Amidopyrroles: from anion receptors to membrane transport agents

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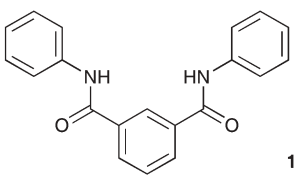
Amidopyrroles have been employed in a variety of anion receptors and sensors. 2,5-Bisamidopyrroles show selective oxo-anion complexation properties in organic solution whilst bis-amides containing dipyrrolylmethane groups form strong complexes with dihydrogen phosphate anions in mixtures of DMSO-d_6 and water. Deprotonation of the 2,5-bisamidopyrrole unit can lead to interesting solid-state structures including the formation of orthogonal hydrogen bonded dimers. Amidopyrrole groups have also been employed in receptors for ion-pairs and in membrane transport agents for HCl.

Introduction

Anions are critical to the maintenance of life with the recognition, transport and transformation of anions involved in almost every biochemical operation. Anions can also have deleterious effects. The discharge of anthropogenic anions such as pertechnetate from nuclear fuel reprocessing processes into the environment is strictly controlled whilst nitrate and phosphate originating from the over use of agricultural fertilizers can lead to eutrophication in inland waterways. Consequently, there has been increasing interest in anion complexation since the seminal report of the first synthetic anion receptor in 1968 by Park and Simmons.[1] A wide variety of receptors that utilise electrostatic interactions, hydrogen bond donor groups, Lewis acid groups and hydrophobic interactions have been employed to bind a variety of anionic guest species over the intervening years.[2] Neutral anion receptors containing hydrogen bond donors are an important subset of the anion binding agents. Amide,[3] urea,[4] pyrrole[5] and other hydrogen bond donor groups have been employed in a variety of both cyclic and acyclic receptors. Pioneering work by Sessler and co-workers at the University of Texas at Austin has shown that both neutral[6] and charged[7] macrocyclic and macrobicyclic pyrrole based receptors display high affinities and selectivities for anionic species both in solution and in the solid-state. In very elegant related work, Schmuck and co-workers have shown that positively charged guanidinio-carbonylpyrroles are excellent carboxylate receptors and have been employed in a variety of receptors for amino-acids[8] and self-assembling systems.[9] Inspired by the work of Sessler and by the work on the anion and neutral guest complexation of very simple molecules based on the isophthalamide skeleton (**1**),[10] we wished to explore the potential of simple neutral amidopyrrole containing species to act as anion receptors.



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2,5-Bisamidopyrroles

Our initial studies focused on synthesising pyrrolic analogues of compound **1**. Our starting point for this work was the

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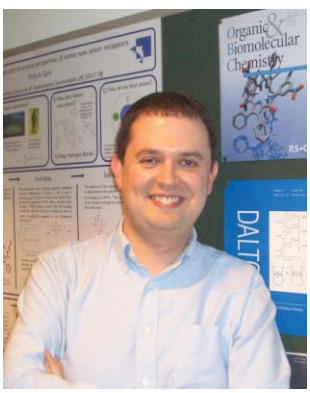


Philip A. Gale

Philip A. Gale was born in Liverpool in 1969. He graduated with a BA (Hons.) in chemistry from Wadham College, Oxford in 1992 (MA (Oxon.) 1995) and a DPhil (for work conducted in Prof. Paul Beer's research group) from Linacre College, Oxford in 1995. He was awarded a Fulbright Post-doctoral Fellowship taken up at The University of Texas at Austin working under the supervision of Professor Jonathan L. Sessler. In 1997 he was awarded a Royal Society University Research Fellowship and started his independent career at the Inorganic Chemistry Laboratory, Oxford. He moved to the School of Chemistry at the University of Southampton in September 1999 as Royal Society URF and Lecturer and was promoted to Senior Lecturer in 2002 and Reader in 2005. His interests in supramolecular chemistry are focused on anionic species and specifically on synthetic anion receptor chemistry and the roles anions can play in self-assembly and in crystal engineering. He was awarded a Society of Porphyrins and Phthalocyanines Young Investigator Award in New Orleans in July 2004 and the 2004 Bob Hay lectureship by the RSC UK Macrocycles and Supramolecular Chemistry Group in January 2005. He is the associate editor of the journal Supramolecular Chemistry and a member of the international editorial advisory boards of Coordination Chemistry Reviews, the Encyclopaedia of Supramolecular Chemistry, Chemistry World and Chemical Communications. In 2004 he joined the International Scientific Committee of the International Symposium on Macrocyclic Chemistry (ISMC).

pyrrole-2,5-bisacid **2** that was originally reported by Friedman in 1965.[11] Reaction with thionyl chloride yielded the acid chloride from which the amides **3** and **4** could be obtained in 18 and 47% respective yields (Scheme 1).[12] The moderate yields of these reactions are due in part to self-condensation of the acid chloride yielding a fused three ring dimer species.[13] However, reasonable quantities of the bis-amides could be made easily by this route. Mono-amides **5** and **6** were also synthesised in order to compare their anion binding ability with that of **3** and **4**.

The X-ray crystal structure of receptor **3** crystallised from acetonitrile solution is shown in Fig. 1(a). The receptor dimerizes *via* the formation of two NH···O=C hydrogen bonds in the solid-state with additional CH···O interactions stabilising the dimer. The dimerization of the free receptors *via* the NH···O=C hydrogen bonding interactions is often observed in the solid state for a wide variety of amidopyrroles. When crystallised from DMSO solution, the receptors adopt a *syn–anti* conformation wherein the DMSO is hydrogen bonded to the pyrrole NH and one of the amide NH groups (Fig. 1b).

Scheme 1 Synthesis of **3** and **4**.

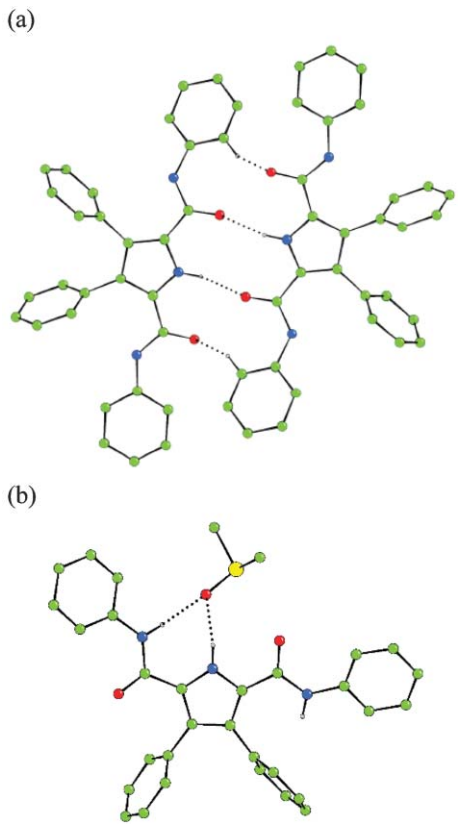
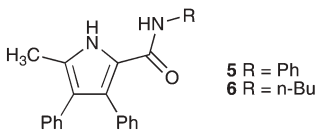


Fig. 1 (a) The X-ray crystal structure of receptor **3** (crystallised from acetonitrile solution) showing the dimer formation (N_{py}···O 3.238(4) Å). (b) The X-ray crystal structure of the complex DMSO solvate of compound **3**. The receptor adopts a *syn–anti* conformation (N_{py}···O = 2.757(4) Å, N_{am}···O = 2.831(4) Å) binding the DMSO molecule *via* two NH···O hydrogen bonds. Colour key: carbon – green, nitrogen – blue, oxygen – red, sulfur – yellow.

Proton NMR titrations were used to investigate the anion-binding properties of **3**, **4** and **6**. Unfortunately solubility (and crystallization) problems hampered these binding studies and a complete dataset could not be obtained for compound **5**. The remaining compounds were studied in DMSO-d_6/0.5% water or acetonitrile-d_3 solution. The results of these studies are shown in Table 1.



The binding studies show that the bis-amides **3** and **4** are selective for oxo-anions over halides under the conditions of the ^{1}H NMR titration experiments. Interestingly, a comparison of the oxo-anion affinity of the analogous bis-amide **4** and mono-amide **6** shows that the oxo-anion affinity of the bis-amide is significantly higher than that of the mono-amide, suggesting that all three of the NH hydrogen bond donors are involved in binding oxo-anions in solution. This was subsequently confirmed in the solid state with the elucidation of the benzoate complex of compound **4** (Fig. 2).[14]

We then decided to append extra hydrogen bond donors to the amidopyrrole in order to assess how these groups would modulate the anion affinity of the 2,5-bisamidopyrrole skeleton. Compounds **7**–**9** were synthesised and their anion binding properties studied.[15] Notably, compound **7** showed a very high affinity for hydrogen sulfate anions ($K > 10^4$ M^{-1}) presumably due to protonation of the amine functionalised receptor by the acidic anion and subsequent binding of SO_4^{2-} by the mono-positive host in DMSO-d_6/0.5% water at 298 K (similar behaviour had been observed previously by Bowman-James and co-workers in mixed amine–amide macrocycles).[16]

Table 1 Stability constants of **3**, **4** and **6** with anionic guests

	Stability constants (M^{-1}) with anions[a]		
Anion	Compound **3** in DMSO-d_6/0.5% water	Compound **4** in CD_3CN (0.03% water)	Compound **6** in CD_3CN (0.03% water)
F^-	74	85[c]	134
Cl^-	11	138[c]	28
Br^-	< 10	< 10	< 10
$H_2PO_4^-$	1450	357	89
$C_6H_5COO^-$	560	2500	202

[a] Anions added as tetrabutylammonium salts. [b] Errors estimated to be < 15%. [c] The amount of water present in the acetonitrile can have a dramatic effect on fluoride/chloride selectivity. In the presence of 0.5% water, fluoride is bound with a stability constant of 37.5 M^{-1} whereas chloride is bound more weakly (K = 12.5 M^{-1}).

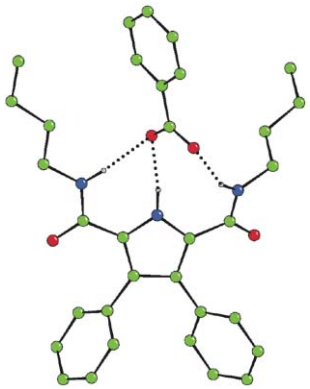
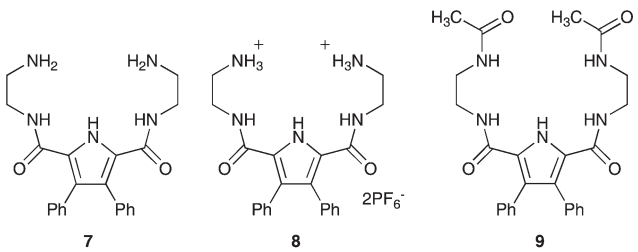


Fig. 2 Crystal structure of the benzoate complex of receptor **4**. One carboxylate oxygen is bound to the pyrrole NH and one amide NH group ($N_{am}\cdots O$ = 2.8638(4) Å, $N_{py}\cdots O$ = 2.7710(4) Å); the second carboxylate oxygen interacts with the remaining amide group through the formation of the third hydrogen bond (distance $N\cdots O$ = 2.7915(6) Å) necessitating this amide to twist out of plane of the pyrrole ring by 34.95(6)°. Colour key: carbon – green, nitrogen – blue, oxygen – red.

Compounds **8** and **9** showed either a low (**8**) or no (**9**) affinity for HSO_4^- under these conditions.



Acidic anion receptors and deprotonation

Modification of the 2,5-bisamidopyrrole skeleton was shown to have a dramatic effect on the affinity and selectivity of these receptors. We next turned our attention to modification of the receptor to include electron-withdrawing chlorine substituents designed to enhance the acidity of the NH protons in the receptor and hence increase the strength of any putative hydrogen bonding interactions.[17] This strategy had been used previously in calix[4]pyrrole chemistry, with octabromofunctionalised calix[4]pyrrole possessing a higher affinity for anionic guests than the non-halogenated parent macrocycle.[18] Receptors **10** and **11** were synthesised from 3,4-dichloro-1*H*-pyrrole-2,5-dicarboxylic acid diethyl ester (originally reported by Martell and co-workers).[19] The crystal structure of compound **10** is shown in Fig. 3 and once again shows dimerization of the receptor in the solid state *via* NH···O hydrogen bonds. Addition of tetrabutylammonium chloride to solutions of **10** in dichloromethane-d_2 and compound **11** in acetonitrile-d_3 or dichloromethane-d_2 gave ^{1}H NMR titration curves indicative of 1 : 1 receptor : anion complex formation. For example, compound **11** binds chloride with a stability constant of K_a = 2015 M^{-1} in acetonitrile-d_3. The 3,4-diphenyl analogue of compound **11**, compound **4**, is a much weaker

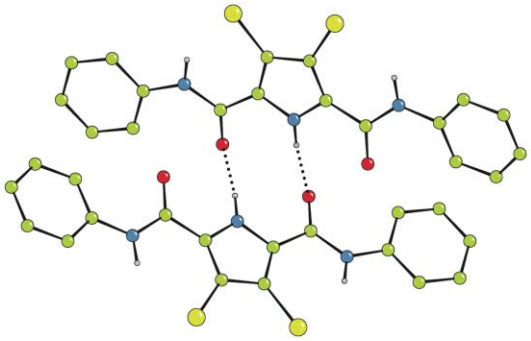
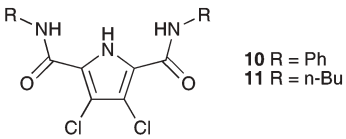


Fig. 3 X-ray crystal structure of **10** revealing NH···O=C hydrogen bonds in the solid state. Colour key: carbon – green, oxygen – red, nitrogen – blue, hydrogen – white, chlorine – yellow.

chloride receptor, binding this anion in acetonitrile-d_3 with a stability constant of 138 M^{-1}.



Upon addition of fluoride anions to solutions of the receptor in acetonitrile-d_3 an unusual titration profile was observed. In dichloromethane-d_2 the unusual titration profile was particularly apparent and is shown in Fig. 4. A downfield shift of the amide NH protons was observed up to the addition of one equivalent of fluoride whilst between one and two equivalents these protons shift upfield. The NH resonance then reaches a plateau at two equivalents. The pyrrole NH proton vanishes during the titration. The unusual titration profile is due to deprotonation of the pyrrole NH proton by the basic fluoride anion. Gunnlaugsson and co-workers have observed deprotonation of an amino group in 4-amino-1,8-naphthalimide based chemosensors upon addition of fluoride.[20] Our findings and those of Gunnlaugsson suggest that care must be taken when binding basic anions with neutral hydrogen bond donor receptors as deprotonation processes may be mistaken for binding.

Deprotonation of the pyrrole NH proton was confirmed by X-ray crystallography. Crystals were grown by slow evaporation of a solution of receptor **10** in acetonitrile solution in the

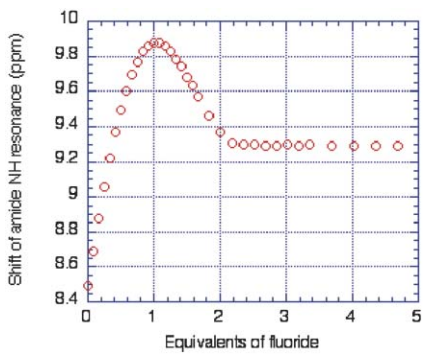
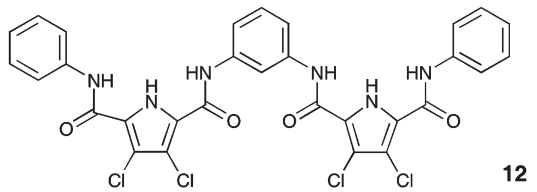


Fig. 4 NMR titration curve for compound **10** (amide NH protons) with fluoride in dichloromethane-d_2.

presence of excess tetrabutylammonium fluoride. The species which crystallised was the tetrabutylammonium salt of the pyrrole anion. Interestingly, the receptor, now in the *syn–syn* conformation, forms a 'Narcissistic' dimer *via* amide NH$\cdots$ N$^-$ pyrrole hydrogen bonds. The hydrogen atoms in this structure were located from the difference map and then constrained during the refinement confirming the deprotonation of the pyrrole ring (Fig. 5). In addition to the N-H$\cdots$N hydrogen bonds there are π–H interactions between the *ortho* phenyl hydrogen atoms and the pyrrole ring in the range 2.4627(42)–2.6401(44) Å.

Orthogonal hydrogen bonded systems such as [(**10** − H$^+$)]$^{2-}{}_2$ are quite rare and we therefore wished to investigate if this supramolecular synthon would occur in other systems containing 2,5-bisamido-3,4-dichloropyrroles upon deprotonation. Consequently pyrrole dimers **12** and **13** were synthesised from 1,3-phenylene diamine and 1,4-phenylene diamine respectively.[21]



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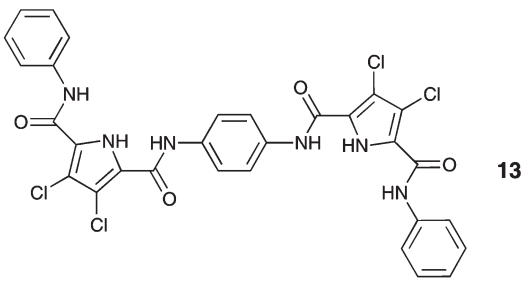

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These compounds proved to be rather insoluble. Addition of tetrabutylammonium anion salts was found to increase solubility allowing the compounds to be fully characterised.

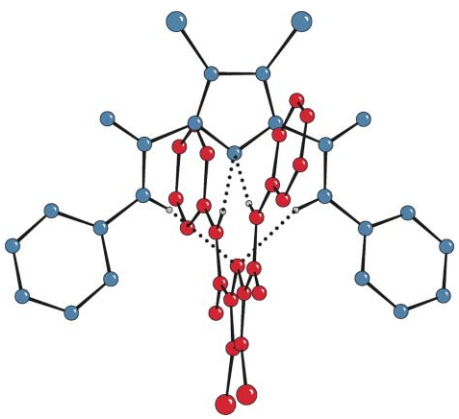


Fig. 5 X-ray crystal structure of the deprotonated form of **10** (tetrabutylammonium salt) revealing NH$\cdots$N$^-$ hydrogen bonds (tetrabutylammonium counter cations omitted for clarity).

Additionally, crystals of the tetrabutylammonium chloride salt of receptor **13** were obtained by slow evaporation of an acetonitrile solution of the receptor in the presence of excess tetrabutylammonium chloride.[22] The complex is shown in Fig. 6 revealing that in the solid state in this complex each chloride is bound by three NH hydrogen bonds.

When the same crystallisation process was repeated with tetrabutylammonium fluoride, once again deprotonation occurred resulting in this case in the formation of continuous chains of hydrogen-bonded pyrrole anion dimers in the solid state (Fig. 7).[21]

However, we have found that the 2,5-bisamidopyrrole anions do not form an interlocked dimer in every case. For example, compound **14** was synthesised and crystals of the tetrabutylammonium salt of the doubly deprotonated molecule obtained in a similar fashion to those of compounds **12** and **13**.[23] The X-ray crystal structure of this salt (Fig. 8) shows that the deprotonated amidopyrrole units adopt the *syn–syn* conformation but do not interlock. We currently have too few examples of crystal structures of these species to understand

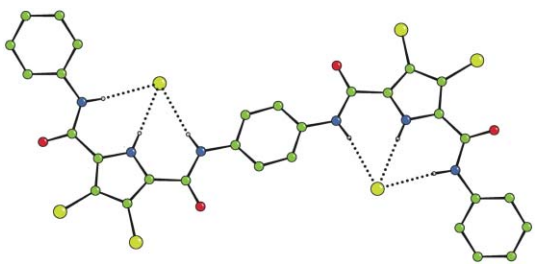


Fig. 6 The X-ray crystal structure of the tetrabutylammonium chloride complex of **13** (counter cation, acetonitrile and non-acidic hydrogen atoms omitted for clarity). Colour key: carbon – green, oxygen – red, nitrogen – blue, hydrogen – white, chlorine – yellow.

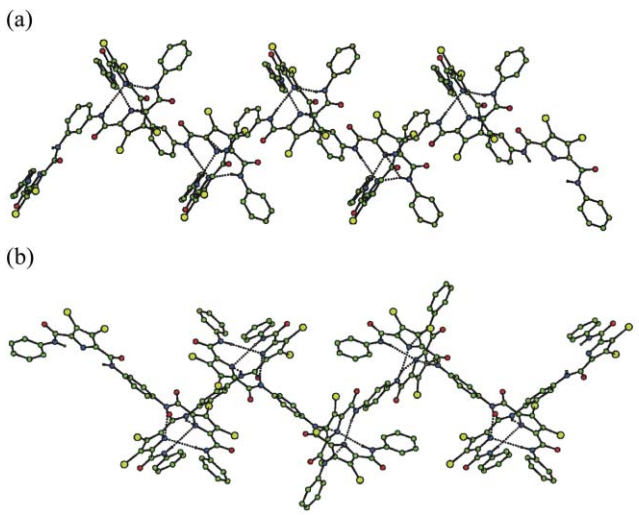


Fig. 7 Crystal structures of the hydrogen bonded polymers formed in (a) the doubly deprotonated form of receptor **12** and (b) the doubly deprotonated form **13**, both as tetrabutylammonium salts. Colour key: carbon – green, oxygen – red, nitrogen – blue, hydrogen – white, chlorine – yellow. Reproduced with permission from *J. Am. Chem. Soc.*, 2002, **124**, 11228. Copyright 2002 American Chemical Society.

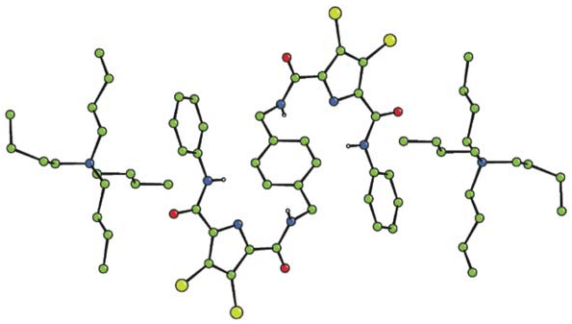
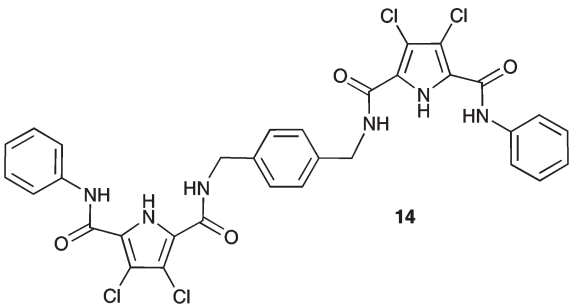


Fig. 8 The X-ray crystal structure of the tetrabutylammonium salt of the doubly deprotonated form of compound **14** (non-acidic hydrogen atoms omitted for clarity). Colour key: carbon – green, oxygen – red, nitrogen – blue, hydrogen – white, chlorine – yellow.

why some species interlock and some do not. However, the fact that the deprotonated form of compound **14** does not contain phenylamides at both the 2- and 5-positions of each pyrrole may decrease the stabilization from CH–π hydrogen bonding in a hypothetical interlocked structure.



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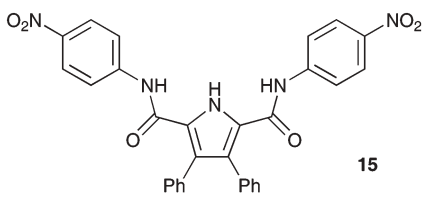
Introduction of chlorine substituents to the 3- and 4-positions of the pyrrole ring did not lead to anion receptors with higher affinities for anions but rather to an orthogonal interlocked hydrogen-bonded array. The other option for the introduction of electron-withdrawing groups is to attach them to the amide substituents rather than to the pyrrole. Compounds **15** and **16** were synthesised by condensation of the pyrrole bis-acid chloride with 4-nitroaniline and 3,5-dinitroaniline respectively.[24]



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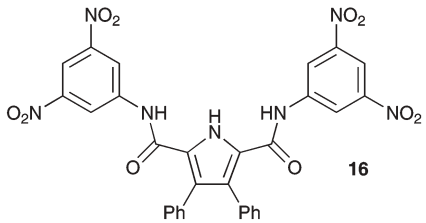


16

Proton NMR titrations with receptors **15** and **16**, and anions were carried out in DMSO-d_6/0.5% water solution. The results showed that receptor **15** possesses a significantly higher affinity for benzoate (4150 M^{-1}) than receptor **3** (560 M^{-1}) under these conditions at 298 K. Under the same conditions, addition of anions to solutions of receptor **16** in DMSO-d_6/0.5% water gave unusual results. Surprisingly, upon addition of fluoride and benzoate, no significant shift in the NH resonance was observed (with the resonance disappearing at higher anion concentrations). However the CH protons on the nitro-aromatic ring do shift downfield in what appears to be a three-stage process for fluoride (Fig. 9). Upon addition of the first two equivalents of anion a curve is obtained that is similar to that observed during the titration of compound **10** with fluoride in dichloromethane.[17] Further addition of anion causes a downfield shift until the plateau is reached after addition of three equivalents of fluoride. This behaviour seems to be consistent with a three step process that may be hypothesized as follows: the first equivalent of fluoride is coordinated by the receptor (causing a significant downfield shift); the second equivalent promotes the deprotonation process due to HF_2^- formation[25] and the third equivalent of fluoride is coordinated by the deprotonated receptor with the participation of the phenyl CH groups that in this receptor are particularly acidic because of the presence of the electron withdrawing groups present in the phenyl ring.

X-ray crystallographic analysis of crystals of **16** grown by slow evaporation of a dichloromethane/methanol solution of the receptor in the presence of excess tetrabutylammonium fluoride, revealed the presence of an adventitious chloride anion coordinated to the deprotonated form of receptor **16** (Fig. 10).

Compound **16** also behaved anomalously upon addition of fluoride anions in acetonitrile solution. An intense blue colour was observed (Fig. 11) which is not observed upon addition of other anions to **16**, or fluoride anions to receptor **15** under the same conditions. We believe this colour is due to deprotonation of the pyrrole in solution. In order to confirm this, receptor **16** was treated with 20 equivalents of tetrabutylammonium hydroxide and, after removing excess base, a dark red material was crystallized from a mixture of diethyl ether/dichloromethane. The crystal structure revealed that this material was the tetrabutylammonium salt of the deprotonated ligand (Fig. 12). Interestingly when the dark red crystals were dissolved in dichloromethane the dark red colour was maintained in solution. However a variety of colours were observed when the compound was dissolved in more polar

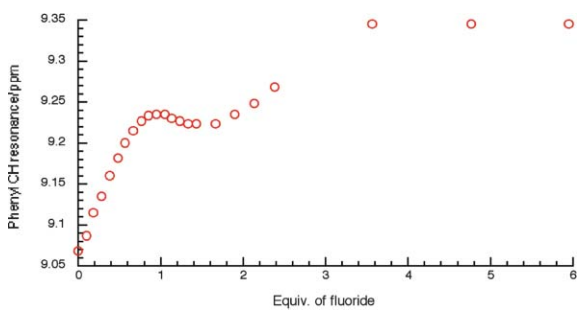


Fig. 9 NMR titration curve of compound **16** with fluoride anions in DMSO-d_6/0.5% water.

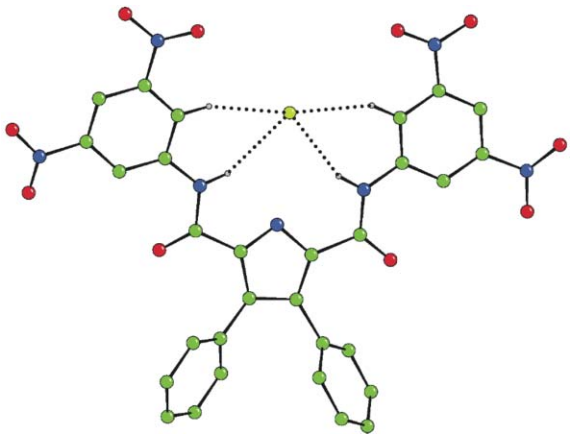


Fig. 10 The crystal structure of the deprotonated form of **16** binding chloride *via* NH and CH hydrogen bonds (two tetrabutylammonium counter cations have been omitted for clarity). Colour key: carbon – green, nitrogen – blue, oxygen – red, chloride – light green.

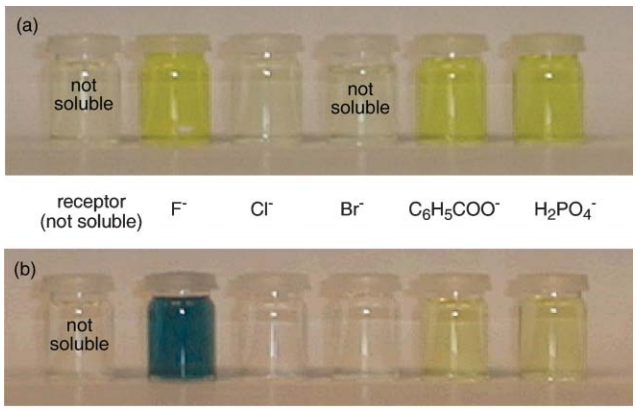


Fig. 11 Solutions of (a) receptor **15** and (b) receptor **16** (2 mM) in acetonitrile with various anionic guests (added as their tetrabutylammonium salt at a concentration of 20 mM). In the absence of an anion, the receptors are not soluble in this solvent but are solubilised upon addition of the anion (with the exception of receptor **2** and bromide).

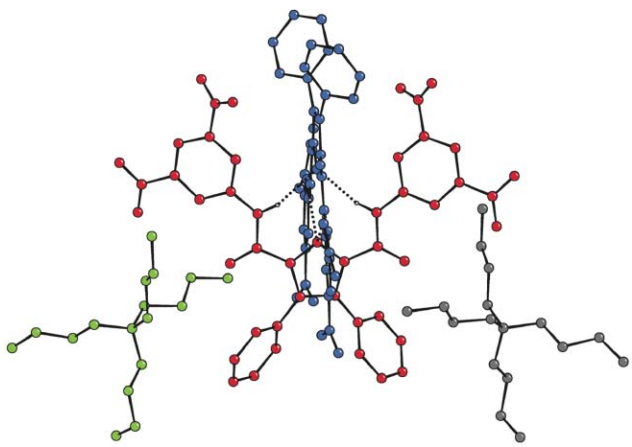
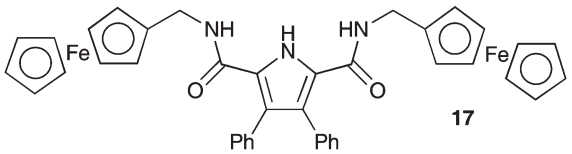


Fig. 12 The X-ray crystal structure of the of the deprotonated form of receptor **16** (tetrabutylammonium salt). Colours represent individual components of the assembly. Non-acidic hydrogen atoms have been omitted for clarity.

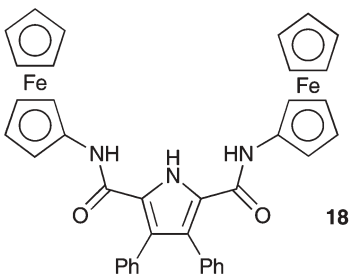
solvents: blue in acetonitrile or acetone, purple in methanol and violet in water. UV/Vis analysis carried out on both an acetonitrile solution of this material and compound **16** in the presence of excess of fluoride, revealed identical UV/vis spectra (with a maximum at 598 nm). This indicates that the deep blue colour is due to deprotonation of the receptor by the fluoride anion and not fluoride complexation.

Redox-active receptors

Thus compound **16** could be regarded as a fluoride selective colorimetric sensor in acetonitrile solution. Redox-sensors for anions have also been constructed from the 2,5-bisamidopyrrole skeleton. Receptors **17** and **18** were synthesised by reaction of either ferrocenylmethylamine or ferrocenylamine with the pyrrole bis-acid chloride (the crystal structure of **18** is shown in Fig. 13 showing dimerization of the receptors in the solid state *via* NH···O and CH···O hydrogen bonds).[26]



17



18

Compound **18** was found to have a higher affinity for anions than compound **17** (Table 2) presumably due to the greater flexibility and lower degree of preorganisation in **17**. Large

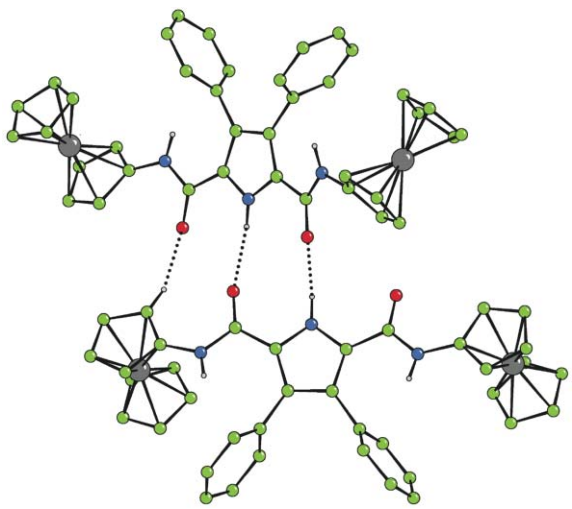


Fig. 13 X-ray crystal structure of **18** showing dimer formation in the solid state *via* NH···O and CH···O hydrogen bonds (N···O 2.795(4) and 3.020(3) Å, C···O 3.2245(5) Å). Colour key: carbon – green, oxygen – red, nitrogen – blue, hydrogen – white, iron – grey.

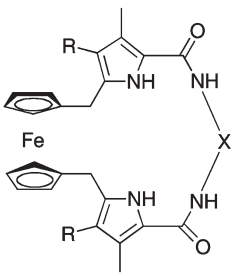
Table 2 Stability constants of receptors **17** and **18** with various anions (added as their tetrabutylammonium salts) in dichloromethane-d_2 and voltammetric shifts in ferrocene/ferrocenium redox couple of receptors in the presence of three equivalents of the anion in dichloromethane

	Compound **17**		Compound **18**	
	K_a (M^{-1})	ΔE (mV)	K_a (M^{-1})	ΔE (mV)
F^-	170	−130	705	−125 and −255[b]
Cl^-	< 20	−75	70	−55
Br^-	< 20	0	< 20	−10
$H_2PO_4^-$	45	[a]	145	[a]
HSO_4^-	45	[a]	75	−40
Benzoate	35	−60	1820	−120

[a] With some anions, the voltammetric wave is seriously distorted as the product of the electrochemical reaction passivates the electrode. [b] Two waves are observed.

shifts in the ferrocene/ferrocenium redox couple were observed upon addition of fluoride to solutions of both compounds in dichloromethane. Compound **18** was found to have a higher affinity for benzoate than **17**, a finding reflected in the greater shift of the redox-couple upon addition of this anion to **18**.

Early examples of amidopyrrole containing anion receptors (**19**–**22**) from Jonathan Sessler's group also contain ferrocene and were used as electrochemical anion sensors.[27]

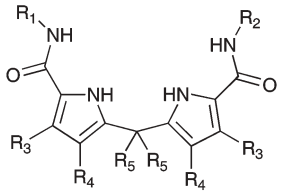


19 R = CH_2CH_3, X = $CH_2(CH_2OCH_2)_2CH_2$
20 R = CH_3, X = $(CH_2)_5$
21 R = CH_3, X = $CH_2CH_2OCH_2CH_2$
22 R = CH_3, X = $CH_2(CH_2OCH_2)_2CH_2$

Stability constants for **20**–**22** were determined by ^1H NMR titrations performed in dichloromethane-d_2/2% DMSO-d_6 and revealed a general increase in the binding affinity for dihydrogen phosphate with increasing numbers of oxygen atoms in the ethylene oxide based linker. Compound **20** does not contain any hydrogen bond acceptor sites and binds the anion with a stability constant of 4050 M^{-1}, whilst compound **21** which contains one oxygen atom has a stability constant of 13200 M^{-1}, and compound **22** which contains two oxygen atoms has a stability constant of 81400 M^{-1} with $H_2PO_4^-$. This substantial increase relative to the number of oxygen atoms in the chain suggests that the oxygen atoms present in the introduced chains are actively involved in the complexation. Square wave electrochemical analyses confirmed that the affinity of the receptors for dihydrogen phosphate increases with increasing numbers of oxygen atoms in the bridging chain.

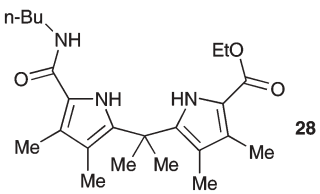
5,5′-Bisamidodipyrrolylmethanes

Moving back from the area of sensors to that of receptors, the crystal structure of the benzoate complex of compound **4** (Fig. 2) showed that one amide NH group had to twist out of plane in order to interact with one of the carbonyl oxygen atoms in the solid state. The observation of this strained conformation led us to consider other amidopyrrole species as backbones for the construction of anion receptors. Bisamidodipyrrolylmethanes such as **23** and **24** contain an sp^3 carbon linker between the pyrrole rings allowing the receptor some flexibility without inducing strain.[28] These species were synthesised by reaction of commercially available diethyl 5,5′-methylenebis(4-ethyl-3-methyl-2-pyrrolecarboxylate) with n-butylamine or aniline in the presence of trimethylaluminium in dry dichloromethane at 35 °C.



23 $R_1 = R_2$ = Ph R_3 = Me R_4 = Et R_5 = H
24 $R_1 = R_2$ = n-Bu R_3 = Me R_4 = Et R_5 = H

25 $R_1 = R_2$ = Ph $R_3 = R_4 = R_5$ = Me
26 $R_1 = R_2$ = n-Bu $R_3 = R_4 = R_5$ = Me
27 R_1 = Ph R_2 = n-Bu $R_3 = R_4 = R_5$ = Me



28

Proton NMR titrations in DMSO-d_6/5% water were used to determine the stability constants of **23** and **24** with a variety of anionic guests.[8] The results, shown in Table 3, show receptors **23** and **24** bind fluoride and benzoate with significant affinities in this solvent mixture with a 1 : 1 receptor : anion stoichiometry. In the case of compound **23**, the addition of aliquots of $H_2PO_4^-$ gave a very sharp titration curve in DMSO-d_6/5% water (under these conditions receptor **3** binds $H_2PO_4^-$ with a stability constant of 350 M^{-1}) and hence the titrations with dihydrogen phosphate were performed in DMSO-d_6/25% water with both compounds in order to obtain reliable stability constant values. These were found to be 234 M^{-1} and 19 M^{-1} for compounds **23** and **24** respectively.

Table 3 Stability constants K_a (M^{-1}) of compounds **23** and **24** with a variety of putative anionic guests (added as tetrabutylammonium salts) at 298 K in DMSO-d_6/5% water (except where noted)[a]

Anion	Compound **23**	Compound **24**
F^-	8990	7560
Cl^-	43	23
Br^-	10	13
HSO_4^-	128	44
Benzoate	424	354
F^{-b}	114	11
$H_2PO_4^{-b}$	234	20

[a] Errors estimated to be no more than ±15%. [b] Measured in DMSO-d_6/25% water.

The high affinity of compound **23** for dihydrogen phosphate is notable as this receptor is neutral, and yet can bind this anion strongly in DMSO-d_6/5% water and still function as a dihydrogen phosphate receptor in DMSO-d_6/25% water. However, unfortunately these compounds were found to be unstable over time in solution, oxidizing to the corresponding dipyrrolylmethene. To overcome this problem, bis-amides **25**–**27** were synthesised which contain a dimethyl substituted '*meso*-carbon'.[29] These receptors again showed a high affinity for dihydrogen phosphate (particularly in the case of the bisphenylamide **25**) in DMSO-d_6/5% water (Table 4). The shifts of compound **25** upon addition of a variety of anions are illustrated in Fig. 14. DFT calculations suggest that the two pyrrole-amide groups bind to different oxygen atoms in the $H_2PO_4^-$ anions (Fig. 15). Thus the extra hydrogen bond donor and flexibility in this class of receptor have allowed this new class of pyrrolic anion receptor to compete with highly competitive solvent mixtures for dihydrogen phosphate, an espcially significant result for a non-macrocyclic receptor. Interestingly, the mono-amide compound **28** complexes $H_2PO_4^-$ but only through the pyrrole-amide NH groups. The pyrrole ester NH group resonance does not shift upon addition of the anion to DMSO/water solutions of the receptor.

Pyrrole-2,5-diacetic acid derivatives

In collaboration with Sally Brooker's group at the University of Otago we have investigated the anion complexation properties of amide derivatives of pyrrole-2,5-diacetic acid.[30]

Table 4 Stability constants K_a (M^{-1}) of compounds **25**, **26** and **27** with a variety of putative anionic guests (added as tetrabutylammonium salts) at 298 K in DMSO-d_6/5% water.[a] No significant shifts were observed upon addition of tetrabutylammonium bromide or hydrogen sulfate

Anion	Compound **25**	Compound **26**	Compound **27**
F^-	124	89	429
Cl^-	< 15	[b]	[b]
Benzoate	41	20	33
$H_2PO_4^-$	1092	81	307

[a] Errors estimated to be no more than ±15%. [b] No significant shift.

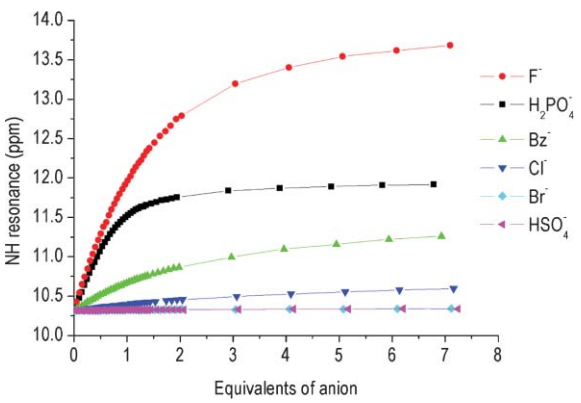


Fig. 14 (a) ^{1}H NMR titration curves for compound **25** with fluoride, chloride, bromide, dihydrogen phosphate and hydrogen sulfate in DMSO-d_6/0.5% water at 298 K. Anions added as their tetrabutylammonium salts.

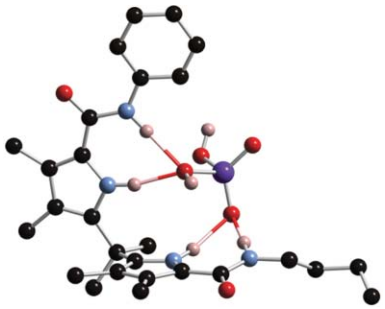
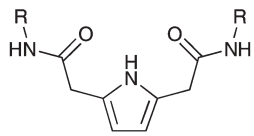


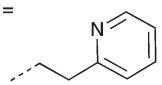
Fig. 15 Structure of the dihydrogen phosphate complex of **27** generated by DFT calculation using Spartan '02.[29] Colour key: carbon – black, oxygen – red, nitrogen – blue, hydrogen – white, phosphorus – purple.

In acetonitrile-d_3 solution, compound **29** showed a high affinity for HSO_4^- and $H_2PO_4^-$ presumably due to a proton transfer occurring between the anion and receptor (similar to that occurring between compound **7** and HSO_4^-). Direct comparison of the other receptors to the first generation 2,5-bisamidopyrroles proved difficult to make as the receptors contain different substituents on the pyrrole rings. However in acetonitrile-d_3, the other receptors show generally similar anion affinities to those of compounds **3** and **4**.

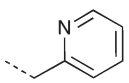


29 R = $CH_2CH_2NMe_2$

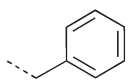
30 R =



31 R =

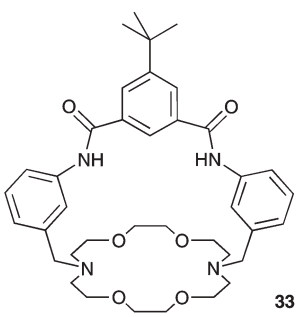


32 R =

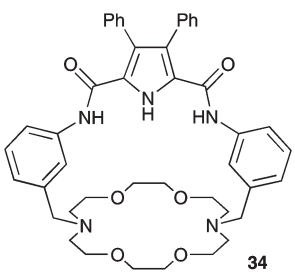


Ion-pair receptors

Recently, in collaboration with Bradley Smith's group at the University of Notre Dame, we have turned our attention to employing amidopyrrole groups in receptors for ion-pairs. Smith's group had previously published a series of papers on ion-pair receptors capable of binding either solvent separated ion pairs[31] or contact ion pairs[32] (such as compound **33**). A pyrrole-containing analogue of this molecule **34** was synthesised and its affinity for chloride measured in the absence of cations and in the presence of one equivalent of either sodium or potassium cations.[33]



33



34

The crystal structure of the receptor (Fig. 16) illustrates the close proximity of the anion-binding pyrrole bis-amide group (bound to a methanol) and the cation binding diaza-18-crown-6 (coordinated to a water molecule). In addition, inclusion of the bis-amide in this macrobicyclic system preorganizes this unit into a *syn–syn* conformation ideal for anion complexation.

The chloride association constants for macrobicycles **33**, **34** and acyclic control pyrrole **3** are listed in Table 5. Compared to macrocycle **34**, the first generation acyclic bis-amidopyrrole **3** has a ten-fold smaller affinity for chloride. This is presumably due to the preorganized cleft conformation in the macrocycle, whereas compound **3** is conformationally flexible. Bis-amidopyrrole macrocycle **34** also has a three-fold higher affinity for chloride than compound **33**. There are two likely contributors to this effect: (a) the presence of the pyrrole NH which can hydrogen bond with the chloride, and (b) the amide NHs in **34** are more acidic than in **33**. The affinity of **34** for chloride is hardly changed by the presence of one molar equivalent of sodium ions but it is increased substantially by the presence of potassium ions. This same trend was observed previously with receptor **33** and attributed to a difference in cation coordination by the receptor crown oxygens.

Receptors **33** and **34** are able to extract chloride salts into weakly polar organic solvents. For example, compound **34** can extract powdered sodium or potassium chloride into deuterated chloroform. Since the free receptor and complex are in slow exchange on the NMR time scale, the extraction process can be conveniently monitored by ^{1}H NMR spectroscopy (with complete receptor saturation taking about a week at room temperature). A notable difference between the NMR spectra for salt saturated receptor **33** and salt saturated receptor **34** is the magnitude of the change in NH chemical shift upon salt complexation. In the case of compound **33** the signal for the two equivalent NHs moves downfield by about 1 ppm upon binding of NaCl or KCl, whereas the signal moves about 2 ppm in the case of **34** reflecting the greater acidity of the amide NHs in **34** and consequently higher affinity for chloride.

Recrystallization of the [**34**·NaCl] complex produced single crystals that were suitable for analysis by X-ray diffraction. As expected the X-ray structure (Fig. 17) shows that the receptor binds NaCl as a contact ion-pair. The Na···Cl distance at 2.65 Å is shorter than the Na–Cl distance in crystalline sodium chloride (2.74 Å)[34] and in the sodium chloride complex of **33** (2.70 Å).[32] The crystal structure illustrates why the pyrrole containing receptor **34** has enhanced chloride affinity relative to **33** as the chloride forms hydrogen bonds to both amide NHs (N···Cl 3.38 and 3.20 Å) but also to the pyrrole NH (N···Cl 3.17 Å).

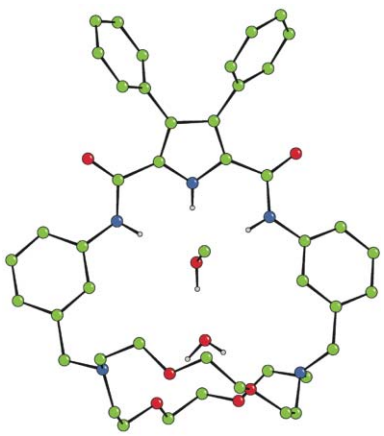


Fig. 16 The crystal structure of receptor **34** (with bound methanol and water). Non-acidic hydrogen atoms have been omitted for clarity. Colour key: carbon – green, oxygen – red, nitrogen – blue, hydrogen – white.

Table 5 Chloride stability constants (M^{-1}) for receptors in DMSO-d_6 at 298 K[a]

Additive	33	34	3
None	34	109	11
+ Sodium[b]	49	128	—
+ Potassium[b]	340	540	—

[a] Chloride added as tetrabutylammonium salt, association constant uncertainty estimated to be ±15%. [b] As tetraphenylborate salt (one molar equivalent).

Membrane co-transport of HCl

Another type of ion-pair currently attracting interest is HCl. A class of natural product, the prodigiosins (which have the general structure **35**),[35] are capable of transporting HCl across lipid bilayer membranes.[36] These compounds have a variety of biological activities including immunosuppression, induction of tumour cell apoptosis, and toxicity against bacteria, protozoa, fungi and malaria parasite.[37] In collaboration with Bradley Smith's group we are developing organic compounds that mimic the HCl co-transport ability of the prodigiosins. As a starting point, we decided to take design cues from the prodigiosin structure and produce relatively simple receptors containing two NH hydrogen bond donor groups (from an amidopyrrole group) and one basic group for protonation (an imidazole in the case of **36** and a pyridine group in the case of **37**).[38] As free bases, the receptors were expected to have weak

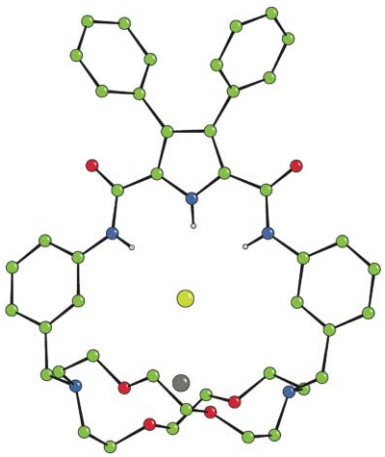
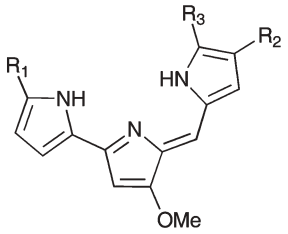


Fig. 17 The crystal structure of the sodium chloride complex of receptor **34**. Non-acidic hydrogen atoms have been omitted for clarity. Colour key: carbon – green, oxygen – red, nitrogen – blue, hydrogen – white, chloride – yellow, sodium – grey.

chloride affinities, but they should form lipophilic HCl complexes in acid. Thus, the receptors were designed to co-transport H^+/Cl^- from an acidic phase through a bilayer membrane to a high pH interface where decomplexation occurs.



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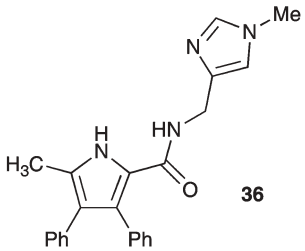
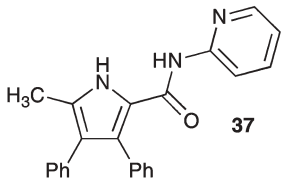


36



37

The X-ray crystal structure of **36**·HCl revealed the formation of a '2 + 2' dimer in the solid state with each chloride bound by three hydrogen bonds; two from the pyrrole (N···Cl 3.24(2) Å) and amide (N···Cl 3.29(2) Å) groups of one receptor and one from the imidazolium group of another (N···Cl 3.10(2) Å) (Fig. 18). A notable feature of the structure is that all the polar and ionic functionality is inside the dimer; whereas, the exterior projects primarily lipophilic groups – an ideal arrangement for solubilising HCl in a lipophilic environment.

The abilities of receptors **36** and **37** to co-transport H^+/Cl^- across bilayer membranes were evaluated at Notre Dame using unilamellar vesicles (200 nm mean diameter) composed of POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine) : cholesterol (7 : 3 molar ratio). A chloride selective electrode[39] was used to measure Cl^- leakage from the vesicles under a variety of different starting conditions. As shown in Fig. 19, addition of receptor **36** (10 μM) induces Cl^- release in a pH dependent manner. After a short induction period, a moderate rate of Cl^- efflux was observed when the pH was 7.2 on both sides of the vesicle membrane, whereas no efflux was observed when both aqueous phases were acidic (pH 4.0). The highest efflux was observed when there was a pH gradient, that is, when the inside aqueous phase was acidic (pH 4.0) and the outside phase near neutral (pH 6.7). Receptor **37** was inactive as a chloride transporter under all of the above conditions.

Receptor **36** was subsequently tested for its ability to deacidify liposomes. The acid sensitive dye, Oregon Green® 514,[40] was encapsulated inside POPC : cholesterol (7 : 3) vesicles at a pH of 4.0 (500 mM NaCl, 5 mM citric acid), and after dialysis to remove untrapped dye, the aqueous exterior phase was quickly adjusted to pH 7.2. Addition of **36** at t = 200 s induced an immediate discharge of the pH gradient,

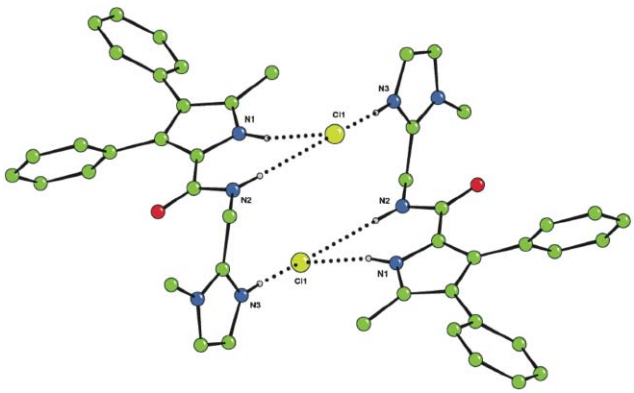


Fig. 18 Crystal structure of HCl complex of **36** showing the formation of a '2 + 2' hydrogen-bonded dimer. Colour key: carbon – green, oxygen – red, nitrogen – blue, hydrogen – white, chloride – yellow.

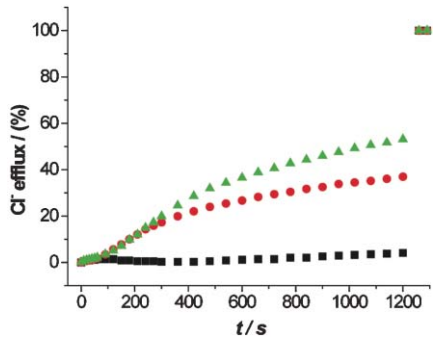


Fig. 19 Cl^- efflux induced by the addition of **36** (10 μM) to vesicles containing NaCl (500 mM), X_1 solution, and dispersed in $NaNO_3$ (500 mM), X_2 solution. ■ X_1 and X_2 = citric acid (5 mM), pH 4.0; ● X_1 and X_2 = citric acid (5 mM), pH 7.2; ▲ X_1 = citric acid (5 mM), pH 4.0, X_2 = sodium phosphate (5 mM), pH 6.7. At t = 1300 s, the vesicles were lysed to produce 100% Cl^- release.

whereas, addition of compound **37** produced no enhancement of the background leakage rate (Fig. 20).

The data are consistent with the transport model shown in Scheme 2. The free base of receptor **36** partitions into the vesicle membrane and diffuses to the interior membrane interface where it forms a lipophilic HCl complex (possibly the '2 + 2' dimer in Fig. 18) that diffuses back through the membrane. Transport is not observed when the exterior phase is also acidic because **36**·H^+ is not sufficiently lipophilic to strongly partition from the bulk external aqueous into the vesicles. The pyridyl analogue **37** does not transport H^+/Cl^- out of vesicles, presumably because it is unable to form a kinetically active HCl complex. We are currently examining whether **36** and related analogues can induce organelle deacidification.

Conclusions

Very simple receptors containing amidopyrroles have been shown not only to be effective acyclic anion binding agents but also to have interesting assembly properties in the solid state. Deprotonation of 3,4-dichloro-2,5-bisamidopyrroles leads in

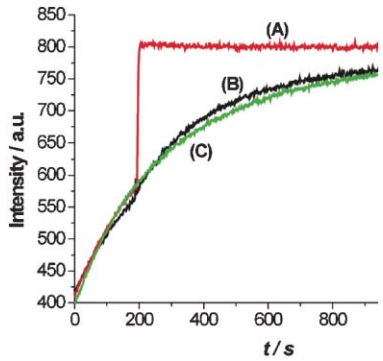
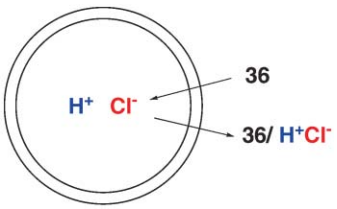


Fig. 20 Change in Oregon Green® 514 fluorescence upon addition of: (A) **36** (10 μM), (B) **37** (8.8 μM), and (C) no receptor, at $t = 200$ s to vesicles containing Oregon Green (10 μM), NaCl (500 mM), and citric acid (5 mM), pH 4.0. The vesicles were dispersed in an external solution of $NaNO_3$ (500 mM), and sodium phosphate (5 mM), pH 7.2.



Scheme 2

some cases to interlocked dimers and new types of hydrogen bonded polymers. Most excitingly, simple imidazole functionalised amidopyrroles function as membrane transport agents for HCl. The ability of compound **36** to induce organelle deacidification is currently being tested. It will be interesting to see if this leads to prodigiosin-like biological activity. By virtue of their simplicity and synthetic accessibility, these anion-binding motifs may find application in a variety of molecular recognition systems. We are currently incorporating this chemistry into metal-based anion receptors and into libraries of receptors for amino-acid recognition. Neutral anion binding groups such as amidopyrroles may also find application in the construction of synthetic channels for anion transport through membranes. We are continuing to pursue the exciting chemistry of these versatile anion-binding groups.

Acknowledgements

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Notes and references

1 C. H. Park and H. E. Simmons, *J. Am. Chem. Soc.*, 1968, **90**, 2431. Interestingly, in 1967 Shriver and Biallas published a report of a boron chelate complexing a methoxide anion: D. F. Shriver and M. J. Biallas, *J. Am. Chem. Soc.*, 1967, **89**, 4261.
2 *Coord. Chem. Rev.*, 2003, Vol. 240 (Ed. P. A. Gale); P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.*, 2001, **40**, 486; *Supramolecular Chemistry of Anions*, (Eds.: A. Bianchi, K. Bowman-James, E. Garcia-España), Wiley-VCH, New York, 1997; J. L. Sessler and W. E. Allen, *Chemtech*, 1999, **29**, 16; F. P. Schmidtchen and M. Berger, *Chem. Rev.*, 1997, **97**, 1609; P. D. Beer and D. K. Smith, *Prog. Inorg. Chem.*, 1997, **46**, 1; J. L. Atwood, K. T. Holman and J. W. Steed, *Chem. Commun.*, 1996, 1401.
3 C. R. Bondy and S. J. Loeb, *Coord. Chem. Rev.*, 2003, **240**, 77.
4 For an early example see: T. R. Kelley and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072.
5 J. L. Sessler, S. Camiolo and P. A. Gale, *Coord. Chem. Rev.*, 2003, **240**, 17.
6 P. A. Gale, P. Anzenbacher, Jr. and J. L. Sessler, *Coord. Chem. Rev.*, 2001, **222**, 57.
7 J. L. Sessler and J. M. Davis, *Acc. Chem. Res.*, 2001, **34**, 989.
8 C. Schmuck and U. Machon, *Chem. Eur. J.*, 2005, **11**, 1109; C. Schmuck and L. Geiger, *Chem. Commun.*, 2005, 772.
9 C. Schmuck and L. Geiger, *Chem. Commun.*, 2004, 1698.
10 S.-K. Chang and A. D. Hamilton, *J. Am. Chem. Soc.*, 1988, **110**, 1318; K. Kavallieratos, S. R. de Gala, D. J. Austin and R. H. Crabtree, *J. Am. Chem. Soc.*, 1997, **119**, 2325; M. P. Hughes and B. D. Smith, *J. Org. Chem.*, 1997, **62**, 4492; K. Kavallieratos, C. M. Bertao and R. H. Crabtree, *J. Org. Chem.*, 1999, **64**, 1675.
11 M. Friedman, *J. Org. Chem.*, 1965, **30**, 859.
12 P. A. Gale, S. Camiolo, C. P. Chapman, M. E. Light and M. B. Hursthouse, *Tetrahedron Lett.*, 2001, **42**, 5095; P. A. Gale, S. Camiolo, G. J. Tizzard, C. P. Chapman, M. E. Light, S. J. Coles and M. B. Hursthouse, *J. Org. Chem.*, 2001, **66**, 7849.
13 R. J. Boatman and H. W. Whitlock, *J. Org. Chem.*, 1976, **41**, 3050.
14 S. Camiolo, P. A. Gale, M. B. Hursthouse and M. E. Light, *Tetrahedron Lett.*, 2002, **43**, 6995.
15 K. Navakhun, P. A. Gale, S. Camiolo, M. E. Light and M. B. Hursthouse, *Chem. Commun.*, 2002, 2084.
16 M. A. Hossain, J. M. Llinares, D. Powell and K. Bowman-James, *Inorg. Chem.*, 2001, **40**, 2936.
17 S. Camiolo, P. A. Gale, M. B. Hursthouse, M. E. Light and A. J. Shi, *Chem. Commun.*, 2002, 758.
18 P. A. Gale, J. L. Sessler, W. E. Allen, N. A. Tvermoes and V. Lynch, *Chem. Commun.*, 1997, 665.
19 R. J. Motekaitis, D. H. Heinert and A. E. Martell, *J. Org. Chem.*, 1970, **35**, 2504.
20 T. Gunnlaugsson, P. E. Kruger, P. Jensen, F. M. Pfeffer and G. M. Hussey, *Tetrahedron Lett.*, 2003, **44**, 8909.
21 P. A. Gale, K. Navakhun, S. Camiolo, M. E. Light and M. B. Hursthouse, *J. Am. Chem. Soc.*, 2002, **124**, 11228.
22 M. E. Light, P. A. Gale and K. Navakhun, *Acta Crystallogr., Sect. E*, 2005, **61**, o1300.
23 M. E. Light, P. A. Gale, K. Navakhun and M. Maynard-Smith, *Acta Crystallogr., Sect. E*, 2005, **61**, o1302.
24 S. Camiolo, P. A. Gale, M. B. Hursthouse and M. E. Light, *Org. Biomol. Chem.*, 2003, **1**, 741.
25 S. Gronert, *J. Am. Chem. Soc.*, 1993, **115**, 10258.
26 G. Denuault, P. A. Gale, M. B. Hursthouse, M. E. Light and C. N. Warriner, *New J. Chem.*, 2002, **26**, 811; S. J. Coles, G. Denuault, P. A. Gale, P. N. Horton, M. B. Hursthouse, M. E. Light and C. N. Warriner, *Polyhedron*, 2003, **22**, 699.
27 M. Scherer, J. L. Sessler, A. Gebauer and V. Lynch, *Chem. Commun.*, 1998, 85; J. L. Sessler, R. S. Zimmerman, G. J. Kirkovits, A. Gebauer and M. Scherer, *J. Organomet. Chem.*, 2001, **637**, 343.
28 I. E. D. Vega, S. Camiolo, P. A. Gale, M. B. Hursthouse and M. E. Light, *Chem. Commun.*, 2003, 1686.
29 I. E. D. Vega, P. A. Gale, M. B. Hursthouse and M. E. Light, *Org. Biomol. Chem.*, 2004, **2**, 2935.
30 R. Li, L. S. Evans, D. S. Larsen, P. A. Gale and S. Brooker, *New J. Chem.*, 2004, **28**, 1340.
31 M. J. Deetz, M. Shang and B. D. Smith, *J. Am. Chem. Soc.*, 2000, **122**, 6201.

32 J. M. Mahoney, A. M. Beatty and B. D. Smith, *J. Am. Chem. Soc.*, 2001, **123**, 5847.
33 J. M. Mahoney, R. A. Marshall, A. M. Beatty, B. D. Smith, S. Camiolo and P. A. Gale, *J. Supramol. Chem.*, 2001, **1**, 289.
34 A. F. Wells, *Structural Inorganic Chemistry*; Oxford Press: Oxford, 1984, 433.
35 A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582.
36 C. Yamamoto, H. Takemoto, H. Kuno, D. Yamamoto, A. Tsubura, K. Kamata, H. Hirata, A. Yamamoto, H. Kano, T. Seki and K. Inoue, *Hepatology*, 1999, **30**, 894; K. Tanigaki, T. Sato, Y. Tanaka, T. Ochi, A. Nishikawa, K. Nagai, H. Kawashima and S. Ohkuma, *FEBS Lett.*, 2002, **524**, 37; T. Sato, H. Konno, Y. Tanaka, T. Kataoka, K. Nagai, H. H. Wasserman and S. Ohkuma, *J. Biol. Chem.*, 1998, **273**, 21455; R. A. Gottlieb, J. Nordberg, E. Showronski and B. M. Babior, *Proc. Natl. Acad. Sci. USA*, 1996, **93**, 654; S. Ohkuma, T. Sato, M. Okamoto, H. Matsuya, K. Arai, T. Kataoka, K. Nagai and H. H. Wasserman, *Biochem. J.*, 1998, **334**, 731.
37 A. J. Castro, *Nature*, 1967, **213**, 903; J. E. H. Lazaro, J. Nitcheu, R. Z. Predicala, G. C. Mangalindan, F. Nesslany, D. Marzin, G. P. Concepcion and B. Diquet, *J. Nat. Toxins*, 2002, **11**, 367.
38 P. A. Gale, M. E. Light, B. McNally, K. Navakhun, K. E. Sliwinski and B. D. Smith, *Chem. Commun.*, 2005, DOI: 10.1039/b503906a, in this issue.
39 A. V. Koulov, T. N. Lambert, R. Shukla, M. Jain, J. M. Boon, B. D. Smith, H. Y. Li, D. N. Sheppard, J. B. Joos, J. P. Clare and A. P. Davis, *Angew. Chem., Int. Ed.*, 2003, **42**, 4931–4933.
40 J. R. Lakowicz, H. Szmacinski and H. Lin, *Anal. Biochem.*, 1999, **269**, 162.

