Artificial Organic Host Molecules for Anions

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Received January 23, 1997 (Revised Manuscript Received May 23, 1997)

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I. Introduction to Molecular Hosts

According to one of Natures most fundamental laws, molecules may be differentiated by having a positive, a negative, or no net charge at all. Although nothing may be known about the distribution of partial charges within the covalently connected framework or about other types of molecular interaction some principal properties (ion exchange behavior, solubility, etc.) of the charged species can be predicted with great confidence. Apparently, the Coulombic forces largely dominate the long-range noncovalent communication between molecules. Notwithstanding, the negatively charged anions like any other molecular species experience attractive forces with their environment irrespective of its chemical nature. The association of anions with some other structurally defined entity, giving what is now called a host−guest complex, appears as a natural consequence of this fundamental interaction and thus does not seem special at all. In quantitative terms, however, one observes great differences in the strength of binding posing the question for the origin of these nonuniform effects. In principle, the pertinent thermodynamic quantity characterizing the molecular association, the binding constant K_{assn}, comprises all direct mutual interactions between the binding partners as well as all changes in the environment (e.g., in the solvent). Both contributions are heavily dependent on the covalent structures of the binding partners and, as such, are subject to molecular design. The development of novel concepts and ideas for studying supramolecular association on this basis has been one favorite objective in chemistry over the past decades.

In the early steps of his career Franz P. Schmidtchen received training in natural product chemistry obtaining the Ph.D. degree with B. Franck (Münster, 1972) followed by a post-doctoral period with H. Rapoport (Berkeley, 1974). On returning to Germany in 1975 (H. Simon, Münich), he embarked on the synthesis of abiotic anion receptors which at that time was a virgin field occupied by just one earlier paper. Some success in this research led to the habilitation (1982), the prestigious Heisenberg fellowship (1983), the chemistry award of the "Göttinger Akademie der Wissenschaften" (1987), and an *ad personam* Fiebiger professorship for Bioorganic Chemistry at Technical University of Münich (1989). Inspired by the intellectual environment, the research interests widened with time and now comprise molecular recognition of anions in all of its facets spanning from fundamental aspects to applications in self-assembly and in homogeneous organometal catalysis in water. The latter is in close connection with a bioorganic area of activity concerning regioselective modification of mature proteins.

Michael Berger was born in 1967 in Wuppertal, Germany. He started studying chemistry at the University of Bonn, Germany, where he received his diploma in 1994 after spending two years at the University of Tennessee in Knoxville, TN. Since 1995, he has been working with Prof. Schmidtchen at the Technische Universität München, on his Ph.D.; in his thesis, he works on the development of novel receptors for oxoanions.

It seems fair to state, however, that attempts to redesign the direct interactions between association partners by far outnumber those which rather address the modification of solvation patterns.

S0009-2665(96)00384-6 CCC: $28.00

In condensed phases, K_{assn} obviously only measures the difference in free energies between two stabilized states, the complex and the separated fully solvated association partners, and does definitely not reflect the total intrinsic free energy of association. Thus, it is well conceivable that some structural modification at a site remote from the place of direct contacts of the association partners may well affect their binding strength. On the other hand, as is particularly true for anions of higher charge, stabilization by solvation is the prerequisite for their mere existence and is mandatory for establishing an association equilibrium between binding partners of defined structures.

In general, the term host describes the ability of a molecular species to bind another one with preference over all of the others and with greater strength than is commonly found as the result from unspecific molecular interactions. This is an operational definition of very broad scope and is, on top, dependent on the experimental situation. Consequently, a compound qualifying as a host for one peculiar guest species in one solvent may completely fail to bind the same guest under different solvent conditions. In order to be of some use in general discussions of intermolecular interactions, the definition of what to consider a host compound must be further restricted. Clearly, there is at present no universal consensus on the catalog of criteria to be met by molecular hosts, but a number of features seem essential, while others which are historically founded do not hold nowadays any more. A prominent example of the latter is the size relation of host and guest. Host−guest interactions were frequently visualized by the lock-and-key metaphor of Emil Fischer which implies that the guest must penetrate into and be wraped by the host structure. Although there are distinct advantages for the encapsulation mode of intermolecular interactions, the experimentally observable result of host−guest complex formation does not require this binding type. Another example refers to the involvement of purely supramolecular interactions in host−guest binding. A number of successful and uniformly accepted host systems bind their guests by covalent bonds and thus do not qualify as supramolecular complexes by definition. Nevertheless, their consideration for the present discussion is appropriate, because the conceptual approach underlying their construction as well as their binding properties and most of the methods for their study are fully coherent with their analogues acting exclusively by noncovalent binding.

Among the criteria characteristic for molecular hosts the rapid establishment of a host−guest binding equilibrium appears mandatory. Again, there is no agreement on quantitative limits, but it is generally expected that equilibration is reached within the usual time periods of the physical measurements. Most artificial systems equilibrate much faster. However, the time criterium translates into an upper limit for the free energy of binding in the complex. A crude estimate for a 1:1 stoichiometric association arrives at $K_{assn} \sim 10^{13}$ M^{-1} ($\Delta G = 18$ kcal/mol). (The rate of bimolecuar association is taken at the diffusion limit of 10^9 M^{-1} s^{-1} and the half-time for dissociation of the complex at $T_{1/2} = 3$ h.) Supramolecular complexes of higher stability, which are well-known in biology (cf., the Avidin−Biotin system: $K_{assn} \approx 10^{15}$ M^{-1}), are quite difficult to recognize and characterize in artificial systems. On the basis of similar reasoning, one can predict that any covalent bond formed in a complex must have a dissociation enthalpy ΔH_{dissn} of less than 25−30 kcal/mol. Thus, a prime target for host design is to enable kinetically labile complex formation, which allows rapid guest exchange. A very proficient strategy in this vein is to arrange several segregated binding sites (or anchor groups) in an array that allows their cooperation in guest binding. In fact, this approach is far spread and has been cited as the fundamental criterion in the definition of molecular hosts. The problematic aspect is how to define an anchor group knowing that in principle every part of the entire structure contributes to overall binding and any structural segregation is ultimately arbitrary and artificial. The latter notion has evoked the view that it is just this aspect of targetted design which promotes a molecularly interacting system to the status of a host−guest system. The attribute "host" thus denotes some purposefully planned architecture, if not already some application, and *a priori* excludes all of the nonmodified natural systems. In view of the great difficulties in developing another clear-cut definition, this criterion appears attractive, but does not encompass the current usage of the term host.

Beyond dispute, however, is the requirement for a host compound to show selectivity in some of its various aspects (substrate-, chemo-, regio-, or stereoselectivity). Most frequently, guest discrimination is measured in the ground state giving a selectivity factor corresponding to the ratio of association constants under a peculiar set of experimental conditions. Guest discrimination may alternatively refer to the *rate of transformation* of competing substrates on a reaction path. Kinetic selectivity in this sense is the ordinary way to direct fluxes in vectorial processes from homogeneous catalyses to guest sensing and signaling.

The selectivity emerges from more- or less-dedicated molecular interactions of the binding partners. Unravelling and characterizing these factors should finally lead to our ability to optimize complexation by insightful and prudent engineering of the host structure. Before this level of skill can be confidently approached fundamental points in general host−guest relationship must be clarified:

What is the chemical nature of the guest to be specifically bound by the host?

In which solvent or other environment is the host−guest binding to take place?

Is there a special purpose that the complexation must serve?

The first question addresses the mutual recognition pattern of host and guest, assuming that the precise definition is mandatory for maximizing the discrimination of similar guest species. Here is the place to include all knowledge about attractive and repulsive interactions, and about complementary shape or preorganization of the host design as well as to consider molecular requirements imposed by the

desired integral molecular properties. Beyond doubt, this process is at the heart of host design and has attracted major attention even to the extent that the other issues on the list have been neglected. This is also the subject readily investigated by molecular modeling[1−3] in docking analyses, although it must be stressed that meaningful comparisons to the true experimental observables require considerable extension beyond energy minimizations.

The inclusion of solvent in the calculations appears as an obligatory supplement, and this touches on the second point in the list. There is no doubt that solvent structuring unavoidably will change on complexation. The net free energy of this process may either favor or hamper host−guest association irrespective of the direct mutual interactions of host and guest. Experimental examples have shown that complex stability even is subject to the shear size of the solvent molecule and differences of orders of magnitude have been documented in a homologous series of chemical similar solvents.[4] One runs no risk by predicting that the incorporation of solvation features to actively shape the binding characteristics will pay off greatly in host design. The rational approach, however, requires solid experimental data of the caloric contributions of the various anchor groups to the total solvation energy in typical organic solvents. Results in this sense are rather scarce at present, although progress in the necessary instrumentation (isothermal titration calorimetry) has placed them within reach.

Answering the third question is less trivial than it seems at first sight. The analysis, however, requires dissection of whether host−guest complexation is aimed at maximizing binding or should rather serve a functional purpose (i.e., some messaging in a signal cascade, a vectorial transport across a membrane, or perhaps a catalytic reaction). Unlike mere binding, the selectivity in all of these processes depends on the ratios of the rates of competing species and thus is a kinetic phenomenon. The situation is very similar to the selectivity problem in living systems which typically operate far from thermodynamic equilibrium. The denotion of selectivity as a ratio of association constants in the ground state breaks down in this case and must be replaced by rate constants characteristic of the overall process. The better binding of one among several competing guests does not necessarily mean that this is the one triggering the host response with the highest selectivity. Instead, it is well conceivable that the better binding guest inhibits host action and thus resembles biological antagonists in its effect. Enzyme models deliver good examples for this kind of behavior, because here it is well recognized that strong substrate binding is detrimental to catalysis.[5,6] The fine art consists of utilizing the intrinsic free energy of host−guest interaction to lower every activation barrier along the trajectory leading to products including the initial binding event to the best degree possible. Since, in general, there are several activation barriers of comparable height occuring on the productive pathway, one can postulate that in the domain of kinetic selectivity a host compound must be capable of organizing all binding groups in optimal complementarity and with a speed matching transitory changing structural determinants of the guest.

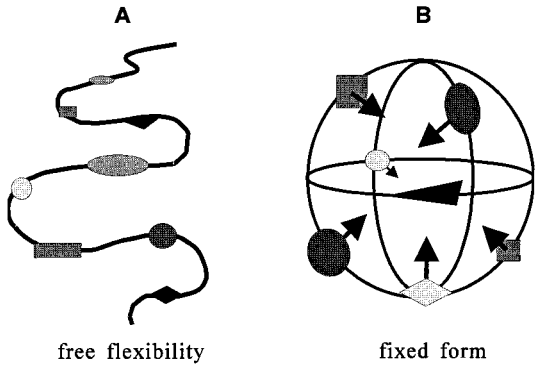


Figure 1. Two different options for the covalent preorganization of a host structure. (A) Various anchor groups linked in linear or branched fashion require a folding process to place them in distinct spatial position. (B) The exact topology and orientation of anchor groups is warranted by virtue of a multiply interconnected framework.

In view of the paucity of reliable experimental information on the dynamics of hosts and guests, it is not surprising that deliberate engineering of their time-dependent complementarity has not been undertaken. There is increasing evidence for correlated dynamic motions in enzyme−substrate complexes;[7−9] yet, analogous investigations for abiotic host−guest systems have not been reported. As a corollary, deliberate engineering of time-dependent host−guest complementary has not been undertaken in spite of early investigations using molecular modeling.[1]

Common to both modes of expressing selectivity is their molecular foundation: They ultimately depend on the differences in the total intrinsic energy of interaction of the host with each member of the ensemble of competing guests. These differences are directly related to the barriers for discrimination of two competitive guests, which in turn can only be high if the attractive free energy is great in absolute terms (i.e., if rather stable complexes are formed). Since most types of interactions are cumulative to a first approximation, one must expect that the total interaction energy will increase the greater the number of independently recognizable substructures (epitopes). Consequently, the binding constants should increase the larger and more diversely structured the guest and the better its functional surface, size, and topological pattern of epitopes can be scanned by the host.

In addition to the chemical nature, the number, or topology of its recognizing groups, the conceptual design of the host determines its binding strength. As pointed out by Cram,[10] a rigid host having all of its anchor groups preorganized in complementarity to the respective guest functions should show strongest binding (Figure 1).

Attempts to implement this concept to real situations meet with severe difficulties in host synthesis, especially for the larger, multifunctional guests, because the set of recognizing groups must be placed and fixed in a predetermined topology and orientation in space. Binding the guest in one peculiar configuration requires the anchor groups to converge

to a binding center which necessitates their placement on macropolycyclic frameworks. Apart from their inherent difficulty of construction, they do not lend themselves to easy modification in case the original layout of anchor groups needs restructuring because of unsatisfactory binding results. Another inherent flaw of rigid hosts is the appreciable risk of slow guest exchange kinetics which would undermine many potential applications even if the host turned out to be a successful and selective guest binder.

It is illuminating to recognize that the natural hosts and receptors (e.g., proteins, nucleic acids, polysaccharides) do not follow the concept of rigid host design, although maximizing the selectivity certainly was under evolutionary pressure. Rather, they follow a modular construction principle in which binding substructures are connected in linear, unbranched, or branched fashion to form chain molecules. The correct placement of the binding modules in terms of topology and orientation is left to a folding process requiring part of the free energy available for guest interaction in the rigid host system. Thus, with the same number and type of binding sites, the foldable host will display inferior selectivity because of the entropic cost of organizing the flexible chain into a defined three-dimensional structure. One can expect, however, that, as is true for the biological examples, the inherent virtues of the flexible chain design could prevail for abiotic hosts as well. In addition to the ready synthesizability and modifyability by chain elongation, shortening, or alteration of the sequence of binding modules, the appealing feature is the conformational flexibility. Hosts designed according to the folding principle most likely will not suffer from slow guest exchange rates. On the other hand, the direct translation of host−guest complex structures found by X-ray crystallography in the solid state to the solution state in which the thermodynamic binding data are collected (i.e., the structure-activity correlation) is much less straightforward and obvious. While for rigid hosts X-ray structures can be assumed valid also in solution with reasonable fidelity and guidelines for host structural improvement can be derived directly, the corresponding conclusions with flexible hosts is less reliable and must be backed by additional evidence (e.g., from a systematic variation of host or guest structures). Nevertheless, the great practical advantages, not the least easy adaption to experimental restrictions (aggregation, solubility, etc.), make the concept of foldable hosts a valuable and useful option.

From the preceding discussion it should be clear that the selection of hosts binding negatively charged species in solution is necessarily subject to some arbitrariness, and we are well aware of borderline cases. Some experts would have included a number of other systems and omitted some of those dealt with here. Intentionally, however, we disregarded systems owing their anion binding ability solely to basic ion pairing. Also, no systems are covered which show anion binding in the crystal or gas phase only. Systems with rapidly equilibrating structures such as micelles, vesicles, and macroions or the selective binding phenomena at phase interfaces are not treated likewise. Moreover, host production by combinatioral approaches might prove to be a powerful strategy for finding novel anion hosts. But since they are poorly defined in structural terms, at present we do not treat them here. The main focus of this review is on the anion binding capabilities of purposefully constructed organic frameworks. Some binuclear inorganic complex systems having anion binding properties and in this respect being closely related to analogous metal-free hosts are discussed as well. But this is only a marginal share of the rich chemistry of polynuclear inorganic complexes with proven anion hosting properties in solution the treatment of which lies beyond the scope of this report.

II. The Guest Species: Anions

The most prominent property of anions distinguishing them from any other guest species is their negative electrostatic charge. It is thus only natural that this also is the prime feature to address if one embarks on the design of specific complexing agents for these guests. Judging from the electron affinities, almost all elements can form stable single-charged anions in the gas phase.[11,12] In condensed phases, especially in the presence of water and oxygen, many elements are more stable at higher oxidation states, which combine with water to form oxoanions in which the net charge is distributed over few atoms. Correspondingly, the charge density is lowered with notable consequences in integral properties. Compared to cations, anions generally show diminished electrostatic interactions with the environment, while their dispersion interactions (based on polarizability) are greatly enhanced. This materializes, namely, in the easier transfer of anions from water to some organic solvent phase. In a two-phase system, the latter ordinarily has the higher polarizability and thus can stabilize the softer anionic species to a greater extent. In many oxoanions, the charge density can be tuned by proton transfer. Proton dissociation from anions (i.e., Brönsted acidity) giving species of higher charge is vital to all biological systems, but it is almost totally confined to condensed phases.[11,12] Recent experimental evidence by electrospray mass spectroscopy confirmed earlier theoretical calculations that doubly charged anions such as SO_4^{2-} which are well-proven species in solution or in salt crystals, require electrostatic stabilization by their environment to warrant their existence. In the gas phase lacking this influence, Coulombic repulsion may lead to the fragmentation of the anion (Coulombic explosion), the expulsion of an extra electron (e^- detachment), or, as for sulfate, proton transfer from a water molecule to give HSO_4^- and OH^-, quite an exotic process when viewed from solution chemistry.[13,14] Of course, multiply charged anions can be obtained even in the gas phase, but the excess electrons must be well separated in the molecular skeleton or must be extensively delocalized like in fluorinated fullerenes.[15] Electrostatic stabilization of anions is particularly efficient in polar protic solvents due to hydrogen-bonding interactions. The solvation energies involved are huge and in some cases such as for isocyanate distinct stoichiometric complexes with solvent molecules of appreciable stability can be detected (K_{assn} (OCN^-, MeOH) = 9 M^{-1}).[16,17] The special interactions of anions with

Table 1. Ionic Size, Experimental Enthalpies, and Gibbs Enthalpies of Hydration for Selected Ions[474−476]

	r [pm]	ΔH_{hyd} [kJ mol^{-1}]	ΔG_{hyd} [kJ mol^{-1}]
F^-	133	−510	−465
Cl^-	181	−367	−340
Br^-	196	−336	−315
I^-	220	−291	−275
$HCOO^-$	156	−432	−335
NO_3^-	179	−312	−300
$H_2PO_4^-$	200	−522	−465
ClO_4^-	250	−246	−430
CO_3^{2-}	178	−1397	−1315
SO_3^{2-}	200	−1376	−1295
SO_4^{2-}	230	−1035	−1080
$PdCl_6^{2-}$	319	−730	−695
PO_4^{3-}	238	−2879	−2765
Li^+	69	−531	−475
Na^+	102	−416	−365
K^+	138	−334	−295
Cs^+	170	−283	−250
NH_4^+	148	−329	−285
$(C_2H_5)_4N^+$	337	−73	0
Ca^{2+}	100	−1602	−505
Zn^{2+}	75	−2070	−1955
Al^{3+}	53	−4715	−4525
Fe^{3+}	65	−4462	−4265
La^{3+}	105	−3312	−3145
Th^{4+}	100	−6057	−5815

water extends beyond the common hydrogen bonding[18] and were noted more than a century ago by Hofmeister.[19] He grouped salts in a sequence according to their capability to precipitate (salt-out) proteins from water. Although various cations also show differences in this respect the more pronounced effects are displayed by anions. In spite of substantial advances in most recent times which correlate the macroscopic trend seen in the Hofmeister series to atomic changes in the hydrogen bonding pattern[20,21] the subtle influence of anions on water structure is far from being clear.

Table 1 gives an overview over the pertinent thermochemical data of important anions in comparsion to some cations along with their radii. One can recognize that common anions are considerably larger than cations and if subjected to the same host−guest binding concept would require larger host structures. When ions have comparable sizes (e.g., F^- and K^+), the anion is more strongly hydrated, again reflecting the peculiar mechanisms of stabilization by hydrogen bonding. If this network is destroyed (e.g., by transfer of negatively charged species to a non-hydrogen-bonding phase), its nucleophilic reactivity is tremendously increased.[2,23] On the basis of this rate effect, the chemistry of desolvated, "naked" anions has evolved,[24] resting on the notion that solvation by protic solvents in particular shields the principally much higher intrinsic reactivity of the anion. The better the solvation, the less intense the interaction with other possible partners. Although this principle applies, it does not suppress the binding of oppositely charged species. Ion pairing, as it is called,[25] is a universal phenomenon and so strong that it needs very dilute solutions ($<10^{-4}$ M) of ions in a strongly solvating solvent (e.g., H_2O) in order to avoid detection.[26] Even the so-called strong electrolytes in water associate to ion pairs or higher aggregates at rather low concentrations,[27,28] so that it is popular to strive to design anionic species minimizing this tendency.[29−31]

Even though aqueous solvation counteracts ion pair formation, in principle it may actually serve as a glue to attract ionic species of the like charge. This is a well-known phenomenon in colloidal systems,[32] although the origin of the effect is still under debate.[33,34] Association, however, may occur with small and simple anions, too. A good demonstration of how powerful and effective hydrogen-bonding solvation really is, is provided by the observation of two chloride ions overcoming electrostatic repulsion to form stable $\{Cl_2{:}H_2O\}^{2-}$ complexes in water.[35] *Ab initio* computational analysis reveals that at least three water molecules bridging both anions are needed to arrive at a stable configuration. This result emphasizes the role of Lewis basicity and stereoelectronics in anion solvation. Lewis basic character in anions is most abundant, although not essential, since a number of well-known anions (AlH_4^-, $B(C_6H_5)_4^-$, *closo*-$B_{12}H_{12}^{2-}$) do not have lone electron pairs and cannot be considered in these terms. Nevertheless, apart from these exceptions, Lewis basicity is the second most important feature of anions to be exploited in the construction of molecular hosts. In combination with the covalently insured topology, it adds directionality to the system and renders it sensitive to the spatial arrangement and orientation of binding groups. This is an indispensible screen to differentiate between anions of very similar size and charge as seen, namely, in the biological distinction of phosphate and sulfate.[36,37] With carboxylates, stereoelectronic differences in the Lewis basicities of syn and anti lone pairs at oxygen have been invoked to explain enzymatic rate acceleration,[38] but now seem less important than originally proposed.[39,40]

Many anions—in particular those of biological interest—contain structural elements that modify the properties of the negatively charged substructure only marginally or even not at all. On the other hand, extra moieties are sometimes deliberately attached to the anion in order to aid in the detection of host−guest complex formation. Most popular in this respect are aromatic moieties, because they may induce changes in NMR chemical shifts that are indicative and characteristically dependent on the complex structure. Less structural information but higher sensitivity can be obtained from the UV spectroscopic or fluorescent analysis of binding in these cases. Although the intrinsic properties of the anionic moiety may not be touched, host−guest complexation is sensible to the overall structure of the guest and the nonionic part may well dominate the binding interactions. Any conclusions about the role played by the anionic substructure will necessarily be flawed unless stringent precautions are taken or contributions from the component structures can be derived from a trend analysis in an ensemble of very similar guests. Although an expert can make an educated guess whether a molecule makes enough interactions with an anionic site of a guest in order to qualify as an anion host, this decision in essence is arbitrary and depends on the desired focus. Here, we concentrate on the host−guest complexation of small inorganic and organic anions up to the size of a nucleotide.

III. Artificial Anion Hosts: The Various Concepts

About 30 years ago, time was set for a serendipitous but nevertheless sharply observed and interpreted finding: The noncovalent encapsulation of halide anions into a preformed molecular cage **1** (Chart 1).[41−43] The spherical anion is held there by an array of hydrogen bonds within a cavity formed in a bicyclic molecular framework **2**. The penetration of the guest into the macrocyclic structure was correctly derived from the systematic variation of host size and was later confirmed by an X-ray crystal structure.[44] This observation of molecular three-dimensional inclusion actually preceded the most successful elaboration of this principle in the cation series (cf., cryptates[45]) and dominated the thinking about host−guest relationships for more than a decade.

Coincidentally, many more X-ray crystal structures of natural enzyme-substrate complexes became available which gave intimate detail on the mode of binding of anionic guests. In fact, the origin for the discrimination of the simple tetrahedral oxoanions phosphate and sulfate by their respective binding proteins was traced back to the ability of the former to act as a hydrogen-bond donor in a delicately balanced network of hydrogen bonds deeply buried in the interior of the protein.[46−49] In spite of this growing insight, the construction of the corresponding hosts for cations evolved more rapidly presumably owing to better established concepts for ligand design and the less expeditious effort in the construction of the generally smaller and putatively topologically less-demanding cations. The slower but steady progress in the construction of anion hosts was monitored by reviews covering either the field in a gross overview[50−61,478] or more specialized parts of it such as guanidinium hosts,[62,63] polypyrrols,[64−67] hosts based on multisite metal complexes,[68−72] cyclodextrins,[73,74] covalently-bonded poly-Lewis-acids,[75] and polyazonia compounds.[76−78]

Following our initial definition, the treatment of anion hosts in this review will categorize the examples according to their primary binding principles into positively charged or electroneutral species. In the subtle interplay of attractive and discriminative interactions necessary to make up a host compound, the former builds preferentially on electrostatic binding. Although electrostatics in the form of ion−dipole interactions including hydrogen bonding may play a decisive role in the latter case as well, this may be supplemented or even overriden by covalent contributions. Examples are provided by anticrown compounds,[75,79] a term denoted to emphasize the reciprocal type of binding between a guest anion and a multisite Lewis acidic host which relies on interaction modes of this type. Of course, the clean and crisp basic modes are frequently merged with more general supramolecular interactions rendering the clear-cut segregation of binding contributions impossible. This is particularly problematic if rather weak total interactions are coupled to very sensitive probes for host−guest association events, such as fluorescence quenching or cyclovoltametry of redox active compounds or the rate of a chemical reaction depending on host−guest complex formation. In order to observe clear effects concentrations of the interaction partners are often applied that change the overall medium so profoundly that the results obtained cannot be honestly compared to the situation in the absence of one or the other partner.[80] As a corollary, the association constants K_{assn} deduced are seriously flawed even if the primary data are analyzed by a suitable stoichiometric model and an acceptable confidence limit is reached. Experience tells us that the literature holds a strong bias in favor of a 1:1 stoichiometric model. Neglecting to consider alternatives combined with a credulous belief in numbers delivered by computer regression analysis very easily may lead to K_{assn} values which are in error by more than an order of magnitude usually biased toward stronger binding. Thus, a fair measure of caution or even scepticism should accompany the evaluation of absolute K_{assn} data. The most significant and reliable binding data beyond doubt arise from trend analyses obtained on ensembles with systematically varied structures.

Chart 1

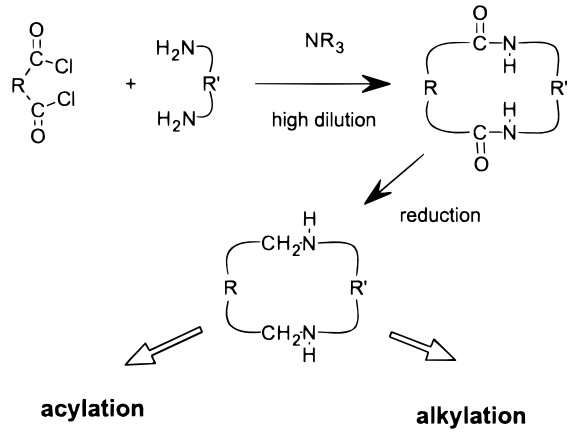
1 n = 9, 10 **2**

IV. Positively Charged Anion Hosts

A. Azonia Compounds

Cationic hosts capable of forming ion pairs with anions in solution are most easily prepared by protonation of suitable basic compounds. Since many anions possess some basic properties as well, host−guest binding in these cases depends on relative proton affinities in interconnected multiple equilibria. In water as a solvent, protonation equilibria are readily established and the corresponding pK_a values of individual groups may be determined from titration curves. It is no surprise, therefore, that water was the solvent of choice to study anion binding to a great variety of protonated polyaza compounds. Due to its high dielectric permittivity ($\epsilon = 78$) and high hydrogen-bond donor−acceptor ability, electrostatic ion pairing is hampered to the extent that significant association at moderate concentrations ($\sim$<0.1 M) can only be observed with multiply charged species. On the other hand, the mutual interaction rapidly increases with charge size so that great thermodynamic stability can be attained on complexation of highly charged ions. Of course, the state of protonation depends on pH, and as a general rule, several differently protonated species constitute the ensemble of hosts at any given value. As a corollary, the host−guest association observed in the actual experiment is an integral event that may be divided by regression calculation into singular contributions from all of the species involved. In this case, the respective association constants may contain relatively large errors. Moreover, it is not straightforward to derive complex structures from the analysis of trends in the binding constants. Relating the

Scheme 1



binding effect to host structure is essential for selectivity development which constitutes the basis of molecular design.

In this sense Park and Simmons[43] opened a door when they described a new type of ion pairing by which a halide guest occupied the central cavity offered by an organic cage compound as in **2**. The derivation of an encapsulation-type process rested on the correlation of the sizes of host and guest and was further supported by the result that association required crossing of an appreciable activation barrier in accord with a process in which the guest invades a collapsed molecular cavity. Gratifyingly, this interpretation was fully confirmed later by an X-ray crystal structure of the inclusion complex of **1**.[44]

This sharply observed but somewhat serendipitous result had a lasting effect on the further development of host−guest chemistry with anions. Guided by the high interest in azacrown ethers and cryptands as cation complexing agents, the convenient preparation of this class of compounds soon reached a high level.[81−83] Following the work of Stetter,[84] azamacrocycles could be readily obtained by condensing an open-chain α,ω-diamine with an α,ω-dicarboxylic acid chloride using high-dilution conditions (Scheme 1). In general, moderate to fair yields of macrocyclic bisamides can be expected which in turn were reduced by $LiAlH_4$ or borane/THF to afford the secondary amines. Further elaboration by alkylation or acylation led to the formation of lariat compounds or polycyclic cryptands that were amenable to protonation and thus could serve as anion hosts.

Biological linear polyamines such as spermine or spermidine are well-known to bind phosphate or polyanions in water at neutral pH values,[85−88] but due to the accumulated charge and flexible texture most likely adopt an extended conformation. Polyprotonated azacrown ethers instead possess a greater charge density and consequently present a higher Coulombic attraction for anion association. On the basis of this concept, it is only rational to place as many ammonium groups as synthetically feasible in close vicinity in order to maximize the electrostatic attraction for the anionic guest. Limitations, however, arise when the distance between cationic centers becomes too narrow. The experimental determination of the pK_a constants for the two most acidic protonation steps in the series **3a**−**c** (Chart 2) reveals that very low pH values are required to convert di- or tricationic ammonium salts to the even higher charged species, if the separation of charge is less than that provided by a propane spacer unit. Aiming at the complexation of biologically important anions under physiological pH conditions, the diminution of host volume by using ethylene connections of cationic centers is not a viable route. Rather, an increase in nominal charge has been attempted by enlargement of the macrocycle[89−99,132−134] or through annexing amino-functionalized side arms pending from smaller azacrown compounds.[100] The macrocycles **4**−**6** are representative examples synthesized by stepwise alkylation, reduction and subsequent ring closure of appropriately substituted tosylamides.[91]

Chart 2

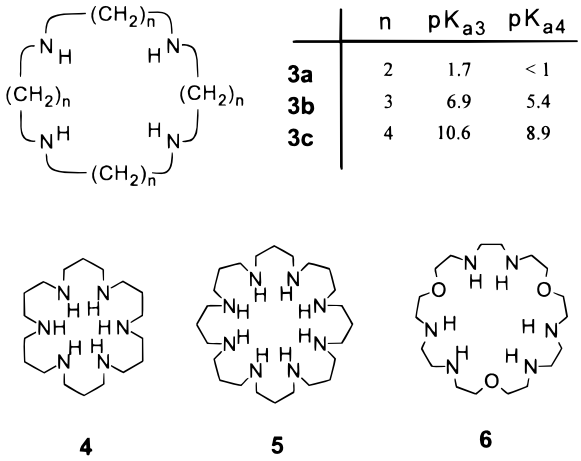
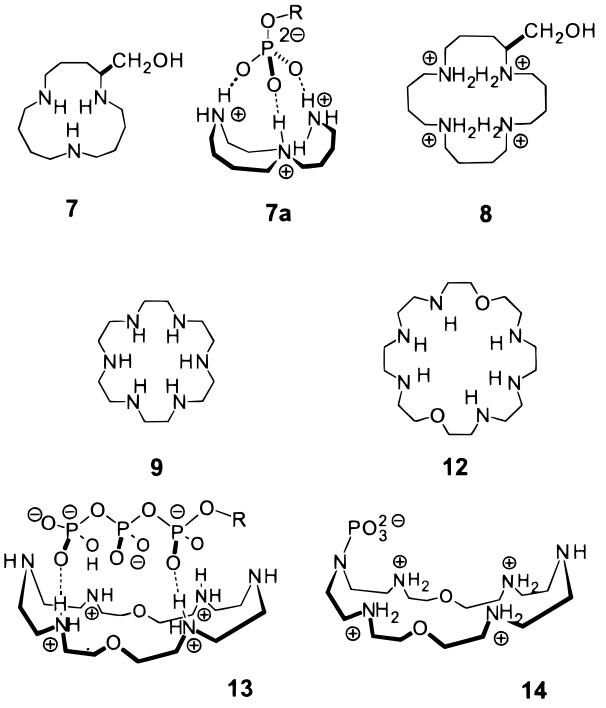


Table 2. Selected Stability Constants log K_{assn} (±0.2) for Anion Binding by Polyammonium Macrocycles 4−6 in Water (n = 0.1 M $(CH_3)_4N^+Cl^-$) As Determined by pH-metric Titration and Regression Calculation[89]

	4·6H$^+$	**5**·8H$^+$	**6**·6H$^+$
oxalate^{2-}	3.8	3.7	4.7
sulfate^{2-}	4.0	4.0	4.5
fumarate^{2-}	2.2	2.9	2.6
squarate^{2-}	3.2	3.6	3.4
citrate^{3-}	4.7	7.6	5.8
1,3,5-benzenetricarboxylate^{3-}	3.5	6.1	3.8
$Co(CN)_6^{3-}$	3.9	6.0	3.3
adenosine monophosphate^{2-} (AMP)	3.4	4.1	4.7
ADP^{3-}	6.5	7.5	7.7
ATP^{4-}	8.9	8.5	9.1

Pertinent binding data with a variety of anions are collected in Table 2 and testify to the anion complexone character of these macrocycles. Coulombic interactions apparently dominate host−guest binding as can be derived from the increase in complex stability with charge. At the same time, only a moderate dependence of the stabilities on structure can be noted. The greatest difference in the stability of any two guest anions of like charge amounts to a factor of 60 only. The preference of an anion for a single host is in line with this observation, equaling a factor of 20 at the most (AMP binding **4** or **6**). In some cases, substantially higher selectivities (up to a factor of 1000) have been noted, for instance, as in the binding of citrate over the more preorganized aromatic tricarboxylates,[101,102] but it appears fair to state that quite mediocre guest discrimination is wide-spread in this class.

Chart 3



The reason this observation is accounted for probably is in the multitude of host−guest binding modes all having rather similar energies and in the inherent flexibility of the monocycles which allows adaption of the host structure to the geometrical needs of the guest at very little energetic cost.

Further support of this view is obtained by the notion that symmetry relations seemingly play a minor role, as can be derived from the complexation of ATP to the ornithine-derived macrocycles **7** and **8** (Chart 3).[103,104] Although **7** offers a complementary topology of H-bonding sites to the locus of highest charge density, the γ-phosphate group of ATP (cf., **7a**), this putatively favorable configuration is not translated into enhanced binding. According to ^{31}P NMR studies, either host undergoes 1:1 stoichiometric interactions involving the γ-phosphate group, but **7** appears to form the slightly more stable complex.

Structure-affinity correlations can best be assessed on the basis of a solid thermodynamic analysis that allows splitting of the Gibbs energy by means of van't Hoff plots or, better, by the more direct method of isothermal titration calorimetry (ITC) into its enthalpy and entropy components. Gelb and Zomba et al.[105,106] undertook the respective analysis with hexacyclen **9** binding chloride, bromide, and a number of oxoanions which revealed entropy-driven host−guest association in water. There is no reasonable doubt that the mutual interaction of oppositely charged host−guest binding partners must result in an enthalpic effect, but in strongly solvating solvents this intrinsic gain in enthalpy is used to release solvent molecules from the interacting sites so that the net enthalpic outcome in close to zero. However, the additional solvent molecules set free by the host−guest association add a positive entropy term which outbalances the intrinsic negative contribution of combining two binding partners in one complex. As a result, the complex stability will increase with

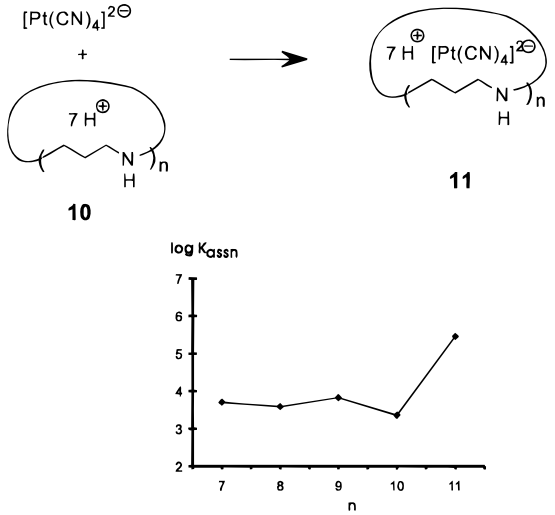


Figure 2. Correlation of the size relation of host and guest as reported by the log K_{assn} value in a series of polyammonium macrocycles complexing tetracyanoplatinate.

increasing temperature. Enthalpy−entropy compensations are a constitutive feature of weak complex formation,[87,88] in particular, in solvents capable of efficient competition to the targeted guest species. In general, this certifies that solvent reorganization contributes a major part to complex stability rather than the direct mutual interaction of host and guest. Of course, this discernment complicates rationalization of structure−stability interdependence, so that subtle features are most easily elucidated when a trend analysis in a receptor series with systematically varied structures is available. A good example is provided by the ensemble of nitrogen macrocycles binding some transition metal complex anions. With a given guest complex, stability diminishes with increasing ring size up to a point where a peculiar threshold size is reached beyond which binding affinity dramatically rises.[78] Supported by additional evidence from photochemical studies and based as well on some X-ray structures,[94] a straightforward interpretation attributes the sudden enhancement of binding to the switch in guest binding mode: When $[Pt(CN)_4]^{2-}$ is taken as an example[95] (Figure 2), its interaction with the smaller and highly charged macrocycles will be of the general ion pairing type in which the guest anion at best will approach up to the periphery of the host. Due to steric repulsion, the Coulombic interactions will be optimal to a fraction of the positive centers only. But if the ring size allows guest encapsulation, which obviously depends on relative dimensions, the anion can slip into the center of the macrocycle and enjoy the best contacts to all positively charged sites resulting in maximal stabilization documented by the increase in complex stability.

The encapsulation process, however, is heavily modulated by the presence and chemical nature of H-bonding donor sites. Naturally, the basic H-bond acceptor guests would be particularly sensitive in this respect. But even the chronically poor H-bond acceptor $[Co(CN)_6]^{3-}$ is not bound at all in solution or in the crystal lattice if the H-bonding donor ability of $([12]aneN_4)^{4+}$ (**10**, $n = 4$) is abolished by quaternization, forming the $[Me_8[12]aneN_4]^{4+}$ octakismethylammonium salt of the same overall charge.[107]

The oxaazacrown ether **12** provides another fine example for the importance of a dedicated network of hydrogen bonds in particular in biomimetic reactions such as phosphoryl group transfer and hydrolysis.[108−121] In a series of well-designed experiments, **12**, much more than closely related analogues, was shown to cleave phosphoric anhydrides. The central nitrogen atom of one hemisphere acts as a nucleophile attacking the phophoryl group and intermittantly forming a phosphoric amide which subsequently serves as a phosphoryl donor to water (hydrolysis) or another oxoanion species (phosphoryl transfer).[111,115] The hydrolysis of ATP (ATPase activity) is influenced by N-methylation in analogous azamacrocycles as well testifying to the requirement of a subtle array of hydrogen-bonding sites.[98,122] Compared to that of real enzymes, the rate acceleration over the spontaneous background rate is minute only (10^2; ATPases reach 10^{10} acceleration factors) and may well be a consequence of multiple nonproductive binding modes of the substrate. Nevertheless, several characteristic features of true enzymes are successfully modeled by **12**[124] such as catalytic turnover, saturation, and inhibition kinetics and the presence of a reasonably defined mechanism that differs from the uncatalyzed reaction. All of the evidence collected support the assumption of a common binding motif[108,117] mediated by a peculiar network of hydrogen bonds. With the aim of utilizing these aza macrocycles for ion sensing or membrane transport, they were attached to polystyrene resin[125] or equiped with C_{16} hydrocarbon chains.[126] This modification does not alter the basic nucleotide-binding features seen in the parent compounds.

The monocyclic hexamines **15** and **16** were designed to recognize dicarboxylic acid anions depending on their maximal extension.[127,128] In neutral aqueous solution, **15** and **16** exist as hexaprotonated cations. The analysis of complex stabilities with a series of dicarboxylates of increasing chain length *m* (Figure 3) reveales a maximum with the guests of intermediate size. Although even quaternary ammonium salts such as **17** show this type of dimensional selectivity to some extent,[129] it is generally much less pronounced than with macrocycles. In spite of their simplicity, the macrocycles obviously set up a size restriction that requires dimensional matching of host and guest in order to obtain optimal contacts of the complementary charged sites. An equivalent barrier is absent in linear hosts that rely on Coulombic attraction only.

Another probe of host−guest complex configuration may be obtained if structure-dependent physical effects can be correlated to the structural modification in a host ensemble. Elaborating on their adventitious finding that cationic ammonium macrocycles moved to the anode in electrophoresis in the presence of citrate, Kimura et al. had recognized this as an early example of what is known now as affinity (or band-shift) electrophoresis[477] and embarked on a thorough investigation. Sensitive electrochemical methods, namely, cyclovoltametry or polarography allowed ready elucidation of the stoichiometry and K_{assn} values of polyammonium salts with oxoanions such as carbonate[51,132,133] or phosphate[134,135] or with

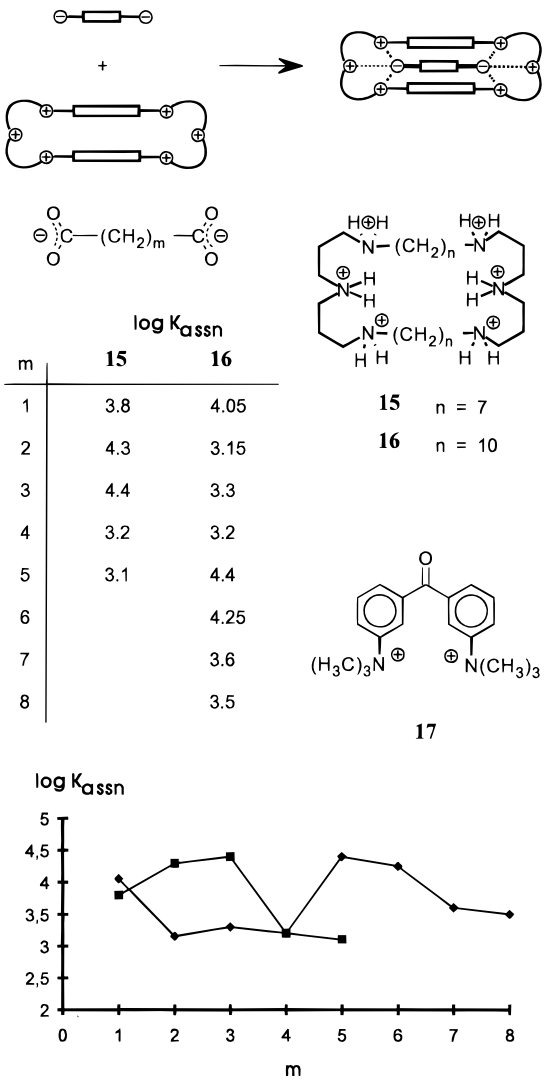
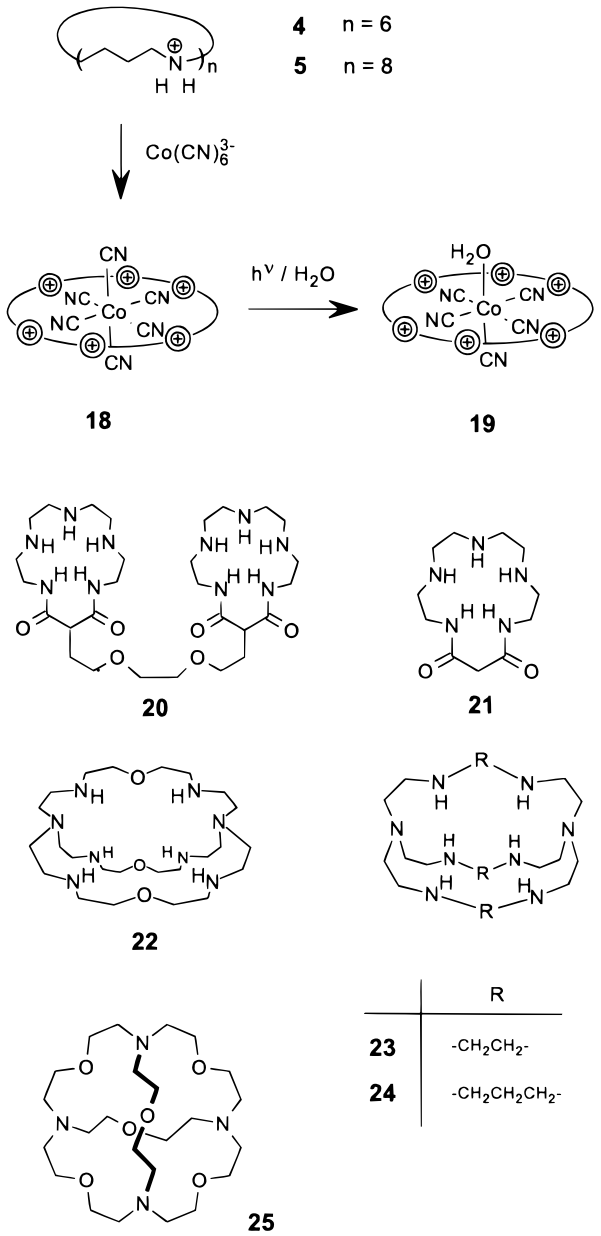


Figure 3. Dimensional matching of polyammonium macrocycles and α,ω-dicarboxylates.[128,127]

cyano complexes of transition metals,[130,131] but could not uncover structural details in the complexes formed. This changed when the photodehydration of $[Co(CN)_6]^{3-}$ in the presence of macrocycles **4** and **5** was investigated.[136−138] The quantum yield of the photodissociation of CN^- from the metal proved to be a function of the macrocycle indicating a shielding effect attributable to complex formation. Moreover, a correlation with the number of cyano sites in direct contact with the ligand and thus the mode of association was derived.

The straightforward conclusion drawn from the studies with simple macrocycles called for more structured interaction modes in order to improve selectivity. Progress on this route could be expected from the synthetically easy covalent connection of two polyammonium macrocycles assuming their cooperative action in anion binding. Further elaboration of their pioneering investigations of oxoanion complexation by macrocycles[132−134,139−141] led the Kimura group to construct host **20** (Chart 4). As expected, the phosphate or citrate binding selectivity was augmented but by factor of 2 only when compared to the parent monocyclic host **21** having the same charge.[142] One-armed connection of binding sub-

Chart 4



structures obviously cannot bring about the preorganization necessary for massive guest selectivity.

An alternative concept for selectivity and stability improvement was aimed at the rigidification of binding sites. Following the original plan of Park and Simmons,[41,42] the Lehn group constructed the bicyclic cryptates **22** and **23** which require somewhat acidic pH values to form the penta- or hexaprotonated species. In this state they give rather stable complexes with a variety of even well-solvated anions in aqueous solution (Table 3).[143−146] The construction principle can be extended to create hosts for effectively transporting anions across liquid membranes.[147]

Comparing K_{assn} values (e.g., for oxalate and malonate),[144,145] it became apparent that strong binding is based on an inclusion process by which the guest anion penetrates into the molecular cavity of the host that is expanded by the electrostatic repulsion of the positive charges. Several X-ray crystal structures confirmed[144,146,148,149] that the guest is fixed by an

Table 3. Host−Guest Association Constants (log K_{assn}) of Anions with Bicyclic Polyammonium Salts As Determined by pH Titration in Water at 25 °C (0.1 M NaOTos)[143−145]

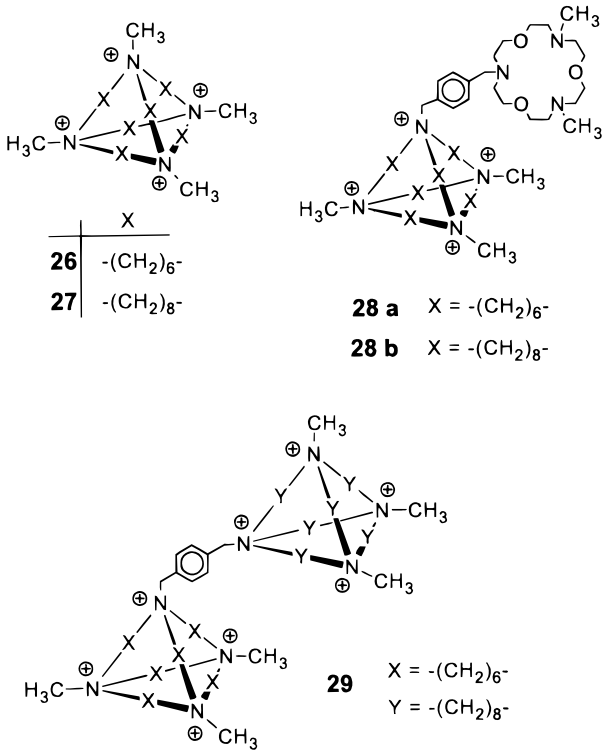
anion	**22**·6H$^+$	**24**·6H$^+$
F^-	4.10	
Cl^-	3.00	1.70
Br^-	2.60	2.20
I^-	2.15	2.40
N_3^-	4.30	
SO_4^{2-}	4.90	4.20
oxalate^{2-}	4.95	4.50
malonate^{2-}	3.10	2.85
AMP^{2-}	3.85	
ATP^{4-}	8.00	

oriented set of hydrogen bonds. Viewing the ellipsoidal shape of the cavity and the topology of nitrogen H-bonding sites, it seems plausible that azide anion having an optimal complementarity to the host shows extraordinarily high complex stability. Spherical anions such as halides fit less well, and their monotonous decrease in binding going from fluoride to iodide argues in favor of hydrogen bonding as a major binding force. When the cavity is reduced in size and the ether bridges are replaced by hydrocarbon chains (i.e., on going from **22** to **24**), the reverse order of halide complex stability is observed accompanied by a general decrease except for iodide. ^{35}Cl NMR was introduced as another analytical tool to study guest exchange equilibria in this series and provided an independent way to determine binding stoichiometries and affinities.[150,151] Considering monocyclic and bicyclic anion hosts of the same chemical nature, it is apparent that the susceptibility of host−guest binding to structural variation is greater the better defined the host structure. This notion applies to guest selectivity as well as to the absolute binding strength. Progress on this track culminated in the construction of the macrotricyclic azacrown ether **25** composed of the aesthetically appealing arrangement of two interwoven polyhedra: a tetrahedron of four nitrogen atoms placed concentrially to an octahedron of oxygen sites. In the first place, this compound was designed as an alkali metal complexone,[152,153] but protonation soon led to the discovery of anion complexes, too.[153,154] A maximum of four protonated ammonium sites can be formed which, in principle, are subject to in−out isomerism. In the presence of chloride counteranions, an array of four hydrogen bonds converges to the cavity center to hold the halide there, as shown by an X-ray structure.[156] Fluoride and bromide but not iodide or any of the polyatomic anions can be encapsulated in a similar mode. The virtues of binding of this host are based upon the same principles that have been pointed out above: A unique geometry and orientation of binding sites in combination with an almost undistortable molecular skeleton warrants high association constants and unprecedented selectivity. The preference of chloride over bromide exceeds a factor of 10^3, and nitrate, having very similar size and hydrogen bond acceptor properties as Cl^- but a distinctly smaller

hydration free energy, which should ease its binding, is totally excluded. Most likely, the lack of shape complementarity accounts for this result. On the other hand, rigid hosts such as **25** suffer from dynamic disadvantages that become apparent in molecular mechanics (MM) and dynamics (MD) calculations:[157,158] When chloride or bromide ions are brought from infinity toward **25**·4H$^+$, they reach an energetic minimum related to a configuration in which the halide is associated to one tetrahedral face from the outside. Invasion into the molecular cavity requires crossing of a substantial barrier (31.8 or 49.8 kJ mol^{-1} for Cl$^-$ and Br$^-$, respectively) mainly reflecting Pauli repulsion of the electron clouds. For geometrical reasons, the radius of the tetrahedral cavity is greater than the radius of a tetrahedral face, and this relaxation of strain favoring the encapsulated state of the chloride guest is clearly seen in gas phase calculations. Bromide in turn experiences only marginal stabilization, and in fact, bromide inclusion has not unambiguously been proven. According to MD calculations for Cl$^-$ in aqueous solution the kinetics of binding to **25**·4H$^+$ are dominated by desolvation of the anion and deformation of the host.[159,160] Recently, an improved synthesis of this appealing host compound has been reported.[161]

Anion binding using protonated polyaza hosts is severely hampered by the restriction to quite acidic pH regions, undermining any study involving the more basic anions. In addition, switching the solvent may shift the pK_a values and may diminish the total charge by deprotonation, thereby affecting anion complexation. Nitrogen quaternization might offer a remedy in this situation, but since hydrogen bonding contributes a major share of the total interaction in the protonated host species, it is not at all granted that peralkylation of nitrogen sites would still given useful anion hosts. This was put to the test with the macrotricyclic quaternary ammonium salts **26** and **27** (Chart 5)[162−165] prepared by methylation of the parent tertiary amines.[163] The construction of the tetrahedral framework followed the same strategy as that for **25**. Both quaternary ammonium compounds were freely soluble in water without detectable aggregation and proved to be hosts for a broad variety of anions in water always adhering to strict 1:1 host−guest stoichiometry.[164−166] On the basis of NMR titration data as well as X-ray crystal structures of **26** with iodide,[167] guest binding occured by inclusion complexation. The same binding mode was reported recently for chloride association of partially quaternized[168] or slightly smaller congeners.[169] With the help of CPK models, the cavity diameters were estimated as spheres of 4.6 Å (**26**) and 7.6 Å (**27**), respectively. As a corollary, iodide, with an ionic radius of 2.2 Å, fits rather snugly into the smaller tetrahedral host **26**. The good fit allows efficient stabilization by dispersion interactions with this halide ion which becomes apparent also in the preferential transport of iodide over chloride in membrane carrier studies.[170] Even larger anions such as *p*-nitrophenolate cannot be complexed by **26**, but only by the bigger host **27** thus providing additional evidence for an encapsulation process. The quaternary ammonium inclusion hosts are chemically rather stable compounds and opened the option to study reacting systems depending on host−guest binding without interference from pH effects.

Chart 5



The two principal alternatives are exemplified in Figure 4: In the monomolecular case, the reacting anion may form an inclusion complex with the host which results in a change in the molecular environment and can translate into a change in reaction rate in complete analogy to any ordinary solvent effect. Of course, the ground and transition states of the reaction undergone by the substrate will be affected to different extents, and overall catalysis or inhibition of the reaction may result. The same reasoning applies in bimolecular reactions. It is obvious that the first reaction partner by virtue of its encapsulation into the host's cavity is shielded from attack by the second substrate, and the corresponding reaction is thus inhibited. If, however, the cavity is spacious enough to incorporate both reaction partners simultaneously, one may observe rate acceleration because of the entropic gathering effect that also forms the basis in micellar catalyses:[171] The reacting substrates are confined to a volume smaller than they had available in bulk solution, and since reaction rate is dependent on concentrations, the concomitant rise in concentration will surface as a rate increase. Supplementing this entropic effect, the host may even stabilize the transition state selectively with respect to the bound ground state by enthalpic interactions, leading to additional rate acceleration. The hydrocarbon character of the cavity lining of **27** suggests that reactions running through highly delocalized, soft anionic transition states in particular are predisposed for the observation of catalytic effects by this host. It did not come as a surprise that nucleophilic aliphatic and aromatic substitutions confirmed this rationale[172−174] and were catalyzed by host **27**, achieving acceleration factors of up to 1700 in some

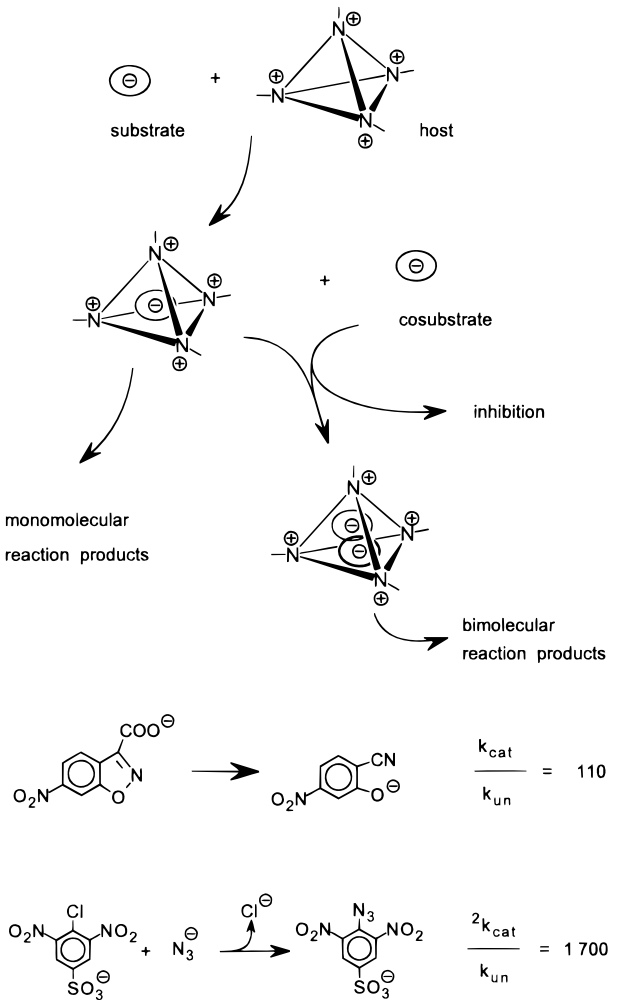


Figure 4. Reaction scheme and two examples for alternative modes of catalysis shown by the quaternary cage receptor **27**.

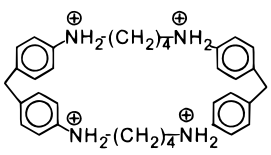
cases.[173,175,176] From the observation that the smaller host **26** invariably inhibited these reactions, one must conclude that the catalyses must happen inside the cavity of **27** since cavity volume is the only feature distinguishing **27**, from the smaller analog. Treatment of the reaction kinetics according to the schemes developed in enzymology revealed a rapid-equilibrium−random-order process, the rate-determining step being the transformation of the ternary complex involving the host and both substrates into the corresponding product complex.[177] In addition to bimolecular reactions, their monomolecular counterparts were analyzed using the same methodology. As an example, the decarboxylation of 6-nitrobenzisoxazole-3-carboxylic acid is easily followed by UV measurements and, because of its cleanliness and great susceptibility for catalytic effects, has frequently been used in the characterization of artificial and protein hosts including catalytic antibodies.[178,179] The quaternary ammonium host **27** showed a 100-fold rate enhancement in decarboxylation resembling β-cyclodextrin in this respect, but also revealed cooperative kinetics.[180] The sigmoidal saturation kinetics observed were found to be due to the formation of a complex with 1:2 host−guest stoichiometry having almost the same decarboxylation rate constant but a higher binding constant in the second step than the 1:1 complex. In the synopsis of all results, host **27** mimics true enzymes in many respects: Chemo- and substrate selectivity, but owing to the achiral topology no stereoselectivity, have been found along with saturation kinetics, inhibition, cooperativity, and turnover. Host **27** contains no catalytically active functionality whatsoever, so that all rate effects must arise from the change in the molecular environment on complexation (i.e., from a microsolvent effect). Chemical stability and the ease of elaboration starting from the parent tertiary amine building block made the macrotricyclic hosts attractive candidates for the development of modular hosts for amino acid zwitterions[181] or biogenic ammonium salts (**28a** or **28b** respectively).[182,183] Further insight into the advantages of assembling various anchor groups into an open-chain receptor were gained and quantitatively evaluated using the ditopic host **29** complexing a series of dianionic dimensional probes.[184,185] The direct comparsion of **29** with the monotopic analog **27** allowed the attribution of a factor of 3 to the gain in binding as a result from the extra interaction in the ditopic receptor, completely in line with previous findings in quite different host systems.[142,181,182]

Larger organic molecules having an overall net negative charge frequently consist of structures which interact with the solvent by quite different basic principles. The covalent junction of hydrophilic ionic moieties to hydrophobic aromatic partial structures, as occuring in nucleotides, is most abundant. Cationic cyclophanes provide a successful basic host design for these guests, since Koga had demonstrated that the macrocycle **30** (Chart 6) formed well-defined inclusion complexes with a number of aromatic guests in aqueous solution[186] and Tabushi had discovered the catalytic effect of the quaternary ammonium cyclophane **31** on the hydrolysis of suitable ester substrates.[187,188]

Triggered by these pioneering reports, a great variety of descendent cyclophanes were prepared and their properties studied, and the field has been extensively reviewed.[123,174,189−192] The general binding principle for anionic guests in water in this series consists of a superposition of the hydrophobic effect and electrostatic attractions.[123,193,194] In many instances, the hydrophobic component dominates the total interaction and the incorporation of aromatic residues as in the nucleotides is particularly favorable.[143,195] Weaker complexes are to be expected if the guest contains the anionic moiety attached to an aliphatic residue.[194] Also, since also guests lacking the anionic charge (e.g., nucleosides) will be complexed with considerable affinity, the role of the charge is only marginal and apparently just modulates the more fundamental hydrophobic interaction. Selectivity and complex stability are influenced by dispersion forces to a great extent, as can be read from the heavy dependence on shape complementarity and steric fit. In many cases, the presence of an anionic moiety just serves to guarantee sufficient water solubility of the guest and exhibits elusive effects on host−guest binding.

Very strong and selective binding of anions containing a combination of hydrophobic and charged moieties as present in many biologically important

Chart 6



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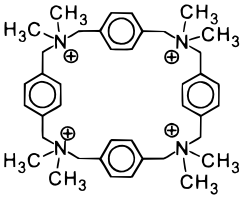

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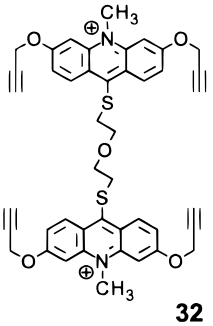

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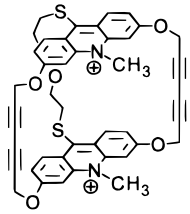

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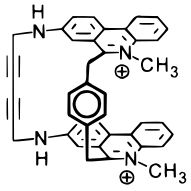

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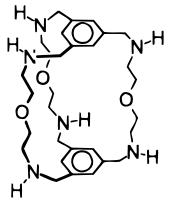

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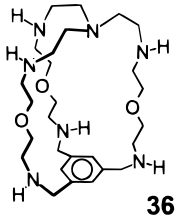

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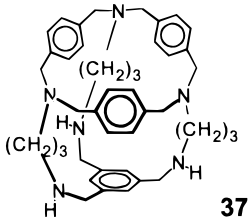

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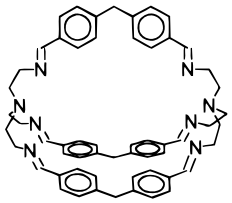

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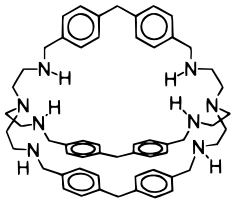


38a

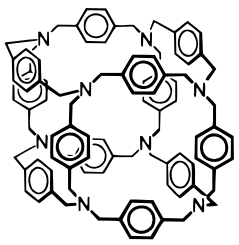
guests can be expected from the design of host compounds satisfying both binding requirements. A step in this direction exploited the well-known fact that planar electron-deficient aromatics such as nucleotide bases stack in a face-to-face mode to positively charged extended aromatic ring systems. This binding motif, when built into the cyclophane framework, can yield very potent hosts for binding nucleotides in water. The acridinium cyclophane **33** prepared by Glaser coupling from the open-chain precursor compound **32**[197] is a shining example: Various planar aromatic carboxylates and nucleotides are complexed in water with log K_{assn} values ranging from 4 to 7.[198,199] Judging from UV measurements, from the host−guest stoichiometry found, and from an X-ray crystal structure, there is little doubt that true inclusion complexation by which the guest is sandwiched between the aromatic walls of the host is in fact occurring. Host **33** appears to be extraordinarily rigid, but suboptimal in its dimensionality as indicated by an amazing observation. Preorganizing two acridinium units in parallel fashion is reflected by a dramatic >100-fold increase in K_{assn} relative to a monoacridinium salt. Nevertheless, the open-chain analog **32** outmatches cyclophane **33** in guest affinity. This points to a misfit of guest and host in the more preorganized structure **33**. Presumably, the distance of the aromatic walls in this host are a little too far apart to make optimal contacts on both faces of the bound guest molecule, and the exceedingly rigid construction prevents the collapse necessary to maximize favorable interactions. The more flexible host **32** in turn needs no distortion to adapt its structure for optimal binding. This series of receptors has been extended to include also the phenanthridinium hosts **34**, which have been shown to form the most stable nucleotide complexes known so far.[200−204] Again, the binding constants are almost unaffected by the size of the anionic charge of the guest, reiterating the dominance of hydrophobic and stacking interactions in this class of hosts. A great variety of open-chain analogues (*seco*-cyclophanes) have been prepared,[205−207] but, in general, they fall short of reaching the affinity of their cyclic congeners in binding aromatic polycarboxylic anions.

Another type of polycyclic cyclophanes was prepared by bridging 1,3,5-trisubstituted benzenes with carbon chains containing secondary amines (**35**−**37**). These compounds can be solubilized in water by protonation,[208,209] and pH-metric determination supplemented by NMR titrations unambiguously showed 1:1 complex formation of **35** with numerous small inorganic anions such as nitrate, chloride, or sulfate. Quite strong binding was observed with log K_{assn} values ranging from 2.5 (monovalent) to 6.0 (divalent anions). This and additional evidence collected from the NMR response with nitrate as a guest, which indicated slow host−guest exchange kinetics, left little doubt that a genuine encapsulation process was in operation. Surprisingly, this was not confirmed by the X-ray crystal structure. The nitrate salt of **35** had all of the anions associated from the outside to the host in the crystal requiring a molecular reorientation similar to an induced fit occurring on dissolution.

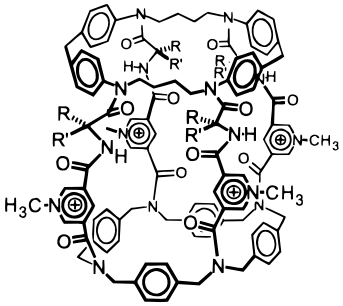
A well-documented recipe for preparing azacyclophanes calls for macrocyclization by imine formation followed by reduction.[202,210−214] Strong but size-dependent complexation of oxoanions is observed with monocyclic[215−217] as well as with bicyclic members such as **38a**[201] of this class. Efficient binding of nucleotides reaching log K_{assn} of 4−5[202] is found in dilute acid and probably is of the inclusion type, as suggested by a number of crystal structures.[201,212]

The monocyclic cyclophanes **30** and **31** serve as parent structures in the conversion into the appealing cubic azaparacyclophanes **39** and **40** (Chart 7).[155,218−223] In water at pH 4, they dissolve to form tetracations which bind anionic fluorescent probes such as ANS **41**. Unfortunately, slow conformational changes severely broaden the ^{1}H NMR signals, undermining any subtle investigation of host−guest binding. However, UV and fluorescent measure-

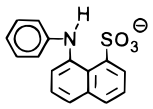
Chart 7



39



40 R = -CH(CH$_3$)$_2$
R' = H



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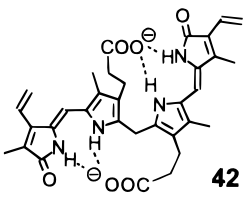
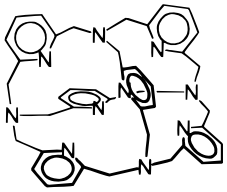
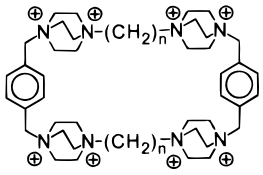


42

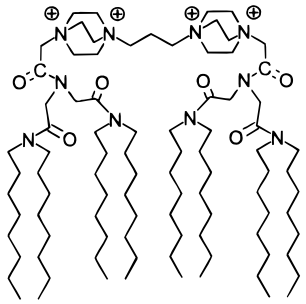


43

Chart 8



44 n = 3, 4, 5



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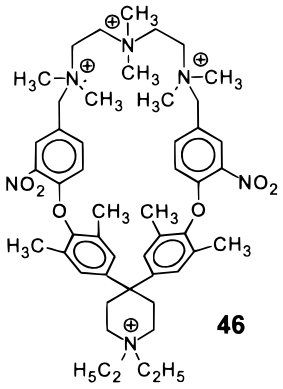
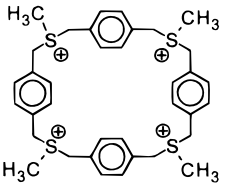


46



47

ments allow the determination of K_{assn} values with a guest series. Comparsion of these data to the respective constants obtained with analogous host having partially opened cages delivers strong arguments for guest penetration into the cavities of **39** and **40**, judging from the weak effect observed on omission of the anionic charge in **41** (this diminishes binding by a factor of 2 only). On the contrary, deletion of the anilino moiety in **41** leads to a dramatic drop in K_{assn} by 3 orders of magnitude (log K_{assn} of 2.0). Owing to the chirality of the amino acids serving as spacer modules in **40**, a helical twist is induced upon the entire molecule. According to CD measurements this leads to preferential binding of one enantiomeric conformation of bilirubin anion **42** over the other.[221] It is well-known that bilirubin forms a mixture of two rapidly interconverting helical conformers in solution. The cubic array of aliphatic nitrogen atoms in **40** was also changed into a tetrahedral one giving the cage compound **43**.[224] In aqueous trifluoroacetic acid (TFA), the host is protonated and then can encapsulate chloride anion, but not the larger halides. The inclusion complex undergoes guest exhchange only slowly on the NMR time scale, indicating a considerable barrier for this process. The K_{assn} value (K_{assn} = 8.4 M^{-1}, 50% TFA/D_2O), however, is distinctly smaller than in the analogous compound **25** conceivably due to the reduced freedom of **43** to adapt its structure to the needs of the guest anion.

For maximizing Coulombic binding while conserving the option for stacking interactions with aromatic guest moieties, the octacationic cyclophanes **44** were designed (Chart 8).[225] Small inorganic anions (Cl^-, Br^-) bind inside the cavity, as evidenced by a crystal structure. Larger organic anions such as ATP or naphthalenesulfonates, however, do not penetrate the host, but rather bind from the outside. As a corollary, the binding constants with ATP do not vary appreciably with the ring size and in absolute terms are of the same magnitude as found with tetracationic quaternary ammonium cyclophanes. The use of diazabicyclooctane (DABCO) building blocks in the construction of host **44** was inspired by the success of this moiety to serve as membrane transfer agent for ATP and other nucleotides after quaternization with hydrophobic moieties.[226−229] Thus, the tetracation **45**[228] like several other compounds of similar design indeed formed 1:1 complexes with nucleotide triphosphates and extract ATP from very dilute aqueous solution into chlorohydrocarbon phases. Their use in membrane transport, however, is severly hampered by their detergenic properties leading to disruption of, namely, liposome vesicles.

The preceding examples clearly show that the accumulation of positive charge is not sufficient to bring about great guest-binding strength. The cationic cyclophane **46**—originally designed as a model for the peptide binding antibiotic Vancomycin—underlines this notion.[230] Although weak binding of a variety of aliphatic and aromatic oxoanions is observed in water, they all associate at the host periphery rather than inside the molecular cavity. Obviously, the attractive electrostatic interactions possible by encapsulation do not match the energetic cost of desolvation required to happen in the inclusion process.

In principle, cationic cyclophanes can also be based on sulfur compounds. The early example **47**, which could bind anionic fluorescent probes such as ANS **41** in water and appeared quite promising for further elaboration,[231] failed in this respect probably due to its chemical instability.

B. Oligopyrrole-Derived Receptors

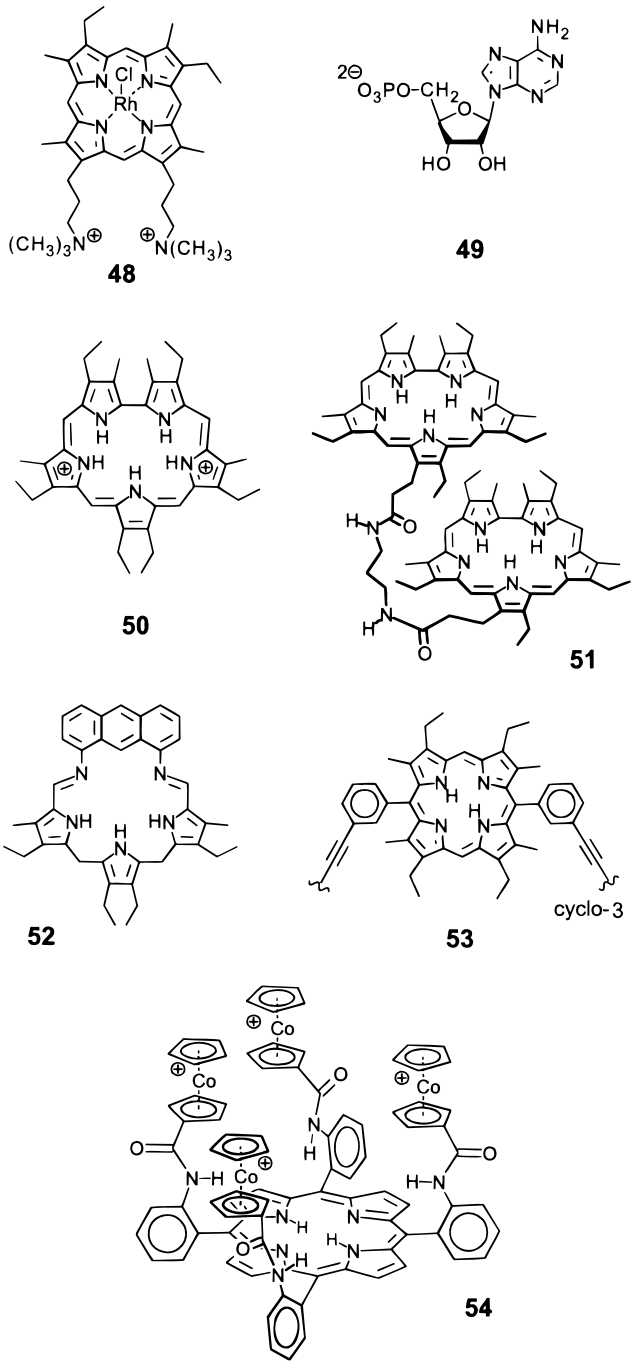
When complexing metal cations, chelating ligands may not fully satisfy the coordination needs of the

central atom but leave a site open for additional ligation of another ligating species that will be readily exchangable. Binding in these cases will be governed primarily by intrinsic preferences that translate directly into selectivity factors. This dedicated single-point interaction between binding partners does not meet our initial definition of a host−guest relationship, but, in some cases, provides a platform to which more modes of interaction have intentionally been added to generate a true host compound living on binding motives that extend well beyond the first ligation sphere of the metal. Prominent examples encompass polypyrrol complexes like metalloporphyrins and -corrins that have been investigated for anion selective sensing and transport.[232] A particularly illustrative case was studied by Ogoshi and Kuroda who supplemented a rhodium(III) porphyrin with two quaternary ammonium sites to give **48** (Chart 9).

The high positive charge serves two functions: First, it prevents these flat molecules from dimerizing by stacking in water thus easing host−guest analysis, and second, it conveys sufficient water solubility to enable a study on the complexation of adenine nucleotides. There is good reason to assume coordination of the nucleotide heterocyclic base to the metal allowing the phosphate group to errect Coulombic interactions with the ammonium moieties. When the various energetic contributions to K_{assn} were dissected, it was discovered that metal ligation holds the major share (estimated as 13.4 kJ mol^{-1}), while for AMP^{2-} the electrostatic attraction between phosphate and ammonium groups contributes 3.3 kJ mol^{-1} only.

The anion-binding capacity of porphyrins is totally dependent on the presence of the metal ion. The free tetrapyrrolic ligand has no anion-binding power[65,67,233] probably due to the small size of the porphyrin cavity which does not allow the use of the convergent N−H dipoles for anion stabilization. Expansion of the porphyrin cavity by the incorporation of more pyrrolic or other spacer moieties appeared as a rational remedy. Following this line, the Sessler group prepared a large number of ring-extended porphyrins[65,67,234−236] among which the sapphyrins were shown to possess anion-binding properties. Sapphyrin **50** contains a unique disposition for anion inclusion based on its planar pentapyrrolic skeleton of aromatic character which forces three N−H bonds to point with their positive ends toward the center of a cavity of ca. 5.5 Å diameter. Another two protons may be added (pK_{a1} = 3.5; pK_{a2} = 9.5) to readily form a symmetric array of hydrogen-bonding sites that is almost perfectly predisposed for anion encapsulation. In fact, the sapphyrin system has been known for over 30 years, but requires considerable synthetic effort in preparation. With the synthetic improvements introduced by Sessler et al.,[64,237] this compound became available in sufficient quantity to enable extensive anion-binding studies. Blessed by serendipity, they discovered that the diprotonated sapphyrin **50** formed a very stable complex with fluoride (K_{assn} = 1 × 10^5 M^{-1}) in methanol solution.[238] As anticipated, the X-ray crystal structure shows the fluoride guest completely encircled by the dicationic

Chart 9



aromatic macrocycle. The extraordinary stability of this arrangement is reflected by selectivity factors of more than 100-fold, discriminating against the heavier halides chloride and bromide which for steric reason cannot be bound in the inclusion mode. The same argument also applies to oxoanions such as phosphate, but these may form chelation-type complexes instead. Various X-ray structures[65,67,239] show one oxygen atom of an anionic phosphate ester moiety in a perching position over the center of the macrocycle. All N−H donor sites can participate in binding the anionic hydrogen bond acceptor leading to moderately stable complexes with these guests in noncompetitive solvents. Even if one NH group is replaced by sulfur or selenium, halide anions can bind to the remaining array of NH dipoles in the diprotonated cation as shown by an X-ray struc-

ture.[240] This general motif could be exploited in a self-assembly process of a porphyrin carboxylate to the carboxylate-binding sapphyrin (K_{assn} 2.6 × 10^3 M^{-1}) monitored by an enhanced energy transfer between the chromophores[241] and, furthermore, for transporting nucleotides from one aqueous solution into another separated by a CH_2Cl_2 liquid membrane employing sapphyrins as carrier molecules.[59,242−246] Sapphyrin, when linked covalently to a solid matrix, is useful in the separation of nucleotides following the scheme of affinity chromatography.[247] Even more promising applications may derive from its demonstrated ability to bind to single- or double-stranded DNA.[248−250] The rich chemistry possible was underlined by the covalent junction of two macrocyclic units to give a dimer **51**[267] that displayed some selectivity in binding dicarboxylic anions. The sapphyrin concept was further extended by variation of the macrocyclic cavity itself. Replacement of two pyrrole rings by a rigid anthracene spacer to give anthraphyrin **52**[251] led to a widened cavity that, when diprotonated, displayed stronger complexation of chloride over fluoride in dichloromethane. In spite of this reverse selectivity, anthraphyrin **52** proved to be an excellent carrier for fluoride in transport studies outmatching even sapphyrin by a factor of 6.

Following a building block approach, Sanders et al.[252] used prophyrins as stiff construction elements. The giant cage molecule **53** was obtained by covalent connection of three porphyrin macrocycles and formed a hexaprotonated cation $[\mathbf{53}\cdot H_6]^{6+}$ with acid. When this compound was codissolved with the heteropolycluster anions $[PW_{12}O_{40}]^{3-}$, $[SiW_{12}O_{40}]^{4-}$, or $[Os_{10}C(CO)_{24}]^{2-}$ in a *m*-nitrobenzyl alcohol matrix and subjected to FAB mass spectroscopy, signals corresponding to 1:1 host−guest complexes were observed in addition to the peaks derived from the free host. Since small anions which should be at least as volatile as the big cluster anions could not be detected in host−guest complexes with protonated **53**, one can conclude that it is the complementarity in size, shape, and charge that cause host−guest association of $[\mathbf{53}\cdot H_6]^{6+}$ and the cluster anions. We believe that this system holds the record in size for guest encapsulations.

Another approach also uses a *meso*-substituted porphyrin as the basic scaffold to which cationic, anion-sensing substructures are attached. The connection of cobaltocenium moieties via carboxylic amide formation to the readily accessible all-cis atropisomer of tetrakis(*o*-aminophenyl)porphyrin gave **54** in 45% yield.[253] In acetonitrile solution, anion complexation with chloride, bromide, nitrate, hydrogen sulfate, or dihydrogen phosphate was detected by NMR, UV, and cyclovoltammetric techniques. Quantitative determination gave K_{assn} values of less than 10^3 M^{-1} and a selectivity factor of about 4.

C. Guanidinium-Based Receptors

The guanidinium group as present in the side chain of arginine is ubiquitous in enzymes that bind anionic substrates and is also involved in the stabilization of protein tertiary structures via internal salt bridges with carboxylate functions. The reason for the strong interaction with oxoanions lies in the peculiar binding pattern featuring two parallel hydrogen bonds in addition to the electrostatic attraction (Figure 5), a structural motif that can be found in many crystal structures of enzyme complexes with oxoanionic substrates as well as in simple guanidinium salts.[254,255] This type of binding appears to form also the basis for the biological activity of quite a number of alkaloids and toxins such as ptilomycalin A and related guanidinium natural products.[63,256,257]

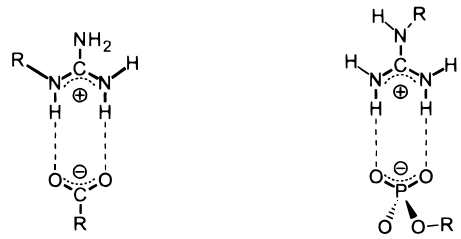


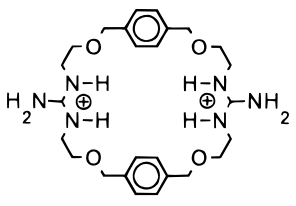
Figure 5. Binding pattern of guanidinium groups with oxoanions found in many X-ray structures of the corresponding salts.

Another feature which makes the guanidinium moiety an attractive anchor group in artificial receptors[258] is the extremely high basicity of guanidine (pK_a = 13.5), which guarantees protonation over a wide pH range. On the other hand, the exploitation in host−guest chemistry is hampered by the very effective solvation of the guanidinium function in water along with the lower charge density as compared to that of ammonium-based receptors, leading to weaker electrostatic interactions. In spite of these disadvantages, the attractive features of the guanidinium group, in an effort to learn from nature, have led to the development of an appreciable number of artificial guanidinium-based receptors for anions.[258]

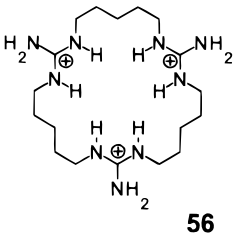
The first examples of macrocyclic guanidinium-based receptors were reported by Lehn et al.[90] who synthesized compounds **55** and **56** (Chart 10). Either of these showed only weak complexation of PO_4^{3-} (log K_{assn} 1.7 (**55**) and 2.4 (**56**) in methanol/water), which was thought to be governed by electrostatic interactions. This was confirmed by a more extensive study[259] of several polyguanidinium hosts revealing that binding of phosphates and carboxylates was influenced by a macrocyclic as well as a chelate effect. Guest selectivity was primarily dependent on the charge density of the anions thus confirming the initial assumption.

Inspired by the enzymatic cleavage of phosphodiesters by, namely, staphylococcal nuclease,[260,261] there is increasing interest in designing receptors that can bind to the monoanionic substrate as well as to the dianionic transition state. Simple bisguanidinium compounds like **57**, synthesized by Hamiltons group[262] were found to complex phosphodiesters (K_{assn} in acetonitrile 5 × 10^4 M^{-1}) and gave rate enhancements for transesterifications by a factor of 300.[263] A monoguanidinium receptor increased the reaction rate only 2.5-fold, indicating the importance of the cleftlike arrangement of the guanidinium groups in **57** for cooperative binding. With the incorporation of a basic side chain, it was hoped that a receptor containing all necessary parts for phosphodiester cleavage would be obtained which was expected to show enhanced catalytic activity.[264] Indeed, **58**, having an intramolecular base, showed a 45-fold

Chart 10



55



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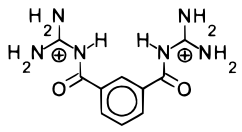
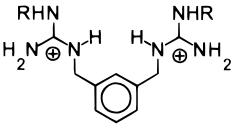
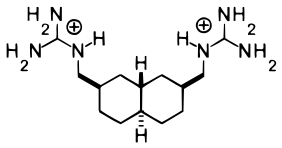


57



	R
58	NMe$_2$
59	H



60

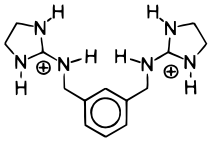


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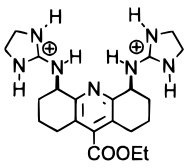
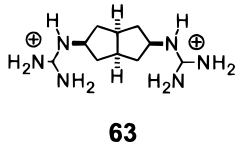
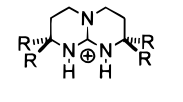
Chart 11



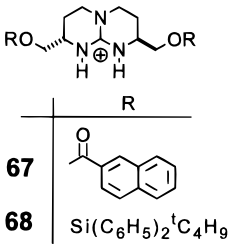
62



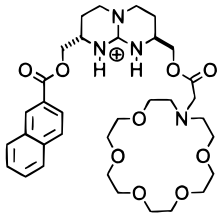
63



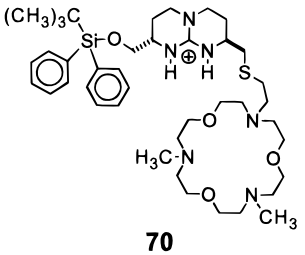
	R
64	
65	OH



	R
67	
68	Si(C$_6$H$_5$)$_2$^{t}C$_4$H$_9$



69



70

higher rate than **59** with added base under comparable conditions.

Similar systems (e.g., **60** and **61**) were also used by Göbel[265,266,268,269] and gave binding constants of about 100 M^{-1} with a cyclic phosphodiester in DMSO. Rate enhancements of up to 4.8×10^3 for **61** in DMF were found.[268] Compound **61** was also shown to bind strongly to the dicarboxylate fumarate ($K_{assn} > 5 \times 10^4$ in DMSO).[270]

Improved complexation can be expected from more preorganized hosts.[271] With this hope in mind, **62** was synthesized by Anslyn et al. and, in fact, gave a binding constant of 8×10^2 M^{-1} with dibenzylphosphate[1] in DMSO (Chart 11).[272] The stronger binding displayed by the *meso*-isomer[273] indicated the cooperative binding mode. Also, **62** was shown to enhance imidazole-catalyzed mRNA hydrolysis by 20-fold in water.[274] Enhanced preorganization was also employed in the design of a receptor for peptides. In **63**, Hamilton used a rigid scaffold to orient two guanidinium groups for interaction with two carboxylates in a spatially fixed arrangement. The 16-mer peptides with two aspartate groups located at different positions along the chain were tested for binding to **63**, and quite strong binding in methanol/water was found.[275] Moreover, a noticable preference for binding to the peptide with three amino acids between the aspartates was also observed and indicated that the peptide most likely formed a helical secondary structure, which was also supported by CD measurements.

In order to improve the binding characteristics, the guanidinium group can be embedded in a bicyclic framework, which should reduce hydration of the charged moiety by the accumulation of hydrophobic hydrocarbon residues as well as improve the predictability of the host−guest orientation. Further manipulation of substituents could then introduce other binding sites to increase specificity of guest binding (Figure 6). The great promise of these bicyclic guanidinium anchor groups has been recognized two decades ago when symmetrically substituted derivatives became available.[276] Thus, even the simple derivative **64** formed an ion pair with *p*-nitrobenzoate of great stability in chloroform (K_{assn} 1.4×10^5).[255] The X-ray structure of **65** revealed formation of the expected host−guest geometry embedded in a larger array of hydrogen bonds.[255] When the first chiral analogues became available[277,278] and the synthesis was improved to give a more reliable and efficient procedure[279−284] (Figure 7), extensive use of these anchor groups could be made for enantioselective recognition, catalysis, and specific transport of substrates across membranes. Recently, further progress was made in the derivatization of the parent bicyclic guanidines (cf. **66** in Figure 7).[285,286] which should lead to a greater variety of host compounds in the future.

The first exploitation of the chirality of these bicyclic guanidines for enantioselective recognition

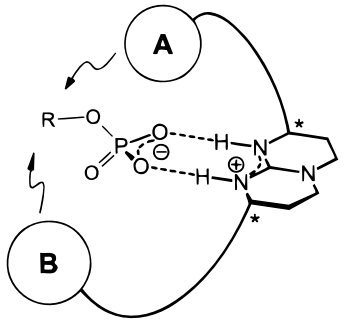


Figure 6. The host−guest binding concept of chiral bicyclic guanidinium groups. Polytopic guest recognition results from attachment of additional anchor groups A and B.

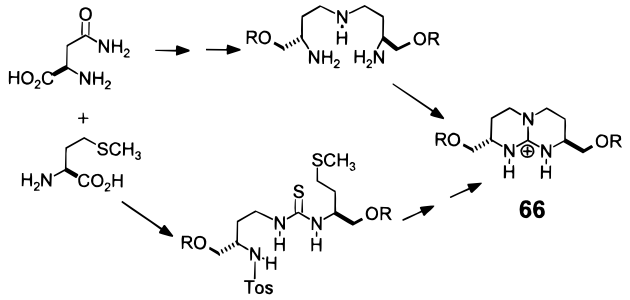
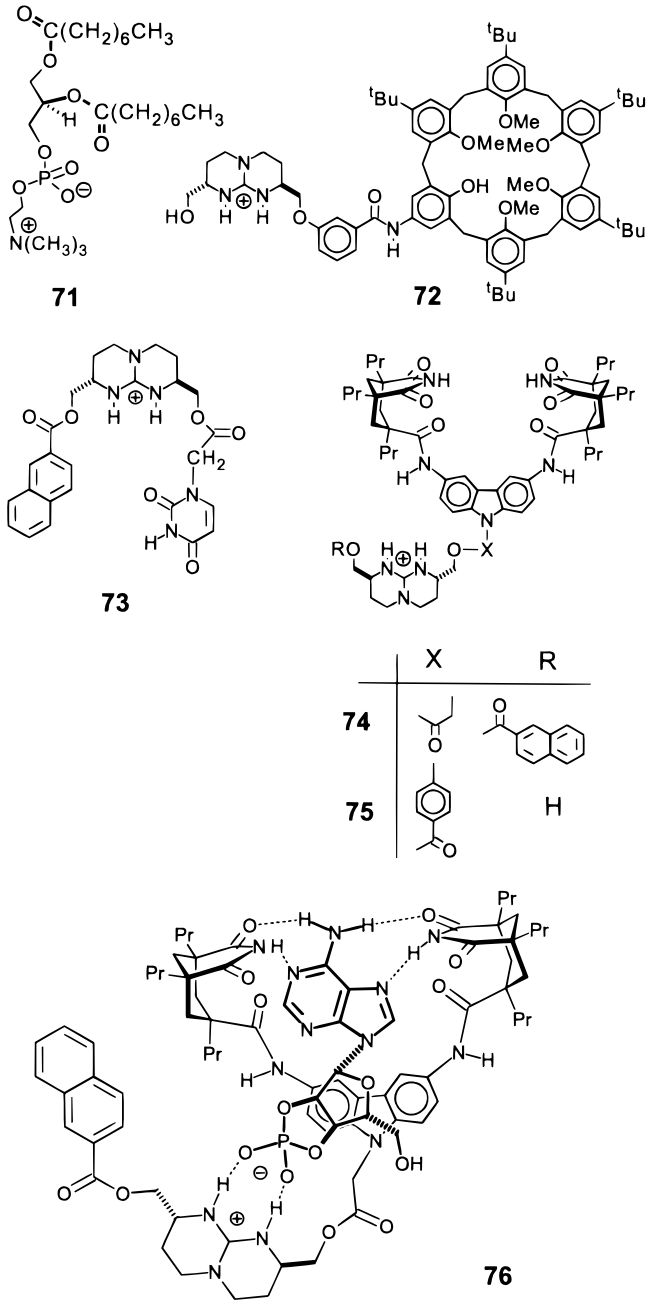


Figure 7. Schematic strategies for the synthesis of chiral guanidinium groups. Starting from chiral amino acids, the target compounds can be prepared in the key step by cyclization of an open-chain triamine or an unsymmetrically substituted thiourea.

was reported by de Mendoza, who attached aromatic moieties to the parent framework giving receptor **67**. Aromatic carboxylic guests could then interact with two different recognition sites comprising guanidinium−carboxylate ion pairing and aromatic π stacking.[287,288] With chiral carboxylates, diastereomeric complexes should be formed, and indeed, it was possible to extract *N*-acetyl- and *N*-BOC-tryptophan from a racemic aqueous solution into $CDCl_3$ with moderate selectivity (17% de (de = diastereomeric excess)). But even the parent anchor group **68** formed diastereomeric host−guest complexes with racemic aliphatic carboxylates such as *N*-acetylalanine or 2-methylbutyrate in acetonitrile.[254] Here, the bulky silyl ether groups seem to be sufficient to form a chiral cleft around the guanidinium binding site.

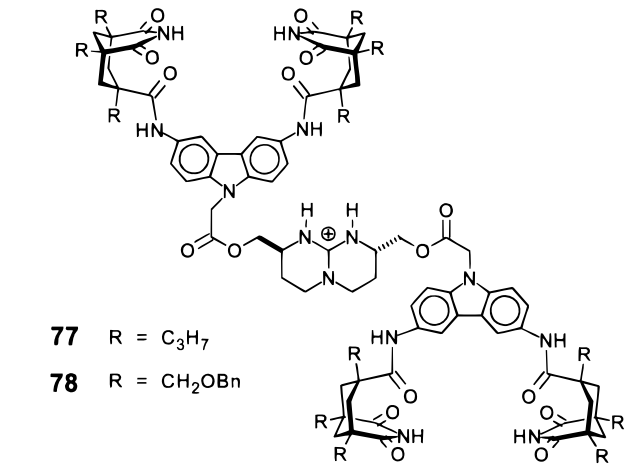
In order to recognize underivatized amino acids in their zwitterionic form, de Mendoza introduced host **69**, which is built upon **67**, but has an additional recognition site for the ammonium moiety.[289] In single-point liquid−liquid extraction experiments, selectivity for aromatic amino acids such as tryptophan and phenylalanine was found supporting a three-point binding mode. Molecular modeling further supported this view and indicated[290] that the guanidinium group contributes about one-half of the total binding enthalpy, while complexation of the ammonium group by the azacrown ether adds another third and the aromatic π stacking with the amino acid side chain the remaining sixth for tryptophan binding. Most remarkably, this host showed exceedingly high enantioselectivity in two-phase liquid extractions and transferred the L-isomer with ca. 80% ee (ee = enantiomeric excess).[290] A similar receptor **70** was used by Gloe and Schmidtchen[291] in a more detailed study on the extraction of ^{14}C-labeled amino acids. Here, a triazacrown ether having an intrinsically better selectivity for the complexation of primary ammonium cations was attached by a stable thioether bridge to the guanidinium anchor function. For the first time, even quite hydrophilic amino acids such as serine and glycine could be transferred to the organic phase, with clean 1:1 host−guest stoichiometry. Maximum extractability was reached at pH 9, indicating that the amino acids were indeed extracted in their zwitterionic forms. Although **70**, in principle, could provide aromatic rings for stacking to an amino acid side chain and thus emulate a three-point binding mode as postulated for **69**, it showed smaller enantioselectivity than **69** (40% ee with phenylalanine). For binding another zwitterionic substrate, dioctanoyl-L-α-phosphatidylcholine (DOPC, **71**), the receptor **72** was recently synthesized with the intention to mimic the antigen binding pocket of an antibody (Chart 12).[292] A calix[6]arene was introduced for binding the tetraalkylammonium function and was linked to a chiral guanidinium unit. In chloroform, quite high binding was determined (K_{assn} 7.3 × 10^4 M^{-1}). NMR data and molecular modeling supported the anticipated binding mode with the calixarene encapsulating the ammonium group adopting a cone conformation.

Chart 12



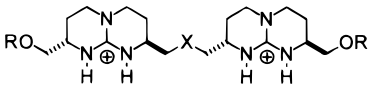
The same idea of using different subunits complementary to specific domains in the guest molecule was used in the design of nucleotide receptors. In **73**, the uracil moiety was expected to recognize adenine via Hoogsteen-type hydrogen bonding in addition to π stacking of the naphthoyl unit.[293] Unfortunately, **73** was too hydrophilic to be used in

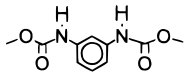
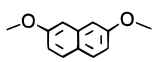
Chart 13



77 R = C_3H_7

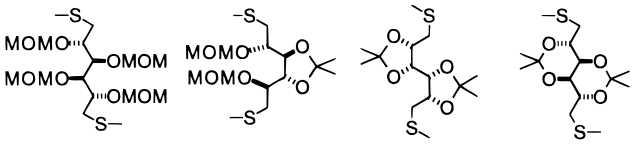
78 R = CH_2OBn



	R	X
79	-$SiPh_2{}^tBu$	
80	H	
81	-$SiPh_2{}^tBu$	
82	H	

R = -$SiPh_2{}^tBu$

MOM = -CH_2OCH_3



83 **84** **85** **86**

extractions, but NMR experiments in DMSO confirmed the expected interactions. Replacement of the uracil by a tweezer-like Kemp acid derivative led to **74**, which was expected to improve binding of adenine by a combination of Hoogsteen and Watson−Crick base pairing.[294] Only a moderate selectivity for cyclic adenosine monophosphates over the corresponding guanosine analogues was found in two-phase extraction experiments and guanidinium−phosphate ion pairing proved essential for extraction. From NMR data, the binding model depicted in **76** was deduced, which combines ion pairing, π stacking with the carbazole spacer and hydrogen bonding with the amide groups. The similar, more hydrophilic receptor **75** was used in an effort to quantify phosphate−guanidinium interactions in water.[295] Rebek concluded that under these conditions the ion pairing contributed about 0.6 kcal/mol on average to the total binding affinity of 3.65 kcal/mol with 2′-3′-cAMP.

Extension of these systems to receptors for di- and oligonucleotides was possible by replacement of the naphthoyl group in **74**, which apparently is not involved in binding, by another adenine recognition site. Thus, the C_2 symmetric host **77** was obtained,[296]

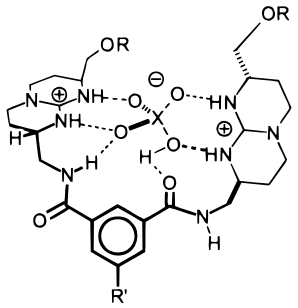


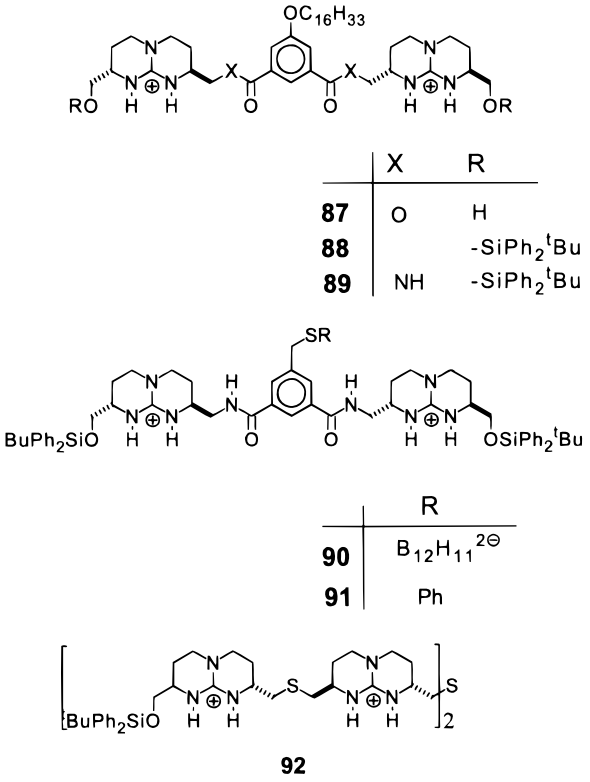
Figure 8. Presumed binding geometry in the interaction of ditopic guanidinium receptors with tetrahedral oxoanions.

which showed high affinity for d(AA) and was able to extract one full equivalent into organic solvents such as dichloromethane (Chart 13). NOE measurements in DMSO indicated that in contrast to the mononucleotide receptors base pairing was predominantly of Hoogsteen-type, which was further supported by molecular modeling studies.[290] Extraction of longer oligonucleotides was possible with the analogous compound **78**, which brought about phase transfer of nucleotides with a molecular weight of up to 25 kDa, provided they contained adenine and, in particular, repeats of ApA, the number of which correlated strongly with extraction efficiency.[297]

When the successful use of the bicyclic guanidinium group for anion recognition was expanded on, polytopic host molecules were developed in the hope of obtaining more powerful and selective receptors for tetrahedral oxoanions in more competitive solvents. The idea of linking two bicyclic guanidinium groups with a linear spacer has been realized in compounds **79**−**82**.[298−302] It was envisioned that, due to the flexibility of the spacer in combination with the chirality of the guanidinium moieties, binding to a suitable tetrahedral anionic guest would initiate a folding of the receptor to arrange the main planes of the bicyclic framework perpendicular to each other (Figure 8). NMR data showed that **79** indeed formed 1:1 complexes with nucleotides in methanol and **80** with deprotected hydroxyl groups even in water.[298] Further evidence for the functioning of these host molecules as ditopic receptors came from the fact that **79** could extract dicarboxylates such as succinate or fumarate, but not monocarboxylates, into an organic phase.

Binding constants for the complexation of several biologically important phosphates in methanol with **81** were found in the region of $(1.8-3.8) \times 10^4$ M^{-1}. Removal of the silyl ether groups apparently led to the formation of complexes of higher stoichiometries in methanol, but in water clean 1:1 complexation was observed with binding constants of up to 10^3 M^{-1}. In a series of dicarboxylates with varying chain length,[301] **81** showed a marked preference for binding malonate over longer or shorter analogues. Obviously, malonate allowed the optimal orientation of the two recognition sites with regard to each other in this series and thus caused the unexpected dimensional selectivity. In order to examine the influence of spacer flexibility on complexation, a series of mannitol-derived spacer units **83**−**86** has been synthesized.[302] But instead of a monotonous trend following

Chart 14



87 X = O, R = H
88 X = , R = -SiPh$_2$^{t}Bu
89 X = NH, R = -SiPh$_2$^{t}Bu

90 R = $B_{12}H_{11}^{2\ominus}$
91 R = Ph

92

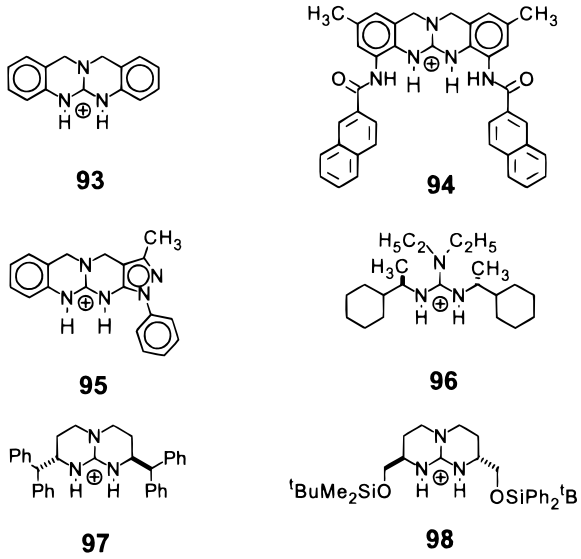
rigidification of the spacer, varying association constants were observed, indicating that spacer flexibility does not play a major role in guest binding.

Exploitation of the binding properties of ditopic receptors in chloroform/water extractions was undertaken using compounds **87**−**89** all having the same anchor groups, spacer units, and hydrophobic tails to enhance solubility in an organic phase (Chart 14). They differ in their terminal group and in the building block connection, which greatly influences their extraction properties.[300] The amide **89**, having bulky silyl ether groups, is the only member in this ensemble capable of extracting oxoanions from very dilute aqueous solutions. The highest preference is shown for sulfate, but nucleotides (AMP, ADP, ATP) were also extracted efficiently into the organic phase.

To combine the positive characteristics of **89** with overall electroneutrality yet preserving high lipophilicity, both being desirable features for membrane transport applications, receptor **90** was introduced.[303] In this interesting molecule, an icosahedral borane cluster served as an intramolecular counteranion to neutralize the positive charges of the guanidinium groups. The noncoordinating nature of the borane and the geometric orientation should prevent an intramolecular collapse of the zwitterion. Instead, however, intermolecular dimerization was found (K_{assn} 250 M^{-1} in DMSO). Nevertheless, association constants for the cyclic oxoanions squarate, croconate, and rhodizonate reached up to (2−3) × 10^4 M^{-1}. Interestingly, the negative charge of the borane cluster seemed to have no effect at all on the overall complexation ability, as was indicated by comparison with the charged host **91**.

One reasonable extension of using bisguanidinium receptors would be the progressive attachment of more bicyclic anchor groups to give a linearly connected host compound. Following this idea, host **92** containing four bicyclic guanidinium units linked by thioether bridges was obtained by de Mendoza.[304] Upon binding to sulfate, the chirality of the guanidinium framework seemed to lead to a helical arrangement of the linear chain around the anions, as concluded from ROESY experiments. When chloride as counterion was exchanged for sulfate, CD measurements also exhibited a noticeable increase in ellipticity and thus helicity that supports this view.

Chart 15



93 **94**

95 **96**

97 **98**

The proven utility of the bicyclic guanidinium core in oxoanion complexation inspired the development of other derivatives. In particular, a number of benzannellated compounds such as **93,**[305] **94**,[306] and **95**[307] (for other examples, see refs 308 and 309) were obtained, which offer more rigid systems for oxoanion binding, as compared to, namely, **68** (Chart 15). But due to the conjugation of the nitrogen sites with the aromatic rings, these compounds are much less basic and therefore restricted in their use to a smaller pH range. Nevertheless, **94** showed strong interactions with carboxylates,[306] and incorporation of **95** into a liquid membrane resulted in an electrochemical sensor for hydrogensulfite in slightly acidic solution with remarkable selectivity, sensitivity and detection range.[310] Despite this impressive result, the more general usefulness of these annellated systems needs further fortification.

The successful complexation of anions led to the idea that anionic transition states and reaction intermediates might also be stabilized by interactions with guanidinium compounds, thus making them act as catalysts. The isolation and X-ray structure of a complex between a bicyclic guanidine and α-nitrotoluene[311,312] confirmed an interaction pattern as sketched in Figure 9 and led to testing of the catalytic activity of a number of guanidines in nitroaldol reactions. Especially, it was hoped that the use of chiral guanidines would lead to enantiomerically enriched products. Compound **96**, for example, effectively catalyzed the addition of nitromethane to isopentanal,[313] but the enantioselectivity was only low to moderate (54% ee at best). Davis synthesized the chiral bicyclic guanidine **97** that had catalytic

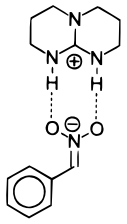
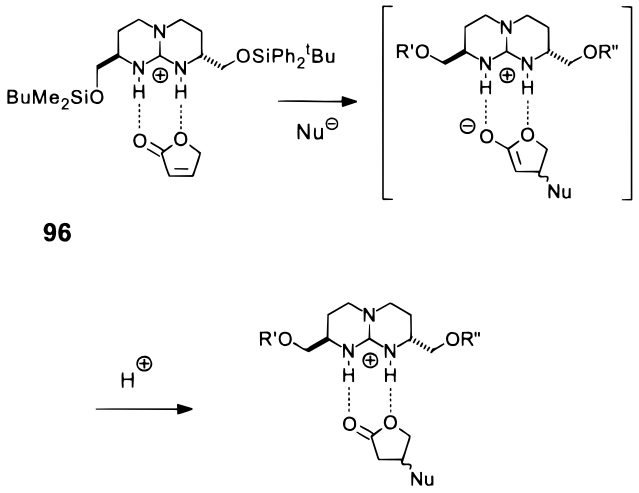


Figure 9. Sketch of the X-ray structure of the ion pair formed from the reaction of a bicyclic guanidine and α-nitrotoluene indicating the peculiar binding mode.[311,312]



96

Figure 10. The concept of catalysis of Michael additions by **96**.[316]

activity in the Michael addition of some nitroalkanes,[314,315] but showed disappointingly low enantioselectivity (ca. 10% ee). In another approach, de Mendoza used **98** to stabilize the transition state in the addition of pyrrolidine to unsaturated lactones (Figure 10). A rate increase corresponding to a factor of 8.4 for the most favorable case was found, but the reaction failed for noncyclic esters, which apparently adopt conformations preventing coordination to the guanidinium cation.[316] A possible chirality transfer from the guanidinium host was not observed.

D. Miscellaneous Cationic Hosts for the Complexation of Anions

The overwhelming majority of organic host compounds interacting by charge attraction with anionic species are based on cationic nitrogen compounds. Very few examples exist which suggest complexation by carbenium-based,[317−321] iodonium,[322] or sulfonium[231] structures. However, the introduction of positive charge into organic frameworks as an alternative to protonation can be very efficiently accomplished by metal cation ligation and in consequence requires the careful design of suitable coordination sites. In this way, hosts with very high charge density at well-defined positions can be constructed and supplemented by additional attractive interaction modes such as hydrogen bonding or solvophobic interactions. Furthermore, the peculiar coordination features of the metal cations can be exploited to assist the electrostatics by some covalent-bonding components. When an organic chelating ligand binds to a metal cation, a mismatch of coordination sites may arise, which not necessarily spoils

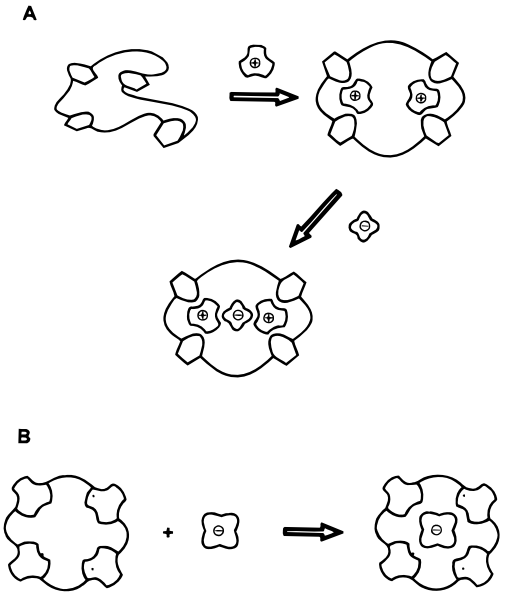


Figure 11. Two different concepts to utilize metals for anion binding. (A) Formation of cascade complexes "Russian doll complexes". The metal species are assembled by coordination to an organic ligand in spatial vicinity but remain coordinatively unsaturated to allow ligation of an anionic guest between them. (B) The metal species are covalently embedded into an organic molecular skeleton.

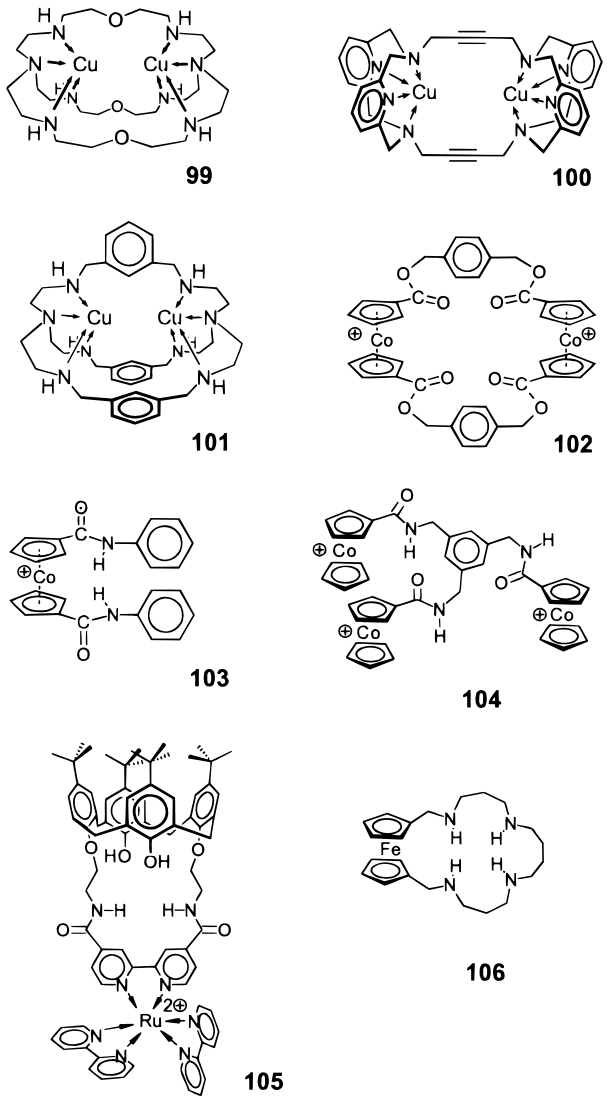
the complexation and may still give thermodynamically stable species. If the potential donor atoms in the ligand outnumber the coordination sites of the metal ion and in addition cannot be arranged to satisfy its coordination needs due to, namely, flexibility restrictions, one observes as a rule polynuclear complexes. Rather frequently these complexes possess open coordination sites that can be filled by anions. Anion binding in these systems is thus widespread. In the perspective of host−guest chemistry, it is often a rather adventitious phenomenon and basically a remedy to arrive at a more stable structure. Viewed from the position of the metal center, this field is frequently connected to second-sphere coordination[323,363] and gains in popularity by applications such as ligand-assisted catalysis.[324] Fundamental in this respect is the formation of cascade complexes[325] (Figure 11) in which the anionic guest is held by ligation to coordinatively unsaturated metal centers themselves being embedded in the organic ligand by coordinative forces. The goal is to tailor ligands in order to impose high barriers for anion discrimination. Of essential importance is the prudent selection of metal cations, since they have to meet multiple requirements. Being the points of direct interactions with the negatively charged guest, they can exert their intrinsic binding preferences, which can be modulated by the chelating ligand in a predictable manner. In addition, the cation of choice should bring in a precise geometry of ligation that would improve structural order and rigidity in the ligand. On top it would be desirable to have guest binding and overall complex formation as independent processes (i.e., the metal complex with the ligand should be kinetically stable while anion binding itself should occur in rapid exchange). Fortunately, this latter caveat is met by most of the chelating ligands used so far. On the basis of these

principles, the lower transition metal cations notably Cu(I), Cu(II), Fe(II), Mn(II), Co(III), Ni(II), and Ru(II) have been preferred, although even the uranyl cation and main group metals have also been successfully employed and there is no obvious limitation to use elements from the entire range of the periodic table. As mentioned above, this concept is in the domain of multinuclear metal complexation and cannot be treated here comprehensively. As a tribute to the importance of this binding principle to the whole area of anion complexation, only a few examples will be highlighted here.

Azacrown ethers and cryptands after protonation make very successful anion hosts (vide supra), but can serve in their basic form as ligands for a number of transition metal cations with well-defined coordination geometries. Bistren **22,** for instance, was shown to complex Cu(II) ions one at each hemisphere of nitrogen sites to give the binuclear complex **99**[326,327] which in spite of the presumed distorted tetrahedral ligation geometry of the metal ions[211] still contains a void space in the center of the structure ready for encapsulation of an anion such as chloride.[326] The binding constants were thoroughly evaluated by precise pH-metric analyses giving K_{assn} (Cl^-) = 3.5×10^3 M^{-1} in water. The chloride anion most likely is bound in bridging mode between the copper ions, because the mononuclear complex having one Cu(II) replaced by two protons and thus being of identical total charge was found to bind chloride more than 100fold weaker. With hydroxide anion the difference between dinuclear and mononuclear complexes is even greater. Differential binding by a factor of 10^8 is obviously due to the particular difficulty of hydroxide to bind to the copper ion safely hidden and shielded in the interior of the ligand. The association of an hydroxide ion is aggravated by 1000-fold when compared to the uncomplexed aquo Cu^{2+} cation thereby showing an "anticryptate effect". This term is justified since the cryptate effect describes the extra amount of binding affinity for a guest acquired by the supply of a three-dimensional cavity. Here, guest binding is disfavored rather than eased, compared to the free solvated cation. Among the binucleating ligands, the macrocycle OBISDIEN **12**[328] holds a prominent position. Compound **12** represents the monocyclic parent compound of **22**, and its Cu^{2+}, Ni^{2+}, Zn^{2+}, and Co^{2+} complexes all have been demonstrated to bind a wide variety of anions including malonate, perchlorate, sulfate,and azide. There is good evidence that anion binding occurs by μ-bridging in every case. Molecular modeling also suggested the same binding mode to occur with pyrophosphate^{4-} complexation in the biscopper(II) complex of **12**.[328] Around pH 8, the unprotonated complex is the dominating species in solution, exhibiting the extraordinary high $K_{assn} = 3.1 \times 10^8$ M^{-1} with this biologically important anion.

Similar binding concepts for anions have been elaborated by Krämer,[329] who demonstrated cyanide binding in the bridging mode by **100** (Chart 16) in acetonitrile solution as well as in the solid state, and by Fabbrizzi et al.[330] Using UV spectrometry, the latter group showed that complex stability with **101** in water in a series of bidentate anions of different

Chart 16



dimensionality ("bite length") does not depend on the chemical nature of the guest, but exclusively on its dimension favoring azide over nitrate by 100-fold.

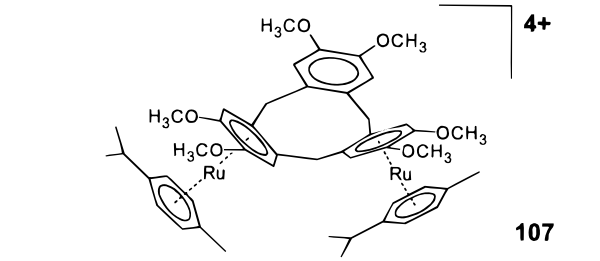
One straightforward application of artificial anion hosts would be their use in the qualitative detection and quantitative determination of selectively bound guest species. This process requires an easily observable signal triggered by the anion-binding event.[331−334] To this end, optical or electrochemical signals appear preferable over, namely, NMR detection methods, although the latter in general transmits more information on the molecular details of the noncovalent interaction and is thus the method of choice for guiding host optimization. The *a priori* incorporation of physical probes into the host structure, however, can be advisable when the application itself is the prime impetus for host development. Along these lines, the utilization of metallocenes, namely, **102** in anion host design was propagated by the groups of Beer[72,70] and Takahashi.[335] These systems possess the virtues of ready accessibility while being reversibly redox responsive, chemically stable, and potentially cationic and, above all, offer the options for easy modifiability and for use as structural building blocks. In particular, cobaltocenium moieties when incorporated into macrocycles

as in **102**[336] or linked by amide connections to a variety of other spacer functions[253,337−340] proved successful in anion recognition. The positive charge of the cobaltocenium unit is certainly helpful but not sufficient to bring about anion complexation and must be supported by hydrogen bonding as was concluded from the lack of guest binding when the secondary amide **103** was replaced by the tertiary *N*-methyl-substituted analogue.[338] Following the building block principle, spacer units such as trisubstituted aromatics (cf., **104)** or calixarenes were combined in various ways with cobaltocenes[341,342] or ruthenium bipyridine complexes[343−345] (e.g., **105**) or were converted into hybrids between the two metal complexes.[346] In every case, anion binding in acetonitrile or dimethyl sulfoxide was clearly visible by optical or cyclovoltammetric methods. Anion-binding strength (K_{assn} < 10^3 M^{-1}) and consequently guest selectivity either remained low to moderate, though, or eluded precise determination. When a redox-active ferrocene unit was covalently incorporated into a polyaza macrocycle to give **106,** the polycation resulting from protonation in water was shown to bind HPO_4^{2-} and ATP anions, causing a cathodic shift of the ferrocene/ferrocenium redox couple by 60−80 mV.[216] A planar chiral cobaltocenium compound was also separated into its enantiomers and shown to form diastereomeric complexes with (+)-camphor-10-sulfonate marking a new access to chiral recognition of suitable anions.[347]

A very elegant extension of the chemistry of arene−formaldehyde condensation products such as cycloveratrylenes or calixarenes was recently introduced by Atwood et al. Arguing that these cage-forming aromatic hosts which usually bind metal cations or neutral organic guests could be inverted in their guest preference toward anions if only strongly electron-attracting groups were attached to the aromatic rings, they prepared η^6-bonded complexes with cationic ruthenium and iridium species.[348−350] In addition to providing highly charged and well-structured cations such as **107** (Chart 17), the metal−arene π bonds lower the electron density sufficiently to enable the uptake of a variety of anions into the bowl-shaped cavity. X-ray crystal structures left no doubt that even oxoanionic guests (e.g., $CF_3SO_3^-$) occupy the central bowl in the most plausible orientation with the hydrophobic portion turned toward the bottom thus exposing the anionic moiety to the solvent. Surprising selectivities in anion extraction have been observed in an analogous host having only two of its rings modified by ruthenium complexation.[348] For instance, $^{99}TcO_4^-$, which is an important ingredient in the nuclear fuel and waste management, could be extracted from saline solutions into nitromethane with preference even to hydrophobic anions as ClO_4^-.[349]

Instead of influencing the electronic properties of preformed organic hosts through metal ligation the host framework itself can be prepared in an informed self-assembly process. A number of metallacyclophanes such as **108**[351−357] have been obtained recently simply by mixing complexes of Pd, Pt, Cd, or Re with bidentated pyridine or cyanoaryl moieties in alcoholic solution. In general, the molecular boxes formed

Chart 17



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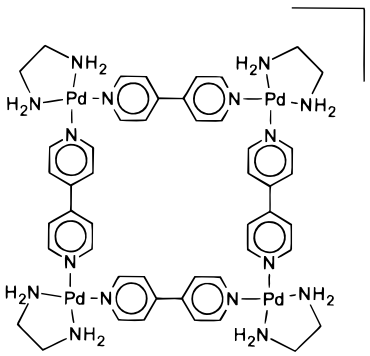

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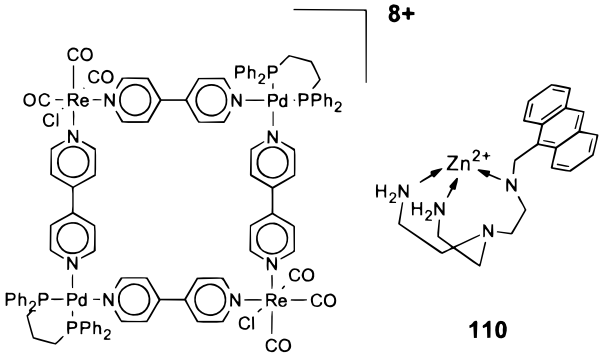
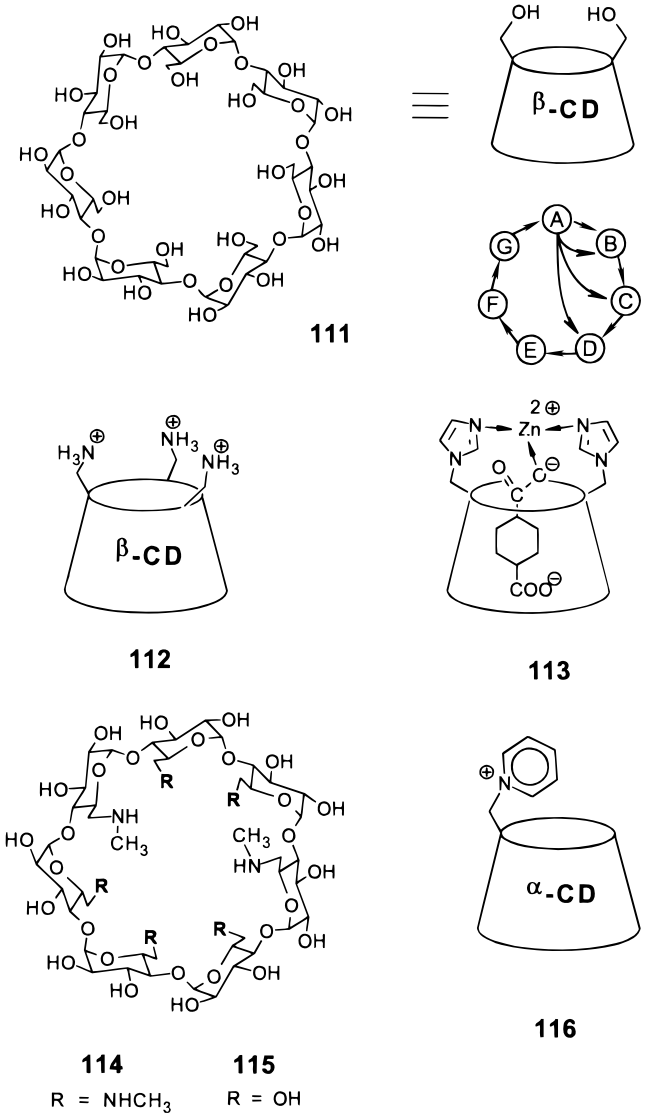


110

109

spontaneously and seemed to be the thermodynamically most stable species. Due to the hydrophobic electron-deficient aromatics encircling the central cavity, it was less surprising that these compounds serve as molecular hosts for electron-rich guests much like the well-established azoniacyclophanes. Their high positive charges insure their water solubility and, in addition to hydrophobic binding, contribute an electrostatic component that was helpful in complexing a variety of aromatic carboxylates.[353] However, unlike the host−guest binding of neutral aromatics, **108** formed complexes of higher stoichiometries with negatively charged guests indicating interactions at the metal centers overlaying the cavity inclusion process. In the rhenium complex **109**, 1:1 stoichiometric binding of ClO_4^- in acetone (K_{assn} 900 M^{-1}) could be detected and resulted in a change of its luminescence, enabling a novel method for sensing this anion.[358] Sensing in particular phosphate anions by their effect on the fluorescence of polycationic anthracene derivatives has been achieved by Czarnik et al.[359−361] Similar systems employing Zn-mediated binding were successful in molecular recognition of carboxylates to **110** in methanol.[362] Although the substrate selectivity can-

Chart 18



not be great within the series of carboxylates visualizing the simple host design, these anions were clearly distinguished from other inorganic anions such as chloride, nitrate, and isothiocyanate and could be detected with good sensitivity.

Cyclic oligomeric α-glycosides of glucose (cyclodextrins), namely, **111** (*β*-cyclodextrin, Chart 18) represent classic examples as host compounds for molecular recognition in water.[364,365] They provide toroidal cavities of variable size which offer a hydrophobic environment rimmed by arrays of highly hydrophilic hydroxy groups. As a general rule, guest molecules not well hydrated in water but of the correct complementary size to fit into the molecular cavity will associate with this class of host compounds. In line with this expectation, some inorganic anions such as ClO_4^-, I^-, and SCN^- but not well-hydrated species (CH_3COO^-, Cl^-, SO_4^{2-}) form weak complexes (K_{assn} 10−50 M^{-1}) with α- or *β*-cyclodextrins (6 or 7 glucose units, respectively).[366−368] The determination of binding enthalpies and entropies from van't Hoff plots, however, rather points to polar interactions of the anionic guest with the cyclodextrin as the prime driving force for complexation.[369] With the advent of reliable methods to further modify these polyfunctional hosts in a regioselective fashion,[370,371] the attachment well-positioned additional binding functions became feasible. Particularly prominent in this respect was the introduction of amino groups in the 6′-position, which after protonation could interact by salt bridging with anionic substructures of the guest. The placement of three ammonio functions in C_3-symmetrical manner on the small rim of permethylated α-CD gave host **112**, capable of binding benzylphosphate at pH 7.0 at least 1000-fold better than either of its constituents (benzyl alcohol or hydrogen phosphate).[372] Somewhat weaker synergism of binding interactions was observed when *β*-CD was modified with two imidazole heterocycles and reacted with zinc to form a coordinatively unsaturated Zink complex. Binding of cyclohexane-1,4-dicarboxylate as sketched in **113** was found to outmatch complexation by the parent ligand by a factor of 6.6.[73,373] Similar results were obtained for the combination of an azacrown ether with *β*-CD-complexing alkali metal salts of *p*-nitrophenolate in DMF.[374]

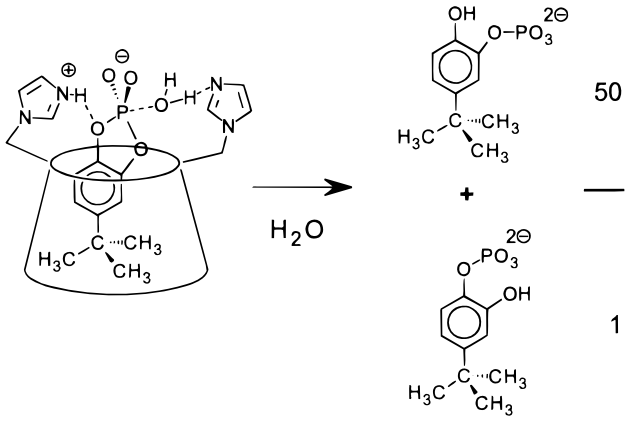


Figure 12. Phosphodiesterase models: Regioselective cleavage of *m-tert*-butylcatechol phosphate by A,B-bis-imidazolyl-*β*-CD. The buffer-catalyzed hydrolysis produces the monoesters in equal amounts.

Bisimidazolylcyclodextrins can also catalyze the cleavage of anionic catechol phosphates (Figure 12) and thus mimic certain nucleases. More than the moderate rate enhancement (ca. 8-fold), it was the impressive regioselectivity of phosphate cleavage that made this model resemble real enzymes. Proton transfer in the general acid−base catalysis of this process could be correlated to the relative spatial disposition of the imidazole heterocycles.[375−377]

Owing to the accumulation of positive charge in the vicinity of the molecular cavity, aminocyclodextrins may serve as molecular hosts for a variety of organic anions such as pyrocatecholates[378] and fluorescent aromatic sulfonates[379] in the enantiorecognition of chiral carboxylates[380,381] and for nucleotides.[382,383] Quite dramatic association constants were calculated for complexation of fully protonated heptamethylamino-*β*-CD **114** and deprotonated nucleotides, with ATP^{4-} hitting the highest mark (K_{assn} 3×10^6 M^{-1}). Although the actual contribution of these equilibria to the *apparent* host−guest association at any given pH is only minor due to the minute concentrations of the individual protonation states, the extreme K_{assn} values reflect the maximum intrinsic interaction energy. The comparsion of [**114**·$7H^+$] and its A,D-disubstituted methylammonio analog **115** revealed

subtle differences in the response to structural variations in the nucleotide (the base, the sugar moiety, and points of connection of the phosphate ester), but underlined the general trend, found also in other host systems, that accumulation of charge is deleterious to guest selectivity. Apparently, different guests may find multiple configurations of very similar energy in the multipole electrostatic field of a highly charged host, so that structural subtleties have no bearing on the overall association. An interesting application reported the use of heptakisamino-β-cyclodextrin as a catalyst for α-H/D exchange in activated carboxylates at neutral pH.[322] The acceleration factors reached 3800 with some α-oxocarboxylates, but with malonate, although being the fastest exchanging anion, a factor of only 150 was marked. No indication of host−guest complex formation was observed. Sulfate, however, but not the more hydrophobic anions bromide and iodide, partly inhibited the exchange process. Progressive replacement of the 6-hydroxy group in α-cyclodextrin by the pyridinium function opened the opportunity to use charge transfer interactions with the negatively charged guest, thus supplementing Coulombic binding.[384,385] Monopyridinium-α-cyclodextrin **116** and a series of higher substituted analogues were shown to bind iodide, SCN^-, or Br^- with respectable affinity in water (K_{assn} approaching 10^6 M^{-1}), while the increase in absorption in the UV spectrum around $\lambda = 300$ nm evidenced charge transfer contributions and could be used for K_{assn} determination.

V. Electroneutral Hosts for Anions

A. Poly Lewis Acid Hosts

The connection of multiple Lewis basic moieties in a preorganized molecular framework, as realized in crown ethers, furnished host molecules capable of binding even the weakest coordinating cations. Adapting the same concept for binding anionic species requires the incorporation of a defined number and type of Lewis acids into a molecular skeleton with their electron-deficient sites exposed for interaction with the lone electron pairs of anions. This is the reciprocal arrangement present in crown ethers and thus the term "anticrown chemistry" has been coined to emphasize this relationship.[79]

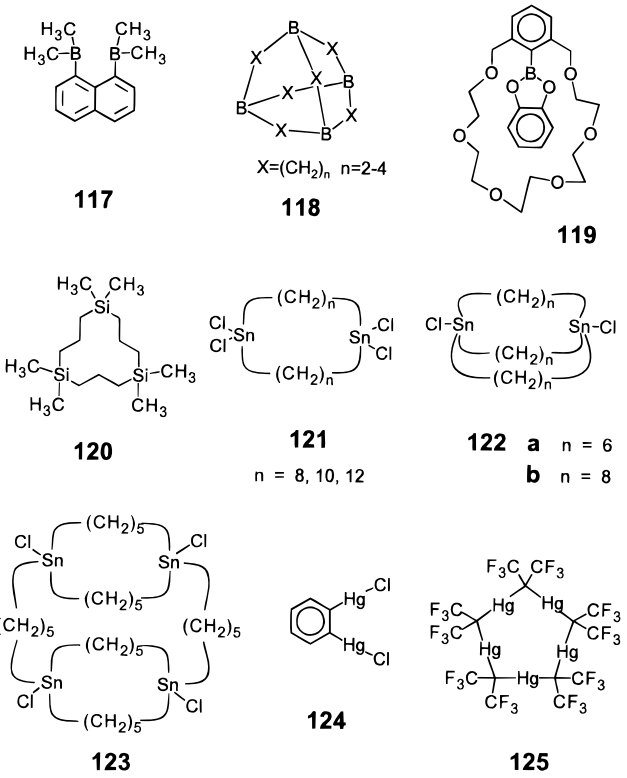
The major advantages in this design of anion hosts derive from their electroneutrality and from the intrinsically more-selective binding mode that ultimately leads to a covalent bond between the binding partners. Electroneutrality is of prime virtue since the internal competition established with the counteranions unavoidably present in cationic hosts and frequently responsible for weak guest binding and poor selectivity is nonexistent. In addition, certain applications such as potentiometric anion sensing by ion selective electrodes require uncharged selective receptors to confine the host to the membrane phase and generate a potential difference between membrane and bulk solution. While pure Coulombic forces just scan size, density, and distance of charge, the Lewis-acid−Lewis-base interaction as it depends on stereoelectronics, symmetry of molecular orbitals, softness, back-bonding ability, etc., provides a much more subtle means to probe molecular properties.

Thus, the construction of suitable poly Lewis acidic hosts can draw on a well-sorted stock that is not accessible for cationic hosts. Lewis acidic hosts, on the contrary, face the problem of competition of almost any solvent with their dedicated guests. Except for the hydrocarbons, all other organic solvents are Lewis bases as well and generally exceed the molar concentration of a guest anion by several orders of magnitude. Solvation design (i.e., the exclusion of solvent from the actual guest binding site while retaining sufficient solvation energy to keep the host and host−guest complexes in solution) is a matter of necessity. Of course, this is more difficult the smaller and more Lewis basic the solvent molecules are. Many examples from biology, namely, metalloenzymes such as superoxide dismutase or carbonic anhydrase which use and convert small inorganic anions, demonstrate this to be feasible and even suggest that it might well be the preferable option if the chemical transformation of small anions is planned. Two conceptually different routes for the incorporation of Lewis acid moieties into host molecules have been followed and realized (Figure 11): The receptor sites can be embedded into the molecular framework using covalent connections requiring a precise synthetic strategy, as usual in target-oriented preparative chemistry, and an intimate knowledge of the chemical reactivity of the Lewis acid sites. On the alternative pathway an organic ligand is prepared that is predisposed to take up the Lewis acidic metal cations in a straightforward complexation step in a defined manner, however, leaving the cation coordinatively unsaturated. This approach has been preferred when implanting transition metal cations, whereas covalent incorporation was chosen when elements from main groups III or IV or mercury was used, all well reputed to form stable covalent bonds.

1. Lewis Acidic Hosts Connected by Covalent Bonds

Proton sponges contain basic amino groups rigidly held in proximity close enough to bind a proton between them. Outstanding basicity and rather slow exchange kinetics characterize this binding motif. In much the same way but with the inverse layout in charge distribution, Katz designed the 1,8-disubstituted naphthalene **117**, having two boron Lewis acids in juxtaposition to one another (Chart 19).[386] As expected, **117** was capable of binding hydride from potassium hydride furnishing an extraordinarily stable borohydride complex that even proved inert toward attack by moderately strong acids or benzaldehyde. As evidenced by an X-ray structure, the hydride atom was located in a bridging position between the boron centers. Although it is clearly not a symmetrical bridge, both boron atoms participate in hydride binding as reflected by their pyramidalization and thereby accounting for the unusual thermodynamic and kinetic stability. Fluoride and hydroxide anions form complexes of very similar structures, supporting the view that **117** acted as a primitive yet very effective bidentate host for small inorganic anions. It was also shown that one borane group could be replaced by a trimethylsilyl moiety without impairing fluoride binding.[387] These experimental results are corroborated by theoretical cal-

Chart 19



culations (AM1) on the complexation of hydride, fluoride, chloride, and oxide anions by the macrocyclic borane **118**.[388] All boron atoms in the parent host were found to be sp^2 hybridized. On anion inclusion, the boron−boron distances are substantially reduced accompanied by partial rehybridization from sp^2 to sp^3 of one or more boron centers. A nice extension of this concept ultimately leads to hosts complexing ion pairs. When a boronic ester was combined with a crown ether as in **119**,[389,390] a ditopic host was formed capable of the simultaneous binding of an anion and a cation potentially favored by synergistic effects. In fact, host **119** solubilized potassium fluoride but not the other potassium halides in dichloromethane. As expected, the X-ray crystal structure confirmed binding of cation and anion at their corresponding sites in the receptor, but at least in the crystal no intramolecular but rather intermolecular association of cationic and anionic substructures in the host−ion pair complex was observed. Qualitative evidence that even weakly Lewis acidic silamacrocycle **120** exhibited selective interaction in transport studies[391] was later supplemented by results from Ito and Tamao et al. who found *o*-bis(fluorosilyl)-substituted benzenes to complex fluoride in acetone at low temperatures with K_{assn} as high as 10^9 M^{-1}.[392,393] The Lewis acidity of the rigidly held bissilyl substructure sufficed to dissolve solid potassium fluoride in acetone or tetrahydrofuran even without the help from cation complexation by crown ethers. Only one ^{19}F signal is observed, indicating very rapid intramolecular scrambling of the various fluoride positions possible. Very similar time-averaging was also observed with cyclic fluorophosphazenes $(NPF_2)_n$ which were shown to bind fluoride in acetonitrile solution and exhibited quasi octahedral coordination of the anionic guest by the inorganic host in the crystal.[394] The initial results promoted investigations of the more acidic germanium[395] or tin(IV)[396,397] analogues. In particular, stanna(IV)macrocycles such as **121** had already been characterized to bind chloride anion in acetonitrile solution.[398,399] However, chloride affinity was only marginally increased by a factor of 2 over the corresponding open-chain pendant. Since binding was almost independent of ring size and 1:1 and 1:2 host−guest equilibria of comparable stability were established, the cooperativity of binding sites could only be minor.

The construction of the bicyclic stanna compound **122a** that exists as the out−out isomer exclusively according to an X-ray structure[400] brought a considerable improvement in selectivity. There is an obvious similarity of **122a** to the bicyclic bisammonium compound **1** of Park and Simmons,[43] the first host shown to bind chloride by encapsulation. In contrast, the metallamacrocycle **122a** proved to be a fluoride host with an K_{assn} in chloroform of $(1-2) \times 10^4$ M^{-1} and showing discrimination against chloride by a factor of 10^5.[401]

In the crystal, fluoride anion occupies the cavity of **122a** making contacts with both tin atoms. The bigger host **122b** instead readily formed a chloride inclusion complex, however, the chloride coordinated to one tin atom only. ^{119}Sn NMR spectra provided a good tool for investigating the complexation dynamics in solution. These studies suggested that the anion hops between the tin atoms crossing an activation barrier of 22.2 kJ mol^{-1}. At any given time, there is only monotopic binding of the guest. It is no wonder that the chloride affinity of **122b** is of the same order of magnitude as in a simple tributyltin chloride. However, cavity dimensions clearly influence complex stability as can be seen within the series of hosts **122**. A smaller or larger host compound (**122**, $n = 7$, 10, 12) gives weaker complexes with Cl^- than **122b** ($n = 8$).[402]

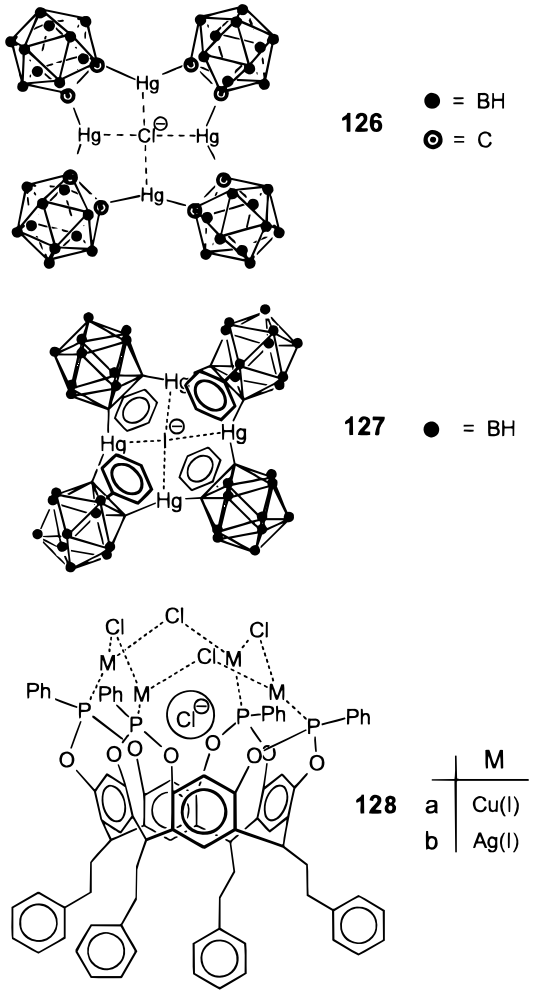
In line with the expectation that absolute binding strength is enhanced the greater the number of Lewis acidic sites synchronically participating in anion binding, the macrotricyclic compound **123** displayed a dramatic gain in chloride affinity. In $CDCl_3$ the binding constant was determined as 500 M^{-1}, representing an increase in free energy of complexation of ca. 8.4 kJ mol^{-1} over the bicyclic analogue **122b**.[403] Additional confirmation of guest inclusion derives from the strict 1:1 stoichiometry that is conserved even with high excess of the guest anion. In host−guest titrations probed by ^{119}Sn NMR, only one signal was observed indicating rapid exchange processes to happen. Organic tin(IV) compounds are known to possess a marked intrinsic affinity for phosphate.[403] This sets the stage for the construction of simple ditopic tin derivatives aiming at the specific sensing of this anion.[405,406] Gratifyingly, rather impressive discrimination factors (up to 100) against even highly hydrophobic guests such as ClO_4^- or SCN^- (which present special problems in anion sensing because of their nonspecific phase transfer behavior) are reported and in combination with the favorable response time observed open a promising perspective in sensing this environmentally important anion,

provided the organic frame holding the tin(IV) atoms can be tailored appropriately.

A great benefit in the use of metals in the construction of artificial hosts derives from their bonding geometries which widen, extend, and sometimes simplify the synthetic routes necessary to arrive at the desired topology of "sticky" anchor groups in space. A peculiarly favorable candidate for use as an architectural element is mercury since it forms unusually stable carbon bonds extending colinearly from the metal. The Lewis acid character of organomercury compounds is due to two empty p orbitals oriented perpendicularly to the metal−carbon axis and to each other. One virtue of this arrangement is its configurational stability because binding a Lewis base to the empty orbitals causes no distortion of the system on stereoelectronic grounds. An early example for binding chloride by a simple organic mercury compound is given by phenylenedimercury dichloride **124**. In the crystal the anion is surrounded and ligated by four mercury centers.[407] A more elaborate system dwelling on the same principle[408] is represented by the 10-membered pentamercuramacrocycle **125**.[409,410] The bonding requirements allow formation of a flat plate-like macro-ring that virtually invites halide ions such as chloride or bromide to associate at the electron-deficient faces. Complexes of 1:2 host−guest stoichiometry are easily formed hosting the halides on both sides of the ring equidistant to all mercury sites. The mutual distance of the two chloride anions perching above the faces of the metallacycle is considerably shorter than the sum of their ionic radii indicating rather strong bonding interactions with the Lewis acidic mercury atoms.

When dilithio-*o*-carborane reacts with mercuric dichloride, the cyclic tetramer **126** in the form of its chloride complex can be obtained in 75% yield (Chart 20).[75,411,412] According to solution NMR investigations and X-ray crystal structural confirmation, the chloride sits in the middle of a square formed by four mercury atoms at the corners. This is the outcome of a templated macrocyclization, because replacement of mercuric dichloride by the mercuric acetate salt gave a cyclic trimer instead.[413] Halide encapsulation into the tetramer appears to give a rather stable complex requiring silver ion for decomposition. The free ligand then undergoes a refolding process arranging all mercury and carbon atoms to fit the seam of a tennis ball. When the free ligand is titrated with iodide in acetone, monitoring by ^{199}Hg NMR furnished evidence for the stepwise formation of 1:1 and 1:2 host−guest associates being in the slow-exchange domain on the NMR time scale. In contrast, the chloride complex followed faster exchange kinetics, and chemical shifts of signals corresponded to weighted averages of the contributing species.[414,415] In solvents of high solvating power (donicity), it is mandatory to strive for exclusion of solvent from the Lewis acidic sites. En route in the present case was the incorporation of aryl rings in order to restrain access to the molecular cavity. The introduction of substituents with the carborane moiety, however, in principle leads to stereochemical scrambling. In the prevailing case, one must expect formation of four

Chart 20



configurational isomers distinguished from each other by the positioning of the set of aryl groups relative to the main plane containing the metal sites (the stereochemical situation is similar the one found in calix[4]arene). Macrocyclization in the presence of HgI_2 yielded one isomer exclusively. This was shown to contain the 1,3-alternate array of phenyl groups depicted in **127**, allowing the substituents on opposing borane clusters to cover and shield the same face of the metallacycle.[416,417] Substituting $HgCl_2$ for the iodide salt yielded a mixture of isomers from which three distinct complexes were isolated and characterized. In every case the chloride guest is encircled in plane by the Hg atoms, while in the iodide complex the anion assumes a perching position above the main plane. It is quite surprising in view of the structural variety and putative fragility at first sight to learn that this class of compounds is obtained reliably and quickly in high yields and lends itself to further structural variation. In synopsis with other desirable properties such as chemical stability and solubility in many organic solvents especially of regioselectively alkylated derivatives[418] in combination with the ease of monitoring the complexation process by ^{199}Hg NMR, this class of compounds holds considerable promise for application both in basic organic chemistry as well as in technology.

2. Lewis Acidic Hosts Based on Metal Cation Coordination

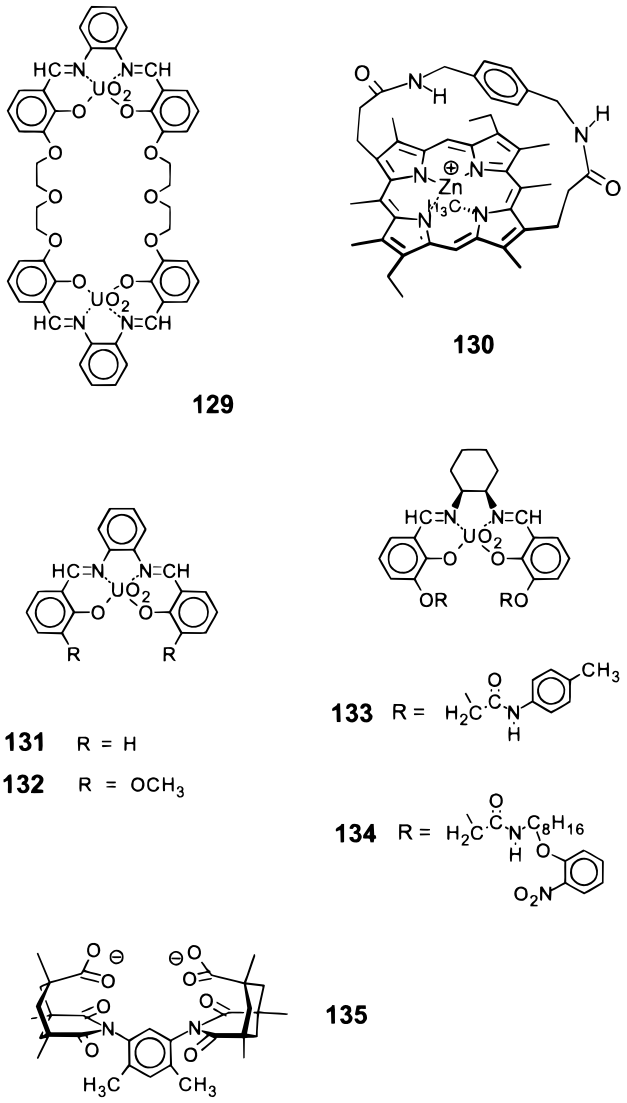
We have already pointed out above that anion complexation following the concept under this headline is at the heart of inorganic coordination chemistry and clearly reaches beyond the scope of this review. A few examples illustrating the basic ideas have also been mentioned in the discussion of positively charged hosts. Here, we want to present a few more systems of overall neutral charge from the most recent literature that may outline the great potential in this approach to artificial anion hosts.

Taking a resorcinarene as a basic scaffold, Puddephatt et al.[419] esterified the hydroxy functions of adjacent rings to arrive at a rigidified phosphonite ligand. Reaction of Cu(I) chloride with this highly preorganized set of phosphorus donor sites gave a neutral tetranuclear Cu(I) complex (**128a**), which turned out to be an anion due to encapsulation of a chloride guest in the center of the cavity formed by the organic bowl and the metal chloride cap. The included guest could be exchanged freely by bromide or iodide in dichloromethane, but not by nitrate or cyanide, the latter leading to destruction. An excess of guest anions caused partial replacement of the bridging halide showing the fragile nature of the copper complex. However, a very similar complex was formed with silver ions which even proved stable enough to assist in driving an organic reaction. Thus, the nucleophilic replacement of iodide in *tert*-butyl iodide by the chloride guest included in **128b** exploited the much greater affinity for I^- to drive this equilibrium reaction to completion within 5 min at 20 °C.[419] The easy accessibility of these electroneutral systems along with their size-selective binding of halides in a unique μ_4 fashion predestines them for many attractive applications in organic chemistry.

Large transition metal cations (e.g., the uranyl cation) hold the virtue of a distinct coordination polyhedron that allows the sincere anchoring of the guest into an organic polychelate while leaving still one coordination site open for additional binding of a Lewis base. This feature was elegantly exploited by Reinhoudt et al.[420] in the construction of the dinuclear complex **129** (Chart 21). A number of dicarboxylates were found by NMR spectroscopic methods to bind to **129** in DMSO with K_{assn} values up to 10^5 M^{-1} (fumarate). Unfortunately, even monocarboxylates such as benzoate ($K_{assn} = 200$ M^{-1}) or dihydrogen phosphate ($K_{assn} = 1500$ M^{-1}) were bound as well, compromising the selectivity of this host to some extent and reflecting the intrinsic affinity of the uranyl system toward anion ligation. This appears to be the electroneutral version of a more general theme represented by ligand **38a** which forms a dinuclear copper(I) cryptate and complexes terephthalate as a polyprotonated host in a highly complementary fashion.[201,211]

The attachment of additional anchoring groups recruited from the rich variety of conventional functional groups used in molecular recognition to Lewis acidic metal complexes offers a promising approach in the promotion of guest selectivity. Some trailblazing attempts are marked by Lehn's coreceptor strategies,[325] the combination of Zn complexes with

Chart 21



cyclodextrins[73,373,374] that we have mentioned already and in anion binding of the protonated monomolecular Cu(II) complexes of the bistren macrocycle (the ligand of **99**).[326] In the end, any ligand containing extra functionality in addition to the groups mandated in metal cation coordination will unavoidably modulate the binding options of an incoming guest. In the qualitative sense, this is a long-standing notion and touches on second-sphere coordination,[323] which lacks the direct interaction with the metal center. Although well established in metal coordination chemistry, the consideration of these secondary interactions in the deliberate design of dedicated host compounds has attracted attention only recently and pushed multitopic receptor development. Covering one face of *N*-methylmesoporphyrin II with an achiral bridge followed by treatment with Zn^{2+} gave enantiomeric zinc−porphyrin complexes **130** that were separated by HPLC.[421] Access to the zinc center is restricted on both sides of the porphyrin but much more so from the backside where the *N*-methyl group completely shields the metal. The front side lined by the strap with the hydrogen-bonding amido groups offers an enforced chiral environment that on binding racemic guests should yield diastereomeric complexes. Taking *N*-acyl-α-amino acid anions as guest

species, a strong enantioselection giving up to 90% ee was observed in extraction experiments (H_2O/$CHCl_3$) that could be traced back to the hydrogen bond donor ability of the guest.

Hydrogen bonding is also a reliable tool for boosting the intrinsic selectivity of uranylsalens **131** and **132** for $H_2PO_4^-$.[422,423] When two extra secondary carboxamide functions were attached to give **133** and **134**, the K_{assn} values of $H_2PO_4^-$ and Cl^- in acetonitrile/DMSO (99:1) increased by an order of magnitude ($K_{assn}(H_2PO_4^-) > 10^5$ M^{-1}) and the discrimination between both hydrophilic anions reached a factor of 100. Host−guest association is entropically driven, and extraordinarily high positive entropies of association (377 J K^{-1} mol^{-1}) have been reported in the complexation of $H_2PO_4^-$ by **131**.[422,423] Obviously, only an unusually drastic desolvation of both binding partners outmatching the inherent negative entropy of association can account for this result. The inspection of the crystal structure reveals that dihydrogen phosphate is coordinated to the uranyl Lewis acidic center and errects supplementary hydrogen bonds to the methoxy and amido functions of the ligand. Many of these complexes contain phosphate as a dimer held together by a pair of hydrogen bonds, so that strictly speaking the 1:1 stoichiometry found may not mirror the actual composition of species in solution. However, even minute amounts of water in DMSO destroy the optimal host−guest configuration, leading to a dramatic drop in the affinity for $H_2PO_4^-$ (K_{assn} = 40 M^{-1} in DMSO/H_2O 9:1 v/v). Transport of $H_2PO_4^-$ across a supported liquid membrane was achieved using **134** as a carrier[424] and thus demonstrated the utility and advantages of this design of electroneutral anion receptors.

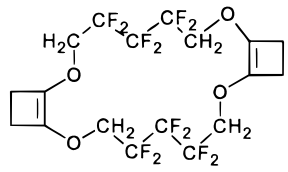
Main group metal cations, in particular Mg^{2+} and Ca^{2+}, are very abundant in natural protein receptors where they play decisive roles in binding anionic substrates, in structure enforcement, or in allosteric switching. Yet, their use in artificial receptors is not well developed at present.[425] Aiming to imitate the ligation environment of magnesium in some phosphatases, the compound **135** was prepared from the parent Kemp acid. In the presence of $Mg(NO_3)_2$ in methanol, a dinuclear magnesium complex is formed[426] containing the metal cations as bridging elements between the carboxylate functions. This topology sets the stage to associate a diphenyl phosphate anion in μ fashion between them. In a series of analogues, the spacing of the Mg centers varies by 0.75 Å signaling enough flexibility in the ligand to accommodate different coordination geometries at the Lewis acidic sites. Adaptation of complex structures appears to be a mandatory requirement to optimize the interaction with transiently changing species as they occur in many vectorial processes from membrane transport to catalysis.

B. Anion Hosts Operating by Ion–Dipole Binding

In the coordination of anions to metal centers, covalent bonding contributes a major component, whereas it is insignificant in ion−dipole interactions which are dominated by electrostatics. As the basic theory of Coulombic forces explains, the ion−dipole interaction has the same dependence on the dielectric environment as the interaction between partners bearing full charges, but is appreciably weaker on an absolute scale and falls off with distance more steeply. The main virtue from the viewpoint of host−guest chemistry, however, is the directionality (i.e., the energy of the interaction of an ion and the electric dipole depends on their mutual orientation). This translates into a structure-making property of dipolar structures that is fundamental, for example, to all molecules of biological importance. Hydrogen bonds are the most prominent and prototypical representatives of dipolar elements and as such guarantee the defined secondary and any higher level of structural organization in proteins and all other biopolymers. All by itself an average hydrogen bond connecting two electronegative atoms can add up to 30−40 kJ mol^{-1} to the attractive interaction of two partners[427] corresponding to roughly one-tenth of the binding energy in a typical carbon−carbon single covalent bond. Of course, this value is subject to grading by solvation, and it is a common observation that the enthalpy of formation of a hydrogen bond in water is near zero. The high dielectric permittivity of water combined with the presence of a delicately balanced network of hydrogen bonds requiring only reorientation but rarely *de novo* formation to satisfy all hydrogen-bonding needs is responsible for this outcome. As a consequence, attraction by hydrogen bonding that serves to glue host and guest together in less-polar solvents may totally vanish on switching to water as the solvent.[436,437] On the other hand, much stronger hydrogen bonds were recognized and triggered a vivid controversial debate on their occurence and exploitation in natural and abiotic receptors.[428−435] In the absence of competitors, hydrogen-bonding groups may be identified that are totally unexpected on the basis of common experience and due to their weakness of interaction would remain undetected otherwise. Fluorocrown ethers, for instance, associate fluoride anions in the gas phase[438] or even in the crystal when it is grown from apolar organic solvents.[439] Several X-ray structures show the anion in a nesting position right in the middle of the macrocycle[136] held in place by four converging C−H···F-H bonds.[439] Apparently, the vicinal CF_2 groups polarize the adjacent C−H bond sufficiently to enable this unusual binding mode. Preorganization of hydrogen-bonding sites appears to be essential as well, because fluoride complexation was not seen with an open-chain analog of **136** (Chart 22).

The main virtues of hydrogen bonding in the design of abiotic anion hosts derive from electroneutrality, from its capability to simultaneously form several bonding relations in bi- or trifurcated arrangements, and from the rich chemistry available for the embedding suitable structural elements into the molecular framework. Judged from the viewpoint of applicability, electroneutrality, as was mentioned above, is a very desirable property, in particular, if membrane transport or potentiometric ion sensing is targeted. The versatility of construction supplemented by the weak but nonspecialized nature of hydrogen bonds opens almost limitless options in receptor design and includes every class of organic compounds. Anion binding will take place and can be detected by the

Chart 22



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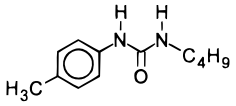

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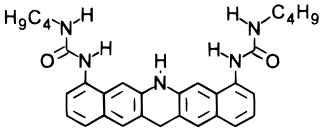

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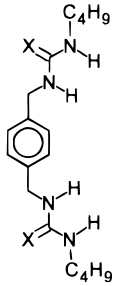


139 **a** X = O

b X = S

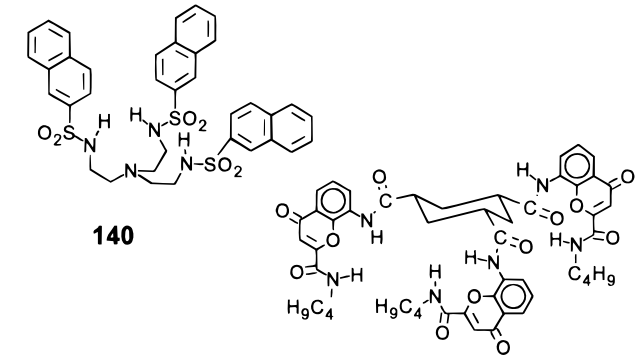
most primitive H-bond donor hosts, provided interference from competitive H-bond acceptors can be suppressed (frequently this is the major obstacle in experimental design). The quality of host design corresponds to the ability to stand up against competing solvation of both binding partners. Evidence that anion binding from the aqueous solution can be achieved only by hydrogen-bonding interactions is provided by biological receptors, sulfate-binding protein being a shining example. This carrier protein demonstrates high efficiency in sequestration of sulfate with $K_{assn} = 10^6$ M^{-1} and discrimination against hydrogen phosphate having the same charge and size by a factor of 10^5. The X-ray crystal structure reveals the molecular basis of this impressive effect.[440] The anion is buried deep in the interior of the protein with the help of seven dedicated hydrogen bonds making donating contacts with the guest. There appears to be no functional group present in the binding cavity that could act as a hydrogen bond acceptor as required for binding HPO_4^{2-} anion. In addition to a number of more subtle influences this fact should account for the selectivity observed. Another contribution to binding affinity might arise from the electrostatic ion−dipole stabilization exerted by a total of four α-helices converging with their N-termini to the binding pocket. Although there is no complete agreement on the involvement of the full length of the helix macrodipole in this ion−dipole interaction, it is undisputed that electrostatic ion−dipole stabilization in fact contributes even if it includes the first turn of the α-helix only.

Very helpful in the rational construction of anion hosts is the availability of quantitative data to characterise relative binding affinities of anions. Kelly et al. reported a useful series describing the complexation of oxoanions such as carboxylate, phosphate, and sulfonate and isosteric oxostructures such as lactone and nitro with the urea-based hosts **137** and **138**.[441] The plausible sequence was found: Greater Brønsted basicity and higher charge of the guest lead to higher complex stability. In an analogous system (**139**), Hamilton et al. had discovered another correlation of improved complex stability and higher acidity of the H-bond donor host.[270] The interdependence is rather flat though in either case.

In contrast, the dependence of host−guest association on solvent is more pronounced. It is well recognized that K_{assn} in general will decrease following the sequence $CCl_4 > CHCl_3 > CH_3CN >$ DMSO/H_2O due to the rise in global polarity, but factorizing the Gibbs enthalpy of association that is readily calculated from the binding constant into its component entropy and enthalpy parts uncovers nonuniform effects that clearly point to more subtle molecular influences. Weak interactions invariably are subject to enthalpy−entropy compensation,[442−444] which in turn comprise the entire molecule and are not restricted to the substructures of host and guest coming in direct contact with each other.[445−447] The role of water in organic solvents leading to specific solvation and thus strong competition in hydrogen-bonding host−guest binding has been unfolded and emphasized by Wilcox.[448] Moreover, the analysis and interpretation of binding data may be further complicated by additional equilibria that are hard to avoid and may falsify the host−guest binding in direct focus. Particularly prone to cause errors are self-dimerization of the host or unspecific ion pairing of the anionic guest with the countercation. Disregard of these factors can easily lead to skew and mostly overoptimistic estimations of binding affinity and may detract from recognizing the true causes of host−guest complexation. In spite of these difficulties, some general conclusions in host design have been advanced and solidly confirmed. Positive effects on binding affinity can be expected from the accumulation of H-bond donor sites in close vicinity to each other for two reasons: This set-up allows to erect a maximal number of H-bonding contacts to the anionic guests resulting in improved binding on enthalpic and entropic grounds.[442−444] The enforced vicinity, on the other hand, allows suboptimal solvation of the individual donor sites only translating into enthalpically more favorable guest binding. Host flexibility is another point of concern. Most organic functional groups serving as strong H-bond donors contain corresponding Lewis basic acceptor sites as well and enter into a self-saturating intra- or intermolecular relation, if host flexibility admits this. As a corollary, guest association would be impaired. Restriction of host flexibility to avoid internal anihilation of anchor functions is part of the preorganization requirement and pays off in enhanced guest affinity.

In many cases, better preorganization means increased expenditure for host preparations. But even rather mobile and readily synthezable hosts may satisfy these intentions. For instance, the flexible tentacle derivative of the polyamine tren **140** (Chart 23) binds chloride, perchlorate, or dihydrogen phosphate in acetonitrile, the latter with the impressive $K_{assn} = 1.4 \times 10^4$ M^{-1}.[449] Adapting the same basic idea, Morán et al. prepared the cyclohexane triscarboxamide **141**, which was found to complex phenyl phosphate dianion with the exceptional $K_{assn} = 1.5$

Chart 23



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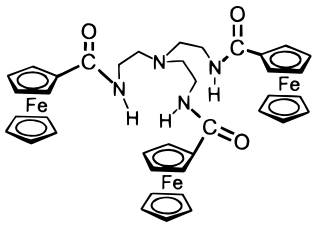
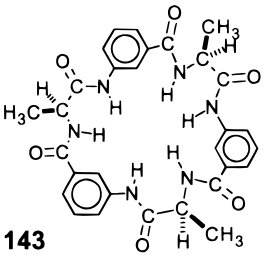


142



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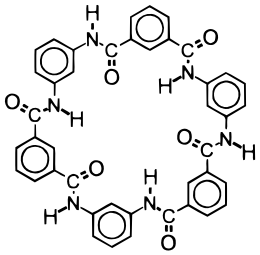

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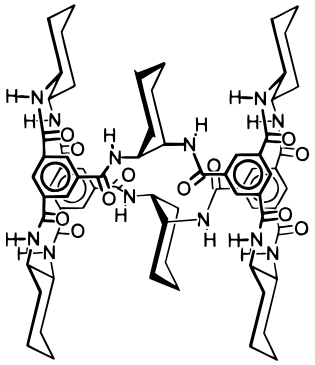


145

$\times 10^4$ M^{-1} in DMSO.[450] The parent chromanon anchor group underwent dimerization in chloroform thus corrupting association of weakly binding guests.[451]

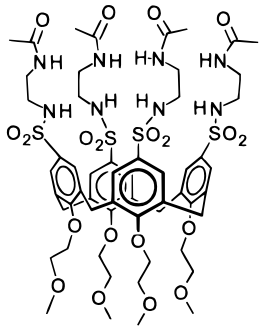
In the same vein but with an electrochemical detection technique, preferential binding of $H_2PO_4^-$ to the ferrocene derivative **142** was observed.[452] Although very plausible host−guest structures can easily be envisaged, and as was true in the former case, too, it appears rather risky to assume just one preferred complex structure to be formed with these highly flexible molecules.

Guided by analogy to the natural receptors one may utilize peptide bond dipoles for anion complexation. Ishida et al. synthesized the cyclic peptide **143**, composed of dipeptide building blocks containing *m*-aminobenzoic acid as a rigid, structure-enforcing element that insures an organized array of H-bond-donating functions to converge to the center of the macrocycle.[453] The UV spectroscopic analysis in DMSO showed *p*-nitrophenyl phosphate to bind with the exceptional $K_{assn} = 1.2 \times 10^6$ M^{-1} adhering to strict 1:1 host−guest stoichiometry. The cyclohexapeptide turned out to be the most potent host, while analogues of larger or smaller ring size were distinctly inferior. Variation of the amino acid side chain revealed its minor importance. Host−guest equilibration occured rapidly on the ^1H NMR time scale affecting all of the amide NH resonances, so that the time-averaged symmetry of the host is not disturbed but does not reveal the true complex structure.

This relates to the involvement of anion−carboxamide complexes in the manufacture of high-strength aramide fibers.[454] Evidence from X-ray crystal structures of aromatic cycloamides complexing $CaCl_3^-$ supports the contention that the increased solubility of amide polymers in amide solvents, which is vital to the polymerization process of aromatic dicarboxylic chlorides with aromatic diamines, results at least in part from anion binding based on N−H hydrogen bonds.[454] Certain metal salts redirect the polymerization reactions, most likely due to a template effect favoring formation of a cyclohexamer **144**. These cyclopeptides may be compared to rigid polycyclic amides directly obtainable in a one-pot reaction (e.g., **145**), which can bind linear amino acid derivatives with exceptional selectivity,[455] but so far have not been tested in the complexation of anions.

Yet another approach to warrant the topological and orientational mutual relation within a set of H-bond donors calls for their attachment to preformed molecular scaffolds. Popular examples holding a well-developed reputation as metal cation complexing agents include the calixarenes that lend themselves to functionalization in predetermined positions and thus present a secure basis for a systematic study on the effects of anion anchor group variation. Connecting sulfonamide functions to the upper rim of calix[4]arene produced **146** (Chart 24) capable of distinguishing HSO_4^- from chloride or nitrate.[456] Discrimination against $H_2PO_4^-$ would be highly desirable but could not be reliably determined though preference for hydrogen sulfate was likely. Surprisingly, joining tethered urea or thiourea moieties to calix[4]arene[457] or its higher congener calix[6]arene[458] giving **147** and **148**, respectively, did not yield the expected phosphate hosts. Instead, both compounds qualified in binding chloride with moderate affinity in chloroform, but **148** also showed strong and regioselective binding of the centrosymmetrical 1,3,5-benzenetricarboxylate ($K_{assn} = 2 \times 10^5$ M^{-1} in $CDCl_3$) while the isomeric 1,2,4- and 1,2,3-substituted congeners were bound 10−100fold weaker, suggesting topological complementarity to be a major factor in host−guest binding. When the urea functions were replaced by another calixarene linked to the first by ordinary amide connections (**149**), binding of oxoanions was greatly diminished.[460] Only fluoride was complexed with decent affinity in the noncompetitive solvent dichloromethane ($K_{assn} = 1330$ M^{-1}), suggesting that oxoanions may be too large to enter into the cavity and experience optimal binding interactions. The enhanced hydrogen bonding power of the urea function was also used in open-chain compounds of very flexible (**150**)[460] and rather rigid spacer units (**151**).[461] In either case, strong binding of oxoanions in DMSO was noted. With **150** binding

Chart 24



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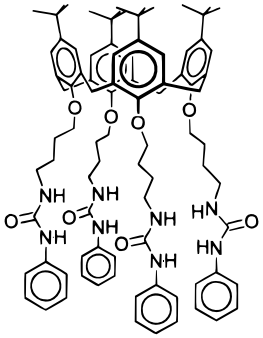

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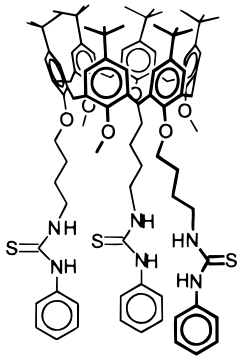

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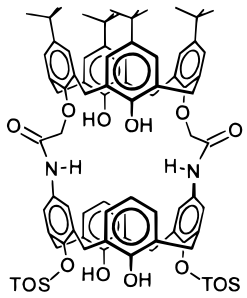

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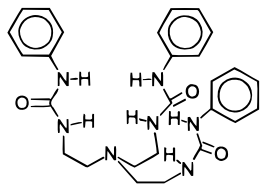

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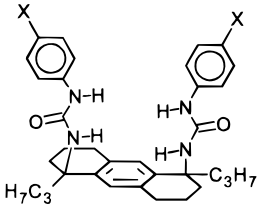
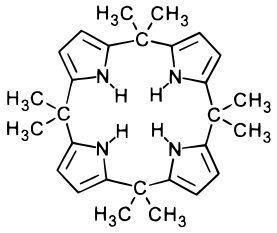


151

tert-phosphate in DMSO, slow equilibration was observed which is a quite unusual feature in these flexible hosts and may point to polymeric structures. Switching to methanol relieved the retardation in guest exchange, although the affinity remained unaltered ($K_{assn} = 1 \times 10^4$ M^{-1}).[461] An interesting dependency of adipate binding to **151** was reported on variation of the *p*-substituent X. Permutating its electronic properties from strong attraction to donation shifted the binding constants by a factor of 40.[461] Obviously, the hydrogen bond donicity of the urea very profoundly affects the overall guest binding.

The calixarene **152** is a well-known compound for over a century and easily obtainable in a one-step condensation from acetone and pyrrole (Chart 25).[462] Now it has been characterized as an electroneutral anion host capable of binding fluoride in dichloromethane ($K_{assn} = 1.7\times10^4$ M^{-1}) with strong preference over chloride ($K_{assn} = 350$ M^{-1}) or dihydrogen phosphate ($K_{assn} = 97$ M^{-1}).[463] X-ray crystal structures gave clear evidence that the 1,3-alternate conformation of the free macrocycle is switched to a

Chart 25



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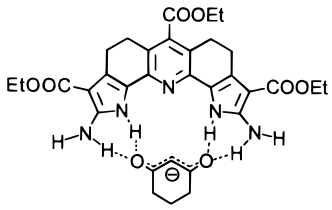

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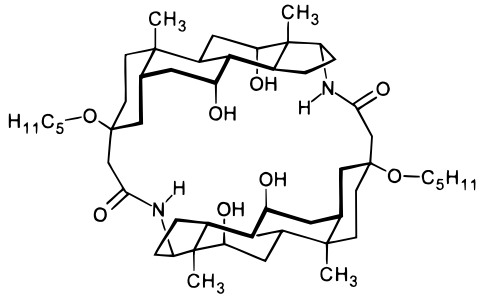


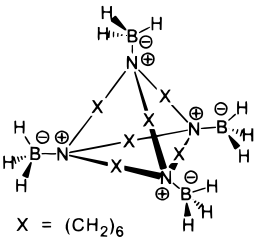
154

cone structure on guest binding enabling cooperative hydrogen bonding of all pyrrole NH groups to the anionic guest. In spite of its small size, even fluoride occupied a perching position above the main plane of the nitrogen atoms. One may expect, thus, that enlarging the macrocycle to the corresponding five- or six-membered calixarene allows encircling the guest in one plane and consequently should boost complex stability.

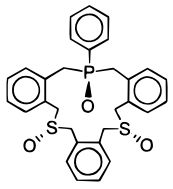
Making use of anion complexation to direct the reactivity was attempted in the construction of a flat, yet concave host shown as a complex with cyclohexanedione enolate anion in **153**.[464,465] As sketched in this drawing and suggested by the related X-ray crystal structure of the picrate complex, the guest anion is bound in the bay region of the neutral receptor by the joint action of four amide-like hydrogen bonds. Binding the enolate anion with preference to the conjugate acid lowered its pK_a in this case by about 1 unit in acetonitrile. This sufficed to demonstrate proton abstraction from cyclohexanedione by pentamethylpiperidine, which is too weak of a base to ionize the substrate in the absence of the host. The effects were weaker than expected by the authors but clearly open the perspective to elaborate this approach into a route with promising utility in organic reaction steering.

Another well preorganized electroneutral hydrogen-bonding receptor was described by Davis recently.[466] The steroid-based macrocycle **154** was designed to donate up to six hydrogen bonds in convergent fashion to a guest anion located near the center of the host structure. The inspection of molecular dimensions, however, suggests that true encapsulation into the ovoid cavity (330 × 220 pm) of even the smallest anion fluoride (the generally accepted diameter of fluoride is around 280 pm) is not likely to happen and only one NH group may be engaged in guest binding at any given time. As expected, the host affinity increased in chloroform the smaller and more basic the halide anion becomes (K_{assn}(F^-, Cl^-,

Chart 26



155



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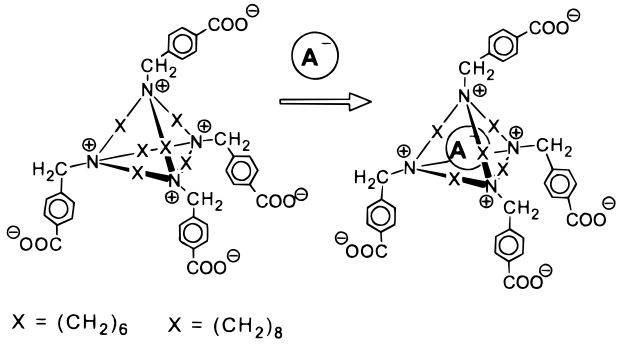
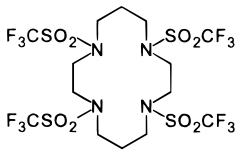


157 **158**



159

Br⁻) = 3220, 990, and 250 M^{-1}, respectively). Preorganization of the H-bond donor sites in a macrocycle proved essential for high-affinity complexation, since an open-chain analog showed much diminished binding. The sensitivity of this binding principle to competition from hydrogen-bonding solvents was apparent though in a LSI-MS experiment using a nitrobenzyl alcohol matrix. Only the bromide complex of **154** could be detected in a mixture containing fluoride and bromide in equal amounts.

In a first approximation, hydrogen bonding is sensitive to the accumulation of negative charge density, for instance, to lone electron pairs in the anionic guest. A fundamentally different means in sensing negative charge employs bond dipoles of heavier, non-hydrogen elements. In order to make use of this interaction principle that in general relies on smaller dipole moments than present in most H-bond donors, the precise preorganization of the host is mandatory. The conceptual idea requires strict orienting of strong but chemically reasonably stable dipolar bonds with their positive ends toward the binding center. Schmidtchen first elaborated this concept building on a macrotricyclic tertiary amine of high connectivity and corresponding rigidity.[467] On reaction with borane/THF, the tetraadduct **155** is produced containing all four borane−amine dative bonds in fixed orientation with their positive ends securely pointing toward the center of the cavity as confirmed by an X-ray structure (Chart 26). This configuration proved profitable since a large number of inorganic anions were successfully complexed by the borane−amine adduct **155** in chloroform solution giving clear evidence for discrimination according to size. In combination with the result obtained by electrospray mass spectroscopy that strict 1:1 stoichiometry was followed in the series of halide complexes, one must conclude that this electroneutral host acted by true guest encapsulation. Similar anion−dipole interactions formed the basis of guest binding by macrocycle **156**.[468] The sulfur and phosphorous oxide dipoles point to the same face owing to the peculiar stereochemistry of the sulfur centers and thus present a parallel alignment.[469] The oposite hemisphere over the macrocycle then exposes a surface of high positive potential open to anion association. While no binding of fluoride, the anion of highest charge density, was detected, **156** readily formed complexes with the other halide anions in chloroform (K_{assn} = 40−60 M^{-1}). The anion-binding event was transmitted to the other face of the macrocycle presenting on an array of oxide functions. These are known to be excellent, but only weakly basic hydrogen-bond acceptors.[470,471] The observation of binding of a primary ammonium cation to **156** thus was no surprise. The diminution of ammonium binding accompanying anion association, however, is less readily explained.[469]

Electroneutral hosts can also arise from the compensation of equivalent numbers of full positive and negative charges. This is the case realized in natural protein receptors which typically contain a considerable number of ionized groups. Their summation regularly gives a net charge near zero (depending on the pH value). The trick played by proteins to arrive at anion-binding structures is to create areas or even cavities in the macromolecular structure that are lined by positively charged residues with none or at most only a few anionic functions present and ready for charge compensation by ion pairing. Of course, the summation to net charge zero requires the existance of domains with excess negative charge, but the differently charged substructures are segregated in the polymeric framework and internal collapse is avoided. Adaptation of this principle for abiotic receptors calls for the creation of zwitterionic structures with distinct positive and negative domains that are held apart and refrained from contact. Following this idea, the zwitterionic compound **157** was designed and prepared by alkylation of the macrotricyclic tertiary amine also being the parent compound in the borane adduct **155**.[472] As expected, **157** showed extraordinary solubility in water indicating undisturbed solvation of the ionic groups testifying indirectly that intramolecular ion pairing is negligable. ^{1}H and ^{35}Cl NMR titration data revealed the formation of stable complexes with the halides and with cyanide (K_{assn} = 300−6 × 10^3 M^{-1}) in water. From the temperature dependence of K_{assn}, the Gibbs enthalpy was split into its component parts. The van't Hoff plots characterized bromide and iodide binding as enthalpically driven processes (ΔH negative) counterbalanced to some extent by a negative entropy contribution. This result is expected in an inclusion process by which the guest strips off at least part its solvent shell in order to enter the host cavity. A novel concept for anion binding inspired by the need to increase ion conductivities in lithium batter-

ies was introduced by Lee et al.[473] A number of open-chain or cyclic trifluorosulfonamides (e.g., **159**) were reported to complex chloride in THF by ion−dipole binding, thus separating the lithium chloride ion pair and leading to 100-fold higher ion conductivities. So far, however, the evidence for the anion complexation capabilities of the nicely simple compounds rests on ambiguous EXAFS studies and requires further fortification by more direct methods.

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CR9603845