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C-H···X-C bonds in alkyl halides drive reverse selectivities in confined spaces

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ABSTRACT

Binding of non-activated alkyl halides (**2**–**20**) in water-soluble cavitand (**1**) through supramolecular forces is here reported, with emphasis on the role of size and polarizability of the halogen atom in the formation of intramolecular C-H hydrogen bonds in confined spaces. Rare reverse affinity in water (RI < RBr < RCl) is surprisingly observed for the more water-soluble short alkyl halides in dynamic open-ended containers. Competitive bindings and theoretical calculations confirm the unusual selectivity and the presence of C-H hydrogen bonds in non-activated systems for the first time, pointing out the importance and effect of subtle forces on molecular recognition in confined spaces.

Weak intermolecular forces such as hydrogen bonds, solvophobic interactions and dispersion forces are usually obvious in host-guest complexation [1,2], but which forces are responsible for the recognition and reactivity in a given system is often a difficult question [3]. We are using open-ended containers such as host **1** as vessels that lead to reactivity of guests that is not normally observed in bulk solution [4]. These are synthetic receptors [5–10] that surround suitable guests [11,12] and act as templates that prevent side reactions in the limited and confined space, miming the action of biological enzymes. The host promotes reactions such as macrocyclization [13–16] or mono-functionalization [17–19] processes that are influenced by binding orientation of the guest in the complex [20,21]. Other investigators of the binding properties and reactivity in supramolecular systems [22–25] include Gibb [26,27] and Yamaguchi [28] who revealed the presence of subtle C-H···X-R hydrogen bonds in the host-guest complexes of cyclic alkyl halides in organic solvents. In both cases, C-H bond(s), involved in the C-H hydrogen bond(s), resulted to be activated for the presence of two adjacent oxygen atoms (-O-CH_2-O-). In aqueous media, Hooley [29] and Yu [30] recently showed binding orientations for encapsulated alkyl halides in open-ended containers showing higher affinity for iodides with respect to relative chlorides. In these, dispersion forces drive the dynamic arrangements of the guests in the cavity and no C-H hydrogen bonds have been observed. Moreover, the higher polarity and consequently higher water-solubility of alkyl chlorides makes their selective capture in water extremely more difficult than the less water-soluble alkyl iodides as reported in the literatures (Table S4 in Supporting information) [29–31]. To the best of our knowledge, no selective capture of alkyl chlorides is reported in presence of iodides in water. Here we report the binding orientation of an expanded group of sample alkyl halides (**2**–**20**) in water-soluble host **1** (Fig. 1) to shed light on their behavior in confined spaces.

Host **1** in solution is held in a receptive vase shape by the two Pd ions at the opposite “corners”. Pd complexation forces a more tight cavity in **1** compared with other hosts based resorcin[4]arenes [29–31], leading to peculiar binding properties. In the absence of Pd, typical resorcin[4]arene cavitands show a dynamic equilibrium between the *vase* and the flattened form called *kite*. *Kite* form is not stable in solution as monomer but it is detected by NMR spectroscopy as dimer, called *velcrand*. Experimental conditions can alter the equilibrium [32] but the *vase* form is always favored in the presence of suitable guests that “solvate” the cavity’s interior. Characteristic signals appear at 5.6 ppm and ~4 ppm in the ^1H NMR spectrum for the methine protons of the *vase* form and *velcrand*, respectively [33]. Mild sonication of **1** (1 mmol/L in D_2O) with alkyl halides gave host-guest complexes that showed ^1H NMR signals for bound guest shifted upfield by the shielding of the aromatic panels of the host. A binding constant (K_A) of 1.5×10^5 L/mol has been determined in **1** by isothermal titration calorimetry (ITC)

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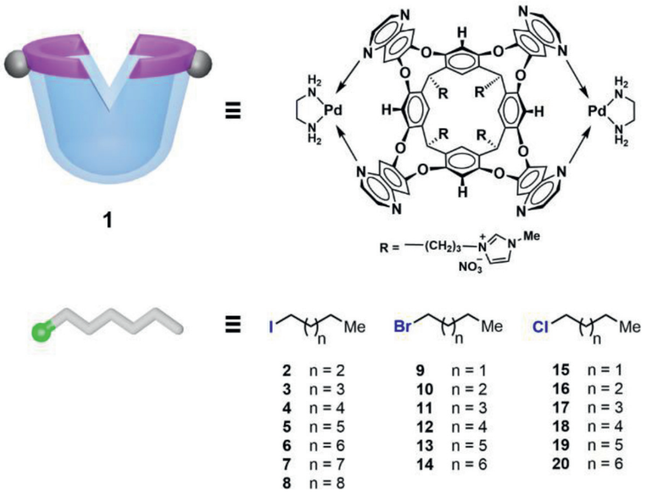

Fig. 1. Cartoon and chemical structure of water-soluble host **1** (Top). Structures of alkyl dihalides guests involved in this study (Bottom). Counter anions (NO_3^-) in **1** has not been reported for better clarity.

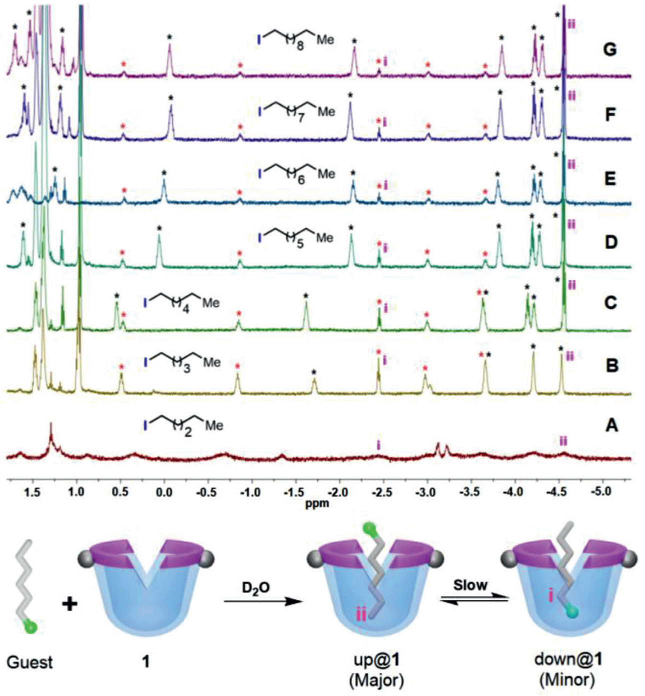

Fig. 2. (Top) Partial ^{1}H NMR (600 MHz, D_2O, 305 K) spectra of host-guest complex between **1** (1 mmol/L in 500 µL) and **1** equiv. (host:guest = 1:1) of (A) **2** ($n = 2$); (B) **3** ($n = 3$); (C) **4** ($n = 4$); (D) **5** ($n = 5$); (E) **6** ($n = 6$); (F) **7** ($n = 7$) and (G) **8** ($n = 8$). (Bottom) Cartoon and equilibria for iodoalkanes@**1**. Peaks from down@**1** and up@**1** are marked with red and black stars, respectively.

for *n*-BuOH [32], while competitive experiments on secondary alkyl halides, using *n*-BuOH as reference, showed comparable binding constants (Figs. S84 and S85 in Supporting information) [19]. The orientation of bound alkyl iodides **(2–8)** was initially investigated (Fig. 2). The guest shows two different orientations in **1**: one with the halogen atom deep in the cavity (down@**1**) and another with the methyl in that position (up@**1**). The narrow space of the host cavity makes the interconversion between up@**1** and down@**1** slow respect to the NMR timescale, leading to separate sets of signals in the ^{1}H NMR spectra (black and red stars, Fig. 2). The linear binding orientation is supported by $\Delta\delta$ calculations (Figs. S56-S64 in Supporting information) with characteristic signals (triplets) detected around −2.5 and −4.5 ppm for down@**1** and up@**1**, respectively (magenta letters, Fig. 2). Moreover, kinetically stable host-guest complexes on NMR timescale are detected in all cases, although broadened signals are observed for bound **2** (1-iodopentane) in **1**, indicative of a relatively fast "in-out" exchange process. Roughly equal amounts of down@**1** and up@**1** (≈50%) were detected for bound **3** (1-iodohexane) (Fig. S69 in Supporting information) while higher amounts of up@**1** (82%) were observed for bound **4** (1-iodoheptane) (Fig. S70 in Supporting information). Polar head ($-CH_2-I$) prefers to be exposed to the polar medium while lipophilic tail occupies the hydrophobic cavity. Indeed, complexes of up@**1** were dominant when even longer guests were involved: 87%, 88% and 93% were detected for **5@1**, **6@1** and **8@1**, respectively (Figs. S71-S74 in Supporting information).

Similar behavior is exhibited by bromides **11**–**13** and chlorides **17**–**19** in **1** (Figs. S75-S80 in Supporting information) but lower percentage of down@**1** was observed for equally long bromides and chlorides with respect to iodides, due to the higher polarizability of the X-C bond (RCl > RBr > RI) and pointing out the importance of the halogen atom in the complex formation and guest orientation (Table S1 in Supporting information). Higher affinity for up@**1** complex is also confirmed by theoretical calculations on bound chloride **17** (Fig. S93 in Supporting information) and bromide **11** (Fig. S94 in Supporting information) in **1**, showing a relative stabilization energy of 1.26 and 0.98 kcal/mol, respectively.

Also, sharp signals are observed for hexyl iodide **3** while bromide **11** and chloride **17** show more broadened signals although their alkyl chains are of the same length (Figs. 3A-C). These results underline their lower affinities for the host and faster "in-out" exchange from the cavity.

No binding was observed for nonyl bromide **14** or chloride **20** while iodide **6** (1-iodononane), shows good affinity for the host cavity (Fig. S54 in Supporting information). Relatively high affinity was also observed for longer iodides **7** (1-iodododecane) and **8** (1-iodounndecane) where kinetically stable host-guest complexes were detected in both cases (Figs. 2F and G). Dispersion forces between halogen atom and host's panels play an important role and stronger interactions are observed in alkyl iodides with respect to bromides and chlorides. Indeed, NMR titration of **3** (1-iodohexane) with **1** shows a K_A of 1.1×10^3 L/mol using acetonitrile as co-solvent (Fig. S87 in Supporting information) while a K_A of 214 L/mol is found for chloride **17** (1-chlorohexane) under same condition (Fig. S88 in Supporting information). As mentioned above, the shortest alkyl iodide **2** (1-iodopentane) shows broadened peaks but the signal pattern in the NMR spectrum is similar to the linear binding observed for longer guests (Figs. 2A-G). Instead, a different signal pattern is detected for bound bromide **10** (1-bromopentane) and chloride **16** (1-chloropentane) in **1**. The most upfield signal is now observed at –4.0 ppm, while for longer guests it is found at –4.57 ppm (Figs. 3D-F). Moreover, fewer signals in the spectrum are present, consistent with a bound guest that moves rapidly inside the cavity, averaging the signals on the NMR timescale. These observations indicate new orientations for bound **10** and **16**, 1–bromo and 1-chloropentane, respectively. A "bent orientation" with asymmetric "*yo-yo* motion" is proposed as a plausible conformation (Fig. 3, bottom). In this conformation, dispersion forces, involving the halogen atom, should be less favored while *gauche–gauche* interactions become predominant, negatively affecting the host-guest complex formation. Simultaneously, intramolecular C-H hydrogen bonds between halogen atom and hydrogen(s) of the lipophilic tail could be potentially allowed, stabilizing the complex. C-H hydrogen bond is experimentally detected in organic solvent in those systems [34,35] where activated C-H bonds, due to the high polarized environment, are observed [27,36-39]. To the

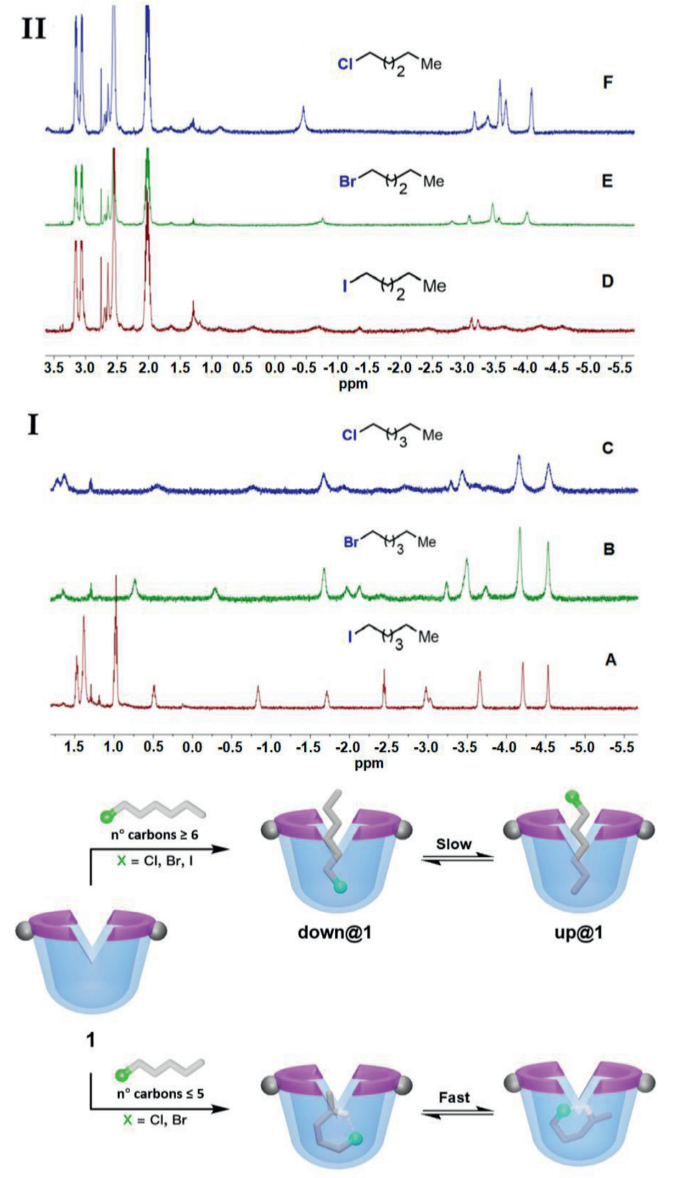

Fig. 3. (Top I) Partial spectra of host-guest complex between **1** (1 mmol/L in 500 µL) and **1** equiv. (host:guest = 1:1) of (A) **3**; (B) **11** and (C) **17**. (Top II) Partial ^1H NMR (600 MHz, D_2O, 305 K) spectra of host-guest complexes between **1** (1 mmol/L in 500 µL) and 1 equiv. (host:guest = 1:1) of (D) **2**; (E) **10** and (F) **16**. (Bottom) Cartoon and involved equilibrium for alkylhalides@**1**.

best of our knowledge, no evidences are reported to support the presence of intramolecular CH hydrogen bonds for non-activated compounds such as hydrocarbons or their derivatives (*i.e.*, alkyl halides).

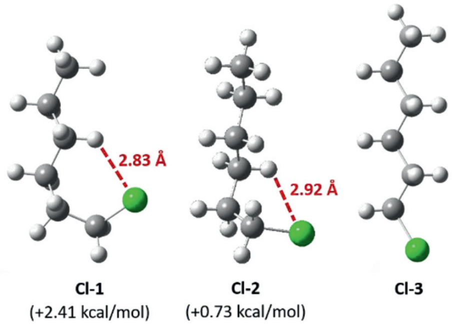

Fig. 4. Structures of most stable conformers, calculated at B3LYP/6–311G(d,p) level of theory in gas phase for guest **17**. CH···Cl distance is reported in red for bent conformers (**Cl-1** and **Cl-2**) while ΔE with respect to linear conformer (**Cl-3**) is reported in parentheses.

Theoretical studies at DFT level of theory (details in Supporting information) on linear alkyl halides reveal how C-H hydrogen bond may be possible in alkyl halides (Fig. 4). Hexyl bromide **11** and chloride **17** have been taken as model alkyl halides for this study. Bent conformer **Cl-1** shows a relative high ΔE (+2.41 kcal/mol) with respect to linear conformer **Cl-3**, leading to exclude its formation in the cavity. Instead, conformer **Cl-2** appears to be more plausible, showing a ΔE of +0.73 kcal/mol (Fig. 4). *Gauche-gauche* interactions are less dominant in **Cl-2** with respect to **Cl-1** while relatively stronger C-H hydrogen bond is observed, due to the higher polarizability of the involved C-H bonds (Fig. 4 and Fig. S91 in Supporting information). Similarly, ΔE of +2.82 kcal/mol and +0.79 kcal/mol have been calculated for conformers **Br-1** and **Br-2** respectively, with respect to linear **Br-3** (Fig. S92 in Supporting information). Moreover, CH···X distances in the bent conformers of 1-chlorohexane (**Cl-1** and **Cl-2** in Fig. 4) and 1-bromohexane (**Br-1** and **Br-2**, Supporting information) have been found shorter compared to the sum of the van der Waals radii that is 3.15 Å and 3.40 Å for **17** (1-chlorohexane) and **11** (1-bromohexane), respectively (Supporting information for details), confirming the importance of the intramolecular CH hydrogen bonds in the stabilization of *gauche* conformers [40]. Bent orientation in **1** and potential C-H hydrogen bond(s) are experimentally confirmed by ^1H NMR spectra and $\Delta\delta$ calculations on bromide **9** (1-bromobutane) and chloride **15** (1-chlorobutane) (Figs. S65-S68). In the light of these results, bound iodide **2** (1-iodopentane), due to the bigger size of the halogen atom and less polarized C-X bond, shows lower affinity for the "bent orientation" (stabilized by C-H hydrogen bonds), leading it to adopt a linear orientation in **1** where dispersion forces are predominant and maximize for iodides. Instead, pentyl bromide **10** and chloride **16**, due to the relative smaller size of the halogen atom, minimize the cost of the *gauche-gauche* interactions, favoring the "bent orientation". Moreover, more polarized C-X bond (I < Br < Cl), observed in chlorides and bromides with respect to iodides, increases the contribution of intramolecular C-H hydrogen bond, leading to further stabilize the "bent orientation" in **1**.

Further calculations on **16@1** in gas phase show a stabilization energy of −2.67 kcal/mol with respect to the isolated systems (Fig. S95A in Supporting information), while positive value (>0 kcal/mol) is found for bromide **10** (Fig. S95B in Supporting information), highlighting a lower affinity for the cavity as pointed out by more broadened peaks for bound bromide **10** in **1** with respect to chloride **16** (Figs. 3E and F). NMR titrations of chloride **16** (1-chloropentane) with **1** showed a K_A of 262 L/mol (Fig. S90) while K_A lower than 200 L/mol is found for iodide **2** (1-iodopentane) (Fig. S89), confirming the higher affinity toward the more water-soluble alkyl chlorides with respect to alkyl iodides (Table S4). Also, direct competition of pentyl iodide **2** and chloride **16** in a solution of **1** definitively showed higher affinity for alkyl chloride, leading to a selectivity for chloride **16** close to 70% determined by NMR spectroscopy (Figs. S83 and S84 in Supporting information). This is the first time that a reverse selectivity has been detected in water for alkyl halides (RCl > RBr > RI) in open-ended containers (Fig. 5).

In summary, higher affinity for alkyl iodides than the respective bromides or chlorides was observed for guest (n° carbons ≥ 6) bound in **1**. This behavior is extreme for longer guests (n° carbons > 8) in which only alkyl iodides are taken up, showing a linear orientation confirmed by $\Delta\delta$ calculations. Unexpectedly, reverse affinity in **1** (RI < RBr < RCl) is instead observed for short

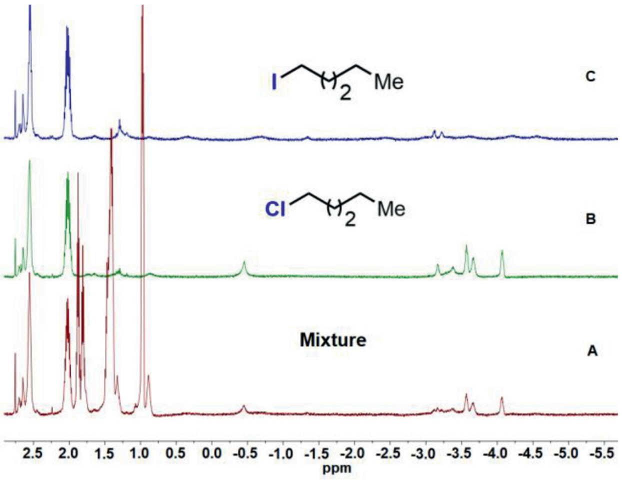

Fig. 5. Partial ^{1}H NMR (600 MHz, D_2O, 305 K) spectra of host-guest complex between host **1** (1 mmol/L in 500 µL) and 2 equiv. of (A) mixture of **2** and **16** (guest ratio 1:1 and host/guest = 1:2), (B) **16** and (C) **2**.

alkyl halides (n° carbons < 6) in which size and polarizability of the C-X bond promote intramolecular C-H hydrogen bond that is maximized in alkyl chlorides, leading to promote a "bent orientation" in **1**. Finally, competitive binding in presence of alkyl iodides in host **1** confirmed rare selectivity toward the more water-soluble alkyl chlorides. We believe, this study points out the importance and effect of subtle forces in lipophilic pockets on molecular recognition and binding selectivity in water, higlighting for the first the role of C-H hydrogen bonds in non-activated aliphatic derivatives.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107834.

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