Recueil Review

Synthetic receptors for anion complexation

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1. Introduction

The construction of host molecules with predesigned architecture is of vital importance for the understanding of selective recognition processes. Artificial host guest systems owe much of their relevance to the analogies which can be drawn with natural receptor systems.

Anion coordination and molecular recognition of anionic substrates by synthetic receptor molecules have been much less studied than cation complexation, despite the important role anions play in chemistry and biology. For example, nucleotide polyphosphates are the basic components in the bioenergetics of all living organisms and di- and tricarboxylate anions are critical species in numerous metabolic processes, including the citric acid and glyoxylate cycles. Several inorganic anions such as nitrate, carbonate, sulfate, and chloride, are present in large amounts in biological systems. In addition, many anions act as nucleophiles, bases, redox agents, and phase-transfer catalysts. Their functions, transfer across membranes, etc. are of the same importance as those of cations and the complexation of anions can bring about changes in chemical reactivity as does cation complexation. To be able to study and mimic the important biological processes involving anionic species receptors are required that complex anions. The challenge in the field of anion complexation is the design of receptors with a high selectivity for biologically important anions like phosphates, (poly)carboxylates, and halides (especially chloride). The design of selective receptors for anions is more demanding than that of cations. Anions have a wide variety of geometries¹. They can be spherical (F^- , Cl^- , Br^- , I^-), linear (CN^- , SCN^- , N_3^-), trigonal planar (CO_3^{2-} , NO_3^-), tetrahedral ($H_2PO_4^-$, HSO_4^- , SO_4^{2-} , ClO_4^-), or octahedral ($Fe(CN)_6^{4-}$, $Co(CN)_6^{3-}$). The difference in geometry between anions is an important factor to account for in the design of selective anion receptors, although it is not easy to synthesize receptor molecules with complementary binding sites in a proper three-dimensional arrangement. Complexation of an ion by a receptor molecule requires the (partial) substitution of the solvation shell of the ion by ligating sites of the receptor molecule. Generally, this is more difficult for anions than for cations as is reflected by the larger differences in Gibbs energies of transfer of anions compared to cations². In addition, the complexation of anions is dependent on the pH of the media.

This review first describes the binding of anions by receptor molecules found in nature, followed by discussion of the various synthetic anion receptors. The synthetic anion receptors are divided into two classes: positively charged and neutral anion receptors. The different positively charged receptors, *e.g.* polyammonium receptors, guanidinium based

receptors, porphyrins, and cobalticinium-based receptors, will be discussed first. The neutral anion receptors are classified on the basis of the type of interaction with the anion, *viz.* ion-dipole interactions, a combination of ion-dipole interactions and hydrogen bonding, or exclusively hydrogen bonding.

2. Anion receptors in nature

In nature, sulfate- and phosphate-binding proteins are important for the active transport of these ions in the cell and organelles. They belong to a class of proteins with molecular mass between 25 000 and 45 000 g/mol that serve as high-affinity receptors for the active transport of various carbohydrates, amino acids, oligopeptides and oxyanions. A very high binding selectivity has been observed in prokaryotic, periplasmic sulfate-^{3,4} and phosphate-^{4,5} binding proteins, with more than 10^4 times higher selectivity for the complexation of sulfate over phosphate and phosphate over sulfate, respectively. The sulfate anion in *Salmonella typhimurium* is bound by seven hydrogen bonds, five from the main chain peptide NH's and the other two from a serine hydroxyl group and an indole NH of a side-chain of tryptophan³. The phosphate anion is bound by the phosphate-binding protein via twelve hydrogen bonds, five from the main peptide chain NH's, two NH's of an arginine side chain, four hydroxyl groups of two serine and two threonine residues, and one of an aspartate side chain⁴. In both cases the anion is completely desolvated and bound exclusively through hydrogen bonds. In addition to hydrogen bonding there is another important driving force for anion binding. In numerous crystal structures of enzyme-substrate complexes the protein backbones are aligned with their amino terminus directed towards negatively charged groups in the substrate. This so-called macrodipole effect also contributes to the stability of the sulfate- and phosphate-anion-binding proteins⁶.

Recently, X-ray crystal structures of complexes of aromatic sulfonates and peptides have been reported in which water molecules are also involved in hydrogen bonding together with peptide NH's⁷.

Native zinc enzymes, such as carboxypeptidase A, bind small inorganic anions like phosphate, Cl^- , N_3^- , and NCO^- by a combination of metal-anion interaction and hydrogen bonding⁸. These hydrogen bonds originate from the peptide chain and from water molecules bound in the active site. Various visual pigments have also been identified as anion binding proteins. Human green and red color vision pigments show

binding of Cl^- , Br^- , NO_3^- , and SCN^- . Although the exact structure of these proteins has not yet been elucidated, a histidine fragment and a lysine residue have been identified as being important for Cl^- binding in the active site⁹.

Ion channels are important for regulatory mechanisms in nature. They are found in plasma membranes of nearly all vertebrate cells and operate in cell volume regulation, transepithelial electrolyte transport, and in tuning of neuronal electrical activity¹⁰. Ion channels that selectively transport Cl^- through the membrane are formed by proteins with a molecular mass of 75–110 kDa. The exact transport mechanism and structures are not completely understood, but these systems also underline the importance of selective anion complexation in nature.

3. Positively charged anion receptors

An obvious approach to the binding of anions is to use positively charged receptors¹¹. In this case the binding force is based mainly on electrostatic interactions, and the selectivity can possibly be enhanced by providing additional binding elements like hydrogen bonding or π - π stacking. Polyammonium anion receptors are the best studied anion receptors and these will be described first, followed by a discussion of guanidinium based receptors. Finally, porphyrin derivatives and cobalticinium based anion receptors will be discussed.

3.1 Polyammonium anion receptors

The first example of anion recognition by a positively charged receptor was reported in 1968 by Park and Simmons¹² who were able to encapsulate Cl^- anions in the tricyclic, diprotonated 1,11-diazabicyclo[9.9.9]nonacosane (**1**). The selectivity is determined by the size of the cavity in relation to the size of the anion.

In close relation with these results, Graf and Lehn¹³ reported anionic cryptates using the tricyclic, tetraprotonated macrocycle **2**. Anions like F^- , Br^- , Cl^- are encapsulated in a tetrahedral array of $\text{N}^+\text{H}\cdots\text{X}^-$ hydrogen bonds but I^- , NO_3^- , CF_3COO^- , and ClO_4^- are not complexed. An almost identical cryptand (**4**) complexes F^- , Cl^- , Br^- , and N_3^- anions. The small F^- anion is tetracoordinated, while the Cl^- and Br^- anions are coordinated in an octahedral array of hydrogen bonds¹⁴. The non-complementarity of these anions with the host is reflected in ligand distortions as revealed by the X-ray crystal structure. Structural complementarity was achieved for the linear N_3^- anion, which is bound by two pyramidal arrays of three hydrogen bonds each interacting with a terminal nitrogen atom¹⁵. Highly selective binding of ADP was

achieved by a simple lipophilic diammonium salt **3**. Extraction of ADP into chloroform was possible¹⁶. More recently, a class of receptors containing lipophilic chains to prevent leaching from organic membranes was reported by Diederich et al.¹⁷ and these ligands transport nucleotide 5'-triphosphates. The recognition properties of O-BISDIEN (**5**) have been studied extensively by Martell and Motekaites¹⁸ and by Zompa and co-workers¹⁹. This ligand is able to recognize a variety of anions (especially ATP, ADP, AMP, pyrophosphate²⁰, and dicarboxylate anions) in its tetra-, penta-, and hexaprotonated form. In the dicarboxylate anion complexes each carboxylate group is bound by four ionic hydrogen bonds. There is a preference for binding of oxomalonate over malonate and oxalate due to the additional hydrogen bonding to the carbonyl oxygen of ketomalonate. Lehn et al.²¹ used O-BISDIEN as a platform for molecular recognition and catalysis. The proposed complex formed between O-BISDIEN and ATP is represented by structure **6**. The tetraprotonated macrocycle recognizes the triphosphate tetraanion of ATP and the acridinium moiety stacks with the adenine moiety of ATP. The remaining free NH group acts as a general base catalyst in the hydrolytic cleavage of the phosphate bond. The double recognition provides a selectivity for ATP compared to the receptor lacking the acridine moiety. An analog of O-BISDIEN in which two furan rings are incorporated was studied by Martell and co-workers²². This hexaazo macrocycle complexes oxalate, malonate, and pyrophosphate anions.

From these studies an important aspect of the polyammonium receptors is revealed: the correct spacing between the nitrogen atoms is of primary importance in the design. Spacing of the nitrogen atoms by three or four carbon atoms provides, at neutral pH, a highly protonated species, a prerequisite for strong complexation. Since the electrostatic interactions mainly govern the binding, the more highly protonated adduct

7 ($n = 0-6$)

8

9

10

11

forms the most stable complexes with guests with the highest negative charge density.

Polyazacycloalkanes (**7**) have been studied extensively by several groups^{23,24} and especially the larger polyaza macrocycles are able to form polyprotonated, highly charged species in the neutral pH region. The tetraprotonated ligand of hexacyclen (**7**, $n = 0$) forms complexes with NO_3^- , Cl^- , ClO_4^- , and Br^- . Due to the steric repulsion between the protonated amino groups, the ligand adopts an elongated elliptical shape and the anions are bound outside the cavity^{19,23}. A study concerning the complexation of $\text{Fe}(\text{CN})_6^{4-}$, $\text{Co}(\text{CN})_6^{3-}$, PtCl_6^{2-} , and $\text{Pt}(\text{CN})_6^{2-}$ (second-sphere complexes) by **7** ($n = 0$ to 6) showed that the inclusion of the anion in the cavity of the ligand depends on the dimensions and conformation of the macrocycle as well as on the geometry of the anion^{25,26,27}. Recently, a triprotonated octaaza cryptand was reported to complex F^- anions²⁸. Also *Lehn* et al.²⁹ synthesized a series of highly charged polyamines containing six or eight nitrogen atoms [**7** ($n = 0, 2$), and **8**]. In their hexaprotonated form ligands **7** ($n = 2$) and **8** complex dianions (SO_4^{2-} , oxalate²⁻, malonate²⁻, AMP), trianions (citrate³⁻, 1,3,5-benzenetricarboxylate, ADP, $\text{Co}(\text{CN})_6^{4-}$), and tetraanions ($\text{Fe}(\text{CN})_6^{4-}$, ATP). The stability constants [$\log(K)$ or β] vary from 2.4 to 4.7 for the dianionic species, from 3.3 to 7.7 for the trianionic species, and from 6.3 to 9.1 for the tetraanionic species. The hexaprotonated ligand **8** forms complexes with the same anions but in most cases with notably higher $\log(K)$ values. With Cl^- anions however, the hexaprotonated ligands **7** ($n = 2$) and **8** form complexes in a 1:2 ratio. In the case of **7** ($n = 2$) $\cdot 6\text{H}^+$, a strong interaction is observed with one Cl^- anion, while the second anion is bound more weakly. In macrocycle **8** $\cdot 6\text{H}^+$ the two Cl^- anions are bound above and below the mean plane of the macrocycle, each by three ammonium groups³⁰. 1,4,7,10,13,16,19-Heptaazacyclohencicosane [**7** ($n = 1$)] possesses a remarkable shape selectivity for tricarboxylate anions in aqueous solution³¹. The selectivity is mainly determined by the host guest complementarity. Although the charge density of 1,2,3-benzenetricarboxylate³⁻ is higher than that of 1,3,5-benzenetricarboxylate³⁻, there is a preference for the latter due to its better complementarity with the receptor. Molecular modeling revealed that, for the complexation of 1,2,3-benzenetricarboxylate³⁻, unfavorable folding of the receptor is required^{31a}. The same group reported the complexation of AMP, ADP, and ATP by a derivative of **7** ($n = 0$) $\cdot 6\text{H}^+$ incorporating a phenyl group³². In addition to electrostatic interactions the phenyl group provided π - π stacking with the nucleobase. *Andrés* et al.³³ reported that a similar polyammonium receptor, incorporating a phenyl ring, is capable of complexing ATP and $\text{P}_2\text{O}_7^{4-}$. *Kimura* et al.³⁴ have studied the anion binding properties of similar compounds **7** ($n = 0$), **9**, and **10**. The triprotonated polyamines form stable 1:1 complexes at neutral pH with polycarboxylates (e.g. citrate³⁻, succinate²⁻)³⁵ and phosphates (e.g. inorganic phosphate, AMP, ADP, ATP)³⁶. The three positive charges in the macrocycle and favorable orientations of the three ammonium hydrogens for hydrogen bonding render **9** and **10** suitable receptors for biologically important polyoxyanions³⁷ such as CO_3^{2-} .

The same group studied macrocyclic dioxopentaamines (**11**) the monoprotonated form of which complexes phosphate and ATP³⁷. A similar compound forms a complex³⁸ with N_3^- . Anion complexation was enhanced by the formation of an intramolecular $\text{NH}\cdots\text{O}=\text{C}$ hydrogen bond.

The incorporation of aromatic moieties into the macrocyclic polyamine system resulted in a class of bis-intercaland receptors (**12**) which recognize planar anionic substrates, such as aromatic carboxylates and nucleotides via electrostatic interactions and additional π - π stacking^{39,40}. A similar hexaprotonated macrotricyclic complexes dicarboxylate anions; the crystal structure of the terephthalate dianion complex shows intracavity binding⁴¹. In line with the latter system, the encapsulation of ClO_4^- and SiF_6^{2-} anions in tricyclic polyammonium macrocycles containing heterocyclic moieties was reported recently by *Nelson* et al.⁴².

Polyammonium macrotricyclic systems (**13**) have been extensively studied by *Schmidtchen*⁴³. These receptors exhibit complexation of Cl^- , Br^- , and I^- anions in aqueous solution. The X-ray crystal structure of the I^- complex shows that the I^- anion is encapsulated symmetrically in a tetrahedral array of $\text{N}^+\cdots\text{I}^-$ interactions⁴⁴. The stability of the complexes depends on the desolvation of the guest entering the cavity. Since this is more demanding for Cl^- than for Br^- and I^- , the Cl^- complex is less stable. The selectivity is $\text{Br}^- > \text{I}^- > \text{Cl}^-$ for **13** ($n = 6$). A similar receptor with shorter polymethylene chains ($n = 5$) shows⁴⁵ a selectivity for F^- . The combination of this receptor with a polyazacrown resulted in a ditopic receptor⁴⁶. The binding of zwitterionic species was achieved with association constants of $50\text{--}250\text{ M}^{-1}$ [in D_2O and in $\text{D}_2\text{O}/\text{MeOD} = 1:9$] and the proposed binding mode is depicted in structure **14**. Complexation of nucleosides, nucleotides, and analogs was achieved by *Schneider* et al.⁴⁷ using a positively charged azoniacyclophane (**15**). Via electrostatic interactions and Van der Waals contributions adenosine is complexed selectively. Complexation-induced ^1H -NMR shifts demonstrate intracavity inclusion for adenine whereas the sugar residues stay outside the cavity. The phosphate groups are bound via four salt bridges. The same researchers used a β -cyclodextrin, functionalized with two or seven positively charged amino groups, as selective host for nucleosides and nucleotides⁴⁸. Via multiple binding, i.e. phosphate recognition by the protonated amino groups, ribose recogni-

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tion in the cyclodextrin cavity, and nucleobase recognition, a selectivity for the 5'-phosphate group, 2'-oxyribose, and adenine was observed. No explanation was given for the observed selectivity for adenine.

Koga et al.⁴⁹ developed receptor **16** which is capable of recognizing sulfonate anions via the formation of two hydrogen bonds by the OH groups and one ionic hydrogen bond with the protonated nitrogen atom of the quinoline^{49a} (or pyridine^{49b}) part of the receptor. In case of the pyridine derivative, the anion complexation results in a 2 + 2 salt formation in the solid state. The same group described a receptor for phosphoric acid monoesters⁵⁰.

Czarnik et al.⁵¹ developed two chelation enhanced fluorescence chemosensors based on an anthracene core substituted with one⁵² or two⁵³ protonated polyamines. These macrocycles (see **17** for the pyrophosphate complex) complex phosphate over sulfate, ATP, citrate³⁻, acetate, and dimethyl phosphate⁵² in aqueous solution and bind pyrophosphate 2000 times more tightly than phosphate⁵³.

Murakami et al.⁵⁴ studied the chirality-based molecular discrimination of protonated cyclophanes bearing L- and D-valine residues, in particular the complexation of bilirubin and pamoic acid.

3.2 Guanidinium based anion receptors⁵⁵

Since anion recognition by positively charged receptors is mainly governed by electrostatic interactions, the stability of

the complex is higher with higher charge density on both guest and host. The disadvantage of polyammonium receptors is the low pH values that are generally required to achieve complete protonation. Although the charge density in guanidinium based receptors is generally lower than in polyammonium-based receptors, the guanidinium group has the advantage that it is protonated over a much wider pH range due to its much higher pK_a . Therefore, guanidinium based anion complexes can be used in a broader pH range. From nature it is known that the guanidinium group is able to recognize anions. Guanidinium is present in the side-chain of arginine and is used in the recognition of the phosphate group of nucleotides via two-point hydrogen bonding⁵⁶. The first application of synthetic macrocyclic guanidines (**18** and **19**) in anion complexation was reported by Lehn et al.⁵⁷ who studied the anion coordination chemistry of polyguanidinium salts with phosphates and carboxylates in aqueous solution⁵⁸. With the stability constants of diethylguanidinium anion complexes a chelate effect was found. A macrocyclic effect was found when the stability constants for acyclic compounds were compared with those of cyclic compounds. The binding is primarily electrostatic and consequently the selectivity is governed by the charge density on the guests. For anions with equal charge, structural effects can induce selectivity, e.g. selectivity for maleate dicarboxylate over fumarate dicarboxylate due to the higher charge density of the maleate dianion. More recently, the complementary binding of phosphates to the guanidinium moiety was exploited by Hamilton et al. Binding of phosphate diesters to bis(acylguanidinium) receptor (**20**) results in a 300-fold increase of the rate of hydroly

of phosphate diesters⁶⁰. A monoguanidinium receptor only increases the reaction rate by a factor of 70, indicating the importance of the presence of two guanidinium moieties. A similar approach was followed by *Anslyn et al.*⁶¹ who used a bisguanidinium cleft in which the guanidinium moieties are preorganized in the form of two 2-aminoimidazoline groups. In DMSO/H₂O mixtures, the binding of dibenzyl-phosphate anions was achieved both in 1:1 and 1:2 host guest stoichiometries. Upon addition of water to the solvent the binding becomes weaker, only 1:1 binding was observed⁶². An increase of the concentration of Cl⁻ anions in the system did not decrease the association with the phosphate anion, which would occur in the case of competition between the binding of Cl⁻ and phosphate. Instead, an increase of the association was observed due to a "salting out" effect⁶³. Compared with free imidazole, rate enhancements of 8 to 20 for RNA cleavage were observed with this receptor⁶⁴.

Schmidtchen et al. have used bicyclic guanidinium receptors in which the guanidinium moiety is preorganized in the cyclic structure (21), as hosts for dicarboxylate anions^{65,66} and phosphates⁶⁷. An X-ray crystal structure of the acetate complex showed two almost linear hydrogen bonds between the acetate anion and the guanidinium hydrogens, indicating an almost perfect complementarity⁶⁵. The bisguanidinium receptor, in which the guanidinium moieties are separated by a naphthyl spacer (21), is able to recognize dicarboxylate anions in MeOH^{66,68}. The same host also shows binding of biologically important phosphates like NAD, AMP, and ATP with association constants of 200–840 M⁻¹ in H₂O and 18000–38000 M⁻¹ in MeOH⁶⁷. In an effort to quantify the effect of freezing internal rotations upon anion complexation more flexible analogs of 21 were designed, in which the naphthyl spacer is replaced by a hexyl spacer and the ether oxygens by sulfur atoms⁶⁹. However, the binding of the dianion of squaric

acid in DMSO-*d*₆ showed no dependency on the host flexibility.

*Lehn and De Mendoza*⁷⁰ achieved chiral recognition of aromatic carboxylate anions in CHCl₃ by a chiral guanidinium receptor (22) with two naphthyl substituents available for additional π - π stacking. The affinity of the guanidinium moiety for the carboxylate group was used by *de Mendoza et al.*⁷¹ to catalyze the addition of pyrrolidine to α,β -unsaturated lactones. The carboxylate anion formed after the nucleophilic attack of pyrrolidine is stabilized by interaction with the bicyclic guanidinium moiety, resulting in an increased rate of the Michael addition. A similar concept was used by *Von Kiedrowski and Terfort* who designed a self-replicating system based on the recognition between 3-aminobenzamidine and (2-formylphenoxy)acetic acid (23)⁷². After the binding between the amidinium group and the carboxylate group the amino group of 3-aminobenzamidine reacts with the formyl group of (2-formylphenoxy)acetic acid resulting in the formation of a molecule that acts as a binding platform for the two additional substrates. In this way the molecule acts as a template for its own formation. A host molecule (24) combining the affinity of the guanidinium moiety for phosphate anions with π - π stacking and Watson-Crick and Hoogsteen base-pairing was reported by *Rebek and de Mendoza*⁷³. Using this receptor the extraction of 2',3'- and 3',5'-cyclic-AMP (cAMP) from water into CH₂Cl₂ was achieved but only a limited selectivity over 2',3'- and 3',5'-cyclic-GMP was observed. The transport of mono- and dinucleotides through liquid membranes was achieved using a similar receptor^{74,75}. A more detailed study concerning the interaction between the water-soluble receptors and cAMP showed that the phosphate-guanidinium interaction leads to a considerable increase in binding affinity for 2',3'- and 3',5'-cAMP⁷⁶. The multi-point binding of ATP and AMP to a guanidinium-functionalized monolayer was reported by *Kunitake et al.*⁷⁷. *Göbel et al.*⁷⁸ used the amidinium moiety (25) to coordinate with phosphoric acid diesters. The hypothesis that this coordination accelerates substitution reactions via an attack of the pendant hy-

droxyl group was studied by using various monoamidinium salts⁷⁹.

3.3 Porphyrin based anion receptors

Porphyrins can act as anion receptors in their protonated form or when containing a metal atom⁸⁰ in the plane of the pyrrole groups. Sessler et al.⁸¹ studied anion binding by expanded porphyrins, for example, sapphyrin (26), rubyrin (27), and anthrapphyrin (28) in their neutral and protonated forms. The diprotonated sapphyrin complexes F⁻ and Cl⁻ anions. In the F⁻ complex the anion is present in the plane of the macrocycle while in the Cl⁻ complex the anions are present above and below the plane of the macrocycle^{82,83}. The association constants (in MeOH) of the halide complexes of sapphyrin (26) are *ca.* 10⁵ M⁻¹ for F⁻ and 10² M⁻¹ for Cl⁻ and Br⁻ anions. In addition to halide binding the diprotonated form of

sapphyrin also shows affinity for phosphate type anions, and sapphyrin facilitated transport of GMP and other nucleotides through a liquid membrane is possible under conditions in which sapphyrin is protonated (pH ≤ 3.5). The monoprotonated sapphyrin (26) is capable of binding monobasic substrates as was proven by X-ray crystal structures of the Cl⁻ and N₃⁻ complexes⁸⁴. Monoprotonated sapphyrins and rubyrins^{85,86} equipped with one or two cytosine moieties are able to transport nucleotides at neutral pH via a combination of electrostatic interactions and base-pairing⁸⁷. Effective separation of oligonucleotides was achieved by a neutral silica-bound sapphyrin⁸⁸, the retention time correlating with the number of phosphate groups. Recently, a neutral bissapphyrin was reported to complex dicarboxylate anions⁸⁹. Furthermore, oligosapphyrins (trimers and a tetramer) were found to be effective receptors for the complexation and membrane transport of nucleotide mono-, di-, and triphosphates with a selec-

tivity for the adenosine-derived nucleotides⁹⁰. Anthraphyrin⁹¹ (**28**) binds Cl^- anions and the X-ray crystal structure of the complex shows that the anion is bound in the protonated center of the cavity. In this system, the affinity for Cl^- is higher than for F^- which is quite different from that observed for diprotonated sapphyrins. Recently, the synthesis of a diaza-18-crown-6 capped sapphyrin was reported and preliminary results show ditopic binding of NH_4F^{92} . The combination of a porphyrin with a calix[4]arene moiety has also been reported⁹³.

Porphyrins bearing cationic substituents in the *meso*-positions associate with aromatic mono- and dicarboxylates and with sulfonates⁹⁴. For these systems the Van-der-Waals interactions prevail over solvophobic interactions. The association energy (ΔG) in water is 5 kJ/mol per salt bridge. Inoue et al. showed that chiral *N*-methylated porphyrin containing zinc(II) and a diamide bridge with a *p*-xylene spacer recognizes amino acid derivatives⁹⁵. The unbridged side of the molecule is blocked by the *N*-methyl group. The high enantioselective recognition is achieved via mutual electrostatic interactions, hydrogen bonding, and Van-der-Waals interactions.

3.4 Cobaltocenium based anion receptors

Beer et al.⁹⁶ have developed a variety of anion receptors based on the combination of positively charged cobaltocenium moieties or neutral ferrocene moieties⁹⁷ with amide substituents. The metal centers provide electrostatic interactions with anionic guests while the amide groups provide hydrogen bonding (**29–31**). The anion recognition has been studied by ^1H -NMR spectroscopy and cyclic voltammetry. Acyclic tripodal ligands (**29**) and acyclic mono- and 1,1'-disubstituted cobaltocenium ligands (**30**) recognize H_2PO_4^- anions in the presence of an excess of HSO_4^- and Cl^- anions⁹⁸. The F^- complex is formed in a 2:1 stoichiometry. The X-ray crystal structure of **30**· Br^- clearly shows hydrogen bonding towards the bromide ion⁹⁹. More elaborate systems were shown¹⁰⁰ to bind Cl^- and Br^- . Recently, this strategy was also applied using calix[4]arene as a molecular platform (**31**).¹⁰¹ These receptors complex Cl^- , Br^- , NO_3^- , and HSO_4^- anions with a 1:2 stoichiometry and adipate²⁻, malonate²⁻, and oxalate²⁻ with a 1:1 stoichiometry^{101b}. These ferrocene or cobaltocenium functionalized ligands¹⁰¹ selectively complex H_2PO_4^- in the presence of an excess of HSO_4^- and Cl^- . The redox active cobaltocenium and ferrocene centers were combined with porphyrins resulting in a class of neutral anion

sensing porphyrin derivatives able to recognize Cl^- , Br^- , NO_3^- , HSO_4^- , and H_2PO_4^- anions¹⁰². Recently, novel ruthenium(II)bipyridine calix[4]arenes were developed as anion receptors. The derivative functionalized at the lower rim with one Ru^{II} Bipy moiety recognizes H_2PO_4^- in the presence of excess of HSO_4^- and Cl^- in a 1:1 fashion. The derivative functionalized at the upper rim displays a 1:2 stoichiometry because it has two Ru^{II} Bipy moieties and two amide bonds¹⁰³. Recently, bis[Ru^{II} Bipy] and Ru^{II} Bipy-metallocene receptors were shown¹⁰⁴ to exhibit selectivity for Cl^- in preference to H_2PO_4^- . A phosphorus containing biferrocene macrocycle recognizes¹⁰⁵ H_2PO_4^- , HSO_4^- , and Cl^- . Atwood et al.¹⁰⁶ reported the complexation of BF_4^- by a calix[4]arene derivative functionalized with four (arene) Ru^{2+} moieties. Of the six BF_4^- anions one is included in the cavity of calix[4]arene.

4. Neutral anion receptors

Anion recognition by neutral receptors can be classified in terms of the interactions involved in the anion recognition. Three classes can be distinguished: (i) receptors that make use of ion-dipole interactions, (ii) receptors combining ion-dipole interactions with hydrogen bonding, (iii) receptors that recognize anions exclusively through hydrogen bonds.

4.1 Anion recognition based on ion-dipole interactions¹⁰⁷

Hawthorne et al.^{108,109} studied the anion recognition properties of a class of carborane supported macrocyclic multidentate mercury hosts (**32** and **33**). The mercury atoms serve as Lewis acids that can bind nucleophilic species. These macrocycles are the charge-reversed analogs of 12-crown-4 and 9-crown-3, respectively, with a preorganized structure. Macrocycle **32** complexes Cl^- and Br^- anions in a 1:1 stoichiometry^{109a} and I^- anions in a 1:2 stoichiometry^{108,109b}. The presence of anions in the cavity maximizes the interaction of four empty Hg p-orbitals with two filled p-orbitals of the anions. Macrocycle **33** binds Cl^- anions. It is believed that the halide anions act as a template for the formation of macrocycle **32** since, in the absence of halide anions, macrocycle **33** is formed.

Katz¹¹⁰ has developed a class of simple 1,8-naphthalenebis(dimethylborane) and 1,8-naphthalenebis(silyldimethylborane) (**34**). The diborane-naphthalenes complex H^- , F^- , and OH^- anions^{110a} and the mixed system F^- anions^{110b}. The unusual

coordination chemistry of phenylene-1,2-dimercury dichloride was studied by Wuest et al.¹¹¹. The X-ray crystal structure^{111a} of the Cl^- complex (**35**) shows that two $\text{C}_6\text{H}_4\text{Hg}_2\text{Cl}_2$ molecules are entwined with an additional Cl^- anion, embraced by a network of four C-Hg-Cl arms to fill the electrophilic cavity formed by the four Hg atoms. Similar receptors, developed by Rothmaier and Simon¹¹², transport Cl^- anions in solvent polymeric membranes selectively over Br^- , SCN^- , ClO_4^- , NO_3^- , and salicylate anions. A sulfite-sensitive solvent/polymeric membrane electrode based on bis(diethyl-dithiocarbamato)mercury(II) complexes was developed by Meyerhoff and Pranita¹¹³. The system responds to anions like SO_4^{2-} , NO_3^- , NO_2^- , Cl^- , ClO_4^- , salicylate, and alkylsulfonates and the response deviates from the order in the classical Hofmeister series¹¹⁴. Br^- and SCN^- are moderate interferents while significant responses to F^- , $\text{S}_2\text{O}_3^{2-}$, and S^{2-} were observed. Newcomb et al.¹¹⁵ have reported a class of macrobicyclic hosts (**36**) containing two chloride- or bromide-substituted tin atoms at the bridgehead positions, linked by 6, 7, 8, 10, or 12 methylene groups. The chloride-substituted tin macrocycles complex Cl^- anions and the bromide-substituted tin macrocycles complex Br^- anions. The selectivity depends on the size of the macrocycle: optimal binding for Cl^- and Br^- takes place with 8 and 10 methylene groups present between the tin centers, respectively. The X-ray crystal structures of the Cl^- complex^{115a} and the F^- complex^{115b,c} revealed that the anions are inside the cavities. The complexation behavior of similar compounds, like tristanacyclododecane, with Cl^- was investigated by ¹¹⁹Sn-NMR spectroscopy by Jurkschat et al.¹¹⁶. Multiorganotin receptors have been used as phosphate selective carriers in polymer-based liquid membranes¹¹⁷.

Reetz et al.^{118,119} studied a class of crown ethers possessing an intra-annular boron atom as the Lewis acid center, which binds both cations and anions. The cation binding occurs through interaction with the oxygen atoms in the crown ether ring and the anion binding occurs via interaction with the boron atom (**37**)¹¹⁸. Ditopic binding of KF, KCN, and KOCH_3 was observed. For KI and KSCN only inclusion of K^+ was observed whereas KCl and KBr were not complexed. Similarly, binding of alkoxide anions by the boron atom and ammonium cations by the crown ether ring (after proton transfer from the alcohol to the ammonium derivative) was observed¹¹⁸. The anion is bound above the plane of the crown ether and the cation is bound below this plane. Selective binding of CH_3O^- over $\text{C}_2\text{H}_5\text{O}^-$ was observed. A different selectivity was obtained with aluminum as the Lewis acidic metal center¹¹⁹. In this case, ditopic binding of LiX and KX

($\text{X} = \text{Cl}, \text{Br}, \text{I}$) was observed while LiF and KF showed no interaction.

Also the uranyl cation has been used as electrophilic center. In our group the anion binding properties of salophen moieties containing a uranyl cation (**38**) were investigated¹²⁰. These neutral uranyl salophen moieties bind H_2PO_4^- anions selectively in a 1:2 stoichiometry. Dicarboxylate anions were complexed by a dinuclear, diuranyl-containing macrocycle¹²¹. Jung and Xia¹²² showed that 12-silacrown-3 (**39**) in bulk liquid membranes transports Cl^- and Br^- ions (with a preference for Br^- over Cl^-) but not F^- and I^- ions. Recently¹²³, an organogermanium macrocycle has been developed for the selective complexation of Cl^- and Br^- . Both the ring structure and the presence of two germanium nuclei are essential for transport. Schmidtchen et al.¹²⁴ developed a neutral macrotricyclic borane-amine adduct (**40**) as host for Br^- , Cl^- , I^- , CN^- , and PF_6^- anions in a 1:1 stoichiometry. Large anions like I^- and PF_6^- can only enter the cavity with difficulty and therefore binding with these anions is relatively weak. The small Cl^- and CN^- anions can easily enter the cavity and this requires only little conformational adaptation of the host. An optimum in the complexation was observed for Br^- . By modifying the positively charged cage with four negative 4-carboxylatobenzyl groups (**41**), an overall neutral host was obtained that is able to recognize anions in water with a preference for I^- anions over Cl^- , Br^- , and CN^- anions¹²⁵.

A theoretical study of anion binding (F^- , H^- , Cl^- , and O_2^{2-}) by organoboron macrocyclic hosts was performed by Jacobson and Pizer¹²⁶. The two classes studied were the bicyclic $\text{B}[(\text{CH}_2)_n]_3$ and the tricyclic $\text{B}_4[(\text{CH}_2)_n]_6$. The former class shows only very limited size selectivity and no preference for any particular guest. In the latter class, $n = 2$ prefers H^- and O_2^{2-} , while $n = 3$ prefers Cl^- and Br^- . A substantial increase in binding energy was observed in complexes in which the anion is bound to more than two boron atoms. Successful

42a: R=CH₃, b: R=p-CH₃C₆H₄, c: R=benzo-15-crown-5 43 R=CH₂C(O)OEt

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anion inclusion in both classes of receptors occurred when the B-B distance decreases (up to 50%) and when partial rehybridization of one or more boron atoms takes place. The anion-boron interaction is more like a covalent bond than a purely ionic interaction and a significant amount of charge is transferred from the anion to the host upon complexation.

4.2 Anion recognition based on ion-dipole interactions and hydrogen bonds

In our group, the neutral uranyl salophen compounds have been further functionalized to enhance the anion selectivity of this class of compounds. Amide functionalized uranyl salophens (**42a-c**) show selective complexation of H₂PO₄⁻ anions¹¹⁹. The UO₂²⁺ ion has a pentagonal bipyramidal coordi-

dination. When encapsulated in a salophen moiety in the plane of the ligand one coordination site is available. In the absence of a guest the free position is occupied by a solvent molecule¹²⁷. However, when a guest containing a nucleophilic group is present (C=O, S=O, P=O, N), this group interacts with the uranyl cation. Receptors **42a-b** exhibit a high selectivity for H₂PO₄⁻. The highest *K*_{ass} value, as determined by conductometry in CD₃CN/DMSO-*d*₆ (99:1), was reported for **42a** (> 5.0 · 10⁶ M⁻¹). Functionalization of the salophen moieties with two benzo-15-crown-5 groups (**42c**) gave a ditopic receptor for KH₂PO₄ and the transport of KH₂PO₄ through a supported liquid membrane has been achieved¹²⁸. By applying the same strategy using the Na⁺-selective calix[4]arene tetraethyl ester as a molecular building block a bifunctional receptor for NaH₂PO₄ was obtained (**43**).¹²⁹

46 X=O, S

47a X=O b X=S

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Attachment of two benzo-15-crown-5 moieties via amide bonds to the lower rim of 4-*tert*-butylcalix[4]arene resulted in the simultaneous complexation of cations (K^+ or NH_4^+) and anions (Cl^- , NO_3^- , HSO_4^- , and $H_2PO_4^-$)¹³⁰. The combination of a uranyl salophen moiety with thymine enables the recognition of cAMP via electrostatic interactions and Watson-Crick base-pairing¹³¹. Gellman et al.¹³² described a macrocyclic phosphineoxide-disulfoxide (**44**) that binds halide anions ($MeOD/CDCl_3$ 2/98) in the order $Cl^- \approx Br^- > I^- > F^-$. These anions appeared to be attached to the positive ends of the $S=O$ and $P=O$ dipoles. In addition, simultaneous binding of monoalkylammonium cations and halide anions is observed. The complexation of the cation orients the dipoles to facilitate anion complexation and vice versa. Functionalization of dibenzo-14-crown-4 with pendant hydroxyl groups facilitates the complexation of $LiNCS$ and $LiNO_3$. In these complexes the anion is bound via the Li^+ cation to the crown ether ring and via hydrogen bonding with the hydroxyl groups¹³³. Kilburn et al.¹³⁴ synthesized a crown ether bridged by a diamidopyridine moiety, able to recognize monopotassium salts of dicarboxylic acids in chloroform, via hydrogen bonding between the acid and the diamidopyridine moiety and electrostatic interactions between a carboxylate anion and the K^+ cation complexed in the crown ether ring (**45**).

4.3 Anion recognition exclusively by hydrogen bonding

The use of hydrogen bonding as the sole interaction for the binding of anions implies that recognition is most pronounced in non-competitive solvents. The advantage of using hydrogen bonds is that a hydrogen bond is directional in character. Correct orientation of the hydrogen bond donors and/or acceptors can provide selective anion recognition.

The urea moiety has been used frequently for the recognition of (di)carboxylate anions and to lesser extent for the recognition of sulfonates and phosphates. Wilcox et al.¹³⁵ has shown that *N,N'*-diarylureas (**46**) bind sulfonates, phosphates, and carboxylates very strongly in $CHCl_3$. This strong binding results in the acceleration of simple alkylation reactions of amines¹³⁶. Hamilton et al.¹³⁷ used simple bis(thio)urea and bisguanidinium receptors (**47**) for the recognition of dicarboxylate anions in highly competitive solvents. The binding by positively charged guanidinium moieties was, as expected, greater than the binding by thiourea moieties which in turn bind more strongly than urea moieties. This is due to the larger acidity of the hydrogens in guanidinium (pK_a 13.9) compared to those in thiourea (pK_a 21.0) and urea (pK_a 26.9). Clefs **47a** and **47b** show substantial binding of glutaric acid anions in $DMSO-d_6$, a highly competitive solvent. In a weakly competitive solvent (5% THF/ $CDCl_3$), the hydrogen

bonding sites are weakly solvated and this leads to a strong enthalpic driving force ($\Delta H < 0$) for binding and a substantial negative entropy term ($\Delta S < 0$). The entropy loss is due to the loss of translational and rotational motion inherent to bimolecular association and to the freezing of bond rotations in the complex. In $DMSO-d_6$, the entropy loss is almost zero due to the desolvation of the binding site upon complexation which compensates for the translational and rotational loss due to complex formation. Addition of D_2O led to a decrease of K_{ass} due to increased solvation of host and guest. However, even at 25% D_2O binding can be detected. A similar approach was followed by Rebek et al.¹³⁸ using a chiral bisurea receptor to achieve chiral recognition in non-polar solvents. Solubilization of an insoluble betaine in $CDCl_3$ was achieved and the 1H NMR spectrum showed that the enantiotopic protons became diastereotopic. However, only very limited enantiomeric recognition was observed.

Recently, Kelly and Kim¹³⁹ reported the relative binding affinity of carboxylate, phosphate, phosphonate, and sulfonate anions, nitro groups, and δ -lactone derivatives by monourea (**48**) and bisurea receptors (**49**). The binding affinity of the monourea **48** decreases in the order: $ArOPO_3^{2-} > ArPO_3^{2-} > ArCOO^- > ArP(OH)O_2^- > ArSO_3^- > \delta$ -lactone $> ArNO_2$ and correlates with the pK_b of the guests. Binding of nitrobenzene was not observed, which is in accord with the fact that the nitro group is a poor hydrogen bond acceptor. Bisurea **49** shows a shape selectivity for isophthalate over terephthalate. The thiourea moiety has also been used as a carboxylate binding site in macrobicyclic receptors for amino acids where additional hydrogen bonding was provided by amide functionalities¹⁴⁰.

The binding of carboxylate anions by a combination of urea moieties and (sulfon)amide moieties has also been reported by

53 R = *n*-octyl, *tert*-butyl

Raposo et al.¹⁴¹ The same authors also reported the complexation of phosphonate anions¹⁴².

A metal template thiourea receptor (50) with a selectivity for glutarate dianions ($K_{\text{ass}} \approx 8.3 \cdot 10^3 \text{ M}^{-1}$ in 5% $\text{D}_2\text{O}/\text{DMSO}-d_6$) was reported recently¹⁴³. The complexation of ruthenium(II) by two terpyridine moieties assembles two thiourea binding sites enabling the binding of dicarboxylate anions. Urethane groups can also act as anion binding sites as was shown for the complexation of acetate¹⁴⁴.

Recently, we have shown that functionalization of the lower rim of 4-*tert*-butylcalix[4]arenes with two or four (thio)urea moieties via a flexible spacer (51) results in a class of receptors¹⁴⁵ with a selectivity for Cl^- in preference to Br^- , I^- , CN^- , and SCN^- . Remarkably, these receptors show no complexation of H_2PO_4^- anions. Functionalization of 4-*tert*-butylcalix[6]arenes with three (thio)urea moieties (52) gave a class of receptors with C_3 symmetry which show a high affinity for tricarboxylate anions with the same symmetry. The thiourea derivative has a strong affinity for 1,3,5-benzenetricarboxylate ($K_{\text{ass}} = 2.9 \cdot 10^5 \text{ M}$, CDCl_3). These receptors also complex halide anions¹⁴⁶ with a preference for Br^- over Cl^- . Functionalization of calix[4]arene tetraethyl ester,

which is selective for Na^+ , with two (53) or four urea moieties at the upper rim, yields a class of bifunctional receptors for MX salts ($\text{M} = \text{Na}, \text{K}$; $\text{X} = \text{Cl}, \text{Br}, \text{I}$). These receptors are capable of solubilizing these salts in chloroform, and cation complexation by the ester groups at the lower rim is a prerequisite for anion complexation by the urea moieties at the upper rim¹⁴⁷. In earlier work, we have shown that simple tris(2-aminoethyl)amine derivatives (54 and 55), in which the hydrogen bond donating and accepting sites are positioned in a tetrahedral orientation, recognize selectively the tetrahedral H_2PO_4^- anion over Cl^- and HSO_4^- anions¹⁴⁸. Calix[4]arenes functionalized with four sulfonamide groups at the upper rim (56) selectively recognize HSO_4^- anions¹⁴⁹. A neutral biscalix[4]arene was recently shown to bind F^- anions¹⁵⁰. The recognition of F^- anions was also achieved exploiting the strong affinity of ferroceneboronic acids (57) for F^- anions¹⁵¹. Using a neutral polyaza cleft Anslyn et al.¹⁵² were able to complex enolate anions in CD_3CN . They found that the higher basicity of the hydrogen bond acceptors does not automatically imply that the complexation becomes stronger. The number of hydrogen bonds also determines the overall strength of association together with the secondary hydrogen bonding interactions and the nature of the host and guest (rigidity, flexibility).

Pascal et al.¹⁵³ reported a cyclophane in which the central cavity is surrounded by three amide groups. Preliminary ^1H -NMR and ^{19}F -NMR spectroscopic studies indicate that there is an interaction with F^- . However, they could not prove that the F^- anion is in the cavity of the cyclophane. Recently, a cyclic hexapeptide containing three non-natural amino acids and three natural amino acids (Ala, Ser) was reported to be a highly efficient receptor for disodium 4-nitrophenyl phosphate in DMSO¹⁵⁴. The binding occurred via hydrogen bonding.

Dixon and Farnham¹⁵⁵ showed that fluorinated macrocycles (58) can act as hosts for F^- anions. X-Ray crystal structures show that the F^- anion is held within the chiral cavity by interaction with four CH_2 groups. The fluorinated groups attached to the CH_2 groups constitute the electronic driving force for fluoride binding. Fluorinated macrocycles¹⁵⁶ were also used in the gas-phase complexation of $\text{O}_2^- \text{F}^-$.

54 R = CH_2Cl , $(\text{CH}_2)_4\text{CH}_3$,
Ar, ArOCH_3 55 R = Ar, ArCH_3 , 2-naphthyl 56 R = ethers, ester or amides
R' = H, *n*-Pr, *tert*-Bu, or $(\text{CH}_2)_2\text{NHC(O)Me}$

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