Steric and electronic factors influencing recognition by a simple, charge neutral norbornene based anion receptor†

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Based on ^{1}H NMR studies, subtle electronic factors rather than pre-organisation dictate the binding stoichiometry of the new, norbornene based, anion hosts 1 and 2 with acetate, however, the binding of dihydrogenphosphate appears to be based solely on steric constraints.

Given the key roles that anionic species play in many biological, chemical and environmental processes[1] it is no surprise that anion recognition and sensing using charge neutral hosts is a rapidly growing area of research within the field of supramolecular chemistry.[2]

Ideal charge neutral receptors have multiple strong hydrogen bond donors, such as amides and ureas, to selectively bind their target;[2,3] as an example, the phosphate binding protein incorporates a total of twelve hydrogen bonds cooperating within the anion binding cavity to ensure both a strong and selective recognition event.[4]

A multitude of rigid sub-units have previously been employed as pre-organising scaffolds including xanthenes, calixpyrroles, cholic acid, and azophenols.[5] Our interest in this field has led us to examine polynorbornanes as pre-organising elements for the construction of neutrally charged anion receptors.[6] Norbornenes are prime candidates for use as molecular scaffolds as they boast an inherent high degree of structural rigidity and are easily constructed through well established Diels–Alder methodologies.[7] The desirable traits of norbornenes as frameworks has led to their use as alternatives to natural reverse turn residues in proteins for self-assembled structure studies.[8]

With an eye to attaching six hydrogen bond donor sites to a norbornene based host, receptors **1** and **2** were designed. As can be seen (Fig. 1), such hosts have a high degree of pre-organisation, yet the anionophoric 'arms' possess an element of flexibility and therefore offer the possibility of binding an anionic guest through the cooperation of all six hydrogen bond donors. Herein the synthesis of the new norbornene based receptors **1** and **2** is presented, as well as the results of the preliminary anion binding assays using ^{1}H NMR titration techniques.

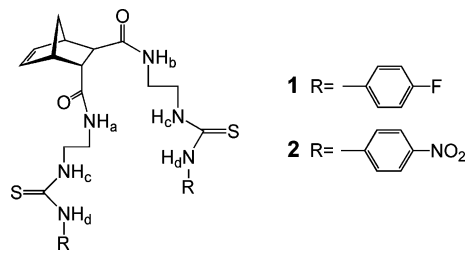
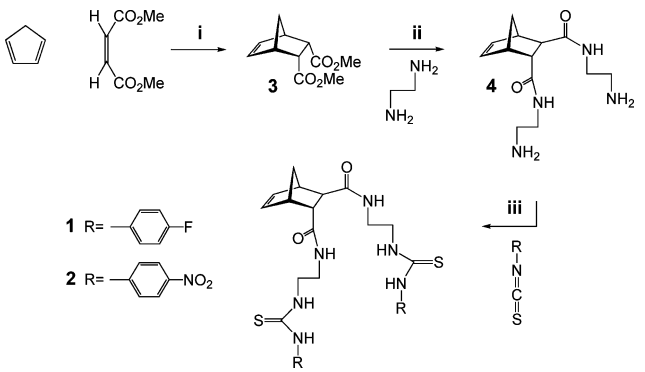


Fig. 1 Structures of the new norbornene based hosts **1** and **2**.

The synthesis of **1** and **2** was accomplished in three steps (Scheme 1) commencing with the Diels–Alder cycloaddition of neat cyclopentadiene with an equimolar amount of dimethyl maleate to give, in quantitative yield, *endo*-2,3-dicarbomethoxy-norborna-5-ene **3**.[7a] Diester **3** was converted directly to the bis-amide product **4**, which was isolated as an extremely viscous orange–brown oil. The conditions required to convert the methyl ester to the amide (100 °C, neat diamine, 19 h) resulted in epimerisation of the *endo*-dicarbonyl compound and the thermodynamically more stable *endo–exo* adduct was obtained.[9] The resultant crude oil **4** was used directly in the next step, where, following reaction with either 4-fluorophenylisothiocyanate or 4-nitrophenylisothiocyanate, receptors **1** and **2** were formed in 69% and 48% yield respectively after chromatographic purification.[10]



Scheme 1 Synthesis of hosts **1** and **2** from cyclopentadiene and dimethyl maleate. *Reagents and conditions*: (i) RT, 5 h, 100% (ii) 100 °C, 19 h, 98% (iii) $CHCl_3$, RT, 24 h, **1** 69%, **2** 48%.

The ability of the new hosts to recognise anions was evaluated by titrating DMSO-d_6 solutions of Br^-, Cl^-, F^-, HSO_4^-, $H_2PO_4^-$ and AcO^- (as their tetrabutylammonium (TBA) salts) against DMSO-d_6 solutions of each host, and monitoring the migrations of the relevant N–H proton resonances using ^{1}H NMR spectroscopy.

Firstly, the spherical halides were investigated and the addition of Br elicited only minor changes in the ^{1}H NMR spectrum (max $\Delta\delta$ = 0.09 ppm after 6.0 equivalents, Table 1). Similar results were obtained for the addition of Cl^-, although the changes observed were slightly larger (max $\Delta\delta$ = 0.74 ppm after 6.0 equivalents). This led to the conclusion that very weak, if any, binding occurred between Br^- or Cl^- and **1** or **2**. On the other hand,

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† Electronic supplementary information (ESI) available: Full synthetic details for receptors **1** and **2**, job and fit plots for binding studies. See DOI: 10.1039/b703626b

Table 1 Maximum observed shifts and calculated binding constants[a]

	Receptor **1** (4-fluorophenyl)			Receptor **2** (4-nitrophenyl)		
	Max $\Delta\delta$/ppm[b]	Log k_1[c]	Log k_2	Max $\Delta\delta$/ppm	Log k_1	Log k_2
Br^-	0.09	—	—	0.06	—	—
Cl^-	0.51	—	—	0.74	—	—
F^-	1.62[d]	—	—	1.35[d]	—	—
HSO_4^-	0.09	—	—	0.04	—	—
$H_2PO_4^-$	1.94	3.6	2.7	1.84	3.1	2.6
AcO^-	3.24	3.8	2.7	3.14	3.3	—

[a] Binding constants were determined from ^{1}H NMR titration data using WinEQNMR software.[12] [b] Maximum chemical shift observed for H_c after the addition of 6 equivalents of anion. [c] All calculated binding constant errors are <13.0%. [d] Values after 1.6 equivalents of added anion.

when F^- was examined, the thiourea N–H resonances became considerably broadened after the addition of only 0.1 equivalents of F^-, yet migrated significantly (max $\Delta\delta \approx 1.62$ ppm after 1.6 equivalents), whereupon, they became indistinguishable from the baseline. Accompanying this signal disappearance was a distinct, successive, colour change from pale yellow through to deep red for receptor **2** (containing the strong electron withdrawing nitro (NO_2) substituent) which was clearly visible to the naked eye. This colour change, likely due to deprotonation, provided evidence that these norbornene-based receptors could function as colorimetric sensors.[6,11] Saturation of the hosts had not been achieved before the N–H signals disappeared, therefore receptor-to-anion stoichiometry and binding constants for F^- could not be accurately determined.

The tetrahedral anions HSO_4^- and $H_2PO_4^-$ were next examined, however when HSO_4^- was added to either of the new hosts only minor changes in the ^{1}H NMR spectrum were observed ($\Delta\delta \approx$ 0.09 ppm after 6.0 equivalents), indicating weak, if any, binding of HSO_4^-. In contrast, upon addition of the $H_2PO_4^-$ anion, significant changes in the chemical shifts of the protons of interest were observed. As expected, the largest shifts were observed for the four thiourea proton resonances, which experienced significant downfield shifts for both hosts **1** and **2** (maximum $\Delta\delta = 1.97$ and 1.84 ppm, respectively, after 6.0 equivalents). When considering the two amide proton resonances, significant changes were also observed and it was of great interest that the changes were not equal (for **1** H_a *endo* $\Delta\delta = 0.39$ ppm, H_b *exo* $\Delta\delta = 1.03$ ppm, Fig. 2). Whilst a 1 : 1 host–guest binding stoichiometry might have been expected, experimental job plot data for the strong binding of both **1** and **2** with $H_2PO_4^-$ indicated that a 1 : 2 host–guest stoichiometry was occurring (Fig. 3). This result suggested that the pre-organised cavity size of the host was inappropriate to accommodate the larger $H_2PO_4^-$ anion, thus the two anionophoric 'arms' act independently to bind one guest each. Although the guests are primarily bound by the thiourea protons, there is undoubtedly a degree of cooperation from the amide protons as evidenced by their significant $\Delta\delta$. Binding constants (Table 1) were determined by fitting the ^{1}H NMR titration data using WinEQNMR.[12]

In the characterisation of the new receptors through multiple 1D and 2D ROESY experiments, it was established that a through space interaction was occurring between amide N–H_a of the *endo* 'arm' of both **1** and **2** and H_1 of the norbornene scaffold (Fig. 5). This interaction suggests that the lack of cooperation of N–H_a when binding $H_2PO_4^-$ to the *endo* 'arm' was based on steric

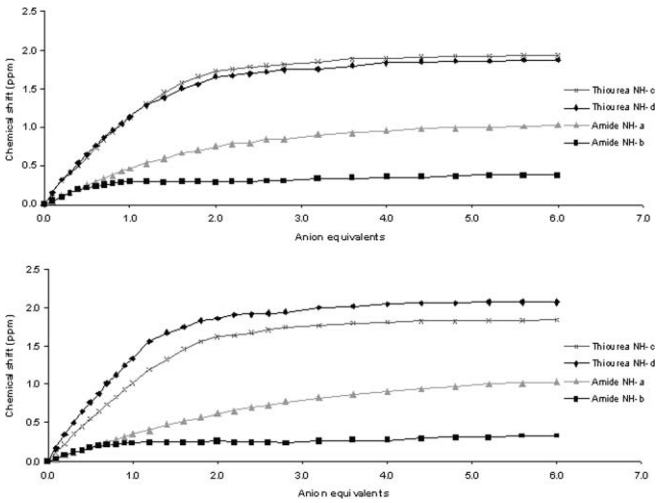

Fig. 2 Changes in the chemical shift of relevant N–H protons within **1** (top) and **2** (bottom) upon addition of $H_2PO_4^-$ in DMSO-d_6.

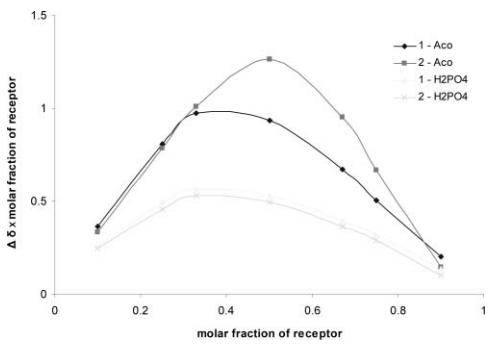

Fig. 3 Job plots for complexation of receptors **1** and **2** with AcO^- and $H_2PO_4^-$ at a total concentration of 12.5 mM.

reasons. Indeed, in kinetic studies examining *endo versus exo* norbornene substituents the *endo* position was found to be less reactive than the *exo* and this difference was justified by steric constraints.[13]

Finally, the trigonal planar AcO^- anion was evaluated. Successive additions to DMSO-d_6 solutions of the two new receptors resulted in considerable changes in the chemical shifts of the thiourea protons (Fig. 4). For receptors **1** and **2** a max $\Delta\delta$ of 3.33 and 3.14 ppm was observed after 6.0 equivalents, respectively (Table 1). As was observed when titrating F^- against receptor

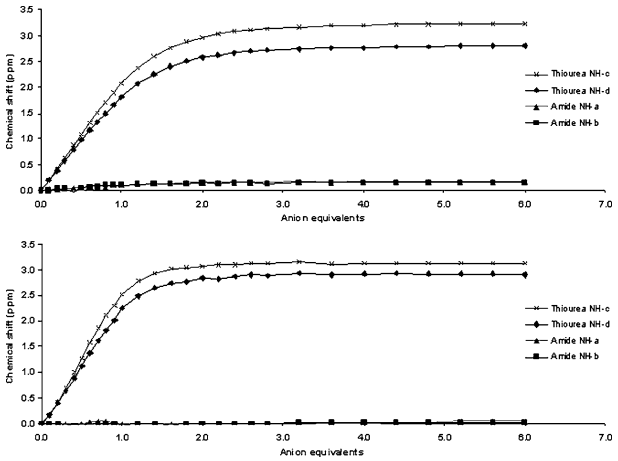

Fig. 4 Changes in the chemical shift of relevant N–H protons within **1** (top) and **2** (bottom) upon addition of AcO^- in DMSO-d_6.

2, a distinct visible colour change accompanied the significant downfield shifts for **2** yet each N–H resonance was still clearly visible in the spectrum after 9 equivalents of the anion had been added.‡ For both receptors, the usual trend of larger shifts for the thiourea proton resonances was observed, however, unlike the titrations for $H_2PO_4^-$, the amide proton resonances essentially remained unchanged (Fig. 4). This was indicative of strong hydrogen bonding between the thiourea protons of the anionophoric 'arms' and the geometrically complementary acetate anions. The lack of variation in the amide proton resonances suggested that the AcO^- anion was binding near exclusively with the thiourea protons.

The job plot data for receptor **1** (Fig. 3) however was not consistent with a 1 : 1 host–guest stoichiometry and indicated a 1 : 2 host–guest arrangement and that the two 'arms' were acting independently and binding a single anion each (Fig. 5). This result was typical for thiourea recognition units as the trigonal planar AcO^- anion complements this hydrogen bond donor system very well.[3a] It was therefore surprising that for receptor **2** the job plot data suggested a 1 : 1 host–guest stoichiometry (Fig. 3), where the anion was bound within the receptor cavity through the cooperation of all *four* thiourea hydrogen bond donors (Fig. 5). Whilst there are numerous examples of a *single* thiourea recognition unit binding a *single* AcO^- anion,[3,14] examples of *two* thiourea units binding a *single* AcO^- are less common and steric complementarity and pre-organisation arguments are usually invoked to explain these examples.[15]

Although it is well understood that a pre-organised binding site is crucial for complementing a guest,[2,3,5] the contradicting host–guest binding stoichiometry of **1** and **2** against AcO^- requires further explanation. The dimensions of the binding site of both receptors are essentially identical given that they have the same level of norbornene based pre-organisation. The only difference is the phenyl substituent: F for **1** and NO_2 for **2**. Therefore, the answer is likely due to electronic rather than steric reasons. When comparing the acidity of *p*-substituted benzoic acids it is intuitive that deactivating (electron withdrawing) groups increase acidity by stabilizing the carboxylate anion, and the opposite is true of activating groups. For example, the pK_a of 4-nitrobenzoic acid and 4-fluorobenzoic acid are 3.43 and 4.15, respectively.[16] In the current study, the same argument explains the increased acidity of the thiourea N–H_d protons (Fig. 5) in receptor **2**. This makes these N–H groups of **2** stronger hydrogen bond donors which in turn, based on the results of this study, better enables the four hydrogen bond donors to cooperatively bind the single AcO^- guest (Fig. 5).

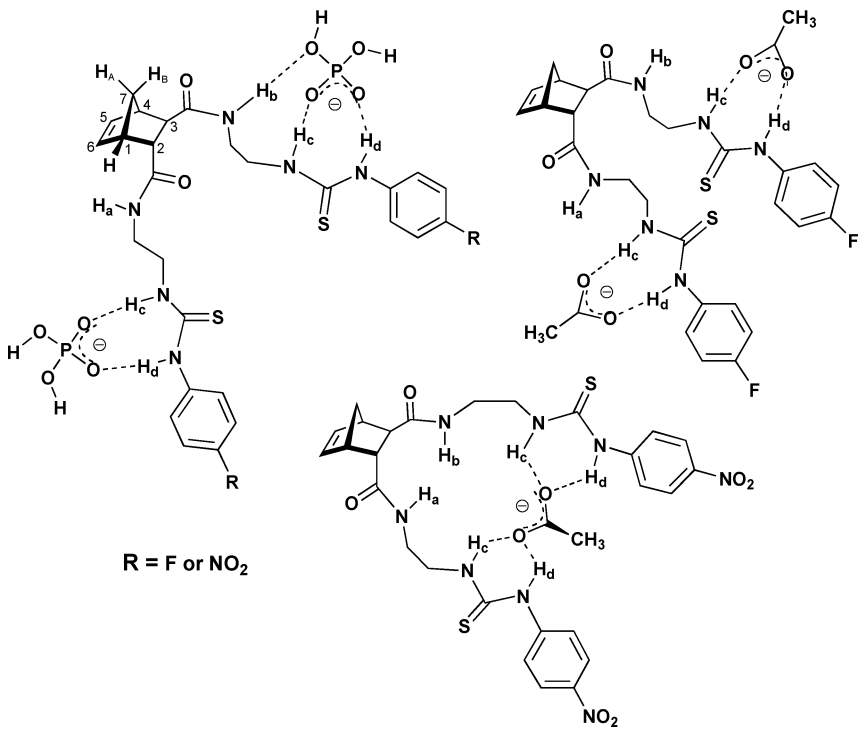

Fig. 5 Proposed binding conformations of both receptors with $H_2PO_4^-$ (top), receptor **1** with AcO^- (top), and receptor **2** with AcO^- (bottom).

In summary, we have designed, synthesised and evaluated two new conformationally pre-organised norbornene-based anion receptors **1** and **2**. These receptors bind $H_2PO_4^-$ in a 1 : 2 fashion with each 'arm' adopting an independent conformation. The unexpected 1 : 2 and 1 : 1 binding of **1** and **2** with AcO^- provides further insight as to how subtle electronic effects can have a major impact on overall host–guest binding. Further investigations into steric and electronic effects in similar pre-organised hosts are ongoing and will be reported in due course.

Notes and references

‡ It was unusual that the colour change was not accompanied by the disappearance of the thiourea N–H resonance (indicative of deprotonation) even when a reasonable excess of the moderately basic acetate anion (9 eq.) had been added. The authors have no definite explanation but suspect very strong H-bonding or a tautomeric equilibrium similar to that observed by Fabbrizzi *et al*.[17]

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10 **Receptor 1**: yield 665 mg (68.7%) of fine white powder; mp 93.2–95.3 °C; δ_H (399.78 MHz, DMSO-d_6, Me_3Si) 1.21 (1H, d, *J* 4.7, $H7_A$), 1.68 (1H, d, *J* 5.3, $H7_B$), 2.54 (1H, s, H3), 2.84 (1H, s, H4), 3.16 (2H, s, H1,2), 3.22 (2H, m, CH_2), 3.34 (2H, m, CH_2), 3.51 (4H, b m, 2 × CH_2), 5.95 (1H, t, *J* 2.2, H6), 6.18 (1H, t, *J* 2.1, H5), 7.15 (4H, m, ArH), 7.36 (4H, m, ArH), 7.68 (2H, b s, Hc), 7.87 (1H, t, *J* 3.3, Ha), 8.07 (1H, t, *J* 3.4, Hb), 9.58 (2H, b, Hd); δ_C (67.94 MHz, DMSO-d_6, Me_3Si): 44.3, 46.2, 47.0, 47.4, 48.1, 49.6, 115.7, 116.0, 126.5, 135.2, 135.8, 137.8, 157.9, 161.4, 173.1, 174.5, 181.4; *m/z* (HRMS) 573.1918 ([M + H]$^+$. $[C_{27}H_{30}O_2N_6S_2F_2 + H]^+$ requires 573.1919). **Receptor 2**: yield 786 mg (47.7%) of fine yellow powder; mp 127.6–129.4 °C; δ_H (399.78 MHz, DMSO-d_6, Me_3Si) 1.21 (1H, d, *J* 5.2, $H7_A$), 1.69 (1H, d, *J* 5.1, $H7_B$), 2.53 (1H, s, H3), 2.87 (1H, s, H4), 3.19 (2H, s, H1,2), 3.28 (2H, m, CH_2), 3.32 (2H, m, CH_2), 3.57 (4H, b m, 2 × CH_2), 5.97 (1H, t, *J* 1.7, H6), 6.19 (1H, t, *J* 1.5, H5), 7.79 (4H, d, *J* 5.4, ArH), 7.94 (1H, s, Ha), 8.13 (1H, s, Hb), 8.17 (4H, d, *J* 5.6, ArH), 8.28 (2H, b s, Hc), 10.24 (2H, b, Hd); δ_C (100.54 MHz, DMSO-d_6, Me_3Si): 14.7, 21.4, 44.5, 46.4, 47.1, 48.5, 49.1, 60.6, 121.8, 125.8, 135.9, 138.6, 143.2, 147.5, 174.1, 175.5, 181.8; *m/z* (HRMS) 627.1803 ([M + H]$^+$. $[C_{27}H_{30}O_6N_8S_2 + H]^+$ requires 627.1809).

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