Structural and Molecular Recognition Studies with Acyclic Anion Receptors†

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ABSTRACT

Acyclic molecules containing amides, ureas, and pyrrole groups have proven to be effective and selective anion-binding agents. In this Account, the structural chemistry of isophthalamide anion complexes, *ortho*-phenylenediamine based bis-ureas, and amidopyrroles, as well as anion-triggered deprotonation processes in neutral anion receptor systems, are discussed.

1. Introduction

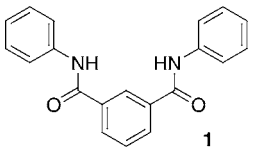
It is now almost 40 years since the first synthetic anion receptor was reported by Park and Simmons in a seminal communication in 1968.[1] Since then, interest in the field has blossomed, and many groups worldwide are tackling the challenges inherent in binding anions.[2] There are many reasons why the development of new selective anion receptor systems continues to be an important goal, including sensor development, environmental remediation, and the selective separation and extraction of chemical species. Additionally, anions are essential components of biological systems. For example, chloride is an important electrolyte in maintaining potentials across cell membranes, and the misregulation of chloride transport through cell membranes by chloride channels is the cause of cystic fibrosis.[3] Transport of chloride as HCl by the prodigiosins through biological lipid bilayer membranes has been shown to uncouple lysosomal vacuolar-type ATPases.[4]

Our research has centered on the synthesis of new simple hydrogen-bond donor systems for anion recognition with a particular focus on structural characterization of anion complexes. This Account will cover four areas of our research program, namely isophthalamides and analogues, bis-ureas, amidopyrroles, and anion-triggered deprotonation.

Philip A. Gale received a B.A. (Honors) in chemistry in 1992, M.A. in 1995, and a D.Phil. in 1995 from the University of Oxford. He then moved as a Fulbright Postdoctoral Fellow to the University of Texas at Austin in 1995, returning to the University of Oxford in 1997 as a Royal Society University Research Fellow and moving in 1999 to the University of Southampton, where he is now a Reader in Supramolecular Chemistry. A major focus of his research is the supramolecular chemistry of anionic species. In 2004, he was awarded a Society/Journal of Porphyrins and Phthalocyanines Young Investigator Award and the Bob Hay Lectureship by the Royal Society of Chemistry (RSC) U.K. Macrocycles and Supramolecular Chemistry Group. He is to be awarded a 2005 Corday−Morgan medal and prize by the RSC.

2. Isophthalamides and Analogues

In 1996, the first report of the use of this group in an anion-binding context appeared, detailing the synthesis of an anion-templated macrocycle containing isophthalamide groups.[5] The following year, Crabtree and co-workers showed that even very simple systems containing the isophthalamide core **1** function as effective receptors for halide anions such as chloride in organic solution,[6,7] while Smith and co-workers showed that boron-functionalized isophthalamides, e.g., **2**, are excellent receptors for anions.[8]



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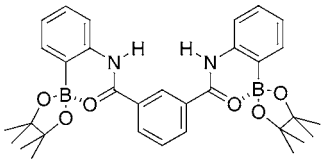

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The ease of synthesis of these systems and their high affinity for anions prompted us to attempt to obtain structural data for a range of anion complexes, because very few X-ray crystal structures of isophthalamide−anion complexes had been elucidated at that time.[6] We therefore synthesized a range of functionalized isophthalamides and attempted to obtain single crystals of anion complexes. Compounds **3** and **4** were synthesized as analogues of the original receptors of Crabtree and co-workers but with enhanced NH acidity because of the presence of electron-withdrawing nitro- or dinitrophenyl groups.[9] The crystal structure of the chloride complex of compound **3** (Figure 1)[10] shows the receptor adopting a similar conformation to that observed previously in a bromide complex that was elucidated by Crabtree and co-workers. The chloride anion lies above the least-squares plane through the central aromatic ring with the angle between the plane through the central aromatic ring, and a plane defined by the anion and amide H atoms is 45.54(4)°, while in the previous bromide structure of Crabtree and co-workers, the angle was found to be 63.63(6)°. The larger size of the bromide anion is also evident in the hydrogen-bond donor−acceptor distances, which were found to be 3.634(4) and 3.436(4) Å for the two N···Br interactions and 3.3239(15) and 3.2367(14) Å for the N···Cl interactions in the chloride complex.[10]

In contradistinction to the chloride complex of compound **3**, the X-ray crystal structure of the fluoride complex of receptor **4** revealed the formation of an unusual "2 + 2" double helix (Figure 2) formed by two isophthalamides wrapping around two fluoride anions via NH···F^- hydrogen bonds, with N−F−N angles of 158.04° and 155.23° and a F^-−F^- separation of 3.716(6) Å (Figure 2).[9] This arrangement results in $\pi-\pi$ interactions between

† This paper is dedicated to Professor Mike Hursthouse on the occasion of his 65th birthday.

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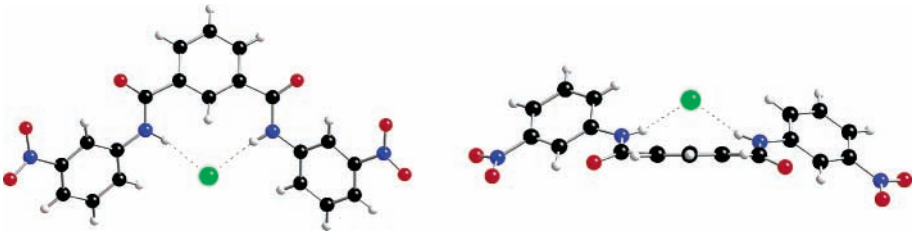


FIGURE 1. Top and side views of the chloride complex of compound **3** (tetra-*n*-butylammonium cations omitted for clarity). The chloride anion is shown in green.

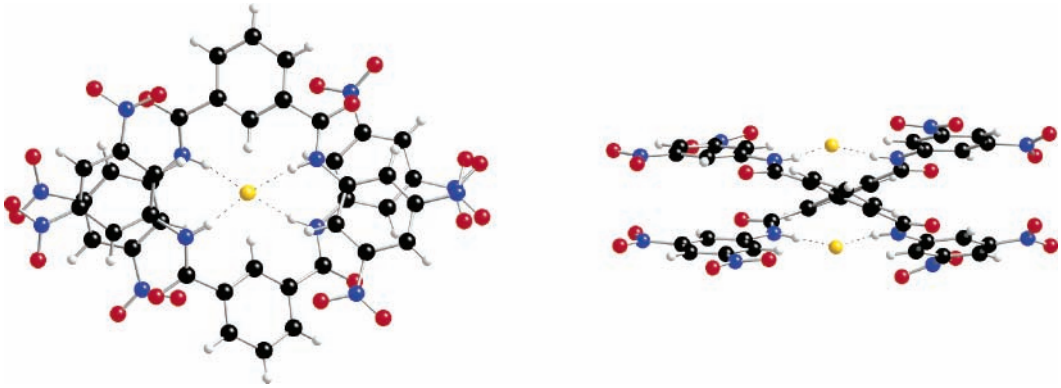
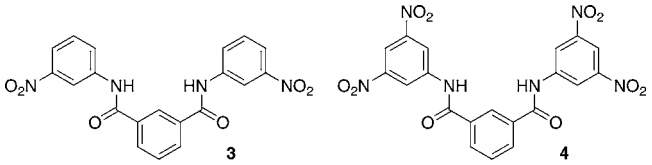


FIGURE 2. Top and side views of the fluoride complex of compound **4** (tetra-*n*-butylammonium cations omitted for clarity). The fluoride anion is shown in yellow.

the terminal nitroaromatic groups of 3.317(8) and 3.361-(8) Å.



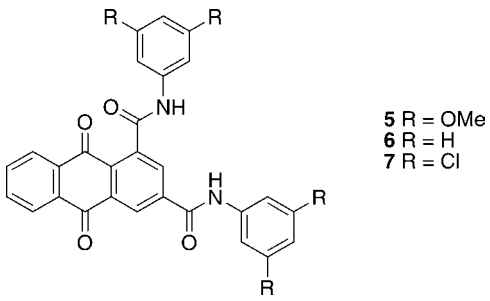
The formation of the fluoride-templated double helix led us to study a variety of functionalized isophthalamides, to explore the generality of this mode of binding. To date, we have not obtained structural evidence of the formation of other helical complexes with simple isophthalamides. However, it occurred to us that "pre-twisting" an isophthalamide-like binding site before complexation might predispose a receptor toward higher order complex formation. Consequently, we synthesized receptors **5**−**7** that are based on a 1,3-functionalized anthraquinone skeleton.[11] These receptors were designed to use the steric interaction between the amide in the 1 position and the anthraquinone oxygen in the 9 position to twist this amide out of the anthraquinone plane and hence form a nonconvergent hydrogen-bonding array that may be amenable to higher-order complex formation with fluoride. Stability constants for a range of anions with these receptors are shown in Table 1. Titrations were conducted in DMSO-d_6/0.5% water with various anions, and stability constants were obtained using the EQNMR computer program.[12] DMSO containing 0.5% water is used to minimize the effect of the titration solution absorbing water from the atmosphere during the titration. In all cases, the addition of aliquots of fluoride gave titration curves that could not be fitted to simple 1:1 or 1:2

Table 1. Stability Constants K_a (M^{-1}) for the Reaction of Compounds 5−7 with Anions Determined by ^1H NMR Titrations in DMSO-d_6/0.5% H_2O with Anions Added as the Tetra-*n*-butylammonium Salts[a]

anions	compound **5**	compound **6**	compound **7**
Cl^-			13
$H_2PO_4^-$	214	198	$K_1 = 1520$, $K_2 = 65$
$C_6H_5CO_2^-$	26	17	160

[a] All titration plots were fitted to a 1:1 binding model unless otherwise stated. Stability constants were given with <10% error.

receptor/anion-binding models. Bromide, hydrogen sulfate, and, in the cases of compounds **5** and **6**, chloride caused insignificant changes to the ^1H NMR spectra of the ligands. Compounds **5** and **6** have very similar affinities for anions, while compound **7** binds anions significantly more strongly, presumably because of the presence of electron-withdrawing chlorine substituents. Interestingly, this compound binds 2 equiv of dihydrogen phosphate with high affinity in this competitive solvent mixture ($K_1 = 1520$ and $K_2 = 65$ M^{-1}). The binding mode of the oxo-anion to this compound has yet to be determined.



The crystal structure of receptor **5** illustrates the twist out of the plane of the amide in the 1 position, resulting

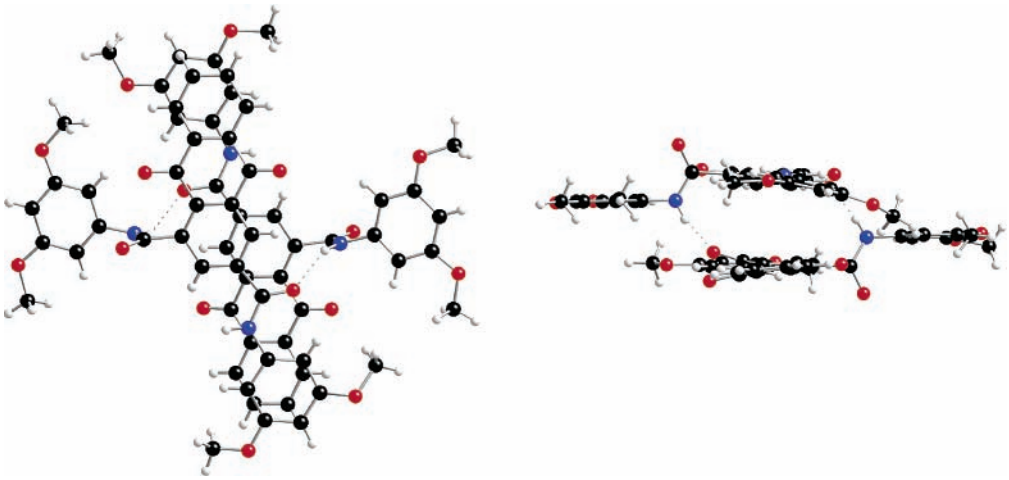


FIGURE 3. Top and side view of the X-ray crystal structure of compound **5**, showing dimerization in the solid state via amide−amide hydrogen-bonding interactions.

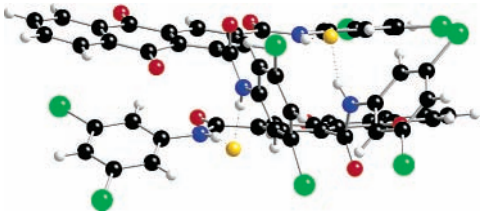


FIGURE 4. X-ray crystal structure of the tetra-*n*-butylammonium fluoride complex of compound **7**, showing "2 + 2" complex formation via amide NH···F^- hydrogen bonds. Fluoride is shown in yellow, and chloride is shown in green.

in the formation of a dimer in the solid state via amide−amide NH···OC hydrogen-bond interactions (Figure 3). There are two crystallographically distinct molecules in the unit cell of compound **5**. The amide in the 1 position is twisted out of plane by 87.14(51)° and 86.89(50)°, while the amides in the 3 position are twisted out of plane by only 15.10(49)° and 23.61(52)°.

The crystal structure of the fluoride complex of compound **7** confirmed that the strategy of using a "twisted" binding site was successful and had resulted in the formation of a "2 + 2" fluoride/receptor complex (Figure 4). As was observed previously in the structure of compound **5**, the amide in the 1 position of compound **7** is twisted out of the plane of the anthraquinone ring (this is particularly clearly illustrated in the side view shown in Figure 3). This NH group forms a hydrogen bond to the fluoride anion bound by the amide in the 3 position of the other receptor in the complex, with N−F distances in the range of 2.574(6)−2.615(6) Å. Additionally, there are CH−F close contacts in the solid state, with C−F distances ranging between 2.789(8) and 3.062(9) Å.

The inclusion of an anthraquinone group in these receptors allows them to be used as electrochemical anion sensors. We have studied the interaction compound **6** with fluoride and other anions in dry DMSO solution using cyclic voltammetry.[13] The cyclic voltammogram (CV) of compound **6** in dry DMSO is shown in black in Figure 5. The shape of this CV was unexpected, because under similar conditions, anthraquinone undergoes two one-

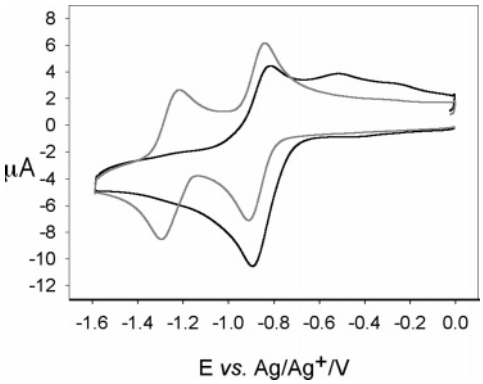


FIGURE 5. Plot showing the cyclic voltammograms recorded for a 1 mmol dm^{-3} solution of compound **6** (black) and 1 mmol dm^{-3} solution of compound **6** in the presence of 5.8 equiv of F^- (gray). All voltammograms were recorded in a 0.1 mol dm^{-3} $TBAPF_6$/DMSO electrolyte at a 3 mm diameter glassy carbon electrode. The data were recorded at a sweep rate of 50 mV s^{-1}.

electron reductions.[14] In the case of compound **6**, electrochemical-modeling studies provided evidence that led us to suggest that intra- and intermolecular hydrogen-bonding interactions stabilize the reduced radical anion and dianion forms of the receptor in dry DMSO, giving rise to the CV shown in black. The addition of a species such as fluoride that can compete with the reduced quinone species for the NH hydrogen-bond donor groups would be expected to switch the electrochemistry to a reduction process more typical of unfunctionalized anthraquinone. As fluoride is titrated into the electrochemical cell, this process does indeed occur with two one-electron reductions being observed in the CV of compound **6** in the presence of approximately 6 equiv of fluoride (Figure 6). Further changes to the electrochemistry occur at higher fluoride concentrations (possibly due to deprotonation) and are currently under investigation.

3. Receptors Based on *ortho*-Phenylenediamine

Inspired by the effectiveness of isophthalamide anion receptor systems, we wished to investigate other simple

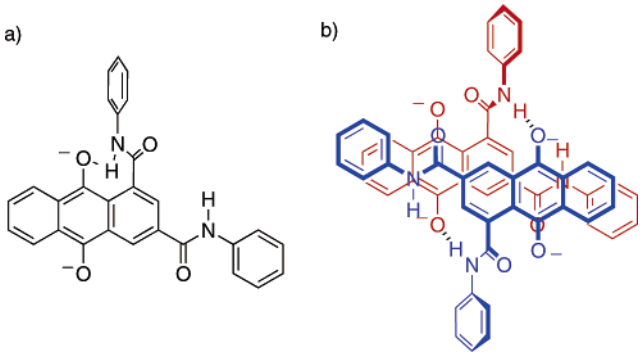


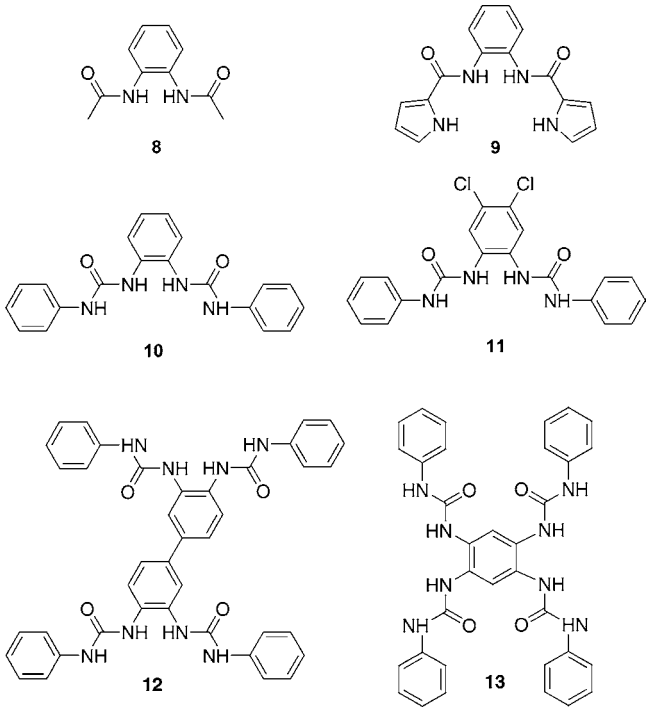
FIGURE 6. Proposed structures of (a) intra- and (b) intermolecularly stabilized reduced anthraquinone **6** species.

Table 2. Stability Constants (M^{-1}) of Compounds 8−11 with a Variety of Putative Anionic Guests (Added as Tetra-*n*-butylammonium Salts) at 298 K in DMSO-d_6/0.5% Water[a]

anion	compound **8**	compound **9**	compound **10**	compound **11**
Cl^-	13	12	43	67
Br^-			<10	<10
$CH_3CO_2^-$	98	251	3210	8080
$C_6H_5CO_2^-$	43	113	1330	2250
$H_2PO_4^-$	149	295	732	4720
HSO_4^-			10	<10

[a] In all cases, 1:1 receptor/anion stoichiometry was observed. Errors were estimated to be no more than ±10%.

hydrogen-bond donor motifs for anion complexation. In 2000, Reinhoudt and co-workers reported the dihydrogen phosphate selectivity of cyclic and acyclic receptors containing two *ortho*-phenylenediamine-based bis-ureas in DMSO.[15] We wished to "extract" the bis-urea unit and investigate the intrinsic anion-binding properties of 1,1′-(1,2-phenylene)bis(3-phenylurea) (**10**)[16] and those of the structurally related compounds **8**[17] and **9**. The anion (but not carboxylate) complexation properties of the amidopyrrole **9** had been reported previously by Cheng and co-workers.[18] Anion-binding studies conducted in DMSO-d_6 containing 0.5% water showed the expected selectivity for oxo-anions based on their higher basicity. Receptor **10** was found to possess a particularly high affinity for carboxylates (Table 2).[19,20] It is interesting to note that across the series of receptors **8**−**10** the ratio of $K_{benzoate}/K_{H_2PO_4^-}$ increases from 0.66 (**8**), through 0.85 (**9**), to 4.39 (**10**). X-ray crystallographic analyses of the fluoride, choride, and acetate complexes of receptor **9** showed that in all cases in the solid state the anionic guests were not bound by all of the available hydrogen-bond donors in the receptor species (Figure 7), with either one (fluoride and acetate) or two (chloride) pyrrole NH groups oriented exo to the anion-binding cavity, forming a hydrogen bond to an adjacent complex. In contradistinction to these results, the X-ray crystal structure of the benzoate complex of receptor **10** (Figure 8) shows the anion bound by all four of the urea NH protons in an essentially symmetrical arrangement. There are two crystallographically distinct complexes in the unit cell with N···O distances of 2.740, 2.818, 2.821, and 2.939 Å in one complex and 2.804, 2.807, 2.827, and 2.872 Å in the other.



Compound **11** contains two electron-withdrawing chlorine substituents on the central aromatic ring and was found to have a generally higher affinity for anions than compound **10** binding benzoate with a stability constant of 8080 M^{-1}. However, the ratio of $K_{benzoate}/K_{H_2PO_4^-}$ is lower at 1.71.[20] Interestingly, the crystal structure of this complex shows that the benzoate anion is not symmetrically bound to the receptor but is instead bound via three hydrogen bonds as shown in Figure 8b, with the presumably more acidic central NH groups both bound to the same oxygen atom (N···O, 2.778 and 2.783 Å) and the other oxygen bound to an "external" NH group (N···O, 2.837 Å) in the solid state.[21]

When two *ortho*-phenylenediamine-based bis-urea groups are combined in a single receptor (e.g., compounds **12** and **13**[22]), complex formation with dicarboxylates leads to the formation of hydrogen-bonded molecular tapes in the solid state (Figure 9).[23,24]

4. Amidopyrroles

As we have already observed from the X-ray crystal structure of the acetate complex of compound **9**, amidopyrroles[25] offer a convergent hydrogen-bonding array suited to binding a single atom in an anion, while urea, which also contains two NH groups, offers anions in a parallel hydrogen-bonding array suitable for binding "Y-shaped" anions such as carboxylate (Figure 10). Our initial studies on amidopyrroles focused on 2,5-dicarboxamidopyrrole receptors such as compound **14**.[26] These receptors proved to be selective for oxo-anions in acetonitrile-d_3 with NMR spectroscopic titrations, with compound **14** in acetonitrile-d_3 revealing selectivity for carboxylates

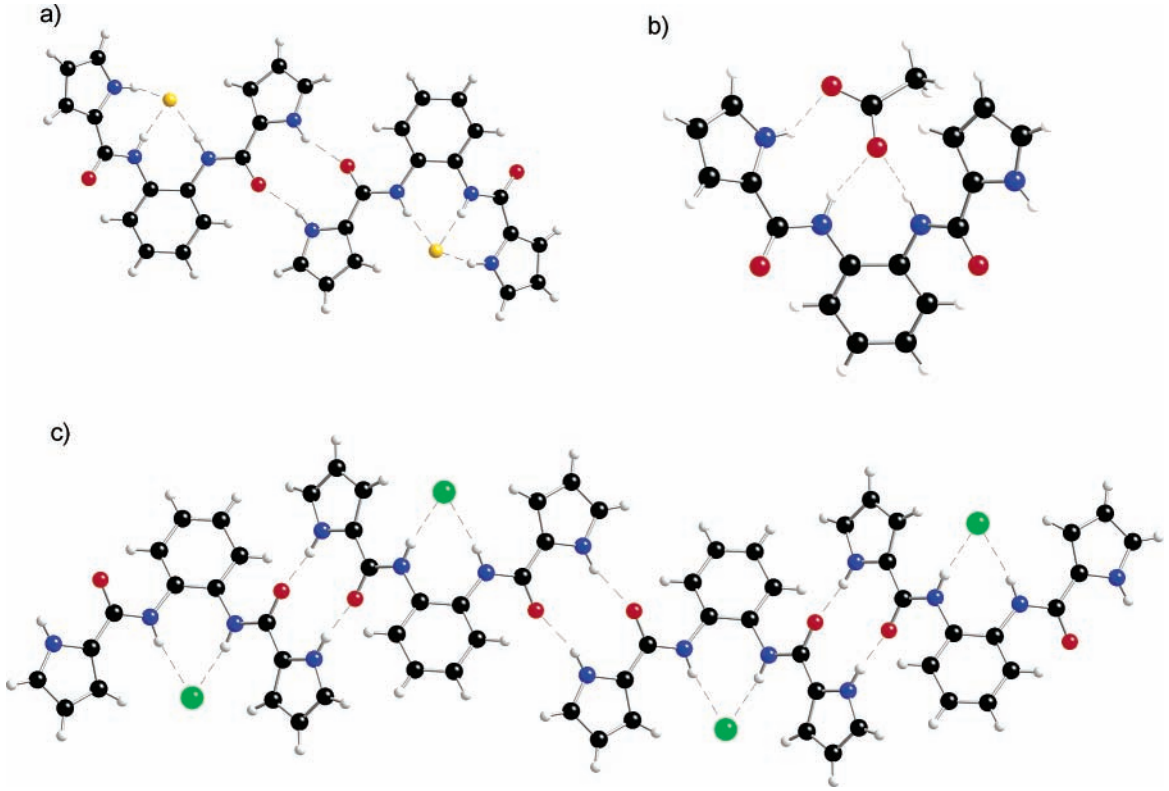


FIGURE 7. X-ray crystal structures of (a) fluoride, (b) acetate, and (c) chloride complexes of compound **9**. Tetra-*n*-butylammonium countercations have been omitted for clarity. Fluoride is shown in yellow, and chloride is shown in green.

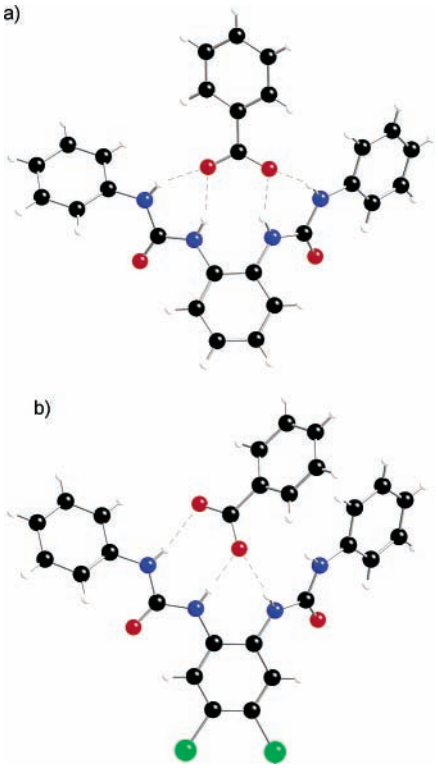
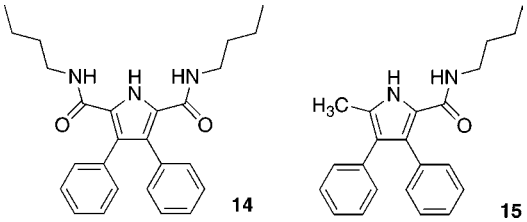


FIGURE 8. X-ray crystal structures of the benzoate complexes of receptor **10** (top) and **11** (bottom). Tetra-*n*-butylammonium countercations have been omitted for clarity.

(Table 3). Mono-amidopyrrole **15** was found to bind benzoate approximately an order of magnitude less strongly than receptor **14**. These data led us to suggest that all three of the NH groups present in receptor **14** are involved in forming hydrogen bonds to benzoate in the solution. Subsequent elucidation of the X-ray crystal structure of the tetra-*n*-butylammonium benzoate complex of compound **14** showed that in the solid-state one oxygen of the carboxylate anion is bound by the convergent hydrogen-bonding array formed by the amidopyrrole, while the second amide group is twisted out of the plane of the pyrrole ring by 38°, forming a third hydrogen bond with the other carboxylate oxygen atom (Figure 11).[27]



The twisted amide bond in this structure led us consider replacing the pyrrole unit in these receptors with a dipyrrolylmethane, because twists around the pyrrole-CR_2-pyrrole (R = H and Me) bonds would induce less strain in the receptor than the twist of an amide bond in the first generation systems. This, in addition to the extra pyrrole NH hydrogen-bond donor group, should lead to the formation of stronger complexes between 5,5′-dicarboxamidodipyrrolylmethanes and oxo-anions than were observed with 2,5-dicarboxamidopyrrole.[28]

Compound **16** was synthesized by the reaction of commercially available diethyl-5,5′-methylenebis(4-ethyl-3-methyl-2-pyrrole carboxylate) with aniline in the pres-

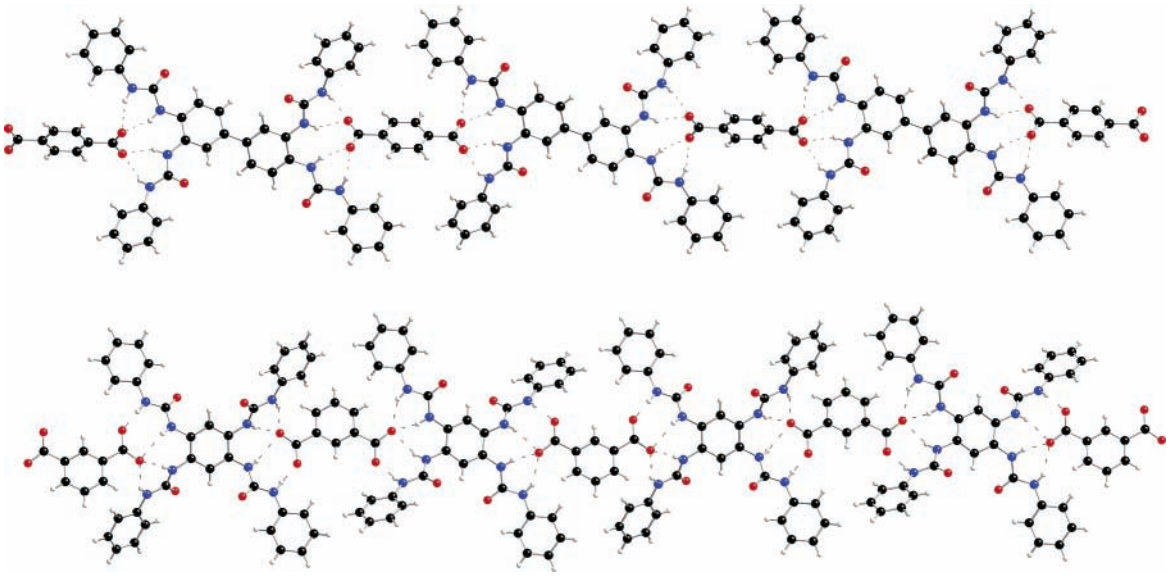


FIGURE 9. X-ray crystal structures of the terephthalate complex of compound **12** (top) and the isophthalate complex of compound **13** (bottom). Tetra-*n*-butylammonium countercations have been omitted for clarity.

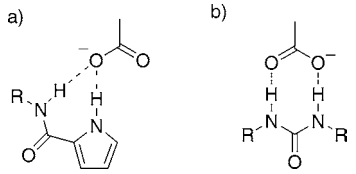


FIGURE 10. (a) Amidopyrroles offer a convergent hydrogen-bond donor array in contrast to (b) urea that offers carboxylate anions a parallel hydrogen-bonding array.

Table 3. Stability Constants K_a (M^{-1}) of Compounds 14 and 15 with a Variety of Anionic Guests (Added as Tetra-*n*-butylammonium Salts) at 298 K in CD_3CN (0.03% Water)[a]

	receptor	
anion	compound **14**	compound **15**
F^-	85	134
Cl^-	138	28
Br^-	<10	<10
$H_2PO_4^-$	357	89
$C_6H_5COO^-$	2500	202

[a] Errors were estimated to be <15%.

ence of trimethylaluminum in dry dichloromethane. This compound was found to have an exceptionally high affinity for dihydrogen phosphate binding this anion with a stability constant of $>10^4$ M^{-1} in the DMSO-d_6/5% water solution. Hence, a higher concentration of water was used to increase the competitiveness of the solvent and bring the stability constant down to a level that could be measured using proton NMR titration techniques. In the DMSO-d_6/25% water solution, the stability constant dropped to 234 M^{-1}. Unfortunately, this compound was prone to oxidation in dichloromethane solution over the course of several days, generating a dipyrrolylmethene. To overcome this instability, receptors **17**−**19** were synthesized that contain two methyl groups attached to the "*meso*-like" carbon between the two pyrrole rings, preventing oxidation.[29] Compound **17** retained selectivity for dihydrogen phosphate over a variety of other anions

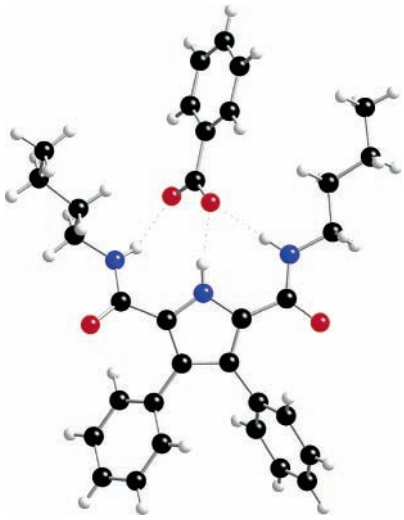


FIGURE 11. X-ray crystal structure of the benzoate complex of compound **14**. The tetra-*n*-butylammonium countercation has been omitted for clarity.

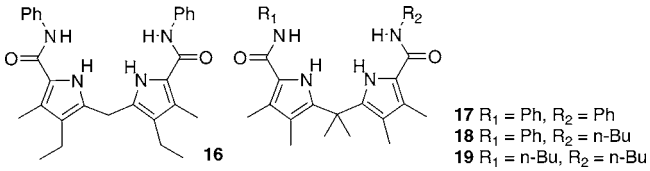
Table 4. Stability Constants K_a (M^{-1}) of Compounds 17−19 with a Variety of Putative Anionic Guests (Added as Tetra-*n*-butylammonium Salts) at 298 K in DMSO-d_6/5% Water[a]

anion	compound **17**	compound **18**	compound **19**
F^-	124	429	89
Cl^-	<15	*b*	*b*
benzoate	41	33	20
$H_2PO_4^-$	1092	307	81

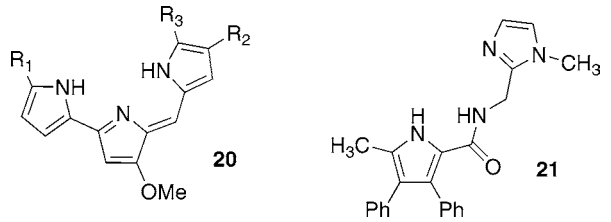
[a] No significant shifts were observed upon the addition of tetra-*n*-butylammonium bromide or hydrogen sulfate. Errors were estimated to be no more than ±15%. [b] No significant shift.

(Table 4); however, the affinity was found to be lower than observed with compound **16**. Nonetheless, compound **17** binds dihydrogen phosphate with a stability constant of 1092 M^{-1} in the DMSO-d_6/5% water solution. A density-functional theory (DFT)-calculated structure of receptor **18** bound to dihydrogen phosphate is shown in Figure

12, illustrating the two convergent hydrogen-bonding arrays coordinating to two of the dihydrogen phosphate oxygen atoms.



Anion complexation by pyrrole-containing receptors also occurs in biological systems. The prodigiosins (molecules of general structure **20**) are a class of natural product that have been shown to possess HCl co-transport properties and have attracted much attention recently because of their range of biological activity from functioning as proton-pump inhibitors to triggering apoptosis and hence having potential anticancer applications. Interest in the synthesis of prodigiosin analogues[30] and in the mechanism of prodigiosin-mediated chloride transport[31] is growing among the supramolecular chemistry community. There is currently some debate over the origin of this biological activity, and hence, we wished to investigate whether other synthetic HCl co-transport agents might have similar effects. Therefore, in collaboration with Bradley Smith's group at the University of Notre Dame, we have designed and synthesized amidopyrroles that function as membrane-transport agents for HCl.[32] The design of compound **21** was inspired by the prodigiosins because the receptor contains two hydrogen-bond donor groups (the amide and pyrrole) and a basic site (the pendant imidazole). On the basis of our previous findings, as a free base, the receptor was expected to possess a weak affinity for chloride but should form lipophilic HCl complexes under acidic conditions. Hence, the receptor should co-transport H^+/Cl^- from an acidic phase through a bilayer membrane to a high pH interface, a pH regime found in membrane-bound cellular compartments such as organelles of the biosynthetic and endocytic pathways, where deprotonation occurs.



Crystals of the HCl complex of compound **21** were obtained by slow evaporation of a dichloromethane/methanol/concentrated $HCl_{(aq)}$ solution of the receptor. The structure reveals the formation of a "2 + 2" dimer with each chloride bound by three hydrogen bonds, two from the amide [N···Cl, 3.29(2) Å] and pyrrole [N···Cl, 3.24(2) Å] groups of one receptor and one from the protonated imidazolium group of the other [N···Cl, 3.10(2) Å] (Figure 13). An interesting feature of the structure is that all of the polar and ionic functionality is inside the dimer, whereas the exterior projects primarily lipophilic

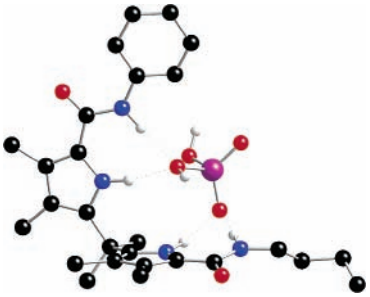


FIGURE 12. Structure of the dihydrogen phosphate complex of compound **18** generated by the DFT calculation using Spartan 2002.

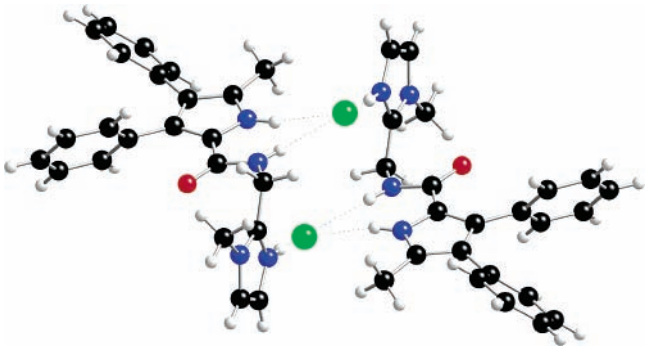


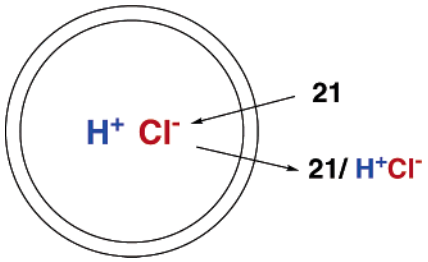
FIGURE 13. X-ray crystal structure of the HCl complex of compound **21**, showing the formation of a "2 + 2" hydrogen-bonded dimer. Chloride is shown in green.

groups, an arrangement that may be important for lipid solubility of the complex.

The ability of receptor **21** to co-transport H^+/Cl^- across bilayer membranes was evaluated at the University of Notre Dame using unilamellar vesicles (mean diameter of 200 nm) composed of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC)/cholesterol (7:3 molar ratio). A chloride-selective electrode was used to measure Cl^- leakage from the vesicles containing compound **21** under a variety of different starting conditions. It was shown that, 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 was near neutral (pH 6.7). The compound was subsequently tested for its ability to deacidify liposomes. The acid-sensitive dye, Oregon Green 514, was encapsulated inside POPC/cholesterol (7:3) vesicles at a pH of 4.0 (500 mM NaCl and 5 mM citric acid), and after dialysis to remove untrapped dye, the aqueous exterior phase was quickly adjusted to pH 7.2. The addition of compound **21** at $t = 200$ s induced an immediate discharge of the pH gradient.

The data are consistent with the transport model shown in Scheme 1. The free base form of receptor **21** partitions into the vesicle membrane and diffuses to the interior membrane interface, where it forms a lipophilic HCl complex (possibly a dimer) that diffuses back through the membrane. Transport is not observed when the exterior phase is also acidic because **21**$-H^+$ is not suf-

Scheme 1



ficiently lipophilic to strongly partition from the bulk external aqueous environment into the vesicles. We are continuing to investigate the HCl co-transport and biological properties of this new class of membrane-transport agents.

5. Anion-Triggered Deprotonation of Neutral Hydrogen-Bond Donors

Electron-withdrawing groups have frequently been employed in synthetic anion receptor systems to increase the acidity of NH hydrogen-bond donors and hence increase the affinity of the receptor for anionic guests. However, in these systems, the electron-withdrawing groups may instead decrease the acidity of the NH groups to such an extent that the receptor becomes susceptible to deprotonation by basic anions. In some cases, it may be difficult to establish a clear difference between these processes. A total of 4 years ago, we discovered that receptor **22** (which contains electron-withdrawing chloro substituents in the 3 and 4 positions of the pyrrole ring) when titrated with tetra-*n*-butylammonium fluoride in dichloromethane-d_2 gave an unusual titration profile of the amide NH groups.[33] A downfield shift of the amide NH protons was observed up to the addition of 1 equiv of fluoride, while between 1 and 2 equiv, these protons shift upfield, with the NH resonance reaching a plateau at 2 equiv of fluoride (Figure 14). The pyrrole NH proton resonance vanishes during the course of the titration. Subsequent preparation of the deprotonated form of the ligand with tetra-*n*-butylammonium hydroxide and analysis of the salt by ^{1}H NMR in dichloromethane-d_2 showed that the amide NH resonances have a chemical shift of 9.3 ppm, suggesting that 2 equiv of fluoride are required to deprotonate the receptor (which was subsequently confirmed to be due

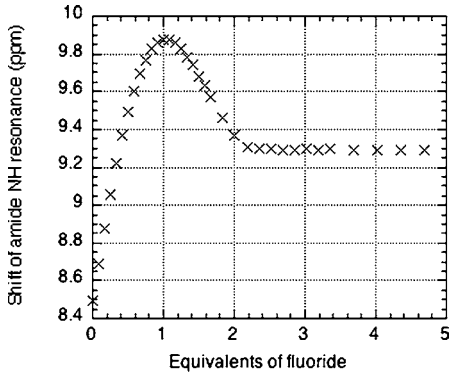
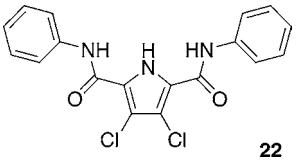


FIGURE 14. NMR titration curve for compound **22** (amide NH protons) with fluoride in dichloromethane-d_2.

FIGURE 15. X-ray crystal structure of the tetra-*n*-butylammonium salt of compound **22**−H$^+$, revealing NH···N$^-$ hydrogen bonds (tetra-*n*-butylammonium countercations have been omitted for clarity).

to the formation of the relatively stable bifluoride HF_2^- anion). Crystals of the deprotonated amidopyrrole were obtained by slow evaporation of a dichloromethane solution of compound **20** in the presence of excess tetra-*n*-butylammonium fluoride. The structure confirmed deprotonation of the receptor (at the pyrrole NH position) and additionally revealed that the deprotonated species is self-complementary, forming an "orthogonally" interlocked structure (Figure 15). The same motif was observed in the solid state with dimers **23** and **24**, which when deprotonated form orthogonally interlocked hydrogen-bonded polymeric structures in the solid state (Figure 16).[34]



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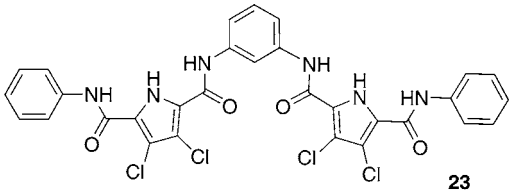

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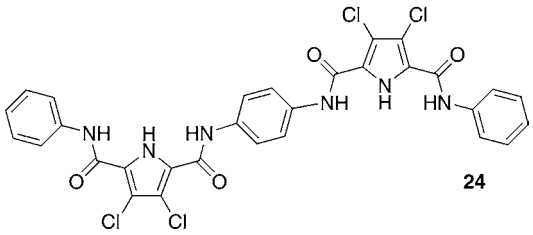


24

Compounds **25** and **26** also contain electron-withdrawing groups, but in contradistinction to compounds **22**−**24**, the groups are attached to the amide positions and not directly to the pyrrole ring. Nonetheless, fluoride was shown to deprotonate the more acidic compound (**26**), a process accompanied by a distinctive and fluoride-specific color change from colorless to blue in acetonitrile solution.[35] To confirm that the color change was due to deprotonation, receptor **26** was treated with 20 equiv of tetra-*n*-butylammonium hydroxide and, after removing

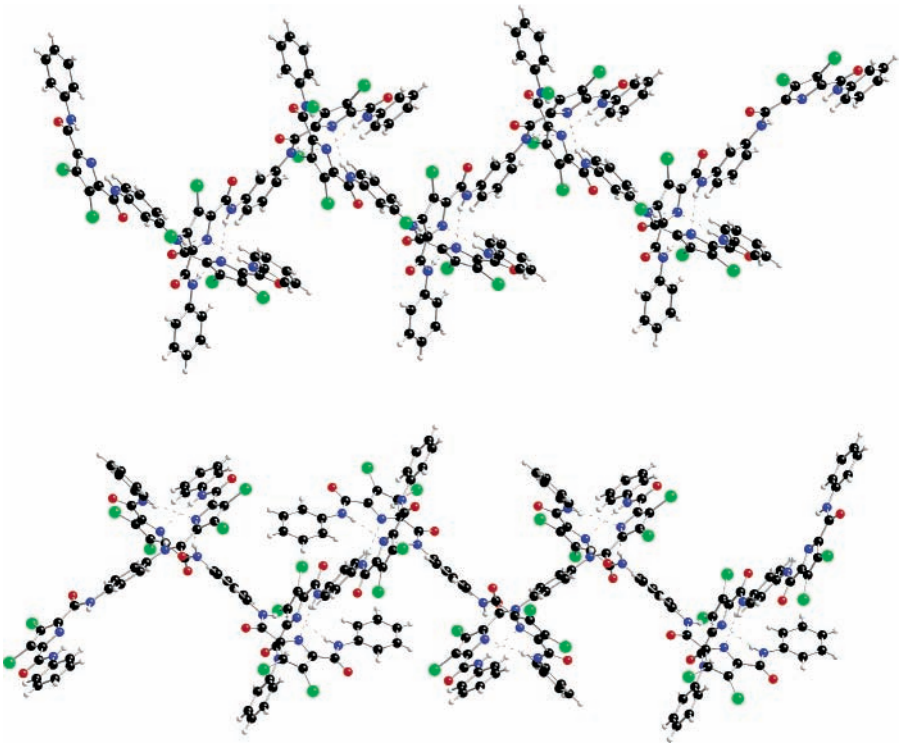


FIGURE 16. X-ray crystal structure of the tetra-*n*-butylammonium salt of compounds **23**−2H$^+$ (top) and **24**−2H$^+$ (bottom), revealing NH···N$^-$ hydrogen bonds leading to hydrogen-bonded polymer formation (tetra-*n*-butylammonium countercations have been omitted for clarity).

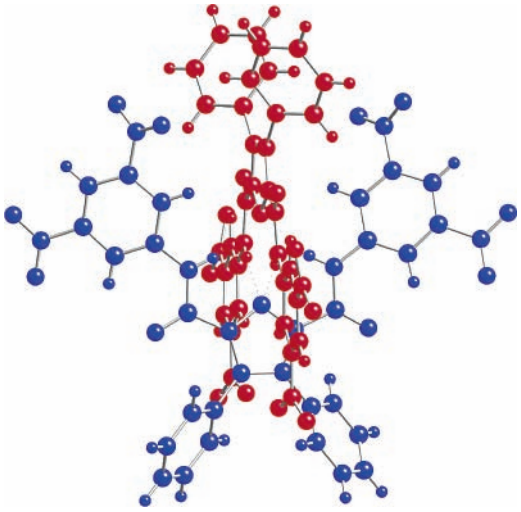
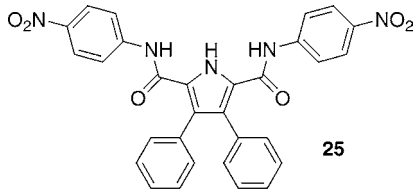


FIGURE 17. X-ray crystal structure of the tetra-*n*-butylammonium salt of compound **26**−H$^+$ (tetra-*n*-butylammonium countercations have been omitted for clarity). The two components of the interlocked structure were rendered in red and blue for clarity.

the excess base, a dark red material was crystallized from a mixture of diethyl ether/dichloromethane. The crystal structure of this material confirms that it is the tetra-*n*-butylammonium salt of the deprotonated pyrrole, and once again, an interlocked hydrogen-bonding motif is observed with NH···N$^-$ distances in the range of 2.97−3.08 Å (Figure 17). The red crystals when dissolved in acetonitrile form a blue solution, confirming that deprotonation and not selective fluoride complexation is responsible for the color change. In the same year, Gunnlaugsson, Kruger, Pfeffer,[36] and co-workers reported an analogous process occurring with a naphthalimide thiourea resulting in a color change from yellow/green to red/purple, and subsequently, anion-triggered deprotonation has been reported by a number of groups.[37]



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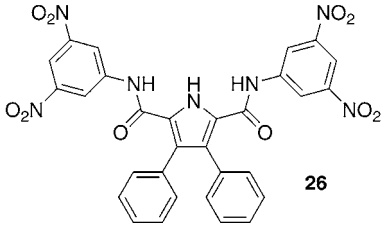


26

Most recently, we have been studying anion-binding processes in amido(thio)urea compounds. Many species containing this hydrogen-bonding motif have been reported to function as colorimetric anion (and often fluoride sensors). We therefore synthesized a series of amido(thio)ureas **27**−**30** with expected increasing acidity and investigated whether the interaction of these species with anionic guests was a binding or deprotonation process.[38] Compound **27** did not interact to any significant extent with anions in DMSO solution, while the more acidic analogue **28** was shown by UV/vis titration methods to bind anions with a 1:1 stoichiometry, with stability constants of 3010 M^{-1} (F$^-$), 5580 M^{-1} ($CH_3CO_2^-$), 1440 M^{-1} ($PhCO_2^-$), and 1060 M^{-1} ($H_2PO_4^-$). Titration of these

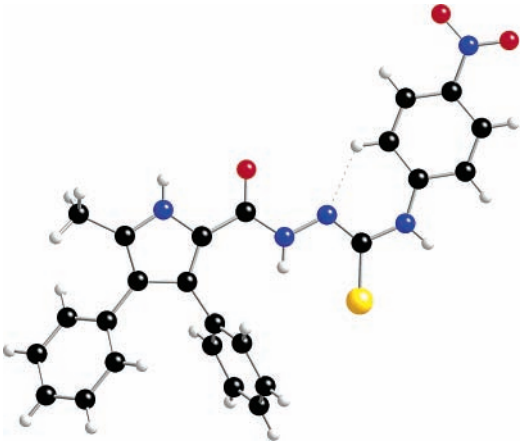
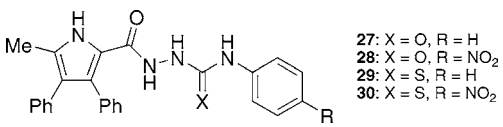


FIGURE 18. X-ray crystal structure of one of the anions present in the unit cell of the tetra-*n*-butylammonium salt of compound **30**. Deprotonation has occurred at a urea NH position.

anions into solutions of compounds **29** and **30** resulted in dramatic changes in the UV−vis spectra of the receptors, with new intense absorption bands appearing at 330 and 430 nm, respectively. The titration profile was a sharp curve reaching a plateau at 1 equiv of the anionic guest. Proton NMR spectroscopic studies showed that the addition of these anions caused the appearance of three sharp NH proton resonances, consistent with a deprotonation process. Red crystals were formed upon slow evaporation of a dichloromethane/ether solution, with compound **30** containing either 1 equiv of tetra-*n*-butylammonium fluoride or 1 equiv of tetra-*n*-butylammonium benzoate (in the latter case, colorless crystals of benzoic acid were also formed). The X-ray crystal structure of the red material showed that the crystals were the tetra-*n*-butylammonium salt of $(\mathbf{30}-H^+)^-$ and that deprotonation of the thiourea had occurred at one of the urea NH positions (Figure 18). A proton NMR titration study the tetra-*n*-butylammonium salt of $(\mathbf{30}-H^+)^-$ in DMSO-d_6 gave an identical spectrum to those obtained after the addition of 1 equiv of tetra-*n*-butylammonium fluoride, acetate, benzoate, or dihydrogen phosphate. When this evidence is taken in concert, it leads us to suggest that these four anions deprotonate compound **30** in DMSO solution.



27: X = O, R = H
28: X = O, R = NO_2
29: X = S, R = H
30: X = S, R = NO_2

Amido(thio)urea compounds have previously been shown to act as colorimetric anion sensors. We have shown here that in contradistinction to a number of other anion-triggered deprotonationation processes only 1 equiv of a basic anion will deprotonate receptor **30**. Care must therefore be taken when studying these compounds by UV/vis titration methods because a deprotonation process may in this case masquerade as a strong 1:1 binding event.

6. Conclusions

The chemistry of neutral hydrogen-bond donor anion receptors is still not fully explored. Structurally simple systems such as the acyclic *ortho*-phenylenediamine bisureas or dicarboxamidodipyrrolylmethanes can possess very high affinities for anionic guests in competitive solvent media. Crystallographic analysis of complex structures has provided us with leads for the design of new receptor systems and has been important in our work in characterizing deprotonated hydrogen-bond donor systems and identifying recurring hydrogen-bond motifs for further study. We are continuing to investigate the binding properties of both acyclic and cyclic anion and ion-pair receptors containing hydrogen-bond donor groups. Applications for these systems in new separation and sensor technologies and in potential future medical applications will continue to drive this work forward.

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