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Differentiation of small alkane and alkyl halide constitutional isomers *via* encapsulation†

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Previously we have demonstrated that host **1** is capable of hydrocarbon gas separation by selective sequestration of butane from a mixture with propane in the headspace above a solution of the host (C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.*, 2006, **128**, 16498–16499). Expanding on the idea of using this host as a means to affect guest discrimination, we report here on NMR studies of the binding of constitutional isomers of two classes of small molecules: hexanes and chloropentanes. Our results indicate that even with these relatively straightforward classes of molecules, guest binding is complicated. Overall, host **1** displays a preference to bind guests with a X–C(R_2)–C(R_2)–Me (X = Cl or Me) structure, and more generally, a preference for branched guests rather than highly flexible, unbranched derivatives. The complexity of binding of these isomers is magnified when considering molecular differentiation between pairs of guests. In such cases, different guests demonstrated different propensities to self-sort; some self-sort exclusively, while others show very little propensity to do so. However, whereas the pool of guests reveals some general correlations between binding strength and structure, no obvious relationship between structure and degree of self-sorting was observed.

Introduction

Although classes of molecules such as cyclodextrins have been key to understanding molecular recognition in aqueous solution,[1–6] there is still much to learn about supramolecular chemistry in this unique medium. How molecules interact with one another in water is intimately tied to their hydration, which is itself governed not just by the functional groups that they possess, but the gross overall form of the solute; even molecules of the same shape but different sizes are hydrated differently.[7–10] This fact emphasizes the point that the tube-like form of cyclodextrins has the possibility of teaching us much about hydrophobic channels in macromolecules, but is less suited as a model of hydrophobic concavity for mimicking the active sites of enzymes. Towards this point, the examination of concave hosts and model concavity has highlighted how very different water molecules that fill such spaces are from the bulk.[11–14] Indeed, even quite far from concave molecules such as cucurbiturils display unusual water molecules within their pockets[15] which undoubtedly influences their binding properties.[16,17]

The consequences of an improved understanding of how concavity folds into host–guest complexation in water are manifold. For biological systems, the advantages of an improved understanding of endogenous systems such as enzyme–substrate pairs are self-evident. This is also true for exogenous pharmaceuticals where, on average, each new drug brought to market costs over $1 billion, with some $600 million of this cost resulting from preclinical studies to identify small-molecule ligands with suitable drug-like properties and receptor affinities.[18] Being able to predict *a priori* what makes a good ligand for a particular cavity can therefore considerably mitigate the costs of this fundamental research and development.

Furthermore, a better understanding of the intimate supramolecular interactions possible with concavity is of utility to non-biological scenarios. Thus, the separation of alkanes in the petrochemical industry – crude petroleum into useful fractions of similarly sized homologues, and the control of the degree of branching within, for example, the C5–C12 (gasoline) fraction obtained from petroleum distillation and/or from cracking and reforming – currently relies on cost-intensive distillation. Replacement technologies involving zeolites and metal organic frameworks (MOFs),[19–22] as well as permeable membranes[23–26] have a bright prospect with respect to hydrocarbon discrimination. However, because of their relatively large pores and difficulties associated with uniformly controlling pore size distribution and shape, host–guest chemistry has a role to play if ideal, single pass separations of structurally very similar molecules are to be realized.

The problem of hydrocarbon separation also dovetails with drug development and our ability to modulate biological

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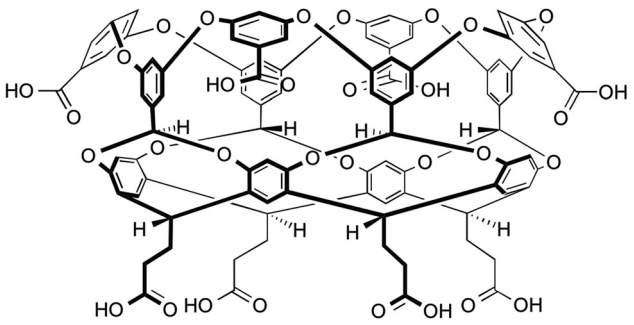
systems. Thus, the rapid increase in constitutional and stereoisomers as a function of increasing molecular size is a telling problem for the fine chemicals industry. To take one straightforward example, for mono-substituted alkanes ($C_nH_{2n+1}X$) the total number of isomers (constitutional and stereo) for the series C3–C6 is 2, 5, 11 and 27, respectively. Not surprisingly, separation can be an issue even with small molecules, which impedes ready access to families of structurally related drug homologues. In short, the confluence of designing molecular concavity and carrying out molecular discrimination in water is of multifarious importance.

Previously, we have demonstrated that the water-soluble deep-cavity cavitand informally known as octa-acid **1**[27,28] is capable of bringing about the separation of mixtures. This host undergoes two distinct kinds of supramolecular events driven by the hydrophobic effect: binding of very small guests, amphiphiles, or anions results in 1 : 1 complexes,[29–33] and binding of hydrophobic guests followed by assembly (dimerization) to form capsular 2 : 1 (or 2 : 2) host–guest complexes.[27] Using the latter, two kinds of separations have been reported on: kinetic resolutions in which the selective encapsulation of one type of guest inside the inner space of a capsule works to protect the guest from a reactive bulk solution,[34] and physical separation in which guests are selectively encapsulated by sequestration from a gas-phase mixture.[29] This first report on gas-phase separation focused on the hydrocarbon gases methane through butane and showed that the smallest of guests formed 1 : 1 complexes, but that the complexation of propane or butane led to the formation of 2 : 2 host–guest complexes. Furthermore, because the association constant of butane was over an order of magnitude larger than propane, butane could be selectively sequestered into the host in the aqueous solution from a gas phase mixture of the two gases.



1

Building on the use of **1** for the separation of hydrocarbon gases, and with an eye on the relevance of small molecule recognition in water, we detail here the complexation of the five constitutional isomers of hexane and the eight constitutional isomers of chloropentane within capsules formed by octa acid **1**. Our results demonstrate how the degree of branching within guests affects their strength of complexation, and reveal that different guests have varying propensities to form homo- (AA or BB) and hetero-guest (AB) 2 : 2 complexes in the presence of a second guest.

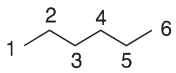
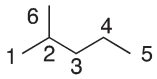
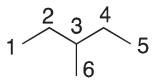
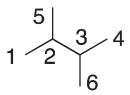
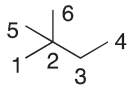
Results and discussion

Our first studies focused on the constitutional isomers of hexane (Table 1). A combination of signal integration and diffusion NMR demonstrated that each guest formed the corresponding 2 : 2 complex with **1** (ESI†). Fig. 1 shows the guest binding region of the complex formed between **1** and 2-methyl-pentane **3**. As expected, the guests signals are all shifted upfield; specifically in this case to reside between δ = −0.44 and −2.54 ppm. In the binding of alkane guests,[35] the largest observed $\Delta\delta$ values for guest signals ($\delta_{bound} - \delta_{free}$) are typically the methyl groups, indicating that they bind most deeply into the tapering base of the binding site. In the case of guest **3**, the $\Delta\delta$ values for each signal (Fig. 1 and S2†) suggest that it is the unique methyl group (C_5) that is preferentially binding down into the base of the cavitand rather than the two equivalent (enantiotopic) methyl groups C_1 and C_6. This interpretation is complicated by the fact that it is possible that only one of the enantiotopic methyls can bind deeply into the pocket at any one time, resulting in a time-average signal arising from the exchange between a deeply bound position and one that is less deep in the pocket; however, the shift in all the signals *en masse* suggest the aforementioned binding preference. More generally, the large $\Delta\Delta\delta$ value for guest binding (1.45 ppm) suggests a significant guest binding preference (conversely, a small $\Delta\Delta\delta$ value is indicative of no preferred orientation). A similar analysis (Fig. S3 and S5†) for guests **4** and **6** indicated that the former had little in the way of preferred guest orientation, while **6** binds primarily with the *t*-Bu group binding down (Table 1).

Subsequently, competition experiments between pairs of guests in this series were performed (Table 2). These experiments revealed that all guest combinations formed hetero-guest complexes whereby two different guests were encapsulated within the same capsule. However, the extent of hetero-guest complex formation was quite variable, ranging from ~2% in the case of guests **2** and **6**, up to 30% in the case of guests **4** and **5**. The total amount of hetero-guest complex formed by each guest when paired with all the others in the series was: **2** (17%), **3** (42%), **4** (73%), **5** (65%), **6** (49%), hinting at the possibility that higher sphericity or lower ovality values (Table 1) correlate with the extent of hetero-guest complex because the more compact a guest is, the less likely it is to interact with the second guest that shares the inner space of the capsule (although *vide infra*).

The formation of varying amounts of hetero-complex precluded the determination of K_{rel} values. Furthermore, because of the very low solubility of these guests in water it was not possible to use Isothermal Titration Calorimetry (ITC) to ascertain the absolute K_a values and thermodynamic parameters for each guest complexation. However, an overall view of the order of guest binding can be garnered by considering the number

Table 1 Structural properties, and orientation for the hexane guests **2–6** within the capsule formed by **1**

Guest[a]	Structure	Surface area[b] (Å^2)	Volume[b] (Å^3)	Ovality (sphericity)[c]	# Me groups	# Rotating C–C bonds[d]	Guest orientation[e]
2		152.1	125.1	1.26 (0.79)	2	3	NA
3		150.5	124.7	1.25 (0.80)	3	2	C_5 Me ↓
4		149.2	124.6	1.24 (0.81)	3	2	No pref.
5		147.6	124.3	1.23 (0.82)	4	1	NA
6		146.8	123.9	1.22 (0.82)	4	1	*t*-Bu ↓

[a] All of the guests were listed and found to be 99% pure. [b] Calculated with Spartan '14 using space filling models from van der Waals contact distances. [c] Ovality calculated using $O = \frac{A}{4\pi\left(\frac{3V}{4\pi}\right)^{\frac{2}{3}}}$ where O = ovality, A = surface area, and V = volume (sphere, O = 1). Sphericity calculated using $\psi = \frac{\pi^{\frac{1}{3}}(6V_p)^{\frac{2}{3}}}{A_p}$ where ψ is the sphericity, V_p is the volume and A_p is the surface area (sphere, ψ = 1). [d] Number of rotating C–C bonds that result in distinguishable conformations, *i.e.*, that do not involve a methyl group. [e] Orientation in the complex as determined by $\Delta\delta$ and $\Delta\Delta\delta$ values from ^{1}H NMR analysis of the free and bound state. Size of arrow indicates strong or slight preference for designated orientation. No pref.: No preferred orientation of the guest.

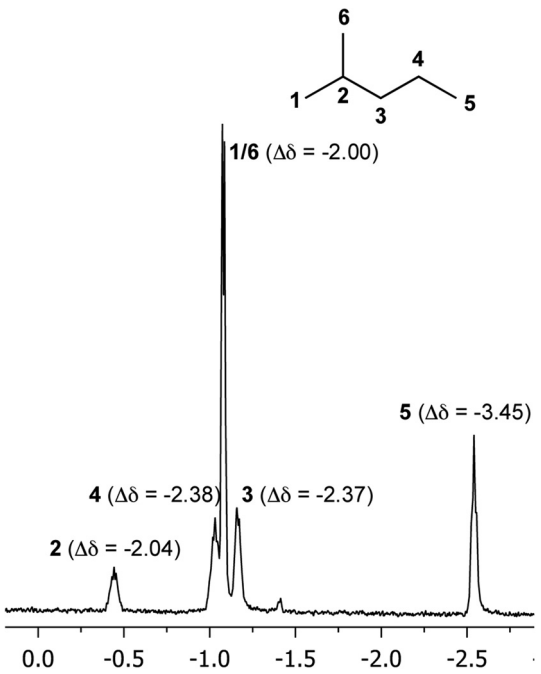


Fig. 1 High-field (bound guest) region of the ^{1}H NMR complex formed between **1** and 2-methylpentane **3**. $\Delta\delta$ values for each signal are shown in parenthesis.

Table 2 Percentage of homo- and hetero-guest complexes formed between host $\mathbf{1}_2$ and the constitutional isomers of hexane

Guest competition[a]	% Homo-complex	% Hetero-complex
2–3	16–78	6
2–4	4–90	6
2–5	4–93	3
2–6	2–96	2
3–4	4–82	14
3–5	3–82	15
3–6	4–89	7
4–5	34–36	30
4–6	25–52	23
5–6	46–37	17

[a] Competition experiments involved combining 1 equiv. of a 1 : 1 mixture of the two guests with 1 equiv. of host 1 at a concentration of 1 mM (10 mM sodium borate buffer).

of times a guest out-competes the other guests in the series (Table 2). Thus we allocated half a point to the guest in question when there was less than 10% of a difference between the amount of complex it formed verses its competitor, and one point when it predominated by more than this amount. From this approach the score for each guest was calculated to be: **2** (0), **3** (1), **4** (2.5), **5** (3.5), **6** (3), indicating the estimated order for the strength for guest binding is: **2** < **3** < **4** < **6** < **5**. Guest **2** is the weakest – it is out-competed by all other guests – whilst guest **3** is the next to weakest. The remaining three guests all bind with similar affinities. Although by this approach guest **5** appears to be the strongest binder, it does tie with **4**. However, **4** is outcompeted by **6**, which itself is outcompeted by **5**. Overall, this order of affinity suggests that binding increases as the ovality decreases, the sphericity increases, the number of

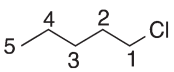
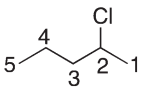
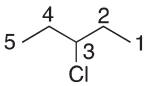
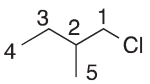
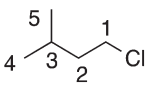
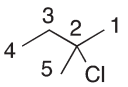
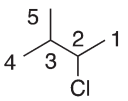
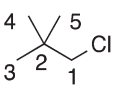
methyl groups increase, and the number of freely rotating bonds that change conformation of the carbon framework decreases (Table 1). Thus, the data suggests that it is not so much how deeply the methyl groups can probe the base of the pocket, but rather how many methyl groups there are to do this (and correspondingly the degrees of freedom of the guest).

On the assumption that all guests have similar hydration thermodynamics, the fact that association constants increase with increased branching of the alkanes suggests that entropic penalties associated with binding play a significant part in the differentiation of these constitutional isomers. Our reasoning is as follows. By and large, as branching increases within different constitutional isomers, the boiling point is seen to decrease due to fewer possible van der Waals' interactions between branched alkanes than between linear alkanes. Correspondingly, the boiling points of the guests **2–6** are respectively: 68, 61, 62, 58, and 50 °C. Thus it would be expected that there are more potential host–guest interactions possible between **1** and **2** than between **1** and strongly binding **5** (and also more guest–guest interactions in the case of the complex of **2** than the complex of **5**). Assuming this to be the case, the enthalpy of complexation for **2** is likely to be more favorable than **5**, but if enthalpy is the controlling factor, the reverse of the observed guesting order would be expected.

On the other hand, the entropy changes of complexation for the different guests can be expected to show the observed trend. Focusing on the structurally extreme cases of **2** and **5**, both can be expected to undergo a similar loss of entropy of translation as a result of internalization within the host. However, the rotational entropic cost associated with encapsulating **5** can be anticipated to be lower than that of **2** because the more rotund nature of the former allows it to rotate more freely within the confines of the capsule. Furthermore, the entropy of vibration penalty for **5** can be expected to be smaller than that of **2** because fewer internal bond rotations are restricted in the bound state. Hence, the anticipated entropy of binding changes for the different guests suggests an order of affinity identical to that observed.

We subsequently turned to the 'isosteric' series of chloropentanes **7–14** (Table 3). As previously alluded, the tetravalency of sp^3 hybridized carbon leads to a bewildering number of constitutional and stereo- isomers, even for

Table 3 Purity, structural properties, and orientation for the chloropentanes **7–14** within the capsule formed by **1**

Guest	Structure	Purity[a]	Impurity	Surface area[b] (Å^2)	Volume[b] (Å^3)	Ovality (sphericity)[c]	7 Termini	Guest orientation[d]
7		99, 99%+	NA	149.3	121.2	1.26 (0.79)	2	C_5 Me ↓
8		95, 96%	**9**	147.6	120.7	1.25 (0.80)	3	No pref.
9		95, 75%	**8**	147.0	120.7	1.24 (0.80)	3	No pref.
10		96, 98%	Unknown	145.6	120.4	1.24 (0.81)	3	C_4 Me ↓
11		NA, 97%	**13**	145.9	120.3	1.24 (0.81)	3	C_4/C_5 ↓
12		98, 99%+	NA	144.5	120.2	1.23 (0.81)	4	C_4 ↓
13		95, 91%	**11**	145.0	120.3	1.23 (0.81)	4	C_4/C_5 ↓
14		99, 99%+	NA	143.9	119.7	1.22 (0.82)	4	Cl ↓

[a] Purities listed are respectively those stated by the supplier and those determined here (^{1}H NMR in $CDCl_3$). [b] Calculated with Spartan '14 using space filling models from van der Waals contact distances. [c] Ovality calculated using $O = \frac{A}{4\pi\left(\frac{3V}{4\pi}\right)^{\frac{2}{3}}}$ where O = ovality, A = surface area, and V = volume (sphere, O = 1). Sphericity calculated using $\psi = \frac{\pi^{\frac{1}{3}}(6V_p)^{\frac{2}{3}}}{A_p}$ where ψ is the sphericity, V_p is the volume and A_p is the surface area (Sphere, ψ = 1). [d] Orientation in the complex as determined by $\Delta\delta$ and $\Delta\Delta\delta$ values from ^{1}H NMR analysis of the free and bound state. Size of arrow indicates strong or slight preference for designated orientation. No pref.: No preferred orientation of the guest.

relatively small molecules; a fact that can complicate the availability of fine chemicals as starting materials and the subsequent synthesis of families of molecules. Indeed, a search of commercial availability suggested that chloropentane is near the size limit of haloalkanes available in all constitutional isomeric forms. Nevertheless, the three chiral derivatives within this family: 2-chloropentane **8**, 1-chloro-2-methylbutane **10**, and 2-chloro-3-methylbutane **13** were only available as racemates (±). Furthermore, ^{1}H NMR spectra ($CDCl_3$,) revealed that two guests were of lower purity than that purported (Table 3). The most extreme deviation was observed with 3-chloropentane **9** (Fig. S24†) which was found to be only 75% pure (c.f. 95% stated); however 2-chloro-3-methylbutane **13** (Fig. S25†) was also noted to be only 91% pure (95% stated). Having limited commercial sources and limited amounts of both materials, we chose to use them as received. This theoretically affects quantitative analysis; however the formation of hetero-guest complexes (*vide infra*) precludes any K_{rel} determinations. In contrast, we believe that the qualitative/semi-quantitative conclusions reached here are not adversely affected by the sample purity.

A combination of ^{1}H and diffusion NMR experiments revealed all guests formed 2 : 2 host–guest complexes upon binding with host **1** (ESI†). As the outcome of these encapsulation processes was dependent on the purity of the guest utilized, we discuss each case individually. Numbering of the carbon atoms follows that shown in Table 3.

Previously, it has been shown that halogen atoms – particularly Br and I – act as strong anchors for guests through formation of four C–H···X–R hydrogen bonds with the crown of benzal hydrogens projecting from the inner wall of the pocket.[36,37] As a result, halogenated derivatives generally adopt a singular binding motif in which the guest is oriented with the halogen pointing down into the base of the pocket. However, the weakest anchor of the halogens is the relatively small chlorine atom, and to date there has been no analyses of whether a primary chloride or methyl group would provide stronger anchoring. Guest **7** (commercial and actual purity 99%) provided such an opportunity. In this case, the $\delta\Delta$ values for the C_1 and C_2 methylene groups are smaller than those of the C_3 and C_4 methylenes, strongly suggesting a preferred orientation with the methyl group down into the deepest part of the cavity. In other words, for guest **7**, the methyl group is a stronger anchor than the primary chlorine atom. The relatively large range of $\Delta\delta$ values ($\Delta\Delta\delta$ = 1.12 ppm) reflects this strong preference.

Guest 2-chloropentane (±) **8** was shown by ^{1}H NMR to be 96% pure with the majority of the contaminant being 3-chloropentane **9** (Fig. S23†). In the complex with **1**, a combination of ^{1}H and COSY NMR experiments (Fig. S12 and S19†) was required to identify all the bound **8** signals, including the relatively far downfield C_2 methine signal at 1.83 ppm. Of note for this guest was the narrow range of $\Delta\delta$ values for bound guest atoms: $\Delta\Delta\delta$ = 0.16 ppm verses 1.12 ppm for **7**, suggesting that **8** has no binding orientation preference inside the host.

The ^{1}H NMR spectrum of the guest binding region of the complex of **1** with **8** also revealed approximately 12% of the corresponding complex with **9**, suggesting **9** formed a stronger complex than **8**. Furthermore, in addition to the complex with **9**, it was possible to detect a slight impurity manifest as small shoulders to two of the large signals from **8**. We attribute these to the corresponding hetero-guest complex (*vide infra*), although there is the possibility that (±) **8** forms diastereomeric complexes (*R*/*R* and *S*/*S* verses *R*/*S*) and that the minor complex is the least stable of the two.

Guest 3-chloropentane **9** was found to be only 75% pure, with the remainder of the sample being 2-chloropentane **8**. The ^{1}H NMR of the complex formed between **1** and **9** revealed that **8** competitively bound with guest **9** sufficiently to form only ~1.5% of its corresponding capsular complex (Fig. S13†); an observation corroborating the idea that of the two guests **9** forms the stronger complex. For guest **9** itself, the diastereotopic protons of the C_2 and C_4 methylene groups appeared at −0.31 ppm, whilst the signals for the C_1 and C_5 methyl groups were located at −1.08 ppm. A COSY NMR experiment (Fig. S20†) was necessary to identify the C_3 methine located at 1.39 ppm. Again, the relatively small $\Delta\Delta\delta$ value for this guest (~0.20 ppm) suggested little in the way of a preferred orientation within the pocket.

In the complex between **1** and guest (±) **10**, 1-chloro-2-methylpentane, the upfield region of the NMR spectrum showed well-defined signals and only the slightest trace amounts of competing impurity (Fig. S14†). The C_5 and C_6 methyl groups of bound **10** possessed the expected doublet and triplet multiplicity, and the C_4 methylene hydrogens were manifest as an apparent pentet. Finally, the C_2 methine was a poorly resolved multiplet, whilst the C_1 methylene was pinpointed at 1.23 ppm with a COSY NMR experiment (Fig. S20†). The lack of any minor peaks in the bound guest region indicated that, as was the case for **8**, the encapsulation of guest (±) **10** did not result in the formation of diastereomeric complexes (*RR*/*SS* and *RS*). The $\Delta\delta$ values suggest a preference for the guest binding ethyl group down, but the relatively small $\Delta\Delta\delta$ value (~0.40 ppm) indicates only a slight affinity for this orientation.

The sample of guest 1-chloro-3-methylbutane **11** (isohexyl chloride) contained 3% of an impurity suspected to be 2-chloro-3-methylbutane **13**. This was confirmed by the corresponding complex between **1** and **11** that showed small amounts of complexation with **13** (*vide infra*). The signals from the encapsulated guest **11** were evident as a large doublet for the enantiotopic C_4 and C_5 methyl groups at −1.26 ppm, a multiplet at −0.56 ppm for the C_2 methylene hydrogens, a broad multiplet for the C_3 methine hydrogen at −0.28 ppm, and the C_1 methylene at 1.47 ppm. A small $\Delta\Delta\delta$ value (~0.12 ppm) confirmed a slight preference for the chlorine up binding conformation (Fig. S15†).

A ^{1}H NMR spectrum of free 2-chloro-2-methylbutane **12** revealed no significant impurities. All of the signals from the encapsulated guest **12** were simply identified from a ^{1}H NMR experiment (Fig. S16†). The C_4 methyl group signal was

evident at −1.26 ppm, the two enantiotopic methyl groups (C_1 and C_5) appeared at −0.46 ppm, and the signal from the C_3 methylene group manifested as a multiplet at −0.21 ppm. The larger $\Delta\delta$ values for the unique methyl group and a relatively small $\Delta\Delta\delta$ value of 0.48 ppm suggests a slight preference for the unique methyl group binding down into the base of the pocket (although the difference in $\Delta\delta$ values for the methyl groups may be caused by time averaging of the C_1 and C_5 signals).

Guest 2-chloro-3-methylbutane **13** was found to be only 91% pure. Accounting for the bulk of the impurity of the commercial sample was 1-chloro-3-methylbutane **11**. However, NMR provided no evidence that at this ratio **11** could compete with **13** for the capsule.

Whereas there was little or no evidence of guest self-sorting for the racemate guests (±)**8** and (±)**10**, ^{1}H NMR (Fig. 2) vividly demonstrated that guest (±)**13** formed a 1 : 1.74 : 1 mixture of the *R*/*R*, *R*/*S* and *S*/*S* capsular complexes. In other words, host **1** and guest **13** showed a slight (53.5% to 46.5%) preference to form the homo- (*R*/*R* and *S*/*S*) verses the hetero-guest (*R*/*S*) complex. For such a structurally straightforward molecule, the guest binding region of the complex between **1** and **13** is remarkably intricate. This arises through three main factors; first, the pair of C_4 and C_5 methyl groups (Fig. 2) of each guest are diastereotopic and therefore magnetically non-equivalent. Second, there are many *enantio*- and diastereotopic relationships amongst ostensibly identical groups between pairs of guests in a complex. Lastly, adding to these complications is that the C_{4h} (*R*/*S*) and D_4 (*R*/*R* and *S*/*S*) complexes are formed in approximately the same amounts.

Identification of the thirteen signals from the bound guests required a combination of COSY NMR and symmetry considerations. To take as an example one of the complexes formed (Fig. 2, beige shading), the COSY experiment (Fig. S21†) revealed coupling between a characteristically downfield C_2 methine at 2.61 ppm and two doublets corresponding to the C_1 methyl groups of both guests at −0.79 and −0.86 ppm. Additionally, coupling of the C_3 methine signals at −0.15 and −0.26 ppm was observed with the three doublet signals from the C_4 and C_5 methyl groups at −1.12, −1.37, and −1.45 ppm. However, the COSY spectrum did not reveal coupling between the C_2 and C_3 methine hydrogens in this (or the other) complex. As the expected cross-peak was evident in the corresponding COSY NMR of the free guest, it is assumed that the kinetics of guest movement within the capsule – which led to considerable broadening of the methine signals – caused this attenuation of the COSY cross-peaks. Nevertheless, it was possible to link the two halves (C_1/C_2/Cl and C_3/C_4/C_5) of each complex by integration of all the respective peaks belonging to each half.

Although COSY NMR and integration revealed two complexes in a 2 : 1.74 ratio, symmetry considerations were necessary to identify which was which. As a starting point, the *meso* *R*/*S* complex belongs to the achiral C_{4h} point group whilst the *R*/*R* (or *S*/*S*) complex belongs to the chiral D_4 point group. An analysis of the many homotopic and heterotopic (enantiotopic and diastereotopic) relationships within each guest and between the two guests of a complex revealed that it is the latter D_4 complex that possesses the more straightforward ^{1}H NMR spectrum.[38] For example, in the case of the C_{4h} (*R*/*S*) complex, the C_1 methyl signal appears as two doublets at −0.79 and −0.86 ppm because of the intrinsic coupling with the methine and because the methyl group of one guest is enantiotopic with respect to the methyl group of the second guest in the capsule (externally enantiotopic). Consequently, in the chiral environment of the inner space of the capsule these

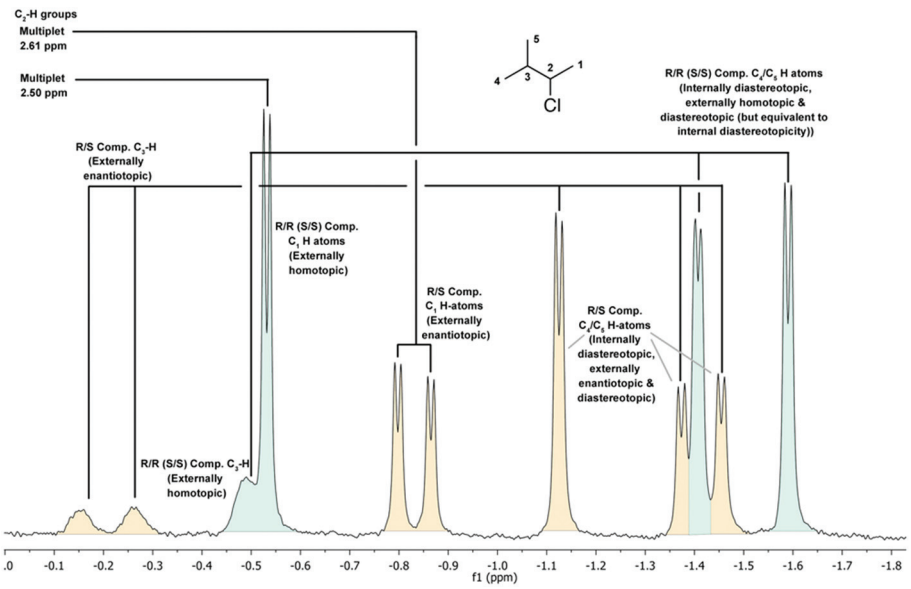


Fig. 2 High-field (bound guest) region of the ^{1}H NMR complex formed between **1** and racemate **13**. The COSY couplings are highlighted. Signals corresponding to the homo-guest complex (*R*/*R* and *S*/*S*) are shown in blue-green, signals for the corresponding *R*/*S* complex in beige.

two methyl groups are magnetically non-equivalent. In the *R*/*S* complex, the C_3 methine groups of the two guests are externally enantiotopic with respect to each other and become non-equivalent in the chiral space of the complex (−0.15 and −0.26 ppm). These two C_3 signals are coupled with those from the diastereotopic C_4 and C_5 methyl groups and would appear as four doublets because of the splitting with the C_3 methine because they are diastereotopic, and are externally heterotopic (*enantio*- and diastereotopic relationships depending on which methyl is compared to which). However, only three doublets are observed. There is apparently degeneracy that collapses one signal into a doublet at −1.12 ppm. A similar breakdown of the supramolecular stereochemistry within the D_4 (*R*/*R* and *S*/*S*) complexes predicts a more straightforward set of signals. For example, the diastereotopic C_4 and C_5 methyl groups are externally homotopic and diastereotopic, but this latter relationship is degenerate with the internal diastereotopicity. Consequently, only two doublets at −1.40 and −1.58 ppm are evident. Likewise, the C_1 methyl groups of the *R*/*R* (*S*/*S*) complex are externally homotopic and only a doublet is observed because of coupling to the C_2 methine. In conclusion, symmetry considerations dictate that the chiral D_4 complex possesses the more straightforward NMR. Hence, considering the COSY and integration data, host **1** preferentially forms the homo-guest (*R*/*R* and *S*/*S*) complexes with **13**.

The ^{1}H NMR of the complex between **1** and 1-chloro-2,2-dimethyl propane **14** was relatively straightforward. As expected, considering its very high purity, **14** showed no signals corresponding to any competing guest. For bound **14**, the C_1 methylene group was evident at 0.93 ppm with the methyl groups apparent at −0.94 ppm. The $\Delta\delta$ values for these two signals were −2.45 and −1.87 ppm respectively, indicating a slight preference for the molecule to bind chlorine down inside the pocket ($\Delta\Delta\delta$ = 0.58 ppm).

Having studied these chloropentanes individually, we then sought to pit them against each other in competition experiments. As with the hexane isomers, the extent of formation of any hetero-guest complex was very dependent on the actual guests paired (Table 4). Thus, the total amount of hetero-guest complex formed by each guest when individually complexed with the others in the series was: **7** (86), **8** (107), **9** (97), **10** (98), **11** (88), **12** (18), **13** (0), **14** (124). Two standout guests in this series are **12** and **13**, that have very little tendency to form hetero-guest complexes. The absoluteness of **13** to self-sort is unique among the guests studied, and this is all the more intriguing because **13** is the only (chiral) guest that, in its complexation with host **1**, demonstrated the formation of both *RR*/*SS* and *RS* diastereomeric complexes. When two guests compete for the host capsule there is an obvious entropic advantage to forming the hetero-guest complex; specifically, there is an entropy of mixing associated with the formation of an AB complex that is absent with self-sorting and the formation AA and BB complexes. If guest **13** gains an entropy of mixing advantage by forming *RR*/*SS* and *RS* complexes with itself, does this nullify any entropic advantage of forming an AB hetero-guest complex with an isomeric guest? At the other extreme, guest **14** formed considerable amounts of hetero-guest complex with all guests except **13**, but all of the other guests formed relatively large amounts of hetero-guest complexes. Overall, in contrast to the hexane isomers where lesser degrees of branching correlated with the formation of homo-guest complexes, there was no obvious correlation between structure and the predisposition to form these AB-type complexes. There is apparently much to learn about the self-sorting of guests inside nano-spaces, and correspondingly how to control bimolecular reactions within such spaces.

As with the hexane isomers, the solubility of these guests precluded the use of techniques such as ITC to determine the absolute thermodynamic parameters of guest complexation. Consequently, to determine an order of preference for complexation, the competition of each guest against the others in the series was examined to ascertain whether it bound with approximately the same affinity (half a point) or bound more strongly (1 point). This approach gave the following: **7** (0.5), **8** (3), **9** (6.5), **10** (6), **11** (2), **12** (0.5), **13** (4), **14** (5.5) indicating the preference for complexation within the capsule formed by **1** as: **7** ~ **12** < **11** < **8** < **13** < **14** < **10** < **9**. Thus guests **7** and **12** are

Table 4 Percentage of homo- and hetero-guest complexes formed between host **1** and the constitutional isomers of chloropentane

Guest competition[a]	% Homo-complex	% Hetero-complex	% Impurity complex
7–8	9–68	19	4 (**9**)[b]
7–9	5–90	5	
7–10	10–80	10	
7–11	31–41	28	
7–12	42–48	10	
7–13*RR*–**13***RS*	15–44–41	0	
7–14	1–85	14	
8–9	20–54	26	
8–10	25–58	17	
8–11	56–34	10	
8–12	92–5	3	
8–13*RR*–**13***RS*	41–32–27	0	
8–14	17–51	32	
9–10	50–29	21	
9–11	70–9	21	
9–12	91–0	0	9(**8**)[c]
9–13*RR*–**13***RS*	86–9–5	0	
9–14	34–42	24	
10–11	69–16	15	
10–12	100–0	0	
10–13*RR*–**13***RS*	84–7–9	0	
10–14	40–25	35	
11–12	89–11	0	
11–13*RR*–**13***RS*	23–40–37	0	
11–14	14–72	14	
12–13*RR*–**13***RS*	0–53–47	0	
12–14	0–100	5	
13*RR*–**13***RS*-**14**	1–1–98	0	

[a] Competition experiments involved combining 1 equiv. of a 1 : 1 mixture of the two guests with 1 equiv. of host **1** at a concentration of 1 mM (10 mM sodium borate buffer). [b] Guest **9** is a minor (~4%) impurity in **8**. As this guest is a much stronger binder than either **7** or **8**, all of **9** is observed to complex to host **1**. [c] As discussed in the text, guest **8** is a stronger binder to host **1** than guest **12**. Consequently, all the host remaining after complexing high affinity **9** is seen to form a complex only with **8**.

the weakest binders, competing only with each other. The next two weakest binders are **8** and **11** and in a direct competition between these guests, **8** is the stronger binder. The remaining guests bind with considerably higher affinity. The strongest binder is **9**, which outcompetes all guests with the exception of **14** (tie). The next strongest binding guest **10** outcompetes all guests except **9**. Guest **14** is the guest with the third highest affinity; it ties with **9** and is outcompeted by **10**. Finally, completing the top half of the affinity table, guest **13** is outcompeted by the three strongest guests **9**, **10**, and **14**, and successfully outcompetes the four weaker binders **7**, **8**, **11**, and **12**.

Whereas the hexane isomers exhibited apparent trends regarding structure and affinity, we did not see analogous correlations between affinity and surface area, volume, ovality, sphericity, the number of termini, the number of C–C (or C–Cl) rotating bonds that results in a conformational change within the carbon framework, the type of alkyl chloride (1°, 2° or 3°), or even the preferred orientation of the guest (Table 3). It is evident that the replacement of a methyl group with a chlorine atom and the concomitant introduction of a significant dipole into the guest leads to a much more complicated system. It is possible that computational calculations might reveal details about guest binding. However, such an approach cannot take into account potential differences in solvation for each guest and would likely be of limited utility. Nevertheless, some interesting observations are worth noting. For example, the two strongest binders, **9** and **10**, have very similar structures with only the interchange of a methyl group and an isosteric chlorine atom relating them. Indeed, the four strongest binding chloropentanes share a privileged 4-atom chain pattern Cl–C(R_2)–C(R_2)–Me; only low affinity guest **12** bucks this trend (Fig. 3, red). On the other hand, very little change is required to greatly modify affinity. For example, swapping a C_1 H-atom of **12** with the C_5 methyl group 'converts' this weakest binder into the strongest binder, namely **9**. Similarly, swapping the Cl atom of **12** with the unique C_4 methyl group converts it into the third best binder **14**. For both these guests it is the "sharper" end of the guest (C_4 methyl in **12** and C_1 chlorine in **14**) rather than the "blunter" end that binds down into the lowest region of the pocket. Hence the reason that **14** binds so much more strongly than **12** may be because the C–Cl dipole of the former roughly opposes the dipole of the host, but in the latter it is roughly aligned with it.[39]

When the two groups of guests are compared (Fig. 3) these structural trends are emphasized. In both classes, the unsubstituted or singly branched derivatives are the weakest and next to weakest guests, respectively. On the other hand, the four best chloropentane and three best hexane guests share the privileged 4-atom chain pattern X–C(R_2)–C(R_2)–Me (X = Cl or Me). Within this group of strong binders there is some interchange in the order of binding affinity that could be attributed to the relationship between the C–Cl dipole of a halo-pentane guest and the large dipole of the host.[39] The one comparison between the two classes of guest that contradicts this weak/strong bifurcation of guests is **12**. Guest **12** (along with **7**) is the weakest binding of the chloropentanes, whilst its isosteric hexane isomer **6** is the next to best guest. The two strongly binding guests **6** and **14**, and the weak binder **12**, all share the same basic structure (R_3CCH_2R) and we attribute the observed binding propensities in terms of the gross overall form of these guests being well suited to the base of the pocket of the host, but that in the case of the preferred binding orientation **12** the C–Cl dipole is aligned with the large dipole moment of the host.

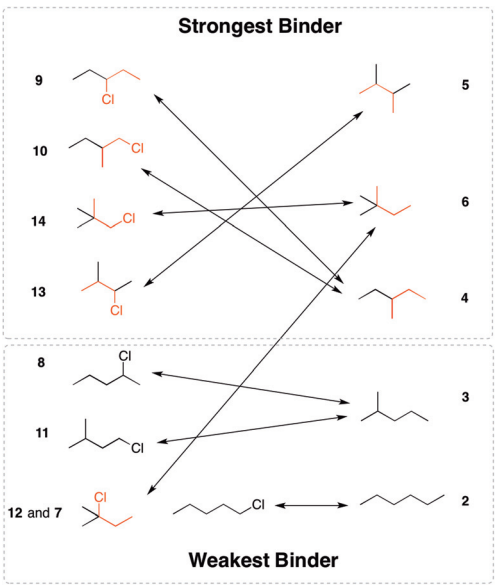


Fig. 3 Pairs of structural similar guests and the relationship between this and binding affinity.

Conclusions

Our results show that even with relatively straightforward classes of molecules – the isomers of hexane and chloropentane – guest binding to the well-defined pocket of host **1** is far from straightforward. There is a preference to bind guests with a X–C(R_2)–C(R_2)–Me (X = Cl or Me) pattern and, more generally still, a preference for the host to bind branched, rotund guests rather than highly flexible, unbranched derivatives. However, the limited solubility of the guests in water precludes detailed examination of the thermodynamics of complexation.

The complexity found in the binding of such simple guests is magnified when considering molecular differentiation between pairs of guests. In such cases, different guests demonstrate different propensities to self-sort. Some guests form very little hetero-guest complexes, whilst others readily do. Guest (±) **13** is an extreme; when forming a complex with **1**, it self-sorts exclusively; potentially because any bonus from the entropy of mixing in forming an AB complex with a constitutional isomer is lost because **13** forms hetero-guest complexes with itself (*RR*/*SS* and *RS* diastereomeric complexes). Overall, although the pool of guests reveals some general

correlations between binding strength and structure, there is no obvious relationship between structure and degree of self-sorting.

These points notwithstanding, our results demonstrate that host **1** is capable of differentiating between these small, constitutionally isomeric guests. These properties may hold application in fine chemicals syntheses and isolations. Consequently, although the physical properties of the guests preclude detailed thermodynamic analysis, and their propensities towards self-sorting are difficult to predict, hosts such as **1** are most certainly capable of the selective uptake and transport of small guests to affect separations. Investigations along these lines are ongoing.

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38 A good analogy to this statement is a comparison between the *meso* (*R*/*S*) and chiral (*R*/*R* or *S*/*S*) cyclopentane-1,3-diols. In the former the C2 methylene hydrogens are diastereotopic with respect to one another. In the latter diol the same hydrogens are homotopic. Similarly, the C1 and C3 methine hydrogens of the meso compound are enantiotopic, whereas the same methine hydrogens in the chiral species are homotopic. In terms of stereotopicity (and hence the multiplicity of the NMR spectrum), the achiral molecule is more complicated than the chiral equivalent.
39 Dipole moments are notoriously difficult to calculate but we estimate using semi-empirical calculations that the core host (host **1** where the rim carboxylates are replaced by hydrogen atoms and the propanoic acid pendant chains replaced with methyl groups) has a dipole moment of ~5 D, the vector of which points out of the portal along the C_4 axis of the host.