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Anion Recognition Using Preorganized Thiourea Functionalized [3]Polynorbornane Receptors

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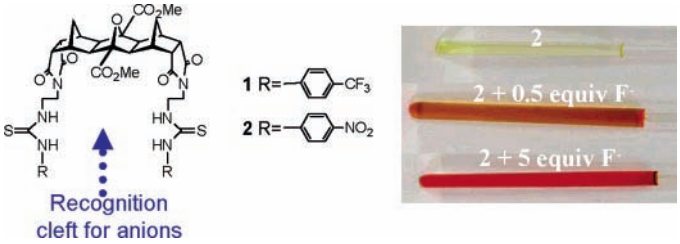
ABSTRACT



A new family of [3]polynorbornane frameworks exhibiting conformationally preorganized aromatic thiourea (cleft-like) receptors have been designed and synthesized for anion recognition. These show excellent affinity for the biologically relevant dihydrogenphosphate ($H_2PO_4^-$) and dihydrogenpyrophosphate ($H_2P_2O_7^{2-}$) anions (among others), which are bound in 1:1 and 2:1 (host:anion) ratio, respectively. Moreover, visually striking color changes accompany guest binding, enabling this family to act as colorimetric anion sensors.

There is currently great interest in the development of supramolecular systems that have the ability to bind and signal the presence of anions, as well as transporting such species across vesicle and cell membranes.[1] Molecules that possess functional groups such as amides, ureas, and thioureas[2−4] as well as guanidinium[4b] and ammonium[4c] derivatives have proven to be particularly effective in this regard as they are able to bind anions using directional hydrogen bonding interactions. Paramount in the design of anionophores are the concepts of preorganization and complementarity. Optimum binding is found for highly rigid

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hosts, with receptor sites preorganized to be complimentary to the respective guest, such as those developed by Davis et al. based on cholic acids.[5] Even though these show strong binding and good selectivity, they often require convoluted and time-consuming syntheses that do not lend themselves to easy modification.[4]

We are interested in anion recognition[2] and have previously employed both anthracene and naphthalimide molecules functionalized with thiourea binding units as luminescent sensors for anions, such as acetate, phosphate, and fluorides, as well as dicarboxylate anions. In this letter, we extend this approach and provide, to the best of our knowledge, the first examples of polynorbornane frameworks preorganized for anion recognition. The cleft-like polynorbornane frameworks are known for their inherent high degree of structural order and, as such, compliment Davis' cholic acid design, yet their synthesis is highly amenable to modification for both size and shape.[5] Appending receptor motifs to these frameworks allows them to be oriented in a specific and predetermined topographical relationship, a feature previously exploited when attaching peptide and intercalator moieties.[6] These frameworks are readily synthesized by the cycloaddition reactions between functionalized cyclobutene epoxides, which ring open under thermal treatment to form carbonyl ylides,[7] and suitable norbornene partners.[8] The methodology is robust, and a range of functionalities are tolerated.[6,7,9] We envisaged that a receptor combining the structural integrity of the [*n*]polynorbornane framework together with proven anionophores, such as ureas, thioureas, and carbamides, would yield a new family of conformationally preorganized anion hosts.[10]

Herein we detail the synthesis of the thiourea functionalized receptors **1** and **2** and report the preliminary anion binding assays of these hosts. For **1** and **2**, we choose the aromatic derived 4-trifluoromethylphenyl and 4-nitrophenyl thioureas as anion receptors, as these electron-withdrawing groups would be expected to increase the acidity of the thiourea protons and hence enhance their anion binding ability through hydrogen bonding. Furthermore, **2** would be expected to display significant color changes upon anion binding due to the concomitant perturbation in the ICT (internal charge transfer) character of the chromophore.

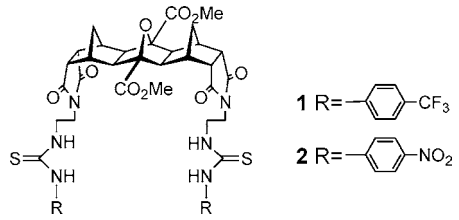
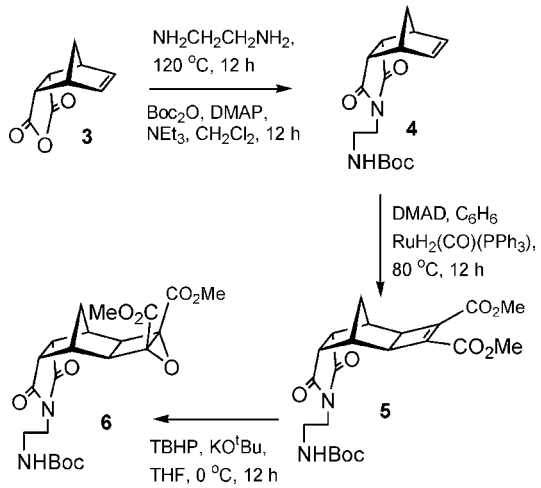


Figure 1. The [3]polynorbornane anion receptors employed within the current study.

The synthesis of **1** and **2** was accomplished in six steps commencing with the Diels−Alder cycloaddition of cyclopentadiene with maleic anhydride to afford *endo*-norborn-5-ene-2,3-dicarboxylic anhydride, **3**, which, following heating in neat 1,2-diaminoethane and treatment with di-*tert*-butyl dicarbonate, gave the crystalline adduct **4** in good yield (Scheme 1). The Mitsudo reaction[11] of **4** provided the

Scheme 1. Synthesis of Cyclobutene Epoxide **6**



cyclobutene diester **5**, which gave **6** in moderate yield (45%) following a modified Weitz−Scheffer epoxidation.[7b,12] Slow evaporation of CH_2Cl_2/EtOAc solutions of **6** yielded crystals suitable for a single-crystal X-ray structure determination, which clearly shows (Figure 2) the cyclobutene ring and the fused epoxide flanked by two methyl ester groups. This arrangement is crucial as it predisposes **6** in such a way that

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(10) Four factors were considered when designing these receptors. (i) Anion size: as most anions of interest are not comparable in size to the large [*n*]polynorbornane framework, hence, only [3]polynorbornanes were employed in this study. (ii) Recognition unit: we chose to use substituted aromatic thioureas as these may be readily tuned to enhance binding affinity. (iii) Symmetry: to facilitate spectroscopic analysis, a highly symmetric framework based on *endo*-norborn-5-ene-2,3-anhydride **3** was chosen. (iv) Rigidity: to maximize the anion−receptor interaction without compromising preorganization, a flexible ethyl spacer was placed between the rigid [3]-polynorbornane backbone and the thiourea receptor units.

(11) (a) Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492. (b) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580.

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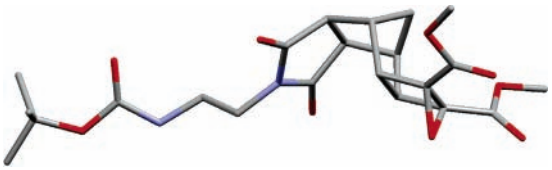
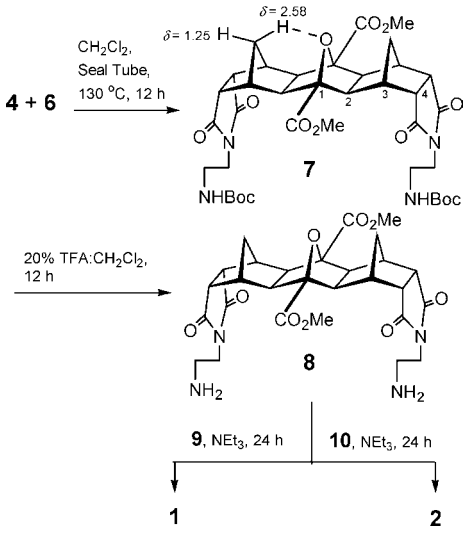


Figure 2. Crystal structure of **6**, as viewed from side-on. See Supporting Information for further details.

subsequent cycloaddition occurs from "below" and ensures the formation of the cleft-like receptor. After successfully synthesizing the requisite epoxide, our attention turned to the 1,3 dipolar cycloaddition reaction (Scheme 2). Heating

Scheme 2. Cycloaddition Reaction to Yield Framework **7**



a dichloromethane solution of epoxide **6** and alkene **4** in a sealed tube overnight afforded the desired [3]polynorbornane framework **7** in 71% yield. The ^{1}H NMR spectrum of **7** was consistent with the proposed structure and consisted of a *tert*-butyl resonance, three methine singlets (δ = 2.02 H_2, δ = 2.56 H_3, δ = 2.97 H_4), a characteristic pair of AM doublets (δ = 1.25 and δ = 2.58) for the nonequivalent bridging protons (δ = 2.58 was assigned to the proton deshielded by the central oxygen; see Scheme 2), two sets of mutiplets (*CH*$_2$, spacer), a clear methyl ester resonance at δ = 3.84, and a broad singlet at δ = 4.87 assigned to the NH protons. Following deprotection with TFA in CH_2Cl_2, reaction with 4-trifluoromethylphenylisothiocyanate (**9**) or 4-nitrophenylisothiocyanate (**10**) gave receptors **1** and **2** in 70 and 45% yield, respectively. The ^{1}H NMR spectra of **1** and **2** were consistent with the proposed structures and displayed clearly resolved thiourea NH resonances and a symmetric *AB* system typical of *para*-substituted benzene derivatives.[13]

The anion binding ability of **1** and **2** was evaluated by titrating DMSO-d_6 solutions of each receptor with anions such as AcO^-, F^-, $H_2PO_4^-$, and $H_2P_2O_7^{2-}$ (as their tetrabutylammonium salts) and monitoring any changes through ^{1}H NMR spectroscopy in the thiourea protons as well as in the aromatic protons. In general, the addition of the anion to the solution of the host gave rise to spectral changes that were in fast exchange and which showed shifts of up to 3 ppm for the thiourea protons. These observations are consistent with the anion interacting with the thiourea protons through hydrogen bonding. We first evaluated the binding of AcO^- to **1** and **2**. On both occasions, an excess of AcO^- was needed to achieve saturation in the thiourea resonances. For instance, for **1**, the two thiourea protons were shifted by 2.86 and 3.15 ppm, respectively, following anion addition. Analysis of the binding isotherms suggested a 1:2 complex formation between **1** and the anion, which is due to linear binding of the ("Y"-shaped) anion to each receptor. Fitting the resulting changes using the program WinEQNMR[14] supported this stoichiometry, with binding constants (log β_1 and log β_2) of 3.5($\pm$0.1) and 2.4($\pm$0.1) for these two interactions. Similarly the binding of AcO^- to **2** gave values of 3.5($\pm$0.1) and 3.0($\pm$0.1), respectively.

A visibly perceptible color change was observed during each titration, which is consistent with the anion hydrogen bonding to the thiourea receptor. This would be expected to affect the efficiency of the ICT character of the resulting *receptor:anion* complex and lead to these spectral changes. Of the anions tested, the strongest color changes were observed for F^-, which showed a distinctive change from light yellow to red (e.g., see graphical abstract).[15]

The changes in the ^{1}H NMR spectra for either **1** or **2** on addition of F^- indicated that hydrogen bonding was not the only contributing factor leading to these color changes. The resonances for the ArN*H* and CH_2N*H* protons had broadened to the point of being unrecognizable after 0.5 and 1.2 equiv of F^-, respectively. These affects are not uncommon on titration with F^-, as we and others have discovered,[2a,b,e,15d,16] as it is sufficiently basic to deprotonate these protons. This finding was supported by the fact that after ca. 2.5 equiv of F^-, the tell-tale peak attributed to $[FHF]^-$ began to appear at ~16.0 ppm[17] and had sharpened to a perfect triplet at 16.1 ppm after the addition of 4.0 equiv of F^-. Consequently, we were unable to accurately determine binding constants from these changes.

The ^{1}H NMR titration data for $H_2PO_4^-$ were much more amenable to interpretation as deprotonation was not an issue here. Regression analysis indicated the most favorable

(13) **1**: Formed as off white solid; mp > 300 °C; HRMS calcd for $C_{44}H_{42}N_6O_9F_6S_2K$ = 1015.1996; found 1015.1947. **2**: Formed as light yellow solid; mp = 197 °C (decompose); HRMS (ES^+) calcd for $C_{42}H_{42}N_8O_{13}S_2Na$ = 953.2210; found 953.2245.

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(15) Color changes in urea-based receptors have been reported, for instance, by: (a) Thiagarajan, V.; Ramamurthy, P.; Thirumalai, D.; Ramakrishnan, T. *Org. Lett.* **2005**, *7*, 657. (b) Jose, D. A.; Kumar, D. K.; Ganguly, B.; Das, A. *Org. Lett.* **2004**, *6*, 3445. (c) Vázquez, M.; Fabbrizzi, L.; Taglietti, A.; Pedrido, R. M.; González-Noya, A. M.; Bermejo, M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1962. (d) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 8909 and references therein.

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(17) Shenderovich, I. G.; Tolstoy, P. M.; Golubev, N. S.; Smirnov, S. N.; Denisov, G. S.; Limbach, H. H. *J. Am. Chem. Soc.* **2003**, *125*, 11710.

binding of $H_2PO_4^-$ to **1** and **2** was in the 1:1 receptor-to-anion stoichiometry and yielded log β values of 3.9(±0.1) and 3.6(±0.1), respectively (Figure 3), rather than 1:2 binding

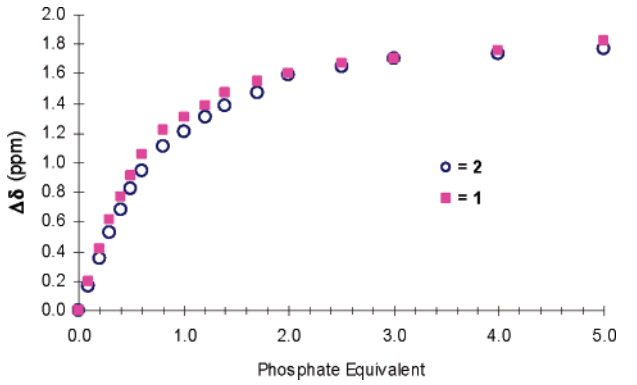

Figure 3. ^{1}H NMR titration results for **1** and **2** against $H_2PO_4^-$; $\Delta\delta$ tracks the changes in the thiourea protons at δ 8.34 and 8.07 for **1** and **2**, respectively.

as in the case of acetate. This suggests that each of the thiourea receptors binds to a single $H_2PO_4^-$, as anticipated, involving four hydrogen bonds.[18]

Having achieved such selectivity, we then evaluated the ability of **1** and **2** to bind bisanions, such as pyrophosphate.[19] The titration of $H_2P_2O_7^{2-}$ against **1** and **2** gave some very interesting and altogether unexpected results. By tracking the changes in the thiourea protons up to the addition of 2 equiv of $H_2P_2O_7^{2-}$, the titration curves (Figure 4) showed

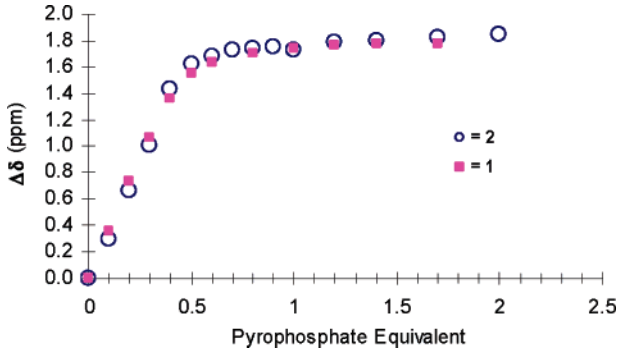

Figure 4. ^{1}H NMR titration results for **1** and **2** against $H_2P_2O_7^{2-}$.

the formation of a 2:1 *receptor-to-anion* stoichiometry. In addition, by monitoring the chemical shifts of the aromatic protons (up to 5 equiv), an identical stoichiometry was obtained. To achieve this stoichiometry, *two* molecules of **1** or **2** must bind a *single* $H_2P_2O_7^{2-}$ anion in a way that might be envisaged to give rise to a self-assembled sandwich

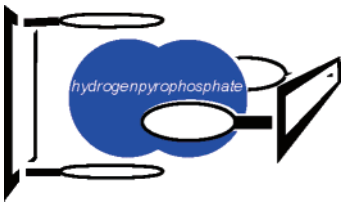

Figure 5. Possible 2:1 (receptor:anion) self-assembled binding arrangement of $H_2P_2O_7^{2-}$ by **1** and **2** depicted in cartoon form.

complex, as depicted schematically in Figure 5. Here, the anion is accommodated in such a way that the two thiourea units in **1** or **2** each coordinate to one phosphate terminus. Regression analysis of the data within Figure 5 determined binding constants that fit the 2:1 binding model, with log β values of 7.9(±0.1) and 7.8(±0.1). This indicates very strong binding.

However, binding of such a magnitude has recently been reported by Molina et al. for phosphate in heteroditopic receptors.[20] One can thus conclude that the nature/structure of these newly developed conformationally preorganized [3]-polynorbornane-based receptors, in conjunction with the nature/structure of the target anion will dictate the binding mode and, hence, the strength of the anion binding

In summary, we have designed, synthesized, and carried out the binding evaluation, using ^{1}H NMR in DMSO-d_6, of two new polynorbornane-based anion receptors. The binding of several anions to these showed that AcO^- formed 1:2 stoichiometric complexes with **1** and **2**, respectively, while $H_2PO_4^-$ gave rise to 1:1 binding and $H_2P_2O_7^{2-}$ formed 2:1 self-assembled structures. We are currently studying other analogues of **1** and **2**.

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Note Added after ASAP Publication. There were minor errors in the text and Scheme 2 in the version published ASAP November 1, 2005; the corrected version was published ASAP November 2, 2005.

Supporting Information Available: Synthetic procedures and characterization of all new compounds; fitting of the ^{1}H NMR data for **1** and **2** for AcO^-, $H_2PO_4^-$, and $H_2P_2O_7^{2-}$ and X-ray crystal structure details (.cif file). This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Otón, F.; Tárraga, A.; Velasco, M. D.; Molina, P. *Dalton Trans.* **2005**, 1159.