Binding of the terephthalate dianion by di- tri- and tetrathiourea functionalised fused [*3*] and [*5*]polynorbornane based hosts†

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The affinity of new di-, tri- and tetrathiourea functionalised fused [*3*] and [*5*]polynorbornane based hosts **1–6** towards terephthalate^{2-} was proportional to the size of the preorganised cleft/cavity imparted by the polynorbornane scaffold. Receptors based on the [*5*]polynobornane framework had greater affinities for the anion due to a higher degree of host:guest size complementarity. Hosts **1–5** formed 1:1 host:guest complexes with the rigid dianion, yet remarkably, host **6** was found to bind two terephthalate guests.

Introduction

Anion recognition has become an active field of research[1] due to the crucial roles that anions play in many fundamental processes; from biochemical transformations, such as the generation of high energy polyphosphate bonds,[2] to environmental pollutants such as nitrates and phosphates which are linked to the eutrophication of waterways.[3]

The key concept of conformational preorganisation as a means to enhance recognition and binding strength was pioneered by Cram.[4] This concept has been adopted by several research groups in the field of anion recognition and a range of functionalised molecular frameworks have been specifically designed, synthesised and evaluated (examples include calix[*n*]arenes,[5] calix[*n*]pyroles,[6] and cholapods[7]) to encapsulate anionic guests.

Research in our laboratory is aimed at extending this arsenal of preorganised hosts for anions through the use of suitably functionalised fused [*n*]polynorbornane scaffolds containing multiple H-bond donors for strong recognition.[8] Such frameworks are readily constructed through the use of a thermal 1,3 dipolar cycloaddition of a norbornene alkene with a cyclobutane epoxide (ACE reaction).[9]

In the current study the size of the [*n*] polynorbornane framework and also the number of H bond donors of the host were varied (Fig. 1, compounds **1–6**) and their interaction with a single anion (terephthalate^{2-}) probed using ^{1}H NMR spectroscopic titration analysis. In this full paper the synthesis of new hosts **3–6** is described, followed by the results of ^{1}H NMR titration binding studies.

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† Electronic supplementary information (ESI) available: Von-Baeyer numbering system used to name the [*n*]polynorbornane scaffolds, additional experimental details, stack plots of ^{1}H NMR titration spectra, and titration isotherms for the internal framework C–H protons. See DOI: 10.1039/b910522k

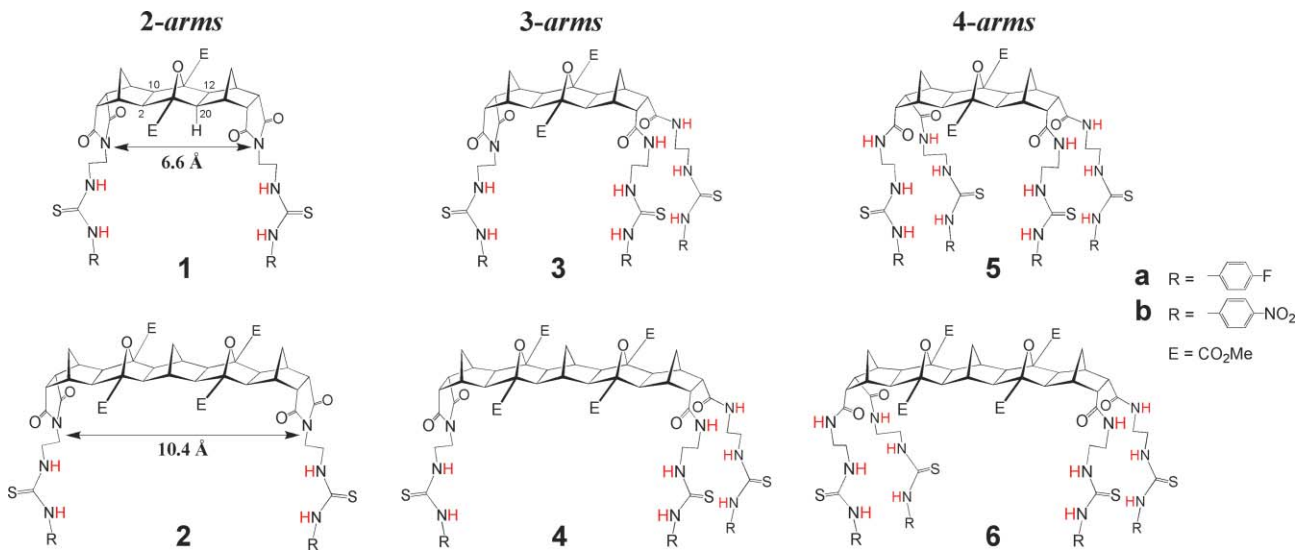


Fig. 1 The structures of the 2, 3 or 4-*armed* [*3*] and [*5*]polynorbornane based hosts **1–6**, * denotes the H-bond donor used for calculations.

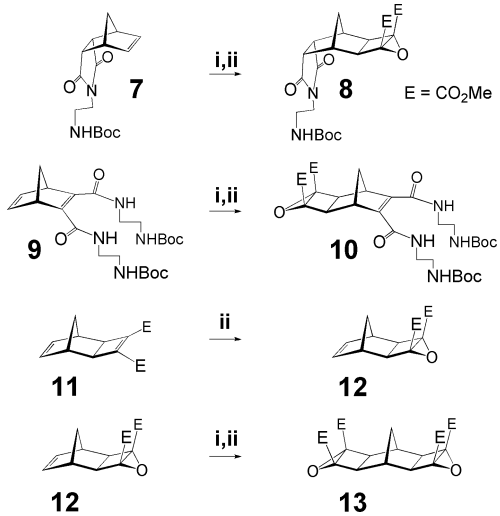
Results and discussion

Design

As illustrated in Fig. 1, all hosts **1–6** were based on either a [*3*] or [*5*]polynorbornane scaffold with 2, 3 or 4 thiourea functionalised anionophoric *arms* covalently attached through flexible ethyl linkers. In the case of the 3 and 4-*armed* hosts **3–6**, amide functionality was also included with the design, potentially providing additional anion recognition units.

Synthesis

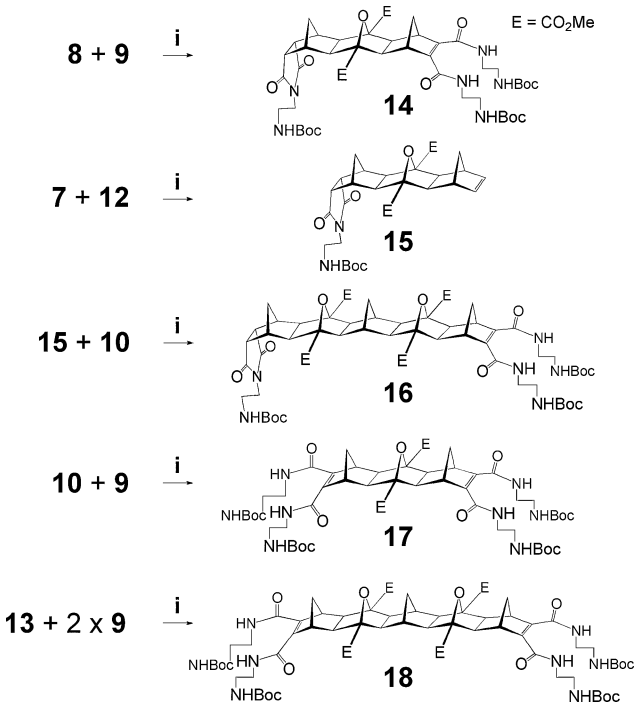
The synthesis of [*n*]polynorbornane frameworks requires the reaction of a norbornene alkene with a cyclobutane epoxide.[9] The necessary epoxides are prepared from norbornene alkenes using Ru catalysed Mitsudo reaction,[10] followed by Weitz–Scheffer epoxidation.[11] The epoxides required herein (**8**, **10**, **12** and **13**, Scheme 1) were manufactured according to this protocol using known norbornene units.[12] In the case of epoxide **12**, cyclobutene diester **11** was used and this was conveniently prepared from quadricyclane and DMAD.[9a,13]



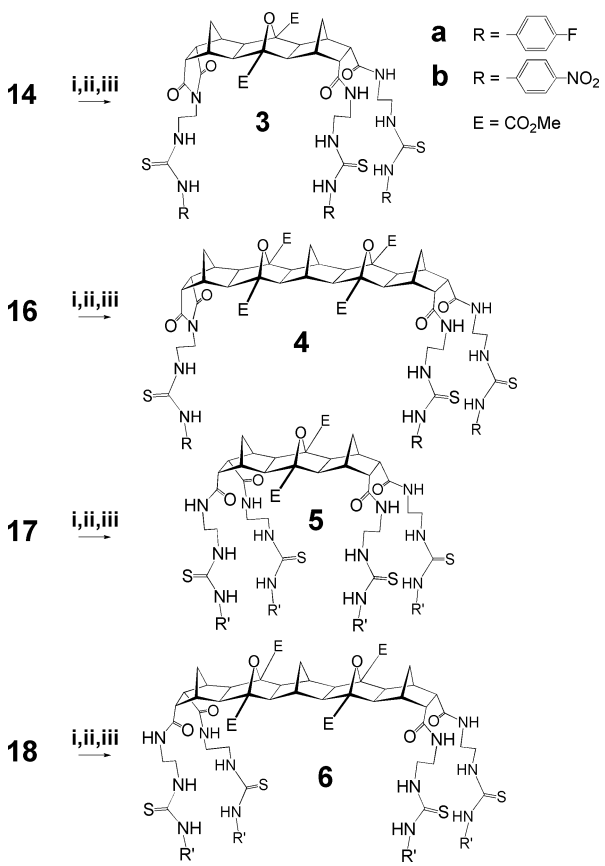
Scheme 1 Synthesis of cyclobutane epoxides. *Reagents and conditions*: (i) DMAD, $RuH_2(CO)(PPh_3)_3$, THF, 70–90 °C, 12–48 h, (ii) TBHP, KO^{t}Bu, THF, 0 °C, 15–28 h.

Synthesis of the *multi-armed* [*n*] polynorbornane frameworks involved in thermal ACE cycloaddition of the cyclobutane epoxides with appropriately functionalised norbornene units (Scheme 2). The reaction typically took between 12 and 72 hours and yields ranged from 35–76%. This series of reactions highlights the versatility of the methodology as from a limited number of norbornenes and cyclobutane epoxides the full suite of desired [*3*] and [*5*]polynorbornane scaffolds including the appropriate number of *arms* were prepared.

The final steps in the synthesis of the hosts **3–6** required a three step protocol (Scheme 3) involving: (i) hydrogenation of the norbornene double bonds using Pearlman's catalyst (giving *endo* product exclusively), (ii) deprotection using 20% trifluoroacetic acid (TFA) in dichloromethane (DCM) to afford the free amines and (iii) subsequent coupling with either 4-nitrophenyl or 4-fluorophenylisothiocyanate to afford the desired hosts. In all cases



Scheme 2 Formation of a [*n*]polynorbornane framework using ACE cycloaddition. *Reagents and conditions*: (i) THF, 140–150 °C, 12–72 h.



Scheme 3 Synthesis of hosts **3–6**. *Reagents and conditions*: (i) H_2, Pd-OH/C, EtOH, 45 °C, 48 h, (ii) 20% TFA/DCM, RT, 2 h, (iii) DIPEA, $CHCl_3$, RT, 20 h, **a** 4-fluorophenylisothiocyanate, **b** 4-nitrophenylisothiocyanate.

Table 1 Maximum observed chemical shifts, host:guest stoichiometries and calculated association constants (log$K$) for hosts **1–6**[a]

	max thiourea NH Δδ (ppm)	max internal CH Δδ (ppm)	H:G	log$K$ (M^{-1})
1a	2.22	–0.02	1:1	3.5 (± 0.23)
1b	3.02	–0.05	1:1	3.8 (± 0.52)
2a	3.26	0.14	1:1	4.4 (± 0.34)
2b	3.61	0.20	1:1	6.0 (± 0.49)
3a	3.11	0.04	1:1	3.2 (± 0.35)
3b	3.47	–0.03	1:1	3.6 (± 0.34)
4a	3.64	0.13	1:1	4.3 (± 0.28)
4b	3.84	0.14	1:1	4.9 (± 0.47)
5a	2.14	0.04	1:1	2.9 (± 0.17)
5b	2.81	0.03	1:1	3.1 (± 0.10)
6a	3.38	0.23	1:2	2.9 (± 0.22) 3.0 (± 0.29)[b]
6b	3.74	0.21	1:2	3.0 (± 0.25) 4.5 (± 0.54)[b]

[a] In each case, the data refers to the thiourea H-bond donor marked with an asterisk (*) in Fig. 1. Association constants were determined from ^{1}H NMR titration data using WinEQNMR,[15] calculated errors < 14.0%, $[H]_i \sim 2.5 \times 10^{-3}$ M. [b] For **6a** and **6b** the binding constants are listed as logK_1 and logK_2.

the target compounds were purified by column chromatography and/or recrystallisation and fully characterised using ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectrometry (HRMS).

Terephthalate^{2-} binding studies

^{1}H NMR spectroscopy titration experiments were conducted to determine how the increased number of prepositioned H-bond donors and various cleft/cavity geometries of hosts **3–6** would effect the ability of these hosts to bind the rigid dicarboxylate guest, terephthalate^{2-}. Solutions of terephthalate^{2-} (prepared as a tetrabutylammonium (TBA) salt)[14] in DMSO-d_6 ($\sim 3.0 \times 10^{-2}$ M) were titrated against DMSO-d_6 solutions of each host ($[H]_i \sim 2.5 \times 10^{-3}$ M) while recording any change in chemical shift of the amide and thiourea N–H resonances. The results of this study, and those of the previous study involving hosts **1** and **2**,[8a] are summarised in Table 1, stacked ^{1}H NMR spectra of these experiments are supplied as ESI.†

Two armed hosts 1 and 2

The investigation of receptors **1** and **2**[8a] revealed that both hosts formed strong 1:1 host:guest (H:G) complexes with terephthalate^{2-}, where the dianion spanned the cleft and was bound cooperatively by both thiourea groups (4 H-bond donors in total). Association constants were calculated for the single step process (H + G ⇋ HG) using WinEQNMR[15] and it was noted that the 4-nitrophenyl functionalised hosts **1b** and **2b** both had a higher affinity for terephthalate^{2-} than their 4-fluorophenyl counterparts **1a** and **2a**. The difference in binding affinity was attributed to the larger electron withdrawing effect of the nitrophenyl substituent (versus the fluorophenyl) inductively increasing the acidity of the adjacent thiourea protons, thereby enhancing their H-bonding ability.

Nevertheless, the dominant factor influencing binding affinity was that of the preorganisation imparted by the [*n*]polynorbornane scaffold; where the [*5*]polynorbornane based host **2b** (log$K$ = 6.0) bound the anion > 100 times more strongly than the [*3*]polynorbornane based host **1b** (log$K$ = 3.8). As illustrated in Fig. 2, this was due to the longer cleft width of host **2** experiencing less *stretching* than host **1** when bound in the host–guest complex, as such receptor **2** better complements the length of the rigid dianionic guest (ca. 7.0 Å).[8a]

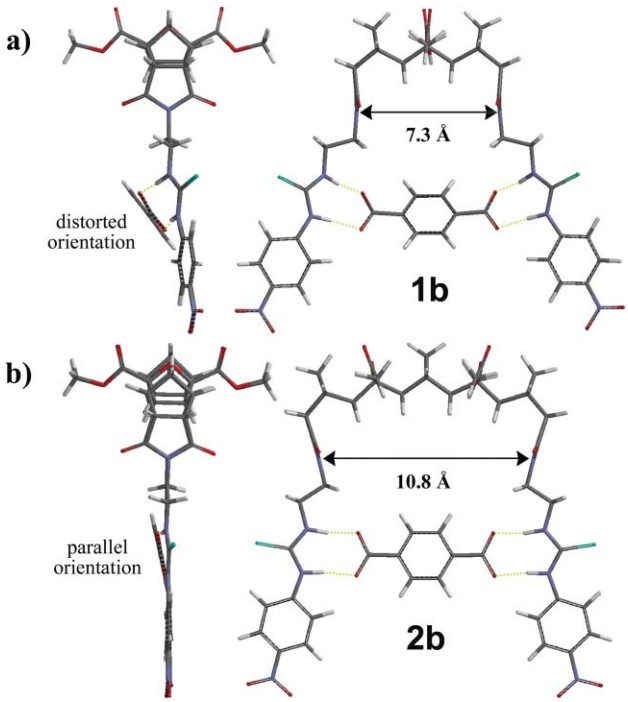


Fig. 2 Molecular models calculated at Hartree–Fock 3–21G(*) level of theory depicting the 1:1 complexes formed between (a) host **1b** and, (b) host **2b** and the rigid aryl dicarboxylate, terephthalate^{2-}.

The interaction of host **2** and terephthalate^{2-} was also monitored by following the internal framework '*endo*' C-H resonances during ^{1}H NMR titrations (for example H2, 10, 12 and 20 in host **1**, Fig. 1). It was found that although the observed change in chemical shift was relatively small (Δδ ~ 0.2 ppm, Table 1,) a definite trend existed,† where both the binding isotherm and Job plot confirmed the formation of a 1:1 complex.[8a] As a downfield migration occurred, it is likely that the CH protons were being deshielded by the *ring-current effect* of the phenyl ring.[16] In contrast, the magnitude of Δδ observed for the internal C–H protons of host **1** was negligible, this can be explained by considering the geometries of the host:guest complexes in Fig. 2.

Calculated at Hartree–Fock 3–21G* level of theory, Fig. 2a shows that in order to accommodate the rigid dianion, host **1** adopts a slightly distorted conformation in which the aromatic ring of terephthalate^{2-} is no longer in the same plane as the host and as such has a reduced capacity to deshield the framework C–H protons.

Three armed hosts 3 and 4

In the case of the new 3-*armed* [*n*]polynorbornane based hosts **3** and **4**, Job plots (Fig. 3) immediately indicated the formation of 1:1 H:G complexes in both cases. Binding isotherms revealed that the terephthalate^{2-} guest was bound solely through the thiourea

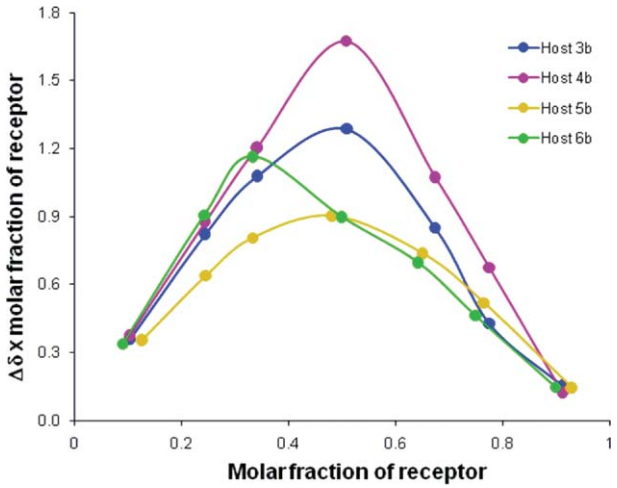


Fig. 3 Job plots of hosts **3b–6b** upon the addition of terephthalate^{2-}.

H-bond donors with no assistance from the amide H-bond donors (Fig. 4). Unlike hosts **1** and **2**, receptors **3** and **4** are not C_2 symmetric and as such a total of five resonances (one for each H-bond donor) could be followed during ^{1}H NMR titration analysis providing additional information regarding possible binding modes.

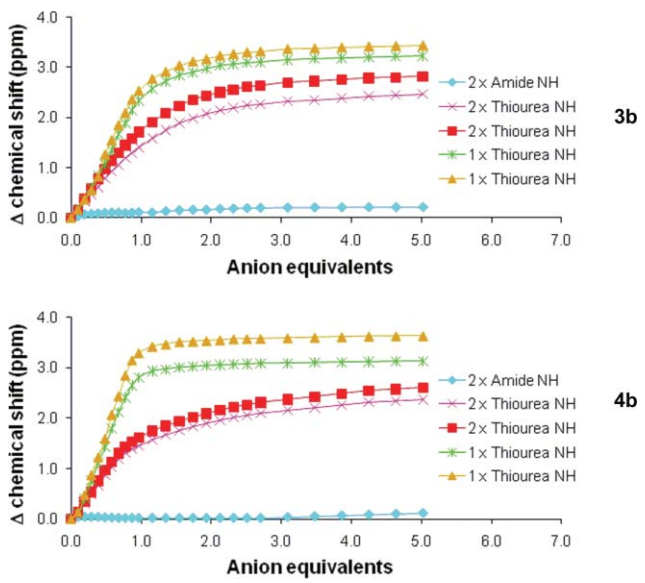


Fig. 4 Titration isotherms of hosts **3b** (top), and **4b** (bottom) upon the addition of terephthalate^{2-} (the coloured curves represent each of the coloured H-bond donors shown in Fig. 5).

These binding isotherms (Fig. 4) clearly show that in both cases the terephthalate^{2-} is bound cooperatively through all 3 thiourea groups (6 H-bond donors in total: *two* from the *single* armed side of the host (orange and green) and *four* from the 2-*armed* side of the host (red and pink) as shown in Fig. 5).

As observed for hosts **1** and **2** the dominant factor governing the binding event was the larger cleft width provided by the [*5*]polynorbonane host **4** which better accommodated the terephthalate guest than the [*3*]polynorbornane based host **3**. This was reflected by the calculated association constants where the affinity

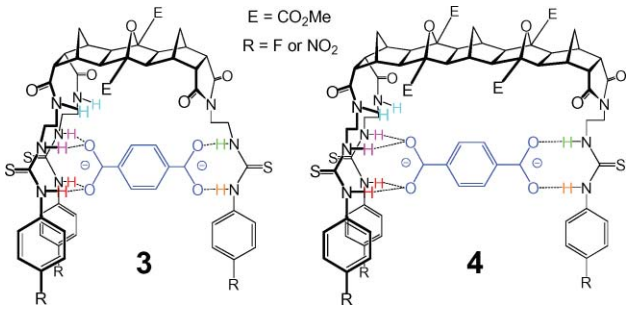


Fig. 5 Proposed binding conformations of the 1:1 complexes formed by hosts **3** and **4** when binding terephthalate^{2-}.

of host **4** (log$K$ = 4.9) for terephthalate^{2-} was greater than that of host **3** (log$K$ = 3.6). Monitoring the internal framework, C–H resonances of host **4**†also revealed a similar trend to that of host **2** where a more pronounced downfield shift was observed due to better accommodation of the guest.

Four armed hosts 5 and 6

In the case of the new 4-*armed* [*n*]polynorbornane based hosts **5** and **6**, it was immediately apparent from Job plot data (Fig. 3) that host **5** exhibited a 1:1 host:guest stoichiometry while host **6** was arranged in a 1:2 H:G complex with terephthalate^{2-}. Binding isotherms (Fig. 6) clearly indicated that both hosts bound the dicarboxylate guests symmetrically through all 4 thiourea groups (8 H-bonds in total), whilst the chemical shifts of the amide H-bond donors remained unchanged indicating little or no participation in the binding event. It was interesting that host **5** bound a *single* terephthalate^{2-} guest, whereas host **6** bound *two* terephthalate^{2-} dianions, forming four H-bonds with each (Fig. 7).

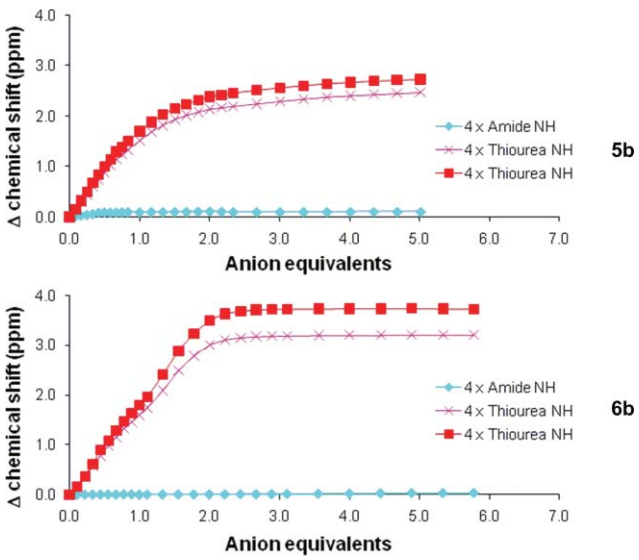


Fig. 6 Titration isotherms of hosts **5b** (top), and **6b** (bottom) upon the addition of terephthalate^{2-} (the coloured curves represent each of the coloured H-bond donors shown in Fig. 7).

The fact that the shifts associated with the thiourea H-bond donors of host **6** were approximately double that of host **5** (at the

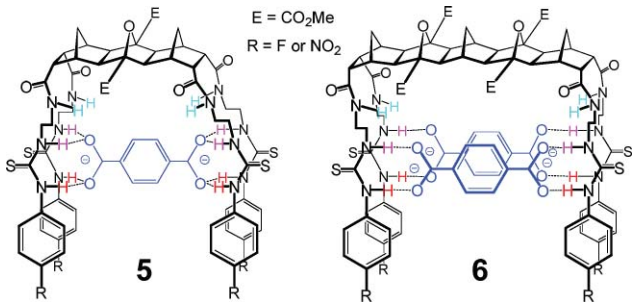


Fig. 7 Proposed binding conformations of the 1:1 and 1:2 arrangements exhibited by hosts **5** and **6**, respectively, when binding terephthalate^{2-}.

equivalence point $\Delta\delta_6 = 3.5$ and $\Delta\delta_5 = 1.8$ ppm), also supported the 1:2 stoichiometry determined from Job plots. When complexed with host **5** the electron density of each of the *two* carboxylates of the *single* terephthalate dianion was being shared between *four* thiourea H-bond donors, compared with host **6**, where each of the *four* carboxylates of the *two* guests were being shared between only *two* thiourea H-bond donors (Fig. 7). As such, the electron density withdrawn from each thiourea H-bond donor of host **6** was approximately double that of host **5**, resulting in a larger downfield shift being observed in the ^{1}H NMR spectrum. Upon re-examination of the isotherm for host **4b** (Fig. 4) a similar trend was observed where the thiourea N–H resonances of the 2 armed side of the host experience a change in chemical shift approximately half that (at the equivalence point) of the N–H resonances at the single armed side. Thus a consistent 'dilutive' effect in the change of chemical shift occurred when a single carboxylate was 'shared' amongst multiple co-operating H-bond donors.

The longer cavity of [*5*]polynorbornane host **6** was able to encapsulate two rigid terephthalate dianions as the guests can both span the cleft parallel to one another (Fig. 8). The 4-*armed* receptors **6a** and **6b** are more flexible than their 2-*armed* counterparts **2a** and **2b**; the thiourea functionalised *arms* of **2a** and **2b** are attached through a rigid five-membered cyclic imide, whereas the arms of **6a** and **6b** are linked through a more flexible amide bond. This enables greater variation in possible binding conformations including a conformation in which the anions can be held sufficiently far enough apart to allow a 1:2 H:G complex to exist with little or no electrostatic repulsion (Fig. 8). This 1:2 binding mode was further supported by re-examination of the internal framework C–H resonances of host **6b** where the magnitude of the downfield shift was approximately double that observed for host **4b**.†

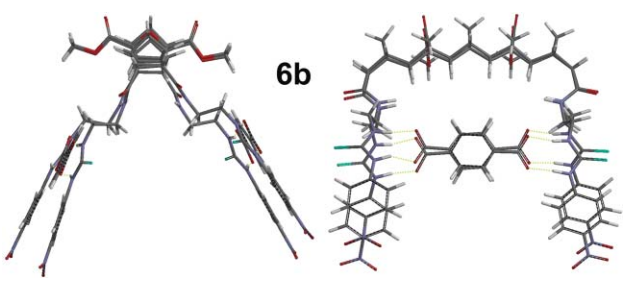


Fig. 8 Illustration of the 1:2 binding of host **6b** with terephthalate^{2-}.

Conclusions

In summary, the successful synthesis of 2, 3 and 4 arm functionalised [*3*] and [*5*]polynorbornane scaffolds **1–6** was accomplished through the successful application of 1,3 dipolar ACE cycloaddition methodology. In doing so the array of preorganised [*n*]polynorbornane based anion hosts has been expanded to include those with binding *pockets* that provide 4, 8 or 12 H-bond donors arranged around cavities of customisable geometric lengths.

Hosts **1–5** bound terephthalate in a 1:1 H:G arrangement, where the 2-*armed* hosts **1** and **2** exhibited symmetrical binding through *four* cooperative thiourea H-bonds (Fig. 2), the 3-*armed* hosts **3** and **4** bound the guest unsymmetrically through *six* H-bonds (Fig. 5) and the 4-*armed* host **5** used *eight* thiourea H-bonds (Fig. 7) to bind the dianion. The only exception to this general trend was host **6** which exhibited a 1:2 H:G stoichiometry; the increased number of H-bond donors coupled with the larger [*5*]polynorbornane scaffold and increased flexibility of the *arms* enabled two terephthalate^{2-} guests to 'coinhabit' the cavity.

In all cases the 4-nitrophenyl derivative of each host had a slightly higher affinity for the guest than the 4-fluoro derivative due to the enhanced H-bonding ability of the thiourea H-bond donors. However, the prevailing factor controlling host–guest affinity was the size of the preorganised cleft/cavity imparted by the [*n*]polynorbornane scaffold, in all cases the [*5*]polynorbornane scaffold provided a cleft/cavity length that better complemented the guest, resulting in increased binding affinities.

Experimental

NMR spectra were collected on either a JEOL EX 270 MHz FT-NMR spectrometer (Tokyo, Japan), or a JEOL EX 400 MHz FT-NMR spectrometer (Tokyo, Japan) where indicated. HRMS was performed with an Agilent 6210 LC/MSDTOF instrument using CH_3CN as the mobile phase. Melting points were determined on a digital Electrothermal® 9200 (UK) heated-block melting point apparatus and are uncorrected. Microanalysis was performed by Chemical and Microanalytical Services Pty Ltd, Belmont, Geelong, 3216. TLC was performed using Merck 60 F254 aluminium backed silica plates. Visualisation employed a UVP Mineralight 254 NM UV lamp or an oxidising dip containing $KMnO_4$ (1.0 g), K_2CO_3 (1.0 g) and H_2O (100 mL). Flash chromatography was performed using Merck Kieselgel 60 (70–230 mesh). General reagents were analytical grade and used as supplied unless otherwise stated. Isothiocyanates were purchased from Aldrich Chemical Co.

General two step protocol for epoxide synthesis

Step 1 Mitsudo reaction. Freshly distilled dimethyl acetylenedicarboxylate (DMAD) (1.3 eq.) was added to a pressure vessel containing the starting norbornene unit (1.0 eq.) and $RuH_2(CO)(PPh_3)_3$ (0.10 eq.) in dry THF. The tube was sealed and the mixture stirred at 70–90 °C for up to 48 h. Following cooling, the pressure vessel was opened, the reaction mixture filtered and the solvent removed under reduced pressure. The resultant crude solid was subject to column chromatography to afford the cyclobutene diester.

Step 2 Epoxidation. A nitrogen-flushed solution of alkene diester (1.0 eq.) in dry THF was cooled to 0 °C in an ice bath before *tert*-butyl hydroperoxide (TBHP) (1.2 eq. of a 1.14 M toluene solution) was added by syringe. Following rapid stirring for 10 min, potassium *tert*butoxide (KO^{t}Bu) (0.25 eq.) was added and the reaction stirred for another 10 min. The ice bath was removed and the solution stirred at RT overnight whereupon aqueous sodium thiosulfate solution (10%) was added and the mixture stirred for a further 30 min. The resultant two-phase mixture was concentrated to 1/3 of its volume, transferred to a separatory funnel and extracted with $CHCl_3$ (×3), the organics combined, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. The crude solid was purified by column chromatography and/or recrystallisation resulting in the requisite cyclobutane epoxide as a white solid.

Dimethyl (1α,2α,6α,7α,8β,12β)-4-(2′-*tert*butoxycarbonylamino ethyl)-4-aza-10-oxapentacyclo [5.5.1.0^{2,6}.0^{8,12}.0^{9,11}]trideca-3,5-dione-9,11-dicarboxylate 8[8a]

Prepared according to a standard two step protocol; *Step 1*: (1α,2α,6α,7α)-4-(2′-*tert*-Butoxycarbonylaminoethyl)-4-azatricyclo[5.2.1.0^{2,6}]deca-8-ene-3,5-dione **7**[8a] (5.002 g, 16.34 mmol), DMAD (2.5 ml, 20 mmol) and $RuH_2(CO)(PPh_3)_3$ (401 mg, 0.436 mmol) in THF (20 ml) at 70 °C for 48 h to give (1.823 g, 3.005 mmol, 94%) the cyclobutene diester as a white powder following chromatographic purification (50% EtOAc/Pet Sp, R_f = 0.26); mp 153.8–154.7 °C; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.37 (9H, s, C(CH_3)$_3$), 1.47 (1 H, d, J = 11.6 Hz, H12), 1.74 (1 H, d, J = 11.6 Hz, H12), 2.79 (2 H, s, H8,11), 2.83 (2 H, s, H1,7), 3.22 (2 H, s, H2,6), 3.33 (2 H, m, NHCH_2), 3.61 (2 H, m, NCH_2), 3.76 (6 H, s, 2 × COOCH_3) and 4.70 (1 H, br s, NH); δ_C(400 MHz; $CDCl_3$; Me_4Si) 27.9, 33.7, 35.5, 37.8, 38.4, 42.0, 47.0, 51.5, 79.0, 140.7, 155.8, 160.1 and 176.5; HRMS: m/z = 449.19030 [M + H]$^+$, $C_{22}H_{29}N_2O_8$ requires 449.19240.

Step 2. The above diester (1.197 g, 2.670 mmol) was epoxidised with TBHP (1.14M, 3.0 ml, 3.4 mmol) and KO^{t}Bu (81 mg, 0.72 mmol) in dry THF (150 ml) for 28 h. Column chromatography (50% EtOAc/Pet Sp, R_f = 0.22) afforded **8**[8a] (854 mg, 1.84 mmol, 69%) as a white solid; mp 190.8–192.2 °C; δ_H(270 MHz; $CDCl_3$; Me_4Si) 1.39 (9 H, s, C(CH_3)$_3$), 1.72 (1 H, d, J = 11.5 Hz, H13), 2.12 (1 H, d, J = 11.5 Hz, H13), 2.37 (2 H, s, H8,12), 3.17 (2 H, s, H1,7), 3.27 (2 H, m, NHCH_2), 3.29 (2 H, s, H2,6), 3.55 (2 H, m, NCH_2), 3.79 (6 H, s, 2 × COOCH_3) and 4.68 (1 H, br s, NH); δ_C(400 MHz; $CDCl_3$; Me_4Si) 27.9, 34.2, 36.4, 38.6, 38.7, 45.6, 47.1, 52.5, 79.5, 141.2, 155.5, 163.3 and 176.2; HRMS: m/z = 465.18621 [M + H]$^+$, $C_{22}H_{29}N_2O_9$ requires 465.18732.

See ESI for the syntheis of epoxides **10**, **12** and **13**.

General ACE coupling reaction

A pressure vessel was charged with equimolar amounts of the desired epoxide and norbornene unit (two eq. in the case of bis epoxides), the minimum amount of tetrahydrofuran (THF) added for dissolution then the vessel sealed and heated at 140–150 °C for up to 72 h. The vessel was then cooled, opened, the solvent removed under reduced pressure, and the crude purified using flash chromatography.

Dimethyl (2β,3α,4α,8α,9α,10β,12β,13α,16α,17β) 6-*tert*butoxy-carbonylaminoethyl-14,15-di[(*tert*butoxycarbonylamino)ethyl carboximido]-6-aza-19-oxa-5,7-dioxoheptacyclo [9.6.1.1^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}] icosa-14-ene-1,11-dicarboxylate 14

Equimolar amounts of epoxide **8**[8a] (902 mg, 1.94 mmol) and norbornene **9**[12] (901 mg, 1.94 mmol) were heated (150 °C) in THF (4 ml) for 70 h. Column chromatography (EtOAc, R_f = 0.37) gave **14** (1.601 g, 1.72 mmol, 89%) as an off-white powder; mp 147.2–150.7 °C; δ_H(270 MHz; d_6-DMSO; Me_4Si) 1.02 (1 H, d, J = 7.8 Hz, H20), 1.18 (1 H, d, J = 9.8 Hz, H18), 1.34 (9 H, s, 1 × C(CH_3)$_3$), 1.36 (18 H, s, 2 × C(CH_3)$_3$), 2.02 (2 H, s, H2,10), 2.24 (1 H, d, J = 8.2 Hz, H20), 2.31 (2 H, s, H13,16), 2.33 (1 H, d, J = 8.2 Hz, H18), 2.43 (2 H, s, H3,9), 3.02 (4 H, s, 2 × CH_2NHCO), 3.04 (4 H, s, H4,8,12,17), 3.11 (4 H, s, 2 × CH_2NHCOO), 3.14 (2 H, s, 1 × CH_2NHCOO), 3.41 (2 H, s, 1 × CH_2N), 3.84 (6 H, s, 2 × COOCH_3), 6.78 (1 H, s, 1 × NHCOO), 6.84 (2 H, t, J = 5.1 Hz, 2 × NHCOO) and 8.89 (2 H, s, 2 × NHCO); δ_C(270 MHz; $CDCl_3$; Me_4Si) 28.3, 28.4, 38.1, 39.0, 40.0, 41.0, 48.4, 48.5, 50.9, 52.8, 53.8, 79.7, 89.1, 148.4, 156.1, 156.7, 164.3, 168.2, 176.9; HRMS: m/z = 929.45020 [M + H]$^+$, $C_{45}H_{65}N_6O_{15}$ requires 929.45024.

See ESI for the synthesis of [*n*]polynorbornenes **15**, **16**, **17** and **18**.

General hydrogenation procedure

A round-bottomed flask was charged with the required [*n*]polynorbornene scaffold, catalytic $Pd(OH)_2/C$, EtOH and equipped with a reflux condenser. This reaction mixture was stirred at 45 °C under a H_2 atmosphere for up to 48 h. After cooling to RT the solution was diluted with EtOH, filtered through celite and solvent removed under reduced pressure. The product was purified using column chromatography.

Dimethyl (2β,3α,4α,8α,9α,10β,12β,13α,14α,15α,16α,17β) 6-*tert*butoxycarbonylaminoethyl-14β,15β-di[(*tert*butoxy-carbonylamino)ethylcarboximido]-6-aza-19-oxa-5,7-dioxo-heptacyclo [9.6.1.1^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}] icosa-1,11-dicarboxylate

The [*3*]polynorbornene **14** (0.891 mg, 0.959 mmol) was subject to hydrogenation conditions in EtOH (30 ml) for 48 h, column chromatography (10% EtOH/EtOAc, R_f = 0.42) gave the 3-*armed* [*3*]polynorbornane scaffold (0.879 mg, 0.944 mmol, 98%) as a white powder; mp 152.1–154.2 °C; δ_H(270 MHz; d_6-DMSO; Me_4Si) 0.81 (1 H, d, J = 9.2 Hz, H20), 1.17 (1 H, d, J = 6.7 Hz, H18), 1.35 (9 H, s, 1 × C(CH_3)$_3$), 1.37 (18 H, s, 2 × C(CH_3)$_3$), 1.81 (2 H, s, H13,16), 2.10 (2 H, s, H2,10), 2.18 (1 H, d, J = 9.4 Hz, H20), 2.33 (1 H, d, J = 8.2 Hz, H18), 2.38 (2 H, s, H3,9), 2.59 (2 H, s, H14,15), 2.72 (2 H, s, H12,17), 2.94 (6 H, s, 2 × CH_2NHCO, H4,8), 3.01 (6 H, br s, 3 × CH_2NHCOO), 3.47 (2 H, br s, 1 × CH_2N), 3.77 (6 H, s, 2 × COOCH_3), 6.59 (2 H, s, 2 × NHCOO), 6.85 (1 H, t, J = 5.4 Hz, 1 × NHCOO) and 7.56 (2 H, s, 2 × NHCO); δ_C(270 MHz; d_6-DMSO; Me_4Si) 28.8, 29.6, 29.9, 34.8, 37.5, 37.8, 38.8, 39.4, 40.8, 43.1, 46.8, 48.3, 49.7, 50.7, 52.7, 78.2, 78.3, 90.4, 156.1, 156.3, 169.0, 171.6 and 177.4; HRMS: m/z = 931.46566 [M + H]$^+$, $C_{45}H_{67}N_6O_{15}$ requires 931.46589.

See ESI for the hydrogenation of compounds **16**, **17** and **18**.

General Boc deprotection and isothiocyanate coupling

The required [*n*]polynorbornane was stirred in 20% TFA/DCM for 2–4 h, then both TFA and DCM were removed under reduced pressure. The resulting crude solid was dissolved in $CHCl_3$ then evaporated to dryness (twice) to ensure complete removal of TFA. The resultant free amine was dissolved in $CHCl_3$, then diisopropylethylamine (DIPEA) and the required equivalents of isothiocyanate added. Following stirring at RT for 18–46 h, the solvent and excess DIPEA were removed under reduced pressure and the resultant solid purified using flash chromatography.

Dimethyl (2β,3α,4α,8α,9α,10β,12β,13α,14α,15α,16α,17β) 6-(4-fluorophenylthioureido)ethyl-14β,15β-di[(4-fluorophenylthioureido)ethylcarboximido]-6-aza-19-oxa-5,7-dioxohepta-cyclo [9.6.1.1^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}] icosa-1,11-dicarboxylate 3a

Dimethyl (2β,3α,4α,8α,9α,10β,12β,13α,16α,17β) 6-*tert*-butoxycarbonylaminoethyl-14β,15β-di[(*tert*butoxycarbonyl-amino) ethylcarboximido]-6-aza-19-oxa-5,7-dioxoheptacyclo [9.6.1.1^{3,9}.1^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}]icosa-1,11-dicarboxylate (690 mg, 0.741 mmol) was deprotected (5 ml, 20% TFA/DCM) in 2 h to yield the free triamine which underwent coupling with 4-fluorophenylisothiocyanate (341 mg, 2.23 mmol) and DIPEA (1.2 ml, 6.9 mmol) in $CHCl_3$ (15 ml) for 20 h. The resultant crude off-white solid was purified by column chromatography (5% EtOH/EtOAc, $R_f = 0.34$) to afford host **3a** (752 mg, 0.689 mmol, 93%) as a white powder; mp 181.1–185.6 °C; δ_H(270 MHz; d_6-DMSO; Me_4Si) 0.83 (1 H, d, $J = 9.1$ Hz, H20), 1.17 (1 H, d, $J = 9.2$ Hz, H18), 1.85 (2 H, s, H2,10), 2.15 (2 H, s, H13,16), 2.21 (1 H, d, $J = 10.2$ Hz, H20), 2.29 (1 H, d, $J = 10.1$ Hz, H18), 2.40 (2 H, s, H3,9), 2.62 (2 H, s, H14,15), 2.84 (2 H, s, H12,17), 3.01 (2 H, s, H4,8), 3.14 (4 H, s, 2 × CH_2NHCO), 3.46 (4 H, s, 2 × CH_2NHCS), 3.60 (2 H, s, 1 × CH_2NHCS), 3.62 (2 H, s, NCH_2), 3.77 (6 H, s, 2 × COOCH_3), 7.17 (6 H, q, $J = 7.2$ Hz, 6 × ArC*H*CF), 7.27 (2 H, t, $J = 6.7$ Hz, 2 × ArC*H*CNH), 7.38 (4 H, t, $J = 6.6$ Hz, 4 × ArC*H*CNH), 7.67 (5 H, br s, 2 × CO*N*H, 3 × CH_2N*H*CS), 9.51 (1 H, s, 1 × ArN*H*) and 9.53 (2 H, s, 2 × ArN*H*); δ_C(270 MHz; d_6-DMSO; Me_4Si) 35.1, 37.7, 38.4, 38.6, 40.9, 42.2, 43.2, 44.1, 46.8, 48.6, 49.6, 50.8, 52.8, 90.5, 115.9, 126.8, 135.5, 159.6, 169.1, 171.8, 177.6 and 181.5; HRMS: m/z = 1090.33996 [M + H]$^+$, $C_{51}H_{55}N_9O_9F_3S_3$ requires 1090.32315.

See ESI for the synthesis of hosts **3b** and **4a**,**b**–**6a**,**b**.

Tetrabutylammonium terephthalate

One equivalent of terephthalic acid (150 mg, 0.903 mmol) was stirred in two equivalents of tetrabutylammonium hydroxide in MeOH (1.0 M, 1.8 ml, 1.8 mmol) for 48 hours. Excess MeOH was then removed under reduced pressure, complete dryness was obtained by heating (70 °C) the crude white solid under vacuum for 2 days to yield (568 mg, 96.9%) a white powder; mp 98.2–102.1 °C; δ_H(400 MHz; DMSO; TMS) 0.93 (24 H, t, J 6.5, CH_3), 1.30 (16 H, sextet, J 7.2, CH_2CH$_3$); 1.57 (16 H, q, J 7.2, CH_2CH$_2$CH$_3$); 3.17 (16 H, t, J 7.8, CH_2CH$_2$CH$_2$CH$_3$) and 7.62 (4 H, d, J 1.7, Ar-C*H*); δ_C(400 MHz; DMSO; TMS) 14.06, 19.78, 23.65, 58.13, 128.06, 142.28 and 169.15.

^{1}H NMR spectroscopy titration technique

A JEOL EX 270 MHz FT-NMR spectrometer (Tokyo, Japan) was employed to conduct the ^{1}H NMR spectroscopy titration experiments. In general, a stock solution of each host was made up to 2.5×10^{-3} M in d_6-DMSO, 600 µl of this solution was then transferred to an NMR tube and the spectrum collected. The chemical shift (ppm) of the resonances corresponding to the amide and thiourea H-bond donors, as well as the internal C–H protons, were recorded. A 5 µl aliquot of the stock guest solution (TBA terephthalate, ~3.0×10^{-2} M in d_6-DMSO) containing 0.1 equivalents (eq.) of terephthalate^{2-} was then added to the host solution by auto-pipette, this solution was briefly mixed in the NMR tube then the ^{1}H NMR spectrum collected. Again, the chemical shift of the resonances corresponding to the amide and thiourea H-bond donors, as well as the internal C–H protons, were recorded, this process was repeated until 2.0 eq. of guest had been added. The aliquot was then increased (10 µl) so that it contained 0.2 eq. of guest, and the procedure repeated until a total of 4.0 eq. of guest had been added. The final additions were made using 20 µl aliquots (containing 0.4 eq. of guest) until a total of 6.0 eq. of terephthalate^{2-} had been added. The data was then plotted as a titration isotherm and the association constant determined through a non-linear regression analysis using WinEQNMR.[15] In cases where the resonances became significantly broadened a *smoothing* function was used to more accurately determine the centre of the peak. Stack plots of the ^{1}H NMR titration spectra are provided as ESI.†

Hartree–Fock molecular model calculations

The molecular models of Fig. 2 were calculated using *Spartan '04* (Wavefunction Inc., California, 2004). Both the hosts and guest were constructed using the *builder* function, the guest was then arranged within the cleft so that each of the carboxylates was in close proximity to the thiourea H-bonding motifs. The *energy minimize* function, which employs Merck Molecular Force Field (MMFF) molecular mechanics to minimize the steric energy, was used to optimize the geometry before the Hartree–Fock calculation was performed using the following constraints and conditions. Properties: total charge–dianion; multiplicity–singlet; Calculation: calculate–equilibrium geometry; at–ground state; with–Hartree–Fock 3–21G(*); start from–initial (MMFF) geometry; subject to–symmetry. Results: host **1b**; CPU time–021:23:53.1; Energy = –4399.62 E_h; host **2b**; CPU time–051:38:45.7; Energy = –5269.56 E_h.

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