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Halogen-Bonded Supramolecular Capsules in the Solid State, in Solution, and in the Gas Phase

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In memory of José Barluenga

Abstract: *Supramolecular capsules were assembled by neutral halogen bonding (XB) and studied in the solid state, in solution, and in the gas phase. The geometry of the highly organized capsules is shown by an X-ray crystal structure which features the assembly of two XB hemispheres, geometrically rigidified by H-bonding to eight MeOH molecules and encapsulation of two benzene guests. To enhance capsular association strength, tuning the XB donor is more efficient than tuning the XB acceptor, due to desolvation penalties in protic solvents, as shown for a tetraquinuclidine XB acceptor hemisphere. With a tetra(iodoethynyl) XB donor and a tetralutidine XB acceptor, the association in deuterated benzene/acetone/methanol 70:30:1 at 283 K reaches* $K_a = (2.11 \pm 0.39) \times 10^5\ \text{M}^{-1}$ *(*$\Delta G = -6.9 \pm 0.1$ *kcal mol*$^{-1}$*). The stability of the XB capsules in the gas phase was confirmed by electrospray ionization mass spectrometry (ESI-MS). A new guest binding site was uncovered within the elongated iodoethynyl capsule.*

Since the first covalent container molecules were introduced by Cram et al. in 1985,[1] different interactions, such as hydrogen bonding,[2] coordinative bonds,[3] ionic interactions,[4] and only recently halogen bonding,[5] have been employed to construct supramolecular capsules.[6] Halogen bonding (XB) is the attractive non-covalent interaction between the electrophilic site of a bound halogen atom and a Lewis base.[7] Supramolecular architectures based on XB interactions have evolved over the recent years in crystal engineering,[8] supramolecular materials,[9] in the construction of rotaxanes,[10] catenanes,[11] macrocyclic hosts,[12] helical foldamers,[13] anion receptors,[14] and catalysts.[15] XB has also become an important tool in medicinal chemistry to develop more active and selective ligands.[16] Recently, we reported on the first example of a XB capsule in solution (**1**···**2**, Figure 1).[5c] XB donor **1** and XB acceptor **2** were constructed from resorcin[4]arene cavitands and assembled to form XB capsule **1**···**2** with a substantial association constant of $K_a = 5370\ \text{M}^{-1}$ ($\Delta G = -4.85$ kcal mol^{-1}), despite the use of XB-competitive solvents, such as deuterated benzene/acetone/methanol 70:30:1 at 283 K.

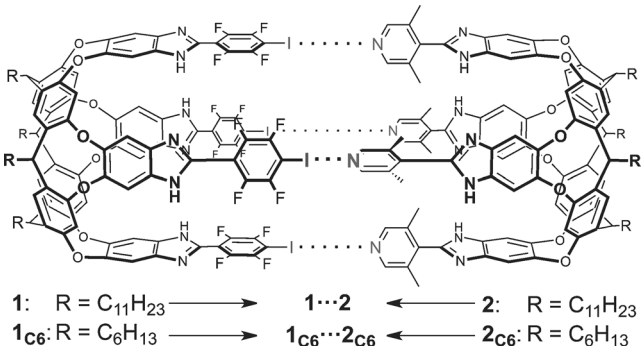

Figure 1. Halogen-bonded supramolecular capsules. **1**···**2** (R = *n*-undecyl) studied in solution[5c] and in the gas phase. $\mathbf{1_{C6}}\cdots\mathbf{2_{C6}}$ (R = *n*-hexyl) studied in the solid state.

Herein, we report a study of XB capsules in the solid state, in solution, and in the gas phase. Each phase reveals different aspects of the fourfold XB through the use of complementary analytical techniques, such as single-crystal X-ray crystallography, NMR binding studies, and electrospray ionization mass spectrometry (ESI-MS), in addition to structural variations of the XB donor and acceptor motifs.

X-ray analysis of dimeric XB capsules is challenging as it is often difficult to obtain suitable single crystals necessary for high quality crystallographic data on supramolecular complexes beyond a molecular weight of approximately 2,000 g mol^{-1}.[5a,e,17] Multicomponent ionic XB architectures with different XB linker units have been reported,[5b,d,18] however, no discrete, neutral, halogen-bonded dimeric capsule has been resolved by X-ray analysis until now. Suitable crystals were obtained for $\mathbf{1_{C6}}\cdots\mathbf{2_{C6}}$, an analogue of **1**···**2** with shorter side chains, by slow vapor diffusion (26 days) from a benzene/MeOH/CS_2 solvent system. The solid state structure (*C*2/*c*, Figure 2) depicts a remarkably ordered 12-components assembly [(benzene⊂$\mathbf{1_{C6}}$·4 MeOH)]···[(benzene⊂$\mathbf{2_{C6}}$·4 MeOH)] with a molecular weight of 4492 g mol^{-1}.

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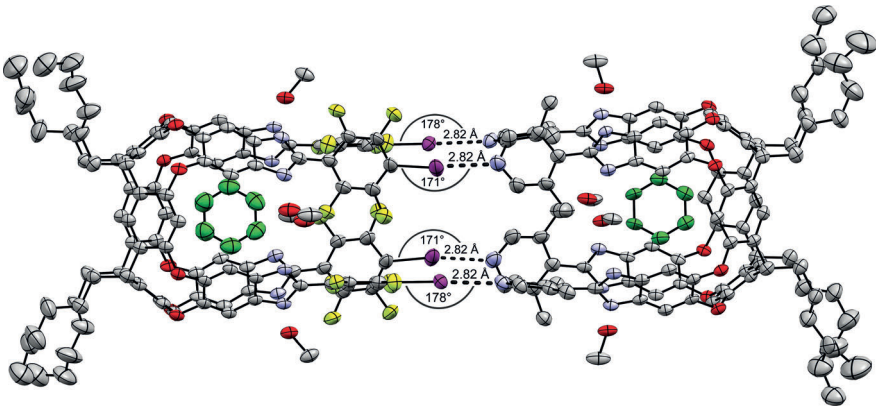

Figure 2. Single-crystal X-ray structure of XB capsule $\mathbf{1}_{C6}\cdots\mathbf{2}_{C6}$. The supramolecular assembly consists of twelve individual components: donor hemisphere $\mathbf{1}_{C6}$, acceptor hemisphere $\mathbf{2}_{C6}$, each encapsulating one benzene molecule (green), and each cavitand is rigidified by four MeOH molecules. ORTEP ellipsoids are set at 40% probability at 100 K. C_{host} gray, N blue, O red, I purple, F yellow, C_{guest} green.[19]

The capsular geometry is in agreement with our initially predicted model obtained by density functional theory (DFT) calculations.[5c] The two XB donor and acceptor hemispheres undergo head-to-head assembly as earlier determined in our solution studies by ^{19}F NMR titrations and 2D-HOESY NMR experiments.[5c] The four halogen bonds have a length of d(I···N) = 2.82 Å and are shorter than the sum of the van-der-Waals radii of the interacting atoms by about 20%. The C–I···N angles are nearly linear (2 × 171°, 2 × 178°), as expected for the strongly directional XB interactions. Each hemisphere complexes one benzene guest deep inside the resorcin-[4]arene scaffold and each hemisphere is stabilized by four MeOH solvent molecules bridging the benzimidazole walls of the cavitand by a circular hydrogen bonding array, as initially shown by Rebek and co-workers.[20] The central unit of capsule $\mathbf{1}_{C6}\cdots\mathbf{2}_{C6}$ is unable to bind guest molecules owing to the intrusion of the aromatic units into the cavity (see the Supporting Information, Figure S3). Independently, Sure and Grimme calculated detailed structural features of this XB capsule by applying optimized D3-dispersion methods to DFT calculations (2% deviation in the d(N···I) distances, see the Supporting Information, Section S3).[21]

The capsular assembly is solely based on fourfold halogen bonding and provides a platform to investigate XB in solution with the aim of exploring the upper limit of XB association constants and to uncover new aspects of that interaction in solution. To investigate the influence of different XB donor and acceptor motifs, we introduced two distinct structural changes from the original XB capsule **1**···**2** with the intention of enhancing association between the hemispheres. The weakly Lewis basic lutidyl moieties of the XB acceptor cavitand **2** were exchanged with quinuclidyl residues, one of the strongest organic XB acceptor motifs known,[22] to afford tetraquinuclidyl cavitand **3** (Figure 3A; for synthetic details, see the Supporting Information, Section S2). The vertical fourfold alignment of the nitrogen atoms was confirmed by an X-ray crystal structure of **3** (Figure 3C). Synthetic incorporation of quinuclidyl derivatives into XB acceptor scaffolds had not been achieved before, despite their attractive XB abilities.[23]

We further intended to strengthen the XB ability of the XB donor hemisphere **1** by installing iodoethynyl(tetrafluorophenyl) moieties to afford hemisphere **4** (Figure 3A). (Iodoethynyl)benzene derivatives exhibit superior XB donor abilities in solution[15d,22c,24] and in the solid state.[25] In fact, pentafluoro(iodoethynyl)benzene···quinuclidine is among the strongest neutral monodentate XB pair in solution ($K_a = 117\ M^{-1}$, cyclohexane, 298 K).[22c] Initial calculations further suggested that the modifications outlined above might increase the binding Gibbs energies of the altered capsule dramatically.[21] Binding experiments to determine K_a for capsule **1**···**3** by ^{19}F NMR binding titration revealed a—for XB interactions unprecedented—slow exchange process relative to the ^{19}F NMR time scale (in deuterated benzene/acetone/methanol 70:30:1, 283 K). When **3** was added to a solution of **1**, a new set of ^{19}F NMR signals for the capsular complex **1**···**3** emerged (Figure 3B) and the association constant was determined to an unexpectedly modest value of $K_{a,\mathbf{1}\cdots\mathbf{3}} = (1.03 \pm 0.11) \times 10^4\ M^{-1}$ ($\Delta G = -5.3 \pm 0.1$ kcal mol^{-1}, see the Supporting Information, Section S4). ^{19}F Diffusion-ordered NMR spectroscopy (DOSY)[26] confirmed the presence of **1**···**3** by a significantly lower diffusion constant relative to single cavitand **1** (see the Supporting Information, Table S12). As we initially hoped to substantially strengthen the XB association with **1**···**3** as compared to **1**···**2**, we turned to analyze the enthalpy–entropy compensation for the binding process by van't Hoff analysis. The formation of capsule **1**···**3** is enthalpy-driven with an unexpectedly low binding enthalpy of $\Delta H = -5.0$ kcal mol^{-1} and a nearly vanishing entropy ($\Delta S \approx 0$ kcal mol^{-1} K^{-1}). This situation is in marked contrast to the thermodynamic profiles of neutral XB interactions,[22c,27] such as in the complexation of **1**···**2** with a larger binding enthalpy of $\Delta H = -12.6$ kcal mol^{-1} and a compensating entropic penalty of $T\Delta S = -7.8$ kcal mol^{-1} (same solvent and same temperature).[5c]

The X-ray analysis of **3** revealed the origin of the slow complexation on the ^{19}F NMR time scale and the modest increase in capsular stability despite the much stronger XB acceptor moiety. The crystal structure ($P\bar{1}$) shows a 10-component assembly consisting of cavitand **3** solvated by eight ordered MeOH molecules and an enclosed benzene molecule. Four of the MeOH molecules participate in the mentioned circular H-bonding array, stabilizing the conformation of the benzimidazole cavity walls. The other four solvate the strongly H-bond-accepting quinuclidine N-atoms (d(O···N) = 2.7–2.8 Å; Figure 3C). The energy barrier for the desolvation of these N-atoms upon capsule formation is substantial and leads to the observed slow exchange kinetics on the NMR time scale.

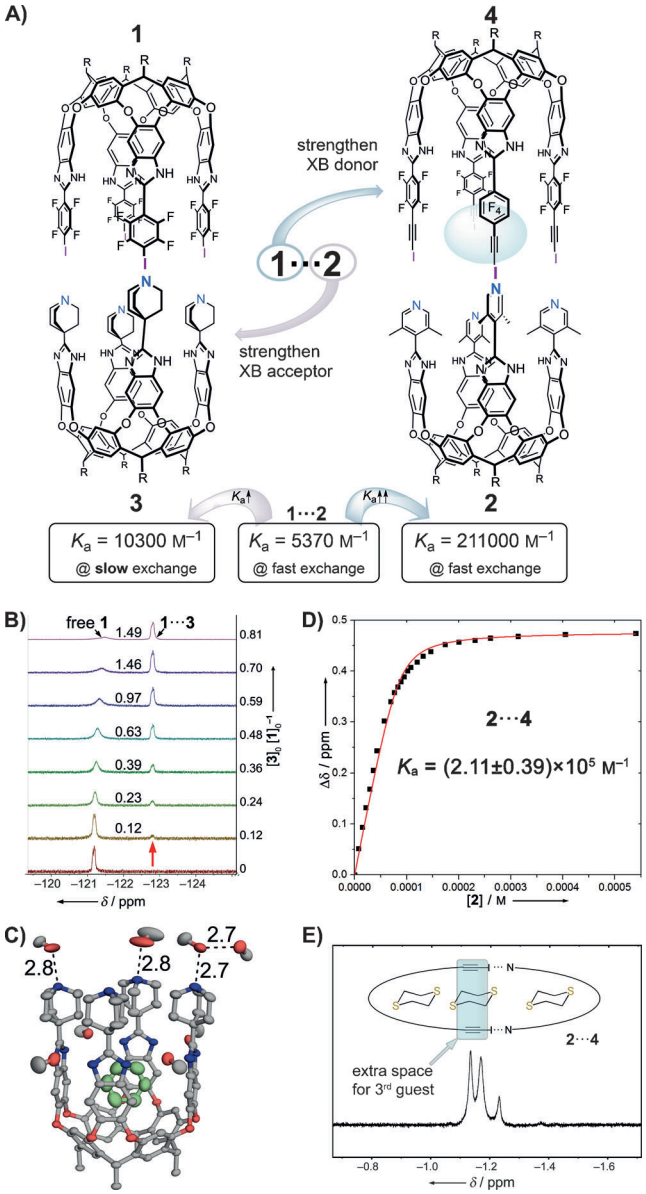

Figure 3. A) Structural tuning of the XB hemispheres in capsule **1**···**2** to tetraquinuclidyl cavitand **3** and to tetra(iodoethynyl) cavitand **4**. The binding constants K_a of the corresponding capsules **1**···**3**, **1**···**2**, and **2**···**4** are given in the boxes (all in $C_6D_6/(CD_3)_2CO/CD_3OD$ 70:30:1, 283 K). B) ^{19}F NMR spectra of **1** ($c_0 = 1.024$ mM) with increasing amounts of added component **3**. Determination of K_a by integration ratios *bound*/*free* (inset values) at slow exchange rates. C) X-ray crystal structure of **3** in complex with benzene and showing eight ordered MeOH solvent molecules, with four of them solvating three of the strongly basic quinuclidyl moieties. The front residue is not solvent-exposed owing to its shielded position in the crystal packing; distances in Å.[19] D) ^{19}F NMR binding titration of **4** with **2**. The complexation-induced change of chemical shift of the signals for the F atoms *ortho* to the iodoethynyl substituents is plotted (c_0(**4**) = 85.5 μM) and fitted to a 1:1 isotherm. E) ^{1}H NMR spectrum of 1,4-dithiane encapsulated in **2**···**4** in [D_{12}]mesitylene (+2% 3,5-dimethylbenzyl alcohol) at 283 K. The iodoethynyl capsule **2**···**4** hosts one additional guest (turquois marked area) compared to **1**···**2** or **1**···**3**.

The moderate, only twofold increase in stability of capsule **1**···**3** compared to **1**··**2** is largely because the strong quinuclidine···MeOH N···HO H-bonds are exchanged by strong N···I halogen bonds, yielding only a moderate enthalpy gain for capsule formation. Gratifyingly, the release of the quinuclidine-bound MeOH molecules into bulk solvent fully compensates for the entropy losses upon capsular assembly. The multidentate XB of highly preorganized hemispheres to capsules thus provides unique insight into solvent effects on the assembly in the presence of competitive solvents.[27] Theoretical Gibbs energy predictions overestimated the binding strength for **1**···**3** ($\Delta G_{theo} = -9.6$ kcal mol^{-1}),[21] probably due to limitations on including explicit solvent molecules.

We anticipated that solvent would be less competitive in the formation of tetra(iodoethynyl) capsule **2**···**4**. Indeed, the ^{19}F NMR binding titration of **4** with **2** occurred at fast exchange kinetics and provided a greatly enhanced XB association, with an association constant of $K_{a,\mathbf{2}\cdots\mathbf{4}} = (2.11 \pm 0.39) \times 10^5$ M^{-1} ($\Delta G = -6.9 \pm 0.1$ kcal mol^{-1}) in deuterated benzene/acetone/methanol 70:30:1, 283 K (Figure 3D). To our knowledge, this is the highest binding constant reported for any neutral organic XB system and can be largely attributed to the strong XB donor ability of the iodoethynyl moieties.

All attempts to characterize the hypothetically strongest iodoethynyl···quinuclidyl XB capsule **3**···**4** by NMR binding titration resulted so far in either precipitation of the material or degradation. The degradation could occur presumably by alkyne de-iodination via iodine transfer to the quinuclidyl N-atom, followed by protic degradation pathways.

ESI-MS experiments were selected as a mild method to characterize the presence and stability of XB capsules in the gas phase.[28] Obtaining ESI-MS signals from neutral XB capsules remained unsuccessful in both the positive and negative ionization mode. As the capsule was shown to host six-membered aromatic and heteroaliphatic guests, *N*-methylpyridinium was chosen as a permanently charged guest to charge-tag[28a,d] the halogen-bonded capsules. Positive-mode electrospray ionization of equimolar solutions of XB capsules **1**···**2**, **1**···**3**, and **2**···**4** with *N*-methylpyridinium tosylate guest **G**·OTs resulted in mass spectra showing the intact heterodimeric capsules with one bound guest **G** as singly charged ions [**G**@(**1**···**2**)]$^+$, [**G**@(**1**···**3**)]$^+$, and [**G**@(**2**···**4**)]$^+$ at *m*/*z* 4733, 4749, and 4830, respectively (Figure 4). Exact masses and isotopic patterns match those calculated. No homodimeric complexes were observed indicating that the heterodimeric capsules are indeed formed due to specific XB interactions of the different cavitand hemispheres (see the Supporting Information, Section S6).

To further explore the guest affinity of **1**···**3** and **2**···**4** in solution, we studied 1,4-dioxane and 1,4-dithiane as guests.[2c,29] As a solvent system, we chose the reported [D_{12}]mesitylene with 2% of 3,5-dimethylbenzyl alcohol at 283 K to compare new binding data of capsules **1**···**3** and **2**···**4** with the reported capsule **1**···**2** (see the Supporting Information, Section S5).[5c]

Guest binding rates are slow on the ^{1}H NMR time scale and encapsulation of guests is indicated by a large upfield shift of the ^{1}H NMR resonances into the negative ppm range. XB capsule **1**···**3** binds two molecules of 1,4-dioxane. Each 1,4-dioxane guest tumbles in the cavity at fast rates and each gives

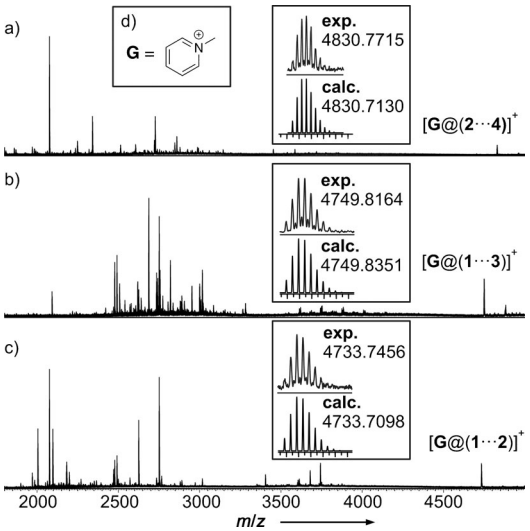

Figure 4. ESI-Q-TOF-HRMS spectra of host–guest complexes of XB capsules a) **2**···**4**, b) **1**···**3**, c) **1**···**2** with d) *N*-methylpyridinium (**G**; 10–100 μM in CH_2Cl_2 plus 3–5% MeOH), and experimental and calculated isotopic patterns (inset). For a detailed discussion of non-labeled signals, see the Supporting Information.

rise to a singlet in the negative ppm region ($\delta_H = -0.72$ ppm and -0.76 ppm) of the ^{1}H NMR spectrum with a total Gibbs binding energy of $\Delta G = -(12.2 \pm 1.2)$ kcal mol^{-1}. Similarly, two 1,4-dithiane guests bind to **1**···**3** with $\Delta G = -(10.9 \pm 1.1)$ kcal mol^{-1}, in agreement with guest binding in **1**···**2** ($\Delta G = -7.5$ and -11.6 kcal mol^{-1} for 1,4-dioxane and 1,4-dithiane, respectively).[5c] When Sure and Grimme explored the inner space of capsule **1**···**2** by quantum chemical methods, a third guest binding site was found near the iodophenyl residues in **1**, which appeared to be significantly less favorable compared with the deeply buried binding sites of the bridged resorcin[4]arene scaffolds.[21] With the incorporation of the capsule-elongating ethynyl units in tetra(iodoethynyl) cavitand **4**, this binding site becomes accessible to a third molecule. Binding of three 1,4-dithiane guests inside the XB capsule **2**···**4** was inferred by three ^{1}H NMR signals in the negative ppm region (Figure 3E). The overall Gibbs binding energy for three 1,4-dithianes amounts to $\Delta G = -(15.3 \pm 1.5)$ kcal mol^{-1}. The additional third binding site is a result of the XB capsule assembly and has not been observed with the monomeric cavitand hemispheres **1**–**4** in solution; only the X-ray crystal structure of **1** showed two benzenes inside the cavitand hemisphere **1**.[5c] When 1,4-dioxane—a guest known to bind weaker to each hemisphere than its thio analogue—was employed in the same encapsulation experiment with **2**···**4**, the third binding site was only partially filled with guest molecules, indicated by a small third ^{1}H NMR signal besides two intense guest signals. The third binding site is only occupied after the deeply buried cavities are saturated and requires strongly binding guests to be filled.

In summary, we present a comprehensive study of halogen-bonded capsules by complementary analytical methods comprising of X-ray crystallography in the solid state, NMR binding titrations in solution, and ESI-MS in the gas phase. The first X-ray crystal structure of a neutral dimeric XB capsule evidenced a fourfold XB geometry between the two hemispheres and encapsulation of two benzene guests. Two novel structural modifications of the XB donor and acceptor motif uncovered large solvent effects on XB capsule formation. The quinuclidyl residues in the free hemisphere **3** are strongly solvated by MeOH molecules undergoing OH···N hydrogen bonding. As a result, the formation of the XB capsule **1**···**3** was found to have a modest association constant in deuterated benzene/acetone/methanol 70:30:1 at 283 K and self-assembly occurs at slow exchange rates on the ^{19}F NMR time scale. In contrast, the tetra(iodoethynyl) cavitand **4** undergoes strong association to the tetralutidyl cavitand **2** ($K_a = (2.11 \pm 0.39) \times 10^5$ M^{-1}) at fast exchange rates. These findings imply for protic solvents that tuning of the XB donor has a greater favorable impact on the strength of XB systems than tuning of the XB acceptor. Through encapsulation of an *N*-methylpyridinium guest as charge-tag, ESI-MS experiments further verified the presence of XB capsules in the gas phase. Guest binding in solution showed Gibbs binding energies down to $-(15.3 \pm 1.5)$ kcal mol^{-1} for three 1,4-dithianes enclosed into the largest capsule **2**···**4**. We expect increased future incorporation of the reported XB motifs in supramolecular architectures and the use of multidentate XB to create efficient binding sites for molecular recognition, transport, and supramolecular catalysis.

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Keywords: halogen bonding · host–guest complexation · mass spectrometry · supramolecular capsules · X-ray diffraction

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Communications

VIP

Halogen-Bonded Capsules

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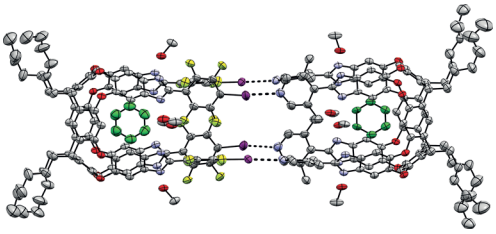
Halogen-Bonded Supramolecular Capsules in the Solid State, in Solution, and in the Gas Phase



We got them all: The geometry of neutral dimeric halogen bonding (XB) capsules is shown by an X-ray crystal structure of a 12-component assembly. The halogen bond donor and acceptor hemispheres were tuned and revealed unprecedented solvent effects, suggesting a new approach for raising the stability of XB assemblies in protic solvents. Stability of the XB capsules in the gas phase was confirmed by ESI-MS.