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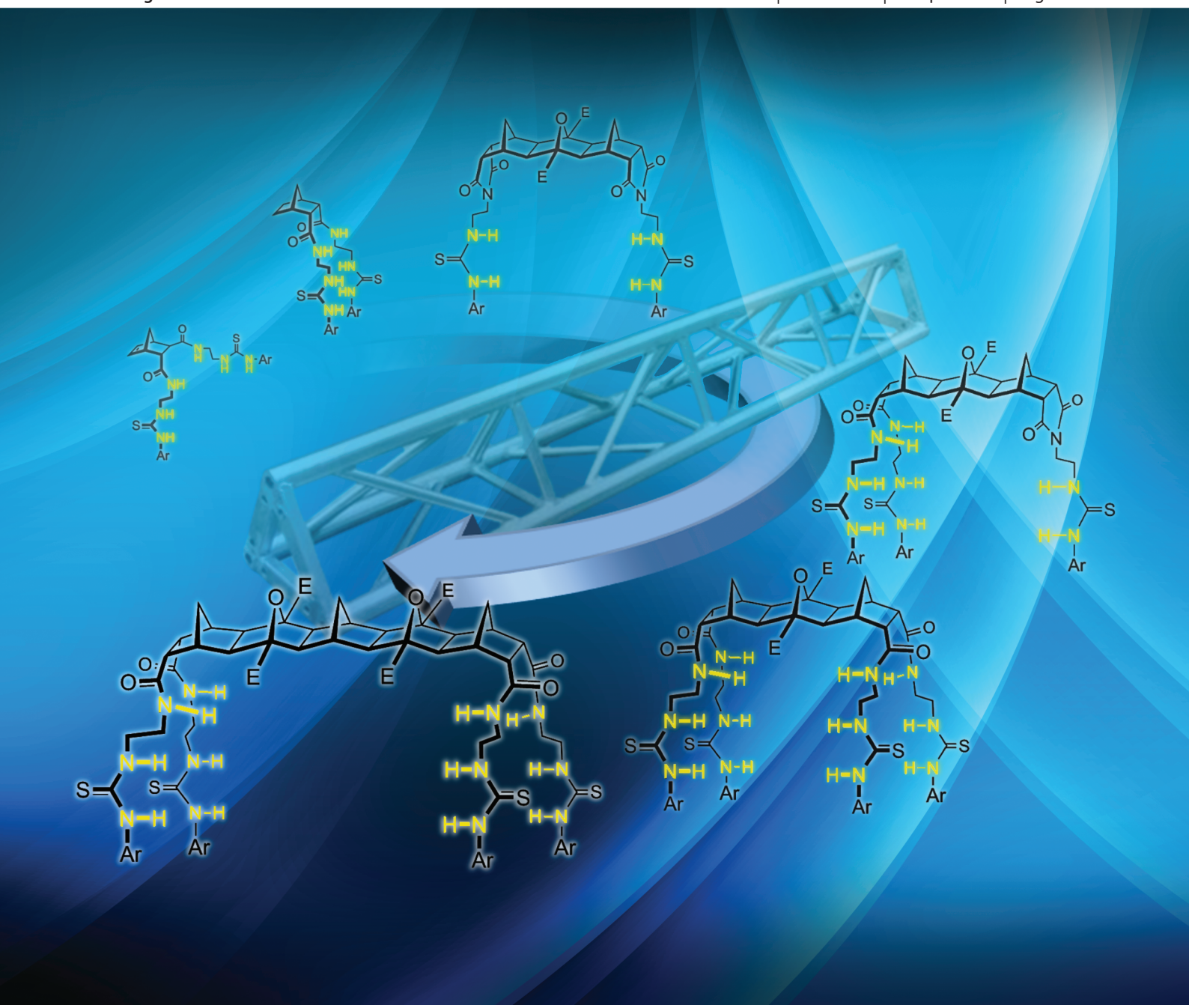

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FEATURE ARTICLE

Frederick M. Pfeffer *et al.*

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Conformationally preorganised hosts for anions using norbornane and fused [*n*]polynorbornane frameworks

Adam J. Lowe,† Benjamin M. Long and Frederick M. Pfeffer*

Norbornane and fused [*n*]polynorbornane frameworks are readily synthesised, can be tailored to a variety of predictable geometries and can be functionalised regiospecifically. As such, these highly preorganised scaffolds offer the supramolecular chemist an excellent starting point when designing hosts for specific guests. This feature article will highlight the evolution of our research from relatively simple norbornane based anion receptors to more sophisticated tetrathioureido functionalised fused [*n*]polynorbornane hosts.

Introduction

In the field of supramolecular chemistry the topic of anion recognition and sensing has become an intense pursuit for a growing number of research groups worldwide.[1] Indeed, as a result of this effort, many excellent examples of hosts for anionic species have been successfully developed.[2]

In many instances new hosts are synthesised and are subsequently evaluated against a broad set of guests to see which of these 'fits' best. One of the principal objectives for undertaking the research featured herein was not to simply unveil a new host in this way but to develop a series of related hosts such that the supramolecular chemist, when faced with a specific guest, can employ a host of appropriate dimensions to complement that guest.

Fig. 1 Norbornane **1** and fused [*3*]polynorbornane framework **2**.

An approach that employs a framework comprised of *n* individual norbornane units (**1**, Fig. 1) fused together to form a [*n*]polynorbornane framework such as **2** is one that can provide hosts that contain a preorganised cleft of predictable dimensions.

This feature article will briefly outline the role of preorganisation in supramolecular chemistry then highlight the recent use of norbornane and in particular, topologically predefined, fused [*n*]polynorbornanes in the recognition of anionic species.

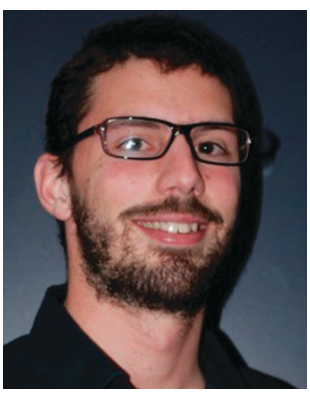
Preorganisation, induced fit, and complementarity

It was Emil Fischer who, in 1894, noted that "only in the case of similar geometrical structure can the molecules approach each other as to initiate a chemical action. . .together like a *lock and key*".[3]

Research Centre for Chemistry and Biotechnology, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, VIC 3217, Australia.
E-mail: fred.pfeffer@deakin.edu.au; Fax: +61 3 5227 1040; Tel: +61 3 5227 1439
† Present address: Digital Biology Center, Bio-Rad Laboratories Pty., Ltd., Pleasanton, CA 94566, USA.

Adam J. Lowe

Adam Lowe completed his PhD under the supervision of Dr Pfeffer in 2009 on the development of norbornenes and [n]polynorbornanes as molecular scaffolds for anion recognition. He is currently senior scientist in the digital biology center of Bio-Rad Laboratories Pty., Ltd. California where he is developing new amphiphiles for use in digital droplet technology.



Benjamin M. Long

Benjamin Long received his BSc (Hons) at Deakin University, Geelong, Australia and is currently completing his PhD under the guidance of Dr Frederick Pfeffer. His research focusses on the use of fused norbornane frameworks for anion recognition as well as the functionalisation of these scaffolds as peptidomimetics.

This pioneering theory of enzyme:substrate binding was modified by Koshland who introduced a flexible *hand in glove* description for the topological adjustment—*induced fit*—that enzyme:substrate complexes undergo in order to achieve the optimum alignment of binding groups.[4]

In the realm of supramolecular chemistry it was Cram who used preorganised spherands and flexible podands to clearly demonstrate that "preorganisation is a central determinant of binding power" and also that the alignment of contact sites between the host and guest—*complementarity*—is crucial for specific recognition.[5] Thus the goal of strong and selective anion recognition by charge neutral hosts can only occur if the host has an array of hydrogen bond donors suitably arranged in a predefined fashion for the guest.

In this context fused [*n*]polynorbornane frameworks again appear well suited as they can be readily synthesised to specific dimensions and can also be easily functionalised to include a variety of H-bond donors

This article will focus on 'larger' scaffolds, nevertheless, researchers will be aware of anion hosts based on 'smaller' scaffolds such as pyrrole,[6] indole,[7] naphthalene,[8] naphthalimide,[9] and anthracene.[10] In addition, suitably functionalised metal templated architectures have also emerged as suitable for anion recognition and the subject has been recently reviewed.[11]

Norbornanes

The norbornane (bicyclo[2.2.1]heptane) framework **1** requires little introduction. It occurs naturally in terpenoid derivatives such as borneol, camphor and fenchone[12] and the cycoladdition methodology developed for its construction won its discoverers, Otto Diels and Kurt Alder, a Nobel prize in 1950.[13] This simple scaffold has enjoyed use in a range of fields where conformational preorganisation is paramount including medicinal chemistry,[14] peptidomimetics[15] and as chiral auxiliaries for asymmetric synthesis.[16]

In the field of supramolecular chemistry tetra-amide norbornenes have been used as photo-switchable ion carriers (Fig. 2).[17] Norbornadiene–quadricyclane isomerisation (**3a–3b**) alters the preorganisation of the four amide groups and has a direct impact on the binding (and in turn transport: organic → aqueous) of a range of cationic guests.[17]

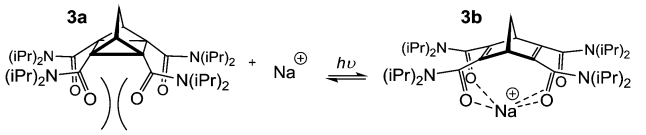


Fig. 2 Photoisomerisation of **3a** to **3b** enables cation recognition and transport from chloroform to water.[17]

Norbornanes and anion recognition[18,19]

To demonstrate that norbornanes/enes could be employed as frameworks for anion recognition, hosts **4–6** were designed (Fig. 3). Each possessed a unique binding cleft flanked by two thiourea arms (throughout this article 2-ureidoethylamido substituents are referred to as arms for convenience).[18,19]

Synthesis of the hosts was achieved using Diels–Alder cycloaddition, amide bond formation and thiourea formation. For example, construction of *endo*/*endo* host **4**[19] (Scheme 1) required cycloaddition of cyclopentadiene with acetylenedicarboxylic acid to afford norbornadiene diacid **7**. Coupling with two equivalents of 2-(*tert*-butoxycarbonylamino)ethylamine using EDCI gave Boc protected diamide **8**. Hydrogenation using $Pd(OH)_2$ afforded norbornane **9** with the desired *endo*/*endo* geometry.

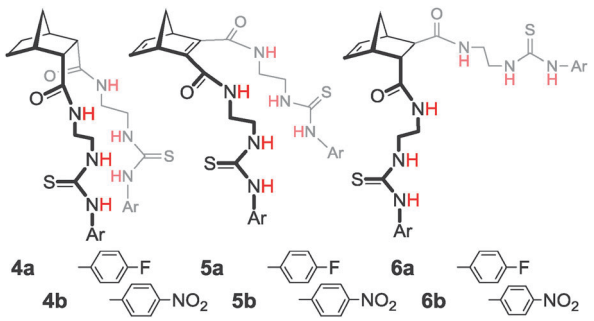
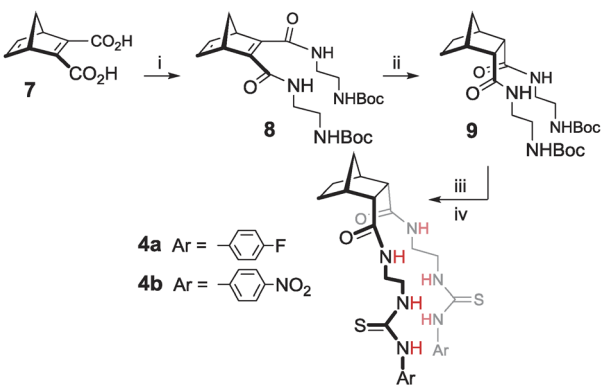


Fig. 3 Norbornane and norbornene based hosts **5–7**.

Frederick M. Pfeffer

Fred Pfeffer completed his PhD in 2001 on the synthesis of peptide functionalised molecular frameworks before moving to Trinity College Dublin for a teaching post then postdoctoral fellowship with Thorfinnur Gunnlaugsson and Paul Kruger on the development of naphthalimide based anion sensors. He returned to Australia in 2004 to take up a lecturing position at Deakin University where he is now senior lecturer. His interests include the development of new antidiabetic and antimicrobial agents as well as supramolecular anion recognition chemistry; in particular the development of conformationally preorganised norbornane based hosts.



Scheme 1 Synthesis of hosts **4**. *Reagents and conditions*: (i) 2-(*tert*-butoxycarbonylamino)ethylamine, EDC, $CHCl_3$, RT, 17 h, 44% (ii) H_2, $Pd(OH)_2$/C, EtOH, RT, 12 h, 99% (iii) 12% TFA/DCM, RT, 3 h, 100% (iv) DIPEA, $CHCl_3$, RT, 18 h, for **4a** 4-fluorophenylisothiocyanate, 93%, for **4b** 4-nitrophenylisothiocyanate, 88%.

Deprotection (TFA/CH_2Cl_2) and reaction with the appropriate isothiocyanate afforded hosts **6a** and **6b**.

Anion binding studies

Within this series (**4–6**) it was predicted that compounds **6a** and **6b** with *endo*/*exo* preorganisation would be more suited to tetrahedral anions such as dihydrogenphosphate and these anions would bind in the larger cleft of these hosts in a 1 : 1 host : guest (H : G) arrangement.

To evaluate host : guest interactions, both ^{1}H NMR and UV-Vis titration experiments were performed in DMSO. Selected results from these binding studies are summarised in Table 1.[19]

Electron withdrawing groups and H : G stoichiometry

Most significant were the results obtained for acetate (Fig. 4). Five of the six hosts bound this anion in a 1 : 2 H : G stoichiometry (common for 2-armed thiourea receptors,[21] indicating that the urea groups are *not* acting cooperatively). However, host **6b** bound acetate with a 1 : 1 H : G stoichiometry. The change from Ar–F to the more electron withdrawing Ar–NO_2 effected a change in H : G stoichiometry from 1 : 2 (for **6a** ArF) to 1 : 1 (for **6b** $ArNO_2$). Hosts **4b** and **5b** also contained the NO_2 substituent but 1 : 2 H : G stoichiometry with acetate was identified. This result implied that it was actually a combination of both the *endo*/*exo* preorganisation of host **6b** and the electron withdrawing nature of the Ar–NO_2 that made host **6b** unique when binding AcO^-.[18,19]

A colour change was noted during the titrations of the hosts containing the nitro group (**4b**, **5b** and **6b**) and UV-Vis titrations confirmed the unusual 1 : 1 H : G stoichiometry of **6b** with AcO^- despite the initial host concentration being significantly lower (*ca.* 5.0×10^{-5} M). Association constants calculated from this data were also consistent with those determined from ^{1}H NMR titrations; **4b** $\log K_1 = 3.7$, $\log K_2 = 3.6$; **5b** $\log K_1 = 3.7$, $\log K_2 = 3.8$; and **6b** $\log K_1 = 3.9$.[18,19]

To the best of our knowledge this was the first example in which a change in an electron withdrawing group (an Ar–F to a Ar–NO_2) could alter the final stoichiometry of the host : guest complex and suggests that H-bonding power can be used to control binding stoichiometry.

Table 1 Maximum observed chemical shifts, host : guest (H : G) stoichiometries and calculated association constants (log *K*) for hosts **5–7**[a]

		4a	4b	5a	5b	6a	6b
Cl^-	max $\Delta\delta$ (ppm)	0.51	0.53	0.48	0.84	0.44	0.53
	H : G	1 : 2	1 : 2	1 : 2	1 : 2	1 : 2	1 : 2
	$\log K_1$	2.8	2.5	2.6	2.9	2.3	2.6
	$\log K_2$	1.2	1.6	1.1	1.1	1.7	1.4
$H_2PO_4^-$	max $\Delta\delta$ (ppm)	1.67	1.74	1.83	1.74	1.94	1.84
	H : G	1 : 2	1 : 2	1 : 2	1 : 2	1 : 2	1 : 2
	$\log K_1$	3.7	3.7	3.9	2.9	3.6	3.1
	$\log K_2$	3.0	2.6	2.2	2.7	2.7	2.6
AcO^-	max $\Delta\delta$ (ppm)	3.15	3.31	2.89	3.27	3.24	3.14
	H : G	1 : 2	1 : 2	1 : 2	1 : 2	1 : 2	1 : 1
	$\log K_1$	3.2	3.8	4.2	3.4	3.8	3.3
	$\log K_2$	2.3	3.0	2.5	3.2	2.7	—

[a] log *K* were determined by ^{1}H NMR titration using WinEQNMR software,[20] (error < 14.0%). Titrations were carried out with initial host concentrations, $[H]_i$, of $\sim 1.2 \times 10^{-2}$ M. Max $\Delta\delta$ obtained from ArN–H after addition of 5.0 eq. of anion.

Targeting dihydrogenphosphate and lipid A[25]

In all cases 1 : 2 H : G arrangements were noted for the binding of $H_2PO_4^-$ by receptors **4–6** (Fig. 5).[18,19] Hosts **4** and **5** bound the guests symmetrically through three H-bonding interactions per arm (two from the thiourea NH's and one from the amide NH), however in the case of the *endo*/*exo* host **6** the binding of $H_2PO_4^-$ to the *exo* arm was by means of three H-bonds, whereas the *endo* arm bound $H_2PO_4^-$ solely through the thiourea N–H groups.

Given that each arm was acting independently in the binding of $H_2PO_4^-$ it was reasoned that this type of host might be capable of binding a diphosphate species such as lipid A.[22] (Fig. 6). Many potent antimicrobial agents interact strongly with the anionic lipid A portion of the bacterial outer membrane lipopolysaccharide (LPS). Examples include the naturally occurring polymyxin and defensin families of peptides.[23] These compounds are facially amphiphilic; they have cationic groups (ammonium or guanidinium) correctly positioned to interact with the anionic phosphate groups of lipid A and hydrophobic residues to penetrate the hydrophobic layer. In order to mimic these features, 'lead' compound **6** was modified to include an octyl 'tail' and guanidine groups for anion recognition[24] (see **10**, Fig. 6). Molecular modelling indicated that the *exo*/*endo* arms could easily span lipid A and bind to both phosphate groups.[25]

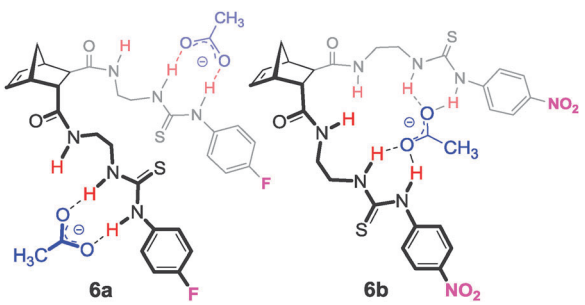


Fig. 4 Proposed 1 : 2 H : G binding conformation of host **7a** with two equivalents of AcO^- and **7b** in a 1 : 1 arrangement with AcO^-.

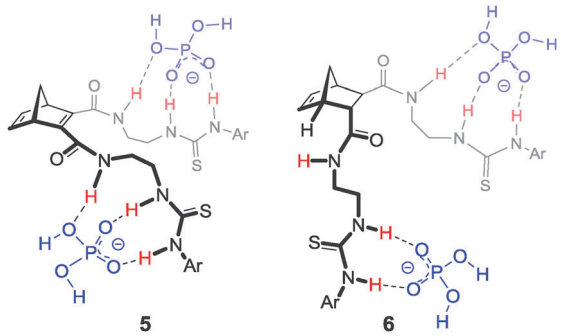


Fig. 5 Proposed 1 : 2 H : G binding conformation of hosts **5** and **6** (also representative of the binding mode of **4**) with $H_2PO_4^-$.

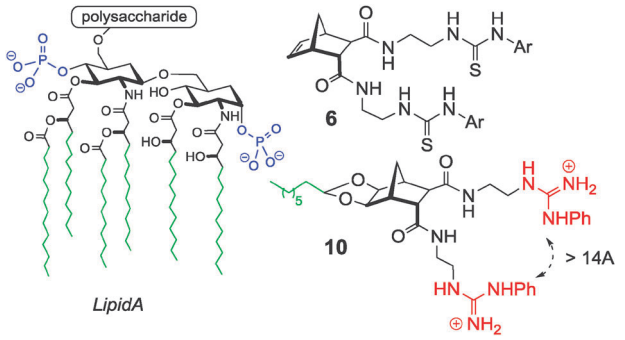


Fig. 6 Structure of Lipid A (phosphate groups highlighted in red). Anion host **6** and custom modified host **10** are shown on the right.[25]

A fluorescent displacement assay confirmed binding to the LPS target and compound **10** had an IC_{50} of 9.5 μM (Colistin IC_{50} = 6.0 μM). Simple disk diffusion studies identified that compound **10** was active (particularly against *Pseudomonas aeruginosa* ATCC 27853) and haemolytic tests confirmed that **10** did not lyse red blood cells at concentrations up to 125 μM.[25]

Preorganised frameworks for anion recognition

Excellent progress in the field of anion recognition has been made using conformationally preorganised frameworks.[22] Particularly well studied are cholic acid and the calix families.[26–36] In the case of the 'cholapods' Davis and others[27–30] have performed comprehensive studies, varying the number of attachment points and also the number and nature of H-bond donors. Strong binding of chloride was noted for these receptors (*e.g.* **11**, Fig. 7)[28] with selectivity resulting from a well preorganised binding site. More recent developments include cationic cyclocholamides such as **12** for anion transport.[29]

Many examples also exist of anion hosts based on the calix[*n*]arenes[30–33] and also the calix[*n*]pyrroles.[34–36] The ability to construct related frameworks in varying sizes is an advantage of the calix based hosts and typically [*n*] = 4 or 6 for these systems (*e.g.* calix[*n*]arene, Fig. 8).[30] Specific examples, Fig. 8, include hosts for sensing[37] (*e.g.* calix[4]arene **13**[35]) and transport[33] (*e.g.* calix[4]pyrrole **14**[36]).

Other examples of preorganised anion hosts include tripodal benzene receptors[38] (*e.g.* **15**,[39] Fig. 9), peptidomimetic trioxazoles[40] (*e.g.* **16**[41]) and macrocyclic C–H receptors[42] (*e.g.* **17**[43]).

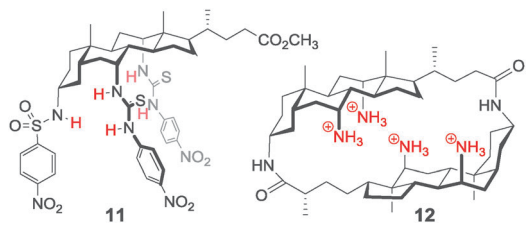


Fig. 7 Examples of anion hosts based on cholic acid.[28,29]

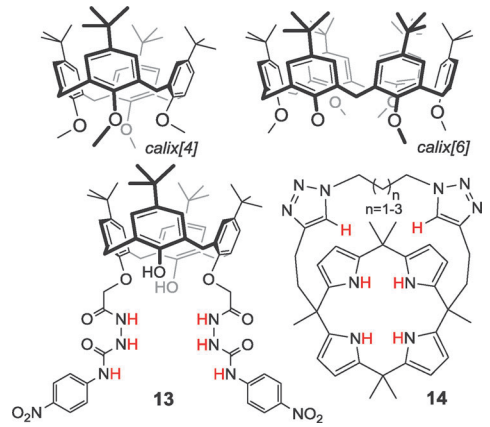


Fig. 8 Examples of functionalised calixarene and calixpyrrole frameworks for anion recognition, sensing and transport.[35,36]

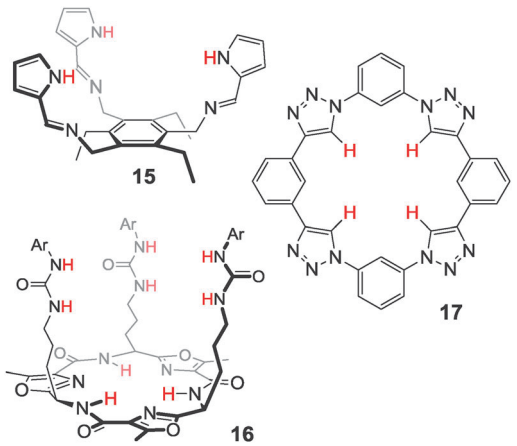


Fig. 9 Examples of preorganised tripods and macrocycle.[39,41,43]

Fused [*n*]polynorbornane scaffolds

A collection of researchers including Warrener, Russell, Paddon-Row and Johnston (amongst others) have produced a remarkable arsenal of frameworks of varying, though predictable, dimensions (including tweezers, clips, binanes, molracs, ladderanes, norbornylogs, alicyclophanes, and regioselectively addressable frameworks).[44] These versatile scaffolds have been used in a number of settings including (i) single molecule conductivity switching (*e.g.* tetrasulfide **18**[45] Fig. 10), (ii) DNA bisintercalators to mimic the properties of ditercalinium (*e.g.* 'staple-like' bisacridine **19**[46]) and (iii) molecular capsules (*e.g.* bisporphyrin tweezers **20**[47]).

Cyclic scaffolds that incorporate aryl fused norbornanes have also been pursued by Stoddart[48] who employed a molecular LEGO approach to constructing 'belts' such as Kohnkene (**21**,[49] Fig. 11). More recent examples include the molecular 'tweezers' and 'clips' produced by Klarner.[50] For example bisphosphate **22**[51] (Fig. 11) binds cationic Lys residues and has been shown to 'unwind' amyloidogenic proteins. Fused polynorbornanes have also recently been used by Clever in the synthesis of metal organic cages[52] (such as **23**,[53] Fig. 11).

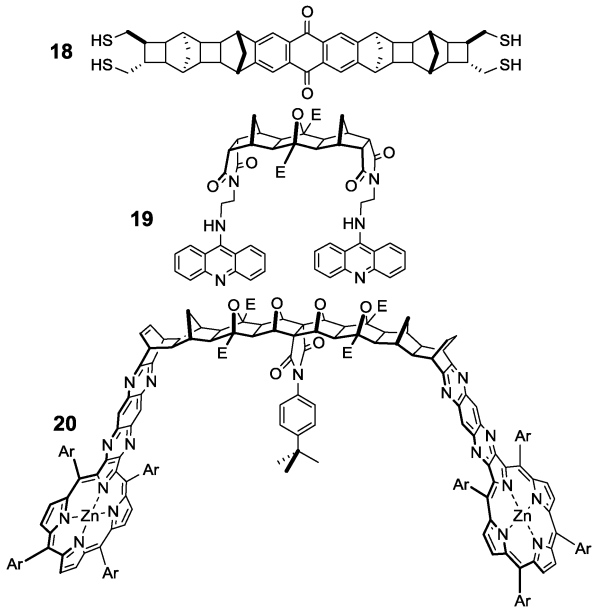


Fig. 10 Examples of fused polynorbornane frameworks.[45–47]

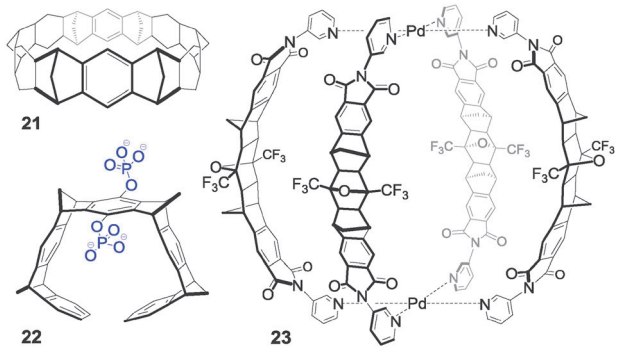
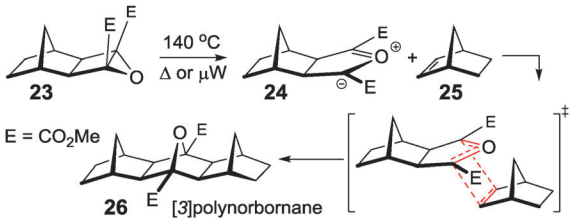


Fig. 11 Examples of fused aryl/norbornane frameworks.[49,51,53]

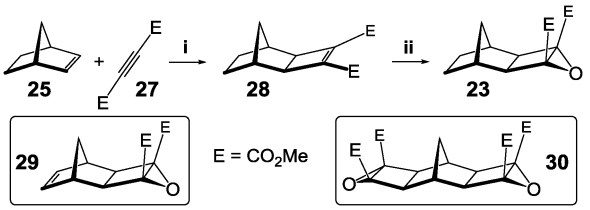
Several cycloaddition strategies have been developed to access these fused polynorbornane structures[44–55] and inventive descriptions such as LEGO[48] are used to describe their construction. Other monikers including 'molecular glue' have been used to describe oxadiazole coupling[54] and also BLOCK as an acronym for 'bonzer little organic construction kit'.[55] All such terminology hints at the modular nature of the various approaches to the ready assembly of these large molecular architectures. The terminology also clearly conveys the '*no atoms wasted*' advantage inherent with a cycloaddition approach.[56]

The ACE reaction

The key cycloaddition to assemble fused [*n*]polynorbornanes is the (2+3) [$\pi4_s + \pi2_s$] 1,3 dipolar cycloaddition of a resonance stabilised, electron deficient, carbonyl ylide (such as **24**, Scheme 2), generated by electrocyclic ring opening of a cyclobutane epoxide (**23**), to a norbornene partner (**25**).[57] This reaction of an *A*lkene with a *C*yclobutane *E*poxide is termed the ACE reaction. More recently a microwave-assisted version of this cycloaddition has been used to effect the transformation in high yields and reduced reaction times (10–15 minutes).[58]



Scheme 2 Mechanism of the ACE cycloaddition of an electron deficient cyclobutane epoxide with a norbornene.[57,58]



Scheme 3 Two step protocol for the synthesis of cyclobutane epoxides. *Reagents and conditions*: (i) $RuH_2(CO)(PPh_3)_3$, THF, 80 °C (ii) TBHP, KO^{t}Bu, THF, 0 °C.

A simple two step methodology has been devised for the construction of the requisite epoxides (Scheme 3). First is the ruthenium catalysed Mitsudo reaction[59] of a norbornene with an acetylene dicarboxylate diester (equivalent to a [2+2] cycloadditon) which affords cyclobutene diesters (such as **28**). This reaction can be performed in a microwave reactor and near quantitative yields are achieved in under 5 minutes.[60] The second step is a modified Weitz–Scheffer epoxidation[61] of this electron deficient alkene using *tert*-butylhydroperoxide (TBHP) with a catalytic amount of potassium *tert*-butoxide in THF.[62] Epoxide **29** and bisepoxide **30** are both routinely used in framework construction and are easily prepared using the protocol of Mitsudo reaction followed by epoxidation.

Fused polynorbornanes are slightly curved in nature (as shown in Fig. 12),[63] but linear variants can be accessed through the use of the dihydrofulvalene 'pincer'.[64] Relatively simple levels of theory (AM1) can efficiently model this arc-shaped

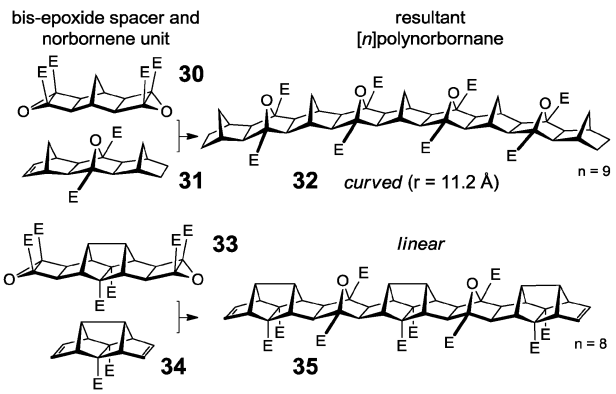


Fig. 12 Examples of [*n*]polynorbornane frameworks with curved and linear geometries as predicted by molecular modelling (*r* is the calculated radius of curvature).[63]

topology[63] giving the molecular architect significant control over final scaffold dimensions.

Fused [*n*]polynorbornanes and anion recognition[65–69]

With the goal of creating a family of new hosts that could be used to target a range of larger and biologically relevant anions, such as dicarboxylates and pyrophosphate, a series of thiourea based anion receptors **36–41** (both symmetric and non-symmetric, Fig. 13) were designed. Using molecular modelling (AM1) it was calculated that the [*3*]polynorbornane **36** spans *ca.* 6.6 Å from imide N to imide N and the [*5*]polynorbornane **37** spans 10.4 Å.[65] Thus the cleft dimensions of these polynorbornanes are significantly different and ideally suited to recognition of larger/longer anions. Again the 2-ureidoethylamido substituents are referred to as arms and as such the hosts will be referred to as 2, 3 or 4-armed [*n*]polynorbornanes, for example host **40a** (Fig. 13) is a 4-armed [*3*]polynorbornane.

Synthesis

Initially the desired 1- or 2-arm Boc protected norbornene unit was prepared. The protected [*3*]- or [*5*]polynorbornane framework was then assembled through the sequence of Mitsudo reaction, epoxidation, and ACE 1,3-dipolar cycloaddition. The final steps in all cases were deprotection then reaction with either 4-nitrophenyl- or 4-fluorophenylisothiocyanate. The two examples in Scheme 4 (2-armed receptor **36** and 4-armed receptor **41**) illustrate the similar approaches.[67–69]

Construction of host **36** (Scheme 4) required norbornene imide **43** which was readily synthesised by heating anhydride **47** with 2-(*tert*-butoxycarbonylamino)ethylamine to give imide **48**.[67–69] The protocol of Mitsudo reaction with dimethylacetylene dicarboxylate (DMAD) followed by Weitz–Scheffer epoxidation gave oxirane **44**. Subsequent ACE reaction of alkene **43** with cyclobutane epoxide **44** resulted in the Boc protected 2-armed [*3*]polynorbornane scaffold **45**. Deprotection then coupling with the desired isothiocyanate gave hosts **36a** and **36b**.

For hosts **38–41** the previously synthesised norbornenes **4** and **5** and their precursors could be used as substrates for the construction of the 3- and 4-armed frameworks. Thus for the synthesis of 4-armed [*5*]polynorbornane host **41** norbornene **8** was employed, and in this case ACE reaction of bis-epoxide **30** with two equivalents of **8** provided the 4-armed [*5*]polynorbornane scaffold **46**. Subsequent hydrogenation, deprotection and coupling with the requisite isothiocyanates afforded hosts **41a** and **41b**.

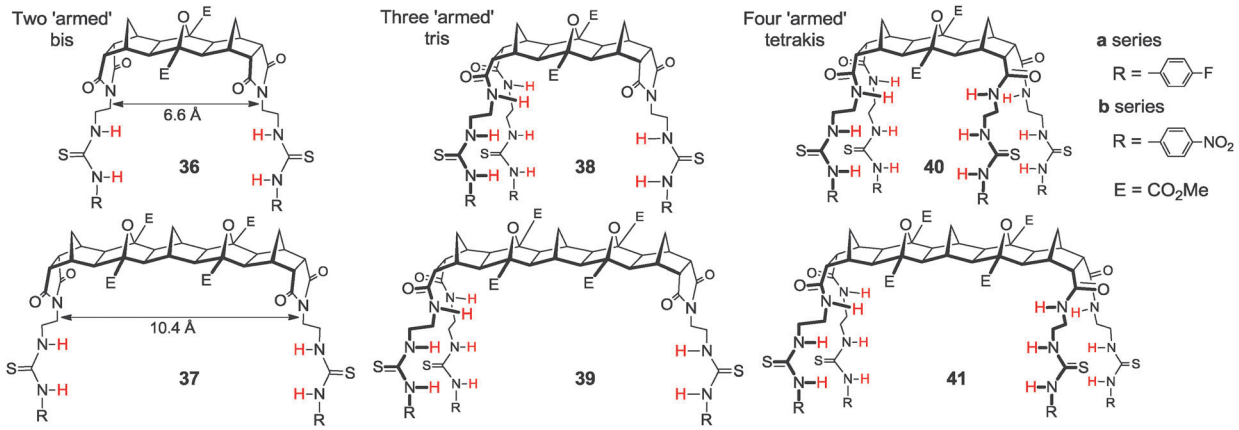
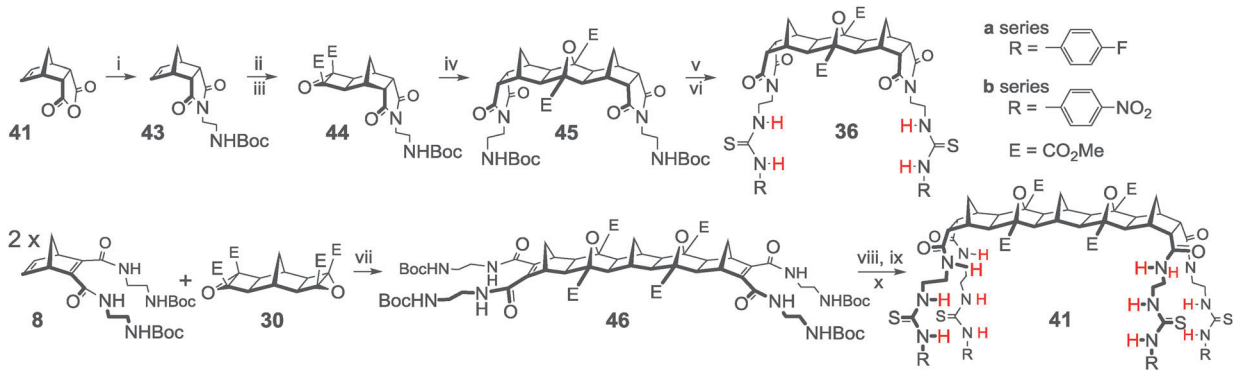


Fig. 13 2,3 and 4-armed [*3*] and [*5*]polynorbornane hosts **36–41**.[67–69]



Scheme 4 Synthesis of hosts **36** and **41**. *Reagents and conditions*: (i) 2-(*tert*-butoxycarbonylamino)ethylamine, $CHCl_3$, 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) DCM, 140 °C, 24 h, 58% (v) 20% TFA/CH_2Cl_2, 4 h, 100% (vi) DIPEA, $CHCl_3$, 23 h, for **36a** 4-fluorophenylisothiocyanate, 84%, for **36b** 4-nitrophenylisothiocyanate, 68% (vii) 2.2 eq. 9, THF, 140 °C, 49 h, 65% (viii) H_2, Pd–OH/C, 48 h 61% (ix) 20% TFA/CH_2Cl_2, 4 h, 100% (x) DIPEA, $CHCl_3$, 24 h, for **41a** 4-fluorophenylisothiocyanate, 92%, for **41b** 4-nitrophenylisothiocyanate, 95%

Anion binding studies

Two armed hosts: size matters[65–67]

As the new [3] and [5]polynorbornane hosts **36–41** have larger binding clefts than the simple norbornane based hosts **4–6**, the set of anionic guests was also expanded to include alkyl dicarboxylates ($^{-}OOC(CH_2)_nCOO^{-}$, n = 1–6) and terephthalate; prepared as TBA salts.[67] These anions were used in ^{1}H NMR titration experiments in DMSO-d_6 and selected results are summarised in Table 2.

Of the results obtained for the 'smaller' anions, the most useful were those obtained from the titrations against $H_2PO_4^-$. For the [3]polynorbornane based host **36** 1 : 1 H : G stoichiometry was observed in both cases, whereas [5]polynorbornane based hosts **37** formed 1 : 2 H : G complexes (Fig. 14). The H : G stoichiometry can be attributed to the shorter cleft width of host **36**; the $H_2PO_4^-$ anion is simply too small to span the cleft of host **37** so cannot be bound cooperatively by the two anionophoric arms, instead each arm binds independently. This notion of the arms acting independently is further supported by the binding constants K_1 and K_2 being similar in magnitude (Table 2).

Table 2 Maximum observed chemical shifts, H : G stoichiometries and calculated association constants (log K) for 2-arm hosts **36** and **37**[a]

		36a	36b	37a	37b
$H_2PO_4^-$	max Δδ (ppm)	2.0	1.9	2.5	2.3
	H : G	1 : 1	1 : 1	1 : 2	1 : 2
	log K_1	2.6	2.9	2.7	3.5
	log K_2	—	—	2.5	3.0
AcO^-	max Δδ (ppm)	3.4	3.5	3.5	3.6
	H : G	1 : 2	1 : 2	1 : 2	1 : 2
	log K_1	2.8	3.2	2.9	3.1
	log K_2	2.3	3.0	2.3	3.0
Succinate^{2-} (n = 2)	max Δδ (ppm)	3.8	3.6	4.1	4.1
	H : G	1 : 1	D	1 : 1	1 : 1
	log K_1	4.5	—	4.8	~5.0
Suberate^{2-} (n = 6)	max Δδ (ppm)	3.7	3.9	3.9	4.0
	H : G	1 : 1	1 : 1	1 : 1	1 : 1
	log K_1	4.8	~5.0	~5.0	~5.3
Terephthalate^{2-} (n = phenyl)	max Δδ (ppm)	3.38	3.51	3.64	3.74
	H : G	1 : 1	1 : 1	1 : 1	1 : 1
	log K_1	3.6	3.7	4.3	~5.5

[a] Max Δδ obtained from ArN–H after addition of 5.0 eq. of anion; log K were determined by ^{1}H NMR titration using WinEQNMR software[20] (*fittingprogram*[70] for terephthalate) with error ≤ 15%. Values for log $K \geq 5$ are indicated as approximate as they are at the limits of accuracy for NMR. Titrations were carried out with $[H]_i$ of ~1.2 × 10^{-2} M. D indicates deprotonation thus H : G stoichiometry and log K could not be determined.

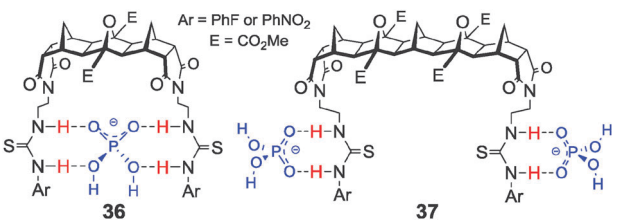


Fig. 14 Proposed binding conformations of host **36** binding one equivalent of $H_2PO_4^-$, and host **37** in a 1 : 2 complex with $H_2PO_4^-$.

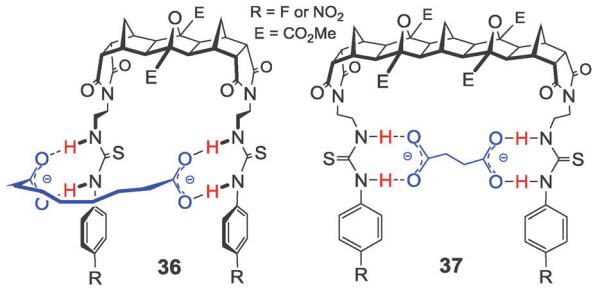


Fig. 15 Proposed binding conformations of the 1 : 1 complexes formed between hosts **36** and **37** and the various length alkyl dicarboxylates.

A trend was expected in which short chain dicarboxylates would complement the [3]polynorbornane host **36** and longer chain alkyl dicarboxylates would prefer the larger cleft of the [5]polynorbornane hosts **37**. However, no such trend was found and in all cases strong 1 : 1 H : G complexes were observed (Table 2). In Fig. 15 two binding arrangements are shown; in the case of the [3]polynorbornane **36** binding suberate it is the flexibility of (i) the arms of the host and (ii) the alkyl chain of the guest that allows a conformation in which a strong host : guest complex forms. In the second example, despite the longer [5]polynorbornane scaffold of host **37** the flexibility of the arms still allows the host to capture the shorter succinate guest. The deliberate allowance for induced fit designed into these receptors was sufficient to over-ride the preorganisation imparted by the rigid scaffold.

The rigid terephthalate guest (7.0 Å long) can only bind strongly to a host with an appropriate cleft width and while a 1 : 1 H : G arrangement for both hosts **36** and **37** was identified there were significant differences between the titration isotherms and the binding constants. Host **37b** bound terephthalate 100 times more strongly than host **36b**.[67] The cleft width of the host was now the controlling factor in the binding of the guest (illustrated in Fig. 16) where the larger cleft of host **37** better complements the width of the rigid dianionic guest.

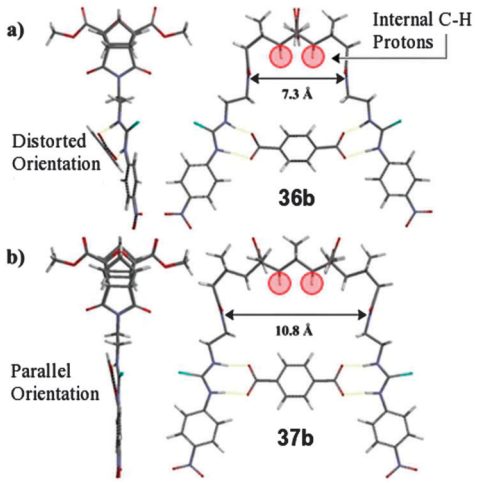


Fig. 16 Molecular model calculated at H–F 3-21G* level of theory depicting the 1 : 1 complexes formed between the rigid aryl dicarboxylate, terephthalate^{2-} and (a) host **36b** and, (b) host **37b**. Internal CH protons highlighted in red.

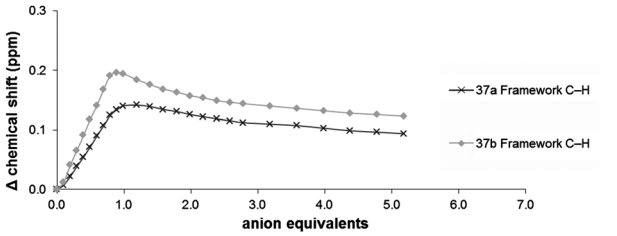


Fig. 17 Titration isotherm for **37** against terephthalate using the internal C–H protons.

These results neatly reinforce the ideas of Cram who in his principle of preorganisation stated that "the more highly hosts *and guests* are organised for binding and low solvation prior to their complexation the more stable will be their complexes".[71]

The interaction of host **37** with terephthalate could also be monitored by following the 'internal' framework C–H resonances as these protons are deshielded by the ring-current effect[72] of the phenyl ring (Fig. 17).[73] Although the observed change was small ($\Delta\delta \sim 0.2$ ppm) the binding isotherm clearly indicated the formation of a 1 : 1 complex (Fig. 17).

3 and 4 armed hosts: multiple H-bond donors[68,69]

The 3- and 4-armed [*n*]polynorbornane hosts **38** and **39** provide up to 12 H-bond donors per host (both thiourea and amide). As such they are ideally suited to larger guests with multiple H-bond acceptor sites and dihydrogenpyrophosphate (H_2ppi^{2-}) and adenosinediphosphate (ADP^{2-}) were also included in the already large list of titrants for these hosts.[69] Selected results are provided in Tables 3 (for 3-arm) and 4 (for 4-arm).

Table 3 Maximum observed chemical shifts, H : G stoichiometry and calculated association constants (log *K*) for 3-arm hosts **38** and **39**[a]

		38a	38b	39a	39b
$H_2PO_4^-$	max Δδ (ppm)	1.9	2.3	1.8	1.6
	H : G	1 : 2R	1 : 2R	1 : 2R	A
	log K_1	3.5	2.7	3.3	—
	log K_2	<1	<1	<1	—
Pyrophosphate (H_2ppi^{2-})	max Δδ (ppm)				
	H : G	1 : 1R	1 : 1R	1 : 1R	A
	log K_1	3.8	4.7	3.4	—
	log K_2	—	—	—	—
AcO^-	max Δδ (ppm)	2.8	3.5	2.7	3.3
	H : G	1 : 2	1 : 2	1 : 2	1 : 2
	log K_1	2.9	3.2	2.9	3.1
	log K_2	2.5	2.5	2.4	2.6
Pimelate	max Δδ (ppm)	3.5	3.2	3.4	3.2
	H : G	1 : 2R	1 : 1	1 : 2R	1 : 1
	log K_1	4.8	4.3	4.5	3.8
	log K_2	2.8	D	2.9	D
Terephthalate (n = aryl)	max Δδ (ppm)	2.14	2.81	3.38	3.74
	H : G	1 : 1	1 : 1	1 : 1	1 : 1
	log K_1	3.0	3.2	4.4	4.9
	log K_2	—	—	—	—

[a] Max Δδ obtained from ArN–H after addition of 5.0 eq. of anion; log *K* were determined by ^{1}H NMR titration using WinEQNMR software[20] (*fittingprogram*[70] for terephthalate) with (error ≤ 15%). Titrations were carried out with $[H]_i$ of $\sim 2.5 \times 10^{-3}$ M. D indicates deprotonation therefore H : G stoichiometry and log *K* could not be determined. A indicates a high degree of aggregation was noted and assessment of the titration data was impossible. R indicates that binding was regioselective or occurred at one end of the framework only.

Table 4 Maximum observed chemical shifts, H : G stoichiometries and calculated association constants (log *K*) for 4-arm hosts **40–41**[a]

		40a	40b	41a	41b
$H_2PO_4^-$	max Δδ (ppm)	1.8	1.8	1.6	2.1
	H : G	1 : 2	1 : 2	1 : 2	1 : 2
	log K_1	2.7	2.8	2.6	2.8
	log K_2	2.6	2.5	2.6	2.4
Pyrophosphate (H_2ppi^{2-})	max Δδ (ppm)	1.1	1.7	1.1	1.7
	H : G	1 : 2	1 : 2	1 : 2	1 : 2
	log K_1	3.0	3.0	4.2	2.4
	log K_2	2.2	3.0	2.5	1.7
AcO^-	max Δδ (ppm)	2.1	2.7	2.0	2.9
	H : G	1 : 2	1 : 2	1 : 2	1 : 2
	log K_1	2.8	2.9	2.7	3.0
	log K_2	2.4	2.7	2.5	2.6
Pimelate	max Δδ (ppm)	3.1	3.2	3.0	3.2
	H : G	1 : 2	1 : 2	1 : 2	1 : 2
	log K_1	~5.0	~5.1	5.1	~5.0
	log K_2	4.6	4.8	4.9	~5.0
Terephthalate^{2-} (n = aryl)	max Δδ (ppm)	3.11	3.47	3.64	3.84
	H : G	1 : 1	1 : 1	1 : 2	1 : 2
	log K_1	2.9	3.0	4.1	~5.0
	log K_2	—	—	3.5	4.4

[a] Max Δδ obtained from ArN–H after addition of 5.0 eq. of anion; log *K* were determined by ^{1}H NMR titration using WinEQNMR software[20] (*fittingprogram*[70] for terephthalate) with (error ≤ 15%). Titrations were carried out with $[H]_i$ of $\sim 2.5 \times 10^{-3}$ M.

Hosts **38** and **39** bound terephthalate in a 1 : 1 H : G arrangement and the guest was bound cooperatively through all six thiourea H-bond donors (no contribution from the amide groups). Due to the unsymmetrical nature of the 3-armed hosts, five H-bond donor signals could be followed throughout the ^{1}H NMR titration (Fig. 18) and as such an increase in the amount of information regarding the binding could be gathered. A global method of calculating binding constants (taking into account all H-bond donors) could also be used to accurately determine log *K*.[70]

It was also noted that the change in chemical shift of the thiourea protons of the one-armed end were approximately

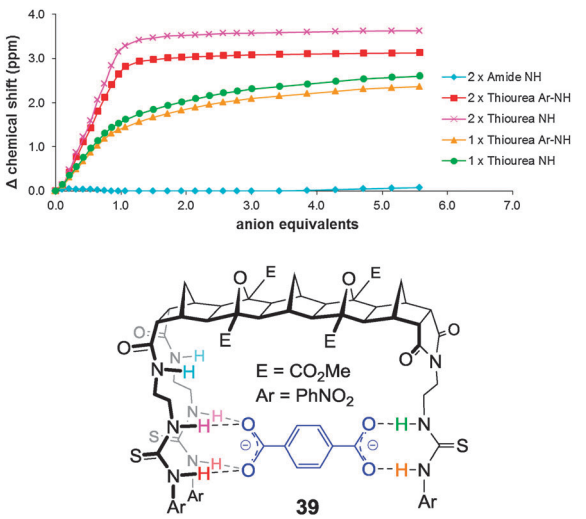


Fig. 18 Titration isotherm of host **39b** upon the addition of terephthalate and proposed 1 : 1 complex formed between the 3 armed [5]polynorbornanes and terephthalate.

double that (at the equivalence point) of the shifts observed for the four thiourea H-bond donors of the 2-armed end. This result reinforces the idea that one carboxylate of the dianion is being bound by both thiourea groups from the 2-armed end of the host while the other carboxylate is being bound by the single thiourea group (Fig. 18).

Regioselective recognition[69]

The most remarkable behaviour for this series of hosts was observed when either alkyl dicarboxylates or pyrophosphate were added to the 3-armed hosts (**38** and **39**). A *stepwise regioselective* binding process occurred in the case of the alkyl dicarboxylates and in the case of pyrophosphate, a H : G complex formed in which the 1-armed end was completely *ignored* and the anion bound exclusively to the 2-armed end.

For the 3-armed hosts with alkyl dicarboxylates the clearest example of the stepwise binding was observed for host **38a** with pimelate (Fig. 19). The binding isotherms indicated that an initial 1 : 1 binding event occurred at the 2-armed end. When one equivalent of dicarboxylate had been added there was little change in the urea protons of the 1-arm end (Fig. 19). When more than one equivalent of dicarboxylate was added no further change was observed at the 2-arm end, however, there was a distinct 'jump' in the N–H signals of the 1-arm end. The isotherm for the 1-armed end after one equivalent is reminiscent of a standard 1 : 1 binding isotherm and indicates modest binding of a second equivalent of pimelate at that end. Hence the overall process can be considered a *stepwise regioselective* process where the first dicarboxylate preferentially binds tightly at the 2-armed end.[69] Modelling (H–F 3-21G*) also supported the binding of the dicarboxylate at the 2-arm end (Fig. 20).[69]

To further demonstrate the regioselective binding of hosts **38** and **39**, mixed anion titrations were conducted. By adding

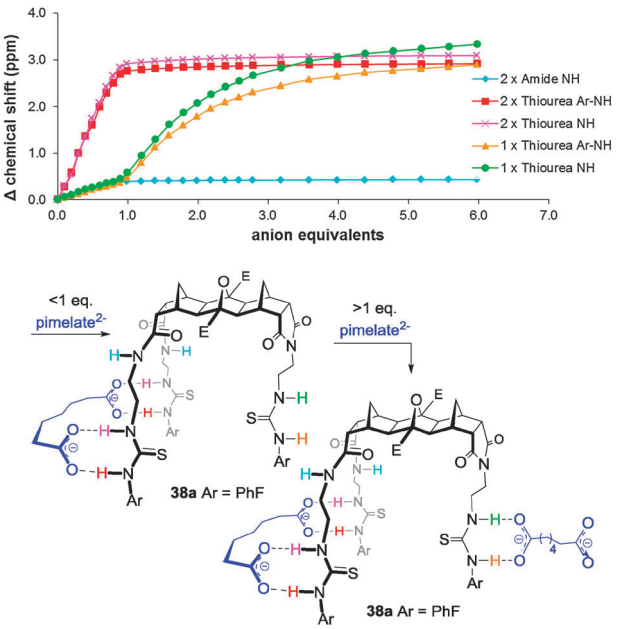


Fig. 19 Titration isotherm of host **38a** with pimelate (above) and an illustration of the stepwise binding process.

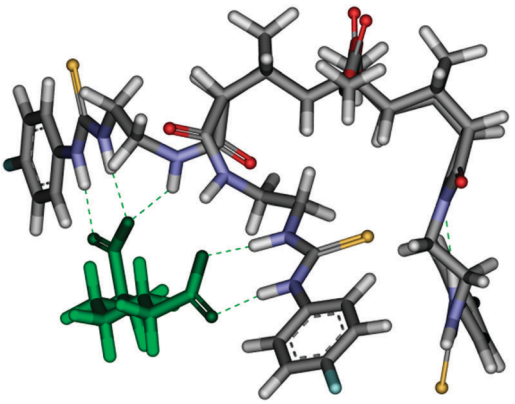


Fig. 20 Molecular model calculated at Hartree–Fock 3-21G* level of theory depicting the 1 : 1 complex initially formed between host **38a** and pimelate.

one equivalent of dicarboxylate (pimelate or malonate) followed by an excess of acetate is was possible to assemble in, a stepwise fashion, pimelate at the 2-armed end then acetate at the 1-arm end.

Our recent investigations into the binding of dihydrogenpyrophosphate (H_2ppi^{2-}) to the [*n*]polynorbornane hosts have used the tributylammonium salt [$(Bu_3NH)_2H_2ppi$] and 3-arm hosts **38** and **39** both bound this form of H_2ppi^{2-} in a 1 : 1 H : G stoichiometry. The binding isotherms (Fig. 21) clearly indicate that the anion interacts with both the urea N–H protons as well as the amide N–H protons of the two-armed end whereas the single armed side appears to be *completely ignored* even when an excess of pyrophosphate was added. Regardless of the size of the binding cleft (either [*3*] or [*5*]polynorbornane) no response from the 1-arm end was noted. The cleft width also had little or no effect on the strength of the binding (Table 3). The contribution from the amide groups was considerable with the magnitude of the observed changes in chemical shift approaching that of the thiourea N–H (Fig. 21).

Due to the regioselective recognition ability of **38** and **39** with pyrophosphate and the stepwise assembly process previously

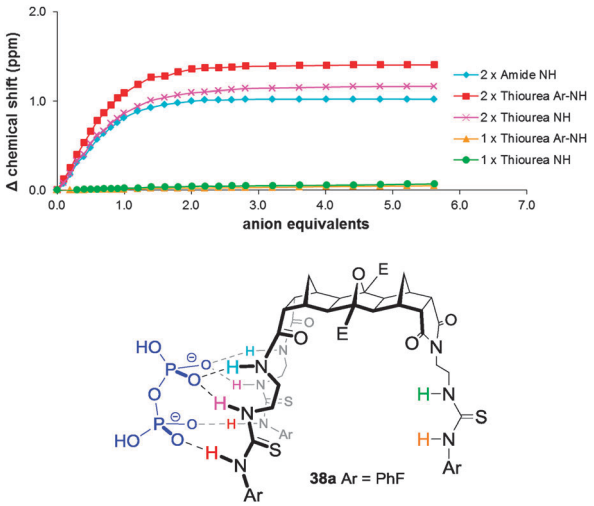


Fig. 21 Titration isotherm of 3-arm host **38a** upon the addition of H_2ppi^{2-} and illustration of the regioselective recognition of H_2ppi^{2-} by the 3-arm host **38**.

accomplished using pimelate/acetate it was envisioned that with pyrophosphate bound at the 2-armed end, the single armed end should be free to bind a smaller anion such as phosphate or acetate. However, upon titration, the single armed end was still ignored, even when an excess of phosphate was added. Even when the anion addition order was reversed (one equivalent of phosphate was added followed by an excess of H_2ppi^{2-}) the isotherm quickly morphed into what would be expected of a pure H_2ppi^{2-} titration.

Both the size of the cleft and the urea electron withdrawing groups (Ar–F or Ar–NO_2) had an influence on the ability of these hosts to regioselectively bind anions. The larger hosts (**39**) showed less selectivity than their smaller counterparts. The *b*-series (Ar–NO_2) also showed less tendency towards regioselectivity than the *a*-series (Ar–F). While the exact cause of the regioselective binding remains unknown, one possibility, the formation of larger symmetric H : G complexes (*e.g.* 2 : 2), has been ruled out using NMR diffusion experiments.

One guest or two?

The last examples to be featured are those of the 4-arm hosts **40** and **41**. In the titrations of dicarboxylates against these hosts a distinct 'inflection' in the binding isotherm appeared at approximately 1.0 eq. of anion (Fig. 22). It was reasoned that up until *ca.* 1.0 eq. of dicarboxylate had been added a 1 : 1 H : G arrangement was preferred then once an excess of anion was added a 'switch' to a 1 : 2 H : G stoichiometry occurred (Fig. 22).

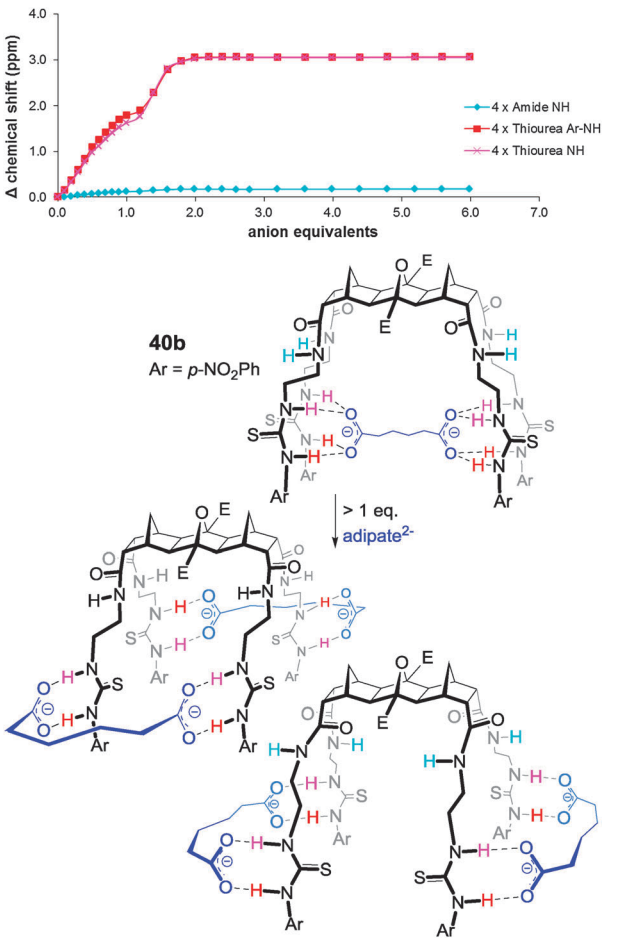


Fig. 22 Isotherm and proposed binding of adipate by host **40b** clearly showing the 'switch' from a 1 : 1 to a 1 : 2 H : G arrangement with an excess of guest.

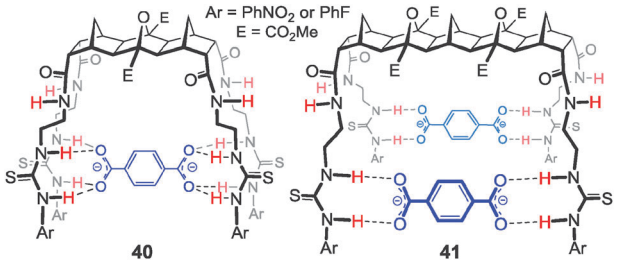


Fig. 23 Proposed 1 : 1 and 1 : 2 binding arrangements of hosts **40** and **41**, respectively, when binding terephthalate.

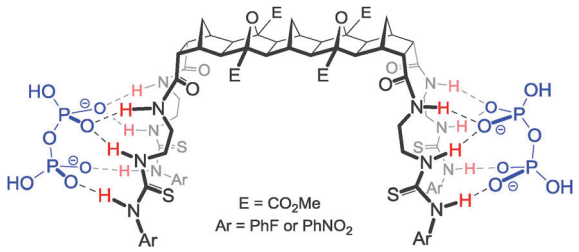


Fig. 24 Proposed binding arrangement of host **41** (also representative of **40**) with two equivalents of H_2ppi^{2-}.

When titrations were performed using terephthalate and the 4-armed hosts a 1 : 1 H : G arrangement was noted for the [*3*]polynorbornane **40** but a 1 : 2 H : G complex for the longer [*5*]polynorbornane **41** (Fig. 23). Host **41** can encapsulate two rigid terephthalate dianions as the ethylene arms can flex away from the framework to minimise electrostatic repulsion between the two terephthalate units.

For H_2ppi^{2-} the titrations and Job plots showed that the 4-armed hosts **40** and **41** bind in a symmetric 1 : 2 H : G stoichiometry. The titrations identified that all 12 H-bond donors of the host were involved and the strength of the 1 : 2 complexes formed was independent of the cavity width of the host as evidenced by log *K* values The combination of results suggests that each side of the host was acting independently and the dianions are not spanning the cleft (Fig. 24).

Conclusions and outlook

The outlook for further applications of norbornanes and [*n*]polynorbornanes in supramolecular chemistry is excellent as the full range of possible framework and cleft geometries is yet to be explored. The group at Deakin is currently developing multicomponent strategies for the rapid construction of [*n*]polynorbornane frameworks and aims to further expand the current range of hosts to include fluorescent signalling moieties and also to use these functionalised frameworks in applications such as organocatalysis.[74] A full series of analogues of the LPS binder **10** are also in preparation. The results of these endeavours will be reported in due course.

Acknowledgements

The authors thank the many excellent researchers in the field for continual inspiration. Particular thanks go to Professors Richard Russell and Thorfinnur Gunnlaugsson for introducing FP to BLOCK chemistry and anion recognition respectively.

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