JOC*Note*

Open-Cage Fullerene Derivatives with 15-Membered-Ring Orifices

Georgios C. Vougioukalakis,[†] Kosmas Prassides,*[,‡] Josep M. Campanera,[‡,§] Malcolm I. Heggie,[‡] and Michael Orfanopoulos*[,†]

Departments of Chemistry, University of Crete, 71409 Iraklion, Greece, and University of Sussex, Brighton BN1 9QJ, UK

orfanop@chemistry.uoc.gr

Received January 27, 2004

Abstract: The addition reaction of the *N*-MEM-ketolactam derivative of [60]fullerene with phenyl, *p*-Br-phenyl, and *p*-MeO-phenyl hydrazines proceeds regioselectively, affording three open-cage fullerene derivatives bearing a 15-membered-ring orifice on the fullerene cage. Both experimental data and theoretical calculations were utilized for the structure determination of the new [60]fullerene adducts.

Since Wudl and co-workers isolated *N*-MEM-ketolactam **1** (Figure 1),[1] the first open-cage fullerene derivative, much attention has been paid to synthetic procedures toward the formation of an orifice in the fullerene shell, sufficiently large to allow encapsulation of small atoms, molecules, or ions such as He, H_2, or Li^+. In this direction, Rubin and collaborators successfully prepared an open-cage bislactam fullerene derivative with a 14-membered-ring orifice by the scission of four bonds of the fullerene cage[2] and succeeded in introducing inside the cage both He atoms and H_2 molecules with yields of 1.5% and 5%, respectively.[3] Additionally, Komatsu and co-workers synthesized the open-cage fullerene derivative **2** (Figure 1),[4] which allowed encapsulation of H_2 molecules in 100% yield at an applied H_2 pressure of 800 atm at 200° C.[5] Also, a new bowl-shaped [60]fullerene derivative was found to spontaneously encapsulate a water molecule into the cage.[6]

Furthermore, a regioselective addition reaction between the α,β-unsaturated carbonyl structure of the open-cage fullerene adduct **3** and aromatic hydrazines was recently reported.[7] The reaction proceeds with migration of two hydrogen atoms from the hydrazine to the fullerene, affording adduct **4**, which has a methylene carbon along the orifice (Figure 2).

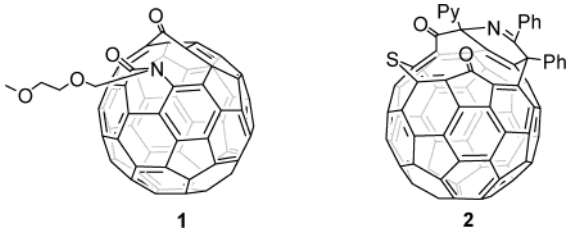


FIGURE 1.

Open cage fullerenes are important members in the fullerene family because of their potential use in the production of endohedral fullerene complexes. Although endohedral fullerenes are currently being produced by utilizing the evaporation of graphite-metal composites, high temperature and high-pressure conditions or high energy plasma insertions into pure fullerenes,[8−10] an alternative methodology could make use of the "molecular surgery" approach, which is based on the chemical creation and then closure of the opening, following the encapsulation of the desired species within the fullerene cage. This has proven to be feasible in the gas-phase generation of $H_2@C_{60}$ during MALDI-TOF mass spectrometry experiments.[5]

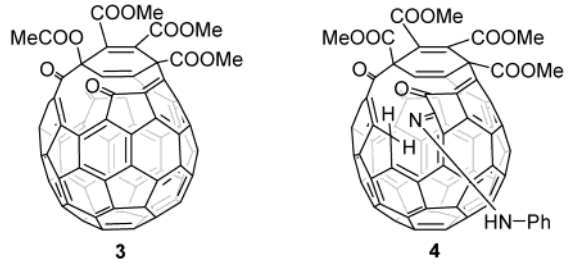


FIGURE 2.

Noting the α,β-unsaturated carbonyl structure of the *N*-MEM-ketolactam **1**, which resembles the structure of **3**, we investigated its reactivity toward the phenyl hydrazines **5a**−**c**. Herein, we report the synthesis and characterization of the three open-cage fullerene adducts **6a**−**c** (Table 1), which have a 15-membered-ring orifice on the fullerene cage. At the time that we finished the preparation of the present manuscript, the reaction of **1** with phenylhydrazine **5a** and 1,1-diphenylhydrazine was reported by Iwamatsu and co-workers.[11] Our data and discussion in this paper will point out that their assumed structural assignment is incorrect.

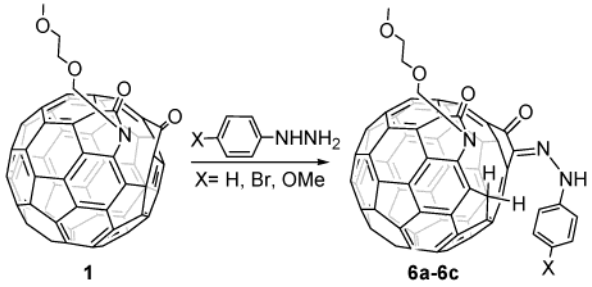
Phenyl hydrazines **5a**−**c** are all commercially available. The reaction conditions and the isolated yields are presented in Table 1. The new open-cage fullerene adducts **6a**−**c** were characterized by ^{1}H NMR, ^{13}C NMR, and NOE-difference experiments as well as MS (MALDI),

[†] University of Crete.
[‡] University of Sussex.
[§] Present address: Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, 43005 Tarragona, Catalonia, Spain.

(1) Hummelen, J. C.; Prato, M.; Wudl, F. *J. Am. Chem. Soc.* **1995**, *117*, 7003−7004.
(2) Schick, G.; Jarrosson, T.; Rubin, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 2360−2363.
(3) Rubin, Y.; Jarrosson, T.; Wang, G.-W.; Bartberger, M. D.; Houk, K. N.; Schick, G.; Saunders: M.; Cross, R. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1543−1546.
(4) Murata, Y.; Murata, M.; Komatsu, K. *Chem. Eur. J.* **2003**, *9*, 1600−1609.
(5) Murata, Y.; Murata, M.; Komatsu, K. *J. Am. Chem. Soc.* **2003**, *125*, 7152−7153.
(6) Iwamatsu, S.-I.; Uozaki, T.; Kobayashi, K.; Re, S.; Nagase, S.; Murata, S. *J. Am. Chem. Soc.* **2004**, *126*, 2668−2669.
(7) Iwamatsu, S.-I.; Ono, F.; Murata, S. *Chem. Commun.* **2003**, 1268−1269.
(8) Shinohara, H. *Rep. Prog. Phys.* **2000**, *63*, 843−892.
(9) Nagase, S.; Kobayashi, K.; Akasaka, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2131−2142.
(10) Stevenson, S.; Rice, G.; Glass, T.; Harich, K.; Cromer, F.; Jordan, M. R.; Craft, J.; Hadju, E.; Bible, R.; Olmstead, M. M.; Maitra, K.; Fisher, A. J.; Balch, A. L. Dorn, H. C. *Nature* **1999**, *401*, 55−57.
(11) Iwamatsu, S, −I.; Ono, F.; Murata, S. *Chem. Lett.* **2003**, *32*, 614−615.

10.1021/jo049842x CCC: $27.50
Published on Web 05/22/2004

TABLE 1. Reactions of *N*-MEM Ketolactam 1 with Substituted Phenylhydrazines 5a−c



hydrazine	X	adduct	yield (%)[a]	reaction time (h)	temp (°C)	hydrazine equiv
5a	H	**6a**	68	1	rt	5
5b	Br	**6b**	37	4	60	6[b]
5c	CH_3O	**6c**	26	4	60	10[b]

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

FT-IR, and UV−vis spectroscopy. The MS spectra of **6a**, **6b**, and **6c** showed the molecular ion peaks, of the 1:1 adducts, at m/z = 963, 1042, and 993, respectively. The solutions of adducts **6a**−**c** in all common solvents are brown, and their UV−vis spectra have characteristic absorptions at 257, 325, 395, and 558 nm. The ^{1}H NMR (500 MHz) spectrum of **6a** is presented in Figure 3, as a representative example of the NMR spectra of the new adducts **6a**−**c**.

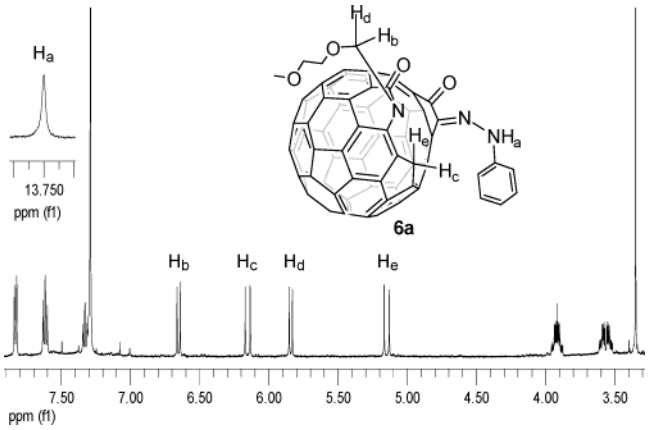
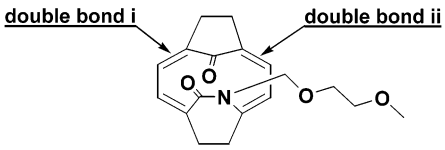


FIGURE 3. ^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of **6a**.

The pair of doublets observed at the ^{1}H NMR spectrum of **6a** at δ 5.13 and 6.13 ppm is attributed to the methylene protons along the orifice, and the D_2O exchangeable singlet at δ 13.74 ppm to the NH proton. The AB system at δ 5.82 and 6.63 ppm is assigned to the two diastereotopic *N*-methylene protons H_b and H_d. The ketone ^{13}C NMR absorption is upfield shifted from 198.5 ppm in the starting material **1** to around δ 188 ppm in the adducts **6a**−**c**, while the lactam ^{13}C chemical shift change is insignificant (the lactam carbon resonance is approximately at 163 ppm). The change in the environment of the ketone carbonyl is also confirmed by IR spectroscopy, with the C=O absorption shifting from 1727 cm^{-1} to near 1670 cm^{-1}, while the shift of the lactam carbonyl position is insignificant. These observations indicate that the bond scission to provide the products occurs at one of the two double bonds (i) or (ii) next to the ketone group, as shown below, in a fashion similar to the reaction between **3** and the corresponding phenyl hydrazines.[7]



The NOE enhancement for H_a during irradiation of the proton H_c (shown in the ^{1}H NMR spectrum of **6a** in Figure 3) was almost twice as large as that during irradiation of proton H_b (1.5% and 0.8%, respectively). Furthermore, the NOE enhancements measured during inverse irradiation (observation of H_c and H_b, while irradiating H_a) were essentially identical. Moreover, all relevant NOEs measured for adducts **6b** and **6c** showed NOE enhancement of the methylene proton on the C_{60} shell twice as large as that of the *N*-methylene one.

To find the most stable conformer of isomer **6a**, a systematic search using molecular mechanics calculations were performed with the Open Force Field (OFF) program in the Cerius^2 package (version 4.2).[12] Afterward, only the most stable conformers were reoptimized employing the Density Functional Theory (DFT) methodology in the AIMPRO program. Although there is a huge number of conformers of isomer **6a**, the most stable ones (0−10 kcal mol^{-1}) are those in which the H_a proton is closer to the H_c proton than to the H_b proton. The most stable conformer of isomer **6a** is displayed in Figure 4. For this, the H_a−H_b and H_a−H_c distances are computed as 3.641 and 2.563 Å, respectively. None of the conformers of the isomer derived from the reaction at double bond (i) allows the H_a proton to be closer to H_c than to H_b. By combining the measured NOEs with the results of the theoretical calculations, we therefore arrive at the structures **6a**−**c** presented in Table 1.

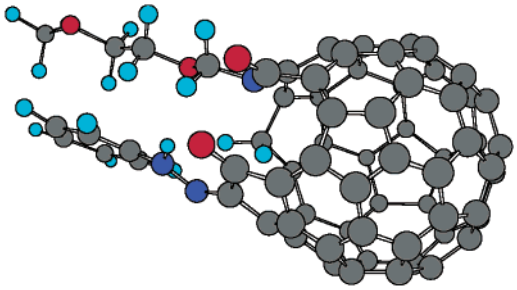


FIGURE 4. Most stable conformer of isomer **6a**.

Although the assignment of both carbon atoms C_a and C_b (Figure 5) is quite difficult even in the starting material **1**,[13] comparison between ^{13}C−^{1}H coupled and selectively decoupled ^{13}C spectra (by irradiating one proton at a time) of **6a**−**c** also leads to the conclusion that double bond (ii) is the one that reacts. In particular, the carbon atom that absorbs at 138.51 ppm (C_a) is

(12) *Cerius2*, version 3.5; Molecular Simulations Inc.: Cambridge, England 1997.
(13) Bellavia-Lund, C.; Keshavarz-K, M.; Collins, T.; Wudl, F. *J. Am. Chem. Soc.* **1997**, *119*, 8101−8102.

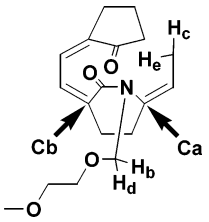


FIGURE 5.

coupled both with protons H_b and H_d and with H_c and H_e (Figure 5). Taking into account that coupling between a carbon atom and a proton can be observed only for carbon atoms that are no more than three bonds away from a specific proton, the proposed structures **6a**−**c** are the only ones possible. If this were not the case and reaction had occurred at double bond (i), the H_b and H_d protons would have been four bonds away from carbon C_b and no coupling between them would have been observed. As a final point, the same trend of reactivity was recently observed for the regioselective sulfur-atom insertion in the central C−C bond of the butadiene unit of **1**, which contains double bond (ii).[14]

Here we emphasize that Iwamatsu and co-workers carried out the reaction between **1** and **5a** in chlorobenzene,[11] whereas ours was in toluene. On repeating their experiment, we again isolated adduct **6a**. An important difference between their conclusions and ours is the structure assignment of the new adduct. They reported that the "most considerable structure" is the one where double bond (i) has reacted, without offering any rationalization or experimental support for such a choice. As we already mentioned, our results and discussion suggest that their structural assignment is incorrect. Indisputable structural assignment would arise from the crystallographic analysis of a single crystal, which it has not been possible to obtain as yet.

In summary, three [60]fullerene adducts with 15-membered-ring orifices on the fullerene cage were synthesized and characterized. The existence of many different functional groups on the rim of the orifice is very promising for further regioselective functionalization and enlargement of the orifice size. Work in this direction is currently under way.

Experimental Section

Synthesis of Open-Cage Fullerene Derivative 6a. Ketolactam **1 (**17.1 mg, 0.02 mmol) was dissolved in degassed, HPLC grade toluene (6 mL) in a 10 mL round-bottomed flask under an argon atmosphere. Phenyl hydrazine (10.8 mg, 0.1 mmol) was added, and the solution was stirred at room temperature for 1 h. The reaction mixture was subjected to chromatography (2% EtOAc in toluene), and the isolated product was washed 2−3 times with acetonitrile HPLC grade (centrifugation at 1500 c/min) to afford 13.1 mg (68%) of **6a** as a brown solid. IR (KBr): ν (cm^{-1}) 2963, 2919, 1672, 1596, 1537, 1480, 1385, 1261, 1092, 1020, 804, 751, 692, 598, 518, 407. UV−vis ($CHCl_3$): λ_{max} (nm) 257, 330, 397, 558. MS (MALDI): m/z 963 (M^+). ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.74 (s, 1H), 7.81 (d, J = 7 Hz, 2H), 7.62 (t, J = 7 Hz, 2H), 7.31 (t, J = 7 Hz, 1H), 6.63 (d, J = 11 Hz, 1H), 6.13 (d, J = 18 Hz, 1H), 5.82 (d, J = 11 Hz, 1H), 5.13 (d, J = 18 Hz, 1H), 3.90 (m, 2H), 3.55 (m, 2H), 3.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.46, 164.38, 156.16, 154.32, 152.46, 150.35, 149.41, 149.40, 149.01, 148.99, 148.96, 147.94, 147.20, 146.73, 146.45, 146.37, 146.34, 146.33, 146.24, 146.11, 146.09, 146.00, 145.90, 145.66, 145.38, 145.08, 144.74, 144.73, 144.31, 144.21, 143.96, 143.88, 143.69, 143.25, 143.11, 142.54, 141.70, 141.51, 139.87, 139.67, 139.49, 139.38, 139.37, 139.17, 138.59, 138.51, 138.19, 137.88, 137.83, 137.60, 135.56, 133.21, 132.50, 131.63, 130.88, 130.13, 129.92, 127.72, 126.58, 125.14, 115.66, 82.55, 71.50, 69.34, 59.06, 42.07.

Synthesis of Open-Cage Fullerene Derivatives 6b and 6c. Ketolactam **1** (17.1 mg, 0.02 mmol) was dissolved in degassed, HPLC grade toluene (6 mL) in a 10 mL round-bottomed flask under an argon atmosphere. Substituted phenyl hydrazine **5b**·HCl or **5c**·HCl (0.12 or 0.2 mmol, respectively) and pyridine (2 equiv relative to the substituted hydrazine) were added, and the solution was stirred at 60 °C for 4 h. After cooling at 0 °C the reaction was washed twice with 2 N HCl and brine and dried with Na_2SO_4. The reaction mixture was subjected to chromatography (2% EtOAc in toluene), and the isolated product was washed 2−3 times with acetonitrile HPLC grade (centrifugation at 1500 c/min) to afford 7.7 mg (37%) of **6b** or 5.2 mg (26%) of **6c** as brown solids. **Data for 6b.** IR (KBr): ν (cm^{-1}) 2915, 1669, 1535, 1476, 1398, 1253, 1085, 1068, 1018, 819, 746, 602, 518. UV−vis ($CHCl_3$): λ_{max} (nm) 256, 322, 392, 556. MS (MALDI): m/z 1042 (M^+). ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.68 (s, 1H), 7.70 (m, 4H), 6.61 (d, J = 10 Hz, 1H), 6.08 (d, J = 18 Hz, 1H), 5.81 (d, J = 10 Hz, 1H), 5.11 (d, J = 18 Hz, 1H), 3.89 (m, 2H), 3.54 (m, 2H), 3.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.31, 164.12, 155.76, 153.96, 152.16, 150.08, 149.16, 149.13, 148.72, 148.69, 147.64, 146.98, 146.48, 146.14, 146.11, 146.08, 145.94, 145.89, 145.84, 145.62, 145.55, 145.39, 145.09, 144.81, 144.46, 144.04, 143.82, 143.59, 143.40, 142.95, 142.83, 142.34, 141.43, 141.16, 139.70, 139.35, 139.12, 138.52, 138.25, 137.89, 137.74, 137.66, 137.60, 137.32 137.23, 133.16, 132.66, 132.61, 132.27, 132.10, 131.32, 130.93, 130.61, 129.86, 128.36, 127.39, 126.42, 117.40, 116.78, 82.30, 71.24, 69.11, 58.83, 41.83. **Data for 6c.** IR (KBr): ν (cm^{-1}) 2913, 1669, 1532, 1507, 1496, 1457, 1398, 1244, 1160, 1085, 1018, 825, 759, 515. UV−vis ($CHCl_3$): λ_{max} (nm) 256, 325, 560; MS (MALDI): m/z 993 (M^+). ^{1}H NMR (500 MHz, $CDCl_3$): δ 13.88 (s, 1H), 7.77 (d, J = 9 Hz, 2H), 7.14 (d, J = 9 Hz, 2H), 6.63 (d, J = 11 Hz, 1H), 6.15 (d, J = 18 Hz, 1H), 5.82 (d, J = 11 Hz, 1H), 5.11 (d, J = 18 Hz, 1H), 3.95 (s, 3H), 3.90 (m, 2H), 3.55 (m, 2H), 3.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.62, 164.81, 159.50, 158.16, 156.67, 155.76, 154.77, 152.86, 150.76, 149.97, 149.86, 149.78, 149.46, 149.44, 149.34, 149.30, 148.40, 147.50, 147.15, 146.92, 146.88, 146.82, 146.79, 146.63, 146.59, 146.55, 146.43, 146.35, 146.12, 145.85, 145.43, 145.19, 145.17, 144.79, 144.74, 144.32, 144.16, 143.71, 143.55, 142.83, 142.12, 141.96, 140.15, 140.12, 140.02, 139.99, 139.80, 139.55, 138.87, 138.64, 138.25, 138.18, 138.05, 136.61, 136.35, 136.16, 133.24, 132.86, 132.08, 130.52, 128.20, 126.69, 117.66, 115.74, 82.97, 71.93, 69.75, 59.47, 56.21, 42.50.

Acknowledgment. Leonidas Zervas Foundation and the Greek National Scholarships Foundation (IKY) are acknowledged for research fellowships to G. C. V. Socrates-Erasmus research graduate program is also acknowledged for financial support to G. C. V., during his three months stay at Sussex University. M.O. thanks the British Council and the Greek Ministry of Education for financial support during his visit to Sussex University (Greek-United Kingdom collaborative scientific visit under cultural program, 2003). J.M.C. thanks Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) of the Generalitat de Catalunya for financial support during his visit to Sussex University.

Supporting Information Available: NMR, FT-IR, and UV−vis spectra and results of the theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049842X

(14) Vougioukalakis, G. C.; Prassides, K.; Orfanopoulos, M. *Org. Lett.* **2004**, *6*, 1245−1247.