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Structure of the Hydration Product of the C_{60}-Di(2-pyridyl)-1,2,4,5-tetrazine Adduct

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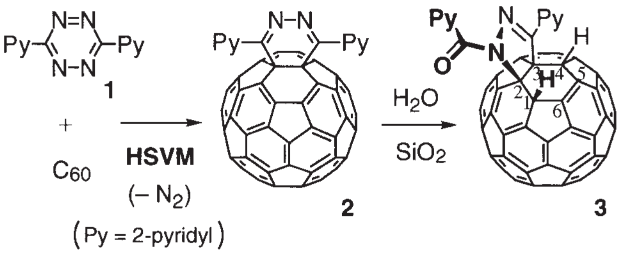
A solid-state reaction of fullerene C_{60} with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine using the high-speed vibration milling technique gives almost quantitatively the monoadduct **2**, which is transformed in high yield upon contact with silica gel to a novel 1,2,3,4-tetrahydro-C_{60} derivative **3** having a 2-pyrazoline ring fused at unusual 2,3-positions of the C_{60} framework. This unexpected product is the result of the addition of a water molecule to an imine moiety of **2**, followed by a series of rearrangements.

Organic functionalizations of fullerene C_{60} using conventional liquid-phase reaction systems with heating and/or irradiation of light have been widely conducted.[1] However, considering the poor solubility of fullerenes in common organic solvents, solid-state reaction systems are quite appealing. Through our extensive studies,[2] we have found that the solid-state reaction of C_{60} is advantageous not only in environment-benignity in avoiding waste materials, such as halogenated solvents, but because of higher yields sometimes observed for the desired products, and also because of the formation of products which can not be produced by liquid-phase reaction. As one of such example, we have reported in Proceedings our preliminary results concerning the solid-state reaction of fullerene C_{60} with 3,6-di(2-pyridyl)-1,2,4,5-tetrazine (**1**), which affords the [4 + 2] cycloaddition / nitrogen-extrusion product **2** in more than 90% yield.[3a] An unexpected product of water addition to compound **2** was also found to form upon purification by chromatography on silica gel.[3] We determined that water addition is followed by an unusual series of rearrangements to give a novel 1,2,3,4-tetrahydro-C_{60} derivative **3**, as shown in Scheme 1. The structure of **3** was based on preliminary X-ray crystallographic data ($R = 0.144$), providing unequivocal bond connectivities for this new compound, but the low quality of the data did not permit a discussion of the bond lengths and geometries.[3a] In a completely independent work from ours, Miller et al. obtained **2** by a liquid-phase thermal reaction in lower yield, and reported that the photochemical rearrangement of **2** affords another type of hydrogenated product.[4] Afterward, they corrected its structure based on analogy to the X-ray structure of an amination product of **2**.[5] During our continued work on the reaction to give the hydration product **3**, we obtained high-quality X-ray crystallography data ($R = 0.0560$), and confirmed that the correct structure of the rearrangement of **2** is actually **3**. Herein we describe the results of our work in detail.



Scheme 1.

Results and Discussion

The reaction of C_{60} with **1** was conducted in the solid-state using our high-speed vibration milling technique (abbreviated as HSVM).[2c] Upon a HSVM treatment of an equimolar mixture of C_{60} and **1** for 1 h, a highly efficient reaction took place and **2** was obtained as a single product in higher than 90% yield, as judged from the ^1H and ^{13}C NMR spectra of the crude reaction mixture. The yield of **2** obtained by the HSVM method is apparently higher than that carried out in toluene at reflux (50–60%).[4] Since this procedure did not require purification, the structure of compound **2** could be determined from its mass and the number of signals in its ^1H and ^{13}C NMR spectra.

Compound **2** is highly sensitive to moisture, particularly upon silica-gel chromatography, and converts to the water addition product **3** in 73% yield based on the starting C_{60} (21% of C_{60} recovered).[6] The general structure of **3** can be deduced from elemental analysis, mass, ^1H and ^{13}C NMR, IR, and UV-vis spectra. The ^1H NMR indicates the presence of two coupled protons directly attached to the C_{60} cage at 6.61 and 6.57 ppm, while the ^{13}C NMR data show four sp^3-carbon signals (79.87, 70.54, 55.45, and 53.93 ppm) and 61 sp^2-carbon signals, indicating that there is no symmetry in this compound **3**. The mass spectrum displays a peak at m/z 945 (M − 1) indicating that **3** is formed by the addition of H_2O to **2**; this was confirmed by the results of the elemental analysis. The IR spectrum has a strong absorption band at 1668 cm^{-1}, indicating the presence of a heteroatom-attached carbonyl group in **3**,

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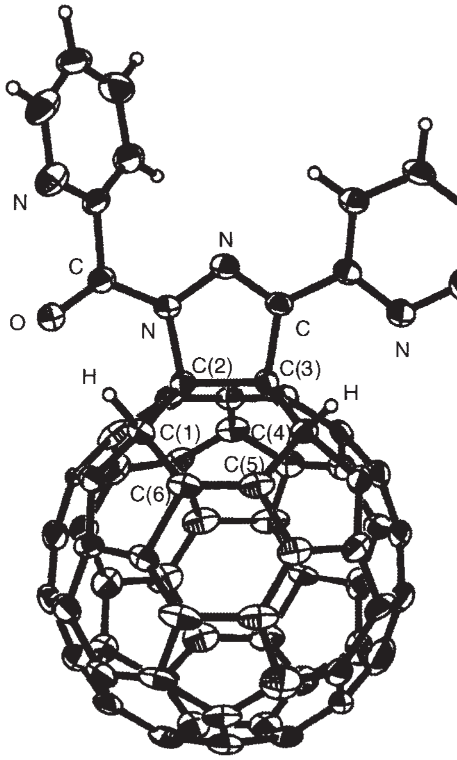
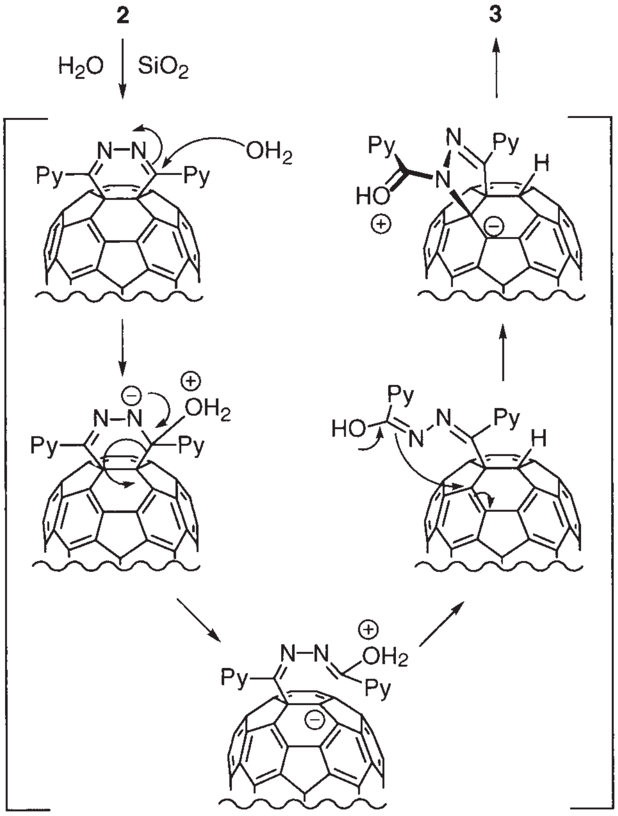


Fig. 1. Thermal ellipsoid plot (50% probability level) for one enantiomer of **3**. Another enantiomer and benzene molecules are omitted for clarity.

in agreement with the ^{13}C NMR signal at 165.25 ppm. Although the water addition was clear from these data, the relative positions of the two fullerenyl hydrogens necessitated an X-ray crystallographic determination.

After much effort with crystal growing, the X-ray structure of **3** was finally determined from a single crystal obtained by the slow evaporation of a benzene solution. Compound **3** was found to be disordered even at -150 °C. After many trials with structural refinements, compound **3** was found to be a disordered racemic mixture after a careful assignment of the atom positions of each enantiomer. There are two overlapped C$_{60}$ cages in a 1:1 ratio found by a refinement of the occupancies of each enantiomer. As shown in Fig. 1, a five-membered ring containing a C=N double bond is fused to the C$_{60}$ moiety at the 5,6 bond of the C$_{60}$ cage; this is a *rare* example in the derivatization of C$_{60}$, since in most of the reported examples, aside from those resulting from nitrogen extrusion,[7] the bonds being formed end up at the primary center of attack, i.e. 6,6 bonds of the C$_{60}$ cage. The bond lengths for C(1)–C(2) and C(3)–C(4) are 1.545(6) and 1.574(8) Å, respectively, which are normal values, but that for C(2)–C(3) is 1.624(6) Å and considerably elongated in respect to the C_{sp^3}–C_{sp^3} bonds. The bond lengths for C(4)–C(5) and C(1)–C(6) are 1.521(5) and 1.512(6) Å, respectively, corresponding to the C_{sp^2}–C_{sp^3} bonds, whereas that for C(5)–C(6) is 1.346(5) Å. C(1), C(2), C(3), C(4), C(5), and C(6) are in a nearly planar arrangement, or may be better described as having a shallow boat geometry with C(1) and C(4) uplifted by 0.134(7) and 0.124(7) Å from the mean plane, respectively.

The addition of a water molecule results in the formation of an amide group through one oxygen atom addition, and the placement of two hydrogen atoms at the 1,4-positions of a six-membered ring. Adduct **3** has the structure of a 1,2,3,4-tetrahydro-C$_{60}$ derivative[8] with a 2-pyrazoline ring fused by its 4,5-positions to the 2,3-positions of the C$_{60}$ moiety.



Scheme 2.

The most probable mechanism for the formation of **3** is described in Scheme 2. The transformation of **2** to **3** is initiated by an attack of H_2O on **2** at a rather hindered, but C$_{60}$ and α-heteroatom-activated imine moiety, which is followed by cleavage of the C_{sp^3}–$C_{fullerene}$ single bond, driven by the unusually low basicity of fullerenyl anions.[9] Proton transfer to the C$_{60}$ cage with the formation of an enolized secondary amide group and an intramolecular addition to a neighboring 6,6 bond, possibly via an electron-transfer step,[8a,10] gives the observed ring fusion. Quenching of the resulting second fullerenyl anion gives compound **3**.

This unusual rearrangement may constitute a straightforward approach to novel heterocycle-fused fullerene derivatives, as was indeed observed by Rubin et al. with several tetrazine derivatives[3b] and by Miller et al. in their recent nitrogen and sulfur-nucleophile addition study.[5] The addition of the parent 1,2,4,5-tetrazine[3b] ($C_2H_2N_4$) leads to a simple formamide analogous to **3** that may show biological activity through protein active site inhibition, such as in HIV-protease.[11] The results in this direction will be reported in due course.

Experimental

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in CS_2–$CDCl_3$ (1:1). The solid-state reactions were conducted using a high-speed vibration mill, which consisted of a capsule and a milling ball made of stainless-steel. The capsule containing the milling ball was fixed in a vibrating arm, which was vibrated vigorously at a rate of 3500 cycles per min.[2c] Fullerene C_{60} was a commercial material ($>$99.5%) purchased from Matsubo Co. All other reagents were commercial materials of reagent grade, and were used as received.

Solid-State Reaction of C_{60} with 3,6-Di-(2-pyridyl)-1,2,4,5-tetrazine. A mixture of C_{60} (50 mg, 0.069 mmol) and 3,6-di-(2-pyridyl)-1,2,4,5-tetrazine (**1**) (17 mg, 0.072 mmol) was vigorously shaken together with a milling ball in a stainless-steel capsule for 1 h by using a high-speed vibration mill under an atmosphere of nitrogen. The resulting brown powder (64.6 mg) was dissolved in CS_2–$CDCl_3$ (1:1) and subjected to NMR measurements. The ^{1}H and ^{13}C NMR spectra showed signals corresponding to adduct **2** as a single product only contaminated by a small amount of unreacted C_{60} (ca. 5%).

2: mp > 300 °C; ^{1}H NMR (CS_2–$CDCl_3$ (1:1)) δ 8.56 (m, 1H), 7.86 (m, 2H), 7.34 (m, 1H); ^{13}C NMR (CS_2–$CDCl_3$ (1:1)) δ 154.76, 153.20, 147.85, 147.32, 147.19, 146.89, 146.40, 146.14, 145.96, 145.37, 145.14, 144.07, 142.95, 142.63, 142.20, 141.49, 141.21, 138.97, 136.42, 134.20, 125.72, 123.83; MS (–APCI) *m*/*z* 928 (M^-).

Rearrangement of Adduct 2 to 1,2,3,4-Tetrahydro[60]fullerene Derivative 3. Product **2** (64.6 mg, 0.068 mmol) obtained by the solid-state reaction of C_{60} (50 mg, 0.069 mmol) was dissolved in CS_2 (10 mL), and the solution was subjected to flash chromatography over SiO_2 (Merck, Silica Gel 60). The elution with CS_2 afforded recovered C_{60} (10.2 mg, 21%), and the elution with CS_2–$CHCl_3$ (1:1) gave compound **3** (47.3 mg, 73%) as a brown powder.

3: mp > 300 °C; ^{1}H NMR (CS_2–$CDCl_3$ (1:1)) δ 8.88 (dt, $J =$ 4.5 and 1 Hz, 1H), 8.77 (ddd, $J = 4.8$, 1.8, and 1 Hz, 1H), 8.18 (dt, $J = 7.8$ and 1 Hz, 1H), 7.96 (dm, $J = 4.8$ Hz, 1H), 7.81 (dt, $J = 1.8$ and 7.8 Hz, 1H), 7.56 (d, $J = 4.5$ Hz, 1H), 7.53 ($J = 4.8$ Hz, 1H), 7.40 (ddd, $J = 7.5$, 4.8, and 1 Hz, 1H), 6.61 (d, $J = 2.1$ Hz, 1H), 6.57 (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (CS_2–$CDCl_3$ (1:1)) δ 165.25, 153.89, 153.13, 151.16, 150.18, 149.78, 148.93, 148.55, 148.50, 148.42, 148.07, 147.75, 147.12, 147.03, 146.80, 146.78, 146.72, 146.39, 146.00, 145.97, 145.47, 145.35, 145.17, 144.87, 144.61, 144.56, 144.23, 144.21, 144.16, 144.09, 144.06, 143.98, 143.94, 143.90, 143.87, 143.84, 143.76, 143.71, 143.49, 143.20, 142.92, 142.80, 142.55, 142.22, 142.16, 141.81, 141.63, 141.41, 141.38, 141.08, 140.61, 139.43, 138.64, 138.28, 137.09, 136.93, 136.20, 136.15, 124.94, 124.46, 124.00, 122.80, 79.87, 70.54, 55.45, 53.93; MS (–APCI) *m*/*z* 945 (M − 1); UV–vis (C_6H_{12}) $\lambda_{\max}$ ($\log \varepsilon$) 210 nm (5.30), 257 (5.02), 291sh (4.73), 430 (3.74), 607 (2.64), 635 (2.55), 662 (2.34), 697 (2.27); IR (KBr) ν 1668 (C=O), 1580 (C=N), 1464, 1444, 1431, 1397, 1317, 1288, 1247, 1215, 1193, 1151, 1096, 1040, 1018, 996, 950, 904, 881, 850, 803, 784, 744, 705, 682, 618, 581, 567, 550, 527, 509, 464 cm^{-1}. Anal. Calcd for $C_{72}H_{10}N_4O$: C, 91.33; H, 1.06; N, 5.92; O, 1.69%. Found: C, 91.01; H, 1.18; N, 5.74; O, 1.78%.

X-ray Crystallographic Analysis of 1,2,3,4-Tetrahydro[60]-fullerene Derivative 3. Crystal data: $C_{72}H_{10}N_4O\cdot(C_6H_6)_2$, FW = 1103.06, crystal size 0.4 × 0.3 × 0.3 mm^3, orthorhombic, space group $P2_12_12_1$, $a = 17.871(2)$ Å, $b = 25.474(4)$ Å, $c = 10.0691(14)$ Å, $V = 4583.9(11)$ Å^3, $Z = 4$, $D_{\text{calc}} = 1.598$ Mg/m^3. Black cubic single crystals of **3** were grown by the slow evaporation of a benzene solution. The intensity data were collected at 123 K on a Bruker SMART APEX diffractometer with Mo-Kα radiation and a graphite monochrometer. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELX-97). The structures of the overlapped and disordered C_{60} cages were restrained to be identical to each other using a SAME instruction ($s = 0.02$). The occupancies of each fragment were refined with constraints that their sum be 1 (0.5236:0.4764). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms connected directly to the C_{60} cage were refined isotropically and other hydrogen atoms were located by calculation. A total of 35423 reflections were measured and 12619 were independent. Final $R1 = 0.0560$, $wR2 = 0.1338$ ($I > 2\sigma(I)$), and GOF = 1.131 (for all data, $R1 = 0.0611$, $wR2 = 0.1366$) for 1360 parameters and 308 restraints.

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