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4-Amino-1,8-naphthalimide-based anion receptors: employing the naphthalimide N–H moiety in the cooperative binding of dihydrogenphosphate

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Abstract—The 4-amino-1,8-naphthalimide-based anion receptor **3** binds dihydrogenphosphate with 1:1 stoichiometry through cooperative hydrogen bonding to a naphthalimide N–H and thiourea N–H groups. This was clearly established from ^{1}H NMR titration experiments in DMSO-d_6 where a substantial shift in the resonance for the naphthalimide N–H was observed concomitant with the expected thiourea N–H chemical shift migration upon successive additions of $H_2PO_4^-$. However, whilst ^{1}H NMR titration experiments indicate that **3** was capable of binding other anions such as acetate, the naphthalimide N–H does not participate and the N–H resonance was essentially invariant during the titration. The lack of cooperative binding in this instance was justifiable on steric grounds.

In the field of supramolecular chemistry, charge neutral anion receptors typically rely on hydrogen bonding as the dominant force driving their interaction with anions. Ideally, a number of judiciously placed hydrogen bond donors will maximise the binding strength to a specific anionic species.[1,2] Nature perfectly illustrates this tenet, for example, with the sulfate-binding protein in which seven dedicated hydrogen bonds cooperate on binding the sulfate to ensure both strong binding and selectivity for this anion.[3]

The rapid detection of anionic species is of great significance given the roles they play in the environment and in physiological systems.[1] Our interest in this field has led us to develop luminescent chemosensors for anions using both cationic and charge neutral receptors.[4] Recently, we synthesised and evaluated the combined thiourea/naphthalimide hosts **1** and **2**, as photo-induced electron transfer (PET) chemosensors for anions (Fig. 1).[5] Indeed, the fluorescence emission of **1** and **2**, which occurs in the green, was quenched upon the addition of either acetate or fluoride (~1 equiv) due to the enhanced PET from the bound thiourea receptor to the excited state of the fluorophore. Moreover, we observed a significant green-to-purple colour change at high F^- concentrations and later established that F^- was sufficiently basic to deprotonate the naphthalimide N–H and that this event led to the observed colour change.[6a] Similar deprotonation effects have also been reported by Gale and co-workers[6b] and more recently by Fabbrizzi and co-workers.[6c]

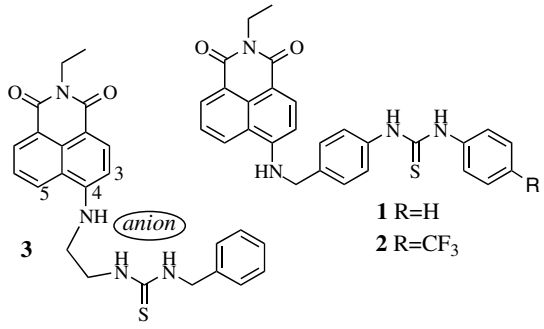

Figure 1. Structures of **1** and **2** and the new naphthalimide host **3**.

Keywords: Supramolecular chemistry; Anion recognition; Hydrogen bonding; Anions; Acetate; Dihydrogenphosphate.
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With the knowledge that the N–H bond is strongly polarised in **1** and **2** it became evident that three N–H groups are capable of interaction with an anionic species: two from the thiourea N–H and the single, *pseudo*-amide, naphthalic amine N–H. However, an unfortunate drawback in the design of **1** and **2** was the incorporation of rigid *para*-substituted aromatic spacers between the thiourea receptor and fluorophore, which rendered the H-bond donors sterically incapable of binding to an anion in a cooperative fashion. Herein, the synthesis of a new 4-amimo-1,8-naphthalimide based host, **3**, is presented along with the evaluation of its anion binding ability by ^{1}H NMR. This more flexible host was designed to test whether both the thiourea H-bond donors *together* with the naphthalic amine N–H may *cooperatively* bind anions. This structurally simple naphthal- imide system was easily prepared and the basic design is amenable to further modification.

The synthesis of **3** was achieved in four steps (Scheme 1) by first reacting 1 equiv of *n*-ethylamine in refluxing toluene with 4-bromo-1,8-naphthalic anhydride, which after aqueous work-up gave the imide **4** in ca. 90% yield as an off-white powder.[5,7] This was followed by nucleophilic aromatic substitution using neat 1,2-diaminoethane to afford amine **5** as a viscous yellow-orange oil in 79% yield. The synthesis of the requisite benzylisothiocyanate **7** was performed using a simple modification of the method of Boas et al.[8] An alternative coupling agent, *N*-ethyl-*N*′-(3-di-methylaminopropyl)carbodiimide hydrochloride (EDCI), was employed in place of benzotriazole-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP). This modification, although requiring a slightly longer reaction time (~72 h), afforded pure **7** in 60% yield after aqueous workup. The reaction of **5** with **7** in chloroform overnight led to the precipitation of **3** in 58% yield.[9]

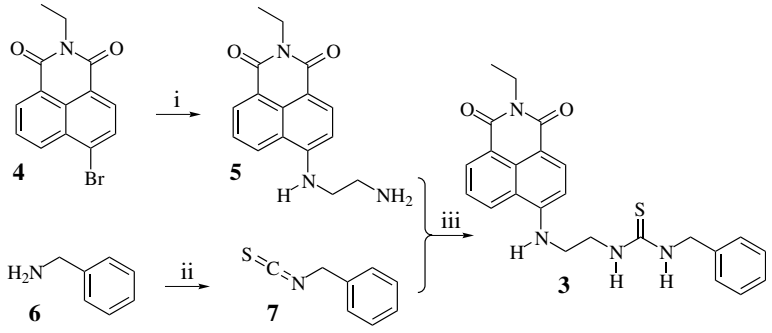
The binding of host **3** to a series of anions was investigated by monitoring the changes in the ^{1}H NMR spectra of DMSO-d_6 solutions of **3** upon addition of AcO^-, $H_2PO_4^-$, F^-, Br^- and I^- (as their tetrabutylammonium salts). The spherical halides were investigated first. However, the additions of either I^- or Br^- afforded only minor changes in the ^{1}H NMR spectrum and we concluded that very weak, if any, binding of these anions occurred.

In the case of F^-, however, the naphthalimide N–H signal became significantly broadened after the addition of only small quantities of the anion and completely disappeared after the addition of only 0.5 equiv. Concomitant with this disappearance was a distinct, visible colour change from yellow/green to deep red/purple. Furthermore, after 2.0 equiv of anion had been added, a new triplet at ca. 16.00 ppm became apparent and was assigned to the formation of the bifluoride $[FHF]^-$ anion[10] in accordance with our previous experience.[6a] The striking colour change and the detection of bifluoride are consistent with F^- mediated deprotonation of the naphthalic amine within **3** rather than binding of the anion to the thiourea moiety.[6a]

In contrast to these changes, the successive addition of AcO^- to DMSO-d_6 solutions of **3** resulted in significant changes in the chemical shifts of several protons (Fig. 2). As anticipated, the largest shifts were seen for the two thiourea proton resonances, which experienced significant downfield shifts of ca. 2.5 ppm, indicative of strong hydrogen bonding between the anion receptor and the acetate anion. Furthermore, significant changes were also seen in the proximate benzylic protons. However, only a small shift in the naphthalimide N–H resonance (along with negligible shifts for the remaining naphthalimide ring protons e.g., H5, Fig. 3) was observed and it can therefore be concluded that it is not involved to any great extent in binding acetate despite the increased flexibility of the host. A plot of $\Delta\delta$H for the thiourea protons versus equivalents of acetate provided isotherms consistent with a 1:1 host/guest stoichiometry (Fig. 3). Furthermore, a binding constant, $\log\beta$, of 3.6($\pm$0.1) was determined when fitting these data with the Win EQNMR programme.[11]

A molecular modelling representation,[12] of the proposed host/guest complex is shown in Figure 4. In the modelled arrangement, the anion binds exclusively to the thiourea N–H protons with no indication of binding to the naphthalimide N–H. Indeed, the anion is at such a distance from the naphthalimide ring that it would be expected to exert little influence upon it, which is consistent with the ^{1}H NMR titration experiment.

The successive addition of the tetrahedral dihydrogenphosphate anion to a DMSO-d_6 solution of **3** also



Scheme 1. Synthesis of host **3** from 4-bromonaphthalic anhydride. Reagents and conditions: (i) Ethylenediamine, 80 °C, 12 h, 79%; (ii) CS_2, EDCI, DIPEA, DMF, 72 h, 60%; (iii) $CHCl_3$, 12 h, 58%.

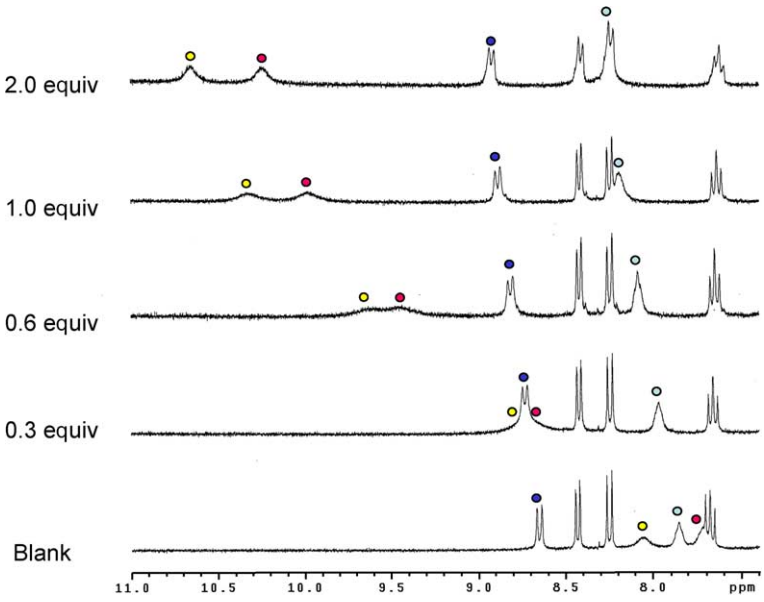


Figure 2. Stack plot of ^{1}H NMR spectra (in DMSO-d_6) of **3** after addition of various quantities of TBA·OAc: Red (●) and yellow (●) track thiourea N–H protons, dark blue (●) tracks H5 of the naphthalimide and light blue (●) tracks the naphthalimide amino N–H proton.

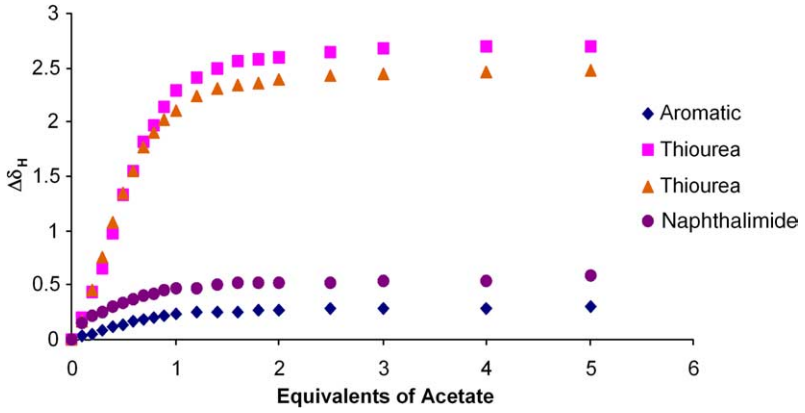


Figure 3. Changes in the chemical shift of relevant protons within **3** upon addition of AcO^{-} in DMSO-d_6.

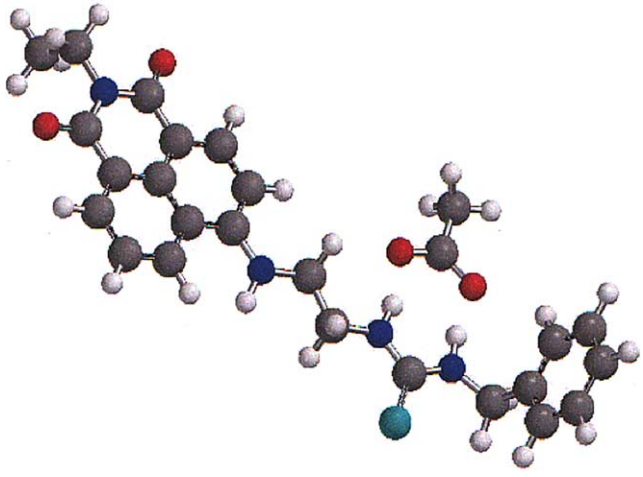


Figure 4. The proposed structure of the 1:1 adduct formed between **3** and AcO^{-} showing H-bonded pairs.

produced significant changes in the chemical shifts of several protons (Fig. 5). As previously observed, the thiourea N–H proton resonances experienced a significant downfield shift of ca. 1.8 ppm, indicative of strong hydrogen bonding of the receptor to the $H_2PO_4^{-}$ anion. A plot of $\Delta\delta$H for several resonances as a function of anion equivalents gave binding isotherms consistent with 1:1 host/guest stoichiometry (Fig. 6). From these changes, a binding constant log β of 3.4($\pm$0.1) was determined.[11] Significantly, and in direct contrast to the results obtained upon the addition of acetate, a large downfield shift of 1.6 ppm was observed for the naphthalimide N–H proton, which is of similar magnitude to that experienced by the thiourea N–H protons. Furthermore, of the remaining protons only that at position 5 of the naphthalimide ring experienced an appreciable shift (ca. 0.5 ppm, see Fig. 6). These observations suggest that the binding event involves the naphthalimide N–H and is occurring quite close to the naphthalimide

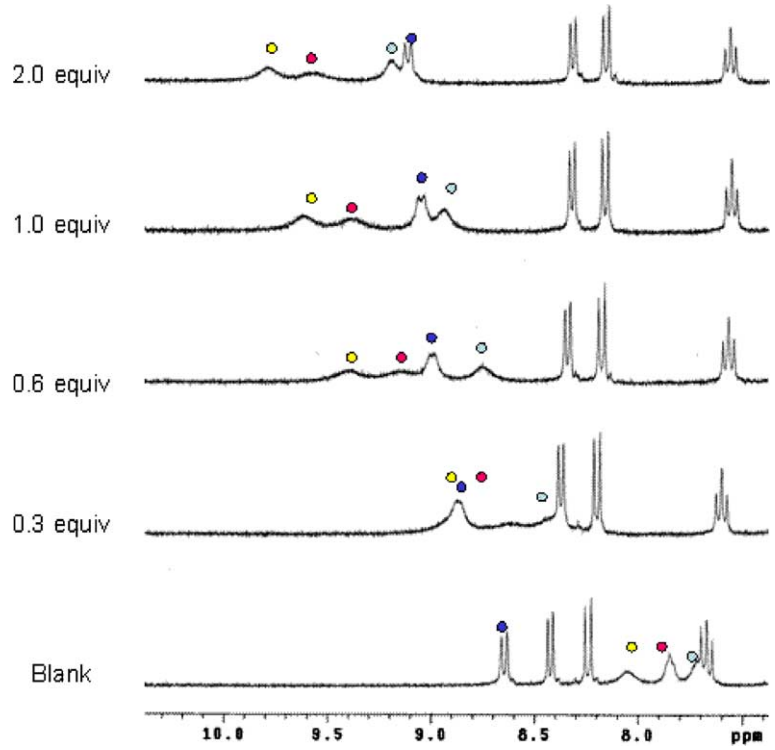


Figure 5. Stack plot of ^{1}H NMR spectra (in DMSO-d_6) of **3** after addition of various quantities of TBA·H_2PO_4. Red (●) and yellow (●) track thiourea N–H protons, dark blue (●) tracks H5 of the naphthalimide and light blue (●) tracks the naphthalimide amino N–H proton.

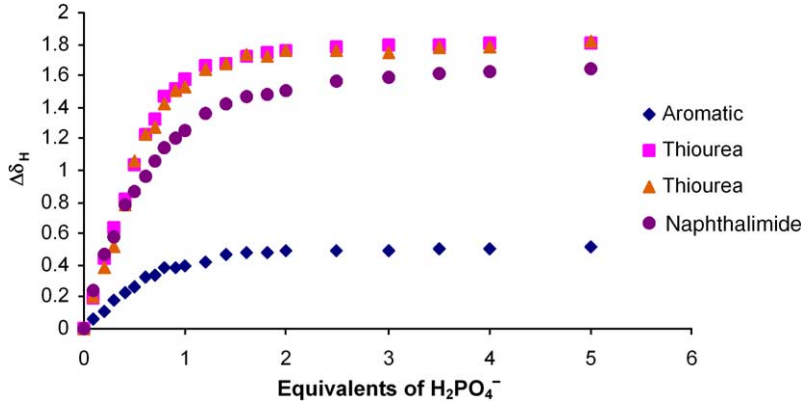


Figure 6. Changes in the chemical shift of relevant protons within **3** upon addition of $H_2PO_4^-$ in DMSO-d_6.

ring system, and that the naphthalimide N–H works in concert with the thiourea protons and cooperatively binds the anion.

Comparing the binding constants observed for AcO^- versus $H_2PO_4^-$, for **3** to that observed previously for **1** and **2** also supports the cooperative nature of the binding event. For **2**, a binding constant of 3.9(±0.1) and 2.9(±0.1) was determined for AcO^- and $H_2PO_4^-$, respectively, which demonstrates that the binding of $H_2PO_4^-$ to **3** is significantly enhanced. To investigate this binding mode further, we carried out a simple molecular modelling determination of the proposed **3**:$H_2PO_4^-$ host/guest complex (Fig. 7). The proposed complex clearly shows the binding of the anion to the naphthalimide N–H, in addition to the two thiourea H-bond donors. The anion is placed at such a distance from the naphthalimide ring that some influence on the naphthalimide H5 proton would be expected and as such, the arrangement proposed in Figure 7 is in agreement with the results of the ^{1}H NMR titration experiment.

It is also important to note that even though the binding constant of receptor **3** for AcO^- ($\log\beta = 3.6$) is less than those determined for receptors **1** and **2** ($\log\beta = 3.9$ and 4.0, respectively),[5] the aliphatic thiourea protons in **3** are not as acidic as the aromatic thiourea protons in either of **1** or **2** due to the absence of electron withdrawing substituents, and hence would be considered less powerful

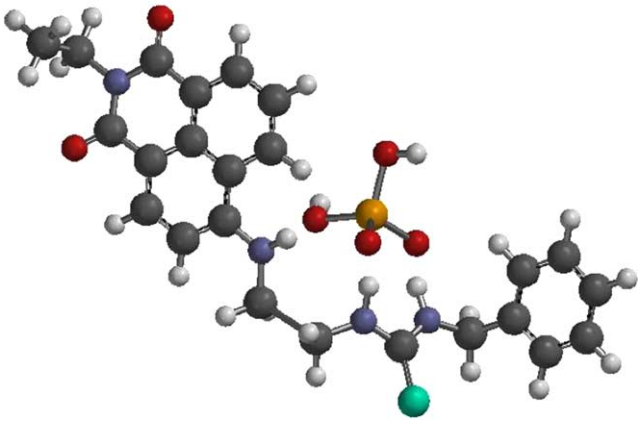


Figure 7. The proposed structure of the 1:1 adduct formed between **3** and $H_2PO_4^-$ showing H-bonded pairs.

hydrogen bond donors. Despite this, the binding of $H_2PO_4^-$ to **3** is stronger than to the simple aromatic thiourea **1** and only the more electron withdrawing trifluoromethyl substituted aromatic thiourea **2** ($\log\beta = 4.0$) is more powerful. This clearly demonstrates the cooperative effect of the naphthalimide 4-amino moiety in **3**.

Unfortunately, even though the hydrogen bonding of $H_2PO_4^-$ to the amine gave rise to large changes in the ^1H NMR, no significant luminescence changes were observed for **3** upon titration with the above anions. This is most likely due to the longer spacer used in **3** compared to that in **1** and **2**, which reduces the PET quenching efficiency. Similarly, the aliphatic-based receptor in **3** is not as electron rich as the aromatic analogue used in **1** and **2**, which would further reduce the PET quenching efficiency.

In conclusion, several specific features of **3** and those of the anions it binds may be used to explain the results observed from ^1H NMR studies. Firstly, the complementarity of the 'Y-shaped' AcO^- anion and the thiourea receptor dictates the preference of AcO^- for this site. The naphthalimide N–H in **3** appears, therefore, to be incapable of cooperatively participating in this interaction on steric grounds and this is supported by the molecular modelling study. However, the tetrahedral $H_2PO_4^-$ anion has two further oxygen atoms available for hydrogen bonding in addition to the two that interact with the thiourea moiety. The increased degree of freedom and the relaxed steric restrictions associated with this allow **3** to use the naphthalimide N–H to participate cooperatively in binding.

In summary, we have shown that naphthalimide N–H and thiourea can cooperatively bind the tetrahedral $H_2PO_4^-$ anion and give rise to significant enhancement in binding affinity in **3** when compared to **1** and **2**. We are currently evaluating frameworks that can elicit a distinctive visible or luminescent response following efficient binding of anions using receptors based upon **3**.

Acknowledgements

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9. *N*-Ethyl-4-[(2′-benzylthioureyl)-ethylamino]-1,8-naphthalimide **3**: Yield 0.71 g (58%), mp 213.6–214.3 °C. Anal. Calcd for $C_{24}H_{24}N_4O_2S$: C, 66.64; H, 5.59; N, 12.95. Found: C, 66.60; H, 5.48; N, 12.84. ^{1}H NMR (DMSO-d_6) δ: 1.15 (3H, t, $J = 6.8$ Hz, NCH_2CH_3), 3.55 (2H, d, $J = 5.9$ Hz, urea–CH_2CH_2), 3.78 (2H, br s, urea–CH_2CH_2), 4.03 (2H, q, $J = 6.8$ Hz, NCH_2CH_3), 4.63 (2H, br s, CH_2Ph), 6.89 (1H, d, $J = 8.7$ Hz, H3), 7.24 (5H, m, Ph), 7.68 (1H, t, $J = 7.3$ Hz, H6), 7.71 (1H, br s, BnNHC(S)N*H*), 7.84 (1H, br s, naphthNH), 8.06 (1H, br s, BnN*H*C(S)NH), 8.24 (1H, d, $J = 8.5$ Hz, H2), 8.42 (1H, d, $J = 7.3$ Hz, H5), 8.64 (1H, d, $J = 8.3$ Hz, H7). ^{13}C NMR (DMSO-d_6) δ: 13.3, 34.3, 42.1, 42.7, 79.1, 103.9, 107.9, 120.1, 121.9, 124.3, 126.8, 127.3, 128.2, 128.5, 129.3, 130.6, 134.1, 150.7, 162.7, 163.5.
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