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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+@C82− 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 Young Chemists. His research interests include the synthesis of fullerene derivatives having novel structures and properties. Koichi Komatsu, FRSC, was born in Kyoto, Japan, in 1942. He studied the synthesis and properties of carborocations at Kyoto University and received his Ph.D. degree under the supervision of Kanji Okamoto in 1974. After postdoctoral work with Robert West in University of Wisconsin, USA, during 1975-1976, he returned to Kyoto. After serving as an assistant professor, lecturer, and associate professor, he was promoted to professor at Institute for Chemical Research of Kyoto University in 1995. He has been awarded the Divisional Award of The Chemical Society of Japan, Alexander von Humboldt Research Award, and the Chemical Society of Japan Award. In 2006 he retired from Kyoto University and moved to Fukui University of Technology as professor. His research interest is focused on the synthesis and properties of novel two- and three-dimensional π-conjugated systems.

Michihisa Murata was born in Kyoto, Japan, in 1978. He studied the chemistry of fullerenes at Kyoto University and received his Ph.D. degree under the supervision of Koichi Komatsu in 2006. After working as a researcher at Kaneka Corp., Japan, he returned to Kyoto. He is currently an Assistant Professor at Institute for Chemical Research of Kyoto University. He has been awarded Inoue Research Award for Young Scientists in 2008. His research interests are in the area of chemistry on novel organic molecules with curved π-conjugated systems.

Yasujiro Murata was born in Kanazawa, Japan in 1970. He studied chemistry at Kyoto University, Japan, and received his Ph.D. degree under the supervision of Koichi Komatsu in 1998. During that time he joined Fred Wudl’s group as a summer student in 1995. After working as a postdoctoral fellow at Kyoto University in Komatsu’s group, he joined Institute for Chemical Research, Kyoto University, as an Assistant Professor during 1999-2006 and then as an Associate Professor since 2006. In 2004, he received The Chemical Society of Japan Award for
water-soluble fullerene derivatives encapsulating a paramagnetic Gd(III) ion. 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 La@C$_{80}$ or nanorods of La@C$_{32}$(Ad) ($\text{Ad} = \text{adamantylidene}$) 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). Although the occupation level of guest is so low as 0.1%, incorporation of an NMR active nucleus, $^3$He, 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 $\pi$-electrons. The NMR signal of $^3$He is also useful as a tool to follow chemical reactions taking place at the exterior of the fullerene cages.

Recent investigation revealed that the reactivity of Xe@C$_{60}$ in [4+2] cycloaddition with 9,10-dimethylnaphthalene is substantially different from that of He@C$_{60}$ because $\pi$-electron cloud of the C$_{60}$ cage is pushed outward by the inside xenon atom. However, a low occupation level of the noble-gas atom within fullerenes (about 0.1%) and difficulty in isolation or enrichment in practical scale 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". 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 C$_{60}$ cage to give compound 1. Unfortunately, however, the opening was found to be not large enough even for the smallest atom, helium, to pass through. Rubin thereafter synthesized bisfulleroid derivative 2 with an eight-membered-ring opening and transformed it into Co(III) complex 3. 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 C$_{60}$

Rubin proposed a strategy 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 C$_{60}$ with butadiene derivative 4 having two azido groups was conducted. 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 C$_{60}$ 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 N$_2$ molecules, and addition of an O$_2$ molecule followed by dehydrogenation.

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 $^3$He atom or a H$_2$ molecule. By treating a crystalline powder of 6 with 475 atm of $^3$He gas at 288-305 °C for 7.5 hours, a $^3$He atom was incorporated at an occupation level of 1.5%. A H$_2$ molecule was also introduced at an occupation level of 5% under the conditions of 100 atm of H$_2$ gas at 400 °C for 48 hours. A highly shielded $^1$H NMR signal for the encapsulated H$_2$ was observed at $\delta = -5.43$ ppm. These results verified the feasibility of the strategy of molecular surgical approach.

Recently, Rubin succeeded in the synthesis of the desired 1,2,3,4,5,6-hexadduct of C$_{60}$, 7, by the reaction of bis-isobenzofuran adduct 8 with Pb(OAc)$_2$ in a substantially low concentration (1.0 $\times$ 10$^{-5}$ M). 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 oxabenzenorbornadiene moieties of 9.

2.2 Bowl-shaped fullerenes
Bisfulleroid derivative 2, 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 and 11, can be readily cleaved via addition of photochemically generated singlet oxygen to give diketone derivatives 12 and 13, respectively, with a 12-membered-ring opening. 28

The opening 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/6-31G* level). When a solution of 14 in 1,1,2,2-tetrachloroethane-d$_2$ (TCE-d$_2$) was heated under 133 atm of H$_2$ gas at 100 °C for 4 hours, encapsulation of a H$_2$ molecule took place to give H$_2$@14 at an occupation level of 62%. Since the activation barrier for the escape of encapsulated H$_2$ is only 23.7 kcal/mol reflecting the large 25

observed at hours, replacement of the H$_2$O molecule inside opening was estimated to be 6.5 Å for a longer axis and 3.8 Å membered-ring opening. 28

δ upfield shifted relative to a signal of dissolved CO gas (δ$_{H2O}$). They showed the occupation level of the H$_2$O molecule to be 84%. The 13C NMR signal of the encapsulated CO was δ$_{H2O} = 174.3$ ppm in TCE-d$_2$, which is 10 ppm upfield shifted relative to a signal of dissolved CO gas (δ = 184.6 ppm in CDCl$_3$). The IR spectrum of CO@15 exhibited two absorptions at ν = 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 CDC$_3$ in the presence of water at 40 °C, the encapsulated CO molecule was gradually released from the cage with concomitant formation of H$_2$O@15 instead. This result indicates that the encapsulation of an H$_2$O molecule within 15 is thermodynamically more favored than that of a CO molecule.

The bowl-shaped compounds such as 14 and 15 derived from C$_{60}$ 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 C$_{60}$ 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 C$_{60}$ with t-butyl hydroperoxide in the presence of ceric ammonium nitrate gives hexaadduct 16. 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. The epoxide moiety in 17 was transformed to vicinal diol by the use of a Lewis acid, B(C$_6$F$_5$)$_3$, 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 diacetoxydibenzenes. 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 bromoacarbonyl moiety by the reaction with Br$_2$ to give 23, and then the reaction of 23 with AgClO$_4$ resulted in elimination of the azo-oxo group to afford tri-oxo open-cage fullerene 24.

Upon $^1$H NMR measurement of 24 in CDCl$_3$-CS$_2$ (1:1), a highly shielded signal was observed at δ = −13.07 ppm. Based on the similarity of the chemical shift to that of H$_2$O@15 (δ = −11.4 ppm) described above, the signal was assigned to an encapsulated H$_2$O 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-butyloxo 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 $^1$H NMR spectrum of 25 exhibited an intense signal of an encapsulated H$_2$O molecule at δ = −12.8 ppm in CDCl$_3$. The occupation level of the H$_2$O molecule inside 25 was 57% at room temperature and it increased up to 88% upon keeping the
solution at −20 °C for several days. The encapsulated H₂O molecule within the fullerene cage of 24 and 25 was also unambiguously confirmed by the X-ray crystallography.

3. Molecular surgical method to endohedral fullerences

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 C₆₀ with 5,6-diphenyl-3-(2-pyridyl)-1,2,4-triazine in 85% yield based on consumed C₆₀ (59% conversion). However, the 12-membered-ring opening in 12 was not large enough even for a molecule of H₂ 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. Since the electrochemistry indicated that compound 12 with two carbonyl groups is even a better π-electron acceptor than C₆₀, 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 °C to give compound 26 having a 13-membered-ring opening as a single product in 77% yield. 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 H₂ 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. In this case, stronger activation by the use of sodium alkaneolinate as a reducing agent was needed. Thus, the reaction of 12 with elemental selenium in the presence of CH₃SNa 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 H₂ molecule

As a guest molecule to be encapsulated in an open-cage fullerene, the smallest molecule, H₂, was selected. When open-cage fullerene 26 was treated with high-pressure H₂ gas (800 atm) at 200 °C for 8 hours in an autoclave, the incorporation of hydrogen inside the cage was realized. The incorporation of hydrogen inside the cage was realized. 38 The incorporation of hydrogen inside the cage was realized. 38

The result of encapsulation of H₂ molecule 27 with a slightly larger opening, the 100% insertion of a H₂ molecule was achieved under slightly milder conditions, that is, with 760 atm of H₂ gas at 190 °C.

In order to directly observe the encapsulated H₂ molecule inside the cage, we conducted an X-ray diffraction study of a single crystal of H₂@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 H₂@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 “flooding” at the center of the fullerene cage of H₂@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 H₂ molecule.

Although H₂@26 was stable at room temperature, encapsulated H₂ was gradually released upon heating its solution in ODCB at the temperatures above 160 °C. The activation energy for the release of the H₂ molecule from the cage of H₂@26 was determined to be 34.2 kcal/mol from the Arrhenius plot of the rate constants obtained at 160 – 190 °C.38 It was also found that the release of a H₂ molecule of H₂@27 was almost three times faster than that of H₂@26 and the activation energy was 32.4 kcal/mol, reflecting the slightly larger opening of H₂@27. Recent investigations demonstrated that the rate of release of the encapsulated H₂ 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, He, 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 He gas (20 atm) at 80 °C for a few hours, He@26 at an occupation level of 0.1% was obtained. By monitoring the release of the He atom from 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 H₂ molecule from H₂@26 by 11.4 kcal/mol. The release of a He atom from He@26 can take place at near room temperature with the half-life of 40.3 hours at 30 °C. Thus, it was required to develop a method to reduce the opening size of 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@C_{60} is 50.4 kcal/mol, which is more than twice as large as that from He@C_{28}, indicating that effective reduction of the opening size of C_{28} has occurred.

Thus, we first conducted the insertion of a He atom within the cage of C_{28} 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@C_{28} in 90% yield as a stable complex. The occupation level of the He atom was 35% based on the mass spectroscopic analysis.

Although the non-covalent interaction between the encapsulated He atom and the fullerene cage of C_{28} had been expected to be almost negligible, the NMR signal of the methine proton of He@C_{28} showed a slight downfield shift by 0.36 Hz as compared to that of empty C_{28}. The methine proton signal of H_{2}@C_{28}, prepared separately, exhibited 1.9 Hz downfield shift relative to that of empty C_{28}. These results demonstrate that the non-covalent interaction of the encapsulated H_{2} molecule with the fullerene cage of C_{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.

3.4 Incorporation of two H_{2} molecules into an open-cage C_{70}

Taking the thickness of π-electron cloud of fullerenes into consideration, the size of the inner cavity of C_{70} 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 C_{60} (3.6 Å in inner diameter). Therefore, it is expected to be possible to insert more than one small molecule through a newly created opening on the surface of C_{70}. However, most studies on this line have previously been made only on C_{60} because of the wealth of knowledge about the chemical reactivity of C_{60} and also due to its higher symmetry. Thus, we challenged to prepare open-cage C_{70} derivative C_{70}H_{2} with a 13-membered-ring opening by applying similar procedures to those used for the synthesis of the C_{60} analogue C_{60}H_{2}. A thermal reaction of C_{70} 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 C_{60} analogue C_{60}H_{2}.

The insertion of H_{2} molecule(s) was carried out by applying 890 atm of H_{2} 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_{6}. This signal was assigned to the resonance of H_{2}@C_{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 H_{2} molecules encapsulated in open-cage C_{29}, i.e., (H_{2})_{2}@C_{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 H_{2}@C_{28} and (H_{2})_{2}@C_{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 H_{2} molecule from H_{2}@C_{29}, monitored at temperatures above 160 °C, was almost as fast as that from the C_{60} analogue H_{2}@C_{60}. 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 H_{2} molecule into the carbonaceous cage of C_{60} at the occupation level of 100%. Subsequently, we developed a method to “suture” the 13-membered-ring opening of H_{2}@C_{26} to complete the molecular surgery operation. 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 H_{2}@C_{60} should be the removal of the sulfur atom. We first conducted an oxidation of the sulfide unit of H_{2}@C_{60} by m-chloroperbenzoic acid in order to make the sulfur atom readily removable. The reaction proceeded at room temperature to give sulfoxide derivative H_{2}@C_{32} almost quantitatively. Then, irradiation of a solution of H_{2}@C_{32} in benzene with visible light at room temperature caused the elimination of the SO unit to give product H_{2}@C_{12} having a 12-membered-ring opening in 42% yield. The encapsulated H_{2} molecule was completely retained throughout these two steps because the two reactions were conducted at room temperature.

This removal of a sulfur atom made the distance between two carbonyl carbons across the opening closer from 3.89 Å for H_{2}@C_{26} to 3.12 Å for H_{2}@C_{12} as shown by calculations (B3LYP/6-31G* level). The reductive coupling of the two carbonyl groups efficiently proceeded by McMurry reaction using Ti(O)_{2}Cl at 80 °C to give product H_{2}@C_{10} with an eight-membered-ring opening in 88% yield. Here, it is to be noted that the MALDI-TOF mass spectrum of H_{2}@C_{10} already exhibited an intense peak of H_{2}@C_{60} together with a smaller molecular ion peak of H_{2}@C_{10}.

The final step to remove all the remaining organic addends on the C_{60} cage was performed by simply heating a powder of H_{2}@C_{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 pure solution containing desired H_{2}@C_{60} (118 mg, 67% yield), contaminated by 9% of empty C_{60}. Subsequently, complete separation of H_{2}@C_{60} from empty C_{60} 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 H_{2}@C_{60} as a pure material after 20 recycles (total retention time, 399 minutes; the retention time for empty C_{60}, 395
minutes). The adsorption mechanism of the Buckyprep column is largely based on the π–π interaction with pyrrole groups in the stationary phase. A very weak van der Waals interaction between the encapsulated H₂ molecule and the C₆₀–π-system must have contributed to this separation. The ¹³C NMR spectrum of pure H₂@C₆₀ exhibited a signal at δ = 142.8 ppm in ODCB-d₄, which is very slightly downfield shifted by 0.07 ppm relative to that of empty C₆₀.

The ¹H NMR signal of the encapsulated H₂ molecule appeared at δ = -1.44 ppm in ODCB-d₄, which is 5.98 ppm upfield shifted from dissolved free H₂ molecule. This value is comparable to the 6.36 ppm upfield shift of a ³He NMR signal downfield shifted by 0.078 ppm relative to that of empty C₆₀. Only the band at 576.7 cm⁻¹ corresponding to an out-of-plane vibration mode, ⁵₃ is higher in energy than that of C₆₀ by 1.0 cm⁻¹. This might be interpreted as evidence of a very slight repulsive interaction between the C₆₀ cage and the inner H₂ molecule. The UV-vis spectrum of H₂@C₆₀ was almost the same as that of empty C₆₀, 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 C₆₀). Only the band at 576.7 cm⁻¹ of H₂@C₆₀, corresponding to an out-of-plane vibration mode, ⁵₃ is higher in energy than that of C₆₀ by 1.0 cm⁻¹.

The cyclic voltammetry and differential pulse voltammetry of H₂@C₆₀ at room temperature exhibited three reversible reduction waves at E₁/₂ = -1.13, -1.54, and -1.99 V vs Fe/Fe⁺ in ODCB and one irreversible oxidation peak at Epa = +1.62 V in TCE, which were virtually the same as those of empty C₆₀. However, when more negative potential was applied using the solution in toluene-acetonitrile (5:4:1), the fourth, fifth, and sixth reduction waves became observable, which were found to be more cathodic than the reduction of empty C₆₀ by 0.04, 0.07, and 0.15 V, suggesting that H₂@C₆₀ becomes more difficult to be reduced as it acquires more than three electrons.⁴⁹

H₂@C₆₀ is thermally stable. Upon heating H₂@C₆₀ at 500 °C for 10 minutes under vacuum, no decomposition or no release of encapsulated H₂ molecule was observed at all.

4. Organic derivatization of H₂@C₆₀

In order to examine the effect of encapsulated H₂ molecule on the reactivity of the outer C₆₀ cage, the solid–state mechanochemical dimerization of H₂@C₆₀ (occupation level of 91%) was conducted under the same conditions reported previously. The dumbbell-shaped dimer, (H₂@C₆₀)₂, was obtained in 30% isolated yield similarly to the reaction of empty C₆₀. Apparently the inside hydrogen does not affect the reactivity of the C₆₀ cage. The NMR signal for the inside H₂ molecule was observed as a singlet at δ = -4.04 ppm, which is 8.58 ppm upfield shifted from that of free H₂ similarly to the case for ³He@C₆₀ (8.81 ppm upfield shift from the signal of free ³He). Three additional fullerene derivatives H₂@33, H₂@34, and H₂@35 were also synthesized and their NMR signals for the encapsulated H₂ molecule in ODCB-d₄ appeared at δ = -3.27, -4.30, and -4.64 ppm, respectively.⁴⁵ Since the values of chemical shift change sensitively according to the difference in structures of the organic addends, the encapsulated H₂ molecule within C₆₀ 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 C₆₀ (occupation level of 0.1%) has been used for this purpose.¹⁵

Furthermore, several organic and organometallic derivatives of H₂@C₆₀ were prepared at the University of Tokyo by the group of Nakamura.⁵⁷ The NMR signals for the encapsulated H₂ molecule appeared at δ = -10.39 ppm for compound H₂@C₃₆ in CDC₁₃-CS₂, δ = -9.79 ppm for potassium cyclopentadienide H₂@C₇₃ in THF-d₈, δ = -10.44 ppm for bucky ferrocene H₂@C₃₆ in CDC₁₃-CS₂, and δ = -10.77 ppm for tetraminofullerene epoxide H₂@C₃₉₉ in CDC₁₃. Although the ¹H NMR chemical shifts for the encapsulated H₂ molecule of amphiphilic derivative H₂@C₃₉₉ were measured in a variety of solvents, such as THF-d₈, DMSO-d₆–toluene-d₈ (1:1), DMSO-d₆, and D₂O–DMSO-d₆ (1:1), no specific solvent effect on the chemical shift was observed.

5. Utilization of the encapsulated H₂ molecule as an NMR probe

Saunders reported that the ³He NMR signal of hexaammonium ³He@C₆₀,⁶ appeared at dramatically high field (δ = -48.7 ppm relative to the signal of free ³He), reflecting the strong shielding effect of C₆₀.⁶–¹³ This was apparently due to the high aromaticity of C₆₀.⁶– Theoretical as well as experimental studies indicated that all of the hexagons and pentagons of C₆₀ showed diamagnetic ring currents. Among the other possible anionic states of C₆₀, dianion C₆₀⁻ is particularly important in synthetic chemistry for introduction of two functional groups on the C₆₀ cage.⁵₈ Although the “2(N + 1)² rule”,⁵⁹ describing the spherical aromaticity of Iₚ-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 C₆₀⁻ prior to our study.⁶⁰

Thus, we carried out the generation of H₂@C₆₀⁻ by using CH₃SN₆ as a reductant in CD₃CN under vacuum. The ¹H NMR signal of the encapsulated H₂ molecule of H₂@C₆₀⁻ was observed at surprisingly low field such as δ = 26.36 ppm. This is downfield shifted by 27.8 ppm relative to that of neutral H₂@C₆₀ (δ = -1.44 ppm in ODCB-d₄).⁴⁷ This result demonstrates that the overall aromaticity within the cage of C₆₀ decreases drastically upon two-electron reduction. The NICS (nucleus independent chemical shifts)⁶¹ calculations (B3LYP/6-31G* level) for all the hexagons and pentagons of C₆₀ 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 C₆₀, 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 fullerene was observed.

The similar reversal was observed even for the dianion of heavily functionalized C₆₀ such as open-cage fullerene H₂@C₆₆. The NMR signal of H₂@C₆₆⁻ was observed at δ = 8.10 ppm in CD₃CN, which is downfield shifted by 15.4 ppm relative to that of neutral H₂@C₆₆ (δ = -7.25 ppm in ODCB-d₄).⁵⁸ 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 C_{60}, in spite of the highly ruptured π-system in H_{2}@C_{60}. While the aromaticity of the spherically conjugated system of C_{60} is proved to be drastically changed when C_{60} acquired extra electrons, the research on the magnetic properties of ionic fullerene are still quite limited. Thus, we prepared dichloromethyl-C_{60} cation and (1-octenyl)-C_{60} anion as these compounds appeared to be well suited for the study of the difference in aromaticity between the nonfunctionalized C_{60} cation and anion. The cation H_{2}@C_{60} was generated in CF_{3}SO_{3}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 H_{2}@C_{60} (\( \delta = -4.62 \) ppm in CS_{2}-CDCl_{3} (1:1)), indicating that the aromaticity of H_{2}@C_{60} was slightly decreased as compared to that of H_{2}. On the other hand, an NMR signal for the encapsulated H_{2} molecule of anion H_{2}@C_{60} was also observed as a stable species in 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 H_{2} (\( \delta = -4.75 \) ppm in CS_{2}-CDCl_{3} (1:1)), indicating the decrease in aromaticity. The relatively small difference in the chemical shifts of the encapsulated H_{2} molecule between H_{2}@C_{60} and H_{2}@C_{60} (absolute \( \Delta \delta \) value, 2.29 ppm) demonstrates that the aromaticity of the fullerene is 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 H_{2}@C_{60} 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 H_{2}@C_{60} upon the \(^{1}H\) NMR measurements were not affected by the presence of molecular oxygen as a paramagnetic species in the solution.\(^{35} \) The \( T_{1} \) values of the encapsulated H_{2} molecule and one of the pyridyl proton of H_{2}@C_{60} in ODCB-d_{8} are 0.2 s and 3.9 s under vacuum and 0.2 and 0.9 s in an oxygen-saturated solution, respectively. In H_{2}@C_{60}, synthesized by complete synthesis and complete restoration of the opening of H_{2}@C_{60}, 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 H_{2}@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 H_{2}@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 H_{2}@C_{60} does not significantly change between the solutions in benzene-h_{2} and benzene-d_{6}. Therefore, the dominating interactions determining H_{2} in H_{2}@C_{60} nuclear relaxation are concluded to be intramolecular. On the other hand, the \( T_{1} \) value for both H_{2} and H_{2}@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 H_{2}@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.\(^{65} \) First, no differences in the triplet life times were observed for C_{60}, H_{2}@C_{60}, and D_{2}@C_{60} upon irradiation of laser pulse. Thus, the interaction of encapsulated H_{2} and D_{2} with the paramagnetic walls of the fullerene is too weak to be determined by triplet lifetime measurements. However, clear differences in reactivity were observed for the quenching of singlet oxygen \(^{1}O_{2}\) by C_{60}, H_{2}@C_{60}, and D_{2}@C_{60}. The absolute quenching rate constants \( k_{q} \) of \(^{1}O_{2}\) by H_{2}@C_{60}, D_{2}@C_{60}, and C_{60} were determined using a time-resolved method in CS_{2} to give the values of \( k_{q}(H_{2}@C_{60}) = 1.5 \times 10^{5} \) M\(^{-1}\) s\(^{-1}\), \( k_{q}(D_{2}@C_{60}) = 0.49 \times 10^{5} \) M\(^{-1}\) s\(^{-1}\), and \( k_{q}(C_{60}) = 0.38 \times 10^{5} \) M\(^{-1}\) s\(^{-1}\), respectively. The results demonstrate that both H_{2}@C_{60} and D_{2}@C_{60} are better quenchers than empty C_{60}. Importantly, the \(^{1}O_{2}\) can sense the difference between encapsulated H_{2} and D_{2}. The rate constants for quenching of \(^{1}O_{2}\) by free H_{2} and D_{2} in CC_{4} were also measured to afford the values of \( k_{q}(H_{2}) = 0.81 \times 10^{5} \) M\(^{-1}\) s\(^{-1}\), \( k_{q}(D_{2}) = 0.024 \times 10^{5} \) M\(^{-1}\) s\(^{-1}\), which are significantly smaller than the values by H_{2}@C_{60} and D_{2}@C_{60}. This is a unique example of an encapsulated guest having a significantly larger rate constant for quenching than the free guest. Since \(^{1}O_{2}\) might form an exciplexes with the outer surface of fullerene, it is speculated that this unique behavior can be attributed to a significant life time to provide an opportunity for \(^{1}O_{2}\) 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 H_{2}@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/\( T_{1} = 1/\tau_{1,0} + R_{l}[S] \), where \( \tau_{1,0} \) is the relaxation time in the absence of paramagnetic relaxant and \( R_{l} \) (M\(^{-1}\) 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 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, H$_2@$C$_{60}$. This method can be applied to the preparation of bowl-shaped compounds by the wide reactions. This molecular surgical operation was shown to be but by the stepwise transformations of fullerenes by organic relaxation effect of the paramagnets is enhanced 5-fold in for this project to be accomplished. For example, see M. Saunders, H. A. Jiménez-Vázquez, B. W. Bangertler, R. J. Cross, J. Am. Chem. Soc., 1994, 116, 3621; D. J. Schuster, J. Cao, N. Kaprinidis, Y. Wu, A. W. Jensen, Q. Lu, H. Wang, S. R. Wilson, J. Am. Chem. Soc., 1996, 118, 5639; R. J. Cross, H. A. Jiménez-Vázquez, Q. Lu, M. Saunders, D. J. Schuster, S. R. Wilson, H. Zhao, J. Am. Chem. Soc., 1996, 118, 11454; M. Rüttimann, R. F. Haldimann, L. Isacs, F. Diederich, A. Khong, H. A. Jiménez-Vázquez, R. J. Cross, M. Saunders, Chem. Eur. J., 1997, 3, 1071; G.-W. Wang, M. Saunders, R. J. Cross, J. Am. Chem. Soc., 2001, 123, 256.


Private communication from H. A. Jiménez-Vázquez, R. J. Cross, and M. Saunders.


