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Reactions of Singlet Oxygen with Enol Esters

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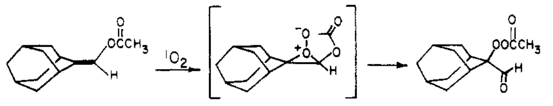
Singlet oxygenation of 1-adamantylideneethyl acetate (4) and 6,6-dimethylcyclohex-1-enyl acetate (7) produces only "ene" reaction products. Photooxygenation of $\Delta^{1,6}$-2-oxabicyclo[4.4.0]decen-3-one (9), in contrast, yields ene, acyl-shifted, and [2 + 2] cycloaddition products. The product distribution resulting from oxidation of 9 indicates that attack of singlet oxygen ($^1O_2$) occurs exclusively on the same side of the double bond as the ester functional group. The bimolecular rate constant for reaction of 9 with $^1O_2$ is found to be ca. 50 times larger than those of 4 and 7. These results are explained most economically by invoking the initial formation of a perepoxide intermediate. In the case of 9, stabilization of the transition state leading to the perepoxide by interaction of the incoming $^1O_2$ molecule with the ester functionally produces the observed rate enhancement and stereospecificity.

Singlet oxygen ($^1O_2$, $^1\Delta_g$) reacts with monoolefins to give either a dioxetane by [2 + 2] cycloaddition or an allylic hydroperoxide by the $^1O_2$ "ene" reaction.[1] The elucidation of the mechanism for these transformations has proven to be a challenging problem. Many of the tools available to chemists have been brought to bear, but there is still disagreement about the details of the reaction coordinate. Some experiments have been interpreted in favor of a concerted reaction,[2] while others are believed to support a stepwise process involving perepoxide,[3] zwitterion,[4] biradical,[5] or reversibly formed exciplex[6] intermediates. To some extent, these differences of opinion may reflect the diversity of the olefinic systems studied.

We have previously reported that the reaction of $^1O_2$ with enol ester 1 gives perester 3 by intramolecular migration of the acyl group[7] (eq 1). This reaction provides a mechanistic probe for the singlet oxygenation of olefins. Product and kinetic studies showed that the mechanism of the acyl-shift, the [2 + 2] cycloaddition, and the ene reactions are best described as proceeding through a common, polar intermediate most simply perceived as the perepoxide 2. We report herein experiments that further define the scope of the acyl-shift reaction and its use as a probe of singlet oxygenation in general.

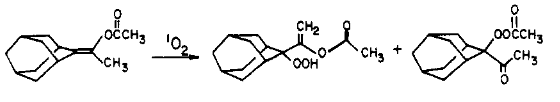


(1)

1 2 3

Results

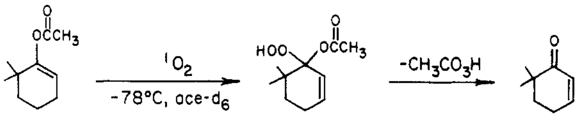
1-Adamantylideneethyl Acetate (4). Singlet oxygenation of enol ester 4 is of interest because this olefin has the competing acyl group and abstractable allylic hydrogens on opposite sides of the double bond. Photooxygenation of 4 at room temperature in CS_2 using tetraphenylporphyrin (TPP) as the sensitizer gives the ene reaction product 5 in 88% yield. A minor product, tentatively identified as acyl-shift product 6, is observed spectroscopically in CS_2 (eq 2). All attempts to isolate this product, however, failed[8] (see Table I).



(2)

4 5 6

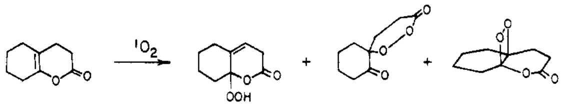
6,6-Dimethylcyclohex-1-enyl Acetate (7). Enol ester 7, which possesses competing groups in a trans relationship, was prepared to define further the acyl-shift competition with the ene reaction. The photooxygenation of 7 is sluggish, and only bleaching of the sensitizer occurs at room temperature. Prolonged irradiation at −78 °C (methylene blue (MB) in acetone-d_6) does result in the oxidation of 7 by the ene pathway to form ene product 8 in quantitative yield (eq 3, Table I).



(3)

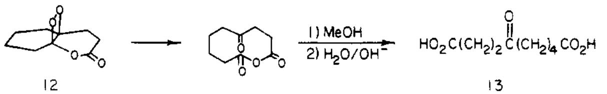
7 8

$\Delta^{1,6}$-2-Oxabicyclo[4.4.0]decen-3-one (9). The acyl group in enol lactone 9 is rigidly held in a favorable position with respect to the double bond for the acyl-shift reaction. Photooxygenation of 9 in a variety of solvents at −78 or 0 °C leads to its very rapid consumption and the formation of ene (10), acyl-shift (11), and [2 + 2] cycloaddition (12) products (eq 4). Peroxides 10 and 11 were fully characterized by the usual methods after isolation. The formation of 12 was inferred from formation of diacid 13 after hydrolysis (eq 5). It is important to note that the ene products that would be formed from the abstraction of the allylic hydrogens in the hydrocarbon ring are not detected (Table I).



(4)

9 10 11 12



(5)

12 13

Kinetic Studies. The bimolecular rate constants for reaction of the enol esters with $^1O_2$ were determined. Two

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(8) The apparent reduction of 6 to the corresponding keto ester was inconclusive because the alcohol resulting from reduction of 5 underwent facile rearrangement to this keto ester.

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Table I. Product Yields for Photooxygenation of Enol Esters 4, 7, and 9

enol ester	solv/senstzr	temp, °C	ene (% yield)	acyl-shift	[2 + 2]
4	CS_2/TPP	23	5 (88)	6 (7)?	
7	$(CH_3)_2CO$-d_6/MB	−78	8 (108)		
9	CS_2/TPP	0	10 (67)	11 (24)	12 (9)
9	CS_2/TPP	−78	10 (64)	11 (34)	12 (8)
9	$(CH_3)_2CO$-d_6/MB	0	10 (56)	11 (29)	12 (12)
9	$(CH_3)_2CO$-d_6/MB	−78	10 (56)	11 (33)	12 (13)
9	CD_3OD/MB	0	10 (62)	11 (22)	12 (16)
9	CD_3OD/MB	−78	10 (61)	11 (22)	12 (14)

Table II. Rate Constants (k_r) for the Reaction of the Enol Esters with $^1O_2$ in Acetone-d_6

enol esters	temp, °C	$10^{-4}k_r$, s^{-1} M^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
1	23	3.4^a		
1	23	2.7^b		
4	23	4.5^a		
7	23	0.8^b		
9	23	100^b	1.1	−31
9	−32	55^b		
9	23	108^a		

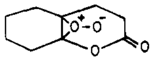
[a] Determined by monitoring the decay of $^1O_2$ phosphorescence following laser flash photolysis at various enol esters concentrations. [b] Determined by competitive photooxygenation.

methods were employed. In the first, the rate of decay of the infrared phosphorescence characteristics of $^1O_2$ was monitored at various enol ester concentrations.[9] This gives k_q, the rate constant for all $^1O_2$ quenching processes (physical and chemical). The second method gives specifically the rate constant for the chemical reaction (k_r) by comparing relative rates of disappearance of the $^1O_2$ substrates during competitive photooxygenation.[10] In all cases studied, k_q and k_r are approximately equal. That is, the enol esters are not efficient physical quenchers of $^1O_2$. The results of the kinetic determinations are collected in Table II. Of particular note is the rapid reaction of 9 in comparison with the other enol esters studied.

Discussion

As noted above, our previous investigation of the singlet oxygenation of enol esters provides evidence of the involvement of a common, polar intermediate in the ene, acyl-shift, and [2 + 2] cycloaddition reactions. A perepoxide intermediate provides the most straightforward explanation of the data. The present results support our earlier conclusions and permit a more detailed description of the reaction coordinate leading to the observed products.

The product distribution resulting from oxidation of enol lactone 9 is particularly interesting. Reaction occurs exclusively on the same side of the double bond as the ester functional group. A similar cis-directing effect has been observed previously for olefins like 3c and for enol ethers.[11] In the latter case, both perepoxide and zwitterionic intermediates have been invoked to explain this effect. Involvement of a perepoxide is supported by incorporating stablilization of the transition state leading to that intermediate by interaction of the lone pair electrons on the oxygen of the enol ether with the LUMO of $^1O_2$.[12] Arguments favoring a zwitterion intermediate incorporate anomeric[13] or steric[14] effects. In the case of enol lactone 9, involvement of perepoxide 14 provides the most economical explanation for the product distribution. It is difficult, for example, to account for formation of 10, the major product, in terms of an open zwitterion intermediate.



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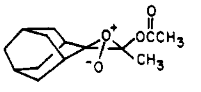

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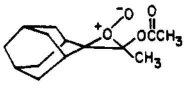

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In contrast to 9, no cis-directing effect is observed for enol acetate 4. In this case, the major product results from allylic hydrogen abstraction opposite to the ester group. A possible reason for this is that the perepoxide 15 is formed in preference to the other isomer 16. This explanation is suspect, however, since there is only a slight rate difference between 4 and 1 (Table II), despite product distribution that are considerably different. A second possibility is that trapping of perepoxide 16 by the acyl group occurs slowly compared with its inversion to 15. Although a zwitterion intermediate can be accomodated in this rationalization, the exclusive formation of 8 from enol acetate 7 seems inconsistent with the involvement of a zwitterion. To account for the exclusive formation of 8 via zwitterion intermediates would require the more stable isomer, which cannot directly yield 8, to be in rapid equilibrium with the other isomer and the product-forming step to 8 to be the solely accessible product-producing pathway. In the only other study of photooxygenation of enol esters, Pusset and co-workers[15] report only formation of two isomeric ene products in nearly equal amounts. This finding is also more consistent with a perepoxide than a zwitterion intermediate.

The rate constant for oxygenation of 9 is considerably greater than that for the other enol esters studied (Table II). Apparently, locking the ester group in a six-membered ring lowers the energy of the transition state leading to suspected perepoxide 14. This may be due to a more favorable orientation of the oxygen lone pair electrons for interaction with an incoming molecule of $^1O_2$ (vide supra). Alternatively, favorable orientation of the carbonyl group may allow stabilization of the developing negative charge in the nascent perepoxide.

The product distribution from photooxygenation of 9 is virtually independent of solvent. This is in contrast to the dramatic solvent effect observed previously in the photooxygenation of 1.[7] In the earlier case, we interpreted the results in terms of hydrogen-bonding interactions of the perepoxide with the solvent. In the present case, the favorable orientation of the carbonyl group may provide intramolecular stabilization of the perepoxide, making hydrogen bonding less effective. In contrast, enol ethers exhibit a pronounced solvent-polarity effect.[3b,16] Also,

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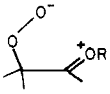
solvent-incorporation products are obtained from photooxidation of enol ethers in methanol.[4b,16] These types of products are not observed for the enol esters. This is reasonably due to the difference in the stability of potential zwitterion intermediates (17 and 18) resulting from these precursors. The zwitterion derived from the ether (17) is expected to be the more stable of the two because of the superior electron-donating ability of the ether functionality.[17]



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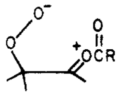

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Photooxygenation of enol ethers and enol esters also respond very differently to temperature. A large effect is observed in the product distribution of enol ethers.[16] We observe no temperature dependence for enol esters (e.g., see **9**, Table I). In this respect, enol esters behave very similarly to unsaturated hydrocarbons.[18] The observation that the product ratio is not a function of temperature implies that there are negligible differences in $\Delta H^{\ddagger}$ for formation of the various products. In other words, the magnitude of $\Delta S^{\ddagger}$ determines the product ratio. Negligible differences in $\Delta H^{\ddagger}$ seem reasonable for a high energy intermediate such as the perepoxide. The magnitude of $\Delta H^{\ddagger}$ for product formation is likely to be small in all cases. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ that we obtain for the rate-determining step (Table II) are similar to those reported for simpler ene reactions.[9b]

Conclusions

Reaction of $^1O_2$ with enol esters possessing abstractable allylic hydrogens generally proceeds by the ene pathway. If, however, the ester functionality is included in a six-membered ring, favorable orientation of the carbonyl group permits the acyl-shift reaction to compete effectively with allylic hydrogen abstraction. The involvement of the ester group of the enol lactone in the stabilization of the transition state of the rate-limiting step is implicated by the large rate enhancement observed. The reaction of $^1O_2$ with enol esters shows no Markovnikov directing effects and no formation of alcohol-incorporation products in methanol solution; product distribution is insensitive to solvent polarity or temperature change. These findings contrast with those reported for enol ethers, suggesting a difference in mechanism which is understood by assuming that a 1,4-zwitterion may be an energetically accessible intermediate for enol ethers but not enol esters. The involvement of a perepoxide intermediate in the reaction of $^1O_2$ with enol esters accounts for the results in a straightforward manner.

Experimental Section

General. THF and DME were distilled from sodium under a N_2 atmosphere, with benzophenone ketyl as indicator. Acetic anhydride was fractionally distilled with the first 10% of the distillate being discarded. All other commercially available reagents were used without further purification.

Photooxygenations were performed using either a 250-W, 24-V Sylvania tungsten–halogen projector lamp or a 400-W General Electric Lucalox sodium lamp. The output of the lamp was filtered with a Corning 3-70 filter to remove light below 490 nm. NMR tubes (5 and 10 mm) were used as the photooxygenation vessels. The tubes were irradiated within a windowed Dewar maintained at the indicated temperature. Oxygen was passed through a drying tube containing anhydrous $CaSO_4$ and molecular sieves, bubbled through the solution being photooxygenated via a Teflon needle, and passed out or a bubbler filled with mineral oil. The outside of the upper portion of the NMR tubes was cooled with dry ice during photooxygenation to prevent solvent evaporation.

GC analyses were carried out on a Varian 3700 gas chromatograph equipped with a linear temperature programmer and a flame ionization detector. A Hewlett-Packard 5900 integrator was used for quantitative analyses. A 6 ft × 0.125 in. glass column containing 5% SE-30 on Gas Chrom Q (100–120 mesh) was used for all GC analyses.

The method for determining k_r by monitoring the decay of $^1O_2$ phosphorescence has been described previously.[9b]

1-Adamantylideneethyl Acetate (4). To a 50-mL round-bottom flask were added 2.17 g (12.2 mmol) of 2-adamantyl methyl ketone,[19] 0.25 g of *p*-toluenesulfonic acid, and 10 mL of acetic anhydride. The flask was fitted with a magnetic stir bar and a distillation head, and the contents were heated at partial reflux so that 5 mL of distillate was collected over a 30-min period. An additional 10 mL of acetic anhydride was added, and the mixture was again heated so that 10 mL of distillate was collected over a 45-min period. Addition and collection of another 10-mL portion of acetic anhydride were performed over another 45-min period. The resulting mixture was poured into a flask containing 50 mL of ether and 50 mL of saturated $NaHCO_3$ solution. Solid sodium bicarbonate was added cautiously, with stirring, until a saturated solution was maintained. The resulting mixture was stirred for 30 min and decanted into a separatory funnel, and the layers were separated. The ether layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residual oil was distilled [104 °C (1 mm)] to yield 2.23 g (83%) of **4** as a cololess oil. The distillate was crystallized from $MeOH/H_2O$: mp 34–35 °C; ^1H NMR (CS_2) δ 1.63–1.99 (m, 12 H), 1.73 (s, 3 H), 1.97 (s, 3 H), 2.57 (br , 2 H); IR ($CHCl_3$) 1730, 1740 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.17. Found: C, 75.98; H, 9.38.

6,6-Dimethylcyclohex-1-enyl Acetate (7). To a flame-dried 100-mL three-neck round-bottom flask fitted with an additional funnel and magnetic stir bar was added, under a N_2 atmosphere, 3.44 g (30 mmol, 35 wt % dispersion, in mineral oil) of potassium hydride. The mineral oil was removed by washing with three 10-mL portions of pentane.[20] The residual pentane was removed under vacuum. To the resulting KH powder was added 5 mL of dry DME. A solution of 2.52 g (20 mmol) of 2,2-dimethylcyclohexanone[21] in 50 mL of DME was added dropwise to the stirring KH suspension over a 10-min period and then stirred for an additional 20 min. The resulting enolate solution was transferred via cannula under N_2 to an addition funnel which was fitted to a 250-mL three-neck round-bottom flask containing 12.6 mL (150 mmol) of acetic anhydride. The enolate solution was added dropwise to the stirring acetic anhydride over a 20-min period, yielding a very viscous, cream-colored mixture. This mixture was poured into a flask containing 200 mL of ether and 200 mL of saturated $NaHCO_3$. Solid $NaHCO_3$ was added until a saturated solution was maintained, and the mixture was stirred for 15 min. The mixture was decanted into a separatory funnel, and the layers were separated. The aqueous layer was washed with two 50-mL portions of ether. The ether solutions were combined, washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residual liquid was distilled [61–63 °C (1.7 mm)], yielding 2.49 g of the crude product. The crude product was fractionally distilled, using a Teflon spinning-band column, to yield 1.55 g of enol acetate **7** [88 °C (17 mm)]: ^1H NMR (CS_2) δ 0.96 (s, 6 H) 1.55–1.74 (m,

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4 H), 2.00 (s, 3 H), 1.98–2.09 (m, 2 H), 5.07 (t, 1 H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.60. Found: C, 71.27; H, 9.70.

$\Delta^{1,6}$-2-Oxabicyclo[4.4.0]decen-3-one (9).[22] A 3.00 g (17.6 mmol) quantity of 2-oxocyclohexanepropanoic acid was dissolved in 150 mL of acetic anhydride. The resulting soltuion was heated at reflux, under a N_2 atmosphere, for 5 h. A 0.17-g (0.89 mmol) quantity of TsOH monohydrate was added, and the mixture was heated at reflux for an additional 1-h period. After cooling to room temperature, the acetic anhydride was removed by distillation at aspirator pressure. The resulting residue was taken up in 300 mL of ether. This ether solution was washed with two 100-mL portions of 5% $NaHCO_3$ followed by 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated under vacuum, to yield 2.54 g of crude **9** as a dark oil. Pure **9** was obtained by flash chromatography[23] (silica gel, 20% EtAc/hexane), followed by Kugelrohr distillation [115 °C (0.7 mm)], as a colorless oil (1.90 g, 71%): ^1H NMR ($CDCl_3$) δ 1.55–1.85 (m, 4 H), 1.98–2.34 (m, 6 H), 2.62 (t, 2 H); IR (neat) 1713, 1765, cm^{-1}. Anal. Calcd for $C_9H_{12}O_2$: C, 71.01; H, 7.96. Found: C, 70.81, H, 8.06.

Keto Diacid 13. To a 25-mL three-neck round-bottom flask equipped with a gas dispersion tube, Teflon stopcock-protected septum inlet, and magnetic stir bar were added 159 mg (1.05 mmol) of enol lactone **9** and 7 mL of methanol. The flask was cooled to −78 °C, and ozone was bubbled through the solution. The addition of ozone was continued for 5 min after the solution became blue. The solution was then purged with N_2 for 5 min, and 0.20 mL (2.7 mmol) of dimethyl sulfide was added. The solution was stirred for 5 min and then allowed to warm to room temperature. After stirring at room temperature for 3 h, the solution was concentrated under vacuum. The residual oil was combined with 15 mL of 2 N NaOH and the resulting solution heated at reflux for 4 h. After cooling to room temperature, the solution was diluted with 25 mL of water and washed with two 20-mL portions of ether. The resulting aqueous layer was acidified to pH 1 with 6 N HCl and extracted with five 30-mL portions of ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 51 mg of crude **13** as a light tan solid. This material was recrystallized ($CHCl_3$): mp 106–107 °C (lit.[24] mp 108.5–109.5 °C); ^1H NMR (acetone-d_6) δ 1.60 (quintet, 4 H), 2.30 (t, 2 H), 2.46–2.61 (m, 4 H), 2.72 (t, 2 H).

Photooxygenation of 4—Isolation of Ene Product 5. A 0.22-g (1.0 mmol) quantity of **4** was combined with 2 mL of a saturated solution of methylene blue in acetone-d_6 and photooxygenated, with the tungsten–halogen lamp, for 1 h. The resulting mixture was dissolved in 15 mL of ether. The ether solution was washed with two 5-mL portions of water and one of brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 0.22 g of crude **5** as a yellow oil. Hexane (0.50 mL) was added to the oil, and the resulting solution was cooled to −15 °C to crystallize **5** as slightly yellow crystals: mp 89–92 °C; ^1H NMR (CS_2) δ 1.48–1.88 (m, 12 H), 2.14 (s, 3 H), 2.16 (br s, 2 H), 5.05 (d, 1 H), 5.16 (d, 1 H), 8.65 (s, 1 H); IR (CS_2) 3370, 1740 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 8.01. Found: C, 67.05; H, 8.02.

Photooxygenation of 7. To a 5-mm NMR tube were added 14.2 mg (0.0845 mmol) of enol acetate **7**, 0.60 mL of acetone-d_6 saturated with methylene blue, and 0.050 mL (4.83 μmol, 0.0966 M, in $CDCl_3$) of a solution of *p*-dichlorobenzene (as an internal standard). The enol acetate was photooxygenated, with the sodium lamp, at −78 °C for 10 h. The resulting solution was peroxidic, as indicated by a positive starch–iodide test. The solution was analyzed by ^1H NMR spectroscopy: enol acetate **7** (64% recovered); enone **8**[25] [δ 1.06 (s, 6 H), 1.83 (t, 2 H), 2.35–2.47 (m, 2 H), 5.80 (d of t, 1 H), 6.96 (d of t, 1 H)], 44% (based on starting material), 108% (based on recovered starting material); acetic acid [δ 1.96] (by addition of authentic acetic acid).

Photooxygenation of 9—Isolation of Ene Product 10. A 141-mg (0.928 mmol) quantity of enol lactone **9** was combined with a 5×10^{-4} M solution of TPP in CS_2 and photooxygenated for 1 h at −78 °C, with the sodium lamp. During this time crude **10** precipitated as a green solid. The resulting mixture was filtered rapidly, and the collected solid was washed with two 2-mL portions of CS_2 which had been cooled to −78 °C. This process yielded 81 mg of crude **10**. Repeated recrystallization (CH_2Cl_2/CS_2) yielded **10** as light green crystals (the green is due to a TPP byproduct, white **10** was obtained by chromatography): mp 92–93 °C; ^1H NMR (CD_3OD) δ 1.23–1.92 (m, 4 H), 2.16–2.50 (m, 4 H), 3.10 (d of d, 2 H, J_1 = 3.49 Hz, J_2 = 2.83 Hz[26]), 5.71 (d of t, 1 H, J_1 = 3.49 Hz, J_3 = 1.91 Hz); ^{13}C NMR ($CDCl_3$) δ 22.3, 25.9, 30.1, 31.3, 35.3, 108.5, 118.5, 132.7, 170.7; IR ($CDCl_3$) 1734 cm^{-1}. Anal. Calcd for $C_9H_{12}O_4$: C, 58.68; H, 6.58. Found: C, 58.55; H, 6.59. Peroxide titer 99% of theory.

Photooxygenation of 9—Isolation of Peroxy Lactone 11. A 537-mg (3.53 mmol) quantity of enol lactone **9** was combined with 3 mL of acetone-d_6 which had been saturated with methylene blue and was photooxygenated, with the sodium lamp, at −78 °C for 3 h. The resulting solution was combined with 417 μL (3.53 mmol) of trimethyl phosphite at −78 °C under a N_2 atmosphere. This mixture was stirred for 15 min and warmed to room temperature. The resulting solution was dissolved in 100 mL of ether and washed with two 30-mL portions of 5% $NaHCO_3$. The ether solution was washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 155 mg of an oily residue. This material was chromatographed (Chromatotron, 1-mm silica gel plate, 33% EtAc/hexane) and recrystallized (EtAc/hexane) to yield 96 mg of **11** as white crystals: mp 65.5–66.5 °C; ^{13}C NMR ($CDCl_3$) δ 22.6, 23.6, 27.3, 36.1, 36.6, 37.9, 108.4, 173.0, 174.7; IR ($CDCl_3$) 1744, 1803 cm^{-1}. Anal. Calcd for $C_9H_{12}O_4$: C, 58.6,; H, 6.58. Found: C, 58.84; H, 6.59. Peroxide titer 91% of theory (**11** reacts with NaI very slowly, 24 h was required).

Photooxygen of 9—Isolation of Keto Diacid 13. A 105-mg (0.691 mmol) quantity of enol lactone **9** was combined with a solution of methylene blue (ca. 10^{-4} M) in MeOH and photooxygenated, with the sodium lamp, at −78 °C for 2 h. The photooxygenation mixture was dissolved in 30 mL of ether, and the resulting ether solution was extracted with two 10-mL portions of 5% $NaHCO_3$. The combined $NaHCO_3$ extracts were acidified with 6 N HCl and extracted with three 10-mL portions of ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residual oil was chromatographed (Chromatotron, 1-mm silica gel plate, 1% AcOH in EtAc/hexane (3:1) to yield 20 mg of a monoester of **13**. This material was dissolved in 1 mL of 2 N NaOH and this solution heated at 110 °C for 1 h. After cooling to room temperature, the solution was acidified with 6 N HCl and extracted with three 15-mL portions of ether. The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 9 mg of an off-white solid. This material has identical spectral properties with those of authentic keto diacid **13**.

Determination of Photooxygenation Product Yields. Unless otherwise indicated, yield determination were performed on 0.50-mL portions of enol ester solutions (ca. 0.2 M) photooxygenated for 30 min, with the sodium lamp.

Yields of acyl-shift product **11** were determined by GC (injector = 180 °C; oven = 3 min at 130 °C and then 10 °C/min to 200 °C; He = 30 mL/min), using tridecane and hexadecane as internal standards. For a given photooxygenation solvent and temperature, at least three independent determinations were made; the reproducibility among independent runs was ±5%.

The yields of ene products **5** and **10** were determined by NMR, by comparison of the integrals of the vinyl hydrogen resonances with those of the internal standard, *p*-dichlorobenzene. Enol acetate **4** was photooxygenated for 1 h, using the tungsten–halogen lamp for determination of the yield of **5**. For **10**, at least three

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[22] This procedure is a modification of one previously reported: Martin, J.; Parker, W.; Shroot, B.; Stewart, T. *J. Am. Chem.* **1967**, 101. Our method provides for in situ isomerization of the exocyclic double bond isomer to **9**.

[23] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[24] Korchak, V. V.; Sosin, S. L.; Morozova, E. M. *J. Gen. Chem. USSR* (*Engl. Transl.*) **1960**, *30*, 922.

[25] By comparison to authentic **8**, which was prepared from 2,2-dimethylcyclohexanone in two steps: (a) Ramirez, F.; Kirby, A. F. *J. Am. Chem. Soc.* **1952**, *74*, 4331. (b) Holysz, R. P. *Ibid.* **1953**, *75*, 4432. In accordance with the DMF/LiCl procedure, 20 h at reflux was required to dehydrohalogenate 2-bromo-6,6-dimethylcyclohexanone.

[26] J_2 apparently represents long-range coupling between the two α-hydrogens and one of the other allylic hydrogens. For a similar example, see: Appel, H. H.; Bond, R. P. M.; Overton, K. H. *Tetrahedron* **1963**, *19*, 635.

independent determinations were made for a given photooxygenation temperature and solvent; the reproducibility among independent runs was ±3%. For photooxygenation of **9** in CS_2 solution, the mixture was combined with 0.50 mL of acetone-d_6 before analysis to dissolve the precipitated **10**.

The yield of the [2 + 2] cycloaddition product **12** was determined by NMR spectroscopy from the integral of the methoxy resonance (δ 3.61) of the mono methyl ester of **13**, with *p*-dichlorobenzene as the internal standard. For photooxygenation in MeOH, the reaction mixture was kept at room temperature for 2 h, the resulting solution was concentrated under vacuum, and the residue was dissolved in acetone-d_6 for analysis. For photooxygenation in CS_2, the reaction mixture was dissolved in 0.50 mL of ether and then added to 3 mL of MeOH, after which, the above procedure for photooxygenation in MeOH was followed. For photooxygenation in acetone-d_6 at −78 °C, the reaction mixture was immediately poured into 5 mL of MeOH and the above analysis procedure performed. For photooxygenation at 0 °C in acetone-d_6, the enol lactone was photooxygenated for 5 min and then immediately poured into 5 mL of MeOH, after which the analysis procedure was performed.

Determination of k_r by Competitive Photooxygenation. The relative rate constants (k_A/k_B) of two ${}^1O_2$ substrates (A and B), when photooxygenated competitively, were determined by using the relationship $k_A/k_B = \ln([A]_0/[A]_t)/\ln([B]_0/[B]_t)$.[10] Enol acetate **1** was photooxygenated in competition with 2-methyl-2-pentene (2M2P). The relative rate of disappearance of **1** and 2M2P was determined by integration of the vinyl hydrogens in the NMR spectrum of these compounds with *p*-dichlorobenzene as an internal standard. The value of k_r for **1** was calculated by using the value of k_r for 2M2P reported by Manring and Foote.[10a] The value of k_r for **7** was determined in the same manner by competition with **1**.

The value of k_r for **9** was determined by its competitive photooxygenation with 2M2P. After photooxygenation, the mixture was reduced with an excess of Ph_3P and analyzed by GC (injector = 220 °C; oven = 3 min at 40 °C and then 15 °C/min to 200 °C; He = 30 mL/min), using tridecane as an internal standard. In this way, the disappearance of **9** and the appearance of the two photooxygenation products of 2M2P (P_1 and P_2) were followed. Using the relationship $\ln([2M2P]_0/[2M2P]_t) = \ln\{[P_1 + P_2]_f/([P_1 + P_2]_f - [P_1 + P_2]_t)\}$ (where $[P_1 + P_2]_f$ = concentration of the sum of the products after complete conversion of 2M2P), the relative rate constants were determined by plotting $\ln\{[P_1 + P_2]_f/([P_1 + P_2]_f - [P_1 + P_2]_t)\}$ vs. $\ln([\mathbf{9}]_0/[\mathbf{9}]_t)$. The response factors of P_1 and P_2 were determined by taking 2M2P to complete conversion and using the values reported by Manring and Foote for P_2/P_1.[10a] The value of k_r for **9** was then calculated from the reported value of k_r or 2M2P.[10a]

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Registry No. **4**, 101470-98-8; **5**, 101470-99-9; **7**, 91056-64-3; **8**, 6553-64-6; **9**, 700-82-3; **10**, 101471-00-5; **11**, 101471-01-6; **13**, 71759-57-4; **13** (monomethyl ester), 101403-81-0; 2-adamantyl methyl ketone, 22635-58-1; 2,2-dimethylcyclohexanone, 1193-47-1; 2-oxocyclohexanepropanoic acid, 2275-26-5.

Kinetics of the Oxidation of Isoquinolinium Cations by Ferricyanide Ion

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The rates of the ferricyanide oxidation of a number of isoquinolinium cations have been investigated in the range pH 11–14 in 20% CH_3CN–80% H_2O at 25 °C (ionic strength 1.0). The oxidation of the 2-methylisoquinolinium cation is kinetically first order in each of ferricyanide ion and isoquinolinium cation but is subject to pronounced inhibition by the ferrocyanide ion reaction product. Second-order rate constants evaluated from initial reaction rates display a pH dependence which is consistent with rate-determining ferricyanide attack on the pseudobase alkoxide ion derived from the isoquinolinium cation. Ferrocyanide ion inhibition is shown to be consistent with this initial electron transfer being a reversible process. Similar observations are made for a number of substituted isoquinolinium cations. Substituent effects are shown to be consistent with electron abstraction from the endocyclic nitrogen atom rather than the exocyclic oxyanion of these pseudobase alkoxide ions. The initially formed radical then undergoes a base-catalyzed deprotonation from C-1, and this is confirmed by deuterium kinetic isotope effects when a deuterium label is present at C-1. The combination of these pH effects leads to ferrocyanide ion inhibition becoming less pronounced with increasing pH. These observations have prompted us to reinvestigate the ferricyanide ion oxidation of some of the 5-nitroisoquinolinium cations that we have previously studied.[1] We find that ferrocyanide ion inhibition is observable when the initial rates of these reactions are examined in the stopped-flow spectrophotometer. Detailed kinetic analysis of these oxidations is shown to be consistent with the reaction scheme detailed above for the 2-methylisoquinolinium cation. In the light of this work, we must now withdraw our earlier claim for rate-determining hydride abstraction in these reactions. Substituent effects on the oxidation of these isoquinolinium cations allow the development of a relationship which can be used to predict the pH–rate profile for the ferricyanide ion oxidation of any isoquinolinium cation for which pK_{R^+} for pseudobase formation is available, provided that steric hindrance from the N substituent is not significant.

There have been recent reports from our laboratory on the kinetics of oxidation of 5-nitroisoquinolinium[1] and acridinium[2] cations by ferricyanide ion in aqueous base. Both of these reactions were characterized by rate laws which appeared cleanly first order in each of ferricyanide ion and heterocyclic cation. Unlike many other ferricyanide ion oxidations,[3–5] these reactions gave no indication

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