PROGRESS IN INORGANIC CHEMISTRY

Edited by

KENNETH D. KARLIN

DEPARTMENT OF CHEMISTRY
JOHNS HOPKINS UNIVERSITY
BALTIMORE, MARYLAND

VOLUME 46

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Progress in Inorganic Chemistry

Volume 46

Advisory Board

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Anion Binding and Recognition by Inorganic Based Receptors

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I. INTRODUCTION

In comparison to cation coordination chemistry, anion coordination is a recent development. The birth of this field occurred in the late 1960s with the synthesis of the first artificial host molecules (1–3). It is perhaps surprising that anion recognition was so slow to begin, bearing in mind the importance of anions in many chemical and biological processes. Specific receptors capable of binding anionic guests are dependent on effectively addressing the characteristic features of anions, such as their negative charge, their size (larger than analogous cations), their wide variety of shapes, and their pH dependence.

Activity in this field during the 1970s and early 1980s was reported in a range of review articles (4–6). These articles outlined the basic principles involved in anion binding, which helped to delineate the arena for further experimental investigations. In the ensuing years, the investigation of anion recognition systems has continued apace (7–15), and involved the development of a whole new range of receptors, many incorporating metal centers. To date, however, there has not been any comprehensive review of this type of anion receptor based on inorganic systems, an omission this chapter intends to rectify.

Anions are of key importance across many fields of scientific life; making their selective binding and sensing a critical research target, as the following illustrative examples indicate:

Chemically, anions have various roles as catalysts, bases and redox mediators. The use of receptors to coordinate anions can alter their chemical reativity (4), and may also be helpful for mixture separation or stabilization of unstable species.

Environmentally, anions pose a considerable pollution problem. In particular, the nitrate anion (used in fertilizers on agricultural land) often pollutes river water to unacceptable levels. This pollution leads to eutrophocation and consequent disruption of aquatic life cycles (16). Radioactive pertechnetate anions also cause a pollution problem in the nuclear fuel cycle. Selective binding and sensing of environmentally sensitive anions is, therefore, an important goal.

Biologically, adenosine triphosphate (ATP), the free energy of life processes, is itself an anion, bound by enzymes in order to perform its many metabolic functions. Deoxyribonucleic acid (DNA) is also a polyanion, its binding by proteins being of great importance in transcription and translation processes. Anion-binding biomimicry could therefore yield much information about fundamental biological processes.

Medically, anions are of great importance in many disease pathways. Cystic fibrosis, a genetic illness affecting a significant proportion of society, is caused by misregulation of chloride channels (17). There is, therefore, a real need for selective halide detection, as established methods of chloride analysis are unsuitable for biological applications (18). Cancer is caused by the uncontrolled replication of polyanionic DNA. Anion-binding proteins have also been implicated in the mechanism of Alzheimer's disease (19).

Many enzymes bind anions very successfully in biological systems; the majority of substrates and cofactors bound by enzymes are anionic (20). It is clearly worth considering the ways in which enzymes carry out this function before going on to discuss synthetic chemical approaches to the problem of anion binding.

II. BIOLOGICAL APPROACHES TO ANION BINDING

A. Binding through Hydrogen Bonding

A recurrent theme in biological chemistry is hydrogen bonding, and the action of receptors for anions is no exception. The crystal structure of the sulfate-binding protein Salmonella typhimurium provides a remarkable example of the coordinative strength of hydrogen bonds for anions (21). The sulfate anion is buried in a cleft 7 Å below the surface of the enzyme. The only stabilization for its dinegative charge is provided by neutral hydrogen-bond donors; peptide groups on the protein backbone are particularly important.

More commonly, there is salt bridge hydrogen-bond formation with a protonated amino group (lysine, arginine, or the N-terminus of the protein) which

provides additional anion stabilization through electrostatic attraction (22). Extensive surveys of the active sites of solely organic, hydrogen-bonding anion-binding proteins have been made (23, 24). Chakrabarti (23) showed that, on average, oxoanions are held by $7(\pm 3)$ hydrogen bonds, of which the protein contributes $5(\pm 3)$ with the rest provided by water molecules.

However, nature is not solely organic as the elegant philosophy of Williams and Frausto da Silva (25) stresses. Frequent use is made of the metal ions available in natural systems to provide additional anion-binding interactions.

B. Metal Ion Based Anion Binding

The guanosine diphosphate (GDP)-bound Ran protein crystal structure (Fig. 1) provides a perfect illustration of how a metal ion can be combined with hydrogen-bonding groups to augment the strength of anion binding and form the focus for an anion-binding pocket (26). (The Ran proteins are located primarily in the nucleus of eukaryotic cells and are involved in protein nuclear import and DNA synthetic control.) The magnesium ion is held in place by four water molecules and two protein residues. This ion binds the anionic GDP substrate in an "end-on" manner. The remaining functionalities of the bound anionic substrate are then satisfied by hydrogen bonding with preorganized sections of the enzyme superstructure.

Lactoferrin, an important iron-binding protein (Fig. 2), synergistically binds carbonate anions and iron(III) (27). The carbonate is bound through a combination of metal–anion coordinate bonds, hydrogen bonds, and electrostatic interactions. It is argued that anion-binding assists iron(III) binding by causing a buildup of negative charge at the iron-binding site.

Many structurally refined enzymes have been found to contain more than one metal ion at the active site. These metal ions are often bridged by an anionic substrate.

Superoxide dismutase (an enzyme for destroying biotoxic superoxide anions) contains copper(II) and zinc(II) ions at its active site, bridged by an imidazolate anion from a histidine residue (28). Phospholipase C has a number of zinc(II) ions at its active site, with two of them being bridged by hydroxide and aspartate (from a protein residue) anions (29). Phospholipase C evolved to bind and hydrolyze negatively charged phosphate esters, illustrating an important principle: the link between anion binding and functioning metal centers. This important concept of function will be returned to at a later stage (Section IV).

Of course, there are many other enzymes that bind anions and many more for which the binding mode is not as yet elucidated. The examples chosen here are merely intended to be illustrative.

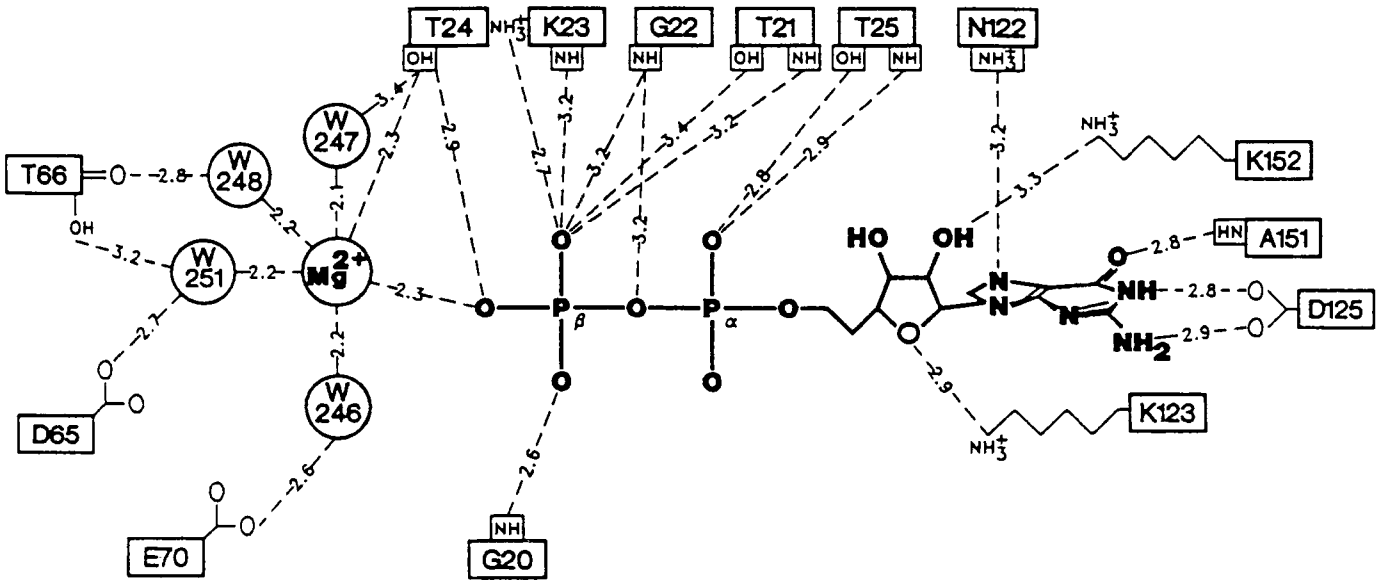


Figure 1. The binding site of Mg·GDP to Ran protein. A schematic drawing of the nucleotide-binding site with selected interactions (dashed lines) between Mg^{2+}, GDP, and the protein, with the corresponding distances (in angstrom units). [Reprinted with permission from *Nature* (K. Scheffzek, C. Klebe, K. Fritz-Wolf, A. Wittinghofer, *374* 378 (1995). Copyright © Macmillan Magazines Limited.]

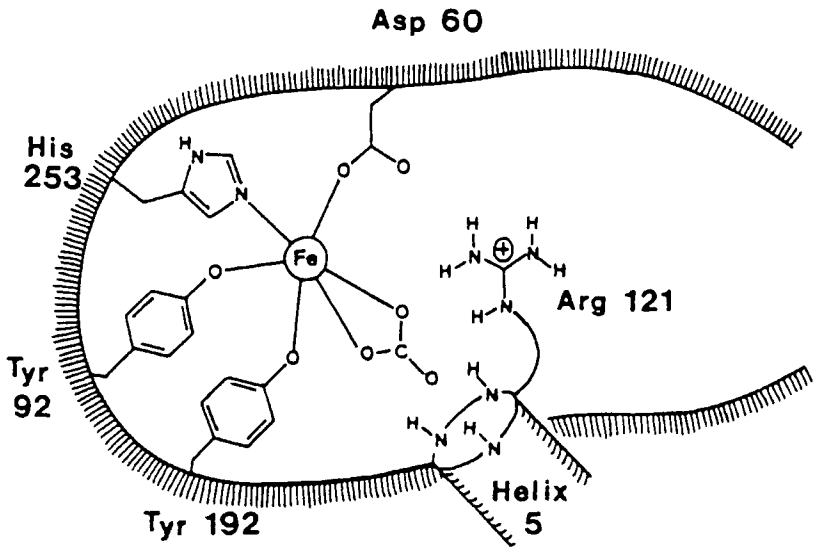
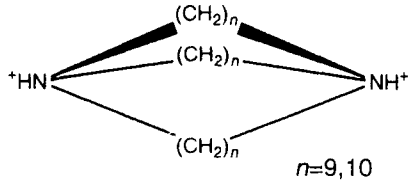


Figure 2. Schematic diagram of the iron- and anion-binding site in human lactoferrin. [Reprinted with permission of (27).]

III. ORGANIC RECEPTORS FOR ANIONS

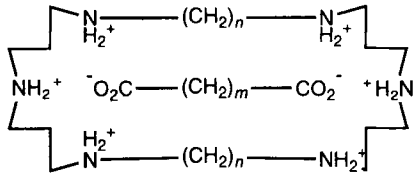
Dietrich's reviews have provided detailed accounts of early approaches to this type of anion receptor (4, 13). This chapter will, therefore, only briefly outline the basic types of organic receptors for anions as they will prove of relevance in understanding some of the recent inorganic systems that form the main body of discussion.

The first synthetic anion receptor (**1**) was based on a protonated nitrogen system (1). Compound **1** was shown to bind anions in the cavity in a "katapinate" manner (with the hydrogen atoms pointed inward toward the anion) (2). The source of interaction with anions in such a system is therefore twofold: electrostatic attraction and hydrogen bonding. Many protonated polyammonium



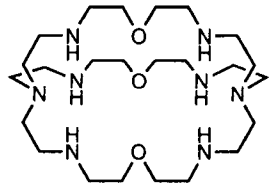
1

macrocycles were subsequently studied for their ability to bind anions, and indeed strong interactions were observed in aqueous solution, especially with carboxylates and phosphates (30–35). Lehn and co-workers (36, 37) in particular, made outstanding contributions in this field of work, synthesizing, for example, compound **2**, which was selective for dicarboxylates of specific chain length (as structure (**2**) illustrated). Compound **3** (BISTREN), when hexaprotonated, selectively bound azide anions due to the elliptical nature of the binding site (38, 39).



n=7 or 10
m=2,3 or 5,6

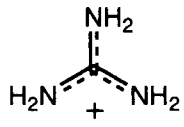
2



3

Unfortunately, polyammonium hosts are limited by the pH range over which they are protonated. This pH range is the same as that at which anions (such as phosphate and carboxylate) also begin to protonate. Consequently, the utility of this class of receptor was limited, thus causing the development of guanidinium based hosts.

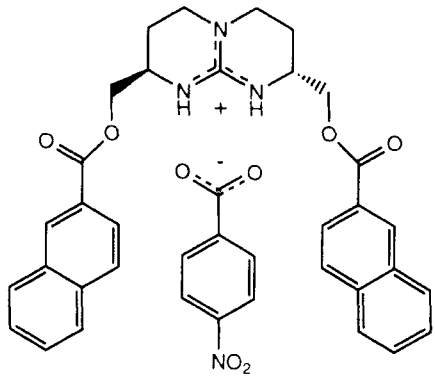
Guanidinium (**4**) is protonated across a wider pH range than polyammonium systems and consequently avoids many of their pH limitations. It is extensively



4

used in enzymatic anion-binding systems [such as Staphylococcal nuclease (40, 41)] in the form of arginine residues. It was therefore a natural choice to be incorporated within organic anion receptors, its action relying, once again, on a combination of electrostatic and hydrogen-bonding interactions. Lehn and co-workers (42) were the first to propose the use of polyguanidinium systems as synthetic anion complexones. The strength of anion binding, however, was less than for analogous polyammonium systems, probably due to the greater charge delocalization across guanidinium.

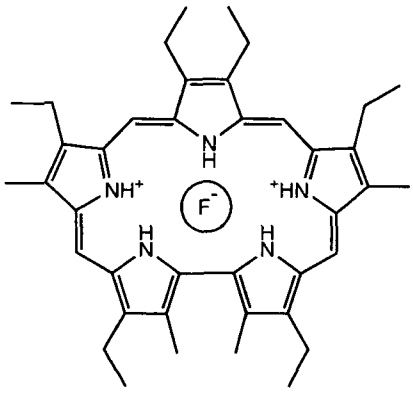
Nonetheless, much excellent use has been made of this system. Receptor **5**, for example, extracts *p*-nitrobenzoate quantitatively from water into chloroform (43), and the chirality of the receptor allows the possibility of chiral anion recognition (44). Guanidinium has also been incorporated into devices, such as a hydrogen sulfite selective electrode (45). Recently, Mendoza and co-workers (46) reported a chiral double helical array of polyguanidinium strands assembled around sulfate templating anions, the first anion centered helical structure.



5

Another method enabling protonation of nitrogenous host molecules at accessible pH values has been developed by Sessler et al. (47), which was based on the ease of protonation of expanded porphyrins. Studies of sapphyrin [an expanded porphyrin (**6**)] yielded a crystal structure of diprotonated host with a bound anion, fluoride, found to be in the plane of the macrocyclic ring. These readily protonated expanded porphyrin systems are now well established as receptors for anions. Compound **7**, for example, elegantly illustrates two-point binding, with the expanded porphyrin binding the negatively charged phosphate group while the nucleic acid base is complementary to the base of the bound substrate (48).

A different approach to the pH problem involved forming permanently positive nitrogen centers by quaternization. This methodology is exemplified by



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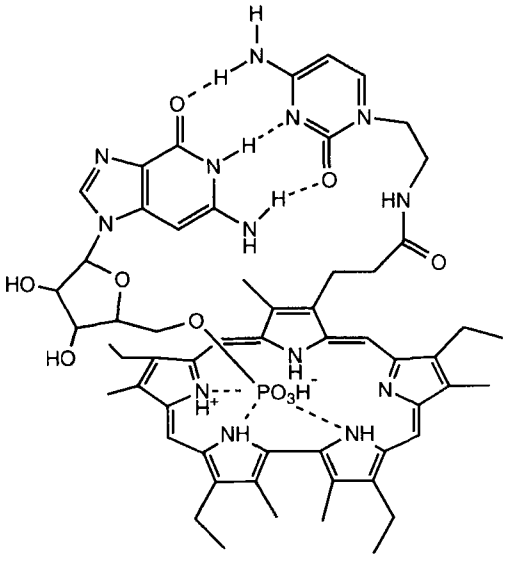
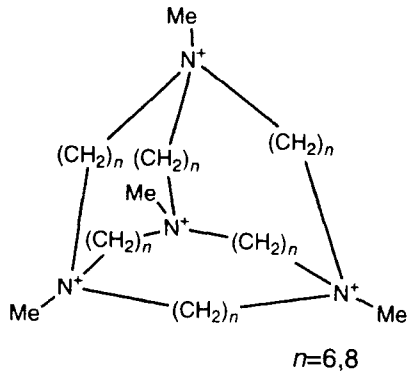


7

Compound **8**, which was synthesized by Schmidtchen (49). This receptor provides a fixed-binding site for anions that operates through a combination of electrostatic and hydrophobic forces (50). The absence of donor protons prevents any opportunity for hydrogen bonding, but the crystal structure of the iodide complex still indicated that the anion-binding site was in the center of the cavity (51). Zwitterionic hosts such as **9**, have also been reported (52, 53). These net neutral hosts prevent the need for the substrate to compete against a



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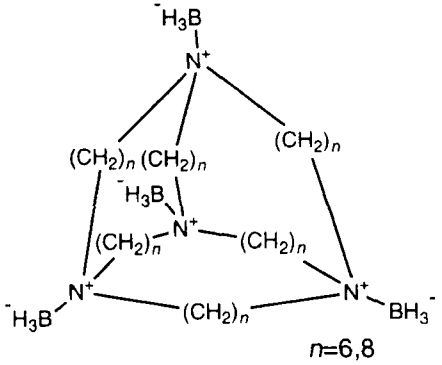
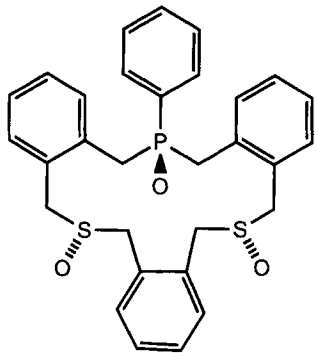


9

counteranion in the binding process, hence enhancing the strength of anion binding.

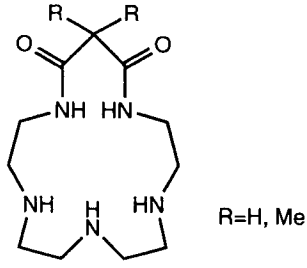
Dipolar electrostatic interactions have also been manipulated for the purposes of anion binding. Macrocyclic receptor **10** was shown to be capable of binding halide anions through interactions with the positive ends of the S = O and P = O dipoles (54). Evidence was also provided for the simultaneous binding of primary alkyl ammonium cations (to the oxygen atoms) and halide anions (to the dipoles). This topic of simultaneous cation and anion recognition is of considerable current interest. Further examples will be encountered during this chapter.

Another way of avoiding the problems of pH range and counterion competition is to use a neutral hydrogen-bonding receptor based on amide functionalities. Peptide groups from the protein backbone are, of course, well known to be involved in enzyme anion binding as discussed earlier. Amide involve-



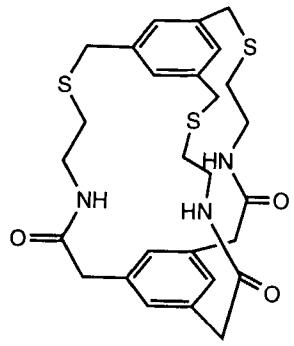
10

ment in the binding of anions by synthetic hosts was first suggested by Kimura et al. (32) for the protonated receptor (**11**). This involvement was later crystallographically proven for azide ion binding (55). In 1986, Pascal et al. (56) prepared **12**, the first purely amide based receptor, which had three amide protons pointed into the cyclophane cavity and showed evidence of fluoride binding in dimethyl sulfoxide d_6 (DMSO-d_6) solution. Since this report, considerable use has been made of amides and, in particular, ureas for the construction of neutral anion receptors (57–61).



R=H, Me

11



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All the receptors discussed so far, however, are based on traditional organic chemistry and while often effective, there are several good reasons for approaching the problem of anion binding from a slightly different, inorganic viewpoint.

IV. INTRODUCTION TO INORGANIC BASED ANION RECEPTORS

The organic receptors illustrated above take their inspiration from the first class of biological receptor to be discussed, utilizing solely organic hydrogen bonds, electrostatic attraction, and hydrophobic forces for anion bindnig. Nature, however, as shown earlier, casts its net wider in search of effective means of binding anions, thus incorporating metal centers into many of its anion receptors. There are several excellent reasons other than pure biomimicry, however, for attempting to incorporate metal centers:

1. *Source of Interactions with Anions.* Metals are usually either positively charged or formally electron deficient. This knowledge leads to either an enhanced electrostatic interaction with negatively charged substrates or the chance for orbital overlap and formation of bonding interactions, thus increasing the stability of any complex species formed.
2. *Structural Factors.* Metal compounds often have precisely defined geometries [e.g., Cu(I)-tetrahedral, Cu(II)-distorted octahedral]. These geometries can be manipulated by the inorganically minded anion recognition chemist to create receptor molecules with well-controlled and interesting relative geometries of ligating groups. This knowledge can be used to enhance selectivity for specifically shaped anions, or create unusual switching and conformational effects on binding.
3. *Incorporation of Functionality.* Metal ions possess a huge range of function, and this is perhaps one of the most compelling reasons for their incorporation into receptor structures. Redox activity, ultraviolet–visible (UV–vis) spectroscopic properties (color), catalytic ability, fluorescent and energy-transfer properties, and radioactivity could all form the basis of potentially useful molecular machines dependent on the recognition of anions. This mechanism could in turn lead to advances in sensor technology (62), anion transport, drug delivery, and catalysis (63); naming only a few applications.

In this chapter, we will try to illustrate the reasons in each case for the incorporation of inorganic centers into the receptors and the advantages conferred to each host by doing so.

In a simplistic treatment, of course, an isolated metal ion could itself be viewed as a receptor for anions as it fulfills the basic criterion of reversible anion binding. The concept of an anion receptor, however, requires a reversal of this metal-centered viewpoint. For the purposes of this chapter, a receptor will be considered as a molecule designed for binding anions, which does so through a combination of bonding interactions (rather than through a single

coordinate bond). The receptors we will discuss are often designed to incorporate anion selectivity and frequently manipulate a variety of noncovalent interactions.

As will be illustrated, the use of inorganic and organometallic chemistry has, in the past 10 years, enabled the development of a rich and exciting range of novel, functional anion receptors. Inorganic anion receptors can be usefully subdivided into four classes dependent on the bonding interactions responsible for anion binding:

1. Neutral receptors based on multiple Lewis acid–anion orbital overlap interactions.
2. Positively charged receptors based on multiple coordination interactions from transition metals.
3. Charged receptors based primarily on intermolecular electrostatic attraction from positively charged metal centers.
4. Receptors incorporating hydrogen-bonding interactions.

V. INORGANIC APPROACHES TO ANION BINDING

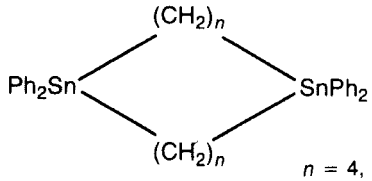
A. Neutral, Lewis Acidic Receptors

Lewis acidic centers are, due to their electron deficiency, capable of interacting with anions through an orbital overlap, causing a bonding interaction. Many novel, neutral receptors incorporating multiple numbers of this kind of anion-binding interaction have been developed.

1. Tin Based Receptors

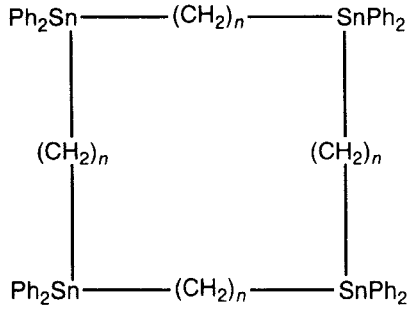
Organotin compounds have been used as neutral carriers for selected anions in membrane electrodes since the late 1960s (64). The compounds generally used, however, were mononuclear tin species such as trioctyl tin chloride. The mechanism of interaction was elucidated to be the formation of a single-bonding interaction between the four coordinate neutral tin center and the anionic guest (65, 66). As such, these molecules do not fall under our criterion of multiple anion-binding interactions for a designed anion receptor.

The first attempts to marshal a multiple number of Lewis acidic tin centers in order to create a receptor specifically for the purpose of binding anions were made by Newcomb and co-workers (67). In 1984 they reported the synthesis of several tin based macrocycles (e.g., **13** and **14**), the first macrocycles to contain Lewis acidic acceptor groups rather than lone-pair donors. Receptor **13** was available in gram quantities making it an ideal receptor for anion-binding in-



n = 4, 5, 6, 8, 10, 12

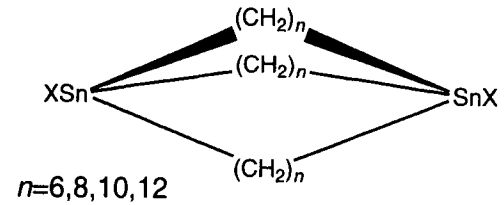
13



14

vestigations. The first coordination study results were reported in 1987 (68). This kind of host was shown to form both 1 : 1 and 1 : 2 stoichiometric complexes with chloride ions in acetonitrile solution. Stability constants ranged from 400–850 M^{-1} with little difference between first and second anion coordination (although some uncertainty was expressed over the reliability of these values). This casts some doubt over whether the tin atoms act cooperatively or independently in this receptor. A small size selective effect was observed (n = 8 binding more strongly than n = 10) and a small macrocyclic effect was observed on comparison with an acyclic analogue.

Macrobicyclic receptors (**15**) were also reported (69). Binding studies indicated kinetically slower binding than with their macrocyclic analogues (probably due to a more enclosed binding site) The stoichiometry of halide ion binding was exclusively 1 : 1 and encapsulation of the guest anion was postulated (70). Nuclear magnetic resonance (NMR) ^{119}Sn studies were used to illustrate that for receptor **15**, with n = 6, the fluoride ion ($K \approx 200\ M^{-1}$) was bound five orders of magnitude more strongly than chloride ions ($K \leq 0.01\ M^{-1}$) in chloroform (71). Crystallography later showed that the fluoride ion was encapsulated within the cavity between the two tin atoms (r_{Sn-F} = 2.12/2.28 Å), whereas in the chloride complex, the ion was strongly bound to one tin center but only weakly interacting with the second (72). For fluoride ions, therefore, the enhancement in binding energy is caused by cooperative interactions with both the tin atoms in the host molecule, making **15** a selective fluoride receptor.

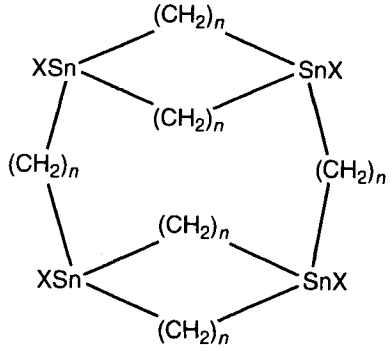


n=6,8,10,12

X=Ph **15a**

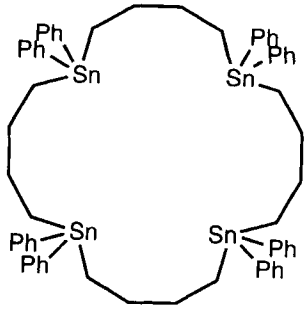
X=Cl **15b**

Receptor **16** was reported to form a 1 : 1 complex with chloride ions in chloroform (K = 500 M^{-1}), exhibiting fast exchange on the NMR time scale (73). Such hosts, containing four tin binding sites, were shown to be considerably more effective than mononuclear organotin compounds for chloride binding. In 1991, Newcomb and co-worker (74) published modeling studies for these tin based hosts as well as a crystal structure of **17**.



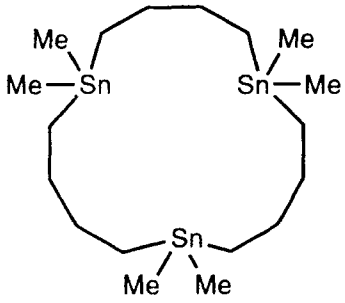
n=4, X=Ph
n=5, X=Ph/Cl

16

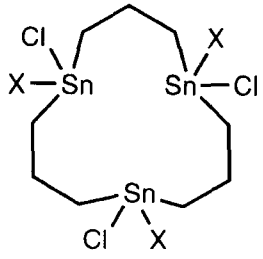


17

The trinuclear receptor **18** and its propyl linked analog **19** have been reported by Jurkschat et al. (75, 76). Receptor **18** was shown to transport chloride and bromide ions from water through dichloromethane, but the process was slow. Crystallography of **19a** indicated chloride binding between a pair of tin atoms, while NMR studies indicated that **19b** involved all three tin atoms in the binding process. No quantitative evaluation of binding affinities was attempted.

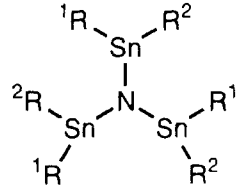


18



X = Cl (**19a**)
X = Me (**19a**)

Compounds such as **20** have recently been reported and crystallographically proven to form Sn–X–Sn intramolecular bridging interactions (77). These biscoordinated bromide and iodide ions are observed to be held with bonds of intermediate bonding length, indicative of cooperative tin multicentered anion binding. Multidentate acyclic organyl tin species have recently been used as phosphate selective carriers in polymer based liquid membranes (78). This result indicates the potential for practical application of organic multitin systems in the field of anion recognition.



20

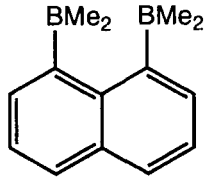
2. *Boron Based Receptors*

Although technically a heteroelement rather than a metal, some interesting Lewis acidic receptors for anions have been based on boron-containing systems. The first evidence for this type of anion receptor was published in 1967, one of the earliest examples of anion binding. Compound **21**, when compared with **22**, exhibited a chelate effect in the binding of methoxide anions (3).

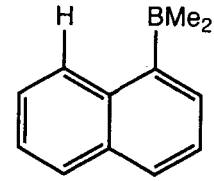
21

22

Katz (79, 80) used **23** as a receptor for anions, studying its interaction with hydride, fluoride, and hydroxide ions. Comparison with **24** once again indicated a chelate effect: compound **23** abstracting hydride or fluoride from complexed **24**. The crystal structure of the hydride sponge **23**, showed the hydride ion bound between the pair of boron atoms with short strong bonds. A crystal structure of the chloride complex was also elucidated and showed the same bridged structure (81).

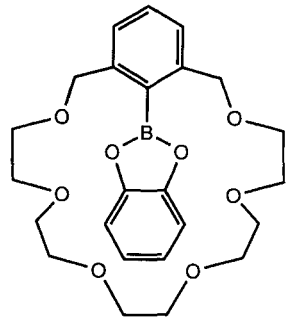


23



24

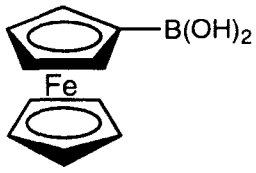
Compound **25** has been synthesized by Reetz et al. (82, 83). It has been used to complex ionic pair species such as KF. The potassium ion is complexed by the crown ether and the fluoride ion is held by a combination of orbital overlap with the Lewis acidic boron atom and electrostatic attraction to the positively charged potassium. This receptor provides an elegant example of the use of a combination of intermolecular forces.



25

A study has also been made of the theoretical propensity of organoboron macrocyclic hosts for anion binding (84). This study indicated that for the hypothetical hosts studied, anion inclusion occurred with cavity shrinkage and partial boron rehybridization. This effect would be expected for these anion receptors, which are dependent on orbital overlap interactions for their mode of action.

Recently, Shinkai and co-workers (85) reported a ferroceneboronic acid receptor (**26**). This receptor showed selective electrochemical recognition of fluoride ions over other halides, the redox potential for the ferrocene unit being perturbed on the addition of F^-. There is, however, only one orbital overlap interaction provided by this host and it is likely the selectivity arises solely due to the "hardness" of the fluoride anion.



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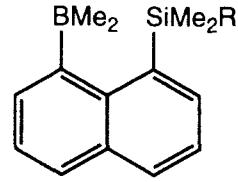


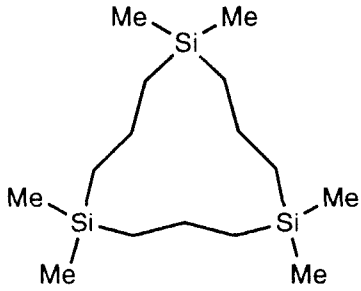
R = Me,OEt,F

27

Compound **27**, a mixed boron–silicon system, was synthesized to investigate the influence of organosilicon on the anion-binding process (86). A fluoride complex was isolated and NMR and crystallographic studies showed that the silicon was involved in binding the anion, but only weakly.

3. Silicon and Germanium Based Receptors

In light of the work carried out on boron systems as described above, a silacrown (**28**) was synthesized in fair yield via nine steps (87). This transported bromide ions more effectively than chloride, but no evidence for the binding mechanism or evaluation of binding affinity was provided. In recent studies, Compound **29** showed, as would be expected, a chelate effect with fluoride ions, exhibiting a high-binding constant (log $K > 9$ in acetone-d_6), which had to be determined via a stepwise procedure (88).



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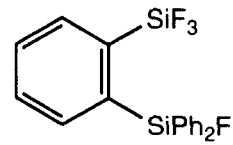
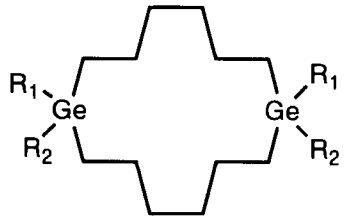


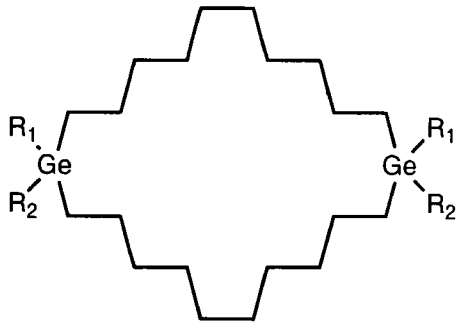
29

Germanium based macrocycles (**30a–b**) have also recently been synthesized (89, 90). Receptor **30b** has been shown to transport chloride ions in preference to bromide, although the degree of transport was only 20% in 35L (H_2O/CH_2Cl_2) (91). The expanded hosts (**31**) have also been synthesized and show similar effects to **30**, indicating that ring size is not the only controlling factor in the anion complexation process (92).



$R_1 = R_2 = Me$ **30a**

R_1=Cl, R_2=Me **30b**



31

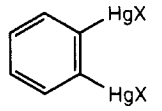
4. Mercury Based Receptors

Perhaps the most eye catching of the receptors utilizing Lewis acidic centers are those based on mercury. Mercury is *sp* (linear) hybridized which has two consequences.

1. Mercury has two empty *p* orbitals available for orbital overlap with guests and consequently binds anions with practically no energetically unfavorable geometric reorganization (unlike Sn, Si, B, and Ge, which have to partially rehybridize on anion binding).

2. Large macrocyclic receptors can be synthesized due to the linear geometry (93).

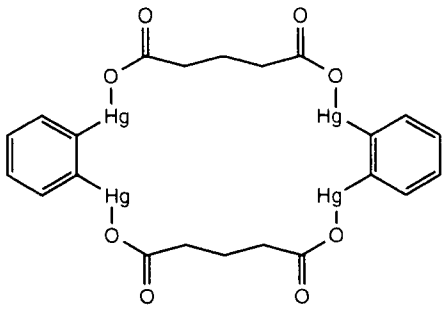
The first literature example of a mercury based receptor (**32**) for anions was analogous to the chelating boron receptor discussed earlier. The crystal structure indicated that two molecules of Compound **32** asociate with one chloride ion, which sits in a four-coordinate binding site. Solution studies, however, gave results indicative of 1 : 1 binding for halide anions (94, 95). This simple



X = Cl,Br

32

receptor unit was subsequently incorporated into macrocyclic structures (**33** and **34**) and investigations indicated interactions with electron-donating molecules such as tetrahydrofuran (THF) (96). Unfortunately, there was no marked enhancement in binding attributable to a macrocyclic effect. Receptor **34** has, however, been further functionalized and built into a polymeric membrane electrode that shows selective response to SCN^- and Cl^-, in the presence of NO_3^- and ClO_4^- (97).



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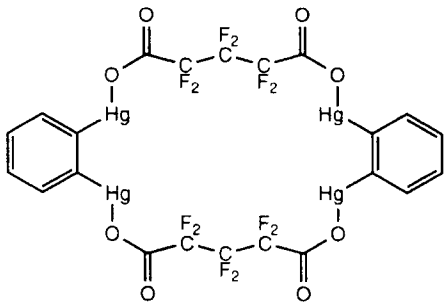
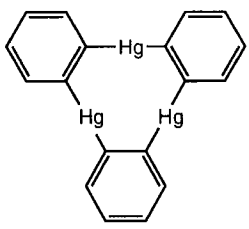


34

Macrocyclic mercury compounds have also been investigated by Shur et al. (98). Receptor **35** was proven to complex halide ions by ^{199}Hg NMR studies but complex isolation failed. On fluorination of the benzene rings yielding receptor **36**, complex isolation became possible (99). As seen from the crystal structure of **36** (Fig. 3), each bromide ion is coordinated to six mercury atoms and is sandwiched between two mercury macrocycles. The Hg—Br distances are 3.07–3.39 Å, shorter than the van der Waals contact but longer than a covalent bond. Receptor **37** was also crystallographically proven to coordinate chloride ions (100). The crystal structure indicated one chloride ion bound above the plane of the macrocycle and one below it, both coordinated by all five mercury atoms (r_{Hg-Cl} = 3.09–3.39 Å). The chloride–chloride distance was short (3.25 Å), probably only tolerated due to the presence of the mercury "sandwich filling."



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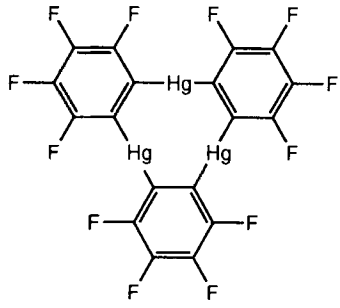

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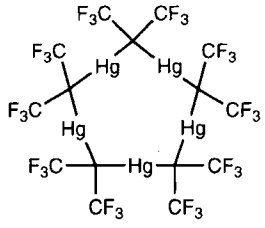


37

Of particular note are the beautiful mercuracaboranes of Hawthorne and coworkers (101), which synthetically link the carbon atoms of carborane cages with mercury atom bridges. Receptor **38** was reported along with the crystal structure of its chloride complex [Fig. 4(a)]. The Hg—Cl bond distances were 2.94 Å shorter than those for Shur's hosts listed above. The square planar coordination of a chloride ion was unprecedented, and analogy was drawn with the lithium selective cation receptor 12-crown-4, the receptor being named [12]mercuracarborand-4 and classed as an "anticrown." It was proposed that the presence of chloride ion during the synthesis templated the formation of

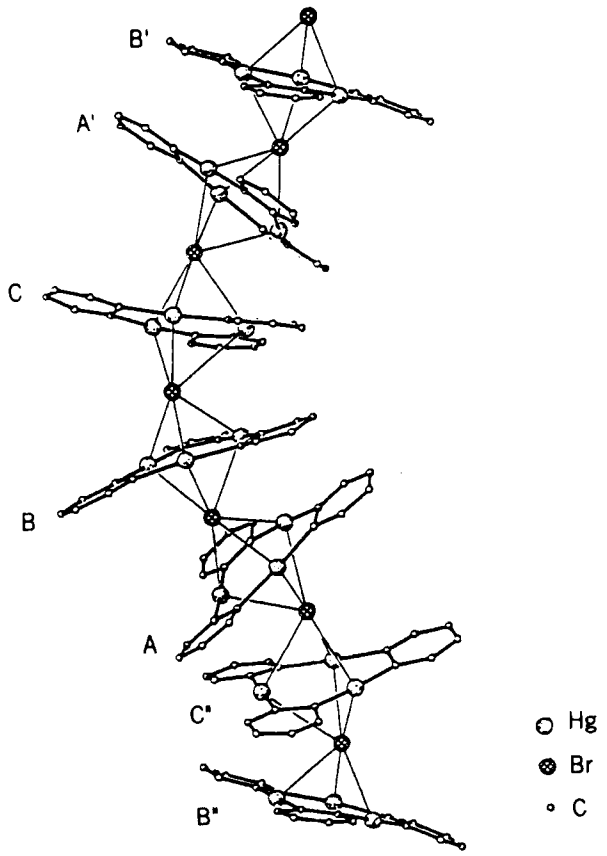
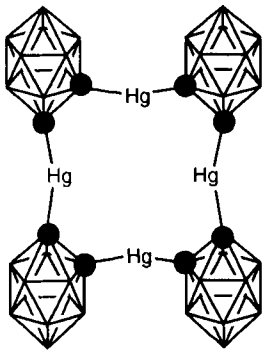


Figure 3. Crystal structure of receptor **36** with bound bromide ions. [Reprinted from *J. Organomet. Chem.*, *418*, C29, V. B. Shur, A. Tikhonova, A. I. Yanovsky, Y. T. Struchkov, P. V. Petrovskii, S. Y. Panov, G. G. Furin, and M. H. Vol'pin. Crown compounds for anions. Unusual complex of tremeric perfluoro-*o*-phenylene mercury with the bromide anion having a polydecker sandwich structure C29, 1991, with kind permission of Elsevier Science SA, Lausanne, Switzerland.]

products avoiding the formation of oligomeric species. When mercuric acetate (incapable of templating) was used in the synthesis, the yield was diminished, providing further evidence for this templated process. X-ray structures have also shown both one and two iodide anions [Fig. 4(b)] bound in the cavity (102, 103). The host has been shown, crystallographically to form a supramolecular aggregate with $[B_{10}H_{10}]^{2-}$, the anion fitting snugly within the binding cavity.

A smaller analogue, [9]mercuracarborand-3 (**39**), has also been synthesized, and evidence has been provided for its interaction with chloride ions (104).



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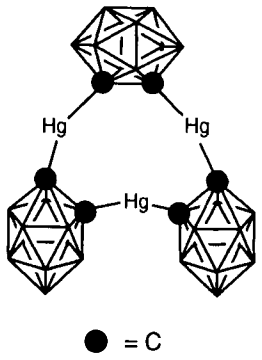
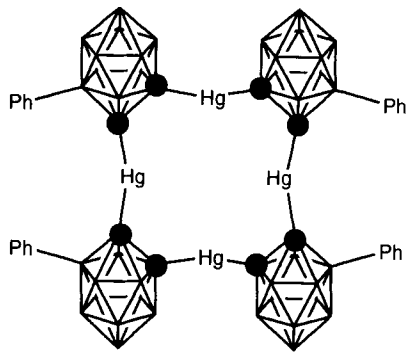


39

Recently, a hexamethyl[9]mercuracarborand-3 derivative has been reported (105). This receptor showed smaller shifts in its ^{199}Hg NMR peaks on anion complexation, probably due to the methyl groups making the mercury centers less electron deficient. Chloride ions formed 1 : 1 complexes, while bromide and iodide formed complexes of 2 : 1 stoichiometry.

A tetraphenyl substituted derivative of [12]mercuracarborand-4 (**40**), which binds one iodide ion in its cavity due to steric hinderance, has been reported. The stereochemistry of the phenyl groups was found to depend on the mercury counteranion used during the synthesis (106). This observation provided yet further evidence for a direct anion templating effect in mercuracarborane syntheses. Most recently, the C—Hg—C link in this type of host has been replaced with a B—Hg—B link, which alters the electron demands of the mercury centers (reducing their electron deficiency) and apparently switches off anion complexation (107).



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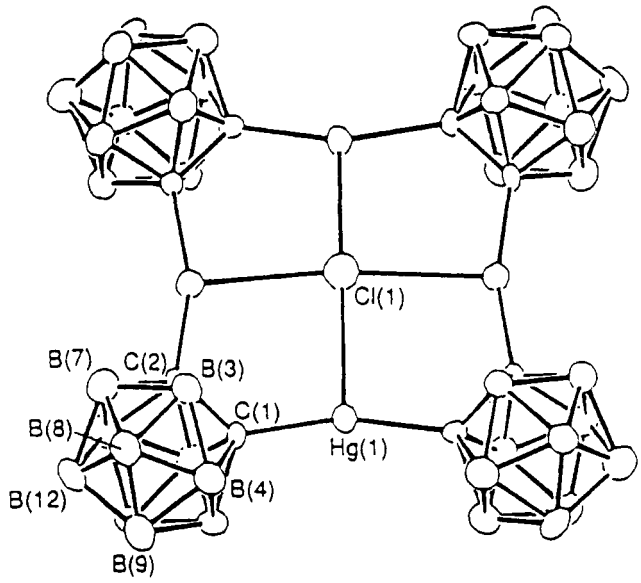
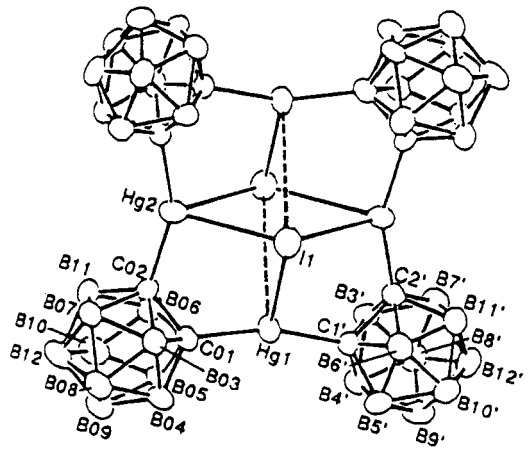


(*a*)



(*b*)

Figure 4. (*a*) Crystal structure of receptor **38** with bound chloride anion. [Reprinted with permission of (101).] (*b*) Crystal structure of receptor **38** with bound iodide anion. The iodide anion is too large to bind in the plane of the mercury crown. [Reprinted with permission from X. Yang, C. B. Knobler, and M. F. Hawthorne, *J. Am. Chem. Soc.*, *114*, 380 (1992). Copyright © 1992 American Chemical Society.]

5. *Summary*

The hosts outlined above generally utilize their metal centers to provide interactions with anions. The orbital overlap between unfilled heteroelement orbitals and filled anion orbitals yields bonding interactions. In the case of the mercury based receptors, the role of the metal atoms is partly structural, with their *sp* hybridization linear geometry specifically yielding large macrocyclic cavities of suitable diameters for anion encapsulation. The metal atoms have often been functionally used as an NMR "handle" on the anion coordination process.

In summary, various Lewis acidic host molecules have been used for the complexation of anions, particularly halide ions, in organic solvents. Stability constants, when elucidated, are often low in magnitude ($K \leq 1000\ M^{-1}$). The exceptions to this rule are those cases where boron or silicon are coordinating to an electron dense "hard" anion such as fluoride, hydroxide, or hydride. In these cases anion binding is strong, but reservations have to be expressed as to the degree of control that can be exerted over the selectivity of the binding process. Lewis acid centers are also well known for their moisture and air sensitivity, leading to a lack of physical robustness. None the less, multidenate Lewis acidic hosts have shown novel anion-binding modes and selectivities and have, as has been illustrated, considerable potential for application into chemical sensor technology.

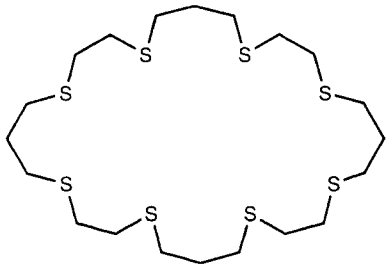
B. Multiple Positively Charged Metal Ion Based Coordinative Receptors

The receptors considered so far have been based on neutral Lewis acidic centers, covalently built into the host framework with organic σ-bonds. Combinations of positively charged metal ions held within one host, however, can also fulfill the function of anion binding by forming multiple coordination interactions with a single cobound anionic substrate. In some ways, these hosts are analogous to the Lewis acidic hosts discussed above, the interactions being based on orbital overlap between the electron-rich anion and empty metal centered orbitals. However, the metal centers are positively charged and are coordinated into the receptor framework rather than held in place by covalent bonds.

The past 25 years have spawned literally hundreds of examples of this type of multimetal center anion coordination. Therefore, rather than being exhaustive, this chapter will attempt to summarize the main types of receptor investigated and analyze their anion-binding potential. A recent review highlighted the general importance of binuclear metal complexes (and concomitant anion binding) in the modeling of biological catalytic processes, and some of the examples contained therein will be returned to later (108).

1. "Robson-Type" Receptors

The first macrocyclic receptors (**41**–**43**) capable of completely circumscribing two metal ions were reported in 1970 (109–111). Receptors **41** and **43** bound two Ni^{II} ions while **42** bound two Cu^{II} ions. No evidence was found of anionic species bridging the metal ions because in these examples the metal ions were either too closely held or were coordinatively saturated. If multimetal anion coordination interactions are to be observed, it is critical that the metal ions involved have vacant coordination sites.



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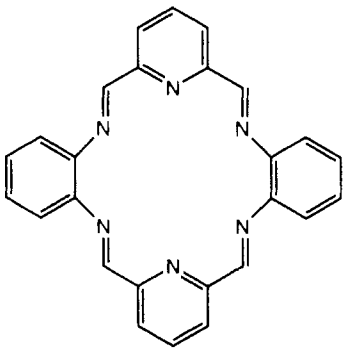

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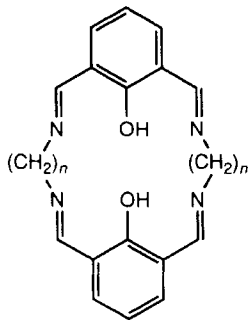
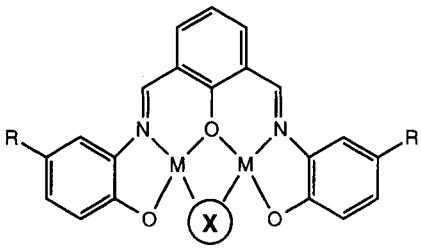


43

To this end, Robson et al. (112, 113) investigated a series of acyclic analogues (**44**) of receptor **41**. As illustrated, these receptors do not coordinatively saturate the two metal ions. Consequently, there is room for a bridging anion X. A variety of alkoxide anions were observed to bridge the pair of metal ions.

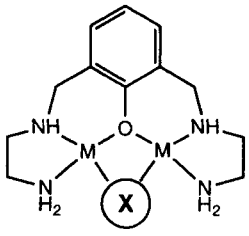
This area of chemistry was particularly fertile in the early 1970s with a whole range of analogous binucleated anion receptors (e.g., **45** and **46**) being synthesized and analyzed either spectroscopically or crystallographically (114–118). A good overview of early binucleated systems, including those with bridging anions, was provided by Groh (119).



$X = EtO^- / PhCH_2O^- / MeO(CH_2)_2O^-$

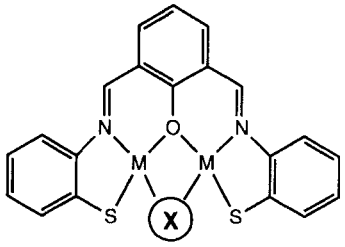
$R = H / Me_3 / Cl / NO_2$

44



$X = OH^- / Cl^- / Br^- / NCS^-$

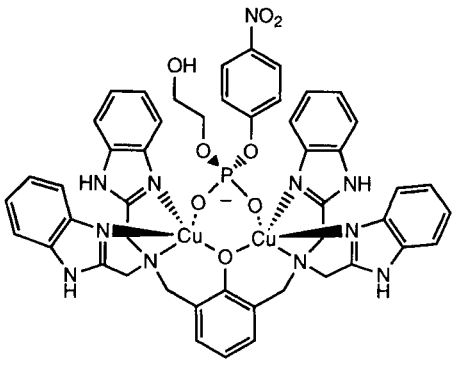
45



$X = NH_2^- / MeO^- / PhCH_2O^-$

46

These acyclic "Robson" systems provided initial evidence for this mode of binding. Recently, a dicopper(II) complex of this type (**47**) was proven to bind phosphate esters and increase their rate of hydrolytic cleavage (120), which

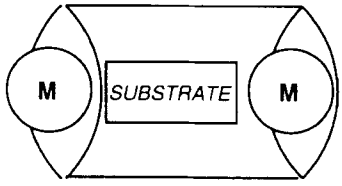


47

indicates the potential of these systems for the incorporation of catalytic function as well as anion recognition properties.

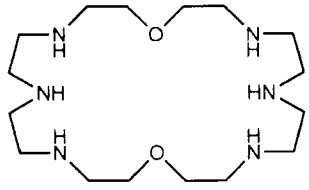
2. *Macrocyclic Receptors*

In three erudite review articles, Lehn (121–123) expounded his early philosophies of supramolecular chemistry. In these articles, he considered the development of generalized multisite receptors such as **48**; analogous with the anion-bridging receptors discussed above. He argued that such receptors would provide an entry into higher forms of molecular behavior normally associated with enzymes, such as cooperativity, allostery, and regulation; describing the bound substrate as being "cascaded." With this assimilation of functional concepts and shift in emphasis from coordination chemistry to "supramolecular" substrate binding, much new attention was focused on these anion-binding systems.



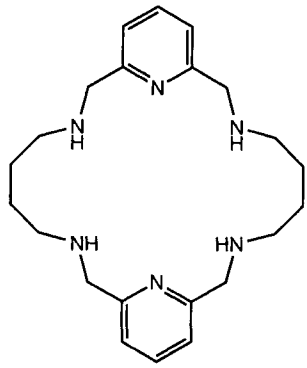
48

Receptors such as OBISDIEN (**49**) when protonated, had already been studied by Lehn and co-workers (30, 31) as organic hosts for anions. OBISDEN



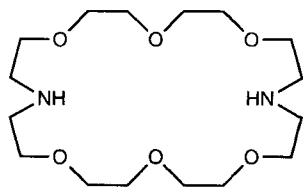
49

was now used in its unprotonated state to bind two metal ions in a coordinatively unsaturated manner and, subsequently, cascade an anion in between them. Receptor **50** was also used to the same end. Along with Lippard and co-workers (124), Lehn found that the biologically important imidazolate anion bridged the bis-copper(II) complex of **49**. Many studies were subsequently made of the potential of this system to act as an effective enzyme model (125–127). The crystal structure of the bis-copper(II)azide complex, however, indicated that cascade complexes were not always formed by such dinucleated receptors (128).

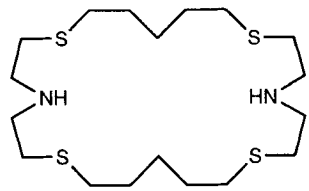


50

A structural study of receptors **51**, **52**, and **49**, showed three different modes of azide complexation to the binuclear copper(II) host (123); 1, 1′ cascaded, 1,3 cascaded, and noncascaded, respectively. These structures indicate that the nature of the macrocyclic framework of the receptor is important in determining the mode of anion coordination. Figure 5(*a* and *b*) shows the crystal structures of **52**, 2 Cu(II)·azide, and **52**, 2Cu(II)·chloride, respectively, for comparison (129). As can be seen, it is the length of the azide bridge that makes cascade complexation possible, whereas for the smaller mononuclear chloride anion this obviously cannot occur. Receptor **49** has also been shown to cascade bind pyrophosphate [as its bis-copper(II) complex] (130) and sulfate [as its bis-iron(II) complex](131). At about the same time, Nelson and co-workers (132) published a similar bis-copper(II) complex structure that cascaded an azide anion.



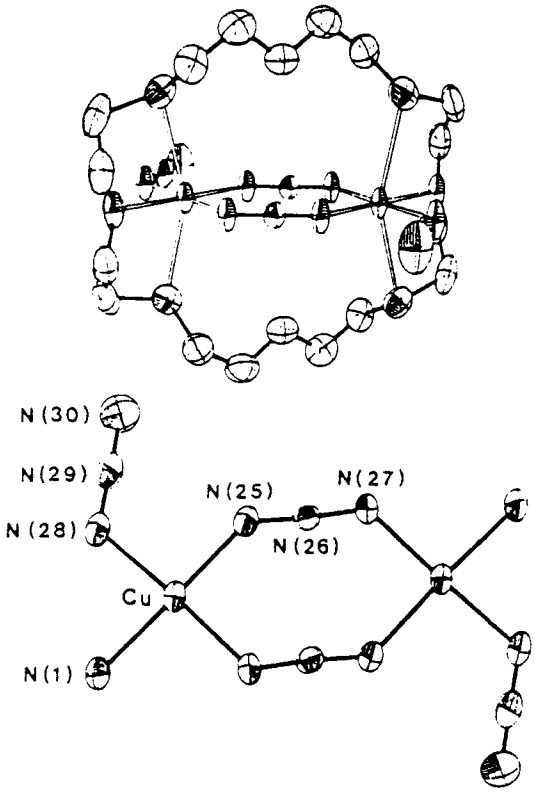
51



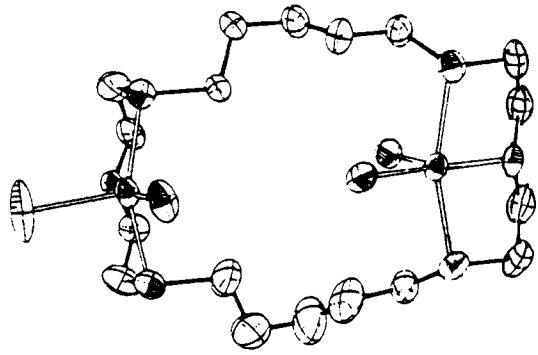
52

In the examples discussed thus far, the coordinating metal sites have had a twofold role. They have (obviously) been the source of interaction with the anion and also played a structural role; their degree of separation influencing the type of anion that can be cascade bound. Martell and Motekaitis (134, 135) have, however, also succeeded in introducing a functional role for the metal centers.

In 1983, it was shown that receptor **49** was capable of binding dioxygen



(*a*)



(*b*)

Figure 5. (*a*) Crystal structure of bis-copper(II) **52** with cascade-bound azide anions. (*b*) Crystal structure of bis-copper(II) **52** with bound chloride anions. [Reprinted with permission from Y. Agnus, R. Louis, and R. Weiss, *J. Am. Chem. Soc.*, *101*, 3381 (1979). Copyright © 1979 American Chemical Society.]