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Binding and selectivity of dihydrogen phosphate by H-bond donors and acceptors in a tripodal-based thiourea receptor

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ABSTRACT

Anion binding properties of a quinoline-based tripodal tris-thiourea receptor have been studied for several oxoanions including perchlorate, nitrate, hydrogen sulfate, and dihydrogen phosphate by ^{1}H NMR and UV–vis titrations in DMSO. Results show that the receptor selectively binds dihydrogen phosphate with a 1:1 stoichiometry. Ab initio calculations based on density functional theory (DFT) suggest that the dihydrogen phosphate is encapsulated within the host's cavity via six NH···O and two N···OH interactions.

Phosphate plays a vital role in a variety of environmental and biological applications.[1,2] For example, it is a widely used component in fertilizer and drug-related industries.[1] In biological applications, the central component of nucleic acids (DNA and RNA) is a phosphate group that plays an important role in many enzymatic reactions.[3] In addition, a phosphate anion is known to interact selectively with phosphate binding protein (PBP), and its structure was crystallographically characterized, showing that the anion at the core of PBP is held with a total of 12-hydrogen bonds.[4] Due to its ubiquitous presence in Nature, there is a growing interest in developing new synthetic receptors with the goal of selectively binding phosphate.[5] In a previous work, an oligopyrrolic-based macrocycle receptor synthesized by Katayev, Sessler, and coworkers was found to complex a di-anionic phosphate showing hydrogen-bond networks similar to those present in the active sites of PBP.[6] Although polyamine-based compounds are good candidates for complexing phosphates in water,[7] they function as H-bond donors only at a certain pH, where the protonation occurs.[8–14] Alternatively, a urea or thiourea-based compound is capable of donating H-bonds for an anion regardless of the solution pH.[15–18] The pK_a of thiourea is 21.1 while that of urea is 26.9 in DMSO.[15] Therefore, the thiourea group is more acidic than a urea group, making a thiourea based receptor more efficient than a corresponding urea-based receptor.[15]

In 1993, Hamilton and coworkers synthesized a simple di-topic host based on a *p*-xylyl framework with urea and thiourea arms, which showed anion binding affinity in DMSO.[19] Several years later, Wu and coworkers showed that a naphthyl-based tripodal thiourea formed a 1:1 complex with $H_2PO_4^-$ and HSO_4^- in DMF.[20] Gale and coworkers recently reported a series of fluorinated tren-based ureas and thioureas showing a strong selectivity for sulfate.[21] In addition, these compounds were shown to function as anticancer agents through a transmembrane transport mechanism of anions in vitro. A *p*-nitro substituted tripodal thiourea reported by Das and coworkers showed anion binding ability in solution, forming a capsular complex with hydrogen phosphate in the solid state.[22] Gunnlaugsson and coworkers reported C_{3v}-symmetrical urea-amide receptors, providing hydrogen-bonding capabilities for phosphate in DMSO-d_6.[23] Fabbrizzi coworkers investigated the interactions of urea/thiourea receptors for anions including phosphates in solution.[24,25] Previously, we reported a tren-based tripodal (*p*-cyanophenyl) urea receptor that binds to $H_2PO_4^-$ (Log$K$ = 4.2) and HSO_4^- (Log$K$ = 3.0) in DMSO-d_6.[26] In the solid state, one hydrogen sulfate is located at the core formed by three hosts via six NH···O bonds ($d_{NH\cdots O}$ = 2.85 to 3.09 Å) and one OH···O bond ($d_{OH\cdots O}$ = 2.57 Å), where the host serves as both H-bond donors and acceptors. Recently, we have

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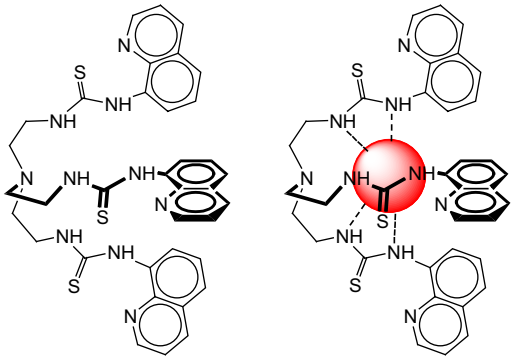

Scheme 1. Receptor **L** (left) and its proposed binding mode with an anion (right).

found that the incorporation of quinoline groups as chromophores in a dipodal urea makes it effective as a chromogenic receptor for optical analysis of anions in solution.[27] We have been further interested in developing chromogenic receptors with an extended dimensionality (e.g., dipod to tripod/macrocycle) that could use their optical signaling for anion sensing in solution. Herein, we report a quinolone-based tripodal tris-thiourea receptor **L** that selectivity binds dihydrogen phosphate in DMSO from the interactions of H-bond donors and acceptors (Scheme 1).

Starting with the tripodal amine (tren), the synthesis of **L** was performed in a two-step reaction as reported earlier.[28–30] Because of the presence of three thiourea units surrounded by a tripodal pocket, this compound can potentially serve as an anion receptor. The receptor **L** is very stable under normal conditions and soluble in DMSO, allowing us to study it for anion binding at room temperature. However, attempts to prepare crystals of **L** with tetrabutyl ammonium salts were unsuccessful.

^{1}H NMR titration of **L** for phosphate was performed using *n*-tetrabutylammonium dihydrogen phosphate (*n*-$Bu_4NH_2PO_4$) in DMSO-d_6. As shown in Figure 1A, the addition of *n*-$Bu_4NH_2PO_4$ to **L** resulted in a significant downfield shift for both NH peaks, indicating the interactions of NH groups of the ligand with $H_2PO_4^-$ in solution. The change in the chemical shift of NH resonances in the NMR spectra, as recorded with an increasing amount of *n*-$Bu_4NH_2PO_4$ solution at room temperature, gave the best fit to a 1:1 binding model.[31] The titration plot is shown in Figure 1B. The calculated association constant (K) of **L** for phosphate was 1130 M^{-1} in DMSO-d_6. This binding constant is higher than that reported by Gale and coworkers for a phenyl based tristhiourea (256 M^{-1}) or a *p*-fluorophenyl based tristhiourea (227 M^{-1}).[21] However, no significant shift was observed after the addition of other oxoanions including HSO_4^-, ClO_4^-, and NO_3^- ions. These results confirm the selectivity of **L** for dihydrogen phosphate in DMSO. Attempts to determine the binding constant in other protic solvent systems, for example, water or DMSO:water (1:1, v/v) were hampered because of the poor solubility of **L** in these solvents, which is a limitation of this ligand for use in an aqueous medium.

The binding ability of **L** for dihydrogen phosphate was also examined by UV–Vis spectroscopy in DMSO. The receptor showed an absorption band (λ_{max}) at 335 nm in the absence of an anion. The addition of *n*-$Bu_4NH_2PO_4$ to the receptor solution resulted in a gradual decrease in the absorption. No appreciable change in λ_{max} was observed for the addition of *n*-$Bu_4NH_2PO_4$. A similar trend was reported previously for a naphthyl-based tripodal thiourea for the binding of dihydrogen phosphate in DMSO.[19] Figure 2A shows the titration spectra, derived from the experiments with a gradual addition of the anion (0–35 equiv). The relative absorbance I/I_0 of **L** (where I_0 and I represent the absorbance of **L** before and after

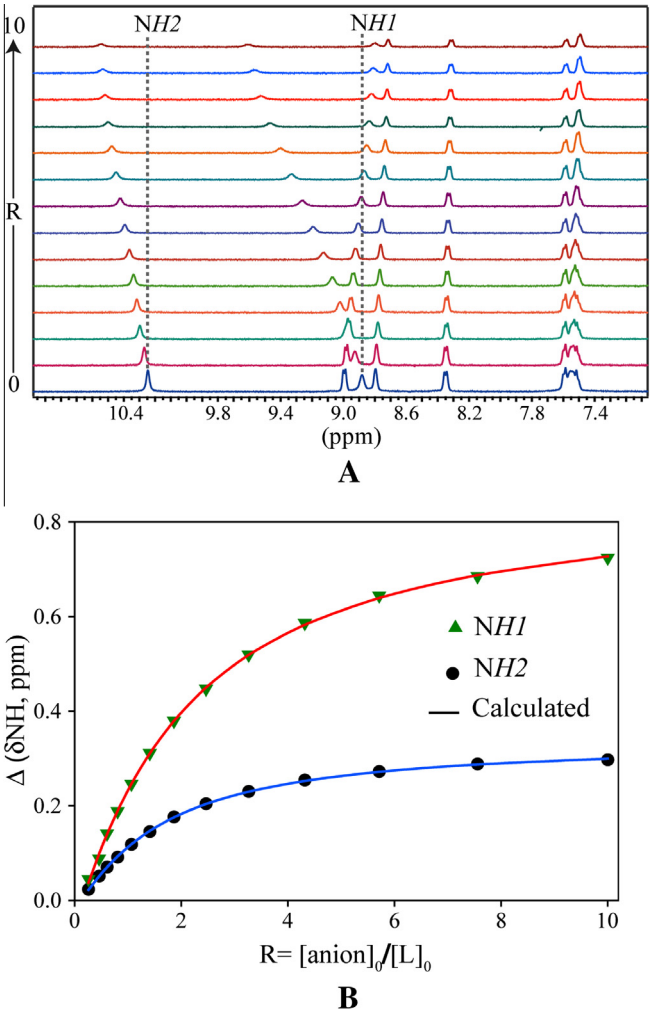

Figure 1. (A) ^{1}H NMR spectra of **L** (2 mM) with an increasing amount of *n*-$Bu_4NH_2PO_4$ (R = [*n*-$Bu_4NH_2PO_4$]$_0$/[**L**]$_0$) in DMSO-d_6. (B) Titration curves of **L** with *n*-$Bu_4NH_2PO_4$ showing changes in the chemical shifts of NH with an increasing amount of anions. H1 = CH_2NHCS and H2 = $CSNHAr$.

the addition of an anion, respectively) upon the gradual addition of *n*-$Bu_4NH_2PO_4$ provided the best fit to a 1:1 association model (Fig. 2B). The binding constant as estimated from the non-linear regression analysis was 1365 M^{-1} (in K); this is slightly higher than 1130 M^{-1} determined from the ^{1}H NMR titrations, which might be the effect of the initial concentrations used for two different techniques.[32] However, the ligand did not show any spectral change when it was titrated with other oxoanions (HSO_4^-, ClO_4^-, and NO_3^-), which is in agreement with the results obtained from the ^{1}H NMR titration.

The binding affinity of **L** for dihydrogen phosphate was further evaluated by ab initio calculations based on density functional theory (DFT). Since an anion–ligand system involves hydrogen-bonding interactions, it is important to choose an exchange-correlation functional that accurately captures these electronic effects. To this end, all DFT calculations were performed using the M06-2X hybrid functional that incorporates an improved description of dispersion energies, an effect which was previously found to be necessary for describing non-covalent interactions.[33] The optimized structure of the dihydrogen phosphate complex is shown in Figure 3, where the calculated binding energy for dihydrogen phosphate is 64.2 kcal/mol. In the DFT-optimized complex, the host loses its C_3 symmetry in order to encapsulate

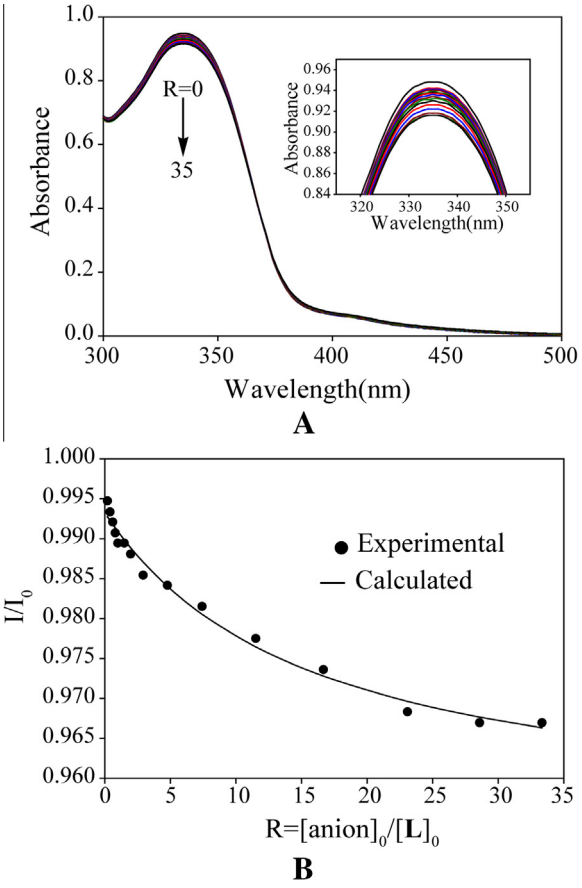

Figure 2. (A) Changes in absorption spectra of **L** (5×10^{-5} M) with an increasing amount of *n*-$Bu_4NH_2PO_4$ in DMSO. (B) Titration plot of change in relative absorbance of **L** with an increasing amount of the anion ($R = 0$–35) at $\lambda_{max} = 335$ nm.

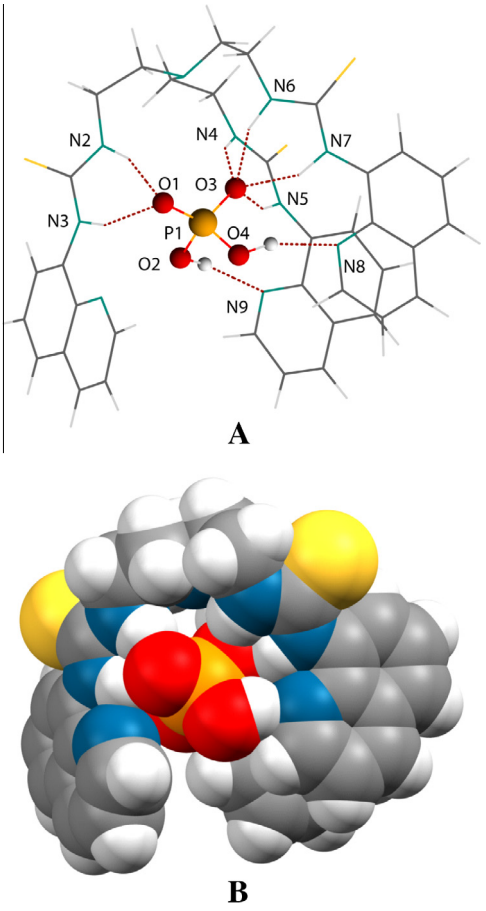

Figure 3. Optimized structure of **L**-dihydrogen phosphate complex showing a (A) perspective view and (B) space filling model.

$H_2PO_4^-$. As seen in Figure 3A, the anion is encapsulated within the cavity and held by six NH···O (2.768–3.934 Å) and two OH···N (2.795 and 2.968 Å) bonds (Table 1). These H-bonding distances are comparable to the reported values observed in the single crystal structure of hydrogen sulfate with tren-based urea (NH···O = 2.85–3.09 Å and OH···O = 2.57 Å).[22] In the complex, one oxygen (O1) is bonded with two NHs of one arm of **L**, while the other oxygen (O3) is held with four NHs of two arms. The later effect drives the two arms closer that are held via π···π interactions. Another important feature in this structure is the participation of two acidic OH groups with the quinoline's nitrogen atoms (N8 and N9) via OH···N interactions. Thus the ligand serves as both an H-bond donor and acceptor in stabilizing the anion complex, which might be a key factor for the high selectivity of **L** for $H_2PO_4^-$ as observed in both ^{1}H NMR and UV titrations.

In conclusion, the tris-thiourea receptor selectively binds dibasic phosphate over hydrogen sulfate, nitrate, and perchlorate in DMSO. As confirmed by DFT calculations, the ligand provides both H-bond donors and acceptors to bind the anion in its cavity. The attached quinoline groups of the ligand have a dual effect: first, they act as chromophores displaying their optical signaling for the sensing of dihydrogen phosphate in solution; second, these groups (through quinolinic N) function as H-bond acceptors for two OH groups present in the dibasic anion. With these excellent anion binding properties of thiourea-based receptors in neutral conditions, this receptor shows promise as a potential sensor for phosphate in other environmental or biological applications.

Table 1
H-bonding distances (Å) in the dihydrogen phosphate complex of **L**

DH···O	D···O (Å)
N2H···O1	2.835
N3H···O1	2.934
N4H···O3	2.841
N5H···O3	2.809
N6H···O3	2.802
N7H···O3	2.768
O4H···N8	2.968
O2H···N9	2.795

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Supplementary data

Supplementary data (synthetic procedure, titration methods, Cartesian coordinates of the phosphate complex of **L**) associated

with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.025.

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