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dihydrogen phosphate receptors

FEATURE ARTICLE
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Nitroalkanes as new, ideal precursors
for the synthesis of benzene
derivatives

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1,3-Diindolylureas: high affinity dihydrogen phosphate receptors†

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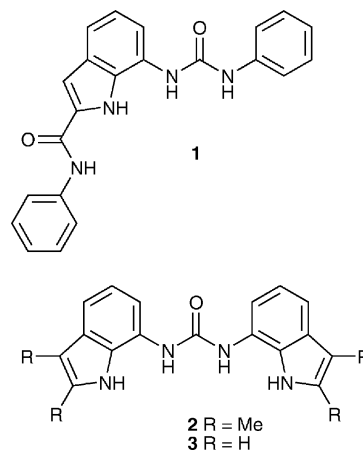
Neutral 1,3-di(1*H*-indol-7-yl)ureas are selective dihydrogen phosphate receptors in polar solvent mixtures (DMSO-d_6–25% water).

There has been much interest recently in the use of indole in synthetic anion receptor systems[1] from the groups of Jeong[2] and others.[3] Indole, like pyrrole, contains a single hydrogen bond donor group and is employed in biological systems to bind anions such as sulfate[4] and chloride.[5] We have used 2,3-dimethylindole in functionalised pyridine-2,6-dicarboxamides and isophthalamides to form fluoride selective receptors,[6] and in collaboration with Albrecht, have explored the use of 2,7-functionalised indoles as oxo-anion receptors.[7] As part of this latter project, compound **1** was synthesised and shown to bind carboxylates (acetate (10^4 M^{-1}) and benzoate (4460 M^{-1})) and dihydrogen phosphate (4950 M^{-1}) in DMSO-d_6–0.5% water at 298 K. However, NMR experiments led us to suggest that oxo-anions do not interact strongly with the amide group in this receptor but do interact with the urea and indole causing significant downfield shifts of these NH protons. This hypothesis was supported by X-ray crystallographic studies of a number of anion complexes. Hence, in an effort to enhance the affinity of this class of anion receptor, we modified our design and report here the anion complexation properties of the symmetrical diindolylureas **2** and **3**, compounds that show a remarkable affinity for dihydrogen phosphate anions in polar solvent mixtures.

Compound **2** was synthesised by reduction of 2,3-dimethyl-7-nitroindole with hydrazine hydrate–10% Pd/C and subsequent reaction with triphosgene in a mixture of dichloromethane and saturated aqueous sodium bicarbonate affording the product in 78% yield.

Proton NMR titration studies were conducted in DMSO-d_6–water mixtures containing 0.5% water with stability constants determined using the EQNMR computer program.[8] The oxo-anions studied bound strongly to the receptor with stability constants greater than 10^4 M^{-1} (Table 1). Chloride and hydrogen sulfate were also bound under these solvent conditions albeit weakly with stability constants of 128 and 50 M^{-1} respectively. 1,3-Diphenylurea[9] **4** was used as a model compound in these studies and it was found that in DMSO-d_6–0.5% water, this compound binds anions significantly less

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strongly than compound **2** (Table 1). Binding studies with compound **2** were also conducted in 10% water, revealing that the receptor has a remarkably high affinity for dihydrogen phosphate in this polar solvent mixture, with a stability constant of 4790 M^{-1} being observed *vs.* a stability constant of 736 M^{-1} with benzoate. When stability constant measurements were attempted in 25% water–DMSO-d_6 mixtures, all the oxo-anion complexes precipitated.
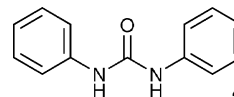
Crystals of the tetrabutylammonium benzoate complex of compound **2** were grown by slow evaporation of a DMSO solution of the receptor.‡ The structure was elucidated by single crystal X-ray diffraction and is shown in Fig. 1. The

Table 1 A comparison of (i) the stability constants (M^{-1}) of compound **2** with a variety of putative anionic guests (added as tetrabutylammonium salts) at 298 K in DMSO-d_6–0.5% water with (ii) the stability constants of 1,3-diphenylurea **4** with various anions in DMSO-d_6–0.5% water. Column (iii) shows the stability constants of compound **2** in DMSO-d_6–10% water. In all cases 1 : 1 receptor: anion stoichiometry was observed. Errors estimated to be no more than ±10%

Anionic guest	Stability constant/M^{-1}		
	(i) **2**[a]	(ii) **4**[a]	(iii) **2**[b]
Cl$^-$	128	31	16
CH$_3$CO$_2^-$	>10^4	1260	567
C$_6$H$_5$CO$_2^-$	>10^4	674	736
H$_2$PO$_4^-$	>10^4	523	4790

[a] Titrations conducted in DMSO-d_6–0.5% water (v/v). [b] Titrations conducted in DMSO-d_6–10% water (v/v).
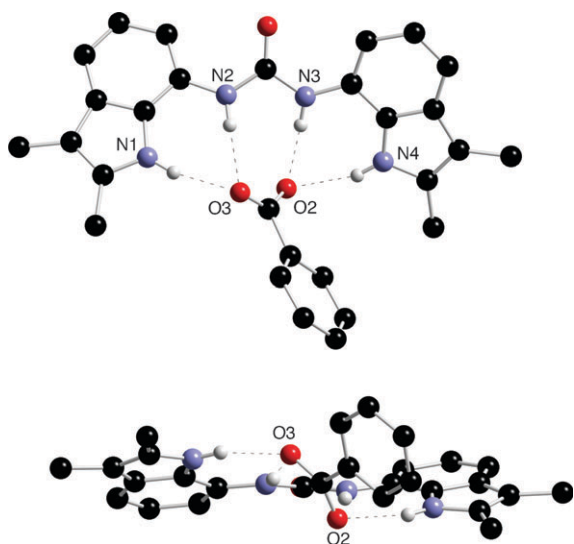
Fig. 1 Top and side views of the X-ray crystal structure of the benzoate complex of compound **2**. Non-acidic hydrogen atoms and counter cations have been omitted for clarity.

benzoate anion is bound by four hydrogen bonds from the receptor, two to each oxygen in the range N$\cdots$O 2.846(8)–2.907(8) Å and bond angles N1–H1$\cdots$O3 161°; N2–H2$\cdots$O3 169°; N3–H3$\cdots$O2 176°; N4–H4$\cdots$O2 159°.

In order to study the anion complexation properties of this hydrogen bonding motif in a more polar solvent mixture, compound **3** was synthesised (in an analogous fashion to compound **2**) in 50% yield, using commercially available 7-aminoindole. Again, proton NMR titration studies were used to determine stability constants with various anions in DMSO-d_6–0.5% water and DMSO-d_6–10% water and in all cases similar affinities were observed to those found for compound **2** (Table 2). However, in DMSO-d_6–25% water, precipitation of the anion complex only occurred upon addition of benzoate anions, allowing stability constants to be determined for acetate and dihydrogen phosphate. Under these polar conditions, it was found that compound **3** binds dihydrogen phosphate with a stability constant of 160 M^{-1} vs. 20 M^{-1} for acetate. The high affinity for dihydrogen phosphate in this very polar and competitive solvent mixture is remarkable for a neutral receptor. We presume the generally high affinity for oxo-anions is due to the cleft-like conformation being the most stable in solution. Favourable interactions

Table 2 Stability constants (M^{-1}) of compound **3** with a variety of putative anionic guests (added as tetrabutylammonium salts) at 298 K in (i) DMSO-d_6–0.5% water, (ii) DMSO-d_6–10% water and (iii) DMSO-d_6–25% water. In all cases binding fitted a 1 : 1 receptor : anion stoichiometry model. Nd = not determined[a]

Anionic guest	Stability constant/M^{-1}		
	(i)	(ii)	(iii)
Cl$^-$	128	17	Nd
CH$_3$CO$_2^-$	>10^4	774	20
C$_6$H$_5$CO$_2^-$	>10^4	521	Ppt[b]
H$_2$PO$_4^-$	>10^4	5170	160

[a] Errors estimated to be no more than ±10%. [b] Precipitation occurred upon addition of benzoate in 25% water.
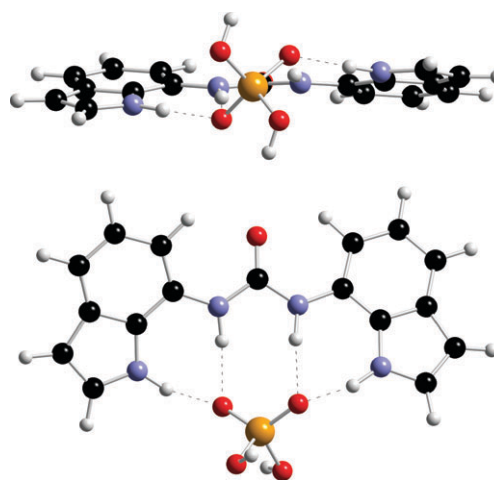

Fig. 2 Side and top views of a DFT calculated structure of the dihydrogen phosphate complex of compound **3**.

between the hydrogen atoms in the 6-positions of the indole with the oxygen of the urea may contribute to this stability.

A DFT calculation[10] of the complex between compound **3** and dihydrogen phosphate (Fig. 2) showed the anion is bound by four hydrogen bonds from the receptor (see ESI for more details†). This may not represent the global minimum energy structure.

The indole group is proving to be a highly effective moiety for anion complexation in synthetic receptor systems. The binding and encapsulation of oxo-anions is an area of increasing importance.[11] We have shown here that 1,3-diindolylureas have a high affinity for oxo-anions and, in particular, dihydrogen phosphate in very polar solvent mixtures. The diindolylurea skeleton is simple to make (in only one or two steps) and functionalise and we are currently incorporating this hydrogen bonding array into a variety of macrocyclic and acyclic anion receptors. The results of these studies will be reported in due course.

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