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Supramolecular Chemistry of Anions

Advances in Anion Supramolecular Chemistry: From Recognition to Chemical Applications

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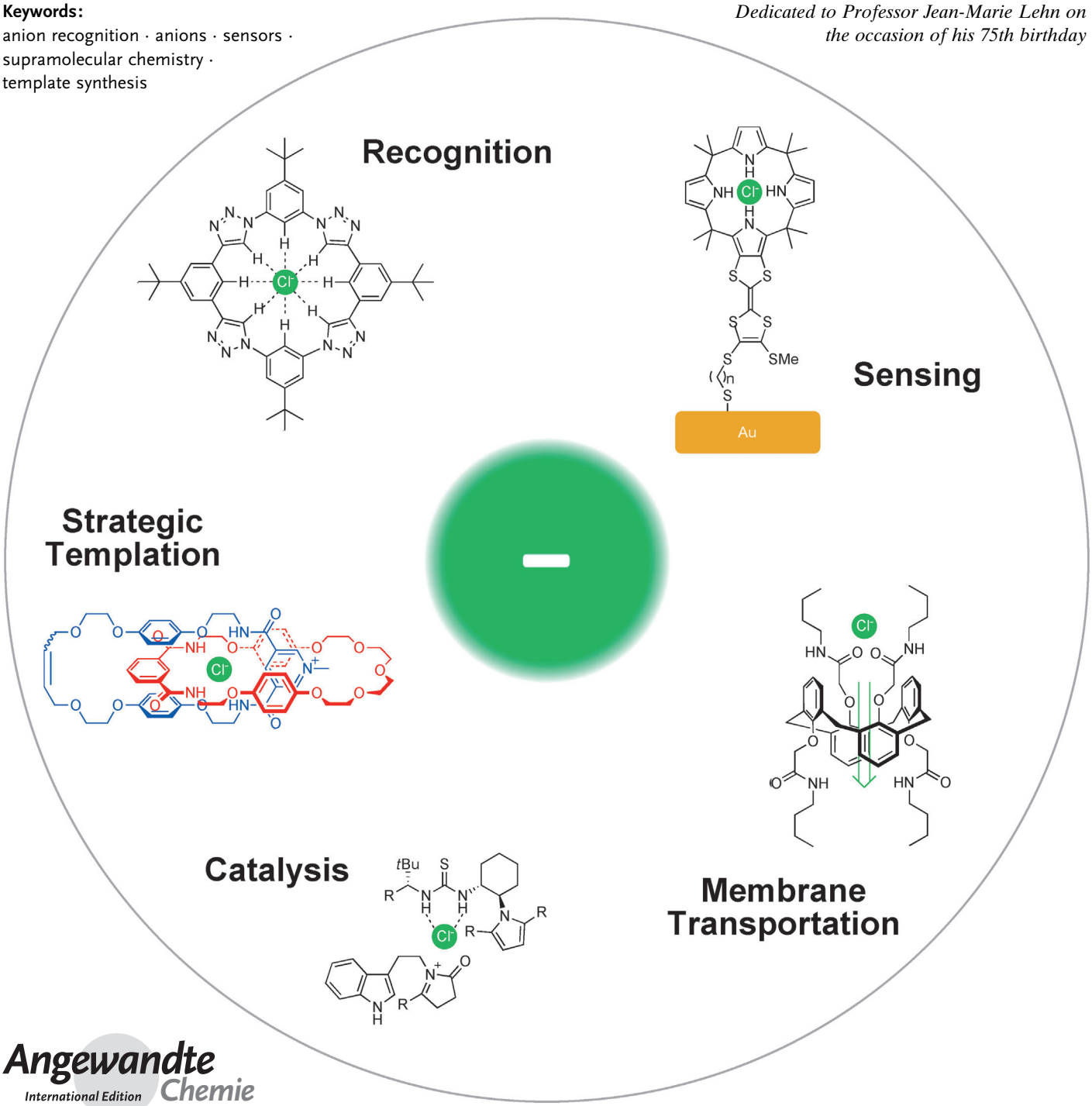
anion recognition · anions · sensors · supramolecular chemistry · template synthesis

Dedicated to Professor Jean-Marie Lehn on the occasion of his 75th birthday



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Since the start of this millennium, remarkable progress in the binding and sensing of anions has been taking place, driven in part by discoveries in the use of hydrogen bonding, as well as the previously under-exploited anion–π interactions and halogen bonding. However, anion supramolecular chemistry has developed substantially beyond anion recognition, and now encompasses a diverse range of disciplines. Dramatic advance has been made in the anion-templated synthesis of macrocycles and interlocked molecular architectures, while the study of transmembrane anion transporters has flourished from almost nothing into a rapidly maturing field of research. The supramolecular chemistry of anions has also found real practical use in a variety of applications such as catalysis, ion extraction, and the use of anions as stimuli for responsive chemical systems.

From the Contents

1. Introduction

Anions have an enormous impact upon our lives. Within our own bodies, the carrier of our genetic information—DNA—is anionic, as are the majority of enzyme substrates and cofactors (e.g. ATP). Amongst the halides, chloride is found extensively in extracellular fluid, with its misregulation being linked to diseases such as cystic fibrosis,[1] iodide is required for the biosynthesis of hormones by the thyroid gland,[2] while fluoride is considered essential for healthy bone and teeth growth, which has led to the (sometimes controversial) artificial fluoridation of water supplies.[3] In the case of other anions, it is well-established that bicarbonate is vital in the maintenance of pH levels in the body, whereas cyanide is highly toxic.

Certain anions have an adverse effect on the environment around us. Nitrate and sulfate are key components in the production of acid rain.[4] Excessive use of phosphates and nitrates in fertilizers has led to eutrophication in waterways.[5] Pertechnetate (a by-product of nuclear fuel reprocessing)[6] and perchlorate (arising from the manufacture of explosives)[7] are two further examples of anthropogenic pollutants, while arsenate is an example of a naturally occurring one.[8] In short, there has been, and still is, considerable motivation for investigating the binding and sensing of anionic species.

In 1968, Park and Simmons described the binding of halide anions by macrobicyclic ammonium cages (Figure 1 a).[9] A year previously, Shriver and Biallas had reported the formation of a chelate between a diboron ligand and a methoxide ion (Figure 1 b).[10] These are generally considered to be the first examples of anion coordination and hence the point of genesis for anion supramolecular chemistry.

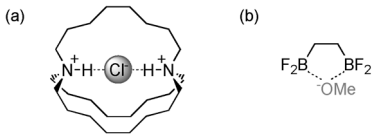

Figure 1. First examples of anion coordination: a) the macrobicyclic ammonium cage of Park and Simmons and b) the boron chelate of Shriver and Biallas.

Initially there was very little progress in the coordination chemistry of anions, in comparison to that of cations, where Pedersen's seminal reports on macrocyclic crown ethers[11] heralded the development of an array of cation-binding ligands, including Lehn's cryptands[12] and Cram's spherands.[13] This lack of development in the field of anion recognition has been attributed, in part, to a number of intrinsic properties associated with anionic species. Anions are larger than their isoelectronic cations, and hence will have smaller Coulombic interactions with an equivalent charged receptor. Anions may be sensitivity to changes in pH, that is, become protonated at low pH values and possibly lose their negative charge. Even simple inorganic anions are known to have a wide range of possible geometries, including spherical, linear, trigonal planar, and tetrahedral. It has also been noted that anions, in comparison to cations, possess high free energies of hydration. The degree of solvation of an anion in water varies from ion to ion, and is reflected by the Hofmeister series. In a hydrophobic binding site, inaccessible to solvent, less hydrated anions are bound more strongly. On the other hand, anions which are more hydrated are typically held more strongly in receptors with open cavities.

Despite these challenges, research on anion coordination gently began to develop momentum. Seminal early contributions came from Lehn and co-workers, who developed a large number of polyammonium receptors, including macrocycles, where optimal binding in aqueous media was observed for dicarboxylate anions of complementary size to the length of

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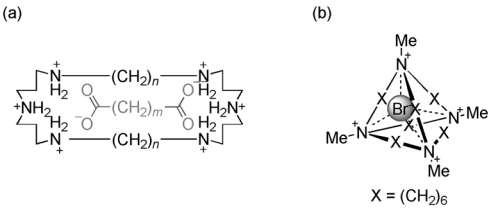


Figure 2. Significant early examples of anion coordination: a) the dicarboxylate binding macrocycle by Hosseini and Lehn and b) Schmidtchen's tetraammonium cage.

the receptor (Figure 2a),[14] and Schmidtchen, who reported innovative quaternary ammonium hosts able to bind halides within their cage structure (Figure 2b).[15] In spite of this slow beginning, anion supramolecular chemistry featured heavily in Lehn's Nobel Prize lecture of 1987.[15]

In 2001, Beer and Gale published a review on anion recognition and sensing[16] which, in particular, highlighted the important advances made in the design and construction of neutral hydrogen bond anion receptors that primarily function in organic solvents, as well as the construction of optical and electrochemical anion sensors.

Developments in anion recognition have subsequently continued to flourish to the extent that today anion supramolecular chemistry has evolved substantially beyond the realms of the chemistry of anion receptors. Although imaginative research continues on the binding and sensing of anions, during the last ten years or so large strides have been made in areas which were new and underdeveloped, such as the use of anions as templates and for transportation and importantly in chemical applications such as catalysis, ion extraction, and responsive materials.

Considering the depth and diversity of anion supramolecular chemistry today, we cannot contemplate producing a comprehensive review of the topic. Instead we seek to provide an overview of the most significant and substantial developments in the field since 2001, as well as providing some indication of where we expect the area to develop in the second decade of this century.[17]

2. Fundamental Advances in Anion Recognition

Previously, anion receptors have been usefully classified by consideration of the type of noncovalent interaction used to complex the anionic guest.[16] Although receptors employing electrostatic interactions are able to bind anions in water, hydrogen bonding, which is considerably weaker, has traditionally been considered insufficient to bind anions in aqueous conditions. The directionality offered by hydrogen bonds, however, means that appropriately designed neutral receptors can be constructed to bind anions with different geometries in aprotic polar solvents. Ureas[18] and amides[19] are popular choices of hydrogen-bond-donating functional groups, partly because of their expedient synthesis. Pyrroles, notably as calixpyrroles, have been shown to be particularly efficient anion receptors in polar organic solvents because of the lack of a competing hydrogen-bond acceptor.[20] Highly effective anion receptors can be produced by combining electrostatics and hydrogen bonding; recent examples of such motifs operable in aqueous solvent media include guanidinium,[21] imidazolium,[22] and pyridinium moieties.[23] Lewis acidic atoms, being electron deficient, are able to bind anions by participating in the formation of a bonding interaction through orbital overlap with an anion, which acts as an electron-donating species. In addition to boron,[10,24] other elements including silicon[25] and tellurium[26] have been employed to generate such anion receptors.

In this Review we do not provide an exhaustive commentary on this research.[27] Here, we concentrate on what may be considered to be the most important fundamental advances in anion recognition since 2001. We first highlight key developments in hydrogen-bonding anion receptors. Hydrogen bonding is widely utilized in a range of anion supramolecular chemistry activities (e.g. as templates and for transportation), and recent developments are often exploited in these applications. Secondly, we discuss the appearance of receptors based on new noncovalent interactions, specifically those using anion–π and halogen bonding.

Nick Evans graduated from Wadham College, University of Oxford with a First Class Masters in Chemistry (2006), before obtaining a DPhil in Inorganic Chemistry (2011), having worked on anion-sensing rotaxanes and catenanes in the group of Prof. Paul Beer. After undertaking postdoctoral research on chiral lanthanide complexes with Prof. David Parker (Durham University), he took up a Lectureship in Chemistry at Lancaster University in 2013. His research involves the development of functional supramolecular systems, with a particular focus on guest recognition and sensing.

Paul Beer obtained a PhD from King's College London in 1982 with Dr. C. Dennis Hall. After a Royal Society European Postdoctoral Fellowship with Prof. Jean-Marie Lehn and a Demonstratorship at the University of Exeter, he was awarded a Lectureship at the University of Birmingham in 1984. In 1990, he moved to the University of Oxford, where he became a Professor of Chemistry in 1998. His research interests cover many areas of coordination and supramolecular chemistry, in particular the binding and sensing of anions by macrocycles and interlocked molecular host systems.

2.1. Critical Developments in Receptors Utilizing Hydrogen Bonding

2.1.1. New N–H-, O–H-, and C–H-Containing Receptors

Neutral squaramides—a particular class of N–H hydrogen-bond donor, that are derivatives of 3,4-diaminocyclobutene-1,2-dione (Figure 3)—were demonstrated to act as effective anion receptors in competitive solvent media (such as DMSO) as early as 1998.[28] Since the turn of the century, numerous examples of squaramide anion receptors have been reported,[29] where their effectiveness is believed to be due in part to an increase in the aromatic character of the squaramide ring upon anion complexation.[30] An illustration is provided by a comparison of diaryl squaramides with their analogous ureas by Fabbrizzi and co-workers.[31] With halides, the di(nitrophenyl)squaramide (Figure 3b) formed considerably stronger complexes (by 1 or 2 orders of magnitude) than the analogous urea receptor in acetonitrile. In contrast, oxoanions were bound by each receptor with almost identical association constants. The enhancement of halide binding by the squaramide was attributed to the presence of convergent C(aryl)–H bonds that can act as additional hydrogen-bond donors.

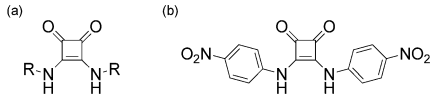


Figure 3. Squaramides as N–H hydrogen-bond-donating anion receptors: a) Fabbrizzi's generic structure of a squaramide and b) the diaryl squaramide receptor which exhibited particular enhancement of halide ion binding in comparison to the analogous urea receptor.

The indole-containing amino acid tryptophan may be found as a N–H hydrogen-bond donor in the anion-binding site of the sulfate-binding protein.[32] The indole functional group, like pyrrole, lacks competing hydrogen-bond acceptors (in contrast to amides and ureas), but is more acidic than its monocyclic counterpart. Indoles, along with carbazoles and indolocarbazoles, are representative examples of heterocyclic N–H hydrogen-bond donors that have been investigated in recent times (typically in combination with other hydrogen-bond donors) as potent anion receptors.[33]

For example, Gale and co-workers synthesized pyridine-2,6-dicarboxamide and isophthalamide molecules which possessed pendent indole groups (Figure 4a).[34] These receptors proved to be highly selective for fluoride over chloride (for example) in [D_6]DMSO/0.5% water mixtures, which was attributed to the "twisted" conformation of the receptor encapsulating the smaller fluoride ion, whereas chloride "perches" on the receptor, as evidenced in a solid-state crystal-structure determination. Previously, Jurczak and co-workers had reported on carbazole/amide receptors (Figure 4b).[35] These molecules were found to bind benzoate and dihydrogen phosphate much more strongly than chloride in [D_6]DMSO/0.5% water. The first reports of anion complexation with indolocarbazoles were made by the Beer research group, where it was demonstrated that, in acetone, simple

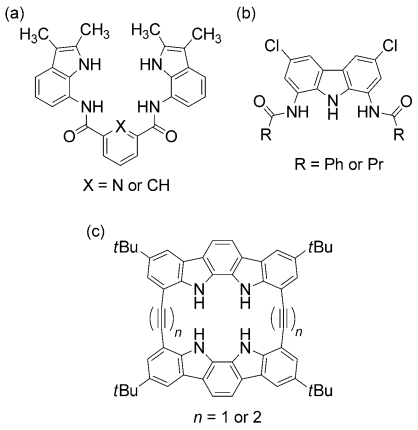


Figure 4. Examples of recent heterocyclic N–H hydrogen-bonding receptors: a) Gale's indole-containing receptors; b) Jurczak's carbazole diamide receptors, and c) Jeong's indolocarbazole-containing macrocycles.

indolocarbazoles bound benzoate strongly (typically $\log K_a > 5$).[36] Jeong and co-workers have since incorporated indolocarbazoles into a range of macrocyclic receptors (Figure 4c).[37] Chloride is bound more strongly by the smaller cyclic receptor (in 10% MeOH/acetone), whereas the larger anions investigated were bound more strongly to the larger receptor, indicative of a degree of complementarity between the host and guest.

Recently, the use of chiral anions to induce helical chirality in N–H hydrogen-bond-donating foldamer anion receptors has been demonstrated. This is exemplified by the tri(indolocarbazole) synthesized by Jeong and co-workers that forms a chiral helix upon coordination to enantiopure 10-camphorsulfonate in dichloromethane, as revealed by circular dichroism (Figure 5).[38] A related example is that of Zhao, Li, and co-workers, who used the chiral glutamate anion to induce helical chirality in a benzamide oligomer.[39]

As already mentioned in the Introduction, protonated bicyclic N–H-containing molecules have been known to bind anions for some 45 years. Interest in such cryptand-like receptors was rekindled by a 1978 report by Lehn and co-workers of an azaoxa cryptand, which was shown to selectively bind the linear azide anion in water.[40] This research area has remained remarkably active, and a large number of bicyclic receptors have even been reported since 2001.[41] Notable among these has been the work of Bowman-James and co-workers, who studied neutral cryptands (prepared by reacting tri(2-aminoethyl)amine, commonly referred to as "tren", with isophthaloyl chlorides), which are able to bind fluoride with $K_a > 10^5\ M^{-1}$ in competitive [D_6]DMSO (Figure 6a).[42] Recently, Mani and co-workers described the ability of polypyrrolic cryptands to also bind fluoride in [D_6]DMSO (Figure 6b).[43] A notable achievement in this field has been the selective recognition of the radioactive pollutant $^{99}TcO_4^-$ by a protonated cryptand in acidic water (Figure 6c).[44] Amendola and co-workers demonstrated by isothermal titration calorimetry that the pertechnetate anion was bound more strongly than either nitrate or chloride by two orders of magnitude.

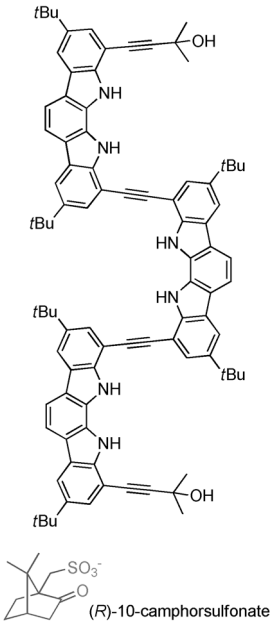


Figure 5. Jeong's indolocarbazole foldamer anion receptor which forms a chiral helix with a positive Cotton effect upon addition of (*R*)-10-camphorsulfonate in dichloromethane.

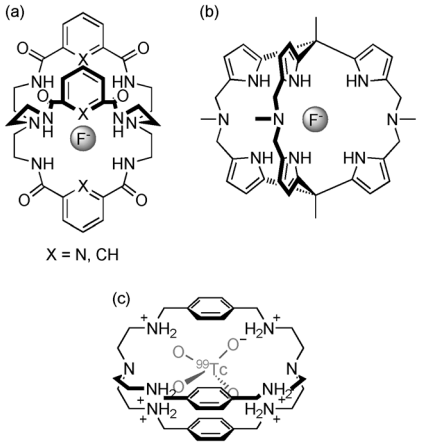


Figure 6. Cryptand-like receptors: a) Bowman-James' polyamide and b) Mani's polypyrrole cages that bind fluoride; c) Amendola's polyaza cage that binds pertechnetate.

The simple, commercially available molecule catechol, has been found by D. K. Smith[45] to be a remarkably potent chloride binder in CD_3CN ($K_a = 1575\ M^{-1}$; Figure 7a). Further study revealed catechol to exhibit greater affinity and selectivity for chloride (over bromide and iodide) than its structural isomer resorcinol (Figure 7b).[46] However, attempts to functionalize catechol with further hydrogen-bond donors proved problematic, with an intramolecular six-membered hydrogen-bonding arrangement found to inhibit anion binding in a number of the receptors prepared (Figure 7c).[47]

Recently it has been recognized that the triazole motif may be utilized as a potent C–H hydrogen-bond donor, with interest in part being driven by the synthetic efficacy of the

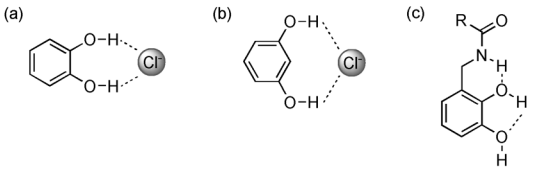


Figure 7. Dihydroxybenzenes as O–H hydrogen-bonding chloride receptors: a) mode of chloride binding of catechol; b) mode of chloride binding by resorcinol, and c) example of a functionalized catechol that has reduced chloride affinity because of intramolecular hydrogen bonding.

Huisgen copper-catalyzed azide-alkyne cycloaddition (CuAAC) "click" reaction.[48] Being similar in size, planarity, and dipolar character to an amide linkage, a 1,2,3-triazole may be considered peptidomimetic. Li and Flood have demonstrated the very strong binding of chloride and bromide by a triazolophane in dichloromethane (Figure 8a).[49] By careful design, a receptor has also been constructed that binds iodide in a 2:1 "sandwich" complex (Figure 8b).[50]

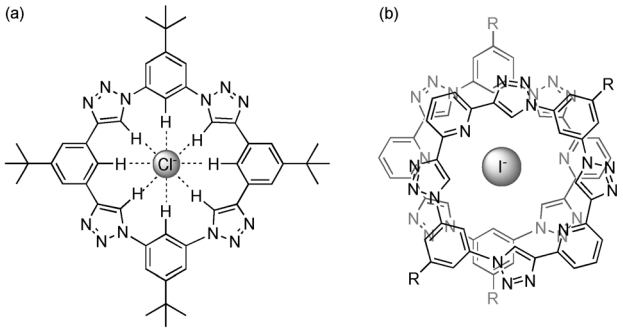


Figure 8. Flood's triazole macrocycles as C–H hydrogen-bond-donating anion receptors: a) the original triazolophane binding chloride and b) an alternative triazolophane that binds iodide in a 2:1 "sandwich" complex.

Contemporaneous with Flood's first seminal reports, the research groups of Craig[51] and Hecht[52] described the formation of halide-templated oligotriazole foldamers in solution. The study by Craig and co-workers revealed their tetratriazole oligomer bound chloride the strongest (in [D_6]acetone), with the 1:1 oligomer/anion stoichiometry confirmed by Job Plot analysis (Figure 9a). By the incorporation of chiral centers onto the backbone, Meudtner and Hecht were able to probe the chiroptical properties of their foldamer: intriguingly the handedness of the helix depended on which halide was present (Figure 9b).

Very recently, Flood and co-workers have demonstrated the ability of an alternative C–H hydrogen-bond donor, cyanostilbene, to bind anions.[53] A pentagonal "cyanostar" macrocycle (Figure 10) has been synthesized which binds large anions (e.g. PF_6^-) as a 2:1 macrocycle/anion sandwich in CD_2Cl_2/CD_3OD (3:2). The same macrocycle was also incorporated into a [3]rotaxane with a dialkylphosphate axle. Further examples of anion-templated rotaxanes will be covered in Section 3.4.

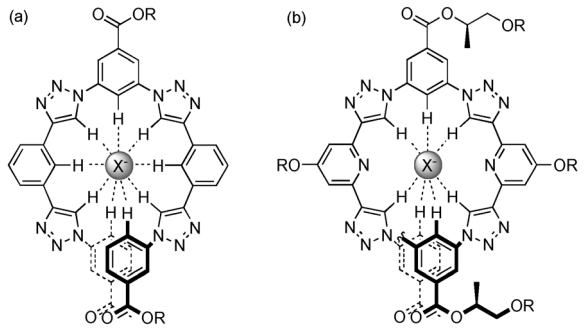


Figure 9. Triazoles as C–H hydrogen-bond donors in anion-templated foldamers: a) Craig's tetrakis(triazole) foldamer and b) Hecht's chiral oligotriazole foldamer.

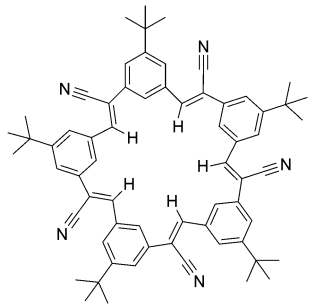
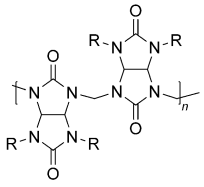


Figure 10. Flood's pentagonal "cyanostar" macrocycle capable of binding large anions in a 2:1 sandwich complex.



n = 2, 3
R = Me, *n*Pr, Benzyl

Figure 11. Sindelar's bambus[*n*]urils capable of binding halide ions by C–H···X^- hydrogen bonds.

Sindelar and co-workers have reported an alternative exploitation of C–H hydrogen-bond donors in a family of cyclic glycouril oligomers termed bambus[*n*]urils (Figure 11).[54] The original bambus[6]uril, was shown crystallographically to hydrogen bond to a chloride ion through 12 C–H···Cl^- hydrogen bonds in the solid state.[54a] An analogue soluble in organic solvents was later found to bind halides very strongly in solution (e.g. $K_a(I^-) = 3.8 \times 10^9\,M^{-1}$), albeit in noncompetitive chloroform.[54b]

2.1.2. Binding in Aqueous Media with Neutral Hydrogen-Bond Donors

The ability of a receptor to operate in aqueous media is essential for medical diagnostics, or for the monitoring of a pollutant in an environmental sample. As already mentioned, it has traditionally been believed that synthetic anion receptors solely employing hydrogen-bond donors are unable to operate in such conditions. However, in the last decade, there have been notable developments in the preparation of neutral receptors capable of functioning in aqueous media.

In a sustained program of research, the group of Kubik has investigated synthetic cyclopeptides containing alternating aromatic and L-proline residues that may act as anion receptors in solvent media with exceptionally high aqueous contents, even in pure (i.e. 100%) water. In their first reports,[55] cyclohexapeptide macrocycles were shown to bind anions in an 80:20 mixture of D_2O and CD_3OD solutions. Whereas the macrocycle bound inorganic anions with a 1:1 stoichiometry in pure DMSO, 2:1 association occurred in aqueous solutions, with the anion being completely desolvated and encapsulated within the sandwich complex (Figure 12a). Furthermore, one of the macrocycles was able to

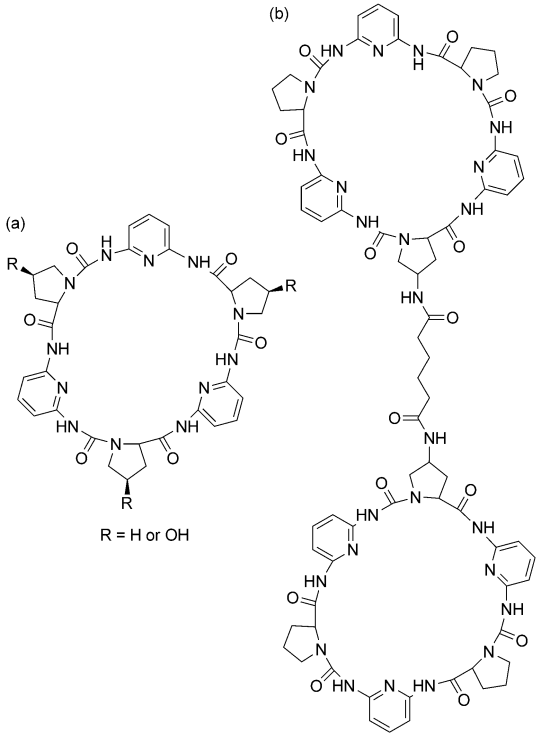


Figure 12. Kubik's cyclopeptide anion receptors: a) the original hexapeptide macrocycles and b) two of the macrocycles covalently linked to form a "molecular oyster".

bind sulfate in pure D_2O, admittedly with a modest association constant ($K_a = 56\,M^{-1}$).[56]

In subsequent work, covalently linking two cyclopeptides with adipic acid allowed for "molecular oyster" receptors able to bind sulfate with $\log K_a \approx 5$ in a 50:50 mixture of H_2O and CH_3OH (Figure 12b).[57] The ability of these receptors to operate in such competitive solvent media has been accredited to hydrophobic interactions between the two cyclopeptide rings that encapsulate the bound anion.[58]

Suk and Jeong have reported the formation of indolocarbazole-based foldamers templated by halide anions in water (e.g. $K_a(Cl^-) = 65\,M^{-1}$; Figure 13).[59] This example is particularly noteworthy, as the required aqueous solubility is achieved by incorporation of negatively charged carboxylate groups into the structure of the oligomer, which provides an electrostatic repulsive contribution that would oppose the anion-binding event.

Gale and co-workers have reported the preparation of dipyrrolylmethane amide receptors capable of binding

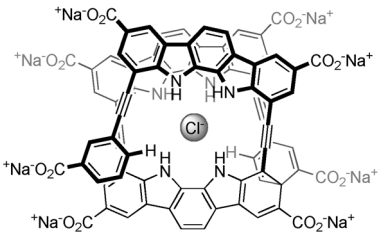


Figure 13. Jeong's water-soluble indolocarbazole foldamer.

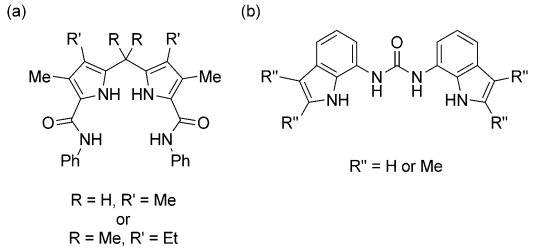


Figure 14. Neutral hydrogen-bonding receptors capable of binding anions in aqueous DMSO solvent media: a) dipyrrolylmethane amide and b) diindolylurea.

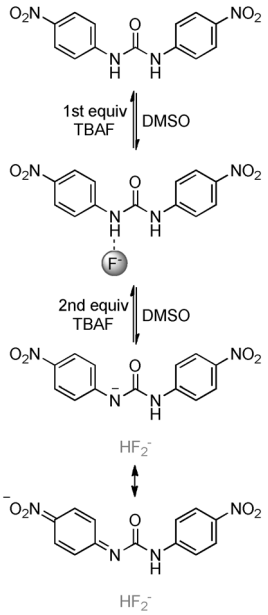


Figure 15. Hydrogen bonding and subsequent deprotonation of an acidic urea derivative by fluoride.

a range of anions in [D_6]DMSO containing 5% water, and in the case of $H_2PO_4^-$ (where R = H, R′ = Me in the receptor) in [D_6]DMSO containing 25% water ($K_a = 234\ M^{-1}$; Figure 14a).[60] In more recent work, combining indole and urea functionalities has resulted in receptors able to bind anions in [D_6]DMSO containing 10% water, with the binding of $H_2PO_4^-$ being observed once again in 25% water solutions ($K_a = 160\ M^{-1}$; Figure 14b).[61]

The binding of anions in water by neutral hydrogen-bond donors is, and will remain, a considerable challenge.[62] For even though these few examples demonstrate that receptors with sufficient hydrogen-bond-donor character can be readily constructed, for such systems to operate in pure water requires sufficient solubility, a property that—to date—has proved difficult to concomitantly incorporate.

2.1.3. Understanding Anion Complexation versus Deprotonation

Electron-withdrawing groups may be added to a receptor to increase the binding strength of hydrogen-bond donors. This increases the acidity of the hydrogen-bond donor, which simultaneously increases the likelihood of the receptor being deprotonated, in particular by basic anions such as fluoride or acetate. In-depth investigations of this effect have been carried out by the research groups of Fabbrizzi,[63] Gale,[64] and Gunnlaugsson,[65] and some illustrative examples are discussed below.

Titration of TBAF into solutions of a simple urea receptor (substituted with electron-withdrawing nitrophenyl groups) in DMSO led to complex behavior being observed beyond simple hydrogen-bond formation (Figure 15).[66] The first equivalent of fluoride titrated forms strong hydrogen bonds with the receptor as expected. However, the addition of a second equivalent results in deprotonation occurring, with formation of a stable HF_2^- ion. The solution turns a deep orange as a consequence of the formation of a charge-transfer state in the deprotonated receptor.

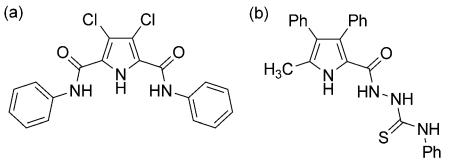


Figure 16. Further acidic receptors deprotonated by basic anions: a) an amidopyrrole and b) an amido(thio)urea.

It has been shown that certain amidopyrrole receptors are also sufficiently acidic to be deprotonated. For example, the receptor in Figure 16a was deprotonated by fluoride in CD_2Cl_2.[67] Once again, two equivalents of TBAF were required for proton transfer, to allow for formation of the stable HF_2^- species. The amido(thio)urea receptor in Figure 16b proved to be so acidic that a greater range of anions caused deprotonation. One equivalent of anion was sufficient to induce proton transfer in the case of fluoride, acetate, benzoate, and dihydrogen phosphate. This process was accompanied by the appearance of a new absorption band in the UV/Vis spectrum of the receptor.[68]

It should be noted that many colorimetric anion sensors previously described are now believed to function through such proton-transfer processes. This should always be kept in mind, particularly if the anion guest species is basic, such as a carboxylate or fluoride.

An appreciation has also begun to develop that an acidic anion may be deprotonated. Titration of excess $TBAH_2PO_4$ into solutions of butyl diindolylurea receptor in [D_6]DMSO (Figure 17) led to the observation of a second set of signals further downfield in the ^1H NMR spectrum. This observation

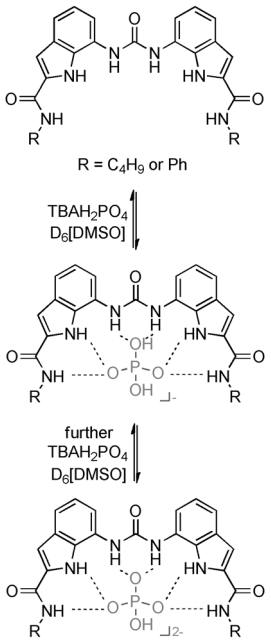


Figure 17. Binding and subsequent deprotonation of dihydrogen phosphate by a diindolylurea receptor.

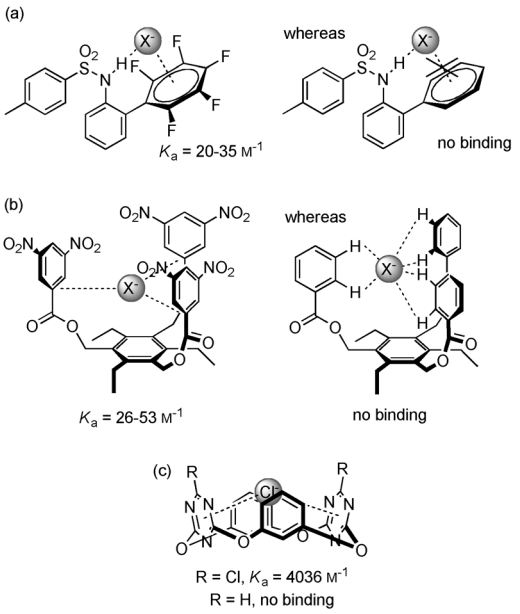


Figure 18. Evidence of anion–π interactions binding halide ions in solution: a) by augmenting hydrogen bonds and b,c) by interacting solely through anion–π contacts.

was rationalized by hypothesizing that the pK_a value of the bound $H_2PO_4^-$ is reduced, which allows for proton transfer to unbound anion. Evidence for this is provided by the solid-state structure of the phenyl analogue of the receptor (grown in the presence of excess $TBAH_2PO_4$), where the coordinated anion is observed to be HPO_4^{2-}.[69]

2.2. Exploiting New Interactions To Bind Anions

2.2.1. Anion–π Receptors

The term anion–π refers to the attractive force between an electron-deficient aromatic π system and an anion.[70] It is believed that the interaction principally consists of electrostatic forces and ion-induced polarization. The electrostatic contribution requires the arene to possess a positive quadrupole moment, thus demanding the arene rings to be substituted with electron-withdrawing substituents.

Evidence for anion–π interactions in the solution phase has only recently been acquired.[71] For example, Berryman et al. prepared two molecules each containing a sulfonamide hydrogen-bond donor, where one possessed a neighboring pentafluorophenyl ring, while the other had an unfluorinated phenyl ring (Figure 18a).[72] They observed no binding of halides with the unfluorinated species in $CDCl_3$. Crucially, weak binding of halides ($K_a = 20–35\,M^{-1}$) was noted with the pentafluorophenyl species. In subsequent studies, Berryman et al. demonstrated that it is possible to recognize halides solely using anion–π interactions (Figure 18b).[73] The substitution pattern of the nitro groups prevents halide ions from hydrogen bonding to the molecule. Despite this, the binding of the halides ($K_a = 26–53\,M^{-1}$) was observed in C_6D_6. The unsubstituted, protic analogue, which is capable of hydrogen bonding (but not of anion–π interactions) possesses no affinity for the halide ions. Wang et al. have reported upon the ability of an electron-deficient tetraoxacalix[2]arene[2]-triazine receptor to bind halide ions (Figure 18c).[74] The dichloro-substituted macrocycle can bind chloride ($K_a = 4036\,M^{-1}$) in CH_3CN, while no binding was observed with the proto analogue, consistent with a binding mode based on anion–π interactions.

An anion–π prismatic receptor has very recently been studied by Wasielewski, Stoddart, and co-workers (Figure 19).[75] The tri(naphthalenediimide) trigonal prism

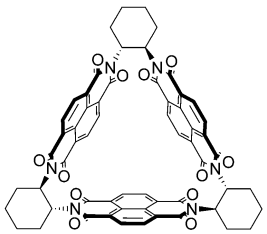


Figure 19. Structure of a tri(naphthalenediimide) trigonal prism capable of binding the triiodide ion by anion–π interactions.

was shown to bind the I_3^- ion with an association constant of $K_a = 25\,M^{-1}$ in CD_2Cl_2. A solid-state structure determination confirms that the anion resides within the prismatic cavity.

Anion–π interactions have perhaps been most notably exploited in the construction of anion–π slides by Mareda and Matile (see Section 5.3). These systems are capable of the transmembrane transportation of anionic species.[76]

2.2.2. Halogen Bonding Receptors

Halogen bonding may be represented by Y−X···D, where X is an electrophilic halogen atom, D is a donor of electron density, and Y is another atom (e.g. C or N).[77] Halogen bonds arise from the appearance of a σ hole at the X end of the Y−X bond, into which electron density may be donated. The strength of the halogen bond follows the trend $X = I > Br > Cl \gg F$. As the electron-poor region sits on the X pole region of the Y−X bond, the halogen bond is considered highly directional, as usually evidenced—but not always[78]—in the solid state. The halogen-bonding interaction has perhaps been most often employed in crystal engineering and liquid crystals. It is perhaps surprising that only in very recent times has the application of halogen bonding to anion recognition begun to be realized.

Taylor and co-workers constructed a receptor containing a convergent array of halogen-bond donors by incorporation of *ortho*-substituted iodotetrafluroroarenes on to a 2,4,6-trimethylbenzene scaffold (Figure 20a).[79] In acetone, this

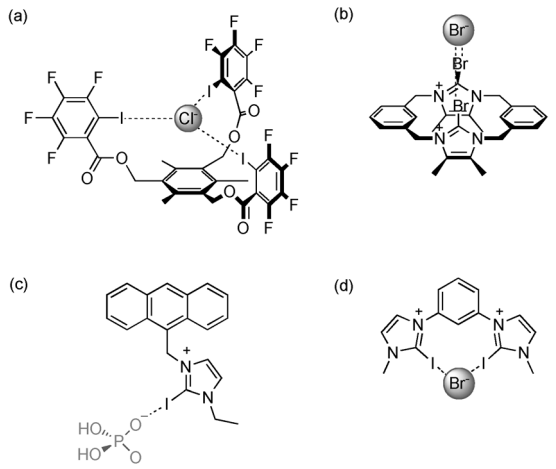


Figure 20. Examples of receptors that employ halogen bonds: a) convergent iodotetrafluoroarenes; b) bidentate bromoimidazoliophane; c) monodentate iodoimidazolium; and d) bidentate iodoimidazolium.

receptor was demonstrated to bind halide ions $Cl^- > Br^- > I^-$, while not exhibiting affinity for the oxoanions HSO_4^- and NO_3^-.

It is possible to achieve anion binding in much more competitive solvent media by utilizing electrostatic interactions. Such charge-assisted halogen bonding is exhibited by the bidentate bromoimidazoliophane in Figure 20b.[80] The *syn* isomer is capable of selectively binding bromide in a 9:1 mixture of CD_3OD and D_2O. The protic, hydrogen-bonding analogue (which lacks *syn*/*anti* isomerism) exhibits weak, unselective binding of halide ions. Analogous halogen-bonding naphthalene-containing macrocycles have also been prepared; in these examples the *syn*-iodo- and bromo-substituted macrocycles are able to act as selective fluorescence sensors of bromide and iodide, respectively, in CD_3OD/D_2O (9:1).[81] A simple iodoimidazolium has also been investigated (Figure 20c), and shown to selectively bind $H_2PO_4^-$ in [D_6]DMSO.[82] Once again the protic analogue exhibits weak, unselective binding of the anions investigated. A comprehensive isothermal calorimetric study of anion binding with di(iodoimidazolium) systems (Figure 20d) has also been carried out in a range of organic solvents. In this study, the entropic contribution to the overall free energy of binding was found to be very important.[83]

The simultaneous employment of halogen and hydrogen bonding to achieve anion binding has also been demonstrated. Taylor and co-workers measured the contribution of halogen bonding to the free energy of anion binding in a di(iodoperfluorobenzoyl)-substituted urea by comparison with a perfluorobenzoyl analogue in CD_3CN.[84] They observed a significantly greater halogen-bonding contribution for the halides compared to dihydrogen phosphate (Figure 21).

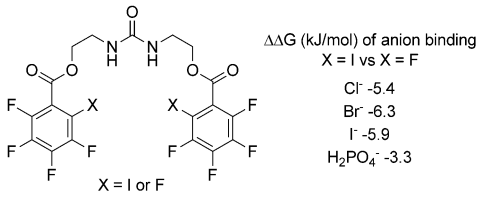


Figure 21. Structures of disubstituted urea derivatives used by Taylor and co-workers to calculate the contribution of halogen bonding to anion binding.

3. Anions as Templates

Up to a decade ago, the use of anionic species as templates in self-assembly had been very much in its infancy, with the majority of examples being of the serendipitous kind. Inspection of the literature from this time reveals various isolated, underdeveloped cases such as Mingos' cage[85] and Lehn's helicate[86] (Figure 22), as well as an earlier report by Hawthorne and co-workers on the role of chloride in the synthesis of anion-binding mercuraborane macrocycles.[87]

In the following years, the preparation of a significant number of anion-templated molecules was reported. Salient examples are now discussed with the focus being specifically on structures constructed by the strategic use of anions as templates. Reviews containing more detailed information on serendipitously produced molecular architectures may be found elsewhere.[88]

Traditionally, templated synthesis has involved a considered iterative process based on design, manufacture, assessment, and re-design (possibly aided by computer modeling). However, the advent of dynamic combinatorial chemistry (DCC) provides a powerful alternative strategy.[89] In the DCC approach, a suitably chosen set of building blocks, which may continuously interconvert, is prepared. The addition of a template (e.g. an anion) to this dynamic combinatorial library (DCL) will lead to a shifting of the dynamic equilibria present, driven by the requirement to minimize the free energy of the entire library, thereby resulting in the amplification of certain product member(s) of the DCL, which may then in turn be isolated. Both of these methodological

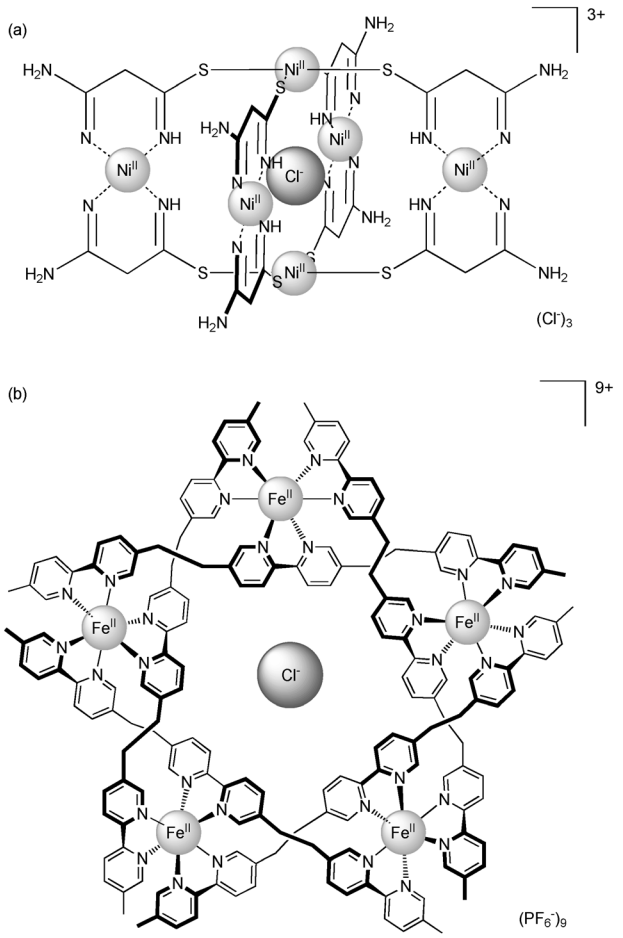


Figure 22. Early examples of anions used as templates: a) Mingos' cage and b) Lehn's helicate.

concepts have been utilized in the construction of anion-templated molecules in the last ten years.

3.1. Anion-Templated Dimeric Complexes and Capsules

The use of anions, with multidentate ligands, to template the formation of dimeric structures has been notably exploited in recent years.

For example, Wu, Yang, and co-workers have reported a coplanar acyclic triurea ligand that forms a 2:1 (L/A^-) complex with either phosphate or sulfate in aqueous DMSO solutions (Figure 23 a).[90] Sulfate was shown by Schubert and co-workers to template the formation of a 2:1 (L/A^-) complex with a triazole-triazolium ligand in acetonitrile through a combination of hydrogen bonding and electrostatic interactions (Figure 23 b).[91] Interestingly, the bis(triazolium) analogue only formed a 1:1 complex with sulfate.

Two classes of tripodal ligands have been widely utilized for the formation of anion-templated dimeric "capsules", namely a) trifunctionalized trialkylbenzenes[92–94] and b) those based on functionalizing tri(2-aminoethyl)amine ("tren").[95–97]

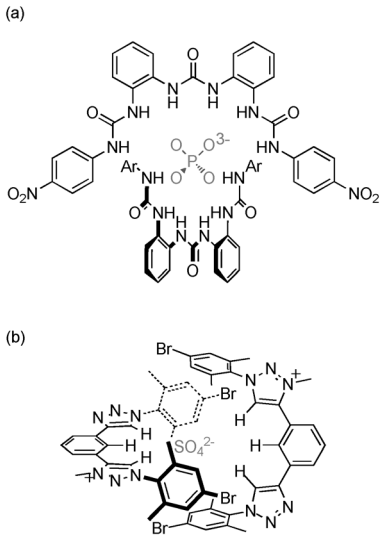


Figure 23. Examples of anion-templated "complexes" using flat ligands: a) Wu and Yang's triurea dimer with a phosphate template and b) Schubert's sulfate-templated triazole-triazolium dimer.

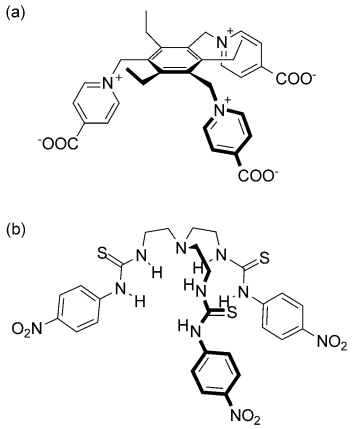


Figure 24. Examples of ligands used in the preparation of anion-templated "capsules" using tripodal ligands: a) Steed's triethylbenzene tripyridinium ligand and b) Das' tren-trithiourea ligand.

A representative example of the first class of tripodal ligands is the zwitterionic tri(pyridinium carboxylate) receptor synthesized by Steed and co-workers (Figure 24 a).[92] A single bromide ion can be encapsulated by two equivalents of the ligand, being augmented by C–H···Br^- hydrogen bonds as identified by X-ray crystallography. In comparison, functionalized tren ligands typically form dimeric complexes templated by polyatomic anions such as phosphate or sulfate. This is exemplified by the tri(thiourea) of Dey and Das, which coordinates to phosphate through 12 hydrogen bonds, once again verified by X-ray crystallography (Figure 24 b).[95]

It is noteworthy that the use of tren-based ligands in industrially useful anionic extraction processes has been demonstrated. Details of these reports can be found in Section 6.2.

3.2. Anion-Templated Macrocycles

The exploitation of anions to template the synthesis of macrocyclic species has been studied intensely over the last decade. Here, it is notable that, from using simple spherical halide ions, the use of (inorganic and organic) polyatomic anions is now being pursued.

The role of chloride in the formation of a di(imidazolium) macrocycle was reported by Alcalde and co-workers (Figure 25).[98] Their investigations confirmed that cyclization

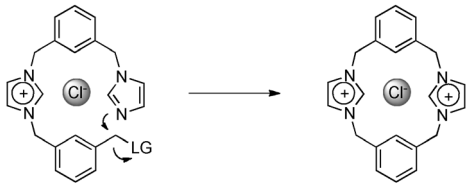


Figure 25. Alcalde's study of the template effect using a chloride ion.

is accelerated by a factor of ten in the presence of chloride. It was proposed that the halide ion hydrogen bonds to the imidazole and imidazolium moieties, thus supporting the arrangement of the molecule in a cyclic-shaped transition state which leads to formation of the macrocyclic product.

The use of a chloride template has also been demonstrated by Böhmer and co-workers in the preparation of a remarkable cyclic hexaurea macrocycle.[99] Reacting the diamine and diisocyanate (Figure 26) in acetonitrile simply yields the triurea macrocycle. However, in dichloromethane the hexaurea macrocycle is also isolated in a yield of 20%. A crystal structure of this macrocycle (grown in the presence of TBACl), revealed a figure-of-eight conformation encapsulating two chloride ions. Evidence of the templating role of chloride in this macrocyclization was provided by the addition of two equivalents of chloride to the reaction mixture, which switched the ratio of formation of the two macrocycles (as determined from crude ^{1}H NMR spectra) from 5:1 to 1:5. Notably, the ratio was found to be 1:3 when bromide was used instead of chloride, but no difference from the halide-free conditions was observed with iodide.

The Sessler research group has reported upon the role of the acid counteranion in the reaction of a 2,6-diamidopyridine diamine and diformylbipyrrole.[100] The use of hydrochloric or hydrobromic acid resulted in a complicated mixture of products, whereas sulfuric acid led to the formation of the [2+2] macrocycle depicted in Figure 27 in 90% yield, aided by the dynamic nature of the imine bond in acidic conditions. In the presence of $TBAHSO_4$ or $TBAH_2PO_4$, the free base of this [2+2] macrocycle converts into the larger [3+3] macrocycle, which is the major product if phosphoric acid is used in the original reaction. Anion-binding studies in acetonitrile revealed that both macrocycles bound $H_2PO_4^-$ and HSO_4^- (both tetrahedral anions) the strongest amongst a range of singly charged anions, including the more basic acetate oxoanion.

Alfonso, Luis, and co-workers have thoroughly investigated the anion-templated synthesis of pseudopeptidic macrocycles by using aromatic dicarboxylates as templates (Figure 28).[101] Di(amidoamines) and aromatic dialdehyde

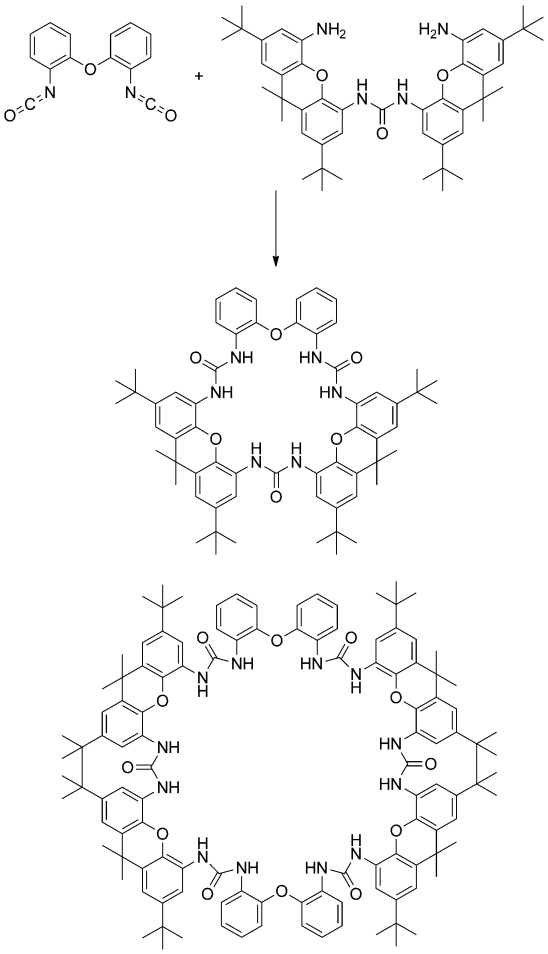


Figure 26. Böhmer's tri- and hexaurea macrocycles, the latter of which is capable of binding two chloride ions in a figure-of-eight conformation.

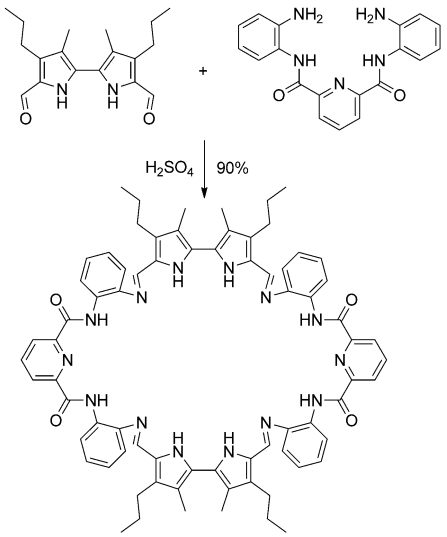


Figure 27. The sulfate-templated synthesis of a [2+2] macrocycle.

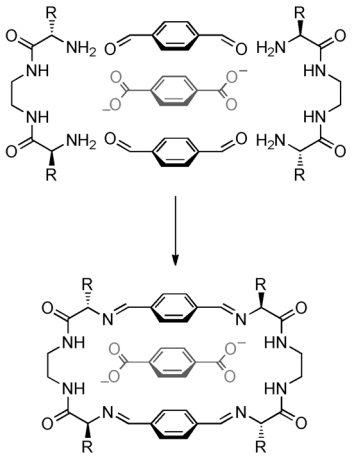


Figure 28. Dicarboxylate-templated synthesis of pseudopeptidic macrocycles by Alfonso and Luis.

precursors were allowed to react in the presence of a dicarboxylate template to form tetraimine macrocycles, which were isolated after in situ reduction of the imine bonds. A notable achievement of this template strategy is the preparation of "structurally disfavored" macrocycles.[101c] This involved taking specific chiral diamines which when reacted with 1,4-benzenedicarbaldehyde without the dicarboxylate template simply form a mixture of long-chain oligomers, whilst their stereoisomers spontaneously macrocyclized. The addition of the dicarboxylate template to the reactions of the "disfavored" substrates led to the formation of the [2+2] macrocyclic product. More recently, replacing the 1,4-dialdehyde with 1,3,5-benzenetricarbaldehyde, and switching the dicarboxylate for a tricarboxylate template, has enabled the efficient synthesis of macrocyclic cages.[101d]

3.3. Anion-Templated Metallo-Organic Cages

Contemporaneous with Mingos' chloride-templated cage described above, McCleverty, Ward, and co-workers described the formation of a tetrahedral metallo-organic cage templated by a tetrafluoroborate anion (Figure 29).[102] The $[M_4L_6]^{8+}$ cage consists of four Co^{II} cations at the tetrahedron vertices, with a di(pyrazolylpyridine) ligand on each edge. The tetrafluoroborate anion occupies the central cavity and forms multiple hydrogen bonds to the methylene protons of the

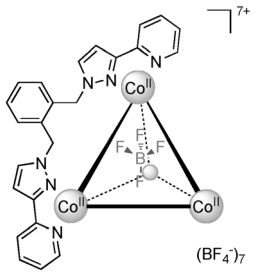


Figure 29. Ward's original tetrafluoroborate-templated $[Co_4L_6]^{8+}$ tetrahedral cage.

bridging ligands. Later, more detailed solution NMR experiments definitively proved the anion functioned as a template, with the cage formed only upon addition of the BF_4^- ion to a mixture of Co^{II} and the ligand.[103] A cage that is formed as a single diastereoisomer was subsequently prepared by use of a chiral bridging ligand.[104]

The original system of Ward and co-workers represents an example of the serendipitous discovery of the anion template effect. The research group of Custelcean, in collaboration with the computationalist Hay, prepared a rationally designed $[M_4L_6]^{8+}$ tetrahedral cage templated by a sulfate ion, which it strongly binds ($K_{app} \approx 6 \times 10^6\,M^{-1}$; Figure 30).[105] In this example, each ligand molecule contains a urea unit, capable of

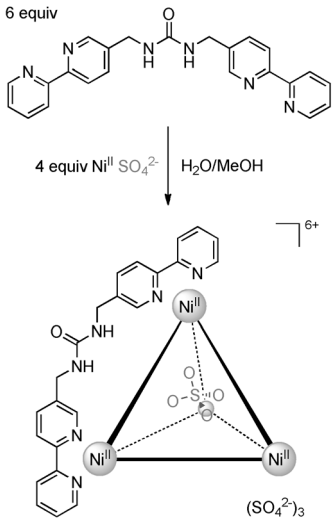


Figure 30. Synthesis of a rationally designed sulfate-templated $[Ni_4L_6]^{8+}$ tetrahedral cage by Custelcean and Hay.

acting as a bidentate hydrogen-bond donor. These were calculated—and found by crystallography—to form 12 hydrogen bonds to the templating sulfate ion. A very similar sulfate-templated cage has also been published by Kaifer and co-workers.[106]

The resulting topologies of anion-templated metallo-organic cages are very often unexpected and not simply limited to tetrahedra. As an illustration, Steel and Sumby have reported a flat prismatic "disclike" $[Ag_6L_2]^{6+}$ cage (L = hexa(2-pyridyl)[3]radialene), where a fluoride ion is encapsulated (Figure 31 a).[107] Fluoride is believed to act as template, due to the encapsulation of the halide ion and the lack of a discrete fluoride ion in the reagents used to prepare the cage. More recently, Su and co-workers have found that a T-shaped pyridyldiphosphine ligand will form "nanotube"-shaped $[Ag_6L_6]^{6+}$ cages in the presence of SbF_6^-; the encapsulation of two anions was proved by crystallography (Figure 31 b).[108]

Recent studies on anion-responsive metallo-organic cages represent one of the most interesting developments in anion supramolecular chemistry. A discussion on this topic can be found in Section 6.3.3.

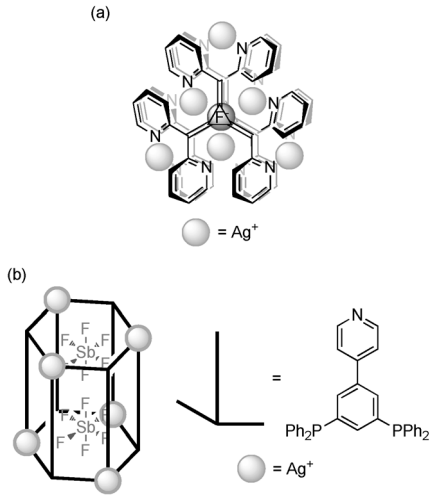


Figure 31. Further examples of anion-templated metallo-organic cage formation: a) Steel's "disclike" $[Ag_6L_2]^{6+}$ cage (viewed from above) and b) Su's "nanotube" $[Ag_6L_6]^{6+}$ cage.

3.4. Anion-Templated Rotaxanes and Catenanes

Two of the most aesthetically pleasing classes of molecules in chemistry are catenanes and rotaxanes. A catenane is a compound that consists of two or more rings that are mechanically interlocked, while a rotaxane consists of one or more macrocycles threaded over an axle, with bulky stopper groups on the axle component preventing dethreading. The first high-yielding syntheses of such species were based on either a copper(I) cation template[109] or donor–acceptor aromatic interactions.[110] The first example of an anion-templated synthesis of a rotaxane was reported by Vögtle and co-workers: a phenoxide "half-axle" component, being held in place by hydrogen bonding to a macrocyclic isophthalamide motif, was trapped by an benzylic electrophile stoppered on one side, with the anionic template being consumed in the synthesis of the interlocked structure (Figure 32).[111]

Related rotaxanes have since been prepared by Schalley and co-workers, where a phenolate-containing thread once again forms a hydrogen bond to an isophthalamide macrocycle, but stoppering in this case furnishes the interlocked structure with the phenolate remaining intact (Figure 33).[112]

In an approach inspired by the copper(I)-templated method of the Sauvage research group, Beer and co-workers synthesized interlocked structures by use of a spherical chloride ion template (Figures 34 and 35).[113] In preparing the rotaxane[114] and in what was the first example of an anion-templated catenane[115] species, the chloride ion is held as part of a tight ion pair with a methylpyridinium diamide motif. The halide ion is coordinatively unsaturated, which means a second, neutral isophthalamide hydrogen-bond-donating species can associate to create an orthogonal array. This assembly is supported by supplementary aromatic donor–acceptor interactions and hydrogen bonding. The use of the Grubbs ring-closing metathesis catalyst facilitated isolation of the [2]rotaxane and [2]catenane in 47% and 45% yield, respectively. The necessity of the chloride ion template is demonstrated by no interlocked product being observed in either case when the hexafluorophosphate salt of the methylpyridinium component is used. By exchanging the chloride ion for the noncoordinating hexafluorophosphate ion it was shown that the resulting unique interlocked cavities selectively bound chloride over more basic oxoanions such as dihydrogen phosphate and acetate in competitive $CDCl_3$/CD_3OD solvent mixtures.

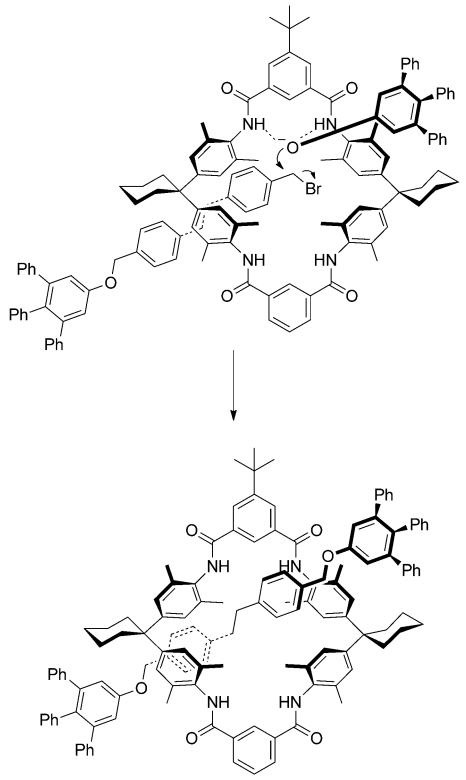


Figure 32. Vögtle's anion-templated rotaxane synthesis.

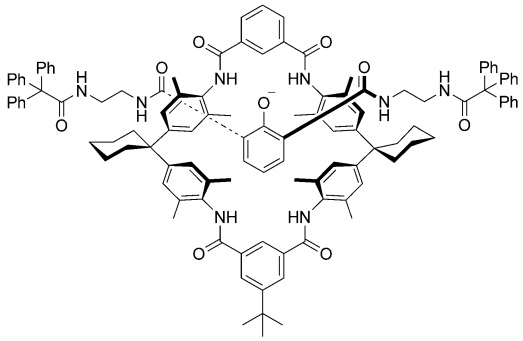


Figure 33. Schalley's phenoxide rotaxane.

Very recently, bis(triazole)pyridinium analogues of these species have been prepared, with both the rotaxane[77] and catenane[78] showing selectivity for the halides (Cl^- to I^-) over dihydrogen phosphate in $CDCl_3/CD_3OD$ (1:1). The pyridinium axle motifs have also been exchanged for imidazolium[118] and triazolium[119] in the construction of further rotaxanes. A rotaxane has also been synthesized where the axle component—an iodotriazolium—coordinates to the

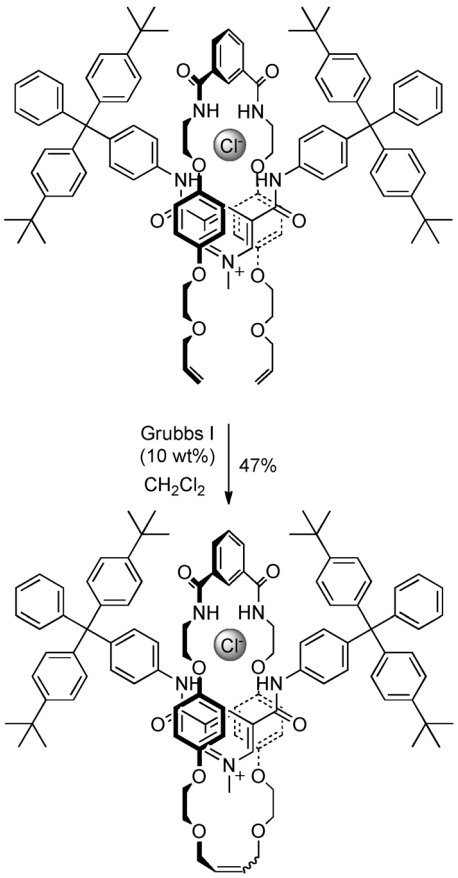


Figure 34. Beer's first synthesis of a chloride-templated rotaxane.

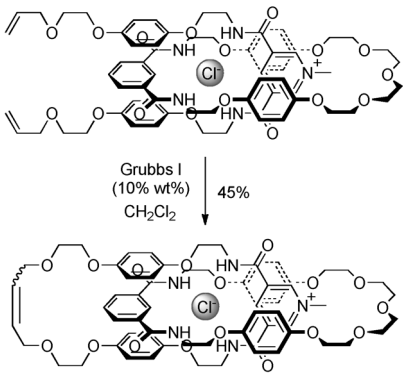


Figure 35. Beer's first synthesis of a chloride-templated catenane.

halide ion by means of a halogen bond (Figure 36).[120] The hexafluorophosphate salt of the iodotriazolium rotaxane bound the halides in the order $I^- > Br^- > Cl^-$ in $CDCl_3$/CD_3OD/D_2O (45:45:10). The authors attributed this trend to the accessibility of the molecular cavity and the weaker competition for the more lipophilic halide by the aqueous solvent media.

Beer and co-workers have also reported upon double cyclization strategies for preparing doubly charged [2]catenanes. For example, two equivalents of methylpyridinium precursors were templated by one equivalent of a chloride

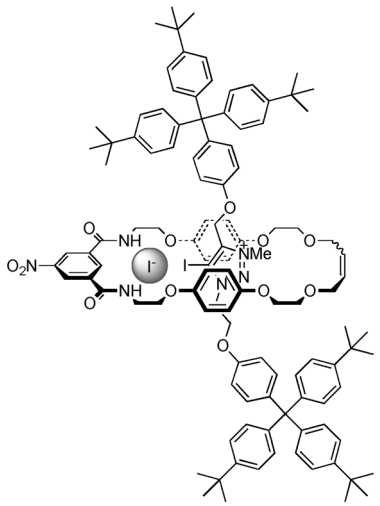


Figure 36. Beer's halogen-bonding, iodide-selective, iodotriazolium rotaxane.

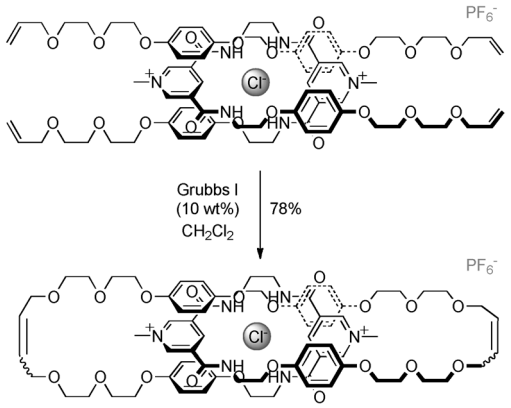


Figure 37. [2]Catenane synthesis with a chloride ion template by double cyclization of methylpyridinium precursors.

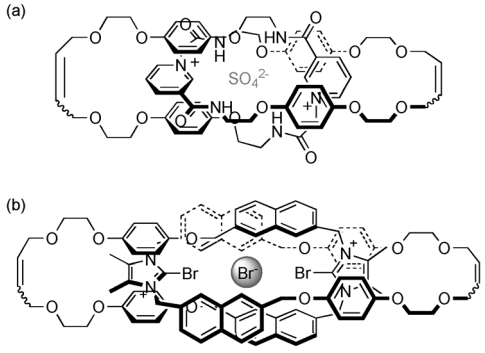


Figure 38. Structures of [2]catenanes prepared by double cyclization around sulfate (a) and bromide templates (b).

ion, which led to catenane formation in a yield of 78% (Figure 37).[121] Further catenanes have been prepared by cyclizing pyridinium nicotinamide precursors around sulfate[122] and bromoimidazolium precursors around bromide ions[123] (Figure 38).

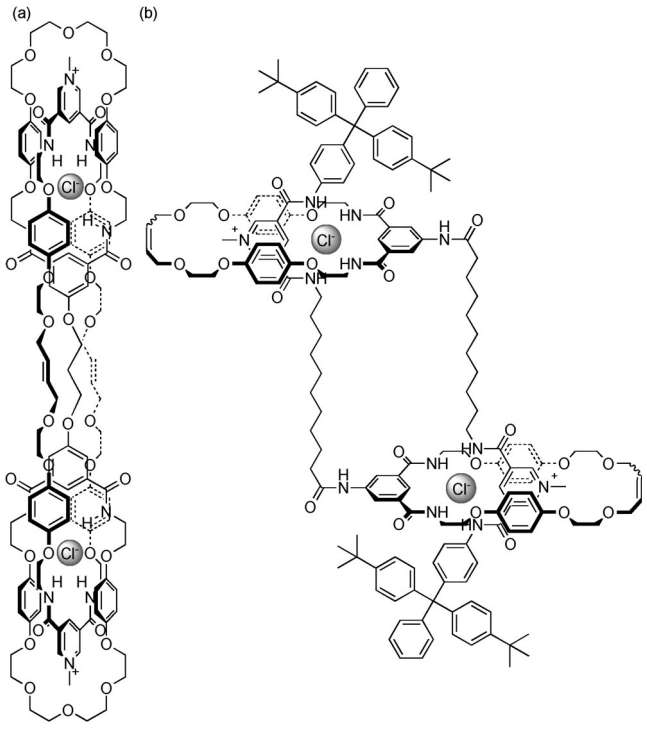


Figure 39. Chloride-templated a) "handcuff" catenane and b) "Janus" rotaxane.

The power of a halide ion template is elegantly demonstrated by the production of exotic structures, including a "handcuff" catenane[124] and a "Janus" rotaxane[125] (Figure 39). In both cases, the essential role of the chloride template was demonstrated by the failure to form the product when the hexafluorophosphate salts of the pyridinium precursors were used.

However, Grubbs catalysts are expensive and intolerant of certain functionalities (e.g. pyridyl). An alternative method has therefore been developed, where a diamine is reacted with a bis-acid chloride in the presence of an axle or macrocycle to produce a rotaxane[126] or catenane[127] (Figure 40). This method was exploited in the synthesis of a doubly charged rotaxane (produced by methylation of the pyridyl rotaxane in Figure 40), which was capable of selectively binding chloride in a 65:35 mixture of $[D_6]$acetone and D_2O.[126b]

A very recent development has been the use of the pyridine-*N*-oxide in place of methylpyridinium to synthesize anion-templated neutral rotaxanes (Figure 41).[128] Here, the rotaxane was prepared by stoppering a pyridine-*N*-oxide axle precursor, threaded through a bis(isophthalamide) macrocycle by using the CuAAC reaction. The presence of a chloride ion was still required for formation of the interlocked structure. Impressively, the isolated rotaxanes were capable of binding halides ($Cl^- > Br^- > I^-$) in $CDCl_3$/CD_3OD/D_2O (45:45:10).

Another example of constructing interpenetrated and interlocked species by using an anion template and neutral components comes from using indolocarbazole. For example, an indolocarbazole may thread through an isophthalamide

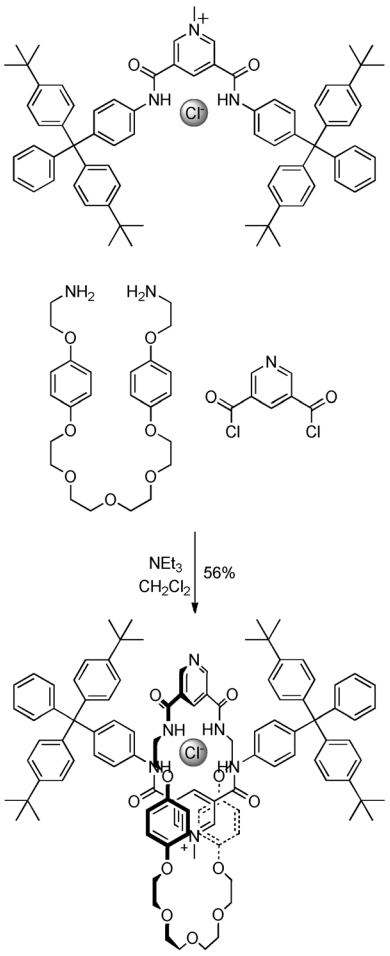


Figure 40. Beer's alternative diacid chloride/diamine "clipping" rotaxane synthesis.

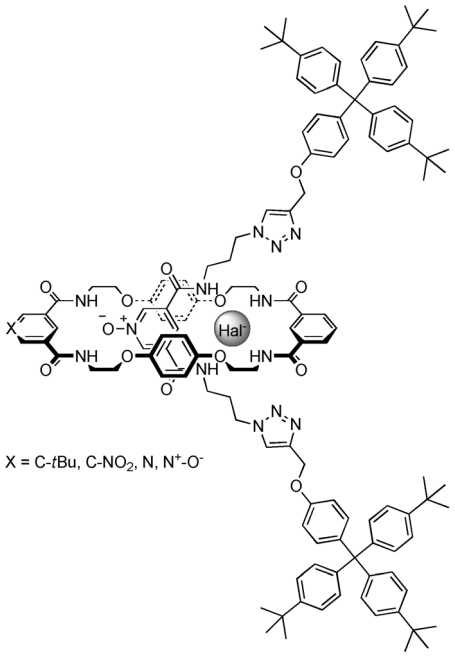


Figure 41. Beer's neutral pyridine-*N*-oxide rotaxane capable of binding halides in aqueous solvent.

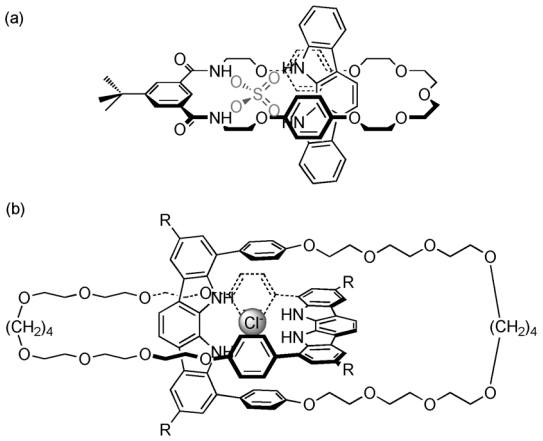


Figure 42. An indolocarbazole-containing anion-templated pseudorotaxane (a) and catenane (b).

macrocycle with either fluoride or sulfate ions acting as the template,[129] and catenanes have been prepared where two indolocarbazole units coordinate around a chloride ion (Figure 42).[130]

To date, the anion-templated synthesis of interlocked molecules has been dominated by the use of spherical halide (in particular chloride) templates. The Beer research group has recently disclosed the preparation of a nitrate-templated rotaxane (Figure 43).[131] By using an axle precursor containing both methylpyridinium diamide and isophthalamide motifs, the polyatomic nitrate anion can template the formation of a pseudorotaxane with an isophthalamide macrocycle, which may be stoppered by the CuAAC "click" reaction. Evidence for the templating role of nitrate was provided by a reduced yield (0–15% compared to 24%) being

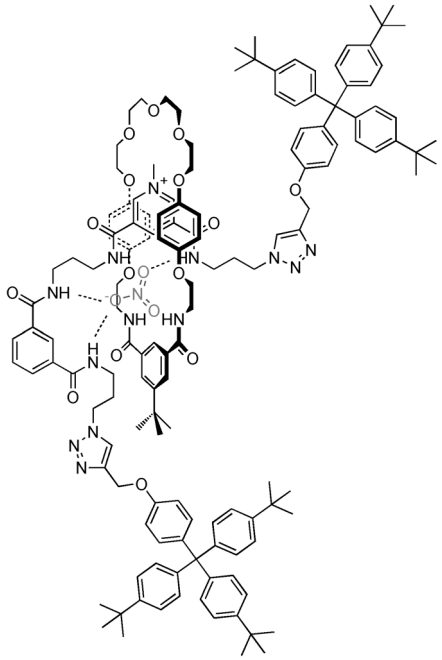


Figure 43. Beer's nitrate-templated rotaxane.

observed when other anions (chloride, bicarbonate, dihydrogen phosphate, and acetate) were used in place of nitrate in the reaction. The rotaxane was demonstrated to selectively recognize nitrate over other singly charged oxoanions (bicarbonate, dihydrogen phosphate, and acetate) in $CDCl_3$/CD_3OD/D_2O (45:45:10).

3.5. The Optimization and Discovery of Anion-Templated Anion Receptors by Dynamic Combinatorial Chemistry

By its very nature, DCC appears to offer an excellent way of preparing receptors for specific guests such as anions.[132] This is illustrated by refinements to the "molecular oysters" receptors of Kubik and co-workers that have been developed in collaboration with Otto.[133] In their first report, a molecule consisting of two identical cyclopeptide macrocycles connected by a single disulfide linker was introduced into a DCL containing a range of dithiol spacers (Figure 44a). Exchange

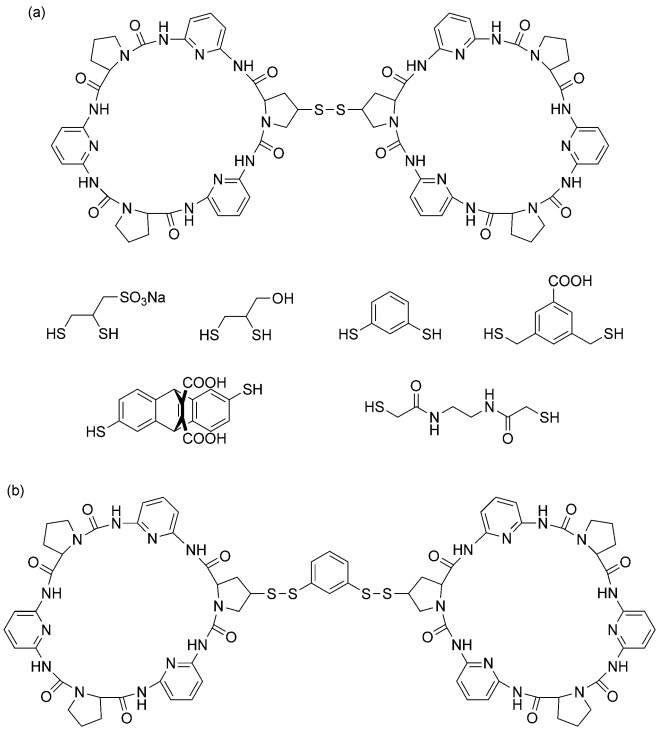


Figure 44. DCC for "molecular oysters" by Kubik and Otto: a) the components of the DCL and b) the structure of the receptor with a single linker possessing the highest association constants for iodide and sulfate.

of the sulfide bonds allowed for a variety of possible receptors to be generated. The addition of iodide or sulfate (as their potassium salts) to the DCL led to specific receptors being favored and amplified (Figure 44a).[133a] After isolation of these receptors, the strongest binding affinities were observed with the receptor depicted in Figure 44b, with association constants of $\log K_a(I^-) = 4.75$ and $\log K_a(SO_4^{2-}) = 6.83$ measured in CH_3CN/H_2O (2:1), which were an order of magni-

tude greater than for the diamide-linked receptor discussed in Section 2.1.2. In a second communication, the use of an alternative library allowed the optimization of a receptor with two linkers between the macrocycles. In this case, one of the amplified receptors was able to bind sulfate with $\log K_a = 8.67$ (in 2:1 CH_3CN/H_2O).[133b]

Beeren and Sanders have since taken the use of DCC one stage further by creating and then investigating novel anion receptors.[134] A library was constructed containing a disubstituted ferrocene scaffold (specifically a dihydrazide), with isophthalaldehyde and 4-methylbenzylhydrazide. The addition of $TBAH_2PO_4$ to the DCL led to magnification of a linear receptor that in fact binds two $H_2PO_4^-$ ions (Figure 45).[135]

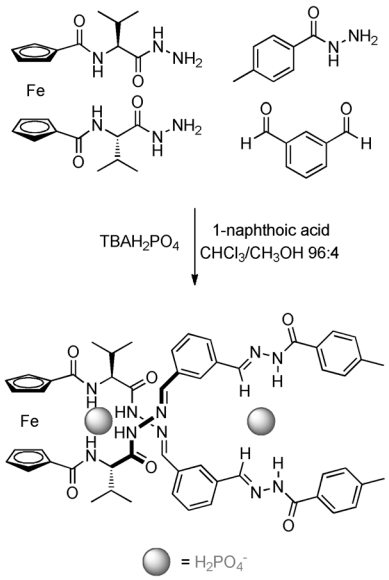


Figure 45. Linear receptor for dihydrogen phosphate by Beeren and Sanders.

4. Progress in Anion Sensing

The importance of anions in biology and their environmental impact has meant that ways to selectively detect and report, that is, sense, the presence of an anionic species, have been intensively investigated. Indeed, this area of anionic supramolecular chemistry saw significant early advances being made, as summarized by Beer and Gale in 2001.[16] Here, we focus on some of the key developments since that date.

Molecular sensors for anions may be classified by the macroscopic response produced upon binding the anion: electrochemical or optical. Optical anion sensors may be further classified as either fluorescent or colorimetric. While fluorescent sensors may be exceptionally sensitive, colorimetric sensors allow for the possibility of detection by the human eye.

4.1. Reporter-Spacer-Receptor Anion Sensors

A popular approach to construct an anion sensor is to link a binding site to a suitable redox-active or optical reporter group, which may be termed the reporter-spacer-receptor approach (Figure 46).

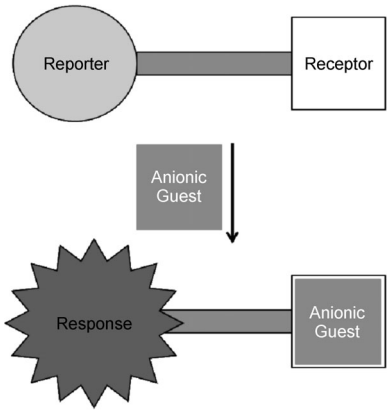


Figure 46. Schematic representation of sensing the binding of an anionic guest by the reporter-spacer-receptor approach.

4.1.1. Electrochemical Anion Sensors

A range of sensors capable of electrochemically detecting anions have been constructed by incorporating the redox-active ferrocene moiety.[136] Anion recognition leads to a cathodic shift of the ferrocene/ferrocenium (Fc/Fc^+) redox couple, as measured by cyclic voltammetry. Although the earliest examples of ferrocene anion sensors were typically based on secondary amides,[137] the metallocene has subsequently been incorporated into a larger number of sensors, where the anion is bound by a variety of hydrogen-bonding groups.[138] An impressive recent example is the ferrocenylurea receptor depicted in Figure 47 which is able to electrochemically discriminate between enantiomers of chiral carboxylate anions in acetonitrile.[139]

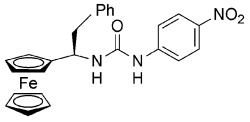


Figure 47. Tucker's chiral ferrocenylurea sensor capable of electrochemically discriminating between enantiomers of a chiral carboxylate anion.

Since the turn of the millennium, a number of alternative redox-active moieties have also been investigated as reporting groups in electrochemical anion sensors (Figure 48). For example, Fabbrizzi and co-workers demonstrated that cathodic shifts of the Co^{II}/Co^{III} bipyridyl redox couple are observed in aqueous acetonitrile electrolyte solutions upon the binding of anions by the convergent array of imidazolium groups in a cagelike receptor (Figure 48a).[140] Meanwhile, Beer et al.

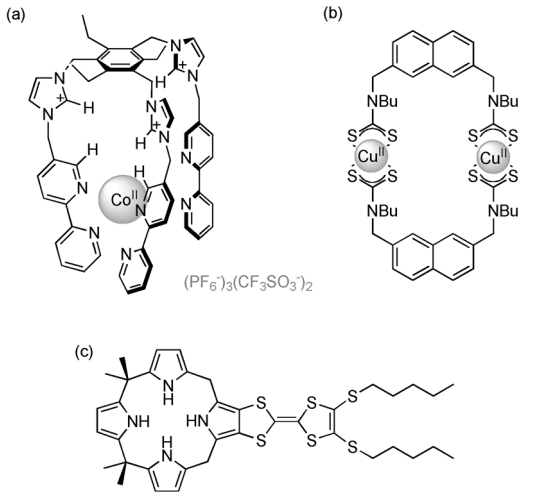


Figure 48. Electrochemical anion sensors: a) Fabbrizzi's Co^{II}-tri(imidazolium) cage, b) Beer's Cu^{II}-dithiocarbamate macrocycles, and c) a TTF-calixpyrrole by Jeppesen and Becher.

have shown that the dithiocarbamate macrocycle depicted in Figure 48b exhibits a cathodic shift in the Cu^{II}/Cu^{III} redox couple upon the addition of dihydrogen phosphate.[141] Non-metallic electrochemical anion sensors have also been synthesized. For example, the redox-active tetrathiafulvalene (TTF) has been fused to a halide-binding calixpyrrole, which allows for the electrochemical sensing of halide ions in acetonitrile (Figure 48c).[142]

4.1.2. ***Optical Anion Sensors***

Many fluorescent anion sensors have been constructed by using the reporter-spacer-receptor approach described above, with a variety of chemical functionality being used as the signaling unit. Examples incorporating organic reporter groups such as anthracene[143] and pyrene,[144] as well as the transition metal luminescent motif Ru^{II} bipyridyl[145] have continued to be utilized.

An addition to these signaling units has been the naphthalimide group.[146] The first naphthalimide-containing anion sensor was described by Gunnlaugsson et al. (Figure 49).[147] The addition of acetate and dihydrogen

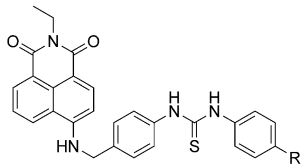


Figure 49. Gunnlaugsson's fluorescent naphthalimide anion sensor.

phosphate to this receptor in DMSO leads to a quenching of fluorescence, as a result of enhanced photoelectron transfer (PET) from the electron-rich thiourea to the naphthalimide.

Another organic chromophore investigated recently as a fluorescent signaling unit is 2,6-bis(arylethynyl)pyridine.[148]

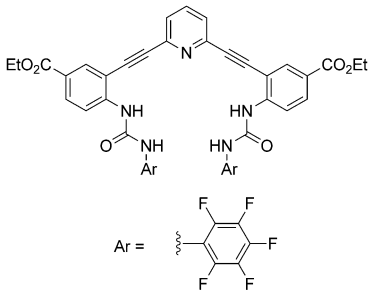


Figure 50. A 2,6-bis(arylethynyl)pyridine fluorescent anion sensor by Johnson and Haley.

Johnson, Haley, and co-workers reported that the receptor in Figure 50 (once protonated) exhibits an "off to on" fluorescence response to added chloride in acetonitrile. Analogous compounds, where the central pyridine is replaced by a benzene ring, have also been found to be fluorescently responsive to anions.[149]

A major aim of anion sensory research has been the development of systems capable of detecting anionic species in biological media. Optical reporter groups have tended to be chosen to maximize sensitivity, while minimizing probe invasiveness. In addition, direct metal–anion coordination allows for operation in highly competitive aqueous environments. Parker and co-workers have used sensitized Ln^{III} complexes to sense anions both in vitro and in cells, with the sharp emission bands of the Eu^{III} (and Tb^{III}) cations allowing for ratiometric analysis, thus avoiding any issues regarding the concentration of the complex. For example, the Eu complex in Figure 51a detects citrate in seminal fluid.[150]

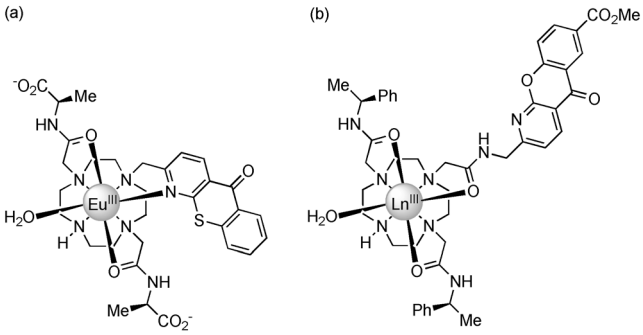


Figure 51. Lanthanide complexes used in the determination of levels of citrate in seminal fluid (a) and mitchrondrial bicarbonate concentration (b).

The remarkable selectivity of the complex in response to citrate over the structurally similar lactate anion—both metabolites which may be found in human fluid media—is vital. As depleted levels of citrate are a symptom of prostate cancer, it has been argued that this complex could be used in cancer screening. Another impressive example has been the study of bicarbonate concentrations in the mitochrondria of living cells by use of a mixture of the Eu and Tb complexes of the same ligand (Figure 51b), which allows for the necessary

ratiometric analysis.[151] Modulation of the Eu emission (by coordination of bicarbonate) is varied by changing the levels of CO_2 in the cell incubation atmosphere.

4.1.3. Interlocked Structures Capable of Selective Anion Sensing

Beer and co-workers have taken their interlocked molecules capable of selective anion recognition and shown that by the appendage and incorporation of reporter groups it is possible to create rotaxanes and catenanes capable of selective sensory responses to anions.

For example, a [2]rotaxane[152] and a [2]catenane[153] with an appended ferrocene unit have been prepared by using a chloride ion template. Their hexafluorophosphate salts demonstrate the selective electrochemical sensing of chloride ions in an acetonitrile-based electrolyte (Figure 52). Specifically, the maximum cathodic shift in the Fc/Fc^+ redox couple was observed upon the addition of one equivalent of the halide ion. With oxoanions, further cathodic shift perturbations were observed upon the addition of excess anion. This observation was rationalized by considering that only chloride is capable of penetrating the interlocked cavity, whereas the polyatomic oxoanions associate at the cavity's periphery.

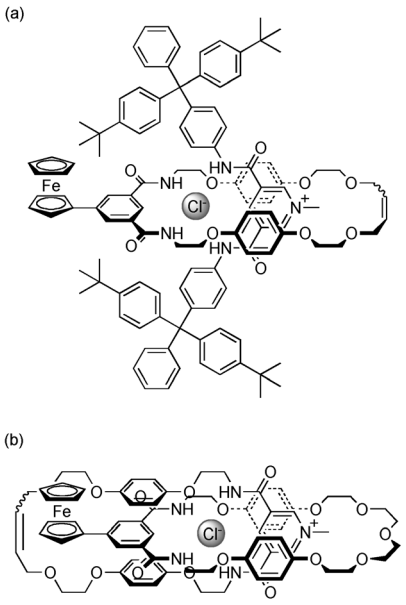


Figure 52. Beer's ferrocene-appended rotaxane (a) and catenane (b) that can selectively sense chloride ions bound within the interlocked cavity.

Luminescent rotaxanes incorporating a 4,4′-diamide-2,2′-bipyridyl macrocycle to allow for complexation of Re^I and Ru^{II} ions have also been reported (Figure 53).[154] The addition of chloride and dihydrogen phosphate to samples of the metalated rotaxanes dissolved in aqueous acetone (containing up to 30% H_2O) led to enhancement of the metal–ligand charge-transfer (MLCT) luminescence. The trend in calculated association constants—chloride being bound more strongly than dihydrogen phosphate—was in agreement with that obtained from ^1H NMR titrations.

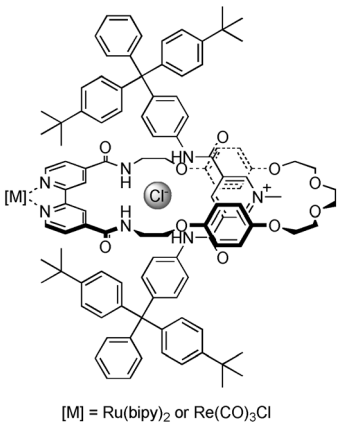


Figure 53. Rotaxane capable of selectively sensing chloride by modulation of the transition-metal/bipyridyl luminescence.

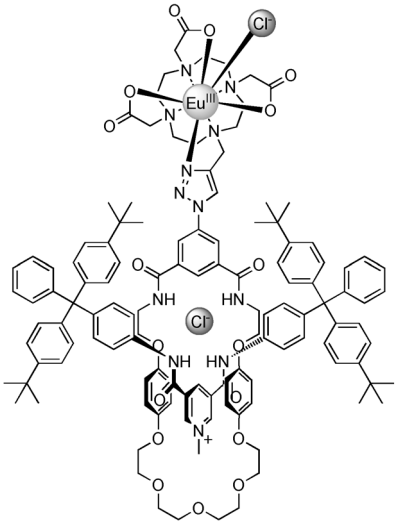


Figure 54. Rotaxane capable of selectively sensing chloride by modulation of the Eu^{III} ion luminescence.

In collaboration with Faulkner, Beer and co-workers have also reported a lanthanide-appended rotaxane that responds to changing chloride concentration (Figure 54).[155] The luminescence behavior is modulated by the binding of the chloride ion first to the ninth coordination site of the Eu^{III} cation, which leads to quenching of the lanthanide emission. This is subsequently restored upon binding of the second equivalent of chloride within the rotaxane cavity.

The ability of higher order interlocked structures to provide alternative modes of sensory selectivity is demonstrated by ferrocene-[156] and naphthalene-functionalized[157] [3]rotaxanes (Figure 55). The Fc/Fc^+ redox couple of the ferrocene rotaxane (Figure 55a) undergoes a cathodic shift upon the addition of up to two equivalents of chloride, consistent with binding of the halide ion within the two interlocked cavities. The addition of sulfate to the free host led to complex, but different, electrochemical behavior; ^1H NMR titrations indicated that the neutral rotaxane binds the dianion in a 1:1 stoichiometry. For the naphthalene

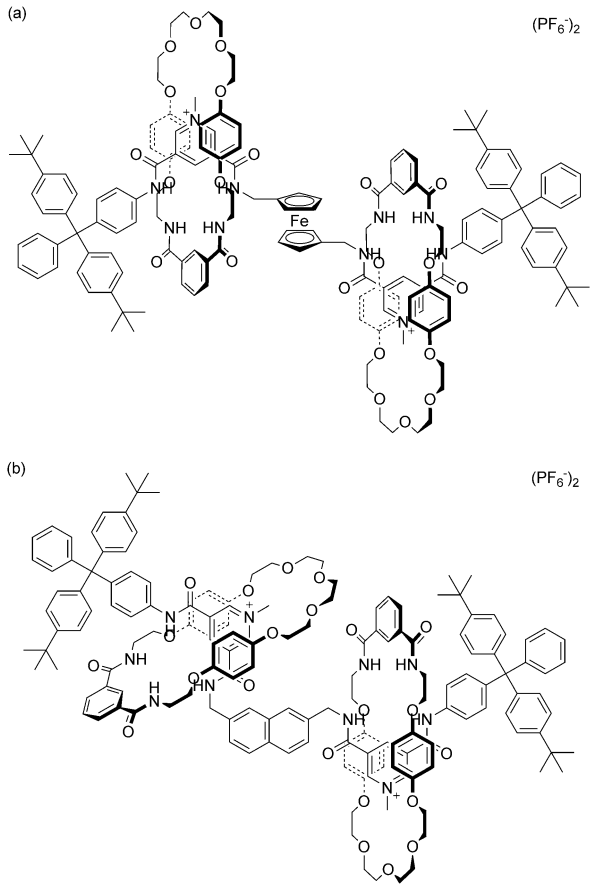


Figure 55. Beer's [3]rotaxanes which can selectively sense anions a) electrochemically and b) by fluorescence.

rotaxane (Figure 55b), the addition of chloride, bromide, and acetate simply led to a modest enhancement of the naphthalene emission. In the case of sulfate, a dramatic quenching was initially observed before restoration and enhancement. This result is attributed to the polyatomic sulfate dianion first coordinating between the two pyridinium units (in a 1:1 binding mode) close to the naphthalene moiety, and then coordinating to each pyridinium moiety separately (in a 2:1 binding mode) and being hence further away from the fluorescent moiety.

B. D. Smith et al. have reported the use of squaraine rotaxane shuttles as reversible optical sensors for chloride ions (Figure 56). In the first report,[158] they demonstrated that the addition of chloride resulted in the tetralactam macrocycle of the rotaxane being displaced, thereby leading to a threefold increase in the deep-red fluorescence emission from the squaraine dye. Removal of the chloride, led to a complete reversal of this process. Prototype dipsticks were prepared (by adsorption of the rotaxane onto reverse-phase silica), which were able to detect chloride ions in aqueous solution. Very recently, an improved shuttle has been reported.[159] Not only containing a more stable dihydroxy-substituted dye, the rotaxane was able to sense anions ratiometrically as a result of anion binding modulating the emission wavelength, rather than changing the emission intensity.

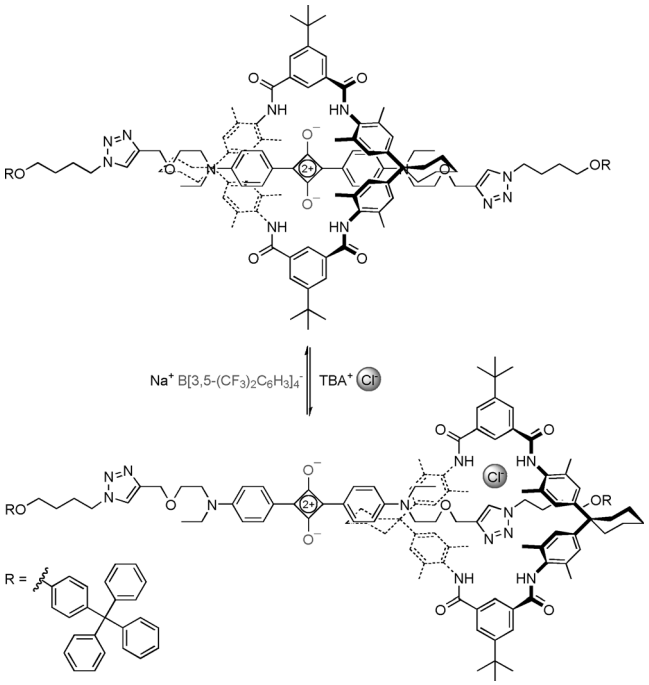


Figure 56. B. D. Smith's squaraine [2]rotaxane shuttle which senses chloride.

4.2. Indicator-Displacement Assays for Anions

An alternative design for optical anion sensors is the use of indicator-displacement assays (IDAs). Here, an indicator is bound weakly by the receptor, so that it is displaced upon addition of guest, thereby giving either a colorimetric or fluorescence response (Figure 57). One of the principal advantages of this approach is the possibility of using different indicators with the same receptor.[160]

The pioneering work on indicator-displacement assays for anions was reported by Metzger and Anslyn just before the start of the new millennium. For example, a 1,3,5-trisubstituted-2,4,6-triethylbenzene scaffold containing three guanidinium groups was shown to selectively sense the levels of citrate in commercially available soft drinks by using 5-carboxyfluorescein as an indicator (Figure 58).[161] Anslyn's research group has also reported a polyguanidinium-appended scaffold that fluorescently sensed inositol triphosphate in methanol[162] and an assay that colorimetrically sensed heparin.[163]

The use of metallic complexes allows for the facile generation of

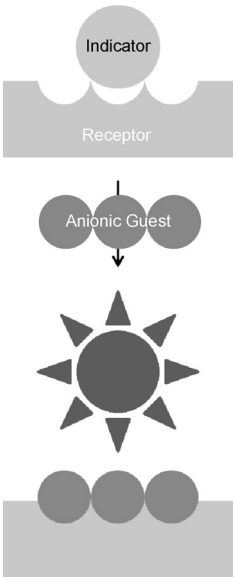


Figure 57. Schematic representation of sensing the binding of an anionic guest by an indicator-displacement assay approach.

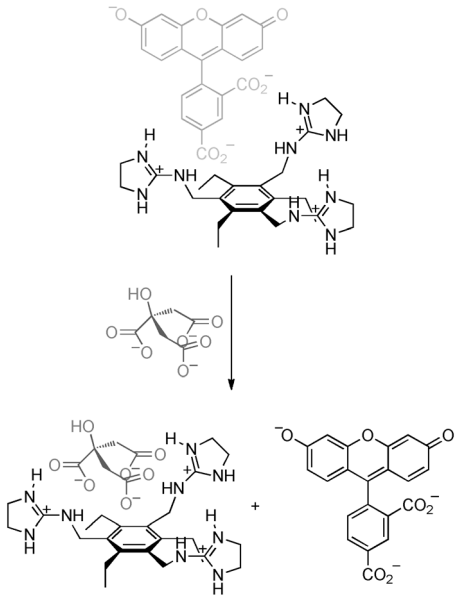


Figure 58. Anslyn's demonstration of IDAs by sensing citrate in aqueous solvent media.

assays that may operate in aqueous solvent media. Fabbrizzi et al. reported upon a dicopper cage that could selectively detect (by fluorescence) bicarbonate in water, by displacement of a coumarine indicator (Figure 59).[164]

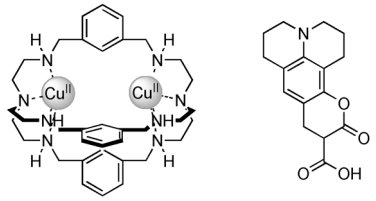


Figure 59. Fabrizzi's dicopper cage (and coumarin indicator) that can selectively detect bicarbonate.

4.3. Anion Chemodosimeters

Chemodosimeters are examples of a third class of anion sensor, which typically provide a colorimetric response (Figure 60). The anion may either form a covalent bond to the receptor, thus causing, for example, a change in the color of the molecule or, alternatively, the anion might catalyze a chemical transformation of the receptor molecule. Considering the irreversible change in the constitution of the "receptor", it is arguable whether chemodosimeters are genuinely supramolecular in nature. For completeness, we provide select examples here to give a flavor of the field.

Two reports of anion chemodosimeters from the research group of Martínez-Máñez are presented in Figure 61. In the first, the cyclization of a yellow pent-2-en-1,5-dione to the magenta pyrylium allowed for discrimination between the olefinic isomers maleate and fumarate, as the *cis* isomer maleate is able to form strong hydrogen bonds to the enol group (significantly enhancing the electron density on the

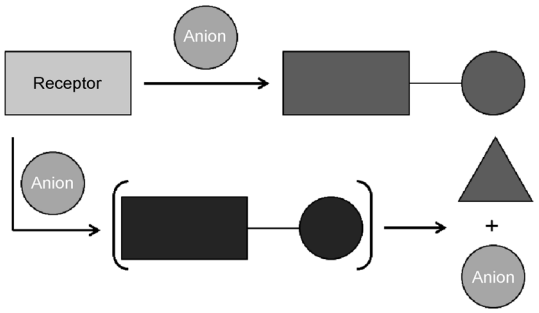


Figure 60. Schematic representation of sensing the presence of anions by chemodosimeters.

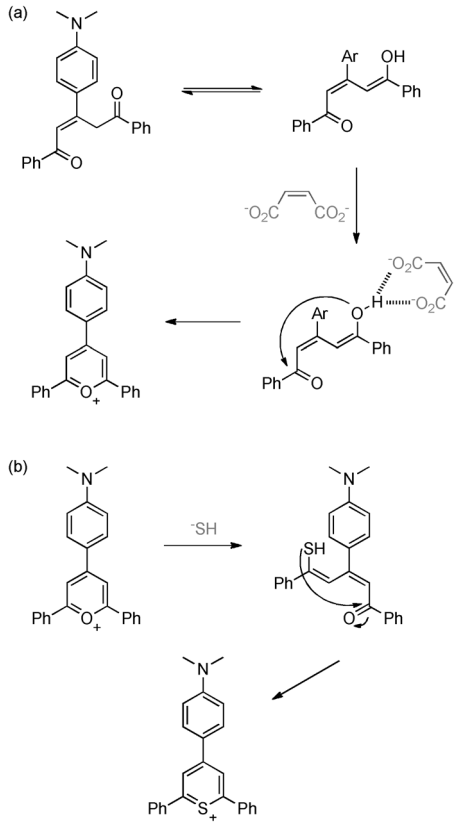


Figure 61. Examples of chemodosimeters that sense a) maleate and b) hydrogen sulfide anions.

oxygen atom), thereby allowing for accelerated cyclization (Figure 61 a).[165] In a second paper, the pyrylium product has been shown to undergo a ring opening followed by a ring closing to form a thiopyrylium upon the addition of the sulfide anion, which is marked by a change in color from magenta to blue (Figure 61 b). Impressive selectivity over a wide range of anions was reported.[166]

The cyanide ion is a very common target for detection by chemodosimeters, as its high nucleophilicity allows for the design of receptors that will selectively react with this particular anion. For example, Sessler and co-workers reported a colorimetric sensor for cyanide based on a benzil analogue (Figure 62). Solutions of the chemodosimeter in

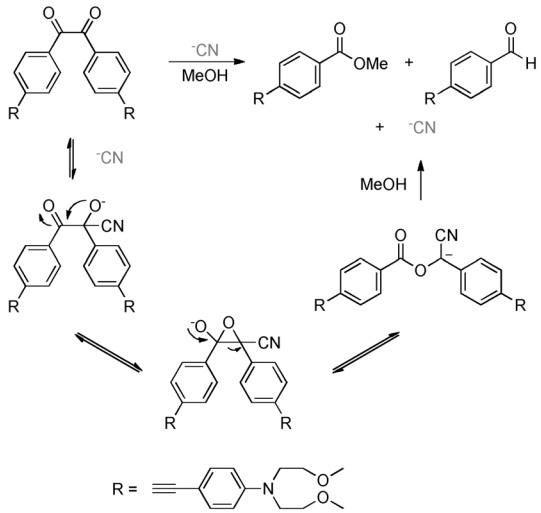


Figure 62. Sessler's benzil chemodosimeter which selectively senses cyanide.

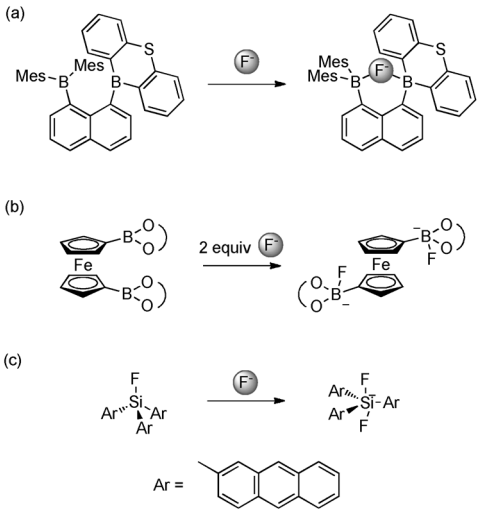


Figure 64. Chemodosimeters for detecting fluoride: a) Gabbaï's diborylnaphthalene; b) Aldridge's diboronate ferrocene molecules, and c) Yamaguchi's trianthrylfluorosilane.

a 70:30 mixture of MeOH and H_2O are yellow, but the addition of low concentrations of cyanide results in the solution becoming colorless, with a high selectivity across a range of anions tested.[167]

Hudnall and Gabbaï have prepared an ammonium borane which is also highly selective for cyanide (Figure 63).[168] In the highly competitive 60:40 mixture of H_2O and DMSO, cyanide

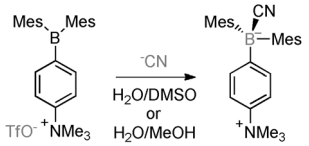


Figure 63. A cationic ammonium borane which is highly selective for the binding and sensing of cyanide.

is bound with $K_a = 3.9 \times 10^8\,\text{M}^{-1}$, while a wide range of halides (including fluoride) and oxoanions exhibit no binding, as evident by monitoring the UV/Vis absorbance of the receptor. In a further experiment it was found that the fluorescence of a 5 μM sample of the receptor is quenched by 1 equivalent of cyanide in a 90:10 mixture of H_2O in MeOH.

Fluoride is another nucleophilic anion that is commonly sensed by chemodosimetric methods. In particular, a vast number of receptors have been prepared which exploit the formation of B–F[169] and Si–F bonds (Figure 64). For example, the diboron naphthalene compound is capable of binding fluoride in a bidentate fashion with an exceptionally high association constant of $5 \times 10^9\,\text{M}^{-1}$ in THF and a change in color from yellow to colorless.[170] The addition of two equivalents of fluoride to the ferrocene diboronate under aerobic conditions leads to a color change from orange to pale green, as a result of the fluoride inducing the in situ oxidation of ferrocene to ferrocenium.[171] In the case of the trianthrylsilane, an enhancement in fluorescence occurs because of alteration of the through-space interactions between the three anthracene moieties upon binding of fluoride (in THF) to the central silicon atom.[172]

4.4. Surface-Attached Anion Sensors

Research into anion sensors has traditionally focused on the design and synthesis of solution-based receptors equipped with appropriate reporter groups. However, receptors attached to surfaces as self-assembled monolayers (SAMs) can exhibit a number of advantages over their solution-phase analogues.[173] First, the receptor is typically more preorganized on a surface, which may lead to amplification of a sensory response. Second, there is the possibility of recycling a surface-attached sensor, and third, by immobilizing a receptor to a surface, it is possible to use a water-insoluble receptor in aqueous conditions.

4.4.1. Surface-Attached Anion Sensors with Reporter Groups

The redox-active ferrocene motif has been used in a number of surface-confined anion sensors. The first example was demonstrated by Astruc and co-workers, where a simple amidoferrocenyl alkylthiolate was adsorbed onto a gold electrode surface, and a large cathodic shift of the Fc/Fc^+ redox couple was observed upon the addition of dihydrogen phosphate.[174] The same research group has also attached amidoferrocenyl alkanethiols to gold nanoparticles, by constructing mixed monolayers of the ferrocene-containing thiol and dodecanethiol.[175] Beer et al. have since demonstrated that immobilization of ferrocene-containing anion receptors to gold surfaces leads to amplification of the electrochemical response (Figure 65 a,b).[176] For example, the ferrocene diamide SAM (Figure 65 a) exhibits a −100 mV cathodic shift in the Fc/Fc^+ redox couple upon addition of chloride, compared to a −40 mV cathodic shift for the receptor dissolved in the electrolyte solution (2:1 CH_2Cl_2/

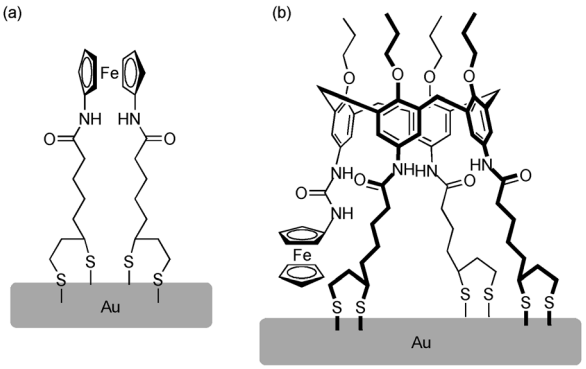


Figure 65. Electrochemical anion-sensing SAMs absorbed on to gold, based on a) ferrocene diamide and b) ferrocenylurea calixarene receptors.

CH_3CN).[176a] The redox couple of the calixarene functionalized with the ferrocenylurea (Figure 65b) undergoes a similar enhancement in the cathodic shift (−115 mV on the surface versus −60 mV in solution, 1:1 CH_2Cl_2/CH_3CN).[176b]

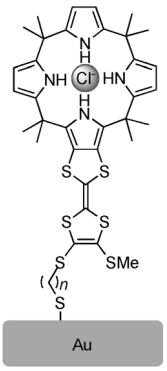


Figure 66. Jeppesen's calixpyrrole/TTF sensor capable of electrochemically detecting chloride.

Jeppesen and co-workers have reported upon a TTF-calixpyrrole chloride sensor adsorbed onto a gold surface (Figure 66).[177] In this case, the chloride-induced cathodic shift of the first oxidation wave of the TTF group in dichloromethane was significantly less than that of the solution-based analogue. This was attributed by the authors to the surface-confined receptor being sterically inhibited from undergoing rearrangement from its ground state 1,3-alternate conformation to the cone conformation that calix[4]pyrroles adopt when binding chloride ions in solution.

Sophisticated redox-active chloride sensors based on rotaxane SAMs have been prepared by Beer, Davis, and co-workers.[178,179] In the first reported system, a ferrocene-appended macrocycle was confined to a surface as part of a rotaxane by use of a thiotic acid appended pentaphenylferrocene-stoppered axle (Figure 67).[178] Upon removal of the chloride template, the rotaxane was able to sense chloride in electrolytic acetonitrile solutions through a cathodic shift in the Fc/Fc^+ redox wave. Excellent selectivity in sensing was observed: with chloride being sensed in the presence of a 100-fold excess of dihydrogen phosphate.

Very recently, an osmium-bipyridyl macrocycle has been incorporated as part of a rotaxane SAM (Figure 68).[179] As before, removal of the chloride template allows for electrochemical sensing of chloride in electrolytic acetonitrile solutions, this time by a cathodic shift in the Os^{II}/Os^{III}-bipyridyl redox wave.

Beer, Davis et al. have also reported an optical surface-attached anion sensor consisting of zinc(II) metalloporphyrins assembled onto gold nanoparticles (Figure 69).[180] These were able to bind chloride and dihydrogen phosphate in

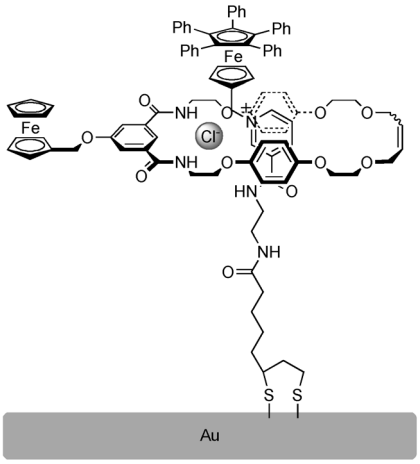


Figure 67. Surface-confined rotaxane capable of selectively sensing chloride by a cathodic shift in the Fc/Fc^+ redox wave.

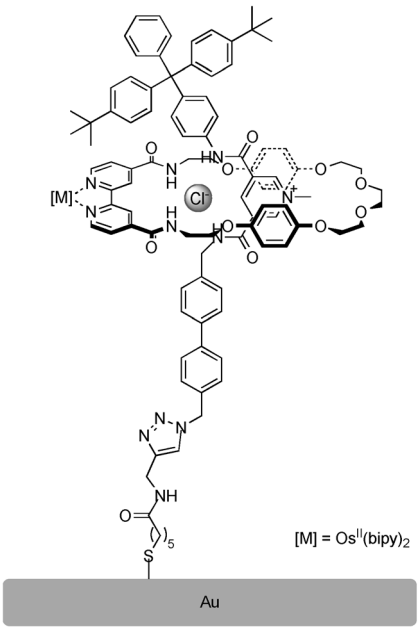


Figure 68. Surface-confined rotaxane capable of sensing chloride by a cathodic shift in the Os^{II}/Os^{III}-bipyridyl redox wave.

dichloromethane and DMSO, as measured by UV/Vis titration experiments, with higher affinities than when the metalloporphyrins were free in solution.

Gunnlaugsson and co-workers have prepared lanthanide complexes on gold nanoparticles for luminescent sensing of phosphate ions in aqueous solution (Figure 70).[181] The sensing of coordinating anions such as carboxylates and phosphates occurs by the switching off of the Eu^{III} emission by displacement of the β-diketone ligand, which acts as an "antenna" for the Ln^{III} ion. Phosphate-containing molecules such as AMP, ADP, ATP, cyclic AMP, or NADP were found to quench the luminescence to a greater degree over other anions. However, complete quenching was only observed with flavin monophosphate.

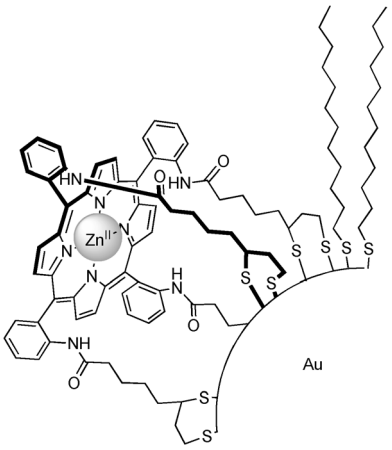


Figure 69. Zinc metalloporphyrin nanoparticle sensor by Beer and Davis capable of optical anion detection.

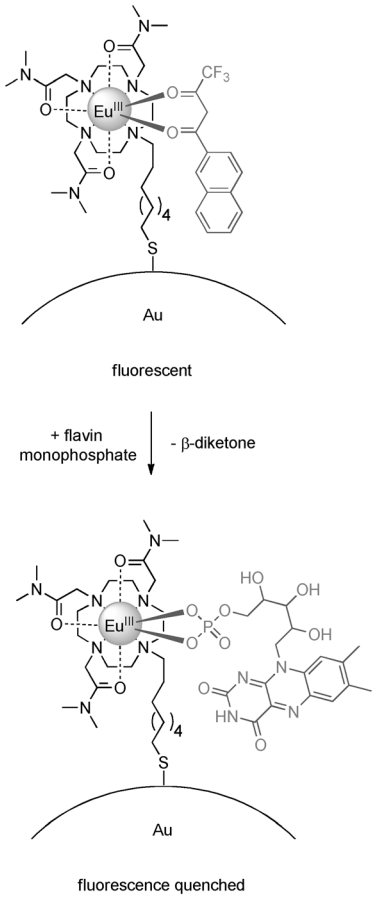


Figure 70. Gunnlaugsson's luminescent lanthanide nanoparticle sensor for optically detecting flavin monophosphate.

Crego-Calama and co-workers produced fluorescent anion sensors by decorating quartz slides with fluorophores and hydrogen-bond-donating groups (Figure 71).[182] Amino functionalities were first introduced onto a glass slide, which were then reacted to append the fluorophore and supporting hydrogen-bonding unit. Impressively, the combination illustrated here was able to selectively sense, in acetonitrile,

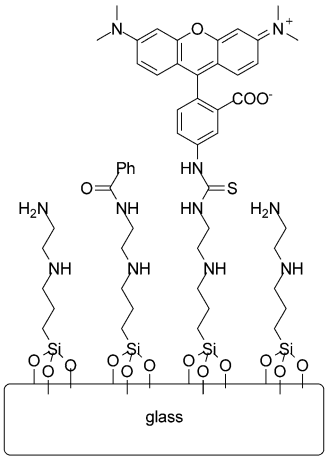


Figure 71. Structure of Crego-Calama's fluorescent acetate-selective sensor constructed on quartz selective.

10^{-5} M^{-1} acetate in the presence of 10^{-4} M^{-1} nitrate and 10^{-3} M^{-1} hydrogen sulfate.

4.4.2. *Surface-Attached Anion Sensors Based on Electrochemical Impedance Spectroscopy*

Electrochemical impedance spectroscopy (EIS) is a technique which allows for the fabrication of a well-established (anion) binding motif onto a suitable surface without need to include a reporter group. The specific quantity measured in an experiment is the charge-transfer resistance (R_{ct}) of a monolayer, which is carried out in the presence of a suitable redox-active couple, which may be a redox-active metal complex or organic molecule. If an anionic guest is bound, a build-up of negative charge occurs in the monolayer, which (for example) repels a negatively charged redox probe, this being detected as an increase in the R_{ct} value.

For example, Zhang and Echegoyen reported upon a trisamide cyclotriveratrylene attached to gold electrodes that could signal the binding of acetate in aqueous solution by EIS (Figure 72).[183] When $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$ was used as the redox probe, a dramatic increase in the R_{ct} value was observed upon addition of acetate, whereas a decrease was observed when $[Ru(NH_3)_6]^{3+}/[Ru(NH_3)_6]^{2+}$ was used. These SAMs proved to be selective for acetate, with the less basic halides not being detected. Selectivity for fluoride was found in a similar system, based on a calix[6]crown-4 scaffold.[184] In both these systems the surface-confined sensor mirrored the anion-binding properties of solution-phase analogues.

4.5. *Detection of Multiple Anions: Sensor Arrays and Pattern Recognition*

Many simple anion sensors are promiscuous, being capable of responding to a range of anions, and so will only be useful as a sensor for a particular anionic species in isolation. Typical "real-world" environmental and biological samples will not conform to this limitation. Even if a sensor is

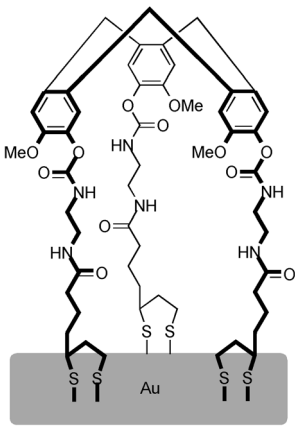


Figure 72. A cyclotriveratrylene SAM which allows the detection of anions by EIS.

able to operate in the presence of other anions, it may be of interest to sense more than one (perhaps even all) of the anions in a sample.

A supramolecular chemistry approach to overcome these issues is to employ a sensor array.[185] This has been demonstrated by Anzenbacher and co-workers, who used eight hydrogen-bond-donating colorimetric sensors (six calixpyrroles, one *N*-confused calixpyrrole, and one anthraquinone; Figure 73) embedded in a polyurethane hydrogel that

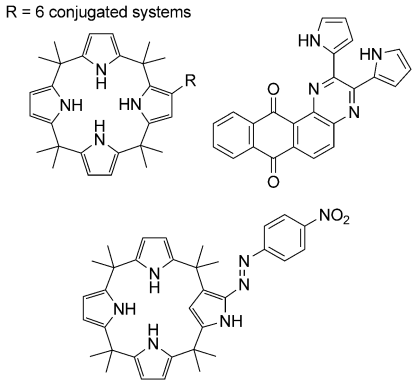


Figure 73. Structures of colorimetric anion sensors used by Anzenbacher to construct a sensor array able to differentiate brands of toothpaste by anionic composition.

enabled the differentiation of ten inorganic anions.[186] The eight sensors were carefully chosen on the basis of their anion association constants determined in organic solvents (the hydrogel desolvates the anions present in the aqueous sample, thus allowing the neutral receptors to function). The colorimetric responses of the array to anions were recorded using an electronic scanner, which facilitated the necessary computational calculations. An application was demonstrated by analyzing several commercial toothpaste brands, which could be differentiated by the quantity of fluoride and other anions present. In the same year, Anzenbacher and co-workers also described a sensor array for detecting phosphate ions in human serum by using eight different (tripodal hydrogen-bond-donating) sensor molecules.[187]

A notable recent example of a ratiometric indicator-displacement assay array capable of colorimetrically distinguishing between ten anions in water has been reported by Feng, Guan et al.[188] The principle behind each IDA used is that a colorimetric indicator chelates a metal cation. Exposure to an anion may lead to the cation being removed from the indicator–cation complex. This event then produces a colorimetric response from the uncomplexed indicator. Nine chelating indicators and eight metal cations were used to construct the 3×6 array, which could analyze anions in "real-world" samples, for example, drinking water or discharged waste streams.

5. Anion Transportation

5.1. Introduction

The investigation of synthetic anion transportation is inspired by the knowledge that a number of diseases are caused by the misregulation of anionic species across the phospholipid bilayers of cell membranes. The most well-known of these is the genetic disorder cystic fibrosis (CF), caused by the dysfunction of the CFTR anion channel in epithelial cell membranes, which impairs the flux of chloride and bicarbonate anions.[1] In addition, it is known that prodigiosins, a family of small naturally occurring molecules capable of anion binding, possess a range of biological activity, including antibiotic, immunosuppressive, and anti-tumor behavior.[189]

In recent times, most studies on anion transportation have used unilamellar vesicles composed of a lipid or a mixture of lipid and cholesterol to simulate the phospholipid bilayers of cell membranes. Anion efflux, as affected by added transporter molecules, may be monitored by use of a) ion-selective electrodes (ISEs), b) encapsulated fluorescent dyes capable of detecting changes in the pH value or anion concentration, and c) NMR spectroscopy. However, real cells have been, and are increasingly, being used in conjunction with whole cell patch clamp or Ussing chamber techniques. For accessible discussions of these experimental methods we refer interested readers to specialist reviews.[190]

Ion transport may be classified by the direction of travel of the ionic species. A uniport mechanism is where a single type of ion is transported, with no other processes occurring at the same time. This process is, therefore, accompanied by the build-up of an electrostatic potential across the membrane. Antiport involves the transport of a species in one direction, with the transport of a second species in the opposite direction. In the case of two anions this will avoid the accumulation of an electrostatic potential. The same effect may be achieved by symport (or cotransport), where two species, specifically a cation and an anion, are transported in the same direction. Strictly, this is ion-pair transportation, but we will cover examples for completeness in the next section.

Here we choose to discuss research on anion transportation based primarily on whether the transporter is either a) a

mobile carrier (molecules that bind and "chaperone" the ion(s) across the bilayer) or b) an anion channel (where molecules are large enough alone, or by aggregation, to span a bilayer).

5.2. Mobile Anion Carriers—"Anionophores"

The design of successful mobile anion carriers, which may be termed anionophores, typically arise from examples of anion receptors.[191] Although the ability to bind the anion guest is essential, another important property to be considered is the lipophilicity of the carrier, as anion transport will occur across a lipophilic medium.

In one of the most established programs on anionophore research, A. P. Davis and co-workers have reported upon the use of derivatives of cholic acid, which possess both hydrogen-bond-donating urea groups and a lipophilic steroid skeleton that can shield a complexed anion (Figure 74).[192] In their first

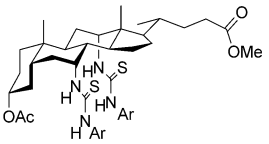


Figure 74. Davis' first cholic acid derived chloride transporter.

studies (in collaboration with B. D. Smith), efflux of chloride ions was monitored by use of an ISE and ^{35}Cl NMR spectroscopy.[193] The strongest binders of chloride were found to be the best transporters of the anion across unilamellar vesicles. In the same report, they used an Ussing chamber to demonstrate that chloride transport was possible across live epithelia, as detected by the creation of a potential difference across the cellular membrane.

A greater range of studies have been subsequently been undertaken, typically incorporating the transporter within synthetic vesicles, and using the fluorescent dye lucigenin to monitor influx of chloride. Interesting results from these investigations include the presence of a positive charge having a deleterious effect on transport,[194] while a cyclic "cholaphane" (Figure 75a) was shown to be a more active transporter.[195] Although a modestly stronger anion binder, the authors attribute the greater transport activity of the cholaphane to the increased shielding of the anion from the solvent. More recently, the same research group has reported the simplification of the structure from a steroid scaffold to

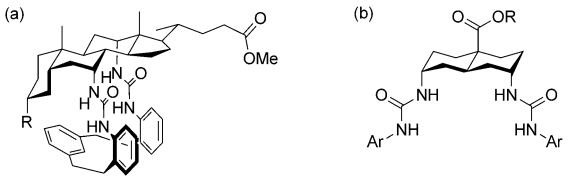


Figure 75. A. P. Davis' "cholaphane" (a) and *trans*-decalin based anionophore (b).

a *trans*-decalin, while retaining high levels of transport activity (Figure 75b).[196] The potentially pharmacologically useful features of this *trans*-decalin structure are its lower lipophilicity (more likely to be deliverable through aqueous environments in vivo) and reduced molecular weight (more "druglike").

There is a considerable body of work describing molecules capable of acting as symportic transporters of the H^+/Cl^- ion pair. For example, Sessler et al. studied the efflux of chloride across synthetic membranes by synthetic prodigiosins and dipyrromethenes using an ISE (Figure 76a).[197] A pH

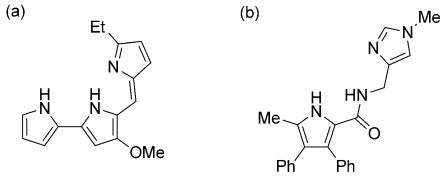


Figure 76. Anionophores capable of H^+/Cl^- transport: a) Sessler's synthetic prodigiosin and b) an imidazole-pyrrole by Gale and B. D. Smith.

dependency, consistent with HCl symport was observed. The research groups of Gale and B. D. Smith have investigated a number of simple prodigiosin mimics, including examples containing pyrrole[198] or 2,6-pyridinedicarboxamide[199] appended with a methylimidazole that could act as a site of protonation (Figure 76b). Chloride transport from vesicles was observed in the presence of a suitable pH gradient, with analogues lacking a protonable site being found to be transport-inactive.

Systems incorporating the tri(2-aminoethyl)amine (tren) functional group have also been studied, as the tertiary amino group may be protonated, while the facile incorporation of hydrogen-bond donors (e.g. amides) allows for chloride complexation. For example, D. K. Smith and co-workers reported triamide-tren molecules were able to transport H^+/Cl^-,[200] while Berezin and Davis described an analogous dicatechol (Figure 77).[201] In the latter case, the presence and

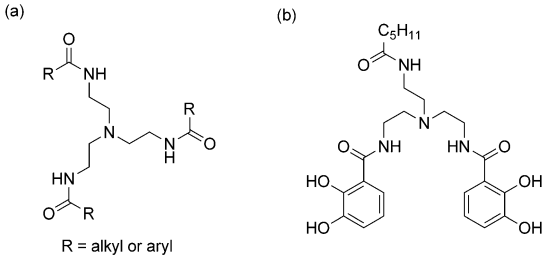


Figure 77. Tren-based anionophores capable of H^+/Cl^- transport: a) D. K. Smith's triamide and b) J. T. Davis' dicatechol.

specific substitution pattern of the catechol appeared to be crucial, for neither the tetramethylated phenol analogue nor the 3,4-isomer were able to transport anions.

Attention has also been paid to the transportation of the bicarbonate ion across bilayers, with a key seminal report on this topic being made by J. T. Davis, Gale, Quesada et al.[202] By studying a selection of natural and synthetic anionophores by use of ISEs and ^{13}C NMR spectroscopy, they verified that Cl^-/HCO_3^- antiport was possible across synthetic membranes. Notably, natural prodigiosins were found to be more effective transporters than the synthetic isophthalamides investigated. Quesada and co-workers have since studied synthetic prodiginines, and shown that the anticancer drug candidate Obatoclax (Figure 78a), was a highly active anionophore able to facilitate chloride/bicarbonate antiport. It was also shown to acidify a GLC4 cell line, and hence have considerable cytotoxic character.[203] Similar behavior was observed in the related, but structurally simpler, tambjamine alkaloids (Figure 78b).[204] Meanwhile, Gale and co-workers have reported that tripodal tri(thio)ureas are capable of Cl^-/HCO_3^- antiport across synthetic membranes (Figure 78c). Notably, the triurea analogues exhibit much lower (if any) transport ability.[205] More recently, the same research group has demonstrated that squaramides can facilitate antiport chloride ion transportation, including Cl^-/HCO_3^- exchange (Figure 78d). In this report, the squaramides were found to be better transporters than analogous thioureas and ureas.[206]

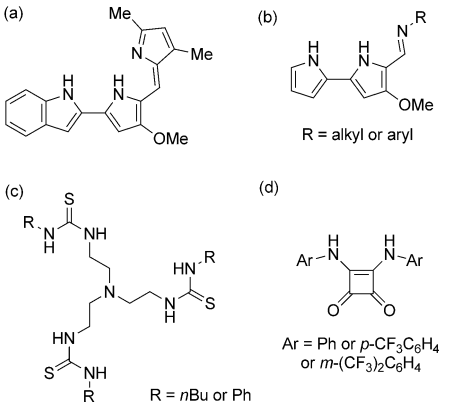


Figure 78. Anionophores capable of Cl^-/HCO_3^- transport: a) Obatoclax, b) tambjamine alkaloids, c) tripodal trithioureas, and d) squaramides.

This interest in the transportation of other biologically relevant anions is a developing research theme. Gale and co-workers have reported that *ortho*-phenylenediamine-based ureas are capable of the antiport transportation of maleate and fumarate (Figure 79a).[207] The same research group has also disclosed that thioureas can act as antiport transporters of lactate and pyruvate (Figure 79b,c).[208] In this case, variation in the transporter structure led to a change in the selectivity of the transportation efficiency; the simpler thiourea-indole (Figure 79b) transported pyruvate more effectively, while the inclusion of an amide (Figure 79c) led to a transporter with greater efficiency for lactate—the authors proposed the presence of an additional hydrogen bond between the receptor and lactate could explain this observation.

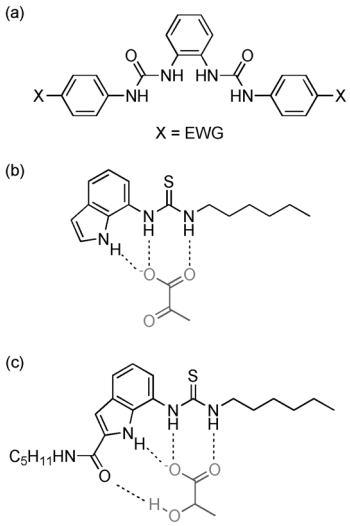


Figure 79. Anionophores for: a) maleate and fumarate, b) pyruvate, and c) lactate.

Sulfate is a highly hydrophilic anion (in part because of its double negative charge), and hence is hugely challenging to transport across a lipophilic membrane. Gale, Jolliffe, Plavec, and co-workers have very recently used ^{33}S NMR spectroscopy to demonstrate direct evidence of sulfate transportation with tri(thio)ureas based on tren or cyclopeptide scaffolds.[209] Specifically, ^{33}S-labeled sulfate, in conjunction with paramagnetic Mn^{2+} and Fe^{3+} ions, allowed for the discrimination of intra- and extravesicular sulfate. By using this technique it was shown that the cyclopeptide cage in Figure 80, could facilitate not only Cl^-/SO_4^{2-} and HCO_3^-/SO_4^{2-} antiport, but Mn^{2+}/SO_4^{2-} symport as well.

Hydrogen bonding has been all but ubiquitous in the anionophores described to date. However, calix[4]arenes that can bind and transport anions by anion–π interactions (Figure 81a) or halogen bonding (Figure 81b) have been prepared by Matile and co-workers.[210] In a more recent communication, the ability of simple, commercially available halogenated compounds to transport anions, by utilizing halogen bonding, has been reported by the same research group (Figure 81c).[211]

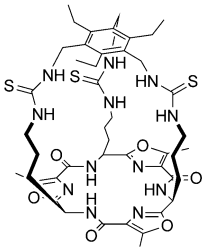


Figure 80. A trithiourea cyclopeptide cage capable of facilitating transmembrane transportation of sulfate.

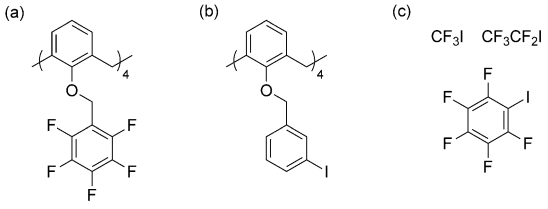


Figure 81. Anionophores that utilize a) anion–π and b,c) halogen-bonding interactions.

5.3. Anion Channels

Considering that nature employs channels to transport anions, it is unsurprising that there has been research into the development of synthetic analogues. Here we provide a few illustrative examples; for further discussions we refer interested readers to specialist reviews.[190]

Tomich and co-workers have been pursuing the preparation of chloride ion transporting channels for some considerable time.[212] Basing their work on the natural spinal cord glycine receptor ion channel, 22-amino acid residue peptides have been synthesized, and found to be selective for chloride, as tested by the planar lipid bilayer method. Gokel and co-workers have reported the use of shorter amphiphilic heptapeptides, which form anion channels upon dimerizing in a bilayer (Figure 82).[213] This research group has been able

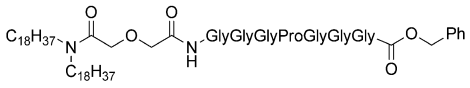


Figure 82. Structure of Gokel's prototype amphiphilic heptapeptide.

to optimize features (e.g. the lipophilic N and C termini and the actual amino acid sequence) of the peptides to maximize the efficiency of chloride transport.[214] Specific examples were also demonstrated (by Ussing chamber experiments) to effect anion transport in epithelial cells.[215]

Relatively small molecules may act as anion channels. For example, J. T. Davis and co-workers have used voltage-clamp experiments to demonstrate that a 1,3-alternate tetrabutylamide calix[4]arene could assemble into channels for the transport of the H^+/Cl^- ion pair (Figure 83).[216] Subsequently, the same research group have reported upon calix[4]arenes existing in partial cone[217] and cone[218] conformations that also form ion channels and permit the transfer of the same ion pair.

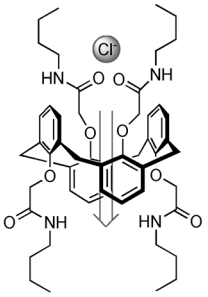


Figure 83. Davis' 1,3-alternate tetrabutylamide calix[4]arene.

Matile and co-workers have been working on anion–π slides.[76] In the archetypal example, rigid, membrane-spanning, *p*-oligo-(*p*-phenylene)-*N*,*N*-naphthalenediimide rods transport chloride across a bilayer by anion–π interactions (Figure 84).[219] More recently, perylenediimide analogues have also been shown to facilitate anion transport.[220]

6. Future Directions: Applications of Anion Supramolecular Chemistry

Here attention is turned to examples of functional applications of anion supramolecular chemistry. Some of these research themes have already reached remarkably high levels of research output, whilst others, in comparison, are somewhat underexplored.

6.1. Anions in Catalysis

6.1.1. Anion Recognition in Asymmetric Organic Catalysis by Using Neutral Hydrogen-Bond Donors

The use of molecules with hydrogen-bond-donating groups as catalysts of asymmetric organic chemical transformations represents an elegant demonstration of how knowledge of anion recognition may be applied to a chemical application. This area has attracted huge amounts of research interest, and we emphasize that what follows merely represents a few highlights from a large number of examples which may be found in the literature.[221]

For example, Jacobsen and co-workers reported upon a thiourea-catalyzed enantioselective Pictet–Spengler cyclization (Figure 85).[222] The proposed reaction mechanism has the chiral thiourea catalyst hydrogen bonding to the chloride counterion of the

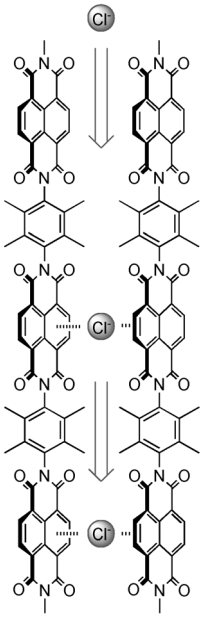


Figure 84. Matile's naphthalenediimide anion–π slide.

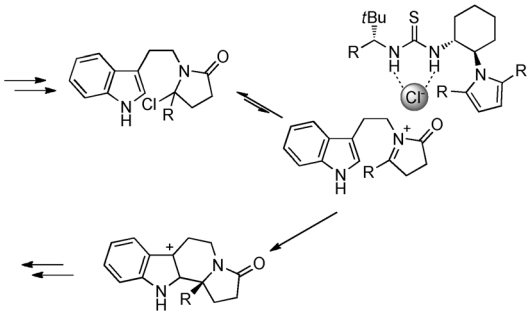


Figure 85. Key mechanistic steps in Jacobsen's thiourea catalyzed Pictet–Spengler cyclization, with a mediating chloride ion.

charged electrophile, thus allowing chiral information to be transferred from the thiourea to the cyclizing molecule. Further reactions where chloride[223] and, alternatively, bromide[224] and fluoride[225] ions are bound by chiral thiourea catalysts have been reported by the same research group.

In a recent study Ooi and co-workers have disclosed that chiral 1,2,3-triazolium compounds can act as cationic organocatalysts in the asymmetric alkylation of oxindoles (Figure 86). Optimization of the catalyst structure and solvent allowed for almost quantitative yields and enantiomeric excesses of up to 97%.[226]

6.1.2. Chiral Anions as Catalysts in Organic Chemistry

Another highly investigated research theme based on anions in catalytic reactions has been the deployment of chiral anions to achieve stereoselective organic transformations.[227] In the majority of cases, these have been axially chiral

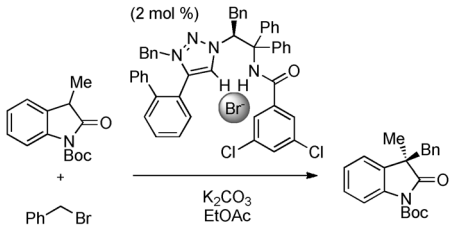


Figure 86. Ooi's asymmetric alkylation of oxindoles, catalyzed by a chiral 1,2,3-triazolium organocatalyst.

binaphthyl phosphate ions. For example, Mayer and List reported upon the transfer hydrogenation of α,β-unsaturated aldehydes using dihydropyridine and 20 mol% of an ammonium binaphthyl phosphate salt, with enantiomer excesses $>98\%$ being observed (Figure 87).[228] Xiao and co-workers

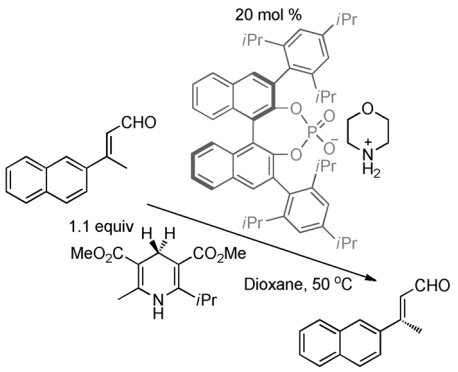


Figure 87. Enantioselective transfer hydrogenation of unsaturated aldehyedes, utilizing a chiral binaphthyl phosphate ion by Mayer and List.

have subsequently demonstrated that an Ir^{III}-catalyzed imine hydrogenation could similarly operate at high levels of enantioselectivity if binaphthyl phosphates were used as counterions to the cationic Ir^{III} organometallic fragment.[229]

Toste and co-workers have also described the use of a chiral binaphthylphosphate ion to mediate the asymmetric ring opening of *meso*-aziridinium and episulfonium ions (Figure 88).[230] The positively charged three-membered rings that are formed in the first stages of the reaction associate with the chiral anion, thus directing the attack of the incoming nucleophilic alcohol and affords enantiomeric excesses $>90\%$.

In contrast, the enantioselective epoxidation of alkenes with a Mn^{III} salen complex reported by Liao and List involves coordination of the chiral anion with the catalytic reagent,

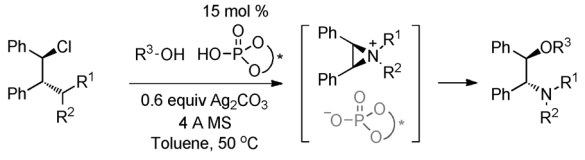


Figure 88. Mechanism of Toste's chiral anion mediated asymmetric ring opening of *meso*-aziridinium ions.

rather than the reaction substrate (Figure 89).[231] After thorough screening, almost quantitative yields and enantiomeric excesses of up to 96% were achieved.

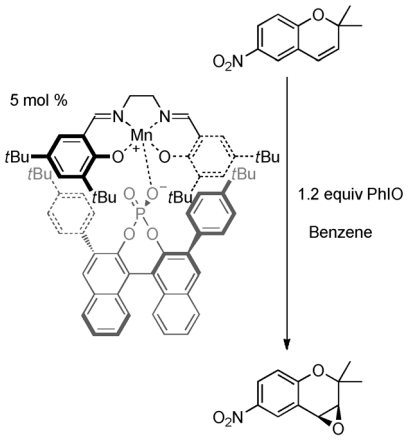


Figure 89. Enantioselective epoxidation of alkenes with a chiral Mn^{III}-salen-phosphate complex by Liao and List.

In a notable departure, Reek and co-workers have investigated the use of chiral carboxylate anions as cofactors in enantioselective catalysis.[232] Specifically, they studied a diphosphine-rhodium complex that contained a di(amidodiindolyl)methane hydrogen-bond-donor array in the ligand structure. Addition of a chiral carboxylate allows for formation a chiral complex (in dichloromethane), which induces enantioselective hydrogenation (Figure 90).

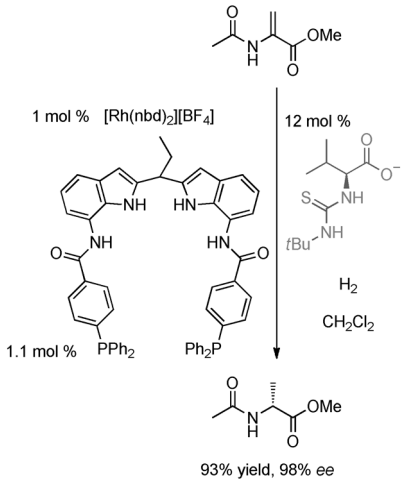


Figure 90. Reek's asymmetric hydrogenation using a chiral cofactor.

6.1.3. Anion Templates in the Synthesis of Catalytic Nanoparticles

Bimetallic core@shell nanoparticles, consisting of a "shell" coating a "core", possess unique catalytic properties. Beer and co-workers have used anion coordination as a novel

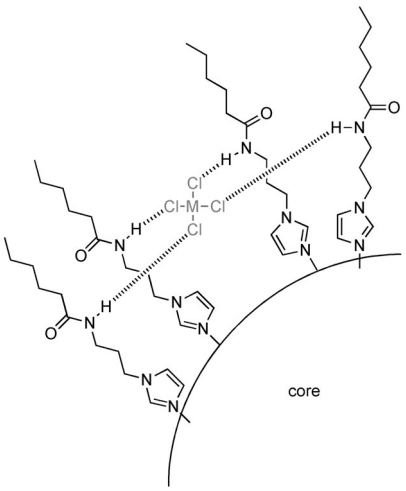


Figure 91. Beer's method of synthesizing core@shell nanoparticles by complexation of the shell metal as an anionic complex by functionalized core nanoparticles.

synthetic method to prepare Au@Pd and Pt@Pd core@shell nanoparticles.[233] First, core nanoparticles are prepared using stabilizing ligands containing hydrogen-bond-donating amides. Then, the shell metal is introduced, in an oxidized form, as part of an anionic $[MCl_4]^{n-}$ complex which is bound by the hydrogen-bond-donating amides (Figure 91). To complete the synthesis, the metal is reduced, thereby yielding the core@shell nanoparticles. The Au@Pd nanoparticles synthesized by this method were shown to be highly efficient in catalyzing the industrially useful conversion of chloronitrobenzene into chloroaniline.

6.2 Anionic Extraction

As stated in the Introduction, a key motivation for investigating anion recognition is the capture and removal of certain anionic pollutants, often resulting from anthropogenic activities, from the natural environment. An excellent demonstration of anionic extraction is provided by Custelcean and co-workers, who have been able to separate sulfate from simulated nuclear waste. The key challenges they faced included the strong hydration of the dianion, the presence of various competing anions, and extreme alkalinity ($pH > 14$). However, a remarkably simple tren-triurea (Figure 92a) can extract sulfate from simulated nuclear waste by crystallization.[234] One equivalent of sulfate ions is bound by hydrogen bonds from two tren-triurea ligand molecules that encapsulate their oxoanion guest (as evidenced by crystallographic structure determination), with sodium ions acting as the necessary counterions.

Similar tren-triurea molecules have also been employed by Tasker, Schröder, and co-workers in the extraction and transport of the $[PtCl_6]^{2-}$ ion (Figure 92b).[235] The industrial isolation of Pt cannot utilize inner-sphere coordination complexes because of the very slow ligand exchange kinetics of the Pt^{IV} cation, and so outer-sphere coordination complexation is required to form neutral anion–ligand systems. As in

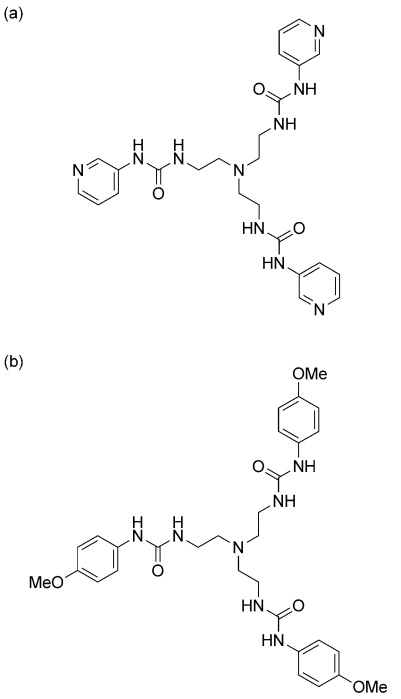


Figure 92. Structures of tren-triureas used by a) Custelcean to extract sulfate from simulated nuclear waste and b) Tasker and Schröder to extract and transport $[PtCl_6]^{2-}$.

the case of the sulfate system developed by Custelcean and co-workers, one equivalent of $[PtCl_6]^{2-}$ ion is bound by two tren ligands, but the tren ligands are protonated, and crystallographical structure determination indicates that only two of the tren "arms" participate in hydrogen bonding with any given anion. The authors were able to demonstrate that this system was able to recover Pt^{IV} from acidic chloride feed solutions.

6.3. Anion-Responsive Materials and Molecules

The generation of systems which respond through a change in a property that is beyond a perturbation leading simply to an optical or electrochemical sensory response is a key area of investigation in supramolecular chemistry today. With their wide variety of geometries, anions offer possibilities which can complement those offered by other classes of chemical or physical stimuli. Although significant progress has been made in developing anion-responsive materials and molecules, this area of research is still in its infancy and has much potential for future development.

6.3.1. Anion-Responsive Gels and Liquid Crystals

A gel is a semi-solid colloidal system, consisting of a fibrous solid network and a solvent that is retained within this solid "structure". A gel will remain in the vessel in which it is residing upon inversion of the vessel; however, upon heating it may pass through a phase transition, equivalent to the melting of a solid, at a temperature denoted T_{gel}.

Molecules containing neutral hydrogen-bond donors and acceptors, for example ureas, may form gels provided the solvent is not too competitive to prevent hydrogen bonding. Anions may be added that compete as hydrogen-bond acceptors, hence disrupting the network and lowering T_{gel}.[236]

For example, Steed and co-workers have reported a set of diureas ($n=2$, 4, 6, 8; Figure 93) that act as gelators in chloroform.[237] The addition of strongly binding anions—such

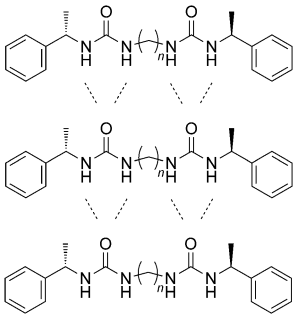


Figure 93. Structure of Steed's diurea gelators, illustrating the hydrogen bonding between individual molecules.

as acetate—reduces the gel strength, and in one case ($n=2$) disrupts gel formation completely. Importantly, a practical use of this phenomenon has been found in the growth of crystals of pharmaceutical molecules.[238] Historically, this application has used hydrogels, which typically require harsh conditions to disrupt the gel phase, which may dissolve the crystals being obtained. The addition of acetate triggers destruction of diurea gelators similar in structure to those shown in Figure 93, thus allowing for easy isolation of the desired crystal.

Anion-triggered hydrogelators have also been reported. For example, Mocerino and Ogden described a proline-functionalized calix[4]arene (Figure 94a) which formed

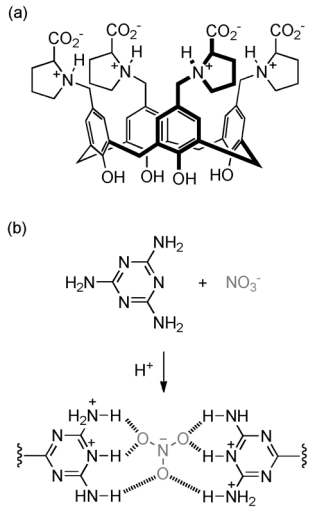


Figure 94. Anion-triggered hydrogelators: a) structure of proline-functionalized calix[4]arene and b) proposed hydrogen-bonding interactions of anion-templated gel structures of melamine and nitrate.

hydrogels in the presence of specific anions; the effect the anion had on gel stability was attributed to the Hofmeister series.[239] Zhang and co-workers demonstrated that protonated melamine will form gels in water with oxoanions such as nitrate, phosphate, sulfate, and ATP (Figure 94b).[240] In both cases, gelation can be switched off by increasing the pH value, which leads to deprotonation of the gelator and loss of the positive charge required to interact with the anion in the competitive aqueous solvent.

Anions have also been used to affect the supramolecular structures of liquid crystals. Kim and co-workers incorporated a guanidinium motif onto the apex of a mesogen to allow interaction of an anion with the molecule (Figure 95).[241] The resulting cation forms supramolecular structures that depend upon the nature of the counterion: hexagonal columnar with nitrate or tetrafluoroborate, rectangular columnar with $HCCCO_2^-$, while a cubic mesophase is observed with chloride. Notably the deprotonated guanidine is not a liquid crystal, but does form a gel phase in dodecane.

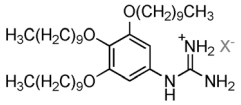


Figure 95. Kim's guanidinium-functionalized mesogen, which exhibits different supramolecular structures depending on the counterion.

6.3.2. *Anion-Responsive Complexes and Molecules*

The effect of anions on the structures and conformational behaviors of single chemical species has also been documented. For example, Yam and co-workers have reported the anion-assisted *trans-cis* isomerization of a Pd^{II}-phosphine complex (Figure 96).[242] Both phosphine ligands contain an

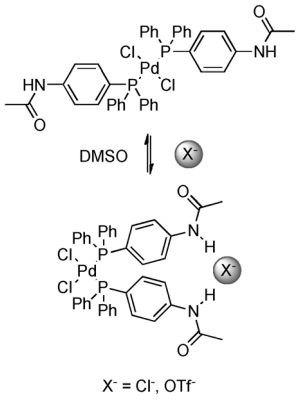


Figure 96. Yam's anion-assisted *trans–cis* isomerization of a Pd^{II}-phosphine complex.

acetanilide functionality, which can form a convergent hydrogen-bonding cleft to an appropriate anion only when *cis* to one another. Hence, in chloroform, the addition of chloride or triflate results in *trans-cis* isomerization, which may be reversed by the addition of DMSO.

Jones and Hamilton have documented the ability of halide ions to control the conformation of hydrogen-bonded diphenylacetylenes.[243] In chloroform, the free diphenylacetylene

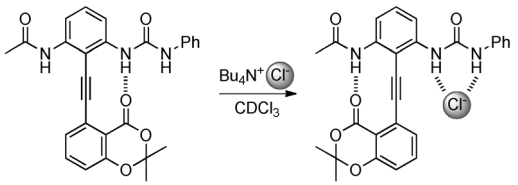


Figure 97. Hamilton's halide-controlled hydrogen-bonded diphenylacetylene.

derivative (Figure 97) exists mainly (ca. 9:1) in the conformation where the ester carbonyl group can hydrogen bond to one of the N–H groups of the acidic urea functionality. A halide ion will bind in preference to the urea, so the addition of chloride results in the phenylacetylene rotating, to allow the ester C=O group to hydrogen bond to the amide N–H group instead.

A principal incentive for the preparation of interlocked architectures is the potential for such molecules to exhibit relative motion of their constituent parts. In recent times, it has been shown that this may be achieved by use of anionic stimuli. For example, Beer and co-workers have reported a pH-switchable catenane (Figure 98).[244] Synthesized by

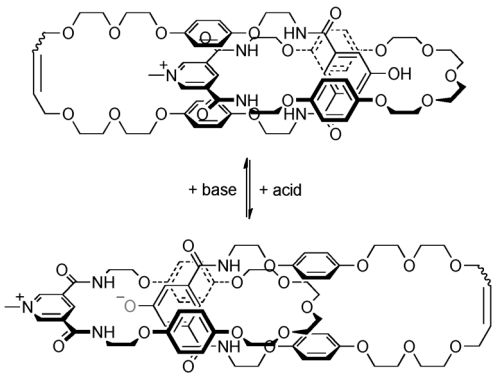


Figure 98. Beer's pH-switchable phenol/phenoxide catenane.

using a chloride ion template and then exchanged to the hexafluorophosphate salt, the catenane contains a phenol which may be deprotonated to generate a phenoxide moiety. The catenane undergoes ring rotation so that the phenolate anion is bound by the pyridinium isophthalamide motif. Reprotonation reverses the process, driven by favorable aromatic donor–acceptor interactions of the electron-poor pyridinium ring with the electron-rich hydroquinones. A pH-switchable phenol-containing rotaxane shuttle has also been reported by Keaveney and Leigh.[245]

Alternatively, the switching of the counterion of a positively charged interlocked molecule may induce molecular motion. For example, Leigh and co-workers synthesized the chloride salt of a rotaxane (Figure 99), where the macrocyclic component initially resides over a pyridinium ring in the axle, as a consequence of electrostatic attraction between the positively charged pyridinium ring and a negatively charged chloride ion coordinated to a Pd^{II} cation bound by the macrocycle.[246] Exchange of chloride for the noncoordinating

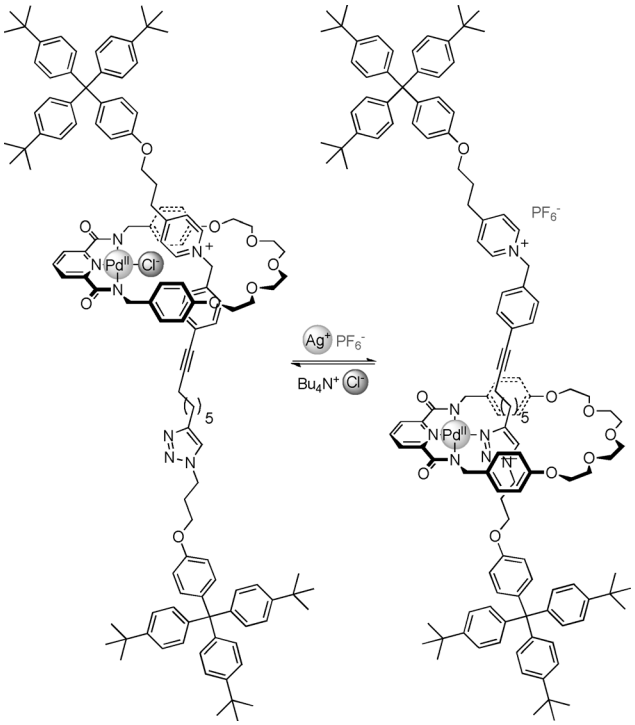


Figure 99. Leigh's molecular shuttle driven by Cl^-/PF_6^- metathesis.

hexafluorophosphate, leaves the Pd^{II} cation coordinatively unsaturated and induces shuttling to the Lewis basic nitrogen atom of the triazole. Reintroduction of chloride returns the macrocycle to its original position. Other rotaxane shuttles, switchable by Cl^-/PF_6^- metathesis, have also been reported by the research groups of Beer[247] and Chiu.[248]

A neutral rotaxane, switchable by the addition and removal of acetate, has been reported by Chiu and co-workers (Figure 100).[249] In $CDCl_3/CD_3CN$ (1:1), the axle of the rotaxane resides with the urea C=O group hydrogen bonding to the 2,6-pyridyldiamide moiety of the macrocycle. In the presence of acetate, the urea N–H groups hydrogen

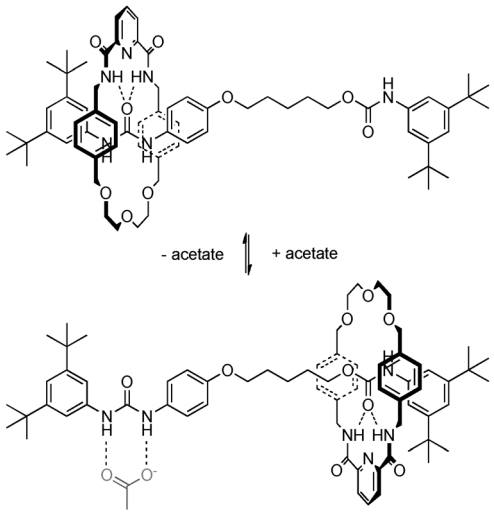


Figure 100. Chiu's acetate-driven molecular shuttle.

bond to the anion, thereby forcing the macrocycle to move and hydrogen bond to the ester C=O group instead.

We note that appropriately designed switchable interlocked molecules have been shown to act as anion sensors. Examples of rotaxane shuttles that provide an optical sensory response to chloride have been reported recently by the research groups of B. D. Smith (see Section 4.1.3)[158,159] and Beer.[250]

6.3.3. Anion-Responsive Transition-Metallo-Organic Cages

Whereas metal-templated organic cages that can act as anion receptors are known,[251] examples that are responsive to anionic stimuli, either by reconstitution of the cage or by disturbing an equilibrium of isomers, have only been reported very recently.

Nitschke and co-workers have described that the reaction of *p*-toluidine, 6,6′-diformyl-3,3′-bipyridine, and $Co(OTf)_2$ produces a $[Co_4L_6]^{8+}$ tetrahedron, where each ligand L is a di(imine)bipyridyl moiety (Figure 101).[252] The addition of

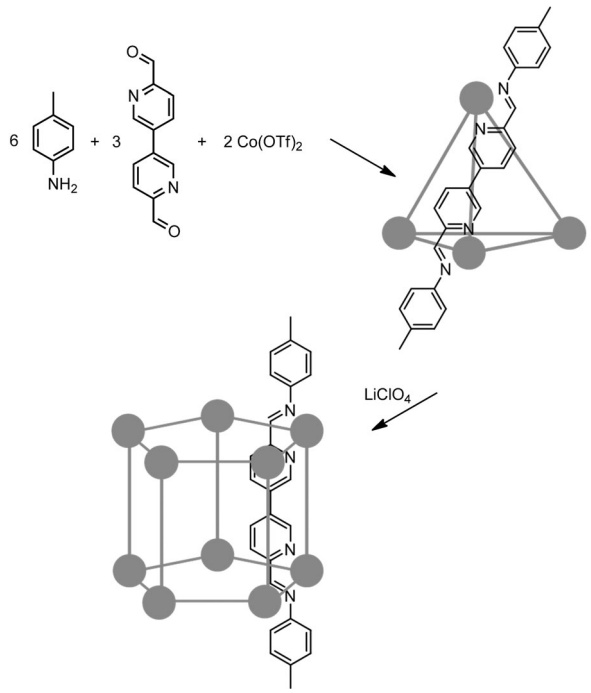


Figure 101. Nitschke's $[Co_4L_6]^{8+}$ tetrahedron and $[Co_{10}L_{15}]^{20+}$ pentagonal prism.

$LiClO_4$ leads to a structural reconstitution to create a barrel-like $[Co_{10}L_{15}]^{20+}$ pentagonal prism, which binds chloride within its structure with an affinity $K > 6 \times 10^5\ M^{-1}$. The same research group has also reported an alternative system, where 4,4′-diaminobiphenyl, 2-formylpyridine, and a Fe^{II} salt are allowed to react. This reaction leads to a $[Fe_4L_6]^{8+}$ tetrahedral cage, which exists as a system of interconverting diastereomers in solution. The addition of anionic guests leads to new combinations of diastereomers, which are able to rotate their bonds to adapt to the particular anion added.[253]

Chifotides, Dunbar, and co-workers have studied the conversion of Fe^{II} di(pyridyl)tetrazine cages with π-acidic cavities by exchange of the anion encapsulated within the self-assembled structure (Figure 102).[254] They first established

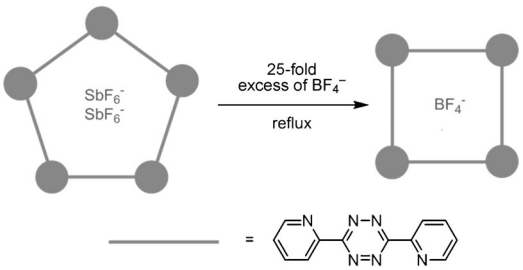


Figure 102. Study by Chifotides and Dunbar of the conversion of a SbF_6^--templated pentagonal cage into a BF_4^--templated molecular square.

that a 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (bptz) ligand forms a molecular square $[Fe_4(bptz)_4(CH_3CN)_8](BF_4)_8$ with the BF_4^- ion and a pentagon $[Fe_5(bptz)_5(CH_3CN)_{10}](SbF_6)_{10}$ with the SbF_6^- ion. X-ray crystallography indicated that a BF_4^- and (two) SbF_6^- ions reside within the cavities of the respective self-assembled structures. It was then demonstrated that it was possible to convert a SbF_6^--templated pentagon into a square by using a 25-fold excess of BF_4^- in acetonitrile at reflux. The failure to achieve this conversion under less-stringent conditions (a 15-fold excess of BF_4^-, stirring at room temperature), suggests that the pentagonal SbF_6^- capsule is much more stable than the square BF_4^- structure.

Clever and co-workers have reported upon the elegant formation of an interpenetrated coordination cage upon BF_4^-/Cl^- metathesis (Figure 103).[255] Formation of a thermo-

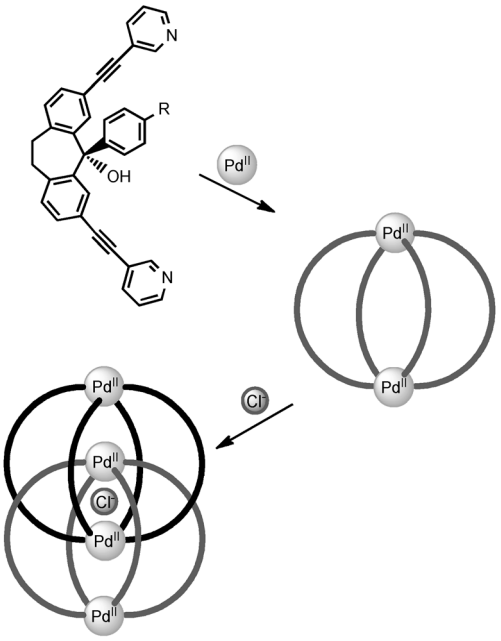


Figure 103. Clever's monomeric cage that can form an interpenetrated dimer upon BF_4^-/Cl^- metathesis.

dynamically stable monomeric $[Pd_2L_4](BF_4)_4$ cage occurs in acetonitrile upon reacting $[Pd(CH_3CN)_4][BF_4]$ with a monodentate dibenzosuberone dipyridyl ligand derivatized with a bulky aryl substituent. The addition of the much smaller chloride ion permits dimerization, thereby resulting in an interpenetrated $[Cl@Pd_4L_8](BF_4)_7$ double cage. The enlarged outer pockets of this double cage show a preference for the binding of large anions such as ReO_4^-.

7. Conclusion and Outlook

In the last ten years or so, since the last review,[16] a vast wealth of anion supramolecular research has been undertaken. Alongside continued interest in anion binding and sensing, the fields of the use of anions as templates and for transportation have flourished. Pleasingly, lessons learnt have been applied to applications such as catalysis, ion extraction, and responsive materials and molecules.

So, what may be achieved in the next ten, twenty, or even fifty years? We foresee exploitation and numerous applications of the "new" anion supramolecular interactions—anion–π and especially halogen bonding. There will undoubtedly be progress in the recognition of anions in aqueous solvent media, noting that the sensing of anions in cells is still very much in its infancy. We anticipate that research on anion transportation will lead to treatments for diseases arising from anion misregulation. Perhaps most ambitiously, anionic species may act as stimuli in highly sophisticated responsive nanotechnological devices and materials, mimicking systems found in nature. Hence, anion supramolecular chemistry will continue to be an exciting, innovative, and productive field of scientific research for many years to come.

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