



An orifice design: water insertion into C₆₀[†]

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Soon after the discovery of C₆₀,¹ the first endohedral fullerene, K⁺@C₅₉B, was proven by Saunders and co-workers in 1991 under mass spectrometric conditions.² To date, a number of endohedral fullerenes encapsulating metal ions, nitrides, and oxides, which are so-called metallofullerenes, have been produced by physical approaches, *e.g.*, laser ablation and arc discharge methods.³ While these approaches could provide endohedral fullerenes albeit only in 0.1% yield, their properties have received growing attention from a wide research area owing to their potential applications in photovoltaic cells (Lu₃N@C₈₀ (ref. 4) and Li⁺@C₆₀ (ref. 5)) and MRI (magnetic resonance imaging) contrast agents (Gd@C₆₀ and Gd@C₈₂).⁶ Additionally, DNP (dynamic nuclear polarization) was recently demonstrated by utilizing Gd₂@C₇₉N, which resulted in increased nuclear polarization of ¹H and ¹³C spins from electron spins by *ca.* 50% at 1.2 K.⁷

In 1997, Rubin advocated an original concept to produce endohedral fullerenes *via* sequential steps: creation of an opening, insertion of small molecules, and closure of the opening.⁸ This molecular surgical synthesis based on organic reactions is conceptually different from physical approaches. Of particular importance is to chemically synthesize endohedral fullerenes encapsulating neutral species that cannot be generated by physical approaches. Since the successful synthesis of the first open-cage C₆₀ derivative in 1995 by Wudl and co-workers,⁹ a number of derivatives with different structural motifs on their orifices have been reported.¹⁰ In the present time, a variety of molecules have been found to be encapsulated inside the fullerene cavities, few of which are able to be restored into the pristine caged structures such as C₆₀,¹¹ C₇₀,¹² and C₅₉N¹³ with retaining the molecule inside. Nevertheless, organic syntheses of such endohedral fullerenes still suffer from low

yielding. To overcome this problem, we focused on an orifice structure which is crucial for trapping a guest molecule as well as for controlling the reactivity of open-cage C₆₀ derivatives. Since the orifice substructure, *i.e.*, ¹ArC–E=C(²Ar)–C(³Ar), originates from a heterocyclic azine (Fig. 1) which is used for the creation of an opening by a thermal reaction with C₆₀,^{11c,14} we considered six hypothetical azines including pyridazines and triazines (**1a–f**) so as to design an orifice suitable both for encapsulation of guest molecules and closure of the opening. Herein, we discuss the molecular design toward efficient synthetic methodology for synthesizing endohedral fullerenes based on theoretical studies as well as experimental demonstration.

With regard to the synthesis of endohedral fullerenes, **INT1** (structure in Table 1) is a key material since it can encapsulate guest molecules such as H₂O,^{11c} H₂,¹⁵ and HF.¹⁶ More importantly, the orifice with a substructure of tetraketone in **INT1** can be zipped up to reduce its orifice size from 16- to 8-membered ring by the reaction with phosphine and/or phosphite.^{11c–e} The plausible mechanism on this closing process was depicted in

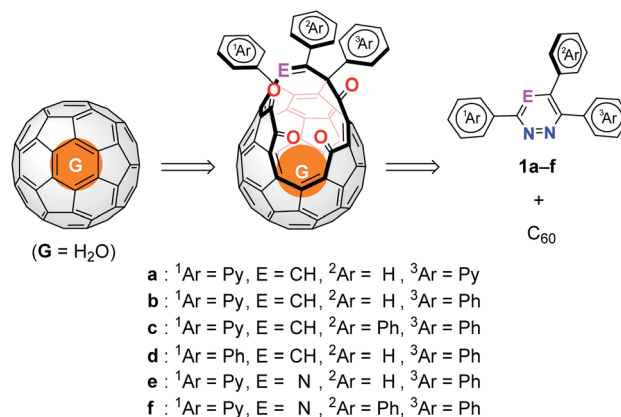
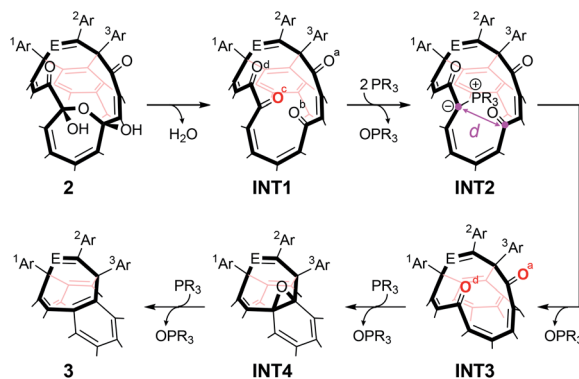


Fig. 1 Retrosynthetic route for endohedral fullerenes (Py: 2-pyridyl group).

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[†] Electronic supplementary information (ESI) available: Detailed synthetic procedures, spectra, and optimized geometries. CCDC 1999283. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra09067k



Table 1 Partial charges q_{NPA} obtained by natural population analysis (NPA), stabilization energies $\Delta\Delta G$, and interatomic distances d (B3LYP-D3/6-31G(d) at 298 K)

Addends	q_{NPA}			$\Delta\Delta G(\text{INT2})^a$ (kcal mol ⁻¹)	$d(\text{INT2})$ (Å)
	O(c)/INT1	O(a)/INT3	O(d)/INT3		
a	-0.465	-0.510	-0.474	0.0	3.35
b	-0.464	-0.502	-0.469	-1.0	3.36
c	-0.467	-0.511	-0.467	+0.1	3.36
d	-0.461	-0.497	-0.469	-1.4	3.34
e	-0.465	-0.501	-0.469	-0.4	3.32
f	-0.464	-0.491	-0.469	-3.3	3.32

^a $\Delta\Delta G(\text{INT2}) = \Delta G(\text{INT2}) - \Delta G(\text{INT2a})$ where $\Delta G(\text{INT2}) = G(\text{INT2}) + G(\text{OPPh}_3) - G(\text{INT1}) - 2G(\text{PPh}_3)$.

Table 1. Firstly, a water molecule would be eliminated from the 13-membered ring of **2** to afford **INT1**. The ring-closing reaction is then initiated by the nucleophilic attack of PR_3 to O(c) in **INT1**, leading to the formation of β -oxo-phosphorus ylide **INT2** (ref. 17) which undergoes intramolecular Wittig reaction to give diketo derivative **INT3**.¹⁸ The further nucleophilic attack of another PR_3 molecule on O(a) and/or O(d) in **INT3** followed by the elimination of $\text{O}=\text{PR}_3$ furnishes epoxide **INT4**.¹⁹ Finally, deoxygenation of **INT4** by PR_3 provides **3** possessing an eight-membered-ring opening. Previously, we used **2a'** (which bears 6-*t*-butylpyridin-2-yl groups instead of 2-pyridyl groups) for preparing **INT2a'**. Even though **INT2a'** could be formed at 100 °C for 3 h, **INT2a'** was significantly decomposed during the conversion into **INT3a'** at 120 °C for 8 h, resulting in 52% yield.²⁰ Thus, open-cage C_{60} derivatives should have an orifice which meets criteria including (i) less polarized carbonyl groups in **INT1** and **INT3** to promote nucleophilic attack of PR_3 to carbonyl O-atoms, (ii) formation of stable ylide **INT2** to suppress undesirable decomposition pathways, and (iii) readily conversion of **INT2** into **INT3**.

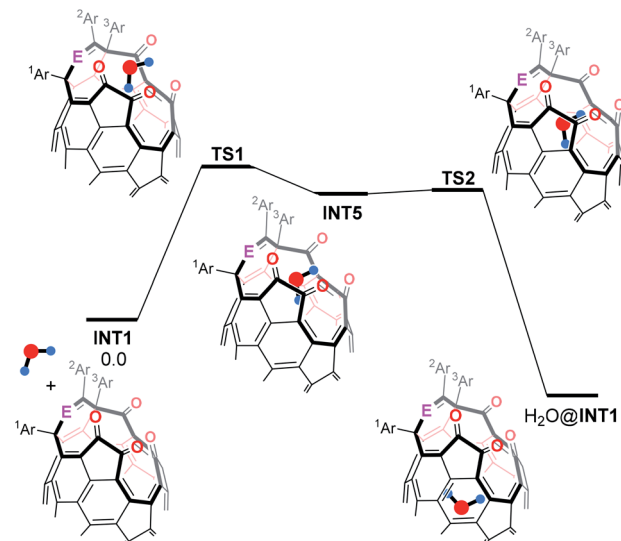
To verify electronic and structural properties of **INT1**, **INT2**, and **INT3**, we performed theoretical calculations at the B3LYP-D3/6-31G(d) level of theory at 298 K (Table 1). From natural charges q_{NPA} of O(c) in **INT1**, the substituent effect is predicted to be not so significant in the initial step. Contrastingly, the q_{NPA} values of O(a) and O(d) in **INT3** are reflected by the opening substructure. Compared with **INT3a** which is a model that we previously synthesized,^{11c} both absolute values of q_{NPA} , except

for O(a) in **INT3c**, markedly decreased, suggestive of increased reactivity of **INT3** by replacing one of Py groups with a less electron-withdrawing Ph group at the ³Ar position. Subsequently, we confirmed thermodynamic properties of β -oxo-phosphorus ylide **INT2**, showing considerable stabilization for **INT2f** ($\Delta\Delta G -3.3$ kcal mol⁻¹) which is superior to others in preventing decomposition. This is probably due to the better orientation for one of Ph groups on the P-atom in **INT2f** via CH/ π interaction with the Ph group at the ²Ar position which is also tightly fixed via an H-bonding with the imine moiety (Fig. S8†). Furthermore, the replacement of an olefin unit with an imine moiety causes decrease in the C(b)⋯C(c) distance by 0.04 Å, implying the positive effect on the intramolecular Wittig reaction in **INT2e** and **INT2f**.

To gain insight into the orifice size of **INT1**, we summarized an energy profile for the H_2O -insertion as shown in Table 2. Interestingly, the H_2O -insertion is predicted to occur stepwisely. Firstly, the H_2O molecule is trapped at a cross-section of the orifice to form **INT5** via **TS1** which is the rate-determining step. Subsequently, the trapped H_2O molecule is encapsulated inside **INT1** via **TS2** to give $\text{H}_2\text{O}@$ **INT1**. Upon seeing activation barriers, the Ph group at the ²Ar position seems not to have considerable influence on the H_2O -insertion, showing the similar ΔG^\ddagger values of 21–22 kcal mol⁻¹. The substantial stabilization of **INT1f** by the H_2O encapsulation ($\Delta G -10.4$ kcal mol⁻¹) would be an advantage to obstruct the escape of the H_2O molecule from the inside. Consequently, the orifice of **2f**, which consists of one Py and two Ph groups with an imine



Table 2 Changes in Gibbs energies (ΔG , kcal mol⁻¹) on a profile for H₂O-insertion into INT1 (B3LYP-D3/6-31G(d) at 298 K)

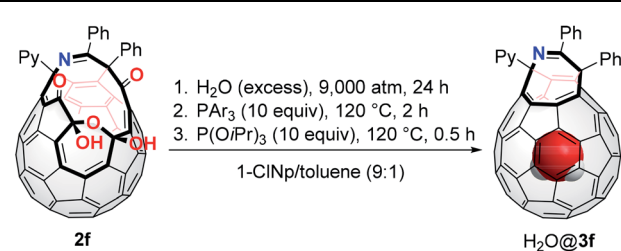


Addends	TS1	INT5	TS2	H ₂ O@INT1
a	+21.6	+17.1	+17.5	-10.0
b	+21.7	+17.2	+17.6	-9.3
c	+21.4	+16.9	+17.2	-8.9
d	+22.0	+17.5	+18.2	-9.7
e	+21.0	+17.3	+17.8	-8.9
f	+21.0	+17.3	+17.8	-10.4

moiety, should be preferable for the synthesis of H₂O@C₆₀ both in terms of reactivity on the closing process and capability of encapsulating a H₂O molecule.

Thereby, we synthesized **2f** by gram-scale reactions including the thermal reaction of C₆₀ with 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (**1f**), photooxygenation,¹⁴ and nucleophilic oxygenation using *N*-methylmorpholine *N*-oxide.^{11c} Recently, we found that β -oxo-phosphorus ylide **INT2a'** bearing a PR₃ unit with a cone angle smaller than 140° is significantly hydrolysed in the presence of water.¹⁷ As to the conversion from **INT3a'** to **3a'**, P(O*i*Pr)₃ was previously found to exhibit high performance.¹⁸ For the efficient synthesis of H₂O@C₆₀, we designed one-pot reaction from **2f** to H₂O@**3f** via three steps commenced with the H₂O-insertion under high-pressure conditions followed by stepwise conversion of the thus formed H₂O@**2f** into H₂O@**INT3f** and then H₂O@**3f**. The results were summarized in Table 3. The H₂O-insertion was conducted using 20 mg of **2f** in a mixed solvent system of 1-chloronaphthalene (1-ClNp) and toluene under 9000 atm for 24 h. For the closure of the opening, we used PPh₃ with a cone angle of 145° (entry 1). Different from **2a'** that required totally 11 h for the conversion into **INT3a'**,²⁰ **2f** was transformed into **INT3f** within 1.5 to 2 h, meeting the criteria (i)–(iii) owing to stable ylide **INT2f** with a shorter C(b)···C(c) distance. The further reaction with P(O*i*Pr)₃ at 120 °C for 0.5 h gave desired H₂O@**3f** in 48% isolated yield with the encapsulation ratio of 98%. Whereas electron-deficient

Table 3 One-pot synthesis of H₂O@**3f** from **2f**^a



Entry	Step 1	Step 2	Yield ^b
1	160 °C	PPh ₃	48% (H ₂ O: 98%)
2	160 °C	P(2-furyl) ₃	21% (H ₂ O: 99%)
3	160 °C	P(<i>p</i> -tolyl) ₃	69% (H ₂ O: 98%)
4	140 °C	P(<i>p</i> -tolyl) ₃	67% (H ₂ O: 65%)
5	120 °C	P(<i>p</i> -tolyl) ₃	68% (H ₂ O: 4%)

^a Conducted using 20 mg of **2f** in a mixed solvent system of 1-chloronaphthalene (1-ClNp) and toluene. ^b Encapsulation ratio was determined by ¹H NMR or mass spectrum.

phosphine P(2-furyl)₃ gave H₂O@**3f** in lower yield (21%, entry 2), the reaction employing electron-rich P(*p*-tolyl)₃ resulted in higher yield (69%) with keeping the 98% encapsulation ratio of H₂O (entry 3). It should be noted that the decreased temperature at the first step drastically influenced on the encapsulation ratio of H₂O: 98% (160 °C, entry 3), 65% (140 °C, entry 4), and 4% (120 °C, entry 5).

The structure of H₂O@**3f** was determined spectroscopically. The molecular ion peak was observed at *m/z* 1020.1255 ([H₂O@**3f**]⁻) in the negative ionization mode by the APCI (atmospheric-pressure chemical ionization) method. The ¹H NMR spectrum of H₂O@**3f** (CDCl₃, 500 MHz) clearly showed a singlet signal at δ -6.11 ppm corresponding to the

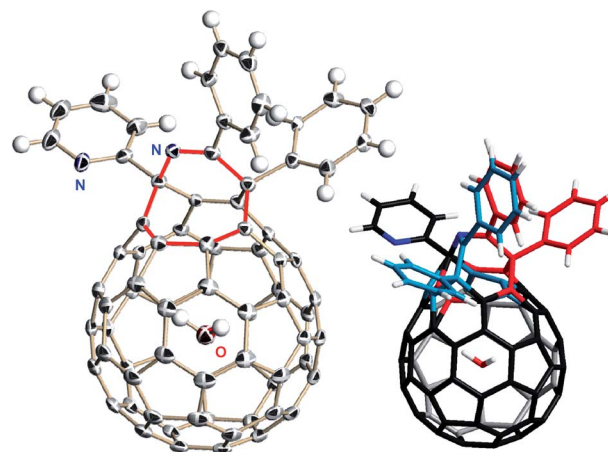


Fig. 2 Single crystal X-ray structure of H₂O@**3f** with showing thermal ellipsoids in 50% probability (left) and disordered structures coloured with pink and light blue for major and minor parts, respectively (right). The benzene molecules co-crystallized with H₂O@**3f** are omitted for clarity.



encapsulated H₂O molecule, bearing the striking resemblance with that for H₂O@3a' (δ –6.09 ppm^{11c,18}). Using H₂O@3f with an occupation level of 60%, single crystals were grown from the benzene/hexane solution by slow evaporation at 5 °C. The solid-state structure was shown in Fig. 2. The water molecule locates at the centre of the cage and its occupancy was refined to be 0.593(8), being in accordance with the ratio determined by ¹H NMR. A crystallographic disorder was seen in the orifice structure which is identical to two parts with sharing the Py group. Their occupancies were refined to be 0.854(2) for the major part and 0.146(2) for the minor part, respectively.

Based on our previous approach to synthesize H₂O@C₆₀ using 2a' in the solid state, the final step has the scale restriction up to 50 mg. Otherwise, the conversion is considerably decreased. For the scalable synthesis of H₂O@C₆₀, we examined one-pot synthesis of H₂O@C₆₀ using 160 mg of 2f. As represented in Scheme 1, 2f was firstly subjected to the optimal reaction conditions as entry 3 in Table 3. To the resultant mixture, methanol was added to obtain the crude precipitate containing H₂O@3f which was further heated at 400 °C under 5 Pa for 2 h, giving H₂O@C₆₀ in 6% isolated yield. Considering the high conversion of 2f into H₂O@3f (Table 3), H₂O@3f should be mostly decomposed during the final step. To avoid undesirable decomposition pathways, the crude mixture was purified, prior to step 4, by silica gel column chromatography which gave H₂O@3f (80% yield) together with complex mixture having higher polarity. Since this complex mixture changed into insoluble solid without formation of H₂O@C₆₀ under the same conditions as step 4, it might hamper the conversion of H₂O@3f into H₂O@C₆₀. With H₂O@3f as a pure form in hand, it was subjected to pyrolytic conditions (Scheme 1). As the results, H₂O@C₆₀ was obtained up to 87% yield and the overall yield from 2f reaches to 70% which is remarkably higher than that obtained by our previous approach (15% from 2a')^{11c} even when compared with Whitby's variant (40% from 2a').¹⁵

In summary, we designed the orifice substructure suitable for the synthesis of endohedral fullerenes on the basis of reactivity toward closing processes and encapsulation properties. Among six candidates, the orifice possessing a phenyl imine moiety (f) was expected to have high affinity to phosphines as well as interaction with the encapsulated H₂O molecule, which is strong enough to prevent its escape from the inside. The thus synthesized open-cage C₆₀ derivative 2f

demonstrated the effective conversion into H₂O@3f via one-pot process, showing high yield up to 80% with nearly quantitative encapsulation of H₂O. The further conversion of H₂O@3f into H₂O@C₆₀ proceeded quite well when H₂O@3f was used in a pure form. The method demonstrated herein could be applied for a variety of endohedral fullerenes in a practical scale.

Conflicts of interest

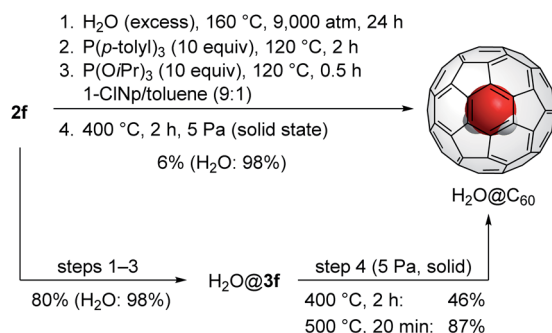
There are no conflicts to declare.

Acknowledgements

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Scheme 1 Synthesis of H₂O@C₆₀ from 2f (160 mg).



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