Photoreactions of 2-(Dialkylamino)ethyl Esters of γ-Oxo Acids via Remote Hydrogen Transfer: Influence of the Stability and Conformational Flexibility of the Biradical Intermediate on Its Chemical Behavior

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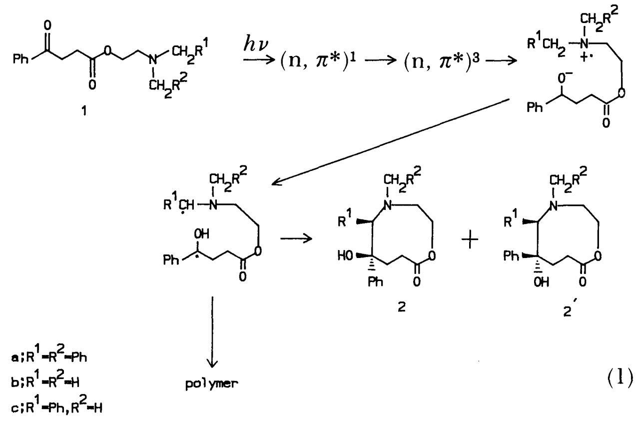
(Received May 8, 1990)

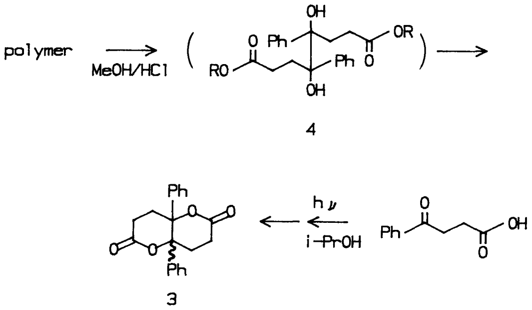
Synopsis. 2-(Dibenzylamino)ethyl 4-phenyl-3-oxobutanoate underwent photocyclization via remote hydrogen migration to give 9-membered azalactones, while 2-(dimethylamino)ethyl 4-phenyl-3-oxobutanoate gave only a polymer. Irradiation of 2-(*N*-methylbenzylamino)ethyl 4-phenyl-3-oxobutanoate gave azalactones via a benzylic hydrogen transfer. No azalactones via methyl hydrogen migration could be detected. The stability and conformational flexibility of biradical intermediates are important factors in the present photocyclization.

Intramolecular hydrogen abstraction by the excited carbonyl group generally occurs through a six-membered cyclic transition state, as in the Norrish Type II reaction.[1] Remote hydrogen abstraction through a large-[2,3] or medium-sized[4–6] cyclic transition state has rarely been observed. We have recently reported the photocyclization of ω-(dialkylamino)alkyl esters of β-oxo acids involving a remote hydrogen transfer.[6] We report here on the photoreaction of 2-(dialkylamino)ethyl esters of γ-oxo acids involving a remote 1,10-hydrogen transfer. The γ-oxo esters showed a somewhat different photochemical behavior from that of the β-oxo esters owing to conformational flexibility.



(1)

Irradiation of **1a** in benzene under nitrogen with a 450 W high-pressure mercury lamp through a Pyrex filter gave azalactone (6-aza analog of 8-octanolide) isomers **2a** and **2a′** in 43 and 14% yield, respectively.[7] Their IR spectra showed the characteristic hydroxyl and carbonyl absorptions (**2a**: 3470 and 1780 cm^{-1}, **2a′**: 3520 and 1770 cm^{-1}). The carbonyl absorptions indicate that there exsist no strong transannular interactions between the carbonyl groups and their nitrogen atoms.[8] The photoreaction of **1** was effectively quenched with 2,5-dimethyl-2,4-hexadiene. The reaction also proceeded in methanol, while the addition of hydrochloric acid prevented the reaction. These results indicate that the primary process in the photoreaction of **1** is intramolecular charge-transfer quenching, similar to the photochemical behavior of amino ketones[9] and ω-(dialkylamino)alkyl esters of β-oxo acids.[6] The Stern–Volmer plots for the formation of **2a** showed a linear relationship, the slope ($k_q\tau$) of which is 24 mol^{-1} l. The lifetime τ of the triplet state of **1a** and $1/\tau$ were calculated to be 4.8×10^{-9} s and 2.1×10^{8} s^{-1}, respectively, assuming a diffusion-controlled rate for k_q (5×10^{9} mol^{-1} l s^{-1}). The $1/\tau$ value is a little bit larger than that of valerophenone ($1/\tau=1.3\times10^{8}$ s^{-1}),[10] though the photoreaction of **1a** involves a 1,10-hydrogen transfer and that of valerophenone involves a γ-hydrogen abstraction. The quantum yields for the formation of **2a** and **2a′** at 313 nm were determined to be 0.43 and 0.14, respectively. These results support the idea of an intervension of the charge-transfer intermediate in the photoreaction of **1a**. The process of the charge-transfer interaction involving the conformational change leading to a suitable conformation for the interaction is presumed to be the rate-determing step, which affects the value of $1/\tau$.



(2)

The photoreactivity of the 2-(dimethylamino)alkyl ester **1b** was very different from that of the corresponding dibenzylamino ester **1a**. Irradiation of **1b** under the same conditions gave only a polymer. No azalactones could be detected. In the case of β-oxo esters, (dimethylamino)alkyl esters showed a similar photoreactivity to (dibenzylamino) alkyl esters.[6] To clarify the polymerization process, alcoholysis of the polymer in the presence of hydrochloric acid was performed. The alcoholysis gave the bicyclic lactone **3**,[11] which might be produced through the pinacol **4**. The lactone **3** was also obtained when 4-phenyl-3 oxobutanoic acid was irradiated in 2-propanol and the reaction mixture was then refluxed in benzene. The polymer seems to be formed through a coupling of biradical intermediates, since the hydrogens on an *N*-methyl group are more reactive than those on an *N*-benzyl group in reactions through proton migration from the alkylamine cation radicals.[12] The following possibility, however, could not be excluded: a pinacol may be formed by the photoreduction of **1b** and contained in the polymer, and the lactone 3 may be produced from the pinacol in the polymer.

The photocyclization of **1** to **2** seems to require a biradical with a stable alkyl radical center, such as a benzyl radical. To ascertain this hypothesis we examined the photoreaction of **1c**, which has *N*-benzyl and *N*-methyl groups. Although proton migration from a methyl group occurs faster than that from a benzyl group in reactions through the alkylamine cation radicals,[12] only azalactones through benzylic proton migration are expected to be produced, due to the stability of the radical centers. Irradiation of **1c** was performed and, indeed, two azalactone isomers, **2c** and **2c′**, through benzylic hydrogen migration were obtained in 26 and 14% yield, respectively.[7] Their ^1H NMR spectra showed a *N*-methyl singlet (δ=2.23 in **2c**, and δ=2.34 in **2c′**).

The requirement of stable alkyl radical centers in azalactone formation seems to suggest that the rather unstable biradical is subject to bimolecular coupling rather than a change in its conformation to that suitable for cyclization. Cyclization demands a specific conformation for the overlap of *p*-orbitals on both radical centers in the biradical intermediate; the process for this demand might compete with a bimolecular coupling process. The substituent effect observed in γ-oxo esters was not observed in β-oxo esters. The absence of the substituent effect in β-oxo esters can be explained in terms of the presence of strong intramolecular hydrogen bonding in a biradical intermediate;[6,13] the hydrogen bonding decreases the freedom of the conformational flexibility and increases the statistical probability of cyclization.

The stability and conformational flexibility of biradical intermediates are important factors in the photocyclization of **1** via a remote hydrogen transfer.

Experimental

IR spectra were recorded with a JASCO A-3 spectrometer. ^1H and ^{13}C NMR spectra were measured with a JEOL FX90Q or a Bruker AM400 spectrometer using tetramethylsilane as an internal standard. An Ushio 100- or 450-W high-pressure mercury lamp was used as the irradiation source. The 4-phenyl-3-oxobutanoates **1a**—**1c** were prepared from 4-phenyl-3-oxobutanoic acid and the corresponding amino alcohol.

General Procedure for Preparative Irradiation of 1a and 1c. A solution of the γ-oxo ester **1** (ca. 3 mmol) in 150 cm^3 of benzene was placed in a flask for immersion irradiation and irradiated with a 100-W high-pressure mercury lamp under nitrogen. After removal of the solvent the residue was chromatographed on silica-gel column. Elution with a mixture of benzene–ethyl acetate (v/v=2/1) gave **2** and **2′**.

(5*RS*, 6*SR*)-4-Benzyl-6-hydroxy-5,6-diphenyl-4-aza-1-oxacyclononan-9-one (**2a**): 43%; mp 127.5—129.0 °C (from a mixture of benzene–hexane); IR (KBr) 3540 and 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.3—2.4 (9H, m, $4CH_2$+OH), 3.03 (1H, d, J=13.7 Hz, CH_2Ph), 3.98 (1H, d, J=13.7 Hz, CH_2Ph), 4.12 (1H, s, CHPh), and 7.2—7.5 (15H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=26.6 (t), 35.2 (t), 52.4 (t), 55.2 (t), 59.0 (t), 70.9 (d), 91.5 (s), 125.1 (d, 2C), 126.9 (d), 127.4 (d), 128.0 (d, 3C), 128.4 (d, 2C), 128.5 (d, 2C), 129.0 (d, 2C), 131.4 (d, 2C), 133.8 (s), 138.9 (s), 142.9 (s), and 176.0 (s). Found: C, 77.87; H, 6.83; N, 3.47%. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49%.

(5*RS*, 6*SR*)-4-Benzyl-6-hydroxy-5,6-diphenyl-4-aza-1-oxacyclononan-9-one (**2a′**): 14%; mp 163.8—165.0 °C (from a mixture of benzene–hexane); IR (KBr) 3520 and 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.1—3.4 (9H, m, $4CH_2$+OH), 3.17 (1H, d, J=13.2 Hz, CH_2Ph), 4.03 (1H, s, CHPh), 4.04 (1H, d, J=13.2 Hz, CH_2Ph), and 7.0—7.4 (15H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=27.9 (t), 33.1 (t), 54.3 (t), 57.2 (t), 61.0 (t), 70.0 (d), 92.6 (s), 124.8 (d, 2C), 126.9 (d), 127.1 (d), 127.3 (d), 127.5 (d, 2C), 128.0 (d, 2C), 128.5 (d, 2C), 129.4 (d, 2C), 131.1 (d, 2C), 133.9 (s), 139.7 (s), 143.1 (s), and 176.7 (s). Found: C, 78.04; H, 6.90; N, 3.38%. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49%.

(5*RS*, 6*SR*)-6-Hydroxy-4-methyl-5,6-diphenyl-4-aza-1-oxacyclononan-9-one (**2c**): 26%; mp 128.0—129.5 °C (from a mixture of benzene–hexane); IR (KBr) 3500 and 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.00 (1H, s, OH), 1.9—2.3 (4H, m, $2CH_2$), 2.23 (3H, s, CH_3), 2.37 (2H, t, J=5.3 Hz, NCH_2), 3.23 (2H, t, J=5.3 Hz, OCH_2), 3.93 (1H, s, CHPh), and 7.2—7.5 (10H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=26.9 (t), 34.2 (t), 37.5 (q), 57.6 (t), 58.0 (t), 76.3 (d), 92.1 (s), 124.7 (d, 2C), 127.7 (d, 2C), 128.1 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 128.6 (d, 2C), 131.1 (d), 133.6 (s), 143.5 (s), and 176.1 (s). Found: C, 73.75; H, 7.13; N, 4.03%. Calcd for $C_{20}H_{23}NO_3$; C, 73.82; H, 7.12; N, 4.30%.

(5*RS*, 6*RS*)-6-Hydroxy-4-methyl-5,6-diphenyl-4-aza-1-oxacyclononan-9-one (**2c′**): 14%; mp 134.5—136.0 °C; IR (KBr) 3400 and 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.2—2.8 (5H, m, $3CH_2$+OH), 2.34 (3H, s, CH_3), 2.37 (2H, t, J=5.4 Hz, NCH_2), 3.74 (2H, t, J=5.4 Hz, OCH_2), 4.06 (1H, s, CHPh), and 7.0—7.4 (10H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=28.4 (t), 34.3 (t), 40.6 (q), 59.3 (t), 60.3 (t), 75.9 (d), 92.9 (s), 125.2 (d, 2C), 127.3 (d), 127.4 (d), 127.8 (d, 2C), 128.4 (d, 2C), 131.1 (d, 2C), 133.8 (s), 143.3 (s), and 177.1 (s). Found: C, 73.77; H, 7.17; N, 4.03%. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30%.

Photoreaction of 1b. A solution of **1b** (1.043 g, 4.2 mmol) in 150 cm^3 of benzene was irradiated under the same conditions described above. After removing the solvent the residue was chromatographed on silica gel. Elution with ethyl acetate gave only a small amount of unknown material. Most of the irradiated mixture could not be eluted out with ethyl acetate. Elution with methanol gave a polymeric material. The polymeric material was refluxed in methanol containing hydrochloric acid. After neutralization with a 0.1 M sodium hydroxide solution (1 M=1 mol dm^{-3}), the mixture was extracted with benzene. The benzene solution was washed with water and then dried over sodium sulfate. After filtration of the drying agent and removing the solvent, the residue was chromatographed on silica gel. Elution with a mixture of benzene–ethyl acetate (v/v=20/1) gave 1,6-diphenyl-2,7-dioxabicyclo[4.4.0]octane-3,8-dione (**3** and **3′**).[11]

3: 5% (based on used **1b**); mp>250 °C; IR (KBr) 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.34 (2H, ddd, J=18.0, 13.5, and 7.5 Hz, 5- and 10-CH_2), 2.13 (2H, ddd, J=18.0, 10.5, and 5.5 Hz, 5- and 10-CH_2), 2.39 (2H, ddd, J=13.5, 10.5, and 7.5 Hz, 4- and 9-CH_2), 2.83 (2H, ddd, J=13.5, 10.5, and 5.5 Hz, 4- and 9-CH_2), and 7.2—7.6 (10H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=28.0 (t, 2C), 31.0 (t, 2C), 88.8 (s, 2C), 127.0 (d, 4C), 128.5 (d, 4C), 128.7 (d, 2C), 139.4 (s, 2C), and 175.8 (s, 2C). Found: C, 74.40; H, 5.63%. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63 %.

3′: 5% (based on used **1b**); mp 176.0—177.0 °C; IR (KBr) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.27 (2H, ddd, J=12.5, 10.0, and 5.0 Hz, 5- and 10-CH_2), 2.37 (2H, ddd, J=17.0, 10.0, and 7.5 Hz, 5- and 10-CH_2), 2.77 (2H, ddd, J=17.0, 10.5, and 5.0 Hz, 4- and 9-CH_2), 3.03 (2H, ddd, J=12.5, 10.5, and 7.5 Hz, 4- and 9-CH_2), and 7.0—7.3 (10H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ=28.7 (t, 2C), 29.9 (t, 2C), 91.2 (s, 2C), 127.6 (d, 8C), 128.7 (d, 2C), 137.8 (s, 2C), and 175.4 (s, 2C). Found: C, 74.41; H, 5.64%. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63%.

The compounds **3** and **3′** (total yield 6% based on used **1b**) were also obtained from the decomposition of the polymer in benzene containing acetic acid instead of in methanol containing hydrochloric acid.

Preparation of the Bicyclic Lactone 3 from 4-Phenyl-3-oxobutanoic Acid. A solution of 4-phenyl-3-oxobutanoic acid (100 mg, 0.56 mmol) in 25 ml of 2-propanol was irradiated under nitrogen with a 450-W high-pressure mercury lamp through a Pyrex filter for 16 h. After removing the solvent, the rsidue was dissolved in 50 ml of benzene and refluxed for 66 h. The solvent was evapolated off. The residue was chromatographed on a silica-gel column. Elution with a mixture of benzene–ethyl acetate (v/v=2/1) gave 65 mg (72%) of 1:1 mixture of **3** and **3′**. Compounds **3** and **3′** were isolated by fractional recrystallization.

Quantum Yield Determination. The γ-oxo ester **1a** was dissolved in purified benzene (ca. 0.05 mol dm^{-3}) and placed in 15×150 mm Pyrex culture tubes. In quenching experiments, the solution also contained appropriate concentrations of 2,5-dimethyl-2,4-hexadiene. The tubes were degassed by three freeze-pump-thaw cycles and then sealed. Irradiation was performed on a "merry-go-round" apparatus with an Ushio 450-W high-pressure mercury lamp. The potassium chromate filter solution was used to isolate the 313 nm line.14) Product analyses were performed using a Gasukuro Kogyo 570B high-pressure liquid chromatograph with a Model 511 single-wave UV detecter (254 nm). A Unishi QC18 colomn (4×250 mm) was used, and a mixture of acetonitrile–water (v/v=3/2) was employed as the moving phase at a flow rate of 9 ml min^{-1}. Phenanthrene was used as a calibrant for the analyses. Valerophenone was used as an actinometer.10)

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7) The configuration of azalactones **2a′**, **2c**, and **2c′** may be determined on the basis of chemical shift of C_6-methine hydrogen in their ^1H NMR spectra. The hydrogen cis to the C_7-phenyl group may be expected to receive a sheelding effect by the phenyl group. However, molecular model inspection indicates that azalactones can take a conformation in which both cis and trans hydrogens to the C_7-phenyl group locate above the benzene ring. So, we could not determine the configuration of the azalactones.

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