Synthetic and Computational Studies on Symmetry-Defined Double Cycloaddition of a New Tris-Annulating Reagent to C_{60}

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For the purpose of doubly functionalizing fullerenes, new tris-annulating reagents **2(*n*)** have been developed. The reagents carry, in one molecule, two cyclopropenone acetals which are connected with an *n*-carbon methylene tether. Upon thermolysis of **2(*n*)** in the presence of C_{60}, the reagent undergoes [3 + 2] cycloaddition reaction twice in a regio- and stereoselective manner to give C_s and C_2 organofullerenes bearing two cyclopentenone acetals. The selectivity varies as the function of the tether structure. The experiments have shown that, in each series of different tether lengths, one can obtain one or two diastereomeric double adducts out of several structural possibilities. The selectivity of the reaction did not conform to the prediction made on the basis of previous knowledge on intermolecular double additions but was found to be correlated to the conformational strain of the tether moiety, which can be estimated by a newly developed "double differential protocol". Systematic studies on the reliability of various computational methods for organofullerenes indicated that certain molecular orbital and molecular mechanics calculations give very reliable structural data while certain others do not.

Introduction

The issues of regio- and stereochemistry occupy the central position in modern chemical research, and despite its I_h symmetry, buckminsterfullerene (C_{60}) does not escape from this problem: any chemical modification of more than two double bonds of C_{60} would create a mixture of various regio- and stereoisomers. It is thus of great interest if one can synthesize a single isomer upon multiple functionalization of C_{60}, especially with *control* and hopefully *prediction* of the regiochemistry so that one can produce a desired regioisomer at will. Such control is not just an intellectual challenge but of practical utility for constructing large molecular structures bearing functional side chains with predefined spatial orientations. We envisage that such molecules will serve as useful tools in the studies of functional catalysis,[1,2] material science,[3] and bioorganic applications[4] (e.g., DNA interactions,[5] enzyme inhibition,[6] and drug delivery reagents[7]).

Organochemical modification of a certain number of double bonds on the sphere of fullerene by 1,2-addition of an X−Y reagent across a C═C bond (Scheme 1) has been widely studied.[8,9] Considerable knowledge has been accumulated on the regiochemistry of the double-addition reaction for cases X = Y,[10] and the "intrinsic regioselectivity" as to the second addition of the reagent (Scheme 1a) has been revealed (electronic and steric effects).[11] A

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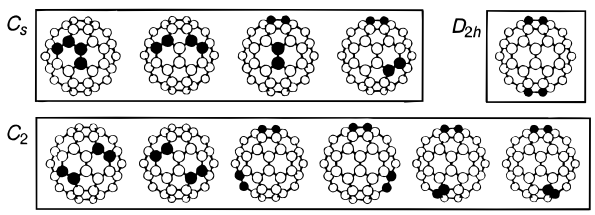
(10) Even double addition of a symmetrical reagent onto two double bonds on C60 would, in principle, produce the 11 structural possibilities (enantiomers inclusive) shown (black atoms indicate the carbon atoms to which X and Y groups become attached).



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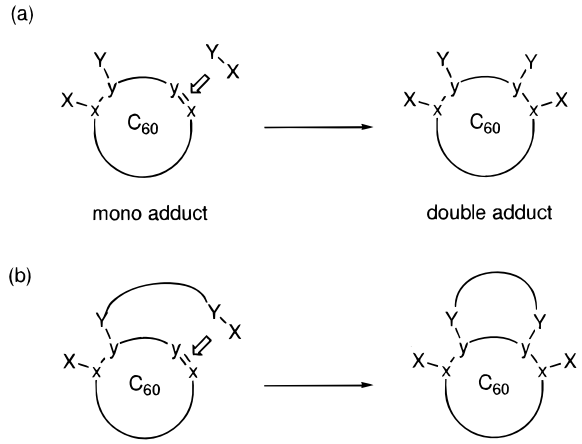
Scheme 1



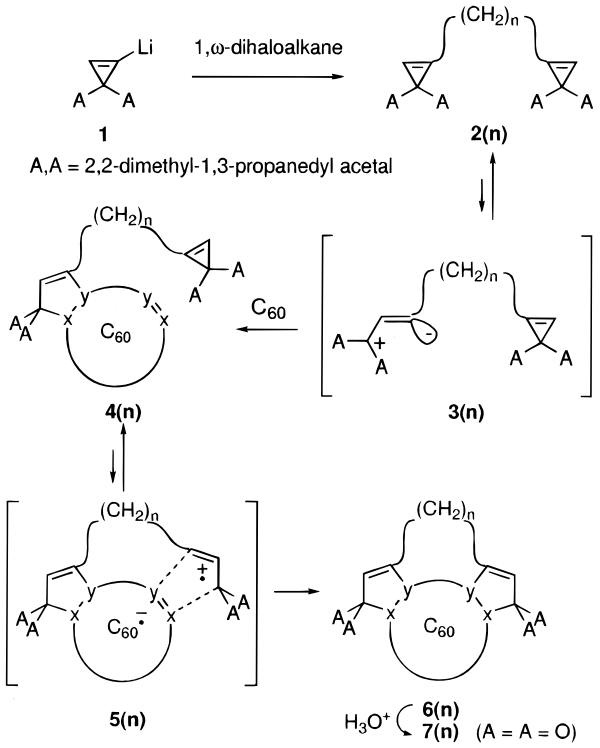
more challenging yet much less explored issue is the control of the addition of structurally complex reagents (Scheme 1a, X ≠ Y): Even for double addition, the number of possible isomers formed in the second addition is as many as 36. Clearly, selectivities must be achieved to control the position, orientation, and absolute stereochemistry of the attachment of the X−Y group to the sphere of fullerene. A simple and effective strategy to reduce the structural possibilities is to link the X−Y reagents with a suitable tether (Scheme 1b).[12] Thus, we have previously communicated that a tethered double-functional reagent (**2(*n*)**) undergoes a single-step double cycloaddition to C_{60}, which takes place in a regiodefined, stereodefined, and symmetry-defined manner as a function of the tether structure.[13,14]

Described herein are the experimental details of this work combined with the computational analysis of the origin of the tether control. The results have demonstrated that the conformational energy of the tether can override the "intrinsic regioselectivity" of the fullerene core and that this preference may be predictable on the basis of the conformational energy of the tether moiety. To offer basic and important information for the research on organofullerenes, we also describe the results of systematic comparison of various computational methods for structural analysis of organofullerene molecules, which revealed inaccuracy of certain methods used in recent studies.

Results and Discussion

1. Synthetic Studies on Bispropanofullerenes. Recognizing the efficiency of convergent synthetic strategies in the construction of complex molecular structures,

Scheme 2



we have developed a new annulating reagent **2(*n*)** for one-step construction of fused tricyclic carbocycles on the fullerene sphere.[15] As reported previously from our group, a series of compounds with various tether lengths can be prepared in one step by coupling of a 1,ω-dihaloalkane with a lithiated cyclopropenone acetal (CPA)[16] (Scheme 2).

The unique feature of this reagent is that thermolysis reversibly[17] generates only a minute amount of vinylcarbene species **3(*n*)** and hence intramolecular carbene dimerization is avoided. We have previously shown that the parent vinylcarbene species undergoes [3 + 2] cycloaddition exclusively to the 6,6-juncture.[18] We also found that second addition of the carbene to the monocycloaddition adduct is not an efficient synthetic reaction and affords a complex regio- and stereochemical mixture upon treatment with an excess reagent. On the basis of Boger's mechanistic analysis,[17b] the cycloaddition may involve a reversible electron transfer to generate a radical ion pair (**5(*n*)**), which then gives the product **6(*n*)**.

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(13) Preliminary communcation: Nakamura, E.; Isobe, H.; Tokuyama, H.; Swamura, M. *J. Chem. Soc., Chem. Commun.* **1996**, 1747−1748.

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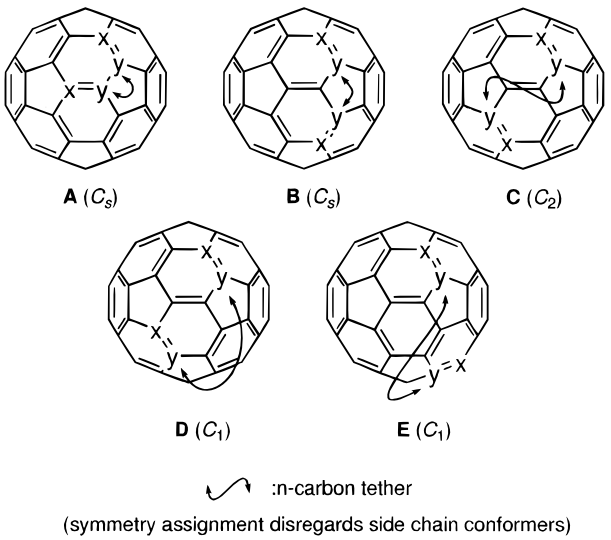
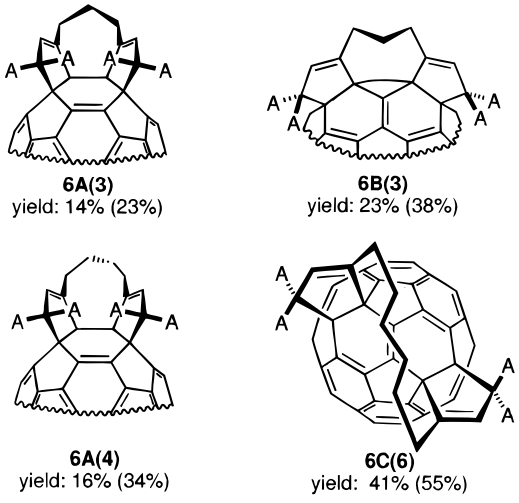
Scheme 3



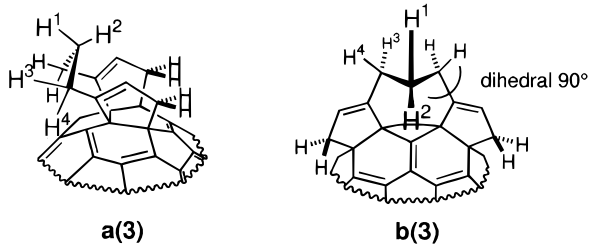


Empirical analysis of molecular models indicated that, for a tether shorter than a six-methylene length, a double-cycloaddition reaction can produce at most five regioisomeric structural types, **A**−**E** (Scheme 3), each of which belongs to the symmetry group shown. The frontier molecular orbital (FMO) analysis according to Hirsch[11] predicts that isomers **A**, **B**, and **E** would be favored and isomer **C** disfavored,[19] while isomer **A** would be sterically prohibited. Double addition to more remote olefins will be simply impossible with a tether having less than six methylene carbons.

The double cycloaddition was achieved simply by heating a mixture of annulating agent **2(*n*)** (1.4 equiv) and C_{60} (40−500-mg scale) in dry 1,2-$Cl_2C_6H_4$ (1.39−13.9 mM) in the presence of 4A molecular sieves under nitrogen, and the desired double-cycloaddition product(s) was isolated by flash column chromatography as a fraction (silica gel, $R_f = 0.5-0.6$ with toluene) next slower moving than recovered C_{60} (R_f = ca. 1.0). The low concentration required by the low solubility of C_{60} contributes to minimize bimolecular reactions, and the various ratio of the concentration in the 1.4−14 mmol range did not change the chemistry at all. Solvent effects on the product selectivity were also very small as studied for **2(3)** with toluene and DMF at 140 °C. A small amount of mono-adduct formed by intermolecular reaction with adventitious water was readily separated by chromatography.

The reaction of **2(3)** (1.39 mM C_{60}) produced two C_s symmetric double adducts in 23 and 14% yields. Both showed fully resolved ^{1}H (at 25−60 °C) and ^{13}C NMR spectra (30 sp^2 C_{60} signals, 26 integrated for 2C and 4 for 1C). The C_s symmetry indicated that two adducts are either **6A(3)** or **6B(3)**. The major product was assigned as **6B(3)** and the minor as **6A(3)** as mentioned in the following paragraph. Acidic hydrolysis of the acetal group proceeded smoothly to afford the corresponding C_s diketones **7A(3)** and **7B(3)** in quantitative yield. Type **A** isomer formed in this reaction is the most sterically encumbered isomer and, to the best of our knowledge, has not previously been observed in cycloaddition reactions.

Both isomers displayed very distinct ^{1}H NMR spectra, which did not change at temperatures between 25 and 100 °C. A conformational search was carried out by the Monte Carlo method as described in the computation section below to find that there exists only one major conformational isomers possible for each structural isomer (i.e., **a(3)** and **b(3)**; others were >2 kcal/mol higher in energy). The $^3J_{H-H}$ coupling for the tether moiety has been calculated with the Altona equation[20] by considering 300 K Boltzmann distribution of all possible conformers. As is seen in Table 1, the most notable feature is the very small coupling constants in the conformer **6B(3)**, and this feature is also found in the experimental data for the major isomer. The experimental spectrum of the minor product shows weak to large coupling between all protons, and this feature was reproduced in the calculated data (Table 1). With such good agreement with experimental and calculated data, we assigned the major product of **6(3)** as the **6B(3)** isomer and the minor product as the **6A(3)** isomer.



The four-carbon-tethered CPA **2(4)** reacted with C_{60} to give a C_s symmetric tricyclic adduct as a single double-cycloaddition product in a diminished yield of 16% (34% based on recovery) (^{13}C NMR: among 30 sp^2 C_{60} signals, 26 integrated for 2 C and 4 for 1 C), together with a large amount of a mono-adduct.[21] While the NMR spectra could not distinguish between **6A(4)** and **6B(4)**, molecular models and computer-assisted structural analysis (vide infra) indicated that **6B(4)** suffers severe steric interference between two allylic methylene groups. The product was hence assigned as **6A(4)**. The cycloaddition with **2(5)** under comparable conditions (as dilute as 0.001

(19) The Hirsch analysis was carried out for methanofullerenes (ref 11), and the propanofullerene (specifically **8**) has the same FMO pictures (see Supporting Information).

(20) Haasnoot, C. A. G.; Leeuw, F. A. M. D.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

Table 1. Calculated Coupling Constants ($^3J_{H-H}$)[a]

	calculated		experimental	
	a(3)	**b(3)**	minor product[b]	major product[c]
H1−H2	2.8	0.3	3.9	0.0
H1−H4	3.9	9.3	1.5	9.4
H2−H3	13.2	11.2	13.2	10.4
H2−H4	2.6	0.3	3.4	0.0

[a] Units are reported in hertz. [b] H1, 2.40 ppm; H2, 2.06 ppm; H3, 2.70 ppm; H4, 3.29 ppm. [c] H1, 1.84 ppm; H2, 2.20 ppm; H3, 2.92 ppm; H4, 2.48 ppm.

M) afforded hardly any trace of the desired double-cycloaddition product with 40% recovery of C_{60}.

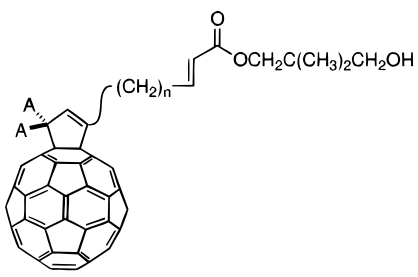
A six-carbon tether was examined next. The double addition with **2(6)** proceeded especially cleanly and selectively to afford a single isomer (41%; 55% based on recovery). The ^{1}H and ^{13}C NMR of **6(6)** (28 sp^2 C_{60} signals with the same intensity) indicated the C_2 symmetry of the adduct, and hence that the product was **6C(6)** (an anti-parallel isomer in footnote 22). Hydrolysis of **6C(6)** afforded quantitatively the diketone **7C(6)**.[22] The double functionalization with this regioselectivity has not been reported previously[13,14a] and must be considered as an important first step toward asymmetric synthesis of C_2 polyfunctionalized fullerene derivatives.[23,24]

As summarized in Figure 1, the double cycloaddition of **2(*n*)** took place regio- and stereoselectivily to give C_s and C_2 organofullerenes. The graphic representation clearly illustrates the dominant influence of the tether structure on the regiochemistry of the second cycloaddition. The above experimental studies have shown that, in each series of different tether length, one can obtain one or two diastereomeric double adducts out of several structural possibilities (Scheme 3). With the short three- and four-carbon tether, two cyclopentene rings were placed at positions most sterically encumbered, and with the six-carbon tether, they were formed with the regioselectivity expected to be the most disfavored on the FMO basis. As illustrated in Figure 2, each of these structural isomers possesses spatial orientation of substituents, which is unique among all the previously known classes of organic molecules.

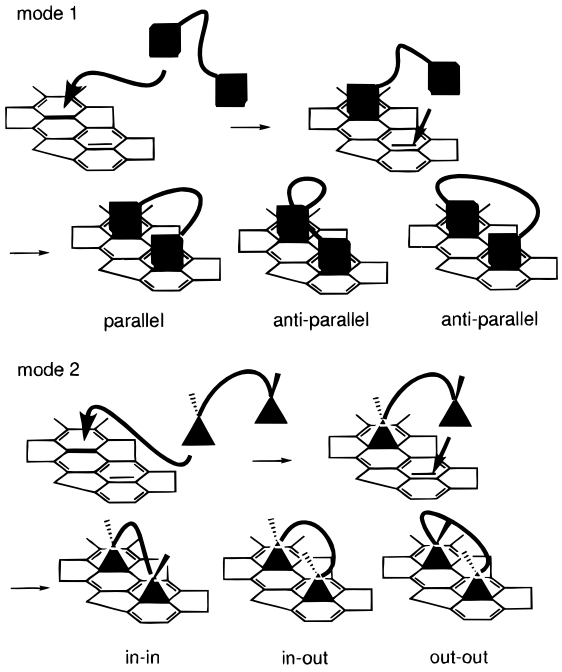
2. Computational Studies. While we found synthetically viable yields and selectivities in the double cycloaddition of the tethered vinylcarbene reagents, we were left uninformed of the reasons for the observed yield and selectivity profiles (Figure 1). Ideally, the activation energy of each possible reaction pathway of intramolecular cyclization is to be obtained with high-level quantum mechanical calculations and to be utilized to predict the yield and the selectivity. However, such calculations, in particular, prediction of the yield and the absolute reaction rate, are not feasible at the present time. On the other hand, analysis of the selectivity (i.e., energy difference) should be easier and perhaps practically more important. A few approaches can be considered to construct predictive protocols without recourse to computational analysis of activation energies.

Among methods to analyze the reactivity of organic molecules, FMO analysis is a popular predictive tool and has been shown to have good correlation to the selectivity of intermolecular multiple addition to fullerenes.[11,25] However, in the tether strategy reported in the above and

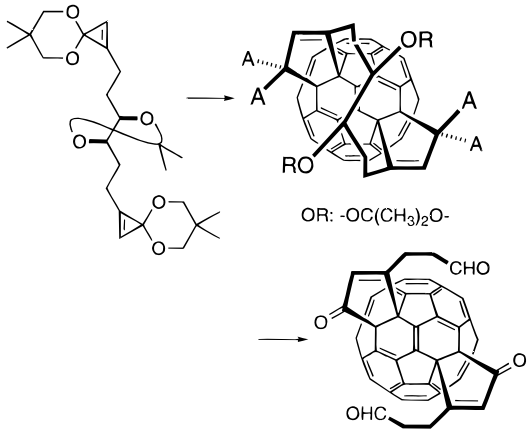
(21) Both the reactions of **2(4)** and **2(5)** afforded a considerable amount of a polar adduct assigned as the mono-adduct below (and its structural isomer due to another mode of vinylcarbene hydrolysis, see ref 17a) by NMR and FAB mass spectra (R_f = 0.1, toluene). Apparently, the double-cycloaddition reactions which leads to the formation of strained medium-size rings could not effectively compete with the reaction of the carbene species with adventitious water.



(22) In the tether directed strategy, there is an interesting structural problem as illustrated for the cycloaddition onto two parallel double bonds in the "naphthalene-like" partial structure on C_{60}. The first involves a case (mode 1) wherein three structural isomers, one "parallel" and two "anti-parallel" isomers, would form (ref. 13 and 14c). In the second mode of addition (mode 2), the tether stretches out perpendicular to the plane of the ring to be constructed and would give us "in-in", "in-out", and "out-out" isomers (ref 14a).



(23) We have also achieved the synthesis of the nonracemic double adduct depicted below (ref 13). Structure determination and optimization of the synthesis is currently carried out, and a full account will be reported in a due course.



(24) Herrmann, A.; Rüttimann, M.; Thilgen, C.; Diederich, F. *Helv. Chim. Acta* **1995**, *78*, 1673−1704.

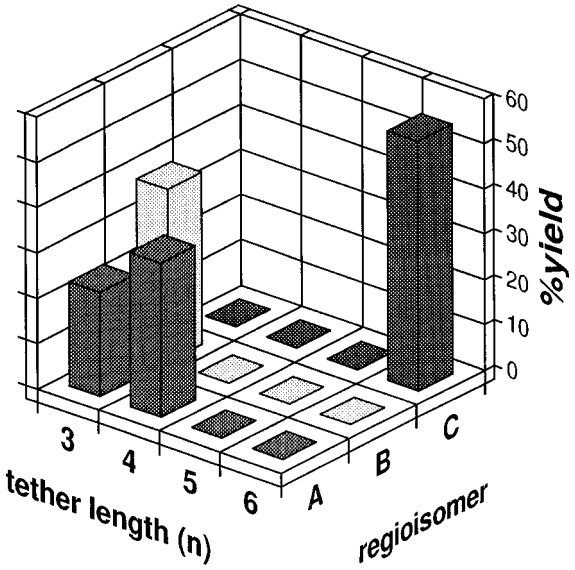


Figure 1. Correlation of tether length and yield of **6(*n*)**. Yields are based on recovered C_{60}.

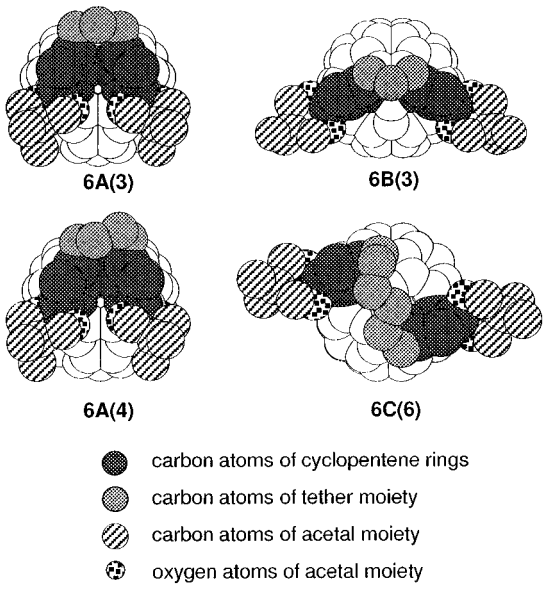


Figure 2. MM2*-optimized structures of bispropanofullerenes **6(*n*)**. Structures are global minima obtained by Monte Carlo computational search. All hydrogen atoms are omitted for clarity.

other studies, the dominant controller of regiochemistry was found to be the tether structure (and hence its energetics).

Estimation of the conformational energy of the tether in a "reactive conformation" is a rather complicated task. One conceptually straightforward approach is to analyze the starting material so as to judge if a certain conformation of the tether directs the reagent moiety on one end of the tether to attack the desired site on the other side of the tether. The utility of this approach has been amply demonstrated in the synthesis of complex natural products[26] and recently for an intermolecular Diels−Alder reaction[27] in fullerene chemistry.[28]

An alternative strategy is the analysis of the product to estimate the strain in the tether. This approach is suitable for the present case, where the structure of the starting material **4(*n*)** shows little resemblance to the reactive intermediate **5(*n*)**, and thus the starting material based approach is impracticable. Obviously, simple comparison of the energies of the products is insufficient, unless thermodynamical control plays the major role in regioselection, which is unlikely in the present case. We have therefore devised a new protocol for sorting out tether's steric energy out of the total energy of the product. In the following paragraphs, we will describe our "double differential approach" toward this goal. While the parent fullerenes have been studied more extensively, the accuracy of various theoretical methods has not been assessed systematically for organofullerenes.

Comparison of the Computational Methods. To start the product-based analysis, we needed to obtain accurate information on the product structures and energies. The accuracy of various theoretical methods has not been assessed systematically for organofullerenes, while the parent fullerenes have been studied more extensively.[8,29] We examined the structure of the monoadduct **8** with the *ab initio* quantum mechanical calculations at the Hartree−Fock level (HF/3-21G), the semiempirical molecular orbital calculations (MNDO, AM1, and PM3), and molecular mechanics (MM2*, MM3*, and Sybyl) and compared the structural data with those of the X-ray structure.[30]

To evaluate the accuracy for the global structure, several structural parameters were examined. Using volume analysis of the MacroModel program, we first calculated the volumes of the molecule within the boundary of the van der Waals radii of carbon atoms based on the atomic coordinates obtained by each method (hydrogens omitted). The volumes based on the X-ray structure, HF/3-21G, MNDO, AM1, PM3, MM2*, MM3*, and Sybyl were 600, 599, 621, 617, 614, 587, 611, and 623 $Å^3$, respectively. Thus, the HF/3-21G and the MM2* structures are 0.4% and 2.2% smaller, and the MNDO, AM1, PM3, MM3*, and Sybyl structures are 3.5%, 2.8%, 2.3%, 1.8%, and 3.8%, respectively, larger than the X-ray structure. The distance (defined as D1 in Figure 3a) between the C−C bond, which is shared in common by the cyclopentene ring and the fullerene core, and the C=C bond, which lies on the opposite side of the C_{60} core, was 7.2−7.3 Å by all methods except by MNDO (7.37 Å) and Sybyl (7.67 Å). Two other distances between two opposing C=C bond. (D2 and D3 in Figures 3a and 3b) showed a comparable trend (note, D1 = D2 = D3 in C_{60}). The detailed data are shown in Table s1 in the Supporting Information. Thus all methods except Sybyl reasonably reproduce the global structure of the propanofullerene **8**, while the Sybyl force field generates a C_{60} core stretched by as much as 0.4 Å.

(25) It must also be noted that theoreticians posed questions as to the viability of the FMO theory in fullerene chemistry, where deeply seated MOs may play important roles. See: Fujimoto, H.; Nakao, Y.; Fukui, K. *J. Mol. Struct.* **1993**, *300*, 425−434. Chikama, A.; Fueno, H.; Fujimoto, H. *J. Phys. Chem.* **1995**, *99*, 8541−8549.

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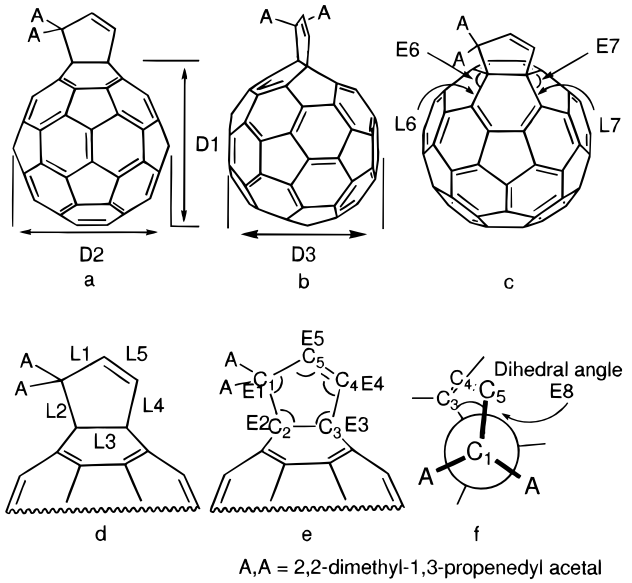
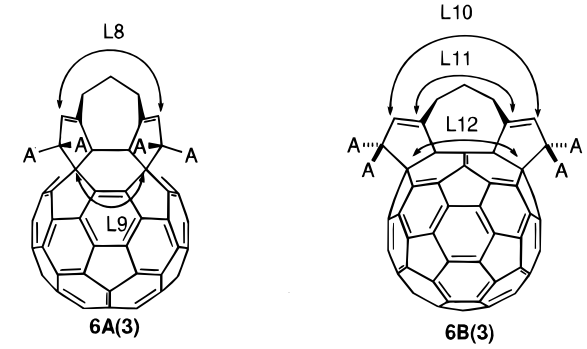


Figure 3. Structural parameters for the monocycloaddition product **8**.



	L8	L9	L10	L11	L12
PM3	4.295	3.131	6.212	3.721	5.119
MM2*	4.370	3.103	6.261	3.764	5.110
Sybyl	4.571	3.305	6.552	4.044	5.376

Figure 4. Selected atom distances of **6(3)**.

Comparison was also made for further details. For the seven C−C bond distances around the cyclopentene ring, all methods reproduced the X-ray data within 2.3% deviation from the experimental value (the detailed data are shown in Table s2 in the Supporting Information). The difference between the X-ray and the HF/3-21G method was remarkably small (<0.6%).

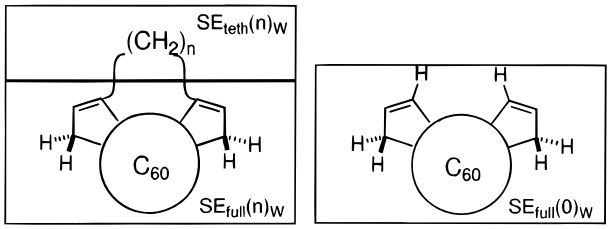
For the bond angles shown in Figure 3 (E1−E7), all methods except Sybyl showed good agreement with the X-ray values (<3.1%), and the HF/3-21G method again showed the best performance (<0.8%) (the detailed data are shown in Table s3 in the Supporting Information). Sybyl's very acute angles for E6 and E7 are the reason for the stretching of the C_{60} core. The dihedral angel C3−C2−C1−C5 (E8) is nearly 0° with all methods except MM3*, which afforded a 12.4° value. Note that this dihedral angle defines the orientation of the methylene tether attached to the C4 carbon.

Further comparison between PM3, MM2*, and Sybyl was made for the double-cycloaddition product **6(3)** (Figure 4). The general tendency remained the same: The first two methods were similar to each other and the Sybyl force field put the two cyclopentene rings far away from each other (L8−L12). The PM3 heat of formation indicates that **6A(3)** is more stable than **6B(3)** by 5.0 kcal/mol. The calculated thermodynamic stability is thus *opposite* to the regioselectivity of the double cycloaddition (**6B(3)** favored over **6A(3)**).

In summary, for all global and local structural parameters, the HF/3-21G method performs extremely well, the PM3 and MM2* methods very well, and the Sybyl force field poorly. Since the HF and semiempirical methods are unsuitable for extensive conformation analysis, we employed the MM2* method in the following studies on the double-cycloaddition products. Additional merit of the MM2* method is that it is very well parameterized for hydrocarbons such as our tether unit. Parenthetically, the good agreement between the X-ray and *ab initio* structures suggests that the crystal structure, in particular, the conformation of the cyclopentene ring, is not much affected by the crystal packing force.

In the following studies, we have replaced the cyclic acetal with a methylene group for the sake of computational facility. For some global minima, we have confirmed that this procedure does not affect the energetics of the structural properties.

Steric Energies of Various Tethers in the Product. In order to estimate the steric energy of the tether moiety in the product, we have developed a "double differential" procedure by processing the MM energies of the double cycloadduct **9** by using **10** as a reference standard.[31]



9 **10**

The steric energy of the *n*-carbon tether moiety for a given isomeric product **W(*n*)** (**W** = **A**−**E**), $SE_{teth}(n)_W$, can be defined as

$$SE_{teth}(n)_W = SE_{total}(n)_W - SE_{full}(n)_W$$

where $SE_{total}(n)_W$ is the total steric energy obtained by MM2* calculations for **9** and $SE_{full}(n)_W$ is the steric energy for **9** excluding the tether. $SE_{full}(n)_W$ is not directly obtainable for the cases $n \neq 0$. For the case $n = 0$ (i.e., without tether), however, this can be readily calculated (i.e., for **10**). Both $SE_{total}(n)_W$ and $SE_{full}(n)_W$, however, contain systematic errors due to improper energetic parameterization of MM2* for organofullerenes (note however that the geometric accuracy, vide supra).[32]

Suppose that the *n*-carbon tether moiety in the isomer **W(*n*)** is fully relaxed and hence the two cyclopentene rings are not deformed as in **W(0)**, $SE_{full}(n)_W$ will be (nearly) equal to $SE_{full}(0)_W$. Naturally, the value of $SE'_{teth}(n)_W$, defined below, derivated from the two structurally different compounds **9** and **10** is theoretically

(31) For the original application of the concept of differential protocol in MO studies, see: Nakamura, E.; Nakamura, M.; Miyachi, Y.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 99−106.

Table 2. Relative Strain Energies $\Delta SE_{teth}(n)$ of the Tether in 6(*n*)[a]

n	A	B	C	D	E
3	3.0	0.0	33.2	75.1	70.1
4	0.0	4.1	7.2	33.0	33.1
5	1.4	12.2	0.0	13.7	13.8
6	10.5	14.2	0.0	6.9	7.0

[a] Units are kcal/mol. The data are based on the most stable tether conformer obtained by Monte Carlo conformational search. Underlined values represent experimentally observed products.

meaningless value (since molecular compositions of **9** and **10** are different from each other).

$$SE'_{teth}(n)_W = SE_{total}(n)_W - SE_{full}(0)_W$$

This systematic error can be eliminated by taking the difference of $SE'_{teth}(n)_W$ among isomers **A**−**E**. If, for instance, **A(*n*)** is the most stable among **W(*n*)**, one can define $\Delta SE_{teth}(n)_W$ as follows

$$\Delta SE_{teth}(n)_W = SE'_{teth}(n)_W - SE'_{teth}(n)_A$$

The relative steric energies of the tether moiety ($\Delta SE_{teth}(n)$) obtained by this "double differential" procedure will give us reasonable measures of the conformational energy inherent to the tether moiety in isomer **W(*n*)**.

The data of the tether strain $\Delta SE_{teth}(n)$ are summarized in Table 2 for the *n* numbers between 3 and 6 and for the isomers **A**−**E**, and one finds that relative energies qualitatively[33] coincide with the experimentally observed product distribution (underlined numbers) for $n = 3$ and 6 (cf. Figure 1). For $n = 4$, a single predominant isomer was obtained and assigned as isomer **A** on the basis of the calculated tether strain (vide infra). For the five-carbon tether, the data predict that isomers **A** and **C** may form, but in experiments, no double-addition reaction took place (very slow second addition). It must be noted that currently available computational methods cannot predict the absolute rate of a reaction.

Conclusion

We have achieved symmetry-defined modification of the C_{60} core structure, with the aid of a new annulation reagent with appropriate tether structure. Clearly, the "intrinsic reactivities" of the double bonds in the initially formed mono-cycloadduct has been overridden by the conformational effects of the tether. Systematic computational studies led to the development of a "double differential" procedure, which is useful for estimating the directing effects of the tether. We expect that the computational method will play vital roles in further optimization of the tether design to maximize the efficiency of the tether control including chirality control.[23] The potential of the new annulating **2(*n*)** in general organic synthesis will be the subject of further studies.

Experimental Section

General. All reactions dealing with air- and moisture-sensitive compounds were undertaken in a dry reaction vessel under a nitrogen stream. Routine flash chromatography on silica gel was performed on Kieselgel 60 (Merck). Analytical thin layer chromatography was carried out using Merck precoated, glass-backed Kiesel 60 F_{254} plates. Gel permeation chromatography was performed on a Japan Analytical Industry LC-908 machine equipped with JAIGEL-1H (20 × 600 mm) and −2H (20 × 600 mm) GPC columns.[34]

Material. Toluene and 1,2-dichlorobenzene were distilled from calcium hydride under nitrogen and stored over molecular sieves. Tetramethylene-tethered bis(cyclopropenone acetal) **2(4)** was synthesized according to the reported procedure.[16]

Trimethylene-Tethered Bis(cyclopropenone acetal) 2(3). To a THF solution (40 mL) of cyclopropenone acetal (2.81 mL, 20 mmol) and HMPA (7.0 mL, 40 mmol) was added *n*-BuLi (1.60 M in hexane) dropwise over 10 min at −78 °C. After 30-min of stirring, 1,3-diiodopropane (0.92 mL, 8.0 mmol) was added and the mixture was stirred for 4 h at −78 °C and 4 h at −40 °C. The reaction was terminated by addition of a pH 7.4 phosphate buffer in THF (1/5 v/v). Aqueous extractive workup afforded a crude product. Purification was performed by silica gel column chromatography (silica gel ca. 120 g, EtOAc/hexane 20%−30% with 0.5% Et_3N elution) gave the titled bis(cyclopropenone acetal) (1.82 g, 50%): IR ($CHCl_3$) 2980, 2830, 1830, 1735, 1470, 1280, 1075, 1025, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 6 H), 1.06 (s, 6 H), 1.97 (q, 2 H, $J = 7.33$ Hz), 2.65 (dt, 4 H, $J = 0.98$, 7.33 Hz), 3.59 (d, 4 H, $J = 10.25$ Hz), 3.63 (d, 4 H, $J = 10.25$ Hz), 7.39 (br s, 2 H). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.02; H, 8.95. Other homologues were synthesized similarly.

Pentamethylene-tethered bis(cyclopropenone acetal) 2(5): IR ($CHCl_3$) 2980, 2830, 1830, 1735, 1470, 1280, 1075, 1025, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.07 (s, 3H), 1.50 (m, 2H), 1.66 (tt, 4 H, $J = 7.81$ Hz), 2.54 (t, 4 H, $J = 7.81$ Hz), 3.59 (d, 4 H, $J = 10.74$ Hz), 3.63 (d, 4 H, $J = 10.74$ Hz), 7.35 (br s, 2 H). Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.08; H, 9.50.

Hexamethylene-tethered bis(cyclopropenone acetal) 2(6): IR ($CHCl_3$) 2980, 2830, 1830, 1735, 1470, 1280, 1075, 1025, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3 H), 1.07 (s, 3 H), 1.43 (m, 4 H), 1.64 (m, 4 H), 2.53 (dt, 4 H, $J = 0.98$, 7.81 Hz), 3.59 (d, 4 H, $J = 10.74$ Hz), 3.63 (d, 4 H, $J = 10.74$ Hz), 7.35 (d, 2 H, $J = 0.98$ Hz). Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.89; H, 9.45. Found: C, 72.66; H, 9.72.

Double Cycloaddition of Bis(cyclopropenone acetal) to C_{60}: Typical Procedure of Double Cycloaddition. Trimethylene-tethered bis(cyclopropenone) acetal **2(3)** (449 mg, 1.40 mmol) and C_{60} (720 mg, 1.00 mmol) were dissolved in *o*-dichlorobenzene (720 mL), and the mixture was heated at 150 °C for 72 h. After the crude mixture was passed through Celite to remove 4A molecular sieves, the solvent was removed under reduced pressure at 50 °C to give a crude product as a black solid (1.20 g). TLC analysis of the crude product indicated the presence of three spots, intramolecular double cycloadducts ($R_f = 0.5$, 0.6: toluene elution), a polar compound ($R_f = 0.1$: toluene elution), and recovered C_{60} ($R_f = 0.9$: toluene elution). The polar compound displayed complexed ^1H NMR spectra, which seems to suggested that it is the product of hydrolysis of the mono-adduct **4(3)**. Product purification was carried out by silica gel column chromatography (silica gel 120 g, elution with hexane, then 50% hexane in toluene, and 20% ethyl acetate in toluene) to afford the products **6A(3)** (145 mg, 0.139 mmol; 14%) and **6B(3)** (236 mg, 0.227 mmol; 23%). Elusion with hexane gave C_{60} (280 mg, 0.39

(32) Since MM2* program is not energetically parameterized for organofullerenes, it will generate two types of errors upon application to the present problem. One is a global error intrinsic to fullerenes: the absolute values of the steric energy calculated, for instance, for the mono-adduct **9** are essentially useless numbers. Another error arises upon application to the double adduct **9** or **10**. There is no guarantee that that the absolute values of steric energies for each isomer of **W** (**W** = **A**−**E**) can be compared with each other because energies for each isomer **W** may be in error.

(33) These values should overestimate the conformational strain in the TS where the tether has more geometric freedom than in the product.

(34) Analytical samples were obtained by purification on GPC HPLC using $CHCl_3$ as eluant, which was always included in the purified products. The content of $CHCl_3$ determined by elemental analysis was confirmed by ^1H NMR analysis of a solution of each analytical sample.

mmol; 39% recovery). Other cycloaddition reactions were carried out in essentially the same manner.

Bispropanofullerene 6B(3): $R_f = 0.50$ (100% toluene); IR (CCl_4) 2949, 2866, 1178, 1103, 806, 791, 750, 742, 526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 6 H), 1.16 (s, 6 H), 2.06 (dt, 1 H, J = 10.4, 15.0 Hz), 2.40 (dt, 1 H, J = 9.4, 15.0 Hz), 2.70 (dd, 2 H, J = 10.4, 14.8 Hz), 3.29 (dd, 2 H, J = 9.4, 14.8 Hz), 3.62 (dd, 2 H, J = 2.1, 11.8 Hz), 3.65 (dd, 2 H, J = 2.1, 11.8 Hz), 3.94 (d, 2 H, J = 11.8 Hz), 3.96 (d, 2 H, J = 11.8 Hz), 6.85 (br s, 2 H); ^{13}C NMR (125 MHz, $CS_2/CDCl_3$ 1/1) δ 21.80 (CH_3), 22.76 (CH_3), 24.91 (CH_2), 29.73, 36.08 (allyl CH_2), 71.94, 72.67 (CH_2), 73.39(CH_2), 78.31, 111.21, 123.98 (CH), 125.98, 127.84, 128.23, 128.35, 129.03, 131.59, 133.13, 136.69, 140.50, 141.56, 142.69, 143.11, 143.79, 144.08, 144.57, 144.86, 144.90, 145.28, 145.36, 145.62, 146.33, 146.55, 146.60, 146.81, 147.52, 147.59, 148.11, 148.95, 155.20, 155.97, 158.16. Anal. Calcd for $C_{79}H_{29}O_4 \cdot 1.25CHCl_3$: C, 80.98; H, 2.48. Found: C, 81.00; H, 2.62.

Bispropanofullerene 6A(3): $R_f = 0.60$ (100% toluene); IR (CCl_4) 2956, 2862, 2362, 2306, 1657, 1460, 1394, 1195, 1018, 530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 6 H), 1.27 (s, 6 H), 1.84 (dtt, 1 H, J = 13.2, 13.2, 3.4 Hz), 2.20 (dtt, 1 H, J = 13.2, 3.9, 1.5 Hz), 2.48 (ddd, 2 H, J = 13.2, 13.2, 3.9 Hz), 2.92 (ddd, 2 H, J = 13.2, 3.4, 1.5 Hz), 3.66 (distorted d, 4 H, J = 11.2 Hz), 3.93 (distorted d, 2 H, J = 11.2 Hz), 3.96 (d, 2 H, J = 11.2 Hz), 6.92 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.05 (CH_3), 23.15 (CH_3), 29.61 (CH_2), 29.83 (CH_2), 31.43, 72.49 (CH_2), 73.38 (CH_2), 74.44, 77.74, 111.67, 124.58 (CH), 132.71, 134.49, 135.14, 136.74, 139.86, 141.63, 143.50, 143.52, 143.79, 144.29, 144.35, 144.41, 144.83, 144.85, 144.89, 144.93, 144.98, 145.64, 145.66, 145.68, 145.74, 146.07, 146.18, 146.73, 147.83, 148.06, 148.52, 148.64, 148.76, 151.09, 153.07; HRMS calcd for $C_{79}H_{28}O_4$ (MH^+) m/z = 1055.2221, found m/z = 1055.3011.

Bispropanofullerene 6A(4): IR (CCl_4) 2949, 2866, 1178, 1103, 806, 791, 750, 742, 526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 6 H), 1.12 (s, 6 H), 2.02 (br s, 4 H), 2.84 (br s, 4 H), 3.56 (distorted d, J = 12.2 Hz, 2 H), 3.85 (d, J = 12.2 Hz, 2 H), 3.90 (d, J =12.2 Hz, 2 H), 6.90 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.10 (CH_3), 22.65 (CH_3), 27.57 (CH_2), 27.92 (CH_2), 29.45, 72.50 (CH_2), 73.51 (CH_2), 74.06, 79.14, 110.60, 125.94 (CH), 131.68, 132.85, 133.18, 136.80, 136.88, 140.42, 141.35, 142.54, 142.76, 143.48, 144.03, 144.43, 144.78, 144.89, 145.25, 145.31, 145.62, 145.76, 146.44, 146.51, 146.64, 146.73, 147.24, 147.52, 147.99, 148.20, 148.23, 148.89, 152.58, 155.82; HRMS calcd for $C_{80}H_{30}O_4$ (MH^+) m/z = 1041.2066, found m/z = 1041.2269.

Bispropanofullerene 6A(6): $R_f = 0.60$ (100% toluene); IR (CCl_4) 2950, 2870, 1180, 1100, 800, 755, 730, 532 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 6H), 1.27 (s, 6H), 1.52 (br s, 4H), 1.84 (br s, 4H), 2.67 (m, 2H), 2.83 (m, 2H), 3.75 (m, 4H), 4.03 (m, 4H), 6.95 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.03 (CH_3), 22.94 (CH_3), 25.61 (CH_2), 26.64 (CH_2), 29.31 (CH_2), 30.21, 71.29, 73.17 (CH_2), 73.62 (CH_2), 78.60, 114.39, 123.19 (CH), 127.56, 133.13, 135.60, 137.59, 138.46, 139.47, 141.70, 141.79, 141.87, 141.92, 143.72, 144.72, 144.83, 144.91, 145.60, 145.75, 146.07, 146.23, 146.26, 146.65, 147.24, 147.64, 147.78, 147.81, 148.77, 149.06, 150.11, 151.48, 151.56. Anal. Calcd for $C_{82}H_{34}O_4 \cdot 1.5CHCl_3$: C, 79.46; H, 2.83. Found: C, 79.70; H, 2.81.

Computational Method. *Ab initio* and semiempirical quantum mechanical calculations were carried out without symmetry assumption with GAUSSIAN 94[35] and Spartan version 4[36] at the Hartree−Fock level using the 3-21G basis set,[37] MNDO, AM1, and PM3 semiempirical levels.[38] Molecular mechanics calculations with MM force fields were performed with MacroModel program version 4,[39] implemented with MM2* and MM3* force fields and a BatchMin program capable of a Monte Carlo conformational search (in vacuo). Molecular mechanics calculations with Sybyl[40] were carried out with the Spartan program. Standard parameters were employed for calculations including alkene parameters for the fullerene sp^2 carbons and alkane parameters for the fullerene sp^3 carbons. Each Monte Carlo search consisted of the generation and minimization of over 3000 structures, with a conformer being kept when it fell within 50 kJ/mol of the current global minimum and does not duplicate any previously stored conformers. This process was repeated at least twice, each time starting from a conformer arbitrarily selected from the most recent coordinate set to test for convergence of the simulation. All the minimization was converged using Polak−Ribiere conjugate gradient minimization followed by line searching by full matrix Newton Raphson convergence. ^1H NMR coupling constants for vicinal protons in the tether have been calculated by the Altona equation as implemented in the MacroModel program.

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Supporting Information Available: Comparison data for various computational method, FMO pictures, and atomic coordinates of the propanofullerene **8** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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