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7,7′-Diureido-2,2′-diindolylmethanes: Anion Receptors Effective in a Highly Competitive Solvent, Methanol

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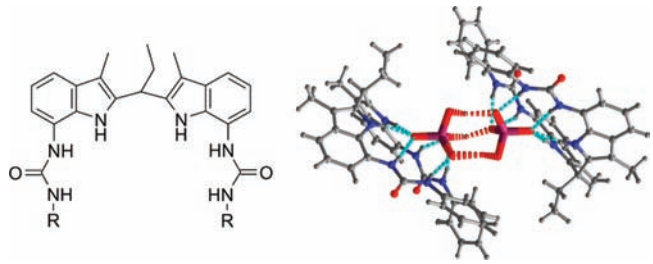
ABSTRACT



Neutral, acyclic, indole-containing ligands bind anions with hydrogen bonds in pure methanol and form an unprecedented phosphate complex in the solid state.

Anion recognition is one of the most vivid fields of supramolecular chemistry.[1] In particular, designing receptors capable of anion binding by hydrogen bonds continues to be an area of active research.[2] Such studies are inspired by the effectiveness of natural systems such as a sulfate-binding protein, which selectively binds a sulfate anion in water with only 7 hydrogen bonds.[3] However, despite ongoing research efforts, anion recognition in protic solvents has been mainly limited to positively charged or metal-containing receptors.[4,5] The remarkable exceptions are mostly macrocyclic receptors, such as, for example, cyclic amides developed by Kubik that bind anions strongly in water[6] or the indolocarbazole-based ligands reported by Jeong.[7] Only recently, acyclic, indole-containing ligands have been published that can function in a DMSO/H_2O mixture containing more than 5% of water.[8−10]

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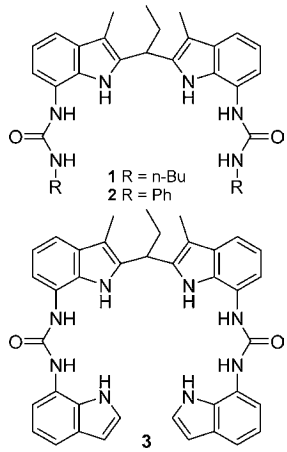
The present study reports new, neutral diindolylmethane-based receptors that are able to form anion complexes even in pure methanol. To the best of our knowledge, this is the first example of a simple, acyclic system that can bind anions with hydrogen bonds in such a highly competitive, polar, and protic solvent.

One of our main research interests has been the application of benzopyrroles in anion recognition.[10,11] In a recent study, we developed a new building block—diindolylmethane—and found simple amides based on this scaffold to be very efficient anion receptors.[10] We therefore decided to further explore this system and designed diureas **1**−**3** using the same building block (Scheme 1).

Scheme 1



7,7′-Diureido-2,2′-diindolylmethanes **1**−**3** were prepared by straightforward application of the classical protocols for urea synthesis: reaction of 7,7′-diamino-2,2′-diindolylmethane[10] with isocyanates for **1** and **2** or with triphosgene and indolo-7-amine in the case of **3**.

The interaction of ligands **1**−**3** with anions in methanol manifests itself in the downfield shift of both urea and indolyl protons' signals (Figure 1), which allowed us to determine

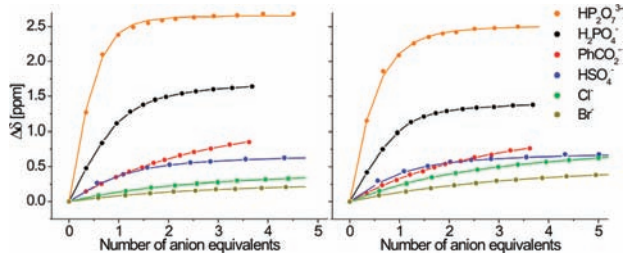


Figure 1. ^{1}H NMR titration experiments for ligand **2**. Chemical shifts of the indole NH (left) and one of the urea protons (right).

stability constants by ^{1}H NMR titration experiments (Table 1). For all anions except pyrophosphate, the titration data fit into a 1:1 model, and such stoichiometry was additionally confirmed by Job plots (see Supporting Information). In the case of $HP_2O_7^{3-}$, Job plots indicate that two ligands are bound to one anion. Although the strong binding of pyrophosphate is apparent, we were able to fit the data into the simple 2:1 model only for the ligand **2**.

Table 1. Anion Binding Constants [M^{-1}] for Receptors **1**−**3** in MeOH-d_3 at 298 K[a]

		stability constant [M^{-1}]		
anion	signal[b]	**1**	**2**	**3**
$H_2PO_4^-$	indole	125	360	235
	urea	135	535	265
HSO_4^- [c]	indole	97[d]	235	78
	urea	99[d]	280	90
$PhCO_2^-$	indole	13	28	39
	urea	15	28	—[e]
NO_3^-		—[f]	—[f]	—[f]
Cl^-	indole	13	37	26
	urea	14	31	21
Br^-	indole	11	29	22
	urea	13	23	15
$HP_2O_7^{3-}$	indole	—[g]	815 (1:1)[h]	—[g]
			10000 (2:1)	
	urea	—[g]	345 (1:1)[h]	—[g]
			12000	(2:1)

[a] Values determined by ^{1}H NMR titration experiments, errors <10%. TBA salts as the source of anions. [b] NH signal used for calculations. [c] Ligands slowly decompose in acidic conditions.[12] [d] Error >10%. [e] Value could not be determined due to broadening and overlapping of signals. [f] Interaction too weak to be measured. [g] Data cannot be fit to a simple 2:1 model; see Supportorting Information. [h] Values for the formation of 1:1 and 2:1 complexes, respectively.

The values of association constants in methanol are remarkable for such a simple system. For comparison, a recently published, amide-based ligand that binds anions strongly in DMSO/H_2O mixtures (Ka for $H_2PO_4^- > 10^4$ in DMSO + 5% H_2O)[10] interacts with anions only weakly in methanol (Ka for $H_2PO_4^-$ is equal to 8). This shows the highly competitive nature of methanol as a medium for anion binding.

Values of Ka calculated for different NH protons are generally in good agreement, showing that both urea and indolyl protons can equally participate in anion binding. It seems that the urea group interacts slightly more strongly with oxoanions and the indole moiety with halides.

Receptors **1**−**3** evidently prefer tetrahedral oxoanions since the strongest complexes are formed with dihydrogen phosphate and hydrogen sulfate.[13] Further inspection of the relative

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(12) Experiments in which HCl aq was added to the solution ligands **1**−**3** or their precursor (7,7′-diamino-2,2′-diindolylmethane) confirmed that the diindolylmethane building block is susceptible to the acidic conditions and slowly decomposes which manifests itself by emergency of red color.

(13) Direct comparison with pyrophosphate is not possible due to the different complex stoichiometry.

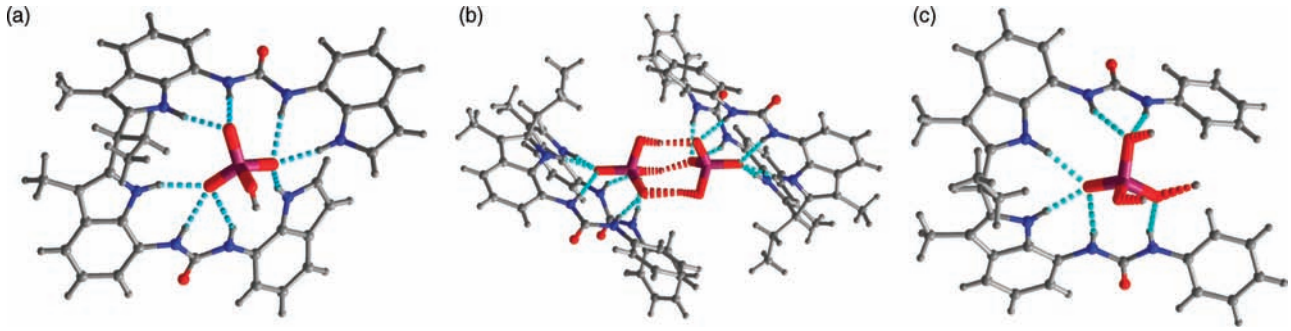

Figure 2. Crystal structures of **3**•TBA_2HPO_4 (a) and $\mathbf{2}_2$•$TBA_3H_3(PO_4)_2$ (b, c); some parts omitted for clarity.

selectivity for anions reveals unusual trends. The most unexpected observation is that ligands **1**−**3** interact with halides as strongly as with benzoate, which is a more basic anion. Also, only moderate preferences are seen for chloride over bromide.

The aliphatic derivative **1** and phenyl **2** show similar selectivity for different anions. Stronger anion binding by **2** can be explained as a result of the higher acidity of its urea protons. The introduction of additional indole subunits in **3** does not improve affinity toward anions but does moderate the selectivity, with the most striking effect in the case of HSO_4^-, whose binding is less favorable.

Slow evaporation of a DMSO solution of the receptor **3** in the presence of tetrabutylammonium dihydrogenphosphate yielded diffraction grade crystals, whose structure was elucidated by X-ray analysis. As shown in Figure 2a, the anion undergoes deprotonation upon crystallization, and the actual complex is formed with HPO_4^{2-}.

A similar process of anion deprotonation upon crystallization has been already observed by Gale for other indole-based ligands.[8b,14] As it was reported, such deprotonation in the solid state may indicate that similar process occurs in the solution.[14] We exclude this possibility in the case of our receptors. The titration data for dihydrogenphosphate fits perfectly into a 1:1 model, and also the symmetrical Job plot clearly indicates a pure 1:1 binding (see Supporting Information).

As the X-ray analysis reveals, the diindolemethane scaffold of **3** adopts a "bent sheet" shape, in a way similar to that observed for the amide analogues of **1**−**3**.[10] All NH groups form hydrogen bonds with oxygen atoms of the anion, and judging by the N−O distances, indole moieties bind the anion more strongly than urea groups. Ligand **3** is capable of binding HPO_4^{2-} with eight complementary hydrogen bonds, so this structure cannot explain its lower affinity toward HSO_4^- as both HPO_4^{2-} and HSO_4^- have similar geometry.

The ligand **3** can be treated as a conjugation of two diindolylurea subunits. The conformation of the first is almost flat, and the anion is located "above" its plane. The second subunit tilts its indole groups in opposite directions and binds the anion with them from "up" and "down" sides. The latter conformation closely resembles the DFT-calculated structure of the phosphate complex with diindolylurea reported by Gale.[9]

We obtained diffraction grade crystal for the complex of **2** in similar conditions. However, X-ray analysis revealed that the complex formed has the actual stoichiometry of $\mathbf{2}_2$•$TBA_3H_3(PO_4)_2$. Such a supramolecule can be described as a 2:1 complex between two ligands **2** and an unusual phosphate dimer—$[H_3PO_4•PO_4]^{3-}$ (Figure 2b). It appears that upon crystallization two phosphate anions are deprotonated, brought together and bridged by three protons, and this "supra-anion" is stabilized by interactions with two molecules of ligand **2**. Both anions are in close proximity, and the P−P distance is 3.68 Å. To the best of our knowledge, there is no precedent of any similar phosphate dimer in the literature. CSD and ICSD databases contain only structures of phosphate anions joined by one or two hydrogen bonds, which leads to a larger distance between phosphorus atoms (around 4.1−4.2 Å).

The ligand geometry is very similar to the one in the complex of **3**, which may indicate that it is the preferred conformation for this class of ligands. All NH protons are involved in interactions with the anions, though a slightly different hydrogen bond pattern is observed than for **3** (Figure 2c). This structure may illustrate a possible binding mode for the observed in solution, complexes of ligands **1**−**3**, and the pyrophosphate anion of 2:1 stoichiometry.

To summarize, we have described new acyclic anion receptors based on a diindolylmethane scaffold. Remarkably, these receptors bind anions in pure methanol even though binding is achieved only by utilization of hydrogen bonds. Structural analysis of the ligand complexes reveals the formation of an unprecedented dimer of phosphate anions, which are stabilized by interaction with two ligand molecules. We are exploring this promising building block further, currently by incorporating it into macrocyclic structures.

Acknowledgment. We would like to thank the Ministry of Science and Higher Education (Project N N204 092735) for support of this work.

Supporting Information Available: Receptor synthesis, crystallographic data (CIFs), titration experiments, and Job plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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