

on KP of the medium of oxidation in a predictable way. We anticipate that products of lipid undergoing autoxidation in a more typical biological environment (membranes, lipid storage pools) will also depend on KP of that environment. Our observations may thus provide a format for further developments in the study of the autoxidation of biologically important compounds.

Experimental Section

High-Pressure Liquid Chromatography. A Whatman 5- μ Partisil analytical silica column was used for analysis of oxidation mixtures. The solvent used was hexane/2-propanol/acetic acid 990:10:1. Arachidonic oxidations could be analyzed before or after reduction of hydroperoxides to hydroxy fatty acids. Similar results were obtained by analysis of the hydroperoxy or hydroxy fatty acids. Further, analysis of hydroperoxy or hydroxy fatty acid methyl esters gave qualitatively the same results as analysis of the free acids. Relative amounts of linoleate products were corrected for their known molar absorptivity, and the arachidonate HPETE products were assumed to have identical ϵ values. This assumption was checked by oxidation of radio-labeled arachidonic acid and isolation of various HPETE products by preparative HPLC. Radioactivity and absorbance of collected fractions were measured and molar absorptivities calculated. The value of ϵ obtained in this way for various HPETE isomers (27000) compares favorably with value obtained for synthetic HPETE's obtained by alternate routes. Comment should be made about *trans,trans*-arachidonic hydroperoxides. 8-*trans,trans*-HPETE, 15-*trans,trans*-HPETE, and 11-*trans,trans*-HPETE have been prepared by alternate routes and were analyzed by HPLC under our standard conditions. The *trans,trans* compounds all elute after the corresponding *trans,cis* isomer, and the 15-*trans,trans*-HPETE is the only compound detected in significant amount at KP > 500 s⁻¹. The 15-

trans,trans compound elutes just after 11-HPETE. Significant amounts of unidentified products are observed in oxidations at low KP in the region of the chromatogram eluting after 8-HPETE and 5-HPETE. The nature of this product mixture, presumably resulting from peroxy radical cyclization, was not investigated here.

Free Fatty Acid Oxidations. Linoleic acid and arachidonic acid were obtained from Nu-Chek Prep or Sigma Biochemicals. Extreme care must be taken to ensure that the fatty acid is not significantly oxidized before an experiment is begun. Significant amounts of oxidation products were detected in some freshly opened samples from Sigma. Oxidations were carried out essentially as described earlier. Extent of oxidation was monitored by titrating hydrogen peroxide (if cyclohexadiene was cosubstrate) and fatty acid hydroperoxide formed with triphenylphosphine. Addition of a known quantity of phosphine to an aliquot of the oxidation mixture was followed by thin-layer or HPLC analysis to determine if all phosphine was oxidized to phosphine oxide. One-half percent increments of phosphine, based on starting oxidizable substrates, were generally added until some phosphine remained unoxidized.

The 9-*trans,cis* and 9-*trans,trans* hydroperoxides of linoleic acid (not analyzed in cooxidations of linoleate and arachidonate) coelute with 8-HPETE. For this reason, side-by-side oxidations were carried out with linoleic acid and arachidonic acid in cyclohexadiene/benzene and arachidonic acid alone in cyclohexadiene/benzene. The amounts of 15-, 12-, 11-, 9-, and 5-HPETE relative to the 13-linoleate could be determined from the first experiment with the 8-HPETE value compared to these other HPETE isomeric hydroperoxides being obtained by the second experiment.

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Mechanism of the Photoepoxidation with and Photodecarboxylation of α -Keto Acids¹

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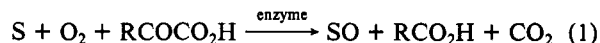
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Abstract: The photooxidation of benzoylformic acid (**1a**) in benzene gave peroxybenzoic acid, hydrogen peroxide, and phenyl benzoate. The addition of α -methylstyrene to the oxidation system afforded the epoxide together with acetophenone as a C-C cleaved product, and the ester yield was significantly increased at the expense of the peracid. The photooxidation of **1a** was not sensitized by methylene blue or other sensitizers, but was efficiently accelerated by pyridine or other weakly basic solvents such as ethers. Pyridine effectively catalyzed the photoepoxidation as well as the photodecarboxylation of **1a** to benzaldehyde. The photoepoxidation gave predominantly *trans* epoxides, and the relative reactivities of olefins were similar to the photoepoxidation with benzoin (i.e., PhCO₂·) and quite different from the peracid epoxidation. Similar results were obtained by other α -keto acids or the corresponding esters. These facts suggest that the photoepoxidation proceeds via radical epoxidation by acylperoxy radical, affording *trans* epoxide predominantly. Contrary to previous reports, the photooxidation of α -keto acids via an ¹O₂ reaction was not substantiated. The photodecarboxylation of **1a** to afford benzaldehyde was selectively catalyzed by water, and its undissociated form was about tenfold more reactive than the corresponding carboxylate ion.

Oxygen atom transfer of oxenoid intermediates are of current interest as models of monooxygenase enzymes;² among them are carbonyl oxides,³ pyridine *N*-oxide,⁴ and unstable cyclic peroxides.⁵ In the study of the photoepoxidation of olefins with α -diketones and oxygen,⁶ acylperoxy radicals have been shown to be effective epoxidizing agents,⁷ based on the fact that α -diketones are not

catalysts but reactants consumed and converted to peracids, etc. The same is true for the photoepoxidation with benzoin.⁸ This led to our interest on the photooxidation of α -keto acids.

In relation to a model reaction of dioxygenases containing α -ketoglutarate (eq 1, S = substrate),⁹ the dye-sensitized pho-



tooxidation of an α -keto acid (**1**) (eq 2) was recently shown to



go by way of singlet oxygen.^{10,11} An intermediate "trioxalene"

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Table I. Photooxidation of and Photoepoxidation with α -Keto Acids in Benzene

	R	R'	conditions ^a	Φ^b (rel Φ) ^b	products (%) ^c			
					RCO ₃ H	PhCO ₂ -Ph	epox-ide	others ^c
1a	Ph	H		0.0066 (1.00) (1.06) (1.10)	80 60 <5 <5 <i>d</i> <i>d</i> <i>d</i>	10 14 15 25 8 <i>d</i> <i>d</i>		H ₂ O ₂ (35%), Ph ₂ (3%) <i>d</i> PhCOMe (50%), PhC(CHO)=CH ₂ (5%) PhCOMe (22%) ROOH ^e (190%) PhCHO (27%) ^g PhCHO (20%) ^h
1b	Ph	Me	0.1 M PhMeC=CH ₂	0.014	58 <5	22 15	21	H ₂ O ₂ (50%) PhCOMe (30%), α -HO ester (20%), PhC(CHO)=CH ₂ (6%)
1c	Me	H	8 mM	0.025	50			H ₂ O ₂ (10%), CH ₄ (~20%)
1d	HO ₂ CCH ₂ CH ₂	H	8 mM in MeCN	0.056	18			H ₂ O ₂ (5%)

^a Irradiation (>320 nm, mainly at 366 nm) of 2 mM α -keto acid in benzene under O₂ at 20 °C for 1 or 2 h unless otherwise noted.

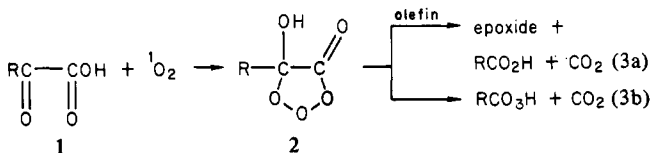
^b Quantum yields for the decomposition of α -keto acid determined using ferrioxalate actinometry. Relative Φ 's were determined by merry-go-round apparatus (average of two or three times determinations). ^c Products were determined by GLC and the yields are based on the keto acid consumed. Peracid and H₂O were titrated iodometrically before and after the reaction with Me₂SO. Carboxylic acid and CO₂ were not determined. A small amount (i.e., within a few percent) of benzaldehyde was also detected in the reaction of 1a and 1b. ^d Not determined. ^e Cyclohexenyl hydroperoxide. ^f *trans*-Stilbene oxide. ^g Recovered stilbene: *cis/trans* = 2. ^h Recovered stilbene: *cis/trans* = 10.

Table II. Effect of Additives on the Photooxidation of 1a in the Presence of α -Methylstyrene^a

no.	solvent	additive ^b	rel rate ^c	products (%) ^d				
				PhCHO	epoxide ^e	PhCOMe ^e	PhCO ₂ Ph	others ^f
1	PhH		(1.0)	1	4	5	2	Ph ₂ (1%)
2		25% DMF	~8	13	44	39	2	Ph ₂ (1%)
3		25% PhOMe	~8	2	24	12	10	PhOH (~8%)
4		25% Ph ₂ O	7	2	35	15	15	
5		0.1 M py	13	16	53	14	30	Ph ₂ (4%)
6	MeCN		1.0	5	6	7		
7		air	0.9	5	5	5		
8		N ₂	0.6	5	<1	1		
9		1 mM MB	1.1	4	6	7		
10		0.1 M py	8	42	31	15		
11		0.1 M py + 1 mM MB	5	26	17	9		
12		25% H ₂ O	15	68	<1	<1		

^a Irradiation of an oxygen-saturated solution of 5 mM 1a and 0.1 M α -methylstyrene. ^b Under oxygen unless otherwise noted. DMF = *N,N*-dimethylformamide, MB = methylene blue, and py = pyridine. ^c Relative rates of the photooxidation of 1a as determined using a merry-go-round apparatus. Averages of two or three determinations. ^d Products were determined by GLC and the % yields are based on charged 1a. ^e Products from α -methylstyrene. ^f Benzoic acid was not determined. Yields (few percent) of PhC(CHO)=CH₂ and PhC(CH₂OH)=CH₂ were always detected.

(2) was postulated to be formed by a nucleophilic reaction of 1 with ¹O₂ and to epoxidize olefins (eq 3a) or to be decarboxylated to peroxy acid (eq 3b).¹⁰ The question here is whether such a



reaction of ¹O₂ to form 2 followed by epoxidation occurs or not. We report herein that the photooxidation of α -keto acids is not a singlet oxygen reaction but proceeds by way of a photochemical α -cleavage leading to an acylperoxy radical which can effectively transfer the oxygen atom to olefins. Pyridine was found to catalyze this photoepoxidation as well as the photodecarboxylation to aldehyde; water catalyzes the latter reaction selectively. After the completion of our study, a communication appeared to show that singlet oxygen does not play a significant role on the basis of a laser flash photolysis.^{12a}

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Results

Photooxidation in Benzene. The photolysis of benzoylformic acid (1a) under O₂ in benzene with >320-nm light at ~20 °C afforded peroxybenzoic acid (80%) in addition to hydrogen peroxide (35%) and phenyl benzoate (10%). A control experiment showed that the reaction of 1a with the peracid or hydrogen peroxide is very slow under the same conditions. When α -methylstyrene was added to the photooxidation system, the olefin was converted into the corresponding epoxide together with acetophenone as a C-C cleavage product, the yield of phenyl benzoate being significantly increased (Table I).

The photooxidation of a mixture of cyclohexene and 1a gave a moderate yield of epoxide (i.e., 12%), but a major product was cyclohexenyl hydroperoxide (190% on the basis of 1a). The product ratio was approximately the same with those from the radical autoxidation of cyclohexene (AIBN-initiated, benzene, 60 °C). Likewise, allylic hydroperoxides were major products in reactions of cyclooctene and 2-octene.

Similar results were obtained by the photooxidation of methyl benzoylformate (1b). Pyruvic acid (1c) and α -ketoglutaric acid (1d) reacted similarly (Table I) and *trans* epoxide was always obtained from *cis*- or *trans*-stilbene at room temperature or at -70 °C. Methane (~20%) was also detected by GLC in the photooxidation of 1c.

Effect of Additives. The effect of additives was examined on the photooxidation of 1a in the presence of α -methylstyrene (Table II). In benzene, the photooxidation of 1a was significantly

Table III. Relative Quantum Yields and Ratios of Photodecarboxylation and Photoepoxidation with **1a**^a

solvent	additive ^b	rel Φ ^c	ratio of PhCHO: epoxide ^d
PhH		1.0	~20:~80
MeCN	0.1 M py	13 ^e	53:47
		(1.00)	64:36
	0.1 M py	8.0	52:48
	0.01 M Dabco	1.0	95:5
	1% H ₂ O	1.7	85:15
	2.5% H ₂ O	10	95:5
	5% H ₂ O	14	99:1
	50% H ₂ O	19 ^f	100:0
	50% H ₂ O, 0.1 M py	1.7	98:2
H ₂ O	50% H ₂ O, pH 8	1.3	98:2
	g	7.3	
	g, pH 1	35	
	g, pH 8	3.4	

^a Reaction with 5 mM **1a** and 0.1 M α -methylstyrene under air; irradiated through a Pyrex glass and NaNO₃ filter solution (i.e., >320 nm). ^b See footnote b in Table I; % means vol % in MeCN. ^c Relative quantum yields (Φ) were determined by GLC analysis at low (i.e., 10–20%) conversions; average of two or three determinations. ^d The ratios of the photodecarboxylation and photoepoxidation were determined from the initial product ratios of PhCHO and α -methylstyrene oxide. ^e The absolute Φ is 0.115. ^f The absolute Φ is 0.20. ^g In the absence of added olefin.

catalyzed by pyridine and weak bases such as dimethylformamide, anisole, and diphenyl ether. The phenol formation from anisole is probably due to the autooxidation of anisole initiated by hydrogen atom abstraction. The photoepoxidation was not effective in solvents such as cyclohexane and methanol. Pyridine was the most effective catalyst, affording high yields of epoxide, benzaldehyde, and phenyl benzoate. Since the selectivity for benzaldehyde decreased gradually as the photolysis proceeded, the aldehyde was also autoxidized probably via initiation by **31** or other radical intermediates. Pyridine catalysis was likewise significant in acetonitrile (Table II), but the accelerating effect was invariable with changing the pyridine concentrations from 0.01 to 0.2 M. Methylene blue (MB), an efficient ¹O₂ sensitizer, did not accelerate the photooxidation but rather retarded the pyridine-catalyzed reaction (entry 11 in Table II). Interestingly, water catalyzed selectively the photodecarboxylation to afford aldehyde; the photolysis of **1a** proceeded likewise under nitrogen (entry 8).

In order to clarify the effect of ¹O₂ sensitizers, the photoepoxidation of *cis*-stilbene with α -keto acids was examined competitively in the presence or absence of MB or Rose Bengal (RB) (conditions: 2 mM α -keto acid, 0.02 M *cis*-stilbene, and 1 mM sensitizer in MeCN or MeOH under oxygen, $h\nu > 320$ nm). Using a merry-go-round apparatus, the relative yields of the resulting trans epoxide were not improved but rather decreased by ca. 20–50% by the addition of MB or RB for all reactions of **1a**, **1c**, and **1d**, where over 95% of the light was absorbed by these sensitizers. In contrast, the dramatic acceleration by pyridine was observed in all cases of α -keto acids.

Competition between Photoepoxidation and Photodecarboxylation. The ratios of photoepoxidation and photodecarboxylation were determined in the presence of α -methylstyrene at an earlier stage (i.e., at 10–20% reaction) of the photooxidation of **1a**. Here, we assumed that the olefin is epoxidized effectively by an epoxidizing intermediate, since the epoxide yield was practically the same either with 0.1 or 0.01 M olefin (see entries 3 and 4 in Table I). As shown in Table III, pyridine catalyzes both reactions similarly, the yield ratio of epoxide: PhCHO being approximately 1.

On the other hand, water selectively catalyzes the photodecarboxylation to aldehyde. In 50% aqueous MeCN, pyridine retarded the photolysis of **1a** simply as a base to dissociate the keto acid **1a** ($pK_a = 1.39$ in water).¹³ Surprisingly, the photo-

Table IV. Relative Reactivities of Olefins in Photoepoxidations and Peracid Epoxidation

olefins	photoepoxidation ^a with PhCOCO ₂ H-		epoxidation with PhCO ₃ H ^d
	py ^b	benzoin ^c	
styrene	0.167	0.123	0.140
α -methylstyrene	(1.00)	(1.00)	(1.00)
β -methylstyrene	2.30	1.95	1.59
β,β -dimethylstyrene	0.70	0.92	3.37
<i>trans</i> -stilbene	0.67	0.76	0.064
cyclohexene	~0.08	0.12	4.31
1-methylcyclohexene	~0.85	1.04	13.6

^a Irradiation through a Pyrex filter for 1 h at ~20 °C under O₂. Relative reactivities were determined by competitive method using GLC and averaged from two or three determinations. ^b Irradiation of benzene solutions containing 0.02–0.1 M olefin, 5 mM **1a**, and 0.1 M pyridine. ^c Reaction in benzene–acetone (4:1), from ref 8. ^d By rate measurements in benzene at 25 °C; ref 8.

decarboxylation of its anion is much slower than the undissociated form. Similar results were obtained in pure water, the relative quantum yield (Φ) being 35 at pH 1 and 3 at pH 8 or 13 (compare with the relative Φ in Table III). The absence of base catalysis by 1,4-diazabicyclo[2.2.2]octane (Dabco) in MeCN (entry 5 in Table III) is probably due to the dissociation of **1a** into a less reactive anion as evidenced by the change in the UV spectra of **1a**.¹⁴

The solvent kinetic isotope effect was determined for the photodecarboxylation of **1a** affording benzaldehyde in water–MeCN (5:95); the resulting effect was $k_{H_2O}/k_{D_2O} = 1.55 \pm 0.13$. This photolysis was efficient ($\Phi \sim 0.14$) and pure PhCDO (above 98%) was easily obtained by the photolysis of **1a** in D₂O–MeCN; the D% depends simply on the molar ratio of **1a** and D₂O used.

Relative Rates of Olefins in the Photoepoxidation. Pyridine is a good catalyst because it accelerates the photoepoxidation by 5–10-fold and at the same time suppresses the acid-catalyzed decomposition of the resulting epoxides. In Table IV are listed the relative reactivities of styrenes and cycloolefins for the photoepoxidation with **1a**. The resulting relative rates are very close to those in the photoepoxidation with benzoin (i.e., with PhCO₃H)⁸ and quite different from the results with molecular peracid. The photoepoxidation with **1a** and pyridine also gave predominantly trans epoxides; both *cis*- and *trans*-stilbenes afforded trans epoxide, and *cis*-2-octene yielded epoxides with a *cis*:*trans* ratio of 3:7, which is similar to the ratio of 2:8 for the photoepoxidation with benzoin.⁸

Discussion

The photolysis of α -keto acids (**1**) has been thoroughly studied under deaerated conditions.^{15–17} In the presence of H donors reductive dimers were obtained.^{15a,18} The photolysis of pyruvic acid (**1c**) gives acetaldehyde and CO₂ in the vapor phase,¹⁹ but affords acetoin in water,^{15a} which is probably produced via the addition of acyl radical to **1c**.^{16b,20} Benzoylformic acid (**1a**) was shown to be photodecarboxylated to yield benzaldehyde in water.^{15a} However, the studies on the photooxidation of **1** in the presence

(14) The UV spectra of **1a** in the presence of Dabco in MeCN is similar to those of the anion in water. The UV spectra in the presence of pyridine in MeCN is at the intermediate stage between the anion and the undissociated form.

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of oxygen are few and the details are not clarified.

Question on the Singlet Oxygen Reaction. It has been reported that photoepoxidation with α -keto acids proceeds by way of a singlet oxygen reaction,¹¹ and a "trioxalone" (**2**) was postulated (eq 3).¹⁰ Our repeated experiments revealed, however, that an $^1\text{O}_2$ sensitizer such as MB or RB rather retarded the epoxidation by 20–50% in MeOH or MeCN ($h\nu > 320$ nm); the pyridine-catalyzed photooxidation was also retarded by MB (entry 11 in Table II).

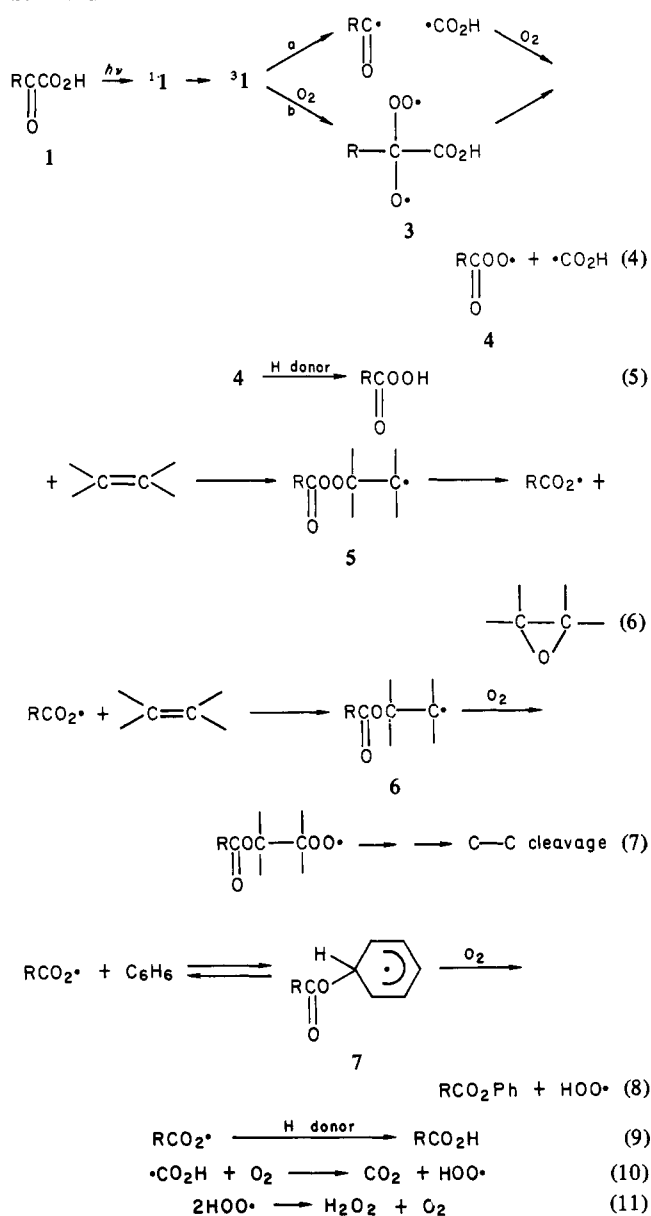
The discrepancy with the previous results may be partly due to the difference of the lamp used. We used a medium-pressure Hg lamp (>320 nm using a filter) while a tungsten lamp (mainly >380 nm) was used in the reported photooxidation.¹¹ Although the authors explained the sensitized oxidation of **1** as an $^1\text{O}_2$ reaction, it was later criticized and explained by an energy transfer from the sensitizer to **1**.^{12b} Indeed, it is not easy to understand the significant acceleration by Dabco, an efficient $^1\text{O}_2$ quencher,²¹ in the photooxidation of **1d** by assuming the sensitized $^1\text{O}_2$ reaction.^{11a} Recently, a laser flash photolysis study^{12a} revealed that triplet sensitizers react with α -keto acids much faster than with $^1\text{O}_2$; the reported small solvent effects (i.e., $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.4\text{--}2$) were also regarded as an evidence against the $^1\text{O}_2$ reaction.

Thus, the reported nucleophilic reaction of **1** with $^1\text{O}_2$ to form trioxalone **2**¹⁰ cannot, at least, be a major reaction as discussed in the following. (i) The sensitized photooxidation of **1d** was not quenched but rather accelerated by Dabco.^{11a} (ii) The photoepoxidation proceeds similarly with ester **1b**. (iii) The photoepoxidation of **1** (>320 nm) was not sensitized by MB or RB where over 95% of the light was absorbed by the dye. (iv) The anion of **1a** was less reactive than the free acid in aqueous MeOH or MeCN. It is not easy to comprehend why a nucleophilic addition of carboxyl group of **1** to $^1\text{O}_2$ is possible, as was reported, only for the case of α -keto acids, the nucleophilicity of which is surely much lower than that of ordinary carboxylic acids. Although we cannot deny the proposed existence of trioxalone **2** at low temperature,¹⁰ the present results at ambient temperature seem not to support the intermediacy of **2** via the $^1\text{O}_2$ reaction.

Photoepoxidation. The photoepoxidation of **1a** in benzene gave peroxybenzoic acid and phenyl benzoate; the addition of α -methylstyrene resulted in the epoxidation and C–C cleavage of the olefin, and interestingly in the increased yield of the ester. The epoxide yields were not decreased by the presence of excess pyridine, a highly reactive substrate for peracid, and the resulting epoxides were predominantly trans. The relative reactivities of olefins are similar to those for the photoepoxidation with benzoin (i.e., $\text{PhCO}_3\cdot$) and quite different from those for the peracid epoxidation (Table IV). All of these results suggest the epoxidation with acylperoxy radical $\text{RCO}_3\cdot$, and reasonable sequences are shown in Scheme I.

The intersystem crossing from $^1\text{1}$ to $^3\text{1}$ is fast and efficient for α -keto acids.^{18a,22} The formation of acyl radicals by the photodissociation of **1** (eq 4a) is also well documented under deaerated conditions;^{16,20,23} moreover, the sensitized photodecarboxylation proceeds regardless of the absence of oxygen.^{11b,12} An alternative pathway (eq 4b) is similar to the photooxidation of α -diketone⁷ and the β -scission of $\cdot\text{CO}_2\text{R}$ is known.²⁴ Although the choice is not conclusive, path 4a seems to be more probable on the basis of the observation of CIDNP spectra of irradiated **1**¹⁶ and the ESR spectra of acyl radicals^{20,23} by the photochemical α -cleavage.

The epoxidation with acylperoxy radical **4** is well known in the coautoxidation of aldehyde and olefin²⁵ and in the photoep-

Scheme I^a

^a Here, $^1\text{1}$ and $^3\text{1}$ represent singlet and triplet **1**; H donor is $\cdot\text{CO}_2\text{H}$, **7**, solvent, etc.

oxidation with benzoin.⁸ That is, the radical epoxidation (eq 6) affords predominantly more stable trans epoxides because of fast C–C rotation in the adduct radical **5**.^{8,25} The benzoyloxylation of benzene (eq 8) is known to be effective under oxygen.²⁶ Since carboxyl radical $\cdot\text{CO}_2\text{H}$ is a potent reducing agent,^{23a,27} it probably reduces oxygen ultimately to H_2O_2 (eq 10 and 11). The reaction of H_2O_2 with **1** was negligibly slow under these conditions.

The epoxide yields were practically the same with 0.01 or 0.1 M α -methylstyrene. On the other hand, the yield of acetophenone, a C–C cleavage product, increased with increasing olefin concentration while the amount of PhCO_2Ph was significantly reduced (entries 3 and 4 in Table I). These facts indicate that the reactions 7 and 8 are competitive. Thus, Scheme I can explain salient features in the photoepoxidation with α -keto acids.

The quantum yields for the photooxidation of methyl ester **1b** ($\Phi = 0.014$) is somewhat lower than that for the photolysis of the

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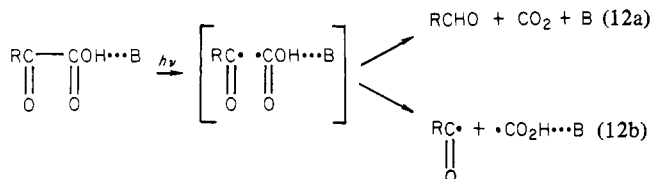
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corresponding ethyl ester in the absence of oxygen ($\Phi = 0.056$).^{15b} This is partly due to the quenching of $^3\mathbf{1}$ by O_2 to afford $^1\text{O}_2$, which was substituted by the photooxidation of $\mathbf{1a}$ or $\mathbf{1b}$ in the presence of α,β,β -trimethylstyrene (0.05 M) yielding allylic hydroperoxides as a characteristic $^1\text{O}_2$ reaction.²⁸ The product ratio of epoxide: $^1\text{O}_2$ products was 60:40, suggesting that about half of $^3\mathbf{1}$ was quenched by O_2 to yield $^1\text{O}_2$.²⁸

Finally, a limitation in the photoepoxidation with $\mathbf{1}$ should be noted. Cyclohexene gave predominantly cyclohexenyl hydroperoxide, and similarly 2-octene or cyclooctene afforded allylic hydroperoxides. These are derived probably from the radical autoxidation of olefins initiated by the hydrogen atom abstraction by $^3\mathbf{1}$, since the reactions via acylperoxy radical (e.g., eq 5-9) are known to afford epoxides selectively.⁸ In fact, the hydrogen atom abstraction by $^3\mathbf{1}$ is fast,^{15a,18a} while the reaction of these olefins with $^1\text{O}_2$ to afford allylic hydroperoxides is much slower. The formation of α -phenylacrolein from α -methylstyrene also supports the radical reaction. Thus, the photoepoxidation with $\mathbf{1}$ is not always an efficient or clean reaction.

Competitive Photodecarboxylation. Many studies have been reported regarding the photodecarboxylation of carboxylic acids. In most cases, carboxylate ions RCO_2^- are much more labile than the undissociated form RCO_2H , suggesting carbanion intermediates R^- .²⁹ A radical formation from the undissociated form was shown for the photolysis of phenylacetic acid in MeOH.^{30a} The photodecarboxylations of carboxylic acids have been classified as a reaction proceeding via carbanion formation, photoionization yielding solvated electron, or α -cleavage to afford radical R^\cdot .^{30b} As discussed below, the third radical pathway is substantiated for the present photodecarboxylation of α -keto acids.

The products from the photooxidation of $\mathbf{1a}$ in benzene or acetonitrile suggest the competition between photoepoxidation via α -cleavage (i.e., free $\text{PhC}=\text{O}$ and hence PhCO_3^-) and photodecarboxylation to form PhCHO as shown in Table III. Since the two reactions are equally catalyzed by pyridine, the photooxidation of $\mathbf{1a}$ probably proceeds via a hydrogen-bonding catalysis leading to both reactions (eq 12). Here the brackets signify a



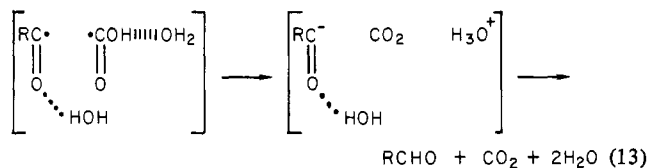
solvent cage. The resultant free acyl radical (eq 12b) is effectively trapped by molecular oxygen to yield an acylperoxy radical leading to the photoepoxidation (eq 6). Since the photolysis is not quenched by oxygen, an efficient triplet quencher, the photochemical α -cleavage should be very fast.

On the other hand, when water is added, the course for the free acyl radical (eq 12b) is dramatically reduced, resulting in the selective decarboxylation to aldehyde (eq 12a). Since a few percent of water is enough to catalyze the photodecarboxylation, water accelerates the reduction of acyl radical with the carboxyl radical $\cdot\text{CO}_2\text{H}$ probably via hydrogen bonding to acyl oxygen in the solvent cage (eq 13). The hydrogen bonding to the acyl radical probably enhances its electron affinity or oxidation power, thus making the oxidation-reduction very effective in the solvent cage. Here the solvent isotope effect from $\mathbf{1a}$ and 5% water in MeCN is a value slightly smaller than normal, i.e., $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.55$. Although solvent isotope effects contain complicated factors,³¹

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it is likely that no proton transfer is involved in the rate-determining step of the present photolysis on the basis of the small isotope effect.

Contrary to those of the ordinary carboxylic acids, the photodecarboxylation of anion of $\mathbf{1a}$ is slower than the undissociated form by a factor of ca. 10. One possible explanation is that the carbanion mechanism to form directly acyl anion and CO_2 is not favored because of the instability of acyl carbanion.³²

In conclusion, the photooxidation of α -keto acids yields acylperoxy radicals leading to photoepoxidation. Pyridine catalyzes the photoepoxidation as well as the photodecarboxylation to aldehyde, while water catalyzes the latter reaction selectively. Finally, it is interesting to note that the acylperoxy radical and/or peroxy acid could be phototoxic species since α -keto acids are important metabolic intermediates³³ and the photolysis is effective in the near-UV around 300 nm.³⁴

Experimental Section

Melting points are corrected and boiling points are uncorrected. UV spectra were recorded with a Hitachi 124 spectrometer, ^1H NMR spectra with a Hitachi R24B spectrometer, and GC-MS spectra with a JEOL D300 GC-MS spectrometer. GLC analyses were performed with a Yanagimoto G180 gas chromatograph with a flame ionization detector using the columns: PEG 20M, 10% on Chromosorb W, 1 m; Silicone OV-17, 5% on Shimalite, 1 m; Porapak QS, 1 m. Biphenyl and propiophenone were used as internal standards.

Materials. Benzoylformic acid ($\mathbf{1a}$) was synthesized from mandelic acid,³⁵ mp 64-65 °C (lit.³⁶ mp 64-66 °C). Methyl benzoylformate ($\mathbf{1b}$) was obtained by KMnO_4 oxidation of methyl mandelate,³⁷ bp 120 °C (1.5 mm) (lit.³⁸ bp 110-111 °C (6 mm)). Other materials were of commercial sources. Solvents were redistilled before use.

General Procedure of Photooxidation. A 3-mL benzene solution of 2 mM $\mathbf{1a}$ in a 10-mL test tube was saturated with oxygen by bubbling its stream for 5 min and irradiated with a 300-W medium-pressure Hg lamp through a 5% NaNO_3 aqueous solution as a filter (i.e., >320 nm) at ~20 °C. After 1 or 2 h of irradiation, peroxybenzoic acid and H_2O_2 were titrated as described previously.³⁹ The peracid was characterized by extraction with aqueous alkali and by the instant oxidation of Me_2SO to sulfone yielding benzoic acid. Products were determined by GLC analyses.

The photoepoxidation of olefins was carried out similarly, and the epoxides were identified by GLC by comparison with the corresponding authentic samples obtained by the epoxidation with peroxybenzoic acid.⁸ Other products were determined by GLC directly and/or after NaBH_4 reduction to the corresponding alcohols.

The reaction of α -keto acids with peracid produced was reported to be instant.^{11a} However, the reaction of $\mathbf{1a}$ with peroxybenzoic acid was very slow in benzene. Although the addition of pyridine accelerated the oxidation of $\mathbf{1a}$ with the peracid, the major reaction was in turn the peracid oxidation of pyridine itself.

The quantum yields for the photooxidation of α -keto acids were determined using ferrioxalate actinometry⁴⁰ and/or a merry-go-round ap-

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paratus. The conversion of α -keto acids was determined by UV and also checked by GLC after methylation with diazomethane.

Photodecarboxylation of 1a in D₂O-MeCN. A mixture of 1a (0.15 g, 1 mmol), D₂O (2 mL), and MeCN (8 mL) in a Pyrex tube was irradiated for 2 h with a 300-W medium-pressure Hg lamp. After

dilution with water, the benzaldehyde produced was extracted twice with 10 mL of CH₂Cl₂, washed two times with water, and dried over Na₂SO₄; GLC analysis showed the formation of benzaldehyde in 95% yield. The NMR spectra showed that the purity of the resulting PhCDO was 99%, which was also ascertained by GC-MS spectra.

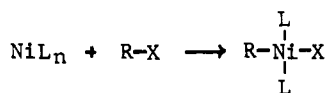
Reaction of Aryl and Vinyl Halides with Zerovalent Nickel—Preparative Aspects and the Synthesis of Alnusone

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Abstract: Zerovalent nickel complexes such as bis(1,5-cyclooctadiene)nickel and tetrakis(triphenylphosphine)nickel react rapidly with aryl and vinyl halides to produce the symmetrical coupling products, a low-temperature analogue of the Ullman reaction. The reaction proceeds through oxidative addition of the organic halide to Ni(0), and the reactivity of the Ni(II) intermediates has been examined. Arylnickel halide complexes decompose rapidly to biaryls in DMF. The coupling of simple vinyl halides proceeds with isomerization of the double bond but 3-haloacrylates give efficient coupling with retention of geometry. Cyclizations to form ortho-bridged biaryls are efficient in simple cases (6-, 7-, 8-, 9-, 10-, and 14-membered rings) but fail with an ortho-disubstituted case. The 13-membered meta-bridged cyclic biphenyl, alnusone, is prepared efficiently with the crucial aryl halide coupling to form the ring proceeding in 50% yield. A side reaction promoted by the presence of protons and with certain ortho-substituted aryl halides is reduction of the aryl halide to the arene. This process can be enhanced by deliberate addition of acid during reaction with Ni(0) and a series of aryl halides underwent successful reduction.

Nickel is relatively unique among the transition metals in that a variety of complexes is easily prepared containing nickel in the zerovalent state.¹⁻³ Like most complexes of low-valent metals from group 8 of the periodic table, the NiL_n species generally



undergo oxidative addition of organic halides (R-X) under mild conditions.⁴ This reaction represents direct formation of a σ -bonded organometal species, in a process reminiscent of the formation of a Grignard reagent. An important difference is the much lower polarization of the carbon-nickel bond and the potential compatibility of the reaction with common polar functional groups such as alcohols, carbonyl groups, etc.

Of particular interest is the ease with which aryl and vinyl halides enter into oxidative addition with Ni(0), Pd(0), and Pt(0).⁵ These halides, which are quite unreactive in classical polar reactions, often add to the zerovalent metals as readily as methyl and primary alkyl halides. While the mechanism of oxidative addition continues to be an active area of study^{6,7} and different metals react by different mechanisms,⁴ it is likely that there is a strong electron-transfer component in the particularly fast reaction of Ni(0) with aryl halides.⁷ We reported in preliminary form the coupling of aryl^{8,9} and vinyl halides¹⁰ promoted by zerovalent nickel and postulated initial formation of aryl- and vinylnickel(II) intermediates. We are prompted to present details of this work including previously unpublished aspects in light of the recent development of a convenient in situ preparation of zerovalent nickel^{11,12} and a study of two important steps in the aryl-aryl coupling method.^{7,13}

The principle of metal-promoted coupling of aryl halides continues to see development, most generally in the Ullman reaction where copper powder serves as the zerovalent metal.¹⁴⁻¹⁷ No

comparably general method exists for coupling of vinyl halides, although certain β -haloacrylates under Ullman-type coupling.¹⁸

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