J|A|C|S
COMMUNICATIONS

Published on Web 12/06/2006

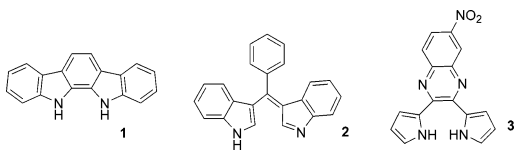
Diindolylquinoxalines: Effective Indole-Based Receptors for Phosphate Anion

Jonathan L. Sessler,* Dong-Gyu Cho, and Vincent Lynch

Department of Chemistry and Biochemistry and Institute for Cellular and Molecular Biology, 1 University Station A5300, The University of Texas at Austin, Austin, Texas 78712-0156

Received October 28, 2006; E-mail: sessler@mail.utexas.edu

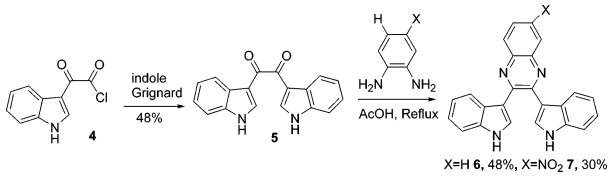
Anions are ubiquitous in biological milieus. Among the most important physiologically relevant anions is inorganic phosphate. Not only does it play a critical role in energy storage and signal transduction,[1] it is recognized as an essential structural element in teeth and bones.[2] On the other hand, elevated serum phosphate levels can result in calcification of tissues[3] and is a recognized problem in patients suffering from chronic kidney failure. Phosphate is also a key pollutant whose role in the eutrophication of waterways is well recognized.[4] This diversity of function has stimulated considerable current interest devoted to the recognition and sensing of phosphate anions.[5] Increasingly, efforts in this area have focused on the use of acyclic small molecule receptors,[4] including those based on amide, sulfonamide, urea, and pyrrole recognition units. While each of these motifs presents certain advantages, there is incentive to explore additional putative binding subunits that could be used to generate new receptor systems. One such motif is indole, a potential hydrogen bond donor that has yet to be exploited extensively in the area of anion sensor development. Indeed, currently only indolocarbazoles, **1**,[6] and bis(indolyl)methane, **2**,[7] are known to the best of our knowledge, and, in the case of the latter system, quantitative binding studies were not fully carried out. Thus, there remains a need to explore the fundamental anion binding properties (e.g., selectivity, affinity) of indole-based receptors. Toward this end, we report here the synthesis of a new series of 2,3-diindol-3′yl quinoxalines (DIQ, **6** and **7**), as well as a comparison of their anion recognition properties to those of our previously reported pyrrole based sensors, 2,3-dipyrrol-2′yl quinoxalines (DPQ, **3**).[8] To the best of our knowledge, this new DIQ system, which relies on β-connectivity, represents the first example of an indole-based small molecule receptor for which evidence of anion binding is available both in solution and in the solid-state. It also provides one of the few structurally characterized neutral receptor−dihydrogen phosphate complexes.[9]



Receptors **6** and **7** require very short syntheses. Although the synthesis of receptor **6** was not clearly described in the literature, the syntheses of 2,3-diindol-3′yl diketone **5**[10] and bis-indole **6**[11] have been published. In the event, we have found that intermediate **5** is easily prepared by the reaction of indole Grignard reagent with indolyl oxaacethyl chloride **4** (Scheme 1). Subsequent reaction between the resulting diketone **5** and either *o*-phenyldiamine or its mononitro analogue gave the final receptors **6** and **7** in unoptimized yields of 48 and 30, respectively.

The association constants (K_a) of receptors **6** and **7** were determined from standard UV−vis absorption titrations carried out in dichloromethane. Figure 1 presents the observed changes in the

Scheme 1. Synthetic Scheme



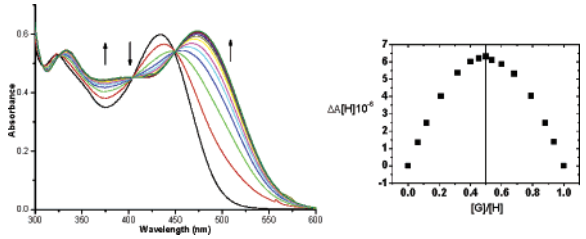


Figure 1. Evolution of the UV−vis spectrum of receptor **7** (3.99×10^{-5} M in dichloromethane) seen during titration with tetrabutylammonium hydrogen phosphate (TBA·H_2PO_4; 0 to 10 equiv). (Inset) Job plot for the interaction between receptor **7** and TBA·H_2PO_4.

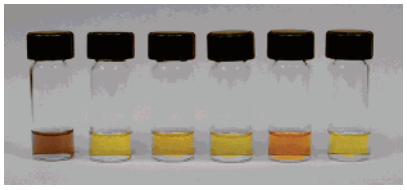


Figure 2. Color changes observed upon the addition of anions (10 equiv) to otherwise identical solutions of receptor **7** (4.34×10^{-5} M in dichloromethane). From left to right; F^- + **7**, Cl^- + **7**, BzO^- + **7**, HSO_4^- + **7**, $H_2PO_4^-$ + **7**, **7**.

UV−vis spectrum of receptor **7** recorded in dichloromethane upon the addition of tetrabutylammonium hydrogen phosphate (TBA·H_2PO_4). In the absence of the anion, an absorption maximum is seen at 434 nm. Upon addition of $H_2PO_4^-$, a large bathochromic shift was observed ($\Delta\lambda_{max} = 40$ nm). The resulting titration revealed several isosbestic points as expected for a 1:1 binding stoichiometry. Similar isosbestic points were also observed during the course of titrations carried out with F^-, Cl^-, HSO_4^-, and BzO^- anions as well (all as TBA salts). This binding stoichiometry was confirmed in solution by Job plots and, in the case of receptor **7** and dihydrogen phosphate anion, by a single-crystal X-ray analysis carried out in the solid state (cf. Figure 3 and discussion below).

Association constants determined from these titrations are summarized in Table 1. An inspection of this table reveals that in the case of receptor **6** the greatest affinity is displayed for dihydrogen phosphate anion, followed by F^- > BzO^- > Cl^- > HSO_4^-. This same table also confirms that, as proved true in the case of the corresponding DPQ systems, the nitro-bearing receptor **7** shows higher affinities across the board than does the unsubstituted system **6**. This result is attributed to the electron withdrawing

10.1021/ja067720b CCC: $33.50

Table 1. Anion Binding Constants (K_a; M^{-1})[a] for Receptors **6** and **7** in Dichloromethane at 22 °C

	3[8]	6	7
F^-	118 000	2100	[b]
Cl^-	65	170	470
HSO_4^-	N.D.	80	250
BzO^-	N.D.	600	2700
$H_2PO_4^-$	80	6800	20 000[c]

[a] Values were determined by UV−vis spectroscopic titrations; errors are <±10%. All anions were used in the form of their respective tetrabutylammonium (TBA) salts. [b] A reliable binding constant could not be determined due to the observation of biphasic behavior. [c] The association constant for the interaction of receptor **7** with $H_2PO_4^-$ was also examined in acetone, acetonitrile, and DMSO; the K_a values are 5600, 2400, and 300 M^{-1}, respectively. N.D. = not determined.

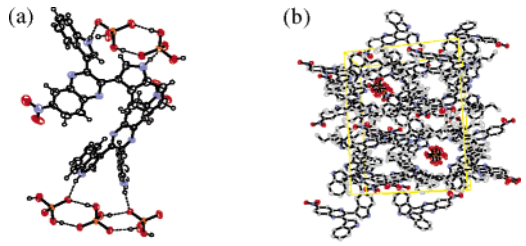


Figure 3. Single-crystal X-ray diffraction structure of receptor **7**·TBA·H_2PO_4. Thermal ellipsoids are scaled to the 50% probability level. Most hydrogen atoms and the TBA cations have been omitted for clarity. (a) View illustrating the two types of phosphate bound receptor **7** complexes found in the solid-state structure; (b) view of the (receptor **7**·TBA·H_2PO_4)$_8$ complex seen in the unit cell.

nitro group, which serves to increase the pyrrole NH acidity. Consistent with this postulate, receptor **7** shows biphasic behavior[12] when subjected to titration with fluoride anion in dichloromethane. Under these conditions, the fluoride anion presumably acts as both a general base and as an anionic substrate (cf. Supporting Information).

Among the anionic substrates for which clean binding behavior is seen, receptor **7**, like its congener **6**, shows good selectivity for phosphate anion ($K_a(H_2PO_4)/K_a(Cl)$ = 42, $K_a(H_2PO_4)/K_a(BzO)$ = 7, and $K_a(H_2PO_4)/K_a(HSO_4)$ = 80). Such a high inherent selectivity was not seen in either the corresponding DPQ systems (K_a(recpt. **7**)/K_a(recpt. **3**) = 250 for $H_2PO_4^-$)[8] or in the indolecarbazole[6] based receptors reported recently by Beer. We ascribe this selectivity to the presence of the β-connectivity linking the two indole motifs to the quinoxaline core; this provides a more open (and potentially less rigid) cavity that is expected to favor binding of this relatively larger anionic substrate.

Further support for the notion that compound **7** can act as a dihydrogen phosphate anion receptor comes from a single-crystal X-ray diffraction analysis of the complex formed between **7** and TBA·H_2PO_4. This structure reveals the presence of two different phosphate−receptor interactions in the solid state. In one complex, a molecule of receptor **7** interacts with two phosphate anions that, in turn, interact with one another via hydrogen bonds. In the other complex, receptor **7** binds three phosphates that again exist in a self-associated network (cf. Figure 3). As the result of these and other hydrogen bonding interactions, a series of infinite phosphate channels and wires is observed in the solid state.[13] Nonetheless, the overall anion-to-receptor binding stoichiometry is 1:1, as expected based on the solution-phase Job plot analyses.

A further notable feature of receptor **7** is that color changes are seen upon the addition of F^- and $H_2PO_4^-$ anions (Figure 2). Such color changes are considered a useful feature of anion receptors in that they allow analytes to be detected easily without recourse to spectrometers.[14]

In summary, the new indole-based receptors **6** and **7** provide a new series of anion receptors that are particularly effective for the dihydrogen phosphate anion. Receptor **7** allows for the visual detection of this anion via the production of a simple, anion-triggered color change (as well as fluoride for which less clean binding behavior is seen). The interaction between $H_2PO_4^-$ and receptor **7** also gives rise to the formation of a unique extended structure in the solid state, leading to the suggestion that systems such as **7** could be used as the basis for new engineered crystalline materials. We are currently studying this possibility while working to produce more elaborate indole-based receptors.

Acknowledgment. This work was supported by the National Institutes of Health (GM 58907 to J.L.S.).

Supporting Information Available: Details describing the synthesis and characterization of compounds **6** and **7**, details of fitting binding curves, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA067720B