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Oxoanion Recognition by a Thiouronium Receptor

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Abstract: The relative binding affinities of various oxoanions for a simple bis(thiouronium) receptor **2** derived from 1,3-bis(aminomethyl)benzene were determined to be $ArPO_3^{2-} > ArOPO_3^{2-} > H_2PO_4^- > ArCOO^- > ArP(OH)O_2^- > ArOP(OH)O_2^- > ArSO_3^-$ in strongly solvating solvent like DMSO on the basis of ^1H NMR titrations. The relative binding affinity of **2** for various oxoanions can be explained on the basis of the Brönsted basicity of substrate oxoanions and complex structures.

In biological systems, the selective recognition of oxoanion substrates such as phosphate and sulfate often takes place by a combination of hydrogen bonds and electrostatic interactions.[1] Synthetic receptors for the biologically relevant oxoanions have recently been developed using these binding forces and others in strongly solvating solvents such as DMSO, methanol, or water by several research groups.[2-5] In particular, bis(urea) and bis(thiourea) groups have been shown to bind dihydrogenphosphate ($H_2PO_4^-$) selectively over various other anions.[4a] Recently, Smith and co-workers showed that polarization of a urea group by intramolecular coordination with a Lewis acidic boronate as shown in **1a** and **1b**, improved acetate binding affinities by up to 3.0 kcal/mol because of larger host dipole moment and the increased positive surface potential at the urea NH residues induced by internal Lewis acid coordination.[6] Therefore we reasoned that the thiouronium group[7] generated by S-alkylation of the thiourea group would possess relatively larger dipole moment and enhanced acidity of thiourea NH residues and therefore can function as a better oxoanion binder compared to the thiourea group.[8]

In this paper, we report on the complexation behavior of thiouronium receptors **2** and **3** for various oxoanions in DMSO, which is a strong hydrogen bonding acceptor and strongly precludes the formation of hydrogen bond based complex.

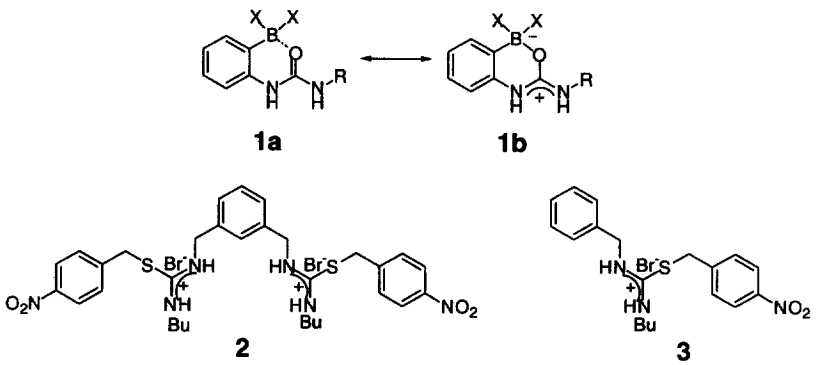

Fig. 1

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Table 1. Association constants of **2** with oxoanions in DMSO-d_6[a]

Oxoanion substrate	pK_a of substrate•H(approx.)[b]	K_a(M^{-1})[c]
$PhSO_3^-$	-6	~5[d]
$PhOP(OH)O_2^-$	1	50(3)
$PhP(OH)O_2^-$	2	150(108)
$H_2PO_4^-$	2	1080(180)
$PhCOO^-$	4	590(130)
$PhOPO_3^{2-}$	6	3700
$PhPO_3^{2-}$	7	4350

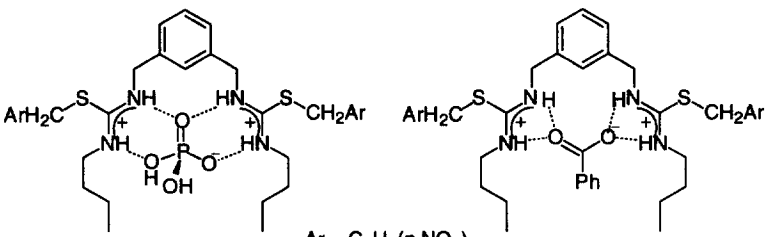
a. Oxoanions were used as their *n*-Bu_4N^+ salts.
b. See refs. 4a and 4b for sources of pK_a data.
c. The number in parenthesis indicates 1:2 complexation constant.
$H + 2G \leftrightarrow HG_2$: K_a (M^{-2}) = $[HG_2]/[H][G]^2$
d. Not accurately determined.

Receptors **2** and **3** were prepared from reaction of *p*-nitrobenzyl bromide with the corresponding bis(thiourea) and mono(thioura) precursors,[4a] respectively.[9] The association constants of sulfonate, carboxylates, phosphate, and phosphonates for thiouronium receptors were determined by proton NMR titrations in DMSO-d_6 (Table 1). For solubility reasons, countercations of anionic guests were replaced by tetrabutylammonium cations.

The new thiouronium receptors bound oxoanions through hydrogen bonding and electrostatic interaction. For the receptor **2**, upfield shifts (~0.5 ppm) of the two different benzylic proton (ArCH_2NH- and Ar'CH_2S-) resonances were observed upon complexation with anionic substrates, while the two different kinds of NH proton peaks rapidly disappeared with increasing anionic substrate concentrations. The relative binding strengths correlate reasonably well with the net charge on the anionic guest, indicating electrostatic interactions as major binding force. Thus, in DMSO-d_6 the dianionic substrates were bound more tightly than their monoanionic counterparts. But that correlation does not explain the difference among substrates possessing the same net charge. The best correlation for the binding strengths of the substrates is with their Brönsted basicity,[4a,4b] as shown in Table 1. Thus, benzensulfonate with the weakest basicity is the weakest binder, and the phosphate and phosphonate dianions with the strongest basicity are the strongest binders.

The one exceptional result was the degree of complexation selectivity for $H_2PO_4^-$. The observed selectivity for $H_2PO_4^-$ can be explained in terms of the complexation geometry. Because $PhCOO^-$ has only two oxygens interacting with the receptor, it must have a different binding mode. The fact that $H_2PO_4^-$ displayed stronger binding affinity than $PhCOO^-$ in spite of its substantially smaller basicity indicated that $H_2PO_4^-$ was not bound in a similar manner to $PhCOO^-$.[4a] Based on the structural similarity to bis(guanidinium)/$H_2PO_4^-$,[2h] bis(thiourea)/$H_2PO_4^-$ and bis(thiourea)/$PhCOO^-$ complexes,[4a] we propose structures **4** and **5** for the complexes of bis(thiouronium) **2** with $H_2PO_4^-$ and $PhCOO^-$, respectively. This hypothesis was also supported by ^1H NMR titration spectra. In fact, the aromatic region signals of the receptor **2** were broad, which indicated that a bis(thiuronium) salt **2** was asymmetrical but slightly distorted in substrate-free condition since two bromides in the anion receptor **2** could play a role of substrate. However, the fact that these signals were sharpened with increasing substrate concentration illustrated that receptor-substrate complex structure was symmetrical as

depicted in **4**. The weaker binding of $H_2PO_4^-$ to mono(thiouronium) receptor **3** (340 M^{-1}) suggested that both thiouronium groups of **2** were involved in complexation as shown in **4**.



4 **5**

Fig. 2

In spite of the same basicity, large difference in K_a between $PhP(OH)O_2^-$ and $H_2PO_4^-$ induced an abstruse problem. It was not clear why phenyl was deleterious, but we might argue that the diminished binding strength of $PhP(OH)O_2^-$ could be rationalzed by the different number of oxygens which could interact with the receptor **2**.

Comparing to thiourea groups as an oxoanion binder,[4a,4c] thiouronium groups turned out to be a relatively stronger binder for oxoanion substrates. For example, a mono(thiouronium) receptor **3** bound acetate in DMSO-d_6 more strongly (K_a = 800 M^{-1}) than a mono(thiourea) (K_a = 340 M^{-1}) and a bis(thiourea) (K_a = 470 M^{-1})[4a], respectively. However, it showed much poorer binding affinity than guanidinium based ones, although it was very similar to those in structure. This fact implied the cationic power of thiouronium was weaker than that of guanidinium, which was well reasoned by relatively large size of sulfur. Since anion basicity is a measure of the propensity to form hydrogen bonds, the observed stability trend suggested that the major importance in the formation of thiouronium-oxoanion complex was hydrogen bond formation rather than electrostatic interaction.

UV absorption experiments in 1,2-dichloroethane showed that the absorbance of **2** above 280 nm increased upon complexation with $H_2PO_4^-$ (K_a = 34000 M^{-1}). In the low $H_2PO_4^-$concentration range (< 2.5 equiv.), a clear isosbestic point was observed. However, the deviation from the clear isosbestic point at high substrate concentration indicated the formation of some amount of 1:2 complexes from one molecule of **2** and two $H_2PO_4^-$ beside the dominant 1:1 complex.

In summary, we have shown that the thiouronium salt can function as an oxoanion receptor and a bis(thiouronium) group can strongly bind $H_2PO_4^-$ in strongly solvating solvent like DMSO. The relative binding affinity of a bis(thiouronium) receptor **2** for various oxoanions can be explained on the basis of the Brönsted basicity of substrate oxoanions and complex structures.

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5. For positively charged receptors using electrostatic interactions, see refs 2a-2i. For neutral receptors having Lewis acid centers, see refs 3a-3f. For neutral receptors having only hydrogen bonding binding sites, see refs 4a-4g.

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9. Selected spectral data for **2** : ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.87 (br, 2H), 9.60 (br, 2H), 8.16 (d, J = 8.3 Hz, 4H), 7.58 (br d, 4H), 7.40-7.00 (m, 4H), 4.66 (s, 4H), 4.56 (s, 4H), 3.34 (m, 4H), 1.55-0.75 (m, 14H); FABMS 637 (M^{2+}-1). **3** : ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (d, J = 8.5 Hz, 2H), 7.55 (br d, 2H), 7.40-7.00 (m, 5H), 4.70-4.50 (m, 4H), 3.33 (m, 2H), 1.55-0.75 (m, 7H); FABMS 358(M^+).