal ions and organic species within the same superstructure.



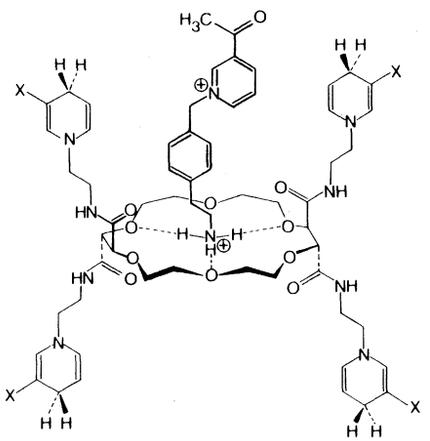
31

Such substances have been obtained by introducing one or two porphyrin or α,α′-bipyridine metal ion binding units as bridges in the macrotricycles of type **23a** through **23d**. These compounds may complex diammonium ions, as in **24**, as well as metal ions (*30, 31, 41*). Simultaneous binding of $^{+}H_3N-(CH_2)_9-NH_3^{+}$ and of two Zn^{2+} cations by such a bisporphyrin metalloreceptor yields the mixed-substrate supermolecule **31**. Complexation of several metal ions gives polynuclear cryptates. Many variations are conceivable involving the subunits as well as the overall macropolycyclic architecture. The simultaneous complexation of organic and inorganic substrates offers the opportunity to induce or adjust physical and chemical interactions and reactions (metallocatalysis) between the metal-centered reactive sites and the cobound molecular substrates. It could also mimic essential features of metalloenzymes. For instance, in species like **31**, activation of the internally bound organic substrate by the metal-porphyrin sites may be envisioned. Also by binding an effector species, the macrocyclic units could act as regulation sites for external interaction with the metal-porphyrin centers, to the point of exerting allosteric control and cooperativity.

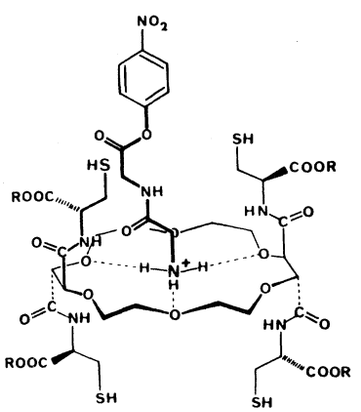
Supramolecular Catalysis

Molecular receptors bearing appropriate functional groups may bind a substrate, react with it, and release the products. This would be called supramolecular catalysis, catalysis within a supermolecule (Fig. 4). The design of efficient and selective molecular catalysts may give mechanistic insight into the elementary steps of catalysis, provide new types of chemical reagents, and provide models, "artificial enzymes," that reveal factors which contribute to enzyme catalysis (*42, 43*).

Enhanced rates were observed for hydrogen transfer from 1,4-dihydropyridyl side chains attached to the macrocyclic ammonium receptor **16** to bound pyridinium substrates, as shown in **32**. This intracomplex reaction was inhibited by addition of a complexable cation that displaced the substrate (*44*).



32



33

Ester cleavage has been induced with the tetra-(L)-cysteinyl derivative of **16**, which binds *p*-nitrophenyl (PNP) esters of amino acids and reacts with the bound species, releasing PNP at various rates. This intracomplex reaction displays substrate selectivity with marked rate enhancement in favor of bound dipeptide esters such as glycylglycine-OPNP in complex **33**. It is inhibited by a complexable metal cation, such as K^+, and it shows high chiral recognition between the enantiomeric dipeptide esters (Gly-(L)-Phe-OPNP and Gly-(D)-Phe-OPNP, the former reacting more than 50 times faster than the latter (*45*).

The development of anion receptor molecules allows molecular catalysis to be performed on anionic substrates of chemical and biochemical interest. Thus, macrocyclic polyamines were found to catalyze ATP hydrolysis, protonated [24]-N_6O_2, **12**, being particularly efficient

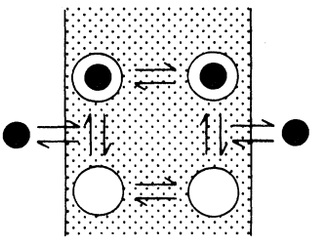


Fig. 5. Schematic representation of carrier-mediated transport through a membrane. Closed circles represent substrates; open circles represent carriers; and closed circles within open circles represent complexes.

(*46*). It strongly binds ATP and markedly accelerates its hydrolysis over a wide *p*H range, probably through a combination of acid, electrostatic, and nucleophilic catalysis. The latter reaction proceeds with an *N*-phosphoryl intermediate, which is subsequently hydrolyzed, a process reminiscent of the enzyme-catalyzed reaction, which gives **12** proto-adenosinetriphosphatase-type activity.

Recent work showed that when **12** is used to catalyze acetylphosphate hydrolysis, appreciable amounts of pyrophosphate are formed. Again an *N*-phosphorylated macrocycle intermediate is generated, which is apparently capable of transferring its phosphoryl group to a phosphate substrate (probably held in proximity), thus achieving the synthesis of inorganic pyrophosphate. This was confirmed by nuclear magnetic resonance spectroscopy and isotopic (^{18}O) labeling experiments. Macrocycle **12** may be considered to display protokinase activity in this process (*47*).

These systems possess a number of properties that supramolecular catalysis should display, that is, properties of an abiotic enzyme (protoase): selective substrate binding, reaction within the supramolecular complex, rate acceleration, inhibition by species competing for the binding site, structural selectivity, and chiral recognition.

Numerous other processes may be imagined. Of particular interest is the development of catalysts capable of realizing synthetic reactions, bond-making rather than bond-breaking processes. For this, the presence of several binding and reactive sites within the molecular catalyst is essential. Thus, coreceptors open the way to the design of artificial molecular cocatalysts of the ligase, metallocatalyst, and enzyme-coenzyme types, which act on two or more co-bound and spatially oriented substrates. In the pyrophosphate generation mentioned above, **12** displays such a cocatalysis function by mediating bond formation between two species.

Transport Processes and Carrier Design

One of the initial motivations of our work with cryptates was to investigate the ability of such complexes to transport cations through membranes (*1, 5*). This led us to explore the chemistry of transport and the design of transport effectors (*42, 48*).

Among the different transport mechanisms, facilitated diffusion, or carrier-mediated transport, consists of the transfer of a substrate across a membrane with the assistance of a carrier molecule (Fig. 5). This cyclic process may be considered as a physical catalysis that effects a translocation on the substrate just as chemical catalysis effects a transformation. The carrier is the transport catalyst, which strongly increases the rate of passage of the substrate with respect to its free diffusion, controls its selectivity, and allows the transport to be coupled to other processes such as proton cotransport (a proton pump) or electron cotransport. The active species is the carrier-substrate supermolecule; and transport is thus one of the basic functional features of supramolecular systems, together with recognition and catalysis.

Depending on internal factors, such as ligand structure or ligand-cation pairing, and external factors, such as the nature of the counterion, the nature of the membrane, or the concentrations of the substrates and carriers, macrobicyclic cryptands of type **1** through **3** were capable of selectively transporting alkali cations, even under conditions where natural or synthetic macrocycles show little activity. The transport rates and the selectivity of the transport for the various alkali cations can be varied by modifying the structure of the cryptand (*49*). Both experimental results and kinetic analysis indicate that there is an optimal binding ability for the highest transport efficiency. Molecular cations, like physiologically active, primary ammonium ions, are transported selectively by macrocyclic polyethers.

Anion carriers may, in principle, be derived from anion receptors. However, this area has been comparatively little explored, although it promises significant developments, for example, the selective transport of organic and biological anions.

The ability to design and to set up coupled transport processes may be clearly illustrated by two examples.

Electron-cation symport has been achieved in a two carrier process in which the electrons and K^+ ions are transported in the same direction, pumped by a redox gradient. This trans-

port is mediated simultaneously by an electron carrier, a nickel complex, and a selective cation carrier, a polyether macrocycle (*50*).

A striking regulation of the selectivity of Ca^{2+} and K^+ transport by *p*H has been achieved with both isomers of the lipophilic dicarboxylate-dicarboxamide macrocyclic carriers of type **16c**. The process involves competitive Ca^{2+} and K^+ symport coupled to back-transport of protons in a *p*H gradient (a proton pump). It displays a change from preferential K^+ transport to preferential Ca^{2+} transport as a function *p*H (*51*). These results demonstrate how appropriate design provides carriers that perform a given function.

Cation passage through membranes may occur through a transmembrane channel rather than a mobile carrier. A solid state model of a K^+ channel is provided by the crystal structure of the KBr complex of **16d** (*52*), and attempts to synthesize a channel structure on the basis of such macrocyclic subunits are under way.

Transport studies provide the means for effector design, analysis of the elementary steps and mechanisms of transport, coupling transport to chemical potentials, energy and signal transduction, models of biological transport processes, and so on. There are a variety of possible applications, for instance, in separation and purification, in batteries, or in systems for artificial photosynthesis. Again, the multiple sites in coreceptors should allow the design of cocarriers capable of transporting several substrates with the transport coupled to electrochemical gradients.

Conclusion

The chemistry of artificial molecular receptors, catalysts, and carriers has produced supramolecular species that effect molecular recognition, catalysis and transport. It has provided insight into the elementary interactions and processes on which these functions are based, and it has an increasing impact on organic, inorganic, and biological chemistry as well as on other fields of science. This chemistry has led to the elaboration of numerous novel structures and made available new properties of abiotic as well as biomimetic interest. Molecules belonging to a number of structural categories other than those described above, have been studied [for example, cyclodextrins (*43, 53*), cyclophanes (*43*), calixarenes (*54*), cavitands (*9, 55*), and catenands (*56*)] (*57*) and many more may be imagined, assisted by the refinement of methods for theoretical molecular design (*58*). The driving force and the selection process of the chemical evolution of these artificial systems rest in the chemist's creative imagination and synthetic (molecular and supramolecular) power.

In combination with molecular layers, membranes and vesicles (*59*), receptors, catalysts, and carriers are necessary elements in the elaboration of chemical microreactors and artificial cells. In another perspective, they may play a key role in the development of an intriguing although still rather futuristic area, which may be termed "chemionics," the design of components, circuitry, and systems for signal and information treatment at the molecular level (*3*). Such prospects offer challenging opportunities for continuously expanding on the words of Marcelin Berthelot in 1860: "La Chimie crée son objet."

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4. A number of the basic concepts and definitions that led to the formulation of supramolecular chemistry have been introduced in the course of the design of receptors for the spherical alkali cations (*1*). General presentations may be found in (*1–3*) as well as in (*30, 31, 42, 48*). The term "Übermolekeln" (supermolecules) was introduced in the mid-1930's to describe entities of higher organization resulting from the association of two or more coordinatively saturated species; see K. L. Wolf, F. Frahm, H. Harms, *Z. Phys. Chem. Abt. B* **36**, 17 (1937); K. L. Wolf, H. Dunken, K. Merkel, *ibid.* **46**, 287 (1940); K. L. Wolf and R. Wolff, *Angew. Chem.* **61**, 191 (1949). We consider that a supermolecule results from binding of substrate to a receptor. This terminology conveys the sense of biological receptor-substrate interactions, with their highly defined structural and functional properties. Furthermore, it is easily converted from one language to another. The "inclusion compound" and "host-guest" designations also cover species that exist only in the solid state (also termed clathrates) and are not supermolecules; see, for instance, F. Cramer, *Einschlussverbindungen* (Springer-Verlag, Berlin, 1954); J. E. D. Davies, W. Kemula, H. W. Powell, N. O. Smith, *J. Inclusion Phenom.* **1**, 3 (1983).
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60. I thank my co-workers, whose skill and dedication allowed us to realize the work surveyed in this article. Their names appear either in the references listed or in the original publications cited in the review articles.