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Neutral anion receptors: design and application

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After the development of synthetic cation receptors in the late 1960s, only in the past decade has work started on the development of synthetic neutral anion receptors. Combination and preorganization of different anion binding groups, like amides, urea moieties, or Lewis acidic metal centers lead to receptor molecules that strongly bind inorganic anions with high selectivity. Combined with neutral cation ligands, ditopic receptors were obtained for the complexation of inorganic salts. The molecular complexation properties of anion receptors has been transduced into macroscopic properties in membrane separation processes and in sensors for selective anion detection.

Introduction

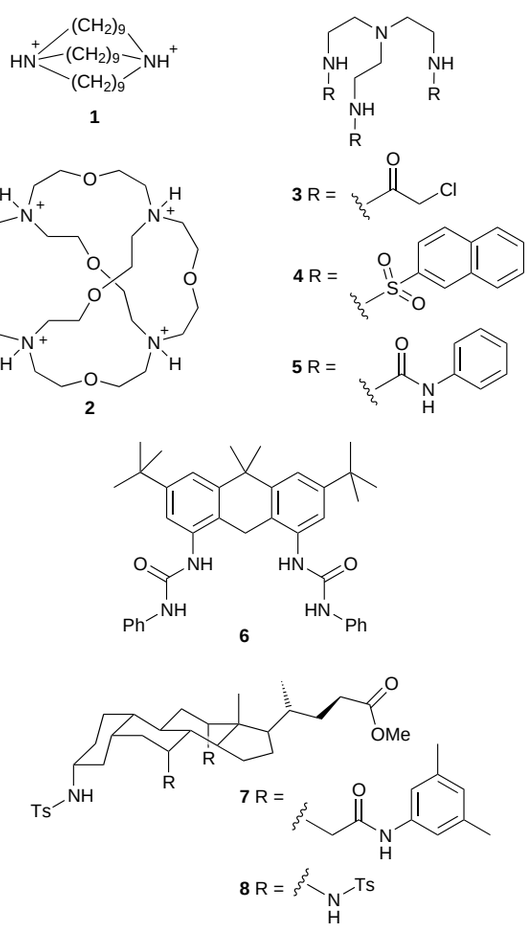
Host–guest systems for ionic species have played an important role in the development of the field of supramolecular chemistry, the chemistry of the non-covalent interactions. The research of Pedersen in 1967 on the complexation of alkali metal ions by crown ethers initiated the development of many other neutral host species for metal ions.[1,2] Compared with the cation receptors, anion receptors were developed much later, although already in 1968 the first synthetic receptor for inorganic anions was reported[3] (size selective binding of Cl^- anions was described with diprotonated 1,11-diazabicyclo-[9.9.9]nonacosane **1**). The field started to develop in 1976 when Graf and Lehn reported that *protonated* cryptate **2** encapsulates F^-, Br^- and Cl^- anions.[4] Since then several other *positively charged* anion receptors have been developed that have protonated nitrogen atoms or metal ions.[5] In these receptors mainly coulomb interactions contribute to the attractive force.

In Nature, the transport of sulfate or phosphate anions through cell membranes is regulated by *neutral* anion binding proteins.[6] The high specificity is due to a recognition site in which the anion is completely desolvated and bound exclusively *via* hydrogen bonds. Furthermore, a so-called macrodipole effect, caused by orientation of the amino terminus of the protein backbones towards the negative guest, contributes to the stability of the complex.[7] This article will focus on the recent developments in the design of synthetic *neutral* receptors for inorganic anions. The individual interactions in these receptors are weaker than coulomb interactions and strongly depend on the directionality of the interaction and on the electron density of the anion. Nevertheless, combination and preorganization of several binding sites can lead to selective neutral receptors for anions.

The neutral anion binding receptors can be divided into two classes: receptors that bind anions exclusively by hydrogen bonding or ion–dipole interactions, and receptors that coordinate anions at the Lewis acidic centers of a neutral organometallic ligand. The corresponding ditopic receptors that are formed by the combination of neutral anion and cation receptor sites are included in the second part of this review. Finally some applications of anion receptors in anion transport and sensing will be discussed.

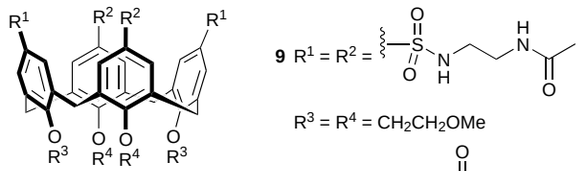
Anion recognition by hydrogen bonding

In an attempt to mimic nature in its high binding selectivity, several anion receptors have been developed with three-dimensional arrangements of hydrogen bond donating moieties, like amides, sulfonamides, and (thio)ureas. Receptor **3**, which has three amido substituents connected *via* a tris(aminoethyl)amine spacer, binds $H_2PO_4^-$ with an association constant of 6100 M^{-1} in MeCN.[8] The increased electrophilicity of the sulfonamide NH moieties in **4**, in combination with preorganization of the binding site by Π-stacking, enhances the $H_2PO_4^-$ binding with **4** ($K_a = 1.4 \times 10^4$ M^{-1}) and results in an almost 400-fold selectivity over HSO_4^-. The tris(aminoethyl)amine spacer was also used to preorganize urea moieties (receptor **5**).[9] This receptor strongly binds PO_4^{3-} ($K_a = 1.4 \times 10^4$ M^{-1} in [$^2H_6$]DMSO) and SO_4^{2-} ($K_a = 3 \times 10^3$ M^{-1}). Reduction of the rotational freedom of the urea substituents with the *cis*-1,3,5-tris(aminomethyl)cyclohexane spacer lowers the PO_4^{3-} association to 1100 M^{-1}. Recently Umezawa and coworkers reported bis(*N*′-phenylthioureylene)xanthene **6**.[10] The rigid spacer prevents the self-association of the urea substituents



and consequently the association constant for $H_2PO_4^-$ is very high. The value of 1.95×10^5 M^{-1} in [$^2H_6$]DMSO was obtained from an NMR titration experiment in competition with 10 equiv. of Cl^- (K_a = 1000 M^{-1}). Davis and co-workers have utilized cholic acid as a building block for neutral anion receptors.[11] Bis-carbamate **7** preferentially binds F^- over other halides, but does not discriminate between chloride or bromide. Functionalization of cholic acid with sulfonamido moieties (**8**) yields a receptor that binds the more basic chloride more strongly than bromide (K_a = 92 000 and 9200 M^{-1}, respectively, in $CDCl_3$).

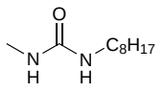
Calixarenes are versatile building blocks that have been used in the design of many cation receptors.[12] Hydrogen bond donating substituents at either the *upper* or *lower* rim yield receptor molecules suitable for anion binding. Functionalization of a calix[4]arene with upper rim sulfonamido substituents leads to a three-dimensional cavity (receptor **9**) which complexes



9 $R^1 = R^2 =$

$R^3 = R^4 = CH_2CH_2OMe$

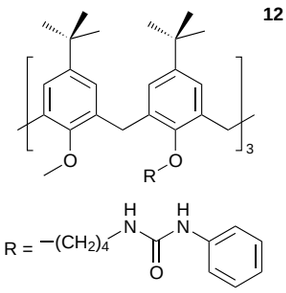
10 R^1 = H, $R^2 =$



$R^3 = R^4 = CH_2CO_2Et$

11 $R^1 = R^2 = Bu^t$,
$R^3 = R^4 = (CH_2)_4NHC(O)NHPh$

12 $R^1 = R^2 = Bu^t$,
R^3 = Pr, $R^4 = (CH_2)_4NHC(O)NHPh$



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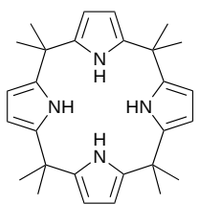

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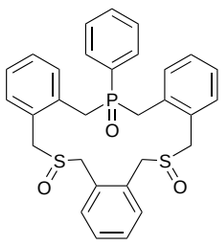

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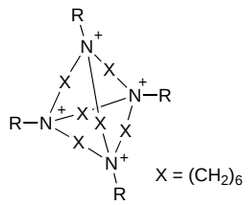
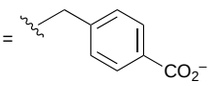


16 $R = BH_3^-$

17 R =



tetrahedral HSO_4^- better than spherical Cl^- or planar NO_3^-.[13] We also introduced octylurea moieties at the upper rim of a calix[4]arene tetra(ethyl ester) yielding calix[4]arene **10**. However, upon addition of Bu_4NCl or Bu_4NBr in $CDCl_3$ no complexation of halide anions was observed.[14] This is due to the strong intramolecular hydrogen bonding between the diametrically positioned urea moieties, stabilizing **10** in a pinched cone conformation.[15] This conformation is stable up to at least 120 °C in $C_2D_2Cl_4$. In contrast to the upper rim functionalized derivatives, calix[4]arenes functionalized at the lower rim with urea substituents bind specifically halide anions. The tetrakis(phenylurea) derivative **11** binds Cl^- and Br^- ions in $CDCl_3$ with association constants of 2015 and 1225 M^{-1}, respectively.[16] The very strong hydrogen bond acceptors F^- and $H_2PO_4^-$ are not bound by **11**. Although bidentate phenylurea derivative **12** has only four hydrogen bond donor sites, the association constants are significantly higher than with **11** and the selectivity for Cl^- over Br^- is enhanced (K_a = 7105 and 2555 M^{-1}, respectively). The extent of inter- and intramolecular hydrogen bond formation is much lower in **12** than in the tetrakis(phenylurea) derivative **11**, favouring the complexation of anions. The larger binding cavity in tris(phenylurea) calix[6]arene derivative **13** reverses the selectivity and Br^- binding is favoured over Cl^-.[17] Beer *et al.* covalently linked the upper and lower rim of two calix[4]arenes with hydrogen bond donating amide bonds.[18] The resulting cavity is too small for encapsulation of $H_2PO_4^-$ or HSO_4^-, but Cl^- and F^- are bound, favouring F^- with one order of magnitude.

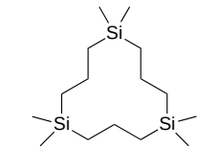
Recently, Sessler and co-workers reported the anion binding ability of calixpyrroles.[19] These *meso*-substituted porphyrinogens are, unlike porphyrinogens with *meso*-hydrogen atoms, stable towards auto-oxidation, and can adopt cone and 1,3-alternate conformations like calix[4]arenes. Crystal structures show that calix[4]pyrrole **14** is fixed in a cone conformation upon Cl^- or F^- binding. The receptor preferentially binds F^- (K_a = 1.7 $\times 10^4$ M^{-1} in CD_2Cl_2) over Cl^- (K_a = 350 M^{-1}) or Br^- (K_a = 10 M^{-1}). Substitution of **14** with electron-withdrawing bromine atoms increases the anion binding (K_a = 2.7 $\times 10^4$ M^{-1} and 4.3 $\times 10^3$ M^{-1} for F^- and Cl^-, respectively).

Phosphine oxide disulfoxide **15** binds halide ions ($Cl^- \approx Br^- > I^- > F^-$) *via* ion–dipole interactions.[20] The association with Cl^-, Br^- (both K_a = 65 M^{-1}) and I^- (K_a = 40 M^{-1}) was investigated by NMR titration in 2 vol% CD_3OD in $CDCl_3$. A similar experiment with F^- induced only small shifts. Also the macrotricyclic borane–amine adduct **16** encapsulates anions driven by ion–dipole interactions.[21] All four borane–amine bonds are in a fixed orientation with the positive ends pointing to the center of the cavity. The small Cl^- and CN^- anions can easily enter the cavity with only a little conformational adaptation of the host. Optimal association was observed for Br^-. Zwitterionic macrotricycle **17** is able to recognize anions in water.[21b] Halides are complexed in a 1 : 1 stoichiometry with association constants from 270 M^{-1} for Cl^- to 6480 M^{-1} for I^-.

Anion recognition with organometallic ligands

Several Lewis acidic atoms have been investigated for binding of anions. In particular, group 14 metals have been used extensively in macrocyclic organometallic anion receptors. 12-Silacrown-3 **18** preferentially binds Cl^- over all other halides in bulk liquid membrane transport experiments.[22] Takeuchi and co-workers investigated several organogermanium macrocycles (receptor **19**) as carrier in bulk liquid membranes.[23] The Lewis acidity of bis-methyl or bis-phenyl substituted germanium was too low for anion transport. The enhanced acidity of methyl(chloro)germanium results in effective Cl^- binding, and transports Cl^- with selectivity over Br^-. Methyl(bromo)-bis(chloro)- and bis(bromo)-germanium are unsuitable due to easy decomposition by hydrolysis. The halide substituted tin centers at the bridgehead position of macrobicycle **20** coordinate with encapsulated Cl^- or Br^-.[24] Optimal selectivity in the case of Cl^- is obtained with eight methylene units between the tin centers; for Br^- a larger cavity is necessary (10 methylene units).

Mercury has also been used for the design of Cl^- receptors. Two phenylene-1,2-dimercury dichloride molecules coordinate with an additional Cl^- anion in the electrophilic cavity that is formed by the four C–Hg–Cl arms.[25] Hawthorne and Zheng studied the anion recognition of carborane-supported multidentate mercury hosts.[26] Cl^- can coordinate with the four mercury atoms in the preorganized cavity of mercuracarborand **21**. Iodide anions are bound in a 1 : 2 host–guest stoichiometry with the I^- ions slightly above and below the plane formed by the mercury atoms.



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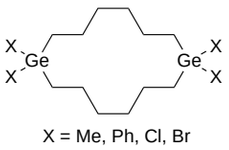

X = Me, Ph, Cl, Br

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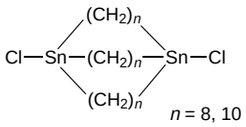

n = 8, 10

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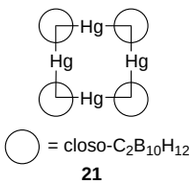

= closo-$C_2B_{10}H_{12}$

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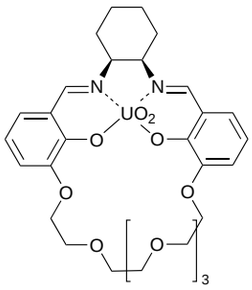

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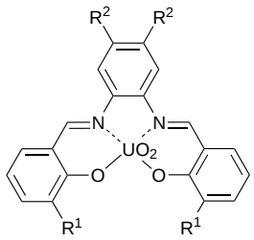
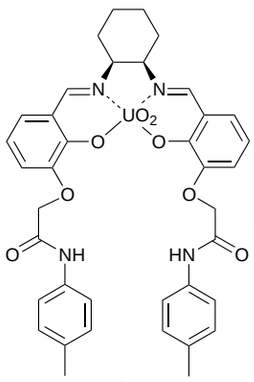


23 $R^1 = R^2 = H$
24 $R^1 = OMe$, $R^2 = H$
25 $R^1 = H$, $R^2 = OC_{12}H_{25}$
26 $R^1 = OMe$, $R^2 = OC_{12}H_{25}$



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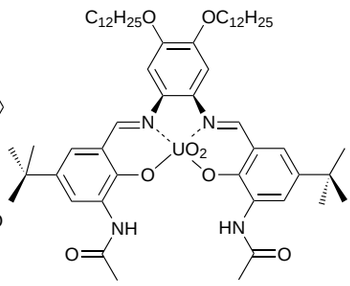

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Katz developed F^- receptors with Lewis acidic boron centers.[27] Both naphthalene-1,8-diylbis(dimethylborane) and (8-trimethylsilyl)-1-naphthyl(dimethylborane) coordinate the anion between the two electron accepting atoms. The boron atom of ferroceneboronic acid binds F^- with an association constant of 1000 M^{-1} (in MeOH–H_2O 1 : 9).[28] The association is reflected in a strong decay in the absorbance at 665 nm. Other ions, like Cl^- or Br^-, hardly affect the absorbance.

In our group we have developed neutral anion receptors based on an immobilized uranyl cation. Complexed in a salophen unit the uranyl cation prefers a pentagonal bipyramidal coordination, with the two oxygen atoms at the apical positions and four of the equatorial positions occupied by the salophen ligand. The fifth equatorial position can coordinate to nucleophilic guest species. This can either be a nucleophilic moiety (*e.g.* C=O or S=O) of a neutral molecule,[29] as we illustrated with the transport of urea with carrier **22** through supported liquid membranes,[30] or anionic species.[31,32] Uranyl salophen **23** binds $H_2PO_4^-$ more strongly than Cl^- (K_a = 1.5 × 10^4 and 4.0 × 10^2 M^{-1} in MeCN–DMSO 99 : 1), which is in accordance with the principle that the hard Lewis acidic uranyl cation favours interactions with hard Lewis basic anions. The advantage of our system is that additional hydrogen bond binding sites can be introduced close to the uranyl center and this makes it possible to improve or change the selectivity in anion binding. Hydrogen bond accepting methoxy substituents (**24**) enhance the $H_2PO_4^-$ over Cl^- selectivity. The crystal structure of the $H_2PO_4^-$ complex of **24** (Fig. 1) clearly shows the additional hydrogen bond between the anion and the methoxy oxygen atom. Salophen **27**, with *N*-(4-methylphenyl)acetamide moieties, has both hydrogen bond accepting ether oxygens and hydrogen bond donating amide functions. This salophen binds $H_2PO_4^-$ by coordination at the uranyl center and three hydrogen bonds. These additional interactions are reflected in the increased association constant for $H_2PO_4^-$ (K_a > 5 × 10^5 M^{-1}). Recently we have synthesized uranyl salophen **28** with hydrogen bond *donating* acetamido moieties close to the uranyl coordination site. The resulting F^- binding is reflected in the selectivity of sensors based on this receptor. According to ^1H NMR titrations in $CDCl_3$ a 2 : 1 host–guest complex is formed in which the fluoride anion is hydrogen bonded to the amide moieties and coordinated to the uranyl centers.

Ditopic receptors, combined recognition of anions and cations

The new neutral anion receptors opened the way for neutral *ditopic* receptors that complex *both* anions and cations. Anion binding, based on hydrogen bonds or coordination to Lewis acids, has been combined with cation binding, *e.g.* crown ethers or calix[4]arene derivatives. We combined the anion binding uranyl salophen building block with several cation ligands. Ditopic receptor **29** binds K^+ between the crown ether substituents, while the uranyl center can coordinate with phosphate.[33] The binding was investigated by ^1H NMR spectroscopy, cyclic voltammetry and fast atom bombardment mass spectroscopy (FAB-MS). The spectra of the latter technique show intense peaks for [**29** + K^+]$^+$ and [**29** + $H_2PO_4^-$]$^-$, while the signal of [**29** + K^+ + $H_2PO_4^-$]$^-$ is also present, which clearly proves the complexation of the salt. In the ditopic receptor **30** a Cs^+ selective 1,3-alternate calix[4]arene crown-6 is combined with a uranyl salophen and this receptor complexes CsCl.[34] Furthermore, the Na^+ selective calix[4]arene tetra(ethyl ester) was linked at the upper rim *via* amide bonds to a uranyl salophen unit.[35] FAB-MS spectra of the NaH_2PO_4 complex of this receptor show intense signals for the receptor + Na^+ and for the receptor + $H_2PO_4^-$.

Also Reetz and co-workers combined Lewis acidic centers with a cation binding crown ether. Boronic acid crown ether derivative **31** forms a ditopic complex with KF when the receptor is added to a suspension of the salt in CH_2Cl_2.[36] Other potassium salts (KBr or KCl) do not exhibit either monotopic or hetrotopic interactions. This selectivity is also observed in

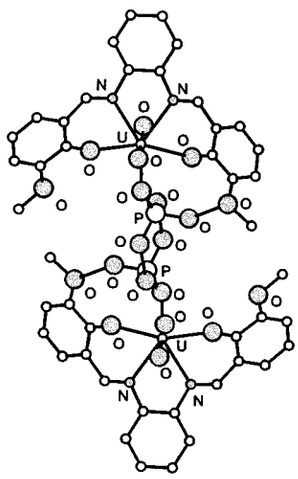
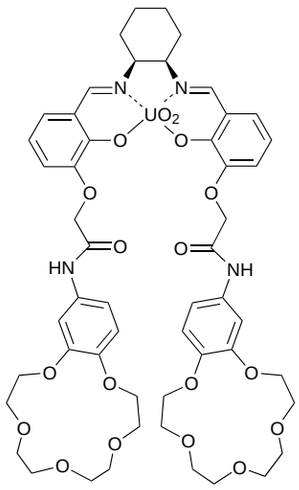


Fig. 1 Crystal structure of the complex **24**·H_2PO_4. Hydrogen atoms are omitted for clarity.



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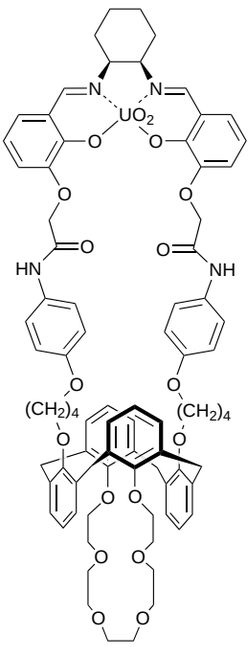

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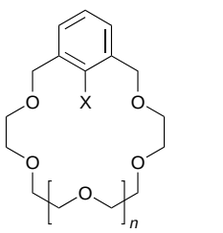
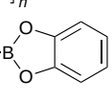
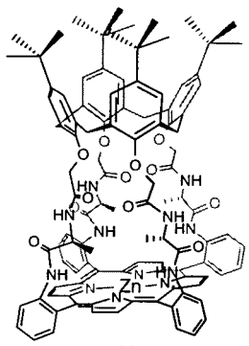


31 n = 2, X = 

32 n = 1, X = $OAlMe_2$

competition experiments, as in a mixture of KF, KCl, KBr and KI, the KF adduct of **31** is exclusively formed. With aluminium phenolate as the Lewis acid (receptor **32**) the selectivity is reversed. With the Li^+ or K^+ salts of F^- no binding is observed, whereas Cl^-, Br^-, or I^- salts all show ditopic binding. Shinkai and co-workers combined a calix[4]arene with a neutral anion binding porphyrin–Zn^{2+} complex (receptor **33**).[37] The two building blocks are covalently linked *via* lower rim amido substituents. The cation (*e.g.* Na^+ or K^+) is coordinated by the four $OCH_2C(O)NH$ linkages and a cavity is formed between the two metal ions. In the case of the K^+ complex strong I^- complexation is observed. For the Na^+ complex the association constant for encapsulation of I^- is lower. This is due to the different electron accepting character of Na^+ and the larger distance between the Zn^{2+} and Na^+ ion. Anion binding porphyrin **34** and cation binding calix[4]arene **35** form a bifunctional receptor by self-assembly.[38] The hydrogen bonds between the diaminopyridine and thymine moieties brings the two recognition sites into close proximity. When no cation is bound in the cavity formed by the ethyl ester moieties, the diaminopyridine fragment interacts with these substituents *via* hydrogen bonding and cannot form the aggregate with the thymine units. Sodium complexation of **35** initiates the self-assembly as it coordinates with the ethyl ester carbonyl oxygen atoms. The self-assembly of the bifunctional receptor enhances the binding of the investigated anion (SCN^-) to the porphyrin. The association constant of the self-assembled complex (**34**·SCN^-)(**35**·Na^+) is 2.5×10^4 M^{-1} in toluene, and is very different from that for free **34** which binds SCN^- only weakly (K_a = 10 M^{-1}).

When we investigated anion binding *via* hydrogen bonds with the above mentioned urea-functionalized calix[4]arene **10** it was observed that cation complexation is essential for anion complexation (positive heterotropic allostery). The tetra ester functionalized lower rim of **10** is a ligand that is highly selective



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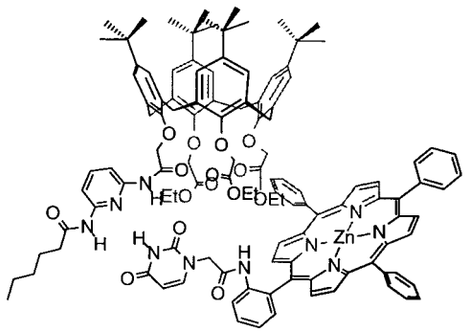
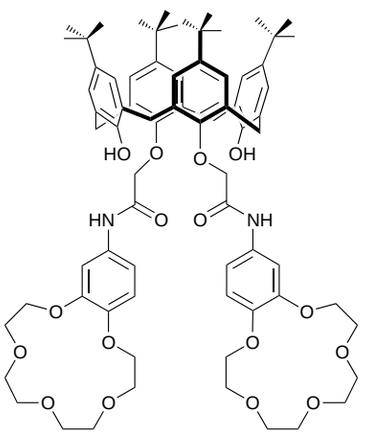


34•35

for Na^+.[39] Upon complexation of Na^+, the conformation of the calix[4]arene is converted from a pinched cone to a symmetrical cone.[14] In this conformation intramolecular hydrogen bonding is not possible and the urea moieties become available for hydrogen bonding to anions. The Na^+ complex of **10** prefers Cl^- binding over the 'softer' Br^- anion. Calix[4]arene **10** is capable of solubilizing simple alkali salts in $CHCl_3$. The selectivity of the cation binding part of the receptor is expressed by the relative amount of Cl^- alkali salt complex that is transferred in liquid–solid extractions. NaCl results in 100% of [Na^+·Cl^-·**10**] complex, but with KCl only partial complexation is observed (29%). No complexation of CsCl is observed, apparently because Cs^+ is too large to fit in the cavity. Beer *et al.* reported NMR studies with the K^+ or NH_4^+ complex of calix[4]arene **36**.[40] K^+ or NH_4^+ form a sandwich complex with the bis(crown ether), rigidifying the hydrogen-bonding arrangement of the two amides and the two phenolic protons in a pseudo-tetrahedral cavity in which Cl^- or HSO_4^- is bound.

Anion transport and sensing

Supramolecular chemistry has always been associated with possible applications. As in the case of cation receptors, anion receptors are now applied as the selector element in separation membranes[41] and in ion-selective electrodes.[42] Recently we have studied anion transport through supported liquid membranes (SLMs). The pores of a microporous film are filled with a solution of anion receptor in *o*-nitrophenyl octyl ether and the film is placed between two aqueous phases: a source phase with the anion to be transported and a receiving phase. The transport of KH_2PO_4 is facilitated by a 1 : 1 mixture of anion receptor **36** and the K^+ selective calix[4]arene crown-5.[43] Salt transport solely by the cation receptor is very low (0.6×10^{-8} mol m^{-2} s^{-1}) due to the low partition of $H_2PO_4^-$. Transport of KH_2PO_4 by **37** alone increases the transport (5.1×10^{-8} mol m^{-2} s^{-1}), but the flux is much larger using a mixture of cation and anion receptor (12.5×10^{-8} mol m^{-2} s^{-1}). A transport selectivity for $H_2PO_4^-$ over Cl^- of 143 for the combination of the cation carrier and **36** is observed. Bifunctional receptor **29** transports CsCl and the flux has been compared with the transport of $CsNO_3$.[34] The interactions of *both* the anion and the cation of CsCl with **29** is reflected in a higher transport rate for CsCl than



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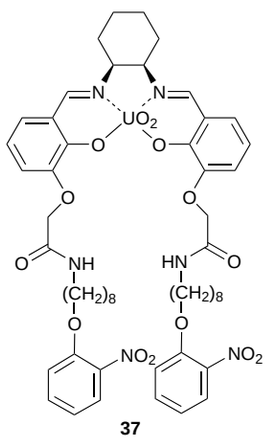

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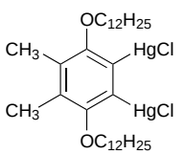

38

for $CsNO_3$. Tsukube *et al.* applied neutral tris(β-ketonate) lanthanide complexes as anion carriers in bulk liquid membrane transport experiments.[44] The transport of Cl^- is more efficient than that of the more lipophilic Br^- I^- or ClO_4^-.

In potentiometric sensors, *e.g.* ion-selective electrodes (ISEs) or chemically modified field effect transistors (CHEMFETs[45]), the molecular interaction between the receptor and the ionic species can be converted into an electronic signal. Most anion receptors applied in potentiometric sensors are organometallic molecules, but recently Umezawa and co-workers reported the application of **6** as a sensor selector.[46] Remarkably, $H_2PO_4^-$ could not be detected as would be expected based on the association constants; instead a moderate Cl^- sensor was obtained. The potentiometric selectivity coefficient *vs.* Br^- ($\log K^{Pot}_{Cl,Br} = 0.4$) reflects almost equal sensitivity for Cl^- and Br^-. Simon and co-workers developed chloride selective electrodes with organometallic trialkyltin derivatives as the neutral anion receptor.[47] With di- or tetra-dentate organotin derivatives the selectivity favours the binding of $H_2PO_4^-$.[48] The sensors show selectivity over the very lipophilic anions, *e.g.* SCN^- and ClO_4^-. Sensors with a high chloride selectivity are based on lipophilic *ortho*-dimercury aromatic compounds like **38**.[49] Chloride is preferred over other halides, as expressed by the potentiometric selectivity coefficients *vs.* I^-, Br^- and F^- of respectively −1.7, −1.4 and −6.6 ($\log K^{Pot}_{Cl,j}$).

Recently in our group we investigated uranyl salophen derivatives as anion receptors in CHEMFETs that are selective for hydrophilic anions.[32,50] For this purpose novel derivatives were synthesized with lipophilic substituents to enhance the solubility in the membrane matrix. The high association constants of uranyl salophen derivatives for $H_2PO_4^-$ could be transduced into sensors with high sensitivity and selectivity for this anion. Application of uranyl salophen **25**, the lipophilic equivalent of **23**, results in sensors that start to respond to $H_2PO_4^-$ at activities $\geqslant 6 \times 10^{-4}$ M. Even in the presence of the more lipophilic NO_3^- anion the sensor is twenty times more sensitive for $H_2PO_4^-$ ($\log K^{Pot}_{H_2PO_4,NO_3} = -1.3$). The introduction of hydrogen bond donating methoxy substituents (receptor **26**) increases the $H_2PO_4^-$ binding and consequently an improved detection limit of 1.6×10^{-4} M is obtained. Also the selectivity in the presence of halides and SO_4^{2-} is further enhanced by a factor 3 to 10. Incorporation of salophen derivative **28** in the CHEMFET membrane gives excellent F^- sensitivity and selectivity. The strong binding of the hydrophilic F^- anion in the small cleft is reflected by the hundred-fold or higher selectivity ($\log K^{Pot}_{F,j} \leqslant -2.0$) for fluoride over other halides, nitrate and sulfate. As shown in Fig. 2, even in the presence of a large excess of the very lipophilic ClO_4^- anion (0.1 M) it is possible to detect F^- at the (sub)millimolar level ($\log K^{Pot}_{F,ClO_4} = -1.7$).

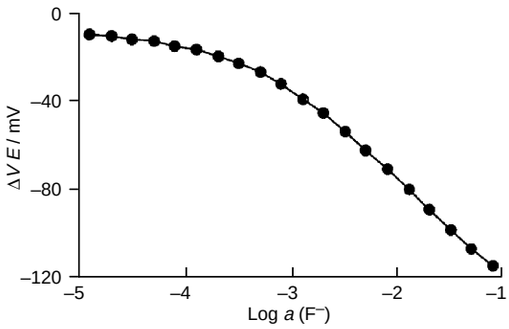

Fig. 2 Fluoride response of CHEMFET with receptor **28** in the presence of 0.1 M ClO_4^- (in 0.01 M MES buffer, pH 6.0)

Conclusions

This article illustrates that neutral anion receptors with high binding selectivity can be synthesized. The organometallic ligands show the highest association constants, but three-dimensional arrangements of hydrogen bond donating ligands are promising recent developments. The combination of anion receptors with cation receptors revealed interesting events like synergistic effects and (positive) heterotropic allostery.

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