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Calixarene-based Anion Receptors

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INTRODUCTION

Anions play a number of fundamental roles in biological and chemical processes and the development of selective synthetic anion receptors is an area of current importance. The use of anions as nucleophiles, bases, redox-active agents and phase-transfer catalysts has led to a desire for receptors which enable stabilisation and separation through co-ordination. The increasing problem of environmental anion pollutants, such as phosphate and nitrate, which lead to eutrophication, and radioactive pertechnetate, a product of the nuclear fuel cycle, is also an area of concern. Biochemically, anions are essential to normal metabolic function, both ATP and DNA being anionic, thus the development of anion binding mimetics will enable investigation of basic biological processes. A number of disease states, including cystic fibrosis, cancer and Alzheimer's disease, involve misregulation of anion function, offering the long term goal of a medical role for anion receptors [1–6].

The development of synthetic anion receptors has been slow in comparison to cation receptors. This is due, in the main, to a number of unique properties of anions that need to be addressed in the design of receptors. These include the negative charge, which is often delocalised over a number of atoms, and the size and shape of anions. In contrast to cations, anions are larger and have diverse topology, being spherical *e.g.* halides, linear such as the dicarboxylates, planar, tetrahedral or octahedral. Binding of anions is also affected by their pH dependence and solvation. For a given anion and cation of comparable size, for example fluoride and potassium, the anion is more strongly hydrated and thus more difficult to desolvate—a pre-requisite for binding.

The first reported synthetic anion receptor was the polyammonium cryptand of Simmons and Park [7], which bound halide anions within a cavity through a combination of electrostatic interactions and directional hydrogen bonding. Further development of organic based systems was slow until the seminal work of Lehn *et al.* who reported a range of polyammonium macrocycles [8] and cryptates [9] with a variety of binding selectivities. The small operational pH range of these receptors was overcome by the design of receptors based on the guanidinium motif [10], and quaternised nitrogen atoms [11]. In recent years, organic-based receptors have been developed which rely solely on hydrogen-bond donors such as amides [12], ureas [13] and pyrroles [14].

Inorganic approaches to anion receptors have been based on the properties of metals, which allow interactions either through favourable electrostatics or orbital overlap.[1d] However, such systems also offer the opportunity of sensing the binding event through redox, colorimetric or luminescent responses. The pioneering work of Newcomb on the design of tin based macrocycles [15] has led to the development of Lewis acidic hosts based on boron [16], silicon [17], germanium [18] and mercury [19]. The 1970s saw great interest in the design of cascade complexes in which bound anions are bridged between positively charged metal centres [20].

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More recently, a number of approaches to anion binding through electrostatic interactions have been investigated using, for example, the cobaltocenium moiety [21] or metal-ion-cornered macrocyclic receptors [22,23].

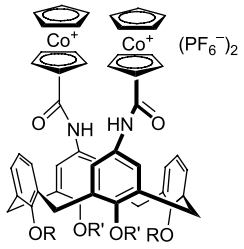
Calixarenes are particularly attractive scaffolds for receptor development, the macrocyclic core being available in a variety of sizes, easily pre-organised into a number of topographies and readily selectively functionalised for the apposite introduction of ligands [24,25]. In this review, we discuss the role of calixarene-based systems in the preparation of selective anion receptors, contrasting the mechanisms employed in inorganic and organic systems to achieve binding. The exciting current area of ditopic receptors for ion-pairs is discussed in detail and the potential for calixarene-based systems to have commercial applications is explored.

INORGANIC-BASED SYSTEMS

Metallocene Calixarene Receptors

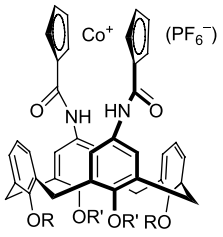
Cobaltocenium-based Receptors

Calix[4]arenes bearing cobaltocenium amide moieties enable enhanced binding of anions through a combination of electrostatic and hydrogen-bonding interactions. In addition, the organometallic centre offers the potential of sensing anions through electrochemical and spectrochemical methods [21].



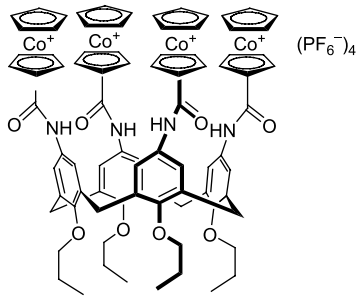
1

a: R = CH_3 R' = H
b: R = H R' = Tosyl
c: R = Tosyl R' = H



2

R = H R' = Tosyl



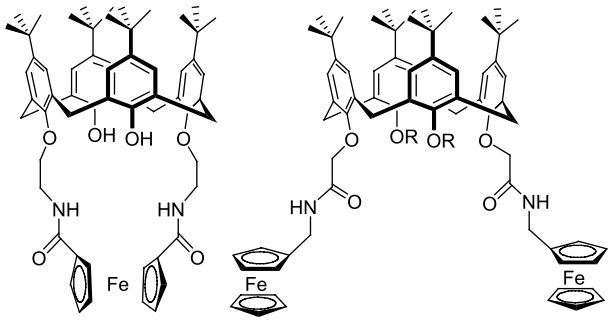
3

The upper-rim difunctionalised receptor **1a** shows selectivity for complexation of dicarboxylates (K_{ass} adipate 11510 M^{-1} in $(CD_3)_2SO$) with a chain-length dependency; complementary NMR spectral shifts indicate that the anion is bound between the two metal centres and within the extended cavity, whereas spherical and tetrahedral anions are bound in a 1:2 host:guest stoichiometry [26,27]. Alteration of both the bulk and the substitution pattern at the lower rim has a significant effect on the anion binding trends observed [28]. Introduction of tosyl groups results in receptors that bind anions in a 1:1 manner and with larger binding constants. The selectivity profile varies between the isomers; when the tosyl groups are *para* to the amide the host **1b** preferentially binds carboxylates with excellent selectivity over chloride whereas the isomer **1c** binds dihydrogen phosphate most strongly and shows reduced discrimination between the anions tested. The bridged receptor **2** is also selective for carboxylates (K_{ass} $MeCO_2^-$ 41520 M^{-1} in $(CD_3)_2SO$) [22,23]. Preliminary binding studies of a tetrafunctionalised host **3** indicate selective binding of dihydrogen phosphate in $(CD_3)_2SO$ [21].

All of the receptors show significant cathodic perturbations of the cobaltocene/cobaltocenium redox couple in the presence of anions (e.g. **2** $MeCO_2^-$, ΔE 155 mV) [29], allowing voltammetric sensing.

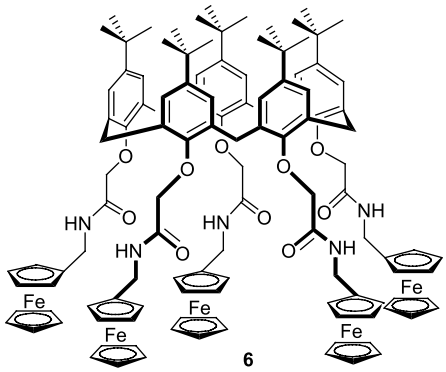
Ferrocene-based Receptors

The ferrocene moiety has also been extensively investigated for the electrochemical sensing of anions [30]. Unlike the similar cobaltocenium receptors, calixarenes appended with ferrocene provide neutral hydrogen-bonding sensing systems. Receptor **4**, in which calix[4]arene is bridged by ferrocene at the lower rim, presents a size-discriminatory binding cavity which allows selective electrochemical sensing of dihydrogen phosphate in the presence of a ten-fold excess of the competing anions sulfate and chloride [31]. The lower-rim calix[4]arene **5a** and calix[5]arene **6** derivatives, despite providing a more flexible binding cavity, still exhibit large cathodic shifts in the presence of anions, 1:1 stoichiometry of binding and selectivity for dihydrogen phosphate [32]. However, the partially functionalised compound **5b** showed no evidence for anion binding which may be a consequence of intramolecular hydrogen bonding from the free phenolic moieties.



4 5

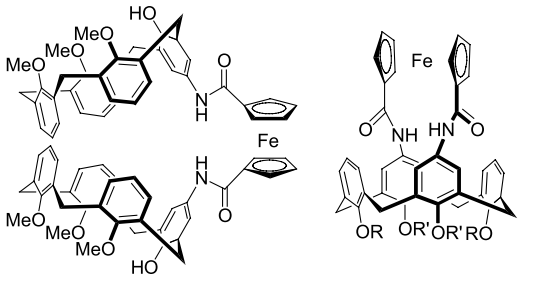
a: R = $CH_2CONHCH_2Fc$
b: R = H



6

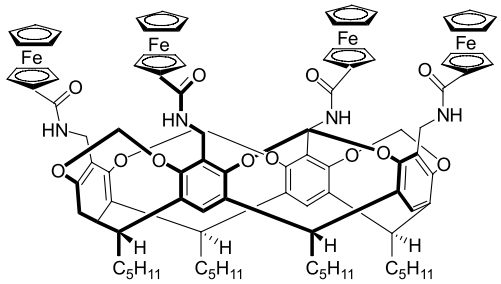
Ferrocene groups have also been appended at the upper-rim of the calixarene cavity. Interestingly, the anion-binding properties, both magnitude of association constant and anion selectivity, of the clam receptor **7** exhibit a marked dependence on solvent [33]. In CH_2Cl_2, benzoate is bound preferentially over both acetate and chloride, whereas in $(CD_3)_2CO$ the selectivity profile is reversed (K_{ass} $MeCO_2^-$ 6000 M^{-1}, Cl^- 5200 M^{-1}, $PhCH_2CO_2^-$ 940 M^{-1} by ^1H NMR). This can be rationalised by considering the Gutman acceptor number of the solvent. In solvents with a higher acceptor number, *e.g.* CH_2Cl_2, the anion is solvated to a greater extent and the solvent competes with the receptor for binding of the anion resulting in low association constants. Additionally, the less charge-diffuse anions are extensively solvated in protic solvents but, in aprotic solvents, preferentially bind to the only source of protons available, the amide groups of the receptor, thus altering the binding selectivity.

In a recent study, the effect of conformational flexibility on the binding of an upper-rim strapped ferrocene receptor has been investigated [34]. Whilst the fixed-cone calixarene **8a** exhibits size-selective binding of halides, the smaller chloride being bound where bromide and iodide give no NMR perturbations, it is unable to bind dihydrogen phosphate. However, the conformationally mobile receptors **8b,c** bind both chloride and dihydrogen phosphate. With these latter receptors, the ratio of partial cone:cone conformation is additionally affected by the presence of anions and tends towards the favouring of the partial cone. Thus it can be postulated that dihydrogen phosphate binding is occurring in the partial cone conformation of the receptor. Electrochemical studies on all the receptors indicate a preference for binding benzoate and acetate over dihydrogen phosphate and chloride [35].



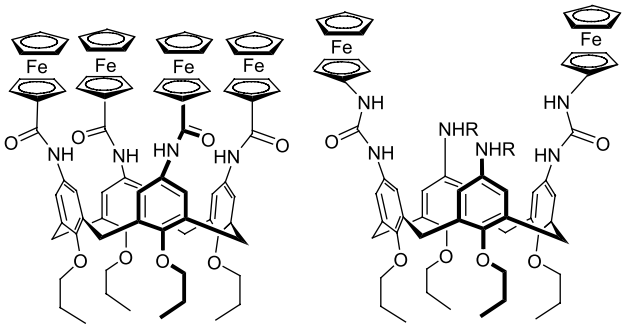
7 8

a: R = R' = CH_2CO_2Et
b: R = CH_3, R' = CH_2CO_2Et
c: R = R' = CH_3



9

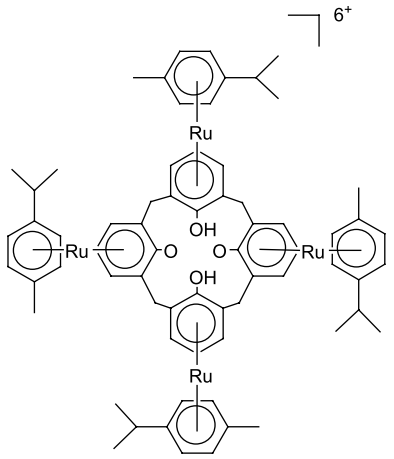
The cavitand receptor **9** has also been reported and forms 1:1 complexes with chloride in which the four ligand arms act co-operatively in binding [36].



10 11

a: R = H
b: R = CONHFc

A comparative study of the binding achieved with ferrocene amide motifs and that with ferrocene urea motifs has been undertaken. Surprisingly, similar association constants are achieved for both receptors **10** and **11b** with a preference for dihydrogen phosphate over chloride despite the presence of more acidic protons in the urea derivative. Less anion discrimination is observed for the 1,3 disubstituted receptor **11a,** which may be a consequence of the receptor flexibility. It is interesting to note that, whilst solution binding studies indicate a 1:1 complexation, in the solid state two benzoate ions are bound and the receptor exhibits a flattened cone conformation [37].



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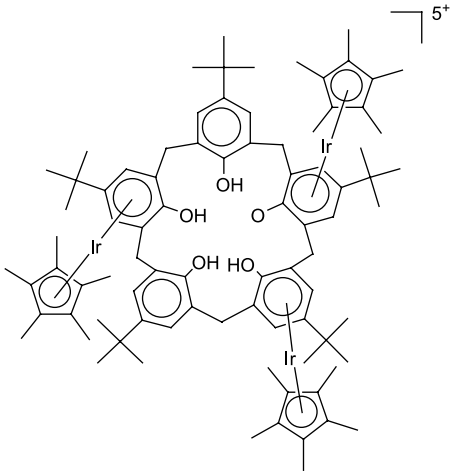


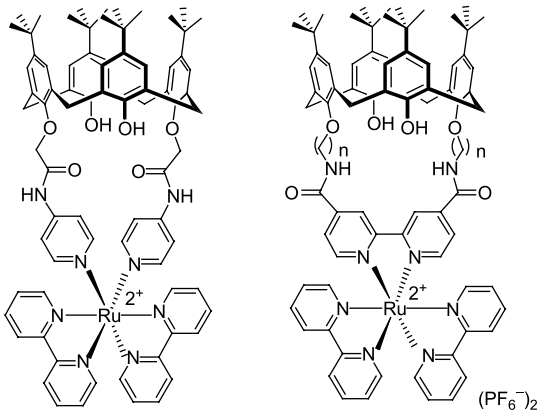
13

π-Metallated Cationic Hosts

The ability of the electron-rich calix[4]arene cavity to bind both neutral and cationic guests is well known [24,25]. Atwood and co-workers have developed a novel approach for cavity anion binding through the introduction of cationic transition metal ions to the outer face of the aromatic rings [38–41]. The subsequent reduction in electron density of the cavity enables size- and shape-selective complexation of anions. Whilst di-metallic hosts show no anion binding due to the residual electron density [31], both iridium and ruthenium tetra-metallic hosts **12** can be prepared which incorporate an anion (e.g. BF_4^-, $CF3SO_3^-$, PF_6^-) within the cavity [39,41]. Solid state studies show the tetrafluoroborate anion to be held deep within the cavity with reduced thermal motion compared to the crystal lattice indicating a good complementarity of fit with the cavity. Metathesis proved successful with a range of anions and ^{1}H NMR solution studies of the triflate host demonstrated a selectivity for halides, with the smaller chloride being bound preferentially (K_{ass} Cl^- 551 M^{-1}, Br^- 133 M^{-1}, I^- 51 M^{-1} in D_2O). The tri-iridium calix[5]arene complex **13** has also been prepared and is able to include a tetrafluoroborate anion, in contrast to the di-metal derivative in which the metallocene rings are distal, here the two adjacent metal centres can act co-operatively to enable anion inclusion [41].

Transition Metal Bipyridyl Based Calixarene Systems

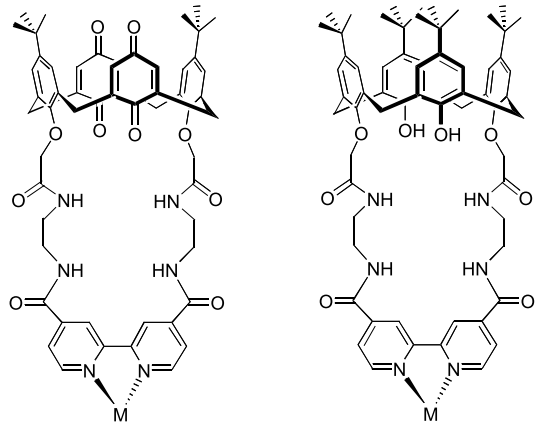
The introduction of ruthenium or rhenium bipyridyl metal centres onto the calix[4]arene cavity enables sensing of anion interactions by electrochemical, UV–visible and luminescence techniques. Whereas the pyridyl based cavity **14** is suitable for binding both chloride and bromide [42], the lower-rim bridged compounds **15a,b** show a cavity size selectivity for dihydrogen phosphate (K_{ass} **15b** 5.2×10^3 M^{-1} in $(CD_3)_2SO$) over sulfate and chloride [43,44]. Electrochemical sensing, through the bipyridyl ligand reduction redox wave, of dihydrogen phosphate binding by **15a** is possible, even in the presence of a ten-fold excess of sulfate or chloride.



14 **15**

a: n = 2
b: n = 3

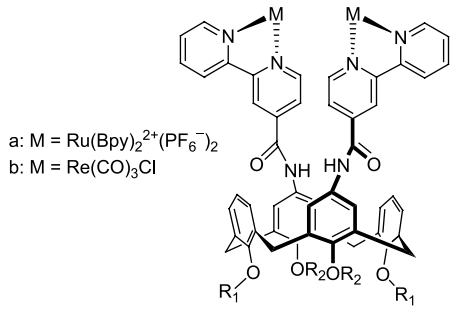
Fluorescence emission has also been developed as a sensing approach with the lower-rim calixquinone receptors **16** and their calixarene analogues **17**. All receptors show 1:1 anion binding with selectivity for acetate over chloride and dihydrogen phosphate (K_{ass} **16a** $MeCO_2^-$ 9990 M^{-1}, Cl^- 1050 M^{-1}, $H_2PO_4^-$ 215 M^{-1} in $(CD_3)_2SO$). Remarkable luminescent emission retrieval effects are observed on anion binding, due to the complexed anion overcoming intramolecular quenched luminescence between the metal centres and quinone moieties. A 500% increase in emission was observed for **16a** with acetate and 60% for chloride [45].



16 **17**

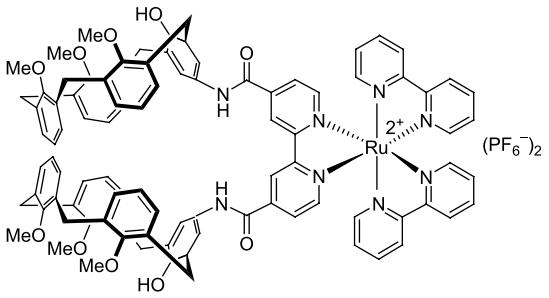
a: M = $Ru(Bpy)_2^{2+}(PF_6^-)_2$
b: M = $Re(CO)_3Cl$

Upper rim derivatives show a dependence on lower rim substitution patterns in their anion binding behaviour. With the conformationally mobile receptor **18** the two binding sites act independently to give a weak ditopic receptor with no selectivity between binding of dihydrogen phosphate and chloride [43]. The introduction of bulky tosyl groups *para* to the amide in both the ruthenium and rhenium receptors **19a,b** enables discrimination of dihydrogen phosphate from chloride (K_{ass} **19a** $H_2PO_4^-$ 4400 M^{-1}, Cl^- 80 M^{-1} in $(CD_3)_2SO$), due to rigidification of the receptor bringing the metal centres closer together [28]. In contrast, the isomeric compounds **20a,b** although able to bind dihydrogen phosphate, showed considerably reduced selectivity over chloride. The clam-like receptor **21** is selective for carboxylates over hard spherical anions, in contrast to non-calixarene analogues, demonstrating once again the importance of secondary interactions with the hydrophobic core in achieving anion selectivity [46].



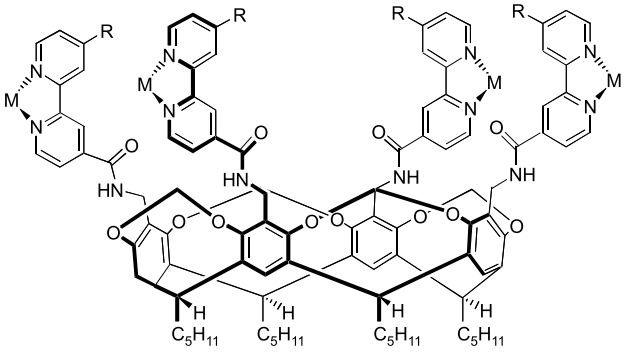
a: M = $Ru(Bpy)_2^{2+}(PF_6^-)_2$
b: M = $Re(CO)_3Cl$

18: R_1 = CH_3 R_2 = H
19: R_1 = H R_2 = Tosyl
20: R_1 = Tosyl R_2=H



21

The ruthenium cavitand **22** shows potential in selective sensing of carboxylates over chloride through absorption and fluorescence emission techniques. An increase in emission intensity is observed on anion binding as a consequence of the increased rigidity of the complex and a decrease of non-radiative decay processes [36].

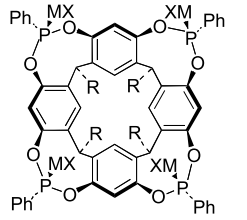


22

a: M = $Ru(Bpy)_2^{2+}(PF_6^-)_2$
b: M = $Re(CO)_3Cl$

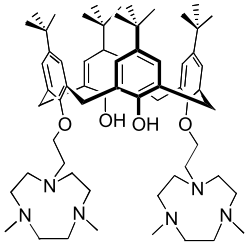
Other Transition-metal-based Calixarene Receptors

Puddephatt and co-workers have described an interesting non-covalent host for anion complexation based on phosphonito-resorcin[4]arenes [47–49]. Complexation of group 11 metals results in a cavitand structure featuring a rim of metal atoms bridged by halides **23**. In the case of gold, the host cavity is occluded by self-inclusion [47] but with both copper [47] **23b** and silver [48] **23c** a fifth halide ion is held in the central cavity by weak interactions. With copper, chloride adopts a rapidly alternating μ_3 binding mode and is easily displaced, in a stoichiometric manner, by iodide which can form four metal halide bonds. The silver host, in contrast, allows μ_4 binding of both chloride and iodide due to the larger atom size and cavity flexibility. Not only is anion exchange possible within the halides but treatment with nitrate allows removal of the encapsulated guest and subsequent binding of small anions, such as S^{2-} and CN^-, which themselves are unable to displace chloride. An interesting consequence of the preferential binding of iodide by **23c** is the acceleration of alkyl halide nucleophilic exchange reactions. Alkyl iodides are converted to alkyl chlorides with retention of configuration. This combined, with an enhanced reaction rate with the more substituted alkyl groups, points towards a mechanism in which the iodide is first extracted by the host in the rate determining step [49].



23

a: M = Au
b: M = Cu
c: M = Ag
X = Cl, Br, I



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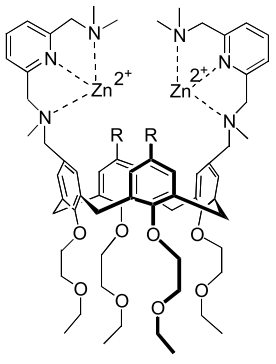


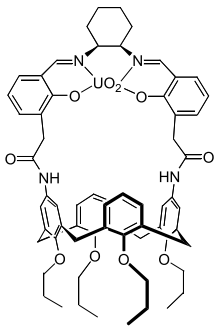
25

a: R = H
b: R = $CH_2N(CH_3)_2$

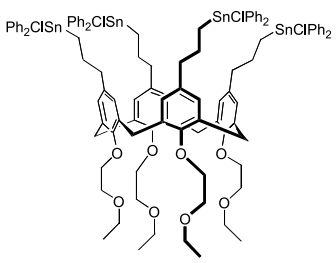
"Cascade" type calixarenes have also been developed, an early example being the solid state complex **24** in which nickel is bound within the triazacyclononane units with three azide 1,1′ end-on bridging ligands between them [50]. Most interest, however, has been focused on the potential of upper-rim derivatives to function as phosphodiesterase mimics [51–56], the phosphate anion being bound by the metal centres in the optimum orientation to allow either intra or intermolecular attack by hydroxide ions. In model studies with the dinuclear Zn-pyridine complexes **25** on the cleavage of (2-hydroxypropyl) 4-nitrophenyl phosphate (HPNP), large rate accelerations are observed in comparison to both mononuclear and non-calixarene analogues, thus demonstrating the importance of the calix[4]arene scaffold both for metal co-operativity and in providing additional stabilising hydrophobic interactions [51]. The pH dependence of catalysis can be fine-tuned through the introduction of additional basic centres to the upper rim of the calixarene (optimal pH **25a** = 7.6, **25b** = 6.8), although the increased bulk additionally reduces binding of the anion for steric reasons [52,55]. Interestingly, enhancing rigidity, as in the case of a lower-rim crown analogue, also reduces catalytic activity as a consequence of reduced strength of anion binding [52].

Lewis Acid Based Receptors

Calix[4]salenes have been reported in which the Lewis-acidic UO_2 centre, in combination with additional hydrogen-bonding amides, provides an effective anion-binding motif [57]. Compound **26** selectively binds dihydrogen phosphate (K_{ass} $3.5 \times 10^2\,M^{-1}$ in $(CD_3)_2SO$) over chloride, sulfate and perchlorate.

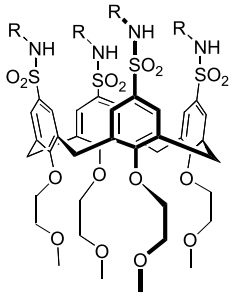


26



27

Lewis-acidic main group metals have also been considered for the preparation of anion receptors. Whilst both silicon [58] and germanium [59] hosts have been prepared, only the complexation properties of the tetratin(IV) receptor **27** have been examined [60]. The length of spacer between the lewis acidic moiety and the calix[4]arene core results in a lack of co-operativity of binding; the host forming a 1:4 complex with chloride as observed by ^{119}Sn NMR. Despite the potential for this host to act in a ditopic manner through cation complexation at the lower rim, no results have thus far been reported.



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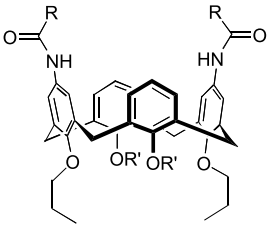
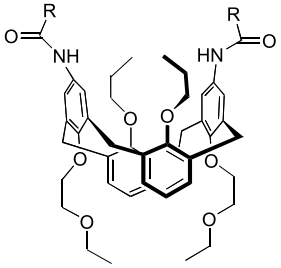


29

a: R = CH_2Cl, R' = propyl
b: R = $CHCl_2$, R' = propyl
c: R = CCl_3, R' = propyl
d: R = $CHCl_2$, R' = methyl



30

a: R = $CHCl_2$,
b: R = CF_3
c: R = C_6F_5

ORGANIC-BASED SYSTEMS

Naturally occurring sulfate- and phosphate-binding proteins show exceptional selectivity (of over 10^4) for the binding of the respective anion. This is achieved solely through hydrogen bonding; the sulfate-binding protein of *Salmonella typhimurium* employs seven bonds from the peptide backbone and from side chains, the phosphate selective protein utilising twelve with secondary stabilisation of the complexes being achieved through a macrodipole effect. Thus, a range of synthetic receptors has been prepared using hydrogen-bond-donor units, such as amides, ureas and thioureas, to bind anions. Receptors based solely on hydrogen bonds are generally only effective in non-polar organic solvents but the directional nature of H-bonds offers advantages in receptor design [1–6].

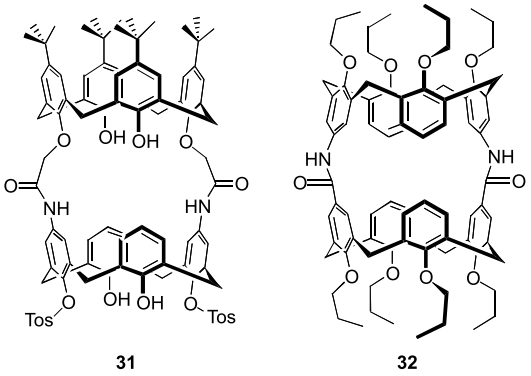
Amide-based Receptors

One of the earliest reports of calixarene-based anion receptors [61] was of a series of tetra-sulfonamides **28**, in which the ligand pre-organisation dictated by incorporation onto the calix[4]arene core results in enhanced selectivity for the tetrahedral sulfate over both planar and spherical anions, in comparison to acyclic analogues.

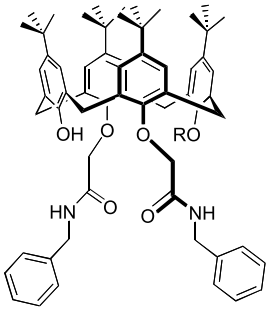
In a preliminary report [62], 1,3-diamido-calix[4]arenes **29a,b** featuring additional electron-withdrawing groups to enhance the acidity of the amide proton, were shown by ^{1}H NMR studies to be selective for 1:1 binding of Y-shaped carboxylates over tetrahedral anions, through the host adopting a pinched-cone conformation in which both amide NH bonds can interact with the anion. With a series of dicarboxylates, only oxalate is bound in a 1:1 manner, through the host reorganising to the opposed pinched cone-conformation, but such distortion is not sufficient to accommodate larger di-anions which bind in a 2:1 stoichiometry. Interestingly, no binding was observed in the perchlorinated derivative **29c**, which the authors proposed was a result of steric crowding. This has been questioned by Stibor *et al.*, [63] who have extensively studied the role of electron-withdrawing groups in anion binding and propose that this absence of binding is likely to be a more general consequence of the lack of an acidic hydrogen on the carbon α to the carbonyl. In an effort to ascertain why the dichloroacetamide **29b** is such an effective host, Ungaro and co-workers investigated the binding properties of

conformationally mobile **29d** and the 1,3-alternate derivative **30a** [64]. With both new hosts a reduction in binding is observed (K_{ass} $PhCO_2^-$ **29b** 5160 M^{-1}, **29d** 100 M^{-1}, **30a** 245 M^{-1} in CH_2Cl_2) however this is still higher than for perflourinated derivatives **30b,c**. Molecular modelling studies, with acetate, indicate that the higher association constants observed for the dichloroacetamide hosts is a consequence of co-operativity between the amide and $CHCl_2$ protons in binding the carboxylate group.

Bis-calix[4]arene hosts have also been developed as potential size-selective clefts for the binding of anions. The head-to-tail receptor **31** [65] forms 1:1 complexes with both spherical and tetrahedral anions but showed high selectivity for binding of the small fluoride anion (K_{ass} F^- 1330 M^{-1}, Cl^- 172 M^{-1} in CH_2Cl_2 by ^1H NMR). In contrast, the head-to-head receptor **32** showed no binding affinity for the larger halides and benzoate anions studied [66].



31 **32**



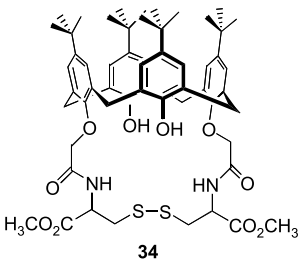
33

a: R = H
b: R = $CH_2CH_2(PhCHCH_2)n$

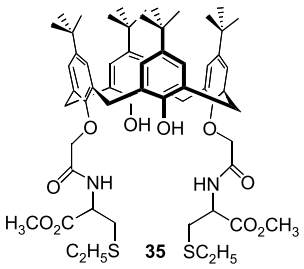
Recently a lower-rim amide receptor has been reported that efficiently extracts dichromate ions from an aqueous phase to a dichloromethane phase. Of particular interest, when the receptor is incorporated into a supported polymer, based on polystyrene, enhanced extraction is achieved at high pH compared to the unsupported ligand (% extraction pH 7 **33a** 4.1, **33b** 27.5) [67].

Peptide-based Systems

An early study of peptide-based systems focused on cyclic peptide motifs with reduced conformational flexibility featuring disulfide bonds [68]. The cyclic peptide **34** binds 4-nitrophenyl phosphate with a considerably higher association constant than the acyclic derivative **35** (K_{ass} **34** 3,900 M^{-1}, **35** 420 M^{-1} in $(CH_3)_2SO$).

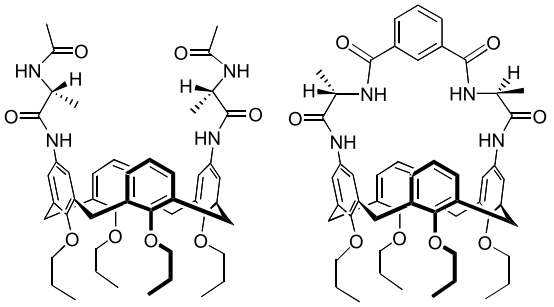


34

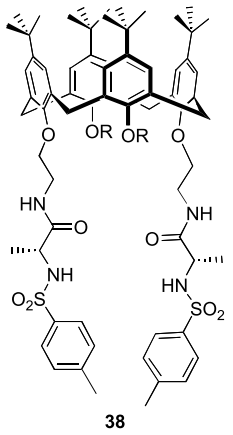


35

Recently, Ungaro and co-workers described C-linked peptidocalix[4]arenes [69–71] with selectivity for complexation of carboxylates and the potential for chiral recognition. In these examples the intrinsically lower acidity of peptide amide protons is balanced by other co-operative non-covalent interactions (π–π, CH_3–π) from the amino-acid side chains. Whilst the flexible receptor **36** show some weak binding of anions, exclusively through the terminal amide bond, intramolecular hydrogen bonding results in low binding constants in non-competitive solvents as significant re-organisation of the host is required for binding. However, a series of more rigid cyclic receptors **37** display greater complexation ability for benzoate and acetate than their acyclic counterparts (K_{ass} $PhCO_2^-$ **37** 44,000 M^{-1}, **36** 680 M^{-1} in $(CD_3)_2CO$) and selectivity for Y-shaped over spherical and planar anions. The selectivity for benzoate over acetate may be due to additional π–π stacking interactions with the aromatic capping moiety. Interestingly, these researchers described for the first time the use of electrospray mass spectrometry (ESI-MS) as a qualitative competitive pre-screening technique for anion binding and demonstrated its value as a basis for quantitative ^1H NMR studies.



36 37



38

a: R = H
b: R = $(CH_2)_2NHCOCH(CH_3)NHSO_2C_6H_5CH_3$

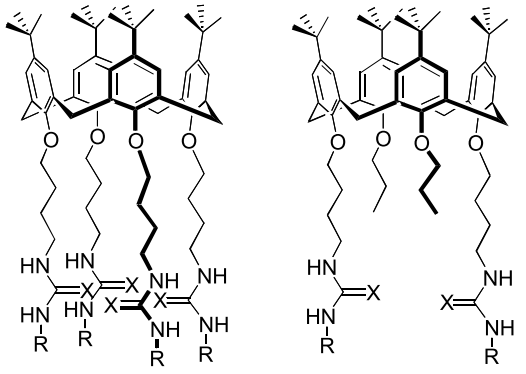
Lower-rim peptide derivatives have also been evaluated [72,73] and proved selective for binding of halides over tetrahedral anions. More interestingly, both the 1,3 disubstituted **38a** and tetra functionalised receptors **38b** are effective complexants of N-tosyl-(L)-alaninate, a binding that may be enhanced through additional $\pi-\pi$ interactions between the tosyl groups.

Urea-based Receptors

Calixarenes bearing urea and thiourea moieties have also been prepared which offer the advantages of increased proton acidity and additional proton interactions with the same directionality which can act co-operatively in binding an anion [1–6,13].

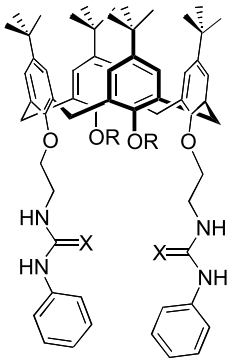
Lower-rim Derivatives

Early work focused on the introduction of both ureas and thioureas through butyl spacers at the lower rim of calix[4]arenes and calix[6]arenes. With the urea-functionalised calix[4]arenes **39, 40**, both FAB mass spectrometry and ^{1}H NMR studies indicated binding of anions in a 1:1 stoichiometry and selectivity for chloride over bromide and iodide [74]. In contrast to a molecular modelling study [75], in which halide anion selectivity was predicted, no binding of fluoride was observed. Interestingly, the di-substituted receptor **40** exhibits both higher binding constants (K_{ass} Cl^- **39** 2660 M^{-1}, **40** 7105 M^{-1} in $CDCl_3$) and enhanced selectivity, despite reduced pre-organisation of the cavity.



39 40

a : X = O, R = phenyl
b : X = O, R = propyl
c : X = O, R = t-butyl
d : X = S, R = phenyl



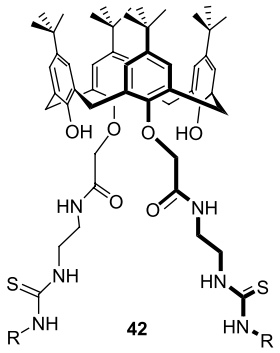
41

a: R = Me
b: R = H
X = O,S

Conformationally flexible di-functionalised calix[4]arenes with shorter spacer groups have also been reported and show a similar selectivity sequence where R = Me **41a**, but reduced binding constants and a lack of selectivity where R = H **41b**, which may be a consequence of intramolecular hydrogen bonding to the urea moieties [76]. Derivatives based on this binding motif have been incorporated into a PVC membrane and proved their potential for the development of chloride ion-selective electrodes [77].

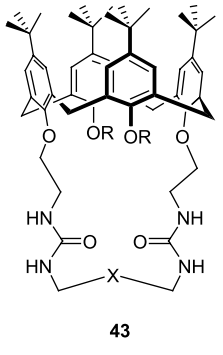
Hybrid receptors **42**, featuring both thiourea moieties and amides at the lower-rim with selectivity for dicarboxylates including adipate and succinate over chloride and dihydrogen phosphate (K_{ass} adipate **42a** 4,640 M^{-1} in $(CD_3)_2SO$), have recently been reported. A 1:1 binding mode was proposed in which the major site

of binding is between the two thiourea moieties with the amide contributing additional stabilisation [78]. The lower rim derivatives **43** are also effective receptors for carboxylates showing selectivity for acetate over phosphate, sulfate and chloride (K_{ass} acetate 722 M^{-1} in $CDCl_3$) [79].



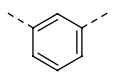
42

a: R = *p*-nitrophenol
b: R = 1-napthyl

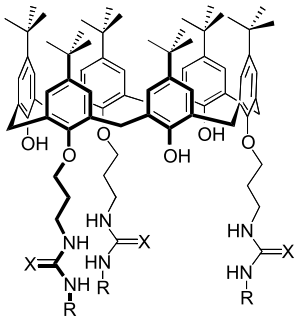


43

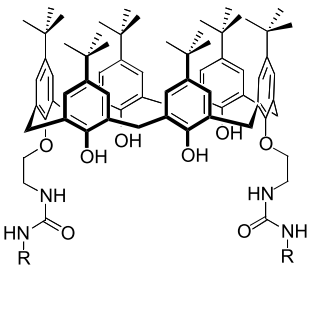
a: X = CH_2
b: X =



The calix[6]arene skeleton offers the possibility of developing tripodal anion receptors for the binding of C_3 symmetrical anions through selective functionalisation at the lower rim. The tris urea derivative **44** shows reverse selectivity to that expected from hydrogen-bonding affinity with bromide bound more strongly than chloride due to the larger cavity size. Larger binding constants were observed for tricarboxylate anions, as a result of the higher charge density and secondary electrostatic interactions, with selectivity for C_3 symmetrical anions which can interact with all six NH protons [80]. The difunctionalised host **45**, in contrast, exhibits the expected selectivity for chloride over bromide, dihydrogen phosphate and acetate [81].



44



45

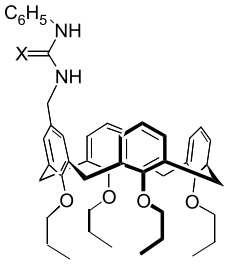
a : X = O, R = phenyl
b : X = S, R = phenyl

The introduction of thioureas would be expected to enhance anion binding due to the increased acidity of the NH protons (pKa urea = 26.9, thiourea = 21.0) [82]. However, in most cases (*e.g.* **39**, **40**), reduced binding constants and decreased anion selectivity are observed. This may be a result of the increased acidity promoting further inter- and intra-molecular hydrogen bonding interactions. Only with calix[6]arene derivative **44b** does introduction of thioureas enhance binding and increase selectivity specifically for planar tricarboxylate anions [80].

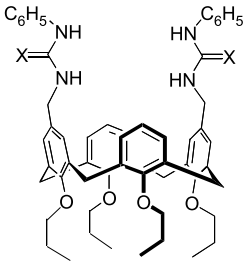
Upper-rim Derivatives

Binding of anions by upper-rim tetra-urea-functionalised calix[4]arenes is a complex situation, such receptors are known to dimerise through hydrogen bond interactions in non-polar solvents to form stable capsules [83]. Thus anion binding involves a two-step process in which the intermolecular interactions initially need to be broken before the anion can bind therefore making measurement difficult. As a result, most studies have focused on selectively functionalised calix[4]arenes which do not undergo the dimerisation process or on first achieving breakdown of the capsule with a competing solvent [84].

The di- and mono-derivatised receptors **46** and **47**, with an additional carbon spacer, showed considerable anion-binding properties with selectivity for carboxylates and no binding affinity for spherical anions [85]. Whilst for **46** the binding constant for acetate was markedly higher than for butyrate and aromatic carboxylates, in all cases the magnitudes are consistent with binding to all four NH protons and stabilisation by additional $CH_3-\pi$ or $\pi-\pi$ interactions with the calix[4]arene cavity. With the mono-functionalised urea and thiourea receptors, selectivity within the carboxylates is reversed; the aromatic carboxylates bind strongly and acetate more weakly. Two binding modes have been proposed with this receptor, acetate binding exo-cavity whilst benzoate and butyrate bind endo-cavity allowing additional stabilisation. In a complementary study [86], inclusion of bulky groups at the lower rim of the calix[4]arene led to di-substituted receptors which showed some selectivity for the binding of fluoride, chloride and bromide over acetate.



46

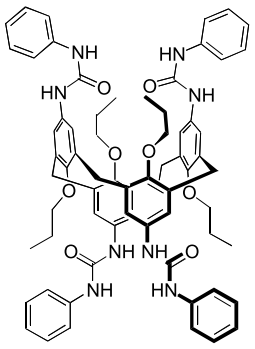


47

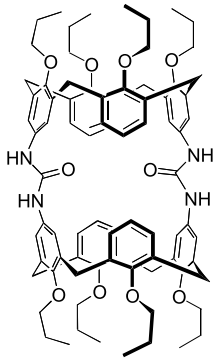
a : X = O
b : X = S

The effect of altering the calixarene core conformation or receptor rigidity on binding has also been investigated. Tetra-urea calix[4]arenes fixed in the

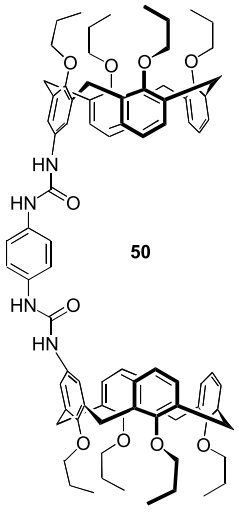
1,3-alternate conformation offer the potential of two distinct binding sites where each anion can interact with four NH protons **48** [87]. However, on complexation of one anion, the distortion of the binding site results in a pronounced negative allosteric effect which precludes additional anion binding at the second face as evidenced by sole formation of a 1:1 complex with expected anion size selectivity (chloride > bromide > iodide).



48



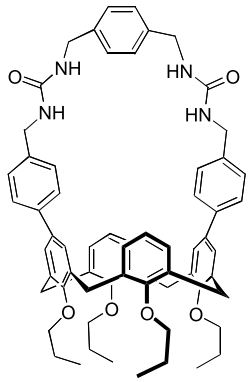
49



50

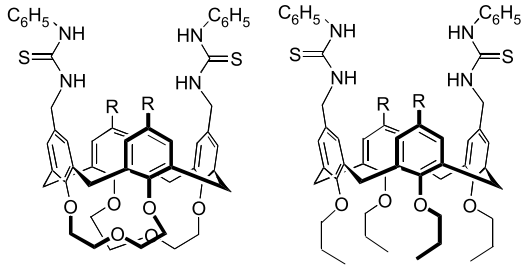
Increasing the rigidity of the receptor results in greater pre-organisation and should give rise to enhanced anion-binding selectivity. Stibor and co-workers have investigated bis-calixarene receptors in which upper-rim urea moieties act as a bridge between the two calix[4]arene cavities [66]. The diurea derivative **49** exhibits selectivity for benzoate over chloride and no binding of bromide and iodide, whereas no selectivity is observed for the mono derivative, illustrating the importance of both co-operativity in binding and size discrimination due to the rigid cavity. The flexible receptor **50** provides two anion-binding sites but complexes of 1:1 stoichiometry were exclusively observed with all anions, which may be a result of the proximity of the binding sites and anion repulsion effects.

Similarly, a rigid extended cavity calix[4]arene receptor **51** has been prepared which, through bridging at the upper-rim with a bis-urea moiety, provides a binding site with selectivity for dicarboxylates over monocarboxylates (K_{ass} benzoate 43 M^{-1}, isopthalate 1100 M^{-1} in $(CD_3)_2SO$) [88].



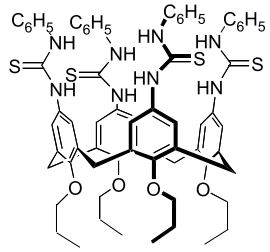
51

A comparative study [89] of tetra-thiourea derivatives provides some interesting results on the effect of rigidity on shape-selective anion recognition. The more rigid cone receptor **52** binds spherical anions more strongly than the flexible derivative **53** (K_{ass} Cl^- **52** 120 M^{-1}, **53** 90 M^{-1} in $(CD_3)_2SO$) but is less able to bind tetrahedral dihydrogen phosphate (K_{ass} **52** 150 M^{-1}, **53** 300 M^{-1} in $(CD_3)_2SO$). Additionally, **54**, in which the urea is conjugated with the aromatic system, only binds chloride, despite the higher acidity of the NH protons.



52 **53**

R = $CH_2NHCSNHC_6H_5$



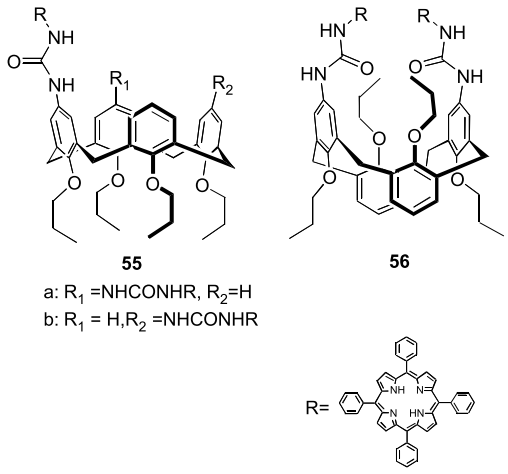
54

Upper-rim urea derivatives of calix[6]arene have also been described as stoppers in rotaxanes [90–92]. Although no binding constants have been reported,

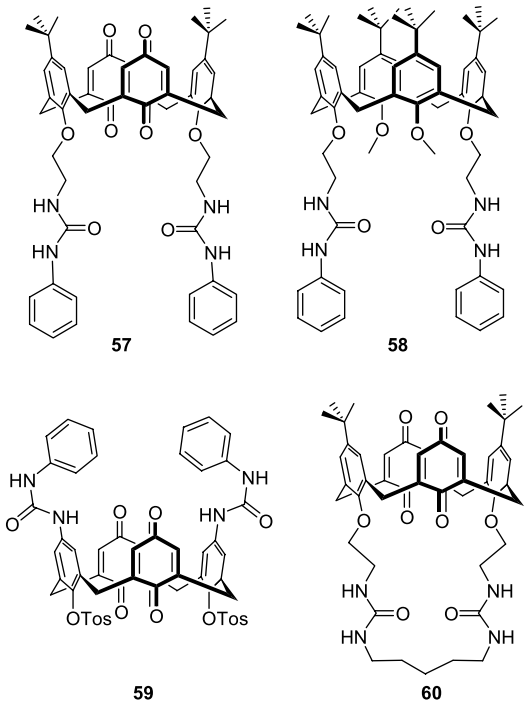
clear evidence for binding of the thread counter-anions by the urea moieties has been shown in ^{1}H NMR studies and it has been postulated that this binding may determine the directionality of rotaxane threading.

Anion Sensing by Calix[4]arene Ureas

The sensing of anion binding by ureas is an important area of research and both optical and electrochemical techniques have been investigated. Stibor and co-workers have recently reported upper-rim urea-based anion receptors **55, 56** which additionally incorporate porphyrin moieties to enable anion detection *via* UV–vis spectroscopy [93]. The Soret band of the porphyrin units displayed changes on anion binding, enabling the calculation of binding constants and determination of binding stoichiometry. All receptors show good binding of chloride and bromide, indicating a degree of flexibility within the binding site, although not sufficient for the binding of the larger iodide and nitrate. It is interesting to note the tolerance of the urea binding sites; comparable binding constants are achieved whether the conformation is cone **55** or 1,3-alternate **56** and whether the calixarene is proximally **55a** or distally **55b** di-functionalised (K_{ass} Cl^- **55a** $5.8 \times 10^5\,M^{-1}$, **55b** $7.6 \times 10^5\,M^{-1}$, **56** 6.6×10^5 in CH_2Cl_2).



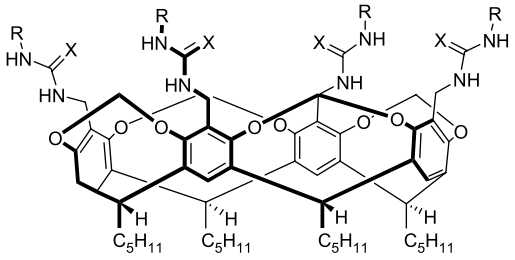
An interesting approach to the electrochemical sensing of anions has been developed by Nam and co-workers: the urea quinones [79,94–99]. Initial studies focused on the selective introduction of two urea moieties at the calix[4]arene lower rim and subsequent oxidation of the unsubstituted aromatics to quinones **57** [95,96,98]. These receptors show significant selectivity for the tetrahedral sulfate anion over spherical anions, *e.g.* chloride, in ^{1}H NMR studies, in a reversal of the selectivity profile of analogous calixureas **58**. Detectable cathodic shifts for the semiquinone-quinone redox couple are observed (ΔE 140 mV for HSO_4^-), enabling sensing, due to stabilisation of the quinone through additional hydrogen-bond interactions from the anion to the oxygen moiety. The selectivity profile of the urea-quinone system can additionally be altered either through introduction of more urea moieties; the mono quinone showing no anion selectivity [94], through introduction of ureas at the upper rim **59** where selectivity in binding of dihydrogen phosphate over sulfate is observed (ΔE 94 mV for $H_2PO_4^-$ and 0 mV for HSO_4^-) [99] or by the incorporation of a lower-rim bridge to give receptor **60** which proves to be acetate selective (K_{ass} $1170\,M^{-1}$ in $CHCl_3$) [79]. Lower-rim derivatives **57**, **58** have been successfully incorporated into PVC membranes for the development of hydrogen sulfite selective ion selective electrodes [100].



Cavitands

Reinhoudt and co-workers have prepared urea and thiourea cavitands **61** which, despite their tendency to dimerise in solution, proved effective hosts for the binding of chloride with formation of much stronger complexes than similar calix[4]-

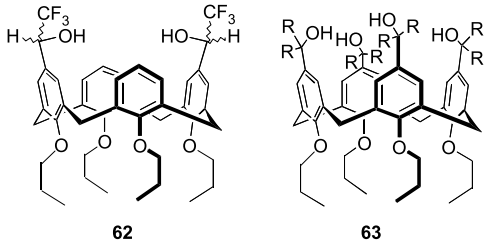
arene ureas (K_{ass} **61** $4.7 \times 10^5\,M^{-1}$, **39** $7105\,M^{-1}$, **40** $2660\,M^{-1}$ in $CDCl_3$) [101]. Additionally, these hosts facilitated membrane transport of chloride across an organic phase, the increased flux observed in the presence of cavitands in comparison to simple thioureas demonstrating the importance of pre-organisation. This work also outlined the use of infra-red studies in the determination of association constants from the changes in the amide stretch band on complexation, the validity of the approach being indicated by good agreement with ^1H NMR measurements [102,103]. A recent molecular modelling study [104] on **61e** indicated that two binding modes are possible. All eight urea protons are involved in the binding of the carboxylate in both cases but with short chain alkyl carboxylates additional binding stabilisation, through CH–π interactions, is achieved through the chain residing in the cavity whereas longer chains bind in an exo-cavity manner.



61

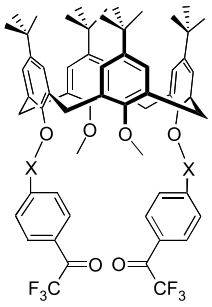
a : X = O, R = *t*-octyl
b : X = O, R = *p*-FC_6H_4
c : X = S, R = *t*-octyl
d : X = S, R = *p*-FC_6H_4
e : X = S, R = propyl

denuded aromatic rings may additionally be involved in binding [88,105].



62 **63**

a: R= C_6F_5
b: R= *n*-Bu



64

a: X = CH_2
b: X= CO

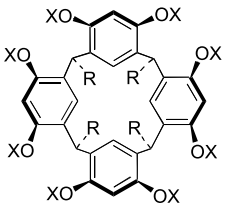
Trifluoroacetyl moieties have also been investigated for anion binding in the lower-rim receptors **64a,b**. For receptor **64a**, the ideal orientation of the complexing groups is achieved enabling selective binding of acetate over the halides and sulfate. However, for **64b** no binding of the anions tested is observed, which is postulated to be a result of an non-convergent binding site [106].

Perfluorated Systems

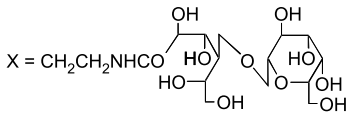
The difunctionalised host **62** displays selectivity for Y-shaped carboxylate anions with a degree of discrimination of chiral guests by racemic and meso hosts (K_{ass} N-lauroyl-L-phenylalanine, racemic $165\,M^{-1}$, meso $40\,M^{-1}$ in $CDCl_3$). In contrast, the tetrafunctionalised perfluoro host **63** binds spherical anions most strongly, with a preference for bromide that can interact with all four hydroxyl groups. Comparative studies with non-fluorinated alcohols indicate that the fluoro moieties are essential for anion binding, suggesting that anion–π interactions with the electron-

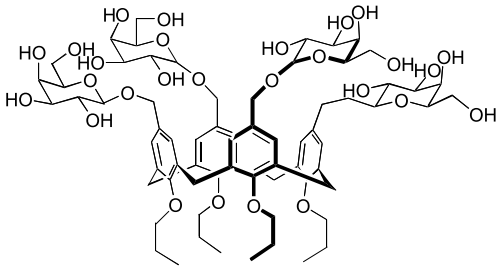
Carbohydrate Containing Systems

Octa-galactose derivatives of resorcin[4]arenes with numerous biological applications have been reported by Aoyama and co-workers [107]. Fluorescence studies indicate that host **65** strongly binds large aromatic anions in a 1:1 stoichiometry through cavity interactions (K_{ass} ANS $2.2 \times 10^5\,M^{-1}$ in D_2O). In contrast, O-linked calix[4]sugars, such as **66**, bind anions only weakly (K_{ass} dihydrogen phosphate $31\,M^{-1}$ in $(CD_3)_2SO$) through interactions with the diol moieties [108].



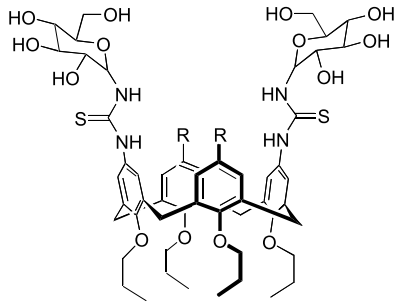
65





66

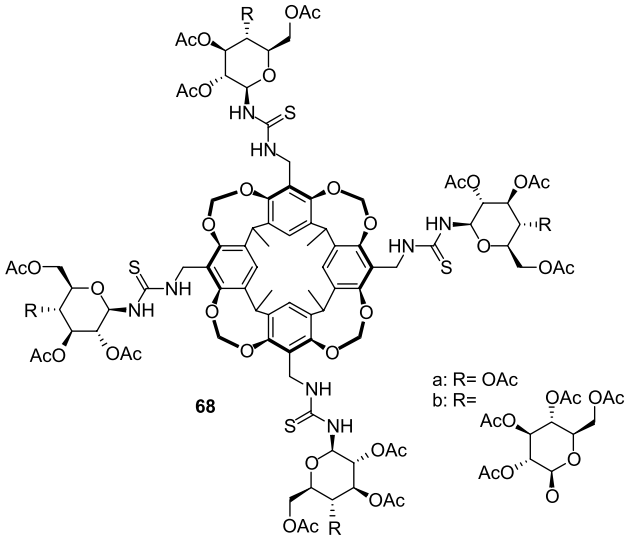
Ungaro and co-workers have reported a thiourea system which incorporates glucosyl units for lectin binding [72,109]. The difunctionalised receptor **67a** shows selectivity for benzylphosphonate (K_{ass} 170 M^{-1} in $(CD_3)_2SO$) over both benzoate and dihydrogen phosphate, indicating that co-operative interactions from both the thiourea and sugar units are important in binding. Whilst broadening of the NMR spectrum precludes determination of association constants for the quadridentate ligand **67b**, competitive ESI-MS studies of simple anions also indicate a preference for dihydrogen phosphate binding.



67

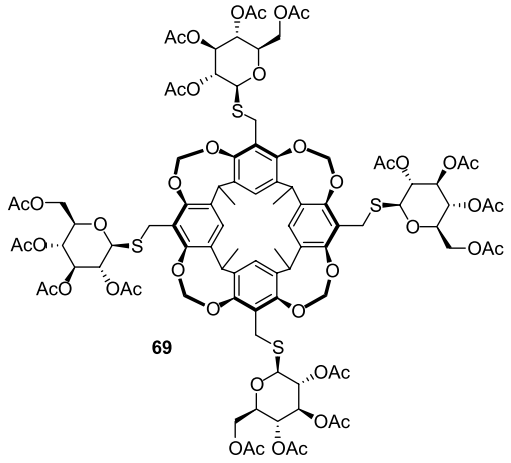
a: R= H
b: R = NHCSNHGlucose

Analogous receptors based on the cavitand skeleton **68** have been reported and in a novel approach ESI-MS, in conjunction with ITC standards, has been used to determine association constants [110]. As with the non-water soluble thiourea derivatives **61e** a preference is observed for the binding of chloride over sulfate and nitrate. Whereas the presence of a single sugar does not affect the magnitude of the binding constant, a significant reduction is observed when the steric bulk is increased by the introduction of disaccharides (K_{ass} Cl^- 4600 M^{-1} **68a**, 15100 **68b** in CH_3CN).



68

a: R= OAc
b: R=



69

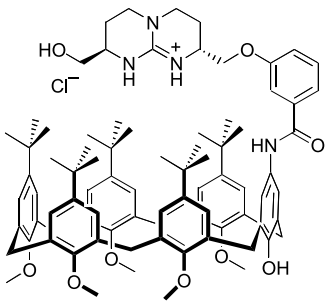
Interestingly, complexation, albeit reduced, is seen in the absence of hydrogen bonding thiourea groups. Compound **69**, containing a sulfide linkage also shows selectivity for the binding of chloride (K_{ass} Cl^- 5200 M^{-1} in CH_3CN) indicating that the glucose unit also plays a part in binding of the anion.

Charged Systems

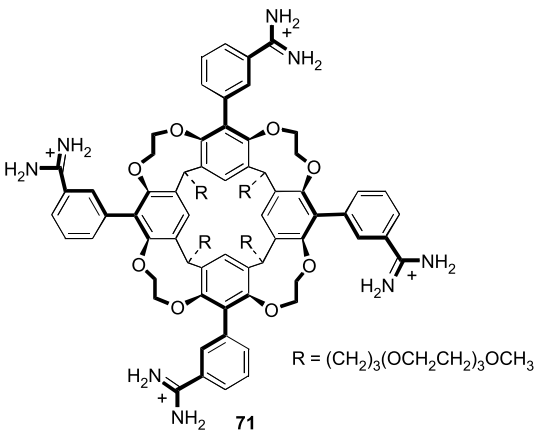
Guanidinium Hosts

Amidinium and guanidinum hosts have been extensively investigated as water-soluble ligands as they are able to form interactions with organic anions both through ion-pairing and hydrogen bonding interactions. In some pioneering work, Mendoza and co-workers [111,112] have described a calix[6]arene-based host **70** that functions as a mimic of the

phosphatidylcholine binding site of the MOPC167 antibody which can catalyse the hydrolysis of 4-nitrophenyl choline carbonate. By tethering a guanidinum motif to the upper rim of a fixed-cone calix[6]arene, a binding site is provided not only for the dihydrogen phosphate anion of phosphatidyl choline but additionally for the quaternary ammonium head group through cation–π interactions with the calixarene core. With organic dihydrogen phosphate anions large association constants of around $7000\,M^{-1}$ in $CDCl_3$ were measured but with phosphatidyl choline, where additive calixarene-based interactions are possible, this rises sharply to $73{,}000\,M^{-1}$. Turnover catalysis of the methanolysis of 4-nitrophenyl choline carbonate is also observed in the presence of the guanidinium hosts, due to their ability to stabilise the anionic reaction transition state, as exemplified by the inhibition of catalysis in the presence of the competitive guest phosphatidyl choline.



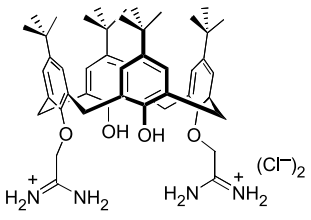
70



71

Cavitand receptors featuring phenylamidinium groups **71** have been developed as water-soluble receptors for dicarboxylates and phosphates, including nucleotides [113]. Whilst isophthalates were found to bind in a 1:2 host:guest ratio, the phosphates were bound in a 1:1 stoichiometry in D_2O. The selectivity observed in the phosphate series for ATP shows the importance of both charge and additional stabilising interactions between the nucleobase and cavitand cavity.

The pre-organisation of other cation and anion receptors onto a calix[4]arene skeleton through anion binding has been described for lower-rim amidinium derivatives **72** [114]. The synthesis of a series of lower-rim calix[4]arene alkyl **73** and bicyclic guanidinium hosts which exhibit recognition properties for nucleotides at the air-water interface has also been reported [115–117]. The proposed binding mode for the receptor involves not only the expected ion-pairing of the phosphate anion with one guanidinium moiety but also, in the case of guanosine, additional stabilisation through hydrogen-bonding interactions with a second guanidinium on the same or an adjacent calix[4]-arene [116].



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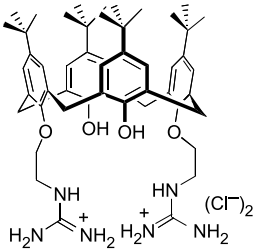
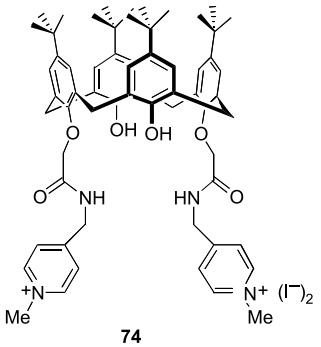


73

Quaternary Ammonium-based Receptors

Quaternary ammonium hosts achieve anion binding through a combination of electrostatic and H-bonding interactions. The flexible redox-active calix[4]arene pyridinium host **74** shows 1:2 host: guest binding, with preference for more basic anions ($H_2PO_4^- > Cl^- \gg Br^- \gg HSO_4^-$) and large cathodic shifts from stabilisation of the positive charge (ΔE 160 mV $H_2PO_4^-$). The cleft receptor **75** forms 1:1 complexes with spherical anions and exhibits a preference for chloride (K_{ass} Cl^- $1015\,M^{-1}$ in $(CD_3)_2SO$) [118].



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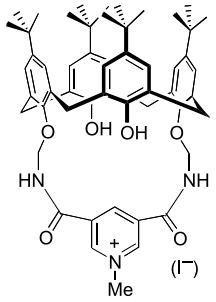
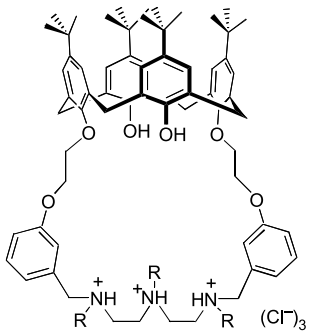


75

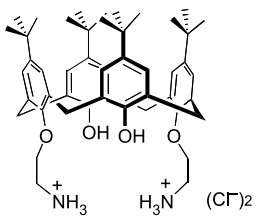
Aza-crown derivative **76a** binds nitrate more strongly than chloride through a directional three-point interaction whereas the methylated analogue **76b** shows no anion-binding ability [119]. The acyclic derivative **77** is a selective proton switchable host for the extraction of chromate and

dichromate from water into chloroform even in the presence of a ten-fold excess of competing anions and oxydianions, the complexed anion being released by addition of base [120,121].



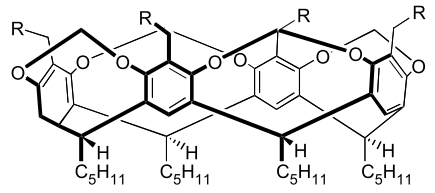
76

a: R = H
b: R = CH_3



77

Charged cavitand receptors have also been developed which, in addition to being water soluble, bind aromatic anions through hydrophobic ($\pi-\pi$, $\pi-CH_3$) and electrostatic interactions. Pyridyl groups can be introduced at the upper rim to give receptor **78a** which binds the tosylate anion more strongly than neutral *p*-cresol (K_{ass} tosylate $5.2x10^2\,M^{-1}$, *p*-cresol $1.1 \times 10^2\,M^{-1}$ in D_2O) [122]. Similarly the quaternary ammonium host **78b** binds dianionic isophthalates more strongly (K_{ass} $10^4\,M^{-1}$ in D_2O) through a two-point electrostatic interaction than aromatic monoanions (K_{ass} $10^2\,M^{-1}$ in D_2O) [123]. The absence of binding in the case of cationic aromatics and reduced anion binding of model ammonium compounds indicates the co-operative role of the ammonium moiety and the calixarene cavity in binding. The imidazolium cavitand **78c** is also selective for dicarboxylates, in particular 1,4-phenylenediacetate (K_{ass} $16.2x10^2\,M^{-1}$ in $(CD_3)_2SO$), and the authors propose a binding mode that involves two imidazole units binding to each carboxylate [124].



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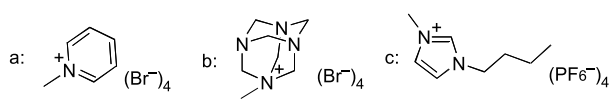
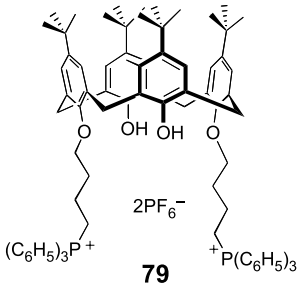


Quaternary Phosphonium-based Receptors

Hosts incorporating phosphonium groups have also been investigated and such an approach offers the dual advantage of using both ^1H and ^{31}P NMR shifts to assess anion binding [125]. From a range of representative anions, receptor **79** selectively binds tetrahedral anions over spherical halides and Y-shaped carboxylates (K_{ass} Cl^- $251\,M^{-1}$, $H_2PO_4^-$ $750\,M^{-1}$ in $CDCl_3$).



79

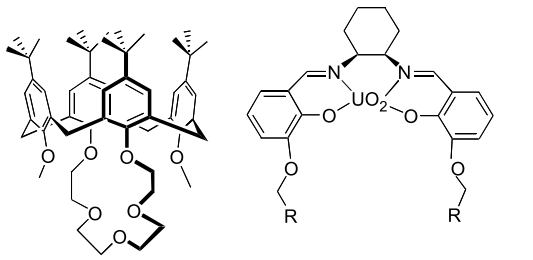
DITOPIC RECEPTORS

The simultaneous binding of an anion and its counter-cation, ion pair recognition, by a bifunctional receptor utilises the positive charge on the cation to enhance the strength of anion binding. This area has recently attracted increasing attention and is of particular interest as it often combines a number of binding strategies in one molecule. Thus, receptors have been prepared that invoke electron-deficient centres, hydrogen bonding and the electrostatic attraction of the counter-cation to enhance anion binding [1–6,126].

Dual Hosts

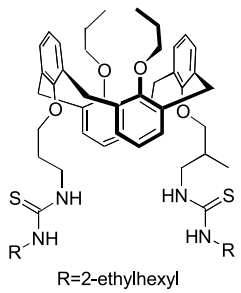
The dual-host approach in which the anion and cation binding sites are provided by two separate molecules is synthetically attractive as each unit can be less complex than if incorporated on the same platform. Calixarenes have mainly been used to provide the cation binding site and the approaches described demonstrate the versatility available.

Calixarenes featuring lower-rim crown[5] units facilitate the transport of KH_2PO_4 across supported liquid membranes, when used in combination with a salophene unit **80**, giving flux rates more than five-fold higher than for the anion-binding unit alone [127].



80

Similarly the 1,3-alternate calix[4]arene crown unit is unable to transport salts but, in combination with a calix[4]arene thiourea **81** as the anion-binding component, does achieve membrane flux [128]. Recently, Parisi and co-workers have described dual hosts in which the cavity of a calix[5]arene acts as a host for a methylammonium cation leading to an exceptional enhancement of anion binding by a calix[6]pyrrole **82** (K_{ass} Br^- $< 10\,M^{-1}$, *n*-$BuNH_3Br$ $2 \times 10^5\,M^{-1}$in CD_2Cl_2) [129].



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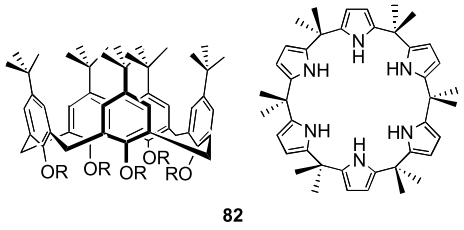
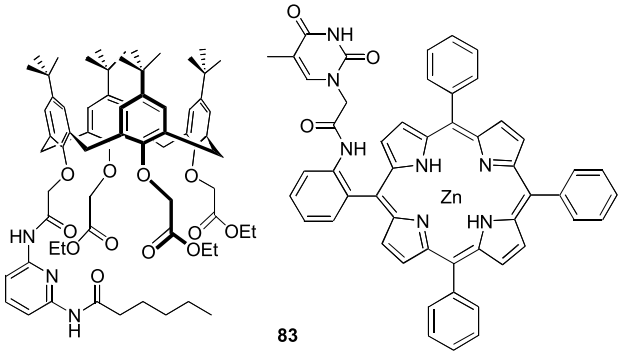


82



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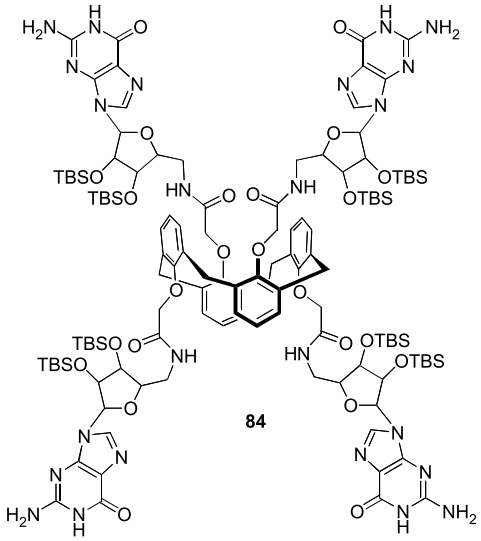


84

Recently Davis and co-workers [132] have reported water-mediated self-assembly of a guanosine derivative of a 1,3 alternate calixarene into a dimeric structure in which the cation binding site is provided by the hydrogen bonded array of the four guanosine motifs and the anion binding site by two lower-rim amide moieties **84**. This dimer extracts a range of alkyl halides with selectivity for bromide over chloride in the presence of either sodium or potassium.

Self-assembled Ditopic Hosts

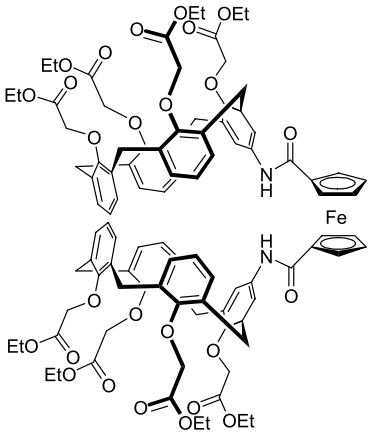
Some interest has been focused on developing ditopic receptors through self assembly of separate anion- and cation-binding sites, despite the synthetic complexity. Combinations of calixarenes derivatised at the lower rim with tetra ester-amide cation binding sites and zinc porphyrin anion binding units have been prepared utilising either diamidopyridine-thymine [130] **83** or melamine-barbiturate [131] motifs. Self assembly of the receptors *via* hydrogen bonding is switched on by cation complexation resulting in enhanced binding of anions *eg*. SCN^- by the zinc ion.

Covalently Bound Ditopic Hosts

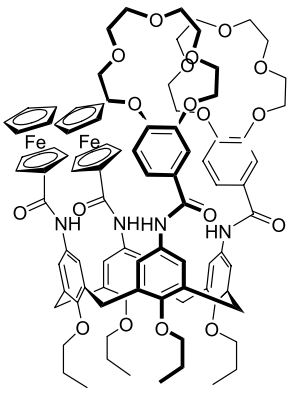
Of the approaches available for binding ion pairs, covalently bound ditopic receptors have been most widely studied. Whilst being synthetically challenging, the additional advantages of allosterism, due to cation binding affecting anion binding selectivity through changes in size and shape of the binding site, and enhanced anion binding, through electrostatic interactions induced by the cation, make these highly attractive systems.

Metallocene-based Receptors

The clam receptor **85** presents two alkali metal binding sites at the calixarene lower-rims and also a ferrocene amide anion binding motif at the upper rim [133]. Selectivity for the carboxylates, benzoate and acetate, over halides can be observed in both ^{1}H NMR and electrochemical studies ($MeCO_2^-$, ΔE 155 mV). This weak binding of anions in the absence of a complexing cation can be rationalised by the ability of the cyclopentadiene rings to rotate and disrupt the anion binding site. On complexation of lithium, however, halide binding can be switched on, due to rigidification of the calixarenes and additional electrostatic interactions (K_{ass} I^- **85** weak, **85.Li**$^+$40 M^{-1}, Br^- **85** 10 M^{-1}, **85.Li**$^+$133 M^{-1} in CD_3CN).



85

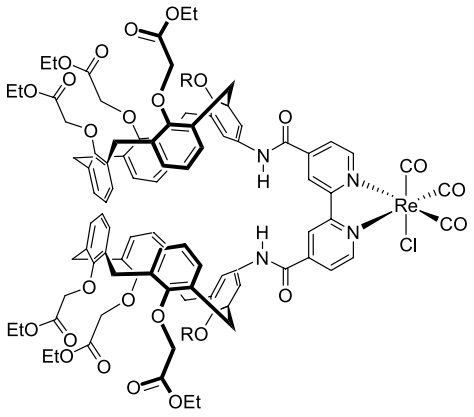


86

For receptor **86**, the cation binding site is provided by two benzocrown[5] units in a 1,2 substitution pattern and the anion binding site by amide moieties [134]. In the presence of two equivalents of sodium, binding of chloride, acetate and hydrogen phosphate anions is reduced (K_{ass} Cl^- **86** 25 M^{-1}, **86.2Na** <5 M^{-1} in 1:1 CD_3CN: $(CD_3)_2SO$), however with potassium, which can form a sandwich complex between the crown units, the anion binding is significantly enhanced (K_{ass} Cl^- **86.K**$^+$150 M^{-1} in 1:1 CD_3CN: $(CD_3)_2SO$) as a result of the rigidification of the anion binding site.

Ruthenium(II) and Rhenium(I) Bipyridyl-based Systems

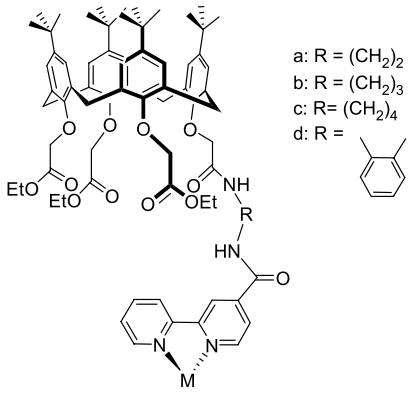
Rhenium clam receptors **87** have also been developed featuring either tri- or tetra-ester functionality at the lower rim [133,135]. Both show 1:1 binding of anions with selectivity for acetate over halides in the presence of non-complexing cations. As with the ferrocene receptor large enhancements in binding of iodide are observed on addition of two equivalents of alkali metal ions. Anion binding is highest for the tetra ester host with sodium, the ideal guest cation, (K_{ass} I^- **87b** 40 M^{-1}, **87b.Na**$^+$320 M^{-1} in CD_3CN) and somewhat reduced for the tri-ester **87a**, in which all cations are more weakly bound.



87

a: R = H

b: R = $CH_2CO_2OCH_2CH_3$



88 M = $Ru(Bpy)_2^{2+}$ $(PF6^-)_2$

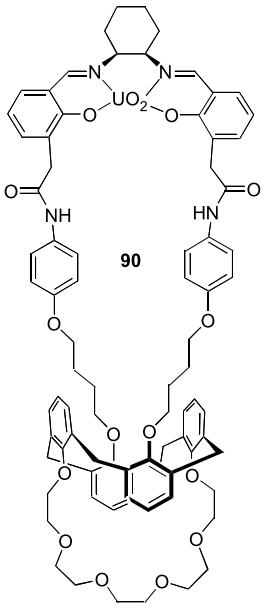
89 M = $Re(CO)_3Cl$

Receptors **88, 89**, which can extract metal salts from water into CD_2Cl_2, feature a lower-rim cation-binding site directly attached *via* a variety of spacers to a metal amide moiety [136]. The ligands weakly bind bromide and iodide from the tetrabutylammonium salts, whereas addition of one equivalent of lithium, sodium or potassium greatly enhances anion binding particularly for the rhenium derivative incorporating an aromatic

spacer. (K_{ass} Br^- **89d** 40 M^{-1}, **89d.Li**$^+$2460 M^{-1} in CD_3CN).

Lewis Acid-based Systems

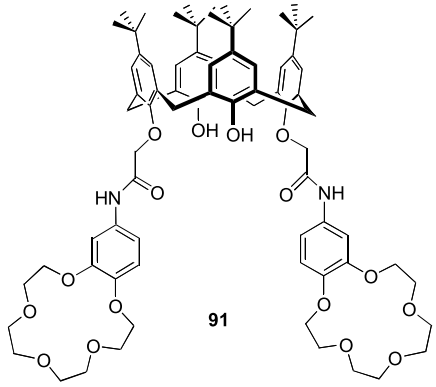
As discussed, dual-host systems using a combination of salophene units and calix[4]arene crowns are effective in transporting salts through supported liquid membranes [137]. Incorporating both units onto the calix[4]arene scaffold results in a receptor **90** which enhances flux of both $CsNO_3$ and CsCl over either an anion binding unit (more than 15-fold for CsCl) or calixarene crown cation binding compound (3-fold for CsCl) alone.

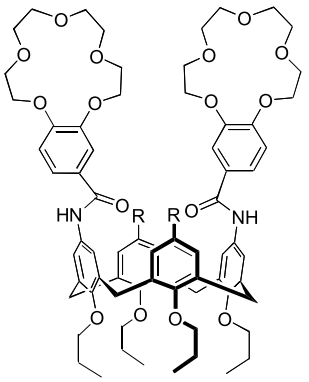


Amide-based Receptors

Compound **91** is an early example of a ditopic receptor based on an amide moiety for anion recognition. Whilst this difunctionalised receptor is unable to bind anions alone, in the presence of potassium or ammonium cations the formation of a sandwich crown complex forces the amide units into a suitable geometry for co-operative binding of anions. 1:1:1 Complexes of host, anion and cation are formed, with a selectivity for dihydrogen phosphate over sulfate, chloride and nitrate [138].

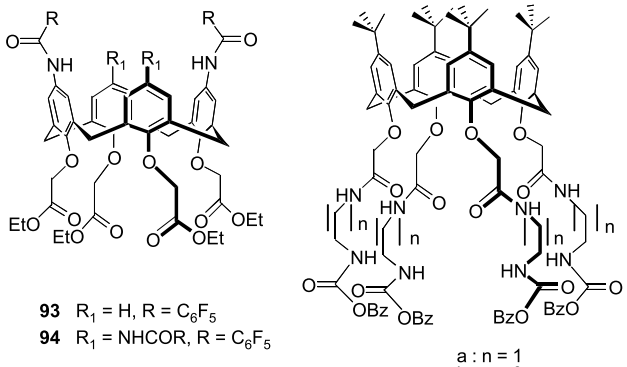
The ability of potassium to form a sandwich complex and alter the anion binding cavity is also evident in the results for receptor **92a** [134]. Whilst the binding of chloride, benzoate and hydrogen phosphate is greatly enhanced in the presence of potassium (K_{ass} $PhCH_2^-$ **92a** 25 M^{-1}, **92a.K**$^+$270M^{-1} in 1: 1 CD_3CN: $(CD_3)_2SO$) it is reduced with sodium which does not bind co-operatively. The role of re-organisation of the receptor in enabling anion binding is additionally confirmed by the absence of cation enhanced binding in the tetra derivative **92b**.





Stibor and colleagues have investigated a number of receptors [63] featuring the sodium-binding [139] tetra-ester ligand arrangement at the lower rim. A marked allosteric response to binding is observed with the di-amide receptor **93**. In the absence of a complexing cation, halides are bound in a 1:2 host:guest arrangement, whilst the dicarboxylate anions, adipate and terephthalate are bound in a 1:1 manner between the two amide units. On complexation of sodium, the receptor rearranges, thus enabling co-operativity of the two amide units in 1:1 binding of halides with selectivity for bromide and abolishing the binding of dicarboxylates. The response on cation complexation is less dramatic for the tetra-amide ligand **94**, although an enhancement in binding of bromide and a reduction for squarate binding is observed. In a different approach, both the anion and cation binding sites are situated at the lower-rim **95**. Weak binding of chloride is observed in the absence of a complexing cation, which increases significantly on simultaneous binding of sodium (K_{ass} Cl^- **95a** 86 M^{-1}, **95a.Na**$^+$681 M^{-1}

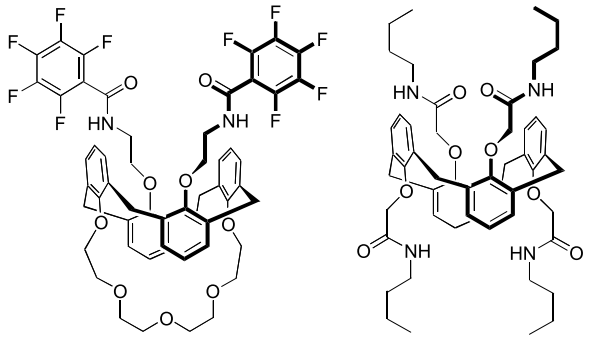
in $CDCl_3$). The strength of anion binding is dependent on spacer length; as the cavity size increases bromide is bound more strongly than chloride.



93 R_1 = H, R = C_6F_5
94 R_1 = NHCOR, R = C_6F_5

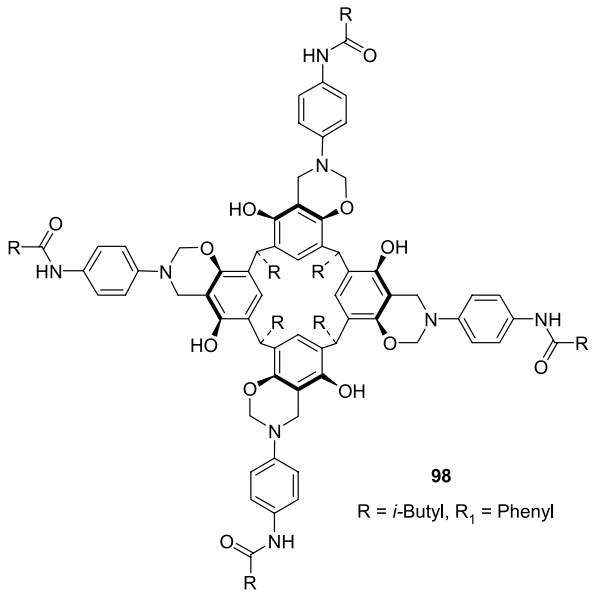
95 a : n = 1, b : n = 3, c : n = 5

More recently, the amide-crown receptor combination has been further investigated, based on a 1,3-alternate calixarene conformation **96** [140]. Solution studies indicate that binding of a potassium cation within the crown enhances binding of acetate (K_{ass} **96** 35 M^{-1}, **96.K**$^+$140 M^{-1} in $CDCl_3$). An interesting 2:2:2 complex is seen in the solid state, in which one NH proton from both calixarenes interact with each anion. Interestingly, the ability for simple 1,3-alternate calixarene-amides to act as ditopic receptors has also been described [141]. Compound **97**, which does not feature a cation-binding site, is unable to bind chloride as the tetrabutylammonium salt but, as evidenced by ^{1}H NMR shifts and bilayer transport studies, is able to bind HCl.



96 **97**

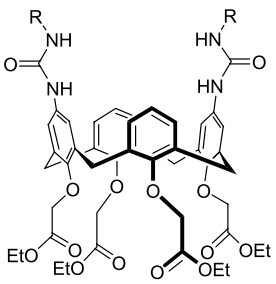
Resorcin[4]arene derivatives **98** have also been studied [142], in which the methylammonium cation is selectively bound within the aromatic bowl through CH–π interactions. Such binding brings the four amide bonds into a co-operative arrangement and 1:1 complexes with chloride, bromide and iodide can be prepared. Metathesis studies indicate a selectivity for chloride over iodide of 10^3 and of bromide over iodide of 25.



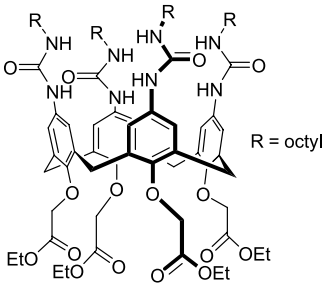
98
R = *i*-Butyl, R_1 = Phenyl

Urea-based Hosts

Some of the earliest examples of ditopic calix[4]arene receptors were based on an upper-rim urea motif combined with a lower-rim tetra-ester binding site. The difunctional receptors **99** are unable to bind chloride and bromide as the tetrabutylammonium salts, but on complexation of sodium, the calixarene core rearranges from pinched cone to cone, reducing intermolecular hydrogen bonding and allowing binding of anions. A similar allosteric effect is seen for the tetradentate receptor **100**; binding of sodium destroys the self assembled calix[4]arene dimer and chloride can be bound strongly in a 1:1 manner (K_{ass} 1×10^4 M^{-1} in $CDCl_3$). The importance of covalently linking the two binding sites is reinforced by the ability of **100** to solubilise alkali metal salts where mixtures of anion binding and cation binding calixarenes cannot [84].

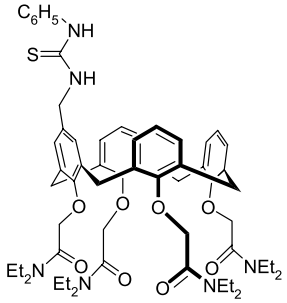


99

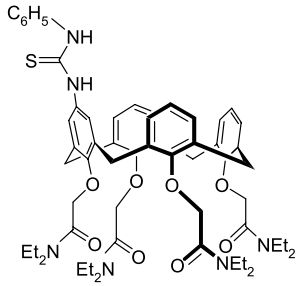


100

The effect of electrostatic interactions in enhancing anion binding in ditopic hosts has been evaluated through comparison of two mono urea derivatives [143]. Receptor **101** in which a CH_2 spacer is inserted between the urea and calix[4]arene selectively binds acetate over other carboxylates and halides, but this binding is reduced on complexation of sodium due to rigidification of the host. In contrast **102**, in which the two binding sites are conjugated, exhibits enhanced binding of anions in the presence of sodium due to the electron withdrawing effect on the NH protons, but interestingly a concurrent reduction in selectivity (K_{ass} $MeCO_2^-$ **102** 940 M^{-1}, **102.Na**$^+$1200 M^{-1}, $PhCO_2^-$ **102** 250 M^1, **102.Na**$^+$1100 M^{-1} in $(CD_3)_2SO$).

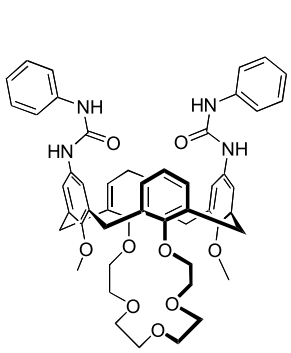


101

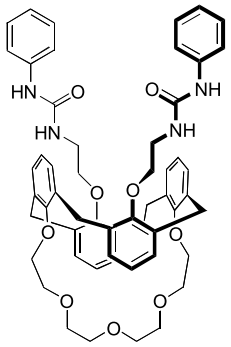


102

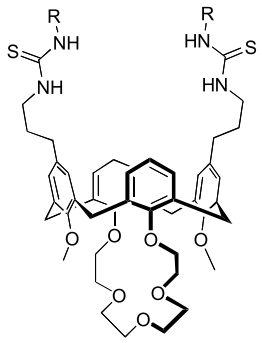
Positive effects are also observed for receptors incorporating a potassium-complexing crown[5] unit. The upper-rim diurea derivative **103** shows selectivity for phosphate over halides with non-complexing cations and, on binding of sodium by the crown moieties, shows substantial anion-binding enhancements (K_{ass} $H_2PO_4^-$ **103** 200 M^{-1}, **103.Na**$^+$1028 M^{-1} in $(CD_3)_2SO$) [144]. For the 1,3-alternate urea derivative, binding of chloride is increased more than five-fold in the presence of the metal cation (K_{ass} Cl^- **104** 1054 M^{-1}, **104.K**$^+$5420 M^{-1} in $CDCl_3$) [145]. The absence of changes in the ^1H NMR signals of the calix[4]-arene core point to the increase being mainly an effect of electrostatic interactions rather than allostery.



103



104

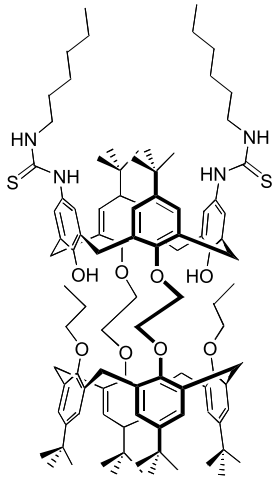


105

R = 2-ethyl hexyl

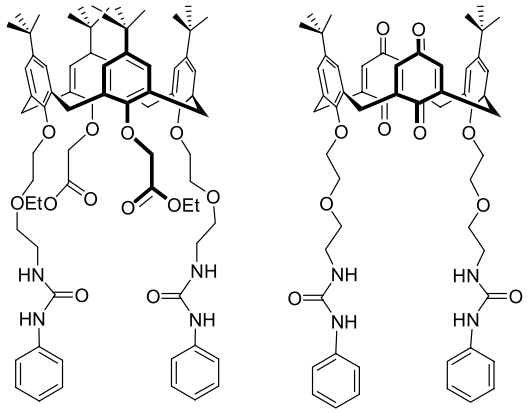
In contrast with the dithiourea crown derivatives **105**, transport of CsCl or KCl across supported liquid membranes can be achieved but, interestingly in this case, less efficiently than with a dual-host approach using two different calix[4]arenes [128].

The calix[4]semitube system has also been exploited in the design of ditopic receptors [146]. Complexation at the lower-rim of sodium or potassium significantly rigidifies the receptor resulting in a considerable enhancement of anion binding, in particular for bromide and iodide (K_{ass} Br^- **106** 20 M^{-1}, **106.Na**$^+$620 M^{-1} in 1: 1 $CDCl_3$: CD_3CN)

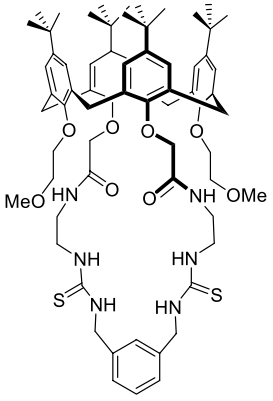


106

Urea derivatives **107**, featuring both cation- and anion-binding sites at the lower rim, bind alkali metals and halides in a 1:1 stoichiometry [147]. The largest enhancements in anion binding are observed for iodide in the presence of the best-fit sodium cation (K_{ass} I^- **107** 24 M^{-1}, **107.Na**$^+$616 M^{-1} in $CDCl_3$). With the diquinone receptor **108** simultaneous binding of sodium by the lower-rim polyether reverses the anion selectivity from a highly selective receptor for tetrahedral anions such as dihydrogen phosphate and hydrogen sulfate to a receptor with enhanced binding and selectivity for halides [148].



107 **108**

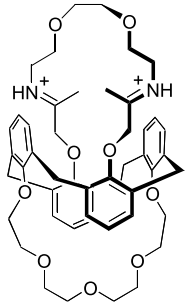


109

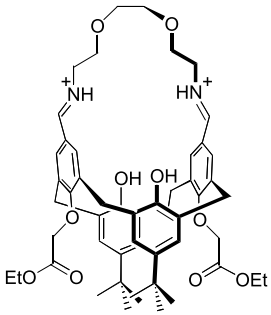
Interestingly, with the bridged receptor **109** a reversal of anion binding selectivities is also observed, from acetate selective to diphenyl phosphate selective, but rather than being a consequence of structural changes within the receptor it appears to be due to the strength of the sodium acetate ion pair and sequestering of the cation from its binding site as binding of the acetate anion is observed after the addition of more than one equivalent [149].

Charged Hosts

Two types of charged ditopic receptors based on Schiff base anion-binding sites have been developed [150,151]. The 1,3-alternate calix[4]arene crown derivative **110** shows proton-switchable binding and transport of dichromate ions. Receptor **111**, featuring a sodium-binding site, is able to extract 70% of dichromate from water into dichloromethane at low pH but extraction tails off to less than 10% at pH 4.5 and greater. Surprisingly, this receptor is unable to extract sodium cations in the presence of dichromate, which is postulated to be due a negative allosteric effect, the receptor adopting a 1,3-alternate conformation on anion binding which disrupts the cation binding cavity.

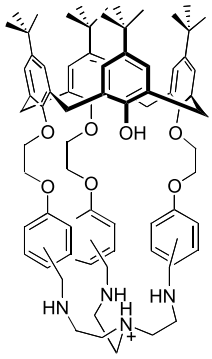


110



111

Capping of the lower rim of calix[4]arene by a tren moiety through glycolic chains [152,153] provides a ditopic receptor in which the potassium cation is preferentially bound. Complexation of numerous anions results in deprotonation, thus precluding measurement of association constants; however, these can be determined for 1:1 binding of bromide, iodide and nitrate in the presence of sodium. The *ortho*-substituted receptor **112a** is nitrate-selective (K_{ass} NO_3^- 190 M^{-1} in CD_3OD), whereas the isomer **112b** is less discriminatory. Co-complexation of potassium enhances binding of both bromide and iodide for **112a**, due to re-arrangement of the tren binding site (K_{ass} Br^- **112a** 84 M^{-1}, **112a.K**$^+$120 M^{-1} in CD_3OD), but decreases the strength of binding of anions by the *para*-substituted receptor.



112
a: *ortho*
b: *para*

CONCLUSIONS

The selective complexation of anions by synthetic receptors offers a great challenge to the modern chemist. The last ten years have seen a great expansion in the design of synthetic anion receptors. In particular, this review has shown that calixarenes are excellent platforms for the incorporation of numerous ligands for co-operative binding of anions. Their unique topology offers not only the potential of designed cavities, through selective functionalisation, but also the fine tuning of binding due to the hydrophobic nature of the cavity. The development of calixarene-based systems has enabled greater understanding of the complex interactions involved in binding, thus offering the prospect of a number of biomedical and commercial applications such as sensors and enzyme mimics. Additionally, recent research into ditopic receptors that can complex both cations and anions has provided a number of systems with membrane transport ability that offer great promise as extractants.

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