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Coordination Chemistry Reviews 250 (2006) 3004–3037
COORDINATION CHEMISTRY REVIEWS
www.elsevier.com/locate/ccr

Review

Receptors for tetrahedral oxyanions

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Received 15 January 2006; accepted 12 April 2006
Available online 25 April 2006

Contents

Abstract

This review covers the field of anion recognition from the perspective of tetrahedral oxyanion recognition. The bulk of the attention is devoted to metal-free systems that are able to effect the recognition, binding or transport of phosphate and sulfate. Particular emphasis is devoted to design criteria that allow for discrimination and selectivity. In this context, a variety of recognition motifs are discussed and, within each receptor class, general paradigms that allow for the construction of receptor systems with high affinity and specificity are noted.

Keywords: Tetrahedral oxyanions; Anion recognition; Artificial receptors

1. Introduction

The selective binding, extraction and separation of anions are frequently invoked as potential solutions to a number of fundamental problems of current interest. Tetrahedral oxyanions are of particular relevance in this regard. Such species are prominent as radioactive contaminants (e.g., pertechnetate), toxic or otherwise troublesome species (e.g., sulfate, chromate, arsenate and phosphate, to name a few) or matrix elements that can interfere with proposed waste treatment processes (e.g., sulfate in the US Department of Energy (DOE) complex). The increasing amounts of phosphates in rivers coming from factories and fertilizers, while perhaps attracting less attention

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doi:10.1016/j.ccr.2006.04.013

than those associated with radioactive waste remediation and storage, also present a problem. These species are leading to the eutrophication of waterways and the production of toxic algal blooms. This makes the problem of detecting and removing phosphates from aqueous solutions of interest. Likewise, the problem of detecting and removing pertechnetate anion from aqueous media is one of challenge and urgency. Pertechnetate anion is the most common form for the long-lived isotope ^{99}Tc ($t_{1/2}$ 2.13×10^5 years) formed from ^{235}U or ^{239}Pu (the yield is 0.6 kg from 1 kg of ^{235}U under conditions of 50% conversion). Unfortunately, this anion possesses good mobility and is appreciated for its ability to migrate readily within the superficial layers of the earth's crust, making pertechnetate anion one of the most dangerous radioactive pollutants known.

Our review will focus on receptors that display a preferential affinity for tetrahedral oxyanions or were made to effect their detection or extraction. Some mention is also made of charged, metal-free receptors possessing affinity for these anions that work as catalysts. The bulk of the attention will be on systems that serve to illustrate viable *design strategies*, as well as on *structure–selectivity relationships*, with the general goal of summarizing in a single review the various determinants that impart high selectivity for tetrahedral anions. Since phosphate anions play a dominant role in biology, it is not surprising that many of the investigators working in this area have concentrated on the binding, transport, extraction and to a lesser extent, reactivity of inorganic and organic phosphates. However, work on such species necessarily touches on the broader problem of tetrahedral oxyanion recognition, and anion binding in the broadest sense of the word.

Recently, a number of reviews have appeared that have focused not just on polyammonium receptors, which are generally considered to be the first well-defined anion receptor motifs [1–3], but also on a number of other recognition subunits. Included among these are amides [4], guanidiniums [5], steroids [6], pyrroles [7,8] and metal-based systems [9]. Other reviews have touched on the general problem of anion-binding chemistry [10–14], and one of the authors (J.L.S.) has recently contributed to a monograph on the subject [15]. In this review, the topic is viewed exclusively through the lens of tetrahedral anion recognition, as noted above. However, as common for reviews of this type, the receptor systems themselves are classified according to the nature of the binding subunit, namely ammonium, pyrrole, guanidinium, amide, amido-amine and mixed (i.e., heterotopic receptors).

2. Anion properties and binding motifs

When building an artificial receptor for tetrahedral anions, as with the design of any supramolecular host system, consideration should be given to the specifics of the targeted anion. In such a context, a primary characteristic of tetrahedral anions is their size and shape. As can be seen from an inspection of Table 1, the smallest common tetrahedral anion is sulfate. This same table also serves to highlight the fact that the difference between sulfate and phosphate is not large. However, in those systems where an effort has been made to discriminate between these two species, it has been found that a slightly larger geometry is needed (e.g., two more carbon atoms in the spacer group between binding motifs) to change the selectivity of the receptor from sulfate to phosphate. Another prototypic anion, pertechnetate (and its homologue perrhenate), is characterized by its ability to undergo a change in geometry, specifically from tetrahedral to hexagonal, in the presence of donor ligands (e.g., acetonitrile, triphenylphosphine) [16,17]. Although not exploited effectively to date, this feature provides a potential "handle" that could be exploited to achieve selective recognition.

A characteristic of some tetrahedral anions that has been used to effect in terms of achieving binding selectivity, is their propensity to undergo protonation. This feature is particularly germane to the design of receptors for phosphates and to a lesser extent those for sulfate. This is because these anions can exist multiple charged states in aqueous media, with the dominant species being a strict function of pH. Since, protonation changes the electron density present on the oxygen atoms and since these atoms are key to the anion receptor recognition process as will become clear in the course of this review, such changes in charge can have a significant effect on both the binding affinity and binding specificity. As can be seen from an inspection of Table 1, which summarizes the pK_a's of these and the conjugate acids of these and other tetrahedral anions, at neutral pH, phosphate-type anions generally exist in two protonated states (mono- and dianionic), whereas sulfate anion is dianionic. This difference can provide a basis for differentiating between phosphates and sulfates and is surely a factor underlying the selectivities seen in biological systems. However, the fact that phosphate anions exist in two dominant forms at neutral pH also adds a level of complexity to the problem of receptor design. One must design systems that favor the binding of one or other protonated forms or, ideally, both. This can prove challenging. Fortunately, such complexities do not plague all tetrahedral anions. For instance, the perchlorate, perrhenate and pertechnetate ions are all mono-anionic over a wide pH range. They can thus

Table 1
Properties of selected tetrahedral anions

Anion	Cl^-	NO_3^-	SO_4^{2-}	PO_4^{3-}	ClO_4^-	ReO_4^-	TcO_4^-
Volume (Å^3) [19]	24.8	24.0	51	56.5	57.9	73.6	73.6
r(X–O) (Å) from X-ray data		1.27	1.45	1.52	1.43	1.65	1.67
pK_a (conjugate acid)	−7	−1.64	−3; 1.9	2.12; 7.20; 10.9	−7	−5.7	−3.8 [20]

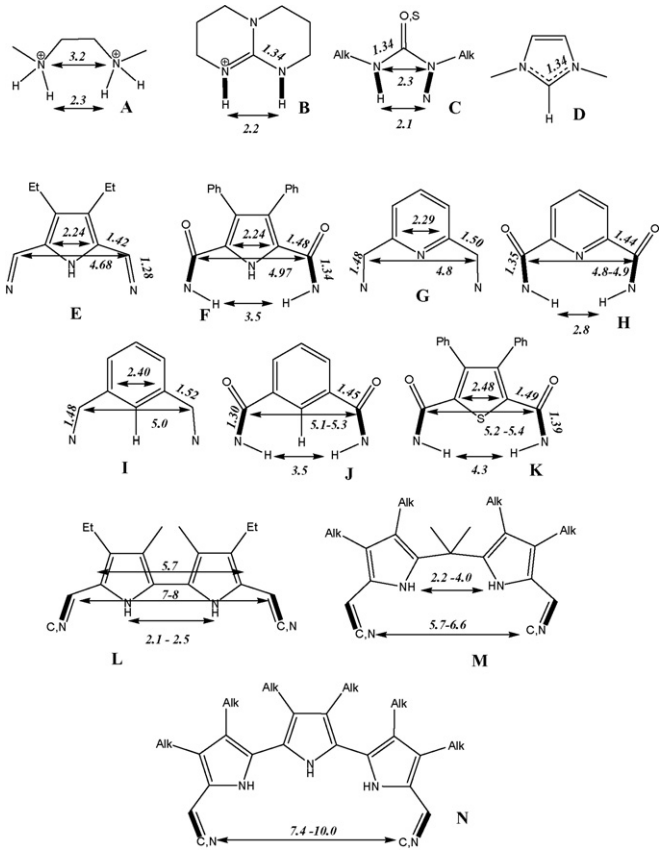


Fig. 1. Some binding motifs and their key geometric features (distances in Å). The values were deduced from X-ray diffraction analyses of receptors produced in the authors' laboratories or described in various review articles [7,8,10–13]. The indicated H–H separations were derived from structures of the free ligands (i.e., not bound to an anion).

generally be used and studied in their dominant monoanionic forms.

Yet another defining feature of anions is their hydrophobicity (or hydrophilicity). According to the Hofmeister series [18], the hydrophobicity of important tetrahedral anions increases according to the progression: phosphate > sulfate > perrhenate ≫ perchlorate and pertechnetate [110]. While other factors are also important, to a first approximation the hydrophobicity of a given anion is a strict function of the (negative) charge on the oxygen atom(s), with a lower charge (or charge density) leading to greater hydrophobicity.

For receptors that do not rely on isotropic binding forces, such as electrostatic interactions, the geometry and direction of the individual recognition elements (e.g., hydrogen bond donors) is critical. Optimizing these factors is required if the best binding is to be achieved between a proposed artificial receptor and its targeted anion. While this process is far from complete in a global sense, a considerable body of data exists. Some of it is summarized in Fig. 1, which shows several well-known binding motifs and the corresponding geometric parameters for anion complexation, as inferred from X-ray diffraction data. The building blocks shown in this figure include polyamines, urea, diamido pyridine, diamino pyridine, benzene, pyrrole, guanidinium, their thio analogues, and various derivatives. Needless to say, the hydrogen bond donors in these motifs differ in their acidity, flexibility and directionality. Therefore, it is not surprising that certain binding motifs display an inherent affinity for a particular set of anions.

Within the cadre of this general consideration, a detailed analysis of the X-ray data allows the following conclusions to be drawn:

(1) With the exception of pyrrole **E**, most of the binding motifs are capable of forming two hydrogen bonds with bound anions. The guanidinium and urea motifs provide NH groups oriented so as to stabilize hydrogen bonds that are almost parallel to one another, with the distance between them being a short 2.1 Å. However, in the case of the urea motif, the NH-derived hydrogen bonds are expected to be slightly bent relative to each other, as is shown by bold lines in Fig. 1. The bipyrrole and dipyrromethane motifs also provide two NH hydrogen bond donor sites. However, these elements contain more carbon atoms between the individual NH subunits and span an H–H distance of between 2.1 and 2.5 Å (structures **L** and **M**).

(2) The distance between the 2 and 5, or 2 and 6 carbon atoms in various bridging aromatic spacer elements vary; this allows the width of the cavity of congeneric systems to be adjusted according to the sequence: pyrrole < pyridine < benzene < thiophene.

(3) The direction of C–C and C–N bonds in diamido functionalized systems (shown in bold in the figure) serves to define the nature of the cavity that each individual binding motif can form when combined with other structure-defining elements. In the case of the 2,6-diamidopyridine motif, for instance, the C–N bonds can orient in such a way that receptors with small inner cavities may be established. The requisite inward pointing conformation is generally stabilized by hydrogen bond interactions involving the amido hydrogen atoms and the pyridine nitrogen center; such conformations lead to structures that are generally more rigid than those based on diamidobenzene. In the corresponding 1,3-diamidobenzene systems outward pointing C–N bonds were observed in a range of X-ray structures, as shown in **J**. Such outward pointing orientations have also been seen in a range of diamide systems containing five-member heterocycles. The net result is that in 2,6-diamidopyridine systems the NH hydrogen bond donors can point in towards each other, whereas in most other systems they do not.

(4) Various polypyrrole building blocks (e.g., dipyrromethane, bipyrrole and terpyrrole) are not equal in terms of the kinds or receptor systems they permit. For instance, although the NH "bite angle" of the dipyrromethane fragment is wider than that of bipyrrole, it can nonetheless stabilize receptors with smaller cavities due to its greater inherent flexibility. The bipyrrole element is more rigid and, as a consequence, the distance between the carbon atoms shown in Fig. 1 is greater in receptors containing this fragment than in the case of those containing dipyrromethane subunits.

3. Pure ammonium based anion receptors

Although there are earlier antecedents in the literature [15], the birth of "anion recognition chemistry" is generally traced to the seminal report of Park and Simmons, wherein simple bicyclic diazakatapinantds were shown to encapsulate halide anions [21]. The spectacular work of Lehn and Kimura in developing polyammonium anion receptors served to stimulate research in the area and, indeed, was the catalyst for what remains a rapidly growing field. Specific motivation for early work with polyammonium receptors came from the recognition that naturally occurring compounds, such as putrescine (**1**), spermidine (**2**) and spermine (**3**), play a critical role in biological anion recognition; such species are involved in the transcription and translation of genetic information, protein synthesis and serve to influence organism growth and development (e.g., cell division, differentiation, embryogenensis, etc.). They have also been proposed as possible photoprotectants for oligonucleotides [22,23], and are well recognized for their ability to bind strongly to phosphate anions and nucleotides [24].

The amino group has a dual nature; it can be protonated and thus serve as a hydrogen bond donor and electrostatic attractive element. However, it can also serve as a hydrogen bond acceptor, which is especially useful for the binding of protonated anions, such as phosphates and sulfates. Not surprisingly, both features have been explored by researchers in the context of efforts to produce synthetic receptors capable of binding selectively to inorganic and biologically important phosphate-type anions. In addition, transport through membranes, modeling of enzymes, such as ATPases [25] and N^{10}-formyltetrahydrofolate synthetase, have been key goals of workers active in this area [26,27].

Representative ammonium-based receptors that bind phosphates and nucleotides, such as ATP, ADP and AMP, are shown in Fig. 2. In this scheme, the receptors (neutral forms) are divided into three classes: naturally occurring polyamines, first generation polyamines and second generation polyamines, that incorporate aromatic rings or which have pre-defined three-dimensional structures.

In aqueous media, the binding event usually involves the protonated form of the receptors operating at or around neutral pH. Subject to this general caveat, there is a remarkable property observed for most macrocyclic receptors containing ethylenediamine bridges; here, up to four protons are generally bound in the pH range 6–10, whereas a fifth proton is bound only at pH values less than 4. For example, in the case of ligands **7**, **10** and **11** the log K_a of the fourth protonation constants are 7.64, 7.09 and 6.98, respectively. By contrast, the corresponding fifth protonation constants (log K_a) are 3.81, 4.79 and 4.11 [28]. Defying this trend, receptors containing propylenediamine bridge display gradually decreasing protonations constants. For example, in 2,6,10,13,17,21-hexaaza[22]metacyclophane [29] the log K_a of the first and sixth protonation constants are 10.78 and 5.24, respectively. Independent of such subtleties, to a first approximation polyamine-containing receptors can be considered as polycations, which can bind anionic species via a combination of three main controlling interactions, namely hydrogen bonding between the receptor and anionic substrate, coulombic attraction and the extent of the geometrical "fit" between the guest molecule and the receptor. Not surprisingly, the coulombic effect is particularly significant; thus, as a general rule, the greater the degree of protonation (on the receptor) the stronger the binding for any given anionic guest [30,31].

Aware that the natural polyamines involved in (oligo)phosphate binding contain nitrogen atoms that are separated by three or four methylene groups and hence function effectively at or around neutral pH, Lehn and co-workers [32,33] suggested that receptors containing either (1) 1,3-propylenediamonium subunits or (2) ethylenediamine units isolated by longer intervening chains would represent effective phosphate binding systems. Presumably, they would provide a nice compromise between the strong binding displayed by ethylenediamine polyammonium salts at acidic pH and the lower efficiency generally displayed by pH-insensitive polyguanidinium salts.

Most of the synthetic receptors designed to favor phosphate binding were tested by measuring their ability to bind prototypic substrates of interest, including inorganic phosphates and various biologically important phosphates, such as AMP, ADP and ATP. Some publications detail the results of more extensive screening involving a range of different phosphate-type substrates. Others detail the ability of the receptor in question to function as a catalyst for ATP hydrolysis.

For most polyammonium receptors, the general binding trend for inorganic phosphates (as determined from potentiometric measurements) is $HPO_4^{2-} \ll P_2O_7^{4-} < P_3O_{10}^{5-}$. This selectivity is highlighted by a comparison of the affinity constants in question. For example, in the case of the pentaprotonated receptors **7** and **10** log K_a(diphosphate)/log K_a(monophosphate) = 6.95 (i.e., 9.35–2.64) and 7.07 (9.94–2.87), respectively, while log K_a(triphosphate)/log K_a(diphosphate) = 0.91 (10.85–9.94) for **10** [28,34,35].

Most of the polyammonium receptors shown in Fig. 2 bind sulfate dianion, as well as oxalate, malonate and other organic anions with association constants that are very similar to those seen in the case of monophosphate anion. In other words, the monophosphate/other oxyanion selectivity ratio is very low. For instance, in the case of the pentaprotonated ligand **10** log $K_a(SO_4^{2-})$/log $K_a(HPO_4^{2-}) = 0.66$ (i.e., 3.53–2.87) [36]. On the other hand, these kinds of polyammonium receptors were found to bind chloride, nitrate and other monoanions very weakly, log $K_a < 2$.

In the case of ligand **6**, both nitrate and chloride anion were found to form complexes with H_4L^{4+} (e.g., $[H_4L{\cdot}NO_3]^{3+}$), as inferred from conductometry and pH potentiometry studies [37]. Adding dimensionality to the ligand and increasing the number of possible hydrogen bonding donors provided receptor **12**, which was found to bind nitrate anions even more strongly [36]. Unfortunately, the sulfate:nitrate selectivity was found to be lower than in the case of ligand **10**.

Another structural modification made in an attempt to produce more efficient receptors involved alkylation of the amino groups. Such alkylation, which modifies the basicity of the nitrogen atoms and the preferred receptor conformation, serves to

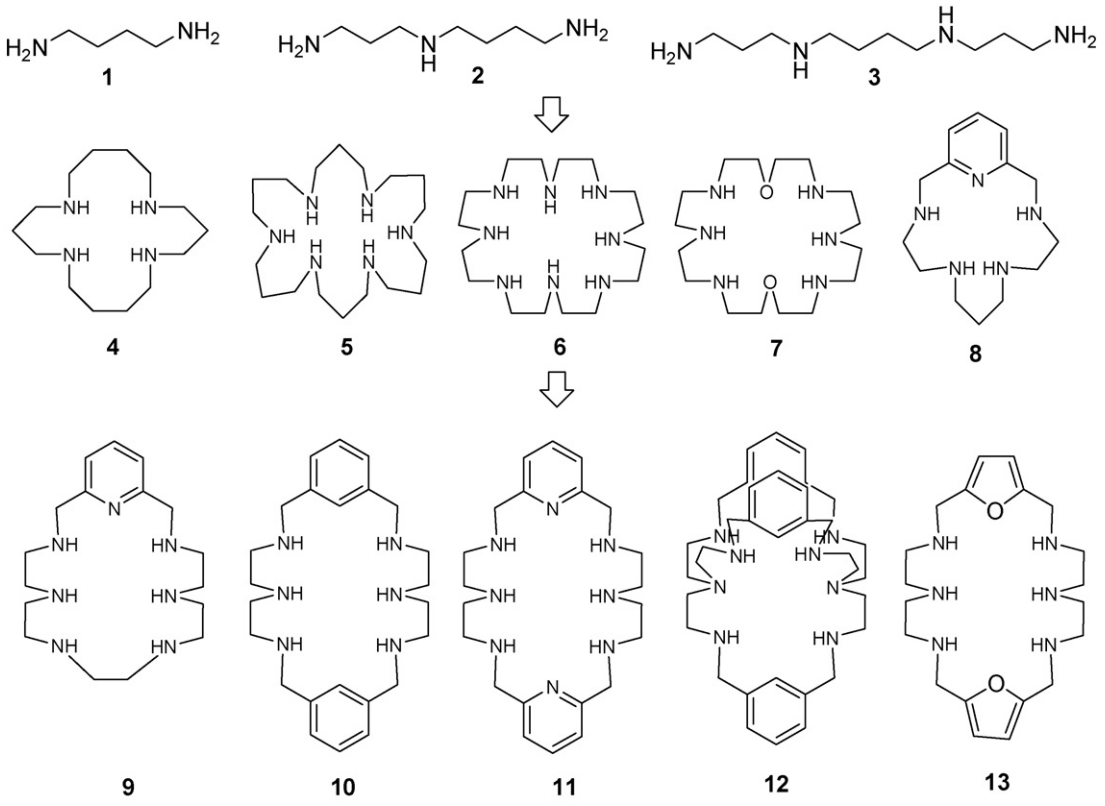


Fig. 2. Hierarchy of structure modifications associated with various synthetic polyammonium-type phosphate binding receptors. For the sake of clarity, these systems are shown in their respective neutral forms.

increase the anion-binding selectivity, albeit not appreciably [38,31].

Fig. 3 shows the crystal structure of the protonated furan analogue **13** bound to a pyrophosphate anion. As can be seen from an inspection of this figure, each macrocycle coordinates the bound anion via a net-like arrangement of hydrogen bonds. Hydrogen bonding interactions involving pyrophosphate anions above and below the macrocycle are also observed.

The copper complexes of polyammonium receptors **7** and **10** were shown to bind inorganic phosphate much more strongly than the corresponding free ligands [28]. These mono copper complexes are stable even when the receptors are in their respective triply protonated states and were found to function as very effective anion receptors in this form. Further protonation leads to a decrease in the binding constants, perhaps as the result of demetalation. In the case of the triply protonated complex $Cu^{2+}\cdot(\mathbf{10})\cdot\mathbf{3H}^{+}$, the effective log K_a's for orthophosphate, pyrophosphate and triphosphate were found to be 12.10, 10.68 and 11.28, respectively. The corresponding bis-copper complexes were also prepared. These complexes were found to bind phosphate anions effectively when not protonated. However, essentially no selectivity was observed between orthophosphate, pyrophosphate and triphosphate.

For the receptors where data is available for both sulfate and phosphate anions, it is possible to analyze the selectivity by calculating the percentage of each anion bound to the ligand as a function of pH in solutions containing equimolar concentrations of sulfate, phosphate and receptor. Using this approach, an inter-

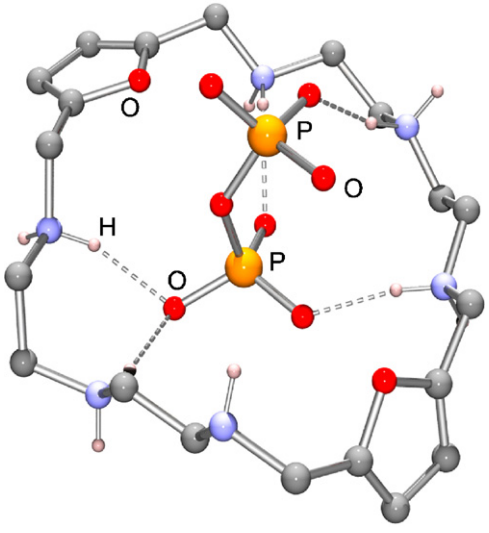


Fig. 3. Geometry of pyrophosphate anion complex of the protonated furan receptor **13**, as inferred from an X-ray diffraction analysis [39]. Most of the hydrogen atoms, as well as water and solvent molecules have been omitted for clarity. In this and other figures, the X-ray data, taken from the cited reference or the CCDC, is ORTEP, POV-ray rendered, with the non-hydrogen atoms presented as spheres. Unless otherwise indicated, the atom codes are as follows: carbon, grey; nitrogen, blue; oxygen, red; phosphorus; orange; sulfur, yellow; halides, green; and hydrogen in pink (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

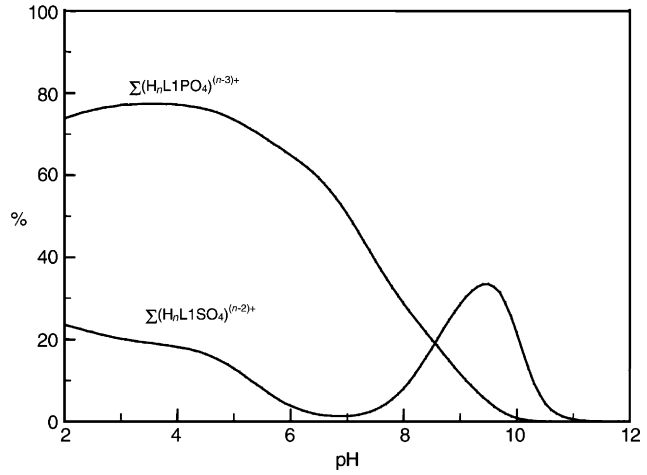


Fig. 4. Total sulfate and total phosphate (as overall percentage) bound, respectively, to the protonated forms of **6**. This figure is taken from [40] and reproduced with permission; copyright 2001, by Royal Society of Chemistry.

esting selectivity pattern was found [40] for ligand **6**. As shown in Fig. 4, in alkaline solution (pH > 8.55), sulfate is selectively recognized in presence of phosphate. However, the selectivity was found to be totally reversed on lowering the pH. Hence, selective recognition of phosphate over sulfate takes place concurrent with an increase in the degree of phosphate protonation. Since this latter protonation leads to a decrease in charge on the anionic substrate, it means that anion selectivity trends are not strictly determined by electrostatic forces, but also regulated by, e.g. hydrogen bonding interactions. In particular, even though SO_4^{2-} and PO_4^{3-} have very similar structures, the former anion displays a lower tendency to undergo protonation. Thus, while both HPO_4^{2-} and $H_2PO_4^-$ are present at neutral pH, the conjugate acid of SO_4^{2-}, HSO_4^-, is formed only in very acidic media (i.e., at pH values approaching 2). As a consequence, there is a large pH range (pH > 2.5) in which sulfate, in contrast to phosphate, acts exclusively as a hydrogen bond acceptor. For this reason, complexation equilibria involving sulfate are generally much easier to interpret than those involving phosphate. Moreover, the ability of the anions to form hydrogen bonds of different types (acceptor only versus acceptor and donor in the case of sulfate and phosphate, respectively) can be used to achieve the selective recognition of phosphate over sulfate, thus mimicking the function accomplished in phosphate binding proteins [41].

Microcalorimetry studies, which allow enthalpic and entropic contributions to be defined, provided further insights into the binding of sulfate and phosphate anions to polyammonium receptors [40]. According to a simple electrostatic model, the formation of ion pairs in an ideal, structureless homogeneous solvent is expected to lead to slightly unfavorable ΔH^0 terms and largely favorable entropic contributions, reflecting desolvation of the interacting species as the result of the charge neutralization that occurs during the host–guest pairing process [42].

Experimentally, it was observed that the binding of sulfate anion to ammonium receptors is endothermic in aqueous media, and promoted by favorable entropic contributions ($T\Delta S^0 > 0$), in agreement with the electrostatic model. In contrast, the corresponding binding of phosphate anion was found to be exothermic and accompanied by a loss in entropy. In order to rationalize these observations, five possible hydrogen bonding scenarios involving amine and ammonium groups interacting with both phosphate and protonated phosphate anions were considered:

$$\text{–N–H}^+\cdots{}^-\text{O–} \quad \Delta H^0 > 0, T\Delta S^0 > 0 \tag{1}$$

$$\text{–N–H}^+\cdots\text{OH–} \quad \Delta H^0 > 0, T\Delta S^0 \approx 0 \tag{2}$$

$$\text{–N–H}\cdots{}^-\text{O–} \quad \Delta H^0 > 0, T\Delta S^0 \approx 0 \tag{3}$$

$$\text{–N–H}\cdots\text{OH–} \quad \Delta H^0 > 0, T\Delta S^0 < 0 \tag{4}$$

$$\text{–N}:\cdots\text{HO–} \quad \Delta H^0 < 0, T\Delta S^0 < 0 \tag{5}$$

Not surprisingly in light of the experimental observations, it was scenario (5), namely the formation of the –N:···HO– hydrogen bonds to the protonated form(s) of a phosphate anion, that was invoked to explain the $\Delta H^0 < 0$, and $T\Delta S^0 < 0$ values found for the interaction of many protonated phosphate anions with polyammonium receptors. In the case of sulfate anion, which is not protonated in the pH range studied (2.5–10.5), these kinds of interactions are not likely. Indeed, only hydrogen bonding of types (1) and (3) are expected in sulfate complexes. Of these two, binding mode (1) is expected to be the predominant one in acidic media, while binding mode (3) should dominate in alkaline media. Both scenarios support the experimental observation that the enthalpic contribution is less favorable in the case of sulfate than phosphate and, indeed, that the binding process is either endothermic or essentially isothermic. Stabilization of the sulfate complexes thus reflects the favorable entropic terms produced as the result of desolvation. Such a consideration leads to the conclusion that the binding of sulfate anions by polyamine receptors containing aromatic groups should be less favored than in the case of the corresponding aliphatic species. This is because the former ligands are generally less solvated in water.

As a matter of fact, the entropic terms obtained for the formation of sulfate complexes with the less charged forms of the aromatic ligands are generally more favorable than the terms obtained for analogous aliphatic receptors. This seemingly counterintuitive result can be explained by the fact that the aromatic systems are more rigid and, thus, undergo a lower degree of structural modification upon complexation. The benefit of this preorganization (relative to the corresponding aliphatic systems) becomes lost at low pH, since upon extensive protonation the aliphatic polyamines also acquire significant rigidity.

The general trend for the binding of adenine nucleotides by polyammonium receptors parallels that seen for the binding of inorganic phosphates (AMP < ADP < ATP). However, the measured stability constants for these nucleotides are usually 10–100 times higher than in the case of simple phosphates. Presumably, this reflects the presence of additional interactions between the adenine base and the macrocycles in question [44]. Most of these interactions involve hydrogen bonds. However, several investigations provide support for the notion that incorporation of aromatic rings in macrocycle structure (as in, e.g. **8**, **9**, **10** and **11**) can increase the affinity by three- to six-fold, a observation

that is consistent with the presence of π-stacking interactions involving the adenine base and the aromatic rings [29].

Often, good selectivity for one of the nucleotides AMP, ADP or ATP is observed at low pH. Generally, this selectivity is substantially reduced at neutral pH. For example, in the case of ligand **10**, the ADP to AMP selectivity is 30:1 at pH 2 but only 5:1 at pH 7. Presumably, these differences reflect electrostatic effects. Consistent with this explanation, the discrimination between ATP and ADP was not found to be as large in the case of **10** as it was for ADP and AMP. Further, it was not found to be as sensitive to pH, going from 5:1 at pH 2 to 4:1 at pH 6. In marked contrast to the free ligand system, the mono copper complex of **10** was found to display an ATP to ADP selectivity of 5:1 over the full 5.5–9 pH range. Likewise, the biscopper complex was found to display a pH independent 10:1 selectivity [28]. Good selectivities were also seen for ligands **4** and **6** at physiological pH [43], with ATP/ADP/AMP selectivity ratios of 700:5:1 and 1400:250:1 being observed for these two receptors, respectively. Interestingly, in the case of ligand **8**, which like **4** and **6** exists in its triply protonated form, LH_3^{3+}, at neutral pH, the selectivity behavior is totally reversed, with the ATP/ADP/AMP selectivity ratio being 0.53:0.66:1. Attempts to increase the selectivity via the synthesis of ditopic receptors wherein two macrocycles are tethered together by a polyethylene bridge proved unsuccessful; this modification served only to increase slightly the binding constants [44].

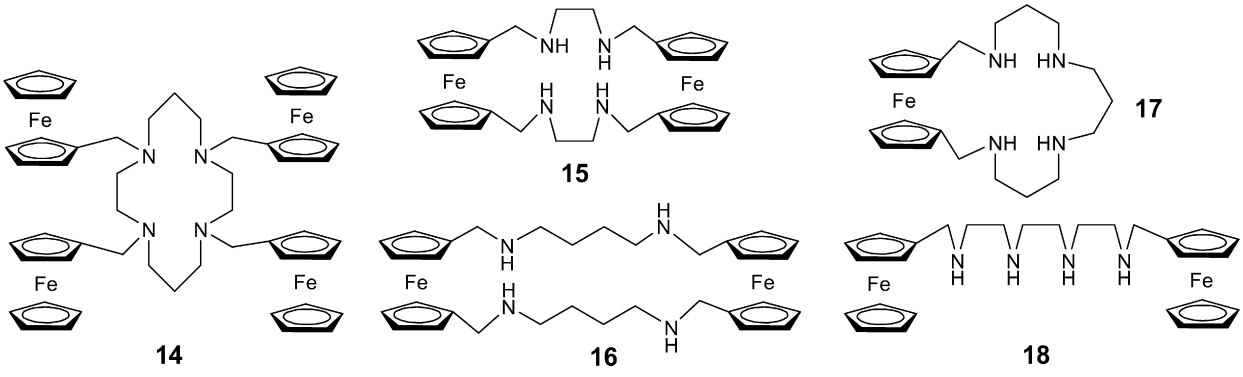
A new class of polyammonium receptors was developed by Beer et al., which can act as chemical sensors for oxyanions, particularly phosphate and sulfate, in water and in THF–water mixtures. These receptors contain redox active groups, such as ferrocene, as well as polyammonium binding sites. They have proved effective in transforming the basic host–guest interaction into a measurable signal, namely a perturbation in the redox potentional of the ligand [45,46].

Table 2
Logarithms of the stability constants corresponding to the interaction of receptors **14–18** with phosphate, sulfate and ATP in water at 25 °C, 0.1 mM tetrabutylammonium perchlorate ($TBAClO_4$) [47]

Reaction (charges omitted for clarity)	**14**	**15**	**16**	**17**	**18**
$H_4L + PO_4 \leftrightarrow H_4LPO_4$	15.55	11.01	12.65	10.36	16.24
$H_4L + SO_4 \leftrightarrow H_4LSO_4$	4.9	3.09	–	2.24	6.94
$H_4L + ATP \leftrightarrow H_4LATP$	10.37	6.98	10.73	4.81	10.80

of **15** (Figs. 5 and 6), it is found that that the sulfate species $[\mathbf{15}{\cdot}H_jSO_4]^{j-2}$ accounts for ca. 90% of the mass balance in the pH range 3–4, whereas the corresponding phosphate complexes represent the main species at neutral and basic pH. Corresponding observations were made in the case of **14** and **17**. Thus, receptors of this type are able to complex sulfate or phosphate selectively as the result of pH modulation. This reflects what was found in the case of the cyclic systems discussed above, but stands in marked contrast to what is seen in the case of most acyclic polyammonium receptors.

For these series of ligands, an electrochemical response was generally seen in the presence of sulfate and phosphate anions. Nitrate and chloride anions did not produce any significant redox potential shift at any pH value. For all of the receptors, sulfate anion produced the greatest cathodic shifts in the redox potential of the ferrocenyl group in the 3–5 pH range, whereas maximum cathodic shifts for phosphate were found at $6 < pH < 8$. Maximum redox potential shifts ($\Delta E_{1/2}$) of 54 and 50 mV were observed for sulfate and phosphate in the case of ligands **15** and **17** at pH 4 and 7, respectively (Fig. 6). Using these kinds of shifts, the authors were able to quantify the binding of sulfate and phosphate to receptors **15**, **16** and **17**. Further, the use of calibration curves of $\Delta E_{1/2}$ versus anion-ligand ratio allowed the concentration of these anions to be calculated in the presence of nitrate, chloride or acetate, at least in the range where a near-linear anion dependent response was observed. As can be seen from an inspection of diagrams (a) and (b) in Fig. 6, such a response for sulfate anion is observed at pH 4, while for phosphate it is seen at neutral pH. This means this latter species can be detected under typical environmental conditions in the presence of other oxyanions. It is important to note that the half-wave potential of the open-chain ligand **18** is also pH dependent but only for sulfate ($pH < 6$); neither, nitrate nor phosphate anions produce any significant change in the redox



pH-metric titrations of the ligands showed that the stability constants for the host–guest complexes involving phosphate are higher than those for sulfate (Table 2). These same studies revealed that ligands **14** and **18** were the best receptors [47]. The selectivity of the receptors was determined from distribution diagrams, specifically by plotting the percentage of free receptor, sulfate-ligand and phosphate-ligand complexes in ternary mixtures as a function of pH. The resulting diagrams revealed differences relative to the corresponding unsubstituted receptor systems (e.g., **6**; cf. Fig. 4). For example, in the case

potential of the appended ferrocenyl group. Such observations support the conclusion that the value of the oxidation potential does not correlate with the observed anion-binding affinities directly, and that the specifics of the molecular structure may play a significant role in determining both the anion selectivities and the observed electrochemical response.

In subsequent work, the Beer group also succeeded in developing a ruthenium bipyridyl polyaza receptor, which was shown to bind and sense phosphate and ATP anions in aqueous solution via MLCT luminescent emission quenching [48].

Anslyn and co-workers have contributed significantly to an understanding of phosphate anion binding. In particular, these researchers synthesized receptors **19** and **20**, rigid systems that were designed to maximize the enthalpy of binding [49]. They also synthesized simplified systems containing just two pyridine rings within the receptor framework and compared them and pyridine with **19** and **20**. Such comparisons were expected to allow the relative contributions of the two binding motifs present in **19** and **20**, namely hydrogen bond donors (ammonium) and hydrogen bond acceptors (pyridine), to be evaluated [50,51]. Towards this end, the authors complemented experimental determinations of binding constants (in chloroform solution) with geometric minimization studies carried out in the gas phase. On this basis, it was concluded that receptor **20**, which contains a larger binding cavity, binds phosphate anions better than the other systems included in the comparison.

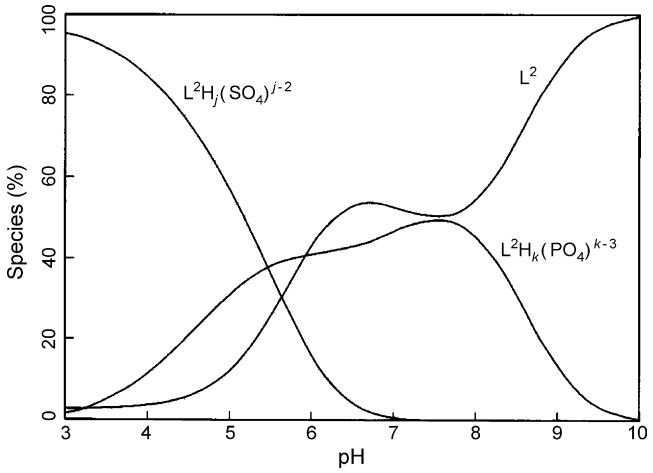
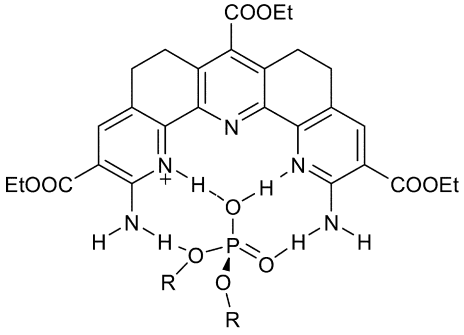


Fig. 5. Distribution diagrams for the ternary system sulfate-phosphate-**15**. The figures are taken from reference [47] and reproduced with permission; copyright 1999 by The Royal Society of Chemistry.

3.1. Hydrolysis of ATP

Lehn and co-workers showed that polyammonium macrocycles can act as supramolecular catalysts promoting the energetically favorable hydrolysis of ATP [52]. This transformation mimics the chemistry promoted by a class of enzymes termed ATPases that can enhance the rate of ATP hydrolysis by 10^{10}-



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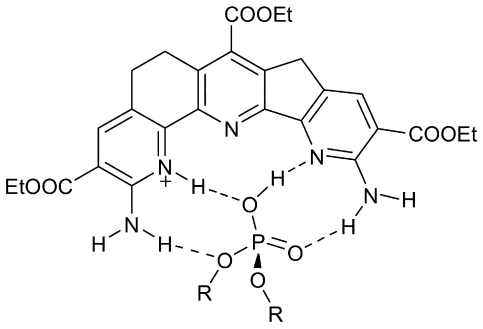

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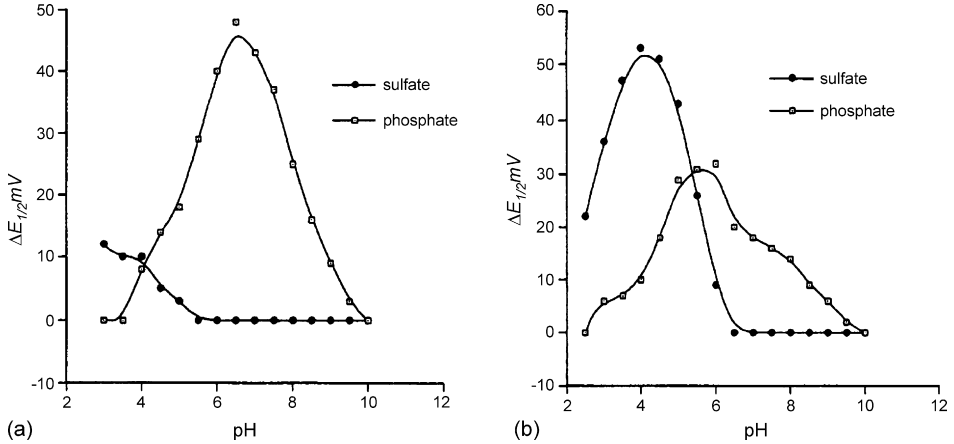


Fig. 6. Redox potential shifts seen for receptors **17** (a) and **15** (b) in the presence of phosphate and sulfate as a function of pH. The figures are taken from reference [47] and reproduced with permission; copyright 1999 by The Royal Society of Chemistry.

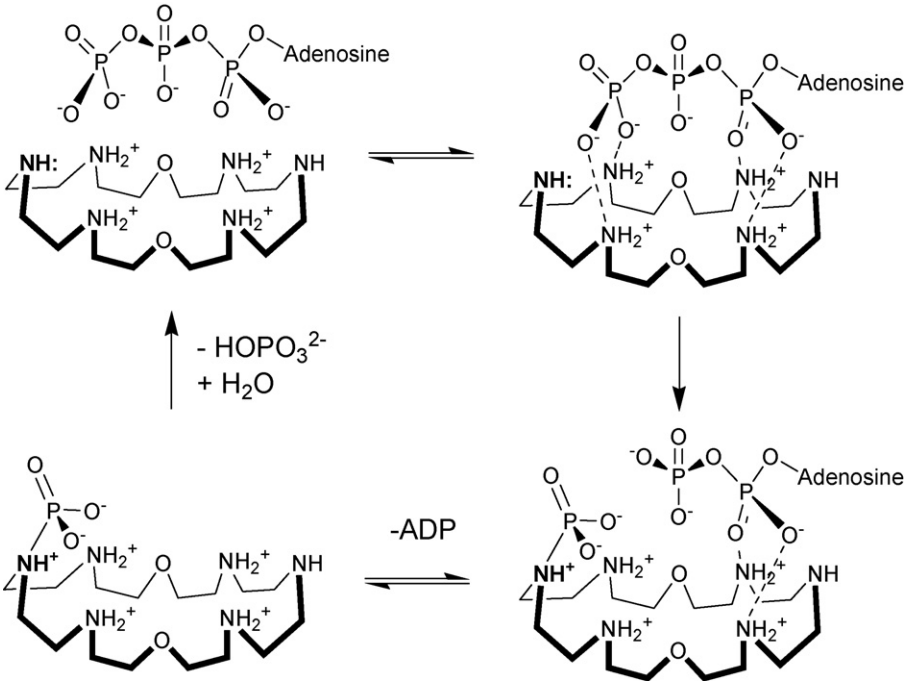
fold. This tremendous rate enhancement provides a challenge to researchers, namely how to construct a synthetic receptor that can bind and activate ATP (or other similar substrates) such that phosphate ester hydrolysis is enhanced. Part of the problem is to find systems that do not interact well with the product of catalysis. It is also important to make sure the initial substrate is bound in such a way that hydrolysis is favored.

Prior to the work of Lehn and Mertes a number of polyammonium macrocycles were known that were found to form complexes that increase in stability as the number of hydrogen bond donor sites increase, presumably reflecting an increase in the number of coulombic interactions as discussed earlier in this review. However, if these coulombic interactions constituted the only factor leading to nucleotide binding, then stable (i.e., inert) complexes would be formed. Fortunately, it was appreciated that hydrogen bonding interactions also contribute to binding and that such interactions can serve to increase the reactivity of the phosphorus center towards nucleophilic attack. Such nucleophilic reagents are present in solution, the most common being solvent water molecules. Also, at all but the lowest pH values there will be some percentage of the amino groups which are not protonated and which can therefore act as nucleophiles. Thus, even though naturally occurring polyamines bind nucleotides but do not catalyze ATP hydrolysis, it was thought that protonated polyammonium macrocycles might act as ATP hydrolysis catalysts.

^{31}Phosphorus NMR spectroscopic analyses were found to be very useful in studying the kinetics of catalysis as well as in detecting intermediates produced during the course of the reaction. Using such methods it proved possible to demonstrate that at neutral pH a neutral (i.e., unprotonated) amino group acts as a nucleophile, as confirmed by the observation that the monophosphorylated derivatives of macrocycle **7** and **11** are seen during the course of the reaction. The mechanism proposed on the basis of these studies is shown in Scheme 1 [30].

The highest rate constants observed for ATP hydrolysis were seen in the case of macrocycles **7** and **11**. At pH 4.4, the relative rates with respect to uncatalyzed hydrolysis at 70 °C are 26.6×10^3 and 34.7×10^3 min^{-1} and at pH 7.4 they are 20.7×10^3 and 3.1×10^3 min^{-1} for receptors **7** and **11**, respectively. Receptor **11** appeared to be the most efficient catalyst at neutral pH, presumably because it contains additional protonation sites within the macrocycle cavity; for this system the rate constant is 310×10^3 min^{-1} at 80 °C [28]. In general at low pH, when the macrocycle is maximally protonated, the rate of hydrolysis is higher than at neutral pH.

Lehn and co-workers were able to show that running the reaction in the presence of different metal salts, which are known to be present in biological milieus, led to an increase in catalytic activity. For instance, enhancement factors of 1.3, 2.4 and 1.4 were seen upon the addition of $MgCl_2$, $MnCl_2$ and $CaBr_2$, respectively, in the case of macrocycle **7**. The authors also found that the macrocycle-catalyzed processes could be treated using normal enzyme kinetic treatments. In particular, the reaction involving **7** was found to be dependent on the formation of Michaelis-like substrate-catalyst complex. The effectiveness of **7** could thus be compared directly with that of ATPase. This comparison served to highlight that system **7** and its analogues, while defining an important achievement in supramolecular chemistry, still fell far short of the goal of matching the natural enzymes. For instance, the turnover rate for **7** in promoting ATP hydrolysis was found to be 0.064 min^{-1}, which is roughly 10^5 times



Scheme 1. Proposed mechanism for ATP dephosphorylation catalyzed by polyammonium macrocycles illustrated in the specific case of **7** [53]. The geometries of the complexes are presumed but not specifically established by experiment or calculation.

slower than the average turnover of 1000 min^{-1} seen for most ATPases [53].

3.2. Hydrolysis of acetyl phosphate

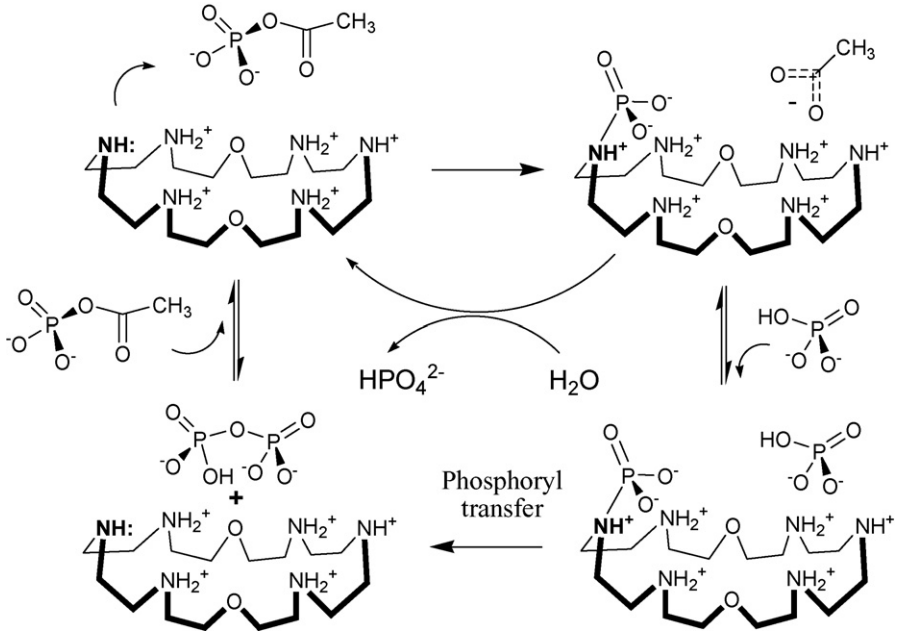
Macrocycle **7** was also found to be an effective catalyst for bond formation. In particular, it was found to hydrolyze acetylphosphate (AcP) and mediate the concurrent synthesis of pyrophosphate (PP). This chemistry was noteworthy because it represented an important step forward in terms of the design of supramolecular catalysts that would provide a potentially useful function, in this case the generation of PP, an energy-rich species that replaces ATP in a number of enzyme catalyzed reactions associated with biological energy conversion [25]. While the dynamics of the reaction were complex, the formation of three expected products was observed, namely P (orthophosphate), PP (pyrophosphate) and an N-phosphorylated macrocycle (phosphoramidate) intermediate. Thus, it was proposed that the key bond-forming step involves the reaction of a phosphorylated intermediate with orthophosphate. Interestingly, the rate of hydrolysis was found to greatest at high and low pH and slowest at or near neutral pH. Based on this observation, it was suggested that the following three factors may contribute to the overall catalytic process: (1) electrostatic catalysis, in which binding overcomes electrostatic repulsion and facilitates reaction between electron-rich species, yielding products of higher total charge than the starting AcP; (2) acid catalysis at low pH by proton transfer within the bound species; (3) nucleophilic catalysis, wherein an unprotonated nitrogen site undergoes phosphorylation via attack on the AcP phosphate ester [31]. The proposed mechanism is shown in Scheme 2. Whether fortuitous or not, this mechanism bears analogy to that proposed for phosphate-dependent acetate kinase.

3.3. Synthesis of ATP

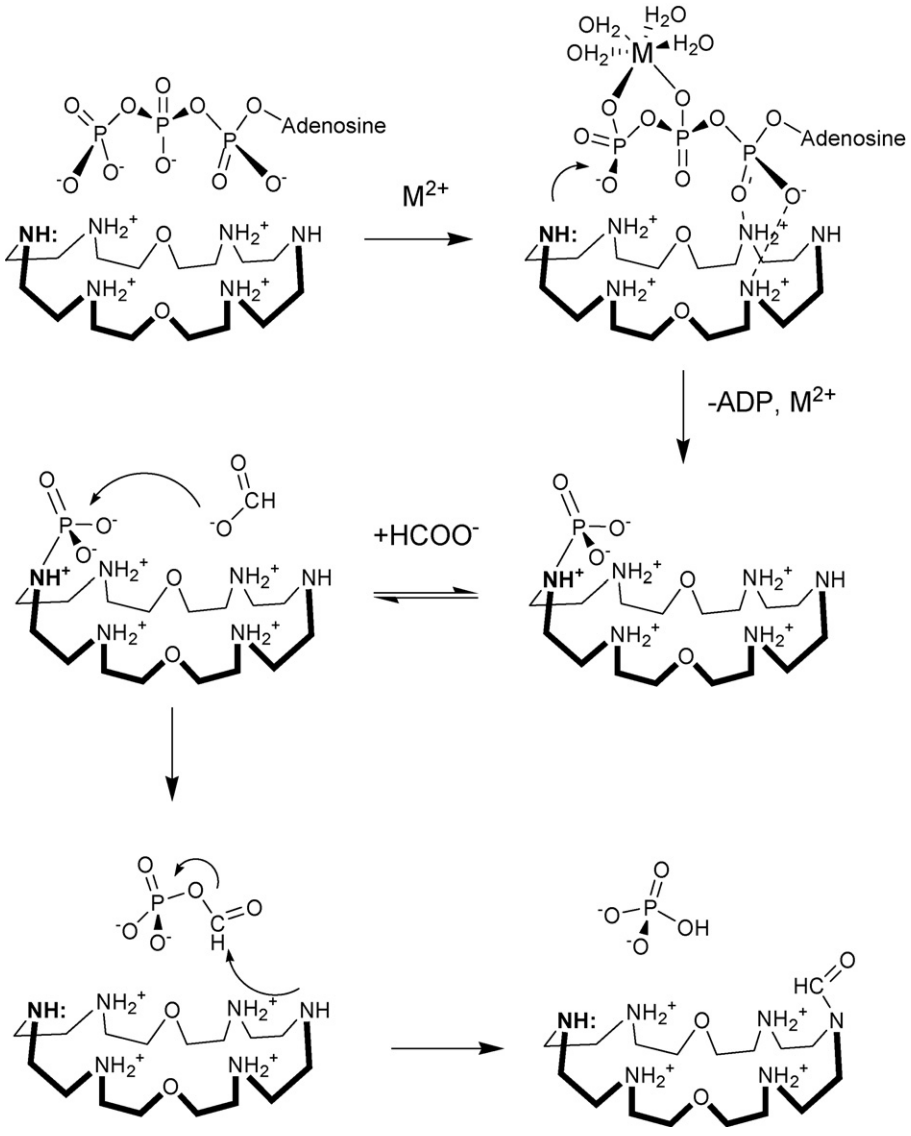
In another example of bond formation mediated by polyammonium macrocycles it was found that addition of calcium or magnesium ions to an aqueous system containing a phosphoryl donor (AcP), an acceptor (P, PP or ADP) and receptor **7**, the hydrolysis of ATP was retarded. Instead, the formation of ATP, PP and PPP (triphosphate) was observed (10^{-2} M at pH 7 at 40 °C) [54]. The key intermediate in the synthesis reaction, as in the hydrolysis process, is thought to be the mono-phosphorylated (phosphoramidate) intermediate of **7**. In analogy to the chemistry detailed in Scheme 2, this intermediate is thought to act as the phosphorylating reagent, reacting via phosphoryl transfer to the bound acceptor species, in competition with hydrolysis. On the basis of detailed studies of the reaction, it was proposed that the phosphorylation event itself involves a ternary complex consisting of this mono-phosphorylated derivative, ADP^{3-} and Mg^{2+} [55].

3.4. Formate activation

In chemistry of a slightly different type, it was found that receptor **7** could also effect activation of formate. This activation process proceeds in the presence of ATP and divalent metal anions (particularly $CaBr_2$ and $MgBr_2$) and results in the formylation of the starting macrocycle [26]. An analogous process, namely ATP-mediated activation of formate resulting in N-formylation, is known to occur in the biosynthesis of N^{10}-formyltetrahydrofolate synthetase. In the case of the model system involving macrocycle **7**, studies showed that the process occurs when either acetyl phosphate and formate or formyl phosphate are used as the carbon source. In the presence of ATP, the phosphorylated macrocycle (phosphoramidate) is again



Scheme 2. Schematic representation of the proposed mechanism of AcP hydrolysis as mediated by macrocycle **7**. All geometries of structures are hypothetical and not explicitly supported by experimental analyses.



Scheme 3. Proposed mechanism of formate activation by macrocycle **7**. As true for related schemes, the geometries of the individual structures are hypothetical.

thought to be the key intermediate (Scheme 3). However, when formyl phosphate is used as the starting material, it is an N-formylated species, rather than a phosphorylated version of **7** that results. This product is produced in almost quantitative yield at pH 7.0. A mechanism of formylation was proposed on the basis of ^{18}O water-labeling studies, as well as studies involving different reagents. The proposed chemistry is outlined in Scheme 3 and entails five steps: (1) complexation, (2) phosphorylation of the macrocycle by ATP, (3) complexation of formate in the other receptor site, (4) reaction of the bound carboxylate in the supramolecular complex with the phosphoramidate group, leading to the complex of formyl phosphate and the macrocycle **7** and (5) formylation of **7** by formyl phosphate, resulting in the transfer of a formyl group to nitrogen and release of phosphate.

4. Metal-based polyamine systems

There are a number of metal containing receptors derived from polyamine systems that, as a rule, were prepared via coordination of one or more Lewis acidic centers (metal cations) to the polyamine ligand. Of particular interest are copper or zinc complexes since these have proved to be highly efficient receptors for oxyanions.

Using a metal coordination-based approach, Anslyn and co-workers have reported a new generation of receptors specifically designed to maximize the enthalpy and entropy of phosphate anion binding in water [56,57]. The approach is shown schematically in Fig. 7(a), a representation that is meant to highlight the fact that these receptors are expected to define a tetrahedral anion-binding cage. In accord with the design expectations, the combination of copper sites, ammonium groups and structural rigidity acts to make receptors **24** and **25** among the most effective and selective phosphate receptors known. They bind phosphate anions in water at neutral pH with binding constants on the order of 2.5×10^4 and $1.5 \times 10^4\ M^{-1}$. The ammonium groups in receptor $\mathbf{24H_3^{3+}}$ have pK_a's of ca. 8.0. Thus, at neutral pH they are protonated and contribute to the attractive columbic interactions between the negatively

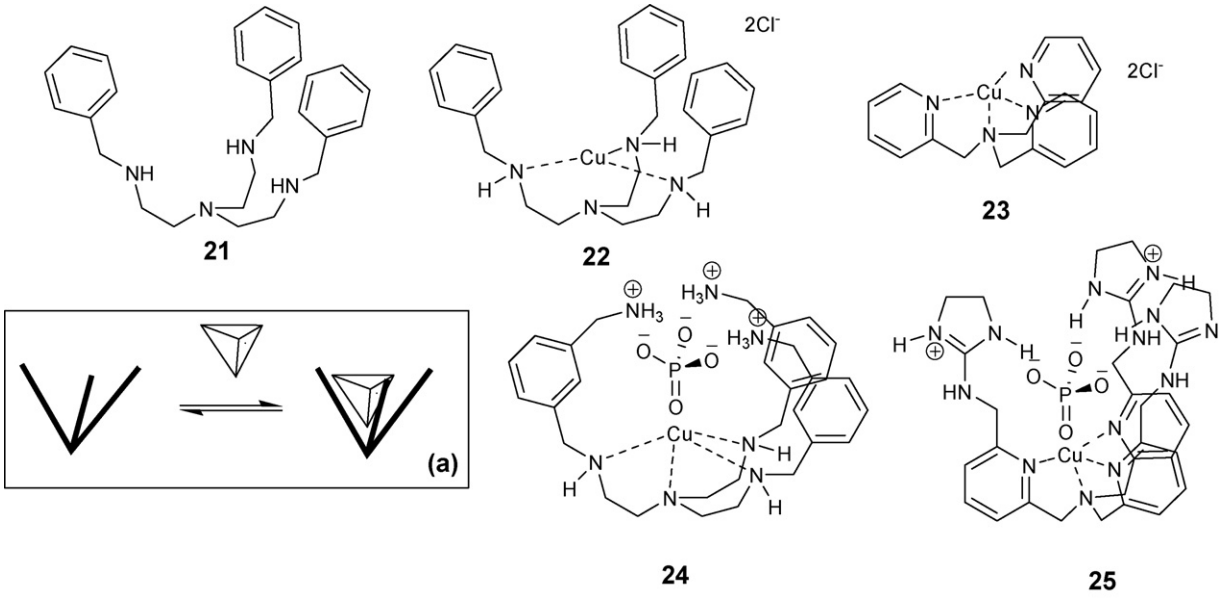


Fig. 7. Design concept for the binding of tetrahedral species using tripodal ligands (insert (a)) and schematic representations of the host–guest complexes ($[\mathbf{24H_3}\cdot PO_4]^{2+}$ and $[\mathbf{25}\cdot PO_4]^{2+}$) formed after phosphate anion binding to the preformed copper(II) complexes, $\mathbf{24H_3}^{3+}$ and **25** (prepared as their chloride salts). Also shown are various control systems.

charged anion and the positively charge receptor. Nonetheless, control studies, involving model systems, such as **22** and **23**, for which binding constants for hydrogen phosphate of 900 and 300 M^{-1}, respectively, were recorded, showed that the major contributor to anion binding is the copper center, a key feature in the host design. Recently, however, it was shown that the ligand itself, in its triprotonated form, can bind sulfate and phosphate anions selectively in chloroform [58].

As can be seen from Table 3, receptor **25** is even more selective for hydrogen phosphate than is $\mathbf{24H_3}^{3+}$. Presumably, this reflects the fact that **25** is built up from pyridine rings and guanidinium fragments and is hence more rigid, making it less prone to bind competing anions, such as ReO_4^-, whose size is incommensurate with that of the receptor cavity. Detailed thermodynamic studies revealed that while the overall Gibbs energies differ only slightly, phosphate anion binding is entirely entropically driven in the case of $\mathbf{24H_3}^{3+}$ whereas it is enthalpy driven in the case of **25**. This observation is rationalized in terms of the fact that solvent organization around guanidinium groups is lower than around ammonium groups; hence, binding to $\mathbf{24H_3}^{3+}$ leads to release of solvent, a process that is entropically favorable. By contrast, a lower enthalpy of solvation in the case of the guanidinium groups leads to a binding process that is enthalpy driven in the case of receptor **25**.

Table 3
Anion-binding affinities (M^{-1}) of receptors $\mathbf{24H_3}^{3+}$ and **25** (both as chloride anion salts) in aqueous solution at pH 7.4 and 25 °C, and receptor $\mathbf{21H_3}^{3+}$(tris toslyate salt) in chloroform at 25 °C

Anion	$\mathbf{24H_3}^{3+}$	**25**	$\mathbf{21H_3}^{3+}$
HPO_4^{2-}	2.5×10^4	1.5×10^4	–
$HAsO_4^-$	2.5×10^4	1.7×10^4	–
ReO_4^-	2.0×10^3	<100	–
AcO^-	<900	<100	–
NO_3^-	<20	<100	35
HCO_3^-	n.d.	<100	–
Cl^-	n.d.	<100	63
SO_4^{2-}	n.d.	<100	–
$H_2PO_4^-$	–	–	1.7×10^2
HSO_4^-	–	–	1.6×10^2

Another approach to phosphate anion binding that has proved very effective in water involves the use of the bis-zinc complexes of pyridine-based ammonium receptors. This strategy, pioneered by Kim and co-workers, draws its inspiration from the active center of alkaline phosphatase [59]. To date, it has led to the development of a colorimetric displacement-type hydrogen phosphate anion sensor [60]. In this case, a precomplexed pyrocatechol violet subunit was used as the color indicator since this dye is known to change color upon the binding to the metals at neutral pH. Therefore, the displacement of the receptor-bound pyrocatechol violet, which occurs upon phosphate anion-binding, leads to a change in color, which may be detected either visually or spectroscopically, as illustrated schematically in Fig. 8 (for the specific case of receptor **26**). The color change only occurs in the case hydrogen phosphate anion; other anions, including sulfate, nitrate, perchlorate, and chloride, do not give rise to an appreciable color change. This sensor system was also found to permit quantitative assays of phosphate-type analytes in biological milieus down to a concentration limit of 10^{-5} M.

Quantitative isothermal titration calorimetry (ITC) studies showed that receptor **26** binds phosphate at neutral pH with an affinity constant of 11.2×10^4 M^{-1}, while pyrocatechol violet is bound with an affinity constant of 5.3×10^4 M^{-1}. The associated thermodynamic parameters indicate that the binding is enthalpically driven, which is considered consistent with a

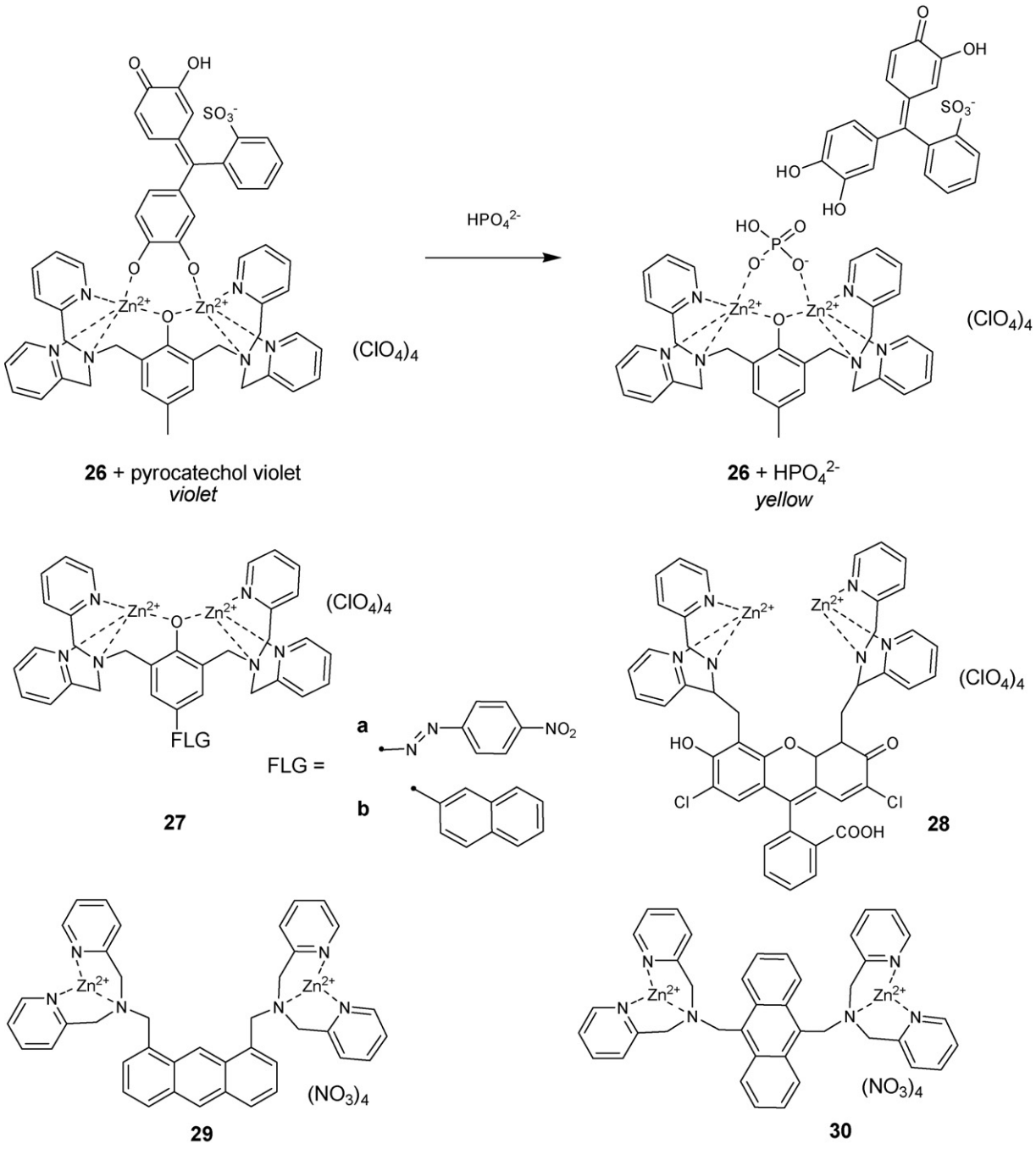


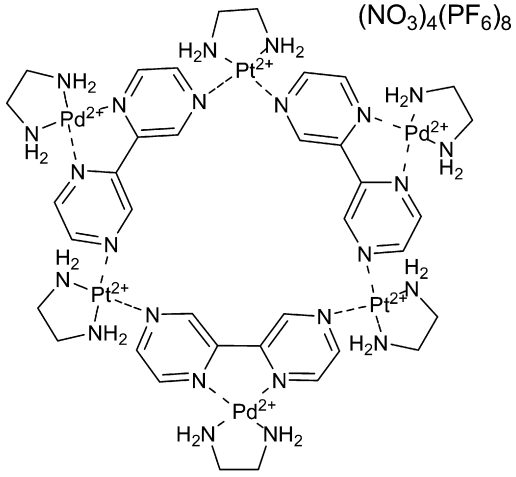
Fig. 8. Schematic illustration of the displacement assay approach believed to be operative in the case of receptor **26**. Also shown are line drawings of various Zn-based anion sensor systems.

strong coordination-type interaction between the substrates and the metal centers.

In subsequent work, a fluorophore reporter group was incorporated directly within the receptor molecule, giving rise to receptors **27a** [61], **27b** [62] and **28** [63]. Quantitative studies revealed that in these systems, pyrophosphate anion binds more strongly (by a factor of $>10^3$) than hydrogen phosphate and that both pyrophosphate and ATP anions are bound extremely well in water at pH 7.4 (binding constants of up to $10^8\,M^{-1}$ being observed). The coordination environment of the pyrophosphate anion complex is shown in Fig. 9.

The anthracene (as spacing group) derived zinc receptors **29** and **30** [64] also displays a high affinity towards monophosphate derivatives (sodium dihydrogen phosphate, phenyl phosphate, methyl phosphate, AMP, and *O*-phospho-L-tyrosine), binding these species with affinity constants on the order of 10^5–$10^4\,M^{-1}$ in water at pH 7.2. Strong affinities for phosphorylated peptides (K_a 10^6–$10^4\,M^{-1}$) were also observed

under these same conditions. This unique property was used successfully to track phosphatase-catalyzed dephosphorylation via fluorescent monitoring.



31

An interesting receptor, showing high sulfate anion selectivity, is system **31**, produced by Lippert and co-workers [65]. This receptor is based on a Pt–Pd heteronuclear complex with 2,2-bipyrazine (bpz). In analogy to the corresponding Cu and Zn complexes, it binds anions via interactions involving the six Lewis acidic metal centers. According to a single crystal X-ray diffraction analysis of $[(en)Pt(bpz)Pd(en)]_3(NO_3)_4(PF_6)_8$, the complex has a scythe-like shape with an inner diameter of about 6 Å (the Pt–Pt distance is 7.88 Å) The hexanuclear Pt–Pd containing receptor has a charge +12 and exhibits a high affinity for tetrahedral anions. This is reflected in the values of the anion-binding constants, as determined by NMR titration analyses in D_2O: SO_4^{2-}, 256 M^{-1}; PF_6^-, 10.6 M^{-1}; BF_4^-, 4.1 M^{-1}; $PtCl_4^{2-}$, no appreciable binding.

5. Pyrrole-based receptors

Calix[4]pyrroles are a class of small, non-aromatic pyrrolic macrocycles that were initially put forward as fluoride anion-binding agents. However, this class of receptors also binds phosphate anions relatively well in aprotic media. For instance, in CH_3CN and DMF calix[4]pyrrole **33** binds dihydrogen phosphate (in a 1:1 stoichiometry) and hydrogen pyrophosphate (forming a 2:1 complex) anions with log K_a values in the range of 4–5. The binding process is mostly enthalpically driven for both anions [66].

As part of a generalized effort to develop the anion recognition chemistry of calix[4]pyrroles, efforts were made not only to effect anion sensing in solution [67], but also to prepare solid supports that would allow anion purification and detection to be achieved using HPLC-based methods [68]. In the context of the first of these goals, several calix[4]pyrrole-anthracene conjugates were synthesized. Among them was receptor **32**, which was found to display selectivity towards $H_2PO_4^-$, Cl^- and F^- ($pK_a > 4$, 1:1, in CD_3CN, as determined by both ^1H NMR spectroscopy and fluorescence quenching methods). The high affinity towards dihydrogen phosphate anion can be explained by the electron withdrawing effect of the appended amido-anthracene functional groups.

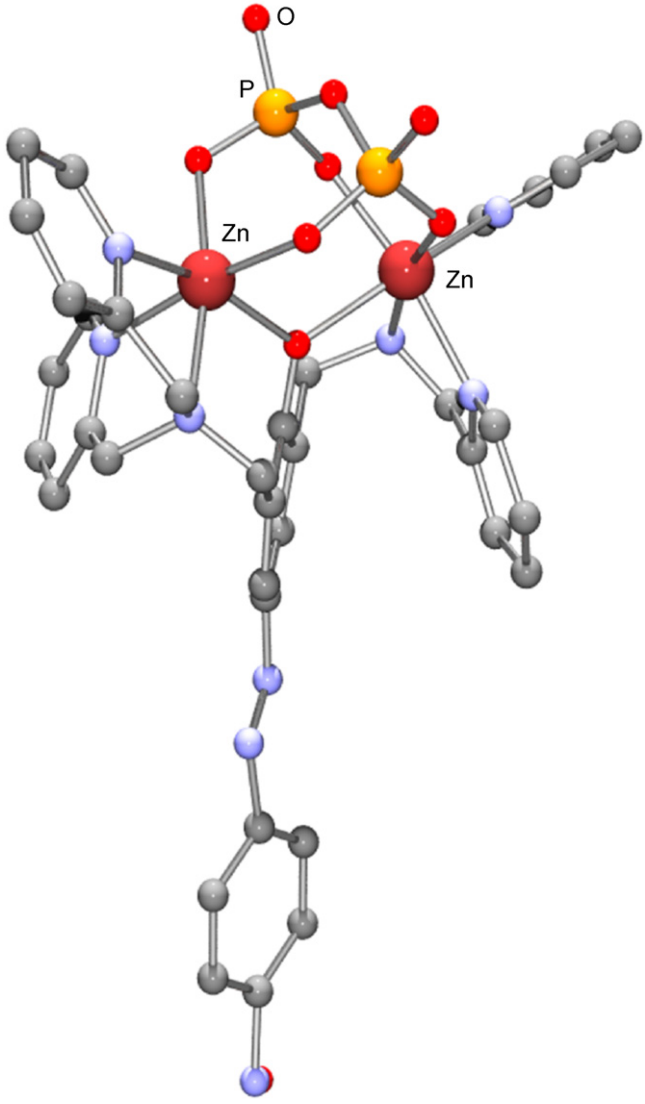
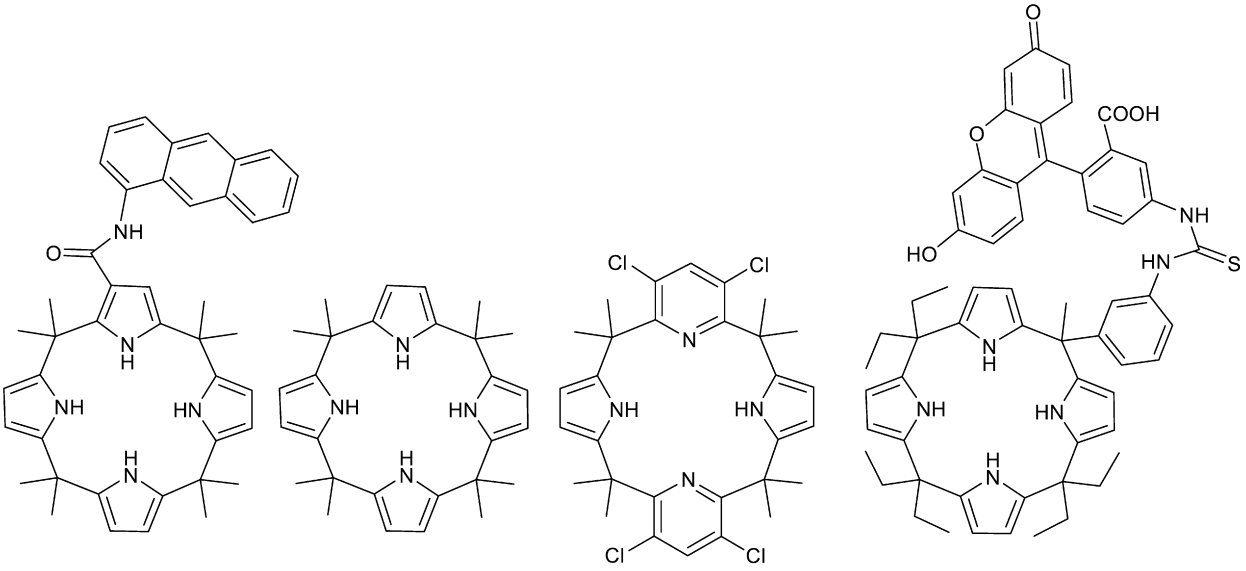


Fig. 9. ORTEP view of the single crystal X-ray diffraction structure of the pyrophosphate anion complex of receptor **27a**. The hydrogen atoms and cations are omitted for clarity. This figure was generated using data originally reported in reference [61].

Calix[4]pyrroles and their pyridine analogues were also used to produce PVC-derived ion selective electrodes (ISEs). At low pH values, system **33**, when incorporated into such ISEs, was found to display a strong anionic response in the presence of chloride, bromide and hydrogen phosphate anions, and to a lesser extent fluoride anion. At high pH 9.0 a non-Hofmeister selectivity sequence was observed, namely $Br^- < Cl^- < OH^- \approx F^- < HPO_4^{2-}$, a observation that was ascribed in part to the fact that the macrocycle coordinates hydroxide anions under these conditions. The modified receptor **34**, containing two pyridine rings, showed better selectivity towards hydrogen phosphate anion at certain pH values. At low pH (<5.5) pyridine is protonated and this receptor displays a strong response for F^- and HPO_4^{2-}. At pH 9.0, however, the

observed selectivity pattern reflects not only the lipophilicity of the anions but also the ability of the receptor to complex each of the targeted anions. The latter determinant tends to dominate with the result that the selectivity is non-Hofmeister, i.e. $F^- < OH^- < Cl^- < Br^- < HPO_4^{2-}$. The main feature of this receptor is thus its pH dependance and its high selectivity towards hydrogen phosphate anions at high pH values. These special protonation features can be potentially exploited to generate ISE systems that are fine-tuned in terms of their anion selectivities by choosing the conditions of experiment. In an effort to overcome the low phosphate-chloride selectivity generally seen for calix[4]pyrroles, Sessler and co-workers sought to reduce the conformational flexibility by putting a substituted phenyl group in one of the meso position [69]. One of the receptors produced via this strategy, **35**, also has a fluorescent label. This permitted anion-binding studies to be carried out via fluorescence quenching. From such titrations, it was determined that the binding affinity of this receptor is extremely high. The affinities of the receptor to the other anions are: $HP_2O_7^{3-}$ ($2 \times 10^6\ M^{-1}$) > $H_2PO_4^-$ ($682{,}000\ M^{-1}$) > F^- ($200{,}000\ M^{-1}$) > Cl^- ($10{,}000\ M^{-1}$) in 96:4 acetonitrile–water. The presence of a small amount of water precludes aggregation of the receptor in solution.



32 **33** **34** **35**

Sapphyrin is one the most important of all known pyrrole-based anion receptors. This pentapyrrolic macrocycle differs substantially from calix[4]pyrrole in that it contains a 22 π-electron aromatic periphery. It also differs by virtue of the fact that it only binds anions in its protonated forms. A number of reviews describing the chemistry of sapphyrins have been published recently [7,8] and thus here the discussion will focus on its oxyanion binding features.

Sapphyrins are often considered to be prototypical expanded porphyrins in that they are larger than this latter class of naturally occurring pigments. In particular, they contain a central cavity that is ca. 25% larger (center-to-nitrogen radius of ca. 2.5 Å) than that found in porphyrins. The larger core size allows the diprotonated form of this macrocycle to remain planar without any significant distortion caused by, e.g. Coulombic or Van der Waals interactions arising from the protons bound within its core. As a consequence, sapphyrin is more basic than porphyrin. Indeed, in contrast to this latter system, sapphyrin remains monoprotonated at neutral pH and doubly protonated at or below ca. pH 3.5 (e.g., for sapphyrin **37** $pK_{a1} = 4.8$ and $pK_{a2} = 8.8$ in aqueous media).

Sapphyrins are known to be highly efficient and selective receptors for fluoride anion relative to both chloride and bromide [70,71]. They have also been used to effect the chiral recognition of dicarboxylates [72] and to act as solution-phase carriers for nucleotides [73,74] and nucleotide analogues [75,76]. It was also found that silica-bound sapphyrin systems provided useful solid supports that allow for the HPLC-based separation of monomeric and small oligomeric nucleotides at pH 7 [77]. In related work, it was likewise established that a water-soluble sapphyrin, **37**, binds DNA in aqueous solution at pH 7 [78,79] (Fig. 10).

The interactions of various sapphyrins (Fig. 10) with phosphate-type anions, including dihydrogen phosphate, phenyl phosphonates and nucleotides, have been extensively studied in solution and in the solid state. The single crystal X-ray structure of the complexes **38**H_2^{2+}·HPO_4^{2-}, **38**H_2^{2+}·2$PhOPO_3^{2-}$ and **38H**$^{2+}$ with cAMP are shown in Figs. 11 and 12. Interestingly, only one phosphate oxygen atom interacts with all five of the NH's present in the doubly protonated sapphyrin core. Related binding motifs were also seen in the case of several 2:1 phosphate anion-sapphyrin complexes, wherein the two anions were found to be coordinated via a single oxygen atom from each of the two bound phosphate anions. These latter were found to be coordinated on opposite faces of the intervening sapphyrin macrocycle [79].

A complicating feature of many sapphyrins is their tendency to undergo aggregation, particularly in polar media. This has made the study of phosphate anion recognition in water challenging. However, it was found that addition of phosphate-containing

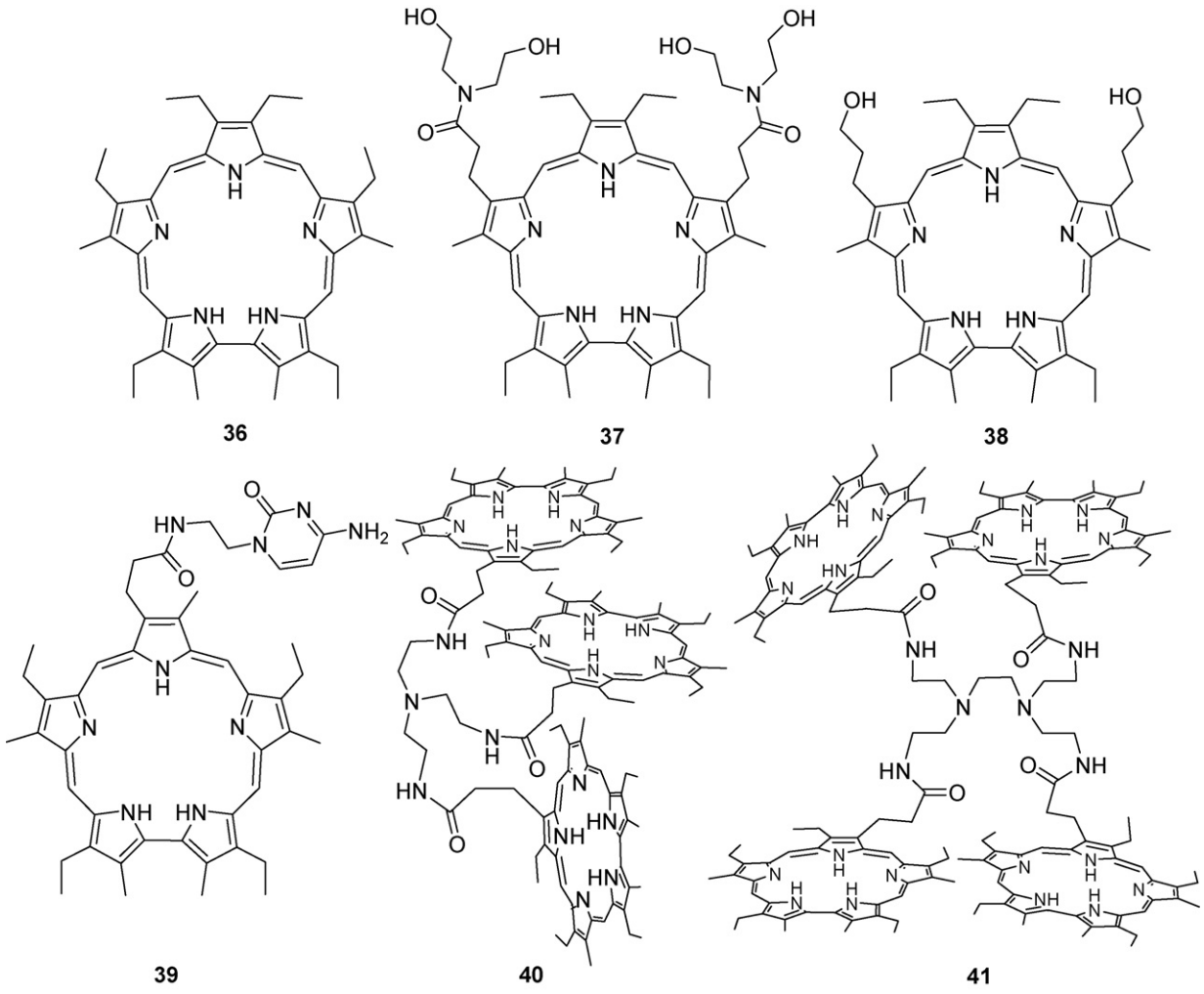


Fig. 10. Representative sapphyrins and oligosapphyrins.

anions to the aggregated form of sapphyrin normally present in aqueous media leads to the formation of first a phosphate-bound dimeric sapphyrin species, followed by generation of monomerized sapphyrin-phosphate complexes at very high phosphate-to-sapphyrin ratios [80].

The situation in organic solvents is generally cleaner, although many phosphodiesters are known to dimerize in organic solvents. Nonetheless, anion-binding titrations involving phenyl phosphate or dihydrogen phosphate were found to give rise to clean binding isotherms and to be readily interpretable in terms of the formation of either 1:1 or 2:1 phosphate-to-protonated sapphyrin complexes [79].

Binding constants for various sapphyrin systems interacting with a range of phosphate anions (as well as other anions) are summarized in Table 4. As a general rule, in almost all solvents protonated sapphyrins bind phosphate-type anionic substrates less well than fluoride anion but considerably more effectively than either chloride or bromide anion. This selectivity reflects, presumably, a combination of charge density and the ability of phosphate-type anions to interact with the protonated sapphyrin core via multiple hydrogen bonds.

Through the use of a U-tube membrane model, consisting of two aqueous phases separated by an intervening organic layer, it was found that protonated sapphyrin **36** acts as an efficient anion carrier for mononucleotides under conditions where octaethylporphyrin does not. It was shown that the transport efficiency and selectivity could be improved by appending a nucleobase recognition unit onto the sapphyrin skeleton. The resulting sapphyrin conjugate, **39**, was found to transport organic-insoluble species, such as GMP through the organic layer. Receptor **39** displays a very high selectivity for GMP (i.e., by a factor of 8–100 relative to AMP or CMP).

In an attempt generate carriers for di- and triphosphate species, various oligosapphyrins, e.g. **40**–**41**, were prepared. Among the resulting species, oligosapphyrin **40**, which is multiply protonated at neutral pH, was found to be an effective carrier for nucleotides diphosphates. By contrast, system **36** was found to be an efficient carrier for nucleotide triphosphates [80].

In addition to generating receptors capable of recognizing and transporting di- and triphosphates, considerable effort was devoted to mapping out the interactions of water-soluble sapphyrins with nucleotides and oligonucleotides. As the result

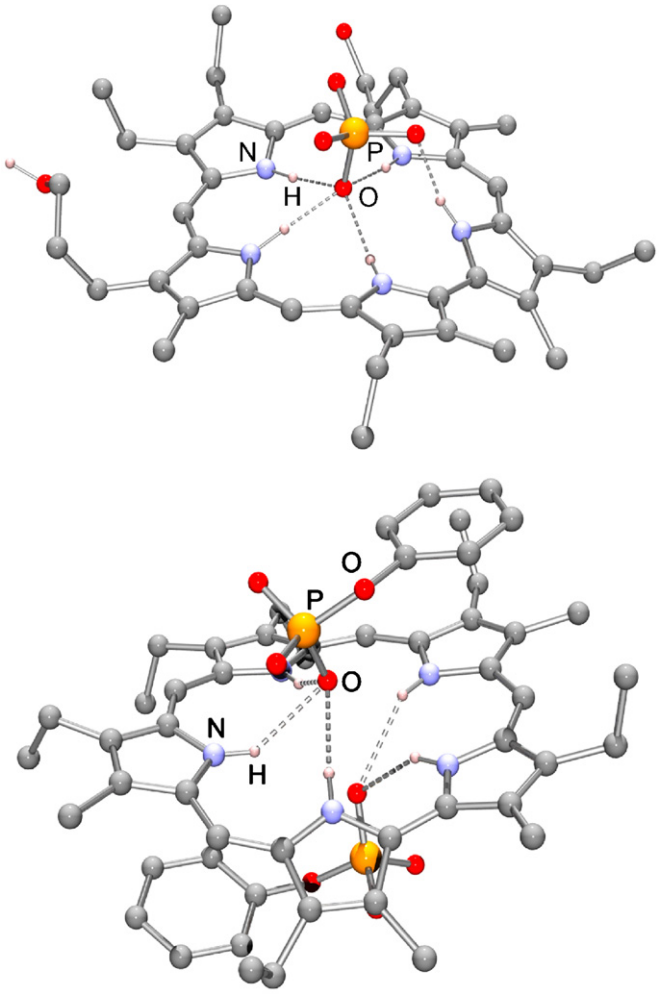


Fig. 11. Views of $\mathbf{38}H_2^{2+}\cdot HPO_4^{2-}$ and $\mathbf{38}H_2^{2+}\cdot 2PhOPO_3^{2-}$ generated from X-ray diffraction data originally published in reference [79]. In these representations, most of the hydrogen atoms have been omitted for clarity.

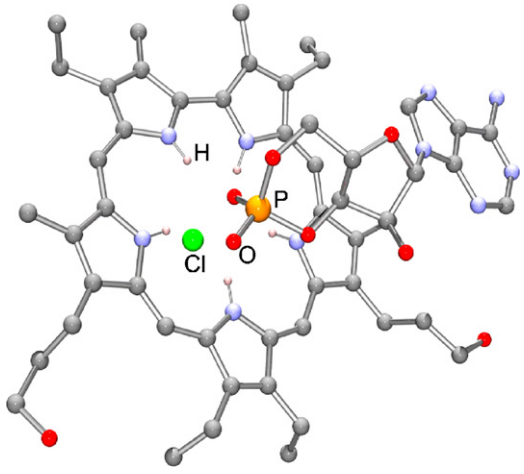


Fig. 12. Views of complex $\mathbf{38}H_2^{2+}$ with cAMP and chloride anion generated from X-ray diffraction data originally published in ref. [74]. In these representations, most of the hydrogen atoms have been omitted for clarity.

Table 4
Binding constants for sapphyrin systems interacting with a range of anionic species

Sapphyrin (analysis method) [7]	Anion	K (M^{-1})
37 (UV–vis)	Solvent: H_2O, pH 6.1 $C_6H_5PO_3^{2-}$	310
36 (UV–vis)	Solvent CH_3OH F^-	2.8×10^5
38 (^{31}P NMR)	$C_6H_5PO_3^{2-}$ H_3PO_4	1.8×10^4 1.3×10^4
39 (UV–vis)	2′-GMP 5′-GMP 5′-AMP 5′-CMP	2.2×10^4 8100 1700 880
36 (UV–vis)	Cl^- Br^- Solvent 5% CH_3OH in CH_2Cl_2 Solvent CH_2Cl_2	100 <100
(fluorescence lifetime)	F^- Cl^- Br^-	$>10^8$ 1.8×10^7 1.5×10^6

of this effort, three basic modes of interaction were defined. The first mode, which is implicated for all phosphate species, involves so-called "phosphate chelation". This mode is exemplified by the solid structures of $\mathbf{38}H_2^{2+}\cdot HPO_4^{2-}$ (Fig. 11) and sapphyrin **38** with cAMP (Fig. 12). It was found that this mode of interaction is specifically characterized by the presence of a Soret-type visible absorption band at 422 nm. The second mode involves a hydrophobic interaction between the macrocyclic ring and the nucleobase(s) present in both monomeric and single-stranded oligonucleotides. This nucleotide-depended interaction is characterized by an absorption feature characteristic of a monomeric sapphyrin species, namely a Soret-like band at 450 nm. The third mode involves what can be considered highly ordered aggregation of sapphyrin to double-stranded, helical nucleic acids at low phosphate-to-sapphyrin ratios. The formation of this organized, aggregated structure is presumably templated by the ordered structure of these double-stranded nucleic acid polymers. It is characterized by a Soret-type absorption band at 400 nm, as well as by a large, induced circular dichroism feature for the achiral sapphyrin chromophore. More qualitative, but nonetheless impressive evidence that sapphyrins can interact with oligonucleotides came from the observation that the addition of sapphyrin **36** to a solution of double-stranded DNA leads to the immediate precipitation of green fibers [78].

Recently, a new class of expanded porphyrins, the so-called cyclo[8]pyrroles (e.g., **42**, derived from 3,4-dimethyl pyrrole) were synthesized. These systems were characterized in the form of their dihydrogen sulfate salts via a variety of methods, including X-ray diffraction analysis. As judged from the latter analyses, the doubly protonated form of **42** has a relatively large central core, with an inner diameter of about 7 Å. Moreover, in the solid state a sulfate dianion is found encapsulated within this inner cavity, being stabilized there via multiple hydrogen bonds (Fig. 13). System $\mathbf{42}H_2^{2+}$ is unique among the various

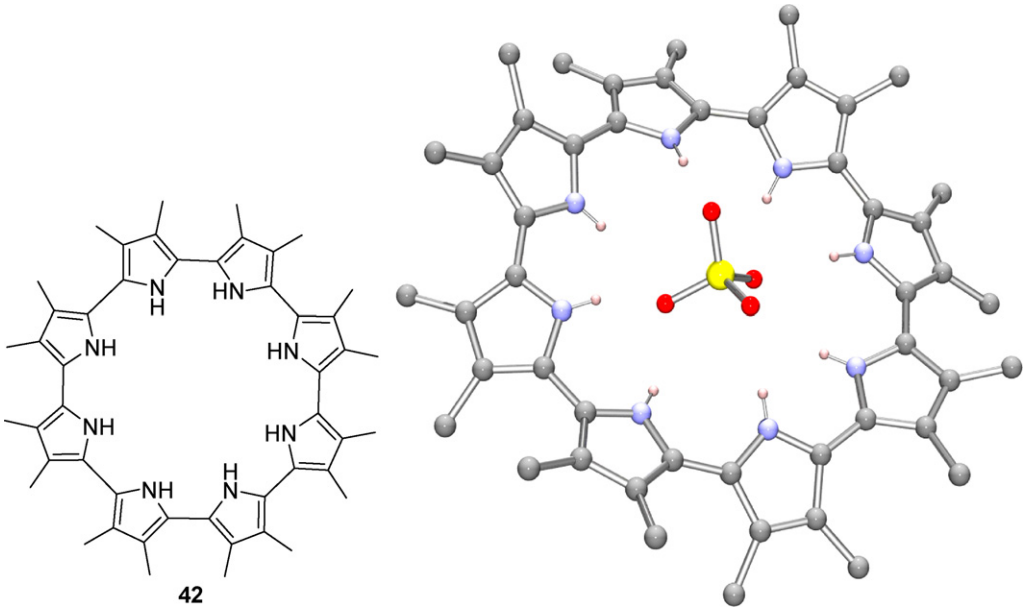


Fig. 13. Views of structure **42** and complex **42**·H_2SO_4 generated from X-ray diffraction data originally published in reference [81]. In these representations, solvent molecules have been omitted for clarity.

expanded porphyrins reported to date in being able to stabilize a well-characterized sulfate anion complex [81]. As a result, studies of this system as a possible selective sulfate anion extractant are currently underway.

6. Amide- and urea-based receptors

Amide and urea NH groups have been employed to produce a wide range of anion receptors. The first amide- and urea-based receptors were produced with the goal of binding halide anions. Subsequently, it was found that phosphate anions bind to these two receptor motifs with almost similar affinity, while other tetrahedral anions do not bind appreciably. While the lack of interference from these latter species is convenient, in point of fact, only careful design provides amide receptors with phosphate anion selectivity. This is because both carboxylate and chloride anions are also bound extremely well by most amide-type anion receptors. In most competition studies, acetate has been used as the test carboxylate anion, and it has been found that even the best phosphate receptors display a selectivity of only 5–10-fold relative to this competing, non-tetrahedral oxyanion.

In contrast to carboxylates, hydrogen sulfate anion is not strongly bound to most amide- and urea-based receptors. The strong discrimination seen in favor of $H_2PO_4^-$ over HSO_4^- is ascribed to differences in the relative basicity and hydrophobicity of these two anions. Especially in DMSO solution (vide infra), amides and ureas can distinguish between these two anions with selectivity factors which approach 3 order of magnitude.

Fig. 14 shows several representative phosphate anion receptors. The best building blocks for such receptors appeared to be 1,3-bis(aminomethyl)benzene, isophthalyldiamide and 2,6-pyridinediamide fragments. A key difference between diamido receptors based on isophthalyl and pyridine subunits is that in the case of the pyridine 2,6-diamido-contain systems, the two amido hydrogen atoms are oriented into the binding cleft as the result of amide NH-pyridine N hydrogren bonding interactions, whereas such an orientation is not stabilized in the case of the isophthalyl-derived species [82].

Among the systems shown in Fig. 14 is compound **43**. This pure amido system shows how tetrahedral species may be bound via the use of tripodal amide-containing ligands in accord with the general scheme illustrated in Fig. 7 above [83]. Receptor **43** is derived from cyclohexane tricarboxylic acid and, as might have been expected, was found to bind phosphate-type anions well. This was demonstrated in a variety of solvents. For instance, the affinity constants, K_a, for the binding of tetrabutylammonium phenyl phosphate were found to be 1.5×10^4 and $8 \times 10^2\ M^{-1}$ in deuterated DMSO-d_6 and CD_3OD, respectively. The corresponding values for dihydrogen phosphate salt were found to be $>10^5$ in DMSO-d_6 and $1.2 \times 10^4\ M^{-1}$ in CD_3OD, respectively. The fact that for this pure amide receptor the binding constants are larger in DMSO than in methanol, means that this latter solvent interferes with the anion-binding process more strongly than does DMSO. Presumably, this reflects its ability to stabilize a variety of competitive hydrogen bonds. Such conclusions have also been drawn in the case of other hydrogen bond-based oxyanion receptor systems, including those based on guanidinium, as discussed later on in this review.

An interesting approach to the construction of amide-type receptors for tetrahedral anions is embodied in receptor **44** [84]. Here, the amido fragments are organized in such a way that six hydrogen bond donors are available for interaction with the four oxygen atoms in mono-, di- or tribasic phosphate. This receptor binds dihydrogen phosphate ($H_2PO_4^-$) and phosphate (PO_4^{3-}) with roughly the same affinity (K_a about $1370\ M^{-1}$ in DMSO-d_6), while showing no appreciable affinity for HSO_4^- or ClO_4^-. The selectivity for dihydrogen phosphate over acetate

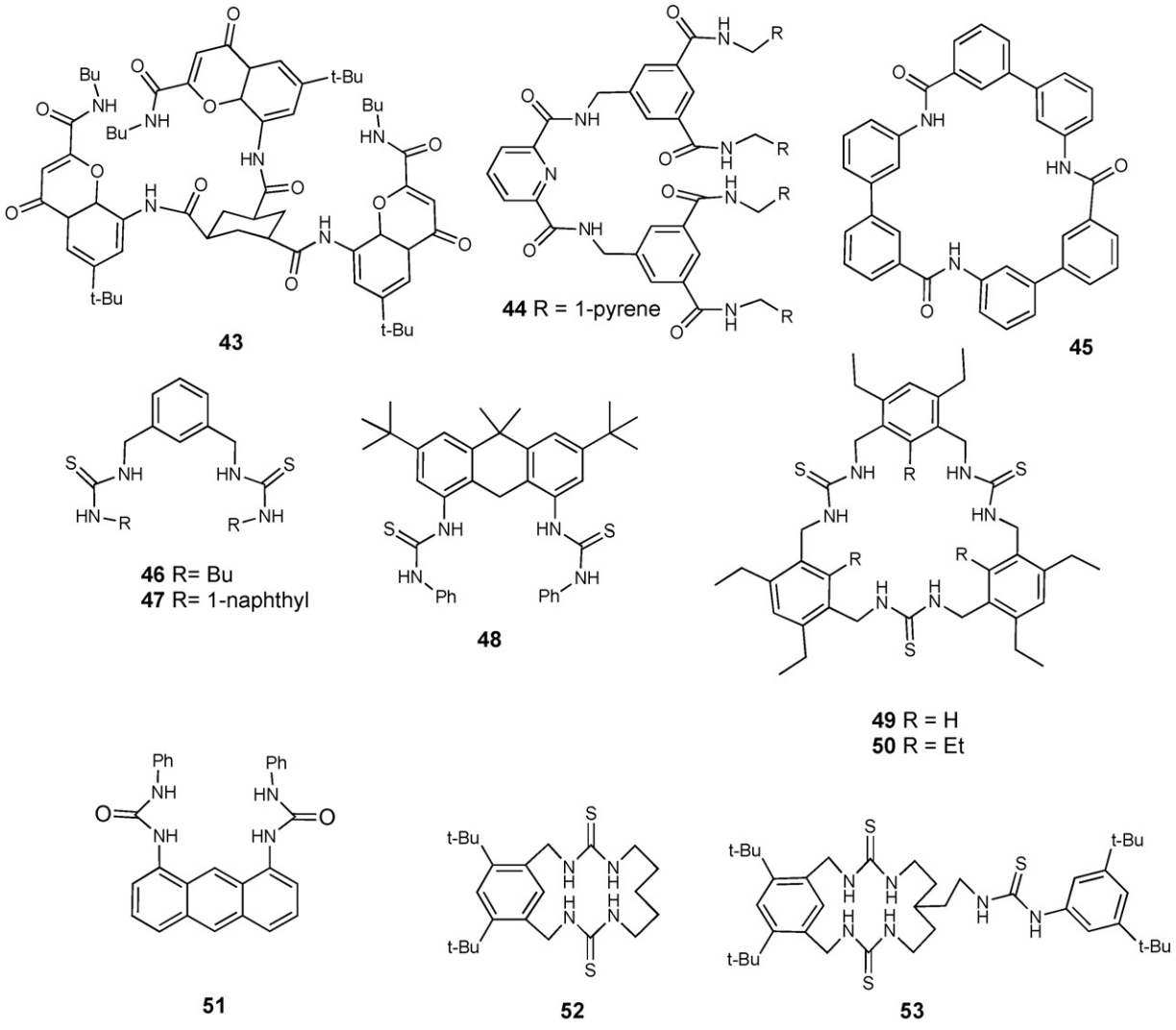


Fig. 14. Examples of amide- and (thio)urea-based anion receptors.

is relatively high in the case of this receptor, being ca. five- to six-fold. A similar design strategy underlies the cyclic amide **45**. In DMSO, this system displays selectivity for dihydrogen phosphate anion over hydrogen sulfate ($K_a = 15{,}000$ and $170\,M^{-1}$, respectively) [85].

Simple bisthiourea receptors, such as **46**, **47** and **48** bind dihydrogen phosphate anion well in DMSO [86]. The best binding and selectivity was observed for systems **47** and **48** derived from aromatic amines and hence possessing the most rigid structures. These receptors bind dihydrogen phosphate anions with affinity constants, K_a, of 4600 and $195{,}000\,M^{-1}$, respectively, in DMSO. In all cases, the following selectivity order (illustrated using data for receptor **46**; K_a values in M^{-1}) was observed in DMSO: $H_2PO_4^-$, 820; AcO^-, 470; Cl^-, 9; HSO_4^-, 2; $NO_3^- < 1$; $ClO_4^- < 1$. Considerable effort was made to rationalize this trend, which mirrors but does not match completely the energies of hydration (all values in kcal/mol), specifically: AcO^-, 9.4; Cl^-, 8.2; $H_2PO_4^-$, 7.6; NO_3^-, 7.1; HSO_4^-, 5.9, ClO_4^-, 4.8. The weak binding of nitrate, sulfate and perchlorate was ascribed to their relatively low hydrogen bond acceptor strength. Moreover, the low affinity seen for chloride was considered to be due to the high solvation effect for this anion in DMSO. Consistent with this latter proposal, it was found that in 1,2-dichloromethane the dihydrogen phosphate and chloride affinities of receptor **46** are almost identical (19,000 and $13{,}000\,M^{-1}$, respectively). Thus, the selectivity for phosphate is very much solvent dependent.

A similar pattern of solvent dependence was seen in the case of receptor **45**. In this case, the chloride, iodide and nitrate anion-binding affinities could be dramatically decreased from $10^5\,M^{-1}$ in $CDCl_3$ to close to nothing in DMSO, with the concomitant effect that selectivity for tetrahedral anions is achieved in the latter solvent system [87]. It is well documented that the polar aprotic solvent DMSO is capable of electron-pair donation, but is not very effective as an electron acceptor (i.e., it can act as a Lewis base but as a Lewis acid). Thus, DMSO solvates acetate, phosphate and sulfate anions in part by interacting with the positively polarized central atoms present in these oxyanions, namely carbon, phosphorus and sulfur. However, because the positively polarized phosphorus atom is surrounded by four

negatively charged/polarized oxygen atoms, with which DMSO does not effectively interact, phosphate anion is not well solvated by DMSO. On the other hand, only two oxygen atoms serve to "protect" the central carbon atom of acetate; this anion is thus better solvated by DMSO. Similar rationalizations can be invoked to explain the high hydrogen pyrophosphate and dicarboxylate anion selectivities seen for related receptors where the spacer group is anthracene. The analogous open-chain control system, receptor **51**, has binding constants of 101,300 and 103,570 M^{-1} in CH_3CN for pyrophosphate and adipate anions, respectively. [88].

The C3-symmetric metacyclophane-based anion receptors **49** and **50** with thiourea groups were also explored as anion complexants [89]. These systems are of interest in that they are very similar, differing only in terms of their inherent flexibility and the degree of steric bulk present within the anion-binding cavity. The more open system, receptor **49**, showed a preference for $H_2PO_4^-$ over AcO^- ($K_a = 800\ M^{-1}$ versus $320\ M^{-1}$). However, the more rigid receptor **50** displays exactly the opposite selectivity profile and an absolute affinity for acetate anion that is increased by ca. 17-fold ($K_a = 1600$ and $5300\ M^{-1}$ for $H_2PO_4^-$ and AcO^-, respectively).

Macrocycles **52** and **53** represent a different series of cyclophane-based cyclic thioureas, but ones that also act as very efficient anion-binding agents. These compounds show the following selectivity profiles in DMSO: $H_2PO_4^- > AcO^- > Cl^- > HSO_4^- > Br^-$. This differs from the order expected on the basis of anion basicity alone, namely $AcO^- > H_2PO_4^- > HSO_4^- > Cl^- > Br^-$. Such observations parallel what was seen in the case of the acyclic urea receptors **46**–**48** and can likewise be rationalized in terms of differences in anion solvation, as well as, more than likely, an optimized level of size and geometry matching for dihydrogen phosphate relative to other anionic guests. In the event, the combination of appropriate design coupled with the presence of three thiourea recognition subunits gives rise to receptors with particularly high affinity for dihydrogen phosphate in DMSO ($K_a > 10^4\ M^{-1}$ for **52** and **53** and related systems) [90].

7. Guanidinium-type based receptors

The guanidinium moiety is an important anion-binding subunit in many biological receptors, particularly in those that interact with RNA. Its unique combination of cationic charge and hydrogen-bond donor properties has inspired the use of this motif in synthetic host–guest systems. Most of these systems combine the guanidinium subunit with amido and amino fragments (Fig. 16). Only a few pure guanidinium receptors are known that were specifically designed to recognize tetrahedral anions, in particular phosphates and sulfates. One example consists of a guanidinium-functionalized monolayer (Fig. 15) reported by Kunitake and co-workers [91]. Here, multiple interactions are exploited to produce a system that binds ATP and AMP roughly 2 orders more strongly in water than the typical ammonium-type macrocycle receptors described above.

Work with guanidinium functionality actually dates back to the early days of anion receptor chemistry. For instance, Lehn and co-workers reported the synthesis of various flexible macrocycles containing several guanidinium fragments. Of the various systems produced, receptor **54** showed the best affinity for PO_4^{3-} anion, $\log K_a = 4.3$, as inferred from pH titration analyses carried out in the presence of phosphate anions in methanol–water (9:1) mixtures. The high affinity was considered to reflect the good charge balance between the anion and

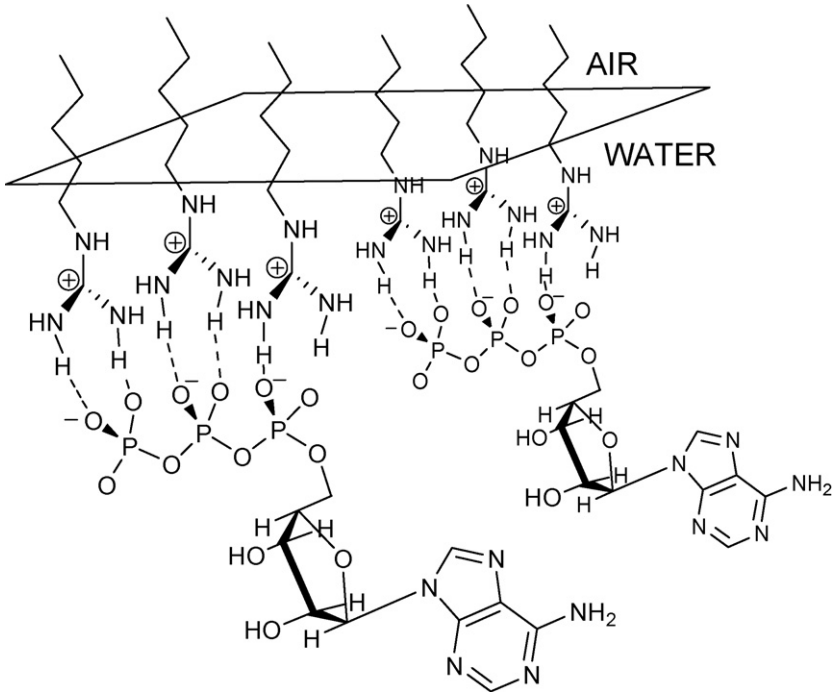
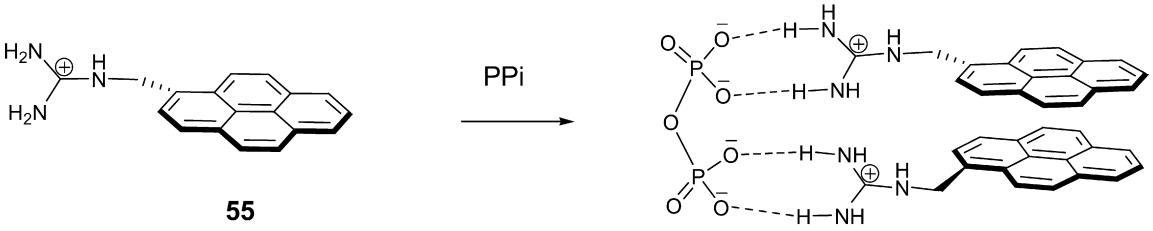


Fig. 15. Schematic illustration designed to show the binding of ATP to a guanidinium monolayer at the air–water interface.

the positively charged guanidinium-based receptor [92]. Later on, the pyrene derived guanidinium receptor **55** was shown to be a highly selective spectroscopic sensor for pyrophosphate anion in methanol. It forms a 2:1 complex with $K_{11} = 1.0 \times 10^4\ M^{-1}$ and $K_{21} = 1.2 \times 10^8\ M^{-2}$. This binding stoichiometry was interpreted in terms of the formation of a sandwich-like pyrene dimer via π-stacking of two receptor molecules and the concomitant coordination of the two guanidinium groups to the pyrophosphate [93].



55

de Mendoza and co-workers have made a number of important contributions in the area of guanidinium-based anion receptor chemistry. In work relevant to the problem of oxyanion recognition, these researchers showed that structure **56**, which combines guanidinium fragments with two carbazoles, is able to bind in seeming cooperative fashion both the phosphate anion and purine nucleus portion of 2′-deoxyadenylyl(3′ → 5′)-2′-deoxyadenosine (*d*(AA)) [94]. The proposed π-stacking between the carbazole subunits with the purine nucleus was supported by NOE NMR experiments. Receptor **56** was found capable of extracting quantitatively dinucleotides from aqueous media into dichloromethane solution (Fig. 16).

Receptor **57**, a polytopic system containing two guanidinium moieties, was reported by Ariga and Anslyn. It was designed with the goal of enhancing the hydrolysis of phosphodiesters via stabilization of dianionic phosphorane intermediate within a positively charged cleft [95]. This system can form four directional hydrogen bonds to two of the oxygen atoms of a bound phosphodiester molecule, species that were found to be complexed well in deuterated DMSO–D_2O mixtures ($K_a = 800\ M^{-1}$ for dibenzyl phosphate in deuterated DMSO at an ionic strength of 0.045 M and $K_a = 700\ M^{-1}$ in deuterated DMSO/D_2O, 67/33, at an ionic strength of 0.516 M). A similar design strategy, wherein acylguanidines were used as the key binding elements, was reported essentially concurrently by Hamilton and coworkers [96]. The resulting receptor, compound **58**, was found to bind diphenyl phosphate (as its tetraphenylborate salt) efficiently in acetonitrile ($K_a = 4.6 \times 10^4\ M^{-1}$).

Two years later, Schmidtchen, one of the early pioneers in the area of anion recognition chemistry, employed an analogous approach to generate phosphate anion receptors **59** and **60**. These systems also rely on the presence of two guanidinium units to form hydrogen bonds to bound phosphate anion oxygen atoms [97]. These two receptors differ in their solubility in water and organic solvents (e.g., DMSO, MeOH) and were studied as their perchlorate or halide (chloride, bromide) salts. The more organic soluble receptor, **59**, was found to have a high affinity for HPO_4^{2-} and 5′-AMP^{2-} in methanol ($K_a = 18{,}300$ and $38{,}000\ M^{-1}$, respectively). Switching the solvent to straight DMSO served to reduce the hydrogen phosphate association constant to one third of its original value. Such an observation is consistent with the dominance of electrostatic binding interactions in analogy to what was found for various amido receptors, as discussed above. Interestingly, however, the binding affinities of the water-soluble receptor **60** in water were found to be smaller than those recorded for **59** in DMSO. In water, the highest binding constants for **60** were observed for HPO_4^{2-} ($K_a = 970\ M^{-1}$) and ATP^{4-} ($K_a = 840\ M^{-1}$).

To provide receptors tuned for the recognition of sulfate, Berger and Schmidtchen elected to decrease the distance between the two guanidinium subunits by using an isophthalimide spacer. This gave rise to receptors **61** and **62**, systems that showed especially high affinities for sulfate in methanol ($K_a > 10^6\ M^{-1}$, in both cases) [98]. Attaching a long chain substituent, as in compound **62**, serves to increase the solubility of the receptor in non-polar organic solvents. This allowed this class of molecules to be used extract sulfate anions from water into chloroform solutions. The process of sulfate complexation is strongly entropy driven and inherently endothermic, as judged from thermodynamic data obtained from ITC measurements. Such observations provide support for the notion that the host–guest complex is less well solvated than the initial combination of free receptor and anion salt. To the extent such a conclusion is true, it suggests that the high sulfate anion affinity reflects a combination of receptor preorganization and efficient hydrogen bonding to the bound anionic target.

Another approach allowing efficient oxyanion complexation was put forward by Yeo and Hong [99]; it involves the use of isothiouronium units as the key anion recognition motifs. Relative to the better-studied guanidiniums, isothiouronium subunits possess relatively large dipole moments and are characterized by higher NH acidities. In accord with design expectations, it was found that compound **63** binds phosphate species strongly in DMSO. The affinity constants (K_a) were found to decrease in the order: $PhPO_3^{2-}$ ($4350\ M^{-1}$) > $PhOPO_3^{2-}$ ($3700\ M^{-1}$) > $H_2PO_4^-$ ($1080\ M^{-1}$) > $PhCOO^-$ ($590\ M^{-1}$) > $PhSO_3^-$ ($5\ M^{-1}$). Notable is the fact that although the phosphate-acetate selectivity is not particularly high, the discrimination between $PhOPO_3^{2-}$ and $PhSO_3^-$ approaches 10^4.

The tripod-based approach to the design of receptors for oxyanions, outlined in Fig. 7 above, has also been used to produce isothiouronium-based receptors [100]. Specifically, the

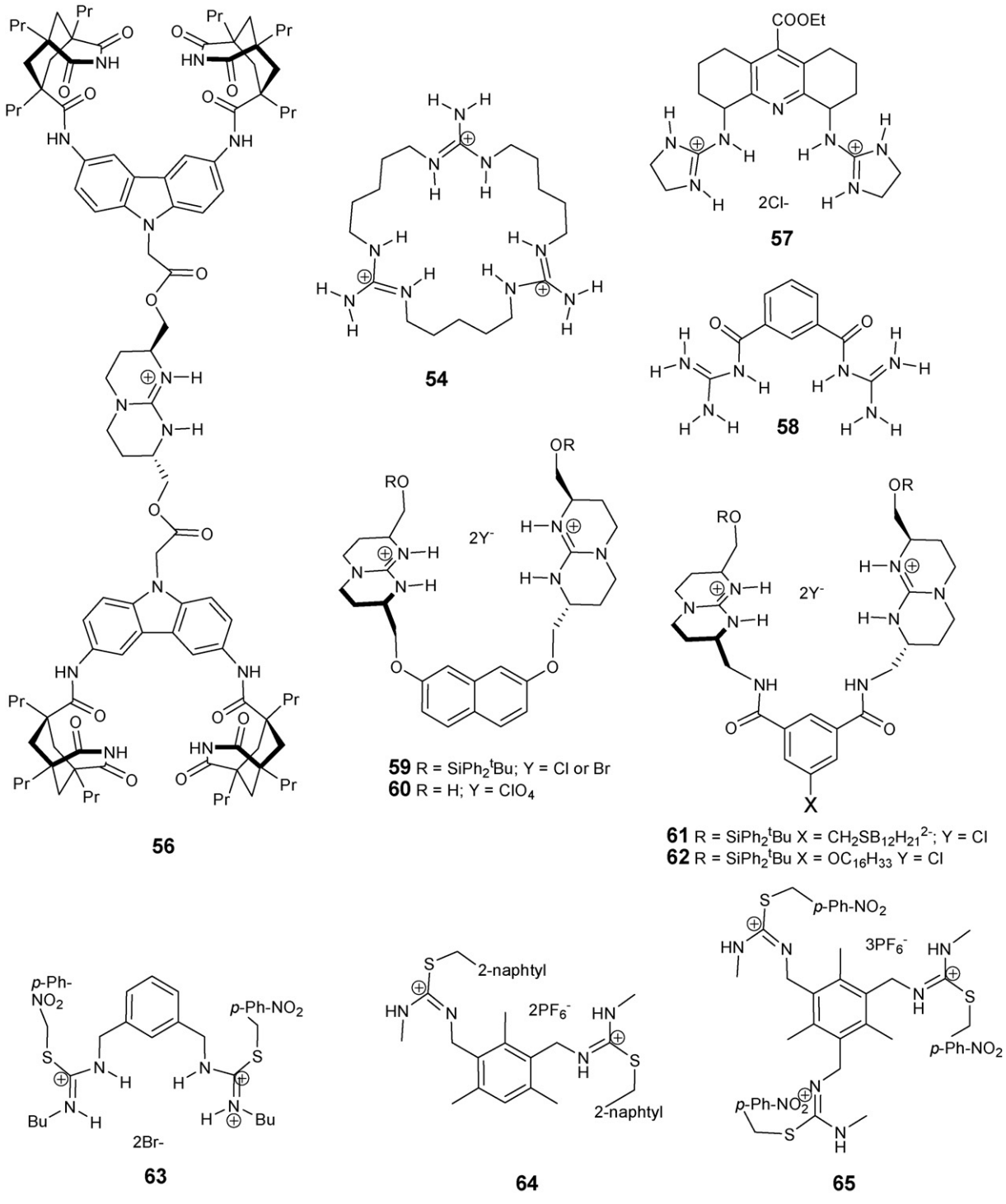


Fig. 16. Selected guanidinium-type anion receptors.

di-functionalized and tri-functionalized receptors **64** and **65** were prepared as their hexafluorophosphate salts and studied in methanol using ITC. Although the disubstituted receptor **64** bears considerable resemblance to receptor **63** (vide supra), it differs from it in that the benzene core is more highly substituted. While data are not available that allow for a direct comparison, receptor **64** binds sulfate (tetramethylammonium salt) with a 1:2 host–guest stoichiometry in methanol and with good affinity ($\Delta G = -6.0$ kcal/mol; $\Delta H = +8.8$ kcal/mol; $T\Delta S = 14.8$ kcal/mol).

In contrast to what is true for the disubstituted control system **64**, the triply functionalized receptor **65** was found to bind sulfate dianion (tetramethylammonium salt) with a 1:1 stoichiometry in methanol and with greater affinity, i.e. $\Delta G = -8.3$ kcal/mol ($\Delta H = +6.4$ kcal/mol; $T\Delta S = 14.7$ kcal/mol; K_a about 10^7 M^{-1}). However, in analogy to what is true for **64**, this binding process

is entropically driven. In any event, the high affinities displayed by **64** and **65** makes it likely that these receptors support the formation of stabilizing hydrogen bonding networks similar to those obtained in the case of receptors **59–62**.

Unfortunately, titration experiments carried out using tribasic phosphate did not give rise to clean binding profiles. This precluded the determination of affinity constants or thermodynamic values. The complexity seen with PO_4^{3-} is thought to reflect the presence of multiple binding sites, as well as the fact that the larger nature of the phosphate anion would favor the formation of complexes with 1:2 and 2:1 host–guest stoichiometries. Thus, even though PO_4^{3-} has a higher charge density than SO_4^{2-} it is not bound cleanly. By contrast, the cavity provided by the conformationally defined receptor **65** is complementary to sulfate dianion in terms of both size and shape.

8. Amidinium and imidazolium-based receptors

Amidinium cation (e.g., structure **66**, protonated amidinium; Fig. 17) is a member of generalized guanidinium family and represents an important motif that has proved extremely useful in preparing receptors for oxyanions. Compared to analogous guanidinium systems, the amidinium NH protons are slightly less basic ($pK_a > 11$). Therefore, amidiniums generally act as better hydrogen donors after protonation. Amidinium-carboxylate salts are of particular interest as model systems for the arginine-aspartate salt bridges found in many biological structures in DNA [101], RNA [102] and in the active site of dihydrofolate reductase [103]. However, to date only a few receptors have been synthesized that act as efficient sensors for biologically important phosphates. In these systems, the general binding pattern involves two hydrogen bonds between one or more oxygen atoms of an oxyanion (e.g., phosphate, competing carboxylate, etc.) and the NH donor sites of the amidinium cation. Not surprisingly given its structure, amidinium cations and systems derived from them generally display a preference for carboxylate anions (cf. Fig. 17, structure **66**, i.e. the complex between pyruvate and benzamidinium).

Eschenmoser and co-workers were the first to provide evidence that amidinium group could be used to effect anion

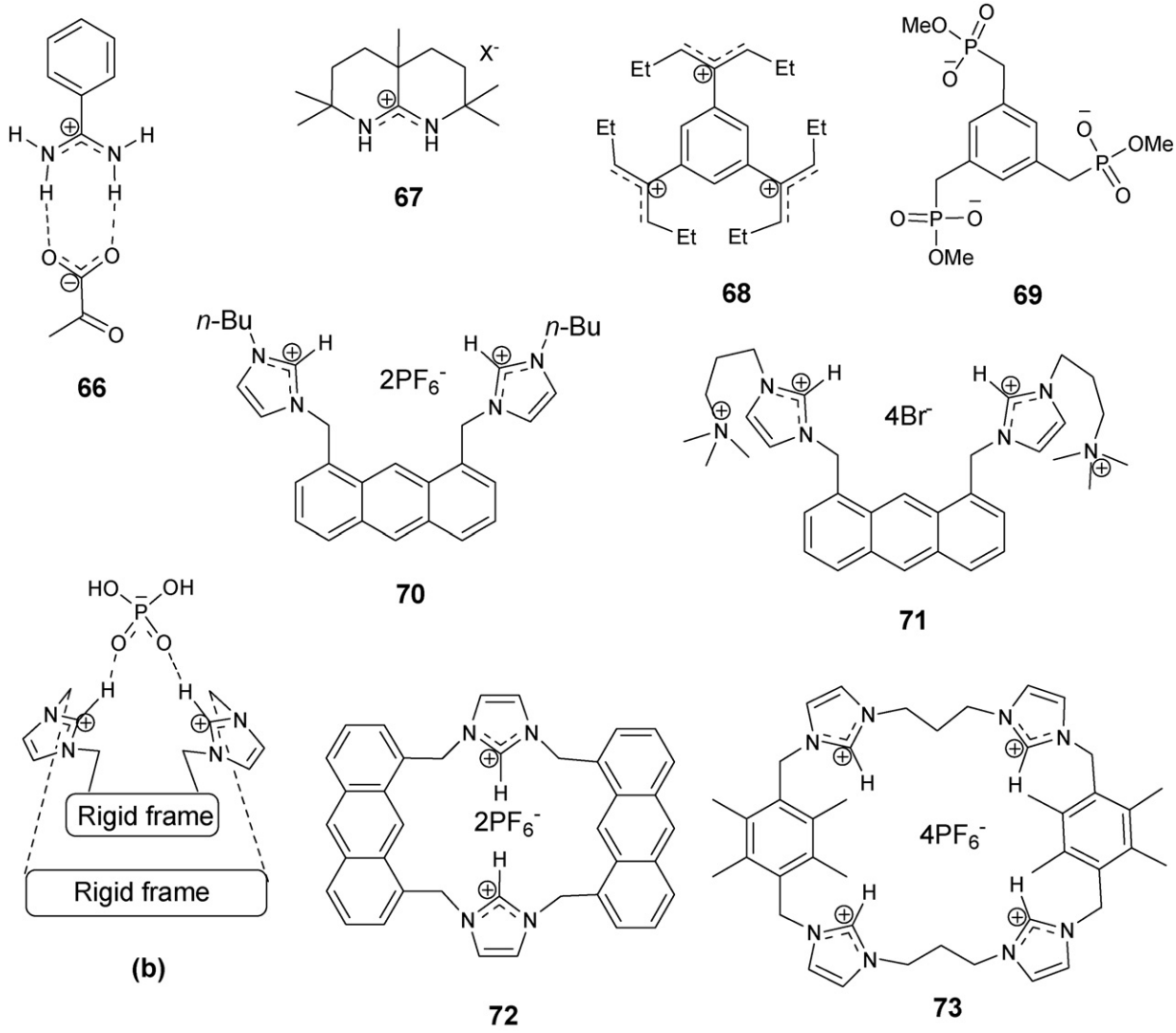


Fig. 17. (a) Selected amidinium- and imidazolinium-type receptors. (b) Design strategy used for developing the dihydrogen phosphate selective receptor **72**.

recognition; they showed that **67** was capable of extracting hydrogen sulfate from an aqueous to an organic phase [104].

An interesting example of an aminidinium-based phosphate receptor was subsequently provided by the work of Kraft and co-workers [105], wherein three ethylated amidinium units are used to generate system **68**, a species that is bound to **69** with a binding constant, K_a, of $1.1 \times 10^6\ M^{-1}$ in CD_3OD solution.

Imidazoliniums, namely 1,3-disubstituted imidazolium motifs, are relatively new cationic subunits for anion recognition. These systems bind anions as the result of both electrostatic interactions and specific $CH^+ \cdots A^-$ type hydrogen bonds, where A^- is anion. As compared to other NH hydrogen bond donor systems (vide supra), imidazolinium-based receptors offer a significant advantage, namely pH-independent (or near independent) binding. However, imidazolinium based systems differ structurally from most other charged anion-binding motifs in that they provide only one directional hydrogen bond. As a consequence, they generally display a preference for spherical halide anions. Nonetheless, several highly phosphate efficient sensor systems based on imidazoliniums are known [15].

Recently, Yoon and co-workers described the new imidazolium-based fluorescent chemosensors **70** and **71** [106,107]. These are cleft-type receptors that bear analogy to the corresponding guanidinium systems (see structures **59**–**65**). They were found to sense biologically important phosphate anions well. In fact, fluorescent titrations of **70** carried out in acetonitrile revealed K_a values of 1.3×10^6, 7900, 4500 and $600\ M^{-1}$ for $H_2PO_4^-$, Cl^-, Br^- and I^-, respectively. The high K_a value and selectivity for dihydrogen phosphate within this set of anions (the corresponding K_a for F^- binding could not be obtained due to inconsistencies in the titration curve) were rationalized in terms of the directional hydrogen-bond interactions provided by the pre-organized and relatively rigid imidazolinium units. Interestingly, receptor **71**, bearing an increased positive charge, does not bind inorganic anions appreciably in water, but displays good affinity for ATP ($K_a = 15{,}000\ M^{-1}$) and GTP ($K_a = 87{,}000\ M^{-1}$), as determined by fluorescent titrations carried out at pH 7.4. Considerably lower affinity was seen for ADP ($K_a = 614\ M^{-1}$) and AMP ($K_a = 121\ M^{-1}$). The selectivity for GTP over ATP was ascribed to the presence of π–H interactions, which were calculated to be more important in the case of GTP than ATP.

Later this same group suggested a conceptually new design strategy for developing a receptor that could have good selectivity for dihydrogen phosphate over fluoride anion (see schematic structure (b) in Fig. 17). The strategy is based on fixing two imidazolinium units within a rigid framework produced by the use of, e.g. an anthracene spacer. The resulting system, macrocycle **72**, displays a high affinity for dihydrogen phosphate anion but is not particularly selective versus halide anions (K_a values in acetonitrile are 1.3×10^6, 340,000, 2000 and $780\ M^{-1}$ for $H_2PO_4^-$, F^-, Cl^- and Br^-, respectively) [108]. In contrast, the analogous (but larger) tetracationic macrocycle, **73**, developed by Sato et al., was found to bind hydrogen sulfate anion preferentially in DMSO-d_6 ($K_a = 8500$, 2230, 1350, 720, 460 and $290\ M^{-1}$ for HSO_4^-, Br^-, $H_2PO_4^-$, Cl^-, I^- and ClO_4^-, respectively) [109].

9. Amido-amine receptors

Beer et al. suggested that the tripodal ligand **74** would be suitable for the binding and extraction of pertechnetate anion [110]. This ditopic receptor (Fig. 18), based on the combination of tris(2-aminoethyl)amine and crown ether motifs, was found to complex sodium cations and to extract perrhenate and pertechnetate anions from aqueous solutions into an organic phase. The distribution coefficient, D, for pertechnetate in test extraction studies (2.3) was found to be rather high, and substantially larger than what is seen for crown ethers alone. Interestingly, the inherent affinity of this receptor for perrhenate was found to be relatively low ($K_a = 60\ M^{-1}$ in $CDCl_3$). On the other hand, addition of sodium picrate serves to boost the binding affinity by more than 10-fold ($K_a = 840\ M^{-1}$ in $CDCl_3$). Three factors likely contribute to this increase: First, complexation of a sodium cation within the crown portion serves to preorganize the ligand for tetrahedral anion guest recognition; second, the bound cation provides additional coulombic stabilization for the co-bound anion; third, the presence of cations increase the acidity of amido hydrogens. At the present time, the relative contribution of these various factors is not known.

Another tripodal amino-urea based receptor, **75**, a system bearing naphthyl amide groups, was developed by Xie et al. [111]. It was studied *inter alia* for its ability to complex tetrahedral oxyanions. It was found that the stability constants in DMF, as determined by fluorescence titrations, are $H_2PO_4^-$ ($40{,}650\ M^{-1}$) and HSO_4^- ($2750\ M^{-1}$). It was suggested that in this receptor system, the presence of the central amino group provides an additional site for protonation and cooperative binding (Fig. 18).

One of the most efficient extractants of pertechnetate anions is system **76** described by Vögtle and co-workers [112]. This amino-urea extractant, which is based on a dendrimer motif, was found to extract both perrhenate and pertechnetate anions from a pH 7.4 aqueous phase into chloroform solution almost quantitatively (percentage distributions into the organic phase of 83.6% and 90.3% for ReO_4^- and TcO_4^-, respectively). At pH 5.4, the extraction percentages increase to 97.7% and 98.8% for these two anions, respectively. Perhaps not surprisingly, this dendrimeric system also proved capable of extracting efficiently various adenosine nucleotides, doing so according to the following selectivity order: ATP > ADP > AMP (extraction percentages of 83.5%, 73.5% and 3.0%, respectively).

A series of new amido-amine macrocyclic receptors, **77**–**82**, were developed by Bowman-James and co-workers. Among them, the isophthalyl-derived ligand **78** is of particular interest. This is because an X-ray diffraction analysis of a single crystal grown from ligand **78** in the presence of tetrabutylammonium hydrogen sulfate ($TBAHSO_4$) revealed that in the solid state this receptor stabilizes an unexpected, 2:1 sandwich-type complex, wherein one SO_4^{2-} dianion is held between two different ligands (Fig. 19). Compound **78**, like many of its congeners was seen to bind dihydrogen phosphate and hydrogen sulfate anions well in DMSO-d_6 (cf. Table 5). It binds these species roughly 2 orders more strongly than nitrate, chloride and iodide in the same solvent and roughly 4 orders of magnitude more effec-

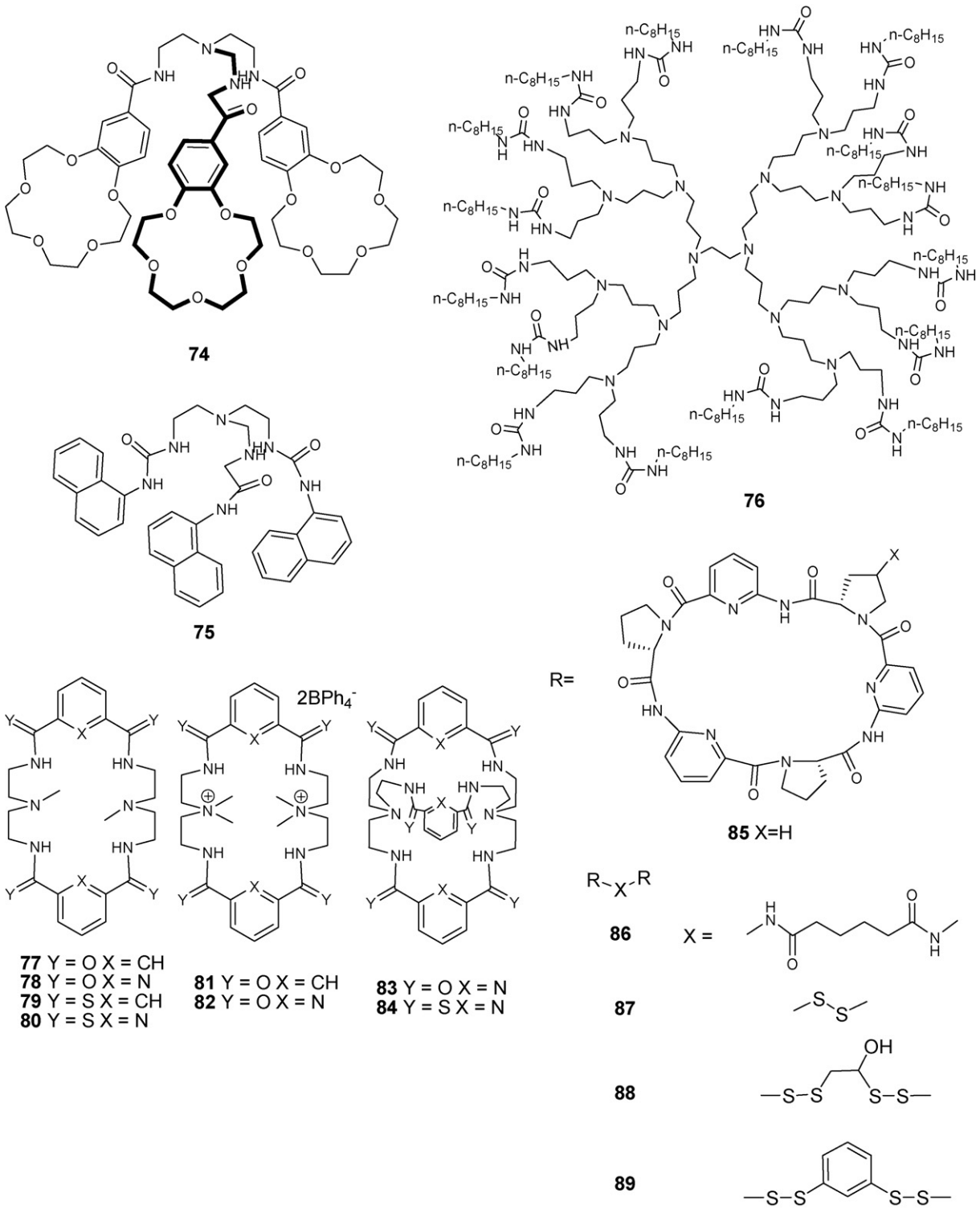


Fig. 18. Amido-amine based receptors.

tively than perchlorate [113]. In the context of this work, efforts were made to enhance the anion-binding affinities of these kinds of receptors. A particular focus was devoted to optimizing the recognition of tetrahedral oxyanion species. This was achieved by alkylating the amino groups and by replacing the bridging benzene subunits by pyridine rings. The use of thioamide linkages rather than amides was also exploited [114]. The results of these optimization efforts are reflected in the high affinity constants ($\log K_a$) obtained for $H_2PO_4^-$ and HSO_4^- binding, as summarized in Table 5.

The data in Table 5 permit a number of very important conclusions about the structure-anion affinity properties of amide-amine receptors to be drawn. First, an increase in binding affinity is observed when a pyridine-diamide fragment is used to replace

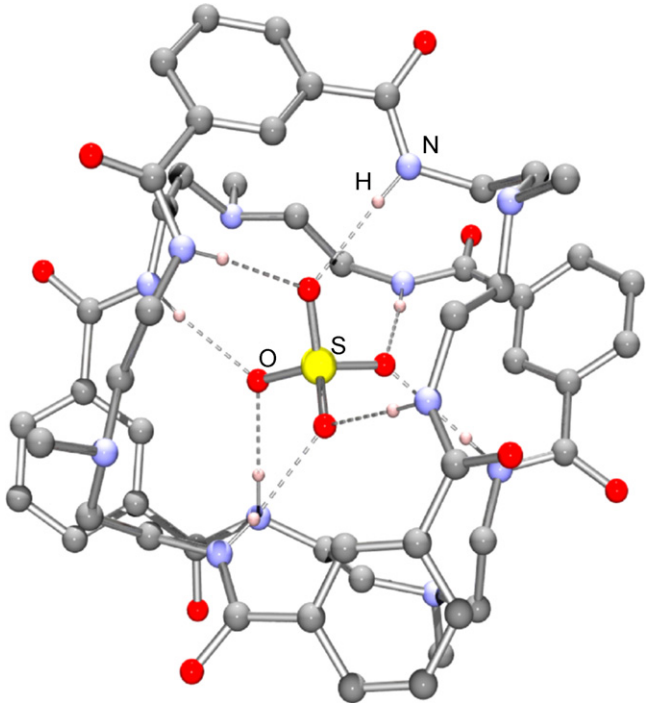


Fig. 19. View of the sandwich-type complex (**78**)$_2$·SO_4(TBA)$_2$. This figure was generated from X-ray structural data originally published in reference [113]. The hydrogen atoms, tetrabutylammonium (TBA) cations and co-bound water molecules have been omitted for clarity.

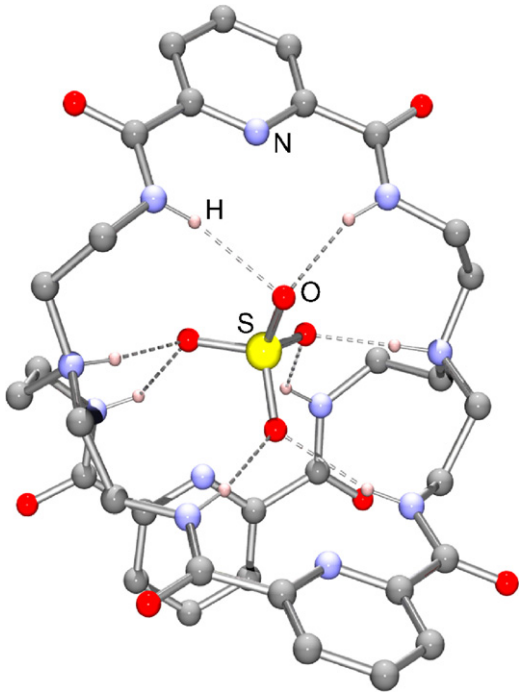


Fig. 20. View of the sandwich-type complex (**83**)·H_2SO_4. This figure was generated from X-ray structural data originally published in reference [117]. The hydrogen atoms and co-bound water molecules have been omitted for clarity.

the corresponding isophthalyl spacer. As in other anion receptor systems, it is suggested that this reflects the fact that the central pyridine nitrogen atom assists in the preorganization of the amide protons via the formation of intramacrocyclic hydrogen bonds. Second, ligands **81** and **82** were found to be more efficient receptors than their neutral analogues, **77** and **78**; presumably, this is due to the added electrostatic attraction present in the charged receptor systems. Third, the use of thioamide linkers serves to increase the binding affinities by almost one order of magnitude relative to analogous amide systems. Interestingly, this latter substitution gives rise to enhanced selectivity for $H_2PO_4^-$ over HSO_4^- in the case of the benzene-derived macrocycles **77** and **79**, but reduces it in the case of the corresponding pyridine systems, **78** and **80** [115].

Recently, Bowman-James and co-workers produced three-dimensional analogues of **78** and **80** (structures **83** and **84**) [115–117]. These systems are the product of an ongoing, rational effort to develop receptors for tetrahedral anions. A single crystal X-ray diffraction structure of the complex **83**·H_2SO_4 reveals that sulfate anion binding in the solid state involves all eight NHs (Fig. 20). The orientation of amide hydrogens is presumably pre-established in a favorable orientation as the result of hydrogen bond interactions involving the pyridine nitrogen long pairs. Although increased affinity and selectivity for oxyanionic substrates can be expected for appropriately designed three-dimensional receptor systems as compared to the corresponding macrocyclic (and hence topographically planar) analogues, in the case of **84** the spherical halide anions, fluoride ($\log K_a > 5$) and chloride ($\log K_a > 3$), compete effectively with the targeted tetrahedral species, phosphate ($\log K_a > 3$) and sulfate ($\log K_a \geq 1.8$) in DMSO (Table 5).

Table 5
Association constants ($\log K_a$) for the binding of dihydrogen phosphate and hydrogen sulfate to macrocyclic polyamide-amine ligands

Anion	77	78	79	80	81	82	83	84
$H_2PO_4^-$	2.92	4.04	4.97	4.63	4.06	5.32	3.40	3.31
HSO_4^-	2.90	2.03	3.15	4.99	–	3.90	1.69	1.83
Cl^-	1.4	2.69	2.02	2.60	3.23	4.75	1.54	3.48
F^-	2.42	2.61	2.85	4.11	2.68	2.04	4.50	5.90
NO_3^-	<1	<1	<1	<1	1.65	2.32	1.93	–
ClO_4^-	<1	<1	<1	<1	1.60	2.40	–	–

The data included in this table are from NMR spectroscopic titrations carried out in DMSO-d_6.

An exciting new class of amino-amide receptors with high selectivity for sulfate anion was reported recently by Kubik et al. [118]. The first receptor of this type, **86**, is derived from L-proline and 6-aminopicolinic acid and consists of two cyclopeptides bridged by a spacer group. The net result is a potential ditopic binding system. The recognition that **86** might prove useful as a ditopic receptor came from earlier studies of the simple cyclopeptide **85**; it was found that this monotopic analogue of **86** forms a 2:1 complex with sulfate. Hence, the thought was that linked systems, such as **86–89** would prove even more efficacious in this regard. In the case of **86**, the stability constants were measured in 50% methanol/water solution by both NMR spectroscopic titrations and ITC analysis; they were found to vary over the 10^5–10^2 M^{-1} range and to decrease in the following order ($\log K_a$ values in parentheses as determined by NMR/ITC measurements): SO_4^{2-} (5.54/4.55) > I^- (3.95/3.79) > Br^- (3.72/3.45) > Cl^-

(2.85/2.85) > NO_3^- (2.11/not determined). A good correspondence between the NMR spectroscopic analyses and ITC measurements was observed. The advantage of the latter studies is that they allowed the associated thermodynamic parameters to be obtained. In particular, for the binding of sodium sulfate, it was found that $\Delta H = -15.0$ kJ/mol and $T\Delta S = 11.0$ kJ/mol. By contrast, for sodium iodide $\Delta H = -13.2$ kJ/mol and $T\Delta S = 8.4$ kJ/mol. From a thermodynamic point of view, receptor **86** thus stands in marked contrast to analogous guanidinium-based receptors, such as **64** and **65**. This is because in the case of **86**, the binding process is driven both enthalpically and entropically.

The monotopic cyclopeptide **85** proved to be a more efficient receptor for sulfate than the ditopic system **86**. Microcalorimetric titrations (e.g., ITC analyses) confirmed the 2:1 binding stoichiometry for the complex of **86** with sulfate, while likewise providing quantitative binding data, namely $\Delta H = -19.3$ kJ/mol and $\log K_T = 6.48$. The observation that the simple macrocyclic control system, **85**, was a better receptor than **86** was an unexpected result. The authors attributed it to the low flexibility inherent in the ditopic receptor. It was thus thought that by choosing a more appropriate linkage, it would prove possible to enhance the binding affinity. Towards this end, the authors made a dynamic combinatorial library (DCL), exposing dimer **87** to several thiols in the presence of oxygen and potassium sulfate using a 2:1 acetonitrile/water mixture as the solvent [119]. Under these conditions, amplification of the two bis(cyclopeptides) **88** and **89** was observed, leading to the inference that both systems bind sulfate anion strongly [120]. In accord with such expectations, receptors **88** and **89** were found to display a 10-fold greater sulfate anion affinity than the first generation system **86**, at least in a 2:1 acetonitrile/water mixture. Such intriguing observations provide support for the notion that the right spacer group can increase significantly the binding affinity of a given type of ditopic receptor.

10. Heterotopic receptors

Phenol has been shown to act as an efficient binding motif in receptors designed to bind tetrahedral anions. In early work by Koga and co-workers it was shown by a combination of X-ray diffraction analyses and NMR spectroscopic studies that bisphenol-containing ligands, such as **90** (Fig. 21), can bind methyl phenyl phosphate via OH hydrogen bond donor groups [121].

In spite of the elegance of Koga's contributions, work with phenol or phenol-derived ligands in oxyanion recognition has involved the use of calixarenes. In some cases, the free phenol sites are implicated in the recognition process, but in most cases their role is more structural, being part of a functionalized molecular framework. A case in point is receptor **91**. This system contains two quinone fragments and two phenolic ethers, which serve as points of attachment for functionalized urea recognition motifs. It shows selectivity for sulfate and phosphate anions (NMR titration in $CDCl_3$, K_a values are HSO_4^-, 2570 M^{-1}; $H_2PO_4^-$, 1010 M^{-1}; CH3COO$^-$, 990 M^{-1}; Cl^-, 830 M^{-1}; ClO_4^-, 85 M^{-1}) [122]. Interestingly, a similar receptor, **92**, derived directly from calix[4]arene, but with two of the oxygen atoms methylated, shows selectivity for chloride and acetate (K_a values are HSO_4^-, 303 M^{-1}; $H_2PO_4^-$, 250 M^{-1}; CH3COO$^-$, 528M^{-1}; Cl^-, 2540 M^{-1}). Presumably, this change in selectivity reflects slight differences in the cavity size of the receptors in question. Consistent with the proposal that small changes in structure can have a substantial effect on binding selectivity was the observation by Beer et al. that, receptor **93**, a system with an ostensibly similar design, showed high selectivity towards dihydrogen phosphate and acetate anion when applied as an electrochemical sensor [123]. In this latter instance, an almost two order of magnitude difference in the selectivity for $H_2PO_4^-$ over HSO_4^- was found in acetonitrile solution. Specifically, the maximal anion-induced cathodic shifts were found to be: 110 mV for $H_2PO_4^-$, <5 mV for HSO_4^- and 40 mV for Cl^-. Most significantly, this receptor was found capable of signaling the presence of dihydrogen phosphate in the presence of a 10-fold excess of chloride and hydrogensulfate anions in acetonitrile solution. Hence, **93** can be used as a dihydrogen phosphate-selective amperometric sensor.

Atwood and co-workers developed calixarene-type receptors that specifically extract pertechnetate from water solution into an organic phase [124]. Representative systems are **94** and **95**, which both rely on the presence of electron-withdrawing metallocenes to enhance the inherent anion-binding affinity. The observed selectivity for extractions into nitromethane was found: $TcO_4^- \geq ReO_4^- > ClO_4^- \gg NO_3^- > SO_4^{2-} > Cl^-$. This selectivity pattern is attributed to a combination of charge, size and shape that makes host nearly ideally optimized for the binding of pertechnetate. Competition studies also showed that **95** is capable of extracting $^{99m}TcO_4^-$ from aqueous solution in the presence of other tetrahedral anions. Efficient extraction is observed at high and neutral pH; however, at low pH values it drops slightly. The molar ratio of the extraction was determined to be 4:1 (host to perrhenate or pertechnetate anions).

The uranyl salen systems developed by Reinhoudt and co-workers represent another very important class of neutral anion-binding receptors. They combine a Lewis acidic meal center with a second binding site based on either amido substituents [125] or a calix[4]arene ring [126]. As a general rule receptors of this type are highly specific for the $H_2PO_4^-$ anion. In the specific case of the preorganized ligands **96**, **97** and **99**, both strong binding ($K_a > 10^5$ M^{-1} 1:1, in MeCN-DMSO, 99:1) and high selectivity in favor of dihydrogen phosphate ion was observed ($K_{rel} > 10^2$ for $H_2PO_4^-$ over Cl^- and $K_a > 10^3$ for $H_2PO_4^-$ over NO_2^- or HSO_4^-) [127] (Fig. 21).

A new strategy for preparing receptors for tetrahedral anions was recently introduced by the authors' groups [128]. In this ongoing collaborative work, simple-to-effect Schiff base bond forming reactions were used to prepare macrocycles containing 2,6-pyridine amide and polypyrrole building blocks (Fig. 22). The advantage of this approach is that it combines known anion recognition motifs with imine functionality that can serve as a further recognition site, either through protonation or via direct interaction with the acid form of an oxyanion (e.g., a P–OH pro-

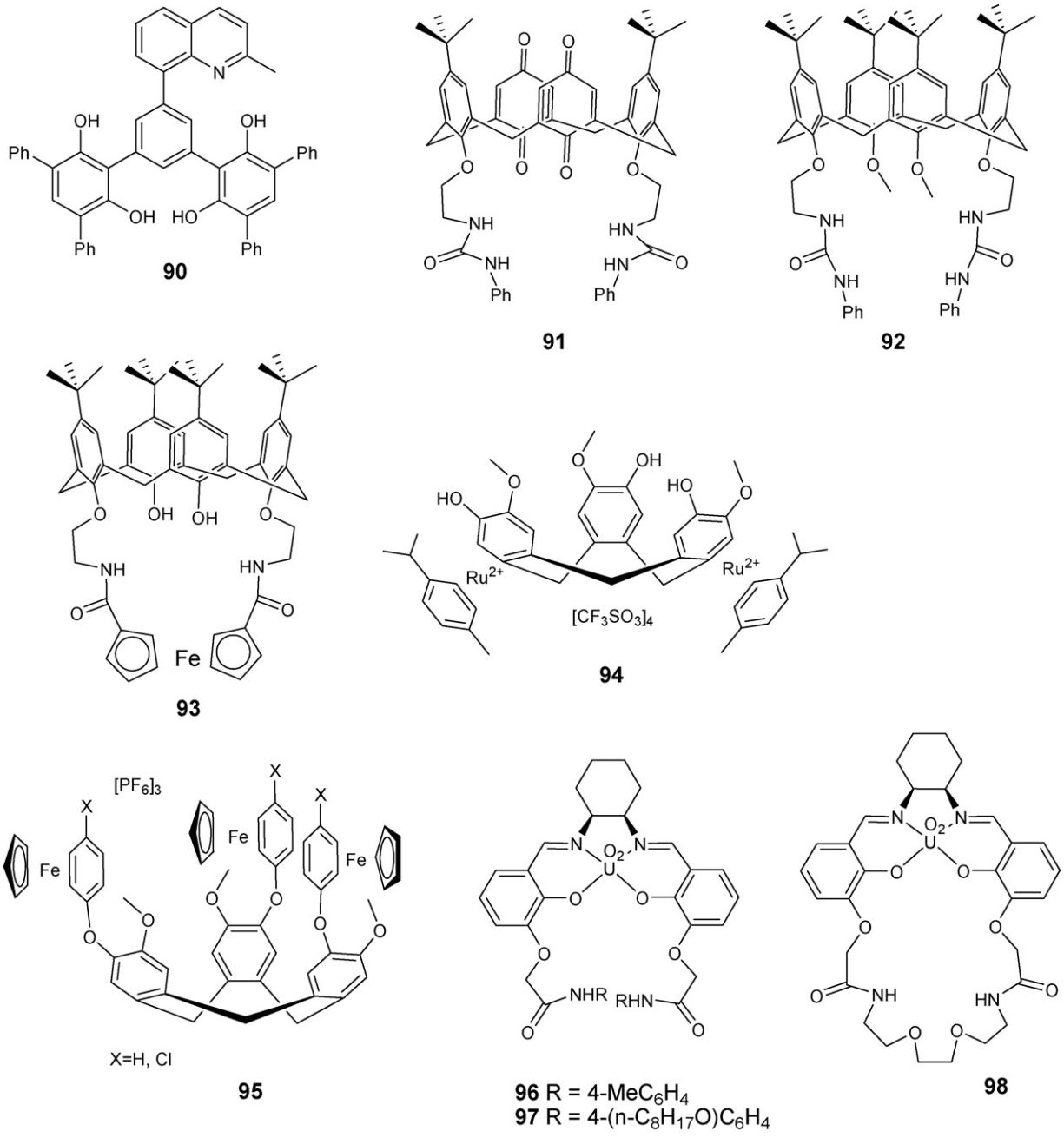


Fig. 21. Selected heterotopic receptors.

ton). The use of these well-defined building blocks also imparts a degree of rigidity to the system.

The first member of this potentially large series of compounds was receptor **99**. It possesses a high affinity for dihydrogen phosphate and was found to bind this particular anionic substrate in a stepwise, 1:2 stoichiometry, as inferred from UV spectroscopic titrations carried out in acetonitrile. Accompanying DFT modeling studies provided support for the existence of two binding sites above and below the macrocyclic cavity that arise, presumably, as the result of facile pyrrole rotation. This receptor was also found to bind sulfate anion well in acetonitrile but have no appreciable affinity for nitrate anion (Table 6). This latter selectivity makes these systems of potential interest in the area

Table 6
Association constants for the binding of representative anions by receptors **99**, **100** and **101**, as determined from UV–vis spectroscopic titrations carried out in acetonitrile at 25 °C

Receptor anion	**99**	**100**	**101**
Cl^-	2000	–	–
CH_3COO^-	38000	12600	26000
HSO_4^-	64000	108000	62500
$H_2PO_4^-$	342000; 26000	29000	191000; 60200

No evidence of binding was seen in the case of bromide or nitrate for any of the systems in question.

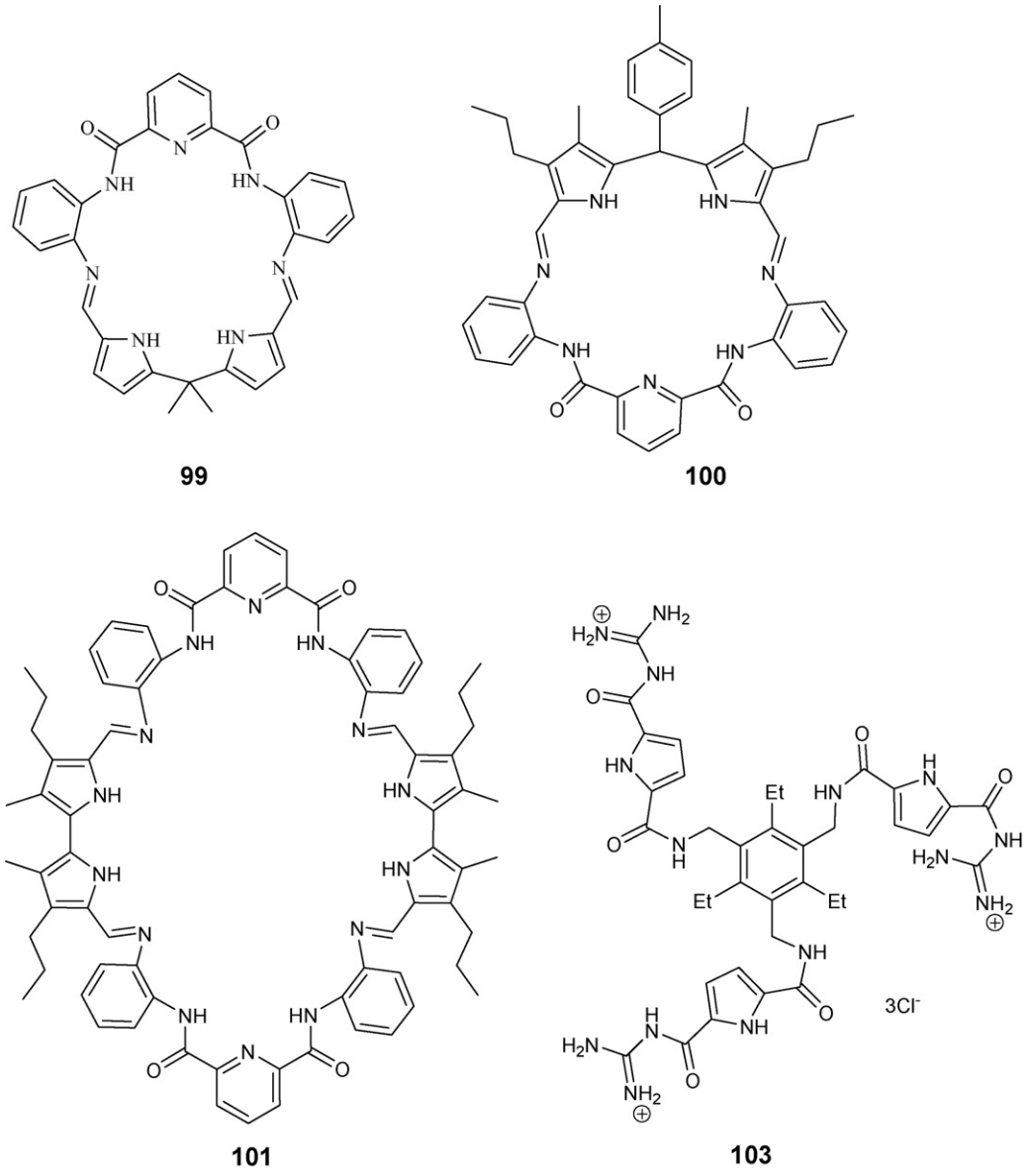


Fig. 22. Selected heterotopic receptors.

of nuclear waste remediation where the selective extraction of sulfate from nitrate rich mixtures is considered beneficial [129] (Fig. 22).

With the goal of simplifying the binding stoichiometry and enhancing the sulfate-phosphate selectivity, a tolyl group was added to the meso-like position of the dipyrromethane fragment. This gave rise to receptor **100**, which was designed to be far more rigid than **99** as the result of a need to avoid potential steric interactions between the tolyl group and methyl subsituents on the pyrrolic three-positions [130]. This structural "fine-tuning" produced a receptor with a high selectivity for hydrogen sulfate anion (ca. 10:1 relative to dihydrogen phosphate in acetonitrile; cf. Table 6). On the basis of theoretical calculations and a single crystal X-ray diffraction analysis of the sulfuric acid salt (Fig. 23), this result was rationalized in terms of an altered cavity geometry and a hydrogen bond donor environment more optimized for the binding of hydrogen sulfate just as was predicted at the time of initial synthetic design.

In the context of the above studies it was discovered that the same kinds of building blocks, namely diformyl pyrrolic precursors and diamines, could be used to effect the combinatorial selection of macrocyclic Schiff base targets when an appropriate anion is used as a template [131]. For example, condensation between a difromyl bipyrrole and a diamine produces the [2 + 2] macrocycle **101** cleanly, but only when the reaction is carried out in the presence of the acid form of tetrahedral oxyanions. The use of other acids leads to formation of a mixture of $[n + n]$ macrocycles, where $n = 1$–4, as well as products presumed to be open-chain oligomers on the basis of mass spectrometric analysis. In acetonitrile, receptor **101** displays binding properties analogous to those of receptor **99**, with the exception that no evidence of chloride binding is seen.

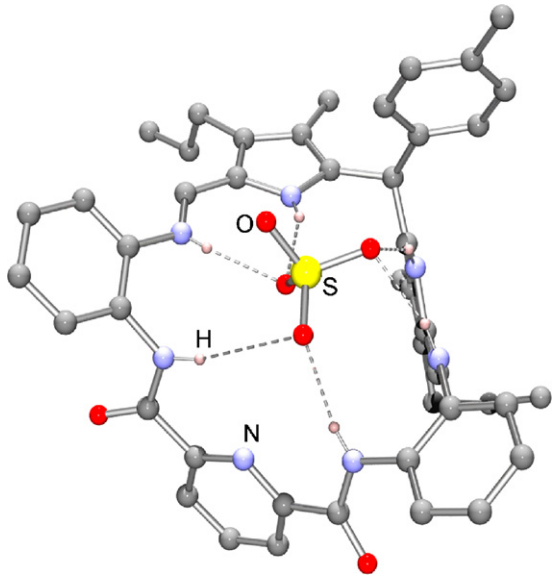


Fig. 23. Single crystal X-ray structure of **100**·H_2SO_4. This figure was generated using data originally published in reference [130]. Most of the hydrogen atoms have been omitted for clarity.

A particularly intriguing property of receptor **101** is that it undergoes rearrangement to produce the corresponding [3 + 3] macrocycle, **107** (instead of [2 + 2]) in the presence of $TBAHSO_4$ or $TBAH_2PO_4$ in acetonitrile, as long as the reaction mixture is allowed to sit for several days in the absence of stirring. Under conditions of greater agitation, the initial [2 + 2] macrocycle precipitates in the form of its anion complex salt. The molecular structure of the [3 + 3] product was confirmed via X-ray diffraction analysis of the sulfuric acid salt; this analysis revealed, not surprisingly, that the bound anion is stabilized in part by hydrogen bond interactions involving all three bipyrrole fragments (Fig. 24).

A different pyrrole-amide receptor, the three-fold symmetric tris-guanidinium system **103**, was reported by Schmuck and

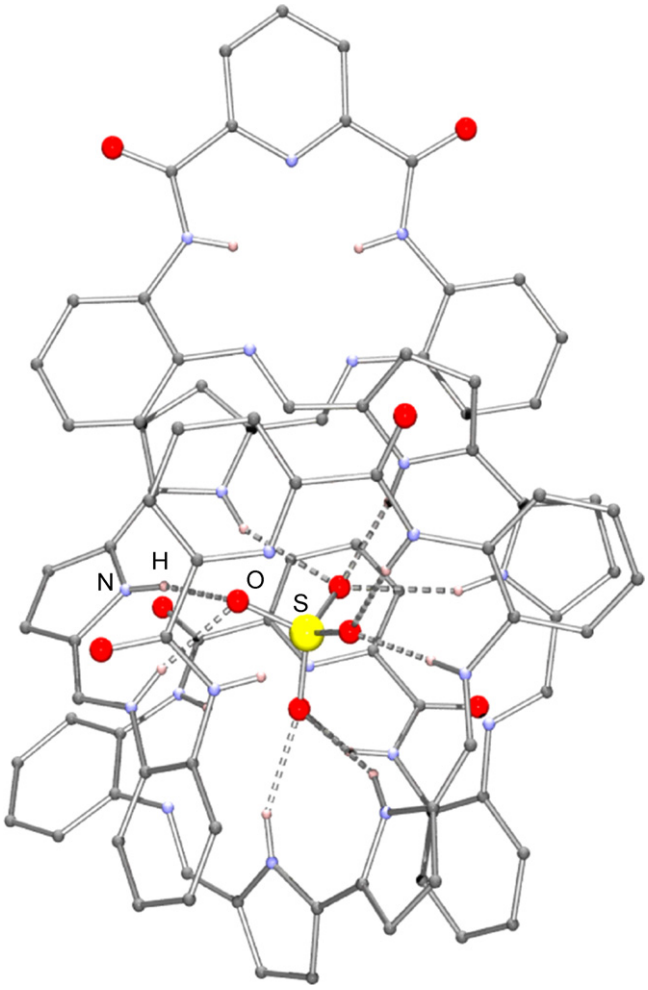


Fig. 24. View of the macrocyclic complex **102**·H_2SO_4. Solvent molecules (CH_3CN and pentane), as well as hydrogen atoms, have been removed for clarity. Dashed lines are indicative of H-bonding interactions.

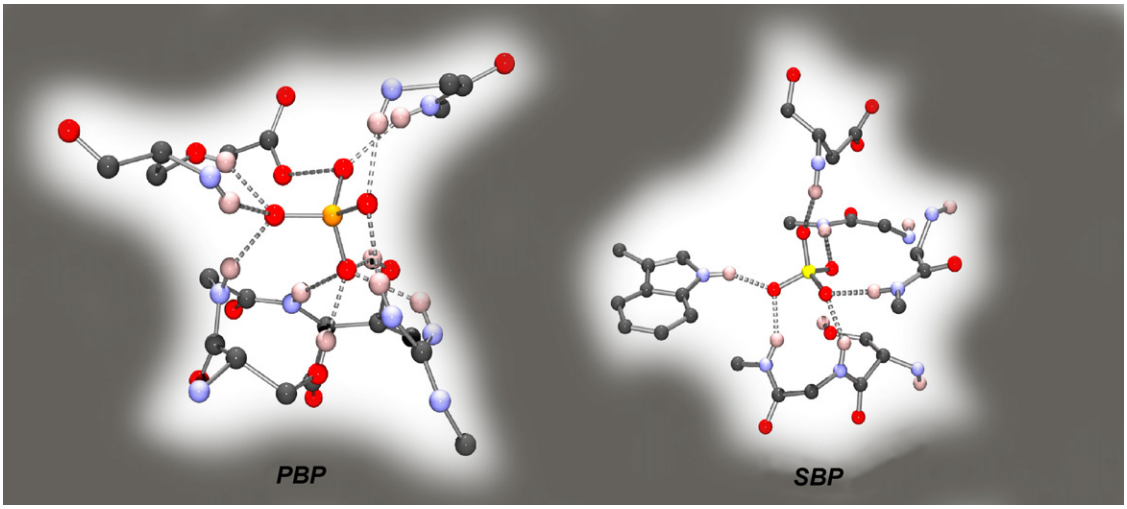


Fig. 25. Hydrogen bonding networks present in the anion bound forms of PBP and SBP, as deduced from X-ray diffraction analyses. Key hydrogen atoms are shown in pink. Most of the remaining hydrogen atoms are not shown for the sake of clarity. This figure was generated using data from the Protein Data Bank as originally published in references [41,134].

Schwegmann [132]. In 30% water–DMSO, this receptor binds phosphorylated carbohydrates with high affinity at pH 4.0. At neutral pH, the binding affinity is roughly two times lower. For example, glucose-1-phosphate and mannose-1-phosphate are bound with $K_a = 25{,}610$ and $25{,}980\,M^{-1}$, respectively, at pH 4 and 12,940 and $14{,}020\,M^{-1}$ at pH 7.4. Model studies of the resulting receptor-substrate complex showed that the two pyrrole motifs are responsible for the binding of the anionic phosphate, while the guanidinium and amido fragments form hydrogen bonds with the OH groups of the sugar.

11. Naturally occuring tetrahedral anion receptors

The most complicated heterotopic receptors are those that are naturally occurring. Perhaps the best studied of these are the phosphate (PBP) and sulfate (SBP) binding proteins. These recognition systems are members of a family of periplasmic proteins that act as initial high-affinity receptors for orthophosphate and sulfate anions [10,41]. Their structures have been characterized by X-ray diffraction analysis [41,133,134], and in both cases an extensive hydrogen bonding network serves to stabilize the bound anions within the active centers (cf. Fig. 25). The cavity of the protein appears to be an exact match to the size and shape of the targeted anions, with the result that they are fully dehydrated and completely bound to the protein. In the case of SBP, no charges are present in the binding cavity. Thus, electrostatic interactions play little or no role in the anion recognition process. Rather, the sulfate dianion is bound through seven hydrogen bonds involving protein-derived NH donor groups.

The cavity of PBP differs considerably from that of SBP. The binding site in PBP contains both hydrogen bond donor and hydrogen bond acceptor groups; together, these stabilize 12 hydrogen bonds with the bound HPO_4^{2-} anion. In addition, to these neutral H-bond donors and acceptors, a carboxylate group from Asp 56 is seen in the binding cavity; it forms a hydrogen bond to the orthophosphate proton (Fig. 26). There is also a positively charged guanidinium group, Arg 135, whose charge is neutralized through formation of salt bridge with the bound phosphate anion and by interacting with the carboxylate side chain of Asp 137 (Fig. 26).

It was initially assumed that the above charged residues contribute significantly to the stability of the phosphate-bound complex. However, Quiocho and co-workers succeeded in characterizing a mutant PBP wherein an Asn residue replaces Asp 137 [135]. The X-ray data analysis revealed the presence of an electronegative Cl^- at this position, which presumably came from the bath solution during crystallization. In the event, binding experiments failed to reveal a dramatic effect on phosphate affinity as the result of these ionic perturbations, leading to the conclusion that hydrogen bonds and other local dipole effects play a dominant role in binding and stabilizing the phosphate-bound anions.

While electrostatic contributions may or not contribute significantly to the overall phosphate anion affinity of PBP, they are certainly considered to be a key to its selectivity. PBP, in obvious contrast to SBP, does not bind sulfate anion. Presumably, this latter anion is excluded due to charge repulsion. Moreover, sulfate lacks the hydrogen atom(s) needed to interact with the Asp56 carboxylate anion and thus derive a positive benefit from this residue. In contrast, SBP can bind phosphate but with much lower affinity due to the lower number of hydrogen bond donors it provides relative to PBP, as well as its smaller cavity size ($K_d = 0.12 \times 10^{-6}$ and 6×10^{-2} M for SO_4^{2-} and HPO_4^{2-}, respectively). A further interesting feature of PBP is that it actually can bind both monobasic ($H_2PO_4^-$) and dibasic (HPO_4^{2-}) phosphate and binds these species rapidly with (rate constants of ca. $10^8\,M^{-1}\,s^{-1}$ at pH 7.0 at low ionic strength); not surprisingly, dissociation rates

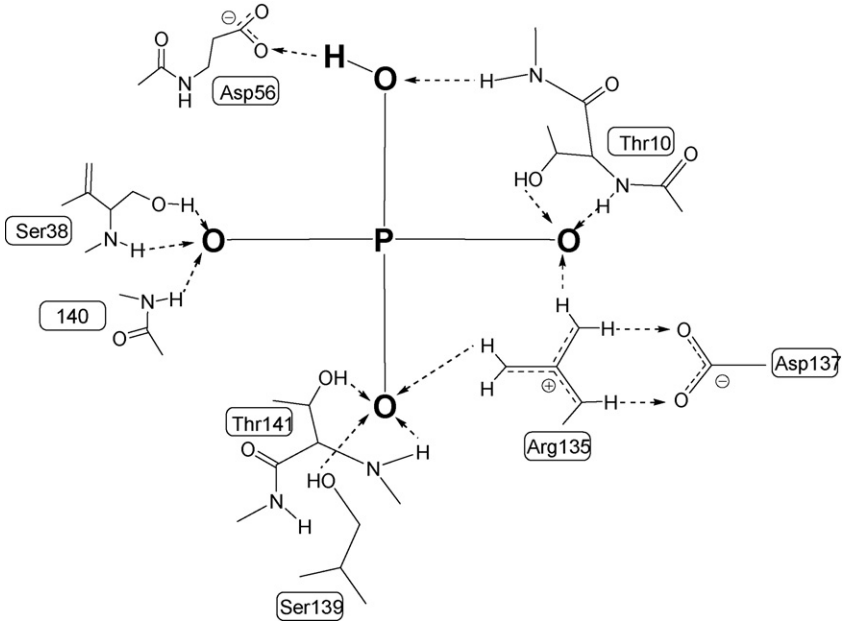


Fig. 26. Schematic representation of the hydrogen bonding network seen in the binding cavity of the phosphate-bound form of PBP.

for inorganic phosphates are low (rate constants of ca. $20\,s^{-1}$) [136].

12. Conclusion

The various systems presented in this review, when considered in concert, serve to underscore the intuitively appealing notion that the size of the binding cavity and the flexibility of the receptor are major factors in determining the selectivity of a given class of anion-binding agent. More rigid systems, with directed hydrogen bonds commensurate with a chosen anionic target, often display the highest affinities and selectivities. For phosphates and sulfates the optimal diameter for the binding cavity is on the order of 6–7 Å, as inferred from X-ray data for a number of different complexes.

Within the context of these general conclusions, important differences are seen for the individual binding motifs. Protonated polyammonium receptors, for instance, are characterized by very high association constants. Moreover, these species typically display a strong preference for doubly charged tetrahedral anions over monoanionic species, such as chloride and nitrate. In this series of compounds, the formation of appropriate copper and zinc complexes can increase both the across-the-board anion-binding affinity, as well as the selectivity for hydrogen phosphate or hydrogen pyrophosphate. In aqueous solution, discriminations in excess of 10^4 relative to chloride, sulfate and nitrate have been obtained using this approach.

In contrast to the electrostatic factors that are critical to the success of polyammonium receptors, pyrrole-based anion receptors rely in large measure on hydrogen bonding interactions involving the pyrrole NH protons. Selectivities are thus often dictated by the Lewis basicity of the anion. As a result most macrocyclic polypyrrole anion receptors bind fluoride anion in preference to phosphate. The latter species can often stabilize a number of hydrogen bond interactions and, in certain cases, interact with the receptor via more than one oxygen atom. As a consequence, good selectivities for phosphate relative the larger halides (chloride and bromide) are usually seen. As a general rule, these systems display little or no affinity for nitrate or sulfate, although this selectivity can be fine-tuned through appropriate molecular design.

Amide- and urea- and containing receptors, when optimized for the purpose, can demonstrate good selectivity for phosphate-type anions. Normally, sulfate anions are not bound well by these kinds of systems. However, competition from acetate and chloride anions is often observed. As a general rule, the thia analogues of these kinds of receptors usually display higher anion affinities, an observation that is ascribed to the presence of more acidic NH protons and their ability to stabilize stronger receptor-anion hydrogen bonds.

Guanidinium-type receptors are especially protean in their binding characteristics. Depending on their design they can be "tuned" to bind selectively either sulfate or phosphate anions. Analysis of the specific receptors in question leads to the conclusion that the guanidinium group does not have a strong inherent preference for a given class of oxyanion. Hence, this motif is particularly attractive since molecular design may be used effectively to obtain highly selective anion receptors. The related anion-binding subunits, namely amidinium and imidazolinium, display an inherent preference for carboxylate and halide anions. Therefore, when working with receptors containing these species, considerable design effort is required to obtain systems with selectivities for tetrahedral oxyanions.

Incorporation of metal centers, as illustrated by several examples discussed in this review, provides an efficient tool for increasing the inherent binding affinity of a receptor; often enhancements of 2 orders of magnitude are seen, especially for phosphate-type anions. The use of this strategy has a further advantage as it often allows the preparation of water-soluble receptors, a characteristic that is common for polyammonium- and guanidinium-type receptor systems.

Heterotopic receptors, which combine different functional groups within a given framework, are far less well studied than anion recognition systems based on a single binding motif. However, it is likely that the use of a heterotopic receptor approach will prove to be an important key in the design of systems that are highly selective for complex anions that are protonated under physiological conditions, such as, e.g. phosphates and phosphate derivatives. Particularly powerful are mixed (thio)amide systems wherein NH hydrogen bond donors are combined with some other recognition group(s). Using such a strategy, the authors of this review have succeeded in generating systems that show very high sulfate-to-phosphate selectivity, something that otherwise has proved quite challenging to achieve.

Acknowledgements

This work was supported by the NIH (grant no. GM 69492 to J.L.S.) and the US Department of Energy (grant no. DE-FG02-04ER63741 to J.L.S.), Russian Foundation for Basic Research (grant nos. 05-03-32684 and 05-03- 08017 to Y.A.U.).

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