Articles

Methyl 1,2-Dihydrofullerenecarboxylate

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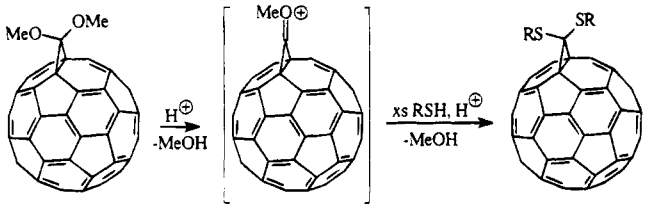
We report the preparation of the title compound, the first fullerenecarboxylic acid derivative, by hydrolysis of dimethoxymethanofullerene. The latter was prepared from dimethoxycarbene and C_{60}. The title ester is quite unreactive; conventional saponification methods, including sulfuric acid, trimethylsilyl iodide, and boron tribromide, failed to transform the ester to acid. A special phase-transfer-catalysis procedure effected hydrolysis but the only characterizable product was buckminsterfullerene (C_{60}).

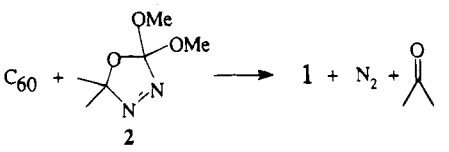
The chemical properties of buckminsterfullerene (C_{60})[1] are being investigated with increasing interest.[2,3] Among the simplest and most versatile derivatives of buckminsterfullerene are the methanofullerenes and fulleroids, where a carbon atom bearing two substituents is added to C_{60}.[4,5] Since the discovery of the HIV enzyme-inhibiting and virucidal properties of a relatively complex water-soluble methanofullerene,[6,7] our group launched a search for simpler, water-soluble methanofullerenes and fulleroids. The methanofullerenone[8] ketal **1** was expected to be a precursor to a large family of water-soluble thioketals because acid-catalyzed transketalizations are known to be driven to completion by the higher hydrolytic stability of thioketals (stable in media of pH < 7) compared to ketals:



1

where R could contain water-solubilizing functionality such as a polyoxymethylene, polyoxyethylene, or polyaminoethylene moieties. Essential to the above strategy was that **1** would undergo normal ketal chemistry. We were not concerned with the cyclopropyl cation–allyl cation rearrangement because, in this particular case, formation of a severely strained bridgehead olefin would impede ring-opening and ensure the integrity of the cyclopropane ring. The intermediate methoxycyclopropyl cation was expected to be somewhat destabilized by the inductive effect of the fullerene.[9]

Scheme 1



2

In this paper we present some properties of the ketal **1**[10] prepared by thermolysis of **2**, Scheme 1)[11] and its conversion to the simplest dihydrofullerene ester (**3**, cf. Scheme 2) as well as some striking properties of the latter.

® Abstract published in *Advance ACS Abstracts,* September 1, 1994.

(1) Krätschmer, W.; Lamb, L. D.; Fostiropoulos, K.; Huffman, D. R. *Nature* **1990**, *347*, 354. Haufler, R. E.; Conceicao, J.; Chibante, L. P. F.; Chai, Y.; Byrne, N. E.; Flanagan, S.; Haley, M. M.; O'Brien, S. C.; Pan, C.; Xiao, Z.; Billups, W. E.; Ciufolini, M. A.; Hauge, R. H.; Margrave, J. L.; Wilson, L. J.; Curl, R. F.; Smalley, R. E. *J. Phys. Chem.* **1990**, *94*, 8634. Taylor, R.; Walton, D. R. M. *Nature* **1993**, *363*, 685.

(2) Fagan, P. J.; Calabrese, J. C.; Malone, B. *Acc. Chem. Res.* **1992**, *25*, 134. Hawkins, J. M. *Acc. Chem. Res.* **1992**, *25*, 150.

(3) Friedman, S. H.; DeCamp, D. L.; Sijbesma, R. P.; Srdanov, G.; Wudl, F.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6506–6509. Sijbesma, R. P.; Srdanov, G.; Wudl, F.; Castoro, J. A.; Wilkins, C.; Friedman, S. H.; DeCamp, D. L.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6510–6512.

(4) Suzuki, T.; Li, Q.; Khemani, K. C.; Wudl, F.; Almarsson, O. *Science* **1991**, *254*, 1186.

(5) Wudl, F. *Acc. Chem.* **1992**, *25*, 157.

(6) Friedman, S. H.; DeCamp, D. L.; Sijbesma, R. P.; Srdanov, G.; Wudl, F.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6506–6509. Sijbesma, R. P.; Srdanov, G.; Wudl, F.; Castoro, J. A.; Wilkins, C.; Friedman, S. H.; DeCamp, D. L.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6510–6512.

(7) Schinazi, R. F.; Sijbesma, R. P.; Srdanov, G.; Hill, C. L.; Wudl, F. *Antimicrob. Agents Chemother.* **1993**, *37*, 1707–1710.

(8) The hypothetical methanofullerenone would be a cyclopropanone with the structure shown below:

(9) Since C_{60} is approximately as strong an electron acceptor as benzoquinone, it is not unreasonable to suspect that its electronegativity would make it an electron withdrawing group by induction.

(10) While some of the chemistry described in this paper was being refereed as a communication, Isaacs and Diederich (Isaacs, L.; Diederich, F. *Helv. Chim. Acta*, 1993, *76*, 2454) published the preparation of **1**.

(11) El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. *J. Am. Chem. Soc.* **1992**, *114*, 8751.

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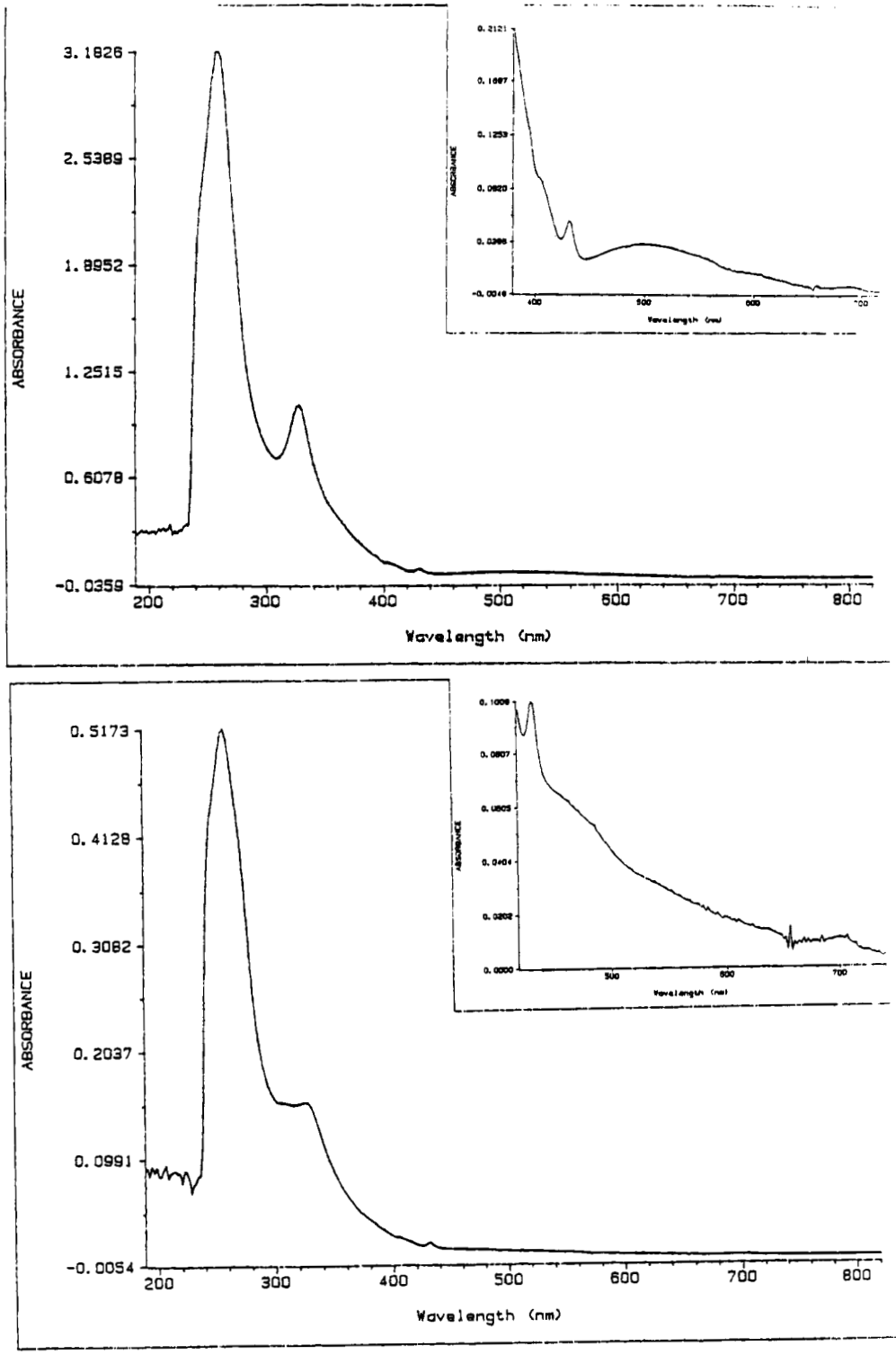


Figure 1. Top, UV–vis spectrum of dimethoxymethanofullerene in hexane; bottom, UV–vis spectrum of **3** in chloroform.

The facile reaction observed above is very likely due to the nucleophilic nature of the dimethoxy carbene intermediate[12] and the well-known electrophilicity of C_{60}.[13]

The ketal **1** was found to be a rather *insoluble* derivative of C_{60}, being only sparingly soluble in most organic solvents but most soluble in carbon disulfide. The UV–vis absorption of $C_{61}(OMe)_2$ is virtually identical to that of other methanofullerenes (Figure 1) and the NMR spectra (^{13}C and ^{1}H) are also consistent with the structure depicted for **1**. The cyclic voltammogram ($E1_{pc}$, −538; $E1_{pa}$, −472; $E2_{pc}$, −896; $E2_{pa}$, −836; $E3_{pc}$, −1366; $E3_{pa}$, 1300 mV vs Ag/AgCl, ODCB, Figure 2) is essentially the same as that observed with Ph_2C_{61}. This result is unexpected in view of the fact that oxygen is a strong electron withdrawing group by induction, especially compared to phenyl. The result is, however, consistent with the observation that there is an effect on the

(12) Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58. (b) Moss, R. A.; Wlostosky, Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443. (c) Kassam, K.; Pole, D.; Warkentin, J. Unpublished observations.

(13) See the whole issue of *Acc. Chem. Res.* **1992**, *25* (3).

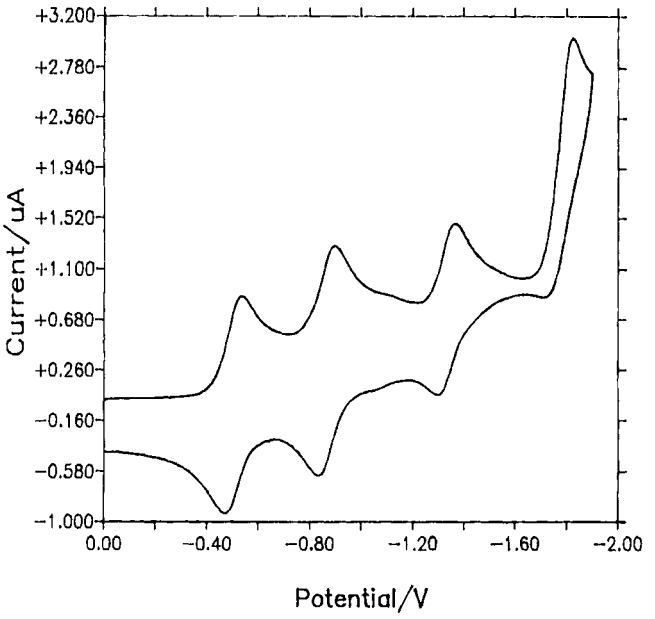


Figure 2. Cyclic voltammogram of dimethoxymethanofullerene in *o*-dichlorobenzene with tetrabutylammonium fluoroborate supporting electrolyte, Pt working and counter electrodes, and Ag/Ag^+ reference. Scan rate 100 mV/s.

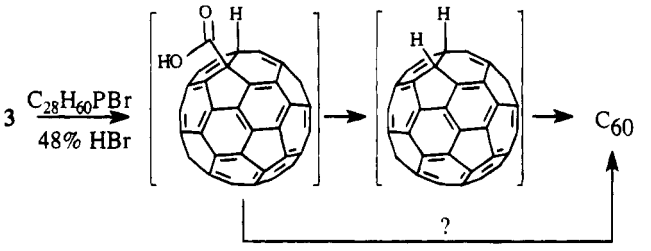
electrochemical properties of methanofullerenes only when the π system of the addend is held rigidly perpendicular to the fullerene "π" system.[14]

Even though crystals of **1** could be obtained from toluene or bromobenzene, a crystal structure elucidation from X-ray data has resisted solution.[15]

We soon learned that the above game plan to obtain the desired target structures was, in fact, flawed. No matter what reagent or conditions were tested, the result was uniform: the only characterizable product produced was the title ester **3**. Scheme 2 describes some of the failed attempts to perform synthetic transformations of the ketal.

The ester **3** is more soluble than its precursor and exhibits only two resonances in the ^1H NMR spectrum (CS_2, $CDCl_3$), δ 7.537 (fullerene CH) and 4.245 ($O-CH_3$), as well as the expected resonances in the ^{13}C NMR spectrum (Figure 3A CS_2, external D_2O), δ 54.13 ($O-CH_3$), 56.74 (fullerene CH),[16] 69.16 (fullerene *C*-CO_2Me), 135–152 (30 resonances, 2 coincidental, fullerene carbons), and 170.68 (ester C=O). From the number of carbon resonances in the fullerene region (32; 31 observed) and the chemical shifts of the saturated fullerene carbons, it is clear that the spectrum corresponds to a fullerene derivative with C_s symmetry, a dihydrofullerene, as depicted for structure **3** above. Further insight into the structure of **3** was gained from the gated proton-coupled ^{13}C NMR spectrum depicted in Figure 3B. This experiment made it relatively easy to assign the methoxy resonance (quartet, J = 147.91 Hz at δ 54.13), the methyne (dihydrofulleryl-H, doublet, J = 139.36 Hz at δ 56.74), and the quaternary dihydrofulleryl-carbonyl (doublet, two-bond coupling, J = 6.04 Hz at δ 69.16). The UV–vis spectrum, while showing the diagnostic 430 nm peak, is broader and the visible region is shifted to the blue. Ester **3** is a stable compound and appears to be the "sink" in attempted transformations of ketal **1**. Also, attempts to perform the usual ester functional group transformations have met with failure.[17]

Attempts to hydrolyze the ester with acid failed (Scheme 3). Even drastic conditions such as heating with trimethylsilyl iodide in chlorobenzene failed to produce the carboxylic acid. However, phase-transfer-catalyzed reaction with hydrobromic acid[18] afforded C_{60}. Presumably hydrolysis to the carboxylic acid occurred, followed by oxidative decarboxylation to the parent fullerene:



Although we did not detect dihydrofullerene[19] in our final product, it is possible either that it was oxidized during workup[20] or that fragmentation to carbon dioxide, hydrogen, and C_{60} may have taken place.

The fulleryl C–H bond is known to be acidic and hence we expected the proton of **3** to exchange readily with deuterium. In fact, no exchange was observed with D_2O (NMR sample in CS_2, heterogeneous D_2O); the exchange occurred only very slowly at room temperature with $NaOD/D_2O$ ($T_{1/2} \approx 5$ days). This could be due to the very nonpolar medium and the heterogeneity of the reaction conditions. Fagan's approximate pK_a determinations were carried out in DMSO,[21] but ester **3** is, unfortunately, insoluble in polar solvents.

Discussion and Conclusion

We and others have observed that functional groups which are very near the surface of the fullerene are rather unreactive.[22] The recalcitrance of the ketal **1** toward hydrolysis is in line with these observations. The question then arises, how is the ketal fragmented to the ester **3** without loss or exchange of methanol, even in the presence of a strong nucleophile such as a thiol or strong

(14) Wudl, F.; Suzuki, T.; Prato, M. *Synth. Met.* **1993**, *59*, 297.

(15) Only 80 reflections were observed and all attempts to obtain higher angle data have failed. This leads us to propose a high degree of disorder. The origin of the disorder could be methyl–oxygen rotations and whole molecule rotations.

(16) These resonances are in the expected range when compared to similar dihydrofullerenes: Fagan, P. J.; Krusic, P. J.; Evans, D. H.; Lerke, S. A.; Johnston, E. *J. Am. Chem. Soc.* **1992**, *114*, 9697. Hirsch, A.; Soi, A.; Karfunkel, H. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 766.

(17) Functional groups close to the surface of the spheroid appear to be rather unreactive. Professor Christopher Foote (private communication, we thank Prof. Foote for the information) was unable to hydrolyze a dimethyldioxolane (Elemes, Y.; Silverman, S. K.; Sheu, C.; Kao, M.; Foote, C. S.; Alvarez, M. M.; Whetten, R. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 351) and Prof. Mark Meier (private communication, we thank Prof. Meier for the information) found a nitrile oxide adduct (Meier M. S.; Poplawska, M. *J. Org. Chem.* **1993** *58*, 4524) to be recalcitrant to typical oxazoline reactions.

(18) Landini, D.; Rolla, R. *J. Org. Chem.* **1982**, *47*, 154.

(19) Henderson, C. C.; Cahill, P. A. *Science* **1993**, *259*, 1885–1887.

(20) Apparently $C_{60}H_2$ is very sensitive to traces of transition metals, reverting in their presence to C_{60}; Henderson, C. C.; Cahill, P. 206th National Meeting of the American Chemical Society, Chicago Illinois, August 1993. It is possible that the reaction mixture was exposed to transition metal salts.

(21) Fagan, P. J.; Krucic, P. J.; Evans, D. H.; Lerke, S. A.; Johnston, E. *J. Am. Chem. Soc.* **1992**, *114*, 9697.

(22) The 2,2-dimethyldioxolane resulting from cycloaddition of dimethyldioxirane on C_{60} could not be hydrolyzed; Prof. Christopher S. Foote, private communication.

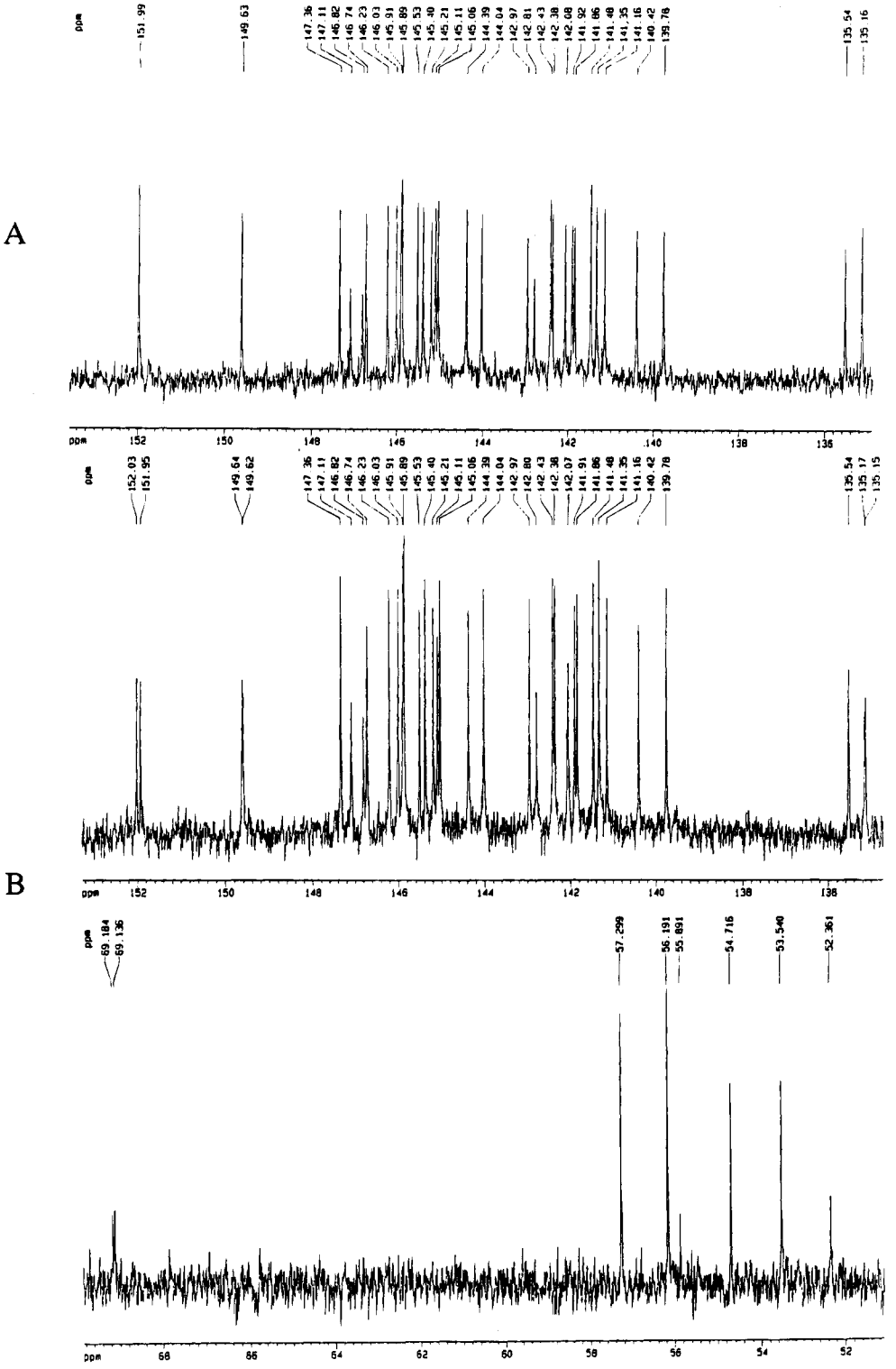


Figure 3. A, ^{13}C NMR spectrum of the fullerene carbon region of **3**. The peak at 142.81 ppm is due to C_{60} as determined by control experiments. B, gated proton-coupled ^{13}C NMR spectrum of the fullerene carbon region (top) of **3** and aliphatic region (bottom) of **3**. The doublet at 69.136 and 69.184 is real and observable only with a well-tuned instrument (Brucker AMX 500 in this case).

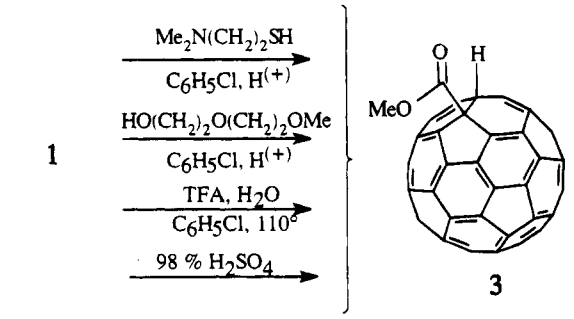
aqueous acid such as TFA or H_2SO_4? A possible interpretation is outlined in Scheme 4.

The above ring-opening may be initiated by an edge protonation of the cyclopropane and assistance from one of the four methoxy lone pairs. An alternate explanation is depicted in Scheme 5.

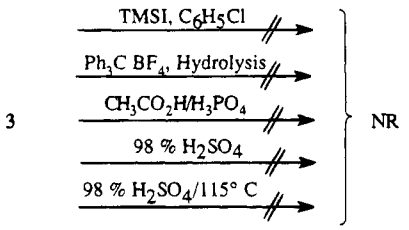
In support of Scheme 4, one can invoke Occam's razor and the fact that cyclopropanone ketals bearing at least one electronegative group are very acid sensitive.[12b] For example, methyl 2,2-dimethoxycyclopropanecarboxylate yields dimethyl succinate as a result of attempted chromatography on silica gel.[12c] On the other hand, there is no precedent for such an "edge-protonated methanofullerene mechanism". The only justification for Scheme

(23) Further support for Scheme 5 rests with the recently discovered acid-catalyzed, quantitative isomerization of [5,6] fulleroids to [6,6] methanofullerenes; Gonzalez Garcia, M.; Hummelen, J. C., unpublished.

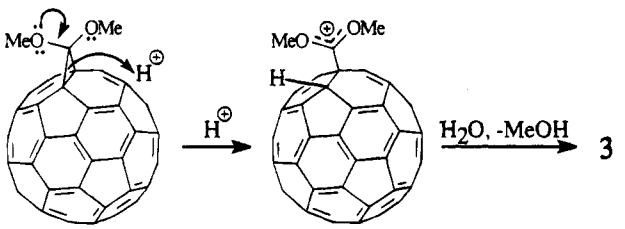
Scheme 2



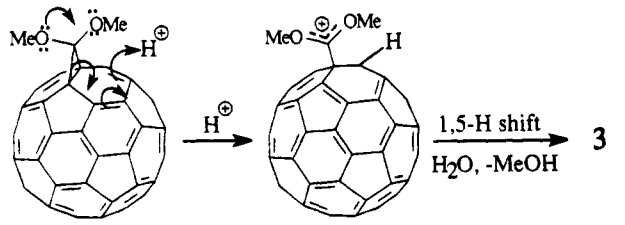
Scheme 3



Scheme 4



Scheme 5



5 is that protonation can occur at a site remote from the sterically encumbered 61st carbon atom.[23] In both schemes (4 and 5), the proton can be "guided" to the protonation site by hydrogen-bonding to one of the ketal's ether oxygens.

A dihydrofullerenecarboxylic acid is expected to decarboxylate readily since loss of carbon dioxide would produce the conjugate base of a relatively strong acid ($pK_a \approx 5.7$),[21] certainly stronger than the conjugate base of a ketone-activated C–H bond ($pK_a \approx 21$),[24] the product of the well-known β-keto acid decarboxylation.

Further chemical properties of the ketal and ester are being investigated and will be the subject of future publications.

Experimental Section

Pulsed Fourier transform 200 MHz ^1H and 125 MHz ^{13}C spectra were obtained in carbon disulfide (99.9% 0.03% v/v TMS, Sigma-Aldrich) and external, coaxial insert, deuterium oxide (99.96% D, Cambridge Isotope Laboratories) using Varian Gemini-200 and Bruker AMX 500 spectrometers. Chemical shifts are in ppm units downfield from Me_4Si as internal reference. Coupling constants are reported in hertz. The assignment of the ^{13}C was confirmed by proton-decoupled and gated proton-coupled spectra. High-resolution FTIR spectra were recorded on a Mattson Galaxy Series 3000 IR spectrophotometer. Solid samples were examined as KBr pellets. UV–vis spectra were measured with a Hewlett Packard 8452A diode array spectrophotometer. UV bands are reported by the maximum wavelength and the absorbance intensity. Cyclic voltammograms were measured with a BAS 100A electrochemical analyzer and a HP 7470A plotter. A three-electrode configuration was employed throughout. All regular and flash column chromatography separations were performed using grade 32–63, 60 Å silica gel available from ICN Biomedicals Co. Mass spectra were recorded on a VG 70-250 HF spectrometer.

Dimethoxymethanofullerene. To a solution of C_{60} (50 mg, 0.07 mmol) in chlorobenzene (20 mL) at 125 °C was added 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline (33.3 mg, 0.21 mmol) in a 5 mL chlorobenzene solution. After the reaction mixture was stirred for 20 h at 125 °C, the chlorobenzene was removed by rotary evaporation. The product was redissolved in a minimum amount of carbon disulfide and purified by column chromatography on silica gel. Unreacted C_{60} was eluted with hexanes/toluene 95:5. The demethoxymethanofullerene was eluted with hexanes/toluene 7:3 (38 mg, 69%): ^1H NMR ($CDCl_3$) δ 4.024; ^{13}C NMR ($C_6D_4Cl_2$) δ 54.63, 84.92, 97.5, 137.64, 141.12, 142.09, 142.31, 142.6, 142.87, 143.14, 143.33, 143.98, 144.2, 144.52, 144.55, 144.72, 144.81, and 145.16; FTIR (KBr) 2959 (w), 2930 (w), 2328 (w), 1539 (w), 1438 (s), 1400 (s), 1216 (m), 1186 (m), 1139 (s), 1116 (s), 1052 (s), 1014 (s), 903 (m), 746 (s), 590 (m), 575 (m), 534 (m), 520 (vs) cm^{-1}; FAB MS, *m/z* 794 (M^+); UV–vis (λ_{max}, hexanes) 260, 328, 430, and 500 nm.

Reaction of Dimethoxymethanofullerene with Trifluoroacetic Acid. Preparation of Ester 3. To a solution of $C_{61}(OCH_3)_2$ (50 mg, 0.063 mmol) in chlorobenzene (15 mL) were added trifluoroacetic acid (0.08 mL, 0.12 g) and distilled water (0.08 mL). The reaction mixture was heated at 110 °C overnight (18 h). The reaction was followed by TLC analysis which showed only one spot with an R_f value of 0.3 (the R_f value of the starting material, $C_{61}(OCH_3)_2$ is 0.41, hexane/benzene 7/3).

After being stirred at 110 °C for 12 h, the reaction mixture was washed with ice–water (3 × 25 mL) and dried over Na_2SO_4, and the solvent was evaporated in vacuo. The crude product was dissolved in a minimum of CS_2 (3 mL) and then precipitated by pouring into excess ether. The product was isolated by centrifugation and some traces of solvents were removed under vacuum, giving rise to 35 mg (71%) of the brown-colored adduct: ^1H NMR (CS_2, external D_2O, 200 MHz) δ 7.54 (s, fullerene CH), 4.25 (s, OCH_3); ^{13}C NMR (CS_2, external D_2O, 125.77 MHz) δ 54.13 (OCH_3), 56.74 (fullerene CH), 69.16 (fullerene *C*–$COOCH_3$), 135.16, 135.54, 139.78, 140.42, 141.16, 141.35, 141.48, 141.86, 141.92, 142.08, 142.38, 142.43, 142.81, 142.97, 144.04, 144.39, 145.06, 145.11, 145.21, 145.40, 145.53, 145.89, 145.91, 146.03, 146.23, 146.74, 146.82, 147.11, 147.36, 149.63, 151.99, 170.68 (ester C=O); FTIR (KBr) ν 2945, 2923, 2873, 1739, 1630, 1512, 1444, 1383, 1232, 1211, 1015 cm^{-1}; UV–vis (chloroform) λ_{max} 275, 325, 430 nm; MS (FD) *m/z* (rel intensity) 780 (100) [M^+].

Reaction of Dimethoxymethanofullerene with 2-(Dimethylamino)ethanethiol. Dimethoxymethanofullerene (0.012 mmol, 9.7 mg) was dissolved in dry chlorobenzene (3 mL), mixed with 2-(dimethylamino)ethanediol (0.07 mmol, 10.08 mg), and chilled in an ice bath. To the ice-cooled reaction was added 3% (w/v) trifluoroacetic acid in chlorobenzene (0.5 mL) slowly. The well-stirred reaction mixture was first warmed to room temperature and then heated at 92 °C overnight. After being heated for 18 h, the reaction was complete as detected by TLC analysis (silica gel; hexanes/benzene 7:3). To the reaction mixture was added CH_2Cl_2 (20 mL), and the resulting solution was washed with 5% aqueous NaOH (5 mL) containing ice–water (20 mL), with brine (20 mL), and with ice–water (2 × 25 mL) before it was dried over Na_2SO_4. Concentration under reduced pressure afforded 8.9

(24) House, H. O. *Modern Synthetic Reactions*; Benjamin: Menlo Park, CA, 1972; p 494.

mg (79%) of the title compound with spectroscopic properties identical to those of the product described above.

Acid Hydrolysis of Methyl 1,2-Dihydrofullerenecarboxylate in the Presence of Hexadecyltributylphosphonium Bromide. To a solution of methyl 1,2-dihydrofullerenecarboxylate (0.22 mmol, 172 mg) in 1,2-dichlorobenzene (30 mL) were added hexadecyltributylphosphonium bromide (0.11 mmol, 54 mg) and 48% HBr (9 mmol, 1 mL). The reaction mixture was allowed to stir at room temperature for a week. No reaction took place. A similar mixture, after being heated at 110 °C for 2 days, was washed with water (3 × 30 mL) and dried over Na_2SO_4. The organic solvent was removed in vacuo and the residue was column-chromatographed (silica, benzene/methanol, 4:1), affording 61% of C_{60}.

Treatment of Methyl 1,2-Dihydrofullerenecarboxylate with Iodotrimethylsilane. Into a solution of chlorotrimethylsilane (0.04 mmol, 4.35 mg, 5.1 mL) and anhydrous sodium iodide (0.04 mmol, 6.00 mg) in distilled acetonitrile (2 mL) was added a solution of methyl 1,2-dihydrofullerenecarboxylate (0.02 mmol, 15.6 mg) in chlorobenzene (10 mL). The cloudy brown reaction mixture was heated at 120 °C for 21 h, and distilled water (5 mL) was added into the reaction mixture with stirring. The precipitate formed was collected by centrifugation, dissolved in CS_2 (3 mL), and reprecipitated from ether. TLC analysis (silica gel, hexanes/benzene 7:3) showed only unchanged starting material.

Treatment of Methyl 1,2-Dihydrofullerenecarboxylate with Triphenylmethyl Fluoroborate. To a solution of triphenylmethyl fluoraborate[25] (0.02 mmol, 6.6 mg) in distilled CH_2Cl_2 (3 mL) was added a solution of methyl 1,2-dihydrofullerenecarboxylate (0.013 mmol, 10 mg) in *o*-dichlorobenzene (6 mL). After the mixture was stirred at room temperature, tetraphenylphosphonium chloride (0.015 mmol, 5.63 mg) in distilled CH_2Cl_2 (2 mL) was added into the reaction mixture. After being stirred at room temperature for 2 days, the reaction was checked by TLC (silica gel, hexanes/benzene 7:3). Since no changes were found, it was heated at 110 °C overnight. TLC analysis showed only unchanged starting material.

Treatment of Methyl 1,2-Dihydrofullerenecarboxylate with Acetic Acid/Phosphoric Acid. To a solution of methyl 1,2-dihydrofullerenecarboxylate (0.01 mmol, 7.8 mg) in dichlorobenzene (7 mL) was added CH_3COOH/H_3PO_4 (4:1 mixture, 4 mL), and the mixture was heated at 145 °C overnight (19 h). According to TLC analysis (silica gel, hexanes/benzene 7:3), there was no change in the reaction mixture.

Treatment of Methyl 1,2-Dihydrofullerenecarboxylate with Concentrated Sulfuric Acid at Room Temperature. Methyl 1,2-dihydrofullerenecarboxylate (0.01 mmol, 7.8 mg) was suspended in concentrated H_2SO_4 (3 mL) in the sonicator. The resulting suspension was poured into ice–water and centrifuged. The precipitate formed was checked by TLC analysis (silica gel, hexanes/benzene 7:3) and showed only unchanged starting material.

Treatment of Methyl 1,2-Dihydrofullerenecarboxylate with Concentrated Sulfuric Acid at 115 °C. Methyl 1,2-dihydrofullerenecarboxylate (0.01 mmol, 7.8 mg) in concentrated H_2SO_4 (5 mL) was heated at 115 °C overnight (18 h). The resulting suspension was poured into ice–water and centrifuged. The precipitate was collected and washed, first with ice–water (15 mL), second with methanol (3 × 10 mL), and finally with ether (2 × 10 mL). The precipitate obtained was checked by TLC analysis (silica gel, hexanes/benzene 7:3). No changes were found.

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