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Efficient Synthesis of Open-Cage Fullerene Derivatives Having 16-Membered-Ring Orifices

Manolis M. Roubelakis,† Yasujiro Murata,‡ Koichi Komatsu,‡ and Michael Orfanopoulos*,†

Department of Chemistry, University of Crete, Voutes 71003 Heraklion, Crete, Greece, and Institute for Chemical Research, Kyoto University, Kyoto 611-0011, Japan

orfanop@chemistry.uoc.gr

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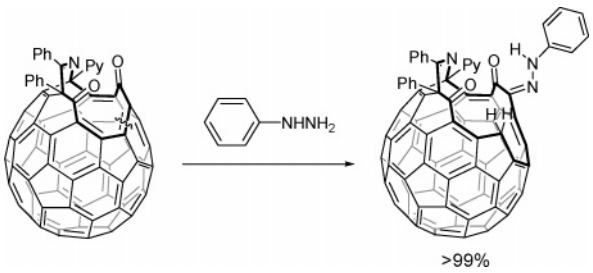

The synthesis of 10 new open-cage fullerene derivatives with a 16-membered-ring orifice is being reported. These compounds, derived from the regioselective addition reaction of an aromatic hydrazine or hydrazone to isomeric diketone derivatives of C_{60}, were isolated in moderate to excellent yields.

Soon after the discovery of [60]fullerene, it was suggested that the cavity of this hollow spherical structure is large enough to incorporate an atom, a small molecule, or an ion, thereby forming endohedral fullerene complexes.[1] The molecular surgery approach proposed by Rubin[2] appears as an alternative to the already known methods[3] of producing such complexes. This method consists of three steps: (i) opening a hole on the fullerene surface by σ-cage bond scission, (ii) insertion of a small atom or a molecule through the orifice, and (iii) restoration of the open-cage sphere. To date, several open-cage fullerenes have been prepared.[4] The first open-cage derivative *N*-MEM-ketolactam **1** (Figure 1) was reported by Wudl.[5] However, even a small atom, such as He, could not pass through the orifice of **1** at a temperature of 200 °C.[2b] The first successful attempt at introducing an atom or molecule inside the fullerene cage was reported in 2001 by Rubin: open-cage bislactam derivative **2** (Figure 1), with an elliptic 14-membered-ring orifice, succeeded in encapsulating inside its cavity both a He atom and a H_2 molecule with yields of 1.5% and 5%, respectively.[6] In addition, open-cage derivative **3** containing both nitrogen and sulfur atoms on its 13-membered-ring orifice (Figure 1), was found to encapsulate H_2 molecules with 100% yield at an applied H_2 pressure of 800 atm at 200 °C.[7]

Recently, the complete restoration of the orifice of H_2@**3** was, for the first time, accomplished by means of chemical transformations. A four-step reaction sequence afforded pristine fullerene encapsulating a hydrogen molecule (i.e., H_2@C_{60}).[8] This is so far the strongest evidence that, in the future, "molecular surgery approach" could constitute a powerful tool in the preparation of other kinds of endohedral fullerenes.

In 2003, Iwamatsu and co-workers reported a regioselective addition reaction between aromatic hydrazines and the open-cage diketone derivative **4** (Figure 2).[9] This reaction proceeded with migration of two hydrogen atoms from the hydrazine to the fullerene, affording adduct **5** (Figure 2), which has a methylene carbon along the orifice. The versatility of this reaction was successfully examined by our research groups. We found that a similar reaction takes place upon treatment of *N*-MEM-ketolactam derivative **1** with phenyl hydrazines.[10] Later on, a similar migrative addition reaction between compound **4** and benzophenone hydrazone, affording the respective adduct **6** (Figure 2), was reported by the same research group.[11]

The α,β-unsaturated carbonyl structure of **4** resembles structure **7** (the precursor of **3**) and its isomeric adduct **8**, both with a 12-membered-ring orifice (Figure 3).[12] Thus, we examined the reactivity of compounds **7** and **8** toward phenylhydrazine (**9a**), *p*-Br-phenylhydrazine (**9b**), *p*-MeO-phenylhydrazine (**9c**), and diphenylhydrazine (**9d**) as well as toward benzophenone hydrazone **12**. Herein, we report the synthesis and characterization of the 10 open-cage fullerene derivatives

† University of Crete.
‡ Kyoto University.

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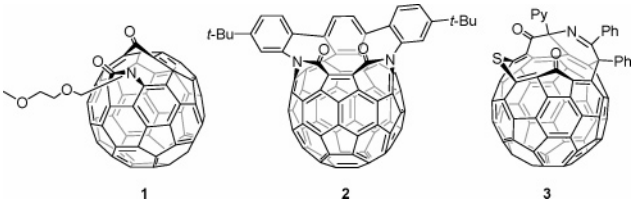


FIGURE 1. Reported open-cage fullerene structures **1**−**3**.

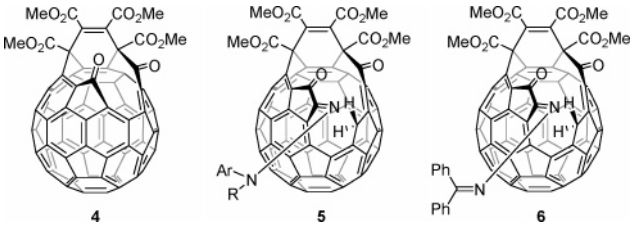


FIGURE 2. Open-cage fullerene derivatives previously reported.

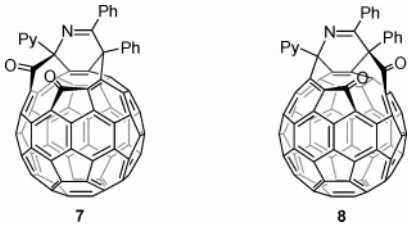


FIGURE 3. Isomeric open-cage compounds with 12-memberd-ring orifices bearing α,β-unsaturated carbonyl structures.

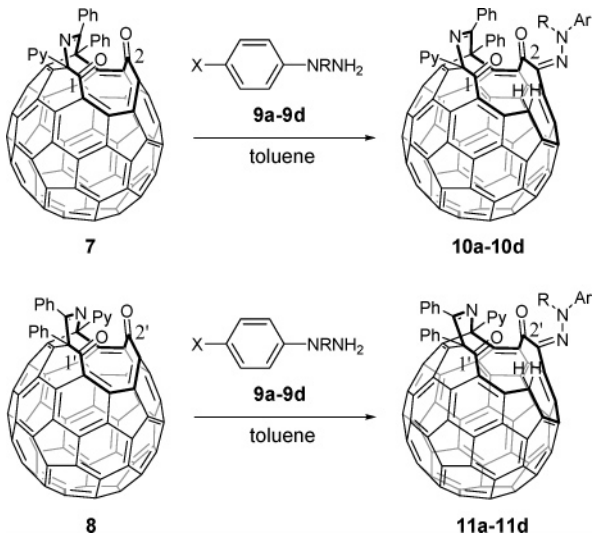
10a−**d**, **11a**−**d**, and **13a**,**b** (Tables 1 and 2) with a 16-membered ring orifice on the fullerene core.

Aromatic hydrazines **9a**−**d** are all commercially available. Reaction conditions and isolated yields are summarized in Table 1. Reactions with isomeric compounds **7** (entries 1−4) and **8** (entries 5−8) proceeded smoothly in toluene giving adducts **10** and **11**, respectively. Unlike the usual low to moderate reactivity of open-cage fullerenes, in this case some derivatives were obtained in high to almost quantitative yields (Table 1, entries 5 and 8).

The reactions of benzophenone hydrazone **12** with **7** and **8** were performed in toluene at 100 °C. Reaction conditions and isolated yields are shown in Table 2. All compounds **10**, **11**, and **13** were characterized by ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H COSY, 2D-HMQC, and DEPT135 experiments as well as MS (MALDI), FT-IR, and UV−vis spectroscopy. The high regioselectivity in these reactions was confirmed by the ^{1}H NMR spectra where the formation of only one single product could be detected.

The MS spectra showed the molecular ion peaks of the 1:1 adduct. The solutions of all adducts in chloroform are brown or red-brown, and their UV−vis spectra have characteristic strong absorptions at 256 and 325 nm, along with some minimum absorptions in the visible region (approximately 436 and 540 nm). The ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **11c** is presented in Figure 4 as a representative example of the ^{1}H NMR spectra of the adducts **10** and **11**. A pair of doublets observed at δ 5.71 and 4.86 ppm (each 1H), with a typical geminal coupling constant of J = 20 Hz, is indicative of the existence of two methylene protons on the same carbon along the fullerene orifice. A D_2O-exchangeable singlet at 14.09 ppm

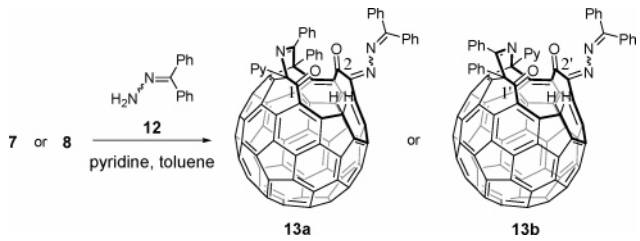
TABLE 1. Reactions of Aromatic Hydrazines 9a−d with Compounds 7 and 8



entry	hydrazine	X	R	*T* (°C)	reaction time (h)	hydrazine (equiv)	product, yield[a] (%)
1	**9a**	H	H	rt	2	5	**10a**, 70
2[b]	**9b**	Br	H	60	4	6	**10b**, 55
3[b]	**9c**	CH_3O	H	60	9	10	**10c**, 53
4	**9d**	H	Ph	60	9	5	**10d**, 85
5	**9a**	H	H	rt	2	5	**11a**, >99
6[b]	**9b**	Br	H	60	4	6	**11b**, 68
7[b]	**9c**	CH_3O	H	60	7	10	**11c**, 79
8	**9d**	H	Ph	60	7	5	**11d**, 93

[a] Based on the amount of isolated adduct. [b] 2 equiv of pyridine relative to hydrazine was added.

TABLE 2. Reactions of Benzophenone Hydrazone with Compounds 7 and 8[a]



open−cage fullerene derivatives	hydrazone (equiv)	product	yield[b] (%)
7	5	**13a**	46
8	5	**13b**	59

[a] 2 equiv of pyridine relative to hydrazone was added; reaction mixtures were heated at 100 °C for 18 h. [b] Based on the amount of isolated adduct.

corresponds to the NH proton. The MeO group resonates at 3.94 ppm. In the ^{13}C NMR spectrum (75 MHz, $CDCl_3$), the two carbonyl carbons were observed at 196.54 and 185.32 ppm (195.31 and 190.36 ppm in **8**, respectively). The two quaternary sp^3 signals characteristic of the fulleroid bridge carbons were observed at 60.44 and 72.75 ppm, regions similar to **8**. Methylene and methoxy carbons were observed at 43.96 and 55.54 ppm, respectively, as was confirmed by DEPT135 and 2D-HMQC spectra.

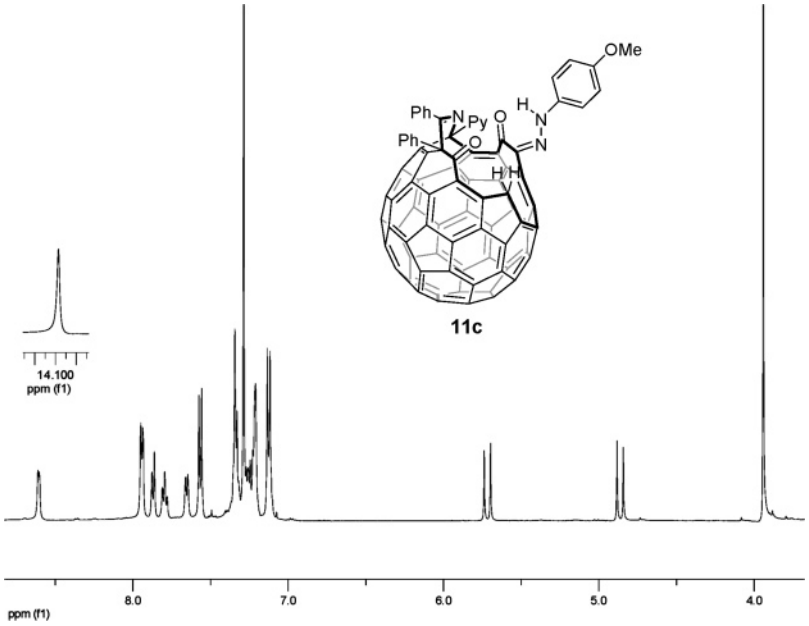
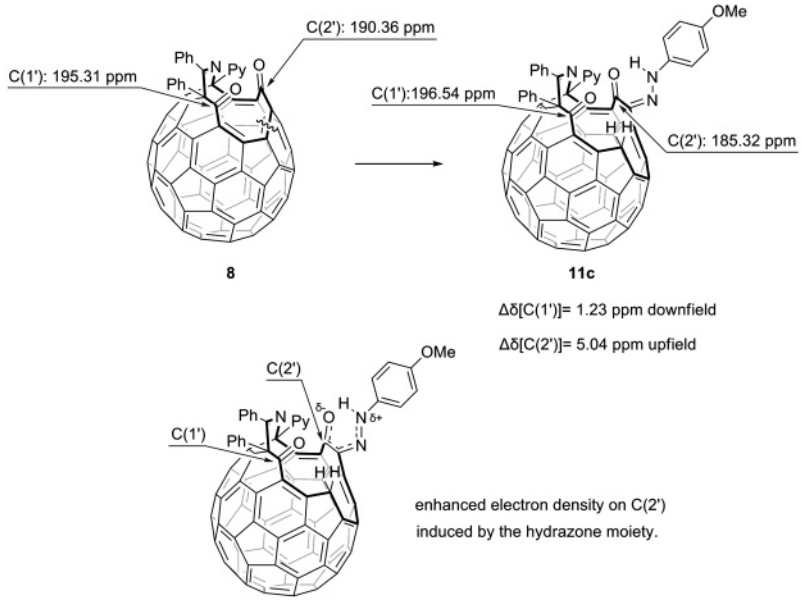


FIGURE 4. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum for **11c**.

SCHEME 1. Upfield Chemical Shift for C(2′) on Going from 8 to 11c



Concerning the regioselectivity of the reactions, it is noteworthy to mention here that the proposed product structures depicted above (Tables 1, 2 and Figure 4) are in agreement with those proposed previously by Iwamatsu.[9,11] Specifically, the C−C double bonds next to carbonyl carbons C(2) of **7** and C(2′) of **8** (Tables 1, 2) are cleaved regioselectively. The similarity of the structures of the starting materials **7** and **8** with **4**, as well as of the spectral data of the products, indicated this attribution. However, additional evidence to the above proposed structures could be the following observation: GIAO-B3PW91/6-311G** calculations reproducing experimental ^{13}C NMR spectra for **7** and **8** allowed the identification of the carbonyl signals to the specific carbons for both compounds.[12] Therefore, for **8**, the signal at 195.31 ppm was attributed to the six-membered-ring carbonyl [C(1′), Scheme 1], while the signal at 190.36 ppm was attributed to the five-membered-ring carbonyl [C(2′), Scheme 1]. On going from the starting material to the 16-membered-ring adduct, in the ^{13}C NMR spectrum, the signal from the carbonyl carbon located next to the reactive double bond will suffer greater upfield chemical shift than the other, due to enhanced electron density on this carbon, induced by the hydrazone moiety in the product (Scheme 1).[13] Thus, for compound **11c**, as mentioned above, the 195.31 ppm signal of C(1′) in the starting material was shifted downfield at 196.54 ppm in the product ($\Delta\delta = 1.23$ ppm), whereas the 190.36 ppm signal of C(2′) was shifted upfield at 185.32 ppm ($\Delta\delta = 5.04$ ppm) in the product (Scheme 1). Consequently, the regioselective scission of the double bond takes place next to the "190.36 ppm" carbonyl group, namely C(2′). Similar comparisons of

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the chemical shifts for the other products led to the same conclusion: the double bond next to C(2) or C(2′) is the one that is ruptured regioselectively.

In conclusion, we have reported the synthesis of ten new open-cage fullerene derivatives with 16-membered-ring orifices, derived from the addition reactions of aromatic hydrazines and hydrazones with two isomeric diketone derivatives of C_{60}. Reactions proceed through regioselective cleavage of a carbon−carbon double bond on the open-cage fullerene skeleton, and, in some cases, almost quantitatively.

Experimental Section

Synthesis of Open-Cage Fullerene Derivatives 10a, 10d, 11a, and 11d. A Schlenk tube was charged with 10.0 mg (0.01 mmol) of **7** or **8** and 3 mL of degassed, HPLC-grade toluene. The resulting solution was stirred under argon atmosphere for 10 min, and subsequently, 5 μL (0.05 mmol) of phenylhydrazine **9a** or 11 mg (0.05 mmol) of diphenylhydrazine **9d** was added. The reaction mixture was stirred at room temperature for hydrazine **9a** or at 60 °C for hydrazine **9d** for 2−9 h (for exact reaction times, see Table 1). The resulting mixture was directly subjected to column chromatography (silica gel, 3% ethyl acetate in toluene; for adduct **10a** due to low solubility in toluene, the polarity of the eluent had to be raised to 20% ethyl acetate in toluene). The isolated product was washed three times with acetonitrile HPLC grade (centrifugation at 1500 c/min) to yield 8.0 mg (70%) of **10a** or 10.4 mg (85%) of **10d** or 11.5 mg (>99%) of **11a** or 11.3 mg (93%) of **11d** as dark brown solids.

Data for 10a. IR (KBr): υ (cm^{-1}) 3369, 3053, 2917, 2848, 1688, 1620, 1594, 1582, 1530, 1481, 1427, 1414, 1259, 1169, 1094, 1062, 998, 748, 695, 559, 540, 506. UV−vis ($CHCl_3$): λ_{max} (nm) 255, 327, 439, 534. MS (MALDI): *m*/*z* 1142 (M^+). ^{1}H NMR (500 MHz, $CDCl_3/CS_2$): δ 13.63 (s, 1H), 8.65 (m, 1H), 7.93 (m, 1H), 7.81 (m, 1H), 7.74−7.70 (m, 4H), 7.47 (m, 2H), 7.36 (m, 1H), 7.22−7.15 (m, 5H), 7.09 (m, 1H), 7.04 (m, 2H), 6.97 (m, 1H), 5.48 (d, J = 20 Hz, 1H), 4.84 (d, J = 20 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3/CS_2$): δ 193.96, 184.05, 153.68, 152.25, 150.98, 149.98, 149.81, 149.68, 149.58, 149.40, 149.09, 148.85, 148.74, 148.70, 148.41, 148.34, 148.28, 148.16, 148.11, 148.04, 147.77, 147.58, 147.43, 146.98, 146.91, 146.52, 145.83, 145.75, 145.65, 144.82, 144.72, 144.17, 144.03, 143.56, 143.31, 143.22, 142.82, 142.76, 142.03, 141.76, 141.16, 140.66, 139.87, 139.16, 138.58, 138.53, 138.37, 138.27, 137.77, 137.72, 137.52, 137.44, 137.41, 136.70, 136.67, 136.58, 136.16, 136.11, 133.77, 132.23, 131.83, 131.29, 130.37, 130.15, 129.14, 128.91, 128.82, 128.65, 128.33, 127.74, 127.51, 127.34, 127.23, 125.40, 123.65, 123.43, 116.27, 76.19, 53.17, 44.29.

Synthesis of Open-Cage Fullerene Derivatives 10b, 10c, 11b, and 11c. A Schlenk tube was charged with 10.0 mg (0.01 mmol) of **7** or **8** and 3 mL of degassed, HPLC-grade toluene. The resulting solution was stirred under argon atmosphere for 10 min, and subsequently 13 mg (0.06 mmol) of **9b**·HCl along with 10 μL (0.12 mmol) of pyridine or 18 mg (0.10 mmol) of **9c**·HCl along with 16 μL (0.2 mmol) of pyridine were added. The reaction mixture was stirred at 60 °C for 4−9 h (for exact reaction times, see Table 1). After being cooled to 0 °C, the reaction mixture was washed twice with 2 N HCl and brine and dried with $MgSO_4$. The resulting mixture was then subjected to column chromatography (silica gel, 3% ethyl acetate in toluene), and the isolated product was washed three times with acetonitrile HPLC grade (centrifugation at 1500 c/min) to yield 6.7 mg (55%) of **10b** or 6.2 mg (53%) of **10c** or 8.3 mg (68%) of **11b** or 9.2 mg (79%) of **11c** as dark brown solids.

Synthesis of Open-Cage Fullerene Derivatives 13a and 13b. A Schlenk tube was charged with 10.0 mg (0.01 mmol) of **7** or **8** and 2.6 mL of degassed, HPLC-grade toluene. The resulting solution was stirred under argon atmosphere for 10 min, and subsequently, 10 mg (0.05 mmol) of **12** along with 8 μL (0.1 mmol) of pyridine were added. The reaction mixture was stirred at 100 °C for 18 h. The resulting mixture was directly subjected to column chromatography (silica gel, 10% ethyl acetate in toluene), and the isolated product was washed three times with acetonitrile HPLC-grade (centrifugation at 1500 c/min) to yield 5.6 mg (46%) of **13a** or 7.2 mg (59%) of **13b** as dark brown solids.

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Supporting Information Available: Characterization data of compounds **10b**−**d**, **11a**−**d**, and **13a**,**b**. ^{1}H and ^{13}C NMR, FT-IR, and UV−vis spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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