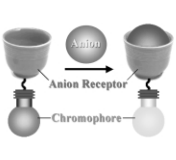
Chromogenic anion sensors



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Received 20th January 2003
First published as an Advance Article on the web 2nd May 2003

Chromogenic sensors for anions generally consist of two parts: anion receptors and chromophores. In this review, 6 types of chromogenic anion sensors are described, namely, NH-based hydrogen bonding, Lewis acid, metal-ion template, transition metal complexes, chromogenic guest displacement and chromoreactands. The first 4 types possess anion receptors attached directly to the chromophores while the guest displacement techniques employ indicators as the ones that were replaced by specific anions. The last type has emerged recently and uses specific reactions between chromogenic hosts or indicators and particular anions to cause dramatic colour changes.

1 Introduction

In the field of supramolecular chemistry, the progress in synthetic receptors for anions has attracted considerable attention in recent decades due to the fact that a large number of biological processes involve molecular recognition of anionic species. It is thus important to develop techniques for quantifying or sensing such anions. Nowadays, the development of colorimetric anion sensing is particularly challenging since visual detection can give immediate qualitative information and is becoming increasingly appreciated in terms of quantitative analysis.

One approach to reach an effective anion sensor for biological anions involves the construction of optical anion sensors. Such a system generally consists of two parts. One part is an anion-binding site employing various combinations of anion receptor units. Anion receptors can be mainly divided into 2 categories: neutral anion receptors and positive-charge anion receptors. Neutral anion receptors employ hydrogen bonding NH-based donors such as pyrroles, amides and urea/thioureas or Lewis acids. Positive-charge anion receptors use ammonium derivatives or guanidinium centers for binding negative-charged anions. The other is the chromophore part which converts the binding events or recognition phenomena to optical signals. These two parts can be either covalently attached or intermolecularly linked to each other.

The concept of chromogenic anion sensors is illustrated in Fig. 1. The ball in the figure can be compared to analytes such as anions and the cup acts like a receptor that is connected to a light bulb. When the ball goes into the cup that fits its shape, the electronic part of the light bulb is perturbed, and the light bulb will give a different colour.

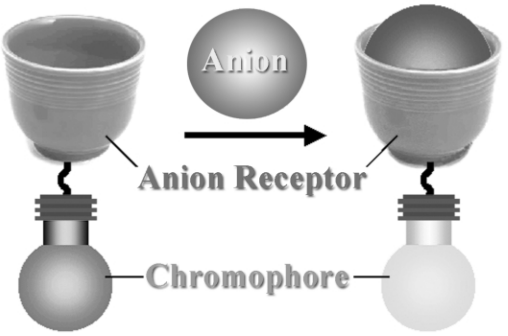

Fig. 1 Operating principle of chromogenic anion sensors.

Chromogenic anion sensors can be divided into two main categories: metal and non-metal chromogenic hosts. For metal-involved chromogenic hosts, the changing colour comes from the colour of metals or metal complexes, especially transition

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DOI: 10.1039/b209598j

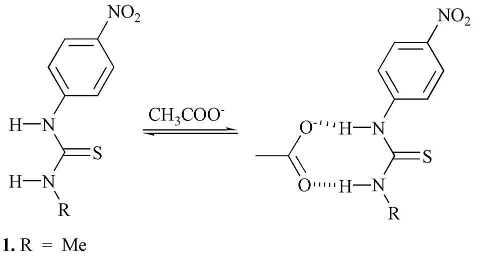
metal ions, as their electronic properties are perturbed upon coordination to anions. The other way to generate a chromogenic sensor is to displace the coordinated chromophore by specific anions. Besides coordination aspects, the colour changes can stem from reactions between chromogenic hosts or indicators and anions. This type of chromogenic anion sensor can be called “chromoreactand”. When the reaction occurs, the conformed-host will definitely change its electronic properties. This, therefore, results in an observable colour change.

This review concerns only chromogenic anion sensors. Those who are interested in general anion receptors and sensors can consult a recent review by Gale.[1]

2 NH-based hydrogen bonding chromogenic hosts

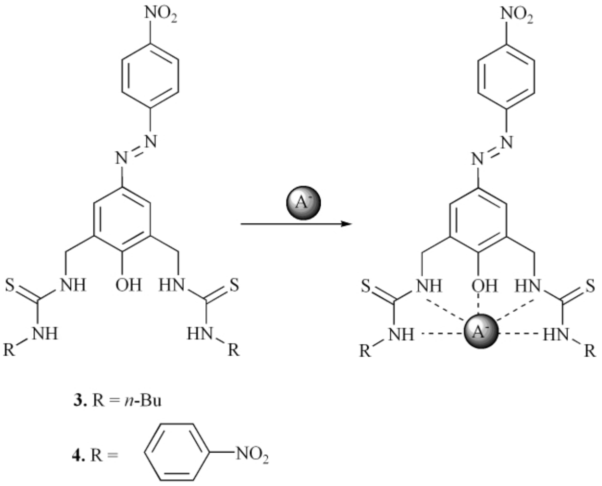
These hosts include simple anion sensor systems containing urea, thiourea, amine, amide, alcohol and pyrrole groups linked to chromophores. Chromophores used in this type of chromogenic anion sensor are mainly organic dyes such as azobenzene, nitrobenzene, indoaniline and anthraquinone or extensively conjugated aromatic compounds such as quinoxaline, oxadiazole and porphyrin. The colour change occurs upon binding of anion guests that affect the electronic properties of the chromophores.

Sessler and Miyaji have investigated a number of commercially available compounds such as 1,2-diaminoanthraquinone, 1,8-diaminoanthraquinone, 4-nitroaniline, 4-nitro-1,2-phenylenediamine, L-leucine-4-nitroanilide, 1-(4-nitrophenyl)-2-thiourea, 4-nitrophenol, alizarin, 2,2′-bi(3-hydroxy-1,4-naphthoquinone), acid blue 45, naphthol AS, 9(10*H*)-acridone and Direct Yellow 50 as anion sensors in organic solvents such as dichloromethane.[2] These compounds contain hydrogen bond donors such as amine, amide, alcohol and urea as anion binding sites. The compounds also contained chromophore subunits (acting as an electron acceptor) whose electronic properties were modified as a result of interaction with a bound anionic substrate (acting as an electron donor).



1. R = Me
2. R = *p*-nitrophenyl

Thiourea is an especially good hydrogen bond donor and is an excellent anion receptor for carboxylate anions. Nishizawa and co-workers prepared thiourea-base chromophores with *p*-nitrophenyl units, **1** and **2**.[3] As a result, compounds **1** and **2** were found to be more highly selective for acetate than other anions in 1% water:99% MeCN. The binding properties of **1** and **2** with acetate showed that increasing the concentration of AcO^- produced a significant bathochromic shift in the UV-vis spectra. The stability constants of the acetate complex of **1** was 5.6×10^3 M^{-1}, much weaker than that of **2**, 3.5×10^5 M^{-1}. It was evident that introducing a *p*-nitrophenyl group into the (*p*-nitrophenyl)thiourea moiety enhanced the hydrogen bonding ability. Likewise, chromophore **2** was then applied to the colorimetric determination of acetic acid in commercially available brands of vinegar. The results agreed well with the specification provided by the suppliers.

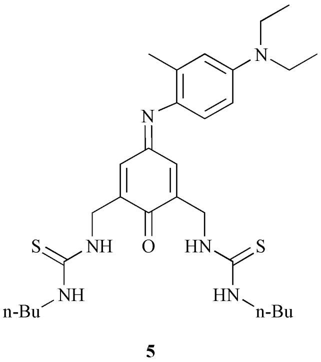


3. R = *n*-Bu
4. R =

Hong and co-workers have recently reported anion coordination with a nitro-azophenol thiourea base sensor, compound **3**.[4] Association constants for anion binding were determined by ^1H NMR and UV-vis titrations in $CDCl_3$. $H_2PO_4^-$ (K_a = 2.6×10^4 M^{-1}) and AcO^- (K_a = 1.9×10^4 M^{-1}) gave stronger complexes with compound **3** than other anions due to their high basicity. Moreover, $H_2PO_4^-$ with four oxygens makes the strongest complexes *via* multitopic hydrogen-bonding interactions and these results agreed with those obtained by ^1H NMR. The large downfield shifts of thiourea NH resonances (> 2.5 ppm) were detected upon complexation with $H_2PO_4^-$ and AcO^-. Broadening of the phenol OH resonance was also observed, indicating its participation in hydrogen-bonding interactions with anions.

In the absence of anions, the UV-vis absorption spectrum of **3** showed an absorption maximum peak at 376 nm. With addition of $H_2PO_4^-$, the peak at 376 nm decreased while a new peak appeared at 529 nm, concomitant with a solution colour change from light yellow to deep red. This may be due to electronic excitation through charge transfer from the donor oxygen of the phenol to an acceptor substituent ($-NO_2$) of the chromophore. The excited state would be more stabilized by anion binding, resulting in a bathochromic shift in the absorption maxima as well as colour change. Changing the substituent at the thiourea moiety of **3** from butyl groups to nitrobenzene groups in compound **4** allowed the easy colorimetric differentiation of F^-, $H_2PO_4^-$ and AcO^- which have similar basicity.[5] The degree of a red shift for **4** was determined to be $H_2PO_4^- >> AcO^- \approx F^- > Br^- \approx Cl^- > HSO_4^- \approx I^-$ in $CHCl_3$. The maximum red-shift value (λ_{max} = 538 nm) for $H_2PO_4^-$ can be understood on the basis of the guest basicity and the structure of the complex.

Later, Hong and coworkers changed the signaling unit in compound **3** from nitro-azobenzene to indoaniline.[6] The compound **5**, a new chromogenic indoaniline-thiourea-based sensor, showed significant colour and UV-vis spectral changes upon binding anions. Upon the addition of $H_2PO_4^-$ or HSO_4^-, the colour of the $CHCl_3$ solution changed from blue-green to deep blue. The association constants obtained from UV-vis



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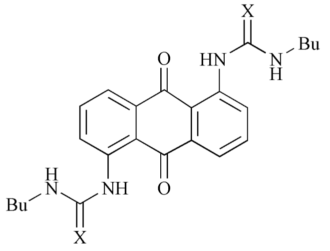
titrations for complexes of **5** with $H_2PO_4^-$ and HSO_4^- in $CHCl_3$ are 1.1×10^4 M^{-1} and 2.5×10^4 M^{-1}, respectively. However, addition of AcO^- or F^-, more basic anions, caused a less intense colour change. In addition, in the case of Cl^-, Br^- and I^-, no detectable colour changes were observed. This sensor, thus, allows the selective colorimetric detection of tetrahedral oxoanions such as HSO_4^- and $H_2PO_4^-$. In the same manner as for compound **3**, compound **5** possesses four NH urea moieties and would preferably bind anions with tetrahedral geometry (HSO_4^- and $H_2PO_4^-$).

Jiménez *et al.* have synthesised the receptors 1,5-bis-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-*N*′-butylthiourea **6** and its urea analogue, 1,5-bis-*N*-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-*N*′-butylurea **7**, by condensation of 1,5-diamino anthraquinone with butylisothiocyanate and butylisocyanate, respectively.[7]



6. X = S
7. X = O

Compound **6** showed a remarkable colour change from orange to brown in acetonitrile or DMSO solution upon adding F^-. The anion was believed to form a 2:1 anion to ligand ratio as shown in Fig. 2.

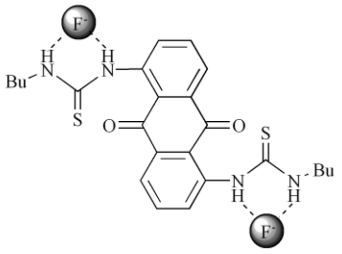
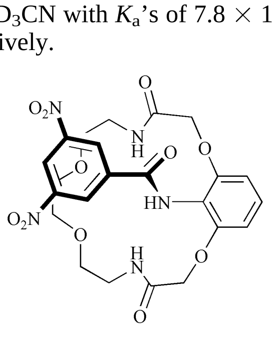


Fig. 2 Proposed hydrogen bond formation between fluoride and receptor **6**.

Besides urea and thiourea, amide groups can also form effective chromogenic anion sensors. Jurczak and coworkers have demonstrated the use of amide groups containing macrocycle **8** as a selective colorimetric sensor for F^-.[8] A DMSO solution of compound **8** showed dramatic colour changes upon addition of F^-, AcO^- and $H_2PO_4^-$ ions. It was found that a colourless solution of **8** turned dark blue (λ = 593, 708 nm), yellow (λ = 375 nm) and yellow (λ = 384 nm) when exposed to F^-, $H_2PO_4^-$ and AcO^-, respectively. However, compound **8** formed a substantially stable 2:1 anion to ligand ratio with F^- in DMSO-d_6 and CD_3CN with K_a's of 7.8×10^6 M^{-1} and 7.5×10^6 M^{-1}, respectively.



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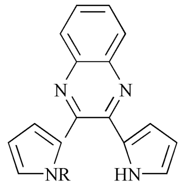
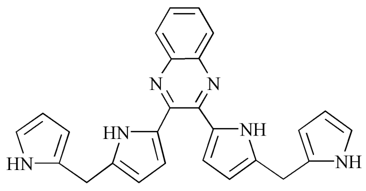
Sessler and co-workers have recently investigated 2,3-dipyrrol-2′-ylquinoxalines derivatives **9** and **10**, as potential anion receptors and sensors.[9] The electronic influence of the functional groups present in the receptor played a crucial role in its recognition and sensing ability. It was found that the receptor **10** had a higher affinity for F^- in dichloromethane with K_a = 1.2×10^5 M^{-1}. The solution underwent a dramatic yellow to purple colour change in the presence of F^-. Furthermore, this system also displayed fluorescence emission spectra that were quenched in the presence of F^- anion.



9. R = H
10. R = SEM



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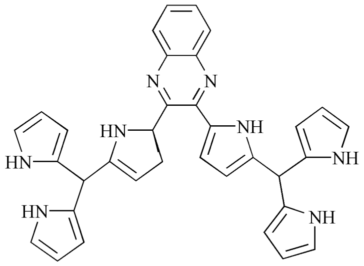

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Later, Sessler *et al.* synthesised two novel quinoxaline derivatives bearing dipyrromethane **11** or tripyrromethane **12**.[10] Both **11** and **12** were found to be much better anion receptors for F^-, Cl^- and $H_2PO_4^-$ than their precursor **10** in CH_2Cl_2. The substantial increase in affinities seen in the case of $H_2PO_4^-$ was ascribed to the greater number of pyrrole NH donors required to bind a larger anion. In addition, ^1H NMR results showed that compound **11** was able to bind anions using 2 modes of structures in CH_2Cl_2, shown in Fig. 3.

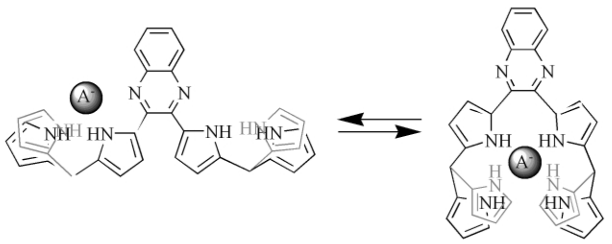
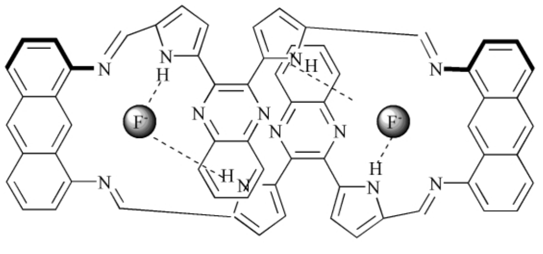


Fig. 3 Proposed anion binding modes of receptor **12**.

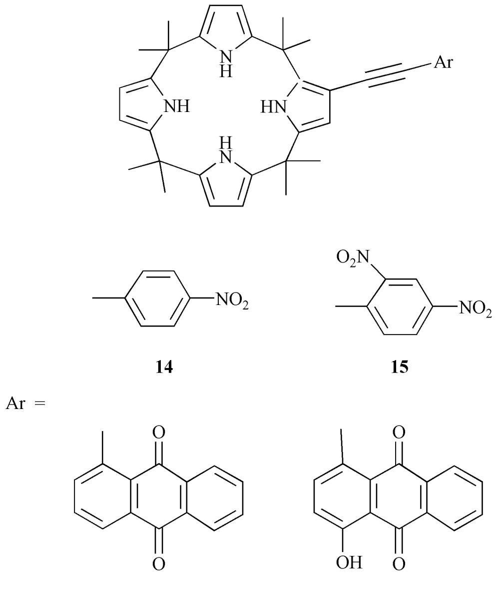
Very recently, Sessler and coworkers have synthesised a quinoxaline-bridged porphyrinoid compound, **13**.[11] Compound



13.2F⁻

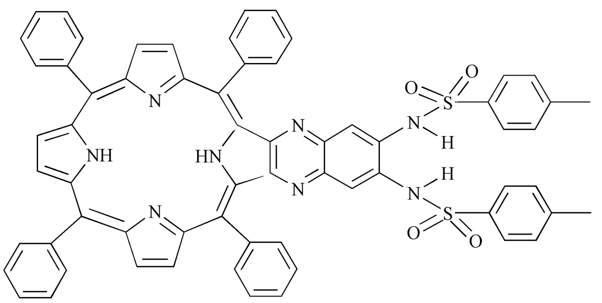
13 is able to bind two F^-. Upon addition of F^- to a 10% DMSO/CH_2Cl_2 (v/v) solution of the compound **13**, the colour of the solution changes from pale orange to red. The binding of the first fluoride anion makes binding the second fluoride anion somewhat more facile. The change in colour is not observed upon addition of > 300 molar equivalents of Cl^-, Br^-, NO_3^- or HSO_4^-.

The calix[4]pyrroles, colourless macrocycles rich in pyrrole NH hydrogen bond donors, are a class of uncharged anion receptors that show considerable promise in the area of anion sensing. The incorporation of nitrobenzene[12] and anthraquinone[13] into the calix[4]pyrroles to create fluoride sensors has been recently reported by Miyaji and co-workers. Both systems bear an appended chromophore directly linked to the calix[4]pyrrole skeleton through a conjugating C≡C triple bond (**14** to **17**). Upon addition of tetrabutylammonium fluoride, solutions of **14** and **15** in dichloromethane turned from pale yellow to intense yellow for **14** and from yellow to red for **15**. Furthermore, when adding tetrabutylammonium fluoride to solutions of **16** and **17** in dichloromethane, the colour of **16** changed from yellow to red, while **17** turned from red to blue. The dramatic colour changes were tentatively ascribed to charge transfer interactions between the electron-rich, calix[4]pyrrole-bound anions and the electron deficient anthraquinone moieties.



14 **15** **16** **17**

Later, Starnes *et al.* synthesised a disulfonamide porphyrin anion receptor **18**.[14] Anion binding was detected by the purturbation of the porphyrin Soret and Q-bands. The Soret band of **18** at 422 nm was red shifted upon addition of anions in CH_2Cl_2 and isosbestic points were observed. Compound **18** was able to bind F^- selectively in a 2:1 anion to ligand ratio with K_{a1} = 255,000 M^{-1} and K_{a2} = 1,700 M^{-1}.



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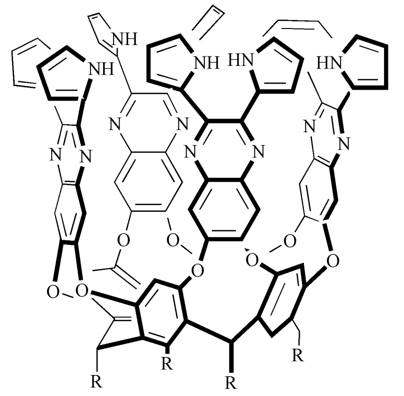
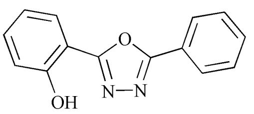
One example of the cavitand-based anion sensors, the open-ended host molecule with a vase shape cavity, was presented by Rebek and co-workers.[15] In this study, cavitand-based dipyrrolyl quinoxaline compound **19**, featuring four anion detecting walls, was synthesised and showed a selective binding for F^- and AcO^- anions in toluene:acetone, 4:1 v/v. A dramatic colour change from yellow to dark red was observed. A band at λ_{max} = 420 nm disappeared and two new bands at λ_{max} = 350 nm and 490 nm emerged in the UV-vis spectrum.



19. R = $(CH_2)_{10}CH_3$

Wang and colleagues have synthesised 2 derivatives of oxadiazole **20** and **21**, which were used as anion fluorescent and colorimetric chemosensors.[16] The two compounds showed high selectivity for $H_2PO_4^-$ and F^- over Cl^- in DMF. It was found that compound **20** changed its colour from colourless to yellow upon addition of F^- or $H_2PO_4^-$ in DMF. Therefore, **20** can be used for the "naked-eye" detection of F^- and $H_2PO_4^-$ in DMF solution in the presence of Cl^-.



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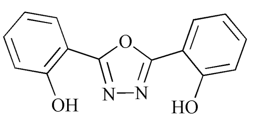

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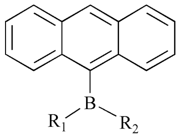
3 Lewis acid chromogenic hosts

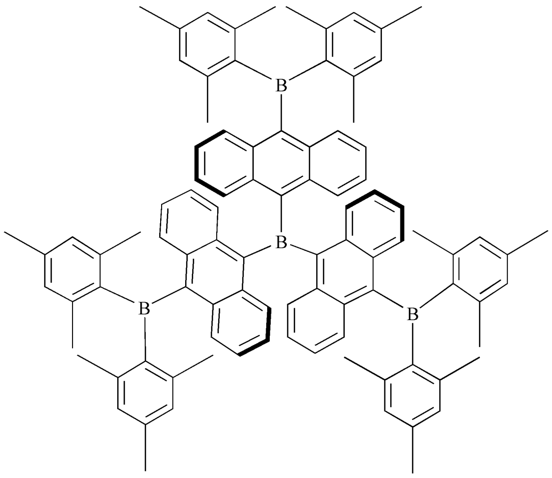
This section involves a type of receptors that require the incorporation of a defined number and type of Lewis acids such as Hg(II), Zn(II) and B into a molecular skeleton with their electron deficient sites exposed for the interaction with the lone electron pair of anions.

Tamao and co-workers reported a new type of multistage sensing of fluoride anion based on boron-containing π-conjugating system **22–25**.[17] The boron atoms in this type of compound possess a unique LUMO in which π-conjugation is divergently extended through the vacant p-orbital of the boron atom. Complexation of the boron π-electron systems with anions would interrupt the π-conjugation extended through the boron atom, resulting in a dramatic colour change. The complexation studies of compounds **22–24** and F^- were done by using UV-vis spectrophotometry. When tetrabutylammonium fluoride (TBAF) was added to a THF solution of each borane, a dramatic colour change occurred from colourless to orange for **22** and from yellow to colourless for compounds **23** and **24**.

However, compound **22** showed a large binding constant towards F^- over compounds **23** and **24**. The more extended π-electron system **25** has four boron atoms in two different



22. $R_1 = R_2$ = 9-anthryl
23. R_1 = 9-anthryl, R_2 = mesityl
24. $R_1 = R_2$ = mesityl



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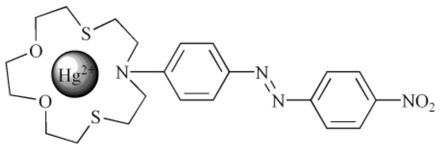
environments. When the concentration of TBAF increased, the absorption at 524 nm decreased and a new band at 474 nm, together with a broad shoulder band around 570 nm emerged, and the colour of solution changed from red to orange. The UV-vis analysis implied that compound **25** were able to bind three F^- ions. The three stepwise binding constants are 6.9×10^4, 9.0×10^2 and 2.1×10^2 M^{-1} in THF. The results suggest that the complexation of F^- in **25** may occur not with the internal boron atom but with the three peripheral boron atoms instead.

Martínez-Máñez and co-workers have showed that the complex of Hg(II) with aza-oxa-thia macrocycle **26** can be used for the specific chromogenic sensing of nitrate.[18] Addition of nitrate anion to an acetonitrile solution of **26** resulted in a shift of the 540 nm band to 490 nm with a concomitant change in colour from red to yellow. UV-vis titrations for the complex of **26** with NO_3^- in CH_2Cl_2 gave a stability constant of log K = 6.2. NMR studies of a **26**-nitrate system showed a slight shift of the signals assigned to the protons *ortho* to the azo group. This shift could be related to the presence of π-stacking interactions between the nitrate ion and the *p*-nitrophenylazobenzene group. The selective sensing of nitrate by **26** has found application in nitrate determination in water.



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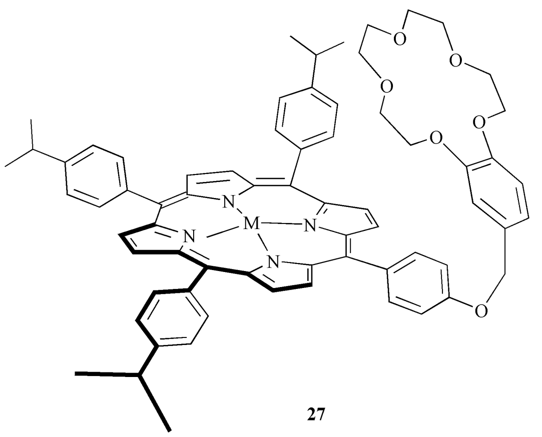
Ditopic neutral receptors composed of both a Lewis acid binding site (zinc porphyrin unit) and a Lewis-basic binding unit (crown ether moiety) **27** and **28** have been reported by Kim and Hong.[19] Such receptors bound only NaCN in a ditopic fashion. UV-visible titrations between the receptors **27** and **28** and NaCN in CH_2Cl_2 resulted in a red shift of the Soret band of the zinc porphyrin units, which were the origin of the colour change from red to green.



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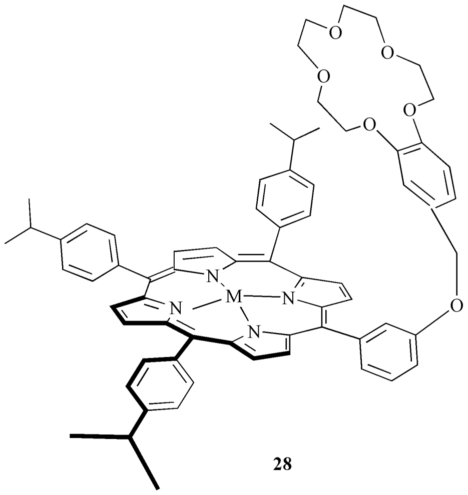

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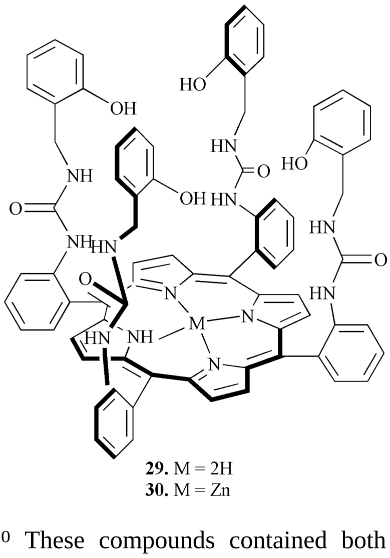
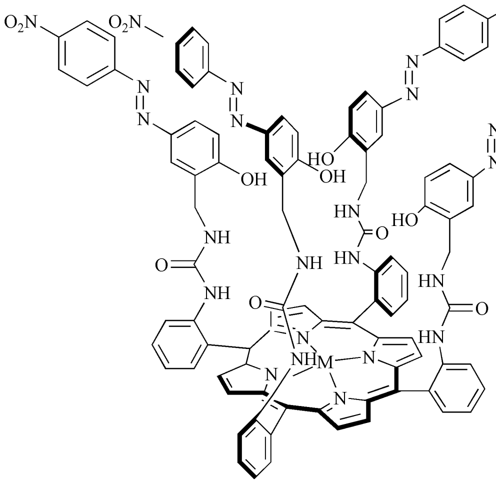


29. M = 2H
30. M = Zn

New colorimetric azophenolurea-containing porphyrin sensors for anions, compounds **29–32**, were reported by Hong and coworkers.[20] These compounds contained both Lewis acid centers and urea anion binding units. Receptors **29** and **30** exhibited good selectivities for AcO^- and $H_2PO_4^-$ in DMSO, while **31** and **32** showed dramatic colour changes for F^- in CH_3CN due to an increased interaction with a nitrophenylazo phenolic OH group.

4 Metal ion-templated chromogenic hosts

The intramolecular enrolment of different binding groups can be readily achieved by a metal template. The basic concept shown in Fig. 4 requires that individual subunits contain both a metal binding region and an anion binding site. Addition of a



31. M = 2H
32. M = Zn

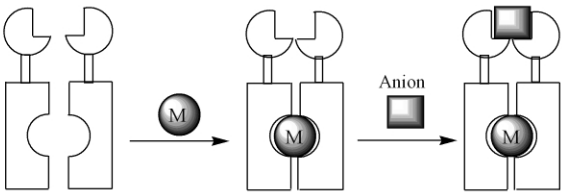


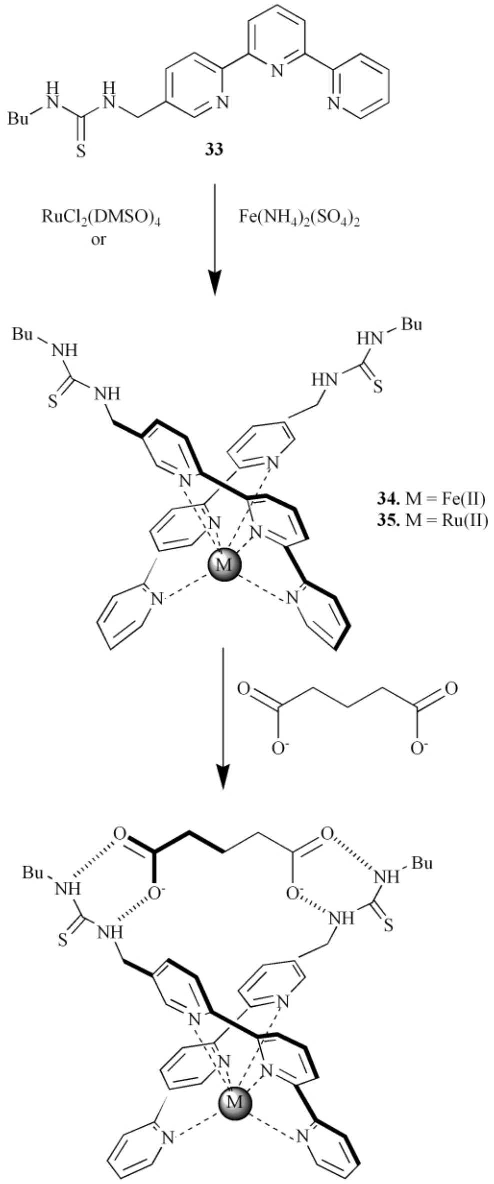
Fig. 4 Schematic of binding site organization by metal template effects.

metal ion will cause the coordination of metal binding regions and the organization of the binding site for anions.

Hamilton and coworkers have synthesised bipyridine bis-thiourea subunit **33** in the presence of Fe(II) or Ru(II) ions.[21] This resulted in the forming of bis-thiourea binding regions of complexes **34** and **35** for binding anions. Preliminary results showed that the complex **35** participated in binding various dicarboxylate anions such as glutarate (K_a = 8.3 × 10^3 M^{-1}), adipate (K_a = 2.9 × 10^3 M^{-1}) and pimilate (K_a = 6.0 × 10^3 M^{-1}) to different extents.

Weiss and co-workers have reported a new receptor for dicarboxylic acids, related guests to dicarboxylate anions, based on the self assembly of functionalized *meta*-catechol **36** around *cis*-[MoO$_2$]$^{2+}$.[22] UV-Vis studies for dicarboxylic acid binding showed 1:1 stoichiometry for the complex formation. The receptor **37** displayed selectivity for C$_4$ and C$_5$ dicarboxylic acids. The stability constants of the complex **37** with C$_4$ and C$_5$ dicarboxylic acids in CH$_3$CN are log *K*'s of 6.1 and 4.3, respectively. This should be explained by the free rotation of the CO–phenyl bond enabling the receptor to adapt to the length of the diacid carbon chain. Furthermore, this receptor exhibited enantioselective recognition of D and L–*N*-CBz-glutamic acid, *via* directed multiple hydrogen bonding and lipophilic interactions with topographical control achieved by the *cis*-[MoO$_2$]$^{2+}$ core.

Hamilton and co-workers synthesised the dicarboxylic acid receptors **38** and **39**.[23] These two receptors consist of a 2,9-disubstituted phenanthroline bearing one or two acylamino pyridine binding sites, which can coordinate to a Cu(I) ion. This arrangement was ideally suited for the strong hydrogen bonding complexation of dicarboxylic acids, and large downfield shifts of the NH resonances were observed in an NMR study. Significant changes in the UV absorption of **38** and **39** in CHCl$_3$ also took place on addition of glutaric acid, with the colour of solution changing from red-orange to orange-red for **38** and orange to red for **39**. The Job's plot showed 1:1 and 1:2 stoichiometries of complex formations between **38** and **39** with dicarboxylic acids, respectively. Binding constants for the complexes of **38** with glutaric acid and pimelic acid measured by ^{1}H NMR in CDCl$_3$ are 4.3 × 10^4 M^{-1} and 1.6 × 10^4 M^{-1}, respectively. The chromogenic effect presumably came from a change in the conjugation of the (benzoylaminopyridyl) side arm of the phenanthroline metal system due to conformational changes on guest binding.

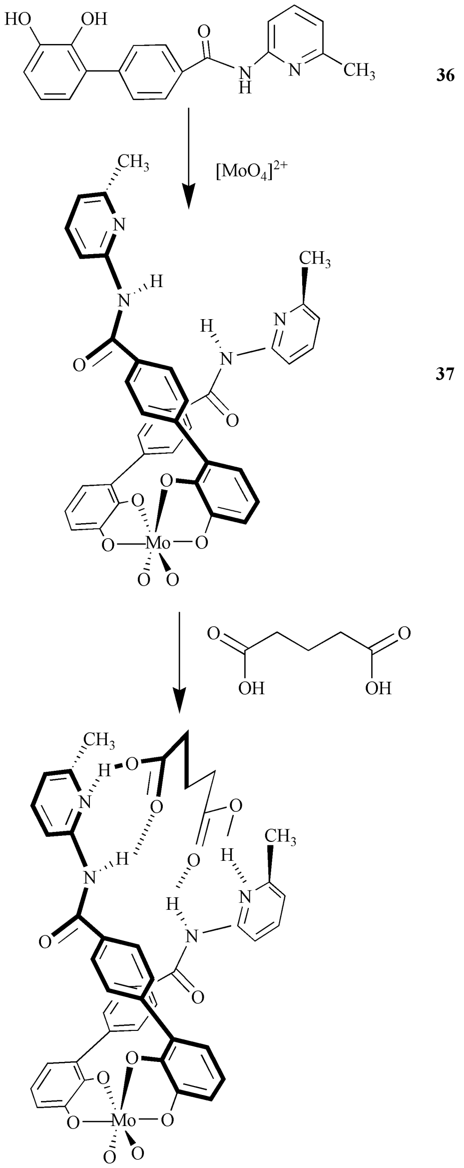


34. M = Fe(II)
35. M = Ru(II)

5 Transition metal complexes as chromogenic hosts

This type of chromogenic sensor utilizes the coordination chemistry of transition metal complexes which have vacant binding sites to bind specific anions or have pendant arms containing anion receptor units. Transition metal complexes already have their own specific colours due to their different electronic structures. Coordinating directly to anions or binding of anions by the pendant arms results in perturbations of their electronic structures and causes colour changes.

Fabbrizzi and co-workers reported the synthesis of dicopper(II) complexes of bis-tren cryptand **40** and **41**.[24] The metal center was coordinated by a tren subunit oriented to a trigonal bipyramidal geometry which had an available binding site for anions at a vacant axial position. These two receptors displayed a special affinity for halide ions that were firmly encapsulated in a 1:1 stoichiometry. Halide inclusions were able to be detected visually by the appearance of an intense, brightly



yellow colour, and development of very strong band centered at 410–440 nm. Moreover, the unique feature of the copper complex with ligand **41** was its ability to accommodate anions by varying size and shape. Not only for halide ions, compound **41** was also able to include linear triatomic anions such as N_3^- (log $K = 4.7$) and NCS^- (log $K = 4.28$). The solution turned pale blue to intense olive green. This was due to the NH–CH_2–C–O torsion angles along the chain arm of 2,5-dimethylfuran behaved as a spring, which controlled the length of the intermetallic cavity.

Beer and co-workers have combined ferrocene and mixed amide–amine moieties for a new anion sensor.[25] The receptor **42** showed a spectacular UV-vis response to the addition of $H_2PO_4^-$ in CH_3CN, which resulted in hydrogen bonding to the amide units near the ferrocene and caused a large UV perturbation. The d–d band at 443 nm showed a hypsochromic shift and a hyperchromic effect. This change was visible to the naked eye with the solution becoming brighter in colour.

Recently, Miyaji and co-workers reported chromogenic molecular switch **43** as a new ditopic ferrocene receptor for anions and cations.[26] Upon addition of F^- to a solution of **43** in acetonitrile, a new absorbance appeared at 472 nm ($K_a = 9{,}340$ M^{-1}). Addition of K^+ to the solution of **43**.$\mathbf{F}^-$ caused a reverse behavior. The colour of the solution turned colourless. This implied that the colour change was controlled by F^- 'switches on' and K^+ 'switches off'. This result was confirmed by NMR studies in CD_3CN. When K^+ was added to the solution of **43**.$\mathbf{F}^-$, large upfield shifts of the proton of the urea-NH occurred and shifted to the position of the free receptor. The results from ^1H NMR and UV-vis studies, therefore, supported the assumption that it was the presence of K^+ in close proximity to the fluoride binding center of **43** that caused the colour quenching process. This receptor may thus be applied as an optical device at the molecular level.

A luminescent Ru(II) metal complex with 2,3-di(1*H*-2-pyrrolyl)quinoxaline receptor **44** was reported by Castellano and colleagues to undergo a red shift in the UV-visible spectrum upon addition of CN^- in CH_2Cl_2/CH_3CN.[27] The low-lying MLCT absorption and the high-energy π–π^* ligand-based absorptions decreased monotonically throughout the addition. These absorption features signified that CN^- anion bound to the metal complex.

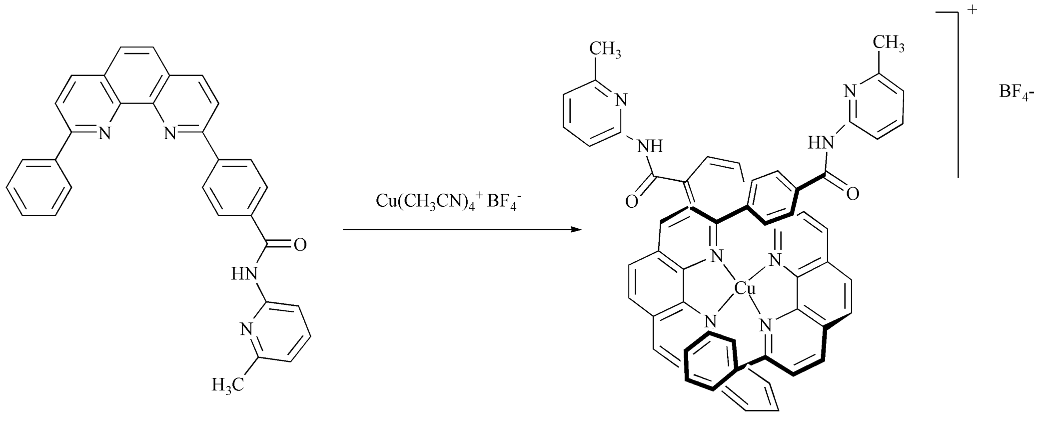
6 Displacement of chromogenic guests

An alternative method to a covalently attached chromophore is a competition between the indicator and the analyte in the receptor unit. An indicator is displaced from the binding site upon addition of an analyte, causing a signal modulation (Fig. 5). In order to create a sensitive sensing strategy, an indicator must give a large absorption change upon addition to the receptor, since the subsequent addition of an analyte must lead to a large change in the opposite direction. The advancement of this method has been described in detail by Anslyn and his colleagues.[28] In this review, the work included in Anslyn's excellent accounts are, therefore, not restated.

Gale and co-workers have discovered a very simple displacement method for a calix[4]pyrrole-based anion receptor.[29] Addition of calix[4]pyrrole **45** to a solution of tetrabutylammonium 4-nitrophenolate in CH_2Cl_2 caused a decrease in intensity of a UV band at 432 nm and calix[4]pyrrole–4-nitrophenolate complex **46** was formed. Upon addition of F^-, 4-nitrophenolate was displaced from the complex, and the colour of the solution changed from colourless to yellow due to the presence of the free nitrophenolate anion.

Heparin, **47**, an anticoagulation reagent, is used during cardiopulmonary bypass surgery. During surgery, heparin is commonly monitored by determining the activated clotting time (ACT). Zhong and Anslyn have recently reported a new designed receptor and sensor for heparin, possessing a novel amino acid with a boronic acid side chain, **48**.[30] This new receptor showed strong binding to heparin with good selectivity. Pyrocatechol violet, **49**, was used as indicator for colorimetric sensor of heparin. The binding of **49** to the receptor **48** in methanol/water caused a colour change from yellow to grayish purple ($K_a = 7.1 \times 10^3$ M^{-1}). When heparin **47** replaced **49** and was bound in the cavity of the receptor **48**, the colour of the solution changed to yellow ($K_a = 3.8 \times 10^4$ M^{-1}).

The detection of anions such as phosphate in water is a challenging task due to the competing solvation effect between water and anions. Han and Kim have recently reported a colorimetric sensor that can detect phosphate anions in aqueous solution at neutral pH.[31] The dinuclear Zn(II) complex of 2,6-bis(bis(2-pyridylmethyl)aminomethyl)-4-methylphenol (H-bpmp), **50**, was synthesised. The Zn(II) H-bpmp is colourless and has good water solubility. In addition, it can bind phosphate very strongly. The authors used pyrocatechol violet **49**, a catechol type pH-sensitive dye, as a chromogenic indicator for the sensor. When the solution of complex **50** was titrated into the solution of the indicator, the colour changed from yellow ($\lambda_{max} = 444$ nm) to blue ($\lambda_{max} = 624$ nm) signifying the binding of pyrocatechol violet to the zinc complex. The addition of phosphate anions to the aqueous solution of the ensemble resulted in a change of the colour from blue to yellow indicating free pyrocatechol violet that was replaced by the anions (Fig. 6).



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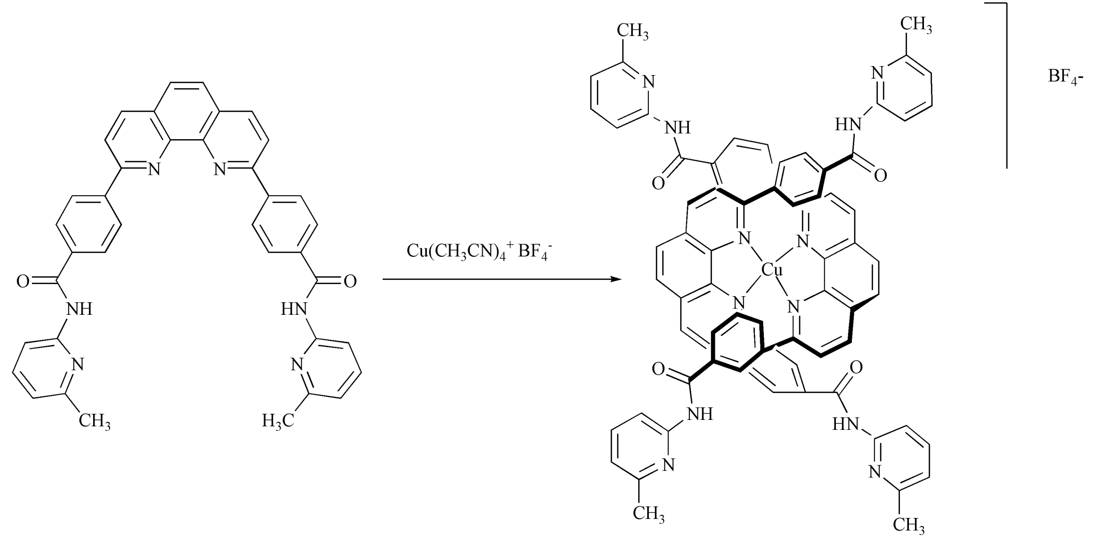

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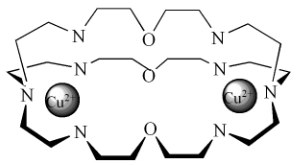

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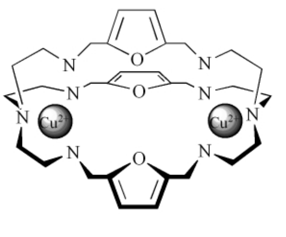

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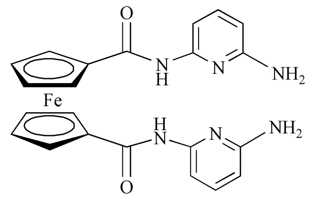

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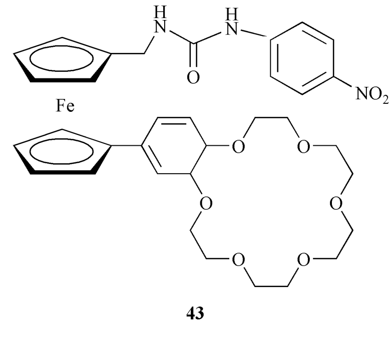

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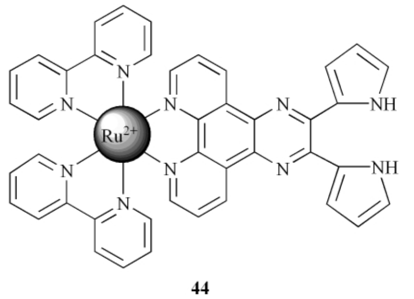

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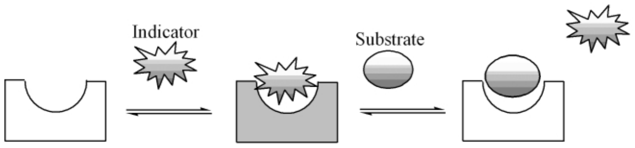
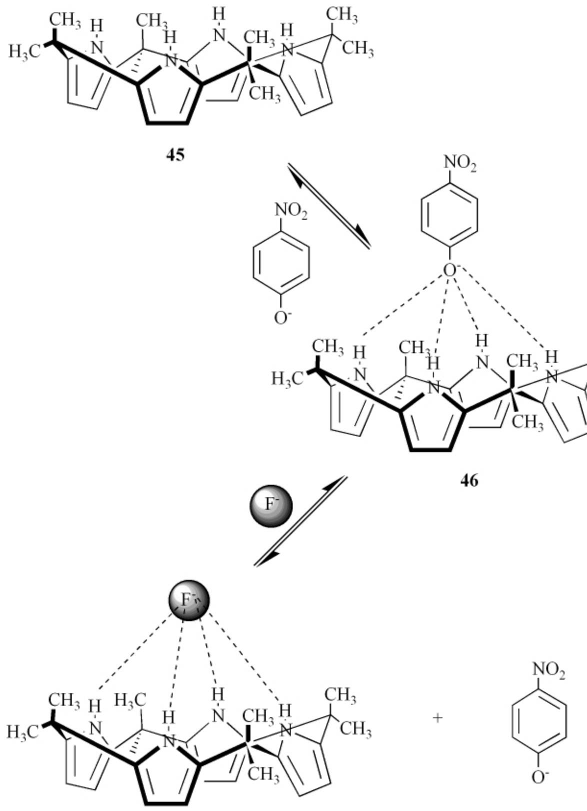


Fig. 5 Schematic operating of displacement method for chromogenic sensor.

This system was very selective for phosphate anions. Other anions failed to cause the colour change.

A similar system for detecting pyrophosphate optically in water was created by Fabbrizzi *et al.*[32] The researchers used the Cu(II) complex of the bisdiene macrocycle, 3,6,9,16,19,22-hexaazatricyclo[22.2.2.2(11.14)]triaconta-1(26),11(12),13,24,27,29-hexaene, **51** as a receptor for binding anion, dyes such as coumarin 343, **52**, and pyrophosphate in their system. The displacement of the dye from the Cu(II) complex by pyrophosphate gave a naked-eye detectable change. The detection of



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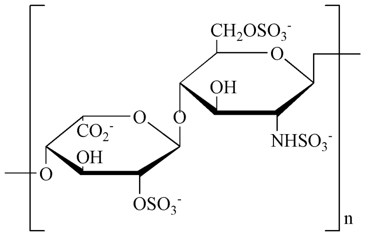

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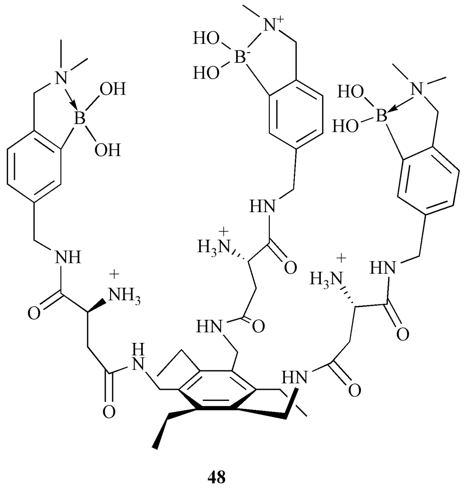

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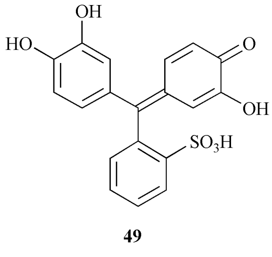

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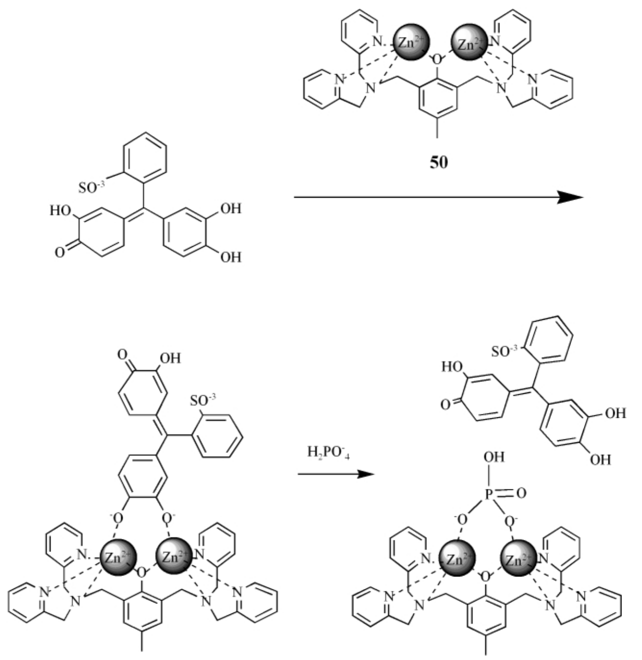

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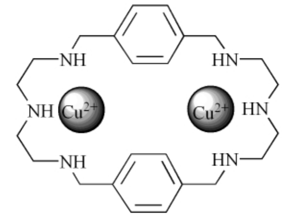
Fig. 6 Schematic representation of receptor **50**.

carbonate in water was also developed by the same researchers; however, the dicopper(ɪɪ) cryptate **41** was used concomitant with coumarine 343.[33]



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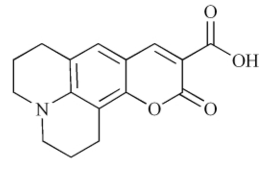

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7 Chromoreactands: concurrent recognition and reaction

Besides the covalent attachment of the chromophore to the receptor units or displacement of a chromogenic guest strategy, one can employ advantages of the selective reactivity between a particular anion and chromogenic hosts, which will display dramatic colour changes. There have been at least five examples of these chromoreactands published recently.[34–38]

Mohr has used 4-*N*,*N*-dioctylamino-4′-formyl-2′-nitroazobenzene, **53**, as a chromoreactand for selective sensing of hydrogen sulfite (HSO_3^-).[34] The aldehyde moiety in **53** is known to interact with hydrogen sulfite by forming a bisulfite adduct as shown in Fig. 7. The conversion of the aldehyde into

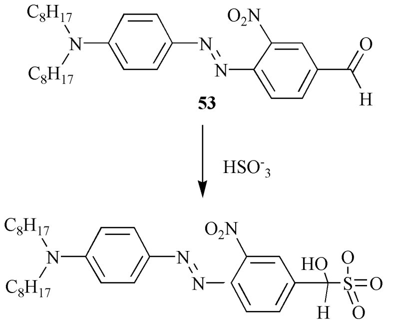

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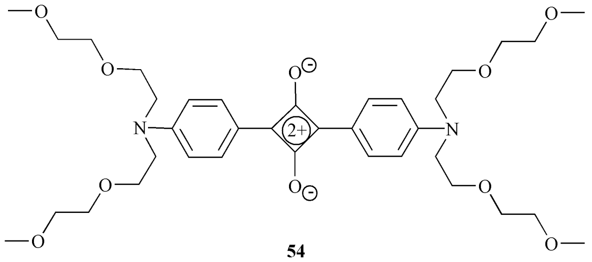
Fig. 7 Chemical structure of receptor **53** for sensing bisulfite and corresponding bisulfite adduct.

the bisulfite adduct can bring about a change in the electron acceptor strength. Consequently, a colour change of the formyl dye upon interaction with hydrogen sulfite can be noticed. The investigator has demonstrated that in a sensor layer composed of the chromoreactand and dioctadecymethylamine in PVC plasticized by 2-nitrophenyloctyl ether, first with plain buffer of pH 4.9 and then with buffer containing 30 mM hydrogen sulfite, a shift in absorbance maximum from 524 nm to 484 nm was observed.

Ros-Lis *et al.* have taken advantage of the selective reactivity towards a particular reaction that certain anions display. The nucleophile characteristics of CN$^-$ allow a reaction with a squarine dye derivative, **54**, that results in a distinct colour change.[35] The chromogenic sensing ability of **54** was studied in acetonitrile in the presence of various anions: F$^-$, Cl$^-$, Br$^-$, I$^-$, NO$_3^-$, H$_2$PO$_4^-$, HSO$_4^-$, AcO$^-$, BzO$^-$, CN$^-$ and SCN$^-$. Only CN$^-$ was able to decolorize **54**. ^{1}H NMR data for **54** in CD$_3$CN upon CN$^-$ addition were consistent with cyanide attack on a carbon of the four-atom squaraine ring next to the phenyl group. This caused the rupture of the electronic decolorization with the consequent disappearance of the 641 nm charge transfer band.



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The transformation of a reactant to another form by changing the pH of the solution can be used as a chromogenic sensor. The 1,3,5-triaryl-1,5-pentanedione derivative, **55**, can be readily transformed into the corresponding pyrylium ion as shown in Fig. 8.[36] Addition of nitric acid to solution of **55** in 1,4-dioxane/water caused a dramatic change in colour from yellow to magenta. The changes in absorption spectrum of **55** at neutral pH upon adding anions such as chloride, bromide, sulfate, phosphate, ATP, ADP, GMP have also been studied. However, the most remarkable effect was observed in the presence of ATP, whereby a bright magenta colour was fully developed. Therefore, **55** is a selective chromogenic reagent for sensing ATP.

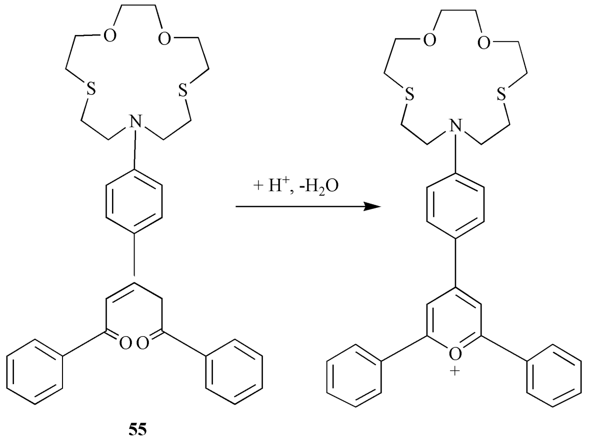
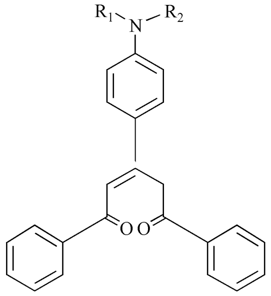


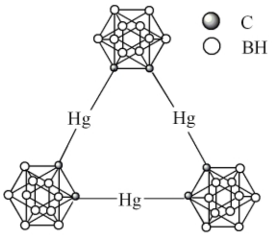
Fig. 8 Transformation of receptor **55** into the pyrylium caion.

Sancenón *et al.* have synthesised a number of colorimetric probes to discriminate between isomeric dicarboxylate anions. A dioxane/water (70:30 v/v) solution of compound **56** at *ca.* pH 6 using 0.01 M HEPES buffer is yellow.[37] Upon addition of oxalate and malonate anions, solutions turn red-magenta. Other dicarboxylate anions such as succinate, glutarate, adipate, pimeate and suberate do not change colour of the solutions, and the solutions remain yellow. The remarkable colour change is a result of the anion-induced selective cyclisation of **56** to give the coloured 2,4,6-triphenylpyrylium cation similar to the one shown in Fig. 8. The solution of **57** in the same solvent and buffer is yellow in the presence of fumarate (a *trans* isomer), but changes colour to magenta in the presence of maleate (a *cis* isomer). Specific colour change occurs because the diacid shaped like a tweezer (*cis* isomer and oxalate) is able to act as chelating ligands towards the hydroxyl group whereas other diacids do not. This shape-induced recognition enhances the ease of cyclisation to the magenta pyrylium cation.



56. R$_1$ = CH$_2$CH$_2$OH, R$_2$ = (CH$_2$CH$_2$O)$_4$CH$_2$CH$_2$OH
57. R$_1$ = R$_2$ = CH$_3$

Bachas and co-workers have reported a highly selective optical sensor for chloride in blood, based on the multidentate Lewis acid ionophore [9]mercuracarborand-3 **58**.[38] Compound **58** incorporates 3 electron deficient mercury centers within a macrocyclic cavity and, therefore, is selective for chloride by such a preorganized cavity. In addition, the compound is chemically stable and hypophilic and, thus, suitable for using as a sensor for Cl$^-$ in blood. This sensor was constructed by embedding the mercuracarborand, a suitable acidic lipophilic dye, **59**, and lipophilic cationic sites in a plasticized polymeric membrane film. The sensing mechanism was based on anion binding by [9]mercuracarborand-3, following by a concomitant protonation of the acid dye to ensure electroneutrality. Such protonation of the proton chromoionophore led to a large change in the absorbance of the optical film.



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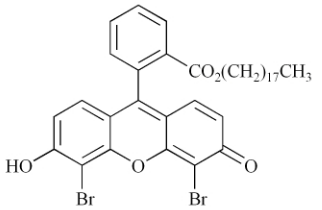

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8 Conclusion

We have summarized 6 types of chromogenic anion sensors. Many anion receptors containing different anion binding sites and a plethora of chromophores have been described. Each type has its own advantages and drawbacks. The NH-based hydrogen bonding-type and Lewis acid-type sensors are simple and easy to use, but they have a limited use in some media such as water. The metal ion template type can be alternatively employed as a switchable ‘on’ or ‘off’ sensor utilizing a metal ion as a switch. The transition metal complex chromogenic hosts are still waiting for new discoveries. The indicator displacement method is a powerful approach in term of analytical aspects, but it is sometimes complicated to use. Therefore, this type of chromogenic sensor, in particular, needs more development. There should be a lot of space to fill in this area. The chromoreactand has only recently emerged and definitely needs more investigation. Overall, chromogenic anion sensing is still a young field waiting for new disclosures. It is yet a long way to bring these synthetic sensors or systems to use practically. We optimistically believe that there is a way to combine the aforementioned approaches to fabricate an ultimate chromogenic sensor for a particular anion.

9 Acknowledgements

This work was financially supported by the Thailand Research Fund (RSA/06/2544 and PHD/00123/2545). CS is a PhD student supported by the Royal Golden Jubilee Program.

10 References

1 P. A. Gale, *Coordination. Chem. Rev.*, in the press.
2 H. Miyaji and J. L. Sessler, *Angew. Chem. Int. Ed.*, 2001, **40**, 154.
3 R. Kato, S. Nishizawa, T. Hayashita and N. Teramae, *Tetrahedron Lett.*, 2001, **42**, 5053.
4 D. H. Lee, K. H. Lee and J.-I. Hong, *Org. Lett.*, 2001, **3**, 5.
5 D. H. Lee, H. Y. Lee, K. H. Lee and J.-I. Hong, *Chem. Commun.*, 2001, 1188.
6 D. H. Lee, H. Y. Lee and J.-I. Hong, *Tetrahedron Lett*, 2002, **43**, 7273.
7 D. Jiménez, R. Martínez-Máñez, F. Sancenón and J. Soto, *Tetrahedron Lett.*, 2002, **43**, 2823.
8 P. Piatek and J. Jurczak, *Chem. Commun.*, 2002, 2450.
9 C. B. Black, B. Andrioletti, A. C. Try, C. Ruiperez and J. L. Sessler, *J. Am. Chem. Soc.*, 1999, **121**, 10438.
10 J. L. Sessler, H. Maeda, T. Mizuno, V. M. Lynch and H. Furuta, *Chem. Commun.*, 2002, 862.
11 J. L. Sessler, H. Maeda, T. Mizuno, V. M. Lynch and H. Furata, *J. Am. Chem. Soc.*, 2002, **124**, 13474.
12 H. Miyaji, W. Sato, J. L. Sessler and V. M. Lynch, *Tetrahedron Lett.*, 2000, **41**, 1369.
13 H. Miyaji, W. Sato and J. L. Sessler, *Angew. Chem. Int. Ed.*, 2000, **39**, 1777.
14 S. D. Starnes, S. Arungundram and C. H. Saunders, *Tetrahedron Lett.*, 2002, **43**, 7785.
15 U. Lücking, D. M. Rudkevich and J. Rebek Jr., *Tetrahedron Lett.*, 2000, **41**, 9547.
16 H. Tong, G. Zhou, L. Wang, X. Jing, F. Wang and J. Zhang, *Tetrahedron Lett.*, 2003, **44**, 131.
17 S. Yamaguchi, S. Akiyama and K. Tamao, *J. Am. Chem. Soc.*, 2001, **123**, 11372.
18 F. Sancenón, R. Martínez-Máñez and J. Soto, *Angew. Chem. Int. Ed.*, 2002, **41**, 1416.
19 Y.-H. Kim and J.-I. Hong, *Chem. Commun.*, 2002, 512.
20 C. Lee, D. H. Lee and J.-I. Hong, *Tetrahedron Lett.*, 2001, **42**, 8665.
21 M. S. Goodman, V. Jubian and A. D. Hamilton, *Tetrahedron Lett.*, 1995, **36**, 2551.
22 I. Prévot-Halter, T. J. Smith and J. Weiss, *J. Org. Chem.*, 1997, **62**, 2186.
23 M. S. Goodman, A. D. Hamilton and J. Weiss, *J. Am. Chem. Soc.*, 1995, **117**, 8447.
24 V. Amendola, E. Bastianello, L. Fabbrizzi, C. Mangano, P. Pallavicini, A. Perotti, A. M. Lanfredi and F. Ugozzoli, *Angew. Chem. Int. Ed.*, 2000, **39**, 2917.
25 P. D. Beer, A. R. Graydon, A. O. M. Johnson and D. K. Smith, *Inorg. Chem.*, 1997, **36**, 2112.
26 H. Miyaji, S. R. Collinson, I. Prokeŝ and J. H. R. Tucker, *Chem. Commun.*, 2003, 64.
27 P. Anzenbacher Jr., D. S. Tyson, K. Jursíková and F. N. Castellano, *J. Am. Chem. Soc.*, 2002, **124**, 6232.
28 S. L. Wiskur, H. Ait-Haddou, J. J. Lavigne and E. V. Anslyn, *Acc. Chem. Res.*, 2001, **34**, 963.
29 P. A. Gale, L. J. Twyman, C. I. Handlin and J. L. Sessler, *Chem. Commun.*, 1999, 1851.
30 Z. Zhong and E. V. Anslyn, *J. Am. Chem. Soc.*, 2002, **124**, 9014.
31 M. S. Han and D. H. Kim, *Angew. Chem. Int. Ed.*, 2002, **41**, 3809.
32 L. Fabbrizzi, N. Marcotte, F. Stomeo and A. Taglietti, *Angew. Chem. Int. Ed.*, 2002, **41**, 3811.
33 L. Fabbrizzi, A. Leone and A. Taglietti, *Angew. Chem. Int. Ed.*, 2001, **40**, 3066.
34 G. J. Mohr, *Chem. Commun.*, 2002, 2646.
35 J. V. Ros-Lis, R. Martínez-Máñez and J. Soto, *Chem. Commun.*, 2002, 2248.
36 F. Sancenón, A. B. Descalzo, R. Martínez-Máñez, M. A. Miranda and J. Sato, *Angew. Chem. Int. Ed.*, 2001, **40**, 2640.
37 F. Sancenón, R. Martínez-Máñez, M. A. Miranda, M.-J. Seguí and J. Sato, *Angew. Chem. Int. Ed.*, 2003, **42**, 647.
38 I. H. A. Badr, R. D. Johnson, M. Diaz, M. F. Hawthorne and L. G. Bachas, *Anal. Chem.*, 2000, **72**, 4249.