Size matters—strong binding of the terephthalate dianion by thiourea functionalised fused [*n*]polynorbornane hosts†

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Received (in Cambridge, UK) 31st January 2008, Accepted 26th February 2008
First published as an Advance Article on the web 18th March 2008
DOI: 10.1039/b801798k

Remarkably strong binding of the new [*5*]polynorbornane based host 2b to the terephthalate dianion is based on size complementarity of the preorganised binding cleft with the rigid dicarboxylate guest.

Abundant in nature, anions are critical to life; indeed the recognition, transport and transformation of anionic species is involved at some level in almost every conceivable biochemical operation.[1] More specifically, dicarboxylates are involved in the generation of high-energy phosphate bonds and numerous metabolic processes including the citric acid and glyoxalate cycles.[2] As such, the construction of selective receptors for these dianionic species is a worthy endeavour.

Size complementarity, as pioneered by Cram,[3] plays a key role when attempting to selectively bind anionic guests as they exist in a wide range of geometries when compared to their simple cationic counterparts.[4] Crystal structures of enzyme–anionic substrate complexes (*e.g.* sulfate/phosphate binding proteins, DNA helicase Rep A) clearly illustrate the importance of preorganisation and size complementarity for selective recognition.[1,5]

Examples of synthetic hosts exhibiting such specific host:guest complementarity are less common, however, highly selective anion recognition has been achieved using a variety of macrocyclic frameworks,[6] calix[*4*]arenes,[7] and cholic acid derivatives.[8]

The design of the hosts employed herein relies on rigid [*n*]polynorbornane frameworks that can, through well established methodologies,[9] be tailored to different sizes. Such scaffolds are therefore ideally suited for constructing hosts to complement a guest of a specific size or shape. Hosts **1** and **2** (Fig. 1) were designed with [*3*]- and [*5*]polynorbornane scaffolds, respectively, and contain two thiourea groups for anion recognition. The short ethylene spacers allow a degree of flexibility for *induced fit*, potentially optimising binding interactions. Previous studies have indicated that electronic properties can have a significant impact on host:guest binding stoichiometry,[10] therefore 4-fluorophenyl and the more electron withdrawing 4-nitrophenyl substituents were included in the design. Herein, the full synthesis of **1** and **2** is presented, followed by the results of anion binding assays performed by means of ^{1}H NMR spectroscopy.

The synthesis of **1**‡ (Scheme 1) required six steps in total. Heating anhydride **3** with *tert*-butyl (2-aminoethyl)carbamate[11] afforded the Boc protected imide **4**.[12] Following Mitsudo reaction[13] of alkene **4** with dimethyl acetylenedicarboxylate (DMAD), the resultant alkene diester was subjected to Weitz–Scheffer epoxidation[14] using *tert*-butyl hydroperoxide (TBHP) to yield epoxide **5**. The [*3*]polynorbornane framework **6** was formed using a 1,3-dipolar cycloaddition between epoxide **5** (which ring opens to form a carbonyl ylide) and alkene **4**. Removal of the Boc groups with dilute TFA produced the free diamine **7** which was reacted with 4-fluorophenyl isothiocyanate, or 4-nitrophenyl isothiocyanate, to produce **1a** and **1b**, respectively.

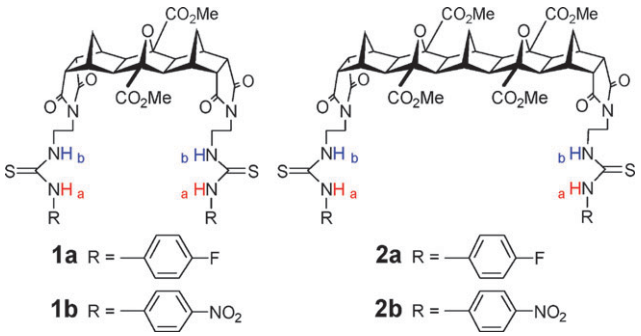
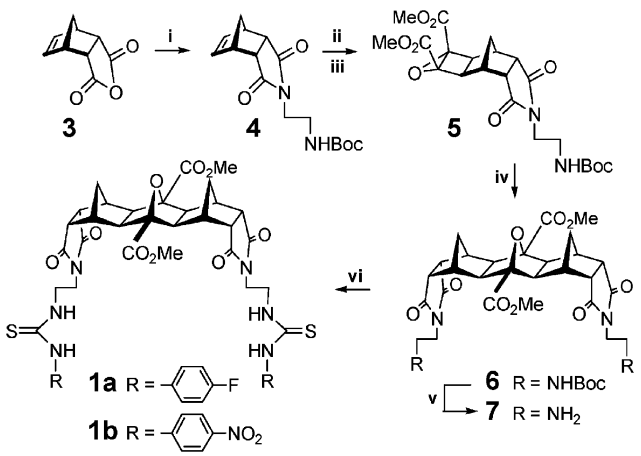


Fig. 1 Structures of the polynorbornane based hosts **1** and **2**.

Synthesis of hosts **2** (Scheme 2) required a total of five steps, and employed similar chemistry. Mitsudo reaction of norbornadiene with *two* equivalents of DMAD afforded the bis



Scheme 1 Synthesis of hosts **1a** and **1b** from *endo*-norborn-5-ene-2,3-anhydride and *tert*-butyl (2-aminoethyl)carbamate. *Reagents and conditions*: (i) *tert*-butyl (2-aminoethyl)carbamate, $CHCl_3$, 120 °C, 12 h, 81%; (ii) DMAD, $RuH_2(CO)(PPh_3)_3$, THF, 70 °C, 72 h, 86%; (iii) TBHP, KO^{t}Bu, THF, 0 °C, 28 h, 69%; (iv) 1.1 equiv. **4**, CH_2Cl_2, 140 °C, 24 h, 58%; (v) 20% TFA–CH_2Cl_2, 4 h, 100%; (vi) DIPEA, $CHCl_3$, RT, 23 h, **1a** 4-fluorophenyl isothiocyanate, 84%, **1b** 4-nitrophenyl isothiocyanate, 68%.

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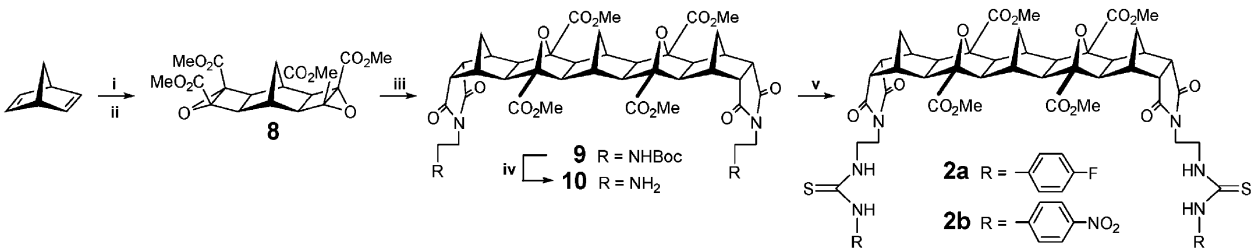
† Electronic supplementary information (ESI) available: Full synthetic details for receptors **1** and **2**, binding isotherms and fit plots for binding studies. See DOI: 10.1039/b801798k



Scheme 2 Synthesis of hosts **2a** and **2b** from norborna-2,5-diene and dimethyl acetylenedicarboxylate. *Reagents and conditions*: (i) DMAD, $RuH_2(CO)(PPh_3)_3$, THF, 70 °C, 24 h, 33%; (ii) TBHP, KO^{t}Bu, THF, 0 °C, 15 h, 54%; (iii) 2.2 equiv. **4**, THF, 140 °C, 41 h, 64%; (iv) 20% TFA–CH_2Cl_2, 4 h, 100%; (v) DIPEA, $CHCl_3$, RT, 24 h, **2a** 4-fluorophenyl isothiocyanate, 92%, **2b** 4-nitrophenyl isothiocyanate, 95%.

alkene diester, which on epoxidation gave the bis epoxide **8**.[15] Again, alkene **4** was used in the cycloaddition; this time two equivalents were heated with bis epoxide **8**, to form the [5]polynorbornane framework **9**. Deprotection followed by reaction with 4-fluorophenyl isothiocyanate, or 4-nitrophenyl isothiocyanate resulted in hosts **2a** and **2b**, respectively.

The ability of the four hosts to recognise the rigid dicarboxylate, terephthalate, was investigated using ^{1}H NMR by titrating solutions of the terephthalate dianion [prepared as a tetrabutylammonium (TBA) salt][16] in DMSO-d_6 against DMSO-d_6 solutions of each host ($\sim 1.3 \times 10^{-2}$ M and also 1.0×10^{-3} M§) while recording any change of the thiourea N–H resonances.

For each of the hosts **1a**–**2b** it was immediately apparent that binding was occurring as all thiourea N–H resonances experienced large downfield shifts (Table 1). Migration approaching 4 ppm with no sign of deprotonation was observed and indicated strong binding between the hosts and the terephthalate dianion. It was noted that during titrations of **1b** and **2b** (Ar–NO_2 substituent) an incremental colour change from pale yellow through to red occurred; this was anticipated and had been observed in previous studies.[10]

Stack plots of the ^{1}H NMR data (Fig. 2) clearly show strongly bound 1:1 host:guest complexes. For host **2b** saturation occurred after 1 equiv. of terephthalate had been added, and once saturated the signals became sharper, indicating high complex stability. It was also noteworthy that the 1:1 stoichiometry beomes 'locked-in', and no further downfield migration of the N–H resonances was observed despite the continued addition of guest. Such a stable state is suggestive of strong binding and the corresponding isotherm (Fig. 3) also depicts this 'quantitative' binding. When the results for **1a** are compared to those for host **2b** it is clear that the titration 'end-point' is significantly sharper for host **2b** than for **1a**, again indicating a very stable host:guest complex.

Job plot data (see ESI†) confirmed the 1:1 host:guest stoichiometry for all four hosts and binding constants for the single step binding of terephthalate [H + G → HG (K)] calculated using WinEQNMR[17] (Table 1) range from host **1a** (log K = 3.5) through to **2b** (log K = 6.0).

Table 1 Observed chemical shifts and calculated binding constants[a]

	[Host] ~ 1.3×10^{-2} M		[Host] ~ 1.0×10^{-3} M	
Host	max. δΔ (ppm)[b]	log K	max. δΔ (ppm)[b]	log K
1a	3.38	2.7 (±0.19)	2.22	3.5 (±0.23)
1b	3.51	3.7 (±0.74)	3.02	3.8 (±0.52)
2a	3.64	4.0 (±1.15)	3.26	4.4 (±0.34)
2b	3.74	5.7 (±1.68)	3.61	6.0 (±0.49)

[a] Binding constants were determined using WinEQNMR software.[17]§ [b] Maximum observed chemical shift observed for H_b after 6.0 equiv. of anion.

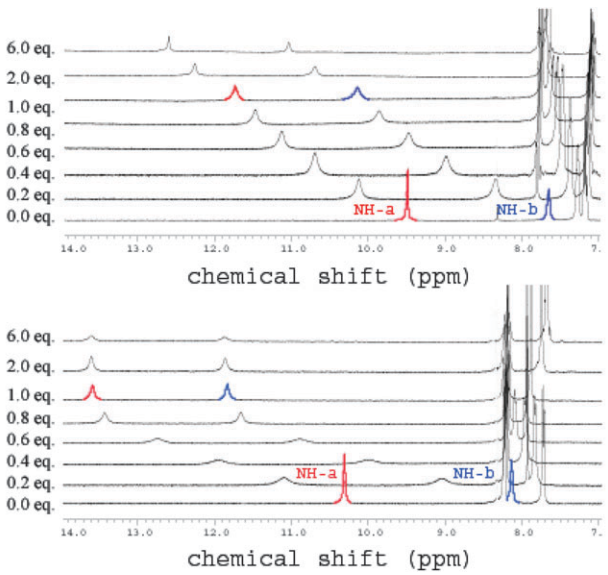


Fig. 2 Stack plots of ^{1}H NMR titrations of hosts **1a** (top) and **2b** (bottom) upon addition of terephthalate dianion in DMSO-d_6 (see ESI† for **1b** and **2a** stack plots).

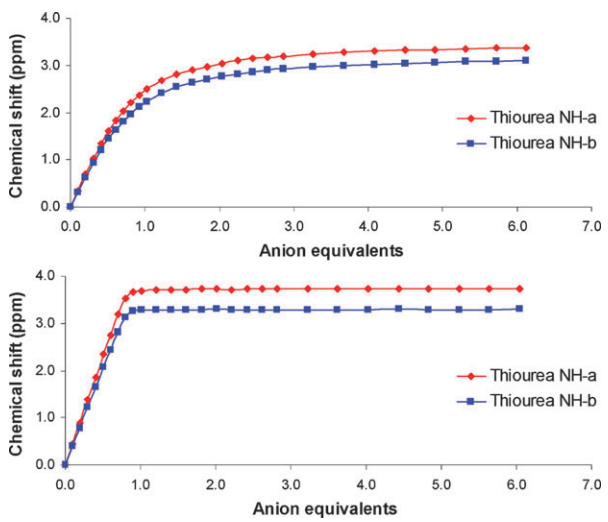


Fig. 3 Titration isotherms for N–H protons within **1a** (top) and **2b** (bottom) upon addition of terephthalate dianion in DMSO-d_6 (see ESI† for **1b** and **2a** binding isotherms).

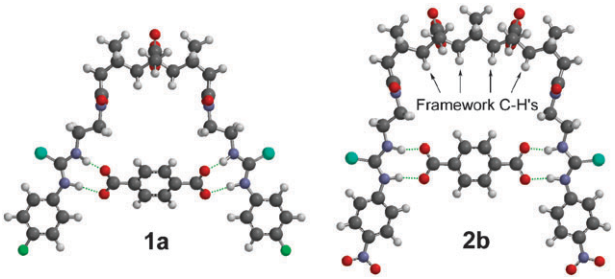


Fig. 4 Energy minimised molecular models of receptors **1a** (left) and **2b** (right) bound to 1 equiv. of terephthalate dianion (see ESI† for molecular models of **1b** and **2a**).

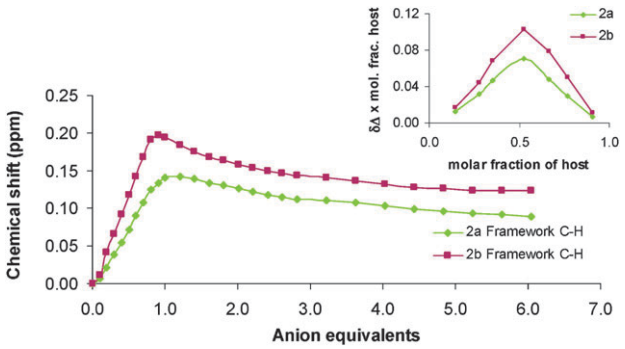


Fig. 5 Job plots (inset) and titration isotherms for framework C–H protons within **2a** and **2b** upon addition of terephthalate dianion in DMSO-d_6.

These results suggest that the cavity sizes of the [*3*]polynorbornane based hosts **1a** and **1b** are too small to encompass the large, rigid terephthalate guest. In order to achieve a 1:1 complex, host **1** must undergo significant backbone *stretching*. Such changes are at the limit of the possible induced fit, and as a result decreased binding strength was observed.[18] In contrast, the larger [*5*]polynorbornane frameworks **2a, 2b** accommodate the terephthalate guest neatly—clearly showing excellent host:guest size complementarity (Fig. 4). As with previous studies,[10] the more electron withdrawing NO_2 substituent elicits the strongest binding.

The inclusion of the guest within the binding cleft of hosts **2a** and **2b** was also established by monitoring the migration of the internal framework C–H protons that face into the binding site (see Fig. 4). Although the change in chemical shift was relatively small ($\Delta\delta \sim 0.2$ ppm), both the binding isotherm and Job plot (Fig. 5) support the 1:1 host:guest stoichiometry. As a downfield migration occurred, it is likely that the C–H protons were being deshielded by the *ring-current effect* of the phenyl ring,[19] and for this to be the case the anionic guest must be symmetrically oriented within the cleft as depicted in Fig. 4. The change in chemical shift of the framework C–H protons of host **1** was insignificant ($\Delta\delta \sim 0.03$ ppm) and this suggested that, unlike host **2**, the orientation of the framework C–H protons was not aligned with the aromatic π-system of the guest—again illustrating the inferior fit of hosts **1a** and **1b** with the guest.

In conclusion, we have designed and synthesised new polynorbornane based hosts, **1a**, **1b**, **2a** and **2b**, and identified that **2b** efficiently binds the large, rigid, terephthalate dianion. The results are a clear illustration of how size complementarity plays a critical role when designing receptors for guests of known dimensions and show that fused polynorbornane based hosts are ideally suited for this task.

Notes and references

‡ Host **1b** has been synthesised previously,[12] however binding assays involving dicarboxylates were not performed.

§ There was no appreciable dissociation of the complex at or near the stoichiometric point (at a concentration of 1.3×10^{-2} M, Fig. 3) despite the competitive solvent DMSO being used. As such large errors (<30%) accompanied the calculated binding constants,[20] repeating titrations at lower concentration (1.0×10^{-3} M) provided more reliable binding constants (error <8.1%).

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