Isolation of the simplest hydrated acid

Rui Zhang, Michihisa Murata, Atsushi Wakamiya, Takafumi Shimoaka, Takeshi Hasegawa, Yasujiro Murata*

Dissociation of an acid molecule in aqueous media is one of the most fundamental solvation processes but its details remain poorly understood at the distinct molecular level. Conducting high-pressure treatments of an open-cage fullerene C\textsubscript{70} derivative with hydrogen fluoride (HF) in the presence of H\textsubscript{2}O, we achieved an unprecedented encapsulation of H\textsubscript{2}O·HF and H\textsubscript{2}O. Restoration of the opening yielded the endohedral C\textsubscript{70}S\textsubscript{8}, that is, (H\textsubscript{2}O·HF)@C\textsubscript{70}, H\textsubscript{2}O@C\textsubscript{70}, and HF@C\textsubscript{70} in macroscopic scales. Putting an H\textsubscript{2}O·HF complex into the fullerene cage was a crucial step, and it would proceed by the synergistic effects of “pushing from outside” and “pulling from inside.” The structure of the H\textsubscript{2}O·HF was unambiguously determined by single crystal x-ray diffraction analysis. The nuclear magnetic resonance measurements revealed the formation of a hydrogen bond between the H\textsubscript{2}O and HF molecules without proton transfer even at 140°C.

INTRODUCTION

One of the most important chemical processes is dissociation of a Brønsted acid in aqueous media accompanied by proton transfer from the acid to H\textsubscript{2}O molecules and solvation of the charged fragments (1). This fundamental event plays a key role in myriad chemical reactions and biological phenomena. However, the detailed mechanism of acid dissociation (2, 3) and the nature of protons in an aqueous environment (4, 5) are rather complex, and still remain to be revealed at the distinct molecular level. Hydrogen fluoride (HF) is the smallest acid and has been studied well, mostly in the gas phase, both theoretically and experimentally (6). One extensively discussed issue on HF is the minimum number of H\textsubscript{2}O molecules that is necessary to solvate an HF molecule resulting in the formation of the solvent-shared ion pair [H\textsubscript{2}O\textsuperscript{+} (H\textsubscript{2}O)\textsubscript{n}F\textsuperscript{-}] (3, 7, 8). However, the central obstacle to resolution of this subject includes the difficulty of preparation of any of the possible HF-(H\textsubscript{2}O)\textsubscript{n} complexes in a pure form with definite components. This is because the high reactivity of HF and the strong hydrogen bond affinity of H\textsubscript{2}O often result in the formation of many types of oligomers, which are in equilibrium with others, rendering their separation and isolation almost impossible (9). To understand this fundamental process, it is highly desirable to construct an ideal system that can elucidate the intrinsic nature of the hydrated HF molecule.

To isolate reactive chemical species, the compounds should be located in an inert atmosphere, preventing interaction and/or reaction from the outer environments. These subnano-sized environments can be found inside fullerenes, which are spherical carbon clusters having a hollow cavity. Very reactive chemical species such as metal ions (10, 11), metal clusters (12), and a nitrogen atom (13) have thus far been encapsulated inside fullerenes. These well-defined supramolecular systems have provided opportunities to study the physical and chemical properties of the encapsulated species at the molecular scale and to use them as functional materials (14). However, selectivity in encapsulated species in addition to fullerene cages are difficult to control because of the reliance of most production methods on harsh conditions (12, 14). In contrast, the “molecular surgery” approach can produce molecule-encapsulating fullerenes with almost-perfect selectivities under mild conditions in solution (15). Using this method, endohedral C\textsubscript{60} encapsulating a single molecule of H\textsubscript{2} (16), He (17), H\textsubscript{2}O (18), and HF (19) was synthesized.

Molecular surgery can also be applied to fullerene C\textsubscript{70} despite difficulties in characterization of products due to low symmetry. Reflecting the larger inner space in C\textsubscript{70} compared to C\textsubscript{60} (20, 21), two small molecules were introduced inside open-cage C\textsubscript{70} derivatives to afford the corresponding doubly encapsulating endohedral C\textsubscript{70}S\textsubscript{8} after restoration of the cage, that is, (H\textsubscript{2}O)\textsubscript{2}@C\textsubscript{70} and (H\textsubscript{2}O)\textsubscript{2}@C\textsubscript{70} (23), respectively. Previously, we reported two open-cage C\textsubscript{70} derivatives, α-13mem (24) and β-13mem (Fig. 1A) (23), both having a 13-membered ring opening with the same functional groups. These compounds were synthesized by a three-step reaction starting from the addition of a pyridazine derivative to the α- and β-bonds of C\textsubscript{70} with total yields of 22% and 2%, respectively. Both openings were enlarged in situ into the 16-membered ring as their C\textsubscript{60} analog (18). The opening of α-16mem is smaller than that of β-16mem, evidenced by the fact that only a trace amount of H\textsubscript{2}O was introduced inside α-16mem, whereas an H\textsubscript{2}O molecule was entrapped almost quantitatively inside β-16mem. Density functional theory (DFT) calculations also supported the smaller size of α-16mem (23). Taking advantage of the efficient synthetic yield of α-13mem, we envisioned that α-13mem would be more suitable as a starting material for novel endohedral C\textsubscript{70}S\textsubscript{8}. Because the size of HF is smaller than that of H\textsubscript{2}O (25), we studied encapsulation of HF into α-13mem with initial intention to synthesize HF@C\textsubscript{70}. Here, we report facile synthesis of HF@C\textsubscript{70} as well as unprecedented formation of (H\textsubscript{2}O-HF)@C\textsubscript{70} and H\textsubscript{2}O@C\textsubscript{70} using α-13mem as a key compound despite the small size of the opening for the insertion of H\textsubscript{2}O.

As shown in Fig. 1B, after optimization of the conditions (vide infra), the high-pressure treatment of α-13mem in the presence of 0.5 equivalence of 70% (w/w) HF in pyridine (HF-Py) (26) and a trace amount of water was conducted in chlorobenzene under 9000 atm at 120°C for 18 hours to afford guest-encapsulating α-13mem (G@α-13mem; G = HF, H\textsubscript{2}O-HF, and H\textsubscript{2}O) in 40% isolated yield after purification with column chromatography. The filling factors of the guests inside α-13mem were determined by the proton nuclear magnetic resonance (\textsuperscript{1}H NMR) analysis: 32% HF@α-13mem, 11% (H\textsubscript{2}O-HF)@α-13mem, 27% H\textsubscript{2}O@α-13mem, and 30% empty α-13mem, respectively. After collecting the products from several batches, closing of G@α-13mem via two-step reactions, without considerable loss of the encapsulated species, gave the corresponding endohedral C\textsubscript{70}S\textsubscript{8}, that is, expected...
HF@C_{70} and unprecedented (H_{2}O-HF)@C_{70} and H_{2}O@C_{70} (figs. S8 to S15).

We confirmed that HF encapsulation into \( \alpha-16\text{mem} \) did not take place in chlorobenzene under ambient pressure at 110°C, in contrast to the case for the open-cage C_{60} (25). Thus, the high-pressure conditions were found to be critical, where the guest species are forced to be “pushed from outside” of the opening of \( \alpha-16\text{mem} \). The experimental conditions and results are summarized in Table 1. Upon checking the time dependence (entries 1 to 4), the filling factor of HF appeared to almost reach a plateau after 14 hours, whereas that of H_{2}O-HF increased slowly and that of H_{2}O was developed rapidly at around 14 hours. These observations suggested stepwise formation of G@\( \alpha-16\text{mem} \), that is, HF@\( \alpha-16\text{mem} \) followed by (H_{2}O-HF)@\( \alpha-16\text{mem} \) and then H_{2}O@\( \alpha-16\text{mem} \). To prevent a high degree of decomposition of the starting materials and the products, a reduced amount of HF-Py at slightly higher temperature gave the better chemical yield of G@\( \alpha-13\text{mem} \) (entry 5). As described previously by Zhang et al. (23, 24), H_{2}O encapsulation did not occur in the absence of HF (entry 6), showing only that pushing from outside was not an effective method of inserting H_{2}O inside \( \alpha-16\text{mem} \). Among the products obtained from entries 1 to 5, (HF)_{2}@\( \alpha-13\text{mem} \) and (H_{2}O)_{2}@\( \alpha-13\text{mem} \) were not detected.

Our experiments considered the insertion mechanisms of HF, H_{2}O-HF, and H_{2}O (as shown in Fig. 2). Because the size of the opening of \( \alpha-16\text{mem} \), which was generated in situ from \( \alpha-13\text{mem} \) by eliminating a water molecule from the bis(hemiketal) moiety, is not large enough for water to pass through, insertion of a smaller HF initially takes place by pushing from outside to give molecular complex A. In earlier work, Gan et al. (27) reported that encapsulated H_{2}O inside an open-cage C_{60} was pulled out by attractive interaction with fluorine atom being present outside the opening, resulting in the release of the H_{2}O. Taking into consideration the similar attractive interaction of the encapsulated HF and the H_{2}O near the opening, the H_{2}O should be introduced into \( \alpha-16\text{mem} \) by the assist of “pulling from inside,” shown as B, to yield C. Then, positional exchange of the lower HF and the upper H_{2}O occurs to afford D. DFT calculations at the M06-2X/6-31G(d) level showed that the required energy for the positional exchange of the HF and H_{2}O in C is 20.8 kcal/mol (tables S3 to S5), which should be possible to occur under the applied conditions. Finally, the resulting HF near the opening escapes to form E. During the cooling process, addition of a water molecule regenerates the \( \alpha-13\text{mem} \) cage to furnish G@\( \alpha-13\text{mem} \).

Because of the complexities in the structures of H_{2}O clusters and hydrated HF, it is very difficult to evaluate energy profiles including A, B, D, and E by DFT studies. In the case of the gas-phase stabilization energy calculated at the MP2/6-311++G(3pd,3df) level, H_{2}O-HF gains more energy (7.3 kcal/mol) than HF dimer (3.9 kcal/mol) and H_{2}O dimer (3.8 kcal/mol) (tables S8 to S15). This stability is considered to play an important role for the formation of C. However, we needed to study another possibility that the presence of an acid would change...
the solvated structures of HF and H₂O before encapsulation to result in facile encapsulation of H₂O. Although a high-pressure treatment in the presence of HCl-Py, instead of HF-Py, under the same conditions was conducted, the resulting products obtained in 64% isolated yield were found to contain only a small amount of H₂O·HF (1.8% filling factor). These results strongly support the hypothesis that both pushing and pulling effects are necessary to achieve encapsulation of H₂O-HF inside α-13mem in a remarkably high yield compared with the doubly encapsulating C₇₀ reported so far (22, 23).

After closure of the openings (Fig. 1B), the high-performance liquid chromatography (HPLC) analysis of the products displayed three peaks corresponding to empty C₇₀, a mixture of HF@C₇₀ and H₂O@C₇₀, and (H₂O-HF)@C₇₀ (as shown in Fig. 3A). The mono-encapsulating HF@C₇₀ and H₂O@C₇₀ appeared at almost the same retention time regardless of the encapsulated species. In contrast, facile separation of (H₂O-HF)@C₇₀ as a pure form was achieved in a preparative scale, showing clear differences caused by the double encapsulation. By the atmospheric pressure chemical ionization mass analysis (APCI MS), we detected (HF)₂@C₇₀ before elution of (H₂O-HF)@C₇₀, albeit in only a trace amount (fig. S16).

The ¹H NMR analysis is a powerful tool to study the structure and dynamics of the isolated H₂O-HF. As shown in Fig. 3B, a signal of the singly encapsulated H₂O at ~27.1 parts per million (ppm) [500 MHz; CDCl₃/CS₂ (1:1); 25°C] coincides with that of our previous report for H₂O@C₇₀ synthesized from different synthetic routes (23), showing strong shielding effects due to C₇₀ cage (22, 23). A doublet corresponding to the singly encapsulated HF was observed at −25.0 ppm with a coupling constant JHF = 507 Hz, whose value is almost the same as that of HF@C₆₀ (19). The ¹H NMR of (H₂O-HF)@C₇₀ displayed a singlet at −25.3 ppm corresponding to the H₂O in addition to a doublet at −17.5 ppm corresponding to the HF. It is noteworthy that both chemical shifts are downfield-shifted compared with those of H₂O@C₇₀ and HF@C₇₀, indicating more positive charges on the protons due to the formation of a hydrogen bond. The shifted value for the HF (δH = +7.5) is larger than that of the H₂O (δH = +1.8), demonstrating that this molecular complex adopts the structure H₂O-HF, in which the oxygen works as a hydrogen bond acceptor, rather than HF-H₂O, in which the fluorine works as the acceptor. In addition, the smaller value of the coupling constant JHF = 443 Hz also supports the structure H₂O-HF, the value being close to those of HF in diethyl ether and dimethyl sulfoxide solutions, JHF = 464 and 410 Hz, respectively (28). Hence, we concluded that this is the simplest hydrated acid. Upon heating the solution in ortho-dichlorobenzene-d₄ (ODCB-d₄), no change in the spectral shape was observed even at 140°C, revealing that no proton transfer takes place between the H₂O and HF on the NMR time scale.

The structure of (H₂O-HF)@C₇₀ was unambiguously determined by the single-crystal x-ray diffraction analysis for the crystals containing nickel(II) octaethylporphyrin and solvent molecules, with almost the same unit cell constants as those of empty C₇₀ (29) and H₂O@C₇₀ (23). As shown in Fig. 3D, the O and F atoms of the H₂O-HF were observed inside the C₇₀ located on the porphyrin. It is the first example of the x-ray structure for doubly encapsulating C₇₀. Here, in contrast to

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**Table 1. Encapsulation of HF, H₂O-HF, and H₂O inside α-13mem under the high-pressure conditions of 9000 atm in the chlorobenzene solution.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>HF-Py (eq.)</th>
<th>Temperature (°C)</th>
<th>Time (hours)</th>
<th>Yield (%)†</th>
<th>Filling factor (%)¹</th>
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</table>

† Isolated yields of the sum of recovered α-13mem and G@α-13mem (G = HF, H₂O-HF, and H₂O) after purification with a column chromatography on silica gel. ¹The filling factors were determined by comparison of the integral values of the encapsulated species (δ−18.2 ppm for HF, −15.6 ppm for H₂O-HF, and −11.8 ppm for H₂O) with that of the organic addends (δ 6.7 ppm for the olefinic proton at the opening) in the ¹H NMR [500 MHz; CDCl₃/CS₂ (1:1)] spectra.

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**Fig. 2.** Insertion mechanism of HF, H₂O-HF, and H₂O into α-16mem with the synergetic effects of pushing from outside by high-pressure conditions and pulling from inside by attractive interaction of HF with the outer H₂O.
The x-ray structure of H$_2$O@C$_{70}$ with dynamic disorder on the position of the O, the O and F in this study did not show any dynamic or positional disorder, demonstrating the perfect alignment of the H$_2$O-HF. Reflecting its dense encapsulation, the averaged longer axis of the C$_{70}$ cage [7.931(1) Å] was elongated by 0.20% compared with that of H$_2$O@C$_{60}$ [7.915(1) Å]. The distance between the O and F was 2.438(2) Å (Fig. 3E). It should be mentioned that the position of H between O and F was geometrically fixed, showing a distance of 1.39(4) and 1.05(4) Å, respectively. Thus, H$_2$O·HF was found to adopt such structure as the proton of HF forms a linear hydrogen bond to the oxygen of H$_2$O, which is in good agreement with the $^1$H NMR results.

To obtain deeper insights, the structure of (H$_2$O-HF)@C$_{70}$ was optimized at the ONIOM-(MP2/6-311++G(3df,3pd):M06-2X/6-31G(d)) level (Fig. 3F). The calculated structure was found to reproduce well the x-ray structure of the encapsulated H$_2$O-HF complex. The H atom between O and F was geometrically fixed, whereas the other two H atoms were geometrically refined, showing a distance of 1.39(4) and 1.05(4) Å, respectively. Thus, H$_2$O-HF was found to adopt such structure as the proton of HF forms a linear hydrogen bond to the oxygen of H$_2$O, which is in good agreement with the $^1$H NMR results.

The chemical shifts of the cage carbons near the H$_2$O are smaller than those near the HF, indicating the polarity of (H$_2$O-HF)@C$_{70}$, which was shown by the gauge-independent atomic orbital (GIAO) calculations (fig. S17). However, this polarity was not obvious on reduction potentials determined by cyclic voltammetry (CV) in ODCB, the first reduction potentials for (H$_2$O-HF)@C$_{70}$ and empty C$_{70}$ being -1.04 and -1.06 V versus a ferrocene/ferrocenium couple (fig. S18). The ultraviolet-visible (UV-vis) absorption in toluene is almost superimposable with that of empty C$_{70}$ (fig. S19). The infrared (IR) bands for the HO= and H–F bonds were not observed, probably due to the shielding effects of the cage, which was the same for H$_2$O@C$_{60}$ (18), HF@C$_{60}$ (19), and H$_2$O@C$_{70}$ (23). However, interesting suppression of the characteristic IR bands of C$_{70}$ was observed for HF@C$_{70}$ and (H$_2$O-HF)@C$_{70}$ (fig. S20).

In summary, the simplest hydrated HF was isolated in a confined subnano space by the use of molecular surgical methods. Compared with the doubly encapsulating C$_{70}$s reported so far, a high efficiency of the encapsulation was achieved because of the synergetic effects of pushing from outside by the high-pressure conditions and pulling from inside with an attractive interaction of the encapsulated HF with the outer H$_2$O, which was supported by the stepwise formation of HF@C$_{70}$, followed by (H$_2$O-HF)@C$_{70}$ and then H$_2$O@C$_{70}$. The NMR studies revealed the rigid structure of the H$_2$O-HF without hydrogen exchange. The single crystal x-ray analysis and theoretical calculations showed the closer contact of the oxygen with the hydrogen of HF compared with that of free H$_2$O-HF.

**MATERIALS AND METHODS**

**General**

The $^1$H, $^{13}$C, and $^{19}$F NMR measurements were performed with the JEOL JNM-ECA 500 and JNE-ECA 600 instruments. The NMR chemical
shifts were reported in parts per million with reference to residual protons, and fluorine of CDCl₃ (δ 7.26 ppm in ¹H NMR, δ 77.0 ppm in ¹³C NMR), tetrahydrofuran (THF-d₈) (δ 67.57 ppm in ¹³C NMR), and hexafluorobenzene (C₆F₆) (δ 164.90 ppm in ¹⁹F NMR). The APCI MS spectra were measured on a Bruker microTOF-Q II. High-pressure experiments were conducted by using the Hikari Koatsu high-pressure apparatus HR15-B3. The HPLC was performed with a Cosmols Buckypep column (4.60 x 250 mm) for analytical purpose and the same columns (two directly connected columns; 200 x 250 mm) for preparative purpose. CV was conducted in an ALS Electrochemical Analyzer Model 620C using a three-electrode cell with a glassy carbon working electrode, a platinum wire counter electrode, and an Ag/0.1 M MgNO₃ reference electrode. UV-vis spectra were recorded with a Shimadzu UV-3150 spectrometer. The IR spectra were collected by using a Thermo Fisher Scientific Magna 550 FT-IR spectrometer equipped with a Harrick Zhang et al. Supplementary material for this article is available at http://advances.sciencemag.org/cgi.

**SUPPLEMENTARY MATERIALS**

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/3/4/e1602833/DC1

**Supplementary Text**

fig. S1. ¹H NMR [500 MHz; CDCl₃/C₆D₆ (1:1)] spectrum of a mixture of HF[α-13mem], (H₂O·HF)[α-13mem], H₂O[α-13mem], and empty α-13mem.

fig. S2. ¹³C NMR [151 MHz; THF-d₈] spectrum of a mixture of HF[α-13mem], (H₂O·HF)[α-13mem], H₂O[α-13mem], and empty α-13mem.

fig. S3. ¹⁹F NMR [470 MHz; CDCl₃/C₆D₆ (1:1)] spectrum of a mixture of HF[α-13mem], (H₂O·HF)[α-13mem], H₂O[α-13mem], and empty α-13mem.

fig. S4. ¹H NMR [500 MHz; CDCl₃/C₆D₆ (1:1)] spectrum of a mixture of HF[α-13mem], (H₂O·HF)[α-13mem], H₂O[α-13mem], and empty α-13mem obtained under the optimized conditions (Table 1, entry 5).

fig. S5. ¹H NMR [500 MHz; CDCl₃] spectrum of a mixture of HF[ε-8mem], (H₂O·HF)[ε-8mem], H₂O[ε-8mem], and empty ε-8mem.

fig. S6. ¹³C NMR [151 MHz; CDCl₃] spectrum of a mixture of HF[ε-8mem], (H₂O·HF)[ε-8mem], H₂O[ε-8mem], and empty ε-8mem.

fig. S7. ¹⁹F NMR [470 MHz; CDCl₃] spectrum of a mixture of HF[ε-8mem], (H₂O·HF)[ε-8mem], H₂O[ε-8mem], and empty ε-8mem.

fig. S8. ¹H NMR [500 MHz; CDCl₃/C₆D₆ (1:1)] spectrum of a mixture of HF[ε-8mem] and H₂O[ε-8mem] (1:1).

fig. S9. ¹⁹F NMR [470 MHz; CDCl₃/C₆D₆ (1:1)] spectrum of a mixture of HF[ε-8mem] and H₂O[ε-8mem] (1:1).

**REFERENCES AND NOTES**


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