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Tetrathiafulvalene diindolylquinoxaline: a dual signaling anion receptor with phosphate selectivity†

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Abstract

Incorporation of tetrathiafulvalene into the backbone of a known neutral phosphate receptor, diindolylquinoxaline, yields a dual optical-electrochemical chemosensor for dihydrogen phosphate that functions in dichloromethane. This system shows selectivity for dihydrogen phosphate over other small anions and can be used to detect the presence of this analyte *via* fluorescence quenching or cyclic voltammetry.

Tetrahedral oxyanion recognition and sensing is of current interest due to the diverse roles that such anions play in biological systems and in the environment.¹ Within this general framework, the ability to monitor the phosphate anion is of particular importance due *inter alia* to the ubiquitous use of phosphates as fertilizers and the role such species can play in the eutrophication of waterways.² This is providing an incentive to develop receptors that can selectively bind and sense phosphate. To date a variety of receptor systems, running the gamut from metal complexes to small molecules employing hydrogen bonding, have been put forward for this purpose.³ While a number of these have proven effective under appropriately chosen conditions, there remains a critical need for systems that display high selectivity and which function with high reliability. The use of so-called dual signaling systems, which allow phosphate anion detection *via* more than one read-out mode, thereby lowering the likelihood of false positives, could help address this need. In pursuit of this goal we report here a tetrathiafulvalene (TTF) functionalized diindolylquinoxaline (DIQ) receptor, **1** (*cf.* Scheme 1). Systems that permit phosphate anion detection *via* both optical and electrochemical means are rare.⁴

Tetrathiafulvalene (TTF), a classic organic redox active unit, has been exploited extensively in recent years as a supramolecular signaling and switching unit. However, it is still relatively unexplored as an electrochemical sensor element in the field of anion recognition.⁵ A seminal report by Becher *et al.* described a mono-TTF-calix[4]pyrrole⁶ (**2**) that proved capable of recognizing halide anions, as opposed to phosphate, electrochemically *via* shifts in the first oxidation potential. Later, Zhu *et al.* developed an amide-based TTF phosphate sensor (**3**).⁷ However, these latter receptors, although elegant and effective, did not function as dual signaling systems. We thus decided to explore the incorporation of a TTF signaling unit into a diindolylquinoxaline (DIQ) framework. DIQs (*e.g.*, **4**) are a class of anion

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receptor with good selectivity for dihydrogen phosphate that were previously reported by our group.⁸ Recently, DIQs were elaborated in a ditopic fashion by Wang and Yan (*cf.* **5**).⁹ However, receptor **1** appears to be the first that combines DIQs with TTF subunits.

Receptor **1** requires a very short synthesis. As illustrated in Scheme 1, condensation of TTF-phenylenediamine **6**¹⁰ with diketone **7**, a precursor that is easily prepared,¹¹ provides receptor **1** in an unoptimized yield of 22%.[‡]

In order to compare the binding affinity of the new TTF-DIQ with the parent unfunctionalized DIQ receptor (**4**),⁸ association constants (K_a) of receptor **1** with various anions were determined *via* standard UV-vis titrations carried out in dichloromethane using the corresponding tetrabutylammonium (TBA) salts. As expected given the analogous nature of the binding site present in these two DIQ-based systems, the new TTF-functionalized system (**1**) was found to display good selectivity and affinity for H_2PO_4^- ($K_a = 6.5 \times 10^3 \text{ M}^{-1}$; $K_a(\text{H}_2\text{PO}_4^-)/K_a(\text{F}^-) = 1:8$; *cf.* Table 1). In fact, the recorded K_a 's for all anions tested proved similar for **1** and **4**, with the exception of chloride, which was found to bind more strongly to **1** than **4** by roughly an order of magnitude. Nevertheless, this latter species was bound less well than H_2PO_4^- (for **1**: $K_a(\text{H}_2\text{PO}_4^-)/K_a(\text{Cl}^-) = 5:9$). It is worth noting that the affinity of receptor **1** for dihydrogen phosphate is the highest reported so far for a TTF-functionalized anion receptor. It is also the only TTF-based system to display phosphate anion selectivity under solution phase conditions. Although system **1** functions in dichloromethane, recent studies have served to reveal that receptors that function in organic media can be useful in sensing anions under aqueous conditions.¹²

Support for the proposed 1 : 1 dihydrogen phosphate binding stoichiometry came from curve fittings and the use of so-called Job plots¹³ (*cf.* ESI[†]), as well as from solid-state structural analyses.

The structure of the complex formed from receptor **1** and $\text{TBA} \cdot \text{H}_2\text{PO}_4$ determined by X-ray diffraction analysis is shown in Fig. 1. It reveals a self-associated network wherein two molecules of receptor **1** interact with two dihydrogen phosphate anions. This self-association behavior, in which interactions between the individual dihydrogen phosphate anions are seen, is similar to what was observed in the case of the ditopic system **5** recently reported by Wang and Yan.⁹

A notable feature of receptor **1** is its ability to sense anions *via* fluorescence quenching of the quinoxaline emission. This was tested in dichloromethane using various TBA salts. As shown in Fig. 2(a), quenching is observed in the presence of H_2PO_4^- , with the effect increasing as a function of dihydrogen phosphate anion concentration. Under the same conditions, only a slight quenching is observed upon addition of F^- , and no noticeable decrease in intensity is seen in the presence of 50 equiv. of Cl^- , BzO^- , or HSO_4^- (Fig. 2(b)), whereas a significant decrease is observed in the presence of H_2PO_4^- .

The TTF-DIQ, receptor **1**, was designed with the goal of detecting anions, specifically dihydrogen phosphate, electrochemically. In particular, it was expected that the direct link between the DIQ anion binding site and the redox active TTF moiety would allow the presence of anions to be sensed *via* changes in the redox potential of the latter subunit. In

[‡]Selected data for compound **1**: ¹H NMR (400 MHz; DCM-*d*₂) δ 8.42 (s, NH, 2H), 8.02 (d, $J = 8.5$ Hz, 2H), 7.92 (s, Ar-H, 2H), 7.43 (d, $J = 8.13$ Hz, 2H), 7.36 (s, 2H), 7.23 (t, $J = 7.02, 6.96$ Hz, 2H), 7.12 (t, $J = 8.11, 6.99$ Hz, 2H), 2.84 (t, $J = 7.09, 7.32$ Hz, -*S*-propyl, 4H), 2.84 (m, -*S*-propyl, 4H), 1.03 (t, $J = 7.31, 7.34$ Hz, -*S*-propyl, 6H) ppm; ¹³C NMR (125 MHz; DMSO-*d*₆) δ 149.7, 138.4, 137.7, 136.2, 128.1, 126.9, 126.0, 122.0, 121.3, 120.4, 120.1, 113.9, 111.9, 110.9, 110.7, 37.5, 22.7, 12.8 ppm. MS m/z : 685.07 [M^+].

[†]Electronic supplementary information (ESI) available: Details of synthetic, experimental, CV studies, UV studies, ¹H-NMR studies, and X-ray crystallography. CCDC 781609. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/c0cc02934c

order to test this possibility, cyclic voltammetric (CV) analyses were carried out. In accord with design expectations, changes in E_1^{ox} and E_2^{ox} were observed upon addition of dihydrogen phosphate (Fig. 3). Specifically, the addition of two equivalents of this phosphate anion (as the TBA salt) yielded a cathodic shift of 112 mV in the first oxidation wave ascribed to the TTF subunit, as well as an anodic displacement of the second oxidation peak. The reduction waves decreased in intensity upon the addition of dihydrogen phosphate and shifted to more positive potentials. These findings are consistent with the suggestion that upon binding to receptor **1**, negative charge from the dihydrogen phosphate anion extends into the TTF core, therefore making the molecule easier to oxidize and harder to reduce, as has been proposed for previous TTF-based anion receptors governed by hydrogen bonding.^{6,7}

Addition of chloride, benzoate, and hydrogen sulfate produced only modest changes in the $E_{1/2}^1$ values, while the addition of fluoride caused a broadening and splitting in the CV features (Table 1). This latter finding is attributed to deprotonation of the indole N–H moieties by the basic fluoride anion under the conditions of the CV experiments. Such a supposition is supported by ^1H NMR spectroscopic studies carried out in $\text{DMSO}-d_6$ and dichloromethane- d_2 (see discussion below and ESI†); it is also consistent with what was found by Wang and Yan in the case of system **5**.⁹

In an effort to understand more fully the interactions between receptor **1** and various anions, ^1H NMR spectroscopic studies were carried out in dichloromethane- d_2 . In the presence of 1.5 equiv. of various TBA salts, the signals for the N–H protons of the indole moieties displayed the most dramatic shifts upon the addition of dihydrogen phosphate (3.88 ppm downfield shift). The addition of benzoate anion also gave a noticeable shift (1.9 ppm), while chloride and sulfate produced only slight downfield shifts. These findings are consistent with anion-dependent changes in the electron density of receptor **1** taking place upon anion addition.

The disappearance of the N–H signal seen upon fluoride introduction is consistent with the proposed deprotonation. Further evidence for this deprotonation was obtained by carrying out analogous ^1H NMR spectroscopic experiments in $\text{DMSO}-d_6$. In this more polar solvent, the N–H signal also disappears upon the addition of TBAH_2PO_4 , while a broadening of the other aromatic signals is also observed. In dichloromethane- d_2 these changes are only seen upon fluoride anion addition.

The relative strengths of the hydrogen bonding interactions between receptor **1** and various anions inferred from these NMR spectroscopic analyses, can be used to explain the respective perturbations in the CV titrations. For example, the phosphate and benzoate anions give rise to the greatest downfield shifts of the indole N–H signals; they also produce the largest cathodic displacements in the first, TTF-centered oxidation potential. Thus, concordant results are obtained from these two disparate measurement methods.

In summary, a new TTF-functionalized diindolyl-quininoxaline receptor, **1**, has been prepared. In contrast to previously reported DIQ systems, this new receptor allows for the detection of dihydrogen phosphate anions in dichloromethane using a dual optical/electrochemical readout approach. In the presence of TBAF, changes are seen that are thought to reflect deprotonation, rather than hydrogen bond mediated receptor–anion interactions. These effects can be readily distinguished *via* spectroscopic means. We thus propose that receptors, such as **1**, that combine a redox active TTF moiety with recognition subunits that permit an optical response will have a role to play in the recognition, detection, and sensing of the dihydrogen phosphate anion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Synthesis of receptor 1.

Fig. 1.

Single crystal X-ray structure of **1**·TBA·H₂PO₄. Top: view of the 2 : 2 complex formed between the receptor and the bound anion. The TBA counter cations have been omitted for clarity and the thermal ellipsoids are scaled to 30% probability level. Bottom: view showing the extended one-dimensional dihydrogen phosphate network within the crystal.¹⁴

Fig. 2.

(a) Fluorescent emission spectra of **1** (2.0×10^{-6} M) recorded in dichloromethane ($\lambda_{\text{ex}} = 468$ nm) before and after the addition of up to 50 equiv. of TBA·H₂PO₄. (b) Fluorescent emission spectra of receptor **1** (1.5×10^{-6} M) recorded upon the addition of 50 equiv. of various tetrabutylammonium anion salts in dichloromethane ($\lambda_{\text{ex}} = 468$ nm).

Fig. 3. Cyclic voltammograms of receptor **1** (2.5×10^{-4} M) recorded in dichloromethane at 298 K with TBA·PF₆ (0.3 M) as the supporting electrolyte in the presence of TBA·H₂PO₄. The potentials were referenced to Ag/AgCl.

Table 1

Apparent affinity constants determined by UV-Vis and ΔE for first redox potentials of the complexes **1**·X (X = anion) determined *via* CV at 298 K

X^-	K_a^a/M^{-1}	$\Delta E_1^{oxb}/mV$
F^-	3.6×10^3	-278^c
$H_2PO_4^-$	6.5×10^3	-112
BzO^-	9.5×10^2	-15
HSO_4^-	3.7×10^2	$+19$
Cl^-	1.1×10^3	0

^aErrors < $\pm 10\%$. All anions used in the form of their tetrabutylammonium (TBA) salts.

^b ΔE_1^{ox} calculated for first oxidation potential after addition of 2 equiv. of anions.

^cValue after suspected deprotonation.