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Aspects of Anion Coordination from Historical Perspectives

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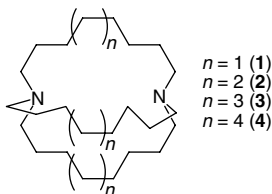
1.1

Introduction

Supramolecular chemistry, the chemistry beyond the molecule, gained its entry with the pioneering work of Pedersen, Lehn, and Cram in the decade 1960–1970 [1–5]. The concepts and language of this chemical discipline, which were in part borrowed from biology and coordination chemistry, can be to a large extent attributed to the scientific creativity of Lehn [6–8]. Recognition, translocation, catalysis, and self-organization are considered as the four cornerstones of supramolecular chemistry. Recognition includes not only the well-known transition metals (classical coordination chemistry) but also spherical metal ions, organic cations, and neutral and anionic species. Anions have a great relevance from a biological point of view since over 70% of all cofactors and substrates involved in biology are of anionic nature. Anion coordination chemistry also arose as a scientific topic with the conceptual development of supramolecular chemistry [8]. An initial reference book on this topic published in 1997 [9] has been followed by two more recent volumes [10, 11] and a number of review articles, many of them appearing in special journal issues dedicated to anion coordination. Some of these review articles are included in Refs [12–52]. Very recently, an entire issue of the journal *Chemical Society Reviews* was devoted to the supramolecular chemistry of anionic species [53]. Since our earlier book [9] the field has catapulted way beyond the early hosts and donor groups. Because covering the historical aspects of this highly evolved field would be impossible in the limited space here, a slightly different approach will be taken in this chapter. Rather than detail the entry of the newer structural strategies toward enhancing anion binding and the many classes of hydrogen bond donor groups that have come into the field, only the earlier development will be described. This will be linked with aspects of naturally occurring hosts, to provide a slightly different perspective on this exciting field.

Interestingly enough, the birth of the first-recognized synthetic halide receptors occurred practically at the same time as the discovery by Charles Pedersen of the alkali and alkaline-earth complexing agents, crown ethers. While Pedersen

submitted to *JACS* (*Journal of the American Chemical Society*) his first paper on crown ethers in April 1967 entitled “Cyclic Polyethers and their Complexes with Metal Salts” [1], Park and Simmons, who were working in the same company as Pedersen, submitted their paper on the complexes formed by bicyclic diammonium receptors with chloride entitled “Macrobicyclic Amines. III. Encapsulation of Halide ions by in, in-1, (k + 2)-diazabicyclo[k.l.m]alkane-ammonium ions” also to *JACS* in November of the same year [54].



These cage-type receptors (1-4) were called *katapinands*, after the Greek term describing the swallowing up of the anionic species toward the interior of the cavity (Figure 1.1). The engulfing of the chloride anion inside the katapinand cavity was confirmed years later by the X-ray analysis of the structure of Cl^- included in the [9.9.9] bicyclic katapinad [55]. However, while investigations on crown ethers rapidly evolved and many of these compounds were prepared and their chemistry widely explored, studies on anion coordination chemistry remained at the initial stage. Further development waited until Lehn and his group revisited this point in the late 1970s and beginning of the 1980s [56–62].

Nevertheless, evidence that anions interact with charged species, modifying their properties, in particular their acid–base behavior, was known from the early times of the development of speciation techniques in solution, when it was noted that

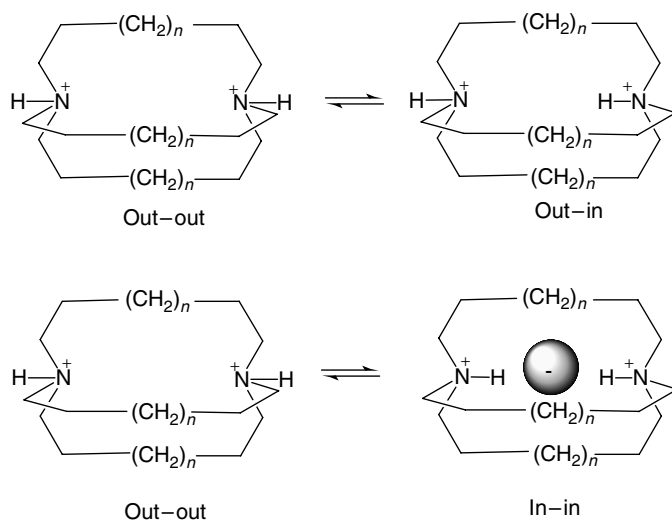
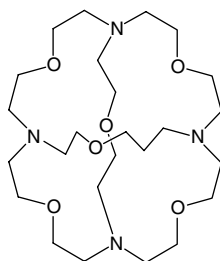


Figure 1.1 In–in and out–out equilibria, and halide complexation in katapinand receptors.

protonation constants were strongly influenced by the background salt used to keep the ionic strength constant [63]. Following these initial developments, Sanmartano and coworkers did extensive work on the determination of protonation constants in water with and without using ionic strength. In this way, this research group was able to measure interaction constants of polyammonium receptors with different anionic species [64, 65]. Along this line, Martell, Lehn, and coworkers reported an interesting study in which the basicity constants of the polyaza tricycle (5) were determined by pH-metric titrations using different salts to keep the ionic strength constant [66]. The authors observed that while the use of KClO_4 did not produce significant differences in the constants with respect to the supposedly innocent trimethylbenzene sulfonate anion (TMBS), the use of KNO_3 and KCl led to higher pK_a values, particularly as more acidic conditions were reached. From these titrations, binding constants of nitrate and chloride with hexaprotonated 5 were determined to be 2.93 and 2.26 logarithmic units, respectively.



5

Similar events were observed in the biological world many years ago. The well-known Hofmeister series or lyotropic series [67] was postulated at the end of the nineteenth century to rank the relative influence of ions on the physical behavior of a wide variety of processes ranging from colloidal assembly to protein folding. The Hofmeister series, which is more pronounced for anions than for cations, orders anions in the way shown in Figure 1.2. The species to the left of Cl^- are called *kosmotropes*, “water structure makers,” and those to the right of

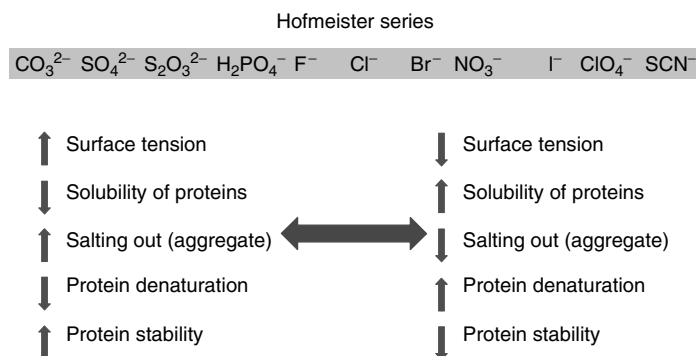


Figure 1.2 Representation of the Hofmeister series.

chloride are termed *chaotropes*, “water structure breakers.” While the kosmotropes are strongly hydrated and have stabilizing and salting-out effects on proteins and macromolecules, the chaotropes destabilize folded proteins and have a salting-in behavior.

Although originally these ion effects were attributed to making or breaking bulk water structure, more recent spectroscopic and thermodynamic studies pointed out that water structure is not central to the Hofmeister series and that macromolecule–anion interactions as well as interactions with water molecules in the first hydration shell seem to be the key point for explaining this behavior [68–72].

In this respect, as early as in the 1940s and 1950s, researchers sought to address the evidence and interpret the nature of the binding of anions to proteins [73]. Colvin, in 1952 [74], studying the interaction of a number of anions with the lysozyme, *calf thymus* histone sulfate, and protamine sulfate proteins using equilibrium dialysis techniques, concluded that although electrostatic charge–charge interactions may be chiefly responsible for the negative free energy of binding, there were other contributions such as van der Waals and solvation energies that can equal or even exceed the charge to charge component.

More recently, the use of X-ray diffraction techniques for unraveling the structure of proteins and enzymes has provided many illustrative examples of key functional groups involved in anion binding. In this respect, the phosphate-binding protein (PBP) is a periplasmic protein that acts as an efficient transport system for phosphate in bacteria. The selection of phosphate over sulfate is achieved taking advantage of the fact that phosphate anion is protonated at physiological pH and can thus behave as both a hydrogen bond donor and an acceptor. The strong binding of phosphate (dissociation constant, $K_d = 0.31 \times 10^{-6}$ M) is achieved through the formation of 12 hydrogen bonds to a fully desolvated HPO_4^{2-} residing inside a deep cleft of the protein (Figure 1.3a) [75]. One of these hydrogen bonds, which is crucial for phosphate over sulfate selectivity, involves the OH group of phosphate as a donor and one aspartate residue as the acceptor (Asp141 in Figure 1.3a). Analogous to PBP, the sulfate-binding protein (SBP) is a bacterial protein responsible for

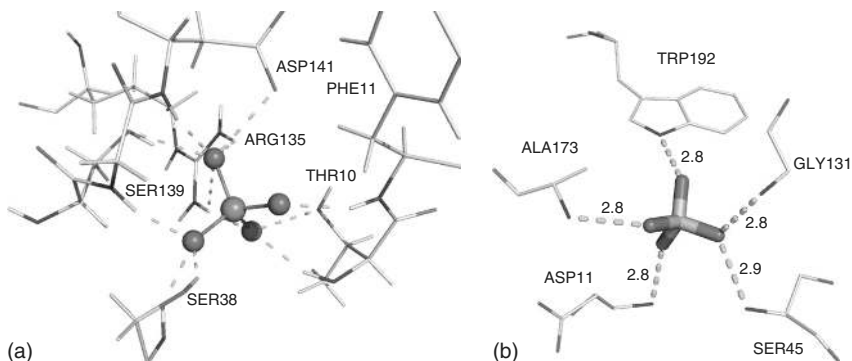


Figure 1.3 Scheme of the active sites of PBP (a) and SBP (b).

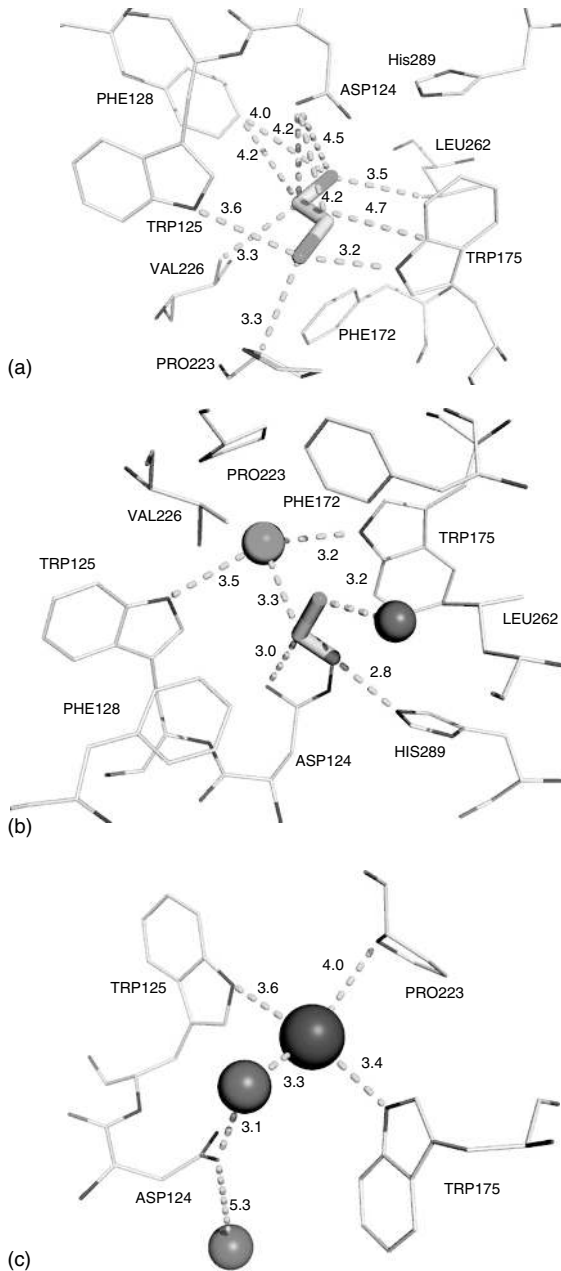


Figure 1.4 Schematic view of the interactions occurring in the active site of dehalogenase: (a) with the substrate before the start of the reaction, (b) with the alkyl intermediate and the chloride ion during the reaction, and (c) with the chloride ion and water molecules after hydrolysis.

the selective transport of this anion. Sulfate binding relies on the formation of a hydrogen bond network in which sulfate accepts seven hydrogen bonds, most coming from NH groups of the protein backbone (Figure 1.3b). The selectivity for sulfate over phosphate is about 50 000-fold in this protein [76].

Another bacterial protein whose crystal structure has revealed interesting binding motifs to anions is haloalkane dehydrogenase, which converts 1-haloalkanes or α, ω -haloalkanes into primary alcohols and a halide ion by hydrolytic cleavage of the carbon–halogen bond with water as a cosubstrate and without any need for oxygen or cofactors [77]. The crystal structure of the dehalogenase with chloride as the product of the reaction shows that the halide is bound in the active site through four hydrogen bonds involving the N ϵ of the indole moieties of two tryptophan residues, the C α of a proline, and a water molecule (Figure 1.4).

One of the most important characteristics of anions is their Lewis base character. Therefore, compounds possessing suitable Lewis acid centers can be appropriate anion receptors. Several families of boranes, organotin, organogermanium, mercurborands, acidic silica macrocycles, and a number of metallomacrocycles have been shown to display interesting binding properties with anions. Examples of this chemistry are included in Figures 1.5 and 1.6 and Refs [78–94].

Anion coordination chemistry and classical metal coordination chemistry have an interface in mixed metal complexes with exogen anionic ligands. Indeed, most of the ligands are anionic species belonging to groups 15–17 of the periodic table. Metal complexes can express their Lewis acid characteristics if they are coordinatively unsaturated or if they have coordination positions occupied by labile ligands that can be easily replaced. If this occurs, metal complexes are well suited for interacting with additional Lewis bases, which are very often anionic in nature, giving rise to mixed complexes. Mixed complexes in which the anionic ligand bridges between two or more different metal centers have been termed, in the new times of supramolecular chemistry, “*cascade complexes*” [95].

Formation of mixed complexes is the strategy of choice of many metalloenzymes dealing with the fixation and activation of small substrates. A classic example is

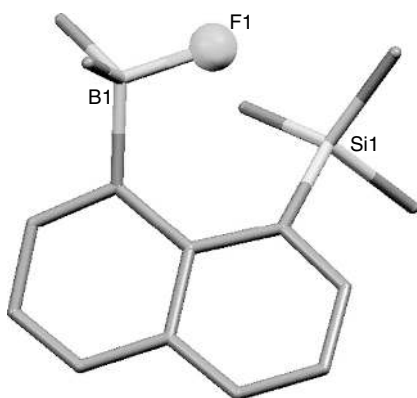


Figure 1.5 ORTEP diagram of the fluoride complex of a boron–silicon receptor. Taken from Ref. [85].

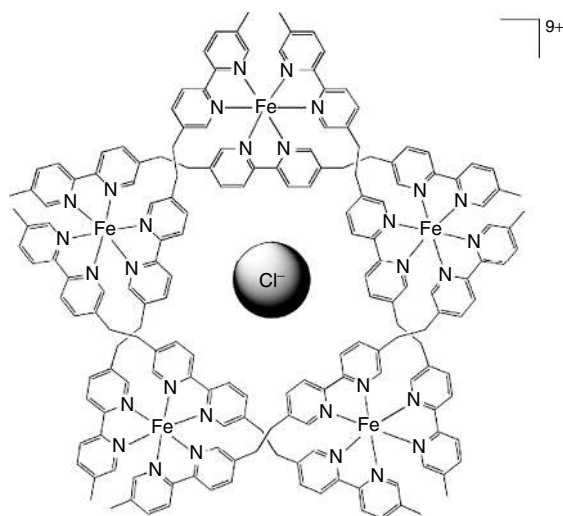


Figure 1.6 Reaction of FeCl_2 and a tris-bipyridine ligand gives rise to a double helix with the chloride as a template [94].

the family of enzymes called *carbonic anhydrases* [96–98]. Carbonic anhydrases are ubiquitous enzymes that catalyze the hydration reaction of carbon dioxide and play roles in processes such as photosynthesis, respiration, calcification and decalcification, and pH buffering of fluids. Human carbonic anhydrase II (HCA II) is located in the erythrocytes and is the fastest isoenzyme accelerating CO_2 hydrolysis by a factor of 10^7 . Therefore, it is considered to be a perfectly evolved system, its rate being controlled just by diffusion. The active site of HCA II is formed by a Zn^{2+} cation coordinated to three nitrogen atoms from histidine residues and to a water molecule that is hydrogen bonded to a threonine residue and to a “relay” of water molecules that interconnects the coordination site with histidine 64 (Figure 1.7). The pKa of the coordinated water molecule in this environment is circa 7, so that at this pH, 50% is hydroxylated as Zn-OH^- , thus generating a nucleophile that will attack CO_2 to give the HCO_3^- form.

The rate-determining step is precisely the deprotonation of the coordinated water molecule and the transfer of the proton through the chain of water molecules to His64, which assists the process.

Phosphatases are the enzymes in charge of the hydrolysis of phosphate monoesters. Metallophosphatases contain either Zn^{2+} or Fe^{3+} or both; one of their characteristics is the presence of at least two metal ions in the active site. *Escherichia coli* alkaline phosphatase contains two Zn^{2+} and one Mg^{2+} metal ions in the active center. In the first step of the catalytic mechanism, the phosphate group of the substrate interacts as a bridging η, η' -bis(monodentate) ligand through two of its oxygen atoms with the two Zn^{2+} ions, while its other two oxygen atoms form hydrogen bonds with an arginine residue rightly disposed in the polypeptide chain (Figure 1.8).

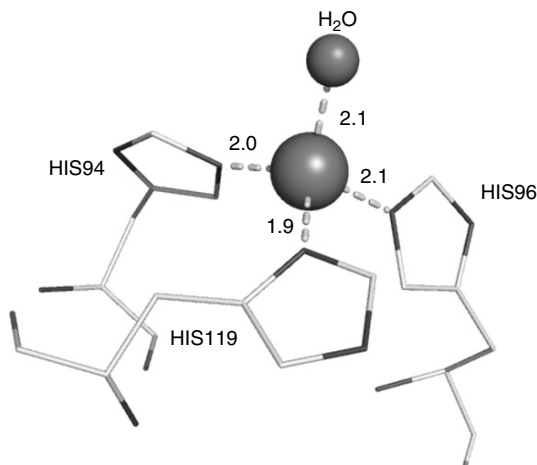


Figure 1.7 Schematic representation of the active site of HCA II showing the tetrahedral arrangement of three histidine residues and a water molecule.

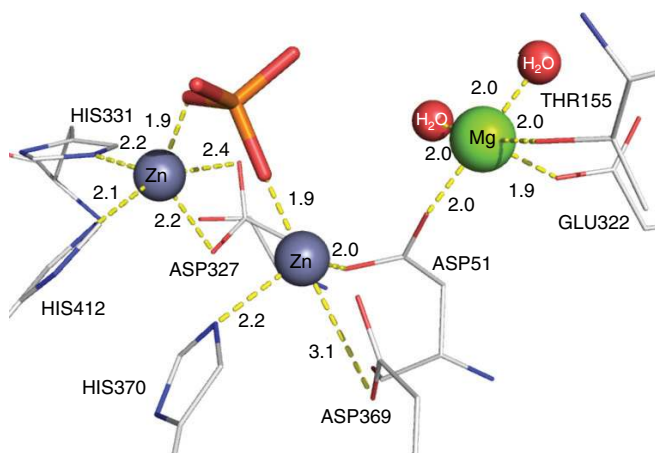


Figure 1.8 Active site of alkaline phosphatases. Adapted from Ref. [99, 100].

A last example that we would like to recall is ribulose-1,5-bisphosphate carboxylase/oxygenase (*rubisco*), which is the most abundant enzyme in nature [101]. *Rubisco* is a magnesium protein that is present in all the photosynthetic organisms participating in the first stage of the Calvin cycle. A lysine residue interacts with CO_2 , forming an elusive carbamate bond, which is stabilized by interaction with the Mg^{2+} ion and by a hydrogen bond network with other groups of the polypeptidic chain (Figure 1.9). The ternary complex formed interacts with the substrate, which is subsequently carboxylated.

In all these examples, anionic substrates bind (coordinate) to a metal ion in key steps of their catalytic cycles, which assists the process as a Lewis acid.

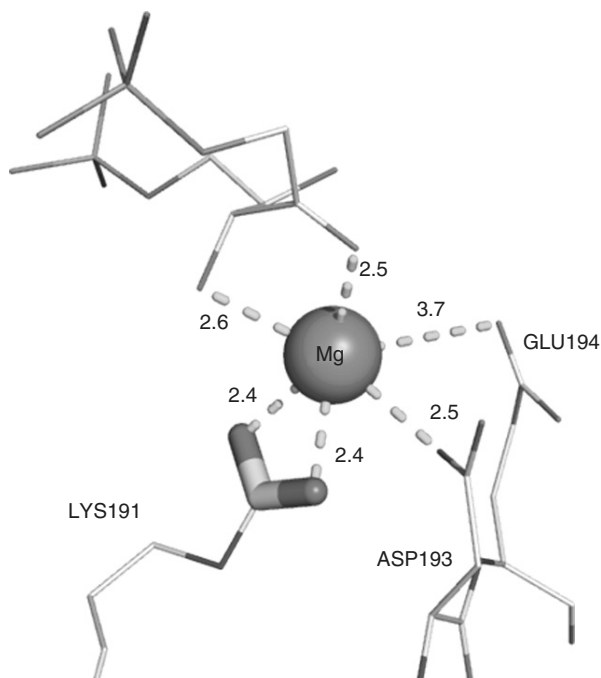
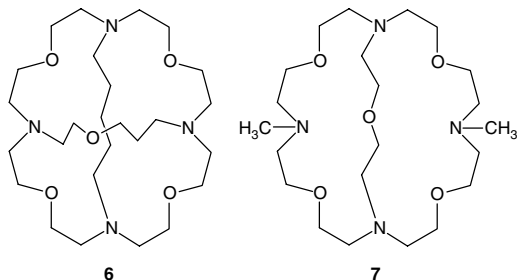


Figure 1.9 Active site of the enzyme *rubisco*. Adapted from Ref. [100].

1.2

Halide and Pseudohalide Anions

Having all these points in mind, there is no doubt that the birth of supramolecular anion coordination chemistry as an organized scientific discipline can be traced back to the work started by Lehn and coworkers in the mid-1970s. The first seminal paper of Lehn's group dealt with the encapsulation of halide anions within tricyclic macrocycles 5–7 [56]. The parent compound of the series 5, already mentioned in the previous section, which is known as the *soccer ball ligand* in the jargon of the field, had been synthesized one year in advance by the same authors [102].

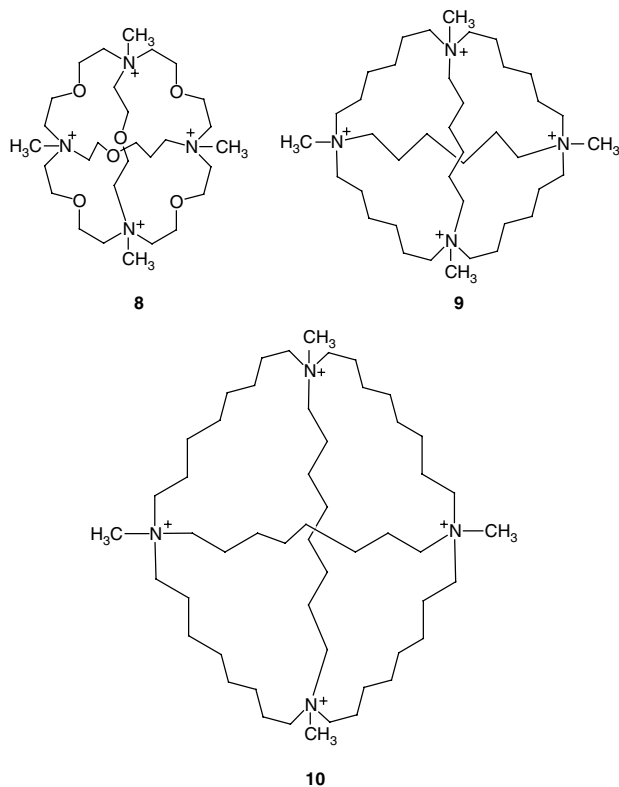


The authors started this paper stating that “Whereas very many metal cation complexes are known, stable anion complexes of organic ligands are very rare

indeed.” By means of ^{13}C NMR, the authors proved the inclusion of F^- , Cl^- , and Br^- within the macrotricyclic cavity at the time when they found a remarkable Cl^-/Br^- selectivity in water of circa 1000.

No interaction was observed with the larger I^- and with the monovalent anions NO_3^- , CF_3COO^- , and ClO_4^- . The crystal structure of $[\text{Cl}^- \subset \text{H}_4(\mathbf{1})^{4+}]$, where the mathematical symbol \subset stands for inclusive binding, shows that chloride was held within the tetraprotonated macrocycle by an array of four hydrogen bonds with the ammonium groups [103]. Years later, Lehn and Kintzinger, in collaboration with Dye and other scientists from the Michigan State University, used ^{35}Cl NMR to study the interaction of halide anions with **5**, **6**, and several related polycycles [61].

This premier study on spherical anion recognition was followed by the work performed in Munich by Schmidtchen, who described the synthesis of a quaternized analog of **5** (receptor **8**) [104]. In the same paper, similar macrocycles with hexamethylene and octamethylene bridges connecting the quaternary ammonium groups placed at the corners of the polycycles were also reported (**9** and **10**).



These azamacropolycycles, whose binding ability does not depend on pH, show modest affinity for halide anions in water. In the case of **9** and **10**, selectivity for bromide and iodide over chloride was found. However, binding is clearly weaker

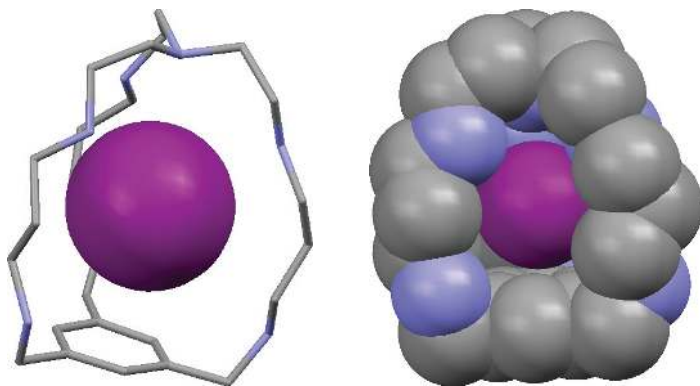
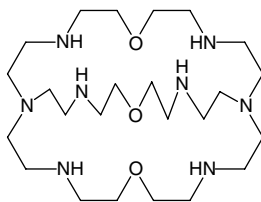


Figure 1.10 Views of the inclusion complex of I^- into the cavity of **9**.

than when auxiliary hydrogen bonding can occur. The crystal structure of an iodide complex with **9**, having hexamethylene bridges, confirmed the inclusion of the anion in the macrotricyclic cavity [105] (Figure 1.10). This series expanded over a wide range of studies illustrating the conceptual utility of these systems for understanding the kinds of binding forces involved in anion coordination [106–118].

Recognition of fluoride came up a little bit later, probably because of the higher difficulties in binding this anion in aqueous solution, which are associated with its high hydration energy in comparison to the other halides. In this respect, it has to be emphasized that most of the pioneering studies in anion coordination were carried out in water. The first stable fluoride complex was obtained with the bicyclic cage nicknamed O-BISTREN (**11**) [119].



11

However, as illustrated in Figure 1.11 [120], the fitting of fluoride within the cavity was not very snug. The anion sits off-center, forming hydrogen bonds with just four of the six ammonium groups of the macrocycle. Consequently, although higher constants were found for the interaction of fluoride with $[\text{H}_6(\mathbf{11})]^{6+}$, the selectivity over the other halides, Cl^- , Br^- , and I^- , was not very large ($\log K$ 4.1, 3.0, 2.6, and 2.1 for F^- , Cl^- , Br^- , and I^- , respectively). In Figure 1.12, it can be seen that chloride fits more tightly into the cavity of **11**. In this case, hydrogen bonds are formed between the encapsulated anion and all six ammonium groups of the cryptand, although some of them are relatively weak.

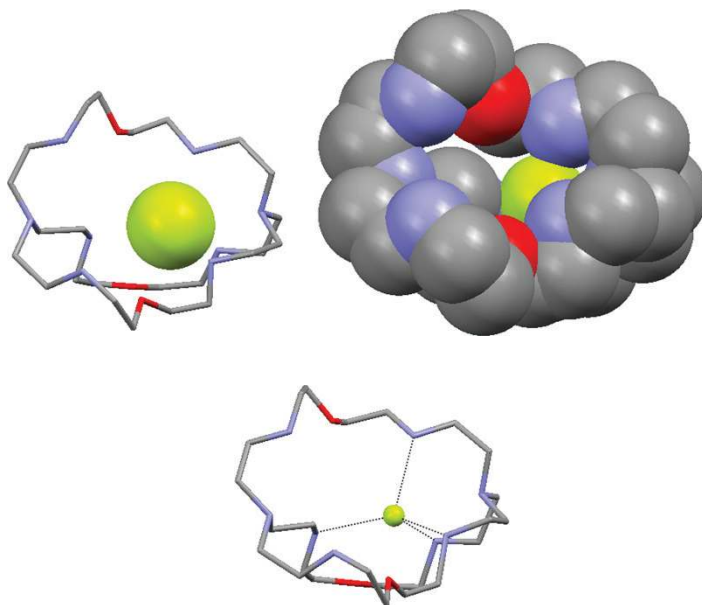


Figure 1.11 Views of F^- included in the molecular cavity of hexaprotonated **11** showing the mismatch in size. Hydrogen atoms have been omitted.

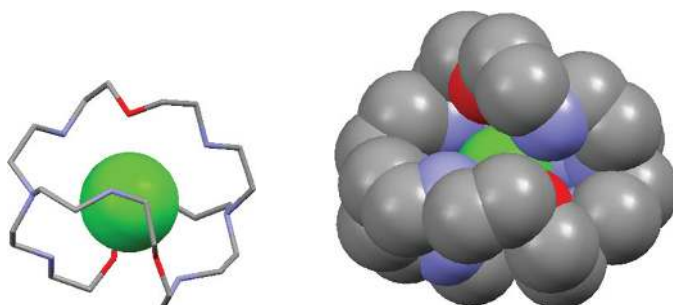
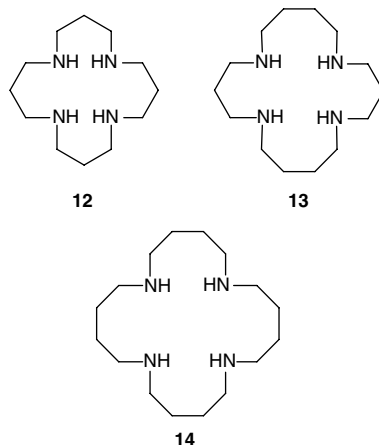
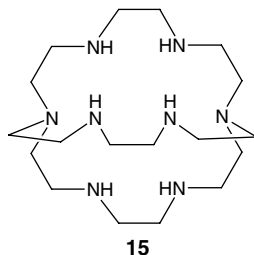


Figure 1.12 View of Cl^- included in the molecular cavity of hexaprotonated **11**. Hydrogen atoms have been omitted.

With respect to fluoride binding, it is worth mentioning that, in 1984, a report by Suet and Handel appeared, describing the ability of different monocyclic tetraazamacrocycles with propylenic and butylenic chains (**12**–**14**) to bind this anion in aqueous solution [121]. The stability constants found for the interaction of fluoride with the tetraprotonated forms of **12**, **13**, and **14** were 1.9, 2.0, and 2.8 logarithmic units, respectively.



In order to obtain a more selective F^- binder, the macrocycle C2-BISTREN was prepared by Lehn and coworkers [122] several years later (15) [123].



The matching in size between fluoride and the cavity was in this case much tighter (Figure 1.13). Unlike in O-BISTREN (11), fluoride accepts hydrogen bonds from all six secondary ammonium groups of the cage 15. Solution studies carried out by Hay, Smith *et al.* in 1995 using potentiometric techniques led to a surprisingly large value of 11.2 logarithmic units for the interaction of the hexaprotonated macrocycle with fluoride anion measured in 0.1 M KNO_3 [124]. The reported F^-/Cl^- selectivity at $pH = 5.9$ expressed as $\log K_s(F^- \text{ complex})/\log K_s(Cl^- \text{ complex})$ was also an exceptionally high 7.5. Lehn and coworkers obtained for this equilibrium a similar value of 10.55 logarithmic units using 0.1 M $(Me_4N)TsO$ as the background electrolyte [123].

The success in obtaining a good fluoride-selective receptor led to the modification of the structure of 15 to obtain receptors that could match the size of the larger halides, Cl^- , Br^- , and I^- (compounds 16 and 17) [123, 125, 126]. However, the results obtained, although pointing in the desired direction, did not show any particularly relevant selectivity. Receptor 18 (C5-BISTREN) prepared by Lehn's group was studied along with 11 by potentiometry in collaboration with Martell and coworkers. Such studies, and the crystal structure of the azide complex [57], gave the first indications of the possibility of the formation of binuclear or higher nuclear anionic complexes with two encapsulated anions or, even better, with the hydrogen bifluoride anion (HF_2^-) (see below for

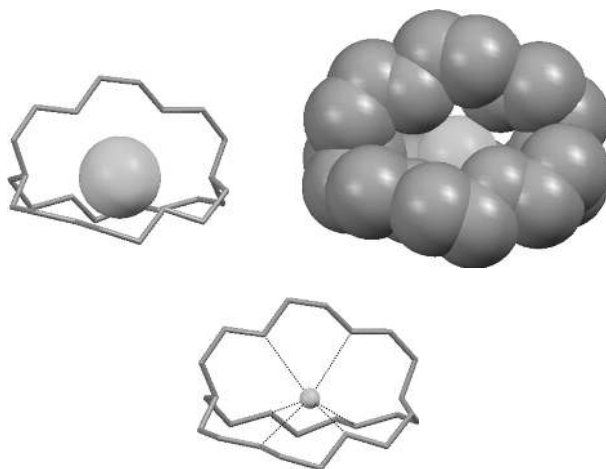
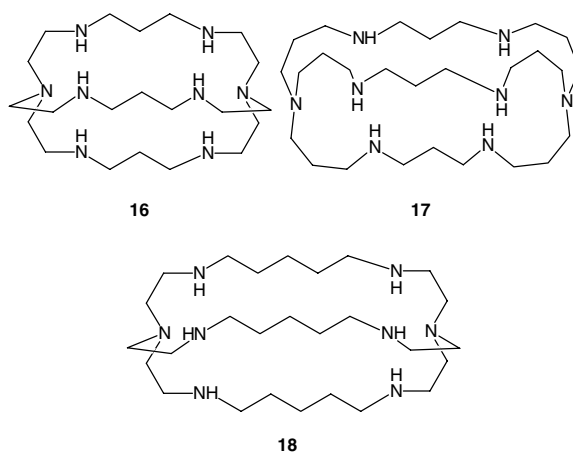


Figure 1.13 Views of the F^- anion included in C2-BISTREN (**15**).



further developments) [127, 128]. The constants for the equilibrium between the hexaprotonated receptor and HF_2^- were 6.4 and 5.2 logarithmic units for **11** and **18**, respectively.

O-BISTREN (**11**) was also the first synthetic receptor for which a crystal structure with an included N_3^- was solved by X-ray crystallography. The azide anion fits perfectly along the internal cavity of the receptor, forming each of its terminal nitrogen hydrogen bonds with the three ammonium groups of each of the two *tren* polyamine subunits of the cage (Figure 1.14) [57].

Fortunately and curiously, this structure and the previously discussed one for fluoride, which have proved to be crucial for the development of the field of anion coordination, were accepted for publication in spite of having R factors of 16.2 and 19.8, respectively.

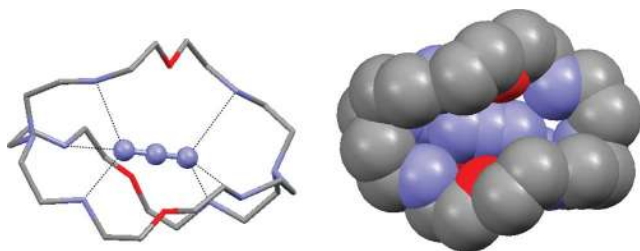
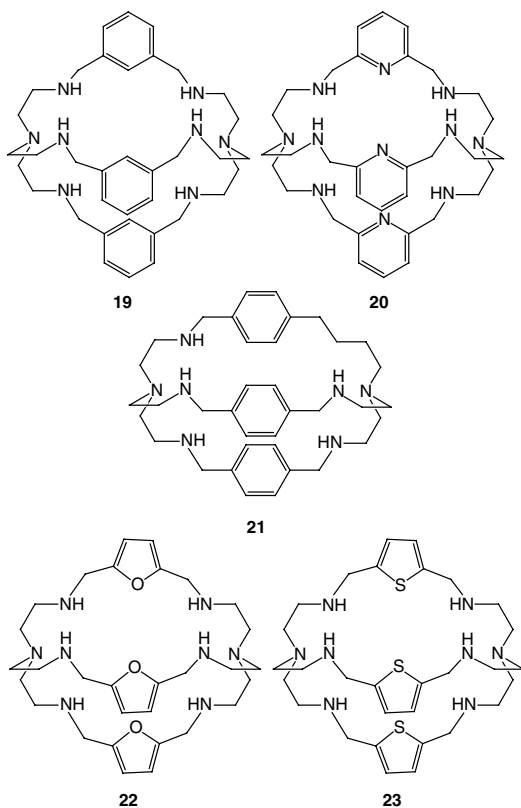


Figure 1.14 Azide anion included in the cavity of receptor 11.



Since these initial findings, many efforts have been devoted to halide recognition with different types of receptors. Among polyammonium receptors, probably the most used have been cryptands obtained by 2 + 3 condensation of the tripodal polyamine *tren* and the corresponding aromatic dialdehydes followed by *in situ* reduction with an appropriate reducing species, often NaBH_4 (19–23). One of the reasons for the large amount of work performed with these receptors is the readiness of its synthesis, which is much more straightforward than those required for preparing cages with aliphatic linkers between the *tren* subunits.

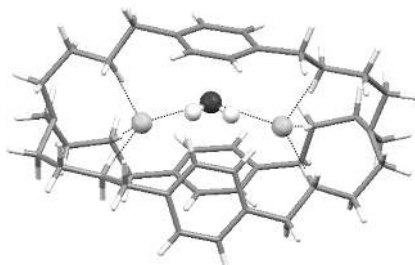


Figure 1.15 View of the fluoride-water cascade complex of $[H_621]^{6+}$.

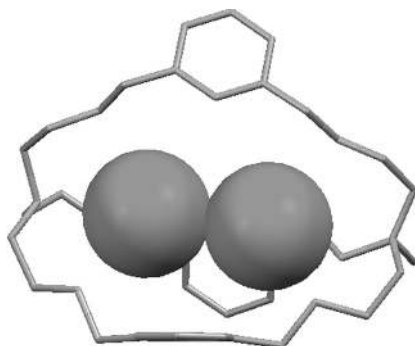


Figure 1.16 Presumed bichloride complex of hexaprotonated **19**, bridging hydrogen not shown.

These latter preps often require tedious protection and deprotection steps in addition to high dilution methods. Examples are receptors **19**–**23**, which are abbreviated as MEACryp, pyridine azacryptand (PyEACryp), PEACryp, FuEACryp, and ThioEACryp following the short names proposed by the late Robert W. Hay from St. Andrews University [129].

Nelson [21], Bowman-James [20, 129], Fabbrizzi [19], and Ghosh [130], among others, have contributed extensively to this chemistry. Perhaps, one of the most interesting developments in this topic has been the crystallographic evidence that this kind of receptors can lodge two halide anions when they are extensively protonated. Figures 1.15 and 1.16 show the crystal structures of hexaprotonated **21** with two fluorides and a water molecule bridging between them forming an anion “cascade complex” [131], and presumably of a bichloride $Cl-H-Cl$ anion included in hexaprotonated **19** [132].

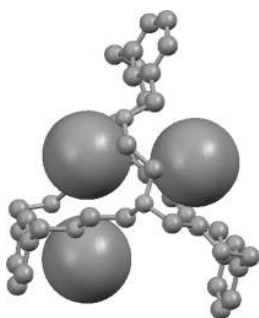
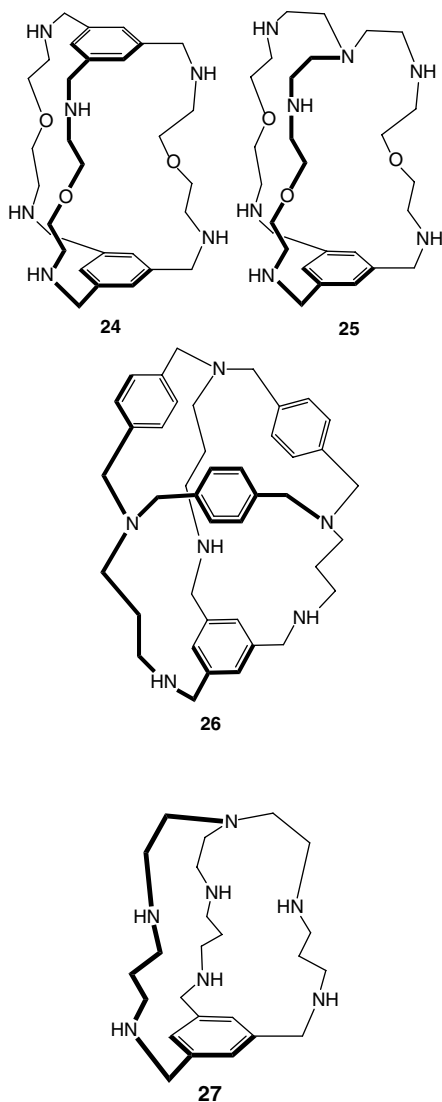


Figure 1.17 View of three bromides partially included in receptor **19**.

Also, in a rather early publication in the field, crystallography was used to prove the almost total inclusion of three bromide anions within the cavity of **19** MEACryp [133] (Figure 1.17).

The polyazacryptands that impose rigidity are a corollary to 1,3,5 trisubstituted benzenes with bridges containing amines (**24–26**). This class of compounds, prepared by Lehn's group [134, 135] for the first time, form 1:1 halide:receptor complexes with a significant stability in water. Recently, crystal structures of anionic complexes have been obtained for a similar receptor **27** developed by Steed *et al.* [136] (Figure 1.18).



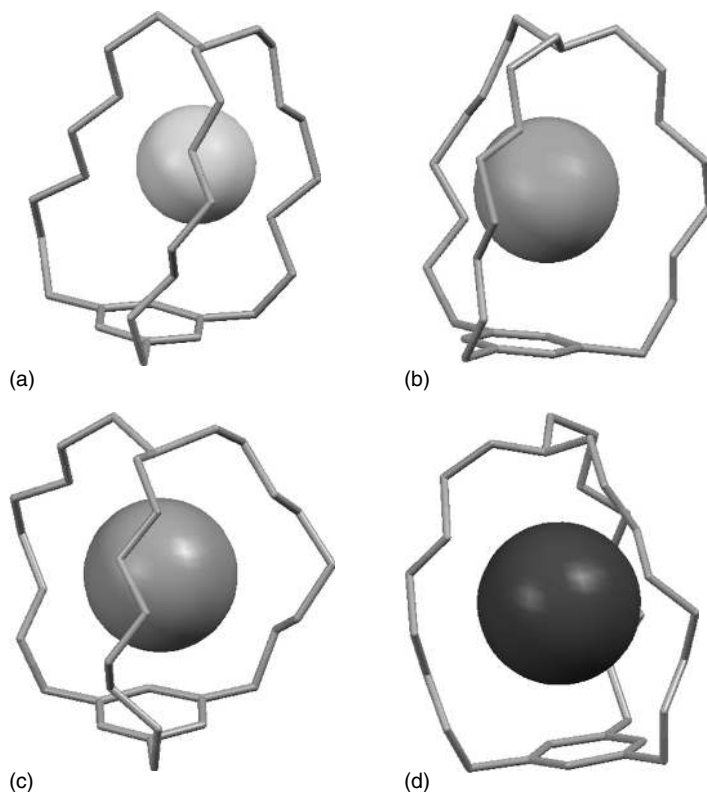
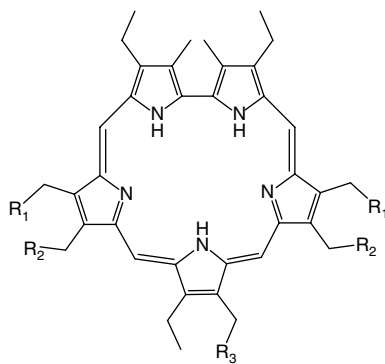


Figure 1.18 Halide anion included in hexaprotonated **27** (a) F^- , (b) Cl^- , (c) Br^- , and (d) I^- .

The initial work in the field was essentially performed with polyammonium receptors to take advantage of their charge. Indeed, the main characteristic distinguishing anions from all other guest species is precisely their negative charge. However, as advanced in Section 1.1, biological receptors, proteins, make use of a combination of binding motifs, which are provided in many instances by the side chains of amino acids and by the amide bonds of their backbones. The environment of protein clefts or pockets, where many binding sites reside, has a pronounced lipophilic character, and therefore, hydrogen bonds become stronger in this ambient condition with reduced water content. On the other hand, extraction strategies of pollutant anions from contaminated aqueous media often require hydrophobic receptors that can be kept soluble in a nonpolar solvent. Moreover, receptors can be grafted in resins or solid supports, making their solubility characteristics less critical.

On the basis of these important considerations, either charged or noncharged receptors containing a variety of hydrogen bonding donor groups came into play.

In this respect, Sessler, Ibers *et al.* [137] were, in 1990, the first to evidence a fluoride anion residing in the central hole of a saphyrin, a $22\text{-}\pi$ -electron pentapyrrolic expanded porphyrin (**28–31**).



28 R₁ = CH₃, R₂ = H, R₃ = H

29 R₁ = H, R₂ = CH₃, R₃ = CH₃

30 R₁ = H, R₂ = CO₂Et, R₃ = CH₃

31 R₁ = H, R₂ = CO₂Et, R₃ = CH₃

Treatment of saphyrin (**28**) as its free base with aqueous HCl in dichloromethane followed by adding silver hexafluorophosphate and crystallizing by vapor diffusion led to the isolation of the diprotonated macrocycle with just one hexafluorophosphate counteranion and another anion located at the center of the macrocyclic hole. On the basis of independent synthesis and ¹⁹F-NMR studies, it was established that the central anion was fluoride. The anion is hydrogen bonded to all five pyrrolic nitrogens of the macrocycle (Figure 1.19).

This first result on cyclic polypyrrole anion receptors gave rise to the evolution of these ligands and to the understanding of their chemistry and applications in a variety of fields [10, 138]. One of the first applications involved the capacity of these hydrophobic compounds for transporting fluoride anions across lipophilic membranes [139].

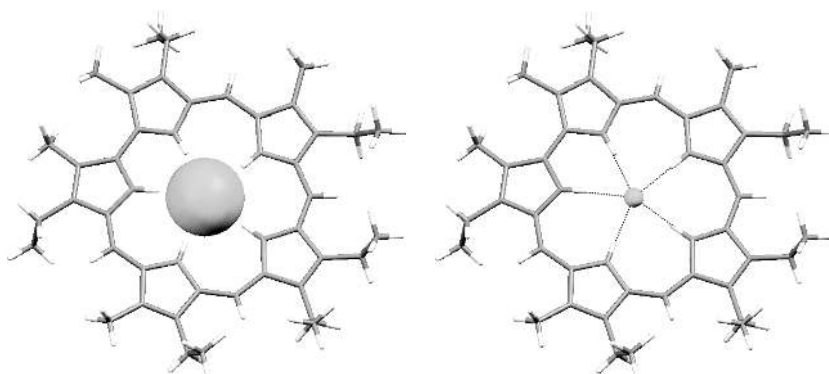
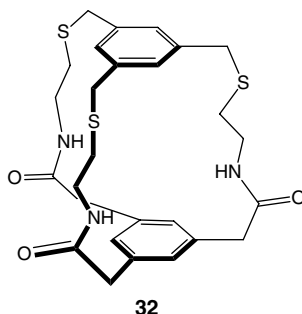


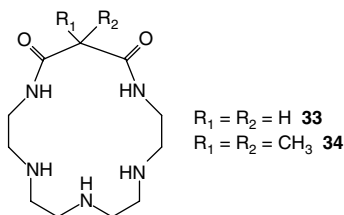
Figure 1.19 Views of the structure of the fluoride complex of diprotonated **28**, saphyrin.

As commented above, another binding motif relevant to anion coordination in proteins is the amide groups constituting the protein backbone. The first time the amide functionality was introduced in the structure of an abiotic macrocyclic receptor probably dates back to 1986 when Pascal, Spergel, and Van Eggen published the synthesis of compound **32** [140].



The authors stated very enthusiastically that compound **32** “may be prepared from the easily accessible precursors 1,3,5-tris(bromomethyl)benzene and 1,3,5-benzenetriacetic acid in a short convergent synthesis, requiring no chromatographic steps, which may be completed in less than 24 h.” In the same paper, the authors indicated that ^1H and ^{19}F NMR studies carried out in $\text{DMSO-}d_6$ suggested an association between the macrocycle and fluoride, although there was no certainty at that time about the inclusion of the anion. Since then, many amide-based receptors have been prepared [22, 23, 26, 29, 50, 53].

Kimura, Shiro and coworkers reported in 1989 amino-amide receptors **33**, **34**, along with a crystal structure of receptor **34**, in which two azide anions were trapped between two macrocycles, forming a sort of hydrogen-bonded sandwich complex [141] (Figure 1.20).



Recently, new cyclic receptors containing mixed amine–amide functions have been developed to take advantage of the charge of the potentially protonated amines and the hydrogen bond formation capabilities of both the amines and the amides [29]. A representative example of this chemistry is provided by the structure of bifluoride or azide anions encapsulated in the cavity of the tricyclic receptor **35** (Figure 1.21).

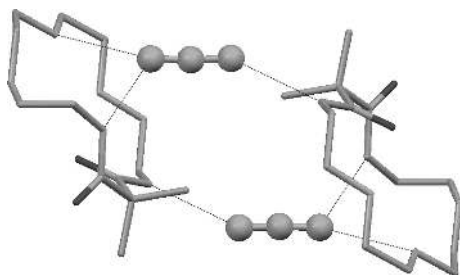


Figure 1.20 Sandwich complex between receptor **34** and azide.

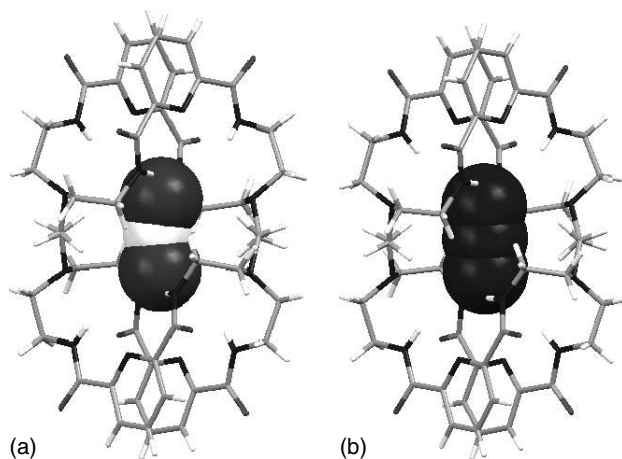
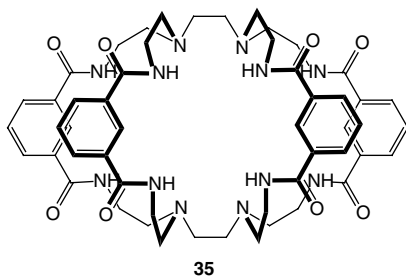


Figure 1.21 HF_2^- and N_3^- anions encapsulated in the tricyclic macrocycle **35**.



Since anions behave as Lewis bases, cyclic or noncyclic receptors containing Lewis acid sites can serve for anion binding. Examples of this chemistry have been advanced in Section 1.1 [78, 81, 83, 85, 87–94], and some other examples are provided in Figure 1.22.

As commented in Section 1.1, the interface between anion coordination chemistry and classical metal coordination chemistry is delimited by the so-called “cascade complexes” [95], a well-known class of multinuclear coordination compounds with bridging ligands. Relevant examples in the field of anion recognition can be found

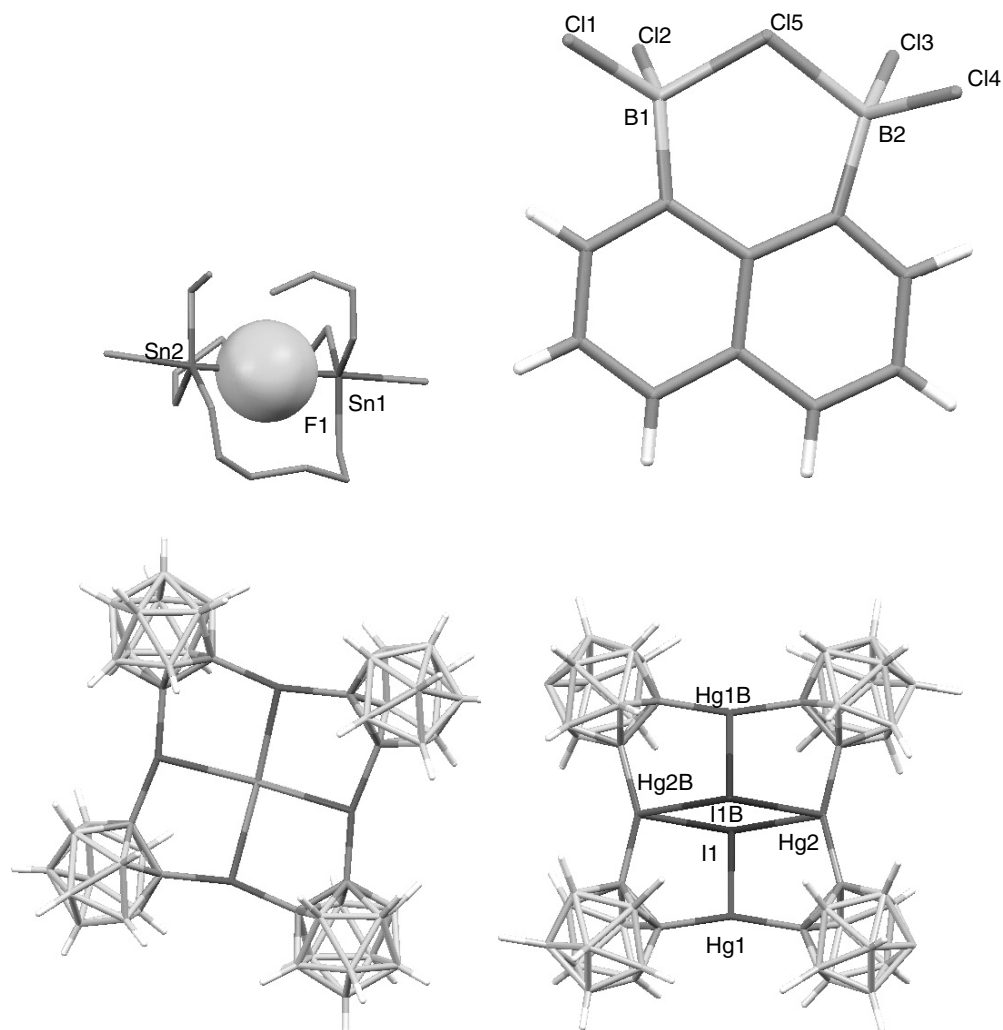


Figure 1.22 Crystal structure of an organotin compound binding fluoride [83] and an organoboron compound binding chloride [86], and of mecuracarborands binding chloride and iodide [78, 79].

in the initial work of Martell and Lehn on O-BISTREN (11) and C5-BISTREN (18), in which, based on disquisitions about the stability constants, a hydroxide and a fluoride anion were postulated to be included within the metal centers [127, 128]. Fabbrizzi and coworkers, among others, have contributed remarkably to this chemistry with several studies and crystal structures. Figure 1.23 collects three representative structures [142–144]. Reviews dealing with this topic are collected in Refs [19, 31, 47, 145].

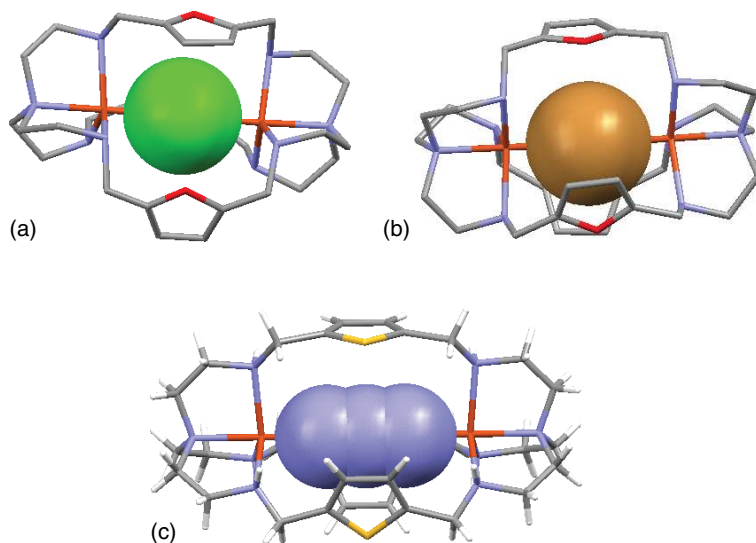


Figure 1.23 View of the “cascade complexes” formed by the binuclear Cu^{2+} complex of **22** with Cl^- and Br^- and between the Cu(II) complex of **23** with Br^- .

1.3 Oxoanions

Oxoanions have triangular, tetrahedral, or more complex shapes resulting from the association of different triangles or tetrahedrons that can be also accompanied by organic residues as in mono- and polynucleotides. On the other hand, if anions are conjugated bases of protic acids, they will undergo protonation processes and their negative charge will depend on their basicity constants. A simple example is provided by phosphate, which displays in water stepwise constants of 11.5, 7.7, and 2.1 logarithmic units for its first, second, and third protonation steps, respectively [146]. Therefore, phosphate exists only as a trivalent anion in a very basic pH range, while at neutral pH it is present in aqueous solution as a mixture of the monovalent and divalent forms. This property can be advantageously used for discriminating between anions of different basicity.

We start this historical description with anions that are conjugated bases of strong acids and that do not change their formal charge with pH.

One of the first studies in this respect was performed by Gelb, Zompa *et al.* on the interaction of nitrate and halide anions with the monocyclic polyamine [18]ane N_6 (**36**) [147]. Apart from deriving stability constants that were relatively low, only slightly above two logarithmic units for the interaction of the tetraprotonated macrocycle with nitrate and below two logarithmic units for its interaction with chloride, the authors described the crystal structure of the compound $[(\text{H}_4[18]\text{aneN}_6)](\text{NO}_3)_2\text{Cl}_2 \cdot \text{H}_2\text{O}$ (Figure 1.24). The nitrates and chlorides are placed

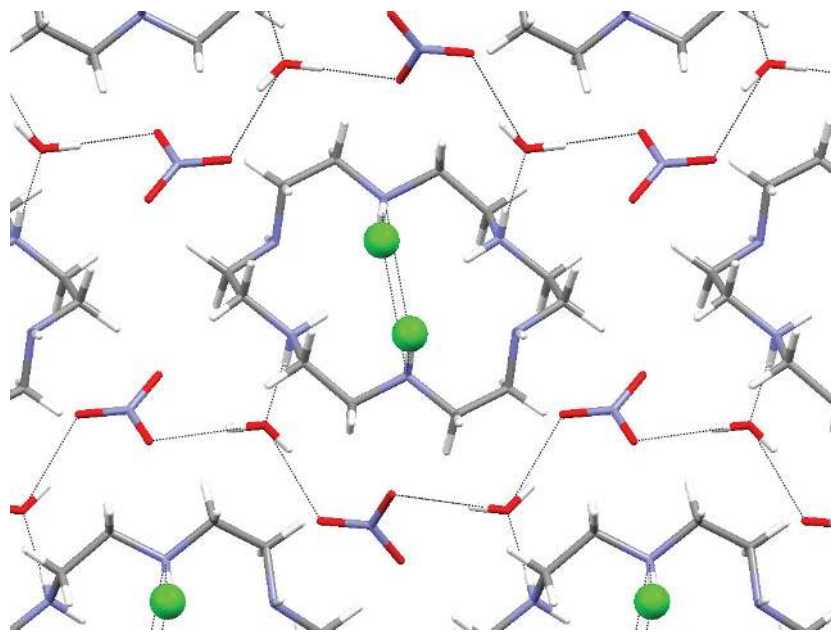
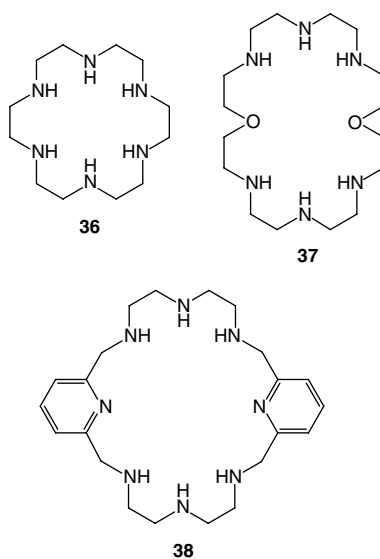


Figure 1.24 View of the hydrogen bonding network in $[H_4(36)](NO_3)_2Cl_2 \cdot H_2O$.

outside the macrocyclic cavity, forming two different hydrogen bonding networks. One of them links the ammonium groups with the nitrate anions through relays of water molecules; in the other, the ammonium groups are directly bound to the chloride anions.



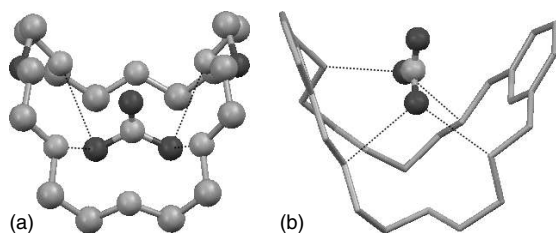


Figure 1.25 Situation of the NO_3^- anion in tetraprotonated macrocycles (a) **36** and (b) **38**.

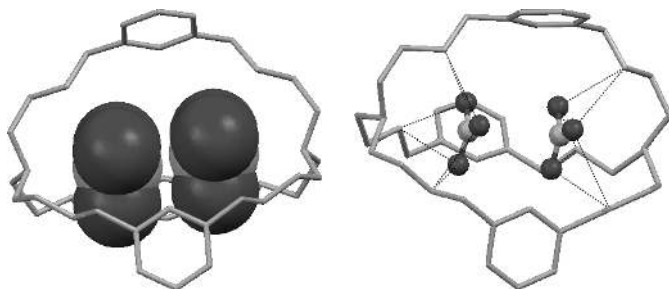


Figure 1.26 Views of the two nitrates included in **19**.

Two related crystal structures that have been more recently reported deserve to be mentioned since they illustrate an inclusive binding of nitrate anion in a monocyclic cavity. The first one is the crystal structure of the 24-membered dioxahexaazamacrocyclic (**37**), usually known as *O-BISDIEN*, with nitrate $[(\text{H}_4\text{37})](\text{NO}_3)_4$, reported by Bowman-James *et al.* [148], and the second one also corresponds to a 24-membered macrocycle with two meta-substituted pyridine spacers $[(\text{H}_4\text{38})](\text{NO}_3)_4$, recently published by Valencia, García-España, and coworkers [149]. In both crystal structures, one of the nitrates is linked through two bifurcated hydrogen bonds to the four protonated amino groups of the macrocycle, which displays a boat-shaped conformation (Figure 1.25). In spite of this similarity, the situation of the nitrate anion with respect to the heteroatoms is different, being symmetrically placed between the two aromatic rings in the pyridine macrocycle.

Azacryptands (**19–23**) can encapsulate nitrate as it was observed crystallographically for **19** (MEACryp) in 1998 [150]. Two nitrate anions were included in the cavity, with a parallel orientation between them (Figure 1.26). Hydrogen bonds were formed between the six secondary amino groups of the cage and all the oxygen atoms of the nitrate anions.

However, the first X-ray crystal structure solved for an oxoanion included in an azacryptand was for a perchlorate. Crystals of perchlorate anion included in the cavity of hexaprotonated **22** (FuEACryp) were obtained serendipitously in the course of an attempt to generate a binuclear manganese complex (Figure 1.27) [151]. Although some disorder obscured the hydrogen bond network of the included perchlorate, the participation of two types of hydrogen bonds, $\text{NH}^+ - \text{O}_{\text{perchlorate}}$ and $\text{NH}^+ - \text{O}_{\text{water}} - \text{O}_{\text{perchlorate}}$, seemed clear. Since this first structure, a number of

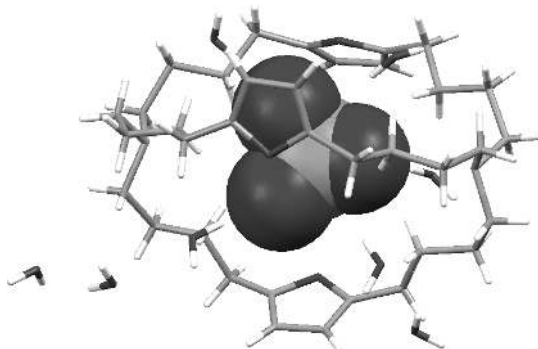


Figure 1.27 View of the perchlorate anion included in the cavity of receptor **22** (FuEACryp) [151].

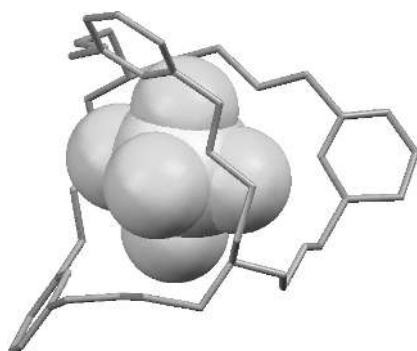


Figure 1.28 View of the anionic complex formed between hexaprotonated **20** and SiF_6^{2-} .

structures of azacryptands have appeared in the literature, in which two main coordination modes are observed that correspond either to inclusive anion binding or to facial binding of three anions similar to that shown in Figure 1.17 for **19**.

In this seminal paper, Nelson's group described another structure in which SiF_6^{2-} was also included in the cavity of **20** (PyEACryp) (Figure 1.28).

ReO_4^- is another anion belonging to this category whose study became relevant because its chemistry parallels that of radioactive $^{99\text{m}}\text{TcO}_4^-$. At the same time

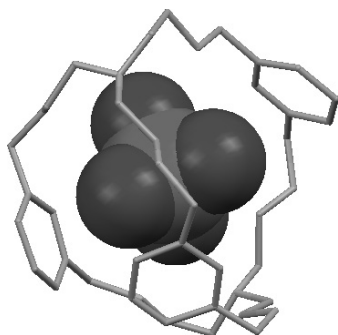
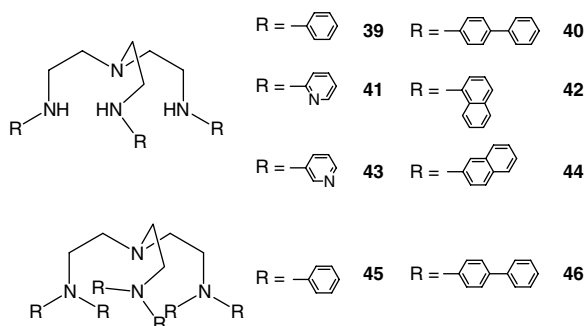


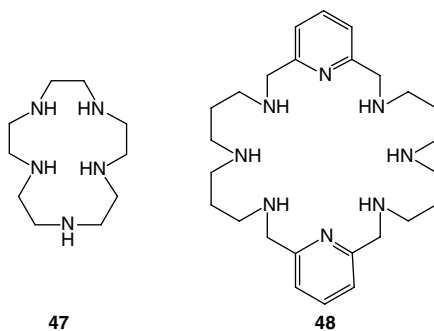
Figure 1.29 ReO_4^- included in MeACryp (**19**).

that $^{189}\text{ReO}_4^-$ itself is of medical interest in connection with specific therapeutic and diagnostic applications [49, 152–154]. Cryptands of this series have also been shown to be capable of interacting with ReO_4^- , including the anion within its cavity as shown in Figure 1.29 for **19** (MEACryp) [155]. These studies were devoted to the extraction of pollutant anions from aqueous media, and to do so, Gloe and Nelson also employed a series of hydrophobic polyamines derived from *tren*, as those seen in **39–46**. The extractabilities observed could not be explained solely on the basis of ligand lipophilicity since the level of protonation also played an important role.



Sulfate anion shows in aqueous solution a protonation step with a pK_a around 1.7 and thus behaves essentially as a divalent anion over a wide pH range, differing from phosphate, which at neutral pH exists as a mixture of mono- and dihydrogenphosphate with formal charges of -2 and -1 , respectively. Therefore, while sulfate can only accept hydrogen bonds, phosphate can both donate and accept hydrogen bonds. As mentioned earlier, this property is advantageously used by transport proteins to discriminate between these two anions.

The same kinds of receptors described for halides have also been traditionally used for binding sulfate. For instance, the monocycle [15]aneN₅ (**47**) [156] has been proved to interact in water with several dianions including SO_4^{2-} . Pyridinophane (**48**) interacts with SO_4^{2-} and SeO_4^{2-} among other anions [157] with $\log K_s$ values of around 3.5.



However, divalent anions having much larger hydration energies than mono-valent anions should be better recognized by cage-type ligands in which the first

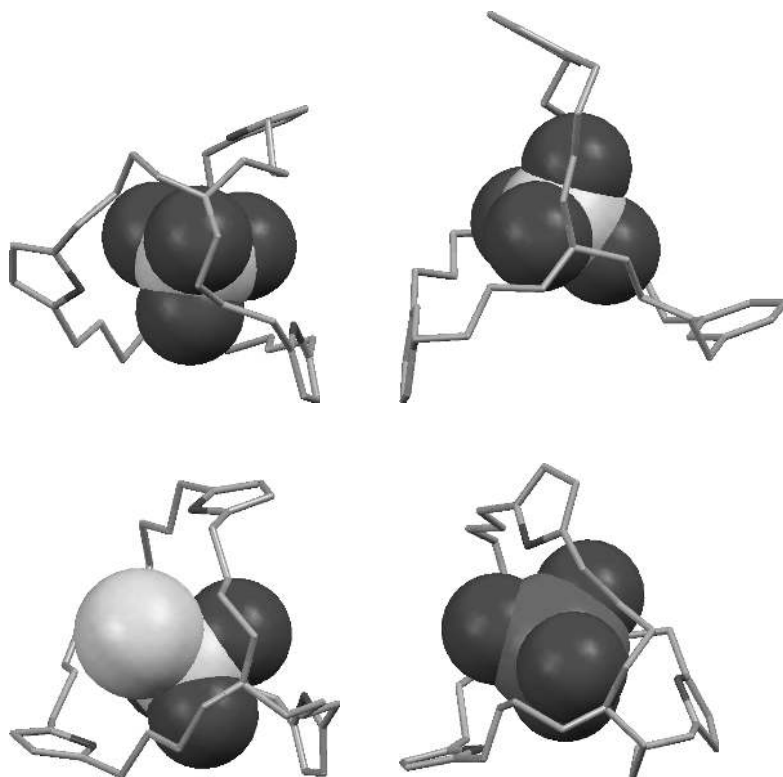


Figure 1.30 Sulfate anion included in the cavities of MEACryp and sulfate, thiosulfate, and chromate anions included in FuEACryp.

hydration sphere of the anion can be completely removed and substituted by the anchoring points of the receptor. In this environment, sulfate reaches a stability constant of 4.9 logarithmic units in its interaction with the hexaprotonated form of O-BISTREN (11) [57]. Compound C3-BISPRN (17), which can take eight protons, was reported to have $\log K_s = 7.45$ for its interaction with sulfate [158].

More recently, the Nelson and Bowman-James groups have published the sulfate crystal structures of FuEACryp (22) [159] and MEACryp (19) [160], respectively. In the same paper [159], Nelson and coworkers reported the crystal structures of thiosulfate and chromate encapsulated in the furan azacryptand (Figure 1.30). Stability constants for the interaction of the hexaprotonated FuEACryp with sulfate were reported to be over seven logarithmic units.

Receptors with amide functionalities can be appropriate for binding sulfate in less polar solvents than water [22, 29]. An interesting crystal structure of a sandwich sulfate complex was reported by Bowman-James' group in 2001 [161] (49, Figure 1.31). The sulfate anion accepts eight hydrogen bonds coming from the amide groups of both macrocycles.

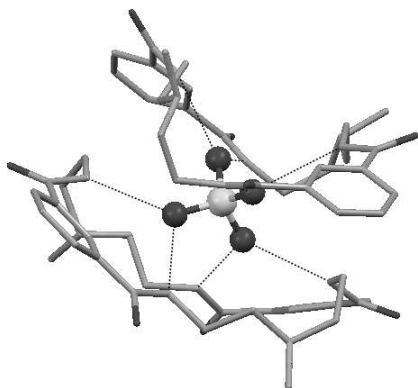
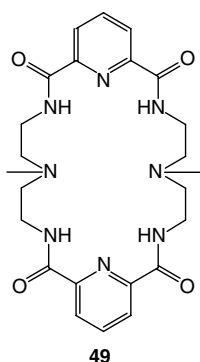


Figure 1.31 Sandwich structure of sulfate anion in macrocycle **49**.



1.4 Phosphate and Polyphosphate Anions

As previously commented, at neutral pH phosphate anions coexist as a mixture of the hydrogen and dihydrogenphosphate anionic forms, and therefore, phosphate can either donate or accept hydrogen bonds at this pH.

Some of the earliest research regarding phosphate recognition was carried out by Lehn's group and implied macrocycles **50**–**52**, which incorporate guanidinium subunits in their framework [162]. Guanidinium groups are present in arginine side chains and are known to have important biological roles related to the maintenance of the tertiary structure of proteins through formation of salt bridges with carboxylate groups and to the binding and recognition of anionic substrates by enzyme receptor sites and antibodies. These roles are based on several important features of this moiety such as its permanent positive charge in aqueous solution at the pH values of biological interest ($pK_a \sim 13.5$) and formation of characteristic pairs of zwitterionic hydrogen bonds (Figure 1.32).

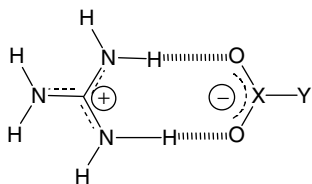
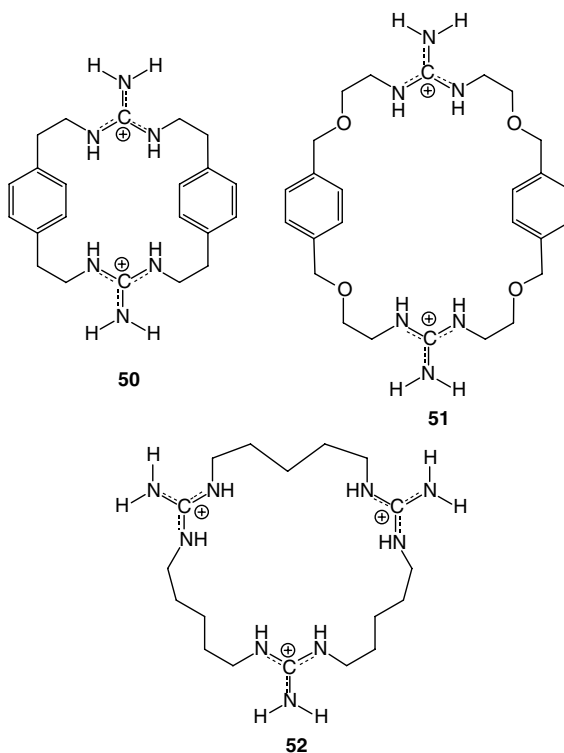
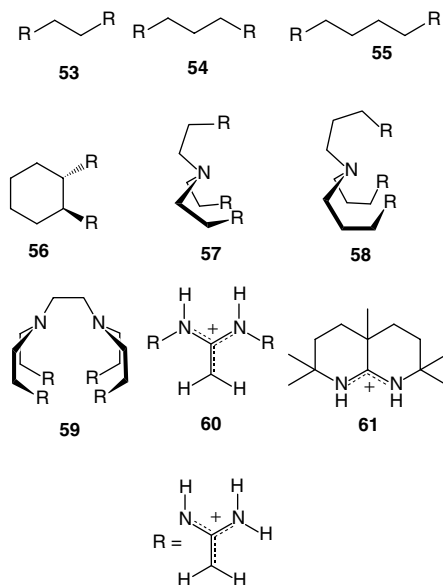


Figure 1.32 Zwitterionic hydrogen bonds formed by guanidinium groups.

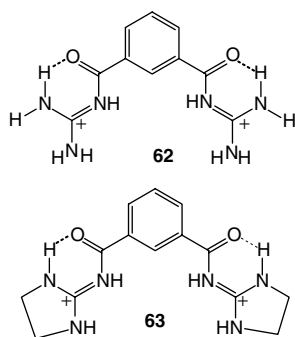


In spite of these appealing properties, the constants reported for the formation of 1 : 1 complexes between the macrocycles **50**–**52** and PO_4^{3-} species in water were not very large; $\log K_s = 1.7, 2.2,$ and 2.4 for **50**, **51**, and **52**, respectively. The authors stated that, although these constants were still low in comparison with those found for alkali cations, compounds **50**–**52** represented a step forward in the design of guanidinium-based receptors for phosphate, polyphosphates, and nucleotide anions. One of the reasons for this low affinity might be charge dispersion through the three possible faces of the guanidinium group. Proceeding with this research line, the same research group [163] prepared a series of polyguanidinium salts as anionic complexones. Several of these ligands are shown in **53**–**61**.



The interaction of these guanidinium-complexone ligands with phosphate, pyrophosphate, and a series of carboxylate and polyacrylate anions was studied by pH-metric titration in pure water and in water:methanol mixtures. The largest constants in water for the interaction with PO_4^{3-} were found for receptors **60** and **61**, which displayed values of $\log K_s$ of about three logarithmic units, while in the case of $\text{P}_2\text{O}_7^{4-}$, constants of 4.3 and 4.1 logarithmic units were retrieved from the pH-metric data for the cases of receptors **57** and **59**. In general, protonation of PO_4^{3-} or $\text{P}_2\text{O}_7^{4-}$ anions to give less negatively charged anionic forms led to stability decreases.

Regarding this kind of receptors, Hamilton *et al.* proposed in 1992 a couple of elegant systems (**62** and **63**) in which internal hydrogen bonding between carbonyl groups of the molecule and the guanidinium moiety induced favorable conformations in the receptors for their interaction with diphenylphosphate (Figure 1.33).



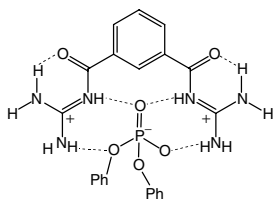
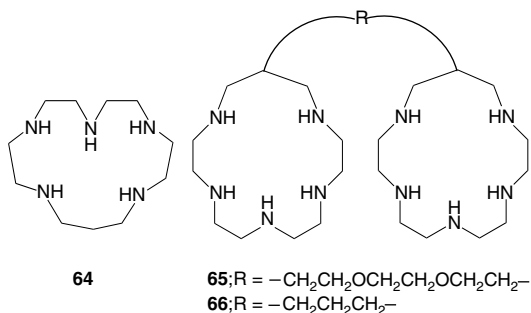
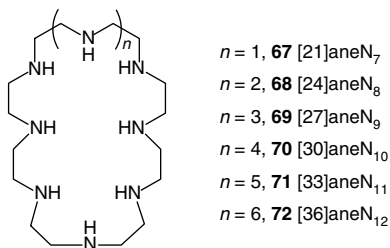


Figure 1.33 Internal C=O–H–N (guanidinium) bonds organizes the receptor for its interaction with phosphate.

Classical azamacrocycles are also appropriate ligands for binding phosphate and polyphosphate anions since the number of protonated and unprotonated amine groups they contain, and thus the overall charge and the number of hydrogen bond donors and acceptors, can be easily controlled by regulating the pH of the solution. Kimura *et al.* described in 1982 the interaction in water of the saturated macrocycles **36** and **64**, in their triprotonated forms, with HPO_4^{2-} , obtaining relatively low values of stability (2.04 and 1.1 logarithmic units, respectively) [99]. The same authors reported years later larger constants for the interaction of the monohydrogenphosphate anion with the tetra- and hexaprotonated forms of the ditopic azamacrocycle **65** (2.9 and 3.8 logarithmic units, respectively) [164].



Macrocycle **36** and larger congeners of the [3k]aneN_k series with K between 7 and 12 were also shown to interact with anions derived from phosphate and pyrophosphate in aqueous solution (**67–72**) [165].



The results obtained for the interaction of phosphate in its HPO_4^{2-} and H_2PO_4^- forms with protonated forms of **70** denoted $\log K_s$ limit values of 1.6 for the equilibrium $\text{H}_4(\mathbf{70})^{4+} + \text{HPO}_4^{2-} = [\text{H}_5(\mathbf{70})\text{PO}_4]^{2+}$ and 3.5 for $\text{H}_9(\mathbf{70})^{9+} + \text{H}_2\text{PO}_4^- = [\text{H}_{11}(\mathbf{70})\text{PO}_4]^{8+}$. For pyrophosphate, the constants were clearly higher, varying from 3.7 logarithmic units for $\text{H}_4(\mathbf{70})^{4+} + \text{P}_2\text{O}_7^{4-} = [\text{H}_5(\mathbf{70})\text{P}_2\text{O}_7]$ to 8.3 logarithmic units for $\text{H}_8(\mathbf{70})^{8+} + \text{H}_2\text{P}_2\text{O}_7^{2-} = [\text{H}_{10}(\mathbf{70})\text{P}_2\text{O}_7]^{6+}$. For a given equilibrium, the

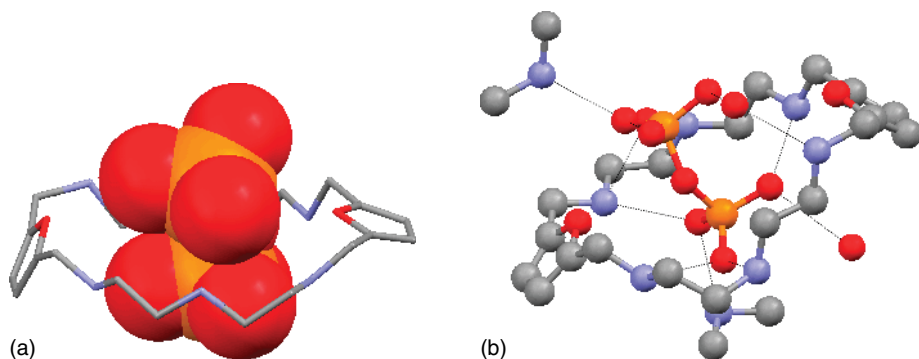


Figure 1.34 (a) View of $\text{H}_2\text{P}_2\text{O}_7^{2-}$ anion included in pentaprotonated $[\text{H}_5(\mathbf{73})]^{5+}$. (b) Hydrogen bond contacts of $\text{H}_2\text{P}_2\text{O}_7^{2-}$ in $[\text{H}_5(\mathbf{73})\cdot(\text{H}_2\text{P}_2\text{O}_7)]\text{Cl}_3\cdot 5\text{H}_2\text{O}$. Parts of the connecting macrocycles are included in the drawing.

progression in the series led to diminished stability constants in agreement with the lower charge density of the receptors as their size is increased. However, in the case of phosphate, this was so until macrocycle [30]aneN₁₀ (**70**) was reached; for [33]aneN₁₁ (**71**), an increase in stability was observed. This was attributed to a likely inclusion of the anion in the cavity. In Section 1.6, similar trends are discussed for metalocyanides.

Finding crystal structures of phosphate or polyphosphate anions fully or partly included in aza monomacrocycles is not frequent. Early examples of such structures were reported by Martell *et al.* in 1995 and 1996 for azamacrocycles **73** and **74** (Figures 1.34 and 1.35) [166, 167]. The first structure reveals that $\text{H}_2\text{P}_2\text{O}_7^{2-}$ binds to pentaprotonated **73** through multiple hydrogen bonds, with one end of the substrate inserting into the macrocycle and the other one extending outside it. Three oxygen atoms of the inside PO_3 unit and one oxygen atom of the outside PO_3 unit form hydrogen bonds to the macrocycle, while the remaining two oxygen atoms of this outside PO_3 unit are hydrogen bonded to oxygen atoms of a pyrophosphate belonging to another binary complex.

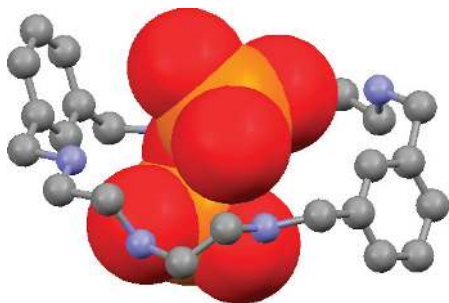
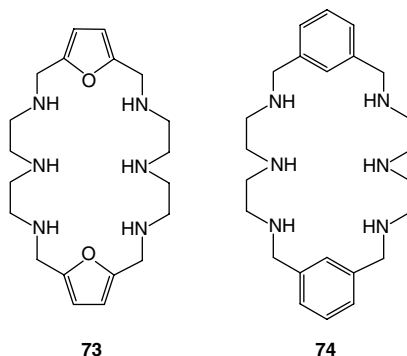
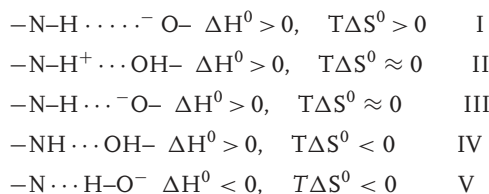


Figure 1.35 View of the $\text{H}_2\text{P}_2\text{O}_7^{2-}$ anion inserted in $[\text{H}_4(\mathbf{74})]^{4+}$.



Tetraprotonated **74** binds $\text{H}_2\text{P}_2\text{O}_7^{2-}$ anions inside the macrocyclic cavity, with each end of the anion hydrogen bonded to the nitrogen atoms of a *m*-xylyldiamine moiety through two of their oxygen atoms and the protonated third nitrogen atom of each end pointing away from the cavity and hydrogen bonded to nitrogen atoms of adjacent molecules. Other representative structural and/or solution studies regarding 2 + 2 azacyclophanes are included in Refs [168–171].

A study on the thermodynamic terms affecting the interaction of polyammonium receptors either of cyclic or acyclic nature with phosphate and pyrophosphate anions in aqueous solution indicated that there were five modes of hydrogen bond motifs in such systems [170, 171]; four of them involve ammonium or amine groups as donors (types I–IV), and just one involves amine groups as hydrogen bond acceptors (type V):



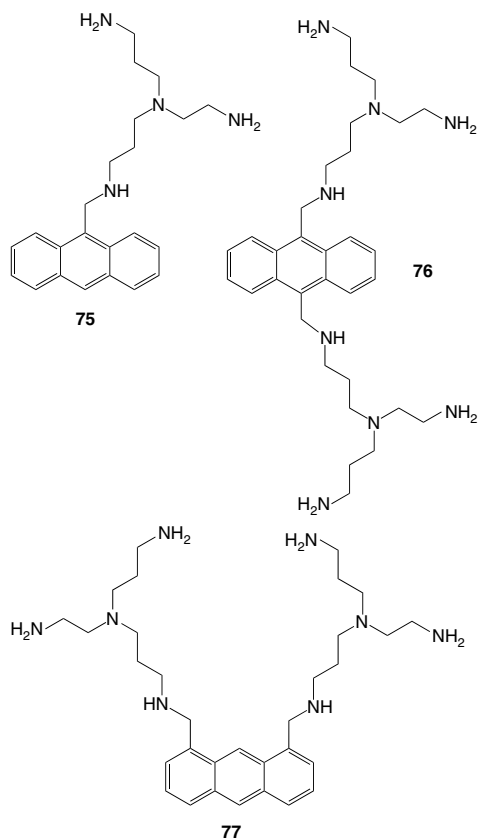
Binding mode I leading to hydrogen-bonded ion pair interactions should be of great importance in association processes occurring in solvents with high dielectric constant, such as water, since they provide synergetic hydrogen bonding and electrostatic attraction.

Type II bonds should be effective only in acidic enough conditions to permit extensive protonation of both the anion and the receptor. Type III bonds will be, however, favored in alkaline media, where both the anion and the receptor are extensively deprotonated. The entropic term associated with this charge transfer process should be favorable. Although types IV and V are possible hydrogen bond modes occurring between amines and compounds possessing $-\text{OH}$ groups, mode V is known to be considerably stronger than mode IV. Hydrogen bonding modes I–IV imply a partial deprotonation of the amino group and a partial protonation of a phosphate oxygen. Since deprotonation of an amino group is a strongly endothermic reaction and protonation of HPO_4^{2-} or H_2PO_4^- or pyrophosphate

anions is weakly endothermic or athermic, formation of hydrogen bonds I–IV should be endothermic, while different contributions depending mostly on the effect the process has on charge separation will be affecting the sign of the entropic term. Conversely, hydrogen bond V, which implies a partial protonation of an amino group and a partial deprotonation of a phosphate oxygen, would be accompanied by a negative enthalpy change and a favorable entropic term.

In the systems studied, I, II, and V are expected to be the principal hydrogen bonding modes with a relative importance directly connected with the extent of proton transfer, which in its turn depends on the N–O separation and the dielectric constant of the medium. Further discussion on this point is included in Chapter 2, devoted to energetics.

The possible use of polyammonium-based receptors as fluorescent chemosensors for phosphate anions was advanced by Czarnik and coworkers in 1989 [172], who proposed that tris(3-aminopropyl)amine derivatives appended with fluorophoric units could be useful for this purpose (75–77).



These authors proposed that monohydrogenphosphate could deliver a proton to triprotonated 75, blocking the photoinduced electron transfer from the amine to the excited fluorophore, producing a chelation enhancement of the fluorescence

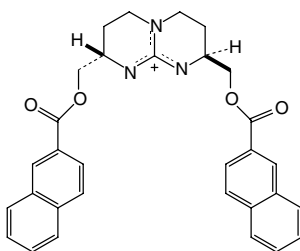
(CHEF) effect. In 1994, Czarnik reported that receptor **77** containing two tripodal polyamine units could operate as a pyrophosphate chemosensor by a mechanism similar to that just described for phosphate [173] (see Chapter 9).

1.5

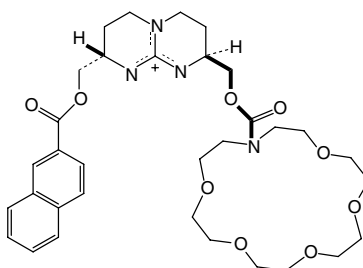
Carboxylate Anions and Amino Acids

The study of carbonate and carboxylate anions emerged in the very early years of the supramolecular chemistry of anions. Guanidinium complexones **53–61** were checked for their capability to bind acetate, maleate, and fumarate in methanol:water 9:1 mixtures, obtaining relatively high stability values in some instances, as in 5.1 logarithmic units found for the interaction of **59** with maleate dianion [163].

On the basis of the guanidinium platform, Lehn, de Mendoza *et al.* reported receptor **78** for chiral recognition of aromatic carboxylate anions [174]. Sodium *p*-nitrobenzoate was quantitatively extracted from water by a chloroform solution of **78**. Extraction experiments of sodium (*S*)-mandelate and (*S*)-naproxenate [(+)-6-methoxy- α -methyl-2-naphthaleneacetate] with **78-SS** and **78-RR** afforded the corresponding diastereomeric salts. Since free amino acids in zwitterionic form (valine, phenylvaline, and tryptophan) were not extracted from aqueous solution by **78**, *N*-acetyl and *N*-*tert*-butoxycarbonyl derivatives of tryptophan were examined. It was observed that extraction of an excess of the racemic salts with **78-SS** afforded in each case two diastereomeric excesses (de) of $\sim 17\%$ for the L-tryptophan derivative.



78



79

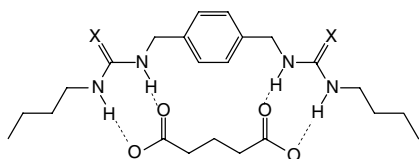
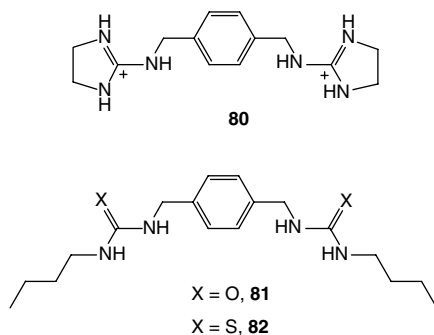


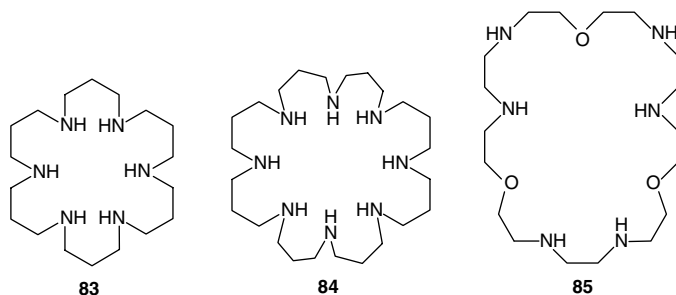
Figure 1.36 Schematic representation of the hydrogen bonding interaction of **81** and **82** with glutamate.

On the basis of this scaffold, a few years later, de Mendoza *et al.* prepared the ditopic receptor **79** for amino acid recognition, including a naphthoyl moiety and a crown ether [175]. Competition liquid–liquid extraction experiments of aqueous solutions containing 13 amino acids showed good selectivity for L-phenylalanine. Chiral recognition was confirmed by NMR since the D-enantiomers were not extracted.

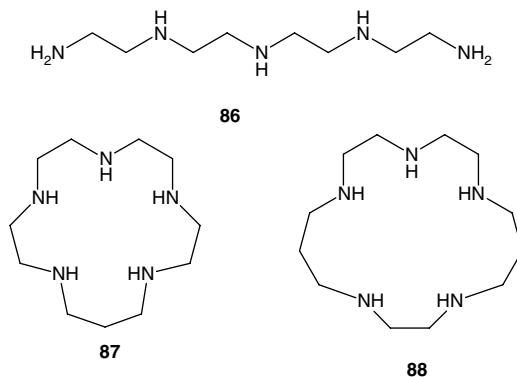
Hamilton and coworkers proved in 1993 that guanidinium receptor **80**, urea, **81**, and thiourea receptors **82** [176] (Figure 1.36) could recognize dicarboxylate anions of matching size in highly competitive solvents such as DMSO. While the association constants of the complex formed between **82** and glutarate in DMSO-*d*₆ determined by NMR ($\log K_s = (1.0 \pm 0.2) \times 10^4 \text{ M}^{-1}$) was 15-fold greater than that obtained for **81**, the constant for **80** was too large to be measured by NMR ($\log K_s > 5 \times 10^4 \text{ M}^{-1}$).



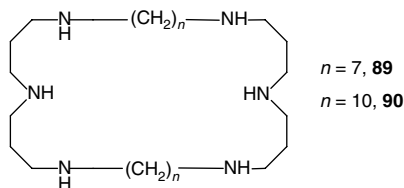
However, polyazamacrocycles were by far the most studied receptors in the early times of anion coordination chemistry. Lehn and coworkers, in their seminal *JACS* 1981 communication, reported the interaction of receptors **83–85** with several di- and tricarboxylate anions, along with sulfate, cyanometallate, and nucleotide anions [58]. Early cyanometallate and nucleotide anion-binding studies are presented in the next two sections.



The values obtained for the interaction of the hexaprotonated forms of **83** and **85** and the octaprotonated form of **84** with carboxylate anions indicated that electrostatic interactions played a major role in both strength and binding selectivity. In the same year, Kimura *et al.* published a polarographic study concerning the interaction of **36**, the open-chain pentaamine **86**, and the cyclic pentaamines (**47**), **87**, and **88** with several mono- and dicarboxylate anions as well as with the tricarboxylate anion citrate [177].



The authors concluded that macromonocyclic pentaamines and hexaamines specifically interact at neutral pH with polyanions having the carboxylate functions at short distances, such as succinate, malate, citrate, malonate, and maleate, but fail to interact with the other dicarboxylates, fumarate, aspartate, and glutarate, and also with the monocarboxylates, acetate and lactate. In the same year, Kimura and coworkers also established electrophoretic protocols for analyzing polyamines using buffers containing di- or tricarboxylates at pH \approx 8. Anomalous electrophoretic behavior of some macrocyclic polyamines migrating in the anode direction in citrate buffer solution at pH \approx 6 was discovered [178]. The same group presented a polarographic study about the interaction in aqueous solution of the hexaazamacrocycle **36** and some of the pentaamines, **47**, **48**, **86–88**, with carbonate anions. Such interaction persisted for some systems even at slightly acidic pH values [179].



Regarding selectivity aspects of dicarboxylate recognition, classic contributions were provided by Lehn's group [60, 180]. Hosseini and Lehn studied the interaction of macrocycles constituted by two dipropylenetriamine chains connected by propyl (**17**), heptyl (**89**), and decyl (**90**) hydrocarbon chains in their hexaprotonated forms with the series of dicarboxylate anions progressing from oxalate to sebacate, which

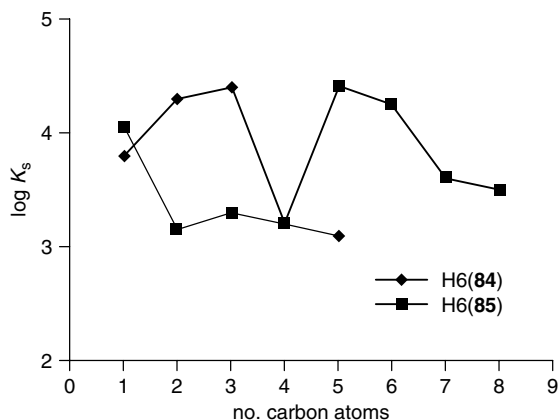


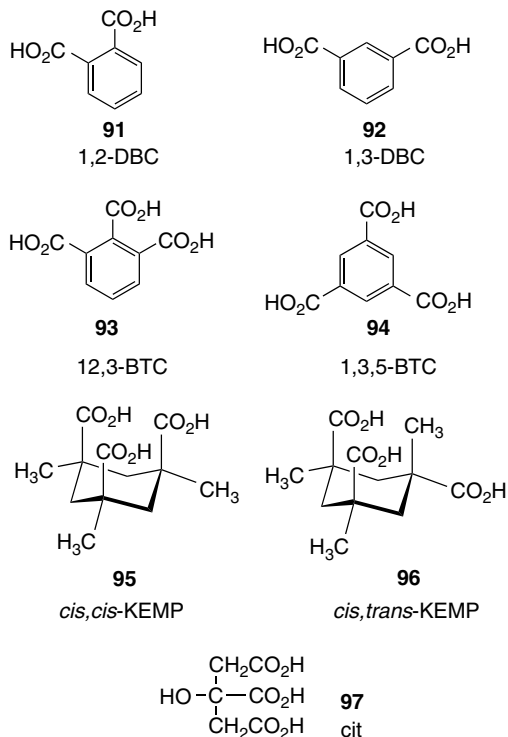
Figure 1.37 Graphical representation of the stability constants ($\log K_s$) of the complexes formed by $[\text{H}_6(\mathbf{89})]^{6+}$ and $[\text{H}_6(\mathbf{90})]^{6+}$ with dicarboxylates ${}^{-}\text{O}_2\text{C}-(\text{CH}_2)_n-\text{CO}_2^{-}$ as a function of the number of carbon atoms (n) between the carboxylate functions. Adapted from Ref. [60].

has seven methylene units between the carboxylate groups. The authors concluded that there exists selectivity depending on the respective chain lengths of substrate and receptor; each receptor, $[\text{H}_6(\mathbf{89})]^{6+}$ and $[\text{H}_6(\mathbf{90})]^{6+}$, shows a marked selectivity peak for a given dicarboxylate (Figure 1.37).

Shape selectivity was found years later by Bianchi, García-España, Luis *et al.* for the interaction of protonated **67** with the anions derived from the isomeric diacids and triacids **91–97** [181, 182] using citrate as a reference for a flexible substrate.

Since the basicities of the different anions explored are very different, a criterion balancing this point had to be adopted. The most appropriate way to compare the interaction of two different anions (anion 1 and anion 2) with receptor **67** is to calculate the distribution of complexed species as a function of pH for the mixed systems Anion **91** - Anion **92–97** and the overall percentages of formation [182, 183]. This method allows establishing selectivity ratios over the pH range studied and does not require any assumption of the location of protons in the interacting species, which is a frequent source of erroneous interpretation of selectivity. Using this approach, the following general selectivity order was found: 1,2,3-BTC > *cis,cis*-Kemp > 1,3,5-BTC > 1,2-BDC > 1,3-BDC > *cis,trans*-Kemp > citric acid. A more detailed discussion of this approach is included in Chapter 2, devoted to energetics of anion coordination.

Bismacrocycles or cryptand-like compounds of appropriate dimensions have been shown to be well-suited ligands for encapsulating dicarboxylate anions with matching size and functionalities. A classic example of this behavior is represented by receptor **98** [184, 185], which forms in aqueous solution fairly stable complexes with dicarboxylate anions of the ${}^{-}\text{O}_2\text{C}-(\text{CH}_2)_n-\text{CO}_2^{-}$ series showing selectivity for adipate ($n = 4$). Moreover, hexaprotonated **86** binds terephthalate with a remarkable



strength ($\log K_s = 60\,000$ at $\text{pH} = 5.5$, $\log K_s = 25\,000$ at $\text{pH} = 6.0$). The higher binding constant obtained at $\text{pH} = 5.5$ should be a consequence of the greater percentage of hexaprotonated **98** existing in solution at this pH . However, the most striking finding in this research was the publication of one of the first crystal structures showing a dicarboxylate anion, in this case terephthalate, included in a bicyclic receptor (Figure 1.38).

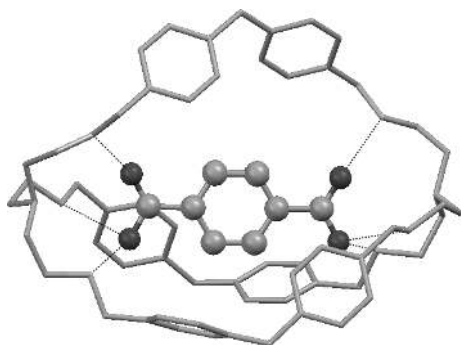
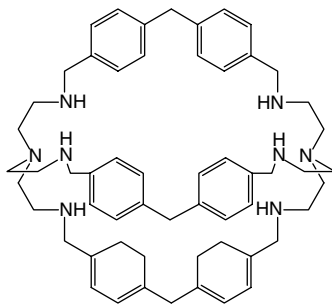
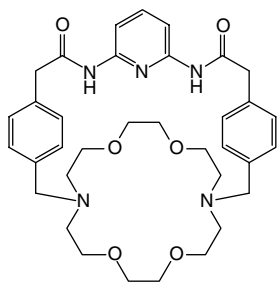


Figure 1.38 Terephthalate dianion included in hexaprotonated **98**.

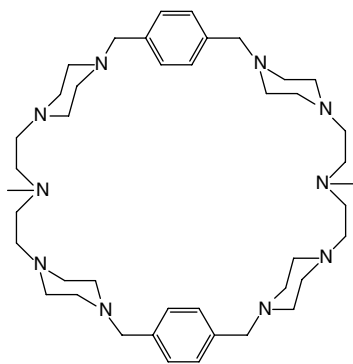


98

A system for the recognition of dicarboxylate anions based on the cooperative interplay of a bis(amidopyridine) hydrogen-bonding donor site and a K^+ -binding site constituted by an 18-membered diazacrown ether unit was proposed by Kilburn *et al.* in the early 1990s (99). NMR studies performed in chloroform proved the interaction of different dicarboxylate anions and amino acids with this receptor [186].



99



100

Cascade complexes formed between coordinatively unsaturated dinuclear metal complexes and α, ω -dicarboxylate anions can also help in recognizing these kinds of substrates. An example of this chemistry was provided by the Florence and Valencia Supramolecular Chemistry groups with the azacyclophane receptor 100.

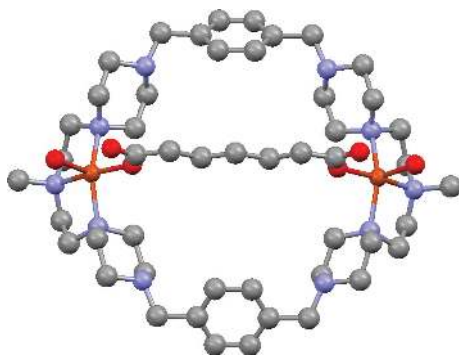


Figure 1.39 Crystal structure of the cascade complex formed by pim^{2-} with the binuclear complex $[\text{Cu}_2(\mathbf{100})(\text{H}_2\text{O})]^{4+}$ [187]. Hydrogen atoms have been omitted.

The coordinatively unsaturated Cu^{2+} centers can catch a pimelate anion as a bridging bis(monodentate) ligand as shown in the crystal structure presented in Figure 1.39 [187].

1.6 Anionic Complexes: Supercomplex Formation

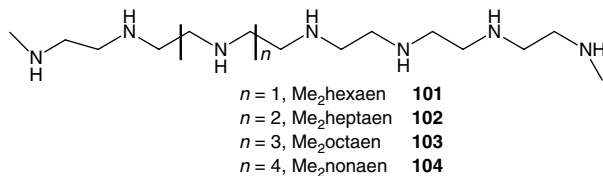
Cyanometallate anions were used as targets very early in anion coordination chemistry. The resulting supramolecular species formed are called *supercomplexes* or *complexes of the second coordination sphere* in which the polyammonium species is placed in the second coordination sphere, interacting electrostatically and through hydrogen bonding and other weak forces with the complex anion. Such an early appearance of cyanometallates as substrates for the interaction with ammonium receptors is not accidental. These anions offer simple ways of analyzing the influence on host–guest affinity of negative charge increases while other factors such as shape and geometry are kept essentially constant. For instance, apart from solvation effects, the only noticeable change when moving from $[\text{Fe}(\text{CN})_6]^{3-}$ to $[\text{Fe}(\text{CN})_6]^{4-}$ is the different net charge of both anions. In the same way, exchanging $[\text{Fe}(\text{CN})_6]^{3-}$ by $[\text{Co}(\text{CN})_6]^{3-}$ should be nonsignificant from a recognition point of view; both anions are octahedral and have a very close size.

On the other hand, the analysis of the changes produced in the electrochemical response of the $[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ redox couple on addition of a given polyammonium receptor is very useful. The simple quasi-reversible electrochemical behavior of this couple permits the derivation of stability constants by an alternative method to pH-metric titration or NMR, which are the most widely used techniques in this area. It has to be emphasized that it is always advisable to use more than one independent technique in order to have reliable descriptions of the anion-receptor systems.

Although formation of ion pairs between hexacyanoferrate(III) and quaternary ammonium salts had already been evidenced in 1965 following the shifts in the ^1H NMR [188] spectra of the ammonium salt following the interaction with the anion, Gross, Lehn *et al.* [59, 62] gave impetus to this topic. The group studied the

changes produced in the cyclovoltamperograms of $[\text{Fe}(\text{CN})_6]^{4-}$ aqueous solutions on addition of increasing amounts of the hexaaza and octaza macrocycles **83** and **84**. Addition of the macrocycles brings about anodic shifts, whose magnitude depends on the stoichiometries of the complexes formed and on their stabilities.

The interaction of the series of large polyazacycloalkanes [21]aneN₇, [24]aneN₈, [27]aneN₉, [30]aneN₁₀, [33]aneN₁₁, and [36]aneN₁₀ (**67–72**) and their open-chain counterparts (**101–104**) in their protonated forms with a series of



cyanometallates and other anionic metal complexes was an illustrative early example of this chemistry presented by the Supramolecular Chemistry groups of Florence and Valencia during the years 1985–1995 [189–196]. The open-chain counterparts were selected so that they had the same number of carbon and nitrogen atoms and the same class of amine groups as their cyclic counterparts [197]. The analysis of the stepwise stability constants for these systems indicated that the chief driving force in cyanometallate–polyammonium receptor binding is charge–charge interaction, which makes it difficult to modulate the selective discrimination of one guest over another. However, a representation of the constants for the equilibria $[\text{Co}(\text{CN})_6]^{3-} + \text{H}_p([\text{3 k]aneN}_k)^{p+} = [\text{Co}(\text{CN})_6][\text{H}_p([\text{3 k]aneN}_k)]^{(3-p)}$ showed that typically the constants for a given protonation degree of the macrocycle (*p*) steadily decreased when going from one macrocycle to the next until [30]aneN₁₀ (**70**) was reached. From there on, an increase in stability was observed (Figure 1.40). This change in the pattern could be attributed to an inclusion of the anion within the macrocyclic cavity, thus favoring shorter charge–charge interactions and the formation of stronger hydrogen bonds.

Inclusion of the anion inside the cavity of the macrocycle was also postulated by early work performed by the groups of Lehn in Strasbourg and Balzani in Bologna on the interaction of $[\text{Co}(\text{CN})_6]^{3-}$ with the polyammonium receptors [24]aneN₆ (**83**) and [32]aneN₈ (**84**) containing all propylenic chains between the nitrogen atoms [198, 199]. These authors observed that the quantum yield of the light-induced aquation reaction of $[\text{Co}(\text{CN})_6]^{3-}$ was reduced to one-third of the initial value in the presence of the octaprotonated receptor $\text{H}_8([\text{32]aneN}_8)^{8+}$, suggesting that inclusion of $[\text{Co}(\text{CN})_6]^{3-}$ into the macrocycle through the equatorial plane had occurred. The four CN[−] groups in the enclosed equatorial plane would be hydrogen bonded to the ammonium groups of the macrocycle and would not be exchanged by water molecules on light excitation (Figure 1.41) [200].

These analyses allowed for structural conclusions to be drawn for a number of systems [201]. Reduction of the quantum yield by half would suggest an interaction of the polyammonium host and the metalocyanide through one of its triangular

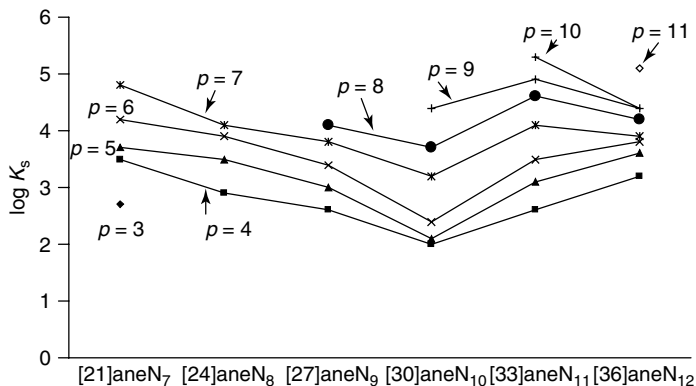


Figure 1.40 Plot of the variation of the constants for the equilibria $[\text{Co}(\text{CN})_6]^{3-} + \text{H}_p([\text{3k}]\text{aneN}_k)^{p+} = [\text{Co}(\text{CN})_6](\text{H}_p([\text{3k}]\text{aneN}_k))^{(3-p)}$ [191]. Reprinted with permission from Ref. [191]. Copyright 1992 American Chemical Society.

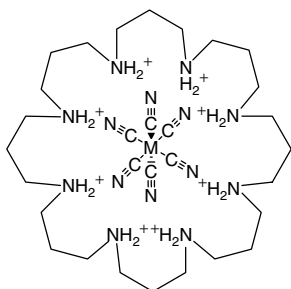
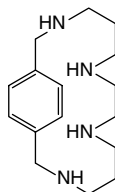


Figure 1.41 Schematic drawing of the inclusion of the equatorial plane of octahedral metalocyanides in the macrocyclic hole of $[\text{H}_8([\text{32}]\text{aneN}_8)]^{8+}$ [198, 199].

faces, while reduction by one-third would imply interaction through one of its edges. Such studies have allowed, for instance, to assume that the interaction between $[\text{Co}(\text{CN})_6]^{3-}$ and hexaprotonated $[\text{H}_6([\text{24}]\text{aneN}_6)]^{6+}$ or the tetraprotonated cyclophane 2,6,9,13-tetraza[14]paracyclophane (**105**) [196] involves one face of the octahedron.



105

Although being relatively small tetraazamacrocyclic **14** intercats strongly with metalocyanides in pure water. In fact, Bianchi, Micheloni, Orioli, Paoletti, and Mangani [202] made direct microcalorimetric studies for the interaction of **14** with $[\text{Fe}(\text{CN})_6]^{4-}$ and $[\text{Co}(\text{CN})_6]^{3-}$, observing that the main contribution

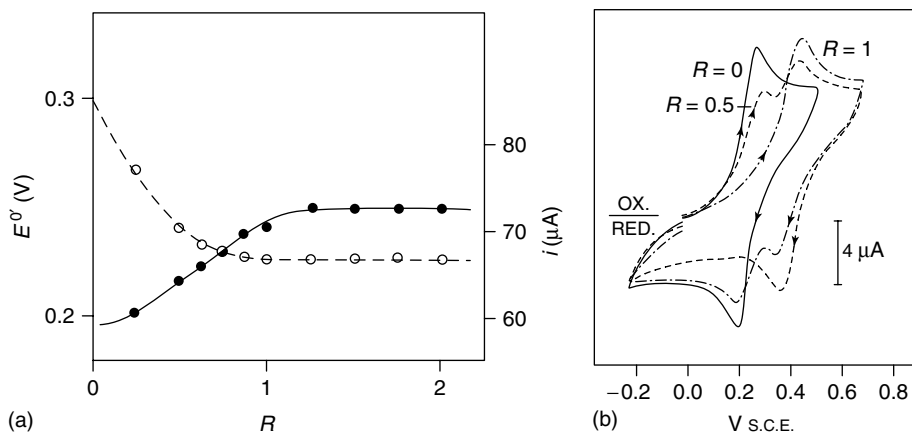


Figure 1.42 (a) Typical effects of the addition of a polyammonium receptor (H_pL^{p+}) on the cyclic voltammogram of $[\text{Fe}(\text{CN})_6]^{4-}$. R is the mole ratio receptor:metallocyanide [195]. Reproduced with permission from the Royal Society of Chemistry. (b) Representation of the

variation of peak potential (continuous line) and peak current (dashed line) versus R for a system polyammonium receptor $\text{H}_p\text{L}^{p+} - [\text{Fe}(\text{CN})_6]^{4-}$. Reprinted with permission from Ref. [191]. Copyright 1987 American Chemical Society.

to the $-4.94 \text{ kcal mol}^{-1} \Delta G^0$ term was coming from the entropic term ($\Delta S^0 = 13 \text{ cal mol}^{-1}$). For both anionic complexes, the enthalpic contribution was slightly exothermic ($\Delta H^0 = -1.1(1) \text{ kcal mol}^{-1}$ for $[\text{Fe}(\text{CN})_6]^{4-}$ and $\Delta H^0 = -2.56$ for $[\text{Co}(\text{CN})_6]^{3-}$).

As noted above, the use of $[\text{Fe}(\text{CN})_6]^{4-}$ allows for the analysis of the systems by cyclic voltamperometry. Figure 1.42 shows the typical behavior of these systems. Addition of the receptor to an aqueous solution of $[\text{Fe}(\text{CN})_6]^{4-}$ yields an anodic shift of the voltammogram until a certain mole ratio $R = \text{receptor} : [\text{Fe}(\text{CN})_6]^{4-}$, normally 1, is reached (Figure 1.42b). From a plot of the variations of the peak potentials versus R it is possible to deduce the stoichiometry of the formed supercomplex. On the contrary, the effect of supercomplex formation is a decrease in the peak intensity due to the formation of the higher molecular weight adducts species.

Distribution diagrams of the species existing in equilibria calculated from the stability constants determined pH-metrically coupled with plots of the variation of anodic peak currents and formal potentials show plateaus in the zones where single species predominate in solution (Figure 1.43). Application of classic voltammetric and polarographic methods permits calculation of the stability constants for the formation of $[\text{Fe}(\text{CN})_6]^{3-}$ adducts. Similar determinations are not possible by means of pH-metric methods because of the very rapid aquation process of the oxidized anion [200]. Table 1.1 shows that, as it could be expected for anions displaying the same charge, geometry, and size, the values of the stability constants for the systems $[\text{Fe}(\text{CN})_6]^{3-}$ -polyammonium receptors were very close to those obtained by pH-metry for the systems $[\text{Co}(\text{CN})_6]^{3-}$ -polyammonium receptors.

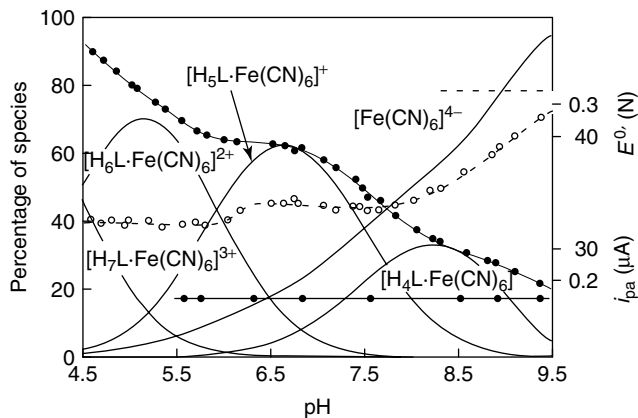


Figure 1.43 Distribution diagram of the species existing in equilibria in the system $[\text{Fe}(\text{CN})_6]^{4-}$: Me₂heptaen and anodic peak currents (dashed lines, open circles) and formal potentials (continuous lines, solid circles) of the couple $[\text{Fe}(\text{CN})_6]^{3-} - [\text{Fe}(\text{CN})_6]^{4-}$ [195]. Reproduced with permission from The Royal Society of Chemistry.

Table 1.1 Logarithms of the equilibrium constants for the supercomplex formation between $[\text{Fe}(\text{CN})_6]^{3-}$ and the polyamines [21]aneN₇ (67) and [24]aneN₈ (68) calculated from cyclic voltammetry data. The corresponding values for $[\text{Co}(\text{CN})_6]^{3-}$ calculated by pH-metric techniques are included by means of comparison [195].

| Reaction ^a | [21]aneN ₇ (67) | | [24]aneN ₈ (68) | |
|--|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| | $[\text{Fe}(\text{CN})_6]^{3-}$ | $[\text{Co}(\text{CN})_6]^{3-}$ | $[\text{Fe}(\text{CN})_6]^{3-}$ | $[\text{Co}(\text{CN})_6]^{3-}$ |
| A + H ₃ L = H ₃ LA | 2.8 | 2.7 | – | – |
| A + H ₄ L = H ₄ LA | 3.4 | 3.5 | 2.9 | 2.9 |
| A + H ₅ L = H ₅ LA | 3.8 | 3.7 | 3.8 | 3.5 |
| A + H ₆ L = H ₆ LA | – | – | 4.4 | 3.9 |

^aCharges omitted.

One of the first supercomplex structures determined by single-crystal X-ray diffraction corresponded to a solid of chemical formula $[\text{H}_8\{[30]\text{aneN}_{10}\}][\text{Co}(\text{CN})_6]_2\text{Cl}_2 \cdot 10\text{H}_2\text{O}$, which evolved from slow evaporation of aqueous solutions of $\text{K}_3[\text{Co}(\text{CN})_6]$ and $[30]\text{aneN}_{10} \cdot 10\text{HCl}$ (70·10HCl) (Figure 1.44) [190]. The crystal structure consisted of octaprotonated macrocycles and two types of hexacyanocobaltate anions placed outside the macrocyclic hole. One of the hexacyanocobaltate anions is hydrogen bonded through four of its six cyanide groups with consecutive macrocycles, forming a chain-like structure. The second

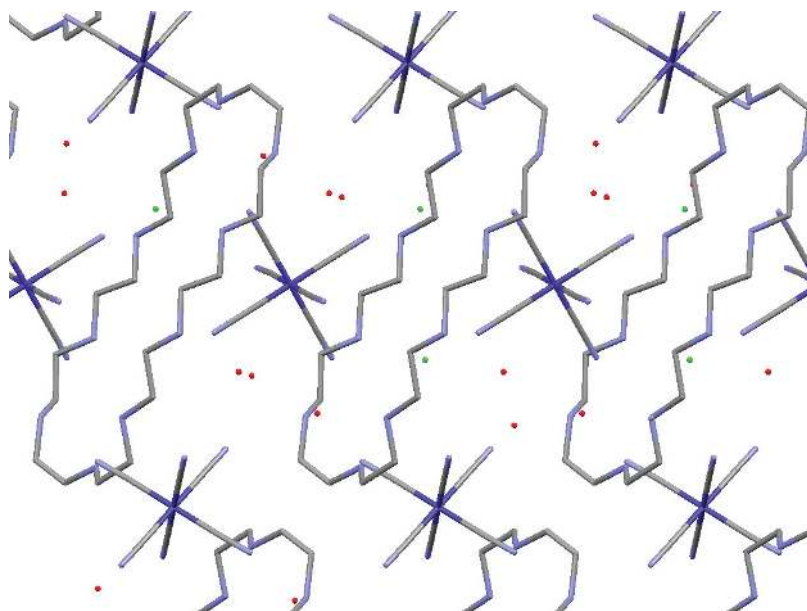


Figure 1.44 Portion of the crystal structure of $[\text{H}_8(70)][\text{Co}(\text{CN})_6]_2\text{Cl}_2 \cdot 10\text{H}_2\text{O}$ showing the two types of hexacyanocobaltate(III) anions [190].

type of hexacyanocobaltate anions interconnects macrocycles of different chains by means of two long hydrogen bonds. The macrocycle adopts an elongated elliptical shape, which is mainly due to repulsions between the positively charged ammonium groups. Interestingly, if this structure were kept in solution, the cyanometallates along a single chain would also provide a diminution of two-thirds in the quantum yield of the photoexcited aquation reaction; four of the six cyanide groups would be stabilized by hydrogen bonds.

In order to get further insight into the characteristics of these interactions and into the inclusive nature of the supercomplexes formed, the studies were extended to other types of anionic complexes [192–194]. The interaction of hexachloroplatinate(IV) anions PtCl_6^{2-} and the macrocycle $[\text{30}] \text{aneN}_{10}$ was studied in solution by means of ^{195}Pt NMR spectroscopy. The shift in the ^{195}Pt signal reaches a constant value (Figure 1.45) for molar ratios $R = [\text{H}_{10}([\text{30}] \text{aneN}_{10})]^{10+} / [\text{PtCl}_6]^{2-} > 1$ because of the formation of 1:1 metal complexes. However, another inflection is observed for $R = 0.5$, suggesting formation of supercomplexes of 2:1 anion:receptor stoichiometry.

The crystal structure of $[\text{H}_{10}([\text{30}] \text{aneN}_{10})][\text{PtCl}_6]_2\text{Cl}_6 \cdot 2\text{H}_2\text{O}$ (Figure 1.46) consists of a complex hydrogen bond network, which involves the hydrogens of the protonated nitrogen atoms of the receptor, PtCl_6^{2-} anions, chloride anions, and water molecules. The complex anions are placed outside the macrocyclic hole.

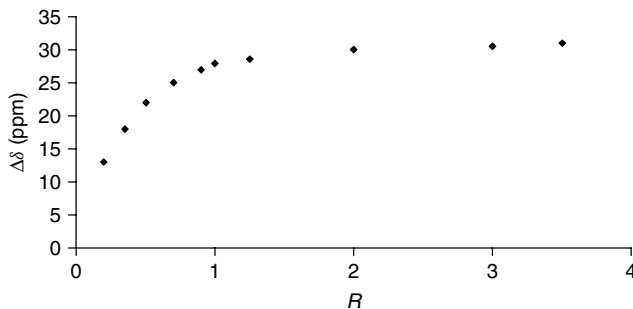


Figure 1.45 Plot of the variation in the ^{195}Pt NMR chemical shifts of PtCl_6^{2-} on addition of increasing amounts of $[\text{H}_{10}([\text{30}]\text{aneN}_{10})]^{10+}$. $R = [\text{H}_{10}([\text{30}]\text{aneN}_{10})]^{10+}/[\text{PtCl}_6]^{2-}$. Reprinted with permission from Ref. [194]. Copyright 1987 American Chemical Society.

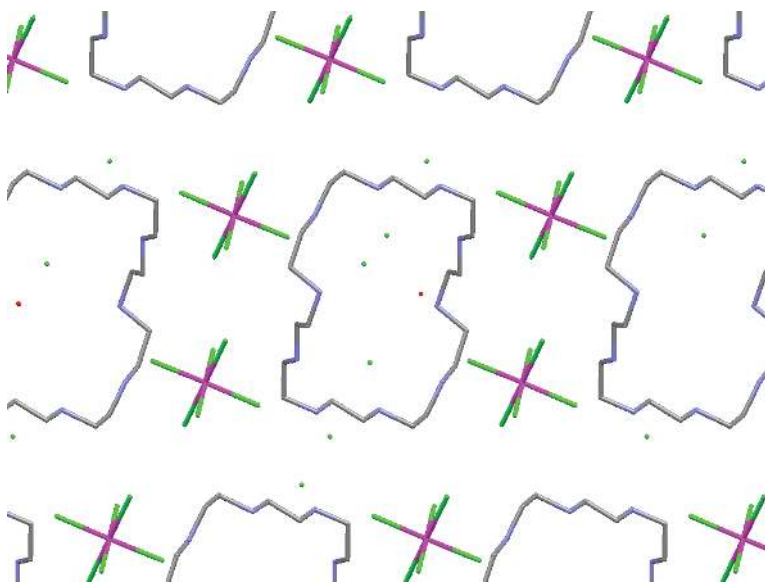


Figure 1.46 Detail of the crystal structure of $[\text{H}_{10}(\mathbf{70})][\text{PtCl}_6]_2\text{Cl}_6 \cdot 2\text{H}_2\text{O}$ showing the outer location of the PtCl_6^{2-} anions. Red dots are water molecules and green are chloride anions [194].

One can imagine that the octahedral shape and the size of PtCl_6^{2-} could hinder its inclusion into the macrocycle. However, at least in the solid state, inclusion was also not detected for the square planar anion $[\text{Pt}(\text{CN})_4]^{2-}$, even if all calculations and models suggested that there was enough free room for this process to occur. The crystal structure of the solid $[\text{H}_{10}([\text{30}]\text{aneN}_{10})][\text{Pt}(\text{CN})_4]_5 \cdot 2\text{H}_2\text{O}$ showed again an array of hydrogen bonds involving the protonated macrocycle and the

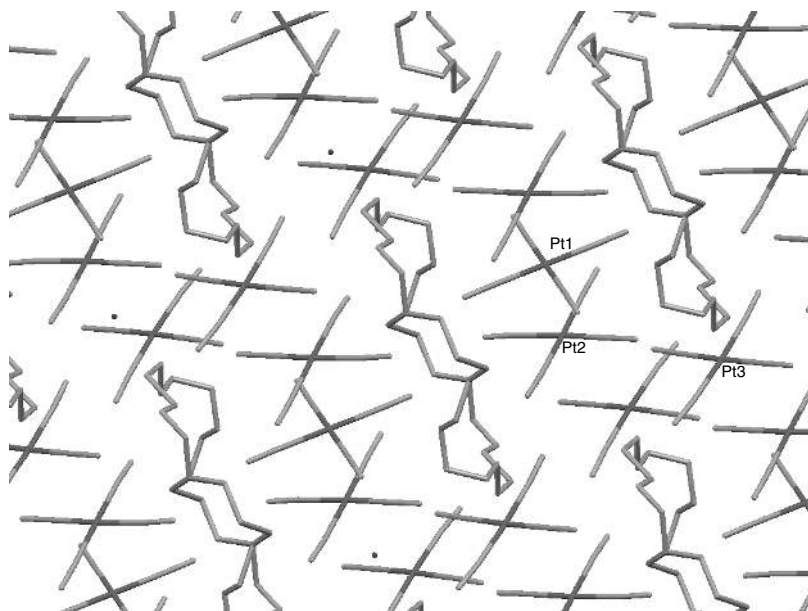


Figure 1.47 Detail of the crystal structure of $[H_{10}([30]aneN_{10})][Pt(CN)_4]_5 \cdot 2H_2O$ showing the three different $[Pt(CN)_4]^{2-}$ anions involved in hydrogen bonding with the decaprotonated receptor [194].

metallocyanide anions whose cyanide groups point directly toward the macrocyclic cavity (Figure 1.47).

Owing to the stronger and more inert character of the Pt-CN bond, it was possible to study these systems by means of pH-metric techniques detecting the formation of 1 : 1 adduct species. A noticeable increase in stability was observed in going from $[30]aneN_{10}$ (70) to the larger $[33]aneN_{11}$ (71), suggesting possible inclusion of the anion within the macrocyclic hole.

As it can be noticed, there is no agreement between the stoichiometries in the solid state and in solution. ^{195}Pt NMR studies in D_2O failed to give information about the formation of adduct species of higher nuclearity because of the precipitation of the polyammonium salts.

A closer relationship between the events coming up in solution and in the solid state occurs, however, in the system $PdCl_4^{2-} - H_{10}([30]aneN_{10})^{10+}$ [192, 193]. Solution studies for the different $H_k([3k]aneN_k)^{k+}$ systems were carried out by batch microcalorimetry in a 0.1 M HCl aqueous medium. The measurements had equilibration times within the timescale of the experiment for $H_6([18]aneN_6)^{6+}$, $H_7([21]aneN_7)^{7+}$, and $H_8([24]aneN_8)^{8+}$ becoming, however, much slower for the next three terms of the series $H_9([27]aneN_9)^{9+}$, $H_{10}([30]aneN_{10})^{10+}$, and $H_{11}([33]aneN_{11})^{11+}$ (Table 1.2). Although all the reactions show slightly exothermic enthalpy terms, the enthalpy changes for $(H_9[27]aneN_9)^{9+}$, $(H_{10}[30]aneN_{10})^{10+}$, and $H_{11}([33]aneN_{11})^{11+}$ are significantly more favorable than for the others. These

Table 1.2 Enthalpy terms and equilibration times for the reactions of fully protonated [3k]aneN_k macrocycles and PdCl₄²⁻ determined in 0.1 M HCl in a BATCH microcalorimeter [192, 193].

| Reaction | $-\Delta H^\circ$ (kcal mol ⁻¹) | Time (min) |
|--|---|------------|
| H ₆ ([18]aneN ₆) ⁶⁺ + PdCl ₄ ²⁻ | 1.5(1) | 20 |
| H ₇ ([21]aneN ₇) ⁷⁺ + PdCl ₄ ²⁻ | 1.5(1) | 20 |
| H ₈ ([24]aneN ₈) ⁸⁺ + PdCl ₄ ²⁻ | 1.6(1) | 20 |
| H ₉ ([27]aneN ₉) ⁹⁺ + PdCl ₄ ²⁻ | 2.9(1) | 120 |
| H ₁₀ ([30]aneN ₁₀) ¹⁰⁺ + PdCl ₄ ²⁻ | 3.9(1) | 110 |
| H ₁₁ ([33]aneN ₁₁) ¹¹⁺ + PdCl ₄ ²⁻ | 3.1(1) | 50 |

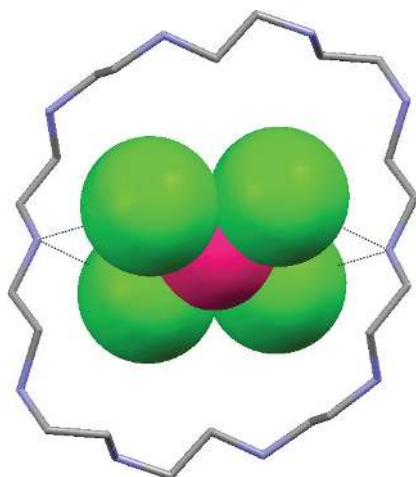


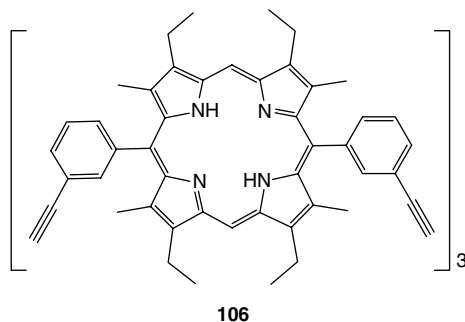
Figure 1.48 Drawing of the cation [(PdCl₄)(H₁₀[30]aneN₁₀)]⁸⁺. Hydrogen bonding is indicated with blue dotted lines. Hydrogen atoms are not shown [192, 193].

experimental evidences suggest that H₂₇([27]aneN₉)⁹⁺ was the first term of the series for which inclusion of the PdCl₄²⁻ within the macrocyclic cavity occurred. The slower equilibration time should account for conformational reorganizations following host–guest interaction.

The crystal structure of [(PdCl₄)(H₁₀[30]aneN₁₀)](PdCl₄)₂Cl₄ (Figure 1.48) shows that one of the PdCl₄²⁻ is included into the ellipsoidal cavity of the deca protonated macrocycle along the shorter axes [192, 193]. The chlorine atoms lie outside of the macrocyclic framework, forming hydrogen bonds with the closest nitrogen atoms of the macrocycle. The outer PdCl₄²⁻ anions also participate in hydrogen bonding with several ammonium groups of the receptors. Although, as previously mentioned, the shape of the macrocycle is largely defined by coulombic repulsions between protonated nitrogen atoms. Attractive charge–charge interactions with the anions and hydrogen bonding also play their role in determining the conformation of the protonated receptor. As a matter of fact, the conformations found in each

of the structures discussed are somewhat different. Thus, it can be stated that the coarse fitting of the macrocyclic conformation is performed by the charge while hydrogen bonding plays a sort of fine tuning.

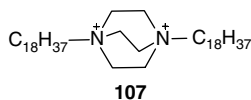
Finally, we would like to remark on the case of the inclusion of the very large anions $\text{PW}_{12}\text{O}_{40}^{3-}$, $\text{SiW}_{12}\text{O}_{40}^{4-}$, and $\text{Os}_{10}\text{C}(\text{CO})_{24}^{2-}$ in the cavity of the porphyrin cyclic trimer (**106**) as established by fast atomic bombardment techniques mass spectrometry by Anderson and Sanders in 1992 [203]. The protonated trimer was found to bind giant clusters in a shape-dependent manner, suggesting the application of separating clusters by size using cyclic hosts of varying dimensions.



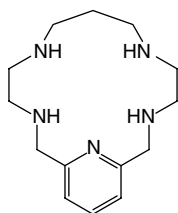
1.7 Nucleotides

The study of the interaction between polyammonium receptors and nucleotides meant a real breakthrough in supramolecular chemistry since it provided an early and definitive biological slant to the field. Organized interconversions among AMP, ADP, and ATP are important since the chemical energy supplied from outside is stored through the formation of highly energetic phosphate linkages. In turn, cleavage of such phosphate linkages provides energy sources for biosynthetic reactions that reverse catabolic pathways and drive active transport through cell membranes against electrochemical gradients.

Acyclic and, in particular, cyclic polyammonium salts from very early proved to be very strong nucleotide binders. In a study performed by Tabushi *et al.* [204], it was shown that the quaternized DABCO with stearyl chains (**107**) was able to transfer ADP very efficiently from an aqueous solution at pHs of 3 and 5 into a chloroform phase. The selectivity found for the transfer of ADP over AMP was explained by the formation of a double salt bridge between the phosphate groups and the quaternized receptor.

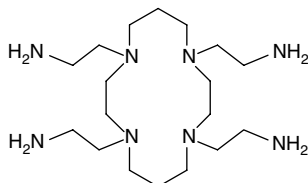


The Lehn and Kimura groups provided very initial evidences of the high interaction between polyammonium receptors with the nucleotides ATP, ADP, and AMP [58, 99]. Lehn's group, in a communication to *JACS* [58], gave stability constant data for the interaction of the hexaprotonated [24]aneN₆ (H₆(**83**)⁶⁺), octaprotonated [32]aneN₈ (H₈(**84**)⁸⁺), and hexaprotonated [27]aneN₆O₃ (H₆(**85**)⁶⁺) with AMP²⁻, ADP³⁻, and ATP⁴⁻. The values obtained by computer analysis of the pH-metric titration curves varied from 3.4 to 9.1 logarithmic units, following the sequence AMP²⁻ < ADP³⁻ < ATP⁴⁻ for each of the three protonated receptors. Kimura *et al.* reported a full paper in *JACS* [99] in which, by means of polarographic techniques, they had explored the interaction with nucleotides of a series of polyazamacrocycles including [18]aneN₄ (**13**), [15]aneN₅ (**47**), [18]aneN₆ (**36**), the mixed amino-amide receptor (**33**), [16]aneN₅ (**87**), and a tetraazapyridinophane (**108**).

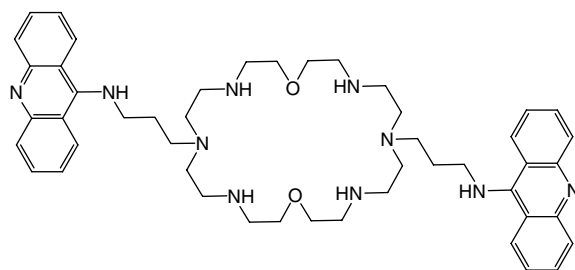
**108**

The polarographically determined association constants in general followed the order mentioned with higher values for the higher charged ATP anion. However, a reverted sequence seemed to be found for the interaction of diprotonated pyridinophane receptor **108** with the three nucleotides. It was soon realized that the length of the hydrocarbon chains between the nitrogen atoms in a monocyclic receptor is a key factor in determining its basicity and consequently its affinity for the anionic species. In this respect, Bianchi, Micheloni, and Paoletti reported that the tetraaza monocycle [20]aneN₄ (**14**), which has butylenic chains between the amino groups and is fully protonated at the physiological pH of 7.4, has a significant affinity for ATP⁴⁻ (H₄(**14**)⁴⁺ + ATP⁴⁻ = H₄(**14**)·ATP, log K_s = 3.81(3)) [205]. Related to this point, Burrows prepared a chiral [18]aneN₄ derivative including an alcohol C-linked side chain, which was proved to interact with ATP by ³¹P NMR [206]. Bis(macrocylic) polyamines **65** and **66** also showed interesting complexing properties toward nucleotide species [164].

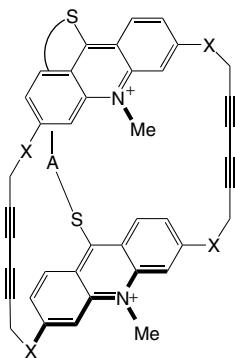
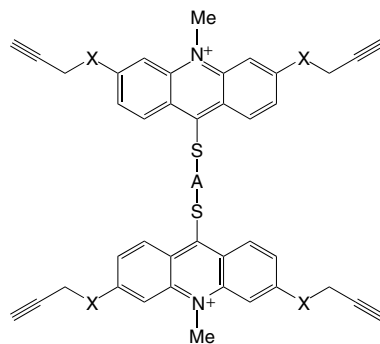
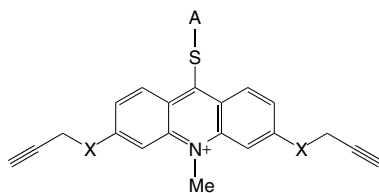
Another strategy in nucleotide binding was based on using tetraazacycloalkanes with pendant arms containing additional ammonium groups such as in receptor **109** [207].

**109**

However, the aromatic rings in the nucleotide structure provide a very important motif for their binding through stacking interactions. With this purpose, Lehn and coworkers [208] prepared receptor **110**, in which acridine moieties were added to the classical receptor O-BISDIEN to take advantage from electrostatic attractions, hydrogen bonding, and stacking interactions.

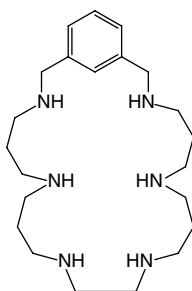
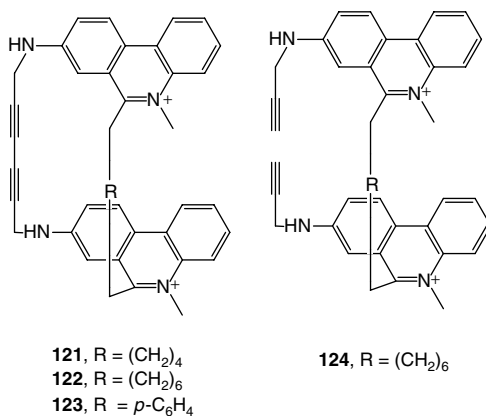
**110**

Lehn and coworkers also prepared a series of bis-intercaland compounds and their reference mono-intercaland partners to see the affinity enhancement provided by this double binding motif [209] (**111–120**).

**111**, X = O, A = $-(\text{CH}_2)_6-$ **112**, X = O, A = $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ **113**, X = O, A = $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ **114**, X = NH, A = $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ **115**, X = O, A = $-(\text{CH}_2)_6-$ **116**, X = O, A = $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ **117**, X = O, A = $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ **118**, X = NH, A = $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ **119**, X = O, A = $-(\text{CH}_2)_2-\text{CH}_3$ **120**, X = NH, A = $-(\text{CH}_2)_2-\text{CH}_3$

Evidence for intercalation was obtained from the hypochromism observed in the UV–vis spectra of the nucleotide–ligand systems. While differences in stability were obtained for the different nucleic bases, the constants obtained for nucleotides containing the same base pair and different phosphate chains were practically the same. For instance, the stability constants for the interaction of AMP^{2-} , ADP^{3-} , and ATP^{4-} with **112** were 3.79, 3.84, and 3.91 logarithmic units, respectively.

The importance of π -stacking in nucleotide binding is even more evident in the case of receptors **121**–**124**. For example, the equilibrium constants for the binding of charged ATP^{4-} , ADP^{3-} , and AMP^{2-} are $\log K_s = 5.80$, 5.65, and 5.38, respectively [210] (**121**–**124**).



125

As was evidenced for **125** by García-España, Luis, and coworkers using ^1H NMR and potentiometric techniques, monocyclic azacyclophanes with appropriate polyamine chains can behave as multipoint binders of nucleotides. While the phosphate chain is a good electrostatic binding point and a hydrogen bond acceptor, the nucleoside part operates as an adequate site for stacking with the aromatic part of the macrocycle [211, 212]. Recently, Bianchi *et al.* [213] have reported a crystal structure for the interaction of the terpyridinophane macrocycle **126** with thymidine-5'-triphosphate (TTP) that assumes many of the binding mechanisms [214] of nucleotides by polyazamacrocycles containing aromatic functions

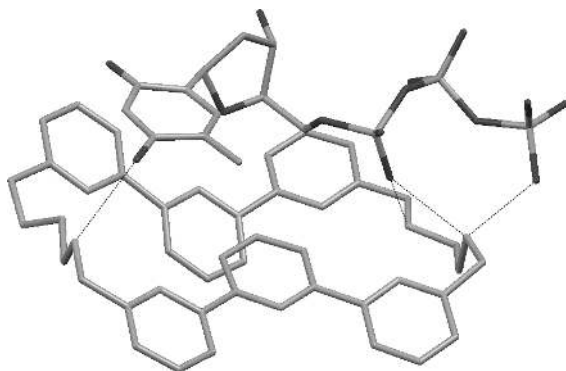
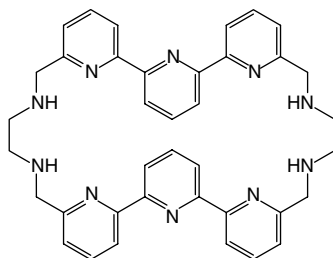


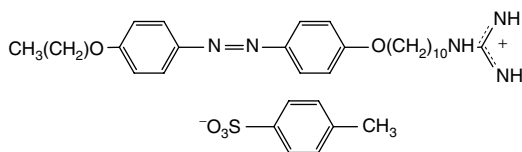
Figure 1.49 View of the crystal structure of complex $[(H_4(126))HTTP]$ showing some of the intermolecular hydrogen bonds between the partners.

(Figure 1.49). This structure is discussed in more detail in Chapter 2, devoted to energetic aspects of anion binding.



126

ATP and AMP binding to guanidinium monolayer formed by **127** was studied by X-ray photoelectron spectroscopy of Langmuir–Blodgett films of the monolayer drawn from substrate-laden aqueous subphases. Binding constants of 1.7×10^7 and $3.2 \times 10^6 \text{ M}^{-1}$ were obtained for ATP and AMP, respectively. The respective site occupations were 0.34 and 0.95.



127

Since macrocycle **37** was found to be one of the most powerful complexing agents for ATP [58, 215], it was attached to polystyrene beads. The modified polymer was able to take up nucleotides, in particular ATP, at neutral and acidic pHs and release them back into the solution at basic pH values.

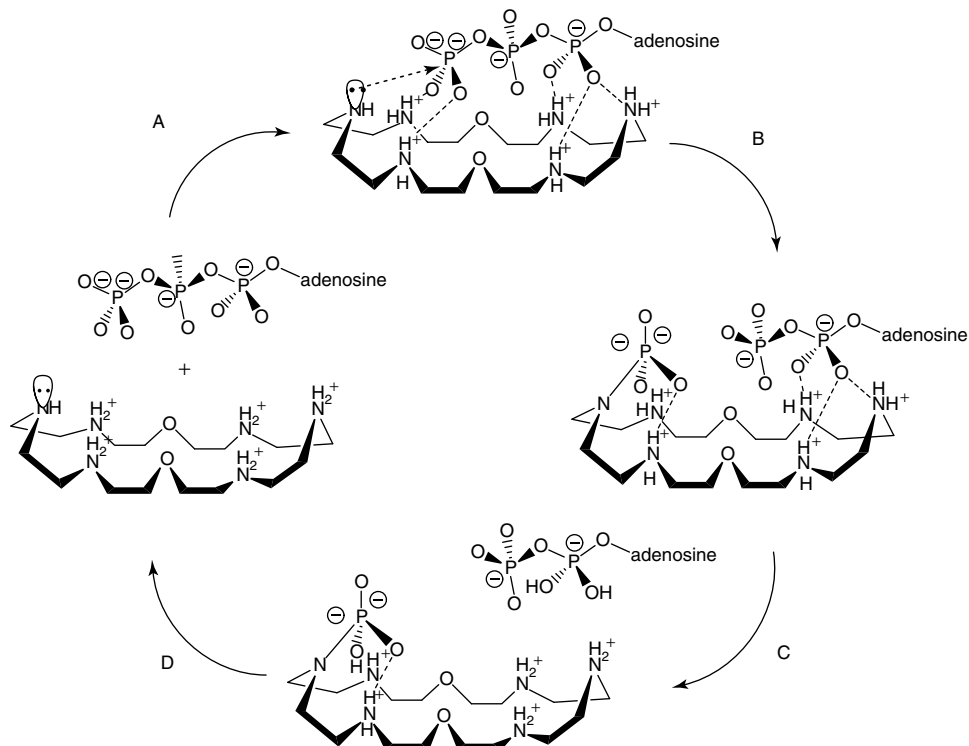


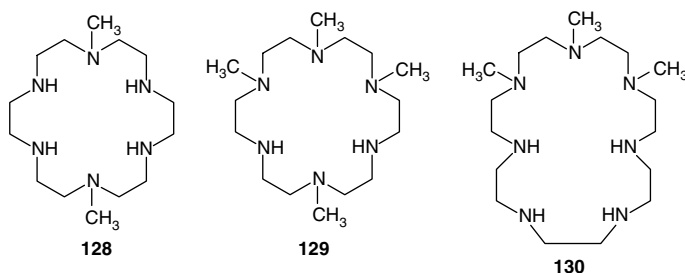
Figure 1.50 Catalytic cycle for ATP in the presence of **37** at neutral pH.

However, the most interesting point of this chemistry concerns the capacity that some polyammonium receptors have for inducing catalytic processes mimicking the behavior of ATPases or kinases. The 24-membered macrocyclic receptor **37** ranks among the abiotic receptors producing highest enhancements of ATP cleavage into ADP and the so-called inorganic phosphate [58, 215–220]. Activation of ATP-cleavage with **37** was observed not only at an acidic pH but also at neutral pH. Under neutral conditions, the hydrolysis of ATP by this receptor was enhanced by a factor of 100. The ³¹P NMR monitoring of the course of the reaction revealed the formation of a transient phosphorylated species, which appeared in the ³¹P NMR spectrum as a singlet downfield shift at 10 ppm with respect to an external H₃PO₄ reference. The hydrolysis of ATP in the presence of protonated **36** proved to be a true catalytic process since for a 10-fold excess of ATP with respect to **36**, the change in the ATP concentration was linear with time in the early period. The products of the reaction of ADP and inorganic phosphate did not interfere with the initial course of the reaction because of their reduced affinity for the protonated receptor.

The authors of this work proposed for ATP hydrolysis catalyzed by **37** the classical mechanism depicted in Figure 1.50. One of the central amines of the bridges is not protonated at neutral pH and performs the nucleophilic attack on the terminal

phosphorous atom (P_γ) of ATP to form the phosphoramidate transient species (steps A and B in Figure 1.50). The electrostatic and hydrogen bonding interactions of the phosphate chain of the nucleotide with the protonated macrocycle places the γ -phosphorous atom and the nonprotonated amine of the partners in a proper position for facilitating the nucleophilic attack. The final steps of the catalytic cycle are the dissociation of the ADP complex and the hydrolysis of the phosphoramidate, not necessarily in this order (steps C and D).

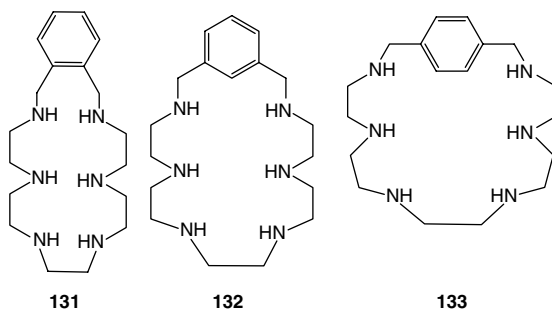
Studies of ATP cleavage conducted with the series of azacycloalkanes [3k]aneN_k ($k = 6-12$) (**36**, **67-72**) revealed the key role played by the macrocycle size [165]. The 21-membered macrocycle [21]aneN₇ (**67**) was shown to be the best catalyst at the examined pHs, with the [24]aneN₈ (**68**) macrocycle providing also very significant rate enhancements. The relevance of macrocyclic size and charge density on rate of catalysis was later checked by introducing structural modifications such as N-methylation of some of the nitrogen atoms in the macrocycles [18]aneN₆ (**36**) and [21]aneN₇ (**67**) [221, 222] to yield macrocycles (**128-130**).



While dimethylated **128** leads to a decrease in the rate of the hydrolytic cleavage of ATP with respect to unmethylated **36**, the tetramethylated **129** produces a significant rate enhancement. On the other hand, trimethylation of [21]aneN₇ (**67**) to give Me₃[21]aneN₇ (**130**) produces a diminution in the rate of the process. Taking into account that methyl groups donate electron density to electronegative atoms and should increase the nucleophilicity of the nitrogens, the slower rate of cleavage must be tightly related to the alteration of the optimal cavity size brought about by the functionalization. However, solvation effects need to be always taken into account in these types of considerations.

Additional evidences supporting the key role played by size cavity in ATP hydrolysis were provided by García-España and coworkers for the series of cyclophane receptors **131-133**.

The critical size required is manifested in the fact that both the ortho (**131**) and para isomers (**133**), containing 20- and 22-membered cavities, yield much poorer ATP cleavage rate enhancements than the meta isomer (**132**) with a 21-membered cavity. This lack of activity is particularly noticeable in the case of the ortho derivative.



^{31}P NMR studies revealed that **132** produced rate enhancements comparable to those of O-BISDIEN (**37**) and slightly lower than those of [21]aneN₇ (**67**), confirming the critical role of size in the catalytic processes (Figure 1.51) [223]. Interestingly enough, the reaction using **131** as a catalyst is not only efficient but also very specific since it stops in the formation of ADP and does not proceed significantly further. Molecular dynamics studies suggest that the optimal size is one at which just the γ -phosphate of ATP perfectly resides at the macrocyclic cavity. Figure 1.52 shows the perfect fitting between the phosphate group and the macrocyclic cavity of **132**.

O-BISDIEN (**37**) exhibited other characteristics of the naturally occurring enzymes, such as the ability to modify the course of reaction and phosphoryl transfer capabilities to other substrates. Protonated **37** was shown to catalyze acetylphosphate hydrolysis and pyrophosphate formation through formation of a

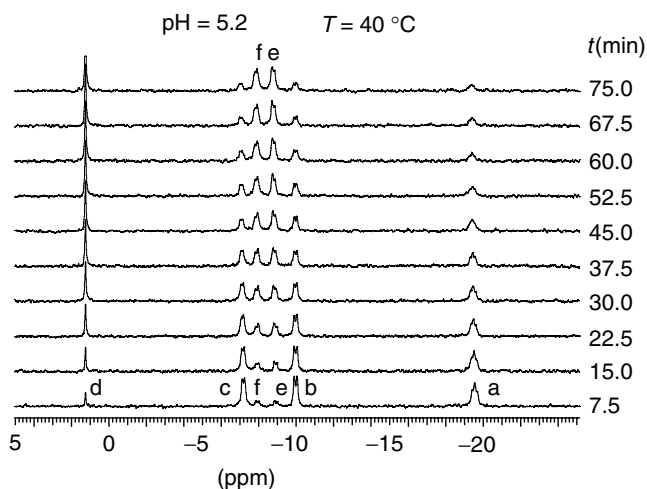


Figure 1.51 Time evolution for ^{31}P NMR spectra of solutions containing ATP and **132** in 10^{-2} M at 40°C and $\text{pH} = 5.2$. (a) P_β (ATP); (b) P_α (ATP); (c) P_γ (ATP); (d) Pi; (e) P_α (ADP); and (f) P_β (ADP) [222]. Reproduced with permission from the Royal Society of Chemistry.

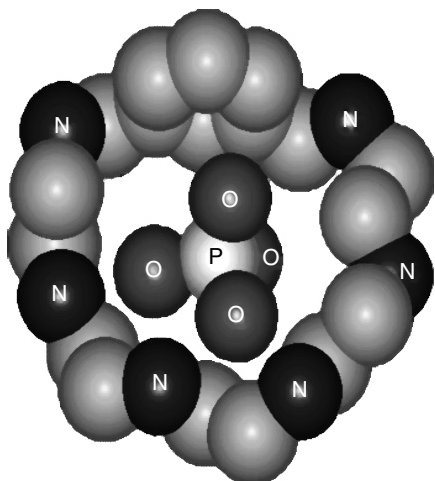


Figure 1.52 Comparison between the size of the macrocyclic cavity of **132** and the γ -phosphate of ATP. The rest of ATP has been obscured for clarity.

phosphorylated macrocycle intermediate, which transfers a phosphoryl group to a phosphate substrate [224]. ATP phosphotransferases, hydrolases, and synthetases, often require mono- or divalent anions in order to carry out their functions. Therefore, to generate systems that resembled even more closely their biological counterpart, protonated **37** was coupled to metal ions [225, 226]. The investigations of the effect of the biologically significant metal ions Ca^{2+} , Mg^{2+} , and Zn^{2+} added to **37** revealed striking influences of the metal ions on ATP hydrolysis and on the formation of the phosphoramidate intermediate and pyrophosphate. While addition of both Ca^{2+} and Mg^{2+} increased the observed percentage of phosphoramidate, only Ca^{2+} provided a significant acceleration in ATP hydrolysis, almost doubling the first order rate constant found for free **37** in the same experimental conditions. Ln(III) also led to a considerable increase in the rate of ATP dephosphorylation. The presence of Mg^{2+} had no apparent effect on the catalytic rate of ATP cleavage, while Zn^{2+} or Cd^{2+} addition to macrocycle-ATP solutions decreased the hydrolytic rate. The most striking finding in this respect was the ready appearance of pyrophosphate in the presence of **37** and either Mg^{2+} , Ca^{2+} , or Ln^{3+} at pH 4.5. No pyrophosphate formation was observed in the absence of metals under these experimental conditions. The pyrophosphate was determined as being formed from nucleophilic attack of inorganic phosphate in solution on the phosphoramidate, aided by metal ion chelation.

Mertes *et al.* indicated that macrocycle **37** was able to activate formate in the presence of ATP and Ca^{2+} or Mg^{2+} ions, yielding as a final product the macrocycle formylated at the central nitrogen of the chain [227]. This finding may represent the first example of a multistep catalytic pathway assisted by a simple macrocyclic host. Furthermore, it resembles what has been proposed to be the pathway followed by N^{10} -formyltetrahydrofolate synthetase in the formylation of the N^{10} nitrogen atom in tetrahydrofolate. The catalytic sequence is presumed to proceed through a formyl phosphate intermediate with the assistance of ATP. The ability of the phosphoramidate intermediate to participate in other phosphorylation reactions

was further confirmed when Hosseini and Lehn proved that **37** in the presence of Mg^{2+} as promoter catalyzed the generation of ATP from acetyl phosphate and ADP in dilute aqueous solution at neutral pH [228]. A more detailed description of the evolution of the catalytic capabilities of the simple 24-membered macrocycle can be found in a 2004 review [229].

1.8

Final Notes

In this chapter, we have provided a descriptive overview of the events that encompassed the birth of the field of anion coordination chemistry along with more recent flashes related to such initial research. However, we would like to apologize for any oversight we may have committed. Since these initial findings, and particularly since the appearance of our previous book in 1997, the anion supramolecular chemistry field has experienced a tremendous explosion. Many new research groups have focused their work in this conceptually new area, and many new receptors have been reported in the last two decades. Hence, as noted at the beginning of this chapter, we have covered only a selected group of the seminal findings, primarily limited to ammonium, amide, and guanidinium donor groups. Furthermore, the wide variety of these new hosts is nothing short of astounding, with many containing within their frameworks binding motifs that allow for recognizing anions in low-dielectric media trying to mimic the clefts or crevices where anion receptors often occur in nature.

Also, the search for biomedical and environmental applications of anion receptors has gained great impetus. Analytical chemistry has also gained great interest in relation to anion detection and quantification, with novel molecules and devices that permit the identification of ever increasingly low amounts of either pollutants or biomedical relevant anionic species. Aspects related to biomedicine and to the importance that anion regulation have in metabolic roles have also become apparent in these years.

The following chapters address new approaches to anion coordination chemistry in relation to the synthesis of receptors, biological receptors, and metalloceptors; energetics of anion binding; molecular structures of anionic complexes; sensing devices; and computational studies addressed to understand the different driving forces responsible for anionic complexation. We hope these chapters will provide the reader an actual picture of the state of the art in many aspects of anion coordination. In short, the future is promising for this exciting and constantly evolving field of supramolecular anion coordination chemistry.

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