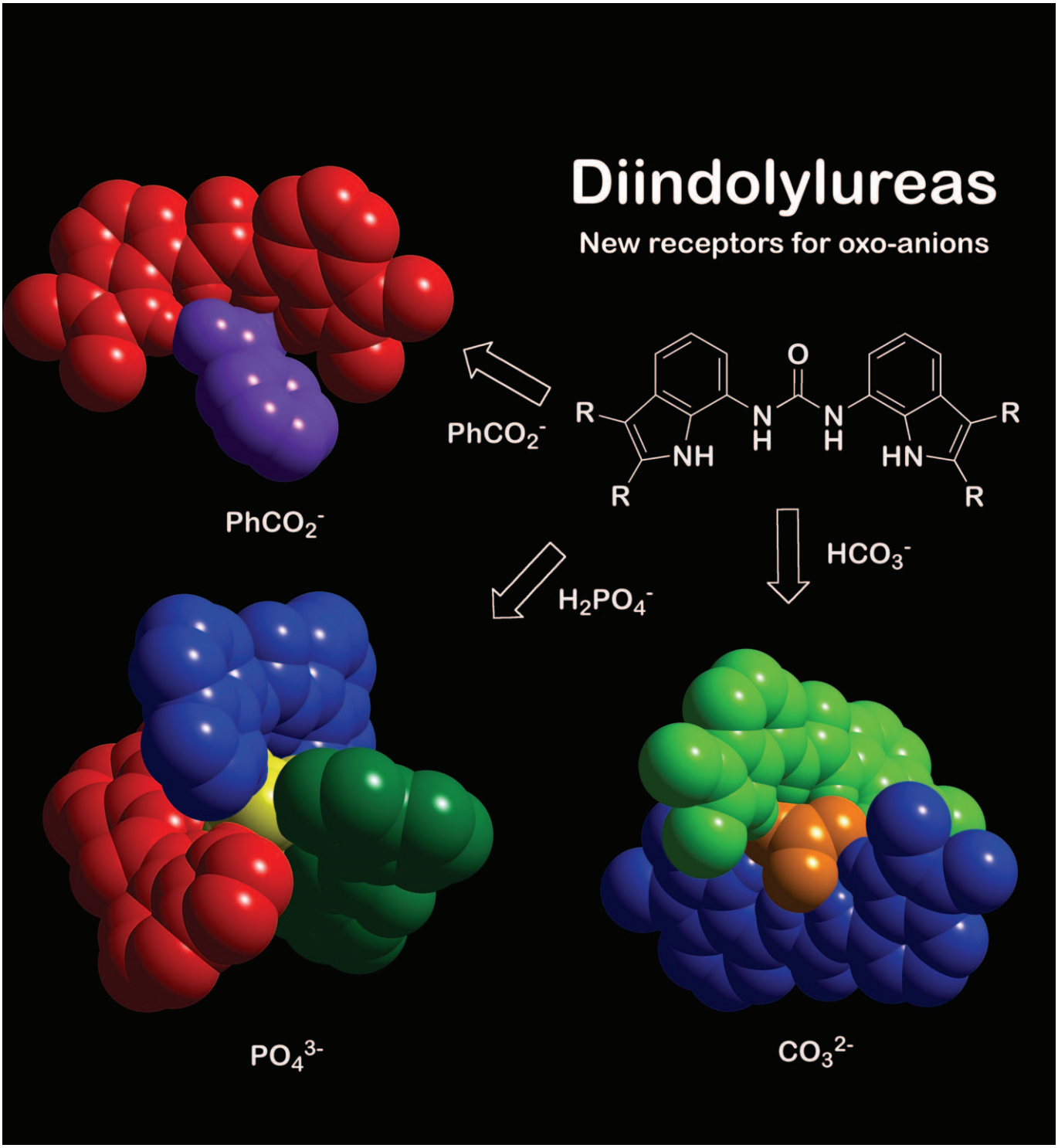
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801639

1,3-Diindolylureas and 1,3-Diindolylthioureas: Anion Complexation Studies in Solution and the Solid State

Claudia Caltagirone, Jennifer R. Hiscock, Michael B. Hursthouse, Mark E. Light, and Philip A. Gale*[a]



Abstract: 1,3-Diindolylureas and thioureas have been synthesised and their anion complexation properties in solution studied. Whilst diindolylthioureas showed only moderate affinities and selectivities, diindolylureas show remarkably high affinity for dihydrogen phosphate in solution for an acyclic, neutral receptor in water/[D_6]DMSO mixtures. These easy-to-make compounds adopt relatively planar conformations in the solid-state and are able to donate four hydrogen bonds and yet not fill the coordination sphere of carbonate or phosphate, allowing two or three receptors to bind to each anion in the solid-state.

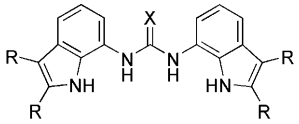
Keywords: anions · indoles · phosphate · structure elucidation · ureas

Introduction

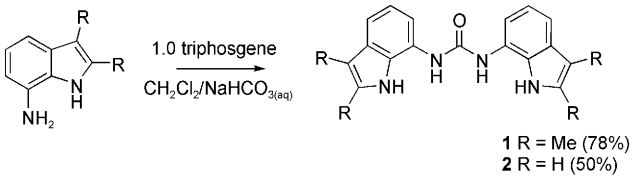
Anion complexation, and in particular anion recognition with neutral hydrogen-bond-donor receptors, has attracted much interest in recent years with a variety of receptors containing amide, urea and pyrrole shown to have high affinities and selectivities for anionic guests.[1] In contrast, it is only since 2004 that indole and related heterocycles, such as carbazole, biindole and indolocarbazole, have been employed as components of neutral anion-receptor systems[2] Indole, like pyrrole, contains a single hydrogen-bond donor group, but is slightly more acidic,[3] and is employed in biological systems to bind anions such as chloride[4] and sulfate.[5] Our interest in structurally simple anion receptors, sensors and transporters[6] lead us to include indole in isophthalamide- and pyridine-2,6-dicarboxamide-based receptors as fluoride selective anionophores[7] and in more flexible receptors containing 2-amidoindoles.[8] In collaboration with Albrecht and Triyanti,[9] we demonstrated recently that 2,7-disubstituted indoles with amide substituents in the 2-position and urea substituents in the 7-position bound oxo anions strongly. However, whilst ^{1}H NMR titration studies showed that the indole and urea groups were participating in hydrogen-bonding interactions with the bound oxo anionic guest, the amide group was only interacting weakly with the bound anion; these data are supported by crystallographic analysis of a number of complexes. We therefore modified the design by removing the amide group and adding an extra indole group, and report here the anion complexation studies with the resultant 1,3-diindolylureas and 1,3-diindolylthioureas **1**–**4**.[10]

Results and Discussion

Diindolylureas **1** and **2** were synthesised by reaction of 2,3-dimethyl-7-aminoindole[7] or 7-aminoindole, respectively, with triphosgene in a mixture of dichloromethane and saturated aqueous sodium bicarbonate affording ureas **1** and **2** in 78 and 50% yields, respectively (Scheme 1). Diindolylthioureas **3** and **4** were prepared by reaction of



1 R = Me, X = O
2 R = H, X = O
3 R = Me, X = S
4 R = H, X = S

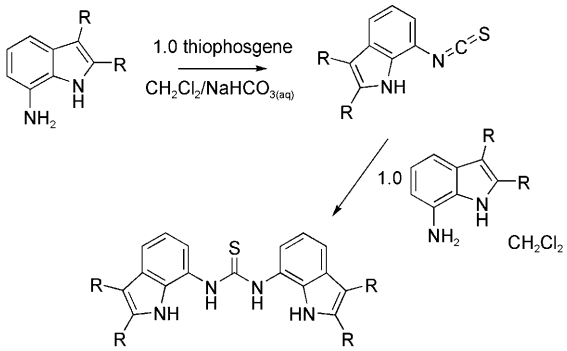


1 R = Me (78%)
2 R = H (50%)

Scheme 1. Synthesis of compounds **1** and **2**.

2,3-dimethyl-7-aminoindole or 7-aminoindole, respectively, with thiophosgene to afford the isothiocyanate followed by reaction with a further equivalent of aminoindole to afford thioureas **3** and **4** in 29 and 83% yields, respectively (Scheme 2).

Anion complexation studies were conducted with compounds **1** and **2** by ^{1}H NMR titration techniques in [D_6]DMSO/water mixtures following the NH proton resonances. Stability constants were determined by using the



3 R = Me (29%)
4 R = H (83%)

Scheme 2. Synthesis of compounds **3** and **4**.

[a] Dr. C. Caltagirone, J. R. Hiscock, Prof. M. B. Hursthouse, Dr. M. E. Light, Prof. P. A. Gale
School of Chemistry, University of Southampton
Southampton, SO17 1BJ (UK)
Fax: (+44) 23 8059 6805
E-mail: philip.gale@soton.ac.uk

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801639.

EQNMR computer program.[11] Selected Job plot analyses showed 1:1 stoichiometry in all cases (see Supporting Information).[12] In [D$_6$]DMSO/0.5% water compound **1** was found to bind oxo anions strongly ($K_a > 10^4\,M^{-1}$), whilst chloride was bound with a stability constant of $128\,M^{-1}$ (Table 1)

Table 1. Stability constants of compound **1** measured in [D$_6$]DMSO/0.5% water and [D$_6$]DMSO/10% water at 298 K by ^{1}H NMR titration techniques.

Anion[a]	[D$_6$]DMSO/0.5% water	[D$_6$]DMSO/10% water
Cl^-	128	16
$CH_3CO_2^-$	$>10^4$	567
$C_6H_5CO_2^-$	$>10^4$	736
$H_2PO_4^-$	$>10^4$	4790

[a] Anions added as tetrabutylammonium salts. Errors in K_a are estimated to be <15%.

and hydrogen sulfate bound weakly ($50\,M^{-1}$). Compound **1** proved therefore to have a significantly higher affinity for oxo anions that *N*,*N*′-diphenylurea.[10] Moving to a more polar solvent mixture, [D$_6$]DMSO/10% water, selectivity for dihydrogen phosphate was observed with $K_a(H_2PO_4^-)/K_a(AcO^-) = 8.5$ (Table 1). Attempts to measure stability constants in 25% water failed due to precipitation of the oxoanion complexes. Compound **2** proved to have similar affinities for anions as compound **1** in mixtures containing 0.5 and 10% water; however, the complexes of this compound with dihydrogen phosphate and acetate proved to be more soluble than those of compound **1**, allowing stability constants to be determined in [D$_6$]DMSO/25% water. Under these conditions selectivity for dihydrogen phosphate is retained with $K_a(H_2PO_4^-)/K_a(AcO^-) = 8$ (Table 2).

Table 2. Stability constants of compound **2** measured in [D$_6$]DMSO/0.5% water, [D$_6$]DMSO/10% water and [D$_6$]DMSO/25% water at 298 K by ^{1}H NMR titration techniques.

Anion[a]	[D$_6$]DMSO/0.5% water	[D$_6$]DMSO/10% water	[D$_6$]DMSO/25% water
Cl^-	128	17	–
$CH_3CO_2^-$	$>10^4$	774	20
$C_6H_5CO_2^-$	$>10^4$	521	precipitate
$H_2PO_4^-$	$>10^4$	5170	160

[a] Anions added as tetrabutylammonium salts.

Crystals of the tetrabutylammonium benzoate complex of compound **1** were grown by slow evaporation of a solution of the receptor in DMSO. The structure was elucidated by single-crystal X-ray diffraction and is shown in Figure 1. The benzoate anion is bound by four hydrogen bonds from the diindolylurea, two to each oxygen atom in the range N···O = 2.846(8)–2.907(8) Å and bond angles N1–H1···O3 = 161°; N2–H2···O3 = 169°; N3–H3···O2 = 176°; N4–H4···O2 = 159°.

Anion complexation studies were also conducted with tetraethylammonium bicarbonate. These studies are not directly comparable with the data presented in Tables 1 and 2 as the counter cation is different;[13] however, the anion bound

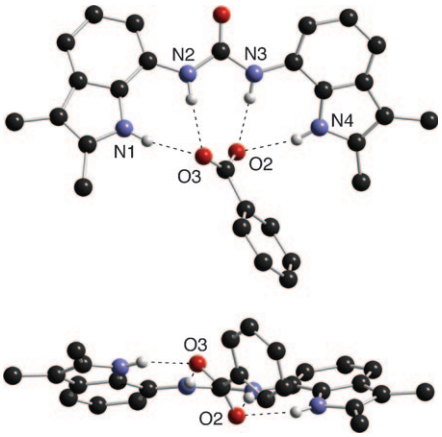


Figure 1. Top and side views of the X-ray crystal structure of the tetrabutylammonium benzoate complex of compound **1**. Non-acidic hydrogen atoms and counter cation omitted for clarity.

with similar affinity as tetrabutylammonium carboxylates with compounds **1** [$K_a > 10^4\,M^{-1}$ ([D$_6$]DMSO/0.5% water); $545\,M^{-1}$ ([D$_6$]DMSO/10% water)] and **2** [$K_a = 9580\,M^{-1}$ ([D$_6$]DMSO/0.5% water); $699\,M^{-1}$ ([D$_6$]DMSO/10% water); $42\,M^{-1}$ ([D$_6$]DMSO/25% water)]. Job plot analysis in 10% water with compound **2** indicated 1:1 complex stoichiometry in solution. Attempts to obtain crystals of the bicarbonate complex of compound **1** were made by slow evaporation of a solution of the receptor in DMSO in the presence of excess tetraethylammonium bicarbonate. Crystals were obtained and the structure elucidated by X-ray crystallography. It was found that the anion was bound as carbonate[14] by eight hydrogen bonds to two equivalents of compound **1** in the solid state with two tetraethylammonium counter cations for each anion complex (Figures 2 and 3). The oxygen atoms O3 and O5 are each bound to three NH groups, with O4 bound to two NH groups. Presumably deprotonation occurs during crystallisation of the complex. The N···O distances were found to be in the range 2.739(2)–2.9382(16) Å and N–H···O angles in the range 151.3–175.1°. The torsion angles

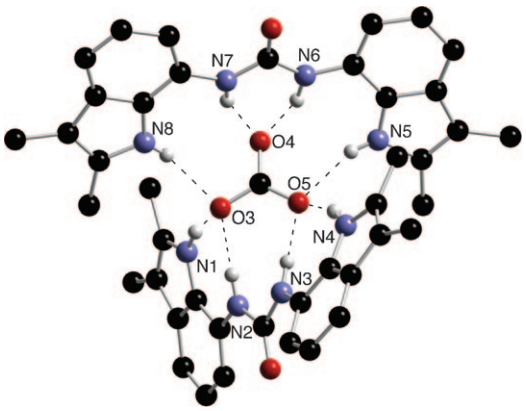


Figure 2. X-ray crystal structure of the tetraethylammonium carbonate complex of compound **1**. Non-acidic hydrogen atoms and counter cations omitted for clarity.

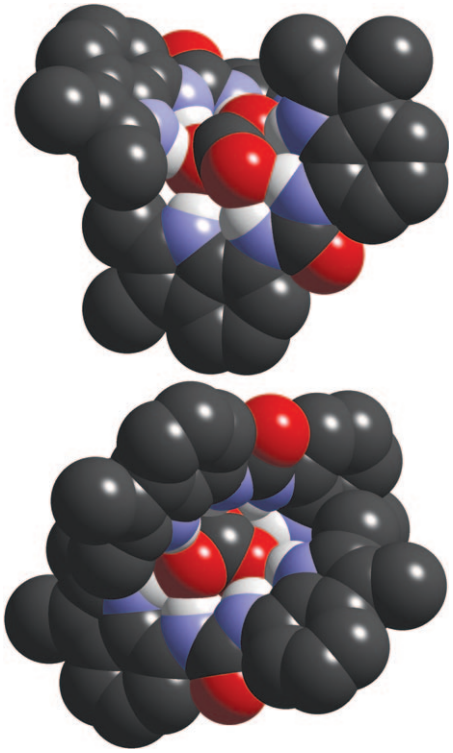


Figure 3. Two space-filling views of the X-ray crystal structure of the tetraethylammonium carbonate complex of compound **1**. Non-acidic hydrogen atoms and counter cations omitted for clarity.

for the urea–indole bonds are in the range 157.89° to 177.38°.

Compound **2** was crystallised in the presence of excess tetrabutylammonium dihydrogen phosphate in [D_6]DMSO/25% water. As with the carbonate structure discussed above, the anion crystallised in its fully deprotonated form (PO_4^{3-}) bound in this case to three equivalents of compound **2** by twelve hydrogen bonds (Figures 4 and 5). Each receptor is bound to three oxygen atoms in the phosphate guest with N1···O2 = 2.762(3) Å, N2···O3 = 2.756(3) Å, N3···O3 = 2.850(4) and N4···O3′ = 2.722(3) Å. Thus each oxygen atom

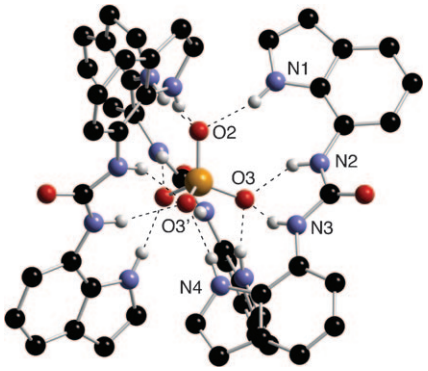


Figure 4. The tetrabutylammonium phosphate complex of compound **2**. Non-acidic hydrogen atoms, solvent and counter cations omitted for clarity.

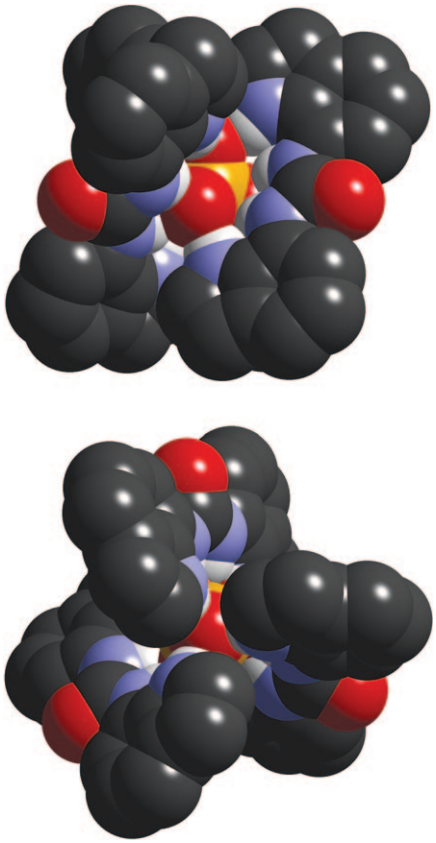


Figure 5. Space-filling side and top views of the tetrabutylammonium phosphate complex of compound **2**. Non-acidic hydrogen atoms, solvent and counter cations omitted for clarity.

accepts three hydrogen bonds. The torsion angles for the urea–indole bonds are 173.82 and 149.16°. To the best of our knowledge this is the only crystallographically characterised example of a fully deprotonated phosphate anion bound to a urea-containing receptor. Recently Custelcean and co-workers reported an example of sulfate SO_4^{2-} bound to two tren-based (tren = tris(2-aminoethyl)amine) trisurea receptors by twelve hydrogen bonds, which may be the optimal coordination number for sulfate.[15] The structure reported here similarly may represent the optimal coordination number for phosphate. Interestingly, in the phosphate-binding protein, bound phosphate accepts eleven hydrogen bonds from the protein and donates one to it (the anion is bound in the monoprotonated form) making a total of twelve hydrogen bonds.[16] A similar 11+1 hydrogen-bond array was observed in the HPO_4^{2-} complex of a protonated Schiff base macrocycle containing amide and pyrrole hydrogen bond donor groups by Katayev, Sessler and co-workers.[17]

Solution binding studies were also conducted with thioureas **3** and **4**. In [D_6]DMSO/0.5% water, a considerably lower affinity for oxo anions was observed together with a loss of selectivity for dihydrogen phosphate (Table 3). We have previously observed lower affinities for anions in a bis-thiourea as compared to an analogous bisurea.[18] This was

Table 3. Stability constants of compounds **3** and **4** measured in [D_6]DMSO/0.5% water at 298 K by ^{1}H NMR titration techniques.

Anion[a]	Compound **3**	Compound **4**
Cl^-	128	74
$CH_3CO_2^-$	2830	1620
$C_6H_5CO_2^-$	514	477
$H_2PO_4^-$	3830	1630

[a] Anions added as tetrabutylammonium salts. Errors in K_a are estimated to be <15%. Indole CH proton resonance was followed during titration due to broadening of the NH proton resonances.

attributed to the larger sulfur atom in the thiourea preventing the receptor adopting a planar conformation. Soós and co-workers have used modelling studies to evaluate the relative energies of a variety of thiourea conformations.[19] One possibility here is that conformational interconversion of the thiourea group in solution reduces the affinity of these receptors for anionic guests.

Crystals of the tetrabutylammonium chloride complex of receptor **4** were obtained by slow evaporation of a solution of the receptor in acetonitrile in the presence of excess tetrabutylammonium chloride. The structure (shown in Figure 6) shows a single chloride anion bound to the four

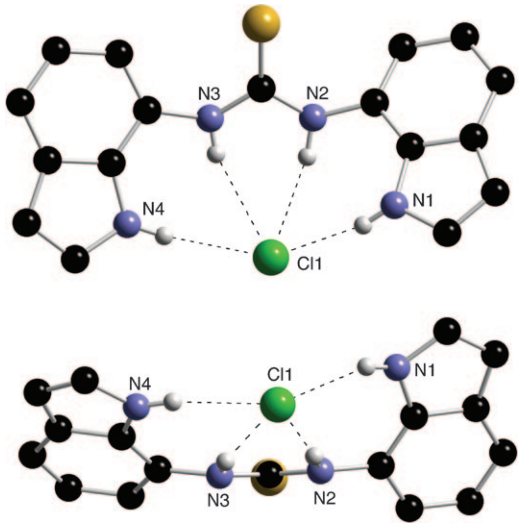


Figure 6. Side and bottom views of the X-ray crystal structure of the tetrabutylammonium chloride complex of compound **4**. Non-acidic hydrogen atoms and counter cation omitted for clarity.

NH groups in the receptor with N···Cl distances in the range 3.187(2)–3.377(3) Å and N–H···Cl angles in the range 159–171°. The structure reveals that the indole groups are twisted out of the plane with torsion angles for the thiourea–indole bond of 122.41 and 142.06°.

Solution studies with tetraethylammonium bicarbonate were also attempted with compounds **3** and **4**. It was found that in [D_6]DMSO/0.5% water compound **3** binds this anion with a stability constant of 477 M^{-1}. Broadening of the ^{1}H NMR spectrum of compound **4** under these conditions prevented the stability constant from being determined. However, crystals of the tetraethylammonium bicarbonate complex of compound **4** were obtained by slow evaporation of a solution of the receptor in wet acetonitrile in the presence of excess anion salt. In this case, in contradistinction to the carbonate complex of receptor **1**, the mixture crystallised as the bicarbonate complex. The HCO_3^- ion is hydrogen bonded between layers of the thiourea complex forming chains along the *a* direction with N1···O2 2.887(4) Å, N2···O2 2.797(4) Å, N3···O1 2.838(4) Å and N4···O3 2.835(4) Å and NH···O angles in the range 152–169° (Figures 7 and 8). The structure again reveals that the indole

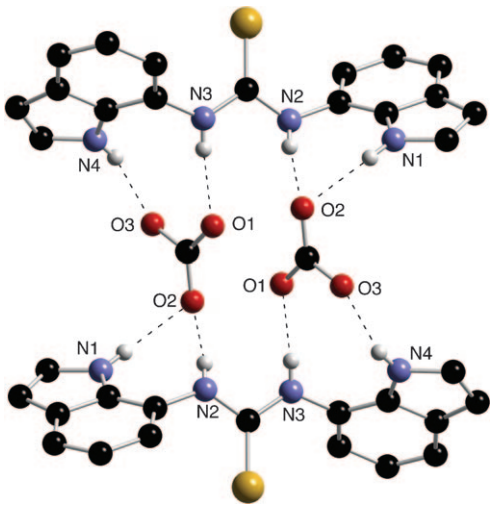


Figure 7. The X-ray crystal structure of the tetraethylammonium bicarbonate complex of compound **4**. Non-acidic hydrogen atoms, and counter cation omitted for clarity.

groups are twisted out of the plane with torsion angles for the thiourea–indole bond of 123.57 and 139.08°. The bicarbonate hydrogen atom was not located, as the exact position of the bicarbonate is not fixed but disordered along the direction of the bicarbonate chain (Figure 8). This can be interpreted as disorder in the position of bicarbonate anion dimers; this is observed frequently in the solid state.[20] This is evidenced in the direction of thermal ellipsoid elongation being along the crystallographic *a* axis (Figure 9), and the presence of sheets of diffuse scattering in 0*kl*.

Conclusions

We have previously shown how controlling conformational changes across a series of receptors can have a dramatic effect on affinity, selectivity and transport ability.[14a,21] In the series of compounds reported here, diindolylthioureas show only moderate affinities and selectivities, whilst diindolylureas have a remarkably high affinity for dihydrogen phosphate in solution for an acyclic, neutral, anion receptor in water/[D_6]DMSO mixtures. These easy-to-make compounds adopt relatively planar conformations in the solid-

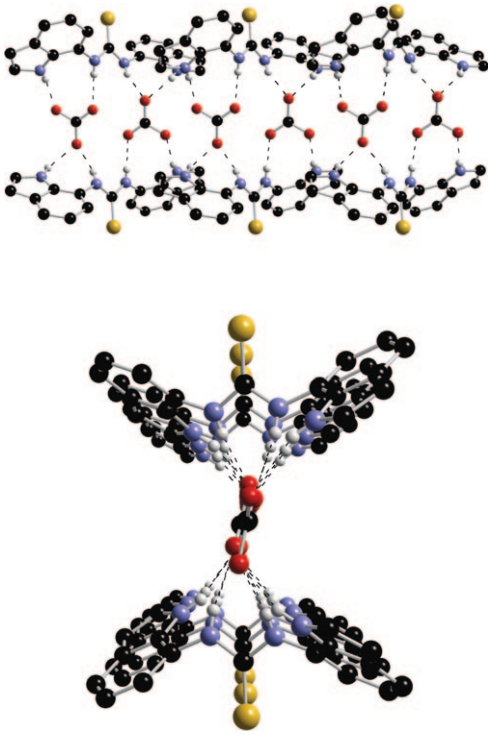


Figure 8. Side and end perspective views of the X-ray crystal structure of the tetraethylammonium bicarbonate complex of compound **4** showing a chain of bicarbonates in the solid state. Non-acidic hydrogen atoms and counter cation omitted for clarity.

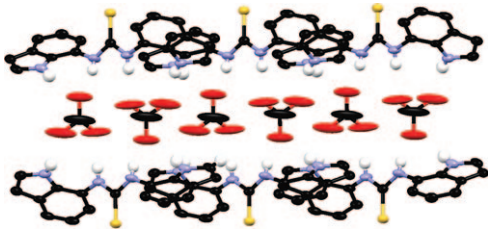


Figure 9. Thermal ellipsoid plot of the bicarbonate complex of compound **4**. Elongation of the thermal ellipsoids along the crystallographic *a* axis is indicative of disorder of the positions of bicarbonate dimers along the chain. Thermal ellipsoids are shown at the 50% probability level.

state and are able to donate four hydrogen bonds and yet not fill the coordination sphere of carbonate or phosphate, allowing two or three receptors respectively to bind to each anion in the solid-state. Consequently these oxo anions are stabilised by eight or twelve hydrogen bonds, which presumably accounts for the deprotonation of these species upon crystallisation. The motif is easy to functionalise and we are currently preparing a variety of acyclic and cyclic anion receptors containing 1,3-diindolylureas. We are also investigating the concentration ranges in which the complexes remain soluble and those in which we obtain precipitation. In addition we are investigating the application of this system in organocatalysis. The results of these studies will be reported in due course.

Experimental Section

General remarks: All reactions were performed in oven-dried glassware under a slight positive pressure of nitrogen. 2,3-Dimethyl-7-aminoindole was synthesised according to a literature procedure.[7] ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were determined on a Bruker AV300 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm), calibrated to the residual solvent peak set, with coupling constants reported in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet. Chemical shifts for ^{13}C NMR are reported in ppm, relative to the central line of a septet at $\delta = 39.52$ ppm for deuteriodimethylsulfoxide. Infrared (IR) spectra were recorded on a Mattson Satellite (ATR). FTIR are reported in wavenumbers (cm^{-1}). Elemental analyses were performed by Medac Ltd. All solvents and starting materials were purchased from commercial sources where available.

^{1}H NMR spectroscopic titrations: A Bruker AV300 NMR spectrometer was used to measure the ^{1}H NMR shifts of the NH protons of the receptors. NMR titrations were performed by adding aliquots of the putative anionic guest (as the TBA, TEA salt in the case of bicarbonate) salt (0.15 M) in [D$_6$]DMSO/water to a solution of the receptor (0.01 M) in [D$_6$]DMSO/water. The titration data was plotted Δppm versus concentration of guest and fitted to a binding model by using the EQNMR computer program.[11]

Crystallisations: Crystallisations were performed by dissolving the receptor (ca. 0.05 mmol) in solvent (2 mL) followed by addition of the anion salt (ca. 0.25 mmol) and allowing the solution to slowly evaporate. Crystals of the phosphate complex of receptor **2** were obtained from the solution used for the NMR titration in [D$_6$]DMSO/25% water in the presence of 5.8 equivalents of tetrabutylammonium dihydrogen phosphate.

1,3-Bis(2,3-dimethyl-1*H*-indol-7-yl)urea (1): 2,3-Dimethyl-7-aminoindole (0.253 g, 1.58 mmol) was dissolved in a mixture of dichloromethane (30 mL) and a saturated aqueous solution of NaHCO$_3$ (30 mL). Triphosgene (0.47 g, 1.58 mmol) was added in portions and the reaction mixture was left stirring under nitrogen atmosphere at room temperature overnight. The organic layer was washed with water, dried over MgSO$_4$, filtered and concentrated in vacuo. The product was obtained by recrystallisation from hot methanol and was isolated as a white solid. Yield: 0.21 g, 78%; m.p. 259 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 2.15$ (s, 6H), 2.33 (s, 6H), 6.88 (t, $J = 7.53$ Hz, 2H), 7.03 (d, $J = 7.53$ Hz, 2H), 7.12 (d, $J = 7.53$ Hz, 2H), 8.44 (s, 2H; NH urea), 10.31 ppm (s, 2H; NH indole); ^{13}C {H^1}NMR (75 MHz, [D$_6$]DMSO): $\delta = 8.5$ (CH$_3$), 11.3 (CH$_3$), 105.6 (C), 113.1 (CH), 113.1 (CH), 118.2 (CH), 123.06 (C), 128.12 (C), 130.5 (C), 131.1 (C), 153.6 ppm (CO); IR (film): $\tilde{\nu} = 3392$ (indole NH stretching), 3247 (urea NH stretching), 1617 cm^{-1} (urea CO stretching); LRMS (ES$^-$): m/z: 345 [M−H]$^-$; HRMS (ES$^+$): m/z calcd for $C_{21}H_{23}N_4O$: 347.1866; found: 347.1870 (error = −0.90 ppm).

1,3-Di(1*H*-indol-7-yl)urea (2): 7-Aminoindole (0.234 g, 1.58 mmol) was dissolved in a mixture of dichloromethane (20 mL) and a saturated aqueous solution of NaHCO$_3$ (20 mL). Triphosgene (0.47 g, 1.58 mmol) was added in portions and the reaction mixture was left stirring under nitrogen atmosphere at room temperature overnight. The organic layer was washed with water, dried over MgSO$_4$, filtered and concentrated in vacuo. The pure product was obtained by recrystallisation from methanol. The product was isolated as a pale grey solid. Yield: 0.15 g, 50%; m.p. 252 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 6.44$ (t, $J = 2.64$ Hz, 2H), 6.94 (t, $J = 7.92$, 2H), 7.08 (d, $J = 7.14$ Hz, 2H), 7.31 (d, $J = 7.92$, 2H), 7.34 (t, $J = 2.64$ Hz, 2H), 8.63 (s, 2H; NH urea), 10.77 ppm (s, 2H; NH indole); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 101.4$ (CH), 113.7 (CH), 115.9 (CH), 119.0 (CH), 124.1 (C), 125.1 (CH), 129.0 (C), 129.4 (C), 153.6 ppm (CO); IR (film): $\tilde{\nu} = 3383$ (indole NH stretching), 3255 (urea NH stretching), 1620 cm^{-1} (urea CO stretching); LRMS (ES$^-$): m/z: 289 [M−H]$^-$; HRMS (ES$^+$): m/z calcd for $C_{17}H_{15}N_4O$: 291.1240; found: 291.1236 (error = 1.52 ppm).

1,3-Bis(2,3-dimethyl-1*H*-indol-7-yl)thiourea (3): 2,3-Dimethyl-7-aminoindole (0.20 g, 1.25 mmol) was dissolved in a mixture of dichloromethane (20 mL) and a saturated aqueous solution of NaHCO$_3$ (20 mL). Thio-

phosgene (0.09 mL, 1.25 mmol) was dissolved in dichloromethane (5 mL) and added dropwise. The reaction mixture was left stirring under argon atmosphere at room temperature overnight. The organic layer was washed with water, dried over $MgSO_4$ and the organic phase was taken to dryness to produce the isothiocyanate as a creamy solid, which was used immediately. A solution of the isothiocyanate (0.16 g, 0.77 mmol) in dichloromethane (20 mL) was then added dropwise to a solution of 2,3-dimethyl-7-aminoindole (0.12 g, 0.77 mmol) in dichloromethane (20 mL). The solution was heated at reflux overnight, then taken to dryness and purified by flash chromatography (dichloromethane:methanol 49:1 v/v). The desired product was isolated as a white solid. Yield: 80 mg, 29%; m.p. 205°C (decomp); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=2.15 (s, 6H; CH_3), 2.34 (s, 6H; CH_3), 6.93–6.86 (m, J=7.92 Hz, 4H), 7.25 (dd, ^1J=2.25 Hz, ^2J=6.39 Hz 2H), 9.26 (s, 2H; NH urea), 10.61 ppm (s, 2H; NH indole); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=8.5 (CH_3), 11.3 (CH_3), 105.6 (C), 115.8 (CH), 118.0 (CH), 118.5 (CH), 122.5 (C), 130.6 (C), 131.1 (C), 131.6 (C), 180.3 ppm (CS); IR (film): $\tilde{\nu}$=3396 (indole NH stretching), 3290 (urea NH stretching), 1152 (thiourea CS stretching); LRMS (ES$^-$): m/z: 361 [$M-$H]$^-$; HRMS (ES$^+$): m/z calcd for $C_{21}H_{23}N_4S$: 363.1638; found: 363.1633 (error=1.32 ppm).

1,3-Di(1*H*-indol-7-yl)thiourea (4): 7-Aminoindole (0.32 g, 2.39 mmol) was dissolved in a mixture of dichloromethane (20 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL). Thiophosgene (0.18 mL, 2.39 mmol) was dissolved in dichloromethane (5 mL) and added dropwise. The reaction mixture was left stirring under argon atmosphere at room temperature overnight. The organic layer was washed with water, dried over $MgSO_4$, and the organic phase taken to dryness. The oil obtained was dissolved in diethyl ether (20 mL) and the isothiocyanate obtained as a brown solid removed by filtration, which was used immediately. A solution of the isocyanate (0.33 g, 1.88 mmol) in dichloromethane (20 mL) was added dropwise to a solution of 7-aminoindole (0.25 g, 1.88 mmol) in dichloromethane (20 mL). The solution was heated at reflux overnight. A light brown solid was then removed by filtration from the solution and dried under reduced pressure. Yield: 480 mg, 83%; m.p. 231°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=6.47 (dd, ^1J=2.94 Hz, ^2J=1.83 Hz, 2H), 6.98 (t, J=7.68 Hz, 2H), 7.06 (d, J=6.93 Hz, 2H), 7.37 (t, J=2.94 Hz, 2H), 7.45 (d, J=7.32 Hz, 2H), 9.51 (s, 2H; NH urea), 11.04 ppm (s, 2H; NH indole); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=101.5 (CH), 118.4 (CH), 118.8 (CH), 119.2 (CH), 123.7 (C), 125.3 (CH), 129.3 (C), 132.0 (C), 180.7 ppm (CS); IR (film): $\tilde{\nu}$=3365 (indole NH stretching), 3300 (urea NH stretching), 1102 cm^{-1} (thiourea CS stretching); LRMS (ES$^+$): m/z: 307 [M+H]$^+$; HRMS (ES$^+$): m/z calcd for $C_{17}H_{15}N_4S$: 307.1013; found: 307.1012 (error=−0.45 ppm).

X-ray structure determinations: Data were collected on a Bruker Nonius Kappa CCD with a Mo rotating anode generator (λ=0.71073) employing phi and omega scans; standard procedures were followed. Lorentz and polarisation corrections were applied during data reduction with DENZO[22] and multi-scan absorption corrections were applied using SADABS.[23] Structures were solved and refined using the SHELX suite of programs.[24] Hydrogen atoms were identified in the difference map and then treated using a riding model, except those attached to nitrogen which were freely refined (with the exception 0126, where they were treated as riding on the parent atom).

*Crystal data for the benzoate complex of compound **1***: $C_{44}H_{63}N_5O_3$, 0.25×0.17×0.06 mm, M_r=709.99, T=120(2) K, monoclinic, space group $P2_1/c$, a=8.5824(3), b=19.9254(9), c=24.182(1) Å, β=95.659(3)°, V=4115.2(3) Å^3, ρ_{calcd}=1.146 g cm^{-3}, μ=0.072 mm^{-1}, min/max transmission 0.979/0.996, Z=4, reflections collected: 31851, independent reflections: 7193 (R_{int}=0.1307), $2\theta_{max}$=25.03°, parameters: 477, largest difference peak/hole: 0.996/−0.440 e Å^{-3}; final R indices [$I>2\sigma I$]: $R1$=0.1469, $wR2$=0.3562; R indices (all data): $R1$=0.2215, $wR2$=0.4147.

*Crystal data for the carbonate complex of compound **1***: $C_{59}H_{84}N_{10}O_5$, 0.4×0.25×0.04 mm, M_r=1013.36, T=120(2) K, triclinic, space group $P\bar{1}$, a=12.8866(8), b=15.5411(7), c=16.4858(10) Å, α=97.235(3), β=109.277(2), γ=108.363(3)°, V=2858.7(3) Å^3, ρ_{calcd}=1.177 g cm^{-3}, μ=0.076 mm^{-1}, min/max transmission: 0.960/0.997, Z=2, reflections collected: 44006, independent reflections: 10101 (R_{int}=0.1315), $2\theta_{max}$=25.02°, parameters: 737, largest difference peak/hole: 1.491/−0.690 e Å^{-3}; final R indices [$I>2\sigma I$]: $R1$=0.0948, $wR2$=0.2441; R indices (all data): $R1$=0.1753, $wR2$=0.2962. Note: One of the tetraethylammonium molecules was disordered and refined with two conformations by using geometric and thermal parameter restraints; however, there were still some extreme ellipsoids and large difference peaks in this area of the structure.

*Crystal data for the phosphate complex of compound **2***: $C_{102}H_{159}N_{15}O_{8.5}PS_{1.5}$, 0.20×0.20×0.20 mm, M_r=1810.5, T=120(2) K, hexagonal, space group $R\bar{3}$, a=24.0023(3), c=32.4801(6) Å, V=16205.2(4) Å^3, ρ_{calcd}=1.113 g cm^{-3}, μ=0.113 mm^{-1}, min/max transmission: 0.968/0.978, Z=6, reflections collected: 33495, independent reflections: 6352 (R_{int}=0.1035), $2\theta_{max}$=25.03°, parameters=417, largest difference peak/hole: 1.380/−0.683 e Å^{-3}; final R indices [$I>2\sigma I$]: $R1$=0.1057, $wR2$=0.2929; R indices (all data): $R1$=0.1285, $wR2$=0.3120. Note: The DMSO was modelled as half occupied and disordered 50/50 over two possible orientations. Its geometry and thermal parameters were restrained. The terminal atom of one tetrabutylammonium arm was modelled as disordered over two possible orientations and the occupancies constrained to total one. These two disorders and partial occupancy of the DMSO explain the apparent close contacts in the structure. The crystal was a non-merohedral twin, but attempts to treat the data as such were unsuccessful. The resulting effect on the intensities has caused some parameters to misbehave, and the R factors to be high.

*Crystal data for the chloride complex of compound **4***: $C_{33}H_{50}N_5ClS$, 0.20×0.20×0.05 mm, M_r=584.29, T=120(2) K, monoclinic, space group Cc, a=14.4760(2), b=14.0106(3), c=16.0360(3) Å, β=93.818(1)°, V=3245.16(10) Å^3, ρ_{calcd}=1.196 g cm^{-3}, μ=0.212 mm^{-1}, min/max transmission: 0.949/0.990, Z=4, reflections collected: 17419, independent reflections: 6742 (R_{int}=0.043), $2\theta_{max}$=27.48°, parameters=381, largest difference peak/hole: 0.208/−0.228 e Å^{-3}; final R indices [$I>2\sigma I$]: $R1$=0.0460, $wR2$=0.0887; R indices (all data): $R1$=0.0557, $wR2$=0.0941.

*Crystal data for the bicarbonate complex of compound **4***: $C_{26}H_{35}N_5O_3S$, 0.20×0.20×0.20 mm, M_r=497.65, T=120(2) K, monoclinic, space group $P2_1/n$, a=7.9556(2), b=16.0231(8), c=19.7617(8) Å, β=95.842(3)°, V=2506.01(17) Å^3, ρ_{calcd}=1.319 g cm^{-3}, μ=0.167 mm^{-1}, min/max transmission: 0.957/0.967, Z=4, reflections collected: 25403, independent reflections: 4423 (R_{int}=0.0679), $2\theta_{max}$=25.03°, parameters=337, largest difference peak/hole=0.430/−0.372 e Å^{-3}; final R indices [$I>2\sigma I$]: $R1$=0.0581, $wR2$=0.1377; R indices (all data): $R1$=0.0822, $wR2$=0.1540. Note: Due to the disorder described above the hydrogen atom of the bicarbonate was not located and it was not included in the refinement.

CCDC-694685 (phosphate complex of **2**), -694686 (benzoate complex of **1**), -694687 (bicarbonate complex of **4**), -694688 (Cl complex of **4**), and -694689 (carbonate complex of **1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Acknowledgements

We would like to thank the EPSRC for a DTA studentship (J.R.H.) and for access to the crystallographic facilities at the University of Southampton. C.C. would like to thank Regione Sardegna for a Master&Back grant.

[1] a) P. A. Gale, S. E. García-Garrido, J. Garric, *Chem. Soc. Rev.* **2008**, *37*, 151–190; b) P. Prados, R. Quesada, *Supramol. Chem.* **2008**, *20*, 201–216; c) G. W. Bates, P. A. Gale; M. E. Light, *CrystEngComm* **2006**, *8*, 300–302, *Struct. Bonding* **2008**, *129*, 1–44; d) J. L. Sessler, P. A. Gale, W. S. Cho, *Anion Receptor Chemistry, Monographs in Supramolecular Chemistry* (Ed.: J. F. Stoddart) Royal Society of Chemistry, Cambridge, **2006**; e) P. A. Gale, R. Quesada, *Coord. Chem. Rev.* **2006**, *250*, 3291–3244; f) P. A. Gale, *Acc. Chem. Res.* **2006**, *39*, 465–475; g) K. Bowman-James, *Acc. Chem. Res.* **2005**, *38*, 671–678; h) P. A. Gale, *Chem. Commun.* **2005**, 3761–3772; i) P. A. Gale, *Coord. Chem. Rev.* **2003**, *240*, 191–221; j) P. D. Beer, P. A.

Gale, *Angew. Chem.* **2001**, *113*, 502–532; *Angew. Chem. Int. Ed.* **2001**, *40*, 486–516; k) P. A. Gale, *Coord. Chem. Rev.* **2001**, *213*, 79–128; l) F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609–1646.

[2] For an overview see: a) P. A. Gale, *Chem. Commun.* **2008**, DOI:10.1039/B809508F; for key papers see: b) P. Piatek, V. M. Lynch, J. L. Sessler, *J. Am. Chem. Soc.* **2004**, *126*, 16073–16076; c) M. J. Chmielewski, M. Charon, J. Jurczak, *Org. Lett.* **2004**, *6*, 3501–3504; d) J. O. Yu, C. S. Browning, D. H. Farrar, *Chem. Commun.* **2008**, 1020–1022; e) F. M. Pfeffer, K. F. Lim, K. J. Sedgwick, *Org. Biomol. Chem.* **2007**, *5*, 1795–1799; f) K.-J. Chang, D. Moon, M. S. Lah, K. S. Jeong, *Angew. Chem.* **2005**, *117*, 8140–8143; *Angew. Chem. Int. Ed.* **2005**, *44*, 7926–7929; g) J.-m. Suk, M. K. Chae, N.-K. Kim, U.-l Kim, K.-S. Jeong, *Pure Appl. Chem.* **2008**, *80*, 599–608; h) D. Curiel, A. Cowley, P. D. Beer, *Chem. Commun.* **2005**, 236–238; i) M. J. Chmielewski, L. Zhao, A. Brown, D. Curiel, M. R. Sambrook, A. L. Thompson, S. M. Santos, V. Felix, J. J. Davis, P. D. Beer, *Chem. Commun.* **2008**, 3154–3156.

[3] F. G. Bordwell, G. E. Drucker, H. E. Fried, *J. Org. Chem.* **1981**, *46*, 632–635.

[4] K. H. G. Verschueren, F. Seljee, H. J. Rozeboom, K. H. Kalk, B. W. Dijkstra, *Nature* **1993**, *363*, 693–698.

[5] J. J. He, F. A. Quiocho, *Science* **1991**, *251*, 1479–1481.

[6] a) P. A. Gale, M. B. Hursthouse, M. E. Light, J. L. Sessler, C. N. Warriner, R. Zimmerman, *Tetrahedron Lett.* **2001**, *42*, 6759–6762; b) P. A. Gale, S. Camiolo, C. P. Chapman, M. E. Light, M. B. Hursthouse, *Tetrahedron Lett.* **2001**, *42*, 5095–5097; c) P. A. Gale, M. E. Light, B. McNally, K. Navakhun, K. E. Sliwinski, B. D. Smith, *Chem. Commun.* **2005**, 3773–3775; d) S. J. Brooks, P. A. Gale, M. E. Light, *Chem. Commun.* **2005**, 4696–4698; e) I. El Drubi Vega, P. A. Gale, M. E. Light; S. J. Loeb, *Chem. Commun.* **2005**, 4913–4915; S. J. Loeb, *Chem. Commun.* **2005**, 4913–4915; f) L. S. Evans, P. A. Gale, M. E. Light; R. Quesada, *Chem. Commun.* **2006**, 965–967; R. Quesada, *Chem. Commun.* **2006**, 965–967; g) G. W. Bates, P. A. Gale; M. E. Light, *CrystEngComm* **2006**, *8*, 300–302; h) S. J. Brooks, P. A. Gale, M. E. Light, *Chem. Commun.* **2006**, 4344–4346; i) S. E. García-Garrido, C. Caltagirone, M. E. Light, P. A. Gale, *Chem. Commun.* **2007**, 1450–1452; j) C. Caltagirone, G. W. Bates, P. A. Gale, M. E. Light, *Chem. Commun.* **2008**, 61–63.

[7] G. W. Bates, P. A. Gale, M. E. Light, *Chem. Commun.* **2007**, 2121–2123.

[8] C. Caltagirone, P. A. Gale, J. R. Hiscock, M. B. Hursthouse, M. E. Light, G. J. Tizzard, *Supramolecular Chem.* **2009**, in press.

[9] C. W. Bates, Triyanti, M. E. Light, M. Albrecht, P. A. Gale, *J. Org. Chem.* **2007**, *72*, 8921–8927.

[10] Aspects of this work have been communicated see: C. Caltagirone, P. A. Gale, J. R. Hiscock, S. J. Brooks, M. B. Hursthouse, M. E. Light, *Chem. Commun.* **2008**, 3007–3009.

[11] M. J. Hynes, *J. Chem. Soc. Dalton Trans.* **1993**, 311–312.

[12] P. Job, *Justus Liebigs Ann. Chem.* **1928**, *9*, 113–203.

[13] D. E. Gross, F. P. Schmidtchen, W. Antonius, P. A. Gale, V. M. Lynch, J. L. Sessler, *Chem. Eur. J.* **2008**, *14*, 7822–7827.

[14] For examples of carbonate bound to macrocyclic hydrogen donor receptors,9 see: a) S. J. Brooks, S. E. García-Garrido, M. E. Light, P. A. Cole, P. A. Gale, *Chem. Eur. J.* **2007**, *13*, 3320–3329; b) R. Custelcean, L. H. Delmau, B. A. Moyer, J. L. Sessler, W.-S. Cho, D. Gross, G. W. Bates, S. J. Brooks, M. E. Light, P. A. Gale, *Angew. Chem.* **2005**, *117*, 2593–2598; *Angew. Chem. Int. Ed.* **2005**, *44*, 2537–2542.

[15] a) R. Custelcean, P. Remy, P. V. Bonnesen, D.-e. Jiang, B. A. Moyer, *Angew. Chem.* **2008**, *120*, 1892–1896; *Angew. Chem. Int. Ed.* **2008**, *47*, 1866–1870; see also b) B. Wu, J. Liang, J. Yang, C. Jia, X-J. Yang, H. Zhang, N. Tang, C. Janiak, *Chem. Commun.* **2008**, 1762–1764. For other crystallographically characterised sulfate complexes see: c) S. O. Kang, M. A. Hossain, D. Powell, K. Bowman-James, *Chem. Commun.* **2005**, 328–330; d) R. Custelcean, V. Sellin, B. A. Moyer, *Chem. Commun.* **2007**, 1541–1543; e) C. R. Bondy, P. A. Gale, S. J. Loeb, *J. Am. Chem. Soc.* **2004**, *126*, 5030–5031.

[16] H. Luecke, F. A. Quiocho, *Nature* **1990**, *347*, 402–406.

[17] E. A. Katayev, J. L. Sessler, V. N. Khrustalev, Y. A. Ustynyuk, *J. Org. Chem.* **2007**, *72*, 7244–7252.

[18] S. J. Brooks, P. R. Edwards, P. A. Gale, M. E. Light, *New J. Chem.* **2006**, *30*, 65–70.

[19] A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.

[20] a) Q. Li, W. H. Yip, T. C. W. Mak, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1995**, *23*, 233–244; b) M. Boiocchi, L. Del Boca, D. Esteban Gomez, L. Fabbrizzi, M. Licchelli, *J. Am. Chem. Soc.* **2004**, *126*, 16507–16514; c) Q. Li, T. C. W. Mak, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *20*, 73–88; d) E. R. Perez, R. H. A. Santos, M. T. P. Gambardella, L. G. M. de Macedo, U. P. Rodrigues-Filho, J.-C. Launay, D. W. Franco, *J. Org. Chem.* **2004**, *69*, 8005–8011; e) T. C. W. Mak, F. Xue, *J. Am. Chem. Soc.* **2000**, *122*, 9860–9861; f) T. Gunnlaugsson, P. E. Kruger, P. Jensen, F. M. Pfeffer, G. M. Hussey, *Tetrahedron Lett.* **2003**, *44*, 8909–8913.

[21] a) P. A. Gale, J. Garric, M. E. Light, B. A. McNally, B. D. Smith, *Chem. Commun.* **2007**, 1736–1738; b) P. V. Santacroce, J. T. Davis, M. E. Light, P. A. Gale, J. C. Iglesias-Sánchez, P. Prados, R. Quesada, *J. Am. Chem. Soc.* **2007**, *129*, 1886–1887; c) M. G. Fisher, P. A. Gale, M. E. Light, *New J. Chem.* **2007**, *31*, 1583–1584.

[22] Z. Otwinowski , W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326.

[23] G. M. Sheldrick, SADABS—Bruker Nonius area detector scaling and absorption correctionotherV2.10.

[24] SHELX97: Programs for Crystal Structure Analysis (Release 97-2). G. M. Sheldrick, Institüt für Anorganische Chemie der Universität, Göttingen, (Germany) **1998**.

Received: August 7, 2008
Published online: October 15, 2008

