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Synthesis of Open-Cage Ketolactam Derivatives of Fullerene C_{60} Encapsulating a Hydrogen Molecule

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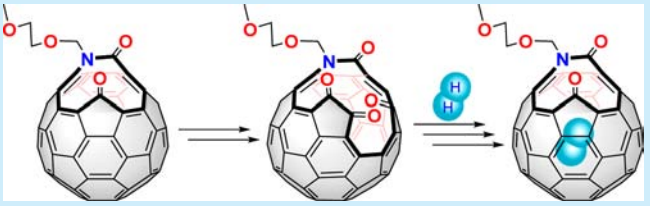
Supporting Information

ABSTRACT: A novel open-cage fullerene C_{60} derivative having a bis(hemiketal) moiety was synthesized by the reaction of C_{60}-*N*-MEM-ketolactam (MEM: 2-methoxyethoxymethyl) with *N*-methylmorpholine *N*-oxide in the presence of water. The structure was clearly determined by single crystal X-ray analysis. Further enlargement of the opening was performed by treatment with trifluoroacetic anhydride to give the tetraketo derivative having a 15-membered ring opening. For H_2-insertion into the cage, the derivative was exposed to a high pressure of H_2. After the encapsulation, the opening size was reduced to the original one while keeping the hydrogen molecule inside the cage. This compound can be a possible precursor for endohedral azafullerenes encapsulating a hydrogen molecule.



Open-cage fullerene derivatives[1] have been attracting considerable attention because they are interesting molecules for host−guest chemistry and can be used as precursors for endohedral fullerenes encapsulating atom(s) or small molecule(s) as well as heterofullerenes.[2] We have previously synthesized several endohedral fullerenes, which encapsulate hydrogen molecule(s),[3,4] a helium atom,[5] and a water molecule,[6] by applying the molecular surgery method.[7] In this method, open-cage fullerene derivatives play an important role, which should meet two requirements for the synthesis of endohedral fullerenes; (a) the opening size is large enough for a guest molecule to be inserted into the cage and (b) the opening can be readily reduced to a smaller one to prevent the escape of the guest molecule.

As shown in Figure 1, C_{60}-*N*-MEM-ketolactam **1** is the first open-cage C_{60} derivative reported by Wudl et al. in 1995[8] and is also known as a precursor for azafullerenes such as $(C_{59}N)_2$[9] and $C_{59}NH$,[10] in which one of the C-atoms of C_{60} is replaced by a N-atom. At the present time, these azafullerenes are the only example of heterofullerenes, for which rational synthetic pathways have been successfully accomplished.[9−11] We expected that, if a small molecule is entrapped inside the $C_{59}N$ cage, magnetically interesting properties, which are different from those for endohedral C_{60}, would be observed due to the unpaired valence electron on the cage of the $C_{59}N$ radical. However, the size of the 11-membered ring opening of **1** is too small even for a helium atom to enter the cage.[8] Thus, enlargement of the opening of **1** is needed for the first step to obtain endohedral azafullerenes.

Regarding the chemical modification of the opening of **1**, structural determination for its derivatives is critical because there are four conjugated reactive olefins **a**−**d** on the rim of the opening. In 2003, the first example was reported by Iwamatsu et al.[12] They synthesized an open-cage C_{60} derivative having a 15-membered ring opening by the reaction of **1** with aromatic hydrazines through the migration of two H-atoms with the regioselective cleavage of a C=C double bond. They also performed the related reaction using *o*-phenylenediamine to give an open-cage C_{60} derivative having a 19-membered ring opening in 2004.[13] Orfanopoulos et al. also reported two ketolactam derivatives having 12- and 13-membered ring openings, which

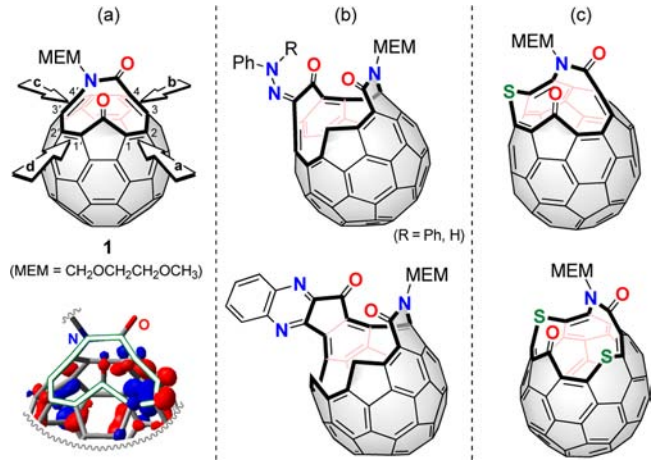


Figure 1. MEM-substituted ketolactam derivatives of C_{60}, having an *n*-membered ring opening: (a) n = 11 as C_{60}-*N*-MEM-ketolactam **1**, reported by Wudl et al. and the LUMO near the opening (B3LYP/6-31G*); (b) n = 15 and 19, reported by Iwamatsu et al.; (c) n = 12 and 13, reported by Orfanopoulos et al.

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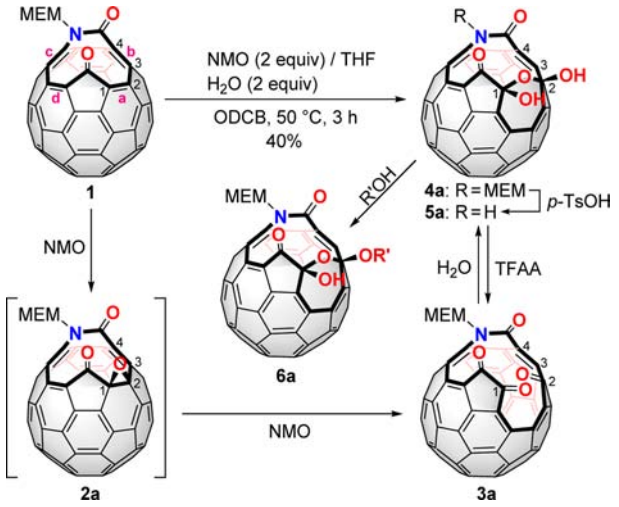
contain S-atom(s) on the rim, in 2004[14] and 2007,[15] respectively. Method development to repair the enlarged opening on these derivatives[12−15] remains a challenging issue. Herein, we report the enlargement of the opening of **1** to provide novel open-cage C_{60} derivatives, their encapsulation of a hydrogen molecule, and the restoration of the opening to the original one.

Our group previously reported a method to enlarge the opening by *N*-methylmorpholine *N*-oxide (NMO) as a nucleophilic oxidant in the presence of a small amount of water.[6] As shown in Scheme 1, we applied this method to **1** in *o*-

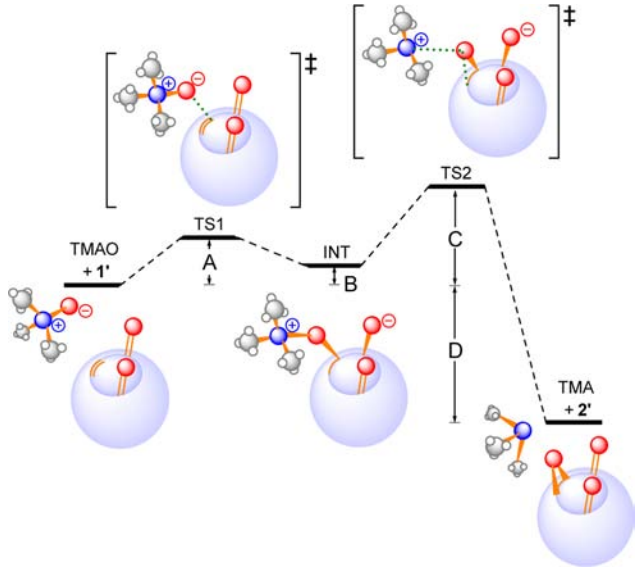
Scheme 1. Synthesis of Novel Open-Cage C_{60} Derivatives



dichlorobenzene (ODCB) to give C_{60}-*N*-MEM-bis(hemiketal) **4a** in 40% yield. Under the same conditions, trimethylamine *N*-oxide (TMAO) instead of NMO resulted in a similar yield (37%) of **4a**. Since **4a** was found to be reactive to methanol, ethanol, and 2-propanol (even trace amounts of ethanol as a stabilizer in chloroform), these alcohols cannot be used as polar solvents for chromatographic purification of **4a**. When **4a** was exposed to these alcohols, formation of monoalkylated derivative **6a** (R′ = Me, Et, or *i*Pr) having a ketal moiety was observed by the ^{1}H NMR and APCI MS spectra. In addition, the HPLC analyses using the Buckyprep (toluene) column revealed that **4a** tends to be adsorbed on the stationary phase and no peak was observed. The Buckyprep-M (toluene) and ODS (octadecylsilyl, toluene/acetonitrile) columns were also unsuitable. The 5PBB column, which is silica-based column modified with pentabromobenzyl groups, is available for the analysis of **4a** (retention time, 14.3 min for **4a** and 22.4 min for **1**; mobile phase, toluene/acetonitrile = 7/3; flow rate, 1 mL/min; temperature, 50 °C; detection, 326 nm). The structure of **4a** was confirmed by APCI MS, ^{1}H and ^{13}C NMR, UV−vis, and IR. The molecular ion peak of **4a** was observed at *m*/*z* 905 with a fragment peak at *m*/*z* 887 corresponding to tetraketo derivative **3a**, which would be formed by the elimination of a water molecule from the rim of the opening under the MS conditions. The ^{1}H NMR spectrum in DMSO-d_6 showed two signals for OH groups at δ 9.46 and 9.63 ppm, and the ^{13}C NMR spectrum in $CDCl_3$ showed two characteristic sp^3-carbon signals corresponding to hemiketal carbons at δ 95.90 and 109.25 ppm. These NMR data support the structure of **4a** shown in Scheme 1.

The theoretical calculations explained the selective formation of bis(hemiketal) that occurred on bond **a**. The epoxidation of **1**, which takes place at one of the C=C double bonds **a**, **b**, **c**, and **d**, is considered to be the first step of this reaction. The theoretical calculations at the B3LYP/6-31G* level of theory[16] demonstrated that the LUMO is relatively localized at the butadiene unit (C1=C2−C3=C4) including bonds **a** and **b** (Figure 1a). Epoxide **2a** formed by the reaction on bond **a** is 9.0 kcal mol^{-1} more stable than the other epoxide formed by the reaction on bond **b**. To discuss more details of the epoxidation with kinetic and thermodynamic perspectives, we investigated the reaction mechanism using model compound **1**′, in which the MEM group was replaced by a methyl group. The calculations were conducted at the M06-2X/6-31G* level of theory with the SMD solvation model[17] in THF. Table 1 summarizes the Gibbs

Table 1. Changes in Gibbs Energies for the Epoxidation of 1′ with TMAO



addition position[a]	epoxide	ΔG° (kcal mol^{-1})[b] A	B	C	D
C1	**2a**′	10.3	4.2	16.2	−33.6
C2	**2a**′	10.3	6.4	22.9	−33.6
C3	**2b**′	11.1	4.2	25.9	−25.4
C4	**2b**′	11.0	6.2	19.1	−25.4

[a]The labeling numbers are shown in Figure 1a and Scheme 1. [b]The changes in Gibbs energies (M06-2X/6-31G* with the SMD solvation model in THF at 25 °C).

energies of the stationary points and transition structures for the epoxidation on the C=C double bonds **a**−**d**. Regarding the nucleophilic attack of TMAO to one of the double bonds on **1**′, formation of each **INT** on C1−C4 seems less selective because all A and B values are quite similar to each other. Then, the sequential elimination of trimethylamine (TMA) from each **INT** was calculated to give product **2a**′ or **2b**′, and the reaction pathway was found to be determined by the value of C. Among the possible reaction pathways, the reaction on C1 needs the least value of C (16.2 kcal/mol), and formation of epoxide **2a**′ is more exothermic than **2b**′ as indicated by the value of D (−33.6 kcal/mol for **2a**′ and −25.4 kcal/mol for **2b**′). These results can explain the regioselective formation of epoxide **2a**, which reacts with the second oxidant to give **3a**. The resulting **3a** affords **4a** by the addition of a water molecule to carbon C2 on the opening.[6]

After many trials, we obtained the single crystal of **4a** from *p*-xylene solution and the solid state structure was unambiguously

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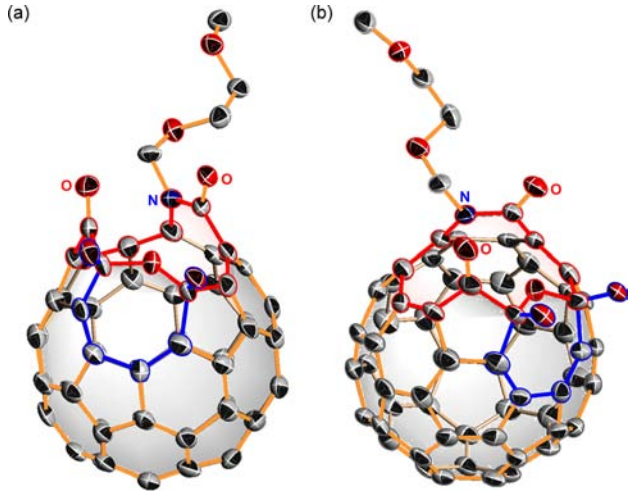

Figure 2. X-ray structure of **4a**: (a) side and (b) front views. Thermal ellipsoids are shown at 50% probability level. Solvent molecules and H-atoms are omitted for clarity.

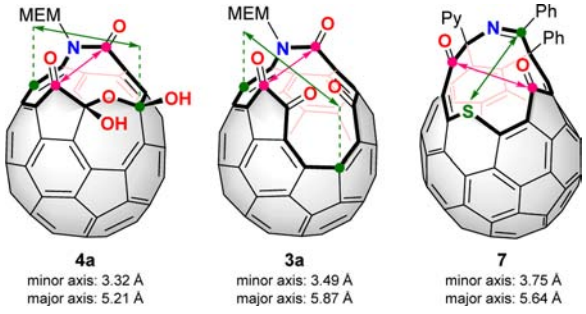

Figure 3. Opening sizes of **4a**, **3a**, and **7**: **4a**[18] and **7**,[20,21] crystal structures; **3a**, calculated structure (B3LYP/6-31G*). The 2-pyridyl group was abbreviated as Py.

determined by X-ray analysis (Figure 2).[18] This is a rare example for the solid-state structure of C_{60} derivatives with a flexible MEM group.[19] It was shown that **4a** has a 12-membered ring opening with an ellipsoidal shape with diameters of 3.319(16) Å along the minor axis and 5.209(18) Å along the major axis (Figure 3). The size of the opening is slightly smaller than that of open-cage C_{60} derivative **7** having a 13-membered ring opening reported by our group (3.75 Å along the minor axis and 5.64 Å along the major axis[20,21]), which can encapsulate a hydrogen molecule efficiently. Therefore, the opening size of **4a** is considered to be insufficient to insert a hydrogen molecule into its cage. For a larger opening, tetraketo derivative **3a** would be a suitable candidate. The theoretical calculations at the B3LYP/6-31G* level of theory showed that **3a** has a 15-membered ring opening with 3.49 Å along the minor axis and 5.87 Å along the major axis, which are close to those of **7**.

The enlargement of the opening of **4a** was investigated through a dehydration reaction from the bis(hemiketal) moiety. The reaction of **4a** with an excessive amount of trifluoroacetic anhydride (TFAA) at rt for 3 h gave tetraketo derivative **3a**, quantitatively. In the presence of water or by column chromatography on silica gel, **3a** readily turned back to **4a**. Other dehydrating agents such as molecular sieves 4A (MS4A) and $MgSO_4$ did not work well, resulting in unrecoverable adsorption on MS4A and/or decomposition. In the case of the reaction of **4a** with *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O), removal of the MEM group took place to give hardly soluble **5a** in 50% yield (Scheme 1). This result is consistent with the report by Orfanopoulos et al. on the reactivity of the ketolactam derivative containing a S-atom in the rim of the opening shown in Figure 1c.[14]

The electrochemical properties of **1**, **4a**, and **3a** were studied by cyclic voltammetry in ODCB (Figure 4). The first reduction

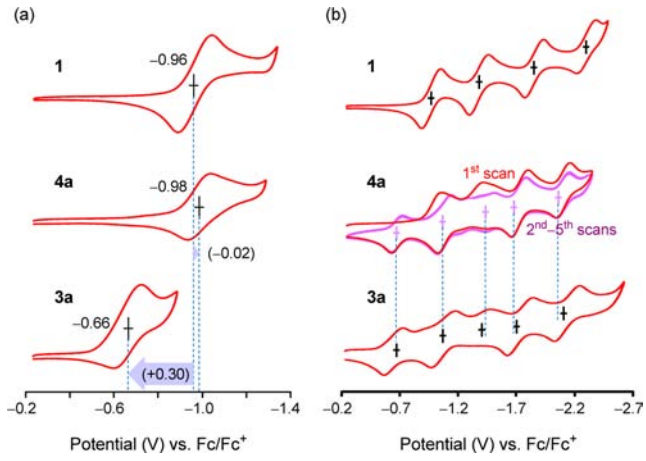

Figure 4. Cyclic voltammograms of **1**, **4a**, and **3a** using 1 mM samples with 0.1 M *n*-$Bu_4N{\cdot}BF_4$ in ODCB at a scan rate of 20 mV s^{-1}. (a) scans for the first redox waves and (b) full scans within the electrochemical window of the solvent.

potential of ketolactam **1** (−0.96 V vs Fc/Fc^+) was close to that of **4a** having a bis(hemiketal) moiety (−0.98 V). On the other hand, the first reduction potential of **3a** (−0.66 V) was anodically shifted by 0.30 V compared with that of **1**, due to the two additional carbonyl groups generated from the bis(hemiketal) moiety, which lead to a significant decrease of the LUMO level. Bis(hemiketal) **4a** showed interesting electrochemical behaviors. After the first scan from −0.23 to −2.3 V for **4a**, the new redox wave was observed at −0.66 V, keeping its appearance in the following scans. Since this reduction potential is the same value as that for **3a**, tetraketo derivative **3a** was probably generated from **4a** after electrochemical reduction followed by elimination of a water molecule in the EC mechanism.

In advance of experiments for H_2-insertion, opening sizes of **3a** and **4a** were estimated by theoretical calculations at the M06-2X/3-21G level of theory. By comparison of the energies required for insertion of a hydrogen molecule, it was shown that **3a** has a larger opening than that of **4a** (total electronic energies; 23.5 kcal mol^{-1} for **3a** and 58.4 kcal mol^{-1} for **4a**).

Thus, H_2-insertion experiments were conducted using both **3a** and **4a** as powders, as well as in ODCB solutions under high-pressure conditions of H_2. It was found that **3a** and **4a** were not stable over 100 °C and some amounts of them thermally changed into MEM-deprotected derivative **5a** and 2-methoxyethylated derivative **6a** (2-methoxyethyl group supposedly came from the eliminated MEM group). However, we found that H_2-insertion into **3a** was possible above 150 °C and that **4a** can be also used as a substrate for H_2-insertion probably due to *in situ* dehydration to give **3a** at this temperature. Under the typical conditions (165 atm, 150 °C, 24 h), the formation of H_2@**3a** and H_2@**4a** were confirmed by ^1H NMR with the encapsulation ratio of 20−30% (Scheme 2). After purification by column chromatography on silica gel, H_2@**4a** was isolated in 48% yield.

Finally, we attempted to reduce the opening size of **4a**. In 2011, we reported a coupling reaction of two carbonyl groups on

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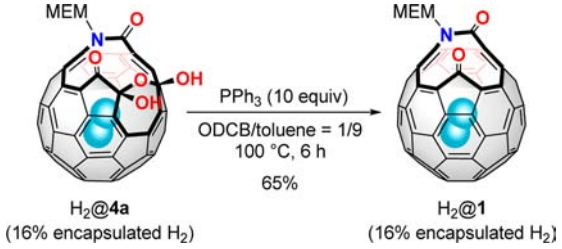
Scheme 2. Synthesis of H_2@3a and H_2@4a

the rim of an open-cage C_{60} derivative by using triisopropyl phosphite.[6] Under similar conditions (at 100 °C in toluene with an excessive amount of triisopropyl phosphite) mono- and di-isopropylated **4a** were formed as byproducts together with desired **1**. In contrast, when triphenylphosphine was used in place of triisopropyl phosphite, **4a** was converted to original **1** in 70% yield without considerable amounts of byproducts. Thus, we applied the same conditions to H_2@**4a** (16% encapsulation) in ODCB/toluene. The isolation of H_2@**1** was successful in 65% yield, maintaining the encapsulation ratio of the original 16% (Scheme 3). This is the first example of a possible precursor of

Scheme 3. Synthesis of H_2@1



endohedral azafullerenes such as $(H_2@C_{59}N)_2$ and $H_2@C_{59}NH$. The proton signals corresponding to the hydrogen molecule encapsulated inside **1**, **3a**, and **4a** appeared at δ −4.63, −5.94, and −5.54 ppm, respectively, which reflects the structural changes of the outer cage.[22]

In conclusion, we synthesized a novel open-cage fullerene derivative having a 12-membered ring opening (**4a**) as well as a 15-membered ring opening (**3a**). With regard to **4a**, the structure was clearly determined by X-ray analysis. H_2-insertion into these compounds was achieved by applying a high pressure of H_2. Finally, we succeeded in the isolation of H_2@**1** by the treatment of H_2@**4a** with triphenylphosphine. This compound is considered to be a precursor for endohedral azafullerenes encapsulating a hydrogen molecule. Further studies on the synthesis of $(H_2@C_{59}N)_2$ and evaluation of its properties are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and spectroscopic data, calculated geometries, and a cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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