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# Macrocyclic anion receptors based on directed hydrogen bonding interactions

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**Contents**



**Abstract**

Natural anion receptors use charge-neutral dipoles to bind small anions with high affinities and selectivities. A convergent and rigid display of hydrogen bond donors such as amide, thiourea and urea functional groups in macrocyclic scaffolds would be one of the most efficient ways to create synthetic anion receptors that mimic natural ones. In this article, we present examples of natural anion receptors and discuss the synthesis of neutral macrocyclic receptors and their anion binding properties.


*Keywords:* Anion binding; Macrocycles; Supramolecular chemistry

## 1. Introduction

Recent advances in chemistry have provided us with the ability to design unnatural molecules, to predict their properties, and to build them. In the field of natural products synthesis, chemists have surmounted delicate molecular structures through the development of novel synthetic methods and, as a result, our knowledge of chemical reactions has been enriched. Nature provides not only target molecules to synthesize but also offers lead structures for the design of artificial receptors. The way in which a natural lead can be improved upon to provide much more effective artificial molecules is well-exemplified in Dervan's elegant work on sequence specific recognition of DNA by polyamides [1]. Although DNA is a polyanionic molecule, electrostatic interactions are not the principal mechanism by which most DNA-binding natural products recognize their target. For example, the antibiotic distamycin contains three amide-linked pyrrole rings and binds preferentially A,T sequences in the hydrophobic minor groove of DNA as an antiparallel 2:1 complex, forming several hydrogen bonds with the DNA bases. Dervan and his coworkers have extended the recognition principle of this natural lead to generate a series of linked pyrrole

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and imidazole derivatives that show highly selective recognition of short sequences of DNA.

Anionic molecules are challenging targets for recognition studies as they possess a wide range of sizes and shapes [2–5]. In contrast to the DNA recognition discussed above, binding directly to charged anionic groups, which are highly solvated in aqueous solution, is essential in the recognition of inorganic or small organic anions. To achieve selective recognition of these anions with synthetic receptors, we can learn a great deal from how nature addresses the problem and can apply the design principles of natural receptors to synthetic ones.

In this paper, we will review examples of anion binding by natural molecules to emphasize how anions can be recognized with convergent arrays of neutral hydrogen bond donors that match the sizes and shapes of anions. We will particularly highlight synthetic macrocyclic receptors in which hydrogen bonding groups are arranged in a convergent and rigid manner. The family of calixpyrroles, a class of anion receptors that falls into this category, is discussed in other articles in this issue and so will not be included in this discussion.

## 2. Natural anion receptors

The anion-bound structures of phosphate binding protein (PBP) from *E. coli* and sulfate binding protein (SBP) from *S. typhimurium* have been determined using X-ray crystallography [6,7]. PBP and SBP are members of a family of periplasmic proteins that act as initial high-affinity receptors for orthophosphate and sulfate anions, respectively, and are involved in the high affinity active transport system to uptake these essential nutrients into bacteria cells. The anion ligand is bound in a deep cleft in the protein and completely buried and desolvated. The precise arrangements of hydrogen bonding groups in the anion binding sites of PBP and SBP exactly match with the hydrogen bonding oxygen atoms of the tetrahedral ligand anions (Fig. 1) and do not allow non-specific binding of other anions. In the PBP–phosphate complex (dissociation constant $K_d = 1 \times 10^{-6}$ M at pH 8.3), the anion is bound by 12 hydrogen bonds including an interaction between the carboxylate from Asp56 and the proton of $HPO_4^{2-}$. As sulfate has no hydrogen bond donor to match with the carboxylate, PBP is unable to bind sulfate [8]. Although the phosphate anion makes a salt-bridge with the Arg135 guanidinium group, which is in turn bound with the carboxylate of Asp137, studies with mutant proteins showed that the phosphate binding is insensitive to the perturbation of this ion-pairing interaction [9]. Selective binding of SBP ($K_d = 0.12 \times 10^{-6}$ M for $SO_4^{2-}$, $6 \times 10^{-2}$ for $HPO_4^{2-}$ at pH 8.3) [10] can be also explained by the lack of hydrogen bond acceptors to pair with phosphate in the anion binding site, whereas sulfate oxygen atoms are bound by seven hydrogen bond donors.

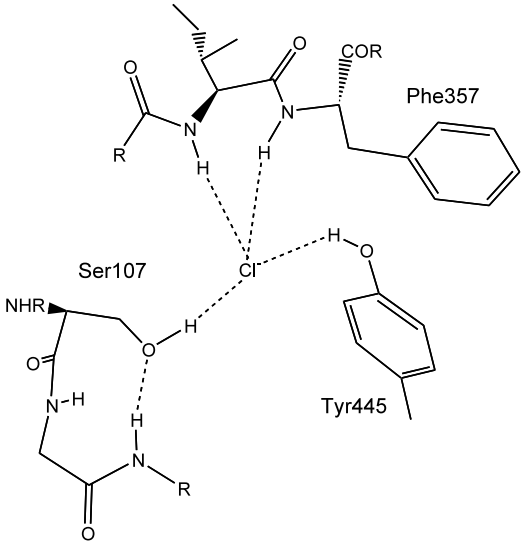



Fig. 2. Schematic diagram of the $Cl^-$ binding site of ClC chloride channel.

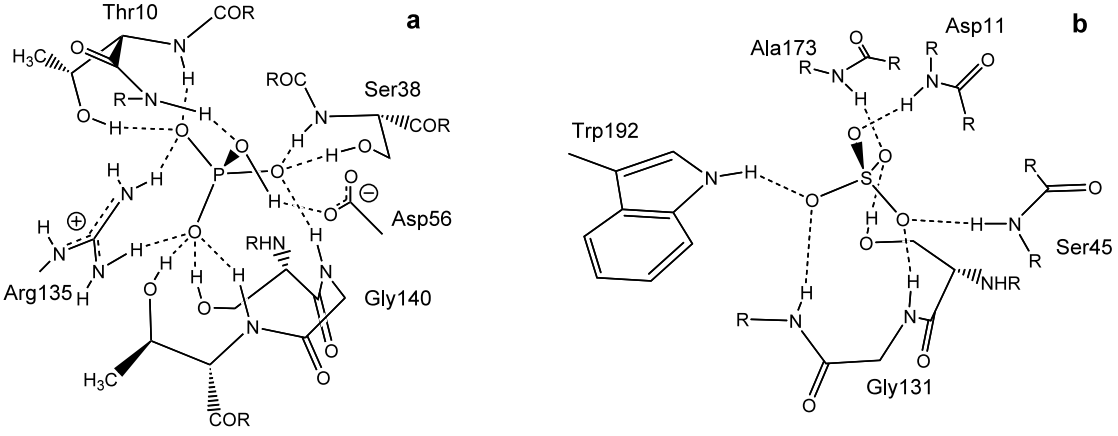



Fig. 1. Schematic diagrams of the hydrogen bonds between (a) PBP and dibasic orthophosphate; (b) SBP and sulfate.

Selective ion transport is crucial for a range of cellular processes and ion channels are the proteins that carry out this vital role. Ion channels must be selective for certain types of ions and transport them with a high rate rather than necessarily bind them with high affinity. Structures of two chloride channels from *E. coli* and *S. typhimurium* have been determined recently [11]. These channels are homodimers with high sequence and structural homologies and each subunit has its own ion-conducting pore. The narrowest part of the pore is formed by highly conserved amino acids and acts as the selectivity filter of the anion channel. $Cl^-$ in this filter is coordinated by backbone amide groups and side chain hydroxyl groups, all located at the N-termini of α-helices (Fig. 2). Anion binding of this type, where charge–dipole, not charge–charge, interactions are exploited, facilitates fast complexation and decomplexation rates and thus fast anion transport through membranes. As in PBP and SBP, hydrogen bonds play critical roles in the formation of a well-ordered binding domain that leads to selective recognition of chloride.

Although there have been no reports on 'small' natural products whose biological function is to selectively bind inorganic anions, the glycopeptide antibiotics of the vancomycin family give us an insight into how small natural receptors can recognize the charged regions of anionic molecules. Vancomycin is produced by microorganism *A. irientalis* and blocks the biosynthesis of the bacterial cell wall by binding to the terminal—Lys-D-Ala-D-Ala sequence of growing peptidoglycan chains (association constant $K_a = 1.5 \times 10^6$ $M^{-1}$ for Ac-Lys(Ac)-D-Ala-D-Ala) [12]. A crystal structure of vancomycin complexed with a peptide ligand shows that the carboxylate of C-terminal D-Ala binds into a pocket of three amide NH groups within the antibiotic (Fig. 3). Two hydrogen bonds and hydrophobic interactions with the alanine methyl groups are additional cooperative interactions between the ligand peptide and vancomycin. Detailed binding studies with ligand analogs and thermodynamic analysis suggest that the binding of carboxylate through convergent hydrogen bonds is the main factor of the high affinity binding [13,14]. A strategy based on the array of hydrogen bonding groups in the right hand ring has been used in synthetic carboxylate-binding analogs of vancomycin [15,16].

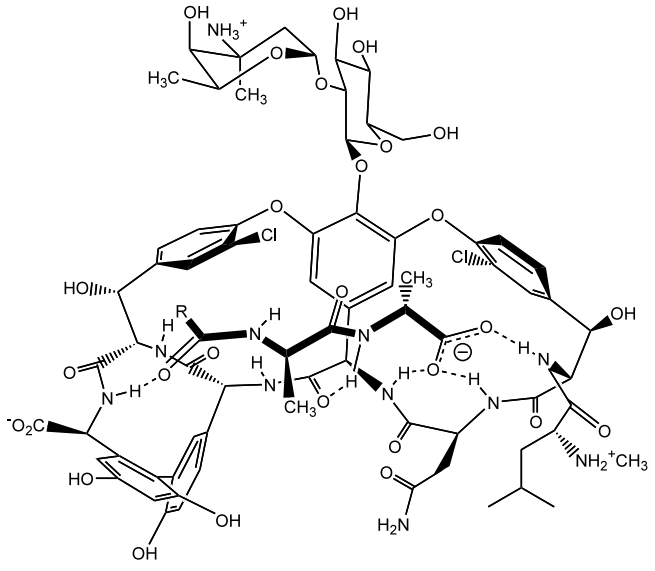


Fig. 3. Schematic diagram of the binding interaction between vancomycin and a peptide with C-terminal D-Ala-D-Ala sequence.

## 3. Macrocyclic receptors

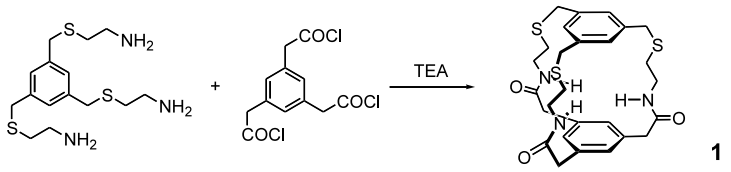
### 3.1. Cyclic amides

In 1986, the first solely amide-based $C_3$-symmetric cage-type anion receptor was reported [17]. The triamine and triacid chloride were reacted with each other to give the triamide cyclophane **1** in 11% yield (Scheme 1). This receptor showed evidence of binding tetrabutylammonium (TBA) fluoride in DMSO-$d_6$, but the result of a quantitative binding study was not reported.

Beer and coworkers synthesized a bis-calix[4]arene receptor in which the upper and lower rims of two calix[4]arenes are covalently linked by hydrogen bond donating amide bonds (Scheme 2) [18]. The calix[4]arene upper rim dinitro derivative was hydrogenated under high pressure and temperature and then the crude product was reacted with the lower rim diacid chloride to give the bis-calix[4]arene **2** and its dicarbonate derivative **3** in 20 and 60% yields, respectively. The cavity size of receptor **2** is too small to encapsulate $H_2PO_4^-$ or $HSO_4^-$, but $Cl^-$ and $F^-$ are bound, favoring the latter with nearly one order of magnitude ($K_a = 1330$ $M^{-1}$ for $n$-$Bu_4^+F^-$ in $CD_2Cl_2$).

The corresponding reaction of the bis-calix[4]arene diacid chloride with cystine dimethyl ester provided the 1+1 and 2+2 cyclization products in 28 and 3% yields, respectively (Scheme 3) [19]. Binding analysis of the 1+1 product **4** with disodium $p$-nitrophenyl phosphate in DMSO using UV–vis spectroscopy was carried out to measure the binding affinity ($K_a = 3900$ $M^{-1}$).

Ishida and coworkers have reported synthetic cyclic peptides containing the unnatural amino acid 3-aminobenzoic acid (Aba) as a rigid element to orient the hydrogen bond donating amide groups to the center of a macrocycle [20]. Three dipeptide building blocks Boc–Xaa–Aba-OH (Xaa: an α-amino acid) were coupled in a stepwise fashion onto an oxime resin using [(benzotriazol-1-yl)oxy]tris(dimethylamino)phosphonium hexafluorophosphate (BOP) as the coupling reagent and macrocyclization was performed on the resin after final removal of the protecting group from the N-terminus (Scheme 4). UV–vis titration experiments in DMSO




Scheme 1. Synthesis of a cage-type anion receptor.

showed that the disodium salt of *p*-nitrophenyl phosphate binds to the receptors with high affinity ($K_a = 1.2 \times 10^6$ $M^{-1}$ for *cyclo*(Ala-Aba)$_3$). Binding affinity was not significantly affected by changing the side chain of the α-amino acid unit. When *p*-nitrophenyl phosphate was added to the cyclic peptide, large downfield shifts of amide-NH $^1$H-NMR resonances were observed consistent with hydrogen bond formation between the anion and the receptor.

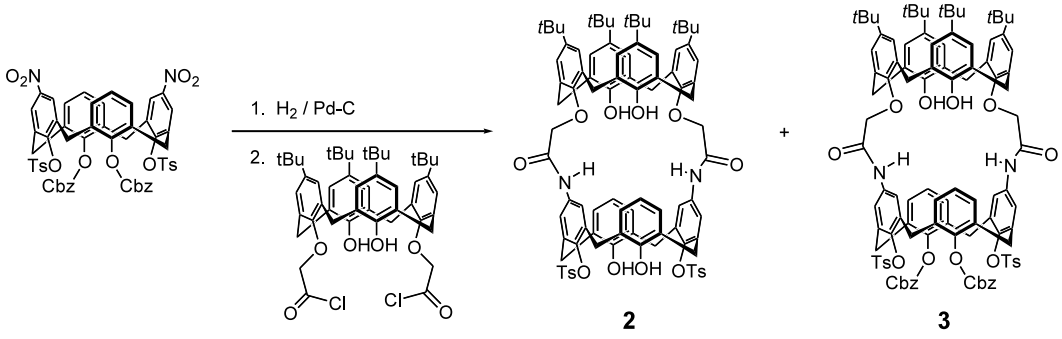
Anslyn and coworkers designed and synthesized a $C_3$-symmetric bicyclic cyclophane for the complexation of nitrate [21]. Two rigid building blocks, 2,6-pyridine dicarbonyl dichloride and 1,3,5-triaminomethyl-2,4,6-triethylbenzene were linked together in 40% yield to give cyclophane **5** where the six amide hydrogens converge into the center of the molecule (Scheme 5). The amide groups act as neutral hydrogen bond donors to the anion π-electron system. $^1$H-NMR titration was used to determine the binding properties of the receptor and the association constant for TBA nitrate was measured as 300 $M^{-1}$ in 25% $CD_2Cl_2/CD_3CN$. Despite its relatively low basicity, nitrate showed enhanced binding due to the size and shape complementarity to the macrocycle. This anion receptor also has been shown to bind planar enolate anions and was used to compare the effects of hydrogen bonding to π-electron systems, as compared with lone pair electrons, on carbon acid p$K_a$ shifts [22].

A cystine-based cyclic amide containing 2,6-pyridine dicarboxamide units has been used as an effective receptor for a number of 1,ω-alkane dicarboxylates [23]. A combination of cystine disulfide bridges and rigid aromatic units introduced several conformational constraints into the cylclopeptide backbone. Macrocycle **6** was prepared from the 2+2 cyclization of L-cystine dimethyl ester and 2,6-pyridine dicarbonyl dichloride in 51% yield with minor products from 3+3 and 4+4 cyclization reactions (Scheme 6). This macrocycle binds to TBA salts of dicarboxylic acids ($(CH_2)_n(CO_2H)_2$, $n = 1, \ldots, 4$) with 1:1 stoichiometry in $CDCl_3$. The highest binding affinity was observed for glutaric acid ($n = 3$, $K_a = 369$ $M^{-1}$).

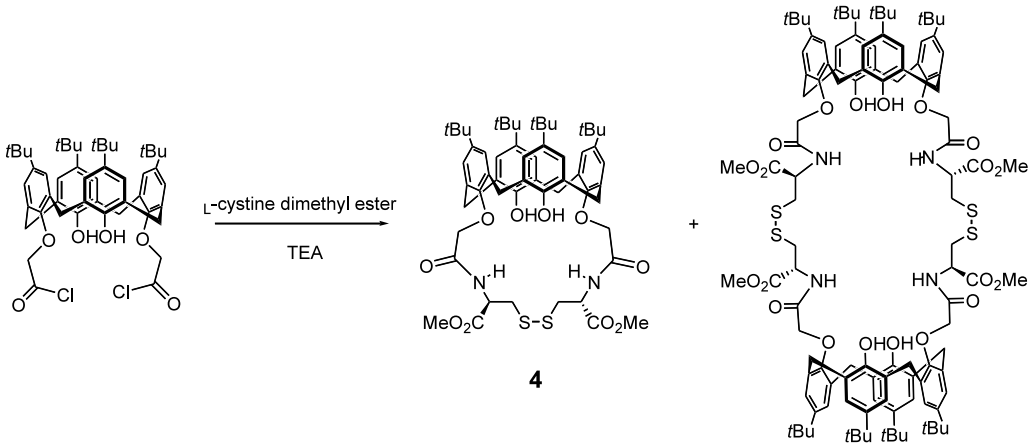
Another cyclic anion receptor containing 2,6-pyridine dicarboxamide units has been synthesized from the reaction between dimethyl 2,6-pyridinedicarboxylate and 1,2-diaminoethane in 51% yield (Scheme 7) [24]. NMR titration experiments showed that macrocycle **7** has highest affinity for TBA acetate ($K_a = 2640$ $M^{-1}$ in DMSO-$d_6$). The crystal structure of **7** complexed with acetate showed that four hydrogen bonds are formed with only one oxygen atom of the carboxylate (Fig. 4).

Vögtle and coworkers have synthesized a series of cyclic amides and used them for anion-templated rotaxane synthesis [25]. Reaction of diamine **8** with isophthaloyl chloride gave macrocycle **9a** in 30% yield (Scheme 8). NMR titration experiments with TBA salts in $CD_2Cl_2$ showed that **9a** strongly binds halides and oxoanions ($K_a = 1.8 \times 10^5$ $M^{-1}$ for $AcO^-$). The anion binding properties of **9a** were exploited in a high yield synthesis of rotaxanes where a bound phenolate nucleophile threads though the macrocycle to react with an electrophile. Cyclic monosulfonamide **9b** showed considerably weaker binding than **9a** under the same condition ($K_a = 1.5 \times 10^4$ $M^{-1}$ for $AcO^-$).

Kubik and coworkers have reported a cyclic peptide made from proline and 6-aminopicolinic acid (Apa) that binds anions in aqueous solvent [26]. The dipeptide building block Boc–Pro–Apa-OH was iteratively coupled to form the linear hexapeptide that was cyclized with 22% yield after N- and C-terminal deprotections (Scheme 9). Chlorotripyrrolidinophosphonium hexa-




Scheme 2. Synthesis of bis-calix[4]arene anion receptors.




Scheme 3. Synthesis of anion receptors containing calix[4]arene and disulfide groups.

fluorophosphate (PyCloP) and O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) were used as peptide coupling reagents. Interaction of macrocycle **10** with halides and other anions was detected by $^1$H-NMR in 80% $D_2O/CD_3OD$ ($K_a = 44$ $M^{-1}$ for benzenesulfonic acid sodium salt). For halides and sulfate, 2:1 complexes were detected by mass spectrometry and a crystal structure of the iodide complex showed that two macrocycles assemble together to hold an anion in the central cavity (Fig. 5).

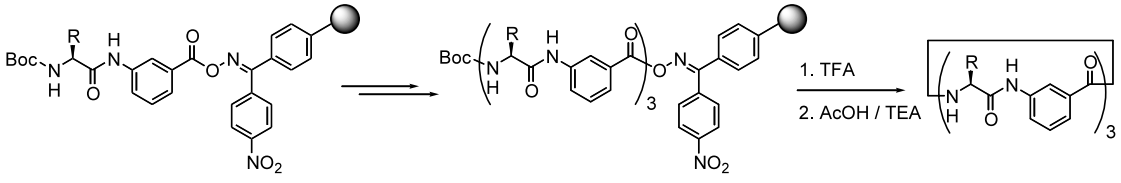
A synthesis of the cyclic trimer of 5-(aminomethyl)-2-furancarboxylic acid and its carboxylate binding properties have recently been reported [27]. Cyclic peptide **11** was synthesized from the monomer in a single step in 65% yield using BOP as the coupling reagent (Scheme 10). The association constant of the cyclic trimer with TBA acetate was measured as 8640 $M^{-1}$ in $CD_3CN$ by using NMR experiments.

We have recently reported the synthesis of rigid macrocycles with $C_3$ symmetry that bind tetrahedral anions with high affinities [28]. Stepwise coupling of 3′-amino-3-biphenylcarboxylic acid monomer using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) gave the linear trimer which was cyclized to macrocycle **12** in 40–60% yields (Scheme 11). This macrocycle projects three hydrogen bond donating amide-NH groups into the central cavity, which is $\approx 5$ Å in diameter. The size of the hole and the skewed arrangement of the three amide protons are well-matched to the size and shape of tetrahedral oxyanions (Fig. 6). In 2% DMSO-$d_6$/$CDCl_3$, **12** forms a 1:1 complex with TBA *p*-tosylate ($K_a = 2.1 \times 10^5$ $M^{-1}$ with R = NHBoc). The even distribution of charge on halides, nitrate, hydrogensulfate and dihydrogen phosphate allows these anions to form 2:1 as well as 1:1 complexes with **12** ($K_{11} = [\mathbf{12} \cdot I^-]/[\mathbf{12}][I^-] = 1.2 \times 10^5$ $M^{-1}$ and $K_{21} = [\mathbf{12}_2 \cdot I^-]/[\mathbf{12} \cdot I^-][\mathbf{12}] = 9.0 \times 10^3$ $M^{-1}$ with R = NHBoc). In DMSO-$d_6$, a more competitive hydrogen bonding solvent, 2:1 complex formation was not observed and tetrahedral anions retained strong binding ($K_a = 1.5 \times 10^4$ $M^{-1}$ for *n*-$Bu_4N^+H_2PO_4^-$, R = NHBoc) while the stability of halide and nitrate complexes decreased significantly.

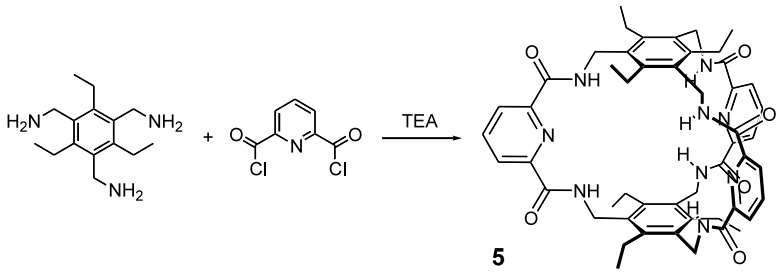
Fluorescent anion sensors showing selective responses to $H_2PO_4^-$ have been developed based on macrocycle **12** [29]. In sensor **13** (Fig. 7), an aminocoumarin fluorophore is integrated into **12** such that it is directly involved in hydrogen bonding to the anion. The anion-binding properties of **13** were similar to those of **12** with high selectivity for tetrahedral ions ($K_a = 2.0 \times 10^6$ $M^{-1}$ for *n*-$Bu_4N^+H_2PO_4^-$ in 1/1 DMSO/1,4-dioxane). Anion binding caused an increase in intensity and red shift of the fluorescence emission of the coumarin. The most remarkable change was the appearance of a second emission band at longer wavelength upon addition of basic anions like $H_2PO_4^-$.

### 3.2. Cyclic ureas and thioureas

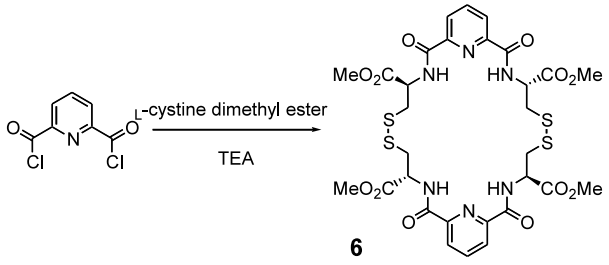
A series of cyclic thioureas has been synthesized and used as anion receptors by Tobe and coworkers [30]. These cyclic receptors have two thiourea groups connected through different spacers to display hydrogen



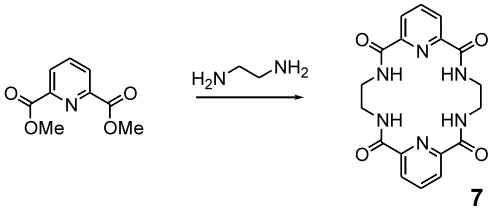

Scheme 4. Solid-phase synthesis of anion binding cyclic peptides.




Scheme 5. Synthesis of a bicyclic cyclophane anion receptor.




Scheme 6. Synthesis of an anion receptor containing 2,6-pyridine dicarboxamide and disulfide groups.




Scheme 7. Synthesis of an anion receptor based on 2,6-pyridine dicarboxamide.

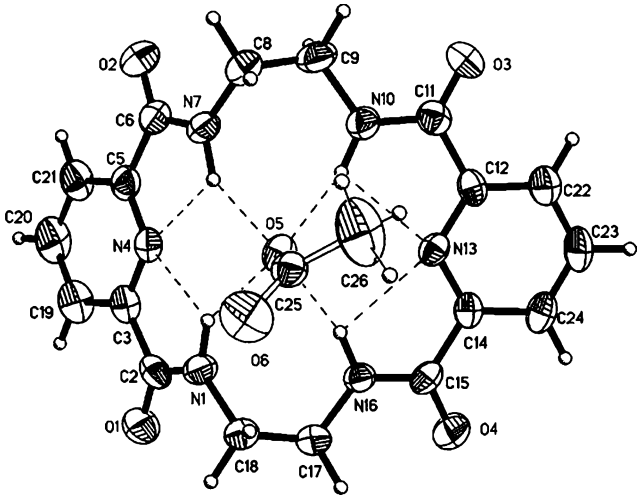


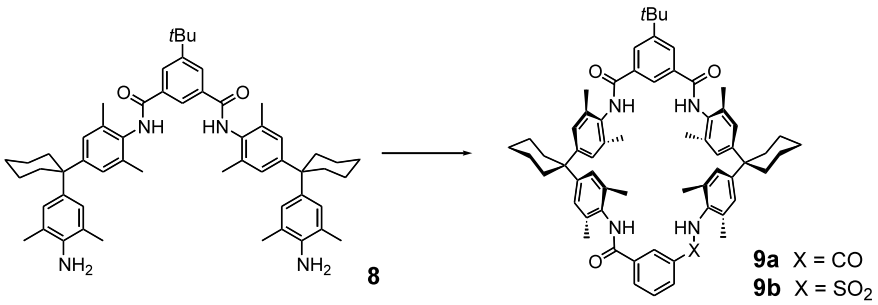
Fig. 4. X-ray structure of $\mathbf{7}\cdot AcO^-$ complex. Reproduced with permission from Eur. J. Org. Chem. (2001) 4031, Copyright 2001, Wiley-VCH.

bond donors in different distances and orientations. Cyclization reactions between corresponding diamines and diisothiocyanates under dilute conditions gave cyclic thioureas in 70–79% yields (Scheme 12). NMR titration studies with TBA salts showed that these receptors selectively bind $H_2PO_4^-$ over other anions and receptor **14** with *meta*- and *ortho*-substituted aromatic linkers has higher binding affinity than the others ($K_a = 1.2 \times 10^4$ $M^{-1}$ for $H_2PO_4^-$ in DMSO-$d_6$).

Macrocycles with three thiourea groups linked through *meta*-substituted phenyl rings have been synthesized and used as anion receptors [31]. The 1,3,5-triethylbenzene group was selected as a linker to preorganize the six hydrogen bond donors for optimal anion binding. Cyclic thiourea **15a** was obtained from the corresponding diamine and diisothiocyanate in 30% yield (Scheme 13) and showed increased binding affinities compared with the less constrained analog **15b** ($K_a = 5300$ vs. 320 $M^{-1}$ for TBA acetate in DMSO-$d_6$).

A cystine-based cyclic urea was reported as another anion receptor derived directly from amino acids. Reaction between L-cystine dimethyl ester and triphosgene under high dilution condition gave cyclic triurea **16** and tetraurea **17** with yields of 37 and 15%, respectively, (Scheme 14) [32]. The anion recognition properties of these macrocylces were studied using NMR and mass spectrometry and cyclic triurea **16** showed selective binding to TBA chloride ($K_a = 2050$ $M^{-1}$ in $CDCl_3$) due to size complementarity.

Chiral recognition of α-hydroxycarboxylate derivatives has been achieved with a macrocycle containing amide and urea groups [33]. Macrocycle **19**, which has a spirobifluorene unit acting as a rigid spacer generating a chiral cavity, was constructed by slow hydrolysis of diisocyante **18** in 60% yield (Scheme 15). The macrocycle showed different binding affinities, which were determined by $^1$H-NMR titration experiments with tetramethylammonium salts in DMSO-$d_6$, for α-hydroxycarboxylate enantiomers ($K_a = 2.8 \times 10^4$ and $1.7 \times 10^3$ $M^{-1}$ for (*R*)- and (S)-mandelate, $3.5 \times 10^4$ and $3.5 \times 10^3$ $M^{-1}$ for (*R*)- and (S)-lactate, respectively). The chiral discrimination was likely explained by steric effects, where the α-hydrogen prefers to be placed in the sterically congested region while the bigger hydroxyl group is placed over one of the aromatic rings of the spirobifluorene group.




Scheme 8. Synthesis of rigid macrocyclic anion receptors.

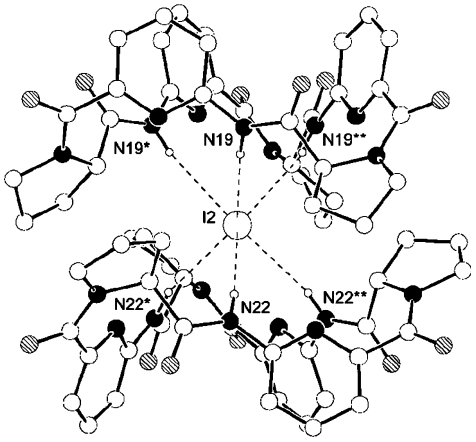
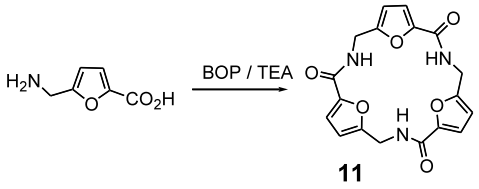



Fig. 5. X-ray structure of $\mathbf{10}_2 \cdot I^-$ complex. Reproduced with permission from Angew. Chem. Int. Ed. Engl. 40 (2001) 2648, Copyright 2001, Wiley-VCH.

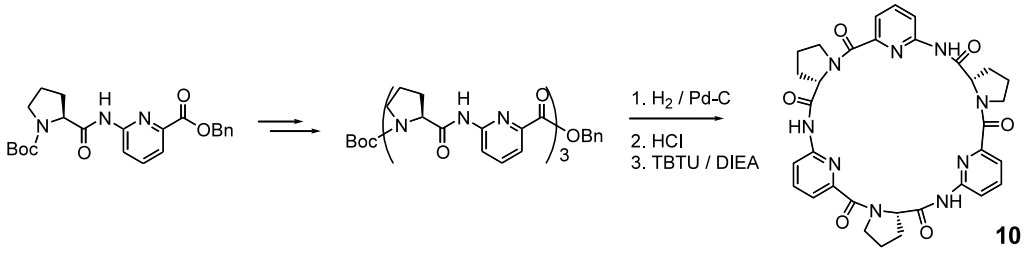



Scheme 10. Cylotrimerizaion of 5-(aminomethyl)-2-furancarboxylic acid.

## 4. Conclusion

Natural anion receptors clearly show how precisely arranged dipoles can be used to bind anions, overcoming high solvation energies. By recruiting multiple binding elements together in a semi-rigid and complementary relationship, natural receptors achieve selective anion recognition with high affinity. The same design principle, convergent arrangement of neutral binding groups in a constrained scaffold to match the functionality of the ligand anion, has been exploited in the preparation of synthetic macrocyclic receptors. Macrocyclic structures are particularly effective in reducing conformational flexibility and preorganizing ligand binding elements, as compared with acyclic molecules. Amide and urea groups, which can be readily constructed using many well-established reactions and reagents, have served not only as hydrogen bond donors but also as constrained linker groups to connect other rigid components of macrocycles, such as aromatic rings or disulfide bridges. Macrocyclization reactions of these types have been executed under various conditions with moderate to high yields. Macrocyclic receptors have been shown to bind various anions in a range of solvents with a certain degree of size, shape and chiral selectivities. These selectivities show the advantages of constructing receptors that employ charge–dipole interactions, which are directional and more dependent on the distance between interaction partners, rather than receptors using charge–charge interactions.

There are many biologically relevant carboxylate, sulfate and phosphate derivatives and the synthesis of artificial receptors for these anions could be achieved in different ways in the future. For example, as in the case of vancomycin family antibiotics, additional recognition elements could be coupled to a macrocyclic anion receptor, which now can be considered as an anion recognition domain or a rigid functional scaffold, to build a receptor for larger anionic molecules. Dipoles directly involved in anion binding by natural receptors are usually bound by other dipoles such as N-terminal




Scheme 9. Sequential synthesis of a cyclic peptide containg proline and 6-aminopicolinic acid.

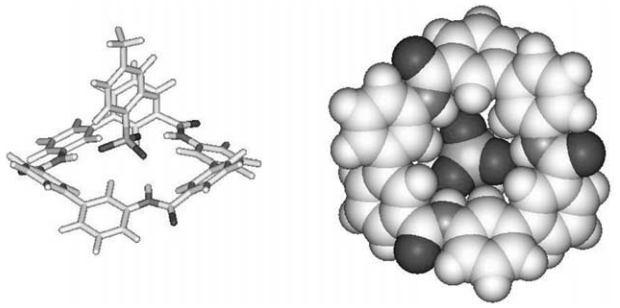
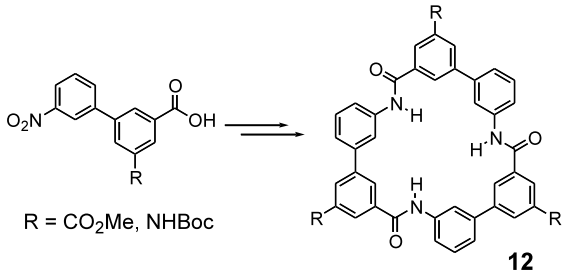
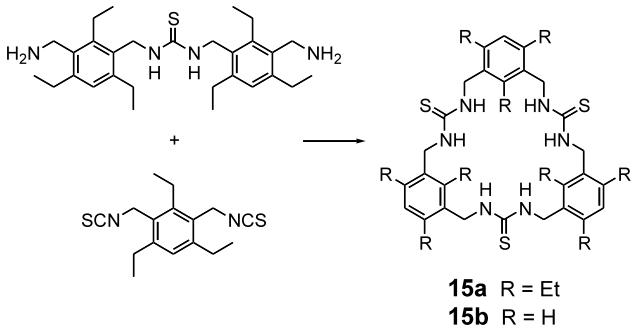


Fig. 6. The calculated structure of the 1:1 complex between **12** and *p*-tosylate anion. R groups are omitted for clarity.

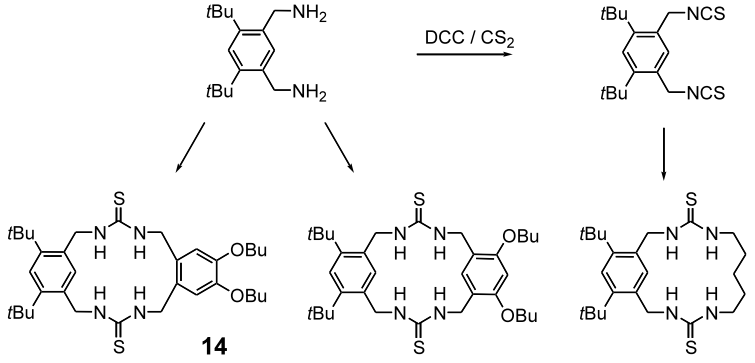



Scheme 11. Sequential synthesis of cyclic trimers of 3′-amino-3-biphenylcarboxylic acids.




Scheme 13. Synthesis of a conformationally constrained cyclic thiourea.

amide groups of chloride channel α-helix macrodipoles and amide groups at the vancomycin dimer interface. These relayed hydrogen bonds preorganize ligand-binding dipoles and increase their polarization to lead to stronger charge–dipole interactions. The same strategy could be applied to synthetic receptors to improve their binding properties. Macrocyclic molecules, which have relatively well-defined conformations to display additional functional groups in a controlled manner, will continue to play an important role in the development




Scheme 12. Synthesis of cyclic anion receptors containing thiourea groups.

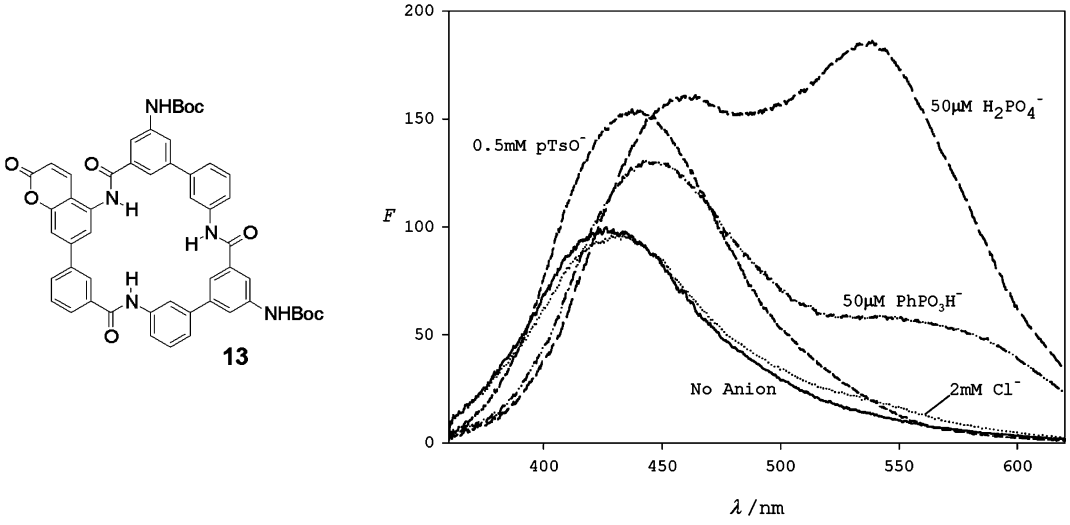
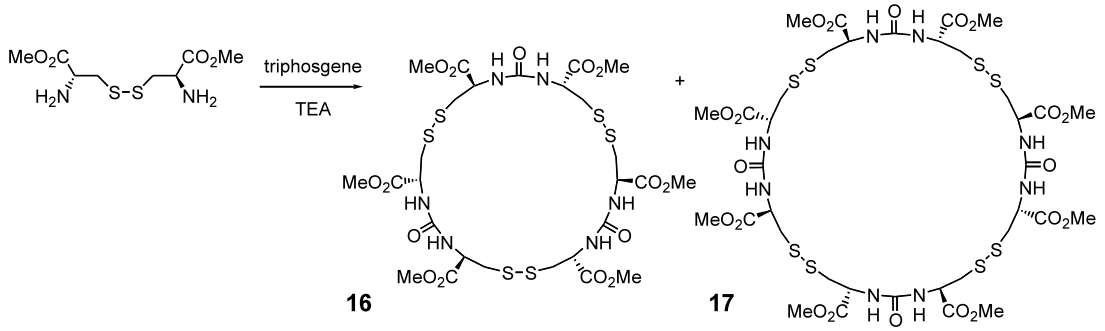
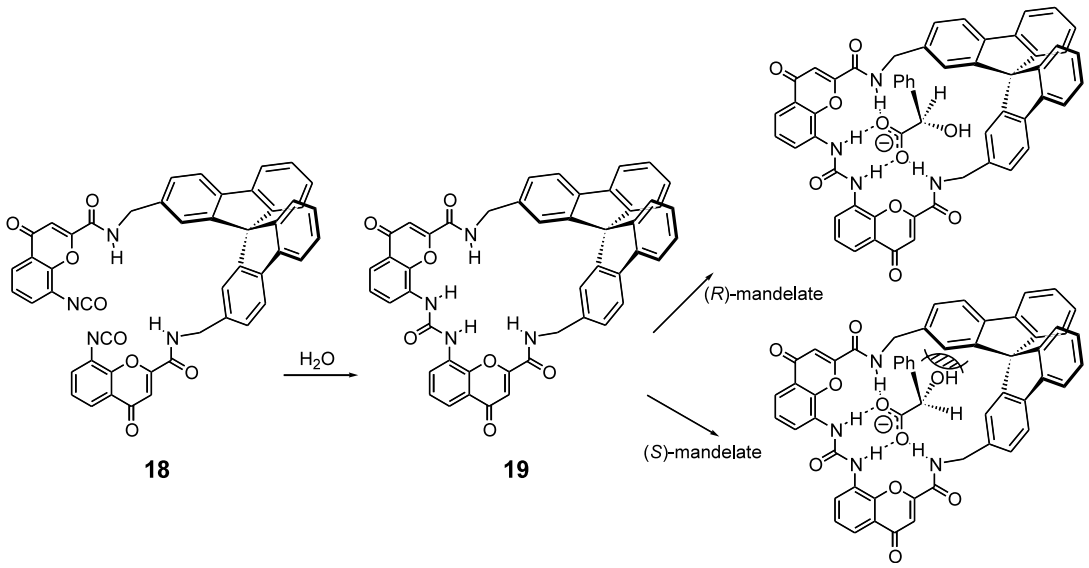



Fig. 7. A fluorescent anion sensor and its emission spectra (3 μM in 1/1 DMSO/1,4-dioxane, $\lambda_{ex} = 320$ nm) with different anions.




Scheme 14. One-step synthesis of cystine-based cyclic oligoureas.




Scheme 15. Synthesis and anion binding of a spirobifluorene containing macrocycle.

of improved synthetic anion receptors, as in other areas of molecular recognition chemistry.

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