Notes

The Effect of Solvent Polarity on the Product Distribution in the Reaction of Singlet Oxygen with Enolic Tautomers of 1-(2′,4′,6′-Trialkylphenyl)-2-methyl 1,3-Diketones

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The reaction of singlet oxygen with olefins has been extensively studied and a number of comprehensive reviews have been published.[1] The olefins with allylic hydrogen atoms undergo ene-type reactions to form allylic hydrogenperoxides. In the ene reaction with substituted olefins, hydrogen abstraction by singlet oxygen takes place preferentially at the more highly substituted side of the double bond (*cis effect*).[2] For cis olefins with a bulky alkyl group, a preference for hydrogen abstraction on the larger alkyl group has been observed.[3] The weakly electrophilic singlet oxygen readily reacts with highly substituted olefins. By contrast, the reactions with electron-deficient systems such as α,β-unsaturated carbonyl compounds are often slow but show a marked regioselectivity.[4] In these systems, hydrogen abstraction takes place selectively on an alkyl group geminal to the electron-withdrawing group. However, the reaction of singlet oxygen with enolic tautomers of 1,3-dicarbonyl compounds, β-hydroxy-α,β-unsaturated carbonyl compounds, has received little attention. The reaction of singlet oxygen with enolic tautomers of 1,3-diketones in the presence of fluoride ion, which enhances the nucleophilicity of enols, gives ketonic products resulting from α-hydroperoxide formation.[5] The enolic tautomers **1** of acyl- and alkoxycarbonylbenzocycloalkenones react with singlet oxygen to give 2-hydroperoxy 1,3-dicarbonyl compounds **2** (Scheme 1).[6] These reactions proceed by the abstraction of hydrogen from the enolic hydroxy group. We report here the effect of solvent polarity on the singlet oxygenation of enolized 1-aryl-2-methyl 1,3-diketones that the abstraction of hydrogen from the enolic hydroxy group decreases substantially with the increase of abstraction from the 2-methyl group as the solvent polarity decreases.

Results and Discussion

We have recently reported that the reaction of singlet oxygen with enolized 1,3-diketones **3a**−**d** using Methylene Blue (MB) as the sensitizer at room temperature in acetonitrile gave the enedione **4a**−**d**, the epoxy ketone **5a**−**d**, and the hydroperoxy ketone **6a**−**d**. In the photooxygenation of **3b**−**d** in methanol under the same conditions, the initially formed enedione **4b**−**d** reacted with methanol to give the corresponding Michael adducts **7** (Scheme 2).[7] In that paper, we proposed that the enedione **4** and the epoxy ketone **5** would arise from the initially formed hydroxyperoxide **8** (Scheme 3). The hydroxyperoxide **8** decomposes to afford **4** with loss of hydrogen peroxide. The hydrogen peroxide thus generated would react with **4** to yield **5**. In the present study, we tried to detect the proposed intermediate **8** by low-temperature experiments. After a carbon tetrachloride solution of **3c** had been photooxygenated below −20 °C until the starting material was completely consumed, the solvent was removed under vacuo below −20 °C. The NMR analysis of the mixture revealed that the reaction proceeded cleanly to give a single product that could be stored below −20 °C but transformed quantitatively into **4c** on standing at room temperature for several hours. The ^{1}H NMR spectrum of the initially formed product at −20 °C showed two singlets at δ 6.22 and 6.59 due to olefinic protons. These peaks gradually disappeared with the gradual appearance of two singlets assignable to olefinic protons of **4c** at δ 5.89 and 6.36 on standing at room temperature. The ^{13}C NMR spectrum of the initially formed product showed a carbonyl carbon peak at δ 207.3. However, the ^{1}H NMR spectrum could not fully explain the structure of **8c** for the initially formed product. The methine proton of isopropyl group appeared at δ 2.1−2.2, fairly high field compared to that of the isopropyl ketone. The ^{1}H NMR spectra of **4c**, **5c**, and **6c** showed the methine proton of the isopropyl ketone group at δ 3.26, 3.02, and 4.38, respectively.[7] On the basis of the NMR data together with chemical behavior, the structure of the initially formed product may be assigned as **9c**.

Although the hydroxyperoxide **9c** was transformed quantitatively into the enedione **4c**, the epoxy ketone **5c** could not be detected on standing the CDCl₃ solution in an NMR tube at room temperature for a long time.

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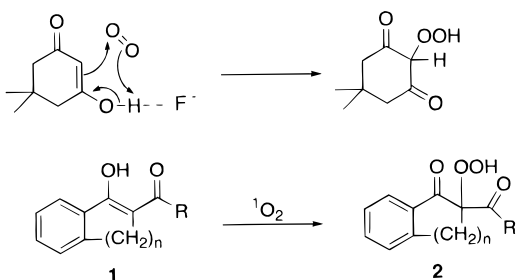
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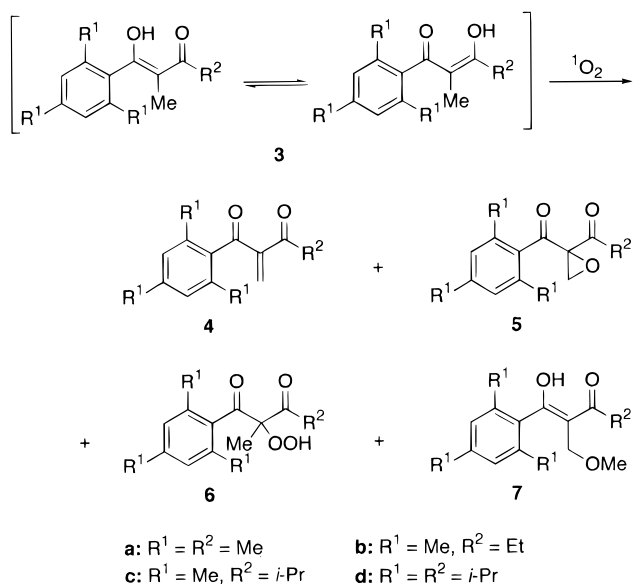(5) Wasserman, H. H.; Pickett, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 4695.

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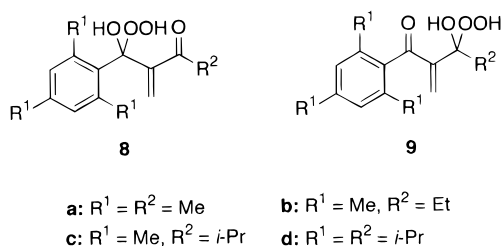
Scheme 1

Scheme 2

a: $R^1 = R^2 = $ Me b: $R^1 = $ Me, $R^2 = $ Et
c: $R^1 = $ Me, $R^2 = i$-Pr d: $R^1 = R^2 = i$-Pr

Scheme 3

a: $R^1 = R^2 = $ Me b: $R^1 = $ Me, $R^2 = $ Et
c: $R^1 = $ Me, $R^2 = i$-Pr d: $R^1 = R^2 = i$-Pr

However, when the hydroxyperoxide **9c** was treated with silica gel immediately after irradiation at low temperature, it was quantitatively transformed into the epoxy ketone **5c**. In this case, no enedione **4c** was detected. On the contrary, the same treatment of the CDCl₃ solution after the hydroxyperoxide **9c** had been completely converted into the enedione **4c** with loss of hydrogen peroxide with silica gel resulted in partial transformation of **4c** to **5c**. These results suggest that the epoxy ketone **5c** was produced from the hydroxyperoxide **9c** by both intramolecular epoxidation and intermolecular process between the enedione **4c** and generated hydrogen peroxide, though the role of silica gel was not at all clear.

To examine the solvent effect of the reaction, we studied the photooxygenation of **3a**–**d** in three other solvents, namely carbon tetrachloride, benzene, and acetone. The product ratios were dependent on solvent polarity. Photooxygenation of **3** in carbon tetrachloride using tetraphenylporphine (TPP) as the sensitizer at room temperature gave **4** and **5**. The hydroperoxy ketone **6** could not be detected. However, the photooxygenation

Table 1. Regioselectivity in the Reaction of Singlet Oxygen with 3[a]

| sub-strate	solvent	sensitizer	distribution[b]				regioselectivity[c]	
			4	5	6	7	(4 + 5 + 7)	6
3a	CCl₄	TPP	31	69			100	
3a	benzene	TPP	17	79	4		96	4
3a	acetone	TPP	3	84	12		88	12
3a	MeCN	MB	44	26	30		70	30
3b	CCl₄	TPP	75	25			100	
3b	benzene	TPP	26	65	9		91	9
3b	acetone	TPP	14	56	30		70	30
3b	MeCN	MB	45	14	41		59	41
3b	MeOH	MB		6	25	40	65	35
3c	CCl₄	TPP	75	25			100	
3c	benzene	TPP	42	43	15		85	15
3c	acetone	TPP	47	32	21		79	21
3c	MeCN	MB	49	9	42		58	42
3c	MeOH	MB		7	27	47	67	33
3d	CCl₄	TPP	100				100	
3d	benzene	TPP	80		20		80	20
3d	acetone	TPP	77		23		77	23
3d	MeCN	MB	60		40		60	40
3d	MeOH	MB			37	52	58	42

[a] A solution of **3** (150 mg) in a solvent (100 mL) in the presence of sensitizer (ca. 10 mg) was irradiated with a 100 W tungsten–halogen lamp through a K₂CrO₄ filter solution until the starting material was totally consumed. [b] Determined by ¹H NMR on the fractions after chromatography of the mixture, integrating olefinic hydrogens of **4**, epoxymethylene hydrogens of **5**, and a hydroperoxy hydrogen of **6**. In the photooxygenation in metanol, the isolated yields were given. [c] Compounds **4**, **5**, and **7** are products arising by hydrogen shift from the methyl group and the compound **6** is that arising by hydrogen shift from the hydroxy group.

of **3** in polar solvents gave the hydroperoxy ketone **6** in substantial amounts together with **4** and **5**. The proportion of **6** increased with decreasing proportion of the sum yield of the enedione **4** and the epoxy ketone **5** as the solvent polarity increased. These products were fully characterized as described previously.[7] The ¹H NMR spectrum of **4** showed two singlets at δ 5.8–5.9 and 6.4–6.6 due to two olefinic protons and that of **5** showed methylene protons of the epoxy ring at δ 2.9–3.2. The hydroperoxy group of **6** appeared at δ 8.9–9.9. The product ratios of the photooxygenation of **3**, which were determined by ¹H NMR spectroscopy on the fractions after chromatography of the mixture, are given in Table 1. The ratios of **4/5** were dependent on the experimental conditions. The proportion of **4** increased with decreasing proportion of **5** when the mixture was passed through a silica gel column after standing at room temperature for several hours because the initially formed hydroxyperoxide **9** was gradually transformed into **4** on standing at room temperature but converted into **5** on treatment with silica gel.

Perepoxide is a possible intermediate of the singlet oxygenation reaction.[8] In our study, four perepoxides **A**, **B**, **C**, and **D** are possible because the starting **3** exists in solution in two cis-enolic forms owing to intramolecular hydrogen bonding[7,9] (Scheme 4). The two enolic forms are in rapid dynamic equilibrium. The perepoxide **C** in which the terminal oxygen atom orients toward the methyl side would be expected to be transformed into the hydroxy-

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Scheme 4

Scheme 5
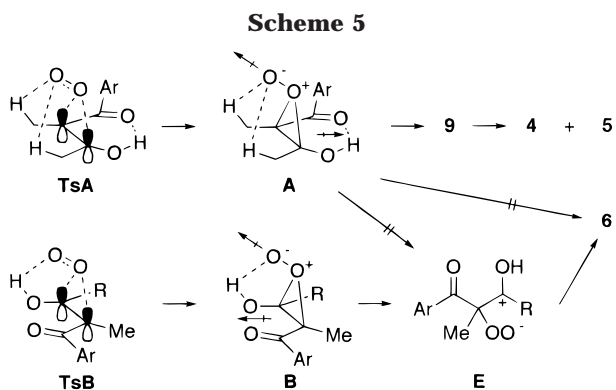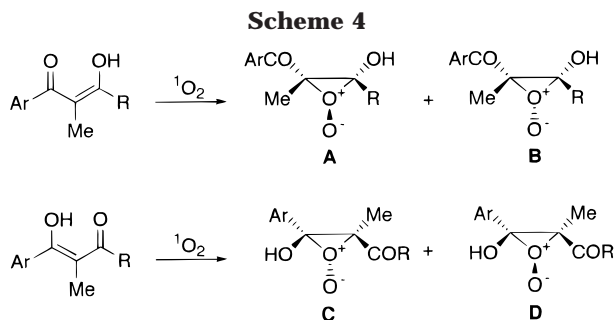
peroxide **8** by a hydrogen shift from the methyl group to the negative oxygen. Similarly, the perepoxide **A** would be transformed into the hydroxyperoxide **9**. However, since the structure of the initially formed hydroxyperoxide was assigned as **9** and not **8**, the perepoxide **C** could be excluded from the possible intermediate. Therefore, the perepoxide **D** may not intervene. The photochemical reaction of benzoylacetone with olefins forms [2 + 2] adducts that are derived largely from the enolic form in which the oxygen adjacent to the phenyl ring is in the enol form.[10] On the contrary, the reaction of singlet oxygen with **3** exclusively took place on the enolic form in which the oxygen adjacent to the aromatic ring is in the keto form. Since the C_1–C_2 site of **3** is sterically more congested than the C_2–C_3 site owing to the bulky 2,4,6-trialkylphenyl group on C_1, the favored attack of singlet oxygen would take place on the C_2–C_3 site. Although the enedione **4** and the epoxy ketone **5** are produced from the perepoxide **A** through the hydroxyperoxide **9**, the perepoxide **A** may be also converted into the hydroperoxy ketone **6** by the hydrogen shift from the alkyl group on the carbon bearing the hydroxyl group or by open of the ring to a cation **E** followed by proton shift (Scheme 5). However, in the photooxygenation in carbon tetrachloride, no hydroperoxy ketones **6** were detected. The geminal selectivity observed in α,β-unsaturated carbonyl system also operates in our system. The perepoxide **B** would be transformed into the hydroperoxy ketone **6** probably via the cation **E**. The enol ethers undergo ene-type reaction with singlet oxygen via the perepoxide intermediate, which opens the ring to the cation stabilized by the presence of ether functionality.[11]

The observed solvent effect on the selectivity of the reaction of singlet oxygen with **3** can be rationalized by

examining the transition states of this reaction. In the transition state **TsA**, the precursor to the perepoxide **A**, the oxygen is placed anti to the hydroxy and carbonyl groups, and the net dipole moment is expected to be smaller than that in the transition state **TsB**, the precursor to the perepoxide **B**, where the oxygen has a syn orientation with respect to the hydroxy and carbonyl groups (Scheme 5). Therefore, the more polar transition state **TsB** is expected to be stabilized better by polar solvents than the less polar transition state **TsA**.[12] The solvent dependence of side selectivity of the ene reaction of singlet oxygen with α,β-unsaturated esters is explained in terms of the stability of perepoxide-like transition states.[12] In the transition state **TsA**, singlet oxygen interacts with both allylic hydrogen atoms on C_2 and C_3. The effective interaction between the hydroxyl group and the partially negatively charged singlet oxygen in the transition state **TsB** requires the coordination of the hydroxyl group with the incoming singlet oxygen.[13] In nonpolar solvents, the intramolecular hydrogen bonding between the hydroxy and carbonyl groups prevents such coordination. In polar solvents, the intramolecular hydrogen bonding must compete with intermolecular hydrogen bonding with the solvent. Consequently, the hydroxyl group can interact with the incoming oxygen by hydrogen bonding through a favorable five-membered ring.[14] Thus, **TsB** is stabilized in polar solvents than in nonpolar solvents, reflecting the increased proportion of the hydroperoxy ketone **6**.

Experimental Section

General Procedure for the Photooxygenation of 3. A solution of the particular substrate (150−500 mg) and ca. 10 mg of tetraphenylporphine or Methylene Blue in 100 mL of a variety of solvents was irradiated with a 100 W tungsten−halogen lamp through an aqueous solution of K_2CrO_4 (0.27 g L^{-1}) and Na_2CO_3 (1 g L^{-1}) at room temperature while a stream of air was passed continuously through the reaction mixture. The course of the reaction was monitored by means of TLC; after all starting material had been consumed, the solvent was evaporated and the residue was fractionated by silica gel column eluting with a mixture of hexane and ethyl acetate (6:1 to 10:1). The composition of each fraction was determined by ^{1}H NMR (see Table 1 for product ratios). Further purification by column chromatography afforded pure samples of enediones **4**, epoxy ketones **5**, and hydroperoxy ketones **6**. The physical properties of these products have been already reported.[7]

Low-Temperature Photooxygenation of 3c. A solution of **3c** (34 mg) and a catalytic amount of tetraphenylporphine in 100 mL of CCl_4 was irradiated below −10 °C by the same manner as described above. After **3c** had been consumed, the solvent was removed under reduced pressure at −20 °C to give the hydroxyperoxide **9c**: ^{1}H NMR (400 MHz, −20 °C) δ 0.99 (3H, d, J = 7 Hz), 1.06 (3H, d, J = 7 Hz), 2.1−2.2 (1H, m), 2.19 (6H, s), 2.32 (3H, s), 6.22 (1H, s), 6.59 (1H, s), 6.88 (2H, s), 8.07 (1H, s), and 10.31 (1H, s); ^{13}C NMR (100 MHz, −20 °C) δ 15.5

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(q), 17.4 (q), 19.3 (q), 21.2 (q), 36.9 (d), 107.4 (s), 128.0 (d), 128.2 (d), 133.2 (s), 134.3 (s), 135.4 (s), 138.0 (t), 138.8 (s), 144.2 (s), and 207.3 (s).

Chemical Properties of the Hydroxyperoxide 9c. The hydroxyperoxide **9c** was poured onto silica gel in a 5:1 mixture of hexane and ethyl acetate, and the mixture was stirred at room temperature for 4 h. The solvent was evaporated after removal of silica gel by filtration. The ¹H NMR analysis revealed the quantitative transformation of **9c** into the epoxy ketone **5c**. The hydroxyperoxide **9c** was dissolved in CDCl₃ in an NMR tube, and the tube was left standing at room-temperature overnight. The ¹H NMR analysis revealed the quantitative transformation of **9c** into the enedione **4c**. This solution was poured onto silica gel in hexane, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated after removal of silica gel. The ¹H NMR spectrum showed that the residue was composed of a 2:3 mixture of the enedione **4c** and the epoxy ketone **5c**.

Supporting Information Available: ¹H NMR and ¹³C NMR spectra of **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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