ducted on 60-mesh silica gel. Authentic samples of both **10** and **11** were prepared by a literature procedure.[8]

NMR Studies. The Er(fod)$_3$ was obtained from the Norell Chemical Co. and used without further purification. ^{1}H NMR spectra were recorded on a Bruker WP-80 spectrometer and carbon spectra on a Varian XL-100 spectrometer, both operating at ambient probe temperature. The paramagnetic shifts reported are the slopes of the molar ratio vs. the induced shift plots after extrapolation to a 1:1 molar ratio. Experimental molar ratios ranged from 2×10^{-3} to 3×10^{-2}. Induced shift experiments were done by the incremental addition of shift reagent to the substrate solution, and both ^{1}H and ^{13}C spectra were run on the same sample. The computer analysis was done on a Xerox Sigma IX computer.

Preparation of 1-d_9. 2,3,5-Trimethylpyrazine (3.5 g) in 60 mL of D_2O (99.7% D) containing 5 mL of 40% NaOD (99.0% OD) was refluxed under dry N_2 for 5 days. The solution was extracted with CH_2Cl_2, the organic layer dried ($MgSO_4$), and the solvent removed under reduced pressure to give 3 g of the deuterated product. The NMR spectrum indicated that only 91% exchange occurred. The above process was repeated with reflux continuing for only 3 days. A workup as above the distillation gave pure product with 98.6% D (the H-6 is taken as 100% of 1 H). The unexchanged residual protons were determined by integration of the spectrum obtained with Er(fod)$_3$. The following residual protons in the three different CH_3 groups were obtained: 2-CH_3, 0.018 H; 3-CH_3, 0.017 H; 5-CH_3, 0.105 H.

Metalation of 1-d_9 with LDA in Ether and in THF. To a solution of LDA (0.01 mol) in ether (80 mL) at 0 °C was added with stirring **1**-d_9 (1.31 g, 0.01 mol) in ether (20 mL). The resulting red mixture was stirred at 0 °C for 20 min. Water (H_2O) was added (50 mL), the organic layer was separated and dried ($MgSO_4$), and the ether was removed under reduced pressure. Distillation afforded pure **1**-d_8. ^{1}H NMR indicated that only 75% of the starting material was metalated. Integration of the spectrum in $CDCl_3$ containing Er(fod)$_3$, after correcting the results for residual protons in the starting **1**-d_9, gave the following distribution of proton in **1**-d_8: 2-CH_3, 0.248 H; 3-CH_3, 0.442 H; 5-CH_3, 0.062 H. The results are shown in Table II as percent incorporation.

The above experiment was repeated in THF (150 mL). Water was added (100 mL), and the product was extracted with ether (5×30 mL). Purification of the product and NMR analysis gave results similar to the above. When the same experiment was carried out at room temperature and the red THF solution was left stirring at this temperature, the red color started to fade after about 8 h.

Metalation of 2,3- and 2,6-Dimethylpyrazines (8 and 9).[8] A solution of **8** and **9** (5.4 g, 0.5 mol of each) in ether (200 mL) was added at 0 °C with stirring to a solution of LDA (0.05 mol) in ether (100 mL). The red suspension was stirred at 0 °C for 20 min. A solution of *p*-methoxybenzaldehyde (6.8 g, 0.05 mol) in ether (40 mL) was added rapidly, and the resulting mixture was stirred for 10 min at 0 °C. Water (50 mL) was added, the ether layer separated, washed with water, and dried ($MgSO_4$), and the solvent removed under pressure. TLC indicated a smooth reaction with mainly products and starting materials present in the crude reaction mixture. A portion of the crude product was separated by preparative TLC, and the two products, **10** and **11**, having the same R_f, were collected. Their ratio was determined by NMR. Complete ^{1}H NMR data for both **10** and **11** have been described in a previous publication.[8]

The above reaction was repeated in glyme as follows. A solution of **8** and **9** (1.08 g, 0.01 mol of each) in dry glyme (30 mL) was added to solution of LDA (0.01 mol) in glyme (70 mL) at 0 °C with stirring. The solution turned red, but no precipitation occurred. The red solution was stirred at 0 °C for 30 min. A solution of *p*-methoxybenzaldehyde (1.36 g 0.01 mol) in glyme (20 mL) was added, and the mixture was stirred at 0 °C for 10 min. Water was added, and the product was extracted with ether. An aliquot was evaporated, and the residue was separated by preparative TLC to give a mixture of **10** and **11** which was analyzed by NMR.

The above experiment was repeated, and the red metalated mixture was stirred at room temperature for 3 h, at which time the red color has almost completely faded. A solution of *p*-methoxybenzaldehyde was added, and the reaction mixture was worked up as above. TLC showed only trace amount of products and mainly unreacted **8** and **9**.

Registry No. **1**-d_9, 85735-49-5; **1**-d_8 (isomer 1), 85735-50-8; **1**-d_8 (isomer 2), 85735-51-9; **1**-d_8 (isomer 3), 85735-52-0; **8**, 5910-89-4; **9**, 108-50-9; **10**, 72725-81-6; **11**, 72725-79-2.

Free Radical Oxidations in Water: Decomposition of Azoinitiators and Oxidation of *p*-Cresol and *p*-Isopropylphenol

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The free radical oxidation of *p*-cresol and *p*-isopropylphenol using peroxy radicals produced by thermolysis of azoinitiators in oxygen at 50 °C in purified water is considered. The major primary products of oxidation of *p*-cresol are the peroxycyclohexadienones and the corresponding hydroperoxides; smaller amounts of two phenolic dimers are also found in each case. A variety of other products thought to result from ortho substitution also were observed but not characterized. The general features of the reactions in water are much the same as observed in organic solvents. Cupric ion causes further reaction of the peroxide products, leading to additional oxidation of phenol and possible formation of some *p*-quinone; Fe^{2+} ion in contrast is a strong inhibitor of phenol oxidation by $RO_2\cdot$.

Introduction and Background

Oxidation of phenols by peroxy free radicals (RO_2) have been studied extensively both in organic solvents, because of their great importance as inhibitors,[1-3] and in water because of their widespread occurrence as aquatic pollutants.[4,5] The main features of inhibition kinetics are well understood, but the detailed chemistry often remains obscure, owing to the complex chemistry. Because oxidations of phenols in water generally are of interest in connection

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0022-3263/83/1948-2133$01.50/0

Table I. Decomposition of ACP and ABN in Water at 50 °C[a]

time, h	$[Azo]_0 \times 10^3$, M	% convn	$k_d \times 10^6$, s^{-1}	r^2
		ACP		
160	0.72	83	3.51 ± 0.17[b]	0.991
74	12.5	55	3.35 ± 0.25[c]	0.987
67	10.3	53	3.0[d]	
		ABN (by HPLC)		
115	0.404	47	1.57 ± 0.06	0.991
167	1.50	60	1.56 ± 0.02	0.999

[a] 95:5 H_2O/AN solvent. [b] By HPLC. [c] By N_2 evolution. [d] NMR experiment.

Table II. Estimation of Azoinitiator Efficiency at 50 °C[a]

time, h	$[Azo]_0 \times 10^4$	$[ArOH]_0 \times 10^5$	$\Delta[ArOH] \times 10^5$	a[b]
		ACP + PC[c]		
23.50	4.00	3.70	1.8	0.18
6.07	1.52	5.20	0.20	0.18
18.00	1.20	22.0	0.40	0.17
		ABN + PIP[c]		
24	4.00	4.00	0.89	0.18
24	4.00	8.00	0.78	0.16
45	4.00	8.00	1.67	0.19
24	4.00	20.00	1.34	0.40
48	4.00	40.00	2.01	0.40
		ACP in NMR[d]		
67	10.3 + O_2	0		0.24
67	10.3, no O_2	0		

[a] Concentrations in M. [b] a for ACP = $\Delta[PC]/[[ACP]_0(1 - e^{-00.0122t})]$; a for ABN = $\Delta[PIP]/[[ABN]_0(1 - e^{-0.0056t})]$. [c] In 95:5 H_2O/AN. [d] In 90:10 D_2/CD_3CN.

with pollutant abatement studies,[4,5] the processes rarely have been subjected to quantitative kinetics or product evaluation.

We report here results of oxidation experiments with *p*-cresol (PC) and *p*-isopropylphenol (PIP) in purified water at 50 °C using peroxy free radicals (RO_2) from two azoinitiators, 2,2′-azobis[2-(methylcarboxy)propane] (ACP) and azobis(isobutyronitrile) (ABN). (This is the common name for 2,2′-azobis(2-cyanopropane).) The study was performed to better characterize the products and kinetics of these reactions, to provide some quantitative insight into free radical oxidations in water, and to set the stage for investigations of peroxy radical reactions with natural phenolic materials and silicate and silica surfaces (reported elsewhere).[6]

These phenols and azoinitiators were chosen because they are reasonably soluble in water (up to 1 × 10^{-3} M), have low rates of volatility from water, and react readily at 50 °C to form products that are readily resolved from one another and detected by high-performance liquid chromatography (HPLC).

Kinetics of Phenol Oxidation by $RO_2\cdot$. Initiated oxidation of phenols by RO_2 in organic solvents follows the general scheme

$$R_2N_2 \rightarrow 2R\cdot + N_2 \qquad (1a)$$

$$aR\cdot + O_2 \rightarrow aRO_2\cdot \qquad (1b)$$

$$RO_2\cdot + ArOH \rightarrow RO_2H + ArO\cdot \qquad (2)$$

$$RO_2\cdot + ArO\cdot \rightarrow RO_2C_6H_5O \qquad (3)$$

$$2ArO\cdot \rightarrow (ArO)_2 \qquad (4)$$

$$2RO_2\cdot \rightarrow (R_2O_2 \text{ or } 2RO\cdot) + O_2 \qquad (5)$$

Reaction 2 typically has rate constants of 10^4 M^{-1} s^{-1} or greater for most phenols in organic solvents,[3] and if ArOH and ArO· scavenges all RO_2, the rate law for loss of ArOH becomes zero order in phenol

$$-d(ArOH)/dt = 2ak_d[Azo]/n \qquad (6)$$

where n varies between 2 and 1, depending on whether reaction 3 or 4 is dominant, and a and k_d are functions only of the azoinitiator, solvent, and temperature.

We evaluated k_d for ACP and ABN in water at 50 °C by following loss of the azoinitiator using HPLC. Good first-order kinetics were found for both initiators (see Table I), and rate constants are slightly faster than those reported in other solvents.[7-10] We estimated a by following the loss of PC or PIP with ACP or ABN under conditions where the principal oxidation sequence follows reactions 1–3, as shown by formation mainly of peroxycyclohexadienone ($RO_2C_6H_5O$) rather than a mixtures of dimers. Under these conditions n = 2 and eq 6 can be rearranged to estimate the value of a:

$$a = \frac{d[ArOH]/dt}{k_d[Azo]} = \frac{\Delta[ArOH]}{\Delta[Azo]} \qquad (7)$$

We also estimated a for ACP in an independent experiment in which we used ^1H NMR to distinguish products resulting from carbon radical recombination from those resulting from self-reactions of RO_2

$$RN_2R \rightarrow (2R\cdot)_{cage} + N_2 \qquad (8)$$

$$(2R\cdot)_{cage} \rightarrow RR + RH + \text{olefin} \qquad (9a)$$

$$(2R\cdot)_{cage} \xrightarrow{O_2} 2RO_2\cdot \rightarrow Me_2CO + MeOH \qquad (9b)$$

$$R{=}CMe_2CO_2Me$$

$$a = k_{9b}/k_8$$

The NMR experiment was done in 10% CD_3CN–D_2O to allow use of 1 mM of ACP needed for NMR measurements. Results for the two kinds of experiments to estimate a are summarized in Table II (see paragraph at the end of paper about supplementary material). About 20–30% of the initially formed R· radicals escape the solvent cage to form $RO_2\cdot$ radicals. These $RO_2\cdot$ oxidize phenols or, in their absence, self-react to form first RO· and then (when R = CMe_2CO_2Me) acetone and methanol; no evidence was found for methyl pyruvate. Thus, the dominant path for cleavage of $\cdot OCMe_2CO_2Me$ (reaction 5) is to cleave out $\cdot CO_2Me$. Methanol found in the NMR experiment with O_2 comes both from hydrolysis, as shown by its formation in the absence of oxygen (6 × 10^{-2} M), and from oxidation (13 × 10^{-2} M); the amount formed by oxidation corresponds closely to the amount of acetone found. The source of H atom to form methanol may be the CD_3CN solvent or disproportionation. Formaldehyde was not detected.

For ACP a is 0.18 ± 0.03 from kinetic experiments (eq 7) and 0.24 from the NMR equipment. For comparison, a is 0.3–0.4 in organic esters at 50 °C for the *n*-butyl ester

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Table III. Oxidation of PC in Water at 50 °C[a]

time, h	$[PC]_0$[b]	$[ACP]_0 \times 10^4$	$\Delta[PC]$[b]	rate × 10^7,[b,c] M/h	n[d]
0.42	1.1 (−7)	1.57	3.9 (−8)	0.93	8.2
1.00	3.2 (−7)	1.21	5.1 (−8)	0.51	~11
1.25	5.4 (−7)	1.57	3.7 (−7)	2.5	2.6
1.72	1.04 (−6)	1.52	5.2 (−7)	3.0	2.4
4.07	5.20 (−6)	1.52	9.8 (−7)	2.4	3.0
18.00	2.20 (−5)	1.20	2.5 (−6)	1.4	3.8
42.00	2.20 (−5)	1.20	6.8 (−6)	1.6	2.8
6.07	5.20 (−5)	1.52	2.0 (−6)	3.2	2.2
18.00	2.20 (−4)	1.20	4.0 (−6)	2.2	2.3

[a] Solvent is 95:5 water/AN; concentration in M. [b] Numbers in parentheses are powers of ten. [c] Rate = $\Delta[PC]/\Delta t$. [d] $n = [0.4[ACP]_0(1 - e^{-0.0122t})]/\Delta[PC]$.

analogue of ACP.[8] For ABN, *a* in water is 0.2 on the basis of eq 7; in many organic solvents *a* is about 0.5 at 50 °C.[9,11] The average value of *a* for both azoinitiators is close to 0.2, a value we have used in all subsequent calculations. Because we noted no effect on rates of loss of phenol when the concentration of oxygen in the void space was increased to 760 torr, we believe that that all of the free carbon radicals formed in reaction 1 are scavenged by oxygen to form RO_2 in reaction 1b. Therefore, most reactions were performed by using air to give oxygen concentrations in water of 2.6×10^{-4} M.[12]

Rates of loss of each phenol were followed over initial concentration ranges of 10- to 500-fold of PIP and PC, respectively, with nearly constant concentrations of azoinitiators. At the lowest concentrations of PC, 1×10^{-7} M, PC was lost very rapidly and was difficult to quantitate. However the pattern of reactivity with each phenol was the same: rates of loss increased initially with increasing phenol concentration up to 10^{-6} to 10^{-5} M phenol and then became zero order in the phenol. With PC the zero-order region begins around 5×10^{-6} M; with PIP the zero-order region is closer to 4×10^{-5} M, and the rate increases again above 2×10^{-4} M PIP. Most experiments gave nearly linear plots of (ArOH) vs. time up to about 25 h, consistent with eq 6 where [Azo] is in large excess of [ArOH]; under these conditions only about 10% of each azoinitiator decomposes. These rate data are summarized in Tables III and IV.

Conversions of phenols in these experiments ranged from 6% to 70%, but most were below 30%. Secondary reactions, especially competitive scavenging of RO_2 by dimer phenols, reduce the reliability of high-conversion reactions. An unexpected complication both for product and kinetic measurements discovered only in studies with PIP is that the purified water (Milli-A system) used in PC and in early PIP experiments contained trace amounts of Cu^{2+} ions, which decomposed some peroxide products. Thus the rate measurement values for PIP loss are too high by about a factor of 2; the *a* values also are too high by this same factor. Figure 1 illustrates the effect on the oxidation rate of treating the Milli-Q water beforehand with either EDTA or Chelex polymer, both of which reduce free metal ion concentrations to less than 10^{-12} M.

Table IV. Oxidation of *p*-Isopropylphenol at 50 °C in Water Free of Metal Ion with 2×10^{-4} M ABN[a]

time, h	$[PIP]_0 \times 10^5$, M	$\Delta[PIP] \times 10^5$, M	rate $\times 10^{11}$, M s^{-1}	n[b]
24	2.00	0.62	7.2	3.2
45	2.00	0.94	5.8	3.8
24	4.00	0.89	10.0	2.3
45	4.00	1.36	8.4	2.6
22	8.00[c]	0.85	10.7	2.1
24	8.00	0.78	9.0	2.6
24	8.00	0.85	9.8	2.3
45	8.00	1.67	10.3	2.1
25	8.00[c]	1.07	11.9	1.9
44	8.00[d]	1.72	10.8	2.0
45	8.00	1.55	9.0	2.4
46	8.00[d]	1.50	9.1	2.4
24	15.00	1.02	11.8	2.0
24	20.00	1.34	15.5	1.5
24	40.00	2.01	23.3	1.0
48	40.00	2.90	16.8	1.3

[a] 95:5 water/acetonitrile treated with 1×10^{-6} M EDTA. [b] $n = \Delta RO_2/\Delta[PIP]$; $\Delta RO_2 = 0.4\ \Delta[ABN]$. [c] Water treated with Chelex resin. [d] $[ABN]_0 = 4.0 \times 10^{-4}$ M.

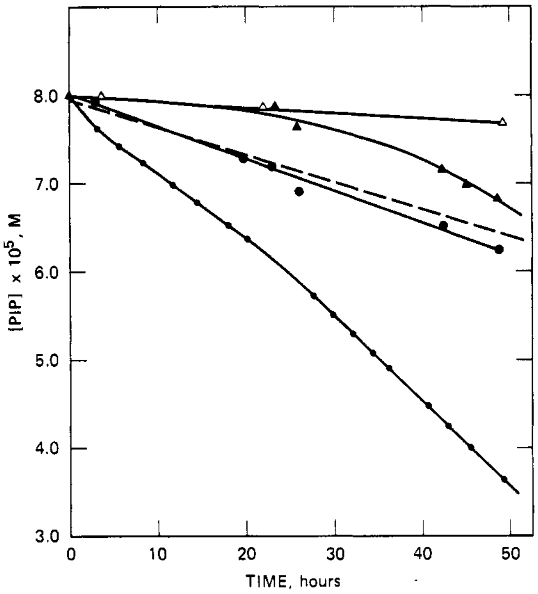

Figure 1. Oxidation of PIP in the presence of Fe^{2+} or EDTA in Milli-Q water: (△) 5×10^{-4} M Fe^{2+}; (▲) 1.7×10^{-4} M Fe^{2+}; (●) 2.7×10^{-5} M Fe^{2+}; (---) 1×10^{-6} M EDTA; (–•–) Milli-Q water.

To further investigate this phenomenon and establish the identity of the active trace metal(s) ions, we examined the effect of Fe^{2+}, Fe^{3+}, Mn^{3+}, Na^+, and Cu^{2+} on oxidations of PIP (Table V). We found that Fe^{2+} at 2×10^{-5} M inhibits oxidation of PIP for several hours. When all of the Fe^{2+} has been converted to Fe^{3+}, oxidation begins at the rate found in water treated with Chelex, which removes metal ions. The stoichiometry of the inhibited reaction of RO_2 with Fe^{2+} was nonintegral (about $3Fe^{2+}/RO_2$), suggesting that as ROOH formed it also oxidized Fe^{2+}. Added Fe^{3+} had no effect on the rate of oxidation of PIP, but Cu^{2+} showed a significant catalytic effect: 1×10^{-5} M increased the rate of oxidation of PIP by about a factor of 2, similar to the rate factor for Milli-Q-treated vs. EDTA-treated water.

Some additional insight into the mechanism of metal ion catalysis in the oxidation was provided by experiments summarized in Table VI. Mixtures of PIP, 2-(hydroperoxy)-2-cyanopropane, and Cu^{2+} or Fe^{2+}, but no azoinitiator, were heated at 50 °C for 4–24 h, and the loss of phenol was measured; control solutions with no metal showed little or no change. The important observation is that although neither Fe^{2+} or Fe^{3+} showed any reaction with hydroperoxide that caused oxidation of the PIP; Cu^{2+} gave a marked rate of oxidation of phenol but only in the

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Table V. Effect of Metals and EDTA on Oxidation Rate of *p*-Isopropylphenol (PIP) in Milli-Q Water at 50 °C^{a}

time, h	metal or EDTA	[M^{n+}], M	[PIP]$_0$ × 10^5, M	Δ[PIP] × 10^5	rate × 10^{11}, M s^{-1}
23.0	none	0	4.00	1.49	18.0
21.0	none	0	4.00	1.80	23.0
20.0	none	0	8.00	1.83	25.0
20.5	NaCl	0.015	4.00	1.35	18.0
24.0	NaClO$_4$	0.20	8.00	2.23	26.0
22.5	Fe^{2}	1 × 10^{-6}	8.00	1.86	23.0
20.0	Fe^{2}	2.7 × 10^{-5}	8.00	0.69	9.6
23.0	Fe^{2}	1.7 × 10^{-4}	8.00	0.12	1.4
22.5	Fe^{2}	5.0 × 10^{-4}	8.00	0.23	3.2
24.0	Fe^{3}	1.0 × 10^{-4}	8.00	2.10	23.0
24.0	Cu^{2+}	1.0 × 10^{-5}	8.00	3.20	37.0
24.0	EDTA	5 × 10^{-6}	8.00	0.90	10.0
21.0	EDTA	2 × 10^{-5}	8.00	0.69	9.1
21.0	EDTA	16 × 10^{-5}	8.00	0.72	9.5

^{a} 95:5 water/AN with 4.0 × 10^{-4} M ABN.

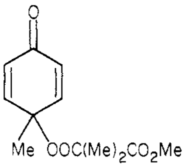
Table VI. Oxidation of PIP with Hydroperoxide and Metal Ions in Chelex Water at 50 °C^{a}

time, h	metal	[metal] × 10^6	Δ[PIP] × 10^5
20.0	none	0	0.05
20.0	Fe^{2+}	2.7	0
20.0	Fe^{3+}	2.7	0
20.0	Cu^{2+}	13	2.8
4.5	Cu^{2+}	2.6	2.7
20.0	Cu^{2+}	2.6	2.7
3	Cu^{2+}	0.25	0.14
24	Cu^{2+}	0.25	0.60
23	Cu^{2+}	2.7^{b}	0

^{a} Reaction mixture consisted of 4 × 10^{-5} M 2-(hydroperoxy)-2-cyanopropane and 8 × 10^{-5} M PIP in 95:5 H$_2$O/AN; concentrations in M. ^{b} No added hydroperoxide.

presence of the hydroperoxide. As little as 3 × 10^{-6} M Cu^{2+} caused a loss of 30% of PIP in 4 h. A reaction time of 24 h gave the same result, indicating that reaction of the metal with peroxide to form radicals is rapid. Neither Cr nor Mn, when added with Cu, gave any added effect. Probably these metals had no independent reaction with peroxide. The reactivity of Cu^{2+} ion added at the parts per billion (3 × 10^{-7} M) was much less marked. The effect of added Cu on the products is discussed below.

Oxidation Products. Several mixtures of ACP and PC were heated in water alone at 50 °C for up to 113 h and were analyzed by HPLC for loss of PC and formation of products. Table VII summarizes the results. The most important product of oxidation of PC by ACP is the peroxycyclohexadienone. At high initial concentration of PC, we also identified some PC dimers as biphenol **2** and Pummerer's ketone **3**,[13] but these products formed only in trace quantities at low initial concentrations of PC. The slight increase (a factor of 2) in *p*-hydroxybenzoic acid with a 10-fold increase in PC is probably within experimental error. Material balances on PC lost are only fair. The proportion of dimers formed increases with increasing initial concentrations of PC.



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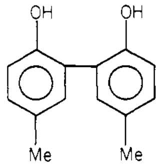

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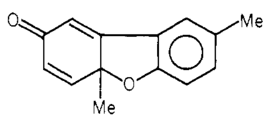

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Table VIII shows products analysis for oxidations of PIP with ABN. The distribution of products as a function of

Table VII. Product from Oxidation of PC with ACP in Water at 50 °C^{a}

time, h	[PC]$_0$	Δ[PC]	[HOPhCOOH]	[peroxy-dienone]	[PC], [dimers]^{b}	material balance,^{c} %
42	220	10	0.23	2.4	0.8, 1.8	73
113	220	13.6	0.38	3.9	0.6, 2.6	79
42	22	0.68	0.073	0.25	trace	48
113	22	1.25	0.18	0.5	trace	54

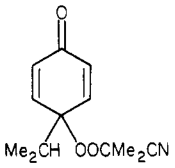
^{a} [ACP]$_0$ = 1.2 × 10^{-4} M; concentrations in M × 10^6. ^{b} Dimers:Pummerer's ketone, biphenol. ^{c} (Σproducts/Δ[PC]) × 100, where dimer = 2[PC].

Table VIII. Products of Oxidation of PIP in Milli-Q Water

additives	[PIP] × 10^5	Δ[PIP] × 10^5	[peroxy-dienone]	[dimers]	[quinone]	balance,^{b} %
none	4.00	1.49	0.40	0.20	0.02	55
none	8.00	1.83	0.13	0.50	0.03	63
0.2 M NaClO$_4$	68.00	2.23	0	0.70	0.07	66
2 × 10^{-5} M EDTA	8.00	0.69	0.45	0	0.01	65
1 × 10^{-5} M Fe^{3+}	8.00	1.96	0.10	0.50	0.05	28
1 × 10^{-5} M Fe^{2+}	8.00	0.69	0.4	0.06		67

^{a} Concentrations in M. ^{b} (Σproducts/Δ[PIP]) × 100, where dimer = 2[PIP].

initial reactant concentrations and the material balances are very similar to results found with PC. Where little dimer was detected by HPLC, the principal product was shown to be the peroxycyclohexadienone 4 by isolation, UV spectral analysis, and analogy with the properties of 1.



4

The small (2–5%) yields of *p*-hydroxybenzoic acid found in the oxidation of PC probably does not arise from direct oxidation of PC at the *p*-methyl group because the phenolic OH is much more reactive.[3,15] A possible source of this acid is oxidation of a quinomethide intermediate formed by reaction of RO_2 or O_2 with the penoxy radical. Further oxidation of this intermediate to the aldehyde and acid are probable, but unproved, processes.

$$CH_3C_6H_4O\cdot + RO_2 \rightarrow CH_2C_6H_4O + RO_2H \quad (10)$$

2-(Hydroperoxy)-2-cyanopropane[14] derived by abstraction of the PIP phenolic hydrogen by $Me_2C(CN)O_2\cdot$ could not be detected by HPLC owing to its weak absorbance. However we confirmed its presence in PIP reaction mixtures by showing that the HPLC eluant at the retention volume corresponding to the elution of authentic hydroperoxide (at high concentrations) contained nearly the expected amount of oxidizing agent as detected by Ce^{4+} fluorescence,[15] about 6×10^{-6} M. An observable HPLC peak eluting in the same position as the hydroperoxide was found by spectral analysis and comparison with an authentic sample to be *p*-benzoquinone. We believe the quinone originates with cleavage of peroxydienone probably by a radical process and possibly initiated by trace Cu^+. However, as shown in Table VIII, quinone appears in most reactions, including those containing EDTA, thus ruling out metal ion catalyzed cleavage as the sole route.

Discussion and Conclusion

The general features of peroxy radical oxidation of unhindered phenols in water are very similar to those reported in organic solvents.[2,3,13,16,17] Inhibition by Fe^{2+} indicates that H-atom transfer from phenol to $RO_2\cdot$ is at least as rapid as in organic solvents. The reaction of Fe^{2+} with $HO_2\cdot$ is reported to have a rate constant of 1×10^5 M^{-1} s^{-1} at 25 °C.[18] If this value applies to reaction of Fe^{2+} with RO_2, we estimate that k_2 has a value of about 10^4 M^{-1} s^{-1}, very close to values for unhindered phenols in organic solvents.[3]

A striking feature of these simple phenol oxidations is the complexity of the product mixtures, shown by the HPLC and mass spectral analyses, and mass balances, which account for only two-thirds of the oxidized phenols. The proportion of peroxydienones and dimers is consistent with the idea that rates of combination of phenoxy and peroxy radicals with themselves and each other is controlled by the relative proportions of phenol and peroxy radical. In contrast, hindered phenols generally exhibit much similar product mixtures made up largely of the corresponding peroxydienones (although some dimers do form when peroxy radicals are scarce).[16,17] This situation seems to be true of oxidations both in organic solvents and in water. Probably the main difference between simple and hindered phenol oxidation pathways lies in the ease of ortho substitution by $RO_2\cdot$ or oxygen[19] in simple phenoxy radicals, followed by cleavage to *o*-quinone and further reaction of these reactive intermediates.

Experimental Section

Reactant Materials and Products. *p*-Cresol and *p*-isopropylpehnol were vacuum distilled or recrystallized from hexane; HPLC analysis showed less than 1% impurities in either phenol. Commercial ABN was used as received; ACP was prepared by the method of Mortimer[20] and recrystallized at low temperature from pentane; mp. 32–34 °C dec. Both azoinitiators were analyzed for available nitrogen by heating them is sealed tubes on a vacuum line for 10–20 half-lives and measuring evolved nitrogen on a Toepler pump; percent N_2 ranged from 94–103%. Solutions of these chemicals in 95:5 water/acetonitrile (AN) were effected by dissolving the phenol and azoinitiator together in pure AN and diluting 5 mL of solution with 95 mL of water.

Water used in these experiments was obtained from a Millipore Corp. Milli-Q purification system. Chelex-treated water was prepared by adding one volume of Chelex-100 resin (Bio-Rad Labs) to five volumes of Milli-Q water, stirring for 2 h, filtering to remove resin, and neutralizing to pH 6 with $HClO_4$.

Pummerer's ketone and 2,2′-dihydroxy-4,4′-dimethylbiphenyl were synthesized and isolated following published methods.[13] *p*-Hydroxybenzoic acid was a commercial sample. 2-(Hydroperoxy)-2-cyanopropane (4) was prepared by the method of Talat-Erben and Onol.[14] The hydroperoxide was purified by preparative HPLC and the liquid hydroperoxide separated from eluant by ether extraction. Iodometric titration gave 107% ROOH. Decomposition of 4 in 0.1 N NaOH gave 98% acetone by HPLC analysis.

4-Methyl-4-[[2-(carboxymethyl)propyl]-2-peroxy]-2,5-cyclohexadienone (1), peroxycyclohexadienone 1, was prepared in millimolar quantities by oxidizing PC with ACP at 50 °C in acetonitrile. The product was isolated by separation and reinjection on an analytical (30 cm × ~4 mm) C18 μBondapak HPLC column and was collected. The separated product fraction (35:65 AN/H_2O) was extracted with five 1-mL portions of CH_2Cl_2, followed by evaporation of the solvent under N_2 to give 0.67 g of white solid; mp 54 °C (4% yield). The product was characterized by ^1H NMR and UV spectra; ϵ_{254} 1270 M^{-1} cm^{-1}. CH analysis, calculated percent, C 60.00, H 6.66; found, C 60.22; H 6.66. The NMR spectrum is simple: δ 6.38 (s), 1.43(s), 4.77(s), and two doublets at δ 6.19, 6.28 and δ 6.85, 6.96. The UV spectrum exhibits a strong band at 237 nm (log ϵ ~4).

4-Isopropyl-4-[(2-cyanopropyl)-2-peroxy]-2,5-cyclohexadienone (4) was isolated from the same kind of reaction mixture used for preparing the hydroperoxide. The toluene mixture was concentrated and repeatedly extracted with 5% AN and 95% H_2O was purified by HPLC and isolated by ether extraction: UV λ_{max} at 233 nm; (95:5 H_2O/AN) IR 6.0, 6.2 cm^{-1} (carbonyl); mass spectrum, *m/e* 135 (M − 100). The loss of the 2-cyanopropyl peroxy moiety (M_r = 100) parallels the loss of oxygen from fragmentation for 4-(hydroperoxy)dienones.[21] The dimer was prepared by HO oxidation of PIP by a method similar to one described by Cosgrove and Waters.[22] The dimer was isolated by ether extraction and purified by preparative HPLC: *m/e* 270 (M), 255 (M − CH_3); UV λ_{max} 244 (ϵ ~3300), 289 (2400); IR 3.1 (s), 6.2, 6.3, 6.7 (s). The dimer was tentatively assigned an ortho to para coupling on the basis of the 244-nm band, which is close to maxima for 2,5-cyclohexadienones and by extraction into water with dilute alkali.

Kinetic Methods. All glassware was baked at 500 °C and maintained sterile in use to avoid biodegradation. Reaction flasks

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were 50- or 100-mL volumetric flasks fitted with threaded necks that were closed with Mininert values (Precision Sample Co).

Blank solutions (no initiator) were heated (additional aliquots stored cold) to demonstrate that no PC or PIP was lost by volatilization. Oxidation experiments were prepared by diluting solutions of ACP or ABN in PC or PIP stock solutions to give the desired concentrations of reactants and heated at 50 ± 0.01 °C. Reaction blanks and oxidized solution were stored at 4 °C in a refrigerator until analyses could be made.

Analytical Methods. We analyzed reaction solutions of PC or PIP by using reverse-phase HPLC with gradient elution. Two Waters Associates M6000A pumps controlled by an M660 solvent programmer were used to pump the solvent through a 4 mm × 30 cm μBondapak C18 column at 2 mL/min. Solvents were high-purity water and Burdick and Jackson "Distilled in Glass" UV-grade acetonitrile (AN) for *p*-cresol. The solvent gradients were 20–35% AN/H_2O for 15 min with linear programming. Analyses were run at 2 mL/min total flow. Detection by UV photometer at 254 nm was with a Shoeffel Instruments SF770 flow monitor or Waters Associates M440 detector. Analyses for ABN or ACP were done at 330 nm.

Field ionization mass spectra were prepared from 10–30 μL of CH_2Cl_2 solutions of compounds injected into the cooled inlet part of the SRI-designed spectrometer. The molecular-weight profile for reaction mixtures was scanned from 90–490 amu. The temperature was raised ~ 2°/min from −30 to 300 °C at 8 kV. Data from repeated scans of 400 amu each were fed into a 4000-channel analyzer, stored, and collectively printed as a single spectrum. Molecular ions (P) or P + 1 peaks were used to detect the presence of ACP coupling products, PC dimers, PC peroxycyclohexadienone and *p*-hydroxybenzoic acid.

An LKB Model 9000 GC/MS with a PDP-11 computer was used to identify the phenol PIP dimer and peroxycyclohexadienone.

^{1}H NMR spectra were measured on a Varian 100-mHz NMR spectrometer.

Acknowledgment. We thank Drs. David Thomas and Sidney "Bud" Buttrill at SRI for preparation of mass spectral data. This work was supported by NSF Grant No. ENV76-11153. Maria Buyco prepared the several drafts of the manuscript.

Registry No. 1, 85553-41-9; 4, 85553-42-0; PIP, 99-89-8; PC, 106-44-5; ACP, 2589-57-3; ABN, 78-67-1; Cu^{2+} ion, 15158-11-9; Fe^{2+} ion, 15438-31-0.

Supplementary Material Available: table of NMR Analysis of ACP decomposition products (1 page). Ordering information is given on any current masthead page.

Stereochemistry of Cyanide Ion Addition to 3,4,5,6-Tetrahydropyridinium Derivatives

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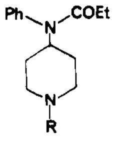
The stereochemistry of cyanide ion addition to 1-alkyl-4-(*N*-phenylpropanamido)-3,4,5,6-tetrahydropyridinium salts **2** was investigated by analysis of the ^{1}H NMR spectra of the isolated α-amino nitriles. The data obtained, together with epimerization studies, indicated that the addition occurred in a stereospecific manner to afford the trans diastereoisomers.

We have previously reported[1] on a convenient synthetic method for the α-cyanation of tertiary amines. The procedure consisted of reacting the corresponding amine oxide with trifluoroacetic anhydride followed by the addition of cyanide ion to the iminium intermediate that had been generated in the reaction. This procedure was successfully applied to a number of piperidine-containing opioids. We now report on the stereochemical consequences of this reaction when conducted on 1,4-disubstituted piperidine derivatives **1**.

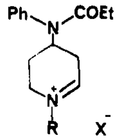


1

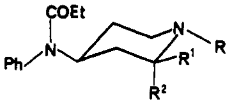
a, R = Me
b, R = CH₂Ph
c, R = CH₂CH₂Ph

Results and Discussion

Since the cyanation procedure using **1** involved the formation of the iminium intermediate **2**, cis and trans diastereomeric products (**3–5**) can be envisaged as arising from the addition of cyanide ion to either side of **2**.



2



a, R¹ = H , R² = CN
b, R¹ = CN , R² = H

3 R = Me
4 R = CH₂Ph
5 R = CH₂CH₂Ph

Moreover, molecular models revealed that both faces of the iminium double bond in **2** are equally accessible to nucleophilic attack when the bulky 4-(*N*-phenylpropanamido) group[2] is in the thermodynamically preferred equatorial conformation.

It was therefore unexpected to find that only one diastereomer **3a** (38%) had formed in this reaction in view

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