Chemoselective Synthesis and Resolution of Chiral [1,9]Methanofullerene[70] Derivatives

Yihan Wang, David I. Schuster,* and Stephen R. Wilson*

Department of Chemistry, New York University, Washington Square, New York, New York 10003

Christopher J. Welch

Regis Technologies, Inc., Morton Grove, Illinois 60053

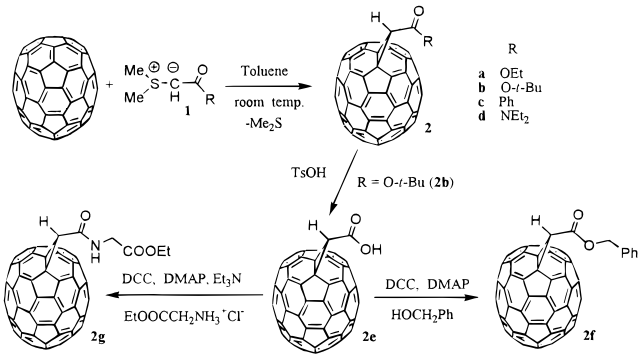
Received June 6, 1996

The unique structure of C_{60} has attracted intense research efforts toward the synthesis and characterization of its derivatives. Possible applications of C_{60} derivatives in the field of biological and materials science have been reported.[1] Much less work has been done on the chemistry of C_{70} due to its lower abundance and higher cost. The lower symmetry of C_{70} gives rise to a more complicated pattern of isomeric structures than for C_{60} upon functionalization of the fullerene core. Both theoretical and experimental data show that the [1,9] and [7,8]bonds[2] are by far the most reactive bonds at [6,6] ring fusions.[3] Most addition reactions favor the [1,9]bond rather than the [7,8]bond,[4] and in a few cases only [1,9] isomers are produced.[5] However, none of the known methods appear to be practical for synthetic purposes. For example, the reaction of diazo compounds with C_{70}, which has been widely used in the functionalization of C_{60},[1c] produces mixtures of isomeric products, which are difficult to separate by flash chromatography.[4e,6] Thus, general methods for the selective functionalization of C_{70} in good yield are needed.

We recently reported a superior synthesis of [6,6]-methanofullerene[60] by reaction of stabilized sulfonium ylides with C_{60}.[7] We now wish to report extension of this strategy to the functionalization of C_{70}, which provides a solution to the isomer problem mentioned above. A toluene solution of sulfonium ylide **1**[8] (1.8 equiv) was added to a solution of C_{70} (1 equiv, 1.2 mM) in toluene (Scheme 1). The reaction was instantaneous at room temperature for entries a, b, and d, while for entry c the reaction was complete in a few minutes at 40 °C. The reactions were monitored by HPLC, which showed the appearance of a monoaddition product together with unreacted C_{70} and small amounts of bisaddition products. Pure monoadducts could be obtained after column chromatography on silica gel. ^{1}H-NMR spectra showed the presence of a single isomer in each case (see Table 1, entries a−d). Only one singlet appeared for the cyclopropane proton for compounds **2a**−**d**, at 3.59, 3.52, 3.67, and 4.43 ppm, respectively, slightly downfield from that of the parent [1,9]cyclopropane $C_{71}H_2$ (2.88 ppm).[4e] The ^{13}C-NMR spectrum of compound **2a** shows peaks for 68 carbons in the sp^2 region, implying C_1 symmetry in the molecule. The two sp^3 carbons appear at 65.33 and 64.23 ppm, respectively, close to those for [1,9]cyclopropane $C_{70}H_2$,[4e] while the other cyclopropane carbon appears at 24.26 ppm. FT-IR spectra of **2a**−**d** in KBr show carbonyl absorption at 1743, 1729, 1684, and 1647 cm^{-1}, respectively. The UV/vis spectra of compounds **2a**−**d** are almost identical to that of [1,9]-$C_{70}H_2$[9] and [1,9]cyclopropane $C_{71}H_2$,[4e] suggesting similar addition patterns on the C_{70} core. These data strongly suggested that these adducts possess a [1,9]-closed structure.[10]

Interestingly, compounds **2a**−**d** are chiral, with a stereogenic bridging cyclopropane carbon. While the analogous C_{60} derivative has a plane of symmetry through the cyclopropane ring, the C_{70} antipodes no longer possess a plane of symmetry due to the asymmetry of the C_{70} core (see Figure 1 for enantiomers of compound **2a**).[11] We have also successfully achieved chromatographic *resolution* of racemic amide **2d** on a chiral (*S*, *S*)-Whelk-O HPLC column (Figure 2).[12] Solutions of the resolved enantiomers of **2d** in $CHCl_3$ show only weak CD signals (Figure 2), since the CD originates in this case from the

Scheme 1



(1) Reviews: (a) Taylor, R.; Walton, D. R. M. *Nature* **1993**, *363*, 685. (b) Diederich, F.; Isaacs, L.; Philip, D. *Chem. Soc. Rev.* **1994**, 243. (c) Hirsch, A. *The Chemistry of the Fullerenes*; Thieme Medical Publishers: New York, 1994. (d) Jensen, A. W.; Wilson, S. R.; Schuster, D. I. *Bioorg. Med. Chem.*, in press.

(2) For original nomenclature of C_{70}, see: (a) Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 813. A new numbering system has been proposed by this author in which [1,9] = [1,2] and [7,8] = [5,6]; see: (b) Taylor, R. *The Chemistry of Fullerene*; World Scientific, Singapore, 1995; Until the new numbering system is widely accepted, we prefer to use the more common convention.

(3) (a) Henderson, C. C.; Rohlfing, C. M.; Cahill, P. A. *Chem. Phys. Lett.* **1992**, *213*, 383. (b) Karfunkel, H. R.; Hirsch, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 7468. (c) Avent, A. G.; Durwish, A. D.; Heimbach, H. W.; Kroto, H. W.; Meidine, M. F.; Parson, J. P.; Remars, C.; Roers, R.; Ohashi, O.; Taylor, R.; Walton, D. M. R. *J. Chem. Soc., Perkin Trans. 2* **1994**, 15.

(4) (a) Hawkins, J. M.; Meyer, A.; Solow, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7499. (b) Smith, A. B., III; Strongin, R. M.; Brard, L.; Furst, G. T.; Romanow, W. J.; Owens, K. G.; Goldschmidt, R. J. *J. Chem. Soc., Chem. Commun.* **1994**, 2187. (c) Meier, M. S.; Poplawska, M.; Compton, A. L.; Shaw, J. P.; Selegue, J. P.; Guarr, T. F. *J. Am. Chem. Soc.* **1994**, *116*, 7044. (d) Herrmann, A.; Diederich, F.; Thilgen, C.; Meer, H.-U.; Muller, W. H. *Helv. Chim. Acta* **1994**, *77*, 1689. (e) Smith, A. B., III; Strongin, R. M.; Brard, L.; Furst, G. T.; Romanow, W. J.; Owens, K. G.; Goldschmidt, R. J.; King, R. C. *J. Am. Chem. Soc.* **1995**, *117*, 5492. (f) Wilson, S. R.; Lu, Q. *J. Org. Chem.* **1995**, *60*, 6496.

(5) (a) Hirsch, A.; Grosser, T.; Skiebe, A.; Soi, A. *Chem. Ber.* **1993**, *126*, 1061. (b) Bingel, C. *Chem. Ber.* **1993**, *126*, 1957. (c) Meidine, M. F.; Avent, A. G.; Darwish, A. D.; Kroto, H. W.; Ohashi, O.; Taylor, R.; Walton, D. R. M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1189. (d) Zhang, X.-J.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4271.

(6) Thus, the reaction of ethyl diazoacetate with C_{70} gave at least four isomeric monoadducts: Wang, Y.; Schuster, D. I.; Wilson, S. R. Unpublished results.

(7) Wang, Y.-H.; Cao, J.-R.; Schuster, D. I.; Wilson, S. R. *Tetrahedron Lett.* **1995**, *36*, 6843.

(8) (a) Speziale, A. J.; Tung, C. C.; Ratts, K. W.; Yao, A. *J. Am. Chem. Soc.* **1965**, *87*, 3460. (b) Ratts, K. W.; Yao, A. N. *J. Org. Chem.* **1966**, *31*, 1185.

(9) Henderson, C. C.; Rohlfing, C. M.; Gillen, K. T.; Cahill, P. A. *Science* **1994**, *264*, 397.

(10) Relevant ^{13}C-NMR data for the parent [1,9]cyclopropane $C_{71}H_2$[4f] are: 64.06 (sp^3), 62.56 (sp^3), 13.80 (methylene). The ^{13}C-NMR spectra of compounds **2b** and **2d** show 68 carbons in the sp^2 region (see the supporting information) together with two sp^3 carbons on the fullerene core. This rules out all open structures, while C_1 symmetry rules out the possibility of [7,8] or [23,24] adducts, both of which possess C_s symmetry.

S0022-3263(96)01070-5 CCC: $12.00

Table 1. Yields and Spectroscopic Data of [1,9]Methanofullerene[70] Derivatives[a]

entry	R	2	% yield	^{1}H-NMR (200 MHz, 2/1 CS_2/$CDCl_3$)
a	OEt	$(C_{71}H_1)COOEt$	60	4.48 (q, J = 7.2 Hz, 2H), 3.59 (s, 1H), 1.54(t, J = 7.2 Hz, 3H)
b	O-*t*-Bu	$(C_{71}H_1)COO$-*t*-Bu	46	3.52 (s, 1H), 1.71 (s, 9H)
c	Ph	$(C_{71}H_1)COPh$	59	8.45−8.40 (m, 2H), 7.78−7.70 (m, 3H), 4.43 (s, 1H)
d	NEt_2	$(C_{71}H_1)CONEt_2$	40	4.00 (q, J = 7.0 Hz, 2H), 3.67 (s, 1H), 3.64 (q, J = 7.0 Hz, 2H), 1.65 (t, J = 7.2 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H)
e	OH	$(C_{71}H_1)COOH$	84	3.65 (s, 1H)
f	OCH_2Ph	$(C_{71}H_1)COOCH_2Ph$	52	7.54−7.30 (m, 5H), 5.43 (s, 2H), 3.63 (s, 1H)
g	$NHCH_2COOEt$	$(C_{71}H_1)COONHCH_2COOEt$	70	6.95 (m, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.29 (d, J = 4.3 Hz, 2H), 3.58 (s, 1H), 1.40 (t, J = 7.1 Hz, 3H)

[a] The cyclopropane protons are underlined.

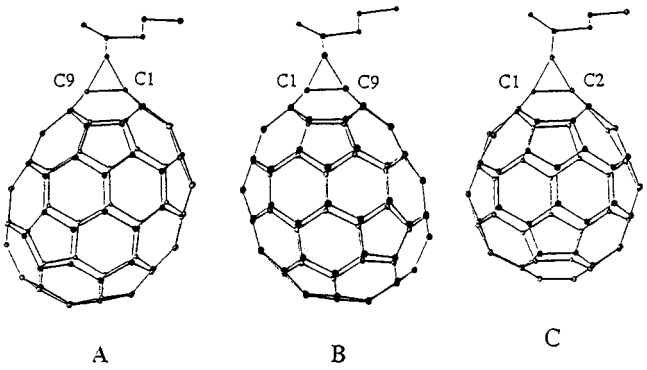


Figure 1. Computer models (CSC chem3D) of the enantiomers of **2a** (**A** and **B**) and their C_{60} analog (**C**). In **C** there is a plane of symmetry through the cyclopropane ring (C1 and C2 are equivalent). In **A** and **B** there is no such plane of symmetry, due to intrinsic asymmetry in the C_{70} core (C1 and C9 are nonequivalent).

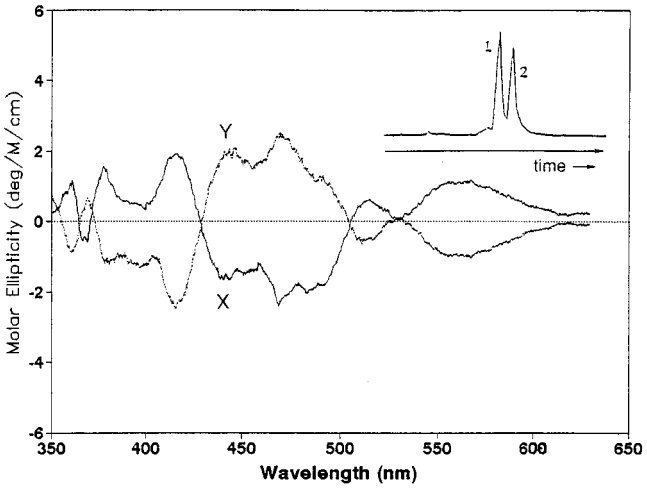


Figure 2. Circular dichroism curves for enantiomers of **2d** (25 °C, 0.28 mM in $CHCl_3$). The insert shows the chiral HPLC chromatogram of racemic **2d** on a (*S*,*S*)-Whelk-O column (eluent: 97/3 toluene/CH_3CN, flow rate 1 mL/min, UV detection at 354 nm, 25 °C). Curve **X** corresponds to peak **2** from chiral HPLC (86.5% ee), curve **Y** corresponds to peak **1** (67% ee).

asymmetric perturbation of a symmetric chromophore.[13] Nonetheless, the near mirror image relationship of the CD curves is apparent. Similar CD curves were seen by Diederich et al. for *diastereomeric* C_{70} derivatives prepared from the addition of *chiral* bromomalonate enolate anions to C_{70}.[14] As far as we are aware, the separation of enantiomers of **2d** represents the first *resolution* of a racemic monoadduct of C_{70}. Similar resolution of **2a**−**c** by this method was unsuccessful.

To illustrate the utility of our synthetic strategy, the *tert*-butyl ester derivative **2b** was hydrolyzed to the corresponding carboxylic acid **2e** in 84% yield using *p*-toluenesulfonic acid under reflux.[15] The carboxylic acid **2e** could be further converted to ester **2f** or amino acid derivatives **2g** in 52% and 70% yield, respectively (Scheme 1). Further functionalization of the carboxylic acid **2e** leading to derivatives with potential biological activity will be reported in due course.

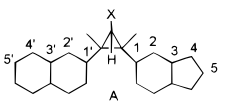
In conclusion, we have demonstrated a new strategy for the functionalization of fullerene[70] that provides a simple chemoselective route to [1,9]methanofullerene[70] derivatives. Amide **2d** could be resolved into enantiomers on a chiral HPLC column, the first example of the *resolution* of a racemic C_{70} monoadduct. The useful synthon [1,9]methanofullerene[70]carboxylic acid was obtained and its further functionalization was illustrated.

Acknowledgment. We thank the NSF (CHE-9400666) and NYU Research Challege Fund for partial financial support of this work. We also thank Mr. D. Qin at Queens College and Mr. Y. Gong at NYU for recording the ^{13}C-NMR spectra, Drs. J. Huang and M. Walters for FT-IR spectra, and Ms. H. Tsao and Dr. N. Geacintov at NYU for CD spectra.

Supporting Information Available: Preparative procedures, ^{1}H-NMR spectra for **2a**,**b**,**d**, ^{13}C-NMR spectra for **2a**,**b**,**d**, ESI-MS spectra for "tagged" **2a**,**b**, UV/vis spectrum for **2a**, FT-IR spectrum for **2e**, HPLC chromatogram for **2c**, C_{70} [6,6] ring fusions, their nomenclatures and Schlegel diagram, and HPLC analysis of separated enantiomers of **2d** on a chiral (*R*,*R*)-Whelk-O column (19 pages).

JO961070K

(11) The symmetry of the C_{70} molecule as a graph[2b] shows differences four to five carbons away from the cyclopropane ring, as shown in structure **A,** below, derived from the Schlegel diagram for C_{70}.[2] The chirality is due to differences in ring size (5- *vs* 6-membered) on each side of the cyclopropane ring, which translates into differences in curvature on the surface. In a more global sense, the chirality is due to a "bulge" on one side of the fullerene core, as shown in Figure 1.



(12) Pirkle, W. H.; Welch, C. J.; Lamm, B. *J. Org. Chem*. **1992**, *57*, 3856.

(13) We have reported CD spectra for various derivatives of C_{60} and have proposed a new sector rule for absolute configuration of C_{60} derivatives. See: Wilson, S. R.; Lu, Q.; Cao, J.; Wu, Y.; Welch, C. J.; Schuster, D. I. *Tetrahedron* **1996**, *52*, 5131.

(14) Herrmann, A.; Ruttimann, M.; Thilgen, C.; Diederich, F. *Helv. Chim. Acta* **1995**, *78*, 1673. In this paper, Diederich et al. reported the chromatographic *separations* of several diastereomeric chiral C_{70} derivatives formed by addition of *chiral* bromomalonate enolates to C_{70}.

(15) Isaacs, L.; Diederich, F. *Helv. Chim. Acta* **1993**, *76*, 2454.