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Cryptates: The Chemistry of Macropolycyclic Inclusion Complexes†

JEAN-MARIE LEHN

Institut Le Bel, Université Louis Pasteur, 67000 Strasbourg, France

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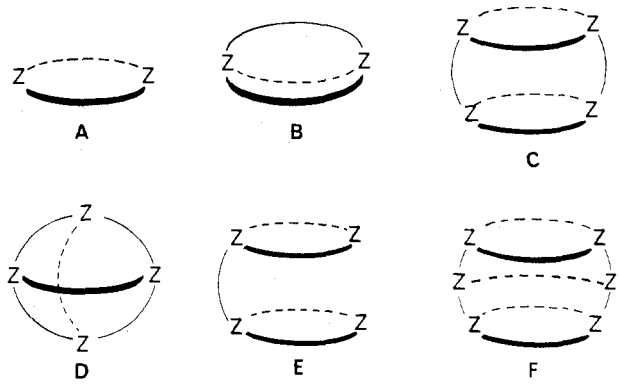
Macropolycyclic molecules are molecules of intermediate size, mesomolecules,[1] which may present a multitude of new properties. Having novel structures, they are often challenging synthetic targets. Whereas macrocycles have been extensively studied for several decades, the chemistry of macropolycyclic systems is much more recent.

Since macropolycycles contain *intramolecular cavities* delineated by molecular segments which may bear various sites for binding and reaction, the most fascinating aspects of their chemistry lie in their ability to form inclusion complexes, to bind selectively substrates, and eventually to perform transport or reactions on the bound substrate. Thus, a field of *supramolecular chemistry* emerges which, based on intermolecular binding forces, expands over molecular recognition processes, receptor chemistry, carrier design, and molecular catalysis.

A vast domain in this general field is the chemistry of macrocyclic and macropolycyclic metal cation complexes.[2-12] Complexes of transition-metal cations have been known for a long time, and in recent years there has been significant attention to synthetic macrocyclic ligands.[7,8,10-12] Whereas only few stable alkali cation (AC) complexes had been identified a decade ago, with the advent of macrocyclic ligands the domain underwent a major mutation from a collection of scattered special cases to a coherent discipline.[2-9]

A major factor to provide impetus to the field has been recognition of the biological role of Na^+, K^+, Mg^{2+}, and Ca^{2+} cations. Another is the discovery of natural macrocyclic antibiotics which display ligand and carrier properties toward alkali cations.[2,8]

During the last decade three main types of AC and alkaline-earth cation (AEC) ligands have been discovered and investigated: the natural acyclic or macrocyclic substances (cyclodepsipeptides, macrolides, etc.),[8] the synthetic macrocyclic polyethers of the "crown" type,[3] and the synthetic macropolycyclic ligands[4] to be discussed here.



Topologically, macrocycles of type A define two-dimensional, circular cavities. Ligands of higher cyclic order contain three-dimensional cavities. Such is the case for macrobicyclic (B) and macrotricyclic ligands; the latter may have either cylindrical (C) or spheroidal (D) topology. These ligands form *inclusion complexes* in which the substrate is contained inside their molecular cavity (or crypt). For this reason we have

Jean-Marie Lehn is Professor at Université Louis Pasteur de Strasbourg, as well as Visiting Professor at Harvard University (on a part-time basis). He was born in 1939 and received both his Licence ès Sciences and Doctorat ès Sciences (with G. Ourisson) from Université de Strasbourg. He did postdoctoral research with R. B. Woodward at Harvard. Besides his work on macropolycyclic molecules and cryptates, his research interests include dynamic nuclear magnetic resonance, theoretical organic chemistry, molecular dynamics and liquid structure, design and synthesis of molecular receptors, and transport processes in organic chemistry.

† Dedicated to Professor R. B. Woodward on the occasion of his sixtieth birthday.

(1) J. M. Lehn, J. Simon, and J. Wagner, *Angew. Chem., Int. Ed. Engl.*, **12**, 578 (1973); *Nouv. J. Chim.*, **1**, 77 (1977) (repetitive mesomolecules may be termed pleionomers; see H. Zahn, and G. B. Gleitzmann, *Angew. Chem.*, **75**, 772 (1963)).

(2) R. J. P. Williams, *Q. Rev., Chem. Soc.*, **24**, 331 (1970).

(3) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972).

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(7) J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, **74**, 351 (1974); R. M. Izatt, D. J. Eatough, and J. J. Christensen, *Struct. Bonding (Berlin)*, **16**, 161 (1973).

(8) Yu. A. Ovchinnikov, V. T. Ivanov, and A. M. Shkrob, "Membrane Active Complexones", Elsevier, Amsterdam, 1974.

(9) F. Vögtle and P. Neumann, *Chem-Ztg.*, **97**, 6001 (1973).

(10) D. H. Busch, *Helv. Chim. Acta, Fasc. Extra. A. Werner*, 174 (1967).

(11) L. F. Lindoy, *Chem. Soc. Rev.*, **4**, 421 (1975).

(12) As compared to the preformed macropolycyclic ligands, clathrochelates have been obtained by template reactions: V. Katovic, L. T. Taylor, and D. H Busch, *J. Am. Chem. Soc.*, **91**, 2122 (1969).

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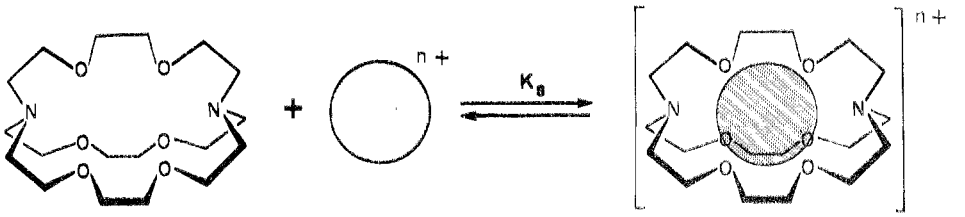


Figure 1. Formation equilibrium of a cryptate inclusion complex between the macrobicyclic ligand [2.2.2] (taken as an example) and a metal cation; K_s is the stability constant of the complex.

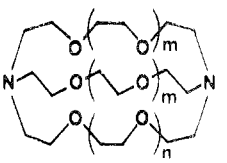
termed such complexes *cryptates*, the ligands themselves being *cryptands*.[4,13-15] They may be designated by the mathematical symbol of inclusion, ⊂, [S ⊂ L], i.e., substrate S included in ligand L.

This Account deals with our work on the design, the synthesis, and the properties of ligands of types B, C, and D; bismacrocycles of type E are obtained in the course of the synthesis of cylindrical macrotricycles C,[16-20] which themselves lead to the macrotetracycles F.[1] One of our initial goals was the complexation of the spherical AC's and AEC's.[4,13,14] Major lines of further development have been the extension to other substrates (transition-metal cations, anions,[21-24] molecules[15,17]) and the design of ligands which may form binuclear complexes in which the location, distance, and arrangement of the cations are regulated by ligand structure.

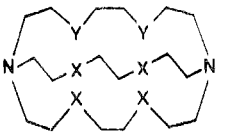
We shall emphasize properties and applications rather than ligand design and molecular recognition aspects (information storage, complementarity, etc.), which have been treated previously.[4]

Macrobicyclic Ligands (Type B) and Their Cryptate Complexes

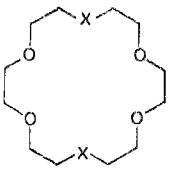
We initially set out to synthesize ligands for AC's and AEC's which would be of the simplest type having higher cyclic order than the macrocycles A, namely, macrobicyclic molecules **1**–**7** of type B.[13] They contain a three-dimensional intramolecular cavity, lined with oxygen and nitrogen binding sites, whose size is governed by the length of the bridges and increases stepwise along the series **1**–**7**.[25] They present a new kind of topological isomerism[21,22] since each bridgehead may be turned either inward or outward with respect to the molecular cavity, leading to the three forms: in-in (*ii*), in-out (*io*), out-out (*oo*).[21] Crystal structures of one representative of each topological type are now available:[26] cryptand **4** [2.2.2] is in the *ii* form, its bis(borane)-amine derivative H_3B[2.2.2]BH_3 is *oo*, and the monoborane derivative of **1**, [1.1.1]BH_3, is of *io* type.



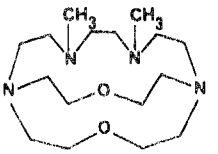
1, [1.1.1], $m = n = 0$
2, [2.1.1], $m = 0$, $n = 1$
3, [2.2.1], $m = 1$, $n = 0$
4, [2.2.2], $m = n = 1$
5, [3.2.2], $m = 1$, $n = 2$
6, [3.3.2], $m = 2$, $n = 1$
7, [3.3.3], $m = n = 2$
8, $HC(CH_2OCH_2CH_2\text{-}OCH_2CH_2OCH_2)_3CH$



11, [2.2.C_8], X = O; Y = CH_2
12, X = O; Y = O, NCH_3
13, X = O; Y = NCH_3
14, X = NCH_3; Y = O
16, X = O; Y = S
17, X = S; Y = O
18, X = Y = S
20, X = O; Y = O, NCH_2COOH
21, X = O; Y = NCH_2CH_2COOH



9, X = NCH_3
19, X = NCH_2COOH or NCH_2CH_2COOH



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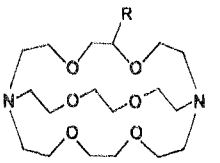

22, R = n-$C_{10}H_{21}$ or n-$C_{11}H_{23}$ or n-$C_{14}H_{29}$

Our next goal was to study the complexation properties of ligands **1**–**7**, especially with AC's and AEC's. Complex formation may be observed directly by following the changes in the proton or carbon-13 NMR spectra of ligands **1**–**7** in the presence of various alkali and alkaline-earth salts.[14] Dissolution of salts in organic solvents in which they are otherwise insoluble, as well as solubilization of insoluble salts in water, becomes possible.[27] Crystal structure determinations of a number of cryptates[28-30] confirm that the cation is located inside the molecular cavity, i.e., the complexes are *cryptates*, with the ligand in the *ii* form.

(13) B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Lett.*, 2885 (1969); B. Dietrich, J. M. Lehn, J. P. Sauvage, and J. Blanzat, *Tetrahedron*, **29**, 1629 (1973).
(14) B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Tetrahedron Lett.*, 2889 (1969); *Tetrahedron*, **29**, 1647 (1973).
(15) Organic cations may also form complexes. The complexes of ammonium salts with macrocyclic polyethers have attracted much attention (ref 3 and references therein; D. J. Cram, and M. Cram, *Science*, **183**, 803 (1974)). Our own work on molecule complexes will not be discussed here (ref 17, 18, and J. P. Behr, J. M. Lehn, and P. Vierling, *J. Chem. Soc., Chem. Commun.*, 621 (1976)).
(16) J. Cheney, J. M. Lehn, J. P. Sauavge, and M. E. Stubbs, *J. Chem. Soc., Chem. Commun.*, 1100 (1972).
(17) J. M. Lehn, J. Simon, and J. Wagner, *Angew. Chem., Int. Ed. Engl.*, **12**, 579 (1973).
(18) B. Dietrich, J. M. Lehn, and J. Simon, *Angew. Chem., Int. Ed. Engl.*, **13**, 406 (1974).
(19) R. Wiest, and R. Weiss, *J. Chem. Soc., Chem. Commun.*, 678 (1973).
(20) J. Fischer, M. Mellinger, and R. Weiss, *Inorg. Chim. Acta*, **21**, 259 (1977).
(21) H. E. Simmons and C. H. Park, *J. Am. Chem. Soc.*, **90**, 2428 (1968).
(22) C. H. Park, and H. E. Simmons, *J. Am. Chem. Soc.*, **90**, 2429, 2431 (1968).
(23) R. A. Bell, G. G. Cristoph, F. R. Fronzek, and R. E. Marsh, *Science*, **190**, 151 (1975).
(24) E. Graf and J. M. Lehn, *J. Am. Chem. Soc.*, **98**, 6403 (1976).
(25) Macrobicyclic polyethers of type **8** with C–H bridgeheads have been reported: A. C. Coxon and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 767 (1977).
(26) B. Metz, D. Moras, and R. Weiss, *J. Chem. Soc., Perkin Trans. 2*, 423 (1976); B. Metz and R. Weiss, in preparation.
(27) For instance, [2.2.2] solubilizes $KMnO_4$ in benzene and dissolves about 50 g of $BaSO_4$/L of water, i.e., an increase in solubility by a factor of about 10^4!
(28) D. Moras and R. Weiss, *Acta Crystallogr., Sect. B*, **29**, 396, 400, 1059 (1973).
(29) D. Moras, B. Metz, and R. Weiss, *Acta Crystallogr., Sect. B*, **29**, 383, 388 (1973).
(30) F. Mathieu, and R. Weiss, *J. Chem. Soc., Chem. Commun.*, 816 (1973).

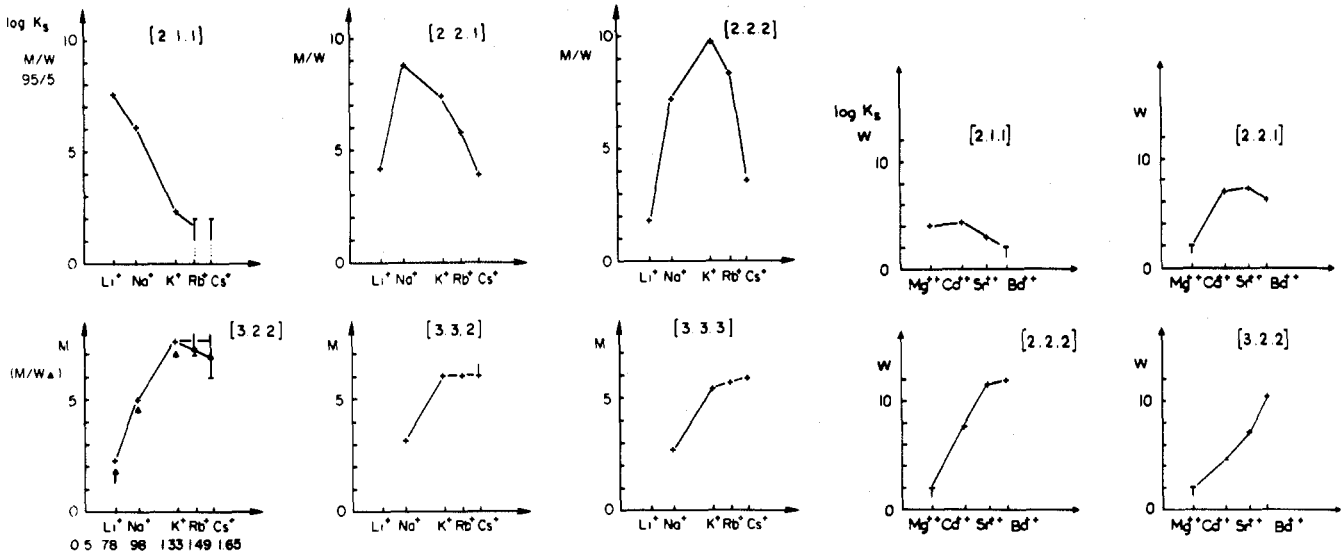

Figure 2. Stability constants (log K_s) of the alkali cryptates (left; in methanol water, M/W, (95:5), or in pure methanol, M, at 25 °C) and of the alkaline-earth cryptates (right; in water at 25 °C) formed by the macrobicyclic ligands **2**–**7**.[31]

Stability and Selectivity of the Cryptates.[31] The spheroidal intramolecular cavity of macrobicyclic ligands should be particularly well adapted to the formation of stable and selective complexes with spherical cations according to the equilibrium shown in Figure 1.

Ligands **2**–**4** form complexes with suitable AC's and AEC's which are several orders of magnitude more stable than those of natural or synthetic macrocycles (Figure 2);[3,8] for instance, $[K^+\subset 2.2.2]$ is about 10^4 times more stable than [$K^+\subset$valinomycin]. The $[Li^+\subset 2.1.1]$ complex is more stable than most Li^+ complexes of anionic ligands[32] despite the fact that [2.1.1] is electrically neutral. The cryptands thus function as receptors for spherical cations and may be considered as models for AC receptor proteins because of their high stability and their slow dissociation rates (see below).

The macrobicyclic topology of the cryptands strongly increases the stability of the complexes. The $[K^+\subset$ 2.2.2] cryptate is more stable by a factor of 10^5 than the K^+ complex of its macrocyclic counterpart; this *macrobicyclic cryptate effect* is even larger than the related macrocyclic effect (Figure 3). The same holds for AEC's: $[Ba^{2+}\subset 2.2.2]$ is 10^5 times more stable than the Ba^{2+} complex of the macrocycle **9** and even more stable than the Ba^{2+} chelates of polyanionic ligands like EDTA and EGTA.[32]

Pronounced and unusual selectivities are found for the cryptates of AC's and AEC's. For almost any pair of AC's there is a ligand among **2**–**7** which has higher selectivity than those previously known, including the natural macrocyclic ligands.[8] An exception is the K^+/Na^+ case, where valinomycin is more selective than [3.3.2] and [3.3.3].

Lengthening the bridges of the macrobicyclic system from [1.1.1] to [3.3.3] leads to a large but gradual change in size of the intramolecular cavity from about 1.2 to 4.8 Å.[4,31] As a result the stabilities of the complexes are greatly affected from one ligand to the other. They

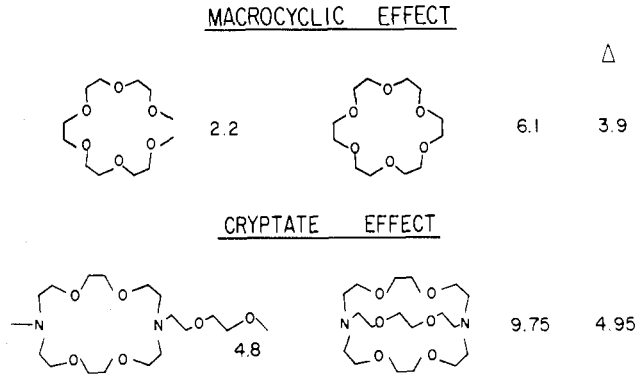

Figure 3. The macrocyclic and macrobicyclic effects (Δ) on complex stability; the values given are the stability constants log K_s of the K^+ complex in methanol (top) and methanol/water (95:5) (bottom).

agree with a simple criterion of *cavity size selectivity*, the preferred cation being that whose size most closely fits the cavity (see Figure 8 in ref 33). The cryptands [2.1.1], [2.2.1], and [2.2.2] thus complex preferentially Li^+, Na^+, and K^+ respectively. They present peak selectivity, being able to discriminate against cations which are either smaller or larger than their cavity; the bicyclic topology renders contraction or expansion of the cavity more difficult than in macrocyclic ligands. Plateau selectivity is observed for the more flexible ligands **5**–**7** which contain large, adjustable cavities. Like macrocyclic antibiotics they have high K^+/Na^+ selectivity but weak K^+, Rb^+, Cs^+ discrimination (Figure 2).

Control over Alkaline-Earth/Alkali Cation Selectivity. Whereas the natural macrocyclic ligands usually complex AC's more strongly than AEC's of similar size, the reverse is true for cryptands **2**–**7**. Control over M^{2+}/M^+ may be achieved by increasing ligand thickness (as in benzo derivatives of [2.2.2]) or by removing binding sites.[34] Thus the Ba^{2+}/K^+ ratio is $\sim 10^4$ and $<10^{-2}$ for [2.2.2] and [2.2.C_8], **11**, respectively. The loss of two oxygen binding sites in [2.2.C_8]

(31) J. M. Lehn and J. P. Sauvage, *J. Am. Chem. Soc.*, **97**, 6700 (1975); when the cation is much larger than the intramolecular cavity, external complexes may be present (see also ref 50).

(32) L. G. Sillen and A. E. Martell, *Chem. Soc. Spec. Bull.*, **No. 17** (1964); **No. 25** (1971).

(33) B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Chem. Unserer Zeit*, **7**, 120 (1973).

(34) B. Dietrich, J. M. Lehn, and J. P. Sauvage, *J. Chem. Soc., Chem. Commun.*, 15 (1973).

as compared to [2.2.2] and the efficient shielding of the complexed cation from the solvent are felt much more by Ba^{2+} than by K^+, reversing the selectivity by a factor of $>10^6$. The effect is clearly of cryptate nature since for the macrocycle **9**, which has the same binding sites as **11** but allows free access of the solvent from top and bottom, the Ba^{2+}/K^+ ratio is similar to that of [2.2.2].[34]

This simple structural transformation $O \rightarrow CH_2$, which retains the cavity size but modifies greatly the binding properties, may also be applied to other cryptands and allow selectivity inversion in other M^{2+}/M^+ couples.

Proton Cryptates.[35] Internal protonation of the ligands leads to proton cryptates which display very slow proton exchange rates[36] in the cases of [2.1.1] and especially of [1.1.1], where the small cavity conceals the protons so efficiently that the deprotonation of the in–in diprotonated species $[2H^+ \subset 1.1.1]$ is very slow even in strong base.[35] Molecular models show that neither H_2O nor OH^- is able to reach into the cavity to remove the cryptated proton(s).

The Cryptate Effect

The results described above illustrate the special complexation properties of macrobicyclic ligands. We can clearly recognize a macrobicyclic cryptate effect characterized by (a) high stability, (b) high selectivity of complexation, and (c) shielding of the complexed cation from the environment. These features may be ascribed to the topology of the ligand which allows complete inclusion of the cations inside the molecular cavity. Efficient cation shielding is illustrated by the solvent independence of the Li^7 NMR signal of $[Li^+ \subset 2.1.1]$.[37]

Effect of Nitrogen and Sulfur Binding Sites. Transition-Metal Cryptates. The replacement of oxygen binding sites in cryptands **2–4** by nitrogen and sulfur sites in **12–18** decreases both the stability and the selectivity of the AC and AEC cryptates.[38,39] Macrobicyclic polyamines like **12–15** provide a means of trapping transition-metal cations inside a molecular cavity, thus imposing unusual coordination geometries and modifying their spectral, redox, and magnetic properties, for instance stabilizing uncommon oxidation states. Transition-metal cations give stable complexes with the small tetraaza cryptand **15** but not with [2.2.2] or its polyaza derivatives **12–14**, whose cavity is too large. $[Co^{2+} \subset 2.2.1]$ forms easily[14] and displays an unusual pentagonal-bipyramidal coordination.[30] Very little is known about *lanthanide cryptates*, although in terms of cavity size [2.2.1] should be well suited and forms a La^{3+} complex. Because of its larger cavity, [2.2.2] might stabiize the Ln^{2+} state.[82]

Attachment of acetic or propionic acid branches leads to macrocyclic and macrobicyclic complexones like compounds **19–21**.[40] With respect to the parent compounds **9**, **12**, and **13**, the anionic sites of these cryptands increase the stability of the AC and AEC complexes and modify the selectivities in favor of the cations of high charge density (Li^+, Na^+, AEC's), thus diminishing cavity size effects on selectivity.

Selective Complexation of Toxic Heavy Metal Cations. The development of new selective ligands for the treatment of heavy metal poisoning and for decontamination by radioactive metals is of great interest for both *environmental chemistry* and *complexotherapy*. The very high Sr^{2+}, Ba^{2+}, Pb^{2+}/Ca^{2+} selectivities confer to [2.2.2] the exceptional ability to decorporate radioactive strontium-85 and radium-224 from rats.[41] It is also effective for lead removal.[42]

An especially illuminating case is the selective complexation of the highly toxic *cadmium* cation while leaving Zn^{2+} and Ca^{2+} untouched. Cryptand **13** displays a very high selectivity ($\sim 10^6$–10^7) for Cd^{2+} with respect to Zn^{2+} and Ca^{2+}, with even higher ratios for lead and mercury. These striking features may be ascribed to the operation of double-parameter (cavity size/binding sites) discrimination: whereas the nitrogen sites of ligand **13** favor both Cd^{2+} and Zn^{2+} over Ca^{2+}, its cavity is too large for strong complexation of Zn^{2+}. At present there seems to be no other ligand displaying such high selectivities for the heavy metal cations. "Cryptatotherapy" may become important for the medical treatment of metal poisoning and for pollution control.

Cation-Exchange Kinetics. The rates and mechanism of formation and of dissociation of cryptates are of interest from several points of view: (i) the general mechanism of cation ligation; (ii) the influence of ligand structure and conformation; (iii) the structural requirements for cation receptor vs. cation carrier properties.

Cation-exchange rates have been studied in many cryptates,[43–47] especially by means of ^1H, ^{13}C, and alkali cation NMR. The following points were noted. (1) Dissociation rates of the most stable complexes are several orders of magnitude slower than those of macrocyclic or antibiotic complexes and decrease as the stability constants increase. (2) Rates of formation are much slower than the rates of exchange of water molecules in the hydration shell but appear to follow the same sequence. (3) The transition state is on the reagent side, i.e., it involves substantial solvation of the cation. (4) Fast exchange rates require low cation solvation energy, ligand flexibility, and not too high complex stability. Conformational changes may occur in the process. The most stable cryptates are cation receptors, releasing the cation only slowly. The less stable ones exchange rapidly and may function as cation carriers (see below). (5) Dissociation may occur via an acid-catalyzed path at low pH.[47]

Enthalpies and Entropies of Cryptate Formation.[48,49] Whereas the chelate effect is usually ascribed to a strong positive entropy of complexation, the alkali

(35) J. Cheney and J. M. Lehn, *J. Chem. Soc., Chem. Commun.*, 487 (1972).
(36) A. J. Kresge, *Acc. Chem. Res.*, **8**, 354 (1975).
(37) Y. M. Cahen, J. L. Dye, and A. I. Popov, *J. Phys. Chem.*, **79**, 1289, 1292 (1975).
(38) J. M. Lehn and F. Montavon, *Tetrahedron Lett.*, 4557 (1972); *Helv. Chim. Acta*, **59**, 1566 (1976); in press.
(39) B. Dietrich, J. M. Lehn, and J. P. Sauvage, *Chem. Commun.*, 1055 (1970).
(40) J. M. Lehn, and P. Vitali, unpublished results.
(41) W. H. Müller, *Naturwissenschaften*, **57**, 248 (1970; W. H. Müller, and W. A. Müller, *ibid.*, **61**, 455 (1974).
(42) Ph. Baudot, M. Jacque, and M. Robin, *Toxicol. Appl. Pharmacol.*, **41**, 113 (1977).
(43) J. M. Lehn, J. P. Sauvage, and B. Dietrich, *J. Am. Chem. Soc.*, **92**, 2916 (1970); E. Kauffmann and J. M. Lehn, unpublished results.
(44) J. M. Ceraso and J. L. Dye, *J. Am. Chem. Soc.*, **95**, 4432 (1973).
(45) J. P. Kintzinger and J. M. Lehn, *J. Am. Chem. Soc.*, **96**, 3313 (1974).
(46) V. M. Loyola, R. G. Wilkins, and R. Pizer, *J. Am. Chem. Soc.*, **97**, 7382 (1975).
(47) B. G. Cox, and H. Schneider, *J. Am. Chem. Soc.*, **99**, 2809 (1977).
(48) G. Anderegg, *Helv. Chim. Acta*, **58**, 1218 (1975).
(49) E. Kauffman, J. M. Lehn, and J. P. Sauvage, *Helv. Chim. Acta*, **59**, 1099 (1976).

cryptates display large favorable enthalpies but unfavorable entropies of formation. The cryptate effect is of enthalpic origin, due to strong interaction of the cations with the weakly solvated polydentate ligands of macrobicyclic topology. The large negative entropies of cryptate formation contain water structure effects since a metal cation is transformed into a bulky organic cation of structure-making type.[49]

Physical Chemistry and Electrochemistry of Cryptates. Cryptates represent a new approach to studies of ionic solvation, since they provide cations isolated in "frozen" coordination shells whose binding sites and geometry may be modified at will. The alkali metal (^{7}Li, ^{23}Na, ^{133}Cs)[37,44,45,50] NMR signal of the cryptates is markedly shifted from that of the solvated cation. The ^{23}Na nuclear quadrupole coupling constants χ of several cryptates[45] obey a linear relationship between χ and the ^{23}Na shift δ ($\chi = \delta\ 0.05 + 1.65$ MHz). Thus, measuring ^{23}Na shifts and relaxation times allows a detailed study of Na^+ solvation (field gradient, cation mobility) in various media.[51] The method should be extendable to other quadrupolar nuclei.

Cryptates open a route to a reliable scale of single-ion free energies of transfer[52] and have electrochemical uses.[53] Electrochemical reduction of AC cryptates occurs at appreciably more negative potentials than those of the free cations.[54]

Cryptates as Counterions. Let us now switch our point of view from the cryptate as a complex between a cation and a ligand to the cryptate as a single entity, a counterion. To the environment, the anions and the solvent, it appears as a spheroidal cationic species of very large size (about 10 Å diameter,[28,29,55] i.e., 6–7 Å larger than Cs^+, 3.3 Å), of low surface charge density, and, as a consequence, interacting with anions and solvent molecules much more weakly than the largest alkali cation Cs^+. $[K^+\subset 2.2.2]$ thus behaves as a "super-heavy" alkali cation.

Strong anion activation may be produced since stabilization of anions either by ion pairing or by solvation is strongly reduced, especially in solvents of low polarity in which cryptate formation facilitates dissolving many otherwise insoluble salts. Whereas the cation in the crown complexes is still accessible for ion pairing with the anion from "top" and "bottom" of the complex (cf. crystal structures[5] and spectroscopic studies[56,57]), this is much more difficult with the well-encased cations in the cryptates. As a result cation–anion separation is more complete and dissociation constants in solvents of low polarity[55,56] are much larger. This difference in exposure to the environment, between a partial and a complete "organic skin", may be expected to play a major role in all properties associated with the anion accompanying the complexed cation. The more complete ion-pair separation in apolar media should enable, so to speak, the study of *gas-phase type chemistry in solution.*

Cryptate Metal Solutions. Metal Anions. Both macrocyclic polyethers and cryptands like [2.2.2] solubilize alkali metals in various solvents, but only the latter yield substantial concentrations of solvated electrons.[56-58]

The most dramatic illustration of the ability of cryptate counterions to stabilize unusual species is the isolation by Dye et al. of the first salt containing an *alkali metal anion*, $[Na^+\subset 2.2.2]Na^-$, as crystals of gold-colored, shiny metallic appearance.[58,59] Its crystal structure has been determined[59] and its ^{23}Na NMR spectrum contains a narrow, upfield Na^- resonance.[60] The electride $\{[Na^+\subset 2.2.2]e^-\}$ and $[K^+\subset 2.2.2]K^-$ have also been observed.[59,61]

A particularly attractive class of substances are anionic clusters, of potential interest in catalysis. With $[Na^+\subset 2.2.2]$ as counterion, it has been possible to isolate and to determine the crystal structures of polyatomic anions of the heavy post-transition metals (Sb_7^{3-}, Pb_5^{2-}, Sn_9^{4-});[62] complexation of Na^+ by [2.2.2] prevents reversion to the starting Na/metal alloy phase.

Anion Activation. Cation Participation. Complexation of the cation of a salt by a cryptand brings about solubilization of the salt, and dissociation or separation of the cation–anion pair leading to anion activation. A large increase in reaction rate may result: activation causes an increase in reactivity of the reagent, i.e., an increase in rate constant, while solubilization increases its concentration. Such anion activation (especially if catalytic) is potentially of interest for energy conservation since processes which usually require heat may become feasible at room temperature.

Strongly basic systems[63] are obtained by addition of [2.2.2] to solutions of sodium *tert*-amylate in benzene or of butyllithium in hexane. The pK_a of the *t*-AmO^- anion, with the potassium cation complexed by cryptand **22**, is approximately 37 or greater.[64] The highly hindered ester, methyl mesitoate, is hydrolyzed at room temperature in the presence of [2.2.2] by powdered KOH suspended in dry benzene or, much more rapidly, by concentrated solutions of KOH in Me_2SO obtained with [2.2.2].[63]

The polymerization of styrene by the cryptate of sodium *tert*-amylate must begin by nucleophilic addition of the alkoxide anion to the carbon–carbon double bond of styrene to give a benzylic anion.[65]

Cryptands are useful in phase-transfer catalysis (PTC), assisting transfer from solid to liquid or from liquid to liquid. Catalytic amounts of [2.2.2] bring about substitution reaction from solid salts.[63,66] The

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lipophilic [2.2.2] derivative **22** or derivatives immobilized on polymer support were found to be highly efficient for salt solubilization[64] and for liquid to liquid PTC in a variety of reactions.[67]

Cryptation makes it possible to ascertain cation participation in ionic reactions.[68,69] Thus the reduction of carbonyl and other functional groups by $LiAlH_4$ is inhibited by cryptation of Li^+ or Na^+ with [2.1.1] or [2.2.1] respectively, showing that coordination of the cation plays a major role.[68] Addition of [2.2.2] decreases the rate of ring opening of ethylene oxide by fluorenylsodium but increases the rate of cleavage by carbazylpotassium in which charge is more localized than in the fluorenyl anion.[70]

These results suggest that cryptate formation may become a powerful criterion of mechanism for ionic reactions involving complexable metal cations. An increase in reaction rate on cryptation of the cation would indicate that the cation was paired with the anion and that separation of the pair causes anion activation. A decrease of reaction rate on cryptation would indicate that the cation assists the reaction by interaction with the transition state, especially with the developing charge. The balance between these two opposite effects is determined by the nature of the reagent anion and the product anion and the relative strength of their interaction with the cation.

Cryptands may be expected to cause major effects in carbanion reactions.[69-71] Carbanion rearrangements and the regioselectivity of carbanion condensations are strongly affected by addition of [2.2.2].[71]

Anionic Polymerization. Anionic polymerization is an ideal field of application for cryptate-induced anion activation since only catalytic quantities of cryptand are required. Both new initiation reagents and new processes have been discovered. The polymerization of a number of otherwise unreactive monomers has been effected using alkali metals or salts in the presence of cryptands.[56,65,70,72]

Cation Transport. Cation transport has been achieved with natural and synthetic macrocyclic molecules[6,8] as well as with macrobicyclic cryptands.[73] It occurs by a carrier-mediated, facilitated diffusion mechanism. Synthetic ligands, which may in principle be modified at will, offer the possibility of governing transport rates and selectivity.[4,6,8] Cryptates cover the whole spectrum from cation receptors to cation carriers and perform selective cation transport in artificial membrane systems.[73] The rates and selectivities of transport depend strongly on the cation, the carrier, and the anion. With neutral carriers, extraction of the salt into the membrane (i.e., the percentage carrier saturation) is anion dependent. [2.2.2], which forms a very stable complex with K^+, carries potassium picrate very slowly; but KCl is transported efficiently by the analogue **22**. Furthermore, [2.2.C_8] (**11**) is an efficient carrier for potassium picrate; thus a simple structural modification transforms a cation receptor into a cation carrier.[73] Similar modification of the Na^+ and Li^+ receptors [2.2.1] and [2.1.1] leads to Na^+ and Li^+ carriers.[73,74]

Fine tuning of the structure of the ligand to the nature of the anion and the membrane may allow the design of selective carriers for regulation of cation levels and transport in organisms (for instance, in lithium therapy of the manic-depressive illness[74]), for recovery, separation and depollution in industrial and environmental applications, etc.

Extraction, Isotope Separation, and Other Applications. Because of pollution problems and increases in the prices of raw materials, the purification and recovery of metals from wastes become more and more important. Cryptands may be of use in specific cases, especially if they are fixed on a polymer support for easy recovery.[67,75] [2.2.2] provides a simple extraction method for purifying Cs^+ (e.g., radioactive ^{137}Cs).

Isotope separation may be envisaged, and remarkable results have been obtained for $^{22}Na/^{24}Na$ with [2.2.1] in methanol.[76] Other cases, such as $^{6}Li/^{7}Li$ and $^{40}Ca/^{44}Ca$, may be visualized. Again cryptand-resins would be of interest. The solubilization properties of cryptands may also find application. Thus solubilization of $BaSO_4$ by [2.2.2][27] may help to unclog oil wells[77] and [2.2.1] should be able to dissolve sodium urate whose crystallization in the joints causes gout.

Cyclindrical Macrotricyclic Ligands. Mononuclear and Binuclear Macrotricyclic Cryptates

Cylindrical macrotricyclic ligands of type C present new topological features with respect to the macrobicyclic ligands B. They are formed by two macrocycles linked by two bridges and 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 and opens the way to the design of systems with specific properties.

A general route has been developed for the synthesis of such structures. It is based on the successive construction of systems of increasing cyclic order: macrocycle, bismacrocycle, macrotricycle.[1] The first macrotricycles to be synthesized, compounds **23–27**, contain oxygen and nitrogen binding sites and should thus be suited for the complexation of AC's and AEC's.

Complex formation of ligands **23–27** with various metal cations can be observed by NMR spectroscopy. Two kinds of complexes may be detected, having either 1/1 or 2/1 cation/ligand stoichiometry. In these cylindrical ligands the two macrocycles may each serve as receptor site for one cation, so that they form both

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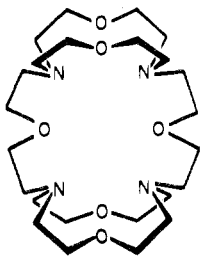

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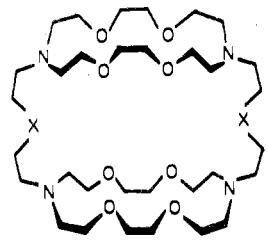
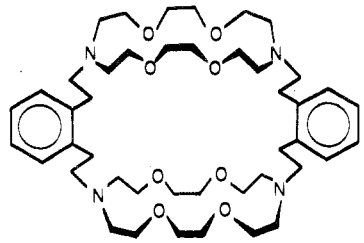


24, X = CH_2
25, X = O
27, X = NH



26

mononuclear and binuclear macrotricyclic cryptates.[17,78]

The 12-membered macrocycles of ligand **23** are too small for cation inclusion into their own cavities. A complexed cation must sit on top of these rings and toward the center of the macrotricyclic cavity. For this reason, a binuclear cryptate has been observed only for the very stable Ag^+ complex. The crystal structure of $[2Ag^+\subset\mathbf{23}]Ag(NO_3)_3^{2-}$ shows that the two silver cations are located inside the central cavity, each bound to one of the rings and at a distance of 3.88 Å.[19]

The larger ligands **24–26** form binuclear complexes with several AC's and AEC's as well as with Ag^+ and Pb^{2+}. The 18-membered rings are big enough for cations like K^+ and Rb^+ to penetrate more or less deeply into their cavities. As a consequence, the cations are further apart and the formation of binuclear complexes becomes easier. In $[2Na^+\subset\mathbf{25}]2I^-$ the Na^+ cations penetrate partially into the macrocycles and are 6.40 Å apart.[20] These structures and ^{13}C NMR data on the 1:1 $Ba(NO_3)_2$/**25** complex[78] suggest that the mononuclear complexes of the tricyclic ligands are nonsymmetric with the cation located on a ring on one side of the central cavity. One can then describe the complexation properties of the macrotricyclic cryptands **23–26** as the successive formation of nonsymmetric mononuclear and symmetric binuclear [3]cryptates represented in Figure 4.

Heteronuclear bimetallic cryptates may also be obtained. With equimolar quantities of $AgNO_3$ and $Pb(NO_3)_2$, ligand **25** forms an equilibrium mixture of the two homonuclear complexes, $[2Ag^+\subset\mathbf{25}]$ and $[2Pb^{2+}\subset\mathbf{25}]$, and of the heteronuclear complex $[Ag^+Pb^{2+}\subset\mathbf{25}]$.[78]

The stability constants of the 1:1 and 2:1 complexes correspond to the equilibria shown in Figure 4. The 1:1 AC complexes of ligand **23** have stabilities comparable to those of macrocyclic ligands except for the larger cations Rb^+ and Cs^+, which probably fit better in the central cavity. The AEC's form remarkably stable complexes.[79] The larger macrotricycles **24–26** show two main features: (i) the stabilities K_{s1} and selectivities of their 1:1 AC and AEC complexes are similar to those of the macrocycle **9**; and (ii) the stabilities and selectivities of the binuclear complexes (K_{s2}, see Figure 4) are similar to those of the 1:1 complexes; it is especially remarkable that K_{s2} for the formation of $[2Ba^{2+}\subset\mathbf{25}]$ is as high as K_{s1} for $[Ba^{2+}\subset\mathbf{25}]$. Both results indicate that the larger macrotricycles contain two almost independent macrocyclic units.[78]

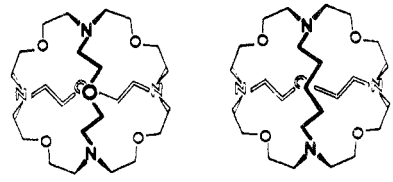
Kinetic processes have been observed in several cases. Temperature-dependent ^{13}C NMR measurements have revealed intramolecular cation exchange in the 1:1 Ca^{2+}, Sr^{2+}, and Ba^{2+} complexes of ligand **23**. The spectral changes observed indicate internal cation exchange between "top" and "bottom" of the molecule. Intermolecular exchange occurs also, but much slower than the internal fluxional process.[79] The same internal process occurs probably in the AC complexes of **23** and in the nonsymmetrical 1:1 complexes of **24–26**, but much faster. These interesting dynamic features of macrotricyclic complexes model the elementary jump process of cations between binding sites in membrane channels.

Cylindrical macrotricyclic ligands incorporating suitable macrocyclic units are expected to form binuclear transition-metal complexes. Regulation of the size of the central cavity via the length of the bridges may produce strong cation–cation interactions at short distances; at long distances, the formation of *cascade complexes* by subsequent inclusion of a substrate between the two metal cations may open a road to binuclear catalysis.

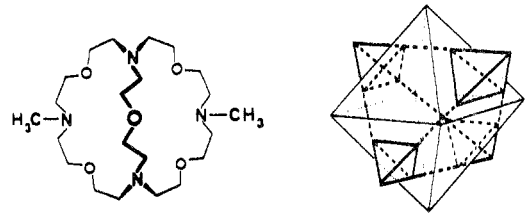
Molecule Complexes. Molecular association has been detected between the large macrotricyclic systems **24** and **25** and fluorescent substrate molecules.[17] These ligands thus function as molecule receptors. Two types of complexation occur: lipophilic cation–lipophilic anion association between metal cation complexes of **24**, **25**, and a fluorescent lipophilic anion, and direct molecular association of the fluorescent probe with the macrotricyclic (and macrotetracyclic) molecules. It is not yet certain that these complexes are of the inclusion type.

Spheroidal Macrotricyclic Molecules

For spherical recognition, macrotricyclic ligands of type D have a particularly attractive topology[4] since they contain a spherical cavity. Two such molecules (**28** and **29**) have been synthesized via a route involving



28 **29**



30 **31**

three high-dilution reactions for the successive construction of a macrocyclic, a macrobicyclic and the final

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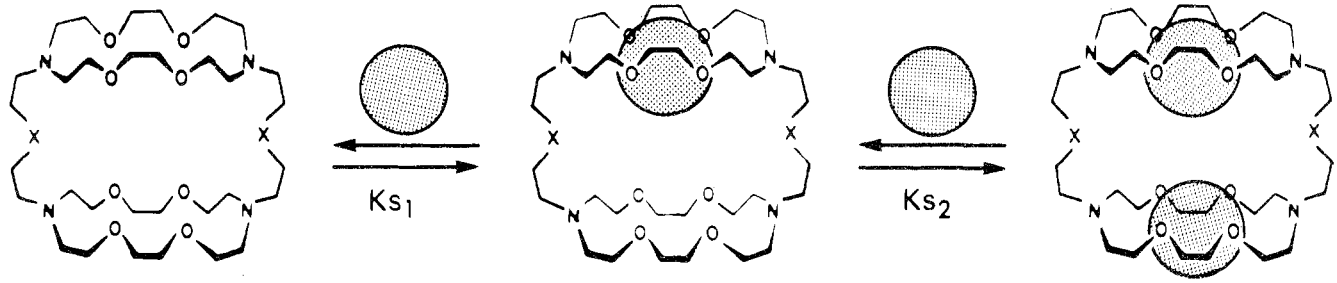

Figure 4. Equilibria for the successive formation of nonsymmetric mononuclear and symmetric binuclear cryptates of the cylindrical macrotricyclic ligand **25**.

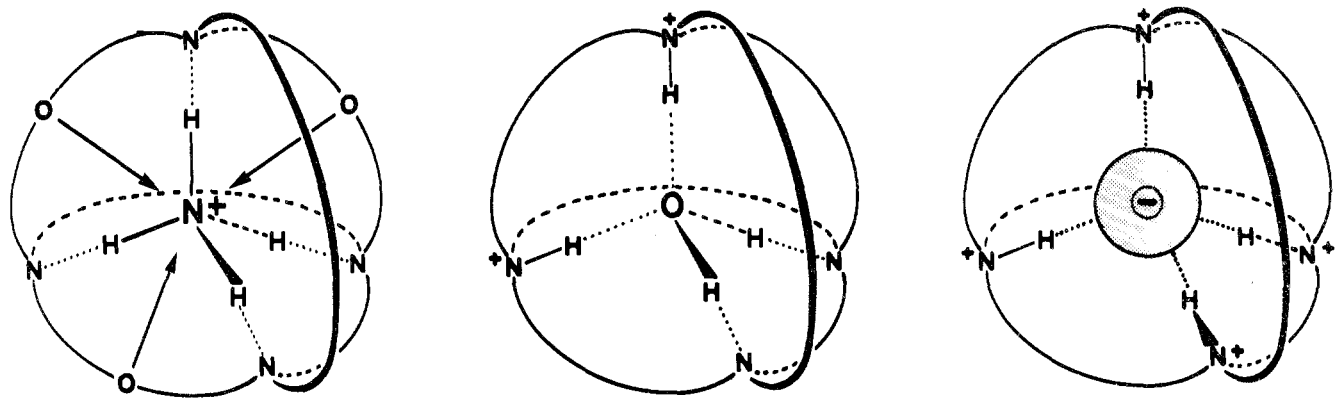

Figure 5. Tetrahedral binding of NH_4^+ (left), H_2O (center), and Cl^- (right) by the spheroidal macrotricyclic ligand **28** (left), its diprotonated form (center), and its tetraprotonated form (right). For the NH_4^+ complex (left) only three of the six possible electrostatic $O \rightarrow N^+$ interactions are shown.

macrotricyclic architecture.[80] The macrobicyclic analogue **30** has been prepared for comparison purposes. Ligand **24** in its i_4 form contains a spherical cavity (of about 1.7-Å radius) lined with ten binding sites in an octahedrotetrahedral arrangement: the four nitrogens are located at the corners of a tetrahedron and the six oxygens are at the corners of an octahedron; the centers of the two polyhedra coincide and the ten corners lie on the same sphere (see **31**).

Spherical Cation Cryptates. Ligands like **28** and **29** have ideal topology for complexing the spherical AC and AEC's. Complexation of K^+, Rb^+, Cs^+, and Ba^{2+} has been observed. These complexes are spherical cryptates, e.g., $[Cs^+\subset\mathbf{28}]$, where the cations are included in the central cavity of the ligand in the i_4 form. The stability constants are high and the Cs^+ complex appears to be the most stable known to date. The cation exchange rates are slow, with high activation energies for dissociation of the complex (of the order of 16 kcal/mol).[80]

Spherical Molecular Cryptates. Ligand **28** forms an inclusion complex with the ammonium cation $[NH_4^+\subset\mathbf{28}]$.[80] It represents topologically the optimal NH_4^+ receptor (Figure 5); the cation forms a tetrahedral array of hydrogen bonds toward the four nitrogen sites, and there are six electrostatic $O\rightarrow N^+$ interactions, one along the bisectrix of each of the H–N–H angles, in agreement with the crystal structure.[81]

Ligand **28** has abnormal acid–base properties ($pK_2 \sim pK_1$), whereas the bicyclic compound **30** behaves as a regular tetramine. The present results indicate that the diprotonated ligand has in fact a water molecule included in its cavity; it is therefore $[H_2O\subset\mathbf{28}\text{-}H_2^{2+}]$ (Figure 5), i.e., a water receptor molecule. The water molecule is held in an ideal hydrogen bonding array with an ice-like, tetrahedral arrangement; it accepts two H bonds from the NH^+ sites and donates two H bonds to the unprotonated amino sites. The abnormal protonation features thus stem from a cooperativity effect mediated by an allosteric effector molecule, H_2O. Finally, NMR data show that proton exchange between $[H_2O\subset\mathbf{28}\text{-}H_2^{2+}]$ and the free ligand is very slow (< 20 s^{-1} at 25 °C). This implies also that water exchange is slow, pointing to a particularly stable water complex. The spherical macrotricyclic cryptands are thus molecule receptors displaying tetrahedral recognition of small inorganic molecules.

Spherical Anion Cryptates. NMR studies as well as measurements with halide ion selective electrodes have shown that the tetraprotonated forms of ligands **28**–**30** complex halide anions, just as diprotonated macrobicyclic diamines form katapinates.[21-23] The halide inclusion complexes are *macrotricyclic anion cryptates*, $[X^-\subset LH_4^{4+}]$ (Figure 5),[24] in which the spherical halide ion X^- is held by a tetrahedral array of N^+–H···X^- hydrogen bonds inside the molecular cavity of the tetraprotonated i_4 form of the ligands **L**, in agreement with the crystal structure of $[Cl^-\subset(\mathbf{28}\text{-}H_4^{4+})]3Cl^-\cdot 7H_2O$.[81] Ligands $\mathbf{28}\text{-}H_4^{4+}$ and $\mathbf{29}\text{-}H_4^{4+}$ may be considered as the topologically optimal receptors for spherical anions. The chloride complexes are very stable (log $K_s \geq 4.0 \pm 0.5$ in water), and the Cl^-/Br^- selectivity is high with both ligands.

The results give evidence for the operation of a marked *macrotricyclic effect:* the stability and selectivity of the Cl^- complexes are much higher for the spherical macrotricyclic ligands than for the macrobicyclic system **30**; this may be attributed to the presence of a closed, rigid cavity, into which Cl^- fits best

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and which resists deformation. F^- is complexed but I^- does not form a stable complex, nor do other anions like NO_3^-, SO_4^{2-}, etc.[24]

The design of cavities acting as receptors for other anions is feasible; the major requirement is to provide suitable electrostatic interactions and the correct array of hydrogen bonds for the anion while hindering as much as possible the hydration of the hydrogen bond donor sites. A new field of coordination chemistry is thus developing: anion complexes of organic ligands.

Prospects

Several lines for future developments may be recognized: (1) the design and synthesis of new types of organic molecules; (2) the construction of specific receptors bearing recognition sites for cations, anions, and molecules; (3) the design of molecular catalysts and selective carriers; (4) the synthesis of ligands bearing several cation-complexing sites and thus forming binuclear or polynuclear complexes in which distance and arrangement of the cations may be regulated via ligand structure; (5) the study of cascade complexes formed by substrate inclusion between metal cations of bi- or polynuclear complexes, which are of interest as bioinorganic models and as catalysts.

As a symbiosis of the architectural power of organic synthesis with the designed manipulation of intermolecular interactions and transformations, the chemistry of macropolycyclic systems may have a broad impact on both fundamental and applied research at the ternary meeting point of three major fields of chemistry: organic chemistry, inorganic chemistry, and biochemistry.

I wish to express my gratitude to the co-workers whose skill and dedication allowed us 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, the Dêlêgation Gênêrale à la Recherche Scientifique et Technique, and the University Louis Pasteur.

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Reactions of Electrophiles with σ-Bonded Organotransition-Metal Complexes

MICHAEL D. JOHNSON

Department of Chemistry, University College, London WC1H OAJ, England

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Mainly because of the need to start with well-characterized substrates, most of the mechanistic studies of the cleavage of carbon–metal σ bonds have utilized isolable, relatively stable, usually diamagnetic, organometallic complexes. Since by their very nature the selected complexes are not very prone to unimolecular decomposition in solution, the overall picture of reaction mechanisms is somewhat distorted, biased in favor of reagent-induced or concerted mechanisms. Nevertheless, such limited studies of mechanism have provided valuable information about ways in which carbon–metal bonds may be cleaved, and much of our present knowledge concerns those reactions promoted by electrophilic reagents. Even within this classification, however, a surprisingly wide range of different mechanisms have been identified and can be ascribed to the versatile character of many organometallic substrates and of electrophilic reagents.

In the field of σ-bonded organotransition-metal complexes, the variety of ligands often required to stabilize the carbon–metal bond ensures that such complexes are frequently polyfunctional molecules containing groups of widely different character, atoms of significantly different electronegativity and any of a range of possible charges. The highest occupied molecular orbital, which usually plays a vital role in these reactions, may be located on the metal, on one of the ligands, or in metal–ligand bonds. Thus the initial stage of a reaction between an organotransition-metal complex and an electrophile does not necessarily involve cleavage of the carbon–metal bond, though such cleavage frequently occurs in later processes.

Electrophiles are also versatile species, but in a different sense: they are also Lewis acids and oxidizing agents. The term *electrophilicity* should imply a kinetic role,[1] often rather narrowly associated solely with substitution processes, whereas Lewis acidity implies the corresponding thermodynamic role. Electrophilicity and Lewis acidity do not necessarily parallel one another, for each is markedly dependent upon the reacting center on the substrate. There have been a number of theories to account for these variations in electrophilicity and acidity, including the hard/soft[2] or class A/B approach,[3] the Edwards combination of proton acidity and redox potential discussed mainly with the nucleophilic center in mind,[4] and the orbital approach

Michael D. Johnson was born in Newcastle-under-Lyme, England. He studied at Southampton University for his B.Sc. degree, and then went on to graduate work there, receiving the Ph.D under N. B. Chapman in 1957. After a year of postdoctoral work with E. S. Lewis at Rice University and a year as a chemist at Imperial Oil Ltd., Sarnia, Canada, Dr. Johnson moved to University College London, where he is now Reader in Chemistry. His research is concerned with the mechanisms of reactions of σ-bonded organotransition-metal compounds, with special interest in homolytic displacement reactions, particularly at carbon centers, and their use in organic synthesis.

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