

# Supramolecular Encapsulation of Tetrahedrally Hydrated Guests in a Tetrahedron Host\*\*

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In memory of George E. Walrafen

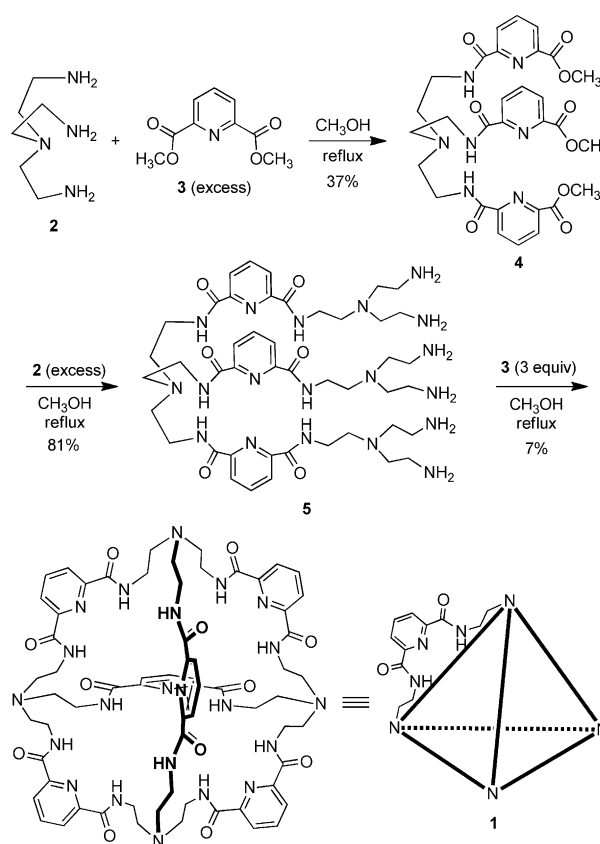
Carefully designed molecular capsules can provide discrete microenvironments capable of trapping targeted guests inside their shielded cavities.<sup>[1]</sup> In so doing, they can stabilize reactive species,<sup>[2]</sup> capture reaction intermediates,<sup>[3]</sup> or collect multiple molecules to study interactions in a cleanroom-like environment.<sup>[4]</sup> While there are reports of elegant tetrahedral capsules based on transition metal frameworks,<sup>[5]</sup> tetrahedral covalent organic capsules comprised of a single molecule are noticeably lacking.<sup>[6]</sup> Herein we describe the synthesis of a tricyclic organic molecular capsule, **1**, that provides an ideal docking site for tetrahedral hydrogen bond coordination. The capsule reproducibly incorporates a tetrahedron of water molecules that holds (solvates) a small guest inside, either a single molecule of water,  $\text{H}_2\text{O} \cdot 4\text{H}_2\text{O} \subset \mathbf{1}$ , or a fluoride ion,  $\text{F}^- \cdot 4\text{H}_2\text{O} \subset \mathbf{1}$ . Essentially, the tetrahedrally positioned bridge-head amine hydrogen bonding sites promote the tetrahedral orientation of the solvation sphere.

Almost 50 years ago Walrafen linked findings from physical data to the structure of the all-important liquid of life, water. He concluded that a very simple pentameric water network could account for many of the observed features in the Raman spectra.<sup>[7]</sup> The five-molecule unit, the “Walrafen pentamer”, takes advantage of the somewhat obvious four hydrogen bonding sites of a central water molecule through tetrahedral coordination to surrounding waters. This simple pentamer also represents the basic structure for solid water phases  $\text{I}_h$  and  $\text{I}_c$ , the two most common forms of ice, and probably for liquid water.<sup>[8]</sup> Since then, many groups have targeted the enigmatic water molecule, often focusing on small water clusters in order to model the more elusive structure of bulk water.<sup>[9,10]</sup> Recently, an elegant example of a lone water molecule in the fullerene  $\text{C}_{60}$  was reported.<sup>[11]</sup> However, such a tetrahedral array for a discrete pentamer cluster enclosed in a capsule-like host,<sup>[12,13]</sup> has not previously been observed.

Along a similar vein, the structural aspects of the aqueous solvation of molecules and ions have also spurred considerable curiosity. Ions are especially of interest because the

electrostatically generated molecule–ion interactions can compete with or add to the normally weaker hydrogen bond associations. Among other applications, a more quantitative assessment of these phenomena can lead to a better understanding of the complexities of ion transport. Anion–water interactions have been less extensively studied, with the exception perhaps of aqueous clusters with halides  $\text{X}^- \cdot n\text{H}_2\text{O}$ .<sup>[14–16]</sup> Herein is reported an excellent dual-purpose model for both water and anion–water interactions, that has been captured in the crystalline state within the cleanroom-like environment of an organic capsule.

The host **1** was synthesized by a simple three-step strategy (Scheme 1). Tris(2-aminoethyl)amine (**2**) was reacted with excess dimethyl 2,6-pyridinedicarboxylate (**3**) to give fragment **4**, which was further reacted with excess **2** to produce **5**. The final completion of the tetrahedron was achieved upon reacting **5** with three equivalents of **3**. The tetrahedron **1** was



Scheme 1. Synthesis of the covalent organic tetrahedral cage **1**.

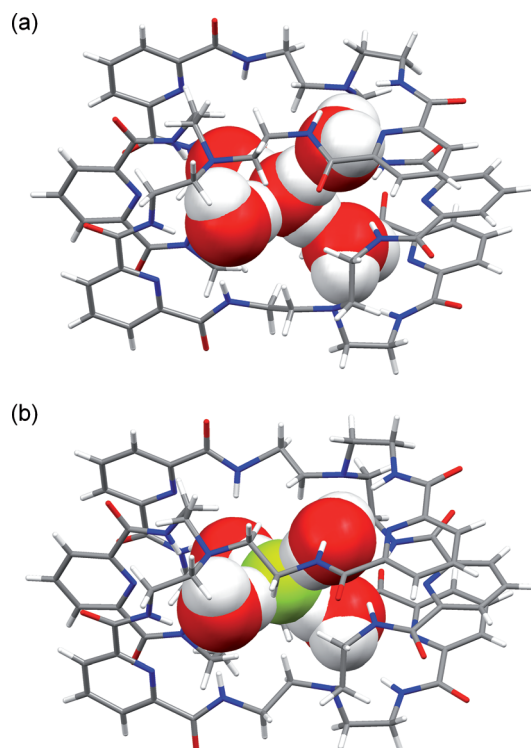
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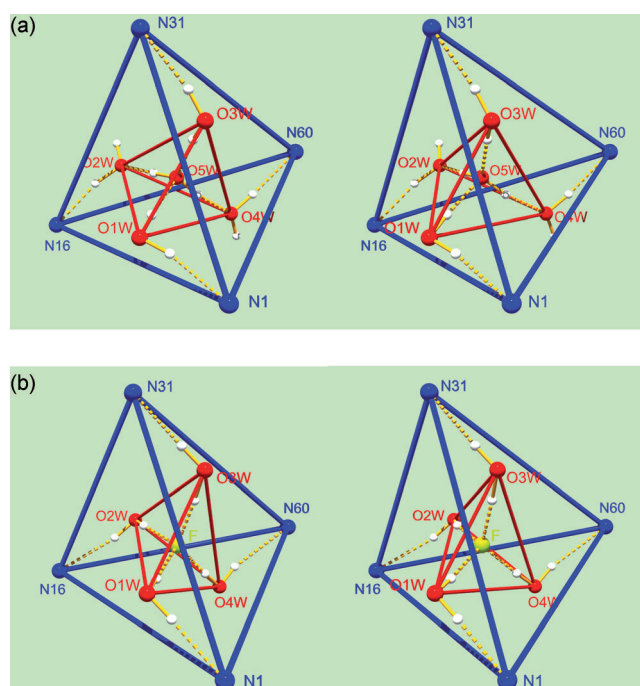
fully characterized by mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy, as well as by X-ray crystallography. Single crystals for the two complexes,  $[\text{H}_2\text{O} \cdot 4\text{H}_2\text{O} \subset \mathbf{1}] \cdot 10\text{H}_2\text{O} \cdot \text{CH}_3\text{CN}$  and  $[\text{F}^- \cdot 4\text{H}_2\text{O} \subset \mathbf{1}] \cdot \text{Me}_4\text{N}^+ \cdot 4\text{H}_2\text{O}$ , were obtained by slow evaporation of an acetonitrile solution of **1** in the presence of excess  $\text{Et}_4\text{N}^+\text{Cl}^-$  and  $\text{Me}_4\text{N}^+\text{F}^-$ , respectively. High-quality X-ray data allowed the location of all of the hydrogen atoms for both encapsulated clusters.

In the structure of the water pentamer, the five-molecule cluster is entirely encapsulated inside the tetrahedral host (Figure 1a), with additional solvent molecules outside the



**Figure 1.** Crystal structures showing encapsulation of the tetrahedral clusters within the tetrahedral cage **1**. a)  $\text{H}_2\text{O} \cdot 4\text{H}_2\text{O} \subset \mathbf{1}$ , b)  $\text{F}^- \cdot 4\text{H}_2\text{O} \subset \mathbf{1}$ . The  $\text{Me}_4\text{N}^+$  counterion in (b) and solvent molecules outside the cavity in (a) and (b) are omitted for clarity. O, red; F, green; N, blue; C, gray; H, white.

cavity. The central water molecule,  $\text{H}_2\text{O}(5\text{w})$ , forms four hydrogen bonds, two acceptor and two donor, as predicted in Walrafen's model (Figure 2a). The hydrogen bonding distances ( $\text{O} \cdots \text{O}$ ) range from 2.649 to 2.751 Å (Table 1a). The  $\text{O}-\text{O}-\text{O}$  angles around the central water molecule range from 78.6 to 133.3°, indicating a distorted tetrahedral array. As predicted by Walrafen, no hydrogen bond interactions exist between the four surrounding water molecules ( $\text{O}-\text{O}$  distances range from 3.480 to 4.952 Å; Table 1b). However, each water molecule has three additional hydrogen bonds to the host. For  $\text{O}2\text{w}$  and  $\text{O}4\text{w}$ , two  $\text{OH} \cdots \text{N}$  bonds are formed, one with the tertiary amine and one with the pyridine, and one  $\text{O} \cdots \text{HN}$  bond with an amide. For  $\text{O}1\text{w}$  and  $\text{O}3\text{w}$ , two  $\text{O} \cdots \text{HN}$  bonds are formed with amides and one  $\text{OH} \cdots \text{N}$  bond with the



**Figure 2.** Stereoviews of the tetrahedral clusters a)  $\text{H}_2\text{O} \cdot 4\text{H}_2\text{O}$  and b)  $\text{F}^- \cdot 4\text{H}_2\text{O}$  with the hydrogen bonding network for both tetrahedral coordination spheres, the four water molecules (red lines), and the four bridgehead amines (blue lines).

**Table 1:** Geometrical parameters [Å, deg] for  $\text{H}_2\text{O} \cdot 4\text{H}_2\text{O} \subset \mathbf{1}$  and  $\text{F}^- \cdot 4\text{H}_2\text{O} \subset \mathbf{1}$ .<sup>[a]</sup>

|  | H <sub>2</sub> O·4 H <sub>2</sub> O⊂1 |          | F <sup>-</sup> ·4 H <sub>2</sub> O⊂1 |          |
|--|---------------------------------------|----------|--------------------------------------|----------|
| a) Hydrogen bond distances and angles to the central H <sub>2</sub> O/F <sup>-</sup> (X) |                                       |          |                                      |          |
|  | O...O5w                               | ∠O—H...O | O...F                                | ∠O—H...F |
| O1w...X  | 2.751                                 | 175.8    | 2.615                                | 169.2    |
| O2w...X  | 2.649                                 | 172.9    | 2.599                                | 160.5    |
| O3w...X  | 2.745                                 | 170.5    | 2.608                                | 176.8    |
| O4w...X  | 2.669                                 | 167.8    | 2.585                                | 176.2    |
| b) Dimensions of the H <sub>2</sub> O tetrahedron  |                                       |          |                                      |          |
|  | O—O                                   | ∠O—O5w—O | O—O                                  | ∠O—F—O   |
| O1w—O2w  | 4.499                                 | 112.9    | 4.741                                | 130.8    |
| O1w—O3w  | 3.480                                 | 78.6     | 3.670                                | 89.3     |
| O1w—O4w  | 4.625                                 | 117.1    | 4.473                                | 118.6    |
| O2w—O3w  | 4.952                                 | 133.3    | 4.282                                | 110.6    |
| O2w—O4w  | 3.799                                 | 91.2     | 3.440                                | 83.2     |
| O3w—O4w  | 4.804                                 | 125.0    | 4.699                                | 129.6    |
| c) Dimensions of 1 <sup>[b]</sup>  |                                       |          |                                      |          |
|  | N—N                                   | ∠N—O5w—N | N—N                                  | ∠N—F—N   |
| N1—N16   | 6.872                                 | 103.5    | 6.927                                | 108.1    |
| N1—N31   | 7.524                                 | 119.0    | 8.066                                | 128.6    |
| N1—N60   | 6.389                                 | 97.7     | 6.754                                | 101.7    |
| N16—N31  | 7.103                                 | 105.6    | 6.286                                | 92.6     |
| N16—N60  | 7.902                                 | 131.3    | 7.472                                | 124.5    |
| N31—N60  | 6.690                                 | 101.2    | 6.966                                | 104.0    |

[a] See Figure 2 for atom labels. [b] Distances between bridgehead tertiary amines and angles involving the central water molecule,  $\text{O}5\text{w}$ , and  $\text{F}^-$ .

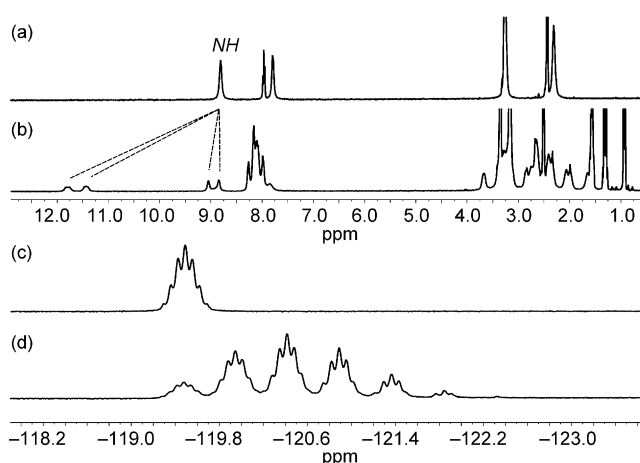
tertiary amine (see Supporting Information). What is clearly important is the formation of the hydrogen bonds with the tertiary (bridgehead) amines of the host ( $\text{O} \cdots \text{N}$ : 2.785, 2.823,

2.838, and 3.051 Å; Figure 2a). This tetrahedral arrangement of bridgehead nitrogen atoms, therefore, appears to play a key role in stabilizing and indeed in promoting the encapsulation of the pentamer. Rather than a perfect tetrahedron, however, the N–N distances are illustrative of a slightly compressed tetrahedron, with the distances between the “base” nitrogen atoms slightly longer (7.1–7.9 Å) compared to the “sides” (6.4–6.9 Å; Table 1c). This encapsulated water cluster is the first example of a discrete tetrahedral water pentamer, i.e., Walrafen’s pentamer, observed crystallographically within a molecular container.

The encapsulated  $F^- \cdot 4H_2O$  complex is isolated as the  $Me_4N^+$  salt, and its geometry is similar to the water pentamer (Figure 1b and Figure 2b). However, because  $F^-$  is a four-hydrogen bond acceptor, the orientation of two of the water molecules is inverted, with O2w and O4w now forming  $OH \cdots F^-$  hydrogen bonds with the central  $F^-$ . As anticipated for  $OH \cdots F^-$  compared to  $OH \cdots O$ , shorter hydrogen bonds are observed (O $\cdots$ F distances range from 2.585 to 2.615 Å, Table 1a). Not surprisingly, therefore, the water coordination shell is pulled more in toward the  $F^-$ . This results in a diminished interaction of the water molecules with the host through hydrogen bonding. Nonetheless, the all-important  $OH \cdots N_{amine}$  hydrogen bonds with the bridgehead nitrogen atoms are all there and range from 2.928 to 2.968 Å. Again, no obvious hydrogen bonding interactions exist between the four surrounding water molecules (Table 1b). The bridgehead amines in the two structures are nearly superimposable and also can be considered as a pseudo-second sphere coordination mode about the  $F^-$ .

In addition to the unusually consistent incorporation of a tetrahedron of water, the two structures exemplify a “freeze frame” capture of the dynamic process of hydrogen bond switching. A fundamental question of importance to both biological and chemical processes is how the process of hydrogen bond making and breaking differs in pure water clusters compared to water–ion interactions. In pure water clusters such as the pentamer, two hydrogen bond donors and two acceptors are anticipated for any of the water molecules, but a single monatomic ion is a four-hydrogen bond acceptor. This switching process is illustrated by the observed reorientation of two of the water molecules in the tetrahedral “solvent” shell from acceptors to donors in the  $H_2O \cdot 4H_2O$  and  $F^- \cdot 4H_2O$  structures, respectively. In aqueous solutions, as opposed to the “frozen” picture in the crystalline state, this dynamic process has been the subject of much interest because water interacts with a multitude of molecular and ionic systems throughout nature.<sup>[17]</sup> We are hoping to shed more light on this process in solution by using advanced  $^{19}F$  and multidimensional NMR techniques and temperature dependence studies, which will be the subject of a future report.

As indicated by  $^1H$  and  $^{19}F$  NMR spectroscopy (Figure 3), the  $F^- \cdot 4H_2O$  cluster is more complex in solution. At room temperature  $F^-$  appears to be held inside the host cavity through direct hydrogen bonding interactions with amide groups. This is evidenced by the splitting of the amide NH singlet signal of the free base into four signals, two doublets downfield, indicating coupling with the fluoride ion, and two



**Figure 3.** a, b)  $^1H$  NMR spectra of **1** (a) and of **1** with equimolar tetrabutylammonium fluoride (TBAF) (b) in  $[D_6]DMSO$ . c, d)  $^{19}F$  NMR spectra of **1** with equimolar TBAF in  $[H_6]DMSO$  (c) and in  $[D_6]DMSO$  (d).

singlets not shifted much from the original amide signal (Figure 3a and b). In non-deuterated  $[H_6]DMSO$ , the complex signal appears as a septet in the  $^{19}F$  NMR spectrum, while in  $[D_6]DMSO$  a stepwise deuterium exchange process results in a series of multiplets (Figure 3c and d).<sup>[18]</sup> Elucidation of the complex deuterium exchange process provides considerable information about the solution structure of the fluoride complex, and the description of the equilibria and also the temperature dependence of binding will be the subject of another paper.

Due to our interest in anion coordination, preliminary anion binding studies of **1** were performed by  $^1H$  NMR titrations in  $[D_6]DMSO$  for the  $nBu_4N^+$  salts of various anions.<sup>[19]</sup> The results show that the tetrahedral cage exhibits the best binding for  $F^-$  and possibly  $H_2PO_4^-$  (Table 2). The latter gives a better curve fit for 1:2 host–anion binding mode, which was also confirmed by Job plot analysis. Attempts to obtain crystal structures of other encapsulated ions, including tetrahedrally shaped ions such as  $HSO_4^-$  and  $H_2PO_4^-$ , have been unsuccessful to date.

**Table 2:** Association constants  $K$  [ $M^{-1}$ ]<sup>[a]</sup> of cage **1** with anions.

| $F^-$      | $Cl^-$ | $Br^-$ | $I^-$ | $AcO^-$ | $HSO_4^-$ | $H_2PO_4^-$              | $NO_3^-$ |
|------------|--------|--------|-------|---------|-----------|--------------------------|----------|
| ca. $10^4$ | 850    | 100    | <10   | 1380    | 70        | 760, 4900 <sup>[b]</sup> | <10      |

[a] In  $[D_6]DMSO$  at room temperature (errors <10%). [b] The stepwise association constant  $K_{11}$  and  $K_{12}$  for the 1:2 L:A binding, respectively.

In summary, a new multicyclic organic host with tetrahedrally arranged bridgehead amines possesses an internal binding site that is selective for tetrahedral clusters of water molecules. Exploration of the chemistry and structure of the new water box **1** reveals at least four exciting findings. First, the dimensions of **1** apparently are perfectly suited to reproducibly encapsulate a tetrahedral cluster of water molecules. We have, to date, isolated four crystals with the same isomorphous structures of the water pentamer or

encapsulated  $F^{-} \cdot 4H_2O$  from independent crystallizations. Second, the internal water capsule can also encapsulate an additional water molecule, resulting in what may be the first crystallographic verification of an isolated water cluster known as Walrafen's pentamer. Further solution studies on these evidently stable basic structural units of a pentameric water cluster may shed light on other physical and chemical properties such as exchange reactions. Third, the acquisition of an isomorphous structure with  $F^{-}$  replacing the central water allows for a closer examination of an isolated aequation sphere of a single halide, providing structural insight to solvation effects. Lastly, the hydrogen bond rearrangement necessitated by switching the internal guest from a neutral  $C_{2v}$  water molecule to a spherical anion allows for examination of the dynamics of hydrogen bond switching within a micro-environment. Further studies are in progress to elucidate the solution structures by using advanced NMR techniques. Taken together these results can impact multiple areas of chemistry and biology by adding to the information base of discrete water structures and solvates.

## Experimental Section

**Tetrahedral cage 1:** 1.47 g (1.5 mmol) of crude product **5** and 0.88 g (4.5 mmol) of dimethyl-2,6-pyridinedicarboxylate were dissolved in 400 mL methanol and heated at reflux for 10 days. Then the reaction mixture was concentrated to remove the solvent and subjected to column chromatography on silica (70–230 mesh, gradient elution 10% to 30%  $CH_3OH$  in  $CH_2Cl_2$  (v/v)) to give 0.14 g (7% yield) **1** as a white solid.  $^1H$  NMR (400 MHz,  $[D_6]DMSO$ ):  $\delta_H$  = 8.83 (s, 12H), 8.00 (t,  $J$  = 7.6 Hz, 6H), 7.82 (s, 12H), 3.36 (s, 24H), 2.39 ppm (s, 24H);  $^{13}C$  NMR (100 MHz,  $[D_6]DMSO$ ):  $\delta_C$  = 163.4, 149.0, 139.7, 124.2, 52.9, 37.6 ppm. Exact mass for  $C_{66}H_{78}N_{22}O_{12} + H^+$  1371.6248, found 1371.6294. Colorless crystals of the complexes,  $[H_2O \cdot 4H_2O \cdot C1] \cdot 10H_2O \cdot CH_3CN$  and  $[F^{-} \cdot 4H_2O \cdot C1] \cdot Me_4N^+ \cdot 4H_2O$ , were grown by slow evaporation of an acetonitrile solution of **1** in the presence of excess  $Et_4N^+Cl^{-}$  and  $Me_4N^+F^{-}$ , respectively. CCDC 838463 and 838464 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

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