

Surgery of fullerenes

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Recent attempts at the synthesis of endohedral fullerenes by organic reactions, so-called “molecular surgery” methods, are surveyed. The creation of an opening on the surface of fullerene cages allowed insertion of He, H₂, H₂O, or CO within the cages. An effective route to “suture” an opening was established to realize new endohedral fullerene, H₂@C₆₀. Further development of this operation as well as the properties and reactions of H₂@C₆₀ are summarized. Also the application of the encapsulated H₂ molecule as an NMR probe for the study of aromaticity of ionic fullerenes is described.

1. Introduction

Endohedral fullerenes, which encapsulate atom(s) or small molecule(s) within the spherical carbon cage, have attracted much attention from viewpoints of not only fundamental curiosity but also applied studies because of their unique electronic structures resulting from the interaction between the fullerene π -system and incorporated species.¹⁻³

The fullerenes encapsulating metal atom(s), so-called endohedral metallofullerenes, were first produced by laser-vaporization of graphite-metal oxides composite materials at the early stage of fullerene research, and later by the use of arc discharge technique.¹⁻³ In these metallofullerenes,

electron transfer from the incorporated metal atom(s) to the fullerene cage gives rise to characteristic behaviors which are totally different from those of empty fullerenes. Just for example as a representative case, La@C₈₂ (@ denotes that the La is encapsulated within the C₈₂ cage) should be better described as La³⁺@C₈₂³⁻ because of the electron transfer to endow La@C₈₂ with paramagnetic character. The redox behaviors of La@C₈₂, studied by cyclic voltammetry, revealed that abilities both as an electron acceptor and as a donor are higher than that of empty C₈₂.⁴ Furthermore, La@C₈₂ can be regarded as a “super atom”, since one-electron oxidation or reduction was shown to take place on the C₈₂ cage while keeping the positive charge of the La atom constant.⁵

It should also be noted that chemical and physical properties of fullerenes encapsulating a trimetallic nitride cluster such as Sc₃N@C₈₀ have been investigated in detail since its discovery by Dorn.⁶ In particular, Sc₃N@C₈₀ was shown to be even applicable as a part of an electron-donor/acceptor system.⁷

Recently, effort was made to develop highly efficient MRI (magnetic resonance imaging) contrast agents by the use of

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water-soluble fullerene derivatives encapsulating a paramagnetic Gd(III) ion.⁸ Besides the high performance as the contrast agent, the Gd(III)-incorporated fullerenes are of great significance from the viewpoint of safety because toxic Gd(III) ion is entirely isolated by the encapsulation in the fullerene cage.

Furthermore, small band gaps of endohedral metallofullerenes make them potential candidates for practical use, for example, in the field of molecular electronics such as thin film organic field effect transistor. Actually, endohedral metallofullerenes such as La₂@C₈₀⁹ or nanorods of La@C₈₂(Ad)¹⁰ (Ad = adamantylidene) have been shown to exhibit the FET properties.

However, development of such applications has so far been hampered by severe limitations of their availability that relied on the hard-to-control method of production. The conventional methods, i.e. arc-discharge or laser vaporization of graphite rods containing metal oxides or carbides, have almost no selectivity in controlling both the cage-size and product distribution. Generally, a pure product can be available only in mg-quantities after tedious separation procedures.

As another types of endohedral fullerenes, fullerenes encapsulating a noble-gas atom, such as helium, neon, argon, krypton, and even xenon were realized by Saunders by treating the fullerene powder under forced conditions (650 °C and 3000 atm of noble gases).¹¹ Although the occupation level of guest is so low as 0.1%,¹² incorporation of an NMR active nucleus, ³He, within fullerene cages has proven to be useful because it provides valuable information about magnetic shielding effect inside the fullerenes caused by ring currents of the spherically delocalized π -electrons.^{13,14} The NMR signal of ³He is also useful as a tool to follow chemical reactions taking place at the exterior of the fullerene cages.¹⁵

Recent investigation revealed that the reactivity of Xe@C₆₀ in [4+2] cycloaddition with 9,10-dimethylanthracene is substantially different from that of He@C₆₀ because π -electron cloud of the C₆₀ cage is pushed outward by the inside xenon atom.¹⁶ However, a low occupation level of the noble-gas atom within fullerenes (about 0.1%) and difficulty in isolation or enrichment in practical scale¹⁷ have apparently hampered the exploration of possibility of the endohedral fullerenes as functional materials. Hence, it is desirable to explore an entirely different approach that would lead to the macroscopic production of endohedral fullerenes.

2. Open-cage fullerenes

Under such circumstances it is quite appealing to produce the endohedral fullerenes by using pristine fullerenes as starting materials. In this connection, Rubin proposed a concept to realize endohedral fullerenes with the use of organic reactions, that is, “molecular surgery”.¹⁸ This approach consists of a series of steps, which are (1) “incision” of the fullerene cage to form an opening on the surface, (2) insertion of some small atom(s) or molecule(s) through the opening, and (3) “suture” of the opening to reproduce the fullerene cage while retaining the guest species.

The development of this approach has been a challenging

task for organic chemists for the past decade. Wudl reported, for the first time, two-step reactions to create an 11-membered-ring opening on the C₆₀ cage to give compound **1**.¹⁹ Unfortunately, however, the opening was found to be not large enough even for the smallest atom, helium, to pass through.²⁰ Rubin thereafter synthesized bisfulleroid derivative **2** with an eight-membered-ring opening and transformed it into Co(III) complex **3**.²¹ These works are unequivocally a stepping stone to the subsequent progress in the technique of incising the fullerene cage. Herein, we summarize recent achievements in the molecular surgical technique with the hope of encouraging the progress in research on the rational chemical synthesis as well as the application of endohedral fullerenes.

2.1 1,2,3,4,5,6-Hexasubstitution of fullerene C₆₀

Rubin proposed a strategy¹⁸ toward “incising” a fullerene cage through saturation of three adjacent C=C double bonds within one hexagonal ring. The subsequent [2+2+2] cycloreversion of the planarized cyclohexane ring was expected to give a fullerene derivative with such a large opening as a 15-membered ring (Fig. 1). Thus, a thermal reaction of C₆₀ with butadiene derivative **4** having two azido groups was conducted.²² This reaction was intended to proceed via initial addition of **4** (involving both a [4+2] cycloaddition and two 1,3-dipolar additions) to the three C=C double bonds in the same hexagon of C₆₀ to form compound **5** with a saturated cyclohexane ring. However, the obtained product was instead bislactam **6** having a 14-membered-ring opening produced through a series of reactions involving rearrangements, extrusion of two N₂ molecules, and addition of an O₂ molecule followed by dehydrogenation.²²

The synthesis of bislactam **6** is of considerable significance because the size of the opening was proved to be large enough for the first time for insertion of the smallest gaseous species such as a ³He atom or a H₂ molecule.²³ By treating a crystalline powder of **6** with 475 atm of ³He gas at 288-305 °C for 7.5 hours, a ³He atom was incorporated at an occupation level of 1.5%. A H₂ molecule was also introduced at an occupation level of 5% under the conditions of 100 atm of H₂ gas at 400 °C for 48 hours. A highly shielded ¹H NMR signal for the encapsulated H₂ was observed at $\delta = -5.43$ ppm. These results verified the feasibility of the strategy of molecular surgery approach.

Recently, Rubin succeeded in the synthesis of the desired 1,2,3,4,5,6-hexaadduct of C₆₀, **7**, by the reaction of bis-isobenzofuran adduct **8** with Pb(OAc)₄ in a substantially low concentration (1.0×10^{-5} M).²⁴ Unfortunately, however, the retro [2+2+2] ring-opening reaction at the strained cyclohexane ring of **7** to afford open-cage fullerene **9** did not take place due to the high activation barrier for this transformation and the thermal instability of product **9** as indicated by theoretical calculations (B3LYP/6-31G**//PM3 level). The origin of the high endothermicity of this ring-opening reaction is attributable to the formation of two strained C=C double bonds in oxabenzonorbornadiene moieties of **9**.

2.2 Bowl-shaped fullerenes

Bisfulleroid derivative **2**,²¹ synthesized by Rubin, possesses bridgehead C=C double bonds at the rim of the eight-membered-ring opening. Komatsu and Iwamatsu independently found that one of these double bonds in the derivatives of **2**: i.e., **10**²⁵ and **11**²⁶, can be readily cleaved via addition of photochemically generated singlet oxygen to give diketone derivatives **12**²⁵ and **13**,²⁷ respectively, with a 12-membered-ring opening.²⁸

The formation of **12** led to the successful achievement of “molecular surgery” as will be shown later, while derivative **13** was found to be a good precursor of various bowl-shaped fullerenes.²⁹

Thus, the opening of diketone **13** was greatly enlarged as reported by Iwamatsu. Although the detailed reaction mechanism is not clear yet, a reaction of **13** with a phenyl hydrazine proceeded at room temperature to give open-cage fullerene **14** having an sp³ methylene carbon within the rim of a 16-membered-ring opening.³⁰ The size of the ellipsoidal opening was estimated to be 6.5 Å for a longer axis and 3.8 Å for a shorter axis (B3LYP/3-21G level). When a solution of **14** in 1,1,2,2-tetrachloroethane-*d*₂ (TCE-*d*₂) was heated under 133 atm of H₂ gas at 100 °C for 4 hours, encapsulation of a H₂ molecule took place to give H₂@**14** at an occupation level of 62%.³¹ Since the activation barrier for the escape of encapsulated H₂ is only 23.7 kcal/mol reflecting the large opening of **14**, release of the H₂ molecule gradually occurred even at room temperature with the half-life of roughly one month.

Although until then the species encapsulated in the open-cage fullerenes had been limited to a He atom or a H₂ molecule, significant progress was made by Iwamatsu in 2004 when he created a huge opening on C₆₀ cage.³² The opening of diketone **13** was greatly enlarged by the reaction with a 1,2-phenylenediamine derivative affording a bowl-shaped compound **15** with a 20-membered-ring opening. The size of the opening was calculated to be 6.5 Å for a longer axis and 4.2 Å for a shorter axis (B3LYP/6-31G* level). Surprisingly, upon ¹H NMR measurement of **15** in TCE-*d*₂, a sharp singlet signal was observed at such a high field as $\delta = -11.4$ ppm even without any intentional procedure for guest incorporation. This signal was assigned to an H₂O molecule encapsulated in **15** based on the results of a D₂O exchange experiment together with elemental analysis. Encapsulation and release of the H₂O molecule in **15** is in equilibrium in TCE-*d*₂, as demonstrated by variable-temperature NMR measurements. They showed the occupation level of the H₂O molecule to reach 75% at ambient temperature while it decreased at higher temperatures. Furthermore, it was demonstrated that the bowl-shaped compound **15** is able to incorporate a CO molecule within the cage.³³ Upon heating a solution of H₂O@**15** in TCE-*d*₂ under 89 atm of CO gas at 100 °C for 20 hours, replacement of the H₂O molecule inside **15** by a CO molecule took place to give CO@**15** at an occupation level of 84%. The ¹³C NMR signal of the encapsulated CO was observed at $\delta = 174.3$ ppm in TCE-*d*₂, which is 10 ppm upfield shifted relative to a signal of dissolved CO gas ($\delta = 184.6$ ppm in CDCl₃). The IR spectrum of CO@**15** exhibited two absorptions at $\nu = 2125$ and 2112 cm⁻¹ indicating that

there exist two orientations in the encapsulated CO molecule on the time scale of the IR measurement. When CO@**15** was kept in a solution of CDCl₃ in the presence of water at 40 °C, the encapsulated CO molecule was gradually released from the cage with concomitant formation of H₂O@**15** instead. This result indicates that the encapsulation of an H₂O molecule within **15** is thermodynamically more favored than that of a CO molecule.

The bowl-shaped compounds such as **14** and **15** derived from C₆₀ are quite attractive as novel host molecules. However, from the viewpoint of “molecular surgery operation”, these compounds have a definite drawback that the restoration of such a severely ruptured π -system to the original structure of C₆₀ seems almost impossible by means of organic synthetic procedures.

2.3 Peroxide-mediated formation of open-cage fullerenes

On the other hand, an approach to other types of an open-cage fullerene using entirely different processes has been reported by Gan and coworkers.³⁴

They recently reported that the reaction of fullerene C₆₀ with *t*-butyl hydroperoxide in the presence of ceric ammonium nitrate gives hexaadduct **16**.³⁵ Subsequent oxidation of **16** by irradiation with visible light in the presence of iodine resulted in the cleavage of the central five-membered-ring and afforded diketone **17** with a nine-membered-ring opening.³⁶ The epoxide moiety in **17** was transformed to vicinal diol by the use of a Lewis acid, B(C₆F₅)₃, giving **18**.

Although attempted oxidation of the vicinal diol moiety in **18** was unsuccessful, aminoketal/hemiketal derivative **19**, obtained from the reaction of **18** with aniline, was found to undergo complex oxidation reactions with diacetoxylidobenzene. That is, the three hydroxyl groups and the amino group of **19** were all oxidized to give product **20** with a large opening divided by an acid anhydride bridge. When **20** was reacted with hydrazine, the bridge across the opening could be cleaved to give compounds **21** and **22** having an 18-membered-ring opening. The amide group of **21** was converted to a bromoazocarbonyl moiety by the reaction with Br₂ to give **23**, and then the reaction of **23** with AgClO₄ resulted in elimination of the azo-oxo group to afford tri-oxo open-cage fullerene **24**.³⁴

Upon ¹H NMR measurement of **24** in CDCl₃-CS₂ (1:1), a highly shielded signal was observed at $\delta = -13.07$ ppm. Based on the similarity of the chemical shift to that of H₂O@**15** ($\delta = -11.4$ ppm) described above, the signal was assigned to an encapsulated H₂O molecule, although the occupation level was less than only 5%.³⁴

The size of the opening of **24** was further expanded by treatment with trifluoroacetic acid in the presence of ferrocene. This reaction removed two *t*-butyl peroxy groups to create an aromatic hexagon, accompanied by insertion of an oxygen atom into the rim of the opening to give **25** possessing a 19-membered-ring opening. It is not surprising that the ¹H NMR spectrum of **25** exhibited an intense signal of an encapsulated H₂O molecule at $\delta = -12.8$ ppm in CDCl₃. The occupation level of the H₂O molecule inside **25** was 57% at room temperature and it increased up to 88% upon keeping the

solution at $-20\text{ }^{\circ}\text{C}$ for several days. The encapsulated H_2O molecule within the fullerene cage of **24** and **25** was also unambiguously confirmed by the X-ray crystallography.

3. Molecular surgical method to endohedral fullerenes

3.1 Cage opening

In this section, we will show a series of reactions which led us to the first successful organic synthesis of endohedral fullerene encapsulating molecular hydrogen according to the molecular surgical method.

As has been mentioned above, we synthesized the open-cage fullerene **12** by the reaction of open-cage fullerene **10** with photochemically generated singlet oxygen. Compound **10** with an 8-membered-ring opening was obtained by the reaction of C_{60} with 5,6-diphenyl-3-(2-pyridyl)-1,2,4-triazine in 85% yield based on consumed C_{60} (59% conversion). However, the 12-membered-ring opening in **12** was not large enough even for a molecule of H_2 to pass through as indicated by calculated high activation energy (51.8 kcal/mol) (B3LYP/6-31G**//B3LYP/3-21G level), and further enlargement of the opening was necessary.

For this purpose, we discovered a novel reaction to insert a sulfur atom into the rim of the opening in **12**.²⁵ Since the electrochemistry indicated that compound **12** with two carbonyl groups is even a better π -electron acceptor than C_{60} , **12** was expected to be activated by a typical electron donor such as tetrakis(dimethylamino)ethylene (TDAE). Thus, in the presence of TDAE **12** was found to react with elemental sulfur in 1,2-dichlorobenzene (ODCB) at $180\text{ }^{\circ}\text{C}$ to give compound **26**³⁷ having a 13-membered-ring opening as a single product in 77% yield.²⁵ The structure of **26** was unambiguously proved by X-ray crystallography. The size of the opening of **26** was 5.64 Å for a longer axis and 3.75 Å for a shorter axis. The calculated activation energy (B3LYP/6-31G**//B3LYP/3-21G level) for the insertion of a H_2 molecule through the opening of **26** (30.1 kcal/mol)³⁸ was lower than that calculated for bislactam **6** (41.4 kcal/mol)²³ in support of the larger opening of **26**. Thus, the encapsulation of a H_2 molecule to **26** was expected to be easier.

The enlargement of the opening of **12** was also found to be possible by insertion of a selenium atom in place of sulfur to the rim of the opening.³⁹ In this case, stronger activation by the use of sodium alkanethiolate as a reducing agent was needed. Thus, the reaction of **12** with elemental selenium in the presence of CH_3SNa in refluxing ODCB afforded open-cage fullerene **27** in 46% yield. The results of X-ray crystallography showed that the size of the opening in **27** was 5.72 Å for a longer axis and 3.88 Å for a shorter axis, which was slightly larger than that of sulfur analogue **26**.²⁵

3.2 Incorporation of a H_2 molecule

As a guest molecule to be encapsulated in an open-cage fullerene, the smallest molecule, H_2 , was selected. When open-cage fullerene **26** was treated with high-pressure H_2 gas (800 atm) at $200\text{ }^{\circ}\text{C}$ for 8 hours in an autoclave, the incorporation of hydrogen inside the cage was realized.³⁸ The

^1H NMR of the resulting material in ODCB- d_4 showed an intense signal of the encapsulated H_2 molecule at $\delta = -7.25$ ppm. The integrated intensity of this signal relative to one of the pyridyl proton signals demonstrated that exactly 100% encapsulation had been achieved. For a selenium analogue **27** with a slightly larger opening, the 100% insertion of a H_2 molecule was achieved under slightly milder conditions, that is, with 760 atm of H_2 gas at $190\text{ }^{\circ}\text{C}$.³⁹

In order to directly observe the encapsulated H_2 molecule³⁸ inside the cage, we conducted an X-ray diffraction study of a single crystal of $\text{H}_2@26$, together with empty **26** as a matching reference, by using synchrotron radiation in Photon Factory at High-Energy Accelerator Research Organization (KEK), Japan, in collaboration with Sawa.⁴¹ The resulting electron-density representations of $\text{H}_2@26$ as well as empty **26** obtained by analysis with a maximum entropy method (MEM) are shown in Fig. 2 as contour maps. These representations clearly demonstrate the electron density that is “floating” at the center of the fullerene cage of $\text{H}_2@26$, while such electron density was not observed at all in the case of empty **26**. The number of electrons of this fragment was calculated to be 2.0 ± 0.1 , exactly corresponding to that of one H_2 molecule.

Although $\text{H}_2@26$ was stable at room temperature, encapsulated H_2 was gradually released upon heating its solution in ODCB at the temperatures above $160\text{ }^{\circ}\text{C}$. The activation energy for the release of the H_2 molecule from the cage of $\text{H}_2@26$ was determined to be 34.2^{38,39} kcal/mol from the Arrhenius plot of the rate constants obtained at $160 - 190\text{ }^{\circ}\text{C}$.³⁸ It was also found that the release of a H_2 molecule of $\text{H}_2@27$ was almost three times faster than that of $\text{H}_2@26$ and the activation energy was 32.4 kcal/mol,³⁹ reflecting the slightly larger opening of $\text{H}_2@27$. Recent investigations demonstrated that the rate of release of the encapsulated H_2 molecule can be well correlated to the opening size on the fullerene cage.⁴²

3.3 Incorporation of a He atom

Next, the insertion of the smallest noble-gas atom, ^3He , within the fullerene cage of **26** was investigated at Yale University by collaboration with Saunders and Cross.⁴³ By heating an ODCB solution of **26** under ^3He gas (20 atm) at $80\text{ }^{\circ}\text{C}$ for a few hours, $^3\text{He}@26$ at an occupation level of 0.1% was obtained. By monitoring the release of the ^3He atom from $^3\text{He}@26$, the activation energy for the release was determined to be 22.8 kcal/mol, which is lower than that for the release of a H_2 molecule from $\text{H}_2@26$ ^{38,39} by 11.4 kcal/mol. The release of a ^3He atom from $^3\text{He}@26$ can take place at near room temperature with the half-life of 40.3 hours at $30\text{ }^{\circ}\text{C}$. Thus, it was required to develop a method to reduce the opening size of $^3\text{He}@26$ in order to prevent the encapsulated He atom from escaping.

We found that, upon sodium borohydride reduction of a carbonyl group in **26**, a transannular ether-forming reaction readily takes place at room temperature to give product **28** in 86% yield.⁴⁴ The structure of **28** was confirmed by the X-ray crystallography. Theoretical calculations (B3LYP/6-31G**//B3LYP/3-21G level) indicated that the activation

energies for release of an encapsulated He atom from He@28 is 50.4 kcal/mol, which is more than twice as large as that from He@26,^{38,39} indicating that effective reduction of the opening size of 26 has occurred.

Thus, we first conducted the insertion of a He atom within the cage of 26 under the conditions of 650 atm of He gas at 90 °C for 24 hours. Then, the resulting material was immediately subjected to the sodium borohydride reduction at –20 to –25 °C to give desired product He@28 in 90% yield as a stable complex. The occupation level of the He atom was 35% based on the mass spectroscopic analysis.⁴⁴

Although the non-covalent interaction between the encapsulated He atom and the fullerene cage of 28 had been expected to be almost negligible, the NMR signal of the methine proton of He@28 showed a slight downfield shift by 0.36 Hz as compared to that of empty 28. The methine proton signal of H₂@28, prepared separately, exhibited 1.9 Hz downfield shift relative to that of empty 28. These results demonstrate that the non-covalent interaction of encapsulated H₂ molecule with the fullerene cage of 28 is larger than that of the encapsulated He atom and the NMR signal of the methine proton outside the cage is a good indicator of the electronic interaction inside the cage.⁴⁴

3.4 Incorporation of two H₂ molecules into an open-cage C₇₀

Taking the thickness of π -electron cloud of fullerenes into consideration, the size of the inner cavity of C₇₀ is estimated to be 4.6 Å along the long axis and 3.6 Å along the short axis, which is larger than that of C₆₀ (3.6 Å in inner diameter). Therefore, it is expected to be possible to insert more than one small molecule⁴⁵ through a newly created opening on the surface of C₇₀. However, most studies on this line have previously been made only on C₆₀ because of the wealth of knowledge about the chemical reactivity of C₆₀ and also due to its higher symmetry. Thus, we challenged to prepare open-cage C₇₀ derivative 29⁴⁶ with a 13-membered-ring opening by applying similar procedures to those used for the synthesis of the C₆₀ analogue 26.²⁵ A thermal reaction of C₇₀ with 3,6-di(2-pyridyl)pyridazine in refluxing 1-chloronaphthalene gave eight-membered-ring compound 30 (40%), and subsequent oxidation with singlet oxygen afforded 12-membered-ring compound 31 (49%). Then, the opening of 31 was enlarged by insertion of a sulfur atom to the rim of the opening using TDAE as a π -electron donor to give 29 (94%). The results of the X-ray crystallography of 29 showed that the opening size of 29 is almost the same as that of C₆₀ analogue 26.²⁵

The insertion of H₂ molecule(s) was carried out by applying 890 atm of H₂ gas at 230 °C for 8 hours. The successful encapsulation of molecular hydrogen was clearly demonstrated by appearance of a new intense signal in the ¹H NMR spectrum at unusually high field, δ = –16.51 ppm in ODCB-*d*₄. This signal was assigned to the resonance of H₂@29 based on the mass spectroscopic data. Noteworthy is that a small signal was also observed at δ = –15.22 ppm. Upon low-temperature NMR studies, this signal completely disappeared by cooling the solution to –60 °C and reappeared as two new signals at –80 °C, which became sharp at –100 °C with the chemical shift of δ = –12.87 ppm and –17.38 ppm.

The observed dynamic behavior is interpreted by assuming the positional exchange of two H₂ molecules encapsulated in open-cage 29, i.e., (H₂)₂@29. The line-shape analysis of the low-temperature NMR spectra gave E_a = 8.0 kcal/mol for this positional exchange. The yield of H₂@29 and (H₂)₂@29 was 97% and 3%, respectively, as estimated from the integrated areas of the NMR signals.

In accord with the results of the X-ray crystallography, i.e., the opening of 29 being almost the same size as that of 26, the rate for the release of a H₂ molecule from H₂@29, monitored at temperatures above 160 °C, was almost as fast as that from the C₆₀ analogue H₂@26.²⁵ The activation energy was determined to be 33.8 kcal/mol.

3.5 Closure of the opening

As described above, we have succeeded in introducing a H₂ molecule into the carbonaceous cage of 26 at the occupation level of 100%.³⁸ Subsequently, we developed a method to “suture” the 13-membered-ring opening of H₂@26 to complete the molecular surgery operation.^{47–51} Prior to this study, there had been no report for the attempt at suturing a once formed opening on the fullerene cage.

Apparently, the first step for the size-reduction of the 13-membered-ring in H₂@26 should be the removal of the sulfur atom. We first conducted an oxidation of the sulfide unit of H₂@26 by *m*-chloroperbenzoic acid in order to make the sulfur atom readily removable. The reaction proceeded at room temperature to give sulfoxide derivative H₂@32 almost quantitatively. Then, irradiation of a solution of H₂@32 in benzene with visible light at room temperature caused the elimination of the SO unit to give product H₂@12 having a 12-membered-ring opening in 42% yield. The encapsulated H₂ molecule was completely retained throughout these two steps because the two reactions were conducted at room temperature.³⁸ This removal of a sulfur atom made the distance between two carbonyl carbons across the opening closer from 3.89 Å for H₂@26 to 3.12 Å for H₂@12 as shown by calculations (B3LYP/6-31G* level). The reductive coupling of the two carbonyl groups efficiently proceeded by McMurry reaction using Ti(0)⁵² at 80 °C to give product H₂@10 with an eight-membered-ring opening in 88% yield. Here, it is to be noted that the MALDI-TOF mass spectrum of H₂@10 already exhibited an intense peak of H₂@C₆₀ together with a smaller molecular ion peak of H₂@10.

The final step to remove all the remaining organic addends on the C₆₀ cage was performed by simply heating a powder of H₂@10 (245 mg) in a vacuum-sealed tube placed in an electric furnace at 340 °C for 2 hours. Separation of the reaction mixture was carried out by flash column chromatography over silica gel eluted with carbon disulfide to afford a purple solution containing desired H₂@C₆₀ (118 mg, 67% yield), contaminated by 9% of empty C₆₀. Subsequently, complete separation of H₂@C₆₀ from empty C₆₀ was achieved by recycling HPLC on semipreparative Cosmosil Buckyprep columns (two directly connected columns; 250 mm length, 10 mm i.d.; mobile phase, toluene; flow rate, 4 mL/min) to give H₂@C₆₀ as a pure material after 20 recycles (total retention time, 399 minutes; the retention time for empty C₆₀, 395

minutes). The adsorption mechanism of the Buckyprep column is largely based on the π - π interaction with pyrenyl groups in the stationary phase. A very weak van der Waals interaction between the encapsulated H_2 molecule and the C_{60} π -system must have contributed to this separation.

The ^{13}C NMR spectrum of pure $\text{H}_2@\text{C}_{60}$ exhibited a signal at $\delta = 142.844$ ppm in ODCB- d_4 , which is very slightly downfield shifted by 0.078 ppm relative to that of empty C_{60} . The ^1H NMR signal of the encapsulated H_2 molecule appeared at $\delta = -1.44$ ppm in ODCB- d_4 , which is 5.98 ppm upfield shifted from dissolved free H_2 molecule. This value is comparable to the 6.36 ppm upfield shift of a ^3He NMR signal for $^3\text{He}@\text{C}_{60}$, suggesting that this nearly 6 ppm upfield shift is a universal value corresponding to the magnetic field at the central position in the C_{60} core. The IR spectrum of $\text{H}_2@\text{C}_{60}$ was almost the same as that of empty C_{60} , exhibiting four absorption bands at 1429.2, 1182.3, 576.7, and 526.5 cm^{-1} (to be compared with 1429.2, 1182.3, 575.7, and 526.5 cm^{-1} for empty C_{60}). Only the band at 576.7 cm^{-1} of $\text{H}_2@\text{C}_{60}$, corresponding to an out-of-plane vibration mode,⁵³ is higher in energy than that of C_{60} by 1.0 cm^{-1} . This might be interpreted as evidence of a very slight repulsive interaction between the C_{60} cage and the inner H_2 molecule. The UV-vis spectrum of $\text{H}_2@\text{C}_{60}$ was almost the same as that of C_{60} .

The cyclic voltammetry and differential pulse voltammetry of $\text{H}_2@\text{C}_{60}$ at room temperature exhibited three reversible reduction waves at $E_{1/2}$ -1.13, -1.54, and -1.99 V vs Fc/Fc^+ in ODCB and one irreversible oxidation peak at E_{pa} +1.62 V in TCE, which were virtually the same as those of empty C_{60} . However, when more negative potential was applied using the solution in toluene-acetonitrile (5.4 : 1) under vacuum at -10 $^{\circ}\text{C}$,⁵⁴ the fourth, fifth, and sixth reduction waves became observable, which were found to be more cathodic than the reduction of empty C_{60} by 0.04, 0.07, and 0.15 V, suggesting that $\text{H}_2@\text{C}_{60}$ becomes more difficult to be reduced as it acquires more than three electrons.⁴⁹

$\text{H}_2@\text{C}_{60}$ is thermally stable. Upon heating $\text{H}_2@\text{C}_{60}$ at 500 $^{\circ}\text{C}$ for 10 minutes under vacuum, no decomposition or no release of encapsulated H_2 molecule was observed at all.

4. Organic derivatization of $\text{H}_2@\text{C}_{60}$

In order to examine the effect of encapsulated H_2 molecule on the reactivity of the outer C_{60} cage, the solid-state mechanochemical dimerization of $\text{H}_2@\text{C}_{60}$ (occupation level of 91%) was conducted under the same conditions⁵⁵ reported previously. The dumbbell-shaped dimer, $(\text{H}_2@\text{C}_{60})_2$,⁴⁷ was obtained in 30% isolated yield similarly to the reaction of empty C_{60} . Apparently the inside hydrogen does not affect the reactivity of the C_{60} cage. The NMR signal for the inside H_2 molecule was observed as a singlet at $\delta = -4.04$ ppm, which is 8.58 ppm upfield shifted from that of free H_2 similarly to the case for $^3\text{He}@\text{C}_{120}$ ⁵⁶ (8.81 ppm upfield shift from the signal of free ^3He). Three additional fullerene derivatives $\text{H}_2@33$, $\text{H}_2@34$, and $\text{H}_2@35$ were also synthesized and their NMR signals for the encapsulated H_2 molecule in ODCB- d_4 appeared at $\delta = -3.27$, -4.30, and -4.64 ppm, respectively.⁴⁹ Since the values of chemical shift change sensitively according to the difference in structures of the organic

addends, the encapsulated H_2 molecule within C_{60} cage can also be used as a good probe to investigate the chemical reactions at the exterior of the cage, just as the ^3He atom inside C_{60} (occupation level of 0.1%) has been used for this purpose.¹⁵

Furthermore, several organic and organometallic derivatives of $\text{H}_2@\text{C}_{60}$ were prepared at the University of Tokyo by the group of Nakamura.⁵⁷ The NMR signals for the encapsulated H_2 molecule appeared at $\delta = -10.39$ ppm for compound $\text{H}_2@36$ in CDCl_3 - CS_2 , $\delta = -9.79$ ppm for potassium cyclopentadienide $\text{H}_2@37$ in THF- d_8 , $\delta = -10.44$ ppm for bucky ferrocene $\text{H}_2@38$ in CDCl_3 - CS_2 , and $\delta = -10.77$ ppm for tetraaminofullerene epoxide $\text{H}_2@39\text{a}$ in CDCl_3 . Although the ^1H NMR chemical shifts for the encapsulated H_2 molecule of amphiphilic derivative $\text{H}_2@39\text{b}$ were measured in a variety of solvents, such as THF- d_8 , DMSO- d_6 -toluene- d_8 (1:1), DMSO- d_6 , and D_2O -DMSO- d_6 (1:1), no specific solvent effect on the chemical shift was observed.

5. Utilization of the encapsulated H_2 molecule as an NMR probe

Saunders reported that the ^3He NMR signal of hexaanion $^3\text{He}@\text{C}_{60}^{6-}$ appeared at dramatically high field ($\delta = -48.7$ ppm relative to the signal of free ^3He), reflecting the strong shielding effect of C_{60}^{6-} .¹³ This was apparently due to the high aromaticity of C_{60}^{6-} . Theoretical as well as experimental studies indicated that all of the hexagons and pentagons of C_{60}^{6-} showed diamagnetic ring currents. Among the other possible anionic states of C_{60} , dianion C_{60}^{2-} is particularly important in synthetic chemistry for introduction of two functional groups on the C_{60} cage.⁵⁸ Although the “ $2(N+1)^2$ rule”,⁵⁹ describing the spherical aromaticity of I_h -symmetrical fullerenes, proposed by Hirsh, predicts that the 62- π -electron system should not have high aromaticity, little had been known about the aromaticity of C_{60}^{2-} prior to our study.⁶⁰

Thus, we carried out the generation of $\text{H}_2@\text{C}_{60}^{2-}$ by using CH_3SNa ⁶¹ as a reductant in CD_3CN under vacuum. The ^1H NMR signal of the encapsulated H_2 molecule of $\text{H}_2@\text{C}_{60}^{2-}$ was observed at surprisingly low field such as $\delta = 26.36$ ppm. This is downfield shifted by 27.8 ppm relative to that of neutral $\text{H}_2@\text{C}_{60}$ ($\delta = -1.44$ ppm in ODCB- d_4).⁴⁷ This result demonstrates that the overall aromaticity within the cage of C_{60} decreases drastically upon two-electron reduction. The NICS (nucleus independent chemical shifts)⁶² calculations (B3LYP/6-31G* level) for all the hexagons and pentagons of C_{60}^{2-} suggested that, upon two-electron reduction, the ring currents of all hexagons become paramagnetic while those of all pentagons become diamagnetic. Because there exist more hexagons than pentagons in C_{60} , the antiaromatic character of hexagons overwhelms the aromatic character of pentagons, resulting in the strong deshielding effect inside the cage. This is the first time that the reversal of aromaticity/antiaromaticity for hexagons and pentagons of fullerenes was observed.

The similar reversal was observed even for the dianion of heavily functionalized C_{60} such as open-cage fullerene $\text{H}_2@26$. The NMR signal of $\text{H}_2@26^{2-}$ was observed at $\delta = 8.10$ ppm in CD_3CN , which is downfield shifted by 15.4 ppm relative to that of neutral $\text{H}_2@26$ ($\delta = -7.25$ ppm in ODCB- d_4).³⁸ The

NICS calculations (B3LYP/6-31G* level) showed that the aromatic and antiaromatic characters of hexagons and pentagons are mostly reversed in the same way as those for $\text{H}_2@\text{C}_{60}^{2-}$, in spite of the highly ruptured π -system in $\text{H}_2@\mathbf{26}$.

While the aromaticity of the spherically conjugated system of C_{60} is proved to be drastically changed when C_{60} acquired extra electrons,^{13,60} the research on the magnetic properties of ionic fullerenes are still quite limited. Thus, we prepared dichloromethyl- C_{60} cation⁶³ and (1-octynyl)- C_{60} anion⁶⁴ encapsulating a H_2 molecule ($\text{H}_2@\mathbf{40}^+$ and $\text{H}_2@\mathbf{41}^-$),⁶⁵ as these compounds appeared to be well suited for the study of the difference in aromaticity between the monofunctionalized C_{60} cation and anion. The cation $\text{H}_2@\mathbf{40}^+$ was generated in $\text{CF}_3\text{SO}_3\text{H}$ as a stable species and the NMR signal of the encapsulated H_2 molecule was observed at $\delta = -2.89$ ppm. The signal was downfield shifted by 1.73 ppm from a H_2 signal of the corresponding neutral compound $\text{H}_2@\mathbf{42}$ ($\delta = -4.62$ ppm in $\text{CS}_2\text{-CDCl}_3$ (1:1)), indicating that the aromaticity of $\mathbf{40}^+$ was slightly decreased as compared to that of $\mathbf{42}$. On the other hand, an NMR signal for the encapsulated H_2 molecule of anion $\text{H}_2@\mathbf{41}^-$, which was also generated as a stable species in $\text{THF-}d_8$, appeared at $\delta = -0.60$ ppm. This resonance was shifted to lower field than that for a H_2 molecule of neutral counterpart $\text{H}_2@\mathbf{43}$ ($\delta = -4.75$ ppm in $\text{CS}_2\text{-CDCl}_3$ (1:1)), again indicating the decrease in aromaticity. The relatively small difference in the chemical shifts of the encapsulated H_2 molecule between $\text{H}_2@\mathbf{40}^+$ and $\text{H}_2@\mathbf{41}^-$ (absolute $\Delta\delta$ value, 2.29 ppm) demonstrates that the aromaticity of the fullerenes are affected to a comparative degree in these cationic and anionic systems.

6. Physical properties of the H_2 molecule inside C_{60}

The encapsulated H_2 molecule in $\text{H}_2@\mathbf{26}$ is isolated from the outside environment by the surrounding fullerene cage because the opening is so small that only a He atom or a H_2 molecule can go through. Actually, the nuclear spin-lattice relaxation time (T_1) of the encapsulated H_2 of $\text{H}_2@\mathbf{26}$ upon the ^1H NMR measurements were not affected by the presence of molecular oxygen as a paramagnetic species in the solution.³⁸ The T_1 values of the encapsulated H_2 molecule and one of the pyridyl proton of $\text{H}_2@\mathbf{26}$ in $\text{ODCB-}d_4$ are 0.2 s and 3.9 s under vacuum and 0.2 and 0.9 s in an oxygen-saturated solution, respectively. In $\text{H}_2@\text{C}_{60}$, synthesized by complete restoration of the opening of $\text{H}_2@\mathbf{26}$, the encapsulated H_2 is completely isolated from the outside. As judged from the difference in chemical shift of ^{13}C NMR ($\Delta\delta = 0.078$ ppm; vide supra), the interaction of the encapsulated H_2 and the outer C_{60} cage in $\text{H}_2@\text{C}_{60}$ appears to exist but should be very weak.

To investigate the nature of such interaction, the T_1 values of H_2 molecule encapsulated in C_{60} cage as well as those of free H_2 molecule were measured in Columbia University by the group of Turro for the first time.⁶⁶ The T_1 values of free H_2 at 300 K were found to depend significantly on the organic solvent, for example, from 1.44 s (benzene) to 0.84 s (CCl_4). A somewhat larger variation of T_1 values was observed for $\text{H}_2@\text{C}_{60}$: from 0.118 s (benzene) to 0.046 s (CCl_4), which are

12-18 times smaller than those for free H_2 . However, the value of T_1 for both H_2 and $\text{H}_2@\text{C}_{60}$ does not significantly change between the solutions in benzene- h_6 and benzene- d_6 . Therefore, the dominating interactions determining H_2 and $\text{H}_2@\text{C}_{60}$ nuclear relaxation are concluded to be *intramolecular*. On the other hand, the T_1 value for both H_2 and $\text{H}_2@\text{C}_{60}$ was found to be temperature dependent with the maximum value observed at ~ 240 K. This kind of temperature dependence of T_1 is consistent with two different relaxation mechanisms dominantly operating at different temperature ranges, that is, below and above 240 K, for both H_2 and $\text{H}_2@\text{C}_{60}$. Qualitatively, the dipole-dipole interaction accounts for the observed increase in T_1 with temperature below 240 K, whereas the spin-rotation interaction accounts for the observed decrease in T_1 with temperature above 240 K. These facts and consideration derived therefrom imply that the H_2 in both environments rotates through large angles between collisions with the solvent shell or with the walls of the C_{60} cage.

Although the encapsulated H_2 molecule in C_{60} is completely isolated from the outside, it can communicate with the outside world.⁶⁷ First, no differences in the triplet life times were observed for C_{60} , $\text{H}_2@\text{C}_{60}$, and $\text{D}_2@\text{C}_{60}$ upon irradiation of laser pulse. Thus, the interaction of encapsulated H_2 and D_2 with the paramagnetic walls of the triplet fullerene is too weak to be determined by triplet lifetime measurements. However, clear differences in reactivity were observed for the quenching of singlet oxygen $^1\text{O}_2$ by C_{60} , $\text{H}_2@\text{C}_{60}$, and $\text{D}_2@\text{C}_{60}$. The absolute quenching rate constants k_q of $^1\text{O}_2$ by $\text{H}_2@\text{C}_{60}$, $\text{D}_2@\text{C}_{60}$, and C_{60} were determined using a time-resolved method in CS_2 to give the values of $k_q(\text{H}_2@\text{C}_{60}) = 1.5 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, $k_q(\text{D}_2@\text{C}_{60}) = 0.49 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, and $k_q(\text{C}_{60}) = 0.38 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, respectively. The results demonstrate that both $\text{H}_2@\text{C}_{60}$ and $\text{D}_2@\text{C}_{60}$ are better quenchers than empty C_{60} . Importantly, the $^1\text{O}_2$ can sense the difference between encapsulated H_2 and D_2 . The rate constants for quenching of $^1\text{O}_2$ by free H_2 and D_2 in CCl_4 were also measured to afford the values of $k_q(\text{H}_2) = 0.81 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, $k_q(\text{D}_2) = 0.024 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$, which are significantly smaller than the values by $\text{H}_2@\text{C}_{60}$ and $\text{D}_2@\text{C}_{60}$. This is a unique example of an encapsulated guest having a significantly larger rate constant for quenching than the free guest. Since $^1\text{O}_2$ might form an exciplexes with the outer surface of fullerenes, it is speculated that this unique behavior can be attributed to a significant life time to provide an opportunity for $^1\text{O}_2$ and the encapsulated H_2 to interact for a considerable period of time.

Interaction of the encapsulated H_2 molecule with another species outside the fullerene cage is also seen for the interaction with nitroxide radicals. In the presence of paramagnet nitroxide radicals, bimolecular contribution to the spin-lattice relaxation rate, $1/T_1$, for the protons of H_2 and $\text{H}_2@\text{C}_{60}$ dissolved in toluene- d_8 were investigated.⁶⁸ The measured relaxation rates depended on the concentration of the nitroxide, $[S]$, according to the relationship: $1/T_1 = 1/T_{1,0} + R_1[S]$, where $T_{1,0}$ is the relaxation time in the absence of paramagnetic relaxant and R_1 ($\text{M}^{-1} \text{ s}^{-1}$) is the second-order relaxation coefficient, or *relaxibility*. It was found that the

relaxation effect of the paramagnets is enhanced 5-fold in $\text{H}_2@C_{60}$ compared to free H_2 under the same conditions.

Concluding remarks

In this article we have outlined recent progress toward synthesizing endohedral fullerenes not by a physical method but by the stepwise transformations of fullerenes by organic reactions. This molecular surgical operation was shown to be effective for realization of a new endohedral fullerene, $\text{H}_2@C_{60}$. This method can be applied to the preparation of endohedral fullerenes encapsulating gas atoms or molecules with sizes comparable or smaller than a H_2 molecule. While the preparation of bowl-shaped compounds by the wide incision of a C_{60} cage provided access to the encapsulation of molecules larger than H_2 , i.e., H_2O and CO , the operation to suture the opening must be a highly difficult task. Of course the most important and ultimate goal of the present method would be to develop a route to the encapsulation of metal atoms affording endohedral metallofullerenes. However, as far as the present method is used, the insertion of metal ions such as Li^+ and Na^+ through the opening is difficult because of their strong coordination with two carbonyl oxygen atoms at the opening. Further development of the technique for the chemical transformations of the fullerene cage will be crucial for this project to be accomplished.

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