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Neutral CH and Cationic CH Donor Groups as Anion Receptors

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Please list the key learning points (up to five) that your review will offer

1. Why are anions important in environmental and biological processes?
2. Why is there growing interest in CH hydrogen bond donors as anion recognition elements?
3. How are CH hydrogen bond donor motifs used to create macrocycles, foldamers and “molecular machines”?
4. What are the nature of the interactions between various types of neutral and cationic CH hydrogen bond donor motifs and different anions?
5. What is the current state of theoretical understanding of CH···anion hydrogen bond strengths and how does this translate into receptor design?

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Neutral CH and Cationic CH Donor Groups as Anion Receptors

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The design and synthesis of anion selective receptors and chemosensors continues to attract considerable interest within the supramolecular community. In recent years, increasing attention has focused on the use of neutral and cationic CH hydrogen bond donors as anion recognition elements. Over the last five years, motifs that support CH···X (X = anion) hydrogen bonds have been actively used in various shape persistent macrocycles, foldamers and "molecular machines". This tutorial review highlights recent developments in host-guest chemistry based on the use of neutral and cationic CH hydrogen bond donors. Also discussed are various structural classifications, including alkyl CH, phenyl CH, triazole-based CH, imidazolium $(CH)^+$ and triazolium $(CH)^+$ hydrogen bond donor systems.

Introduction

Anions are ubiquitous in the natural world and a critical concern in the context of environmental chemistry. Sulphate is prominent as a constituent of acid rain.[1] Nitrate is a wide-spread contaminant in ground water as the result of agricultural fertilizer runoff.[2a] Arsenate and fluoride are present in certain well waters.[2b,c] Phosphate in waterways, arising from both industrial and agricultural activities, leads to the eutrophication of waterways and the production of toxic algal blooms.[2d] Pertechnetate, a radioactive product of nuclear fuel reprocessing, constitutes a potential pollution hazard.[2d] Anions are also critical to the maintenance of life and play important roles in a range of biological processes. ATP and other high-energy anionic phosphate derivatives are at the centre of power processes as diverse and important as biosynthesis, molecular transport, and muscle contraction.[1] Pyrophosphate is the product of ATP hydrolysis under cellular conditions and is involved in DNA replication catalyzed by DNA polymerase.[2e] Misregulation of chloride anion transport is also implicated in a number of diseases, including cystic fibrosis.[2f]

Given the importance of anions, it is not surprising that considerable effort with the supramolecular chemistry community has been devoted to the synthesis of receptors that can recognize, sequester, extract and sense selectively anionic species. Related effort has been devoted to understanding the interactions between guest anions and host anion receptors.[1] Traditionally, systems incorporating neutral species (e.g., Lewis acids and hydrogen bond donors) or charged species (e.g., transition metals and protonated nitrogen motifs) have been used in this regard.[1] A wide array of donor groups have been used for hydrogen bonding-based anion recognition in synthetic receptors, including amines, ammoniums, pyrroles, ureas and amides.[1,2g] There is also a wide range of anion-binding receptors that contain metal atoms, such as Lewis acidic anion-binding sites and transition metal-based anion coordination sites.[1,2h] Recently, however, the importance of CH···anion hydrogen bonds in biological and artificial anion recognition has come to be appreciated. This review is designed to summarize recent progress in the area of synthetic CH hydrogen bond donor-based host guest chemistry.

Alkyl and aryl CH bonds are present in the overwhelming majority (97%) of organic compounds.[3] Moreover, CH hydrogen bonds were first described in 1935,[4] nearly concurrent with reports detailing more traditional hydrogen bonds.[5] However, they were mentioned only occasionally in the literature until a systematic study involving the crystal structures of purines and pyrimidines was carried out in the

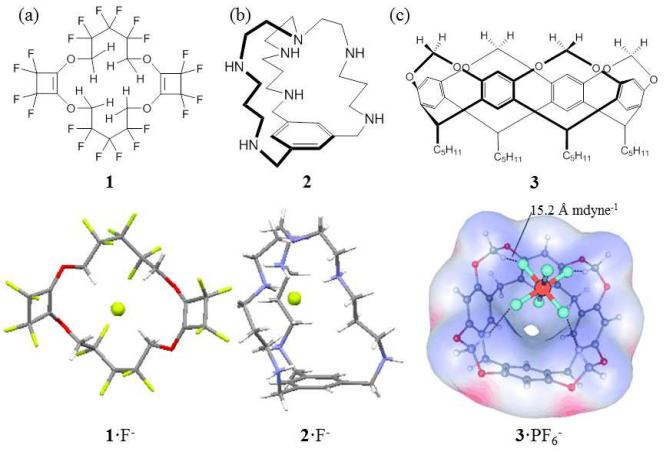
1960s.[6] Further investigations of CH-based hydrogen bonds suffered a setback after strong objections were raised against their importance. Renewed interest in the topic came after a landmark analysis of crystallographic data revealed evidence for CH hydrogen bonds,[7] investigations that culminated in their being highlighted in Desiraju and Steiner's authoritative text on weak hydrogen bonds.[8] A seminal aspect of this latter publication is the suggestion that the strength of CH···X^- (X = anion) bonds could approach those based on more traditional hydrogen bond donors.

Neutral CH hydrogen bond donor motifs

Compared to the more traditional NH and OH donors, it took longer to appreciate the importance of noncovalent interactions involving CH hydrogen bond donors. The importance of this motif for anion recognition was first proposed on the basis of solid state crystallographic analyses, wherein close CH···anion contacts were observed.

Alkyl CH donors

In the early days of supramolecular chemistry, Farnham, Dixon and coworkers reported a novel macrocyclic polyether **1** that acted as an unusual neutral host that was capable of binding a fluoride ion (Scheme 1a).[9] X-ray crystal structure analysis revealed that the central fluoride was held within the chiral cavity of an effective C_2 symmetric system through interactions with four CH_2 groups. A tris(dimethylamino)sulfonium (TAS) cation served as a lid for the complex, and presumably plays a role in stabilizing the bound anion. The fluorine atoms attached to the aliphatic $-CH_2-$ groups were considered responsible for enhancing the CH hydrogen bond interactions that serve to bind the fluoride anion. Upon binding, the 18-membered ring **1** undergoes a substantial change in conformation; presumably, this allows this receptor to provide four neutral CH···fluoride anion hydrogen bonds. Base on an NMR spectral study, it was proposed that central fluoride anion was bound tightly. Ab initio calculations on a model of the anion complex indicated a minimum-energy geometry similar to that observed in the crystal structure of the salt. Interestingly, multiple pathways for enantiomerisation were found, with the preferred pathway depended upon the temperature.

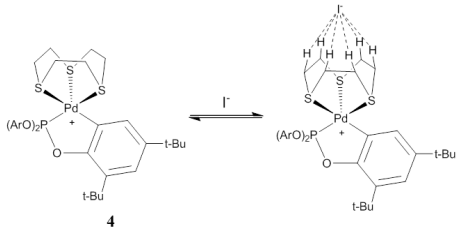


Scheme 1 CH···anion interactions observed in (a) the fluorinated macrocyclic ether **1** and (b) the macrobicyclic azaphane **2**, and, (c) the B3LYP/6-31++G(d,p)-optimized structure of the resorcinarene-based cavitand **3**. Note: These and other X-ray structures were produced using data downloaded from the Cambridge Crystallographic Centre. The structure of **3·PF_6^-** is reproduced with permission of Wiley from ref. 11. Copyright 2008.

A preorganised macrobicyclic azaphane **2** was reported by Steed and coworkers in 2004.[10] Compound **2** was prepared *via* a tripod-tripod cyclization reaction involving the reaction between 1,3,5-tris-bromomethyl-benzene and the aliphatic tripodal hexatosylated polyamine, followed by the reduction of the resulting bicyclic tosylamine. Solution phase binding studies in water revealed that compound **2** in its hexaprotonated form displays a high selectivity for fluoride anion over the chloride anion (log K_{F^-} / log K_{Cl^-} > 5), whereas no evidence of binding in aqueous solution was observed in the case of the bromide and nitrate anions. The remarkably strong and selective binding of the fluoride anion was ascribed to a combination of three NH- and three aliphatic CH-based hydrogen bonding interactions (Scheme 1b). The high degree of preorganisation exhibited by azacyclophane **2** was thought to compensate for the lower intrinsic anion affinity of the unactivated CH hydrogen bond donors. Single crystal X-ray structural studies confirmed the formation of 1:1 anion-bound complexes with the fluoride, chloride, bromide, and iodide anions. The solid state binding of the bromide and iodide anions was ascribed to a dramatic enhancement in the affinity for these halide anions under the very low pH conditions brought about during crystallisation.

In 2008, the Schalley group analysed resorcinarene-based cavitands of general structure **3** and reported interactions between anions and aliphatic CH hydrogen-bond donors in acetone or acetone/methanol mixture.[11] On the basis of mass spectrometric experiments in combination with theoretical calculations, the authors suggested that suitably positioned CH subunits could complex anions provided that they are polarized by neighbouring electronegative heteroatoms. It was proposed that cavitand **3** provides a geometric arrangement that allows four converging CH moieties to support anion binding (Scheme

1c). It was found that one specific cavitand was able to solvate a sulphate dianion well enough to prevent electron autodetachment. On this basis, it was concluded that the interaction between neutral host containing CH hydrogen bond donors and anionic guests could be substantial.



4

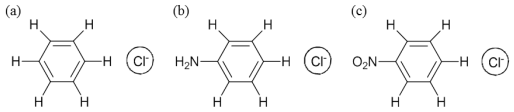
Scheme 2 Complexation of iodide ion by the palladacyclic receptor **4**.

In the same year, a novel organometallic receptor **4** was synthesized by Bedford, Tucker, and coworkers. This system was found to bind anions in organic media (chloroform) and in the solid state, with complexes stabilized through a series of C–H···halide interactions, as evidenced by ^{1}H NMR spectroscopy, X-ray crystallography, and computational models.[12] Adding aliquots of $Bu_4N^+Cl^-$ to a solution of receptor **4** in $CDCl_3$ induced a significant downfield shift in the *endo* proton signal. Based on these analyses, a degree of dissociation was inferred in the case of the chloride complex. This effect was much less marked for the corresponding bromide anion salt and was not observed in the case of iodide (Scheme 2). This allowed a binding constant (K_a) for I^- of 2.2×10^3 M^{-1} (±10%) to be determined. Job plots provided support for the proposed 1:1 binding stoichiometry.

In 2009, Hay and Pedzisa used electronic structure calculations, carried out at the MP2/aug-cc-pVDZ level, to determine CH···Cl^- hydrogen bond energies for a series of XCH_3 donor groups in which the electron-withdrawing ability of X was varied over a wide range of values.[13] They found that the aliphatic CH···Cl^- hydrogen bond strength ranged from -3.6 to -21.9 kcal/mol. These results were used to rationalize why aliphatic CH donors had been observed to function as effective binding sites in solution and led to the generalized suggestion that CH···anion contacts should be considered as possible contributors when evaluating the overall denticity of an anion receptor.

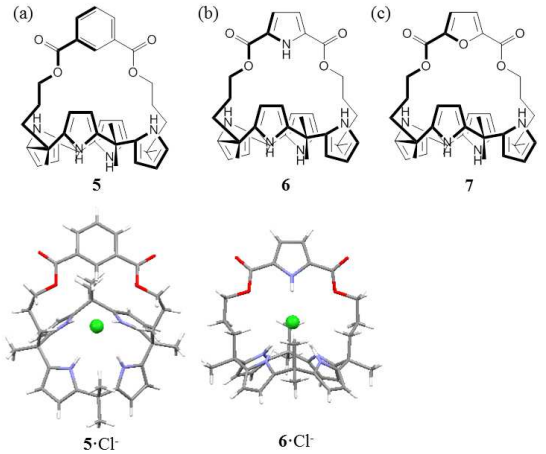
Phenyl CH donors

As with other donor systems, the strength of a CH hydrogen bond depends on the acidity of the proton in question.[14] Aryl CH protons, such as those present in C_6H_6, are appreciably more acidic than those in alkanes.[15] It follows that aryl-based receptors should form stronger anion complexes than those based on alkanes. In aliphatic systems, the CH proton acidity is strongly enhanced by the presence of substituents that would stabilize the conjugate anion through inductive or resonance effects. Based on a combination of theoretical calculations, examination of crystallographic data, and analyses of experimental binding energies, Hay and Bryantsev reported in 2005 that in the absence of electron-withdrawing substituents, simple arenes (Scheme 3a) would stabilize hydrogen bonds with anions that could exceed 50% of the strength of those formed by OH and NH donor groups and that even with *p*-NH_2 substituents such CH entities should be considered as bona fide anion recognition sites (Scheme 3b).[16] Later in the same year, Hay and Bryantsev reported that when electron-withdrawing substituents were present, the aryl CH group (Scheme 3c) was a strong hydrogen bond donor, exhibiting hydrogen bond strengths comparable to those obtained with OH and NH donor groups.[17]



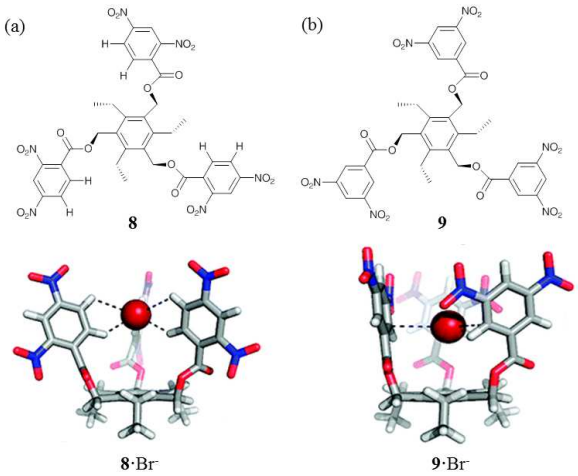
Scheme 3 Schematic representations of benzene-chloride ion interactions.

In 2008, diametrically strapped calixpyrroles bearing benzene, pyrrole, or furan moieties in the strap, compounds **5**, **6**, and **7**, respectively, were reported by Sessler, Hay, Lee and coworkers (Scheme 4). These systems were found to be effective chloride anion receptors as inferred from solid state structural analyses, solution phase binding studies, and theoretical analyses.[18] In this instance, isothermal titration calorimetry (ITC) was used to quantify the interaction between the chloride anion (studies as the TBA salt in acetonitrile at 25 °C). It was found that, as compared to unsubstituted calix[4]pyrrole, an order of magnitude higher affinity was seen in the case of the phenyl strapped system **5**. This enhancement was ascribed in large measure to the presence of an addition aryl CH hydrogen bond donor in the case of the phenyl-strapped calixpyrrole receptor (**5**). The introduction of an additional NH hydrogen bond donor into the strap **6** enhanced the chloride affinity by an order of magnitude relative to **5** ($K_a = 2.2\times10^6$ and 1.8×10^7 M^{-1}, for **5** and **6**, respectively). Conversely, the affinity of the furan analogue **7** was found to be an order of magnitude lower than that of **5**, as reflected in the observed K_a value (1.9×10^5 M^{-1} for **7**). The results provided support for the contention that CH···Cl^- hydrogen bonding interactions are energetically significant and that this type of contact contributed substantially to the overall Cl^- binding energetics in the case of **5**.



Scheme 4 Single crystal X-ray diffraction structures of the chloride anion complexes of the strapped calix[4]pyrroles **5** and **6**; the structure of the anion-free furan system **7**.

In the same year as the Sessler, Hay, and Lee study, the Johnson group reported a series of tripodal receptors, **8-9** (Scheme 5), that relied on preorganised electron-deficient aromatic rings to bind halide anions in organic solvents *via* both weak σ anion-to-arene interactions and CH···X^- hydrogen bonds.[19] This team made extensive use of ^{1}H NMR spectroscopy to quantify the binding interactions in solution and to elucidate the specifics of the receptor-anion interaction. DFT calculations and ^{1}H NMR titrations carried out in benzene provided support for the conclusion that the substitution pattern in **8-9** was critical to defining the nature of the binding mode. The 2,4-dinitro-substituted receptor **8** was found to stabilize the bound halide anion through primarily aryl CH···X^- hydrogen bonding interactions, while anion complexes of the 3,5-dinitro-substituted receptor **9** were stabilized primarily *via* weak σ interactions (Scheme 5). From these observed binding mode differences, it proved possible to differentiate between aryl H-bonds and anion/arene π contacts.



Scheme 5 Optimized geometries (B3LYP/DZVP) of **8** highlighting the aryl CH···anion hydrogen bonding interactions with the bound anion a comparison with the weak σ binding mode inferred in the case of **9**. The structures of **8·Br**$^-$ and **9·Br**$^-$ are reproduced with permission of the American Chemical Society from ref. 19. Copyright 2008.

In 2009, Coletti and Re carried out high level ab initio calculations on the binding of halide ions (F^-, Cl^-, Br^-, I^-) to benzene.[20] They calculated energies and enthalpies for the in-plane minamised geometries, corresponding to the halide anion being bound *via* single or double hydrogen bonds to the aromatic CH moieties. For benzene-fluoride, the interaction was fairly strong, with a linear single bonded geometry being the most stable structure (ΔH_{298}=-15.3 kcal/mol). For the chloride, bromide, and iodide adducts, a simultaneous interaction of the halide ion with two adjacent aromatic hydrogens proved more stable. This gives rise to bifurcated interactions of moderate strength (with ΔH_{298} values ranging from -8.3 to -6.1 kcal/mol). The strength of these interactions (in particular those involving the fluoride and chloride anions) led to the suggestion that aryl CH···anion bonds could contribute to the overall binding in complex receptor systems.

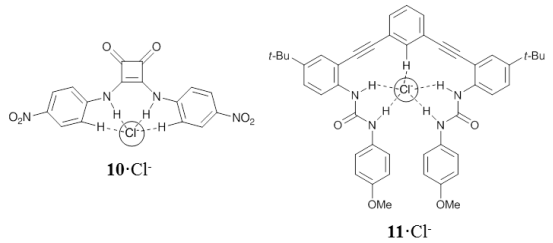
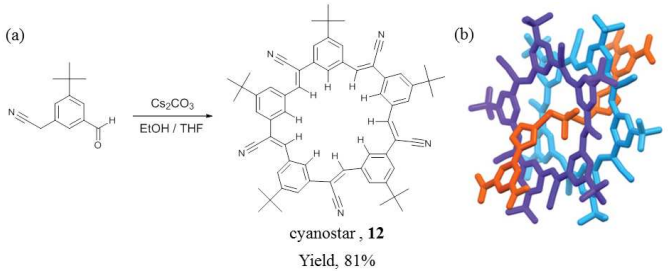


Fig. 1 CH···chloride ion interactions in the squaramide-based receptor **10** and the phenyl-acetylene receptor **11**.

In a separate study, the Fabbrizzi group observed the interaction of a neutral squaramide-based receptor **10** (Fig. 1), equipped with two 4-nitrophenyl substituents, with halides and oxoanions in acetonitrile.[21] UV/Vis and ^{1}H NMR spectroscopy titrations provided support for the formation of 1:1 hydrogen bonding complexes with all the test anions included in the study. X-ray diffraction analyses of the chloride and bromide complex salts confirmed the 1:1 stoichiometry in the solid state and revealed the presence of bifurcated hydrogen bond interactions between the squaramide-based receptor **10** and the halide anions. These interactions involved both amide NH and aryl CH donors (Fig. 1). Quantitative studies revealed that complexes of **10** with halides were one to two orders of magnitude more stable than the corresponding complexes obtained using the analogous urea-based receptor. This was ascribed to the presence of aryl CH hydrogen bond donors.

In 2013, Johnson, Haley and coworkers developed a new phenyl-acetylene receptor **11** (Fig. 1) containing a carbon-centered hydrogen bond donor that, in conjunction with two stabilizing urea moieties, was proposed to contribute to anion

binding.[22] The presence of an unusual CH···Cl^- hydrogen bond was supported by the observation of large ^{1}H NMR chemical shifts in water-saturated chloroform and by a short, linear CH···Cl^- contacts in the solid state. Computational modelling studies led to the conclusion that substitution with electron withdrawing groups could increase the energies of benzene-derived CH hydrogen bonds to the point where they rival the strength of those based on pyrrole NH donors.



Scheme 6 (a) One-pot synthesis of cyanostar **12**; (b) X-ray crystal structure of the [3]rotaxane formed from cyanostar **12**. The structure of the [3]rotaxane is reproduced with permission of Nature Publishing Group from ref. 23. Copyright 2013.

Later in 2013, a high-yielding, one-pot and multigram-scale synthesis of C_5-symmetric macrocycles of general structure **12** was reported by Flood and coworkers.[23] These systems, produced *via* Knoevenagel condensations, were termed "cyanostars" (Scheme 6a). Detailed studies of these systems provided evidence that the electropositive cyanostilbene-based CH groups could be used as hydrogen bond donors and that these receptors would complex normally weakly coordinating anions. The shallow bowl shape and the electron-deficient nature of the cyanostilbenes was thought to provide a π surface that is suitable for interacting with various anions in the form of 2:1 sandwich complexes. In mixed apolar–protic solvents (40% methanol in dichloromethane), log $\beta_2 \approx 12$ and $\Delta G \approx -70$ kJ mol^{-1} values were determined for several large anions (BF_4^-, ClO_4^- and PF_6^-) that are typically considered to be weakly coordinating. The large size of the cyanostar cavity allowed formation of a [3]rotaxane templated around a dialkylphosphate (Scheme 6b). X-ray diffraction structural analyses confirmed the rings-in-rod structure of a representative [3]rotaxane in the solid state and revealed short (< 3 Å) CH···O (phosphate) hydrogen bonds.

Triazole-based CH donors

The advent of so-called click chemistry spawned efforts to exploit 1,2,3-triazoles as highly polarized donors capable of stabilizing neutral CH···anion interactions. In recent years, this chemistry has emerged as an exceedingly important approach to anion binding. It has benefited from both synthesis and conceptual advances, including the creation of foldamers, shape persistent receptors, fluxional systems, and mechanically locked species, that have served to extend the traditional frontiers associated with anion recognition chemistry.

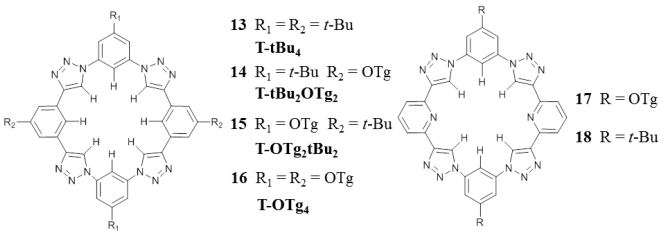
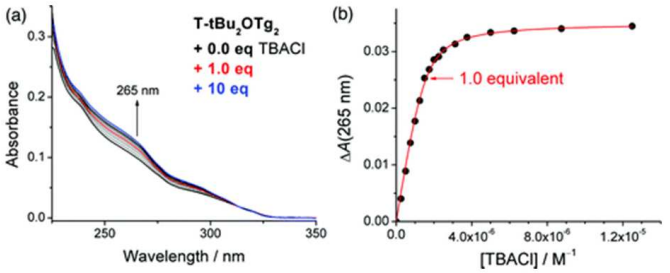


Fig. 2 Structural formulas of [3_4]triazolophanes bearing a variety of substituents **13-16**, and pyridine-containing triazolophanes **17-18**.

In 2008, the Flood group reported a shape-persistent macrocycle **13** (Fig. 2) that was prepared using a sequence of Sonogashira and "click" reactions in an overall yield of 27%.[24] This receptor was found to bind the chloride anion with a 1:1 stoichiometry, as determined from UV-Vis spectral titrations using tetrabutylammonium chloride (TBACl) as the anion source (K_a = 1.3×10^5 M^{-1} in CH_2Cl_2, 298 K). A Job-plot provided further support for the proposed 1:1 binding stoichiometry. In a complementary ^{1}H NMR spectroscopic experiment, macrocycle **13** was titrated with TBACl. This led to a 0.73 ppm downfield shift in the triazole proton signals. A geometry optimization study carried out at the HF/3-21G*level provided support for the notion that the chloride ion was held within the plane of macrocycle **13**. The ability to bind the chloride anion well was ascribed to the preorganized shape of the macrocycle, the ideal size of the inner cavity, and the cumulative effect of multiple weak CH hydrogen bonds.

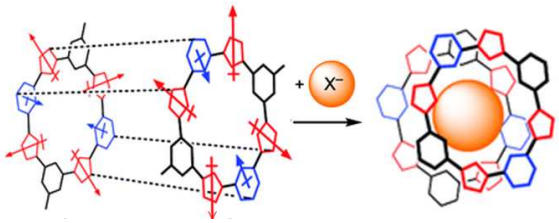


Scheme 7 (a) Representative UV changes observed upon titration of triazolophane **14** (**T-tBu_2OTg_2**) (1.5 μM, CH_2Cl_2) with TBACl and (b) the fit of the absorption changes at 265 nm to a 1:1 isotherm. Reproduced with permission of the American Chemical Society from ref. 3. Copyright 2008.

Table 1 Association constants (K_a) for halide binding (TBA salts) with various triazolophanes (determined using UV spectroscopy) in CH_2Cl_2 at room temperature.

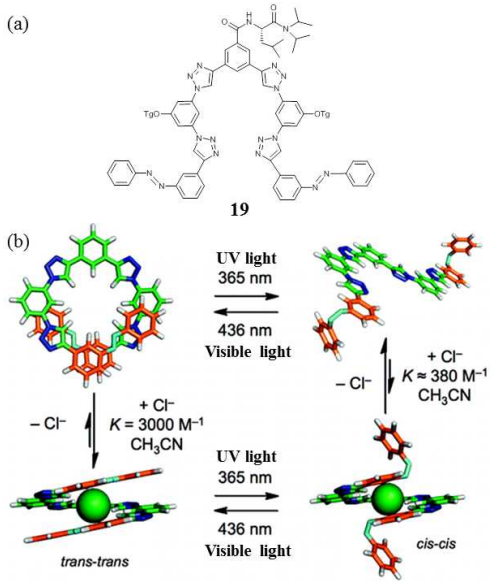
	K_a (UV) (M^{-1})			
Halide	**13** (**T-tBu$_4$**)	**14** (**T-tBu$_2$OTg$_2$**)	**15** (**T-OTg$_2$tBu$_2$**)	**16** (**T-OTg$_4$**)
F^-	280,000 ± 30,000	230,000 ± 20,000	150,000 ± 5000	200,000 ± 20,000
Cl^-	11,000,000 ± 2,000,000	5,100,000 ± 400,000	3,700,000 ± 700,000	2,900,000 ± 300,000
Br^-	7,500,000 ± 900,000	4,200,000 ± 300,000	1,900,000 ± 200,000	1,700,000 ± 200,000
I^-	17,000 ± 1000	19,000 ± 2000	5000 ± 200	4000 ± 400

This series of shape-persistent [3$_4$]triazolophanes was extended by Flood group to create analogues of **13** (i.e., **14-16**; Fig. 2) bearing various combinations of *t*-butyl and triethylene glycol (OTg) substituents on the phenylene linkers. Systems **14-16** were built up in a modular manner from simple building blocks.[3] The halide binding affinities were determined by means of UV-Vis titrations (*e.g.*, **14**, Scheme 7). The fixed size of the central cavity allowed for the selective recognition of the Cl^- and Br^- anions (as the TBA salts) and with high affinity (K_a>10^6 M^{-1} in CH_2Cl_2). These two anions were bound more tightly than the F^- and I^- anion by 1.5 and 3 orders of magnitude, respectively (Table 1). This selectivity was rationalized on the basis of size considerations. The binding affinity could be tuned by as much as 1 kcal/mol by replacing the *t*-butyl groups present in **13** by an increasing number of OTg groups. Compared to an open chain foldamer analogue, it was inferred that in this set of receptors preorganization played a central role in enhancing the anion binding affinity. On the other hand, each electron-donating group on the phenylene spacer served to reduce the anion binding affinity. Based on these results and others, the authors suggested the following order of CH H-bond donor strengths: triazole > N-linked phenylene > C-linked phenylene.



Scheme 8 Representations of the opposing dipoles that are thought to participate in the formation of **17**$_2$·X^-. Reproduced with permission of the American Chemical Society from ref. 25. Copyright 2008.

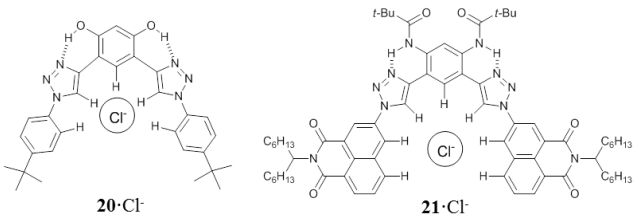
Later in 2008, triazolophanes that incorporate pyridyl subunits in place of phenylenes (i.e., macrocycles **17** and **18**; Fig. 2) were reported by the Flood group. These receptors showed a heightened propensity to form 2:1 sandwich complexes with halide anions.[25] Binding studies carried out in CH_2Cl_2 using TBA salts and technique (NMR and UV-Vis) methods served to confirm that the pyridyl units acted to destabilize the 1:1 triazolophane complexes; presumably, this reflects the presence of destabilizing N:···:X^- electron pair repulsions. Proton NMR spectroscopic analyses provided evidence for the presence of sandwich complexes wherein the macrocycles are oriented such that the dipoles on the pyridyls are directed inward and those of the triazoles are directed outward (*i.e.*, Scheme 8). The authors found that the OTg solubilizing groups on the phenylene system **17** favoured dimerization as compared to compound **18**. Modest cooperative effects (favouring formation of a 2:1 receptor:anion complex) were observed for the relatively smaller F^-, Cl^-, and Br^- halide anions. These effects were increased in the case of the I^- anion, for which high positive cooperativity and improved overall stability of the sandwich complex was observed.



Scheme 9 (a) Chemical structure of chiral aryl-triazole foldmer **19**. (b) Proposed cycle of photodriven binding and release of chloride anion by foldmer **19**. This proposed cycle is reproduced with permission of the American Chemical Society from ref. 26. Copyright 2010.

In 2010, a chiral aryl-triazole foldmer with two azobenzene end groups **19** (*i.e.*, Scheme 9a) was synthesized by the Flood group.[26] In this case, light could be used as a stimulus to trigger the wavelength-dependent release and then reuptake of chloride ions from non-aqueous solutions. The authors also found that the predominantly *trans* forms were more preorganized and stable than the *cis* forms; they also proved more suited for chloride anion binding, as inferred from molecular modelling studies and titration experiments. These latter experiments revealed a ~10-fold reduction from a K_a = 3000 M^{-1} upon *trans*-to-*cis* isomerization in CH_3CN (*i.e.*, Scheme 9b). The relative order in the chloride affinities was as predicted, namely: **19**$_{trans\text{-}trans}$ > **19**$_{cis\text{-}trans}$ > **19**$_{cis\text{-}cis}$. Control of chloride levels using UV light was found to be effective in switching the conductivity of an electrolyte solution from high to low levels. In the absence

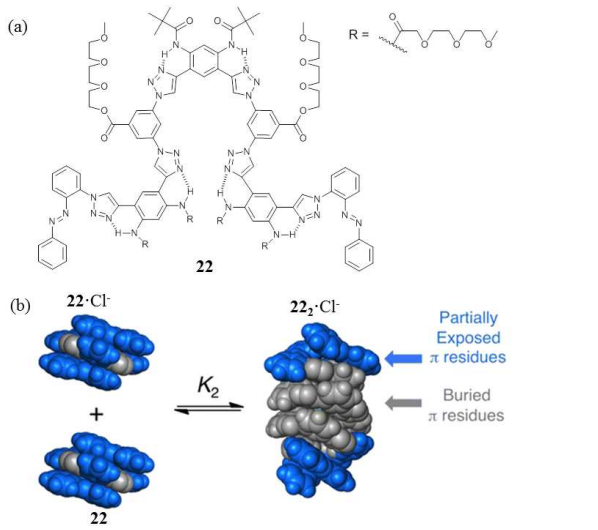
of receptor **19**, the conductivity of a test salt solution was found to be 158 μS cm^{-1}. Upon addition of $\mathbf{19}_{trans\text{-}trans}$, the conductivity decreased to 128 μS cm^{-1}. Irradiating the sample with UV light produced an enhancement in the conductivity to 135 μS cm^{-1}, an effect ascribed to the increase in the free chloride concentration as this anion was released from the lower affinity *cis*-dominated receptor forms. Irradiation with visible light lowered the conductivity (130 μS cm^{-1}) reflecting recapture of the free chloride anion by the *trans*-dominated form of the receptors.



20·Cl⁻ **21**·Cl⁻

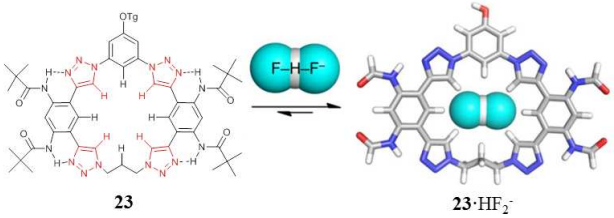
Fig. 3 CH···chloride ion interactions stabilised by the aryl-triazole pentad and naphthalimide aryl-triazole receptors **20** and **21**, respectively.

In 2010, the Flood group also reported an aryl-triazole pentad **20** (Fig. 3), which was preorganised as the result of intramolecular hydrogen bonds between the hydroxyl groups and N^3 of the triazole subunit.[27] This receptor displayed the dual hydrogen bond donor and acceptor properties expected for systems containing 1,2,3-triazoles. It was found to bind chloride anions with a K_a of 46800 ± 2500 M^{-1} in CH_2Cl_2. A related motif, receptor **21** (Fig. 3), was reported by the same group in 2011. In this case, strong Cl^- binding in CH_2Cl_2 was also observed. This strong binding was ascribed to a combination of 1) receptor preorganization from the apparent intramolecular amido NH···N^3 triazole H-bonds and 2) the presence of two polarized naphthalimide CH donors that contribute to anion stabilization.[28] DFT calculations were used to analyse the 1,8-naphthalimide present in this system. It was concluded that the parallel alignment of the CH donors in a urea-like array led to anion stabilization that surpassed that of 1,2,3-triazole alone.



Scheme 10 (a) Chemical structure of aryl-triazole foldamer **22**; (b) molecular models of chloride anion complex of foldamer **22** showing the buried π surfaces present in what are effectively single and double helices. Space-filling models of the foldameric species involved in the binding equilibrium K_2 using colour to distinguish the residues that are partially solvent exposed (blue) from the ones that are effectively buried (grey). The molecular models are reproduced with permission of the American Chemical Society from ref. 29. Copyright 2013.

In an effort to create a system capable of extracting the chloride anion from aqueous milieus, Flood and coworkers created an aryl-triazole foldamer **22** (*i.e.*, Scheme 10a). In this system, reported in 2013, hydrophobic interactions were considered responsible for organizing and stabilizing the artificial receptor in mixed organic-aqueous solutions.[29] The formation of a strongly bound 2:1 Cl^--bound double helix-like complex was observed in 25% water-acetonitrile v/v (log β_2 = 12.6). Anion binding remained strong (log β_2 = 13.0) as the water content was increased to 50%. This stoichiometry and the stability of the 2:1 complex was rationalised in terms of a double helix arrangement allowing ~80% of the π surfaces to be buried in an hydrophobic environment, as compared to the putative alternative single helix, in which only ~50% of the π surfaces would be buried (Scheme 10b). This conformational arrangement was thought to create a solvent-excluding microenvironment capable of stabilising strong CH···Cl^- hydrogen bonds. On this basis, the authors concluded that hydrophobic collapse served to offset the penalty of dehydrating the Cl^- anion.



Scheme 11 Chemical structure of macrocycle **23** produced through computer-aided design and representation of the complex **23**·HF_2^- as optimized at the M06-

2X/6-31+G(d,p) level; the view shown is designed to show the preferred bifluoride orientation. The structure of the complex **23**·HF_2^- is reproduced with permission of the American Chemical Society from ref. 30. Copyright 2014.

In 2014, the Flood group used computer-aided molecular design to facilitate the creation of a new anion receptor **23** (Scheme 11) capable of complexing the bifluoride anion with high affinity.[30] Anion binding is abetted by CH hydrogen bond interactions provided by both the 1,2,3-triazole and phenylene subunits. Compared to the parent triazolophane **14** in which the bifluoride anion is tilted, the more flexible receptor system **23** allows the bifluoride anion to be bound in a non-tilted binding mode (Scheme 11). This geometric arrangement was thought to account in part for a bifluoride anion affinity equal to that seen for the chloride anion in both the gas phase and in solution (CH_2Cl_2).

Over the last several years a number of other groups have contributed to the development of the triazole subunit as a useful motif in anion recognition chemistry. For instance, in 2008, the Craig group demonstrated that oligomer **24** (Fig. 4) would fold to provide a cavity that would stabilize intermolecular interactions between the electropositive CH 1,2,3-triazole sites and electron-rich guests, including anions.[31] Chloride-induced folding was confirmed *via* 2D NOESY experiments in acetone-d_6, as well as through molecular modelling studies.

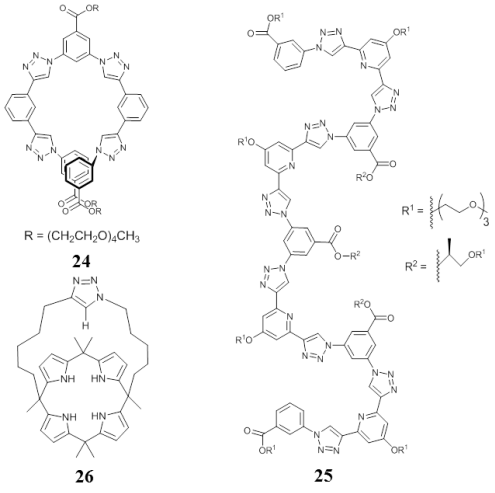
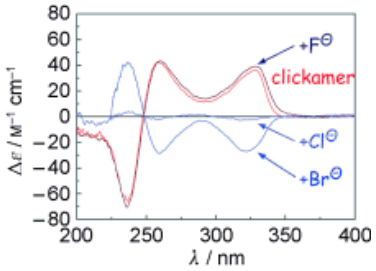


Fig. 4 Chemical structures of the 1,4-diaryl-1,2,3-triazole oligomer **24**, "clickamer" **25**, and triazole-strapped calix[4]pyrrole **26**.



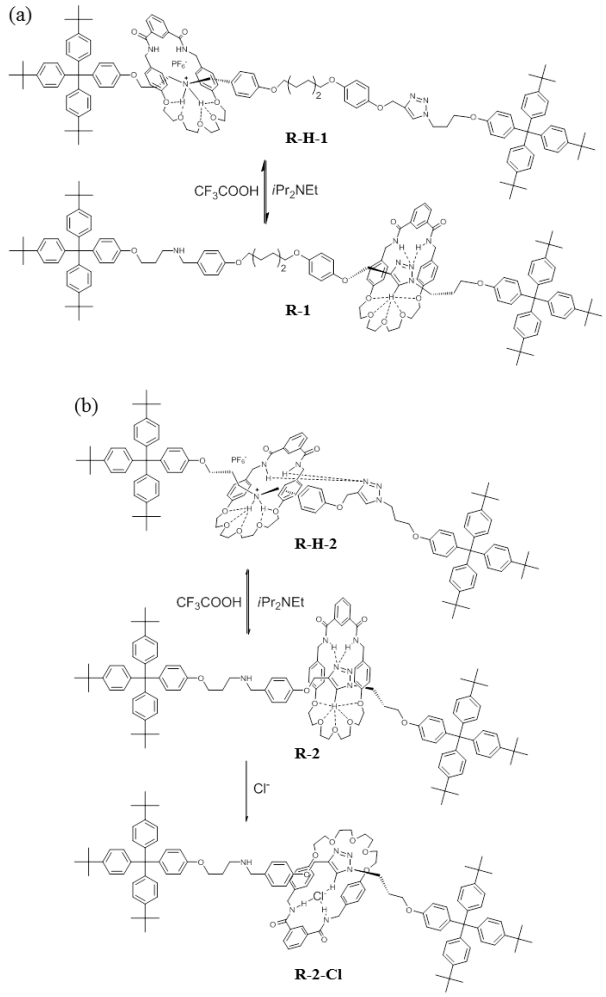
Scheme 12 Optical response of "clickamer" **25** (8×10^{-6} M, 75 vol% water in acetonitrile, 25 ℃) to various halide ions: KF, KCl and KBr (all at neutral pH). Reproduced with permission of Wiley from ref. 32. Copyright 2008.

Likewise in 2008, the Hecht group reported a novel family of responsive foldamers **25** (Fig. 4) and detailed their folding behaviour under a variety of conditions.[32] Of particular note is that these systems, termed "clickamers", were found to undergo an unprecedented helix inversion when exposed to inherently achiral halide ions (KF, KCl, KBr) in a water/acetonitrile mixture at neutral pH. The size of the halide anion played an important role in defining the interaction with the helix. For instance, the addition of fluoride ions to oligomer **25**, led to a slight increase in the intensity of the circular dichroism (CD) spectrum as compared to the anion-free spectrum. Conversely, exposure to chloride ions caused an inverted signature and a reduction in the CD intensity. Finally, the addition of bromide ions gave rise to an increase in the CD spectral intensity but also produced an inverted spectrum (Scheme 12).

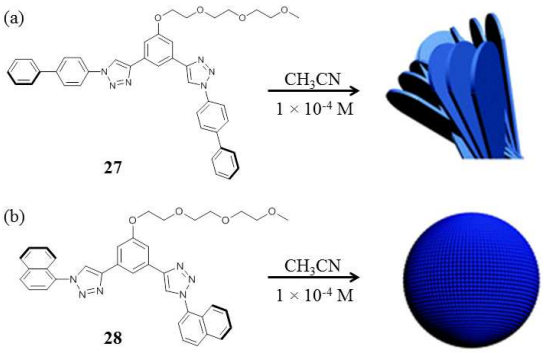
"Click" chemistry was used to introduce a triazole strap into a calix[4]pyrrole by Gale and coworkers giving rise to a hybrid pyrrole–triazole anion receptor **26** (Fig. 4).[33] When studied in acetonitrile solution using TBACl as the chloride anion source, the enthalpy of chloride binding to receptor **26** proved substantially more negative than what was seen for unfunctionalized calix[4]pyrrole under identical conditions. This is as would be expected given the participation of an extra triazole–derived CH···chloride hydrogen bond. Gale and coworkers also found that the strapped calix[4]pyrrole **26** functioned as a chloride transporter in synthetic POPC and POPC–cholesterol vesicles. Depending on the choice of counter cation employed, evidence for two limiting transport mechanisms was observed, namely ion-pair co-transport and chloride-nitrate antiport. In contrast, the parent calix[4]pyrrole acted only as a caesium cation-chloride anion co-transporter.

In 2009, the Li group reported two novel multilevel switchable [2]rotaxanes **R-1** and **R-2**. These systems, containing an ammonium and a triazole "station", were constructed *via* a CuI-catalyzed azide–alkyne cycloaddition (i.e., "click" reaction).[34] In the case of [2]rotaxane **R-1**, which contains a C6-chain bridge between the two hydrogen bonding stations, high selectivity for the ammonium cation station was observed when the system was protonated *via* the addition of trifluoracetic acid in acetonitrile (Scheme 13a). The encircling macrocycle was

able to interact with both recognition stations when the bridge between them was shortened, as in the case of system **R-2** (Scheme 13b). Upon deprotonation by addition of an organic base, both [2]rotaxanes **R-1** and **R-2**, were found to favour an arrangement wherein the macrocycle was bound to the triazole recognition site. This latter preference was ascribed to the presence of hydrogen bond interactions between the triazole nitrogen atoms and the amide groups present in the macrocycle. Upon the addition of chloride anion (in the form of its TBA salt), [2]rotaxane **R-2** was found to undergo a conformational change ascribed to the cooperative recognition of the chloride anion stabilized by favourable hydrogen-bond interactions derived from both the macrocycle isophthalamide amide and thread-centred triazole CH protons (Scheme 13b).

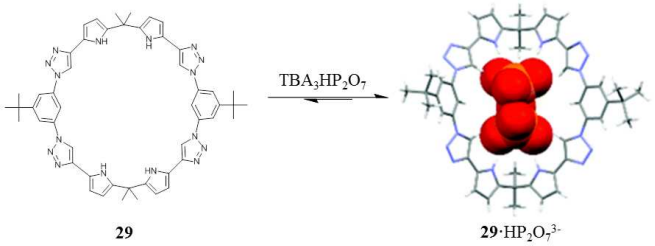


Scheme 13 Different binding modes observed for the [2]rotaxanes **R-1** and **R-2** in acetonitrile as observed in the presence of various added chemical stimuli. The chloride anion was added in the form of its TBA salt.



Scheme 14 Chemical structures of the biphenyl triazole naphthalene triazole receptors **27** and **28**; and schematic illustration of the supramolecular structures formed as the result of their self-assembly in polar acetonitrile. Flat lamellae are formed from **27** (a) and spheres are formed from **28**. The self-assembly structures are reproduced with permission of The Royal Society of Chemistry from ref. 35. Copyright 2011.

Sánchez and coworkers examined the geometry of compound **27** decorated with lateral biphenyl moieties.[35] As demonstrated by X-ray structural studies, this system proved highly planar with a syn conformation for the 1,2,3-triazole rings. It was also seen to self-assemble into flat lamellae in acetonitrile (*i.e.*, Scheme 14a). In contrast, compound **28**, produced by the same group, contains lateral naphthalene units that are considered responsible for a more distorted geometry that finally results in the formation of spherical objects upon self-assembly in acetonitrile (*i.e.*, Scheme 14b). The addition of a bromide anion to these two receptors in chloroform induced formation of an H-bond stabilized anion-bound array wherein a U-like conformation of the receptors is seen. This change in conformation is ascribed to the presence of slightly polarized aromatic CH and triazole CH hydrogen bonds with the anion.



Scheme 15 Chemical structure of pyrrolyl-based triazolophane **29** and single-crystal X-ray structure of its pyrophosphate anion complex **29**·$HP_2O_7^{3-}$.

In 2010, a pyrrolyl-based triazolophane **29** (Scheme 15), incorporating CH and NH donor groups, was reported by the Sessler group.[36] In the solid state, the authors found that this receptor bound the pyrophosphate anion in a clip-like fashion *via* a combination of NH and CH hydrogen bonds (Scheme 15). Standard UV-Vis spectroscopic titrations provided support for the pyrophosphate anion being bound to receptor **29** strongly in chloroform at 300 K ($K_a = (2.30 \pm 0.40) \times 10^6$ M^{-1}) and with a 1:1 binding stoichiometry. The receptor showed selectivity for

the pyrophosphate trianion, followed by $HSO_4^- > H_2PO_4^- > Cl^- > Br^-$. When the authors titrated a solution of receptor **29** with up to 10 equiv. of $TBA_3HP_2O_7$, they found that the signals for the pyrrole NH, the triazole CH, and the endocyclic hydrogen atom of the N^1-linked phenyl unit in the ^1H NMR spectrum shifted downfield by 5.09, 1.96, and 1.22 ppm, respectively. The trends observed in the NMR spectral studies were thus consistent with the intrinsic strength of the various H-bond donor groups as inferred from electronic structure calculations, namely pyrrole NH > triazole CH > benzene CH.

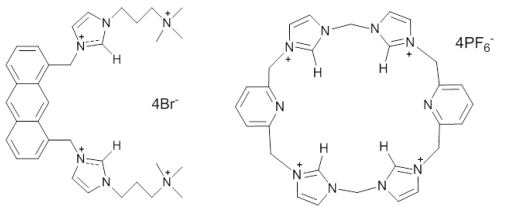
Cationic CH hydrogen bond donor motifs

Traditionally, positively charged motifs used for anion recognition have been nitrogen-based (e.g., ammonium, protonated pyrrole, and guanidinium). As a general rule, these groups interact strongly with anions in aprotic media as the result of both $(NH)^+\cdots A^-$ hydrogen bonds and electrostatic interactions. In recent years, several cationic subunits for anion recognition have been introduced. Among the most prevalent of these are the 1,3-disubstituted imidazolium and 1,4-disubstituted 1,2,3-triazolium cations. Receptors based on the imidazolium and triazolium cations stabilize the corresponding anion complexes *via* a combination of electrostatic interactions and $(CH)^+\cdots A^-$ hydrogen bonds. Imidazolium and triazolium–based receptors offer a significant advantage, namely the possibility of pH-independent binding, compared to most systems based on cationic NH-based hydrogen bond donors.

Imidazolium

In 2004, Yoon, Kim, and coworkers reported a new water-soluble imidazolium anthracene derivative **30** (Fig. 5).[37] This system was not only capable of differentiating between the structurally similar compounds GTP and ATP, it also acted as a fluorescent chemosensor for GTP in aqueous media (pH = 7.4, 10 mM HEPES). Evidence for strong $(CH)^+\cdots A^-$ hydrogen bonding interactions were noted in the case of this receptor.

On the basis of fluorescent titration experiments, receptor **30** was considered to benefit from a chelation-enhanced fluorescence (CHEF) effect in the case of ATP, with relatively smaller CHEF effects being seen for ADP and AMP. On the other hand, the sensing of GTP achieved by **30** was ascribed to a chelation-enhanced fluorescence quenching (CHEQ) effect that was coupled with a slight red-shift in the emission. It was proposed that the guanine base in GTP acts as a fluorescence quencher. Essentially no fluorescent changes were observed when 300 equiv. of pyrophosphate, $H_2PO_4^-$, F^-, or Cl^- (as their TBA salts) were added to host **30** at pH 7.4 in 50 mM HEPES. From the fluorescent titrations, association constants of 87000, 15000, 610, and 120 M^{-1} (errors <10%) corresponding to the interaction of **30** with GTP, ATP, ADP and AMP, respectively, were calculated. In all cases, the formation of 1:1 complexes was inferred from Job-plot analyses. On this basis it was concluded that the selectivity of host **30** for GTP is about 6 times that for ATP, and over 100 times that for ADP and AMP.

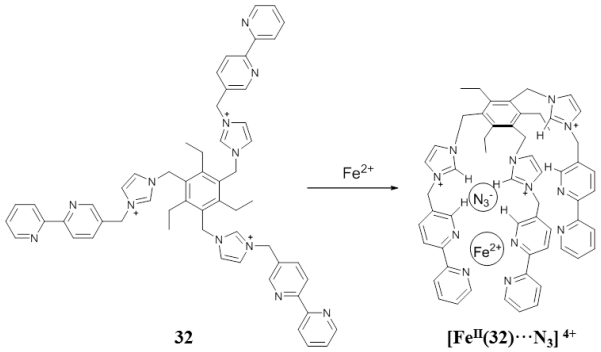


30 **31**

Fig. 5 Chemical structures of the imidazolium anthracene host **30** and calix[4]imidazolium[2]pyridine **31**.

In 2005, Kim cooperated with Hwang and others to synthesize the calix[4]imidazolium[2]pyridine **31** (Fig. 5).[38] This system contains an array of positively charged units and proved to be an effective receptor for the F^- anion (studied as its TBA salt in DMSO-d_6). A single crystal structural analysis of the fluoride anion complex revealed that in the solid state macrocycle **31** adopts a chair-like conformation with all four imidazolium $(CH)^+$ groups pointing towards the centre of the macrocyclic ring. Strong $(CH)^+\cdots F^-$ interactions serve to anchor the fluoride anion within the resulting cavity.

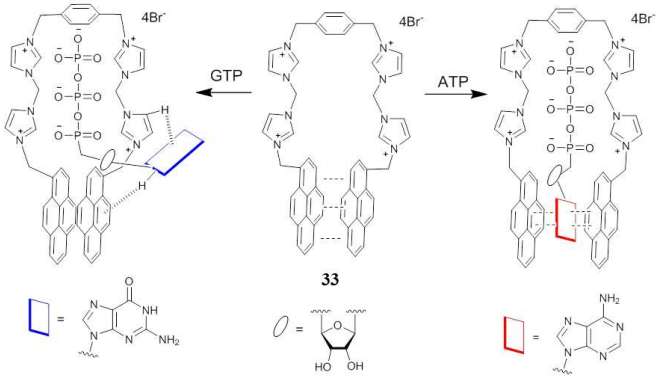
The interactions of receptor **31** with various TBA anion salts were quantified by means of ^1H NMR spectroscopic titrations. These studies, carried out in dry DMSO-d_6, involved monitoring the changes in the chemical shift of the $(CH)^+$ imidazolium proton as a function of added salt. The addition of an equimolar amount of TBAF induced a large downfield chemical shift ($\Delta\delta$ = 1.77 ppm) in this resonance. The further addition of TBAF caused no other significant changes in the chemical shift. Job-plot analysis provided support for the proposed 1:1 binding stoichiometry. The resulting binding constant, calculated using the HOSTEST program, was found to be $K_1 = 28900\ M^{-1}$. This value proved to be 10 times higher than for the corresponding Cl^- salt and over 100 times higher than the corresponding values for the Br^- and I^- TBA salts, which were analysed in the same way.



32 $[Fe^{II}(32)\cdots N_3]^{4+}$

Scheme 16 Chemical structure of the trisimidazolium tripod **32**. Also shown is the capping of this system with a $\{Fe^{II}(bpy)_3\}^{2+}$ subunit to produce a receptor effective for N_3^- anion recognition. This latter interaction is shown schematically.

In 2006, Fabbrizzi and coworkers reported a trisimidazolium based tripodal host **32**. This nitrogen-rich framework could be capped with a $\{Fe^{II}(bpy)_3\}^{2+}$ subunit to produce a receptor that could bind small anions (bpy = 2,2'-bipyridine) (Scheme 16).[39] Rod-like "pseudohalides" (i.e., N_3^-, NCO^-, and NCS^-) and spherical halide (Cl^-, Br^-, and I^-) anions were found to interact with the metal cation-containing cage *via* hydrogen bond interactions involving all six of the available CH donor groups (three imidazolium CH and three pyridyl CH groups). As judged from analyses carried out in CH_3CN-H_2O (4:1, v/v), the N_3^- ion (studied as its sodium salt) formed the most stable inclusion complex ($K = 5.0 \times 10^5$ M^{-1}), proving rough 80 times more stable than the corresponding Cl^- anion complex ($K = 6.3 \times 10^3$ M^{-1}).

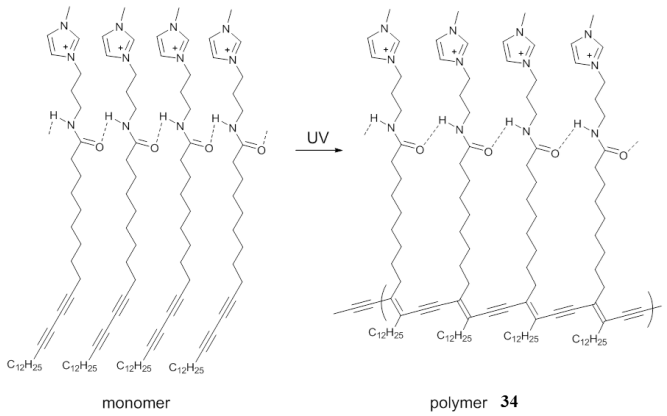


Scheme 17 Proposed binding mode for the ATP and GTP complexes of the pincer-like, benzene-bridged sensor **33**.

In 2009, a new water soluble, fluorescent imidazolium receptor, **33**, was reported by the Yoon and Kim groups. This system proved capable of selectively recognising the biologically important triphosphate, ATP, over other structurally similar nucleoside triphosphates in aqueous media (20 mM HEPES, pH 7.4) at pH 7.4.[40] The observed discrimination in favour of ATP was rationalised in terms of stabilising ionic hydrogen bonds between the imidazolium $(CH)^+$ subunits and the triphosphate group, as well as π-π donor-acceptor interactions involving the pyrene subunit of the receptor and the bound adenine base.

Receptor **33** displayed two distinct and well-known fluorescent spectral features characteristic of pyrene moieties. Specifically a peak at 375 nm was seen that could be attributed to the emission of a pyrene monomer, as well as a peak at 487 nm ascribable to excimer formation. Quenching of the excimer features was seen upon the addition of nucleoside triphosphates in aqueous media. The extent of quenching was found to follow the following order: ATP ≈ GTP > TTP ≈ UTP > CTP. On the other hand, only ATP induced a large enhancement in the intensity of the monomeric emission feature (λ = 375 nm). By monitoring the ratio between the monomeric and emission features, ATP could be distinguished from other structurally similar nucleoside triphosphates. The association constant for ATP was calculated to be 1.03×10^4 M^{-1} (error < 15%) in 20 mM HEPES. The authors also found that monitoring the fluorescent intensity ratio for ATP (I_{375} / I_{487}) allowed for the selective sensing of ATP in the presence of ADP and AMP.

On the basis of fluorescence measurements, NMR experiments, and theoretical calculations, the authors proposed that guanine, cytosine, thymine, and uracil interact with a stacked pyrene-pyrene dimer, a binding mode that serves to quench the excimer fluorescence. On the other hand, adenine could intercalate between the two pyrene moieties (Scheme 17). The resulting separation between the pyrene moieties would give rise to an enhancement in the pyrene monomer fluorescence, as seen by experiment.

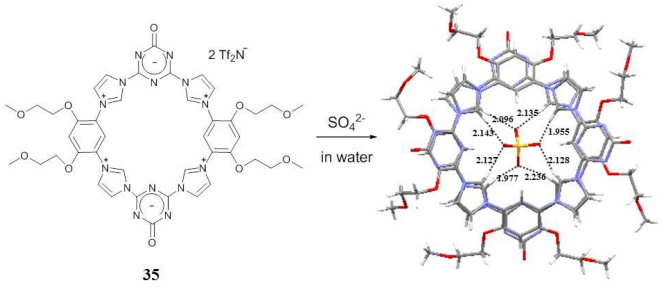


Scheme 18 Self-assembly and polymerization of a diacetylene-containing monomer that leads to formation of the imidazolium-based polydiacetylene polymer **34** under conditions of UV illumination.

In 2010, the Yoon and Lee groups reported the synthesis of an imidazolium-based polydiacetylene (PDA) **34**.[41] This polymer was found to adopt a thin-film structure and act as an effective and reversible colorimetric sensor in aqueous media (20 mM HEPES, pH 7.4). In particular, unique colour changes were seen in the presence of a variety of anionic surfactants. Associated changes in the fluorescence features were also observed. Polymer **34** was obtained by subjecting a highly ordered suspension of the corresponding self-assembled monomers to UV irradiation for 30 seconds (Scheme 18). As obtained in this way, the PDA polymer **34** was deep-blue. However, toggling between limiting blue and red forms could be achieved reversibly by heating between 25 and 50°C. Presumably, these colour changes reflect changes in head group interactions. The colorimetric response of polymer **34** to both surfactants and simple anion salts was also examined at room temperature. While the anionic surfactants (sodium dodecyl sulphate (SDS), sodium dodecyl carboxylate (SDC), sodium

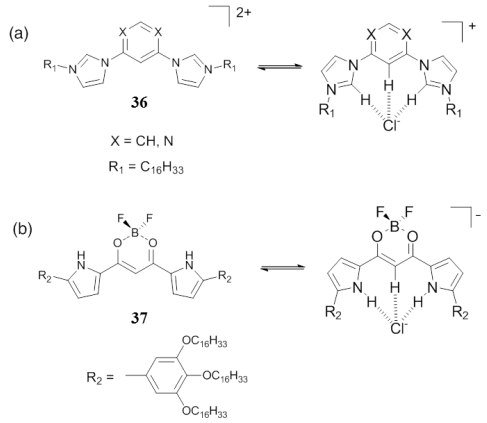
dodecyl phosphate (SDP), and sodium dodecylbenzene sulfonic acid (SDBS)) induced colour changes, no changes were observed in the presence of other anionic species, including F^-, Cl^-, Br^-, and I^- (studied as their sodium salts), or in the presence of neutral (Triton X-100) or cationic surfactants (e.g., cetyltrimethylammonium chloride (CTAC)). The four anionic surfactants tested produced different colour changes: SDS induced a blue-to-yellow transition, SDC and SDP induced a blue-to-orange transition, and SDBS produced a blue-to-red transition.

The authors provided a mechanistic rational for the observed colorimetric changes. Specifically, it was suggested that the strong imidazolium $(CH)^+\cdots I^-$ ionic hydrogen bonding interactions that are an inherent feature of polymer **34** were disrupted when anionic surfactants were added. This scission acts to release the strain energy imposed on the alkyl side chains generated during polymerization. Thius, in turn, was thought to lead to changes in the orientation of, and interactions between, the individual p orbitals that comprise the conjugated framework. The net result is a change in the overall colour.



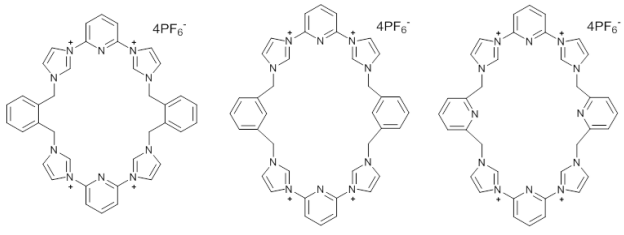
Scheme 19 Tetrakisimidazolium macrocycle **35** and its structure of the 2:1 complex formed in the presence of the sodium sulphate in $CH_3CN/CH_3OH/H_2O$ (1:1:4, v/v/v), as inferred from a solid state single crystal X-ray diffraction analysis.

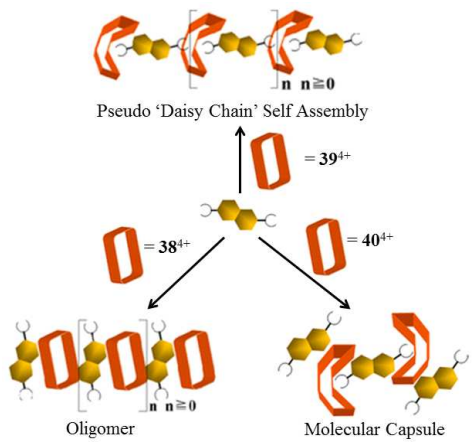
In 2013, the rigid tetrakisimidazolium macrocycle **35** was examined by the You and Gao groups.[42] This system was found to bind the highly hydrophilic sulphate dianion as a 2:1 complex in water. On the basis of a fluorescence titration study in 10 mM HEPES at pH 7.4 using sodium sulphate as the anion resource, an association constant of 8.6×10^9 M^{-2} was calculated. A single crystal X-ray diffraction analysis revealed that in the solid state the sulphate dianion is encapsulated within a pseudo-hexahedral cavity created by the sandwich-like arrangement of two orthogonally packed macrocycles. The presence of eight hydrogen bonds between the C2 hydrogen atoms of the imidazolium units and the oxygen atoms of the sulphate anion were inferred from the structural parameters (Scheme 19). The presence of π–π donor acceptor interactions between the phenyl and the triazinonide rings, as well as a variety of charge-assisted hydrogen bonds between the peripheral chains and the rigid backbones of the macrocyclic rings, presumably contribute to the overall stability of the structure. It was suggested by the authors that the flexible peripheral chains serve to protect the bound sulphate anion from potentially competitive interactions with solvents, such as water.



Scheme 20 Chemical structures of (a) the positively charged anion receptor **36** and (b) the electronically neutral anion receptor **37**. Also shown are schematic representations of their proposed Cl^--binding modes.

In 2013, Maeda, Seki, and coworkers reported a set of phenylene- and pyrimidine-bridged bis(imidazolium) dicationic anion receptors of general structure **36** and noted that these systems form monocationic receptor−Cl^- complexes.[43] Under conditions of the experiment, a free chloride anion is present as the result of charge balance considerations. It was also found by this same group that the pyrrole-based neutral anion receptors, such as **37**, could capture the free Cl^- anion to form a negatively charged receptor−Cl^- complex (Scheme 20). The ion pair of the resulting positively and negatively charged planar receptor−Cl^- complexes could produce a supramolecular gel in octane, adopting a lamellar self-organized structure in its xerogel state.





Scheme 21 (a) Chemical structures of the tetraimidazolium macrocycles **38-40**; (b) Schematic representation of the binding modes between hosts **38-40** and the 2,6-naphthalenedicarboxylate dianion. The exact binding mode was found to depend on the specific choice of receptor. The structures of the binding modes are reproduced with permission of the American Chemical Society from ref. 44. Copyright 2013.

Later in 2013, it was reported that the macrocyclic tetraimidazolium receptors **38-40** (*i.e.*, Scheme 21a), developed by Sessler, Gong and coworkers, could be exploited to complex the 2,6-naphthalenedicarboxylate dianion in DMSO. It was suggested that the resulting complex was stabilized by a combination of CH···anion hydrogen-bonding, anion–π, and π–π donor–acceptor interactions.[44] Depending on the specific choice of receptor, a diversity of structures containing the 2,6-naphthalenedicarboxylate dianion were obtained. For instance, with **38** an oligomer was found. In contrast, a pseudo 'daisy chain' was found with **39**, while a molecular capsule was stabilized with **40** (Scheme 21b). This diversity was rationalised in terms of these congeneric systems being inherently flexible, with the nature of the species formed thus being highly dependent on the choice of the bridging group present in the receptor.

Triazolium

1,4-Disubstituted 1,2,3-triazolium rings are attractive as anion recognition motifs due to their potential ease of synthesis and the fact that they can stabilize in principle what are expected to be strong $(CH)^+$…anion hydrogen bonds. However, in contrast to neural triazoles, relatively little work has been devoted to the use of this subunit for the purpose of anion binding. In 2008, Kumar and Pandey synthesized several bile acid-based cyclic and acyclic 1,2,3-triazolium systems (*e.g.*, **41a,b** and **42**; shown as its $H_2PO_4^-$ complex) using the "click" reaction between an appropriately chosen azide and an alkyne (Fig. 6).[45] As a general rule, high selectivity for the $H_2PO_4^-$ ion with respect to either various halide anions or the acetate anion was observed.

The anion binding properties of receptors **41a**, **41b** and **42** were studied by monitoring the ^{1}H NMR spectral changes caused by the addition of TBA salts of various test anions to a $CDCl_3$ solution containing the receptor in question. Significant downfield shifts were observed for the C(5)–H proton of each triazolium moiety. This is as would be expected were the triazolium C(5)–protons forming $(CH)^+$···anion hydrogen bonds. Significant downfield shifts were also observed for the bridging methylene protons, leading to the suggestion that they also interact with the bound anions. On the basis of these titrations, it was concluded that the acyclic receptor **42** displays a much higher affinity (K_a = 1920 M^{-1}) and selectivity toward the $H_2PO_4^-$ ion than do the cyclic receptors **41a** and **41b**. The selectivity trend proved to be $H_2PO_4^- > Cl^- > F^- > Br^- > I^- > CH_3CO_2^-$. The higher affinity of receptor **42** for $H_2PO_4^-$ ion was attributed to the greater flexibility of this acyclic system, which allows it to adapt a geometry suitable for binding the tetrahedral $H_2PO_4^-$ anion.

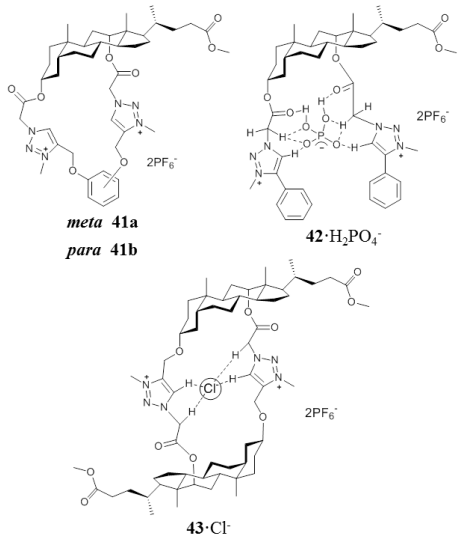
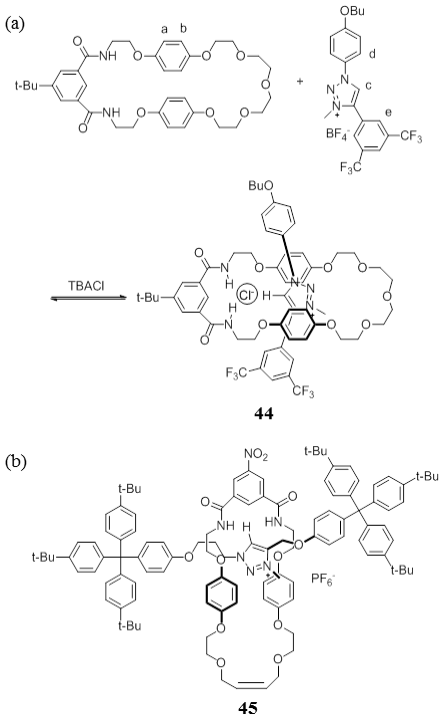


Fig. 6 Chemical structures of cyclic bile acid-based 1,2,3-triazolium receptors **41a** and **41b**, acyclic 1,2,3-triazolium receptor **42**, bile acid-based "click macrocycle" **43**; and the proposed $(CH)^+$···anion interactions present in the dihydrogen phosphate and chloride anion complexes of **42** and **43**, respectively.

Later, the Pandey group reported a bile acid-based macrocycle **43** (Fig. 6) that was likewise prepared using click chemistry.[46] This 1,2,3-triazolium derivative of macrocycle **43** was found to be highly selective for the chloride anion. In $CDCl_3$ solution using the TBA salt, the binding constant, K_a, was calculated to be 3700 M^{-1} as deduced from ^{1}H NMR spectroscopic titrations. In this solvent and using the same counter cation, the observed binding trend was $Cl^- > HSO_4^- > H_2PO_4^- > F^- > Br^- > CH_3COO^- > I^-$.

In 2009, the Beer group reported that the versatile triazole forming click reaction could be used not only as a covalent linker in the preparation of interlocked architectures, but could be further transformed into a new class of potent triazolium anion receptors by alkylation.[47] In the presence of chloride and bromide templating anions, the triazolium motif formed

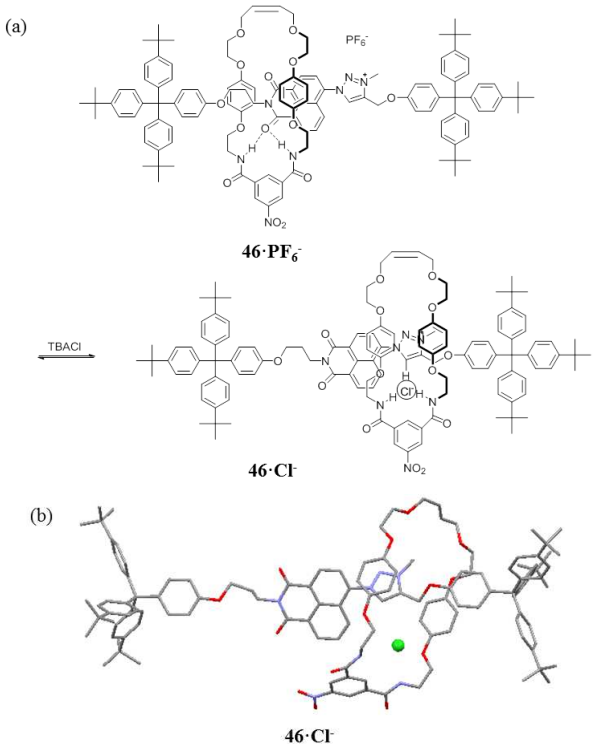
pseudorotaxanes with a neutral isophthalamide macrocycle. This chemistry was used to prepare what at the time was considered to be the first triazolium-based [2]rotaxane **44** (Scheme 22a). The authors also studied in preliminary fashion the anion binding features of the rotaxane host system **45** (Scheme 22b), studies that revealed a rare selectivity preference for the bromide anion over the chloride anion. The larger bromide anion also proved to be a more efficient templating agent for the initial rotaxane synthesis.



Scheme 22 (a) Anion-templated pseudorotaxane **44** formed from a isophthalamide macrocyle and a triazolium thread; (b) chemical structure of the triazolium [2]rotaxane **45**.

A ROESY NMR spectroscopic study of a 1:1:1 mixture of isophthalamide macrocycle, triazolium thread, and TBACl was conducted in acetone-d_6 to provide evidence for the formation of the pseudorotaxane **44**. Evidence for through-space interactions between the hydroquinone protons a,b and the triazolium CH proton c, and the aromatic protons d,e was obtained detected, leading the authors to suggest that the triazolium thread interpenetrated through the annulus of the macrocycle in the presence of the chloride anion (Scheme 22a). Similar perturbations of chemical shifts were detected when TBABr was added to an equimolar mixture of the triazolium thread and the isophthalamide macrocycle in acetone-d_6. This was taken as an indication that pseudorotaxane formation was possible using Br^- as a template.

The Beer group also attempted to synthesize the first triazolium rotaxane **45** by means of a Grubbs' catalyst-mediated ring-closing metathesis (RCM) linking of a bis-vinyl appended acyclic precursor around a stoppered triazolium axle in the presence of a chloride anion template. Preliminary chloride and bromide anion titration experiments with rotaxane **45** were undertaken in 1:1 CD_3Cl/CD_3OD. In this relatively competititve solvent mixture, this rotaxane was found to bind the bromide anion (K_a = 970 M^{-1}; TBA salt) approximately an order of magnitude more strongly than chloride (K_a = 90 M^{-1}).

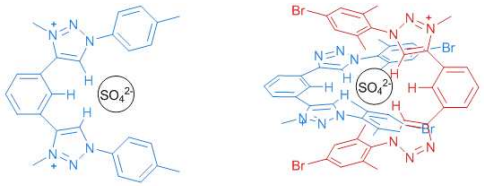


Scheme 23 (a) Anion-induced molecular shuttling exhibited by rotaxane **46·PF_6^-**; and (b) single crystal X-ray structure of rotaxane **46·Cl^-**

The Beer group has made a number of seminal contributions to anion-based mechanically bonded systems. Recently, they reported a receptor system **46·PF_6^-** (*i.e.*, Scheme 23a) that incorporates a naphthalimide triazolium motif. This receptor produces a chloride-anion bound rotaxane **46·Cl^-** as the result of unidirectional, anion-induced shuttling in chloroform (Scheme 23a). Support for the proposed processes came from ^{1}H NMR and UV/Vis spectroscopic analyses.[48]

In this case, a dual stimulus-induced response was observed, with both the nature of the anion and the solvent serving to modulate the properties of the system. Complete macrocycle translocation only occurred upon the recognition of the strongly bound smaller halide anions (chloride and bromide). It was proposed that anion complexation and a conformational change to a structure suitable only for certain guests was responsible for this selectivity.

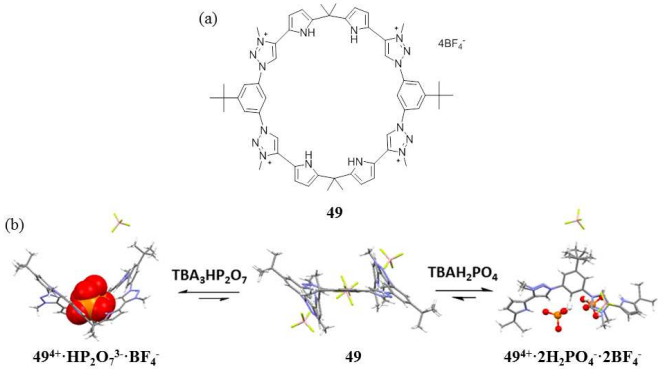
A solid-state crystal structure of the rotaxane **46·Cl**$^-$ provided further support the proposed solution-phase conformational changes (Scheme 23b). The chloride-induced shuttling behaviour of the rotaxane was demonstrated to be reversible upon addition of silver hexafluorophosphate, which served to induce precipitation of AgCl, thus restoring the original form of the receptor.



47·SO$_4^{2-}$ **48$_2$·SO$_4^{2-}$**

Scheme 24 Schematic representations of the proposed (CH)$^+$···SO$_4^{2-}$ interactions present in the mono-tridentate complex **47·SO$_4^{2-}$** and bis-tridentate complex **48$_2$·SO$_4^{2-}$**.

Schubert and coworkers have exploited click syntheses to create systems containing triazole and triazolium moieties, such as the tridentate receptors **47** and **48** (Scheme 24).[49] As so-called electronically inverted ligands, the triazolium motifs were able to complex the sulphate anion *via* a combination of hydrogen bonding and electrostatic interactions. The formation of mono- **47·SO$_4^{2-}$** or bis-tridentate **48$_2$·SO$_4^{2-}$** complexes (Scheme 24) in the presence of TBA sulphate in acetone-d_6/methanol 4:1 and acetone-d_6 solvents, respectively, could be achieved by controlling the degree of triazole methylation. The nature of the complexes was inferred from NMR spectroscopic analyses, as well as supporting computational studies.



Scheme 25 (a) Chemical structure of the pyrrole-based triazolium-phane **49**; (b) single crystal X-ray structures of compound **49**, complex **49^{4+}·HP$_2$O$_7^{3-}$·BF$_4^-$**, and complex **49^{4+}·2H$_2$PO$_4^-$·2BF$_4^-$**.

In 2013, the Sessler group reported the pyrrole-based triazolium-phane **49** (Scheme 25a). This system was prepared *via* the tetraalkylation of a macrocycle originally prepared *via* click chemistry.[50] It displayed a high selectivity for tetrahedral oxyanions relative to various test monoanions and trigonal planar anions in mixed polar organic–aqueous solvent media (e.g., acetone/H_2O 2:3). This selectivity was solvent dependent and was less pronounced in acetonitrile. Single crystal X-ray diffraction analyses of the mixed salts **49**, **49^{4+}·HP$_2$O$_7^{3-}$·BF$_4^-$**, and **49^{4+}·2H$_2$PO$_4^-$·2BF$_4^-$** provided support for the notion that receptor **49** could bind the pyrophosphate and phosphate anions in the solid state (Scheme 25b). Detailed solution phase studies, carried out in polar media, were consistent with this conclusion.

The fact that the motifs in question were contained within a relatively flexible macrocyclic framework in the case of **49** allowed for a direct comparison of the relative importance of NH–, CH–, and (CH)$^+$–anion interactions. Theoretical calculations were carried out in with the chloride anion in an effort to understand the influence of solvent on the intrinsic hydrogen bonding ability of the donor groups (pyrrole N–H, benzene C–H and triazolium C–H). The host–guest interactions between receptor **49** and representative tetrahedral oxyanions were further analyzed by ^{1}H NMR spectroscopy, and the findings proved consistent with the differences in the intrinsic strength of the various H-bond donor groups inferred from the electronic structure calculations carried out in methanol, namely that (CH)$^+$–anion interactions are less important in an energetic sense than neutral CH–anion interactions in polar media. These findings have important implications for future receptor design, particularly systems designed to recognize anions in highly polar organic media or aqueous environments.

Conclusions

The present review provides an overview of recent efforts to exploit CH···anion hydrogen bond donor motifs within a single receptor to achieve the recognition of particular anionic substrates. Although only the focus of intense study over the course of the last half dozen years, neutral and cationic CH hydrogen bond donors are now well established as important motifs in the host-guest chemistry of anions. To date, they have been actively explored in various shape persistent macrocycles, foldamers, self-assembling and dynamic species, and molecular machinery. Nevertheless, as compared to more classic supramolecular systems, the chemistry of neutral or cationic CH hydrogen bond donors is still in its infancy. It is thus viewed as an area with tremendous growth potential for future receptor design. CH-based systems have been shown to rival more traditional NH hydrogen bond donors for their anion recognition potential. Moreover, CH bonds are present in the overwhelming majority (97%) of organic compounds,[3] making it likely that new CH hydrogen bond donor motifs beyond those detailed in this review remain to be discovered and exploited for the purpose of anion recognition.

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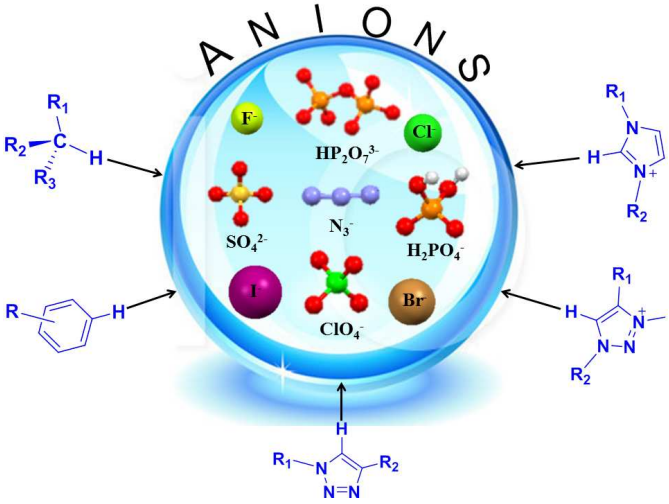
TOC Graph



Neutral and cationic CH hydrogen bond donors have been actively used in various shape persistent macrocycles, foldamers and "molecular machines".

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