An optimised scalable synthesis of $H_2O@C_{60}$ and a new synthesis of $H_2@C_{60}$†

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New high-yielding synthetic routes to the small-molecule endo-fullerenes $H_2O@C_{60}$, $D_2O@C_{60}$ and $H_2@C_{60}$ 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_2O 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[5,6] and nuclear magnetic resonance (NMR).[3,5,7] The stability and homogeneity of endofullerenes such as $H_2@C_{60}$ and $H_2O@C_{60}$ 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.[7] Apart from their intrinsic interest, such observations may underpin new routes to the generation of nuclear hyper-polarization, 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 endo-hedral molecule. The final (reclosure) stage is the most difficult and has been accomplished only by Komatsu and Murata using two different routes leading to $H_2@C_{60}$ (8 steps, 8% overall yield),[1] and $H_2O@C_{60}$ (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 $H_2O@C_{60}$ 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 **$H_2O@1$** is then reduced with $(^iPrO)_3P$ to **$H_2O@3$** which in turn is pyrolysed under vacuum to produce $H_2O@C_{60}$ (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.
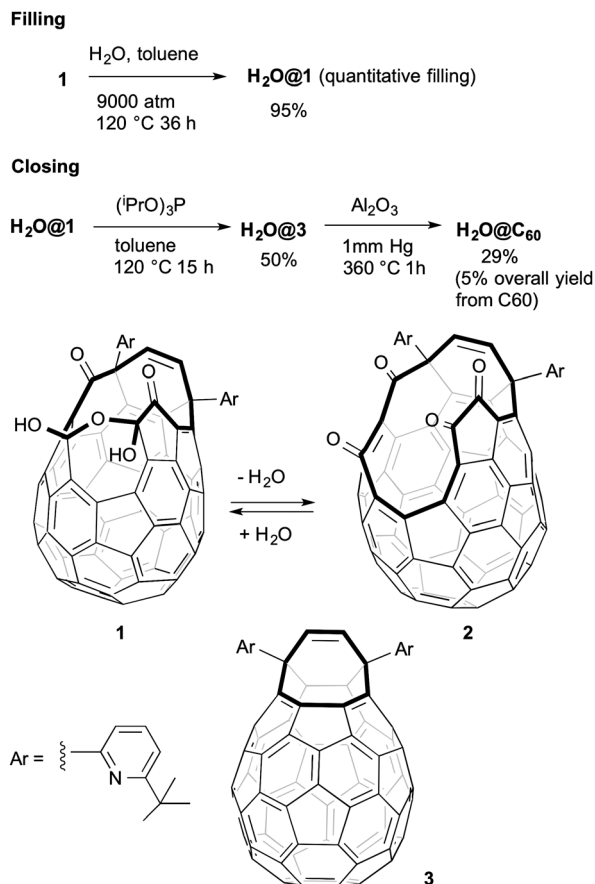
Heating a solution of **1** in toluene in an NMR tube in the presence of water (5.6 equiv.) at 120 °C reached a maximum of 23% incorporation after 36 h reflecting the equilibrium situation. Increasing reaction time further gave substantial decomposition. Changing to a sealed tube which could be uniformly 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-chloronapthalene, 67%).

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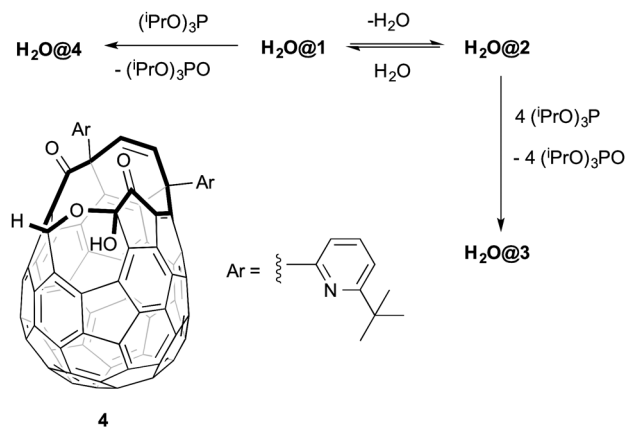*E-mail: rjw1@soton.ac.uk*

Filling

Closing

Scheme 1 $H_2O@C_{60}$ synthesis.[2]

Scheme 2   Reactivity of $H_2O@1$ and $H_2O@2$ towards triisopropyl phosphite.

Using 1-chloronapthalene as the solvent and lowering the temperature to 100 °C gave 78% H_2O incorporation after 48 h providing a practical alternative to high pressure procedures. The same process can be extended to the synthesis of $D_2O@1$ but to avoid contamination with $HDO@1$ and $H_2O@1$ it was necessary to pre-form 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-chloronapthalene, addition of D_2O and heating as above gave $D_2O@1$ with no $HOD@1$ or $H_2O@1$ visible by ^{1}H NMR spectroscopy. Compound 2 was recently isolated using a different protocol.[13]

In an effort to complete the synthesis of $H_2O@C_{60}$ our attention turned to suturing $H_2O@1$. Unfortunately when compound $H_2O@1$ was reacted with $(^iPrO)_3P$ the expected product $H_2O@3$ was isolated in only 34% yield. The same reaction mixture yielded 31% of the novel compound $H_2O@4$. The structure of the latter can be deduced from the appearance in the ^{1}H 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 4 is inert to $(^iPrO)_3P$ and $H_2O@4$ 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 $(^iPrO)_3P$ at room temperature to afford compound 3 in 33% yield without contamination by 4. It is likely that under the reported closure conditions[2] it is a mixture of $H_2O@1$ and $H_2O@2$ formed *in situ* which are reacting with $(^iPrO)_3P$ to give varying mixtures of $H_2O@4$ and $H_2O@3$ (Scheme 2).

In order to overcome this side reactivity of $H_2O@1$ towards alkyl phosphites we looked at alternative reagents and found that reaction with excess Ph_3P at 120 °C cleanly gave compound $H_2O@5$, isolated in 84% yield. Compound $H_2O@4$ was not formed and, even with longer reaction times, reduction to compound $H_2O@3$ was not observed. No endohedral water was lost in the formation of $H_2O@5$ for which this reaction provides the first synthesis. Compound $H_2O@5$ could be reacted with excess $(^iPrO)_3P$ to give $H_2O@3$ which was isolated after chromatography in 84% yield. In comparison with the reported direct reaction with $(^iPrO)_3P$,[2] the yield of $H_2O@3$ 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 $H_2O@3$ into $H_2O@C_{60}$. The reported yield of 29% was achieved by vacuum pyrolysis (360 °C) of $H_2O@3$
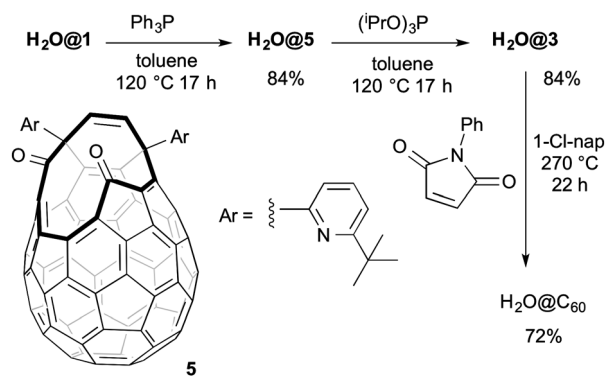
Scheme 3   Optimised suturing procedure of compound $H_2O@1$ to give $H_2O@C_{60}$.
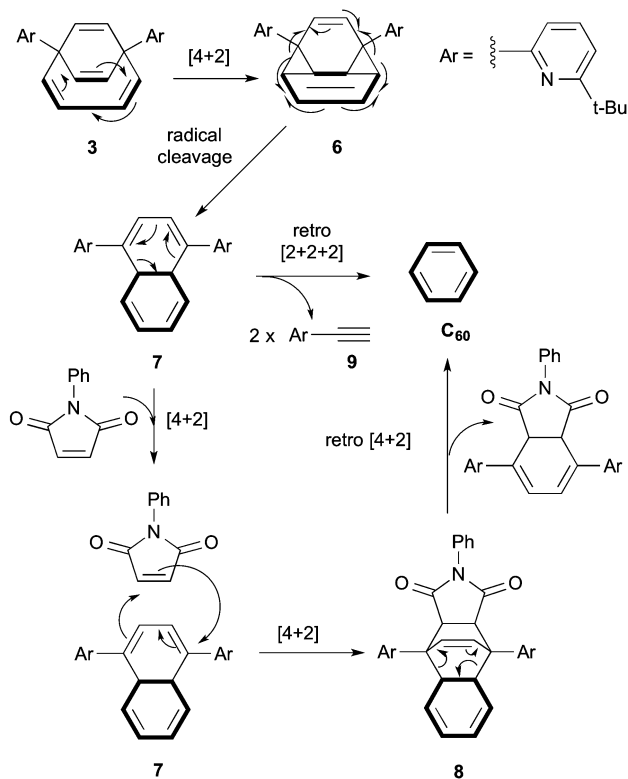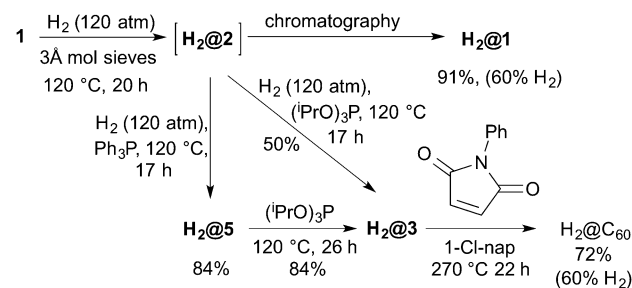
Scheme 4 Proposed mechanism for the conversion of **3** into C_{60}. The C_{60} skeleton other than the orifice carbons (solid line) has been omitted for clarity.

Scheme 5 Synthesis of $H_2@C_{60}$ from **1**.

dispersed on dry neutral alumina.[2] 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.[1] Given the efficiency of the opening/closure described above a more convenient synthesis seemed possible. Incorporation of molecular hydrogen into **2**

(formed *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 *cf.* 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.[1]

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 $(^iPrO)_3P$ 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 $(^iPrO)_3P$ or Ph_3P 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[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 $(^iPrO)_3P$ at room temperature gave the reduced product **4** and $H_2O@4$ was a major by product during the $(^iPrO)_3P$ induce closure of $H_2O@1$ to give $H_2O@3$. Dehydration of hemi-acetal **1** to give tetraketone **2** before reaction with $(^iPrO)_3P$ 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 $(^iPrO)_3P$ 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/retro-Diels–Alder sequence which gave substantially higher yields than the known pyrolysis 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.

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