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Formation of 4-Hydroxy-3-(oxan-3-yl)coumarin from Photochemical Reaction between 4-Hydroxycoumarin and 3,4-Dihydro-2*H*-pyran and MO Analysis

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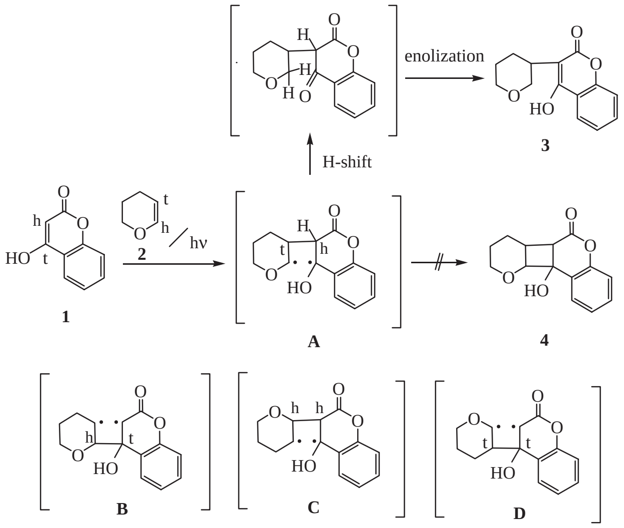
Photochemical reaction of 4-hydroxycoumarin with 3,4-dihydro-2*H*-pyran gave 4-hydroxy-3-(oxan-3-yl)coumarin whose formation was explained by considering a hydrogen shift and successive keto–enol isomerization from a head–tail biradical intermediate (**A**). The reaction mechanism was confirmed by molecular orbital analysis to be induced by intermolecular hydrogen bonding between the 4-OH and pyran oxygen at the transition state.

Coumarin photochemistry has been providing an intriguing subject of synthetic and mechanistic interest. In particular, photochemical cycloaddition reactions of coumarins with cyclic and acyclic alkenes are interesting because they usually give [2 + 2] cycloadducts regioselectively.[1–7] Some of the adducts are converted to ring-enlarged derivatives by cleavage of the cyclobutane ring.[3,8] The origin of regiochemistry and head–head (hh)/head–tail (ht) ratio in cycloalkenone–alkene [2 + 2] photoadditions, remains of great interest in this area.[9] We have confirmed using the PM3-CI level that species specificity and regioselectivity in the photocycloaddition of some conjugated cyclic dienones are mainly controlled by the interaction between the frontier molecular orbitals (FMOs). For example, the peri- ([2 + 2] or [4 + 2]), site- (3,4- or 5,6-addition), and regioselective photoadducts in the triplet photoreactions of 2-pyrones with electron-deficient or electron-rich alkenes are considered to be formed through regioselective 3-β or 6-β two-center interactions in the first-step, and periselective ring-closures from biradical intermediates.[9c,10] Site- and stereoselective [2 + 2] cycloadditions between 2-pyrones and maleimide in the solid state have also been analyzed by MO transition state (TS) calculations and have been determined to proceed via interactions of the singlet excited state of 2-pyrone with the ground state of maleimide.[11] To our knowledge, there have been no investigations by MO analysis of photochemical reactions between coumarins and alkenes.

In this communication, we report a unique synthesis using photochemical reaction of 4-hydroxycoumarin (**1**) with 3,4-dihydro-2*H*-pyran (**2**) that instead of affording a [2 + 2] cycloadduct yields 3-substituted 4-hydroxycoumarin. Also reported is MO analysis of the reaction mechanism. A solution of **1** and five equimolar amounts of **2** in acetonitrile in the presence of benzophenone as a sensitizer was irradiated for 24 h with a 400-W high-pressure mercury lamp through a Pyrex filter under a nitrogen atmosphere. After removal of the solvent, the residue was chromatographed on silica gel using ethyl acetate–hexane (1:1 v/v) as eluent to afford the product **3** in 50% yield (Scheme 1), which showed IR absorbance at 1690 cm^{-1} (α,β-conjugated carbonyl group) and four nonequivalent methylene protons (δ 1.60 and 1.75, 1.94 and 2.02, 3.71 and 4.24, and 3.97 and 4.21) in the ^{1}H NMR spectrum. Finally, the structure of **3** was unambiguously confirmed by X-ray crystallographic analysis as 4-hydroxy-3-(oxan-3-yl)-coumarin, since a colorless single crystal was obtained by recrystallization from diethyl ether (Figure 1). There was no other signal except product **3** and starting materials present in the



Scheme 1. Photoreaction of **1** with **2**.

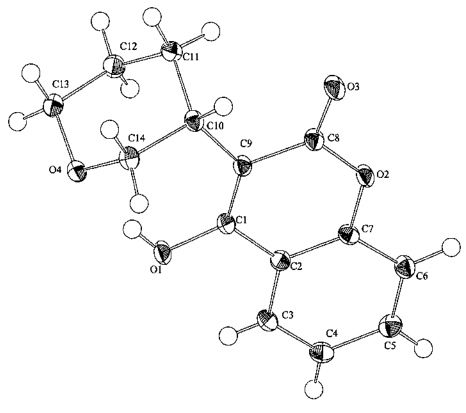


Figure 1. ORTEP drawing of compound **3**.

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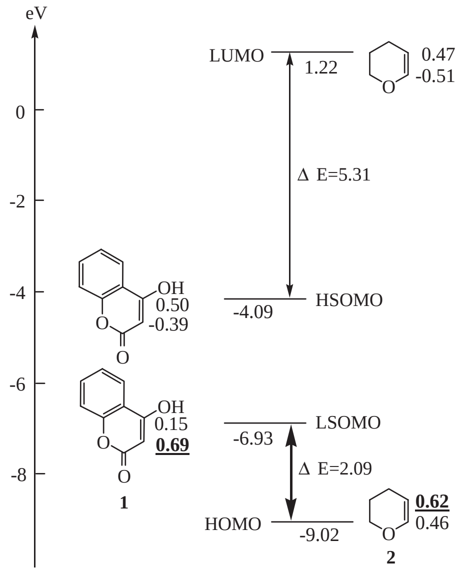

Figure 2. Frontier MO data for triplet photoaddition of **1** with **2** by use of MOPAC-PM5 level.

^{1}H NMR spectrum of the reaction mixture. A solution of **1** with five equivalents of **2** in acetonitrile (63 mM) was irradiated for 8 h in the absence and presence of equimolar benzophenone using a UV cut filter under 350 nm (ε values of **1** and benzophenone at 350 nm in acetonitrile are 7 and 170, respectively). The calculated yields of **3** were 7% and 17%, respectively, by ^{1}H NMR analyses using pyrazine as an internal standard.[12] It was suggested that product **3** was formed via a triplet excited state of **1** from the above results.

Although the photoreaction of 4-hydroxycoumarin (**1**) with cyclohexene gives a [2 + 2] cycloadduct (similar to **4**),[3] similar reaction of **1** with **2** afforded 4-hydroxy-3-(oxan-3-yl)coumarin (**3**). On the basis of the structure of **3** determined by X-ray diffraction analysis, the formation of **3** was reasonably explained from a similar consideration of the triplet photoreaction mechanism between 2-pyrone and alkenes[9c] by way of biradical intermediate **A** followed by a hydrogen shift and successive keto–enol isomerization. It was clarified that the hydrogen shift took place in preference to cyclobutane formation in this system. The inferred presence of intermediate **A** (instead of **B**, **C**, or **D** in Scheme 1) also suggests that the first step of the photoaddition between triplet **1** and **2** is a head–tail (ht) addition and such addition orientation can be explained by the LSOMO–HOMO interaction of the narrow energy-gap and larger coefficients shown in Figure 2.[10] The preference of the ht addition between triplet **1** (HOF: $-149.0\,\mathrm{kJ\,mol^{-1}}$) and **2** (HOF: $-156.9\,\mathrm{kJ\,mol^{-1}}$) and the pathway were confirmed by MOPAC-PM5 transition state analysis of the photoreactions.[13] Figure 3 shows the first-step TS structures and the energies (**AA** and **CC**) for **A** (ht radical) and **C** (hh radical). The TS energy of **AA** is lower than that of **CC**, and the structure of biradical **A** has conformations whose 4-OH of **1** are close to 2-C of **2** ($r_{\mathrm{OH–C}} = 3.20\,\text{Å}$) caused by a hydrogen bonding between the 4-OH and pyran oxygen ($r_{\mathrm{OH–C}} = 2.80\,\text{Å}$). The hydrogen transfer is then inferred to happen easily as shown in Scheme 1. The hydrogen-bonding effect can also be inferred from the following TS analysis of photocycloaddition between triplet **1** and cyclohexene (**5**).[3] The TS energy ($-180.7\,\mathrm{kJ\,mol^{-1}}$) (Figure 4, structure **E**) from the same initial geometry was a local minimum and higher than the true TS energy ($-201.3\,\mathrm{kJ\,mol^{-1}}$) (Figure 4, structure **F**), and the distances between the 2-C of **5** and 4-OH of **1** in the structures of **E** and **F** were not close because of no hydrogen bonding and repulsion by 3-CH$_2$ of **5**. Accordingly, the formation of product **3** is also evidence of the regioselective photoreaction pathway.[13]

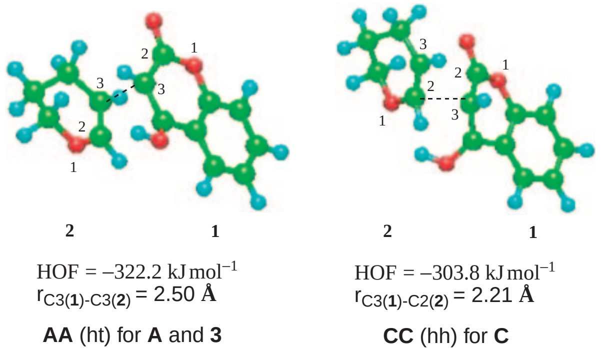

Figure 3. First-step transition state structures and energies of (triplet **1** + **2**) photoaddition by MOPAC-PM5 method.

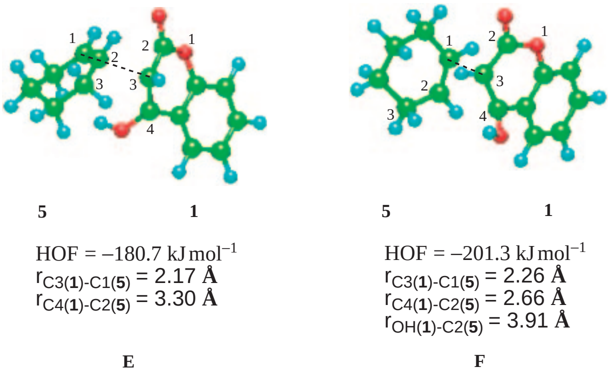

Figure 4. First-step transition state structures and energies of (triplet **1** + **5**) photoaddition by MOPAC-PM5 method.

We have reported that TS structures of the triplet photocycloadditions are twisted in comparison with singlet photoadditions.[14] The photochemical result of this paper suggests control of the structure and reaction direction by an intermolecular hydrogen bonding.

Experimental

4-Hydroxy-3-(oxan-3-yl)coumarin (3). A solution of 4-hydroxycoumarin (**1**) (2.0 g, 12 mmol), 3,4-dihydro-2*H*-pyran (**2**) (5.2 g, 62 mmol), and benzophenone (0.45 g, 2.5 mmol) in acetonitrile (200 mL) was irradiated under nitrogen for 24 h at room temperature and the residue was chromatographed on silica gel using ethyl acetate–hexane (1:1 v/v) mixture to give **3** (1.6 g, 50%). **3**: mp 99–102 °C (from Et$_2$O); ^{1}H NMR (CDCl$_3$) δ 1.60 (1H, br d, $J = 13.6$ Hz), 1.75 (1H, qt, $J = 4.4$, 13.6 Hz), 1.94 (1H, tt, $J = 4.4$, 13.6 Hz), 2.02 (1H, br d, $J = 13.6$ Hz), 3.40 (1H, br s), 3.71 (1H, td, $J = 1.6$, 12.4 Hz), 3.97 (1H, dd, $J = 3.2$, 12.4 Hz), 4.21 (1H, d, $J = 12.4$ Hz), 4.24 (1H, dd, $J = 3.6$, 12.4 Hz), 7.27 (2H, m, Ph), 7.50 (1H, t, $J = 8.4$ Hz, Ph), 7.93 (1H, d, $J = 8.4$ Hz, Ph), 12.11 (1H, s). ^{13}C NMR (CDCl$_3$) δ 22.6, 27.9, 33.1, 69.3, 69.7, 104.8, 115.8, 116.8, 123.5, 123.6, 131.3, 151.9, 161.1, 164.0. IR (KBr) 1690 $\mathrm{cm^{-1}}$ (C=O). LR-FABMS m/z 247 ($\mathrm{MH^+}$). HR-FABMS ($\mathrm{MH^+}$) Calcd for $C_{14}H_{15}O_4$ 247.0970. Found: 247.0966.

All geometry optimizations and TS calculations at ground states and excited triplet states were performed using PM5 to give heat of formation (HOF), etc.,[13] which are available in the molecular orbital package WinMOPAC 3.5 by Fujitsu Ltd.[15]

Single-crystal X-ray diffraction analysis of **3**. Crystal structure data for **3**: formula $C_{14}H_{14}O_4$. $M_r = 246.26$, crystal dimensions $1.00 \times 0.77 \times 0.58\,\mathrm{mm^3}$, monoclinic, space group $P2_1/c$ (#14), $a = 9.5925(3)$ Å, $b = 11.0832(3)$ Å, $c = 11.6146(3)$ Å, $\beta = 108.327(2)°$, $V = 1172.18(6)$ Å^3, $Z = 4$, $\rho_{\mathrm{calcd}} = 1.395\,\mathrm{g\,cm^{-3}}$, $2\theta_{\max} = 54.9°$, $T = 110\,\mathrm{K}$, R (Rw) $= 0.069$ (0.150) for 2679 reflection data with $2\sigma < 54.91°$ and 163 parameters, GOF = 1.03. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC-669436 for compound No. **3**. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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