Small-Molecule Encapsulation

Release of the Water Molecule Encapsulated Inside an Open-Cage Fullerene through Hydrogen Bonding Mediated by Hydrogen Fluoride

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Abstract: A reversible wetting/dewetting procedure is reported for an open-cage fullerene with an 18-membered orifice. In a homogeneous mixture of $H_2O/EtOH/CHCI_3$, water was encapsulated into the cavity of the open-cage compound quantitatively at 80 °C. Addition of aqueous hydrogen fluoride into the water-encapsulated complex removed the encapsulated water completely at room temperature. H-bonding between the trapped water and fluoride is shown to play a key role for the water release process.

Water in nonpolar cavities has been extensively studied to understand the hydrophobic effect and to explore possible applications.^[1-3] Water in the nonpolar interior channel of proteins has been suggested as the mediator for proton transfer.^[4] Aquaporins transport water across biological membranes selectively through hydrogen-bond-guided water movements.^[5,6] Protons have been shown to move with high mobility along the linear water hydrogen bonds inside a carbon nanotube.^[7] Carbon nanotubes can also act as low-friction conduits for the flow of water.^[8-10] Hydrogen bonding between the trapped water molecules with the interior was observed to stabilize the carbon anion on the cage skeleton.[11] Open-cage [60]fullerenes^[12-14] have been shown to act as molecular containers for a single water molecule.^[15] The molecular nature of opencage fullerenes allows their study in detail with conventional methods such as NMR, MS, and single crystal X-ray diffraction analysis. We have been interested in the preparation and prop-

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erties of open-cage fullerenes.^[16] Herein we report the quantitative encapsulation and removal of a single water molecule in an open-cage fullerene with ethanol and hydrogen fluoride, respectively.

The cavity volume of open-cage fullerene is suited to fill just one water molecule as shown by theoretical calculation^[17] and experimental results.^[18] The size and shape of the opening and functional group(s) on the rim of the opening are the key determining factors for the water encapsulation process.^[15] Water encapsulation easily took place at room temperature with a trace amount of water in the solvent during purification if the opening is large enough and with suitable hydrophilic groups such as carbonyl groups on the rim of the orifice. Heating the open-cage fullerene in a mixture of aromatic solvent and water is usually required if the opening is relatively small. In most cases the encapsulation ratio can only reach around 80%.^[19-21] Murata et al. have achieved quantitative water encapsulation for an open-cage [60]fullerene by heating the compound in toluene/water at 120 °C for 36 h under high pressure (9000 atm).^[19]

Compound **1** was previously characterized by spectroscopic data.^[22] Its single-crystal X-ray diffraction structure (Figure 1) has now been obtained, and it confirmed the previous structure assignment.^[23] The water encapsulation ratio was only around 30% after routine purification procedure owing to its relatively small orifice size. To increase the water content, we



Figure 1. Single-crystal X-ray structure of compound $H_2O@1$. The water encapsulation ratio is 31% as determined by ¹H NMR spectroscopy integration. Ellipsoids are set at 50% probability; hydrogen atoms are omitted for clarity.

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heated its CDCl₃ solution with water at 80 °C. The water encapsulation ratio increased to 80% after 18 h. Heating **1** in a mixture of toluene and water gave similar encapsulation ratio. To further increase the water content, we added some ethanol to the CDCl₃/H₂O mixture to make a homogeneous solution instead of separated CDCl₃ and water phases. The heating process was followed by ¹H NMR, which indicated a quantitative encapsulation after 18 h at 80 °C. The relatively small opening also allowed the detection of the molecular ion signal of H₂O@1. Unlike the presence of both empty and water filled molecular ion signals in partially filled samples, the mass spectrum of the ethanol assisted sample showed only the molecular ion signal of H₂O@1 (Figure 2), in good agreement with the ¹H NMR-derived quantitative water encapsulation.



Figure 2. ESI-HRMS spectra of 1, $H_2O@1$, a mixture of $1 + H_2O@1$ and 2.

A partial removal of the encapsulated water in H₂O@1 can be readily achieved by heating it in a dry solvent or evaporation of its solution under vacuum. Complete removal of the encapsulated water was achieved through an unexpected hydrogen fluoride mediated procedure. In an effort to encapsulate hydrogen fluoride in compound $\mathbf{1}^{\text{\tiny [24]}}$ we treated a mixture of 1 and H₂O@1 with aqueous hydrogen fluoride (Scheme 1). The addition product 2 was produced slowly instead of the expected hydrogen fluoride encapsulation product HF@1. ¹H NMR spectra of 2 showed clearly that there is hardly any detectable signal for trapped water, which should appear in the high-field range above 0 ppm owing to the shielding effect of the fullerene cage. The conversion of 1 into 2 was slow and the reaction usually stopped after around 50% conversion. To make sure that both the empty 1 and water filled $H_2O@1$ can form compound 2, we used three different samples of 1 with 25%, 50%, and 80% water encapsulation ratio, respectively, all of which gave the same yield of 2 without water trapped in the cavity. Compound 2 is not stable and decomposes to empty compound 1 in a few days. Treating 2 with $B(C_6F_5)_3$ eliminates hydrogen fluoride to give empty 1 in 10 min. Trifluoroacetic acid could also convert 2 into 1.



on recovered starting material Yields are quantitative as followed by ¹H NMR

Scheme 1. Reversible water encapsulation and removal processes.

The mass spectrum of **2** (bottom spectrum in Figure 2) showed the monohydrofluoride adduct ion as a weak signal together with empty **1** as the major signals, indicating that the H-bond bound hydrogen fluorides can be eliminated under the ESI-mass spectrum conditions. The ¹H-decoupled ¹⁹F fluorine NMR spectrum (top spectrum in Figure 3) of **2** showed two



Figure 3. ^{19}F NMR spectra of 2 in CDCl3 (470 MHz). Above: ^1H decoupled; below: ^1H coupled.

doublets. The high-field signal at -205.10 ppm is most likely due to the fluorine atom that is well-shielded by the fullerene cage. The ¹H-coupled ¹⁹F fluorine NMR spectrum (bottom spectrum in Figure 3) showed a quartet at -119.25 ppm and an apparent triplet at -205.10 ppm, which are due to coupling to the bridging proton (coupling constants 75 and 157 Hz, respectively) and coupling between the two different fluorine atoms (coupling constant is 157 Hz). The substantial difference of coupling constants between ¹H and the two fluorine atoms is in agreement with the structure assignment for **2**, in which

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the hydrogen is closer to the terminal fluorine atom in the F…H—F moiety.

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In the reaction of 1 and H₂O@1 with aqueous HF to form 2, two unstable species 3 and H₂O@3 could be observed by carrying out the reaction in CDCl₃ and monitoring the progress by ¹H NMR spectrum. As in the ¹H NMR spectrum of 1 and H₂O@1, there is no detectable difference in the range from 0 to 10 ppm between the empty 3 and water-filled H₂O@3 except the trapped water signal. Attempted isolation resulted in its decomposition back to compound 1 and H₂O@1. To confirm the speculation that 3 and H₂O@3 are due to protonation of 1 and H₂O@1, we treated CDCl₃ solutions of 1 and H₂O@1 with various acids, including CF₃COOH, HCl (aqueous), and HCl (gas) (Figure 4). All the acids resulted in a pair of *tert*-butyl sig-



Figure 4. ¹H NMR spectra of reactions between $1 + H_2O@1$ and different acids in CDCl₃ (for full spectra, see the Supporting Information).

nals at 1.35 and 1.25 ppm, which are the same as that of **3** and $H_2O@3$. The extent of protonation is dependent on the acidity of the acid. Weak acids can only result in partial protonation. Quantitative protonation was observed by bubbling HCl gas into the solution. The water encapsulation ratio of **3** remains the same as that of the starting compound **1** in both cases when we treated two samples of **1** with 54% and 13% water encapsulation ratios with different acids separately. This result

indicates that the protonation process does not result in release of the trapped water molecule. Comparison of UV/Vis spectra of $1 + H_2O@1$ and $3 + H_2O@3$ (protonated by HCl gas) showed no significant change except slight increase or decrease in the absorption coefficients.

Whitby et al. have recently successfully inserted hydrogen fluoride into the cavity of an open-cage [60]fullerene by treating the open-cage compound with hydrogen fluoride in pyridine (HF·Py, 70% w/w).^[24] The hydrogen fluoride encapsulation ratio can reach 50%. The ¹H chemical shift of a HF encapsulated open-cage [60]fullerene appears at -6.55 ppm, with a 19 F coupling constant of 508 Hz. Inspired by this result, we treated 1 (30% water encapsulation ratio) in $CDCl_3$ with HF·Py and monitored the reaction by ¹H NMR spectroscopy. As in the above reaction with aqueous hydrogen fluoride, protonation product 3 and H₂O@3 were observed. However, there was no detectable formation of 2 or any other HF addition product, and the water encapsulation ratio of 1 remained unchanged. Therefore, the presence of the basic pyridine inhibits the addition of HF to compound 1. However, when we treated completely empty 1 with HF·Py (70% w/w) at room temperature, we observed four peaks at -7.50, -7.53, -8.52, and -8.74 ppm in the ¹H NMR spectrum. The relative intensities of these four peaks indicate that they are due to two doublets centred at -8.01 ppm (-7.50/-8.52 ppm) and -8.14 ppm (-7.53/-8.74 ppm) with a coupling constant of 506 Hz and 505 Hz, respectively. In light of Whitby's work, we assign these two doublets to the cation HF@3 and HF@1 (Scheme 2), re-



Scheme 2. Encapsulation of hydrogen fluoride in 1.

spectively. The HF encapsulation ratio is around 5% as determined from the integrals. Attempts failed to increase the encapsulation ratio by changing the solvent and the temperature. Density functional theory (DFT) calculations at the M06-2X/6-31G** level of theory indicate that the binding energy of H₂O and HF is -42.39 and -21.31 kJ mol⁻¹ respectively in the equilibrium structures of H₂O@1 and HF@1. The much smaller binding energy of HF is probably responsible for the difficulty in its encapsulation.

Hydrogen bonds with a fluorine atom in organic molecules as the acceptor have been well studied, and controversial evidence has been reported concerning their presence.^[25,26] Recent results strongly support that such organic fluorine

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hydrogen bonds C–F···HX are possible and play an important role in the functional properties of fluoro organic compounds. Paquin et al. have reported that water accelerates alkyl fluoride substitution through hydrogen bonding.^[27] Hydrogen bond like weak interactions were observed between the trapped water molecules and fluorine atoms bound on the inner wall of single wall carbon nanotubes through ab initio molecular dynamics simulations.^[28]

The present hydrogen fluoride assisted removal of trapped water from $H_2O@1$ probably involves fluorine hydrogen bonding as the key step as shown in Scheme 3. Addition of hydro-



Scheme 3. Possible pathway for the hydrogen fluoride assisted release of trapped water in H₂O@1.

gen fluoride to $H_2O@1$ forms the intermediate **A**. The trapped water moves up from the centre of the cavity to form the hydrogen bond with the added fluorine atom analogous to the hydrogen bond in compound 2. Hydrogen fluoride then replaces the "activated water" to form compound 2. The driving force for water to escape the cavity is probably more favourable hydrogen bonding with other water and/or hydrogen fluoride molecules in the solvent.^[29, 30] In hydrogen fluoride solution, the concentration of (HF)₂ is relatively high because the hydrogen bond in HF_2^- is the strongest known hydrogen bond.^[31] In the formation of compound **2**, addition of $(HF)_2$ to H₂O@1 to form intermediate B is also possible. Just like A, B loses the trapped water molecule through the H-bonding assisted process. The DFT M06-2X calculations predict that the energy change for the reaction from H₂O@1 to A and B is 33.57 and 108.05 kJ mol⁻¹, and -14.91 and -105.54 kJ mol⁻¹, in enthalpy and Gibbs free energy, respectively. So, the pathway through intermediate **B** is possible, through **A** is infeasible.

Another possible route for the escape of trapped water from $H_2O@1$ involves acid-catalysed formation of a hydrated ketone moiety between the trapped water molecule with one of the three carbonyl groups on the rim of the orifice. Dehydration of the hydrated ketone moiety then releases the trapped water molecule. This pathway appears unlikely from the HCl protonation experiment shown in Figure 4, in which the encapsulation ratio remained unchanged. To obtain further information

concerning this possibility, we heated 1 in toluene and H_2O^{18} to obtain a mixture of 1 and $H_2^{18}O@1$ in about 20:80 ratio, as shown by an ESI-MS spectrum. Treatment of this mixture with HF and subsequent decomposition with $B(C_6F_5)_3$ gave compound 1 without any ¹⁸O remaining in the molecule. This result indicates that the carbonyl groups in 1 are not involved in the escape of the trapped water molecule. The imino group plays the key role in the hydrogen fluoride assisted removal of trapped water.

In summary, a reversible wetting/dewetting procedure is reported for an open-cage fullerene with an 18-membered orifice. Both the encapsulation and removal processes are quantitative (as determined by NMR spectroscopy) under relatively mild conditions. Addition of ethanol to the organic solvent containing the open-cage compound is shown to facilitate the encapsulation process. The imino group on the rim of the orifice is crucial for the fluorine hydrogen bond based removal of the trapped water molecule. Hydrogen fluoride adds to the imino group, and subsequent fluorine hydrogen bonding with the trapped water activates the water removal process.

Experimental Section

Preparation of H₂O@1: Three drops of water was added to a solution of compound 1 (8.2 mg, 0.0077 mmol) in 5 mL CDCl₃. EtOH was added carefully drop wise into the solution to make a homogeneous solution without the precipitation of compound 1. The resulting solution was stirred at 80 °C in a sealed tube for 14 h. Water (5 mL) was added to the solution and the organic phase was removed under reduced pressure at 30 °C. CDCl₃ (3 mL) was added to the residue, about 1 mL of which was used for ¹H NMR measurement. After the NMR sample was recovered, the solvent was evaporated in vacuo, and the residue was washed by 20 mL hexane 3 times to afford H₂O@1 (8.0 mg, 0.074 mmol, 96%).

2: HF (3 mL, 30% aqueous solution) was added to a solution of compound **1** and H₂O@**1** (28.3 mg, 0.026 mmol) in 8 mL CDCl₃. The resulting solution was stirred at 20 °C for 30 h. The reaction was monitored by both TLC and ¹H NMR spectroscopy. The ¹H NMR sample was poured back into the original reaction system together with 0.5 mL 30% HF. The reaction was stopped with excess aqueous NaHCO₃ and washed with water (5×5 mL). The organic layer was dried over anhydrous Na₂SO₄ and directly chromatographed on silica gel eluting with toluene/ethyl acetate (20:1) to recover the starting material (12.5 mg), then CH₂Cl₂/MeOH (20:1) eluted the product as a red band which was collected and evaporated under 30 °C to give compound **2** (11.4 mg, 0.034, 35%, 72% based on recovered starting material). Yield of **2** was quantitative based on ¹H NMR monitoring.

For details of other procedures and spectroscopic data, see the Supporting Information.

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