Cycloaddition of Dipolar Trimethylenemethane to C_{70} Promoted by a Trace Amount of Water

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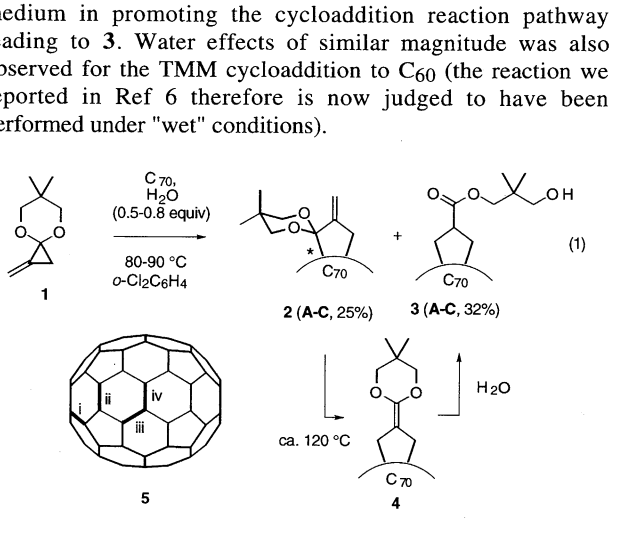
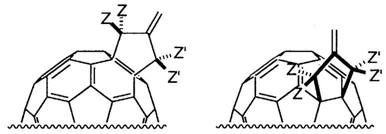
Thermal cycloaddition of a dipolar TMM to C_{70} at 80-90 °C in a "wet" solvent affords a mixture of the acetal **2** and the C_{70}-carboxylic acid ester **3.** The former (as well as its C_{60} analog) undergoes isomerization to the latter at 120-160 °C.

The synthesis of functionalized organofullerenes is a rapidly growing area of scientific research,[1] and organofunctionalized C_{60} derivatives have been recognized to be valuable molecules for various applications in material[2] and biological sciences.[3,4] We have previously reported that a dipolar trimethylenemethane (TMM) generated by mild thermolysis of the methylenecyclopropane **1**[5] serves as a highly useful reagent for the functionalization of C_{60},[6] and that the [3 + 2] cycloaddition reaction of the TMM provides an access[7] to water-soluble C_{60} derivatives useful for bioorganic as well as material science. Of particular note is the ease of incorporation of ^{14}C-label into the carbon skeleton of the TMM species, which have proven to be of vital importance for elucidation of the *in vivo* behavior of bioavailable fullerenes.[8] The demonstrated utility of the TMM reaction in C_{60} chemistry prompted us to investigate the reaction with higher fullerenes.[9] We report in this Letter that the TMM reaction with C_{70} produces, in good combined yield, a mixture of exomethylene acetal **2** and ester **3** by cycloaddition in the flag pole region. Noteworthy is the thermal cleavage of the (asterisked) C–C bond in **2**, which is directly connected to the fullerene core. High temperature thermolysis of **2** hence results in structural isomerization of one isomeric series **2** to the more stable series **3**. Thus, the sequential cycloaddition/isomerization reactions of the methylenecyclopropane **1** with C_{70} afford only the isomer **3**. In addition, we found an intriguing effect of water in the medium in promoting the cycloaddition reaction pathway leading to **3**. Water effects of similar magnitude was also observed for the TMM cycloaddition to C_{60} (the reaction we reported in Ref 6 therefore is now judged to have been performed under "wet" conditions).

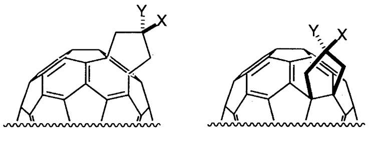


The dipolar TMM generated from the methylenecyclopropane **1**[10] reacts with C_{70} efficiently. Thus, heating a solution of **1** (93 mg, 0.60 mmol) and C_{70} (420 mg, 0.50 mmol) in o-$Cl_2C_6H_4$ (210 mL) containing water (4.7 mg, 0.26 mmol; measured by Karl-Fischer water titrator) at 80-90 °C for 37 h afforded **2** and **3** in 25 and 32% yield, respectively, together with ca. 30% recovery of unreacted C_{70} (eq 1).[11] The ester **3** formed by in situ hydrolysis of the initial cycloadduct **4** (structural assignment by analogy to previous experiments, Ref 5). It must be noted for the formation of **3** (but not that of **2**) the cycloaddition reaction proceeded reproducibly only when a sub-equimolar amount (0.52-0.83 equivalent to C_{70}) of water was present in the reaction mixture. The yield of **3** dramatically decreased from 32-36% to 7-10%, when only 0.05-0.12 equivalent of water was present in the medium (or with large excess of it because of trapping of TMM, Ref 5 and 13). Since C_{70} possesses a very low reduction potential ($E_{1/2}$ = -0.41 V vs. SCE[12]), it is likely that the present cycloaddition reaction involves single electron transfer (SET) from the TMM to C_{70}. Successful competition of the SET-cycloaddition reaction of the TMM against protonation was noted previously.[13] While the origin of the water effects awaits further studies, the difference in the effects of water in the formation of **2** and **3** suggests that the two products form via two independent pathways.



2A and/or **2B** (C_s) **2C** (C_1)

Z, Z = $OCH_2C(CH_3)_2CH_2O$, Z', Z' = H or
Z, Z = H, Z', Z' = $OCH_2C(CH_3)_2CH_2O$



3C (C_1) **3A** and/or **3B** (C_s)

X, Y = H, $CO_2CH_2C(CH_3)_2CH_2OH$

HPLC analysis of the products on an ODS column revealed that the cycloadduct **2** was composed of a 4:1:5 mixture of three isomers (denoted as isomers **2A-C** in the order of elution on HPLC). Similarly, **3** was a 1:3:6 mixture (**3A-C**) of three isomers. The two out of three isomers of **3** (**3B** and **3C**) could be separated pure by preparative HPLC on an ODS column using 20% CH_2Cl_2/i-PrOH as mobile phase, and they were assigned as the adducts due to cycloaddition to bonds i and ii (*vide infra*).[14] The isomeric mixture of **2** could not be separated by any means. However, the thermal isomerization of the isomers of **2** to an isomeric mixture containing **3A** and **3B** suggested that **2** is also due to cycloaddition to bonds i and ii (i.e., **2A**, **B**, and **C**).

From the following ^{1}H and ^{13}C NMR analyses of **3B** and **3C**, we concluded that the reaction took place at the flag pole region (*i.e.*, bonds i and ii) of C_{70}. Thus, in the ^{13}C NMR spectrum of **3B**, the sp^3 carbon of C_{70} appeared at 59.19 ppm, and total 30 peaks of double intensity, 1 peak of quadruple intensity, and 4 peaks of single intensity at 125-155 ppm region were observed, indicating C*s* symmetry of the molecule. ^{1}H NMR of **3B** was also consistent with C*s* symmetry, where the cyclopentane methylene protons appeared as two set of signals at 2.86 (br t, *J* = 12.8 Hz) and 3.22 (br dd, *J* = 12.8, 5.4 Hz). In the ^{13}C NMR spectrum of **3C**, the resonance of the sp^3 carbon of C_{70} appeared at 61.17 ppm and 62.77ppm, and total 68 peaks were assigned in the sp^2 region (125-160 ppm), indicating C*1* symmetry. Among the possible reactive bonds at the 6,6-ring juncture of C_{70} (i-iv in **5**), the thermal reaction to C_{70} so far reported[5,15] only took place at bonds i and ii, both of which are by far the shortest bonds in C_{70}. The TMM additions at bonds i and iii followed by hydrolysis of the ketene acetal should afford C*1* adducts and those at ii and iv should give C*s* adducts. From this analysis, we assigned **3C** as the product due to addition to i and **3B** as that to ii. The minor isomer **3A** was tentatively assigned as a stereoisomer of **3B**.

We found that the isomer **2** undergoes irreversible thermal isomerization to **3** at temperatures higher than that required for the cycloaddition. Thus, heating a *o*-$Cl_2C_6H_4$ solution of pure **2** (a 4:1:5 mixture of three isomers **2A-C**) at 100 °C for 2 days and at 120 °C for 10 days resulted in nearly exclusive formation of **3** (a 1:3:6 mixture of **3A**, **3B**, and **3C**). Little trace of C_{70} or other products formed. Unlike in the cycloaddition reaction, we found no influence of water (0.1-2.4 equiv) in the medium for the rearrangement reaction. In parallel experiments (at 130 °C for 1 day and 160 °C for 2 days) performed for the C_{60} adduct, we observed the same rearrangement taking place in 82% yield. There are two mechanistic possibilities for this rearrangement, namely, full cycloreversion of **2** back to TMM and fullerene, and ionic or radical cleavage of the asterisked bond in **2** followed by internal rotation. The fact that the rearrangement (examined for the C_{60} adduct) takes place smoothly in benzyl alcohol, which rapidly traps the TMM,[5] and with little trace of fullerene regenerated excludes the former possibility. In support of the latter possibility, we may point out that the heterolytic instability of C–C bond between fullerene core and an acetal carbon has been reported for a four-membered ring analog of **2**.[16] In contrast to the reaction reported in ref 16, however, we could not detect any trace of product due to irreversible heterolysis of the C–C bond in benzyl alcohol (cf. Ref 16) and hence consider that a long-lived ionic intermediate is not involved in the rearrangement.[17]

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[14] Spectral data; **3B**: ^{1}H NMR (500 MHz, $CS_2/CDCl_3$ = 1/2) 0.96 (s, 6 H), 2.34 (s, 1 H, OH), 2.86 (br t, *J* = 12.8 Hz, 2 H), 3.22 (br dd, *J* = 12.8, 5.4 Hz, 2 H), 3.31 (s, 2 H), 3.36-3.44 (m, 1 H), 4.03 (s, 2 H); ^{13}C NMR (125 MHz, $CS_2/CDCl_3$ = 1/2) 21.42 (2 C), 36.38, 42.15, 46.02 (2 C), 59.19 (2 C, C_{70}), 68.08, 69.80, 125.13 (2 C), 131.19 (2 C), 131.29 (2 C), 1331.93 (2 C), 132.24 (2 C), 140.68 (2 C), 141.16 (2 C), 142.51 (2 C), 143.79 (2 C), 144.28 (2 C), 144.34 (2 C), 144.43 (2 C), 144.69 (2 C), 145.17 (2 C), 145.32 (2 C), 145.83 (2 C), 145.90 (2 C), 146.60 (2 C), 146.70, 146.77 (2 C), 147.06 (4 C), 147.29 (2 C), 147.87 (2 C), 148.06 (2 C), 148.09 (2 C), 148.96 (2 C), 148.97, 149.08 (2 C), 149.27 (2 C), 149.72 (2 C), 150.43, 151.57 (2 C), 153.57 (2 C), 154.19 (2 C), 154.68, 172.89. **3C**: ^{1}H NMR (400 MHz, $CS_2/CDCl_3$ = 1/1) 1.01 (s, 6 H,), 2.02 (br s, 1 H, OH), 3.03 (distorted t, *J* = 12.2 Hz, 1 H), 3.11 (ddd, *J* = 12.7, 5.4, 1.5 Hz, 1 H), 3.24 (distorted t, *J* = 12.5 Hz, 1 H), 3.38 (s, 2 H), 3.36-3.44 (m, 1 H), 3.60 (ddd, *J* = 12.5, 5.4, 1.5 Hz, 1 H), 4.11 (s, 2 H); ^{13}C NMR (125 MHz, $CS_2/CDCl_3$= 1/1) 21.47 (2C), 36.35, 41.23, 42.51, 46.66, 61.17 (C_{70}), 62.77 (C_{70}), 68.08, 69.83, 125.19, 128.10, 128.88, 131.05, 131.06, 131.08, 131.10, 131.36, 131.40, 133.50, 133.51, 133.68, 133.69, 136.62, 136.89, 139.66, 140.01, 140.23, 140.36, 142.71, 142.76, 142.98 , 143.02, 143.08 (2 C), 143.16, 143.21, 145.61, 145.65, 145.72, 146.09, 146.10, 146.86 (2 C), 146.88, 147.02, 147.24, 147.30, 147.46, 148.53, 148.58, 148.69, 148.84, 148.89, 149.15, 149.20, 149.25, 149.30, 149.53, 149.60, 149.64, 149.72, 149.96, 150.01, 150.50, 150.53, 150.56, 150.60 , 150.62, 150.99, 151.01, 151.23, 151.26, 151.33, 154.40, 155.48, 158.89, 160.43, 172.84. Anal. (for a 1:4:7 mixture of **4A**, **4B**, and **4C**) Found: C, 83.84; H, 1.71%. Calcd for $C_{79}H_{16}O_3{\bullet}(CHCl_3)_{1.1}$: C, 83.85; H, 1.50%.

[15] Photochemical disilirane addition to C_{70} occurred at bond iv; T. Akasaka, E. Mitsuhida, W. Ando, K. Kobayashi, and S. Nagase, *J. Am. Chem. Soc.*, **116**, 2627 (1994).

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[17] The driving force of the isomerization may simply be strain release. PM3 calculation of model compounds of C_{60} adducts revealed that the exomethylene adduct is 11.7 kcal/mol less stable than the ketene acetal adduct (SPARTAN ver. 2.0: Wave function, Inc., Irvine, CA, 1991).