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Anion–Anion Proton Transfer in Hydrogen Bonded Complexes

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Dedicated to the 150th Anniversary of Japan–UK Diplomatic Relations

Abstract: Complexation of dihydrogen phosphate by an anion receptor containing six hydrogen bond donor groups has been shown to reduce the pK_a of the bound anionic species to such an extent that addition of further aliquots of dihydrogen phosphate result in deprotonation of the bound species with the resultant formation of a monohydrogen phosphate receptor complex. X-ray crystallographic studies confirm monohydrogen phosphate complex formation in the solid state. In this way, this study explains the formation of complexes with unusual stoichiometries when investigating the binding of dihydrogenphosphate anion to hydrogen-bonding receptors.

Keywords: anions · crystallography · hydrogen bonds · NMR spectroscopy · supramolecular chemistry

Introduction

Proton transfer processes from acidic hydrogen bond donor receptors to basic anions, such as fluoride and dihydrogen phosphate, have been shown to compete with anion complexation processes in a variety of hydrogen bond donor systems by our group,[1] Gunnlaugsson and co-workers,[2] Fabbrizzi and co-workers,[3] and others.[4] We recently reported that 1,3-diindolylureas form particularly stable complexes with oxo-anions in [D_6]DMSO/water mixtures.[5] This work led from an initial collaborative project with Albrecht and Triyanti on 2,7-disubstituted indoles containing urea substituents in the 7-position and amide substituents in the 2-position that were found to bind oxo-anions strongly.[6] Proton NMR titration studies on these compounds in [D_6]DMSO/0.5% water showed that the indole and urea groups were participating in hydrogen bonding interactions with the bound oxo-anions but that the amide group in the 2-position did not interact significantly with the guest species. This was also observed in X-ray crystal structures of the anion complexes of these systems. The design of the second generation diindolylurea compounds built on these findings by removing the amide group in the 2-position and adding an extra indole moiety to produce a symmetrical receptor containing four hydrogen bond donor groups. These compounds were found to be selective receptors for dihydrogen phosphate anions in [D_6]DMSO/water mixtures over carboxylates and chloride. Single crystal X-ray diffraction of crystals obtained from a [D_6]DMSO/water solution of the receptor in the presence of excess tetrabutylammonium dihydrogenphosphate showed that three of these receptors could assemble around a single phosphate PO_4^{3-} anion in the solid state binding it by means of twelve hydrogen bonds.[5b] Similarly crystallizations with tetraethylammonium bicarbonate and a diindolylurea resulted in the crystallization of deprotonated carbonate bound by two diindolylureas through eight hydrogen bonds. Thus whilst 1:1 complexation was apparently observed in solution, in the case of dihydrogen phosphate and bicarbonate, proton transfer was taking place at some point in the crystallization process from the bound anion to a more basic species. It occurred to us that the receptors in this case may be reducing the pK_a of the bound anionic species (by forming 12 and 8 hydrogen bonds to phosphate and carbonate, respectively) resulting in proton transfer from the bound anion to further added aliquots of the same anion free in solution. Thus this is a related process to those observed previously,[1–4] but in this case,

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it is the bound anion that is deprotonated by the free anion in solution, not the receptor. Multiple hydrogen bonds in these complexes presumably act in concert to lower the pK_a. Hence we designed new receptors containing 6 rather than 4 NH hydrogen bond donor groups (by attaching amides to the 2-positions of a diindolylurea) in order to see whether this deprotonation process could be observed directly in solution.

Results and Discussion

Compounds **1–4** were synthesized by a simple three-step synthesis (Figure 1). Commercially available 7-nitroindole-2-carboxylic acid was coupled to an amine (benzylamine or

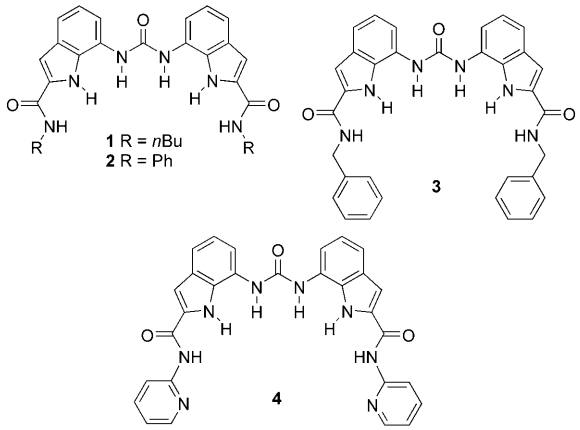
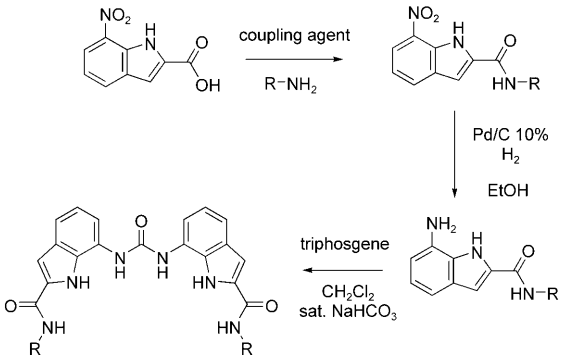


Figure 1. Chemical structures for **1–4**.

pyridin-2-ylmethanamine) using CDI to afford 2-carboxamido-7-nitroindole derivatives in 90 and 80% yields, respectively. Coupling with *n*-butylamine or aniline was performed using our previously published procedures.[6] The nitro-derivatives were reduced using H_2/Pd/C 10% affording the amines which were coupled with triphosgene in a two phase CH_2Cl_2/sat $NaHCO_{3(aq)}$ mixture to afford the urea derivatives **1–4** in 49, 30, 56, and 55% yields, respectively (Scheme 1).

Apparent stability constants of compounds **1–4** with a range of anionic guests were determined by ^{1}H NMR titration techniques in [D_6]DMSO/0.5% water or [D_6]DMSO/10% water. The results are shown in Tables 1–4. The stability constants for carboxylates generally show good agreement between those determined by the shift of the urea NH protons and those determined by the shift of the indole CH protons in the 6-position of the indole ring (the indole NH broadens upon addition of anions in many cases). The receptors were found to have a low affinity for chloride but to strongly bind the oxo-anions studied. Whilst the binding isotherms for carboxylates fit to a 1:1 binding model, the binding of dihydrogen phosphate is more complex and in many cases could not be adequately fitted (possibly indicative of a



Scheme 1. Synthesis of receptors **1–4**.

Table 1. Apparent stability constants determined by ^{1}H NMR titration techniques with compound **1** in [D_6]DMSO/water mixtures at 298 K following urea NH and indole CH (6-position) groups. Errors < 15% except where noted.

Anion[a]	CH (0.5% water)	Urea NH (0.5% water)	CH (10% water)	Urea NH (10% water)
Cl^-	166	22	n.d.	n.d.
BzO^-	$>10^4$	$>10^4$	1020	1100
AcO^-	$>10^4$	$>10^4$	462	–[b]
$H_2PO_4^-$	–[c]	–[c]	$>10^4$	2310
HCO_3^-	$>10^4$	2468	809	395

[a] Anions added as tetrabutylammonium salts except bicarbonate which was added as the tetraethylammonium salt. [b] NMR spectrum indicates conformational changes during the titration (see the Supporting Information). [c] Fast and slow exchange. n.d. = not determined.

Table 2. Apparent stability constants determined by ^{1}H NMR titration techniques with compound **2** in [D_6]DMSO/water mixtures at 298 K following urea NH and indole CH (6-position) groups. Errors < 15% except where noted.

Anion[a]	CH (0.5% water)	Urea NH (0.5% water)	CH (10% water)	Urea NH (10% water)
Cl^-	79	< 10	n.d.	n.d.
BzO^-	$>10^4$	–[d]	639	481
AcO^-	$>10^4$	8460	–[c]	1422
$H_2PO_4^-$	107	–[d]	–[b]	–[b]
HCO_3^-	2250 (±17%)	–[d]	728	–[d]

[a] Anions added as tetrabutylammonium salts except bicarbonate which was added as the tetraethylammonium salt. [b] Isotherm could not be fitted to a 1:1 or 1:2 binding model. [c] A shoulder appears a urea NH resonance possibly indicating the formation of an unsymmetrical complex. [d] Peak broadening prevented a stability constant from being obtained in these cases. n.d. = not determined.

deprotonation process occurring). In the case of compound **1**, the NMR titration with dihydrogen phosphate shows both fast and slow exchange processes (vide infra). Examination of the shifts of the urea NH, amide NH, and indole C6 CH protons show that across the series of compounds, upon addition of carboxylates, the amide NH and indole CHs shift downfield, and in 0.5% water solution, reach a plateau at one equivalent of anion indicating strong binding. However, the amide NH groups either do not shift at all or shift downfield continuously and do not reach a plateau (see Figure 2 for compound **1** and benzoate). These results are evidence

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Table 3. Apparent stability constants determined by ^{1}H NMR titration techniques with compound **3** in [D$_6$]DMSO/water mixtures at 298 K following urea NH and indole CH (6-position) groups. Errors $<15\%$ except where noted.

Anion[a]	CH (0.5% water)	Urea NH (0.5% water)	CH (10% water)	Urea NH (10% water)
Cl^-	–[b]	–[d]	n.d.	n.d.
BzO^-	1490	1580	303	284
AcO^-	$>10^4$	$>10^4$	278	293
$H_2PO_4^-$	–[c]	–[d]	2960	812
HCO_3^-	1420	–[d]	319	–[d]

[a] Anions added as tetrabutylammonium salts except bicarbonate which was added as the tetraethylammonium salt. [b] No shift. [c] Isotherm could not be fitted to a 1:1 or 1:2 binding model. [d] Peak broadening. n.d. = not determined.

Table 4. Apparent stability constants determined by ^{1}H NMR titration techniques with compound **4** in [D$_6$]DMSO/water mixtures at 298 K following urea NH and indole CH (6-position) groups. Errors $<15\%$ except where noted.

Anion[a]	CH (0.5% water)	Urea NH (0.5% water)	CH (10% water)	Urea NH (10% water)
Cl^-	–[b]	<10	n.d.	n.d.
BzO^-	2430 ($\pm 19\%$)	4760	298	304
AcO^-	$>10^4$	$>10^4$	485	544
$H_2PO_4^-$	–[c]	–[d]	256	245
HCO_3^-	7660	–[d]	149	–[d]

[a] Anions added as tetrabutylammonium salts except bicarbonate which was added as the tetraethylammonium salt. [b] No shift. [c] Isotherm could not be fitted to a 1:1 or 1:2 binding model. [d] Peak broadening. n.d. = not determined.

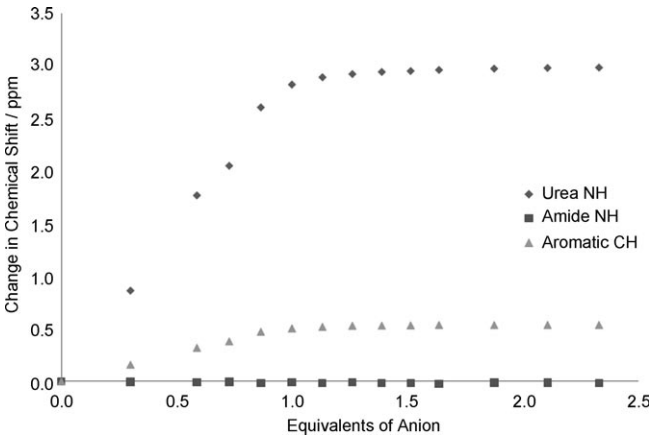

Figure 2. ^{1}H NMR titration of compound **1** with tetrabutylammonium benzoate following amide NH, urea NH, and the aromatic CH in the 6-position of the indole ring.

that supports the hypothesis that carboxylates bind strongly to the receptors, as shown in Figure 3c. The amide NH groups do not interact with the bound carboxylate. The continuous downfield shift of the amide NH group in some cases may be a result of the amide NH pointing out of the binding cavity of the receptor and weakly binding further aliquots of carboxylates weakly through a single hydrogen

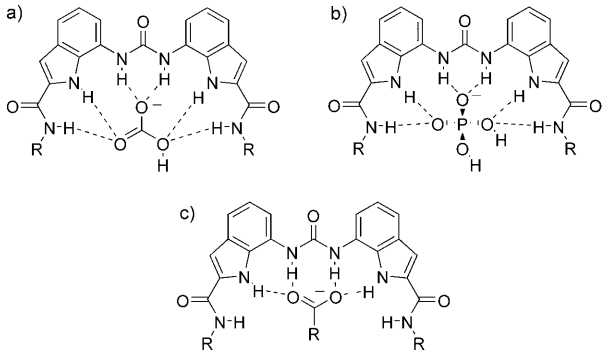

Figure 3. Proposed binding modes of bicarbonate, dihydrogen phosphate, and a carboxylate with a bis-amide functionalized diindolylurea.

bond as was observed with the 2,7-disubstituted indoles studied previously.[6]

However, in contradistinction to the results with carboxylates, addition of bicarbonate or dihydrogen phosphate caused downfield shifts of the amide NH groups (see Figure 4 for compound **1** and bicarbonate) in addition to the

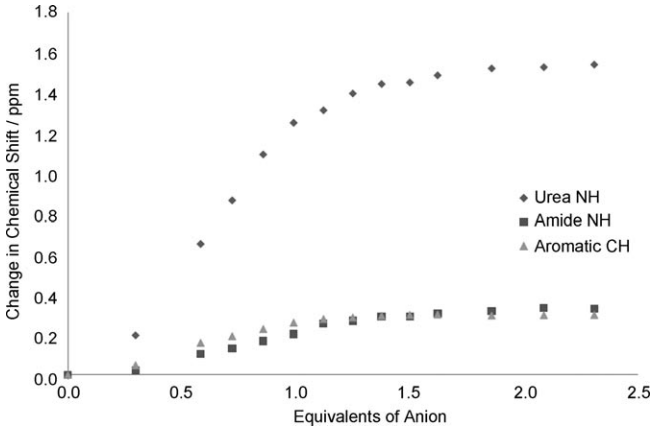

Figure 4. ^{1}H NMR titration of compound **1** with tetraethylammonium bicarbonate following amide NH, urea NH, and the aromatic CH in the 6-position of the indole ring.

urea NH, C6 indole CH groups. These results are evidence to support the binding modes proposed for bicarbonate and dihydrogen phosphate shown in Figure 3a and b, in that these oxo-anions can bind to all the NH groups in the receptor. However, the extra hydrogen bonding interaction to bicarbonate versus carboxylates is not reflected in a higher affinity of these receptors for HCO_3^-.

We further investigated the apparent slow exchange process observed upon addition of dihydrogen phosphate to receptor **1** in [D$_6$]DMSO/0.5% water. We observed shifts of the amide NH groups up to 1.0 equivalent of added anion, followed by the emergence of new peaks in the ^{1}H NMR spectrum as further aliquots of dihydrogen phosphate were

added. One possible explanation for this behavior is the formation of a 1:1 complex at low anion concentrations which is fast on the NMR timescale and at higher concentrations of dihydrogen phosphate, the formation of a 2:1 anion/receptor complex which is slow on the NMR timescale. However, we noted that the new proton resonances which appeared in the ^{1}H NMR spectrum were shifted downfield by a considerable margin to those present in the presumed 1:1 complex (in one case by over 2 ppm). This led us to consider other possible processes and in particular deprotonation of the bound anion. Compound **1** contains six hydrogen bond donors and thus potentially has a greater ability to modulate the pK_a of a bound anionic guest species than simple diindolylureas if all six hydrogen bond donors complex an anionic guest. Consequently, we considered whether the new peaks that appear after addition of 1.0 equivalent of $H_2PO_4^-$ could arise from a proton transfer between the bound dihydrogen phosphate and the more basic free dihydrogen phosphate, resulting in the formation of a monohydrogen phosphate complex in solution. The double negative charge on this anion would result in the formation of a stronger complex and in a greater downfield shift of the NH groups as compared to the dihydrogen phosphate complex. In order to confirm that the new peaks corresponded to the HPO_4^{2-} complex, tetrabutylammonium hydroxide was titrated into a solution of the receptor in the presence of 1.4 equivalents of dihydrogen phosphate (Figure 5). The new peaks were

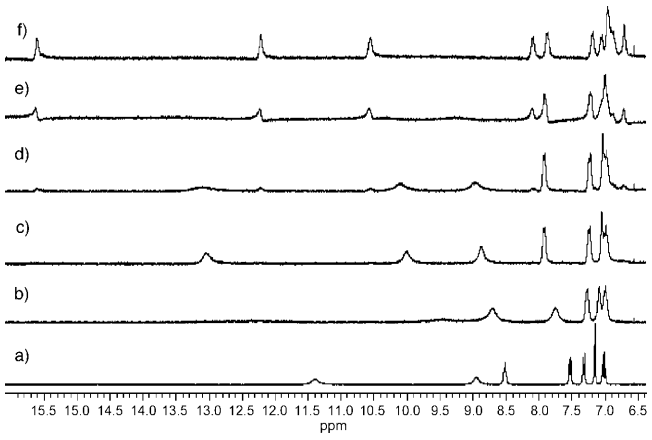

Figure 5. ^{1}H NMR titration with compound **1** in [D_6]DMSO/0.5% water. a) Free receptor; b) 0.6 equivalents TBA H_2PO_4; c) 1.0 equivalent TBA H_2PO_4; d) 1.4 equivalents TBA H_2PO_4; e) 1.4 equivalents TBA H_2PO_4+0.7 equivalents TBA OH; f) 1.4 equivalents TBA H_2PO_4+1.4 equivalents TBA OH.

found to increase in intensity, a finding consistent with the formation of a greater proportion of the monohydrogen phosphate complex in solution. This was also observed in [D_6]DMSO/10% water. A model experiment conducted in the absence of dihydrogen phosphate did not result in the formation of these NH resonances (see the Supporting Information). New peaks were not observed upon addition of dihydrogen phosphate to solutions of compounds **2**, **3**, or **4**. It is possible that steric interactions in these complexes reduce the degree of stabilization of monohydrogen phosphate as compared to that in the complex with receptor **1**. However, the fact that either broadening of the NH resonances upon addition of dihydrogen phosphate or a binding isotherm that could not be fitted to either 1:1 or 2:1 anion/receptor binding models, in these cases, suggests that proton transfer processes may also be occurring but that the equilibrium between the mono- and dihydrogen phosphate complexes is fast on the NMR timescale. For example, a titration with dihydrogen phosphate followed by addition of hydroxide with compound **4** in [D_6]DMSO/10% water shows that hydroxide causes further downfield shifts of the NH proton resonances rather than the evolution of new resonances (see the Supporting Information). Discrepancies between stability constants determined using 1:1 binding models following different proton resonances in the cases of dihydrogen phosphate and bicarbonate complexation may be a result of proton transfer processes occurring in these systems, in addition to anion complexation.

Further evidence for proton transfer comes from solid-state single crystal X-ray diffraction studies. Crystals of receptor **2** were grown by slow evaporation of a DMSO solution of the receptor in the presence of excess tetrabutylammonium dihydrogen phosphate. Interestingly, the receptor crystallized as the hydrogen phosphate (HPO_4^{2-}) complex as shown in Figure 6 with three of the phosphate oxygen atoms hydrogen bonded to the six NH groups with bonds N1···O5 2.734(5) Å, N2···O5 2.668(5) Å, N3···O7 2.804(4) Å, N4···O7 2.842(5) Å, N5···O6 2.660(5), and N6···O6 2.763(4) Å see Scheme 2.

Conclusions

Compounds **1**–**4** form stable complexes with oxo-anions such as carboxylates, but with dihydrogen phosphate and compound **1**, a proton transfer process takes place between bound and free dihydrogen phosphate in solution resulting in the formation of a monohydrogen phosphate complex that is slow on the NMR timescale. Crystallization of compound **2** with tetrabutylammonium dihydrogen phosphate results in the formation of the monohydrogen phosphate complex of the receptor with the anion bound by six NH···O hydrogen bonds. Presumably the fact that these receptors are able to form multiple hydrogen bonding interactions with the bound guest reduces the pK_a of the oxo-anion resulting in proton transfer to the unbound anion in solution. We propose that deprotonation of protonated oxo-anions bound by multiple hydrogen bonds by further addition of the same anion to the complex in solution may be a general process that cannot easily be observed using ^{1}H NMR titration techniques unless there is slow exchange between the different protonation states of the bound guest as we observed with compound **1** and $H_2PO_4^-$/HPO_4^{2-}. We found that dihydrogen phosphate binding often cannot be easily

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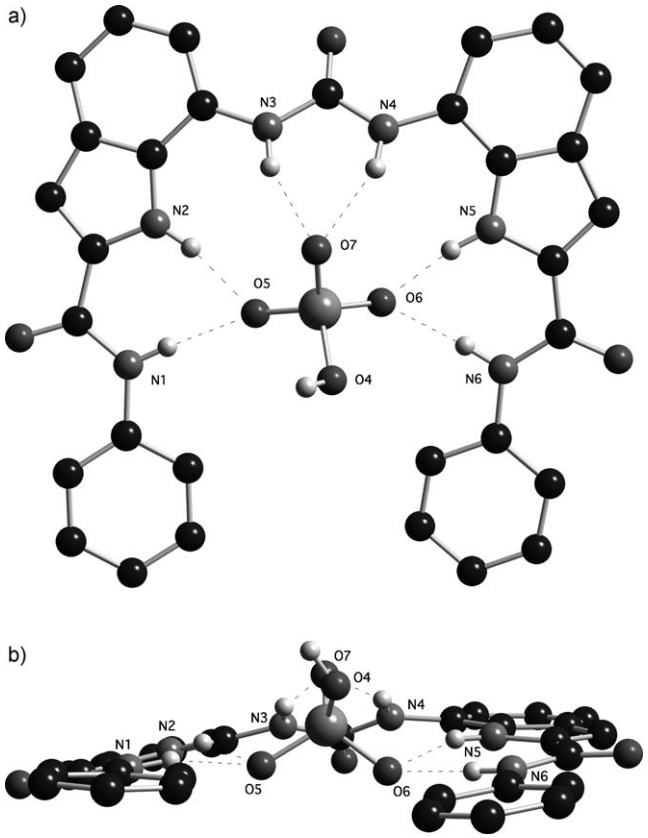
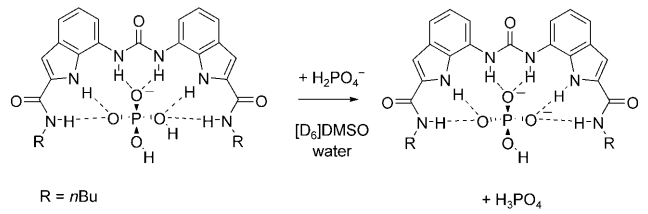


Figure 6. Top and side views of the hydrogen phosphate complex of compound **2**. Tetrabutylammonium counter cations, water and non-acidic hydrogen atoms have been omitted for clarity.



Scheme 2. Addition of dihydrogen phosphate to the dihydrogen phosphate complex of receptor **1** causes deprotonation of the bound anion and the formation of a monohydrogen phosphate complex.

fitted to a 1:1 binding model and it may be that similar proton transfer processes occur in other dihydrogen phosphate–receptor complexation processes.[8] Hence care must be taken when interpreting stability constant data with this class of common oxo-anionic species in organic solution. Additionally, the demonstration that non-covalent binding can modify the acidity/basicity of an anion might also indicate that the anion's reactivity can change significantly on binding—this may be useful in the development of new catalysts (to enhance the reactivity of both anionic and neutral substrates based on phosphates) or other technological processes.

Experimental Section

General

All reactions were performed using oven-dried glassware under slight positive pressure of nitrogen/argon (as specified). ^{1}H NMR (300 MHz) and ^{13}C{^{1}H} NMR (75 MHz) spectra were determined on a Bruker AV300 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C{^{1}H} NMR (100 MHz) spectra were determined on a Bruker AV400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm), calibrated to the solvent peak set. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet. Chemical shifts for ^{13}C{^{1}H} NMR are reported in ppm, relative to the central line of a septet at $\delta = 39.52$ ppm for deuterio-dimethylsulfoxide. Infrared (IR) spectra were recorded on a Matterson Satellite (ATR). FTIR are reported in wavenumbers (cm^{-1}). All solvents and starting materials were purchased from chemical sources where available. NMR titrations were performed by adding aliquots of the putative anionic guest (as the TBA or TEA) salt (0.15 M) in a solution of the receptor (0.01 M) in [D$_6$]DMSO to a solution of the receptor (0.01 M).

^{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 salt, or TEA salt in the case of bicarbonate) salt (0.15 M) in a solution of the receptor (0.01 M) in [D$_6$]DMSO to a solution of the receptor (0.01 M). The titration data was plotted as Δppm versus concentration of guest and fitted to a binding model using the EQNMR computer program.[7]

***N*-benzyl-7-nitro-1*H*-indole-2-carboxamide**: 7-nitroindole-2-carboxylic acid (0.410 g, 1.99 mM) and CDI (0.405 g, 2.50 mM) were dissolved in chloroform (50 mL). The reaction mixture was heated at reflux for 3 h under argon. Benzylamine (0.10 mL, 1.90 mM) was dissolved in dry chloroform (20 mL) and then added dropwise to the stirring reaction mixture. The reaction mixture was heated at reflux for 72 h under argon. The reaction mixture was diluted with DCM (30 mL), washed with water (2×15 mL), and then dried with magnesium sulphate. The reaction mixture was reduced in vacuo and then purified by column chromatography (5% ethyl acetate/DCM) to yield a yellow solid (0.511 g). Yield: 90%; m.p.: 173 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 4.55$ (d, $J = 5.6$ Hz, 2H), 7.24–7.40 (m, Ar CH, 6H), 7.44 (s, 1H), 8.22 (t, $J = 8.4$ Hz, 2H), 9.50 (t, $J = 5.7$ Hz, NH, 1H), 11.38 ppm (s, NH, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 42.5$ (CH$_2$), 106.6 (ArCH), 119.9 (ArCH), 121.1 (ArCH), 127.0 (ArCH), 127.5 (ArCH), 128.4 (Ar CH), 128.8 (ArC), 130.6 (ArCH), 130.9 (ArC), 133.1 (ArC), 134.5 (ArC), 139.0 (ArC), 159.5 ppm (CO); IR (film): $\tilde{\nu} = 3457$, 3380, 3085, 2963, 1650 cm^{-1}; LRMS (ES$^-$): *m*/*z*: 294.2 [*M*−H]$^-$; HRMS (ES$^+$): *m*/*z*: exp: 318.0855 [*M*+Na]$^+$; calcd: 318.0848 [*M*+Na]$^+$

***N*-(2-pyridin-2-yl)-7-nitro-1*H*-indole-2-carboxamide**: 7-nitroindole-2-carboxylic acid (0.200 g, 0.970 mM) was dissolved in dry chloroform. CDI (0.193 g, 1.19 mM) was added to the stirring reaction mixture. The reaction mixture was heated at reflux for 2 h under argon. A solution of 2-aminopyridine (0.092 g, 0.967 mM) in chloroform (5 mL) was added dropwise to the stirring reaction mixture. The reaction mixture was heated at reflux for 22 h. The reaction mixture was washed with water (2×15 mL) and then dried with magnesium sulphate. The reaction mixture was then reduced in vacuo and purified by column chromatography (10% ethyl acetate/DCM) to yield a yellow solid. Yield: 80%; m.p.: 194 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 7.20$ (ddd, $J = 7.3$ Hz, 4.74 Hz, 0.92 Hz, 1H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.71 (s, 1H), 7.88 (dt, $J = 7.3$ Hz, 1.8 Hz, 1H), 8.20–8.31 (m, 3H), 8.43 (dd, $J = 2.4$ Hz, 1.1 Hz), 11.57 (s, NH, 1H), 11.97 ppm (s, NH, 1H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 109.2$ (ArCH), 114.7 (Ar CH), 120.0 (2 ArCH), 121.7 (ArCH), 129.3 (ArC), 130.7 (ArCH), 130.8 (ArC), 133.2 (ArC), 134.1 (ArC), 138.3 (ArCH), 148.0 (ArCH), 151.9 (ArC), 158.4 ppm (CO); IR (film): $\tilde{\nu} = 3382$, 3345, 1671 cm^{-1}; LRMS (ES$^-$): *m*/*z*: 281.2 [*M*−H]$^-$; HRMS (ES$^+$): *m*/*z*: exp: 283.0831 [*M*+H]$^+$ calcd: 283.0831 [*M*+H]$^+$

7,7′-carbonylbis(azanediyl)bis(*N*-butyl-1*H*-indole-2-carboxamide) (1): The synthesis of 7-nitro-*N*-butyl-1*H*-indole-2-carboxamide is taken from

a method described by Bates et al.[7] *N*-butyl-7-nitro-1*H*-indole-2-carboxamide (0.25 g, 0.96 mM) and a Pd/C 10% catalyst (0.03 g) were suspended in ethanol (25 mL). The flask was evacuated and the mixture placed under a hydrogen atmosphere and stirred vigorously for 3 h. After this time the palladium catalyst was removed by filtration through celite and the filtrate taken to dryness and placed under reduced pressure. This gave a white solid. Assumed yield: 100%. The white solid was dissolved in a two-phase solution of sat. $NaHCO_3$ (20 mL) and DCM (20 mL). This solution was stirred vigorously under nitrogen at room temperature and triphosgene (0.30 g, 1.00 mM) added in two equal aliquots. The solution was allowed to stir overnight. The two-phase solution was then filtered and the white solid was sonicated in water (250 mL) for 30 mins. A white solid was then collected by filtration and washed with DCM (20 mL) and diethyl ether (20 mL). Yield: 49%; m.p.: 138°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=0.92 (t, J=7.3 Hz, 3H), 1.36 (dd, J_1=6.93 Hz, J_2=13.5 Hz, 2H), 1.54 (t, J=7.0 Hz, 2H), 3.33 (m, 2H), 7.01 (t, J=7.7 Hz, 1H), 7.16 (s, 1H), 7.32 (d, J=8.0 Hz, 1H), 7.51 (d, J=7.3 Hz, 2H), 8.51 (s, NH, 1H), 8.88 (s, NH, 1H), 11.37 ppm (s, NH, 1H); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): δ=13.7 (CH_3), 19.6 (CH_2), 31.3 (CH_2), 38.4 (CH_2), 102.8 (ArCH), 113.7 (ArCH), 116.0 (ArCH), 120.2 (ArCH), 124.9 (ArC), 128.0 (ArC), 128.6 (ArC), 131.7 (ArC), 153.1 (CO), 160.8 ppm (CO); IR (film): $\tilde{\nu}$=3340, 3270, 1640, 1560 cm^{-1}; LRMS (ES$^-$): m/z: 487.4 [M−H]$^-$; HRMS (ES$^+$): m/z: exp: 489.2604 [M+H]$^+$; calcd: 489.2609 [M+H]$^+$.

7,7′-carbonylbis(azanediyl)bis(*N*-phenyl-1*H*-indole-2-carboxamide (2): The synthesis of 7-nitro-*N*-phenyl-1*H*-indole-2-carboxamide is taken from a method described by Bates et al.[7] 7-Nitro-*N*-phenyl-1*H*-indole-2-carboxamide (0.20 g, 0.71 mM) and a Pd/C 10% catalyst (0.02 g) were suspended in ethanol (25 mL). The flask was then evacuated and the mixture placed under a hydrogen atmosphere and stirred vigorously for 3 h. After this time the palladium catalyst was removed by filtration through celite and the filtrate taken to dryness and placed under reduced pressure affording a white solid. 7-Amino-*N*-phenyl-1*H*-indole-2 carboxamide (0.18 g, 0.71 mM) was dissolved in a mixture of DCM (20 mL) and a saturated aqueous solution of $NaHCO_3$ (20 mL). Triphosgene (0.28 g, 0.95 mM) was added in portions to the two-phase solution and the mixture was left stirring under a nitrogen atmosphere overnight. The organic layer was diluted with DCM (100 mL), washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The pure product was isolated by sonication in MeOH (5 mL) for 3 mins and removed by filtration. The product was isolated as a white solid. Yield: 30%; m.p.: 174°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.05–7.15 (m, 4H), 7.36–7.43 (m, 6H), 7.51 (d, J=1.8 Hz, 2H), 7.60 (d, J=7.7 Hz, 2H), 7.84 (d, J=7.7 Hz, 4H), 8.97 (s, urea NH, 2H), 10.30 (s, amide NH, 2H), 11.62 ppm (s, indole NH, 2H); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): δ=104.5 (ArCH), 114.3 (ArCH), 116.3 (ArCH), 120.3 (ArCH), 120.5 (ArCH), 123.7 (ArCH), 125.0 (ArC), 128.6 (ArC), 128.8 (ArCH), 131.3 (ArC), 138.9 (ArC), 153.2 (CO), 159.7 ppm (CO); IR (film): $\tilde{\nu}$=3289, 1661 cm^{-1}; LRMS (ES$^-$): m/z: 527.5 [M−H]$^-$; HRMS (ES$^+$): m/z: exp: 551.1794 [M+Na]$^+$; calcd: 551.1802 [M+Na]$^+$

Bis(benzyl-7-nitro-1*H*-indole-2-carboxamine)-urea (3): *N*-benzyl-7-nitro-indole-2-carboxamide (0.243 g, 0.824 mM) was dissolved in ethanol (20 mL). Palladium on carbon 10% (0.025 g) was added. The reaction vessel was evacuated and placed under a hydrogen atmosphere and stirred at room temperature for 6 h. The reaction mixture was then filtered through celite and reduced in vacuo to yield a white solid. Assumed yield: 100%. The white solid and triphosgene (0.051 g, 0.171 mM) were dissolved in a two-phase solution of DCM (50 mL) and saturated sodium bicarbonate solution (50 mL) and stirred at room temperature for 2 h. The two-phase solution was then filtered. The resulting grey solid was sonicated in water (500 mL) for 1 hr. A white solid was collected by filtration and washed with water (2×25 mL), DCM (10 mL), and diethyl ether (2×25 mL). Yield: 56%; m.p.: 162°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=4.53 (d, J=5.85 Hz, 4H), 7.02 (t, J=7.9 Hz, 2H), 7.20–7.38 (m, J=7.7 Hz, 14H), 7.52 (d, J=7.7 Hz, 2H), 8.89 (s, NH, 2H), 9.13 (t, J=5.9 Hz, NH, 2H), 11.46 ppm (s, NH, 2H); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): δ=42.2 (CH_2), 103.4 (ArCH), 113.3 (ArCH), 115.9 (ArCH), 120.3 (ArCH), 125.2 (ArCH), 126.8 (ArC), 127.3 (ArCH), 128.1 (ArC), 128.3 (ArCH), 128.5 (ArC), 131.4(ArC), 139.6 (ArC), 153.2 (CO), 161.0 ppm (CO); IR (film): $\tilde{\nu}$=3290, 1635, 1575 cm^{-1}; LRMS (ES$^-$): m/z: 555.3 [M−H]$^-$; HRMS (ES$^+$): m/z: exp: 557.2294 [M+H]$^+$; calcd: 557.2301 [M+H]$^+$

Bis((2-pyridin-2-yl)-7-nitro-1*H*-indole-2-carboxamine)-urea (4): (2-pyridinyl-2-yl)-7-nitroindole-2-carboxamide (0.179 g, 0.635 mM) was dissolved in ethanol (50 mL). Palladium on carbon 10% (0.030 g) was added. The reaction vessel was evacuated and then supplied with hydrogen and stirred at room temperature for 6 h. The reaction mixture was then filtered through celite and reduced in vacuo to yield a white solid. Assumed yield: 100%. The white solid and triphosgene (0.037 g, 0.125 mM) were dissolved in DCM (50 mL) and saturated sodium bicarbonate solution (50 mL) and stirred at room temperature for 2 h. The organic phase was separated and reduced in vacuo. The resulting brown solid was sonicated in water (500 mL) for 1 h. The solid was filtered and washed with water (2×25 mL) and diethyl ether (2×25 mL). This yielded a white solid. Yield: 55%; m.p.: 219°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=7.06 (t, J=7.7 Hz, 2H), 7.17 (dd, J=6.6 Hz, 4.8 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.59 (d, J=7.7 Hz, 2H), 7.70 (s, 2H), 8.25 (d, J=8.4 Hz, 2H), 8.41 (d, J=3.7 Hz, 2H), 8.97 (s, NH, 2H), 10.95 (s, NH, 2H), 11.65 ppm (s , NH, 2H); ^{13}C{^{1}H} NMR (75 MHz, [D$_6$]DMSO): δ=105.8 (ArCH), 114.6 (ArCH), 116.6 (ArCH), 119.5 (ArCH), 119.7 (ArCH), 120.5 (ArCH), 125.0 (ArC), 128.6 (ArC), 129.0 (ArC), 130.6 (ArC), 138.2 (ArCH), 148.0 (ArCH), 152.0 (ArC), 153.1 (CO), 160.0 ppm (CO); IR (film): $\tilde{\nu}$=3269, 1644, 1539 cm^{-1}; LRMS (ES$^-$): m/z: 529.2 [M−H]$^-$; HRMS (ES+): m/z: exp: 531.1879 [M+H]$^+$; calcd: 531.1893 [M+H]$^+$.

Crystallization

Crystallizations were performed by dissolving ca. 0.05 mmol of receptor **2** in 2 mL of DMSO followed by addition of approximately 0.25 mmol tetrabutylammonium dihydrogen phosphate and allowing the solution to stand.

X-ray Structure Determination

Data were collected on a Bruker Nonius KappaCCD with a Mo rotating anode generator (λ=0.71073) employing phi and omega scans; standard procedures were followed. Lorentz and polarization corrections were applied during data reduction with DENZO[9] and multi-scan absorption corrections were applied using SADABS.[10] The structure was solved and refined using the SHELX suite of programs.[11]

Crystal data for the monohydrogen phosphate complex of compound **2**·TBA_2HPO_4.2H_2O: $C_{63}H_{101}N_8O_9P$, 0.18×0.05×0.02 mm^3, M_r=1145.49, T=120(2) K, Triclinic, space group P-1, a=13.9084(5), b=16.5116(5), c=16.5971(4) Å, α=65.864(2)°, β=72.349(2)°, γ=71.014(2)°, V=3224.48(17) Å^3, ρ_{calc}=1.180 Mg m^{-3}, μ=0.102 mm^{-1}, T_{min}=0.9818 T_{max}=0.9980, Z=2, reflections collected: 48032, independent reflections: 11275 (R_{int}=0.0900), $2\theta_{max}$=25.00°, Parameters=768, largest difference peak and hole=0.748 and −0.753 e Å^{-3}, final R indices [I>2σI]: $R1$=0.0931, $wR2$=0.1597, R indices (all data): $R1$=0.1586, $wR2$=0.1914. CCDC 734479 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

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