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Regioselective Intramolecular Nucleophilic Addition of Alcohols to C_{60}: One-Step Formation of a *cis*-1 Bicyclic-Fused Fullerene

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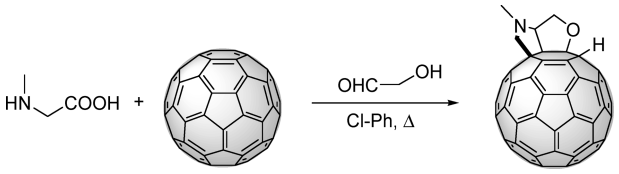

The first example of intramolecular nucleophilic addition of an alcohol to a fullerene double bond is described. In particular, the straightforward one-step reaction of commercially available sarcosine, hydroxyacetaldehyde, and [60]fullerene, in refluxing chlorobenzene, affords a structurally complex novel pyrrolidinofullerene endowed with a furan ring simultaneously fused to both the pyrrolidine and fullerene moieties, which has been spectroscopically and electrochemically characterized. The 2-fold cyclization reaction occurs in a totally regioselective stepwise process leading exclusively to the *cis*-1 isomer. Theoretical calculations (DFT and ONIOM approach) predict that, in contrast to the previous examples with phenols, which require the existence of an intramolecular H-bond and the presence of a methyl group on C-2 of the pyrrolidine ring to afford the cyclized pyran-fused pyrrolidinofullerenes, the formation of the oxygen pentagonal ring is highly favored and does not present such structural constrains. Actually, the 5-*exo*-*trig* cyclization reaction involving the nucleophilic attack of the hydroxyl group to the fullerene surface is moderately exothermic although it has a substantially high energy barrier in accordance with the fact that high temperatures have to be reached to obtain the final product.

Introduction

Fullerenes, the first and best known molecular carbon allotropes,[1] are among the most studied systems in chemistry during the last two decades and, therefore, their chemical reactivity is nowadays well established.[2] However, because of the interest of these carbon materials in the search for practical applications, new reactions involving different covalent and supramolecular chemical protocols for preparing tailor-made fullerenes are currently being reported.[3]

Fullerene derivatives endowed with oxygen through a direct C−O bond are among the less explored and elusive compounds. Thus, in contrast to some well-known oxygen-containing derivatives such as fullerene epoxides, other derivatives like acetals, hemiketals, or ketals are clearly underdeveloped.[4]

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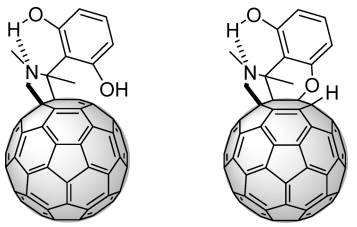

I II

FIGURE 1. Chemical structures of the open pyrrolidinofullerene (**I**) bearing a 2,6-dihydroxyphenyl substituent and the dihydropyran-fused pyrrolidinofullerene (**II**) formed by intramolecular nucleophilic addition of the hydroxyl group to the fullerene double bond.

Fullerene derivatives bearing oxygen-containing heterocycles, such as isoxazolines and oxazolines, have also been reported in the literature, in which the oxygen atom is directly linked to the fullerene surface.[5] Furthermore, isoxazolino[4,5:1,2][60] and [70]fullerenes undergo a retrocycloaddition affording pristine fullerenes.[5j]

Polyhydroxylated fullerenes (the so-called fullerenols or fullerols) are another group of oxygen-containing fullerene derivatives that only recently have been synthesized in a controlled way.[6] Furthermore, as a singular case, the simplest unsubstituted fullerene-fused dihydrofuran has not been reported so far.

In a program directed to the synthesis of novel chemically modified fullerenes from suitably functionalized pyrrolidino[3,4:1,2][60]fullerenes,[7] we have recently reported the first observation of an intramolecular nucleophilic addition of the hydroxyl group of a phenol to a double bond of the C_{60} sphere assisted by the H-bond formed between the pyrrolidine nitrogen and a second hydroxyl group (Figure 1). This intramolecular H-bond was considered to be an essential requirement for achieving the favorable geometry and close proximity of the second OH group to the reactive fullerene double bond. Furthermore, the presence of a methyl group on C-2 of the pyrrolidine ring (similarly to the Thorpe−Ingold effect) was determined to be a key factor for optimizing the geometry of approximation of the O—H group to the fullerene C=C and for the success of the reaction.[8]

Interestingly, an hexagonal oxygen containing heterocyclic ring (dihydropyran **II**) was obtained as a consequence of the atoms chain length existing between the reactive OH phenolic group and the fullerene double bond (**I**), through a 6-*exo*-*trig* cyclization process.[9]

In this paper we report on the straightforward 5-*exo*-*trig* cyclization reaction carried out in a simple one-step synthesis from commercially available starting materials affording a new tetrahydrofuran-fused pyrrolidino[3,4:1,2][60]fullerene (**11**). Interestingly, the nucleophilic addition of the nonisolated intermediate alcohol **10** to the fullerene double bond forming a new pentagonal ring is highly favored, thus avoiding the many structural and electronic requirements (see above) needed to form the oxygen-containing hexagonal heterocycle from phenols.

The reaction mechanism of the intramolecular nucleophilic addition of the hydroxyl group to the fullerene double bond has been theoretically investigated at the density functional theory (DFT) level by using the two-layered ONIOM approach. This study reveals a more favorable formation of the pentagonal ring when compared to that of the previously reported 6-membered oxygen-containing dihydropyran ring.

Results and Discussion

Our first goal was directed to the preparation of new pyrrolidino[3,4:1,2][60]fullerenes suitably functionalized with a hydroxymethyl group able to further react with the fullerene double bond. Therefore, the first chemical strategy was to obtain compound **3** by refluxing in chlorobenzene the commercially available methyl serinate hydrochloride **1** with formaldehyde **2** in the presence of C_{60}. The design of fulleropyrrolidine **3** was made considering the presence of the ester group on C-2 of the pyrrolidine ring in order to favor the subsequent cyclization process, as previously observed in related systems (Thorpe−Ingold effect). Furthermore, it should be expected that spontaneously compound **3** could cyclize to compound **4** by further in situ intramolecular nucleophilic addition of the OH group to the fullerene double bond. However, the only compound obtained from the reaction resulted in the unexpected fulleropyrrolidine derivative **7** in which a new oxazolidine ring has been formed (Scheme 1).

Formation of bicyclic compound **7** can be accounted for by the condensation reaction of the amino of the glycine moiety and the carbonyl group of formaldehyde to yield intermediate **5**, which spontaneously cyclizes to oxazolidine **6**. Further reaction of **6** (bearing the glycine moiety) with formaldehyde generates in situ the required azomethyne ylide, which reacts as a 1,3-dipole with [60]fullerene to afford fulleropyrrolidine derivative **7** in moderate yield (20%).

The chemical structure of fulleropyrrolidine **7** was confirmed by spectroscopic techniques. In particular, the ^{1}H NMR spectrum shows, in addition to the presence of the methyl ester group, the presence of the methylene protons of the pyrrolidine ring, which appear as two doublets centered at 5.06 and 4.94 ppm. Furthermore, we have observed the

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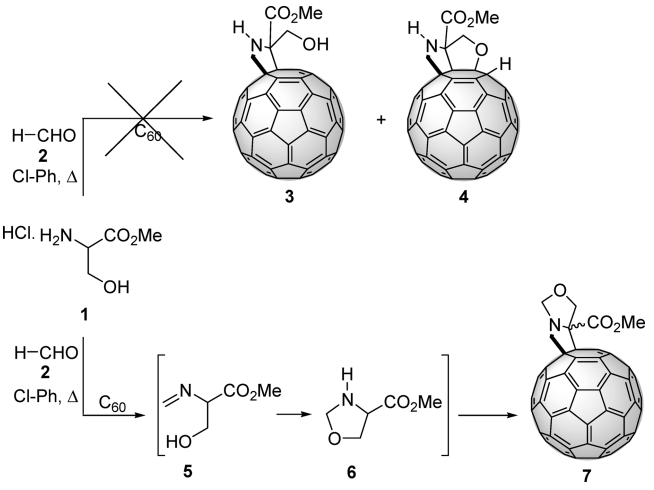
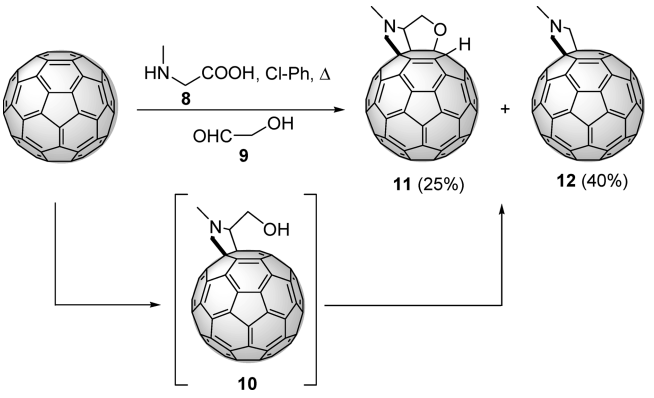
SCHEME 1. Synthesis of Unexpected Oxazolidine-Containing Fullerene 7 from Hydroxymethylglycine Hydrochloride (1) and Formaldehyde in the Presence of [60]Fullerene



SCHEME 2. Synthesis of Fulleropyrrolidine 11 from Nonisolated Intermediate 10 through an Intramolecular Nucleophilic Addition of the Hydroxyl Group to the Fullerene Double Bond



NOE effect between the proton at 4.94 ppm and the proton at 5.11 ppm. This observation indicates that the coupled signals at 5.11 and 5.32 ppm correspond to the methylene group simultaneously attached to the oxygen and nitrogen atoms; in the HSQC this methylene group, as expected, is coupled with the most deshielding sp^3 at 87.2 ppm, due to the presence of the two electronegative heteroatoms (see Figure S3 in the Supporting Iinformation).

Since the chemical approach in which the hydroxymethyl group belongs to the starting aminoester **1** leads to the undesired compound **7** in which the cyclization occurs with the pyrrolidine ring rather than with the fullerene double bond to form an oxazolidine ring, we turned our strategy to the use of an aldehyde endowed with the hydroxymethyl group as in compound **9**.

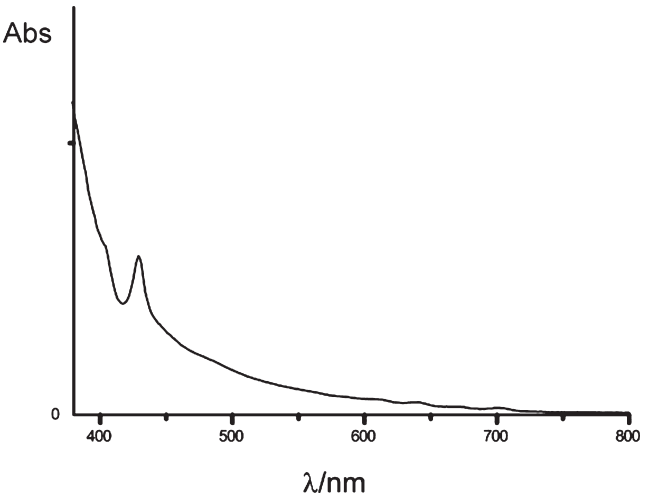


FIGURE 2. UV−vis spectrum of compound **11** in CH_2Cl_2.

Thus, reaction of commercially available *N*-methylglycine **8** (sarcosine) with hydroxyacetaldehyde **9** and C_{60} in refluxing chlorobenzene by following Prato's procedure[10] afforded the desired cyclized compound **11** in 25% yield. Interestingly, intermediate fulleropyrrolidine **10** bearing the hydroxymethyl group was not observed. This experimental finding is a clear indication of the favorable geometrical approach between the reactive O−H and fullerene double bond. A favored 5-*exo*-*trig* cyclization[9] by intramolecular nucleophilic addition of the O−H group to the adjacent double bond of the fullerene leads to the formation of the unprecedented compound **11** in which a tetrahydrofuran ring is simultaneously fused to the pyrrolidine and fullerene moieties (Scheme 2).

The structure of **11** was confirmed by spectroscopic and analytical techniques. Thus, in addition to the signals corresponding to the *N*-methyl (2.89 ppm) and two methylene groups (3.99 and 4.69 ppm for CH_2−N; 4.49 and 4.82 ppm for CH_2−O), the ^{1}H NMR spectrum of this compound showed the typical signature of the hydrogen on the fullerene skeleton, which appears as a singlet at 6.34 ppm, in good agreement with other related fullerenes bearing a hydrogen atom on their surface.[8,11]

The electronic spectrum of compound **11** exibits the typical features of a *cis*-1 regioisomer with an intense absorption at $\lambda = 428$ nm (Figure 2).

To the best of our knowledge, this is the first example reported on the addition of the O−H group of a neutral alcohol to a double bond of the fullerene sphere, affording in a totally regioselective and siteselective manner the *cis*-1 isomer[12] in which the oxygen atom is linked to the fullerene carbon adjacent to the pyrrolidine ring.

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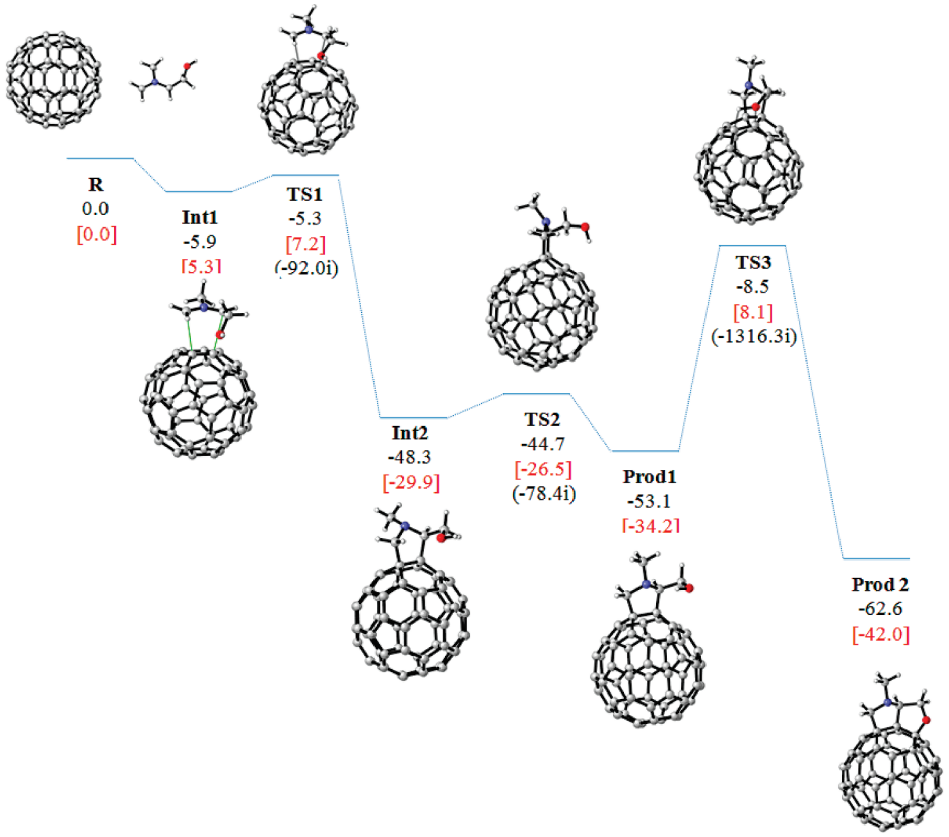

FIGURE 3. ONIOM2(B3LYP/6-31G(d):SVWN/STO-3G) reaction energy profile (Gibbs free energies in square brackets and red color, and the imaginary frequencies of the TSs in parentheses) for the reaction of azomethine ylide and C_{60}.

As is shown in Scheme 2, compound **11** is obtained together with the parent unsubstituted fulleropyrrolidine **12**,[13] which is obtained as the main reaction product (40% yield). Although the formation of this compound lacking the hydroxymethyl moiety from **10** is not clear, other related cases—probably involving a radical mechanism—have been reported in the literature.[14]

The electrochemical properties of the novel compound **11** have been studied by cyclic voltammetry (CV) in *o*-DCB/MeCN (4:1) as solvent at room temperature, using tetrabutylammonium perchlorate as the supporting electrolyte (see the Supporting Information).

As is well-known, saturation of a double bond of the pristine fullerene core results in a raise of the LUMO energy level and, therefore, the reduction waves are shifted toward more negative potential values, thus slightly reducing the accepting ability, as it occurs in fulleropyrrolidine **12** when compared to pristine [60]fullerene.[15]

Thus, as expected, furan-fused pyrrolidinofullerene **11** showed two reversible and a third quasireversible reduction waves ($E^1_{1/2} = -0.81$ V, $E^2_{1/2} = -1.21$ V, and $E^3_{pc} = -1.82$ V)

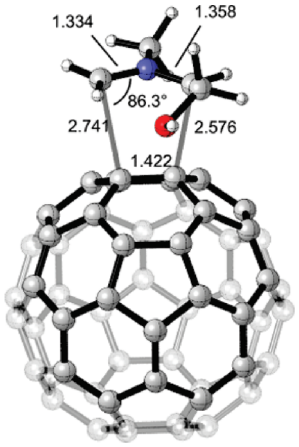

FIGURE 4. Optimized structures (ONIOM2(B3LYP/6-31G(d):SVWN/STO-3G)) for **TS1** with the most relevant distances and angles (in Å and in deg). The atoms treated at the high level in the ONIOM approach are those colored and darkened.

at values more negative than those of pristine C_{60} (−0.70, −1.11, and −1.57 V). However, these values are similar to those of pyrrolidinofullerene **12** (−0.82, −1.19, and −1.71 V) despite the saturation of a second fullerene double bond in **11**, which should raise to still higher values the LUMO level, thus cathodically shifting the reduction potential values. The presence of the electronegative oxygen atom, however, compensates to some extent for the saturation of the second fullerene double bond in **11**, resulting in reduction potential

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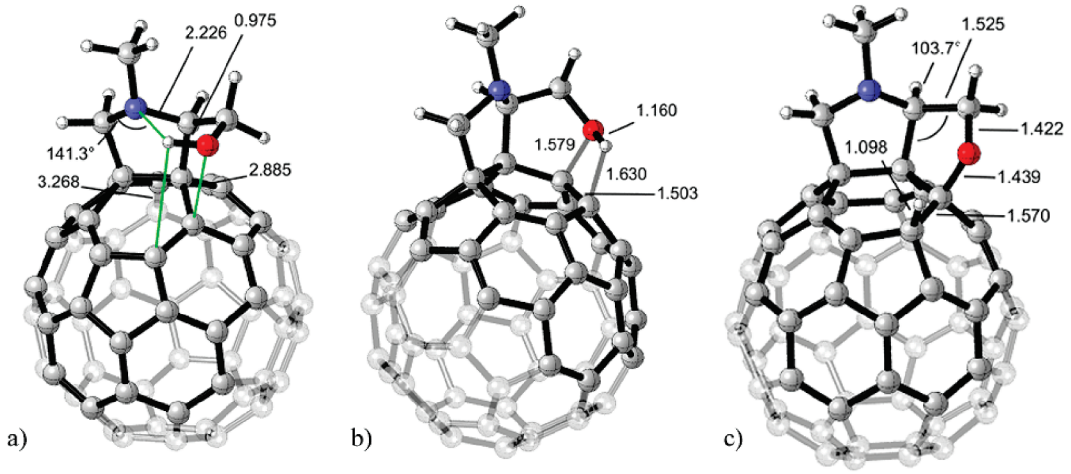

FIGURE 5. Optimized structures (ONIOM2(B3LYP/6-31G(d):SVWN/STO-3G)) for (a) **Prod1**, (b) **TS3**, and (c) **Prod2** with the most relevant distances and angles (in Å and in deg). The atoms treated at the high level in the ONIOM approach are those colored and darkened.

values similar to those obtained for the related monoadducts. This experimental finding has previously been observed in similar examples in which the presence of electronegative atoms or electron-withdrawing groups significantly influences the reduction potential values determined for a variety of organofullerenes.[16]

Theoretical Calculations

As shown above, the intramolecular nucleophilic addition of the hydroxyl group of the 1,3-dipole substituent to the fullerene surface is observed experimentally. The reaction mechanism of the whole path has been theoretically described by means of the ONIOM approach. Figure 3 shows the relative energies and Gibbs free energies of the transition states (TSs), reaction intermediates, and products found.

The first step of the reaction involves the 1,3-dipolar cycloaddition of the 1,3-dipole to the fullerene surface, followed by the intramolecular nucleophilic attack of the hydroxyl group of the dipole substituent. The 1,3-dipolar cycloaddition reaction is extremely favored—the reaction energy calculated with respect to separated reactants is -48.3 kcal mol^{-1}. The TS involving the cycloaddition reaction present negative activation barriers as compared to those involving isolated reactants (-5.3 kcal mol^{-1}). However, Gibbs free energies give an activation barrier of 7.2 kcal mol^{-1}. A reactant complex (**Int1**, see Figure 3) has been localized that is -5.9 kcal mol^{-1} more stable than the corresponding isolated C_{60} and 1,3-dipole although it is less stable in terms of Gibbs free energies by 5.3 kcal mol^{-1}. The activation barrier for the 1,3-dipolar cycloaddition referred to the later reactant complex (**Int1**) is 0.6 and 1.9 kcal mol^{-1} in electronic and Gibbs free energies, respectively. Figure 4 shows the optimized structure for the TS involving the 1,3-dipolar cycloaddition (**TS1**), where the most relevant distances and angles have been represented. As can be seen, a concerted but asynchronous TS is found.

Full optimization of each TS has been done by slightly shifting the geometry of the TS in either sense of reactants or products following the direction of the transition vector (the eigenvector corresponding to the negative eigenvalue). Although this is not equivalent to performing an intrinsic reaction coordinate (IRC), it gives a first idea of which reactants and products are connected through a given TS. The TS involving the 1,3-dipolar cycloaddition (**TS1**) has been shown to lead to cycloadduct **Int2**, which is 4.8 kcal mol^{-1} less stable than the more favorable cycloaddition product for the 1,3-dipolar reaction (**Prod1**). The highest stability of **Prod1** with respect to **Int2** is basically due to the formation of a weak hydrogen bond between the hydrogen atom of the hydroxyl group and the nitrogen atom of the pyrrolidine ring (the H−N distance is 2.226 Å, see Figure 5). The TS converting **Int2** to **Prod1** presents an activation barrier of 3.6 kcal mol^{-1} (or 3.4 kcal mol^{-1} in Gibbs free energies). The 5-*exo*-*trig* cyclization of the hydroxyl group to the fullerene surface that transforms the product of the 1,3-dipolar cycloaddition (**Prod1**) to the final adduct (**Prod2**) is exothermic by 9.5 kcal mol^{-1} (7.8 kcal mol^{-1} in Gibbs free energies).

Figure 5 shows the optimized structures of **Prod1**, **TS3**, and **Prod2** where the most relevant distances and angles have been marked. In **TS3**, the oxygen atom of the hydroxyl group and the carbon atom of the fullerene surface that will be finally bound are 1.579 Å apart. The distance between the hydrogen atom of the hydroxyl group and the carbon atom of C_{60} is 1.630 Å. Interestingly, in a previous paper the 6-*exo*-*trig* cyclization was produced in an organofullerene bearing a phenyl substituent with two hydroxyl groups in an ortho configuration.[8] The TS involving the nucleophilic attack of one of the hydroxyl groups to the C_{60} surface presented considerably larger O−C and shorter H−C distances (1.808 and 1.528 Å for O−C and H−C, respectively) as compared to the distances found for the 5-*exo*-*trig* cyclization. This difference might be attributed to the different nature of the 5- and 6-membered cycles formed. The energy barriers for the 5- ($\Delta G^{\ddagger}=42.3$ kcal mol^{-1}) and 6-*exo*-*trig* cyclization ($\Delta G^{\ddagger}=39.7$ kcal mol^{-1}) differ by only ca. 2.0 kcal mol^{-1}. Although the latter activation barriers are substantially high, both reactions are experimentally feasible. Recently, it has been found that a single point (SP) energy calculation using the new DFT functional M06-2X[17] at the optimized ONIOM-(B3LYP/6-31G(d):SVWN/STO-3G) (i.e., M06−2X/6-31G(d)//ONIOM(B3LYP/6-31G(d):SVWN/STO-3G)) gives a good approximation to the experimental activation barrier for the Diels−Alder reaction of C_{60} with cyclopentadiene.[18] So, we have decided to perform a SP M06-2X/6-31G(d)//ONIOM-(B3LYP/6-31G(d):SVWN/STO-3G) calculation for the present reaction. Using this method we have obtained an activation barrier for the 5-*exo*-*trig* cyclization reaction of 44.1 kcal mol^{-1}, which is quite close to the ONIOM2(B3LYP/6-31G(d):SVWN/

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STO-3G) value. So we conclude that the activation barrier for the 5-*exo*-*trig* reaction is high, which is in line with the relatively high temperatures used in experiment.

Summary and Conclusions

In summary, we report the first example of the intramolecular nucleophilic addition of the hydroxyl group to the fullerene double bond adjacent to the pyrrolidine ring, in a totally regioselective process, affording the *cis*-1 isomer. In contrast to the previous examples with phenols, which require the existence of an intramolecular H-bond and the presence of a methyl group on C-2 of the pyrrolidine ring to afford the cyclized compound, the formation of the oxygen pentagonal ring is highly favored and occurs spontaneously in a one synthetic step. These results are underpinned by theoretical calculations (DFT) which show that the 1,3-dipolar cycloaddition reaction involving the formation of the pyrrolidino ring is an exothermic process with a low activation barrier. The 5-*exo*-*trig* cyclization reaction involving the nucleophilic attack of the hydroxyl group to the fullerene surface is also moderately exothermic but it has a substantially higher energy barrier in accordance with the fact that high temperatures have to be reached to obtain the final product.

This new and facile reaction opens the way to the preparation of a variety of new heterocycle-fused fullerenes from readily available alcohols. Work is currently in progress to explore the scope of the reaction with other alcohols and heteroatoms such as sulfur (−SH) and nitrogen (−NH) as nucleophilic reagents.

Experimental Section

Full geometry optimizations have been carried out with the two-layered ONIOM approach,[19,20] using the Gaussian 03 program.[21] The density functional theory (DFT) SVWN method[22,23] together with the standard STO-3G basis set[24] was used for the low-level calculations, and the hybrid density functional B3LYP method[25−27] with the standard 6-31G(d) basis set[28,29] was employed for the high-level system. All systems were treated with the spin-restricted formalism. The choice of DFT methods was based on previous studies which showed that DFT (and in particular B3LYP together with the 6-31G(d) basis set) give reasonable descriptions of the reaction mechanism of pericyclic reactions.[30−37] Hessians were computed to determine the nature of stationary points (one or zero imaginary frequencies for transition states and minima, respectively) and to calculate unscaled zero-point energies (ZPEs) as well as thermal corrections and entropy effects by using the standard statistical-mechanics relationships for an ideal gas from which Gibbs free energies have been calculated at 298 K.[38]

Preparation of Fulleropyrrolidine Derivative 7. A solution of Et_3N (101 mg, 1 mmol) and methyl serinate hydrochloride (155 mg, 1 mmol) was stirred at room temperature for 30 min. This mixture was added to a solution of formaldehyde (30 mg, 1 mmol) and C_{60} (180 mg, 0.25 mmol) in toluene (150 mL) and was refluxed for 1 h and 30 min. After the solution had cooled to room temperature, the solvent was removed in vacuo, and the crude product was purified by flash chromatography over silica gel, using toluene as eluent, to obtain product **7** in 20% yield. ^{1}H NMR ($CDCl_3$, 298 K, 700 MHz) δ 3.90 (s, 3H, CH_3), 4.89 (d, 1H, J = 10.6 Hz, CH_2−O), 4.94 (d, 1H, J = 9.2 Hz, CH_2−N), 5.06 (d, 1H, J = 9.2 Hz, CH_2−N), 5.11 (d, 1H, J = 6.0 Hz, N−CH_2−O), 5.21 (d, 1H, J = 10.6 Hz, CH_2−O), 5.32 (d, 1H, J = 6.0 Hz, N−CH_2−O); ^{13}C NMR ($CDCl_3$, 298 K, 175 MHz) δ 53.1, 65.6, 70.3, 70.9, 74.6, 86.1, 87.2, 135.0, 135.5, 137.1, 137.12, 139.4, 139.7, 140.5, 141.6, 141.7, 141.8, 141.88, 141.9, 142.1, 142.2, 142.23, 142.3, 142.7, 142.77, 142.79, 142.8, 143.2, 143.22, 144.3, 144.4, 144.5, 144.7, 144.9, 145.3, 145.4, 145.5, 145.56, 145.6, 145.7, 145.8, 145.9, 146.07, 146.1, 146.2, 146.3, 146.4, 146.5, 147.3, 147.4, 150.6, 150.7, 154.3, 154.7, 171.0; FTIR (KBr, cm^{-1}) 526, 700, 1110, 1262, 1741; HRMS (ESI) calcd for $C_{66}H_9NO_3Na$ 886.0480, found 886.04746.

Preparation of Compound 11. A mixture of hydroxyacetaldehyde **9** (15.61 mg, 0.13 mmol), C_{60} (180 mg, 0.25 mmol), and sarcosine (89 mg, 1 mmol) in chlorobenzene (150 mL) was refluxed for 2 days. After the solution had cooled to room temperature, the solvent was removed in vacuo and the crude product was purified by flash chromatography over silica gel, using initially CS_2 as eluent (to separate the unreacted fullerene), then with toluene, and, finally, with toluene/ethyl acetate (9:1) to obtain product **11** in 25% yield together with *N*-methylfulleropyrrolidine **12** in 40% yield.[13]

Spectral Data for Compound 11. ^{1}H NMR ($CDCl_3$, 298 K, 500 MHz) δ 2.89 (s, 3H, CH_3), 3.81 (d, 1H, J = 3.0 Hz, CH−N), 3.99 (d, 1H, J = 9.2 Hz, CH_2−N), 4.49 (dd, 1H, J = 10.8, 3.0 Hz, CH_2−O), 4.69 (d, 1H, J = 9.2 Hz, CH_2−N), 4.82 (d, 1H, J = 10.8 Hz, CH_2−O), 6.34 (s, 1H, H−C_{60}); ^{13}C NMR ($CDCl_3$, 298 K, 125 MHz) δ 39.8, 58.5, 65.5, 67.0, 70.5, 74.8, 81.7, 94.6, 128.1, 135.0, 135.8, 136.0, 138.0, 138.9, 140.7, 141.0, 141.4, 142.1,

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of fulleropyrrolidines **7** and **11**, MS spectrum of compound **11**, cyclic voltammogram of compound **11**, and *xyz* optimized Cartesians coordinates for all minima and transition states located. This material is available free of charge via the Internet at http://pubs.acs.org.