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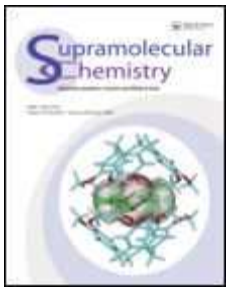

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Recent Advances in Macrocyclic and Macrocyclic-based Anion Receptors.

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The interest in anion coordination chemistry has growth enormously in the last few years. Macrocyclic and macrocyclic-based architectures are at the forefront of the development of new anion receptors. This minireview is intended to illustrate some of the goals achieved recently in this field highlighting examples appeared in the literature over the period 2005-2006.

Keywords: macrocyclic compounds; calixarenes; anion receptors; hydrogen bonds

Dedicated to Prof. David N. Reinhoudt on the occasion of his 65th birthday

INTRODUCTION

Anion coordination chemistry is rapidly becoming a mature field within the realm of supramolecular chemistry [1-7]. There are numerous reasons to boost this interest. Anions play pivotal roles in many biological processes: for instance, it is estimated that 70% of coenzymes and substrates are of anionic nature, "energy currency" at the cellular level is based in anionic nucleotides, RNA and DNA are polyanions, chloride transport across cellular membranes contributes to diverse physiological processes and so on. This in turn implies that misregulation of anion function is the origin of a number of diseases which, on the other hand, results in potential therapeutic applications for anion receptors. Separation and extraction processes are very important from the environmental point of view. Nitrates and phosphates are widely used as fertilizers which produce an increase of the concentrations of these anions in waterways that may lead to eutrophication problems. Vitrification processes involved in the remediation of nuclear waste is hampered by the presence of small quantities of sulfate, thus, removal of this anion from those complex mixtures is currently of great interest. Pertechnetate is an anionic radioactive contaminant produced in nuclear plants. Cyanide is a very toxic anion yet widely used in mining operations.

There are several types of non-covalent interactions used in anion coordination: hydrogen bonds, electrostatic interactions, metal coordination and lewis acid interactions, hydrophobicity and combinations of these forces. The usually weak nature of these motifs means that anion binding relies in multiple interactions to achieve strength and selectivity. In this regard, macrocyclic hosts and macrocyclic platforms decorated with a number of binding units present obvious advantages for the production of anion receptors. Researchers have employed this strategy since the beginning of the development of this field, and, for example, the first anion receptor reported in the literature was a macrobyciclic ammonium host [8]. A plethora of macrocyclic and macrocyclic-based receptors have been reported since then, and this minireview highlights some examples appeared in the literature over the period 2005-2006. It is not intended to be a comprehensive compilation but to illustrate some of the goals achieved recently through selected references.

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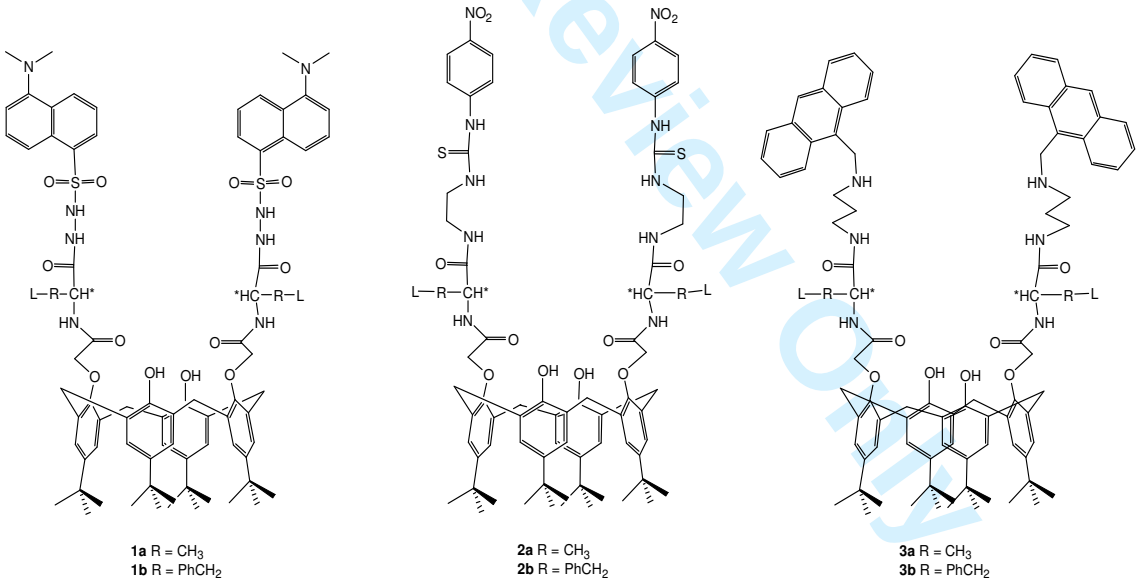
Calixarene-based Receptors

Calixarenes provide optimal scaffolds for the preparation of anion receptors because of their preorganization and ease of functionalization. Recently, two review articles covered this subject [9,10]. He and coworkers prepared several chiral calix[4]arene derivatives bearing chiral aminoacid residues attached to the lower rim, equipped with anion binding units and fluorophore or chromophore proves for the chiral recognition of different substrates. Compounds **1a**,**b** are equipped with fluorescent dansyl groups connected through hydrazide spacers to the calixarene scaffold [11]. The enantioselective recognition of alanine and phenylalanine anions was studied by fluorescence and ^{1}H NMR titration experiments. These compounds showed good enantioselective recognition for L-Ala and Phe anions. Similar chiral calix[4]arene derivatives **2a**,**b** bearing thiourea groups were tested for the chiral recognition of α-phenylglycine. The association constants were calculated by means of UV/Vis titration experiments in DMSO showing that these compounds are selective for α-phenylglycine over other competitive analytes like mandelate or dibenzoyltartrate and form 1:1 complexes with these anions by multiple hydrogen bond interactions. The enantioselectivities of **2a** and **2b** are moderate and opposite, with K_L/K_D = 4.76 for **2a** and K_D/K_L= 2.84 for **2b** [12]. Another pair of calixarenes **3a**,**b** equipped with antracene moieties as fluorescent probes and amine/amide hydrogen bond donor groups were evaluated for their recognition properties towards D and L-malate by fluorescence and ^{1}H NMR titration experiments in chloroform. Those receptors form 1:1 complexes with malate, binding D-malate with preference over L-malate with enantioselectivities (K_D/K_L) of 4.34 for **3a** and 10.41 for **3b** [13].



Chen and co-workers prepared the calix[4]arene derivative **4** bearing an amide macrocycle in the lower rim equipped with a disulfonoantracene group [14]. This compound presented a remarkable affinity and selectivity for dihydrogenphosphate anion. The binding event is signalled by an enhancement of the fluorescence intensity of the host, and job plot experiments revealed a 1:2 host to guest stoichiometry for the supramolecular complex, with an association constant of 5.48×10^9 M^{-2} in acetonitrile. A related upper rim bridged calix[4]arene was shown to be selective for acetate by the same authors [15].

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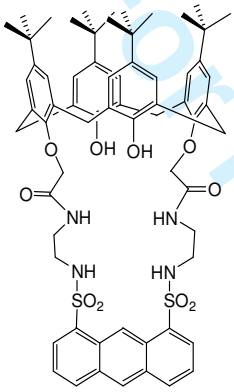
Pyrene has been used by a number of authors as fluorescent reporter group in different calixarene-based anion receptors. Kim and co-workers prepared the calix[4]triazacrown **5**, which is well suited to both anion and cation recognition [16]. This compound selectively binds fluoride signalled by a decrease of the fluorescence emission of the pyrene groups due to PET effects. The association constants were calculated to be 2.04×10^{4} M^{-1} in acetonitrile. The same authors reported the use of the calix[4]arene **6**, in a 1,3 alternate conformation and equipped with two amide groups conjugated to pyrene units, as a selective chemosensor for fluoride [17]. Hydrogen bonding interactions with this anion result in the formation of a static excimer which exhibits an enhanced fluorescence emission. The K_a was calculated at 2.5×10^{2} M^{-1} in acetonitrile.



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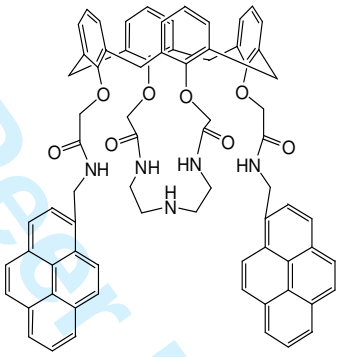

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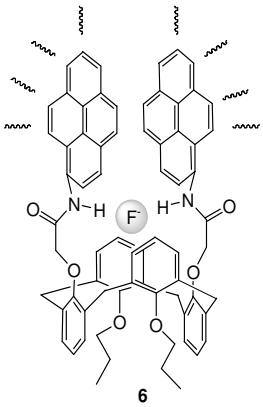
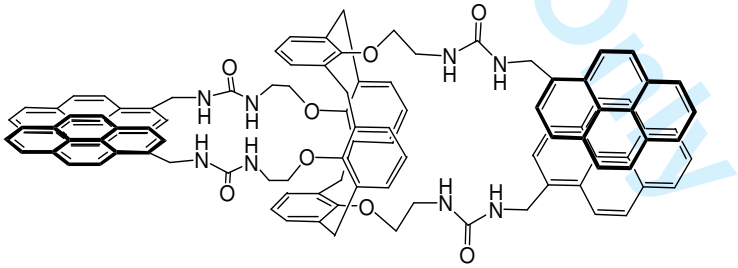


6

Diamond and coworkers prepared the 1,3 alternate calix[4]arene **7**, tetrasubstituted with urea groups as anion binding motifs and pyrene units as reporting fluorophore moieties [18]. This compound showed a selective response for chloride over eleven common anions, with a sharp decline of the excimer emission and an increase of the monomer emission. This is explained in terms of the unstacking of the pyrenes upon anion complexation. The association constant was found to be 2.4×10^{4} M^{-1} in acetonitrile-chloroform (95:5 v:v) mixtures. This compound has a limit of detection of 8×10^{-6} M for chloride under these conditions, making it a potential candidate to be incorporated into real-world sensing devices.



7

Matthews, Gunnlaugsson *et al.* prepared the calix[4]arene derivative **8** equipped with amidourea substituents in the lower rim and studied its binding ability towards different anions in DMSO by means of UV/vis titration experiments. They showed that this compound strongly binds fluoride, dihydrogenphosphate and pyrophosphate in a 1:1 fashion without deprotonation and with concomitant colour changes [19]. Dramatic colour changes in the presence of basic anions such as fluoride, acetate and dihydrogenphosphate were also observed by Chen *et al.* in their studies involving

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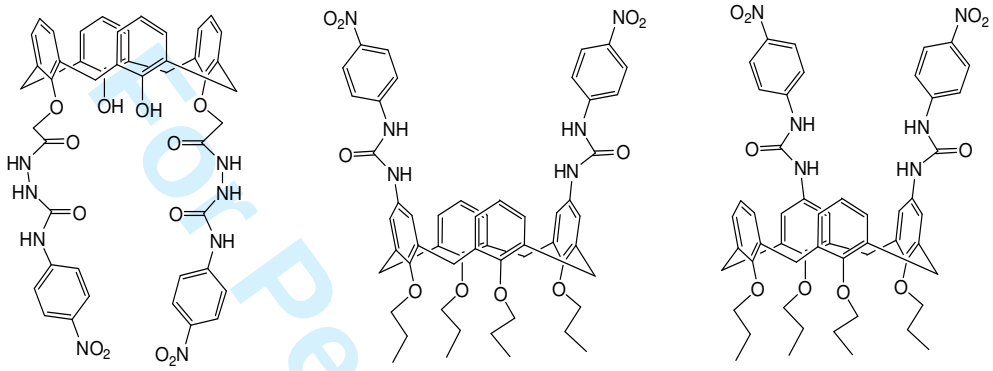
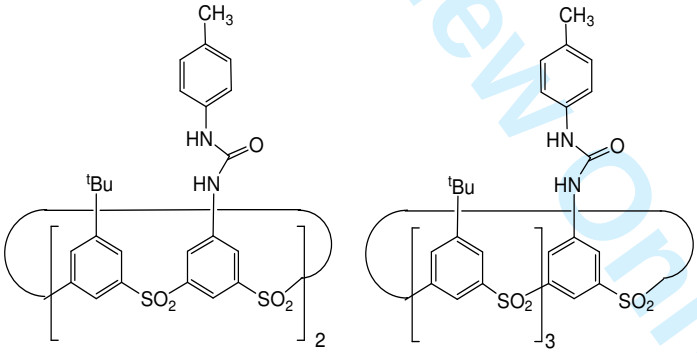
different calix[4]arene derivatives equipped 4-nitrophenyl-azo groups in the upper rim [20]. These calixarenes thus allow the sensing of these anions in acetonitrile.

Lang, Lothák, and co-workers synthesized two upper-rim functionalized calix[4]arenes **9** an **10** with 4-nitrophenylureas in the 1,2 and 1,3 positions [21]. UV/vis titration experiments in dichloromethane revealed high affinities for all the studied anions with association constants in the 10^6 M^{-1} range for **9**. Surprisingly a 2:1 receptor:anion binding stoichiometry for the receptor **10** was found, as a result of the anion induced dimerization of this compound in solution, with β_{21} in the 10^9-10^{11} range.



8 9 10

The same authors also explored the anion binding properties of thiacalix[4]arene derivatives **11** and **12** bearing one or two urea groups in the upper rim [22]. The binding constants were measured in mixtures of chloroform:acetonitrile-d_3 (4:1 v:v) by ^{1}H NMR titration experiments and were found to be much higher to that reported for tetrakis-(phenylureido)calix[4]arene fixed in a 1,3-alternate conformation. For benzoate, the K_a was calculated at 5.0×10^4 M^{-1}, 2.3×10^4 M^{-1} and 1800 M^{-1} for **11**, **12** and the parent 1,3-alternate calix[4]arene respectively [23].



11 12

Nabeshima and co-workers studied the calix[4]arene derivative **13** bearing a polyether chain connected to a bipyridine unit through a urea group in the 1 and 3 positions [24]. This molecule thus possesses three potential binding sites for hard cations (polyether chain on the lower rim), soft cations (bipyridine moiety) and anions (urea groups). While **13** showed weak affinity for anions such as NO_3^-, $CF_3SO_3^-$ and BF_4^- (notoriously poor hydrogen bond acceptors), **13**•Na^+ and **13**•Ag^+ displayed association constants towards these anions enhanced by factors of 30 and 90 times respectively. The simultaneous binding of sodium and silver cations in **13**•Na^+•Ag^+ dramatically increases the affinity for these anions up to 1500 times against **13**, owing

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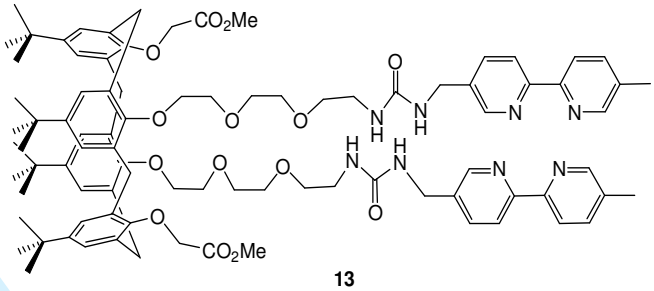
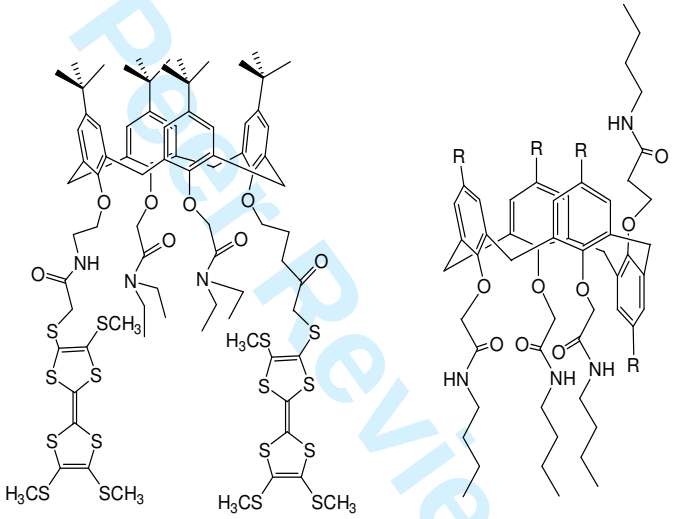
to both electrostatic and allosteric effects. Thus demonstrates the stepwise regulation of the recognition of anions using two different cations as effectors.



13

The electrochemical detection of dihydrogenphosphate was achieved by Sallé and co-workers using a calix[4]arene derivative equipped with amide groups in the lower rim and two pendant tetrathiafulvalene units **14** [25].



14

15 R = H
16 R = *t*Bu

Several reports highlight the possibilities of using calixarene derivatives in biological applications. Davis and co-workers reported the transmembrane chloride transport activity in liposomes of two simple calix[4]arene derivatives **15** and **16** in a partial-cone conformation bearing *N*-butylamide groups [26]. This type of compounds may self-assemble in the membrane to form anion channels. Subtle changes in the structure of these compounds resulted in dramatic differences of their transport activity. Thus **15** is an active transmembrane transporter, whereas **16**, bearing tercbutyl substituents in the aromatic rings, is inactive. Remarkably, **16** is able to quench the transport activity of **15**, most probably because of the formation of inactive heteroaggregates in the membrane. Ungaro reported several calixarene derivatives functionalized with guanidinium groups on the upper rim and alkyl chains on the lower rim [27]. These compounds are able to bind to DNA and condense it as demonstrated by direct visualization using AFM. Condensation is dependent on the conformation and lipophilicity of the calixarene. Calix[4]arenes equipped with four guanidinium groups and hexyl or octyl chains in cone conformation were shown to mediate cell transfection. Schrader prepared the calix[4]arene dimers **17** and **18** equipped with six protonable amine groups on the upper rim and linked through a diamide bridge [28]. These

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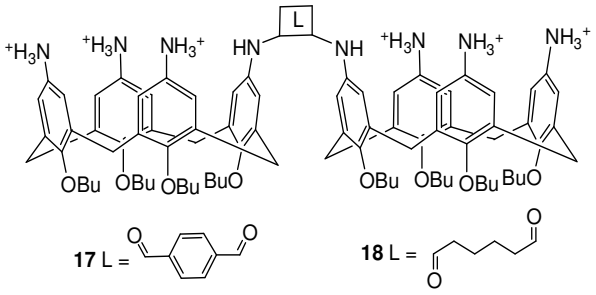
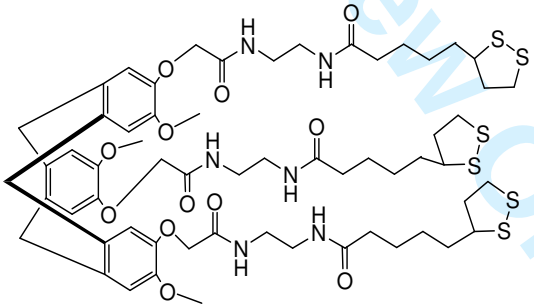
compounds were found to bind double strand DNA and RNA in buffered aqueous solutions.



Calixarenes as anion receptors also find applications in materials chemistry. For example, Wieczorek employed urea decorated calix[4]arenes as additives in polyether electrolytes acting as anion receptors [29]. These compounds modify the ionic transport from almost anionic, through mixed up, to purely cationic within the same polymer system.

The related aromatic platform ciclotriveratrilene has also found application in the design of anion receptors. Echegoyen *et al.* prepared a tripodal CTV-based **19** with amides as anion binding motifs and appended thiotic esters designed to be deposited onto gold surfaces [30]. The binding ability of this receptor was examined in solution, showing good affinity for acetate anion and weaker interactions with dihydrogenphosphate. The receptor was deposited onto gold electrodes forming self assembled monolayers (SAM). The anion sensing properties of the monolayers were examined by impedance spectroscopy confirming the selective binding of acetate anion on the surfaces, proving the usefulness of this method to sense anions in aqueous media by a receptor lacking electrochemical or fluorescent active centres. The same author reported similar strategy for the effective sensing of fluoride using calix[6]arene derivatives with a rigidified bridging crown-4 unit [31].



19

Steroid-based Receptors

Steroids such as cholic acid provide a preorganized scaffold which can be readily equipped with anion binding units yielding potent anion receptors. Davis pioneered the work on this field and has recently published a review article covering this subject [32]. In the last two years interest in this class of receptors continue and several author published reports involving this type of compounds. Davis investigated the binding properties of a wide range of cholic acid derivatives (cholapods) equipped with different hydrogen bond donor groups such as amides, sulfonamides, urea and thiourea moieties as anion binding motifs appended to the steroid scaffold, varying the number of

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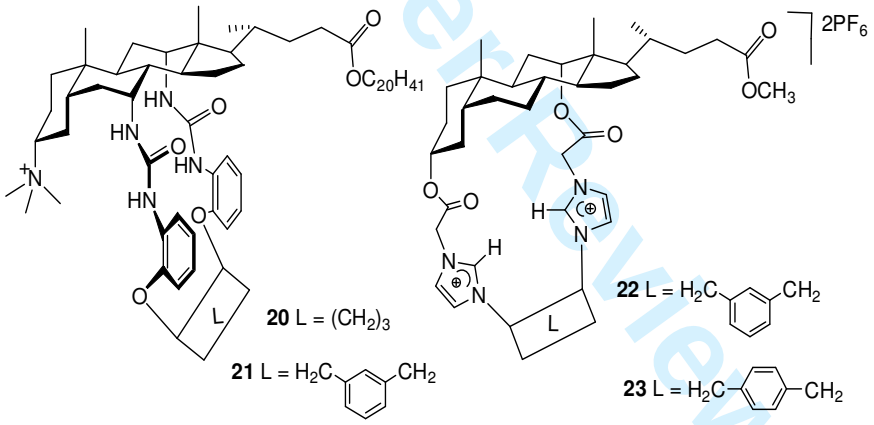
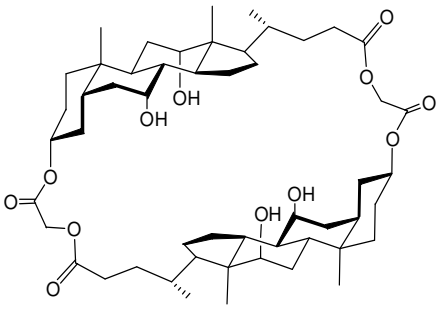
hydrogen bond donors from three to six. These compounds showed very high affinities towards halides, nitrate, perchlorate, acetate or ethylsulfate in wet chloroform, with association constants ranging from 10^4 – 10^{11} M^{-1} [33]. There is much scope to tune the properties of these compounds, and two derivatives **20** and **21** with appended macrocyclic bis-urea units were tested in anion extraction experiments [34]. Rigidification of the binding site with a *m*-xylylene spacer in **21** reduces the flexibility of the binding site yet retaining the preference for chloride. The shorter propyl spacer in **20** would favour smaller anions. Anion extraction experiments showed that both hosts behave as smart anion transfer carriers, and especially in the case of **21** this compound is able to overcome the Hofmeister series to a remarkable extend. Pandey prepared other cholic acid derivatives with a macrocyclic anion binding unit, composed by two imidazolium groups linked by a *m*-xylylene **22** and *p*-xylylene **23** spacers [35]. Binding constants for these receptors were calculated by means of ^{1}H NMR titration experiments in $CDCl_3$ and showed different selectivities. Thus **22** displayed the highest association constant value with fluoride with K_a = 2400 M^{-1} (F^-), 1980 M^{-1} (Cl^-), 1470 M^{-1} (Br^-), 150 M^{-1} (I^-), 470 (AcO^-), whereas **23** is selective for chloride with K_a= 930 M^{-1} (F^-), 12000 M^{-1} (Cl^-), 7600 M^{-1} (Br^-), 300 M^{-1} (I^-), 900 (AcO^-). The macrocyclic dimer **24** studied by Row and Maitra was found to bind fluoride using O-H and C-H groups present in its interior surface [36].





24

Pyrrole-based Macrocycles

First reported in 1886 [37], the tetrapyrrolic macrocyle *meso*-octamethylcalix[4]pyrrole has been extensively used as anion receptor since the seminal work reported by Sessler *et al.* [38]. Nevertheless, its potential as ion pair receptor has only been recently discovered. Moyer, Sessler, Gale, and coworkers presented a complete collection of X-Ray structures showing the inclusion of large, diffuse cations such as cesium or

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imidazolium cations in the electron-rich cup defined by the calix[4]pyrrole upon anion coordination (Figure 1) [39]. This result highlighted the importance of the salt employed in the anion binding experiments and Sessler, Schmidtchen, Gale, and coworkers presented a detailed study of the interaction of octamethylcalix[4]pyrrole with different chloride salts in several solvents such as DMSO, acetonitrile, nitromethane, 1,2-dichloroethane and dichloromethane by means of isothermal titration calorimetry (ICT) and ^{1}H NMR titration experiments [40]. The stability constants obtained from NMR and ITC experiments were generally concordant, although these values are strongly solvent dependent, ranging from 10^2-10^5 M^{-1}. The importance of the countercation chosen is highlighted in the case of the experiments performed in dichloromethane, with K_a= 3.7×10^4 M^{-1} for tetraethylammonium chloride down to 4.3×10^2 M^{-1} in the case of tetrabutylammonium chloride. These differences are attributed to ion-pairing effects and the interaction of the cations with the calix[4]pyrrole cup. The ion pair recognition properties of both calix[4]pyrrole and N-confused calix[4]pyrrole have been employed in crystal engineered networks [41,42]

Please insert here figure 1

FIGURE 1 X-Ray crystal structures of octamethylcalix[4]pyrrole supramolecular complexes with: a) CsF, b) CsCl, c) CsBr, d) Cs_2CO_3 , e) $CsEtOCO_2$ (space filling representation), f) $CsEtOCO_2$ (coordination network). Reproduced with permission from *Angew. Chem. Int. Ed.* **2005**, *44*, 2537 (Figure 1). Copyright 2005, Wiley.

Sessler reported the anion binding properties of several fluorinated calix[n]pyrroles (n=4,5,6) **25**-**27** [43]. Polarization of the pyrrole N-H groups as a result of the electrowithdrawing fluorine susbtituents resulted in an enhanced anion affinity compared to regular octamethylcalix[4]pyrrole. Binding constants were calculated in acetonitrile and DMSO using ^{1}H NMR and ICT titration experiments, which showed that the F-calix[4]pyrrole **25** display the higher affinities towards anions, whereas the larger members of the family favour the larger anions in a relative sense.

Lee and co-workers prepared the strapped calix[4]pyrrole **28** bearing a coumarin unit as fluorophore reporting unit [44]. The fluorescence of this system was examined and it was found that both water and sodium produced an enhancement of the fluorescence intensity, while addition of anions such as chloride, bromide and acetate reverse this effect. ^{1}H NMR experiments in acetonitrile-d_3 revealed that the anions reside inside the central cavity. The association constants were obtained from fluorescence titrations in acetonitrile containing an excess of $NaPF_6$ with values of 2.3×10^6 M^{-1} (Cl^-), 1.0×10^5 M^{-1} (Br^-), and 1.3×10^6 M^{-1} (AcO^-). The dual fluorescence response of this system to anions and cations suggests its function as a molecular logic gate, in which the fluorescence is only enhanced in the presence of cations and absence of anions.

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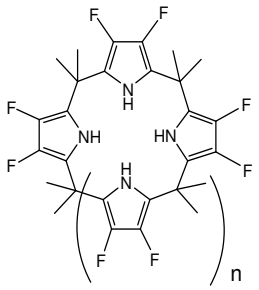
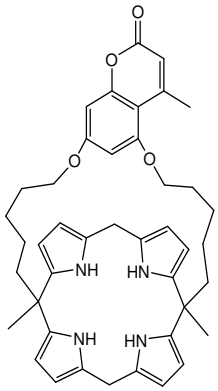
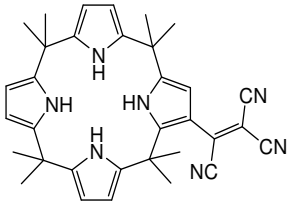


25 n = 1
26 n = 2
27 n = 3



28

In a series of papers, Anzenbacher Jr. *et al.* prepared several octamethylcalix[4]pyrrole **29**-**31** derivatives with different chromophores attached [45, 46]. These compounds were shown to undergo dramatic colour changes upon addition of the basic anions such as fluoride, acetate, and pyrophosphate in competitive solvents. More importantly, they have been shown to be useful sensors for antipyretic carboxylates in plasma-like aqueous solutions. Moreover, these sensors can be embedded in polyuretane films responding to such carboxylates and avoiding interactions with blood plasma protein carboxylates.



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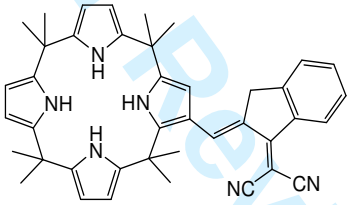

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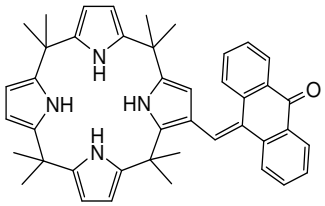

31

The related nitrogen-confused macrocycles were also employed by the same authors for sensing purposes, and two pairs of chromogenic octamethylcalix[4]pyrrole (OMCP) and nitrogen-confused octamethylcalix[4]pyrrole (NC-OMCP) **29**, **32**-**34** were reported [47]. Availability of the alpha position in nitrogen-confused octamethylcalix[4]pyrrole makes functionalization of these derivatives easier than regular octamethylcalix[4]pyrrole. Anion binding in (NC-OMCP) is shown to occur through three pyrrole N-H groups and the β-CH group of the inverted pyrrole, in a cone-like fashion similarly to the octamethylcalix[4]pyrrole. Nonetheless there are differences in the anion affinity of these compounds, and NC-OMCP derivatives presented a higher selectivity for carboxylate anions. Interaction with anions resulted in naked-eye detectable colour changes which were used to prepare microassays to sense anions in competitive aqueous media.

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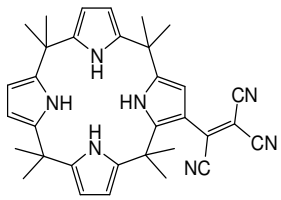

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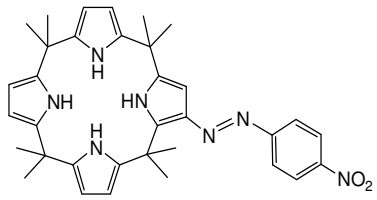

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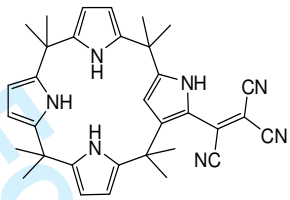

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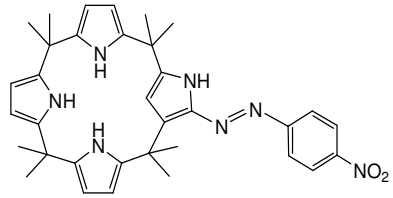
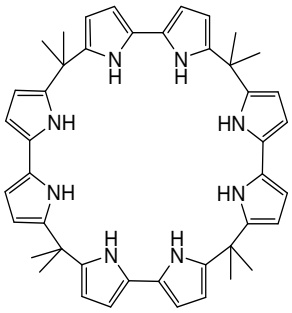


34

Sessler *et al.* explored the anion binding properties of bigger members of this polypyrrole macrocycle family, for example the calix[4]bipyrrole **35** [48]. This compound is the analogous to calix[4]pyrrole containing bipyrrole units as building blocks. Despite its size, this compound is able to adopt a conformation in which the anion is nested inside the macrocyclic cavity, interacting with the eight N-H pyrrole groups, as seen in the solid state structures of the supramolecular complexes of **35** with TBACl and TBABr. The binding constants of **35** with different anions were calculated by ^{1}H NMR and ITC titration experiments in acetonitrile and found to be 2.9×10^6 M^{-1} (Cl^-), 1.1×10^5 M^{-1} (Br^-), 56 M^{-1} (I^-), 450 M^{-1} (NO_3^-). In the case of chloride, this value represent roughly 20 times those calculated for the smaller calix[3]bipyrrole and calix[4]pyrrole [49]. It is worth noting that **35** did not show appreciable interactions with these anions in DMSO solution, presumably because solvation effects in this solvent. By using 1,3-bis-(pyrrol-2-yl)benzene as building block, calix[n]bispyrrolylbenzenes **36**-**38** were synthesized [50]. Along with a solid-state characterization of the macrocycles and supramolecular complexes with anions, the association constants towards Cl^-, Br^-, NO_3^- and HSO_4^- (as their TBA salts) were calculated by ITC titration experiments in 1,2-dichlorethane. **36** was found to bind these anions with much higher affinity than calix[4]pyrrole, being the highest K_a 2.1×10^7 M^{-1} corresponding to bromide, which is explained in terms of cavity size of this compound. **37** and **38** display lower affinities for anions compared to **36**, showing the highest affinity for chloride with K_a values 8.2×10^4 M^{-1} and 2.4×10^5 M^{-1} respectively.



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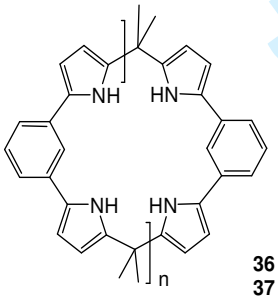
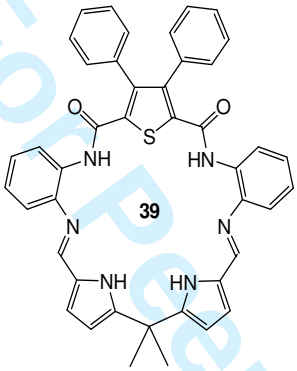


36 n = 1
37 n = 2
38 n = 3

In collaboration with the group of Ustynyuk, Sessler and coworkers also developed shift base macrocycles derived from 2,5-diamidothiophene and dipyrromethane and bipyrrole units [51]. The greater flexibility of macrocycle **39**, due to the linker between pyrrole units, resulted in interesting differences in their anion binding properties compared to **40**. Association constants were determined by means of UV titration experiments in dichloroethane and revealed that more flexible **39** displayed higher affinity than **40**, favouring anions with similar volume such as chloride (16600±900 M^{-1}), nitrate (15400±2100 M^{-1}) and hydrogensulfate (18900±1000 M^{-1}). On the other hand, the more rigid host **40** favours the larger anions, reversing the bromide (7100±900 M^{-1})/chloride (3300±300 M^{-1}) selectivity compared to **39**.



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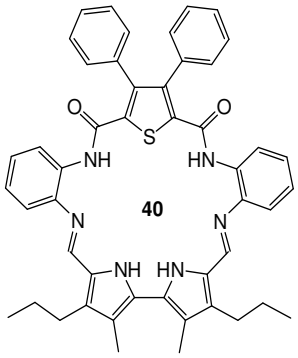
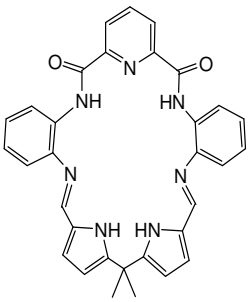


40

The same authors studied the anion binding properties of several 2,6 diamidopyridine-dipyrromethane hybrid macrocycles **42**-**44** [52], similar to the previously reported **41** [53]. These compounds bear a tolyl group in the *meso* carbon of the dipyrromethane unit which rigidified its structure to a certain extend compared to **41**. Oxidation and reduction of this macrocycle provided straightforward access to the parent compounds **43** and **44**. The anion binding properties of these compounds were evaluated performing UV/vis spectroscopic titrations in acetonitrile (Table 1). Compound **42** displayed good selectivity for hydrogensulfate over the other anion tested. Small differences when comparing with **41** resulted in an enhanced selectivity for this anion discrimining the tetrahedral dihydrogenphophate and hydrogensulfate. Presence of additional hydrogen bond donor groups in a more flexible scaffold makes **43** a good receptor for the spherical chloride, whereas fewer hydrogen bond donors and rigidification of the macrocycle in **44** resulted in the receptor only weakly interacting with bromide.



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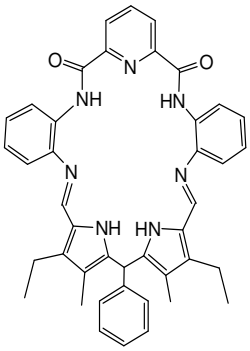

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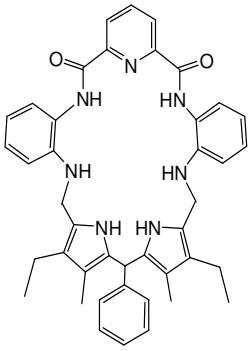

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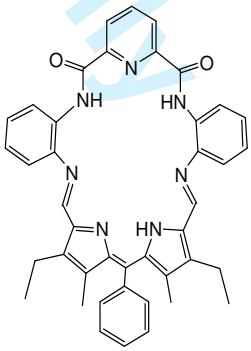

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Table 1. Binding constants K_a (M^{-1}) of receptor **41-44** with different anions (added as their tetrabutylammonium salts) in acetonitrile at 23 ºC.

Anion	**41**	**42**	**43**	**44**
Br^-	a	a	a	2760±380
NO_3^-	a	a	a	a
Cl^-	2000±20	a	116000±11000	a
CH_3COO^-	38000±3000	12600±450	67000±9900	a
HSO_4^-	64000±2600	108000±17000	4700±960	a
$H_2PO_4^-$	34200;26000[b]	29000±1900	15500±1750	a

[a] No apparent binding as reflected in the lack of changes in the UV-vis titration experiment.
[b] 1:2 receptor:anion binding stoichiometry observed, the values refer to the first and second binding event

Amide-based Macrocycles

Amide-based macrocycles remain among the most popular designs for anion hosts [54-56]. Jurczak *et al.* presented a complete study on the structure-affinity relationships in neutral macrocyclic amides derived from 2,6 pyridinedicarboxylic acid, isophthalic acid, and aliphatic α,ω-amines of different lengths **45**-**49** [57]. Both solid-state and solution experiments offered insights in the anion binding behaviour of this class of macrocycles. Preorganization of the amide groups towards a *syn-syn* conformation on the pyridine derivatives result in a higher affinity compared with the parent isophthalamide-based macrocycles. In this case, the lack of preorganization results in intramolecular hydrogen bonds, which, although may be disrupted upon anion coordination, substantially lowered the affinity for these guests. Macrocycle size correlates with anion binding affinity as a compromise of preorganization, which demands shorter spacers between anion binding units, and ability to adjust to a guest, requiring longer, more flexible spacers. Pyridine-based 20-membered macrocycle **46** was found to be the best anion receptor in test, with representative K_a (M^{-1}) values in DMSO-d_6 calculated by means of ^{1}H NMR titration experiments being 1930 (Cl^-), 150 (Br^-), 3240 (AcO^-) and 7410 ($H_2PO_4^-$). Rybak-Akimova *et al.* investigated the size effects in 1:1 macrocycle compounds **50** and **51**, obtained by condensation of 2,6 pyridinecarboxylic acid ester and 2,4,7,10-tetraazadecane and 1,5,9-triazanonane respectively [58]. The 15 membered macrocycle **50** is found to bind fluoride in DMSO solution with an association constant of 5.8×10^2 M^{-1} whereas the smaller 14 membered macrocycle **51** does not interact with this anion.

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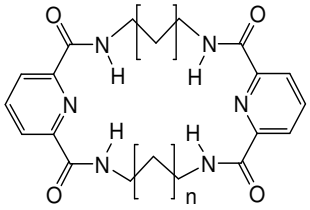

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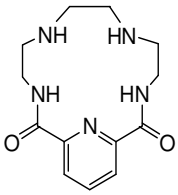

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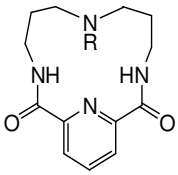
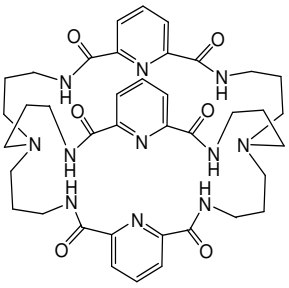


51

Bowman-James and co-workers have presented detailed studies in bicyclic and tricyclic amide-based hosts in both solution and the solid state [59]. For example, the bicyclic amidocryptans **52** and **53**, derived from tris-(3-aminopropyl)amine and 2,6-pyridinedicarbonyl dichloride [60]. Compound **53** was obtained by quaternization of the amine bridges of **52** employing MeI. ^{1}H NMR titration experiments in DMSO-d_6 revealed that **52** is selective for fluoride (K_a>10^5 M^{-1}), whereas **53** showed the highest affinity towards dihydrogenphosphate (K_a=12000 M^{-1}), although in this case the binding constant for fluoride could not be calculated owing to severe broadening of the N-H signals during the experiment. Solid state structures of chloride and sulfate complexes of **52** and chloride and acetate complexes of **53** showed a quite different binding mode. **52** adopted a folded conformation with two loops pointing in one direction and the other in the opposite direction, whereas quaternization of the amino groups in **53** had a profound effect in the coordination mode, adopting a bowl-like shape with the three loops pointing in the same direction.



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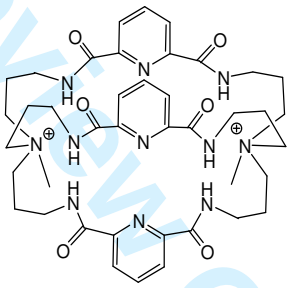

53

The first example of a solid state structure of a bifluoride anion encapsulated in a macrocycle was also reported by the same authors (Figure 2) [61]. They prepared the tricyclic cryptand **54** by linking two monocyclic tetraamide macrociclcyc units by ethylene spacers. Binding studies in DMSO-d_6 revealed a high selectivity for FHF^- (K_a=5500 M^{-1}) over other anions such as $H_2PO_4^-$ (K_a=740 M^{-1}), N_3^- (K_a=340 M^{-1}) and AcO^- (K_a=100 M^{-1}). The solid state structures of sulfate complexes $[H_8\mathbf{55}SO_4]^{6+}$ and $[H_2\mathbf{56}SO_4]$, containing the non-preorganized ammonium cryptand **55** and the amide cryptand **56** were also presented [62]. Both hosts are able to encapsulate a sulfate anion. The more preorganized **56** displayed eight hydrogen bonds, employing all the available amide groups, whereas biding is less efficient with **55** which only used five ammonium groups.

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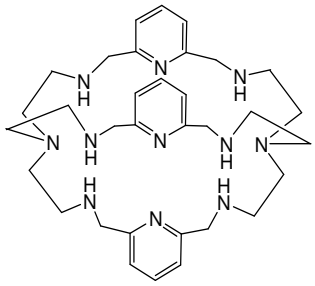

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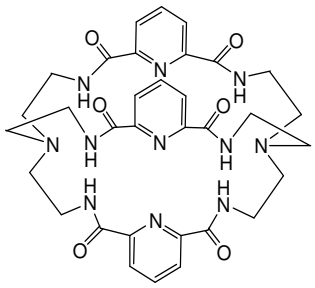
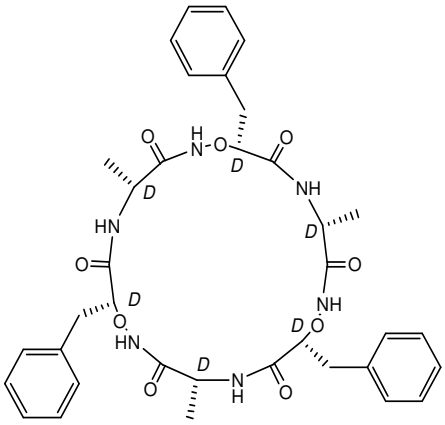


56

Please insert here figure 2

FIGURE 2 X-Ray crystal structure of the bifluoride complex of **54**. Reproduced with permission from *Angew. Chem. Int. Ed.* **2006**, *45*, 1921 (Figure 1a). Copyright 2006, Wiley.

Several authors studied cyclic peptides as anion receptors [63,64]. Yang and Wu reported the cyclic hexapeptide **57** containing amide and aminoxy amide groups [65], which adopts a highly C_3 symmetrical conformation by means of intramolecular hydrogen bonds. ^{1}H NMR titration experiments in dichloromethane-d_2 revealed that this compound formed 1:1 complexes with anions, which are bound by the aminoxy amide groups, and displaying a high selectivity for chloride, with association constants [M^{-1}] for Cl^-, Br^-, I^- and NO_3^-: 15000±1500, 910±43, 51±3, and 440±42 respectively. In agreement with these results, this compound is able to extract chloride anions from aqueous solutions into chloroform.



57

Other Non-charged Macrocycles

Jeong *et al*. reported two indole based macrocycles **58** and **59** displaying four convergent N-H indole groups within a flat and rigid structure [66]. These compounds displayed very high affinities for anions in acetonitrile solutions, forming 1:1 complexes with all the studied anions but bromide and iodide which are found to form 1:2 host to guest complexes. Representative K_a values [M^{-1}] as calculated by UV/vis titration experiments are: 2.0×10^8 (**58**, F^-), 5.6×10^6 (**59**, F^-), 5.9×10^6 (**58**, AcO^-), 6.5×10^6 (**59**, AcO^-), 2.1×10^6 (**58**, $H_2PO_4^-$), 3.2×10^6 (**59**, $H_2PO_4^-$), 1.5×10^6 (**58**, Cl^-), $2.1.\times10^6$ (**59**, Cl^-). Remarkably, these compounds display slow exchange equilibriums in the NMR time scale at room temperature with different chemical shifts for the N-H groups of the

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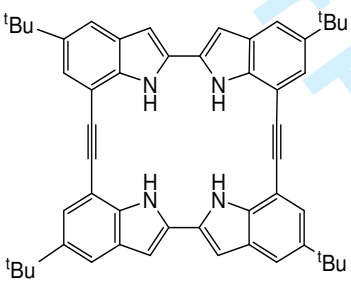
complexes, allowing the identification of the anions under these conditions on the basis of the ^{1}H NMR shifts of the complex.

The use of subphthalocyanines as chemodosimeters for the sensing of cyanide has been reported recently. Martínez-Máñez *et al*. reported the use of the subphthalocyanine **60** as a chromogenic probe for the detection of anions [67]. **60** reacts with basic anions such as fluoride, acetate, dihydrogenphosphate and cyanide in acetonitrile resulting in the degradation of the macrocycle and a naked-eye bleaching of the solution. By adjusting the nucleophilicity of the anions employing mixtures acetonitrile/water 5%, a selective response for cyanide can be obtained. These experiments can be performed in buffered acetonitrile:water 1:1 mixtures with detection limits for cyanide of 10 ppm at pH=7 and 0.1 ppm at pH =9.4. Palomares, Torres and co-workers also published a related approach [68].



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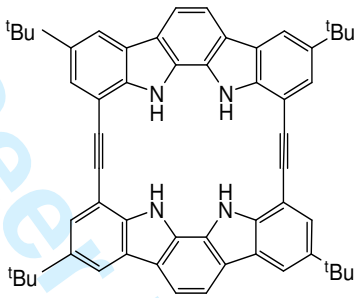

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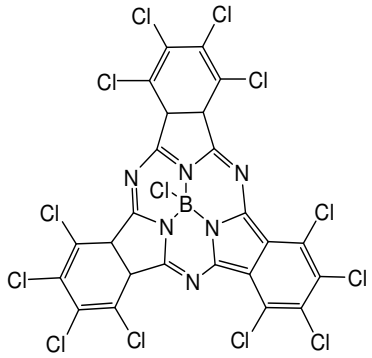

60

Charged Macrocyclic Receptors

Recent reviews by García-España and co-workers, and by Gloe *et al.* summarizes the development of macrocyclic polyammonium receptors for the recognition of different anions in aqueous solution [69,70]. Bencini and co-workers designed the phenantroline containing polyammonium receptor **61** [71]. A combination of hydrogen bonds, charge-charge interactions and π-π stacking leads to the selective recognition of ATP over GTP, TTP and CTP in aqueous solution. Moreover, the binding event is signaled by the selective quenching of its fluorescence by this nucleotide. Pina, García-España *et al.* reported the macrocycle **62**, containing two appended naphthalene units which selectively recognizes citrate over all the other components of the Krebs cycle by changes in the fluorescence emission spectra [72]. Although all the components of the Krebs cycle can interact with the host, citrate would be able to block the macrocycle arms through hydrogen bonding interactions sitting above the cavity of the receptor, thus enhancing the fluorescence.

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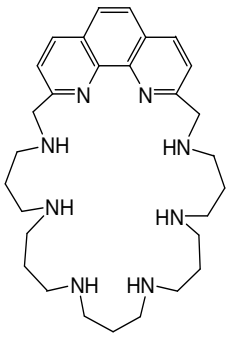

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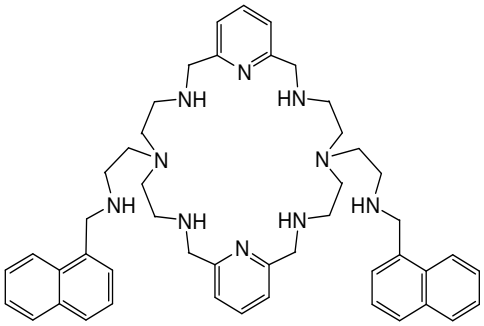
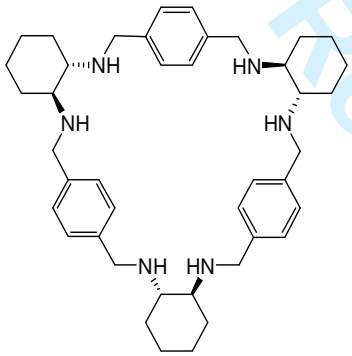


62

Introducing chiral building blocks allow the enantioselective recognition of substrates. Luis, García-España *et al.* studied the interactions of the macrocycle **63**, formed by three *trans*-(1R,2R)-diaminocyclohexane units connected by *p*-xylylene spacers, with three different tricarboxylic acids in water over a range of pH [73]. The complementarity between the macrocycle and 1,3,5-bencenetricarboxylic acid resulted in a marked selectivity for this guest over the other tricarboxylic acids with differences in log K_a of ca. 2.0 at pH 4. Gotor, Alfonso and co-workers studied the enantioselective recognition of malate dianion by the chiral macrocycle (R,R)-**64** [74]. This receptor is found to form strong 1:1 complexes with both malate enantiomers throughout the whole pH range, although complexes with the *S* enantiomer are more stable that those formed with the *R* enantiomer, with K_S/K_R varying from 11.50 at pH 10 to 3.89 at pH 2.



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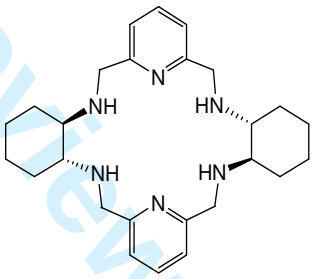

64

Imidazolium-containing macrocyles as anion receptors have also been explored by different authors [75]. Beer and co-workers prepared several tetrakis-imidazolium and tetrakis-benzoimidazolium macrocyles **65**-**68** of different sizes [76]. The anion binding properties of these compounds were evaluated by means of ^{1}H NMR titration experiments in acetonitrile-d_3/water 9/1 mixtures. Macrocycles **66** and **67** exhibited selectivity for fluoride anion with K_a>10^4. All the macrocycles bind benzoate in a 1:2 host:guest fashion, whereas cavity size effect was demonstrated by the affinity of **68**, the largest macrocycle synthesized, towards iodide, which is the highest among all the macrocycles studied.

Hwang, Kim and coworkers prepared a calix[4]imidazolim[2]pyridine **69** and studied the anion binding properties both in solution and in the solid state [77]. This compound was found to bind fluoride in a 1:1 stoichiometry with a binding constant of 28900 M^{-1} in DMSO-d_6. The solid state structure of **69**-$F(PF_6)_3$ showed the fluoride anion interacting with the four $(C\text{-}H)^+$ groups sitting in the centre of the cavity. All the other studied anions are found to form 1:2 host:guest complexes both in solution and in the solid state.

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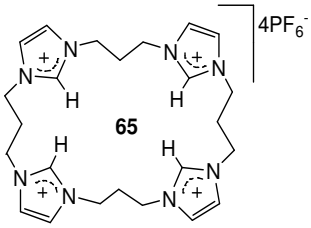
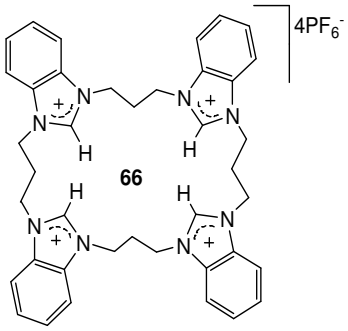
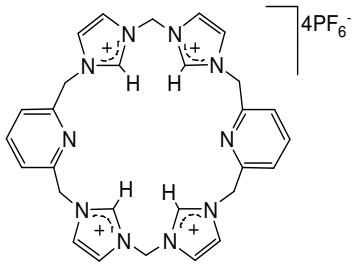
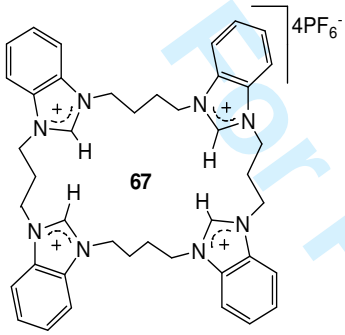
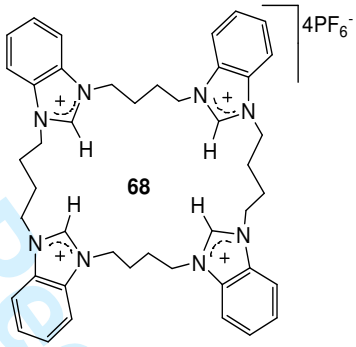


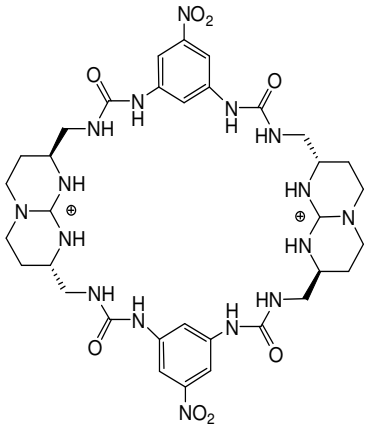








Schmidtchen prepared the macrocycle **70**, derived from two chiral guanidinium groups connected through four urea units [78]. The enantioselective binding of (L,D) tartrate dianion and (L,D) aspartate monoanion as their tetraethylammonium salts in acetonitrile was investigated by isothermal titration calorimetry experiments. The association constants for both pairs of enantiomers were found to be very similar. Nevertheless, discrimination between enantiomers is reflected in significant differences in the observed entropies of association, which is not translate into enantiodifferentiation because this effect is compensated by the differences in the enthalpy of the process. The enantioselective recognition of the chiral carboxylate naproxen using a chiral urea-based macrocycle was reported by Caballero and coworkers [79].



CONCLUSION

As illustrated by the examples contained in this minireview, macrocyclic and macrocyclic-based anion receptors continue attracting a great deal of attention from the research groups interested in the anion coordination chemistry arena. Some important advances toward the understanding of structural design of anion receptors have been

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made. Demanding tasks such as chiral recognition, anion binding in competitive media by neutral receptors, selective sensing and recognition or biological applications are starting to be addressed. Nevertheless, further advances towards practical applications in those fields are much needed and it is likely that progress will continue at good pace.

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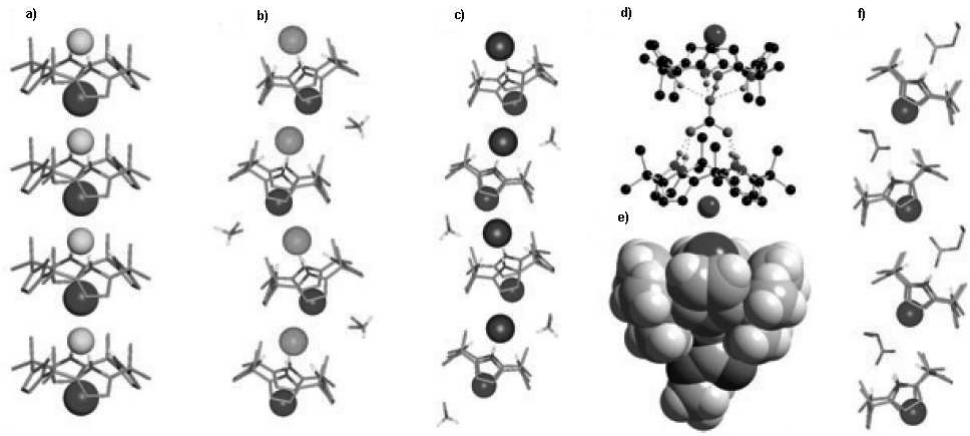

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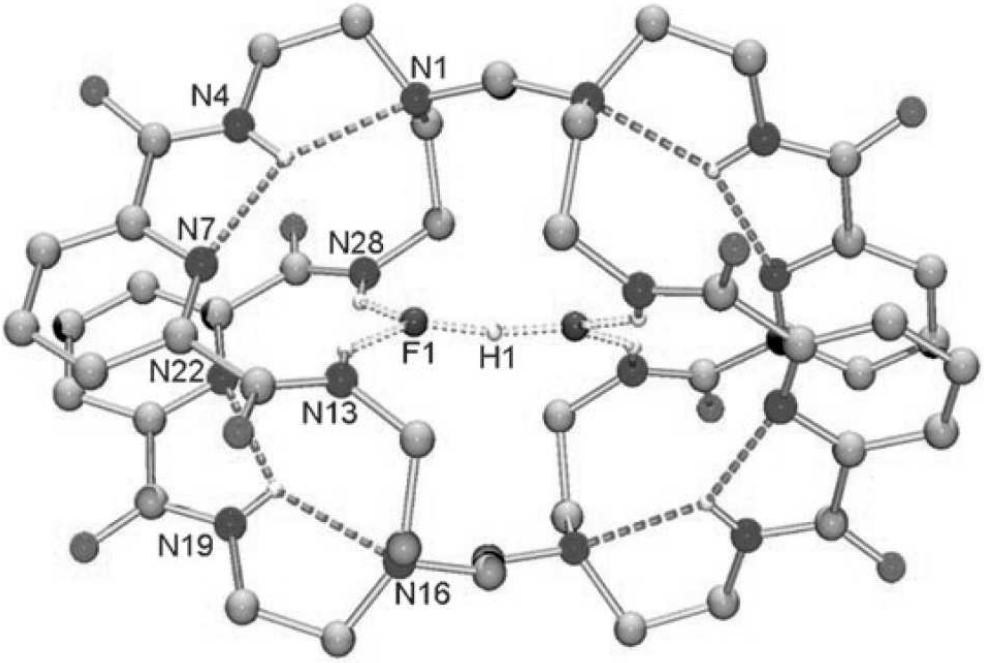

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