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Factors Influencing Anion Binding Stoichiometry: The Subtle Influence of Electronic Effects

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Six new, charge-neutral norbornene-based receptors **1a**,**1b**–**3a**,**3b** were prepared, and their ability to interact with simple anions in DMSO was investigated using ^{1}H NMR and UV/Vis spectroscopy. Binding of dihydrogenphosphate by the six receptors appeared to be based solely on steric constraints. In contrast, the binding stoichiometry of **3a** and **3b** to acetate was controlled by subtle electronic factors.

Introduction

Hosts for the selective recognition of anionic species are highly sought after as anions are essential to many biological, chemical and environmental processes.[1] As such, there is great current interest in the development of strong and selective artificial anion receptors for use as enzyme mimics, catalysts, extractants and molecular probes for medicinal diagnostics and monitoring of anionic pollutants.[2–4]

Neutral receptors are of great importance in anion recognition as they are the most abundant in nature, and can be designed to have high selectivity for a specific target.[5,6] Charge-neutral receptors use hydrogen bonding as their primary mode of interaction; examples of neutral receptors include thiourea, urea, amide, sulfonamide and/or pyrrole groups.[7] Among these, the urea and thiourea functional groups have proven to be particularly useful and are amongst the most commonly employed.[8–10]

Ideally, exceptionally strong complexation is achieved through the active cooperation of multiple, prepositioned, hydrogen bonds in a preorganised binding cavity.[11–13] Specific geometries can be exploited by arranging the hydrogen-bond donors around the acceptors in three-dimensional space.[14] If the host's *preorganised* binding cavity complements the guest's geometry, then high *selectivity* can be achieved.[13]

Attaching hydrogen-bond donor units to a suitable molecular scaffold is a common method for achieving preorganisation of the binding cavity.[15] A diverse number of scaffolds have previously been employed for this purpose, including naphthalenes,[16–18] benzene rings,[19] calixpyrroles,[20] calixarenes,[21] indoles,[22] cholic acid,[23] azophenols,[24] and various other macrocycles.[14,25] In most cases the predefined cavity geometry allows these hosts to discriminate between guests of differing shape and overall size.

Norbornenes have only sparingly been utilised as scaffolds for supramolecular applications,[10,26] which is surprising considering they boast an inherent high degree of rigidity, are readily synthesised through well-known Diels–Alder cycloadditions[27,28] and can be tailored to contain multiple points that can be functionalised with relative ease. Furthermore, established cycloaddition methodologies[29] can also be exploited to create fused [*n*]polynorbornane frameworks for the purpose of encapsulating larger anionic, and possibly neutral, guests.[30,31]

Herein the full synthesis of a family[10] of norbornene-based receptors **1**–**3** is presented, followed by the results of anion-binding studies using ^{1}H NMR and UV/Vis titration techniques.

Results and Discussion

Design

A family of six receptors **1a**–**3b** (Figure 1) were designed; all receptors contained two thiourea-functionalised ethylene "arms". The ethylene spacers introduced an element of flexibility in the anionophoric "arms" to allow optimum binding through induced fit. In order to study the influence of receptor-site prepositioning, receptor **1** was designed with two *endo* "arms", receptor **2** with the "arms" oriented by the alkene and **3** with an *endo*/*exo* combination. As such, each host has a unique degree of preorganisation imparted by the rigid norbornene. The design offers the possibility of binding an anionic guest within the preorganised cleft through the cooperation of all six hydrogen-bond donors.

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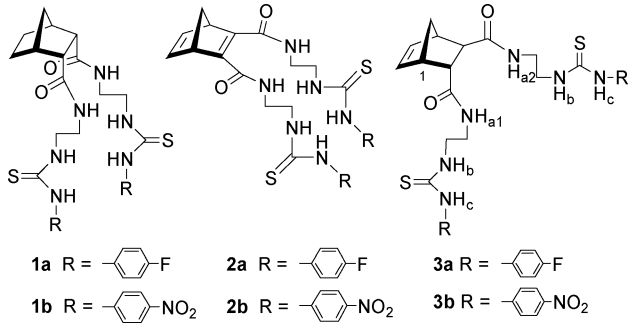
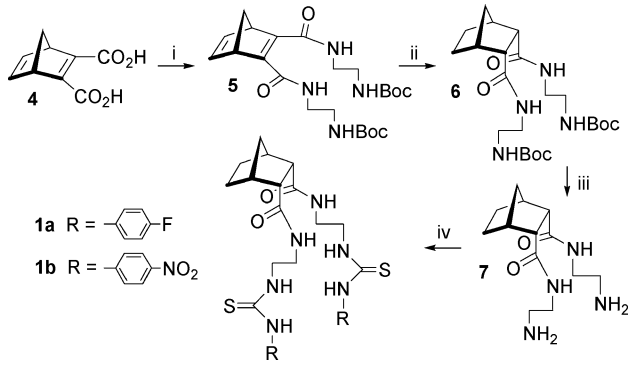


Figure 1. Structures of the new norbornene-based receptors **1**–**3**.

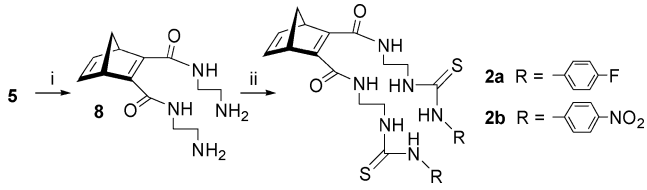
Synthesis

To accomplish the synthesis of **1**, five steps were required (Scheme 1) commencing with the Diels–Alder cycloaddition of cyclopentadiene with acetylenedicarboxylic acid[32] to produce norborna-2,5-diene-2,3-dicarboxylic acid[27] **4** in quantitative yield. The diacid **4** was then coupled with *tert*-butyl (2-aminoethyl)carbamate[33] using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC). The resulting alkene **5** was subsequently hydrogenated in the presence of palladium hydroxide, producing the norbornane *endo*-bis(amide) **6**. The deprotection of **6** was sensitive to TFA concentration but the optimum conditions (12% TFA in DCM) provided quantitative yields of the free primary bis(amine) **7** which was used directly in the final step. Nucleophilic attack by the primary amino groups of **7** on either 4-fluorophenyl isothiocyanate or 4-nitrophenyl isothiocyanate produced receptors **1a** and **1b** in 93%, and 88% yield, respectively, after chromatographic purification.



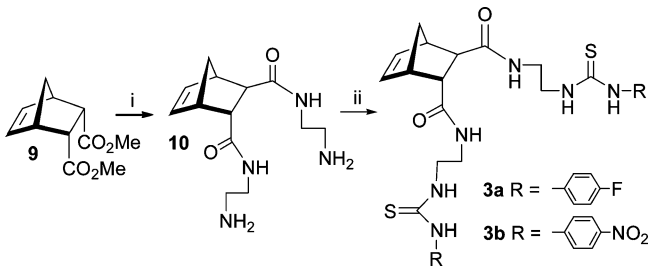
Scheme 1. Synthesis of host **1**. Reagents and conditions: (i) *tert*-butyl (2-aminoethyl)carbamate, EDC, $CHCl_3$, room temp., 17 h, 44%; (ii) Pd–OH/C, EtOH, room temp., 12 h, 99%; (iii) 12% TFA/DCM, room temp., 3 h, 100%; (iv) 4-fluorophenyl isothiocyanate (for **1a**)/4-nitrophenyl isothiocyanate (for **1b**), DIPEA, $CHCl_3$, room temp., 18 h, 93% (for **1a**)/88% (for **1b**).

Starting with bis(amide) **5**, only two steps were necessary to synthesise receptor **2** (Scheme 2). The first of which was deprotection utilising 12% TFA/DCM to form bis(amine) **8**, followed by coupling with either 4-fluorophenyl isothiocyanate or 4-nitrophenyl isothiocyanate, resulting in receptors **2a** and **2b** (both in 76% yield) after chromatographic purification.



Scheme 2. Synthesis of host **2** from precursor **5**. Reagents and conditions: (i) 12% TFA/DCM, room temp., 3 h, 100%; (ii) 4-fluorophenyl isothiocyanate (for **2a**)/4-nitrophenyl isothiocyanate (for **2b**), DIPEA, $CHCl_3$, room temp., 18 h, 76% (for **2a**)/76% (for **2b**).

Three synthetic steps were required to accomplish the synthesis of receptor **3** (Scheme 3). The Diels–Alder cycloaddition of neat cyclopentadiene with dimethyl maleate afforded dimethyl norborn-5-ene-2,3-*endo*-dicarboxylate (**9**) in quantitative yield. Diester **9** was directly converted into the diamine **10**, and the conditions required to convert the methyl ester to the amide (100 °C, neat ethylenediamine, 19 h) resulted in epimerisation of the bis(*endo*-carbonyl) compound, and the thermodynamically more stable *endo*/*exo* adduct was isolated.[34] After reaction of the bis(amine) **10** with either 4-fluorophenyl isothiocyanate or 4-nitrophenyl isothiocyanate, receptors **3a** and **3b** were obtained in 69% and 48% yield, respectively, after chromatographic purification.



Scheme 3. Synthesis of host **3**. Reagents and conditions: (i) ethylenediamine, 100 °C, 19 h, 98%; (ii) 4-fluorophenyl isothiocyanate (for **3a**)/4-nitrophenyl isothiocyanate (for **3b**), $CHCl_3$, room temp., 24 h, 69% (for **3a**)/48% (for **3b**).

^{1}H NMR Titration Studies

When examining hydrogen-bonding interactions ^{1}H NMR spectroscopy is an extremely powerful tool as it provides a means of monitoring the electron density surrounding each potential hydrogen-bond donor present in the host. Conclusions can then be drawn as to which *individual* protons are involved in the interaction, as well as the extent to which they participate.[18,35]

To assess the ability of the new hosts to bind anions, [D_6]-DMSO solutions of Br^-, Cl^-, F^-, HSO_4^-, $H_2PO_4^-$ and AcO^- [as their tetrabutylammonium (TBA) salts] were titrated against [D_6]DMSO solutions of each host (ca. 1.2×10^{-2} M) while recording any observed migration of the relevant N–H resonances.

Initially, the spherical halides were evaluated; however, the addition of both Br^- and Cl^- elicited only minor changes in the ^{1}H NMR spectrum (Table 1). For Br^-, an average downfield shift ($\Delta\delta$) value of 0.10 ppm was ob-

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

		Br^-	Cl^-	F^-	HSO_4^-	$H_2PO_4^-$	AcO^- (NMR)	AcO^- (UV/Vis)
1a	max $\Delta\delta$[b]	0.10	0.51	1.51[c]	0.08	1.67	3.15	–
	$\log K_1$	–	–	–	–	3.66	3.15	–
	$\log K_2$	–	–	–	–	3.00	2.24	–
1b	max $\Delta\delta$[b]	0.11	0.53	1.54[c]	0.12	1.74	3.31	–
	$\log K_1$	–	–	–	–	3.73	3.82	3.67[d]
	$\log K_2$	–	–	–	–	2.60	2.95	3.63[d]
2a	max $\Delta\delta$[b]	0.09	0.48	1.24[c]	0.08	1.83	2.89	–
	$\log K_1$	–	–	–	–	3.94	4.18	–
	$\log K_2$	–	–	–	–	2.24	2.51	–
2b	max $\Delta\delta$[b]	0.14	0.84	1.34[c]	0.06	1.74	3.27	–
	$\log K_1$	–	–	–	–	3.16	3.40	3.70[d]
	$\log K_2$	–	–	–	–	2.53	3.19	3.75[d]
3a	max $\Delta\delta$[b]	0.09	0.44	1.62[c]	0.09	1.94	3.24	–
	$\log K_1$	–	–	–	–	3.63	3.92	–
	$\log K_2$	–	–	–	–	2.65	2.78	–
3b	max $\Delta\delta$[b]	0.04	0.53	1.35[c]	0.04	1.84	3.14	–
	$\log K_1$	–	–	–	–	3.73	3.27	3.95[d]
	$\log K_2$	–	–	–	–	2.46	–	–

[a] Binding constants were determined from ^1H NMR titration data using WinEQNMR software,[37] with calculated errors of <14.0%. All ^1H NMR titrations were carried out with initial host concentrations of approximately 1.2×10^{-2} M. [b] Maximum chemical shift observed for H_c after addition of 6.0 equiv. of anion. [c] Values after addition of 1.6 equiv. of anion. [d] Binding constants determined from UV/Vis titrations using non-linear least-squares curve fitting,[38] with calculated std. dev. $\sigma < 1.3\%$. All UV/Vis titrations were carried out with initial host concentrations of approximately 5.0×10^{-5} M.

served for all hosts (after 6.0 equiv. of anion). Although the shifts for Cl^- were more significant, a lack of a consistent trend in the data meant calculating binding constants was not viable. These results suggested that very weak, if any, binding occurred between Br^- or Cl^- and any of the new hosts.

In contrast, upon addition of F^- significant broadening and considerable downfield migration of the N–H resonances occurred immediately, with maximum $\Delta\delta$ values ranging from 1.24 to 1.62 ppm (Table 1). Again, stoichiometries and binding constants could not be calculated, as saturation of the hosts had not been achieved before the resonances became indistinguishable from the baseline (after 1.6 equiv.). A distinct, successive colour change from pale yellow to deep red was observed during the titrations of the nitro-substituted hosts. This colour change, which was clearly visible to the naked eye and due to deprotonation (FHF^- triplet observed at δ = 16.12 ppm),[8] provided evidence that these norbornene-based receptors could function as colorimetric sensors.[30,36]

After the spherical halides, the tetrahedral anions HSO_4^- and $H_2PO_4^-$ were investigated; however, adding HSO_4^- resulted in insignificant changes in chemical shift (Table 1), suggesting weak, if any, binding of HSO_4^-. On the other hand, upon addition of $H_2PO_4^-$, considerable $\Delta\delta$ values were observed for the entire family of receptors **1**–**3** (Table 1) with a maximum $\Delta\delta$ value of 1.94 ppm recorded for **3a**, which indicated that strong binding of $H_2PO_4^-$ was occurring. As anticipated, the four thiourea protons of each receptor experienced the largest shifts, but there were also significant migrations associated with the two amide protons of each receptor (Figure 2). It was of great interest that in the case of the *endo*/*exo* host **3** the $\Delta\delta$ value of the two amide proton resonances was not equal (**3a**: H_{a1}-*endo*: $\Delta\delta$ = 0.39 ppm, H_{a2}-*exo*: $\Delta\delta$ = 1.03 ppm; Figure 3). Although a 1:1 host/guest binding stoichiometry might have been expected, given the capability of the more flexible two-"arm" system to encompass the larger multiple hydrogen-bond acceptor anion $H_2PO_4^-$, job plot data[13,38] showed a clear 1:2 host/guest binding stoichiometry in all cases (Figure 4).

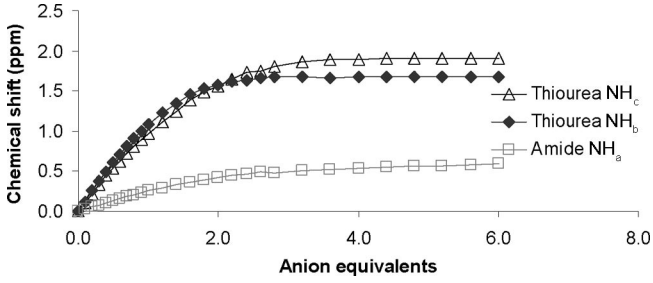


Figure 2. Changes in the chemical shift of relevant N–H protons within **1a** (1.25×10^{-2} M) upon addition of $H_2PO_4^-$ in [D_6]DMSO (also representative of receptors **1b**, **2a** and **2b**, see Supporting Information for individual binding isotherms).

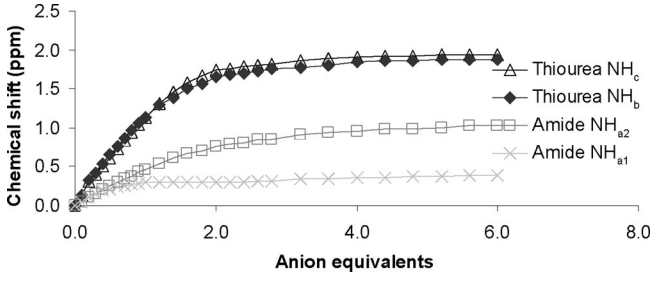


Figure 3. Changes in the chemical shift of relevant N–H protons within **3a** (1.24×10^{-2} M) upon addition of $H_2PO_4^-$ in [D_6]DMSO (also representative of receptor **3b**, see Supporting Information for binding isotherm).

This implied that the two anionophoric "arms" act independently to bind one guest each, and that the preorganised cleft of the host was inappropriate to accommodate the larger $H_2PO_4^-$ anion. The considerable thiourea proton shifts suggest the guests were primarily bound by the thiourea protons; however, a definite contribution from the amide protons was evidenced by their significant $\Delta\delta$ value. Binding constants for the two-step binding process [H + G $\rightarrow$ HG (K_1), HG + G $\rightarrow$ HG_2 (K_2)] were determined by fitting the ^{1}H NMR titration data using WinEQNMR[37] and are reported as log K_1 and log K_2 (Table 1).

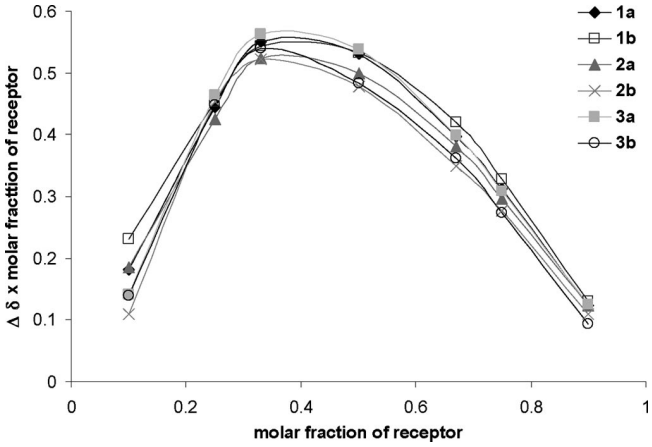


Figure 4. Job plots for the complexation of receptors **1**–**3** with $H_2PO_4^-$ at a total concentration of approximately 1.2×10^{-2} M in [D_6]-DMSO.

It was established by multiple 1D and 2D ROESY experiments (see Supporting Information) that a through-space interaction was occurring between the amide N–H_{a1} of the *endo* "arm" of **3** and H_1 of the norbornene scaffold (Figure 5). This interaction suggests that the lack of cooperation of N–H_{a1} when binding $H_2PO_4^-$ to the *endo* "arm" is likely due to steric reasons. In kinetic studies examining *endo*- versus *exo*-norbornene substituents, the *endo* position was found to be less reactive than the *exo* position, and this difference was justified by steric constraints;[40] such conclusions support our findings.

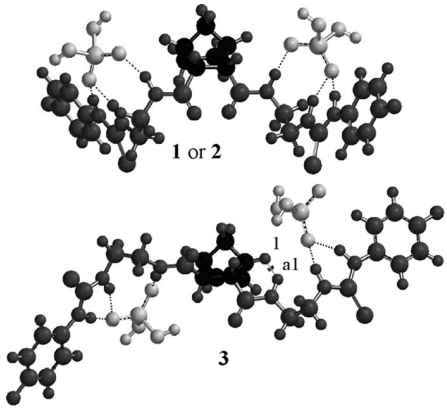


Figure 5. Energy-minimised molecular models[39] of receptors **1** or **2** with 2 equiv. of $H_2PO_4^-$ (top), and receptor **3** with 2 equiv. of $H_2PO_4^-$ (bottom).

The final anion to be evaluated was the trigonal-planar AcO^- anion. It was immediately apparent that the receptors were binding AcO^- strongly due to the large $\Delta\delta$ values recorded for **1**–**3** (max $\Delta\delta$ = 3.31 ppm for **1b** after 6.0 equiv. of added anion; Table 1). As was noted when titrating F^- against the nitro-substituted receptors, a distinct visible colour change accompanied the significant downfield shifts, yet each N–H resonance was still clearly visible in the spectrum after 9 equiv. of the anion had been added, ruling out complete deprotonation as a cause for the colorimetric response. For all six receptors, the expected trend of larger shifts for the thiourea proton resonances was observed; however, the amide proton resonances remained unchanged (Figure 6). This indicated strong hydrogen bonding between the thiourea protons of the anionophoric "arms" and the geometrically complementary acetate anions, with no contribution from the amide protons.

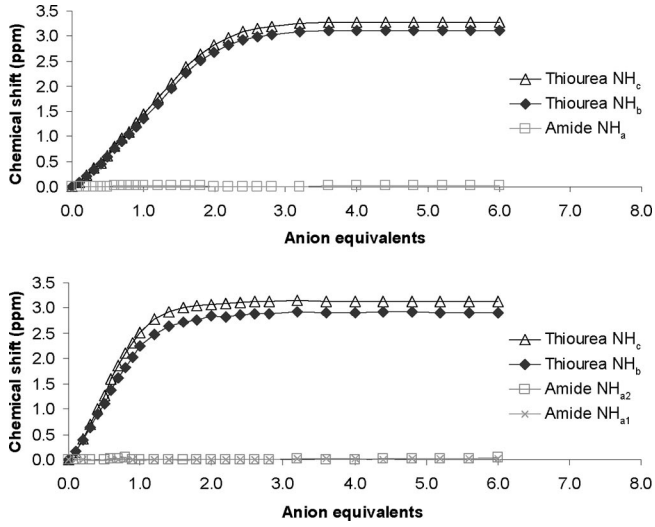


Figure 6. Changes in the chemical shift of relevant N–H protons within **2b** (top, 1.24×10^{-2} M) and **3b** (bottom, 1.16×10^{-2} M) upon addition of AcO^- in [D_6]DMSO (**2b** is also representative of receptors **1a**, **1b**, **2a** and **3a**, see Supporting Information for individual binding isotherms).

The job-plot data for receptors **1**, **2** and **3a** (Figure 7) are consistent with a 1:2 host/guest arrangement, and again a scenario where the two "arms" are acting independently to bind a single anion each was proposed (Figure 8). It was therefore surprising that for receptor **3b** the titration isotherm (Figure 6) and the job-plot data (Figure 7) clearly suggested a 1:1 host/guest stoichiometry where the anion was bound within the receptor cavity through the cooperation of all *four* thiourea hydrogen-bond donors (Figure 8). The trigonal-planar AcO^- anion complements the thiourea hydrogen-bond donor system very well,[3,6] and, as such, there are numerous examples of a *single* thiourea recognition unit binding a *single* AcO^- anion.[41] On the other hand, examples of *two* thiourea units binding a *single* AcO^- anion, as observed for receptor **3b**, are less common, and preorganisation arguments are usually invoked to explain such instances.[16,42]

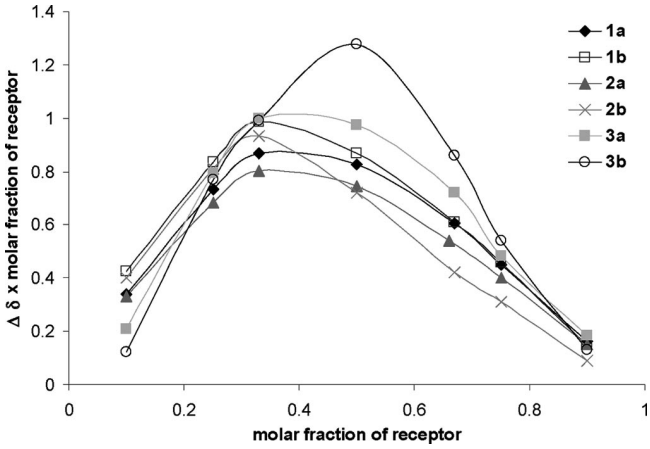


Figure 7. Job plots for the complexation of receptors **1**–**3** with AcO^- at a total concentration of approximately 1.2×10^{-2} M in [D_6] DMSO.

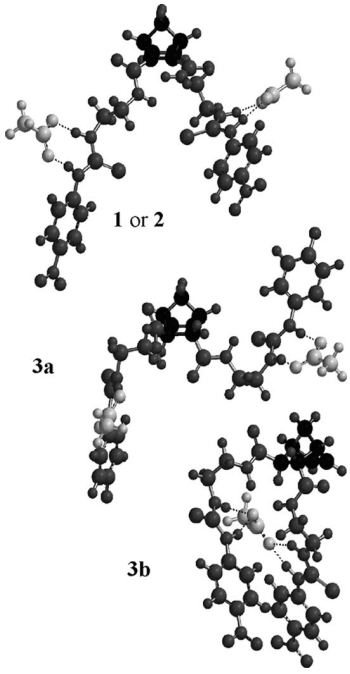


Figure 8. Energy-minimised molecular models[39] of receptors **1** or **2**, and **3a** with 2 equiv. of AcO^- (top), and receptor **3b** with 1 equiv. of AcO^- (bottom).

The contradicting host/guest binding stoichiometries determined for receptors **3a** and **3b** with AcO^- requires justification. Preorganisation cannot be the sole factor influencing host/guest stoichiometry as the cleft-like binding site for both receptors is essentially identical given that they have the same rigid norbornene scaffold. Indeed, they are effectively identical except for one feature – the phenyl substituent: F for **3a** and NO_2 for **3b**. Therefore, electronic factors are likely to play a role when accounting for the observed results. By using the acidity of *p*-substituted benzoic acids as an example, deactivating (electron-withdrawing) groups increase the acidity by stabilizing the carboxylate anion; the opposite is true for activating groups. Indeed, the pK_a of 4-nitrobenzoic acid and 4-fluorobenzoic acid are 3.43 and 4.15, respectively,[43] and this same concept can be used to explain the increased acidity of the thiourea N–H_c protons of receptor **3b**.

Although the hydrogen-bonding ability of hosts **3a** and **3b** depends on a number of contributing factors, such as electrostatic interactions, bond geometries and solvent polarity, this study suggests that increased hydrogen-bond donor strength through substituent effects can prove significant when considering host/guest binding stoichiometry. As the experimental evidence supports receptor **3b** binding a single AcO^- guest through all four thiourea hydrogen-bond donors (Figure 8), it genuinely appears that the combination of steric and electronic properties of this host make **3b** unique within this closely related family.

UV/Vis Study

UV/Vis absorption spectroscopy is another important tool when examining host/guest interactions; this technique can be employed whenever the coordination of a guest is accompanied by a spectral change of the host. Although information regarding individual hydrogen-bond donors is not provided, this method does enable a "global picture" of the binding event to be established. As such, UV/Vis spectroscopy is often used for determining host/guest binding stoichiometries and association constants.[4,44]

During the ^1H NMR studies, addition of AcO^- to the nitro-substituted hosts (**1b**, **2b** and **3b**) resulted in a progressive colour change from pale yellow to a deep red. When these titrations were monitored using UV/Vis absorption spectrometry [the AcO^- anion was added to DMSO solutions of the **b** series of receptors (5×10^{-5} M) as a TBA salt] a new absorption band at 480 nm was gradually enhanced, while the intensity of the absorption band at 362 nm correspondingly decreased (Figure 9). The origin of the colour change could be ascribed to the charge-transfer

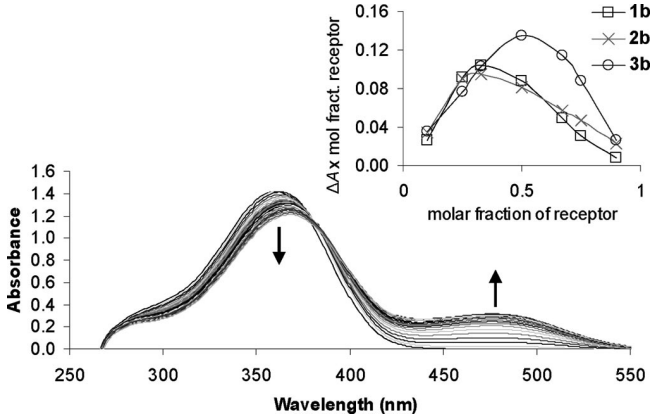


Figure 9. Job plots (inset) and UV/Vis absorption spectra of receptor **3b** (DMSO, 5.0×10^{-5} M) upon the addition of 6.0 equiv. of AcO^- anion in 0.2-equiv. increments (also representative of the spectra obtained for both **1b** and **2b** under the same conditions, see Supporting Information for individual spectra).

interactions between the electron-rich donor nitrogen atoms of the thiourea units and the electron-deficient *p*-nitrophenyl moieties.[17,18,45] A clear isosbestic point was observed at 383 nm indicating the reversible formation of a complex between the host and guest was occurring.[46]

Job plots (Figure 9) confirmed the unusual 1:1 host/guest binding stoichiometry of receptor **3b** with AcO^-, while still supporting the 1:2 host/guest binding stoichiometries determined for both receptors **1b** and **2b** with AcO^-. Binding constants were also calculated from the UV/Vis data (Table 1).[38,43,45] Overall, these values were slightly larger than those calculated from ^{1}H NMR spectroscopic data, this could be due to a number of factors including self-aggregration and oligomerisation, which are less prominent in the more dilute solutions employed in UV/Vis titration experiments. As expected, **3b** had the largest calculated binding constant of the **b** series of receptors, indicating that AcO^- was bound most strongly by this receptor. The strong binding was likely due to the cooperation of all four thiourea hydrogen-bond donors stabilising the host/guest complex as depicted in Figure 8.

Conclusions

We have designed, synthesised and evaluated the anion binding ability of six new, conformationally preorganised norbornene-based receptors **1a**,**1b**–**3a**,**3b**. Receptors **1** and **2** bind both $H_2PO_4^-$ and AcO^- in a 1:2 host/guest stoichiometry regardless of preorganisation and electronic factors. Receptor **3** also binds $H_2PO_4^-$ in the 1:2 fashion, however each "arm" adopts an independent conformation due to the steric constraints imparted by the norbornene scaffold. The unexpected 1:1 binding of **3b** with AcO^- provides further insight as to how subtle electronic factors can have a major impact on overall host/guest binding stoichiometries.

These subtle electronic factors showcase the prospect that deliberately "tuning" the acidity of the hydrogen-bond donors can markedly influence the selectivity. Investigations into [*n*]polynorbornane frameworks employing these simple receptors as building blocks are currently underway, and the results of these studies will be reported in due course.

Experimental Section

General: NMR spectra were collected with either a JEOL EX 270 MHz FT-NMR spectrometer (Tokyo, Japan), or a JEOL EX 400 MHz FT-NMR spectrometer (Tokyo, Japan), where indicated. UV/Vis spectra were measured using a Varian Cary Eclipse 300 Bio UV/Vis spectrophotometer. HRMS was performed with an Agilent 6210 LC/MSDTOF instrument using CH_3CN as the mobile phase. Melting points were determined with 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. Peptide coupling agents and isothiocyanates were supplied by Aldrich Chemical Co.

Norborna-2,5-diene-2,3-dicarboxylic Acid (4):[32] Freshly cracked cyclopentadiene (0.923 g, 13.96 mmol) was added dropwise with stirring to a solution of acetylenedicarboxylic acid (1.592 g, 13.96 mmol) in 1,4-dioxane (5 mL). This reaction mixture was stirred under nitrogen for 12 h, a water bath was used to maintain room temperature throughout the exothermic reaction. TLC analysis indicated complete consumption of the starting materials and the formation of a single pure product **4** (R_f = 0.54, 25% methanol/ethyl acetate) as a white crystalline solid in a quantitative yield (2.516 g, 100%). No further purification was required for subsequent steps; m.p. 158.2–159.2 °C. ^{1}H NMR (270 MHz; $CDCl_3$, TMS): δ = 2.16 (d, J = 6.9 Hz, 1 H, CH_2), 2.28 (d, J = 7.4 Hz, 1 H, CH_2), 4.19 (s, 2 H, CHCH$_2$), 6.92 (s, 2 H, CH=CH) ppm. ^{13}C NMR (270 MHz; $CDCl_3$, TMS): δ = 54.37, 73.17, 142.32, 157.84, 166.84 ppm. HRMS: m/z = 203.0268 [M + Na]$^+$; $C_9H_8NaO_4$ requires 203.0320.

***tert*-Butyl (2-Aminoethyl)carbamate:**[33] A solution of di-*tert*-butyl dicarbonate (5.154 g, 23.62 mmol) in 1,4-dioxane (5 mL) was prepared and added dropwise over 30 min to a solution of ethylenediamine (5.0 mL, 74.6 mmol) in 1,4-dioxane (45 mL). This reaction mixture was then stirred at room temperature for 4 h during which time a white precipitate formed. The suspension was filtered and the filtrate concentrated under reduced pressure to afford a clear oil (3.675 g, 97.1%). ^{1}H NMR (270 MHz; $CDCl_3$, TMS): δ = 1.35 [s, 9 H, C(CH_3)$_3$], 2.69 (q, J = 5.5 Hz, 2 H, CH_2NH$_2$), 3.08 (q, J = 5.8 Hz, 2 H, CH_2NH), 5.12 (br. s, 1 H, NH) ppm. ^{13}C NMR (270 MHz; $CDCl_3$, TMS): δ = 28.42, 41.89, 43.43, 44.85, 156.30 ppm. HRMS: m/z = 161.1155 [M + H]$^+$; $C_7H_{17}N_2O_2$ requires 161.1290.

Di-*tert*-butyl [Norborna-2,5-diene-2,3-diylbis(carbonyliminoethane-2,1-diyl)]biscarbamate (5): A solution of norborna-2,5-diene-2,3-dicarboxylic acid (**4**) (0.400 g, 2.220 mmol) and EDC (0.851 g, 4.439 mmol) was prepared in dry $CHCl_3$ (5 mL), 2-(*tert*-butoxycarbonylamino)ethylamine (0.711 g, 4.438 mmol) was then added and the mixture stirred for 48 h. The reaction mixture was further diluted with $CHCl_3$ (10 mL) then transferred to a separating funnel. The organic phase was washed with water (3 × 30 mL), dried ($MgSO_4$), filtered, then concentrated to dryness under reduced pressure. The crude product was purified using flash chromatography with gradient elution (0–10% methanol/ethyl acetate, R_f(prod.) = 0.64; ethyl acetate) to afford **5** as a white powder (0.452 g, 43.8%); m.p. 196.1–197.2 °C. ^{1}H NMR (270 MHz; $CDCl_3$, TMS): δ = 1.37 [s, 18 H, 2 × C(CH_3)$_3$], 1.86 (d, J = 6.2 Hz, 1 H, CHCH_2), 1.98 (d, J = 4.7 Hz, 1 H, CHCH_2), 3.05 (t, J = 5.7 Hz, 4 H, 2 × CH_2NHCO), 3.17 (t, J = 5.7 Hz, 4 H, 2 × CH_2NHCOO), 4.01 (s, 2 H, 2 × CHCH$_2$), 6.88 (s, 2 H, 2 × NHCOO), 6.89 (s, 2 H, CH=CH), 9.25 (s, 2 H, 2 × NHCO) ppm. ^{13}C NMR (270 MHz; $CDCl_3$, TMS): δ = 28.76, 39.84, 47.54, 54.08, 71.08, 78.27, 142.88, 153.38, 156.30, 164.68 ppm. HRMS: m/z = 465.2713 [M + H]$^+$; $C_{23}H_{37}N_4O_6$ requires 465.2713.

Di-*tert*-butyl [Norbornane-2,3-*endo*-diylbis(carbonyliminoethane-2,1-diyl)]biscarbamate (6): To a solution of the diene **5** (0.170 g, 0.366 mmol) in ethanol (20 mL), a catalytic amount of palladium hydroxide on activated carbon was added. A gas bladder was used to provide and maintain a hydrogen blanket over the reaction mixture which was subsequently stirred at room temperature for 12 h. The reaction mixture was filtered through Celite atop a Büchner funnel, then the solvent removed under reduced pressure to yield **6** as a white powder (0.170 g, 99.2%); m.p. 209.8–211.4 °C. ^{1}H NMR

(270 MHz; $CDCl_3$, TMS): δ = 1.21 (d, J = 8.1 Hz, 2 H, 2× *exo*-CHCH_2CH_2), 1.35 (s, 2 H, CHCH_2), 1.37 [s, 18 H, 2× C(CH_3)$_3$], 1.76 (d, J = 6.9 Hz, 2 H, 2× *endo*-CHCH_2CH_2), 2.33 (s, 2 H, 2× CH$_2$CHCH$_2$), 2.69 (s, 2 H, 2× *exo*-CH), 2.91–3.10 (m, 8 H, 2× CH_2CH_2), 6.64 (s, 2 H, 2× NHCOO), 7.54 (s, 2 H, 2× NHCO) ppm. ^{13}C NMR (270 MHz; $CDCl_3$, TMS): δ = 24.61, 28.78, 39.12, 41.89, 47.39, 78.13, 156.10, 172.49 ppm. HRMS: m/z = 469.3151 [M + H]$^+$; $C_{23}H_{41}N_4O_6$ requires 469.3026.

***N*,*N*′-Bis(2-aminoethyl)norbornane-2,3-*endo*-dicarboxamide (7):** A mixture of 12% TFA/DCM (5 mL) was added to the bis(amide) **6** (0.220 g, 0.469 mmol), then stirred at room temperature for 3 h, while being monitored by TLC. Complete consumption of **6** was apparent by this time, and excess solvent and TFA were removed under reduced pressure to yield **7** as an off-white solid (0.113 g, 100%). This material was used directly in subsequent steps.

***N*,*N*′-Bis[2-({[(4-fluorophenyl)amino]carbonothioyl}amino)ethyl]-norbornane-2,3-*endo*-dicarboxamide (1a):** The bis(amine) **7** (0.220 g, 0.469 mmol) was added to a solution of 4-fluorophenyl isothiocyanate (0.144 g, 0.940 mmol) and ethyldiisopropylamine (0.49 mL, 2.79 mmol) in $CHCl_3$ (5 mL). This reaction mixture was stirred at room temperature for 18 h before being concentrated to dryness under reduced pressure. The crude product was purified using flash chromatography (5% methanol/ethyl acetate; R_f = 0.51) to afford **1a** as a white powder (0.252 g, 93.4%); m.p. 130.1–132.9 °C. $C_{27}H_{32}F_2N_6O_2S_2$ (574.20): calcd. C 56.43, H 5.61, N 14.62; found C 56.36, H 5.72, N 14.56. ^{1}H NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 1.24 (d, J = 4.1 Hz, 2 H, 2× *endo*-CHCH_2CH_2), 1.24 (d, J = 4.9 Hz, 1 H, CHCH_2), 1.39 (d, J = 5.7 Hz, 1 H, CHCH_2), 1.71 (d, J = 4.2 Hz, 2 H, 2× *exo*-CHCH_2CH_2), 2.36 (s, 2 H, 2× CH$_2$CH), 2.75 (s, 2 H, 2× *exo*-CHCH), 3.18 (d, J = 5.5 Hz, 4 H, 2× CH_2NHCO), 3.46–3.54 (m, 4 H, 2× CH_2NHCS), 7.13 (t, J = 8.8 Hz, 4 H, 4× Ar-CHCF), 7.37 (t, J = 6.8 Hz, 4 H, 4× Ar-CHCNH), 7.65 (br. s, 2 H, 2× Ph-NH), 7.75 (s, 2 H, 2× NHCS), 9.56 (s, 2 H, 2× CONH) ppm. ^{13}C NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 24.64, 39.67, 42.18, 48.98, 115.66, 115.88, 126.31, 135.86, 158.38, 160.78, 173.03, 181.35 ppm. HRMS: m/z = 575.2048 [M + H]$^+$; $C_{27}H_{33}F_2N_6O_2S_2$ requires 575.2074.

***N*,*N*′-Bis[2-({[(4-nitrophenyl)amino]carbonothioyl}amino)ethyl]-norbornane-2,3-*endo*-dicarboxamide (1b):** As for **1a**, using bis(amine) **7** (0.200 g, 0.427 mmol), 4-nitrophenyl isothiocyanate (0.154 g, 0.855 mmol), and ethyldiisopropylamine (0.45 mL, 2.58 mmol) in $CHCl_3$ (5 mL) afforded **1b** as a yellow crystalline solid (0.235 g, 87.6%); 5% methanol/ethyl acetate, R_f = 0.39; m.p. 151.9–154.2 °C. $C_{27}H_{32}N_8O_6S_2$ (628.19): calcd. C 51.58, H 5.13, N 17.82; found C 51.61, H 5.16, N 17.71. ^{1}H NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 1.23 (d, J = 4.2 Hz, 2 H, 2× *endo*-CHCH_2CH_2), 1.24 (d, J = 6.1 Hz, 1 H, CHCH_2), 1.39 (d, J = 5.8 Hz, 1 H, CHCH_2), 1.73 (d, J = 4.4 Hz, 2 H, 2× *exo*-CHCH_2CH_2), 2.38 (s, 2 H, 2× CH$_2$CH), 2.78 (s, 2 H, 2× *exo*-CHCH), 3.24 (d, J = 5.7 Hz, 4 H, 2× CH_2NHCO), 3.47–3.58 (m, 4 H, 2× CH_2NHCS), 7.78 (d, J = 8.7 Hz, 4 H, 4× Ar-CHCNH), 7.83 (s, 2 H, 2× CONH), 8.15 (d, J = 7.2 Hz, 4 H, 4× Ar-CHCNO$_2$), 8.16 (s, 2 H, 2× NHCS), and 10.22 (s, 2 H, 2× Ph-NH) ppm. ^{13}C NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 24.62, 37.89, 44.70, 47.84, 121.08, 125.07, 142.35, 144.86, 146.72, 162.35, 173.24, 180.71 ppm. HRMS: m/z = 629.1941 [M + H]$^+$; $C_{27}H_{33}N_8O_6S_2$ requires 629.1964.

***N*,*N*′-Bis(2-aminoethyl)norborna-2,5-diene-2,3-dicarboxamide (8):** As for diamine **7**, using diene **5** (0.321 g, 0.691 mmol) yielded **8** as an off-white solid (0.165 g, 99.6%). This material was used directly in subsequent steps.

***N*,*N*′-Bis[2-({[(4-fluorophenyl)amino]carbonothioyl}amino)ethyl]-norborna-2,5-diene-2,3-dicarboxamide (2a):** The bis(amine) **8** (0.057 g, 0.237 mmol) was added to a solution of 4-fluorophenyl isothiocyanate (0.091 g, 0.594 mmol) and ethyldiisopropylamine (0.25 mL, 1.44 mmol) in $CHCl_3$ (3 mL). This reaction mixture was stirred at room temperature for 18 h before being concentrated to dryness under reduced pressure. The crude product was purified using column chromatography (ethyl acetate, R_f = 0.45) to afford **2a** as a white powder (0.102 g, 75.6%); m.p. 165.4–167.9 °C. $C_{27}H_{28}F_2N_6O_2S_2$ (570.17): calcd. C 56.83, H 4.95, N 14.73; found C 56.78, H 4.99, N 14.69. ^{1}H NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 1.90 (d, J = 6.2 Hz, 1 H, CHCH_2), 2.01 (d, J = 5.8 Hz, 1 H, CHCH_2), 3.38 (d, J = 3.1 Hz, 4 H, 2× CH_2NHCO), 3.59 (br. s, 4 H, 2× CH_2NHCS), 4.06 (s, 2 H, 2× CHCH$_2$), 6.92 (s, 2 H, CH=CH), 7.14 (t, J = 8.8 Hz, 4 H, 4× Ar-CHCF), 7.36 (t, J = 5.3 Hz, 4 H, 4× Ar-CHCNH), 7.77 (br. s, 2 H, 2× NHCS), 9.42 (s, 2 H, 2× CONH), and 9.57 (s, 2 H, 2× Ph-NH) ppm. ^{13}C NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 43.62, 71.10, 115.71, 115.94, 126.58, 135.70, 142.92, 153.53, 158.49, 160.89, 164.83, 181.45 ppm. HRMS: m/z = 571.1705 [M + H]$^+$; $C_{27}H_{29}F_2N_6O_2S_2$ requires 571.1761.

***N*,*N*′-Bis[2-({[(4-nitrophenyl)amino]carbonothioyl}amino)ethyl]-norborna-2,5-diene-2,3-dicarboxamide (2b):** As for **2a**, using bis(amine) **8** (0.178 g, 0.741 mmol), 4-nitrophenyl isothiocyanate (0.334 g, 1.854 mmol), and ethyldiisopropylamine (0.78 mL, 4.48 mmol) in $CHCl_3$ (5 mL) afforded **1a** as a yellow powder (0.353 g, 76.3%); ethyl acetate, R_f = 0.40; m.p. 181.1–184.2 °C. ^{1}H NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 1.91 (d, J = 6.1 Hz, 1 H, CHCH_2), 2.03 (d, J = 6.3 Hz, 1 H, CHCH_2), 3.41 (d, J = 4.1 Hz, 4 H, 2× CH_2NHCO), 3.64 (d, J = 5.0 Hz, 4 H, 2× CH_2NHCS), 4.15 (s, 2 H, 2× CHCH$_2$), 6.93 (s, 2 H, CH=CH), 7.80 (d, J = 9.1 Hz, 4 H, 4× Ar-CHCNH), 8.16 (d, J = 9.4 Hz, 4 H, 4× Ar-CHCNO$_2$), 8.43 (s, 2 H, 2× NHCS), 9.44 (s, 2 H, 2× CONH), and 10.29 (s, 2 H, 2× Ph-NH) ppm. ^{13}C NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 38.52, 43.96, 54.18, 71.24, 121.17, 125.03, 142.13, 142.93, 146.69, 153.58, 164.92, 180.92 ppm. HRMS: m/z = 625.1623 [M + H]$^+$; $C_{27}H_{29}N_8O_6S_2$ requires 625.1651.

Dimethyl Norborn-5-ene-2,3-*endo*-dicarboxylate (9): Freshly cracked cyclopentadiene (1.837 g, 27.79 mmol) was added dropwise with stirring to dimethyl maleate (4.006 g, 27.79 mmol). This reaction mixture was stirred under nitrogen for 8 h, a water bath was used to maintain room temperature throughout the exothermic reaction. TLC indicated complete consumption of the starting materials and the formation of a single pure product [35% ethyl acetate/petroleum ether (boiling range 40–60 °C), R_f = 0.41] as a clear oil in a quantitative yield (5.842 g, 100%). No further purification was required for subsequent steps. ^{1}H NMR (270 MHz; $CDCl_3$, TMS): δ = 1.33 (d, J = 6.8 Hz, 1 H, CHCH_2), 1.44 (d, J = 6.9 Hz, 1 H, CHCH_2), 3.12 (s, 2 H, 2× *exo*-CHCO), 3.26 (s, 2 H, 2× CH$_2$CH), 3.58 (s, 6 H, 2× CH_3) and 6.23 (s, 2 H, CH=CH) ppm. ^{13}C NMR (270 MHz; [D$_6$]DMSO, TMS): δ = 46.32, 48.12, 51.59, 134.97, 138.02, 172.98 ppm. HRMS: m/z = 233.0812 [M + Na]$^+$; $C_{11}H_{14}NaO_4$ requires 233.0790.

***N*,*N*′-Bis(2-aminoethyl)norborna-2,5-diene-2,3-dicarboxamide (10):** A solution of the diester **9** (550 mg, 2.62 mmol) in neat ethylenediamine (3.0 mL, 45 mmol) was prepared in a 25-mL round-bottomed flask equipped with a reflux condenser. After stirring at 100 °C for 18 h, excess ethylenediamine was removed under reduced pressure to yield an extremely viscous orange/brown oil (682 mg, 97.9%). This material was used directly in the following steps.

***N*,*N*′-Bis[2-({[(4-fluorophenyl)amino]carbonothioyl}amino)ethyl]-norborn-5-ene-2-*endo*,3-*exo*-dicarboxamide (3a):** To a solution of the *endo*/*exo*-bis(amine) **10** (500 mg, 1.88 mmol) in dry $CHCl_3$ (3.0 mL), 4-fluorophenyl isothiocyanate (719 mg, 4.69 mmol) was added in a single portion. This reaction mixture was stirred under nitrogen at room temperature for 24 h before removal of excess solvent under reduced pressure resulted in a crude yellow solid. The crude product was purified by flash chromatography (10% 2-propanol/ethyl acetate, $R_f = 0.61$) to yield a white powder (665 mg, 68.7%); m.p. 93.2–95.3 °C. ^{1}H NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 1.21 (d, J = 7.9 Hz, 1 H, CHCH_2), 1.68 (d, J = 7.6 Hz, 1 H, CHCH_2), 2.51 (s, 1 H, *exo*-CH_2CHC*H*), 2.84 (s, 1 H, *exo*-CH_2C*H*), 3.16 (s, 1 H, *endo*-CH_2CHC*H*), 3.17 (s, 1 H, *endo*-CH_2C*H*), 3.22 (m, 2 H, *exo*-CONHCH_2), 3.34 (m, 2 H, *endo*-CONHCH_2), 3.51–3.62 (br. m, 4 H, 2× CSNHCH_2), 5.95 (t, J = 3.5 Hz, 1 H, *endo*-CH=C*H*), 6.18 (t, J = 3.2 Hz, 1 H, *exo*-CH=C*H*), 7.15 (t, J = 8.8 Hz, 4 H, Ar-C*H*CNH), 7.36 (t, J = 5.0 Hz, 4 H, Ar-C*H*CF), 7.68 (br. s, 2 H, 2× N*H*CS), 7.87 (s, 1 H, *endo*-CON*H*), 8.07 (s, 1 H, *exo*-CON*H*), 9.57 (s, 2 H, 2× Ph-N*H*) ppm. ^{13}C NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 44.08, 46.02, 47.26, 47.75, 48.05, 49.21, 115.24, 115.67, 116.01, 126.46, 135.20, 135.78, 137.79, 157.87, 161.43, 173.10, 174.54, 181.35 ppm. HRMS: m/z = 573.2015 [M + H]$^+$; $C_{27}H_{31}F_2N_6O_2S_2$ requires 573.1918.

***N*,*N*′-Bis[2-({[(4-nitrophenyl)amino]carbonothioyl}amino)ethyl]-norborn-5-ene-2-*endo*,3-*exo*-dicarboxamide (3b):** As for **3a**, using *endo*/*exo*-bis(amine) **10** (701 mg, 2.63 mmol) and 4-nitrophenyl isothiocyanate (1.008 g, 5.59 mmol) in dry $CHCl_3$ (5.0 mL) yielded a yellow powder (786 mg, 47.7%); 10% methanol/ethyl acetate, R_f = 0.35; m.p. 127.6–129.4 °C. ^{1}H NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 1.21 (d, J = 7.8 Hz, 1 H, CHCH_2), 1.69 (d, J = 7.5 Hz, 1 H, CHCH_2), 2.53 (s, 1 H, *exo*-CH_2CHC*H*), 2.87 (s, 1 H, *exo*-CH_2C*H*), 3.17 (s, 1 H, *endo*-CH_2CHC*H*), 3.18 (s, 1 H, *endo*-CH_2C*H*), 3.25 (m, 2 H, *exo*-CONHCH_2), 3.35 (m, 2 H, *endo*-CONHCH_2), 3.55–3.68 (br. m, 4 H, 2× CSNHCH_2), 5.98 (t, J = 4.1 Hz, 1 H, *endo*-CH=C*H*), 6.19 (t, J = 2.2 Hz, 1 H, *exo*-CH=C*H*), 7.78 (t, J = 8.0 Hz, 4 H, Ar-C*H*CNH), 7.94 (s, 1 H, *endo*-CON*H*), 8.13 (s, 1 H, *exo*-CON*H*), 8.19 (t, J = 9.2 Hz, 4 H, Ar-C*H*CNO_2), 8.28 (br. s, 2 H, 2× N*H*CS), 10.25 (s, 2 H, 2× Ph-N*H*) ppm. ^{13}C NMR (400 MHz; [D$_6$]DMSO, TMS): δ = 38.45, 38.67, 44.20, 46.61, 47.34, 47.58, 48.15, 49.32, 60.64, 121.79, 125.78, 135.89, 138.56, 143.19, 147.48, 174.08, 175.47, 181.82 ppm. HRMS: m/z = 627.1807 [M + H]$^+$; $C_{27}H_{31}N_8O_6S_2$ requires 627.1808.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR binding isotherms, job plots and fit plots (WinEQNMR) of hosts **1**–**3** when titrated against both $H_2PO_4^-$ and AcO^-, as well as the UV/Vis spectra, job plots and fit plots of hosts **1b**, **2b**, and **3b** when titrated against AcO^-; a ROESY spectrum and an articulated description of the simulations conducted to obtain the energy-minimised molecular models.

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