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Fullerenols

Facile Synthesis of Isomerically Pure Fullerenols and Formation of Spherical Aggregates from $C_{60}(OH)_8$**

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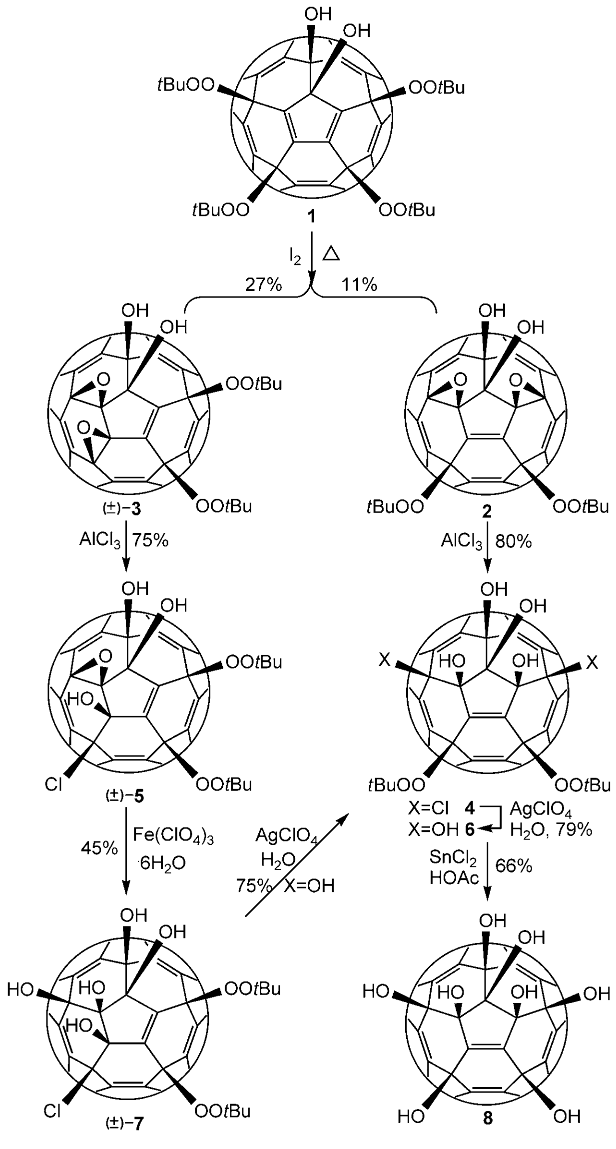
Polyhydroxylated fullerene (fullerenol or fullerol) is among the best studied fullerene derivatives. A number of methods have been reported for its synthesis including both acidic[1] and basic hydroxylation methods.[2] Recently, fullerenols with an estimated 36–40 hydroxy groups were prepared through further hydroxylation of $C_{60}(OH)_{12}$.[3] The excellent radical scavenging ability and low toxicity of fullerenols make them efficient antioxidants for potential medicinal applications.[4] In addition, fullerenols are also good visible-light sensitizers. For example, fullerenol-modified titania catalyzes photooxidative and photoreductive conversions, including degradation of pollutants and production of hydrogen under visible light.[5]

In spite of extensive studies on their preparation and application, the precise structure of fullerenols remains unknown. Fullerenols used in all the known studies are complicated mixtures of compounds. It is impossible to isolate isomerically pure fullerenols even after exhaustive purification procedures. Thus, the exact number of OH groups and their relative locations on the cage are not determined. Hemiketal moieties are present in some cases.[6] Fullerenols prepared by reaction of C_{60} with aqueous NaOH solution were shown to be structurally and electronically complex radical anions.[7] To understand details of their bioactivity and develop practical fullerene-based medicines, the purity and identity of fullerenols is of crucial importance. New methods are needed to prepare isomerically pure multihydroxylated fullerenes. Here we report the preparation of the first isomerically pure multihydroxylated fullerene by reactions involving fullerene mixed peroxides.

Compound **1** was prepared from C_{60} in two steps as we previously reported.[8] Thermolysis converted two of the four peroxo groups in **1** into two epoxy moieties (Scheme 1). Addition of iodine improves the yields of **2** and **3**, presumably by reacting with radical species from thermolysis. The two epoxy groups in **2** were opened to give the vicinal chloro and hydroxy groups in **4** by treating it with $AlCl_3$. However, the same reaction with **3** only cleaved the less hindered epoxy group to form **5**. The remaining epoxy group in **5** was transformed into a vicinal diol moiety by treating it with hydrated iron(III) perchlorate. Compounds **4** and **7** were both



Scheme 1. Formation of fullerenols.

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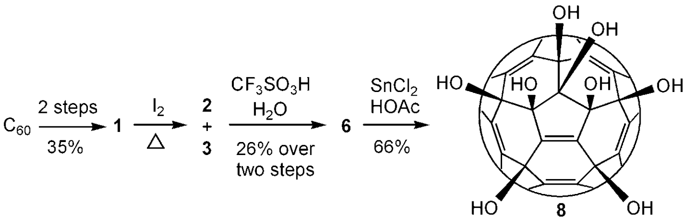
converted into the hexahydroxy derivative **6** by reaction with silver perchlorate in the presence of water. Finally the two remaining peroxo groups in **6** were reduced to hydroxy groups by tin(II) chloride to give fullerenol **8** with eight hydroxy groups.

Reactions of fullerene mixed peroxides depend significantly on the reactivity of the reagents and local structure of the peroxo groups. Reduction of the peroxo groups in **6** with tin(II) chloride gave a good yield, but the same reaction with other peroxo compounds such as **1** gave complicated mixtures. Similarly, hydrated iron(III) perchlorate could not convert **2** or **3** in THF directly into hexahydroxylated **6** by opening the two epoxy groups, even though it could transform the epoxy group of **5** into a vicinal diol moiety. The two peroxo groups in compounds **2** to **6** could not be converted into epoxy groups by thermolysis or photolysis.

Spectroscopic data are in agreement with the structures depicted in Scheme 1. Compounds **2**, **4**, **6**, and **8** are C_s-symmetric according to their ^{1}H and ^{13}C NMR spectra. The C_1-symmetric nature of **7** shows that the epoxy group in **5** must be located between the hydroxy groups. The isomer of **5** with the epoxy group on the same hexagon as the peroxo group would give a C_s-symmetric compound in the reaction with iron(III) perchlorate. However, these NMR data cannot determine the relative locations of the Cl and OH groups in **4**, **5**, and **7**. Mechanistic considerations support the proposed structures with the Cl atom on the outside.[9] In Lewis acid promoted epoxy opening reactions, the intermediate cation with positive charge on the outside pentagon should be favored, since two adjacent double bonds stabilize the cation, as opposed to just one double bond if the cation is located on the central pentagon.

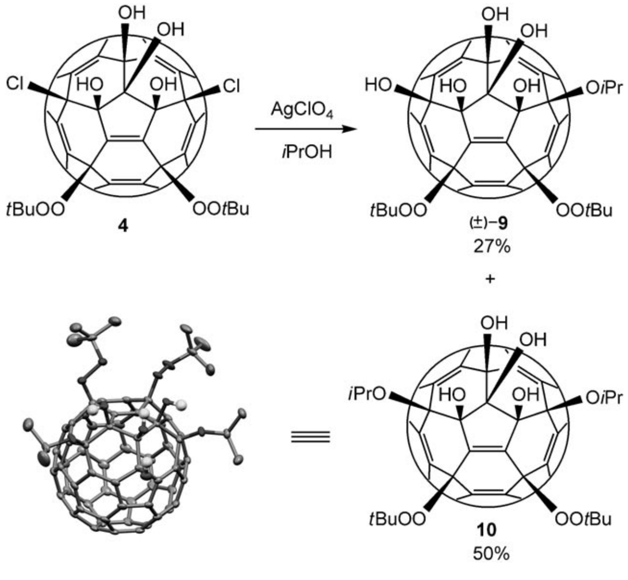
To obtain conclusive evidence about the locations of Cl and OH groups in **4**, **5**, and **7**, we tried to grow single crystals under various conditions. Conversion of the Cl groups in **4** into isopropoxyl groups proved to be successful (Scheme 2). Single crystals of **10** were obtained by slow evaporation of its solution in CS_2/hexane. The X-ray structure confirmed that the two isopropyl groups are on the outside. Thus the two Cl atoms in its precursor **4** should also be on the outside. Replacement of the Cl atoms must follow a S_N1 mechanism. It is unlikely for any rearrangement process to be involved. The double bond on the central pentagon of **10** appears to be the shortest bond on the cage (1.328 Å). Unlike other curved double bonds on the cage, this double bond is essentially planar, with torsion of less than 0.2°.

Octahydroxy fullerene **8** is of interest for possible applications. To improve its yield, a more efficient procedure was developed (Scheme 3). Here the unseparated mixture of isomers **2** and **3** was treated with trifluoromethanesulfonic acid to form hexahydroxy fullerenol **6**, which was then converted into **8** as in Scheme 1. The final yield of **8** is 6% starting from C_{60}.



Scheme 3. Preparation of fullerenol **8**.

Location of all OH groups in the same hemisphere renders fullerenol **8** $C_{60}(OH)_8$ amphiphilic. The assembly behavior of $C_{60}(OH)_8$ in aqueous solution differs from that of charged fullerenes $C_{60}Ph_5K$ reported by Nakamura, Chu et al.[10] in which the OH groups are less hydrophilic and are distributed on the fullerene surface with the capacity to form intermolecular hydrogen bonds.[11] Laser light scattering studies indicated that the assembly of fullerenol in aqueous solution is highly concentration dependent. As shown in Figure 1 A, $C_{60}(OH)_8$ formed aggregates with a hydrodynamic radius R_h of about 100 nm at 1.0×10^{-5} mol L^{-1} in pure water. An AFM image (Figure 1 B) indicated that the morphology of the aggregates is spherical. The height of the dried aggregate of about 6 nm is much smaller than R_h in aqueous solution, and suggests that the aggregate formed in



Scheme 2. Synthesis and X-ray structure of **10**. For clarity hydrogen atoms on the methyl groups are not shown.

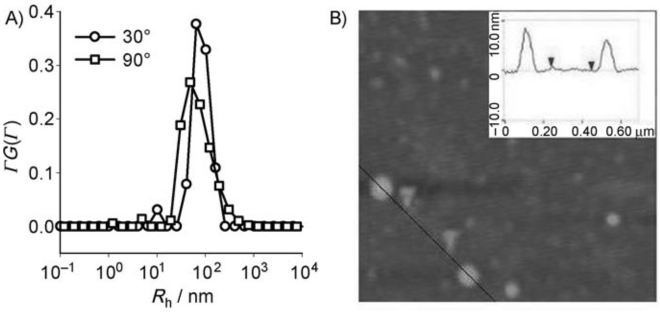


Figure 1. A) Hydrodynamic radius distribution and B) AFM image of fullerenol $C_{60}(OH)_8$.

solution is of low density. Since the aggregate is much larger than $C_{60}(OH)_8$, it contains multidomains rich in either OH groups or fullerene shells; therefore, $C_{60}(OH)_8$ has the potential to serve as carrier for hydrophobic or hydrophilic drugs.

In summary, we have prepared a series of fullerene derivatives with 2–8 hydroxy groups. The process involves direct reduction of peroxo groups to hydroxy groups and thermolysis of peroxo groups to epoxy groups, which were further converted into hydroxy groups by hydrolysis. The octahydroxy fullerene $C_{60}(OH)_8$ is slightly soluble in water, exhibits amphiphilic behavior, and forms spherical aggregates in water. Potential applications of the fullerenols prepared here, such as biological activity, will be investigated in future studies.

Experimental Section

6: I_2 (500 mg) was added to a stirred solution of **1**[8b] (793 mg, 0.714 mmol) in toluene (200 mL) at room temperature under nitrogen atmosphere. The resulting solution was stirred and heated for 16 h in an oil bath at 110 °C. The solution was concentrated to 10 mL at 55 °C under reduced pressure. The concentrated solution was purified by chromatography on a short silica gel column with toluene as eluent to remove I_2. Then the solvent was changed to toluene/petroleum ether/ethyl acetate (20/10/1). The first, red band was unchanged compound **1** (283 mg). The remaining second and third red bands were washed down with toluene/ethyl acetate (10/1), and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (150 mL), and water (30 μL) was added. CF_3SO_3H (3 μL) dispersed in chloroform (2 mL) was added to the stirred solution at 25 °C. The reaction was monitored by TLC. After about 25 min, the reaction was quenched by adding water. After washing three times with water, the oil layer was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was subjected to chromatography on a silica gel column with chloroform/methanol (100/1) as eluent. The major red band was compound **6** (189 mg, yield 26 %, or 41 % based on recovered **1**). Characterization data: ^{1}H NMR (400 MHz, [D$_8$]dioxane/C_6D_6): $\delta = 1.41$ (s, 18 H), 6.64 ppm (br, 6 H); ^{13}C NMR (100 MHz, [D$_8$]dioxane/C_6D_6, all signals represent 2 C except where noted): $\delta = 151.36$, 148.76, 148.61, 148.53, 148.47 (3 C), 148.43 (4 C), 148.23, 148.02 (6 C), 147.78 (1 C), 146.27, 145.04, 144.60, 144.15, 143.60 (4 C), 143.39, 143.36, 143.32, 143.10, 143.06, 142.61, 139.82, 138.42, 83.05, 81.85, 81.14, 81.08 (1 C), 75.90, 74.36 (1 C), 26.33 ppm (6 CH_3); IR (KBr): $\tilde{\nu} = 3413$, 2976, 2929, 1629, 1387, 1363, 1188, 1151, 1116, 1055, 730 cm^{-1}; ESI-HRMS calcd for $C_{68}H_{24}NaO_{10}$ $[M+Na^+]$: 1023.1262; found: 1023.1240.

8: Compound **6** (35 mg, 0.035 mmol) was dissolved in a mixture of $CHCl_3$ (28 mL) and MeOH (7 mL). Anhydrous $SnCl_2$ (796 mg, 4.2 mmol) and HOAc (242 μL, 4.2 mmol) were added. The resulting solution was stirred for 1 h at 50 °C. The reaction was quenched by adding water. The precipitate was separated by centrifugation and washed with water three times and then with 2 N HCl. The solid was subjected to chromatography on a silica gel column with THF/chloroform/water (30/10/1) as eluent. The main yellow band was compound **8** (20 mg, 66 %). Characterization data: ^{1}H NMR (400 MHz, [D$_6$]DMSO) no conclusive signals; ^{13}C NMR (100 MHz, all signals represent 2 C except where noted): $\delta = 151.58$ (4 C), 151.33, 151.02, 148.22, 148.14, 148.05, 148.02, 147.94 (1 C), 147.84, 147.72, 147.73, 147.49, 147.31 (1 C), 146.71, 144.52, 144.17, 144.03, 143.72, 143.59, 143.39, 143.27, 143.15, 142.74, 142.43, 141.27, 140.60, 83.33 (1 C), 82.11, 75.31, 73.90 (1 C), 71.73 ppm; IR (KBr): $\tilde{\nu} = 3333$, 1621, 1377, 1109, 1043 cm^{-1}; UV/Vis (1,4-dioxane): 256, 271, 349, 391 nm; ESI-HRMS calcd for $C_{60}H_7O_8$ $[M-H^-]$: 855.0146; found: 855.0188.

Crystal data for **10**: crystal size $0.26 \times 0.21 \times 0.16$ mm, triclinic, space group $P\bar{1}$, $a = 13.412(3)$, $b = 14.052(3)$, $c = 14.563(3)$ Å, $\alpha = 86.59(3)$, $\beta = 84.70(3)$, $\gamma = 64.58(3)°$, $V = 2467.7(9)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.563$ Mg m^{-3}; $T = 173(2)$ K; 33 305 reflections collected, 11 293 independent ($R_{int} = 0.0449$) included in the refinement; max./min. transmission 0.9711/0.9536; refinement by full-matrix least-squares method on F^2; final R indices $[I > 2\sigma(I)]$: $R1 = 0.0733$, $wR2 = 0.1895$, R indices (all data): $R1 = 0.0792$, $wR2 = 0.1955$.

CCDC 767434 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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