An optimised scalable synthesis of $\text{H}_2\text{O}@\text{C}_{60}$ and a new synthesis of $\text{H}_2@\text{C}_{60}$†

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New high-yielding synthetic routes to the small-molecule endofullerenes $\text{H}_2\text{O}@\text{C}_{60}$, $\text{D}_2\text{O}@\text{C}_{60}$ and $\text{H}_2@\text{C}_{60}$ are described. The use of high temperatures and pressures for the endohedral molecule incorporation are avoided. A new partial closure step using PPh$_3$, and final suturing using a novel Diels–Alder/retro-Diels–Alder sequence are amongst the advances reported.

The molecular structure of C$_{60}$ fullerene consists of a carbon cage enclosing a spherical cavity with a diameter of approximately 3.5 Å. Small-molecule endofullerenes encapsulate a single small molecule such as H$_2$ or H$_2$O within the cavity.$^{1,2}$ The encapsulated molecule behaves as a confined quantum rotor, displaying a rich energy level structure,$^3$ which may be studied by neutron scattering$^{4,5}$ infrared spectroscopy$^{6,6}$ and nuclear magnetic resonance (NMR).$^{3,5,7}$ The stability and homo- geneity of endofullerenes such as $\text{H}_2@\text{C}_{60}$ and $\text{H}_2\text{O}@\text{C}_{60}$ allows the convenient and precise study of important physical phenomena such as nuclear spin isomer conversion.$^{5,7,8}$ It is possible to detect the endohedral interconversion of ortho and para-water, and to show that the conversion is a bimolecular process even under cryogenic conditions, with neighbouring pairs of ortho-water molecules interacting so as to generate a pair of para-water molecules.$^9$ Apart from their intrinsic interest, such observations may underpin new routes to the generation of nuclear hyperpolarization, analogous to the chemical reactions of para-enriched hydrogen gas.$^9$ The high demand for these unique substances has highlighted limitations of the current methods for their preparation. The synthetic route to endofullerenes has been described as “molecular surgery,”$^{10}$ and involves three stages; (i) opening and progressive widening of an orifice in the C$_{60}$ cage through exohedral reactions, (ii) introduction of a small molecule through the orifice into the cavity, (iii) further reactions leading to reclosure of the C$_{60}$ cage and encapsulation of the endohedral molecule. The final (reclosure) stage is the most difficult and has been accomplished only by Komatsu and Murata using two different routes leading to $\text{H}_2@\text{C}_{60}$ (8 steps, 8% overall yield),$^1$ and $\text{H}_2\text{O}@\text{C}_{60}$ (6 steps, 5% yield) respectively.$^2$ Both syntheses require specialised high pressure equipment for the endohedral molecule incorporation step. Herein we report more efficient and practical routes to these important molecular systems.

The key feature of the $\text{H}_2\text{O}@\text{C}_{60}$ synthesis is that the open-cage derivative 1, having a 13-membered orifice, can be converted in situ into its dehydrated form 2 that has a 16-membered orifice. Compound 2 is able to incorporate a water molecule but is easily re-hydrated, reducing once again the size of the orifice trapping the guest molecule inside the cage. Compound $\text{H}_2\text{O}@1$ is then reduced with (PrO)$_3$P to $\text{H}_2\text{O}@3$ which in turn is pyrolysed under vacuum to produce $\text{H}_2\text{O}@\text{C}_{60}$ (Scheme 1).

The reported route$^2$ to the open fullerene 1 worked well but we lacked the equipment to apply the very high pressures (9000 atm) used to efficiently encapsulate the water molecule. It was already known that compound 1 could incorporate water (8%) under atmospheric pressure$^2$ and that higher filling factors could be achieved under similar conditions in other open fullerenes bearing larger orifices.$^{11}$ Published studies on the filling of hydrophobic cavities by water molecules suggested that an increased filling factor could be as well achieved by changing variables other than pressure.$^{12}$ On these premises we investigated the filling of 1 under low pressure conditions.

Heating a solution of 1 in toluene in an NMR tube in the presence of water (5.6 equiv.) at 120 °C reached a maximum of 23% incorporation after 36 h reflecting the equilibrium situation. Increasing reaction time further gave substantial decomposition. Changing to a sealed tube which could be uniformly heated to prevent condensation in cooler regions increased incorporation to 45%. Using a large excess of water did not significantly change incorporation. Changing to other aromatic solvents demonstrated increased incorporation (benzene, 39%; ortho-dichlorobenzene, 61%; 1-chloronaphthalene, 67%).
Using 1-chloronaphthalene as the solvent and lowering the temperature to 100 °C gave 78% H2O incorporation after 48 h providing a practical alternative to high pressure procedures. The same process can be extended to the synthesis of D2O@1 by pre-forming the dehydrated compound 2 by refluxing a toluene solution of 1 for one hour, passing the condensed solvent through a column of activated 3 Å molecular sieves. Subsequent removal of solvent to give 2, dissolution in 1-chloronaphthalene, addition of D2O and heating as above gave D2O@1 with no HOD@1 or H2O@1 visible by 1H NMR spectroscopy. Compound 2 was recently isolated using a different protocol.13

In an effort to complete the synthesis of H2O@C60 our attention turned to suturing H2O@1. Unfortunately when compound H2O@1 was reacted with (iPrO)3P the expected product H2O@3 was isolated in only 34% yield. The same reaction mixture yielded 5% of the novel compound H2O@4. The structure of the latter can be deduced from the appearance in the 1H NMR spectrum of a singlet at δ 7.80 ppm from the proton present on the rim of the orifice and a broad signal at δ 5.21 attributable to the single hydroxyl group. The DFT-GIAO calculated spectra suggest the formation of regioisomer 4. Compound 4 was the only product isolated (76% yield) when 1 was reacted with (iPrO)3P at room temperature. Compound H2O@4 is inert to (iPrO)3P and H2O@4 does not lose its endohedral water molecule upon heating. A somewhat similar reactivity towards alkyl phosphites has been reported for another open-cage fullerene, and the mechanism of the reduction studied theoretically.14 Pre-formed 2 reacted with (PrO)3P at room temperature to afford compound 3 in 33% yield without contamination by 4. It is likely that under the reported closure conditions it is a mixture of H2O@1 and H2O@2 formed in situ which are reacting with (PrO)3P to give varying mixtures of H2O@4 and H2O@3 (Scheme 2).

In order to overcome this side reactivity of H2O@1 towards alkyl phosphites we looked at alternative reagents and found that reaction with excess Ph3P at 120 °C cleanly gave compound H2O@5, isolated in 84% yield. Compound H2O@4 was not formed and, even with longer reaction times, reduction to compound H2O@3 was not observed. No endohedral water was lost in the formation of H2O@5 for which this reaction provides the first synthesis. Compound H2O@5 could be reacted with excess (PrO)3P to give H2O@3 which was isolated after chromatography in 84% yield. In comparison with the reported direct reaction with (PrO)3P,2 the yield of H2O@3 afforded in the two step process, is higher overall (69%) (Scheme 3).

Our attention finally turned to the last step of the closure – the conversion of H2O@3 into H2O@C60. The reported yield of 29% was achieved by vacuum pyrolysis (360 °C) of H2O@3.
dispersed on dry neutral alumina. Unfortunately in our hands we could isolate only traces of the product. A reasonable mechanism involves an initial [4+2] intramolecular cycloaddition to give strained intermediate 6 which rearranges via radical cleavage (formally a retro-[4+4] cycloaddition) of the strained C=C cyclopropane bonds generating intermediate 7. Finally, a retro-[2+2+2] cycloaddition leads to the extrusion of the side aromatic groups and formation of the C_{60} structure (Scheme 4).

The last step (7 to C_{60}) is likely to have the highest activation energy. We postulated that a lower energy reaction profile could be followed in presence of N-phenylmaleimide, a strong dienophile that was expected to react readily with the intermediate 7 in a [4+2] cycloaddition to afford adduct 8 which is a good substrate for a retro [4+2] cycloaddition to regenerate the C_{60} structure. These predictions were confirmed experimentally by reacting compound H_2O@3 with N-phenylmaleimide in 1-chloronaphthalene under reflux conditions. After 20 hours a clean conversion to H_2O@C_{60} was observed and column chromatography afforded the product in 90% yield. Further purification by sublimation gave pure H_2O@C_{60} in 72% overall yield (Scheme 3). The same route has been followed to complete the synthesis of D_2O@C_{60} in identical yield.

Komatsu has reported the synthesis of H_2@C_{60} in 8 steps and 8% overall yield via insertion of H_2 into a different cage-opened fullerene at 800 atm and 200 °C. Given the efficiency of the opening/closure described above a more convenient synthesis seemed possible. Incorporation of molecular hydrogen into 2

(formed \textit{in situ} from 1 using 3 Å molecular sieves) at 120 °C and 120 atm H_2 for 20 h gave H_2@1 after work-up with a 60% filling factor. The lower temperature (120 °C of 200 °C) allowed reasonable incorporation at moderate pressures. It is likely that we would obtain complete filling at the high pressures (800 atm) used previously. In order to test if the system could be closed without the loss of the endohedral hydrogen molecule, a mixture of H_2O@1 and H_2@1 was reacted with (PrO)P in refluxing toluene. All the endohedral hydrogen was lost while all the water was retained inside. The problem was overcome by carrying out the phosphite reaction under hydrogen pressure. Thus compound 1 was heated to 120 °C in o-dichlorobenzene under hydrogen pressure (120 atm) in the presence of molecular sieves to give H_2@2 (60% H_2 incorporation). The bomb was then depressurised and (PrO)P or PrH_p was added before pressurising with hydrogen again and heating to 120 °C overnight. The reactions afforded 60% filled H_2@3 in 50% yield and 60% filled H_2@5 in 84% yield respectively. Both H_2@3 and H_2@5 can be reacted in an analogous way as already described for H_2O@3 and H_2O@5 to isolate 60% filled H_2@C_{60} (Scheme 5).

In conclusion a systematic study of the H_2O@C_{60} synthesis developed by Murata\textsuperscript{2} has been carried out. It has been demonstrated that 78% incorporation of H_2O and D_2O into compound 1 can be achieved without the need for high pressure equipment. Treatment of hemiacetal 1 with (PrO)P at room temperature gave the reduced product 4 and H_2O@4 was a major by product during the (PrO)P induce closure of H_2O@1 to give H_2O@3. Dehydration of hemiacetal 1 to give tetraketone 2 before reaction with (PrO)P at room temperature gave 3 without formation of 4. A new partial closure procedure from H_2O@1 using PPh_3 allowed H_2O@5 to be isolated for the first time, and subsequent deoxygenation with (PrO)P gave H_2O@3 in improved overall yield. A new method for closing the fullerene H_2O@3 to afford H_2O@C_{60} was developed using a Diels–Alder/retno-Diels–Alder sequence which gave substantially higher yields than the known pyrolys method, and was readily scalable. Overall pure sublimed H_2O@C_{60} (78% H_2O incorporation) was synthesised in 15% yield from C_{60}. D_2O@C_{60} uncontaminated with HOD@C_{60} was made in similar yield. The same synthetic route has been successfully applied to the formation of H_2@C_{60} the large size of the orifice of compound 2 enabling a 60% incorporation of H_2 at 120 °C and 120 atm. These advances will lead to a greatly improved availability of the important molecular endofullerenes H_2O@C_{60} and H_2@C_{60}, and their isotopologues.

Scheme 4 Proposed mechanism for the conversion of 3 into C_{60}. The C_{60} skeleton other than the orifice carbons (solid line) has been omitted for clarity.
Notes and references