A deuterated deep-cavity cavitand confirms the importance of C–H···X–R hydrogen bonds in guest binding†

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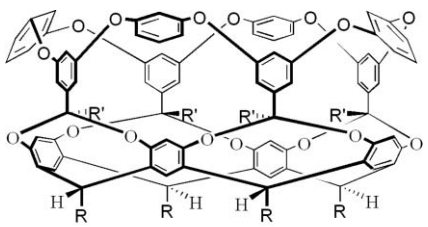
A deuterated cavitand host was examined for its affinity to a series of guests; for halogenated, preorganized guests binding was significantly stronger than the corresponding protium host.

The weighing-up of the different components that make up hydrogen bonds: electrostatic (ES), polarization (PL), charge transfer (CT), exchange repulsion (EX), and dispersive interactions (DI),[1] results in a wide range of bonding types. The most familiar of hydrogen bonds, for example $[F\cdots H\text{–}F]^-$ or amide N–H···O=C, are dominated by a large ES component that out-weighs significant EX. In contrast, in weak hydrogen bonds such as C–H···O=C interactions both the ES contribution and EX components are greatly reduced and PL, CT and DI become important contributors.[2–4] Although these types of weak hydrogen bonds are generally accepted by the supramolecular community, there is still debate regarding weak donor–weak acceptor type hydrogen bonds at the end of the hydrogen bond regime. In this contribution we address C–H···X–R (X = halogen) interactions,[5–7] and examine the use of isotope substitution to probe these interactions.

Host **1** (Fig. 1) binds a variety of guests, but the presence of one or more halogen atoms greatly enhances association (R–I > R–Br > R–Cl).[8–12] For example, the ΔH° for complexing 1-iodoadamantane is 6.7 kcal mol^{-1} higher than adamantane.[11] The fact that polar guests such as cyanoadamantane bind weakly suggests that (molecular scale) dipole–dipole interactions do not play a significant role in the strong binding of halogenated guests. Rather, NMR and X-ray crystallography suggest that C–H···X–R hydrogen bonds between the benzal hydrogens of the host and halogen atom of the guest are important for strong binding and the preferred "halogen down" binding orientation.[8,11] Thus, the observed order of complexation comes about in part because halogen atoms of increasing size can simultaneously form more hydrogen bonds with the crown of electron deficient, benzal hydrogens of the host (Fig. 2), with iodo-derivatives binding the strongest because the halogen atom can simultaneously form four C–H···X–R interactions.[8] To confirm this we have targeted deutero-host **2**, and report here on its synthesis and properties. A comparison with its protium counterpart confirms the existence of these normally weak interactions and reveals something about the other factors important in guest complexation.

The synthesis of the deuterated host **2** (Scheme 1) paralleled the synthesis of **1**.[8] Metal–halogen exchange upon 1,3,5 tribromobenzene (**3**) and quenching with DMF-d_7 gave aldehyde **4**, which upon bromination with BBr_3 gave 3,5-dibromobenzal bromide (**5**). Reaction of **5** with the phenethyl footed octol **6** gave deep-cavity cavitand **7**. Regardless of the choice of base, some deutero–protio exchange was noted to occur in this step (NMR). To counter this, the normal reaction solvent dimethylacetamide was replaced with dimethylsulfoxide-d_6. This minimization of adventitious protons resulted in product **7** with greater than 90% deuterium at the benzal position. Finally, Ullmann ether reaction conditions utilizing resorcinol as the bis-nucleophile gave host **2**. Under these forceful conditions, there was no exchange of the deuterium atoms suggesting that the observed exchange in the formation of **7** arose not through the product, but either the benzal bromide bridging material, or bridging intermediates. The latter were implicated by the absence of exchange when the benzal bromide was treated to the reaction conditions in the absence of the resorcinarene.



1 R = CH_2CH_2Ph R' = H
2 R = CH_2CH_2Ph R' = D

Fig. 1 The protio and deutero hosts.

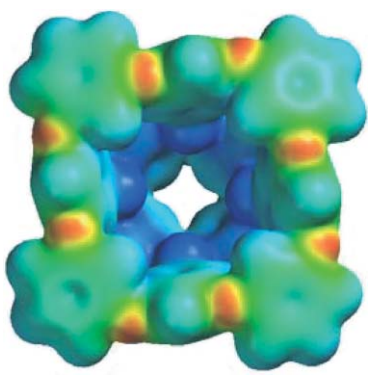


Fig. 2 Potential density map of host **1**.[13]

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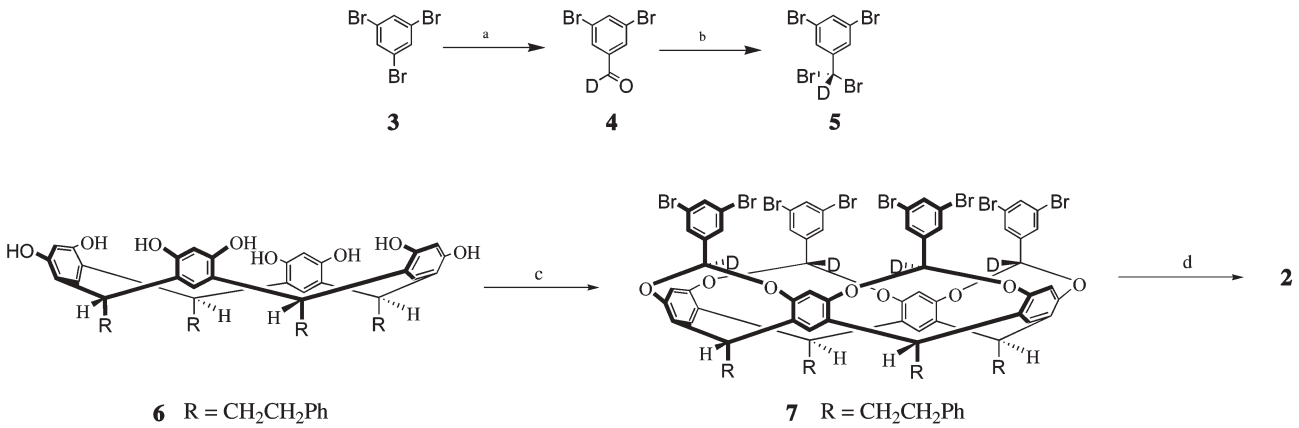

Scheme 1 Conditions are: (a) *n*-BuLi, ether, −78 °C, then DMF-d_7, then H_3O^+. (b) BBr_3, CH_2Cl_2. (c) Bridging material **5**, K_2CO_3, DMSO-d_6. (d) Resorcinol, K_2CO_3, CuO, pyr, Δ.

Table 1 Association constants for **1** and **2** in DMSO-d_6[a]

	K_a/M^{-1}	
Guest	**1**	**2**
Adamantane	790	763
Cyanoadamantane	160	151
Bromocyclopentane	82	86
Iodocyclopentane	226	246
Bromocyclohexane	208	198
Iodocyclohexane	923[b]	1390
Bromocycloheptane	419	448
Iodocycloheptane[c]	2230	3370
Bromocyclooctane	1330	1230
Iodocyclooctane[c]	5960	7920
2-Bromoadamantane	11 300	18 100
exo-2-Bromonorbornane	610	837

[a] Errors associated with respective K_a determinations are ±10% for an average of at least two titrations. [b] A previous determination[11] reported a value of 580 M^{-1}. [c] See supplementary material for synthesis and NMR spectral data.

We examined the binding properties of **2** using a variety of halogenated compounds (Table 1). As a reference, adamantane and cyanoadamantane were also included in the list of guests. With the exception of iodocycloheptane and iodocyclooctane, all guests were commercially available. The iodocycloheptane and iodocyclooctane were themselves synthesized in 64 and 72% yield respectively, the former by a Fienkelstein reaction upon the corresponding bromide, the latter from treatment of cyclooctanol with TSMCl and NaI (see Supporting Information†).

For host **1**, the inner benzal protons are ideal reporters for the determination of binding constants. In the absence of these, no single set of protons could be used for all the guests examined. Hence, two sets of protons were used: either those in the 2-position of the "uppermost" resorcinol rings (the *endo* positions[14]), or those in the 2-position of the "lowest" resorcinol rings. Crosschecks with complexes where either proton could be used demonstrated that both reporters gave the same K_a values. However, to eliminate the possibility of errors arising from using these alternative reporters instead of the benzal protons, previously reported binding constants for five of the guests[11] were determined using the new reporters. Without exception these K_a values were within agreement.[15]

Table 2 ^{1}H NMR derived thermodynamic parameters for 2-Br-adamantane binding to **1** and **2** at 298 K in DMSO-d_6[a]

Host	ΔG/kcal mol^{-1}	ΔH/kcal mol^{-1}	$T\Delta S$/kcal mol^{-1}
1	−5.5	−8.6	−3.1
2	−5.8	−10.9	−5.1

[a] Values calculated from at least two K_a determinations (error ±10%).

As anticipated, there was essentially no difference between the association constants for adamantane or cyanoadamantane binding to hosts **1** and **2**. However, of the four, iodinated guests examined, three bound significantly[16] more strongly to host **2**; only the smallest iodinated guest, iodocyclopentane, failed to differentiate between the hosts. On the other hand, only the two largest and preorganized brominated species, 2-bromoadamantane and *exo*-2-bromonorbornane, bound more strongly to **2**. The four smaller and/or less preorganized bromine derivatives had essentially the same binding constants to either host. A Van't Hoff plot for the complexation of 2-bromoadamantane indicated that these changes in K_a arise through changes in the enthalpy of complexation (Table 2).

That many of the guests examined bind more strongly to **2** than **1** confirms the importance of C–H···X–R hydrogen bonds in these complexes. The increases in association upon deuteration are in accord with experimental/theoretic studies of small systems in the gas phase[17] or in matrices,[18] and most recently, in solution studies of orientational isomerism within supramolecular capsules.[19] In the former, the increase in association has been pin-pointed to the influences of the zero-point vibrational energy (ZPVE) change on one or more intermolecular vibrational mode.

The results described here demonstrate that there are two general classes of guests. Large, preorganized guests that pack the cavity well bind more strongly to deuterated host **2**, while smaller guests are not influenced by deuteration. Additionally, the border between these two groups is dependant on the halogen atom of the guest; relatively small iodinated guests can differentiate between the two hosts while their corresponding bromides do not. Why do smaller guests not "notice" deuteration of the host? This lack of recognition must arise through a decrease in residency time of the halogen atoms in the crown of benzal groups, but many factors

likely lead to this phenomenon. Thus, small guest size would lead to increased mobility within the pocket and perhaps co-habitation with solvent, while a lack of guest preorganization may lead to preferred conformations of the guest that are ill-suited to halogen atom complexation in the crown. Teasing out these factors is however difficult.

More generally, it is noteworthy to ask why, considering the "weakness" of C–H···X–R hydrogen bonds, do halogenated guests bind so strongly to **1** or **2**? For both hosts, the most important structural feature is undoubtedly the size and pre-organization of the crown of convergent, benzal hydrogens. Although weak donors, the acetal C–H groups can work in unison without the host paying a significant entropic penalty. From the perspective of Morokuma's decomposition method, another structural feature probably augments one the of "strengths" of weak donors; the relatively small EX component associated with bonding.[1] Thus, the lone pairs on the acetal oxygens all lie in the outer surface of the host, a feature that must minimize the electron density in the vicinity of the C–H bond, and therefore minimize the (already small) EX component. This would allow significant binding even if the ES component of C–H···X–R hydrogens bonds is as small or smaller (more likely) than C–H···O=C interactions. However, quantifying these roles and those of the PL, CT and DI components lies beyond the scope of this work.

In conclusion, a comparison of deuterated host **2** and its protio counterpart **1** confirms that C–H···X–R hydrogen bonds play an important role in the complexation of large guests within these hosts. This comparison also demonstrates that smaller and more flexible guests have less of a tendency to form these interactions. Their greater mobility and flexibility result in a decreased residency time in the converging, deeply located benzal array of the host.

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