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Oxidation of Styrene Derivatives by $S_2O_8^{2-}$–Cu^{II} in Acetic Acid and Acetonitrile. Reaction Paths in Oxidations via Radical Cations

Cheves Walling,* Gamil M. El-Taliawi,[1] and Kalyani Amarnath

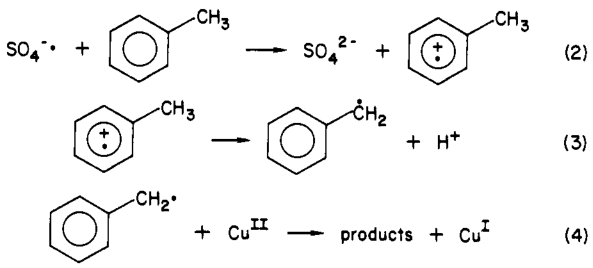
Contribution from the Department of Chemistry, University of Utah,
Salt Lake City, Utah 84112. *Received April 30, 1984*

Abstract: β-Aryl carbonyl compounds are major products in the oxidation of a variety of styrene derivatives by $S_2O_8^{2-}$–Cu^{II}. Evidence is presented that they arise via oxidation to a radical cation, nucleophilic addition of water to give a β-hydroxyalkyl radical, Cu^{II} oxidation to epoxide, and finally acid-catalyzed rearrangement. Data on oxidation of alkyl aromatics with additional functional groups are presented. With ether and amino groups, oxidation occurs at the functional group even when it is remote from the aryl nucleus. These and previous data are summarized to give a coherent picture of the various paths by which aryl side chains may be degraded via initial radical cation intermediates.

Extensive evidence indicates that the oxidation of aromatic side chains often involves, as an initial step, the formation of an aromatic radical cation, followed by proton loss to yield a benzylic radical, or by some other side-chain fragmentation. Such a path has been proposed for oxidations involving OH· and $SO_4^{-}\cdot$ radicals,[2-5] a variety of higher valence metals such as Co^{III},[6] anodic oxidations,[7] and several other processes.

Oxidations employing $S_2O_8^{2-}$–Cu^{II} in slightly aqueous acetic acid or acetonitrile provide a convenient system for generating and studying such radical cation reactions, and we have recently reported results with a variety of alkylbenzenes[8] and (hydroxyalkyl)benzenes.[9] The overall reaction is a redox chain, e.g., for toluene oxidation

$$S_2O_8^{2-} \longrightarrow 2SO_4^{-}\cdot \qquad (1)$$



$$Cu^{I} + S_2O_8^{2-} \longrightarrow Cu^{II} + SO_4^{-}\cdot + SO_4^{2-} \qquad (5)$$

In this scheme the side-chain cleavage (eq 3) (which, with more complex side chains, may also involve C–C bond scission) depends solely upon the properties of the radical cation, but the final products are determined by the oxidation of an intermediate radical by Cu^{II} (step 4). It now appears that this oxidation actually involves the formation of a transient organocopper species (formally Cu^{III}) as originally proposed by Kochi,[10] which, depending upon its structure, can decompose in a number of ways: by loss of a β-proton to yield olefin, by ligand transfer from Cu to C, by solvolysis to yield a carbocation with accompanying rearrangements, or by internal displacement by another functional group.[11]

Table I. Oxidations of Styrene and Phenylacetaldehyde

conditions[a]	HOAc	AN	AN[d]	AN–OAc	HOAc[e]	AN[e]
% conversion	58	49	97	9.7	63	58
products[b]						
PhCHO	17	33	68	76	27	66
$PhCH_2CHO$	45	67	32	24		
PhCH=CHOAc	24[c]					
PhCH(OH)-CH_2OAc	14					
$PhCH_2OAc$					61	3
$PhCH_2OH$					12	31

[a] 2, 2, and 1 mmol of substrate (styrene unless noted), $(NH_4)_2S_2O_8$, and $Cu(OAc)_2$ in 5 mL of acetic acid (HOAc) or acetonitrile (AN) + 1 mL of H_2O, 0.5–2 h at 100 °C; OAc indicates 5 mmol of NaOAc present; percent conversion indicates percent of substrate consumed. [b] As percent of substrate reacted. [c] Equal quantities, two isomers. [d] 4 mmol of $S_2O_8^{2-}$. [e] Phenylacetaldehyde substrate.

Table II. Oxidations of 1,1-Diphenylethylene (DE) and Stilbene (S)

substrate	DE	DE	DE	S
conditions[a]	HOAc	AN	AN–OAc	HOAc
% conversion	70	57	27	55
products				
PhCHO				6
Ph_2CO	13	30	60	
Ph_2CHCHO	87	70	40	13
$PhCH_2COPh$				3
PhCH(OAc)CHOHPh				78

[a] Cf. Table I.

Thus β-hydroxy radicals are oxidized to epoxides,[12] while, as we have shown,[9] more remote hydroxyls can give rise to a variety of larger ring ethers. When it is possible, β-proton loss is often the chief path of decomposition of such organocopper species, and, consistent with this, we found that styrenes were commonly major initial products of oxidation of substrates with side chains of two or more carbons.[8,9] Accordingly, it was of interest to examine the further oxidation of a variety of styrenes, to map out in more detail the successive steps in the degradation of complex side chains.

This paper describes our results, together with the oxidative behavior of some other side-chain functional groups. Finally, we summarize our findings to date in terms of the side-chain cleavage patterns of different types of radical cation, relative rates of oxidation of initial substrates and intermediate products, and new data supporting the reaction scheme proposed.

Results

Styrene Oxidations. Unless indicated, oxidations were carried out at 100 °C in 5:1 acetic acid (or acetonitrile)/water, using 1:1:0.5 $S_2O_8^{2-}$/substrate/$Cu(OAc)_2$, and products analyzed by

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[1] Visiting Associate Professor, University of Cairo, Cairo, Egypt.
[2] Norman, R. O. C.; Storey, P. M. *J. Chem. Soc. B.* **1970**, 1099.
[3] Snook, M. E.; Hamilton, G. A. *J. Am. Chem. Soc.* **1974**, *96*, 860.
[4] Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125.
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[7] Eberson, L.; Nyberg, K. *Acc. Chem. Res.* **1973**, *6*, 1777.
[8] Walling, C.; Zhao, C.; El-Taliawi, G. M. *J. Org. Chem.* **1983**, *48*, 4910.
[9] Walling, C.; El-Taliawi, G. M.; Zhao, C. *J. Org. Chem.* **1983**, *48*, 4914.
[10] Kochi, J. K.; Bemis, A.; Jenkins, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 4038, 4616.
[11] For a general discussion, cf.: Kochi, J. K. In "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 11.
[12] Buxton, G. V.; Green, J. C.; Higgins, R.; Kongi, S. *J. Chem. Soc., Chem. Commun.* **1976**, 158.

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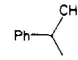
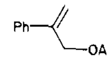
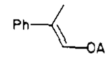
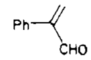
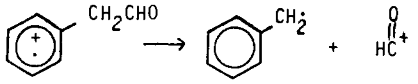
Table III. Oxiation of α-Methylstyrene

conditions[a]	HOAc	HOAc–OAc	AN	AN[b]	AN–OAc
% conversion	97	81	79	37	12
products					
	91	13	58	56	9
PhCOCH$_3$	9	14	41	27	59
		62			
		4			13
			1	23	17

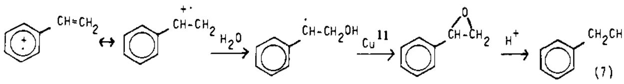
[a] Cf. Table I. [b] No H_2O added.

GC-MS as described further in the Experimental Section. Results for styrene, 1,1-diphenylethylene, and stilbene appear in Tables I and II. It may be noted that here and in subsequent tables, while material balances are generally good, the amount of substrate actually oxidized is quite variable, since some $S_2O_8^{2-}$ is consumed by further oxidation of intermediates and attack on solvent. The tables show that the major products from styrene oxidation are phenylacetaldehyde and benzaldehyde, while 1,1-diphenylethylene correspondingly gives diphenylacetaldehyde and benzophenone. Phenyl- and diphenylacetaldehyde are evidently initial products and are subsequently cleaved to benzaldehyde and benzophenone, respectively. Thus, in the runs in acetonitrile in Table I, the benzaldehyde/phenylacetaldehyde ratio increases with increasing oxidant, and the cleavage occurs readily when phenylacetaldehyde itself is oxidized. The reaction thus parallels the facile cleavage of β-arylalkanols,[9] since it also leads to stable radical and cationic products


(6)

and the products of oxidation of phenylacetaldehyde itself are essentially those observed from benzyl radicals derived from other precursors.[8]

The mechanism of initial formation of the phenylacetaldehydes is less obvious, but, as we shall see, formation of β-arylaldehydes or ketones is, in fact, characteristic of most styrene oxidations. The following sequence appears plausible Reversible hydration


(7)

of radical cations is well established,[3,5,6] epoxides are known products of the Cu^{II} oxidation of aliphatic β-hydroxy radicals,[12] and aryl-substituted epoxides readily rearrange in acid media. In acetic acid, addition of acetate must compete with addition of water to the radical cation, accounting for the vinyl and hydroxy acetate products observed in that solvent. Oxidation of stilbene, Table II, supports such an epoxide intermediate, since, if $S_2O_8^{2-}$–Cu^{II} is first decomposed in acetic acid, stilbene oxide then added, and the mixture heated, essentially the same mixture of addition and rearrangement products is observed.

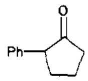
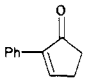
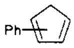
Results of oxidations of α- and β-methylstyrene and allylbenzene are listed in Tables III and IV. The first two show a similar pattern, giving high yields of α-phenylpropionaldehyde and phenylacetone, respectively, under most conditions but products consistent with acetate addition to the radical cation when oxidations were carried out in the presence of added acetate ion. Again the facile cleavage of α-phenylpropionaldehyde was demonstrated, since its oxidatiion in acetic acid gave a 6:5 mixture of acetophenone and α-phenylethyl acetate as sole products.

Table IV. Oxidation of β-Methylstyrene (BM) and Allylbenzene (AB)

substrate	BM	BM	BM	AB	AB
conditions[a]	HOAc	HOAc–OAc	AN	HOAc	AN
% conversion	55	63	55	28	26
products					
PhCHO	12	11	12	23	64
PhCOCH$_2$CH$_3$	1.5	7			
PhCH$_2$COCH$_3$	82	10	88	62	21
PhCH=CHCH$_2$OAc		8[b]			
PhCH(OAc)CH=CH$_2$		64			
unidentified				15	15

[a] Cf. Table I. [b] Two isomers.

Table V. Oxidation of 1-Phenylcyclopentene

conditions[a]	HOAc	HOAc–OAc	AN	AN–OAc
% conversion	64	65	50	23
products				
	94	80	90	23
	6	14	10	5
	Tr	6		72

[a] Cf. Table 1.

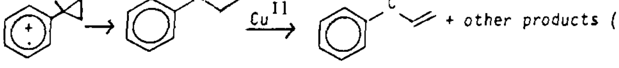
Allylbenzene is less readily oxidized than β-methylstyrene, as indicated by lower conversions and lower reactivity in competitive reactions (see below). Major products are again benzaldehyde and phenylacetone, together with a small amount of an unidentified product.

Oxidation products of some phenylcycloalkenes and alkanes are listed in Tables V–VIII. 1-Phenylcylopentene (Table V) gives high yields of 2-phenylcyclopentanone under most conditions, but 6% of what is evidently a phenylcyclopentadiene in acetonitrile–acetate. This is the least acidic medium we have employed, so proton loss from the radical cation may be favored, but the exact path of this sort of a dehydrogenation is obscure. With indene (Table VI) 2-indanone is the major product in acetonitrile, but in acetic acid 3-indenol is produced instead, either by competitive loss of an allylic proton from the radical cation or by an alternate rearrangement of the epoxide. Similar oxidation of indane gives not only indene, but also appreciable 1-indanone and 1-indanyl acetate. Evidently in the Cu^{II} oxidation of the 1-indanyl radical, some substitution competes with β-elimination.

With six-membered rings, dehydrogenation becomes a more important reaction path. With 1-phenylcyclohexene (Table VII) phenylcyclohexadienes and biphenyl are major products, together with some 2-phenylcyclohexanone and its cleavage product, 6-phenyl-5-hexenal. Apparently phenylcyclohexane is initially oxidized chiefly to 1-phenylcyclohexene, which is evidently quite stable in acetonitrile, but is further oxiddized in acetic acid.

1,2-Dihydronaphthalene as another six-membered ring olefin was not examined directly, but oxidation of tetralin (Table VIII) shows that it is a major initial product and is converted in turn to β-tetralone and naphthalene.

Finally, the oxidation of phenylcyclopropane was examined, since electrolytic oxidation in methanol is reported to give 1-phenyl-1,3-dimethoxypropane, and the nature of the ring opening is of interest.[13] Table IX shows that in acetic acid 1-phenyl-1-acetoxycyclopropane is formed in high yields, as would be expected if proton loss was the chief cleavage path of the initial radical cation. Ring opening is more extensive in acetonitrile Here, proton loss should have led to 1-phenylcyclopropanol as the initial product, and we suggest that ring opening involves its further oxidation, aided by relief of ring strain and analogous to the behavior of other benzylic alcohols.[9]


(8)

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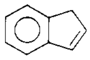
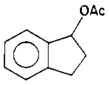
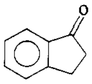
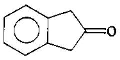
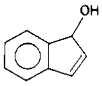
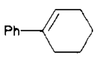
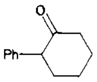
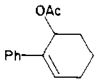
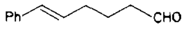
(13) Shono, T.; Matsumura, Y. *J. Org. Chem.* **1970**, *35*, 4157.

Table VI. Oxidation of Indene and Indane

substrate	indene	indene	indene	indane	indane	indane
conditions^a	HOAc	AN	AN–OAc	HOAc	HOAc–OAc	AN
% conversion	62	84	34	54	62	34
products						
				80	58	77
				4	27	
	3	2	28	16	13	35
	20	98	66			
	77		6			

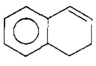
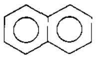
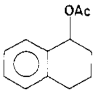
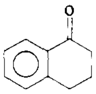
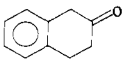
^{a} Cf. Table I.

Table VII. Oxidation of 1-Phenylcyclohexene and Phenylcyclohexane

substrate		hexene	hexane	hexane
conditions^a	HOAc	AN	HOAc	AN
% conversion	70	47	24	21
products				
			7	~100
PhC_6H_7^{b}	29	23	28	
PhPh	29	43	21	
	1.4		9	
unknown	9	16	11	
	6			
	25	18	24	

^{a} Cf. Table I. ^{b} Phenylcyclohexadienes (3 isomers).

Table VIII. Oxidation of Tetralin

conditions^a	HOAc	HOAc–OAc^b	AN
% conversion	34	71	45
products			
	53	40	70
	26	22	12
		38	
	9		
	12		18

^{a} Cf. Table I. ^{b} No water added.

Oxidations Involving Other Side-Chain Substituents. Our previous work has shown that side-chain substituents, hydroxyl and carbonyl groups, strongly influence the competition between benzylic C–H and C–C scission of radical cations. We have now examined several other functional groups, with the significant finding that often oxidation may occur at the functional group, even when it is quite remote from the benzene ring.

Table IX. Oxidation of Phenylcyclopropane

conditions^a	HOAc	HOAc–OAc	AN	AN–OAc
% conversion	40	75	71	59
products^b				
AcO Ph	73	76		
PhCHO	11	6	16	17
$PhCOCH{=}CH_2$	12	8	49	17

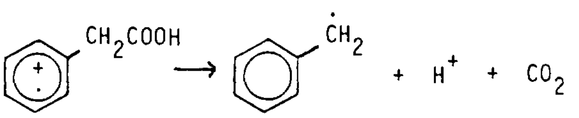
^{a} Cf. Table I. ^{b} Several other minor products detected.

Table X. Oxidation of β-Phenylpropionic Acid

conditions^a	HOAc	AN	AN–OAc
% conversion	66	55	48
products^b			
benzaldehyde	1.4	3	8
benzyl acetate		13	
ethylbenzene	25	49	45
styrene	26	8	11
β-phenylethyl acetate	2	2	
phenylacetaldehyde		9	11
2-chromanone	26		6

^{a} Cf. Table I. ^{b} Plus several additional minor and unidentified products.

The ready decarboxylation of the radical cation of phenylacetic acid is well established in aqueous solution[4]



(9)

and we obtain the same results in acetic acid and acetonitrile, leading to benzyl acetate or benzyl alcohol and benzaldehyde as major products. On the other hand, oxidation of γ-phenylbutyric acid gives δ-phenylbutyrolactone in high yield, presumably via initial loss of a benzylic proton followed by cyclization during collapse of the intermediate organocopper species, again paralleling results in water.[14,15]

Oxidation of β-phenylpropionic acid provides an interesting intermediate case (Table X), since here decarboxylation and proton loss evidently compete. Styrene, ethylbenzene, β-phenylethyl acetate, and phenylacetaldehyde are clearly decarboxylation products, while 2-chromanone must arise from benzylic proton loss, paralleling the formation of chroman from 3-phenylpropanol.[9] The striking observation is that decarboxylation is still the major

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(14) Clerici, A.; Minisci, F.; Porta, D. *Tetrahedron Lett.* **1974**, 4183.
(15) Walling, C.; Camaioni, D. M. *J. Org. Chem.* **1978**, *43*, 3266.

Table XI. Oxidation of Benzyl Methyl Ether

conditions	HOAc	HOAc–OAc[b]	AN[b]	AN–OAc[b]
% conversion[a]	36	82	74	63
products				
benzaldehyde	96	86	81	41
benzyl acetate	3			
methyl benzoate	1	13	18	59

[a] Cf. Table I. [b] Average of 2 runs, ±3%.

Table XII. Oxidation of 1-Phenylethyl Methyl Ether

conditions[a]	HOAc	HOAc–OAc[b]	AN[b]
% conversion	42	62	63
products			
acetophenone	68	91	91
1-phenylethyl acetate	28	7	2
1-phenylethanol	3	2	6

[a] Cf. Table I. [b] Average of 2 runs.

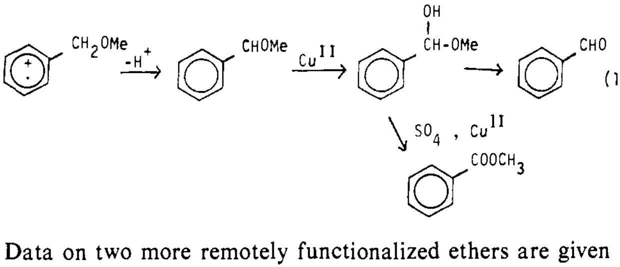
Table XIII. Oxidation of 2-Phenylethyl Methyl Ether

conditions[a]	HOAc	HOAc–OAc	AN	AN–OAc
% conversion	57	55	58	57
products				
benzaldehyde	12	8	13	4
benzyl acetate	17	21	1	15
benzyl alcohol	4		9	
phenylacetaldehyde	2		36	35
2-phenylethyl acetate	16	4	1	
2-phenylethanol	4	19	28	33
X[b]	36	46		2
Y[b]	10		9	

[a] Cf. Table I. [b] Unidentified high-boiling products, see text.

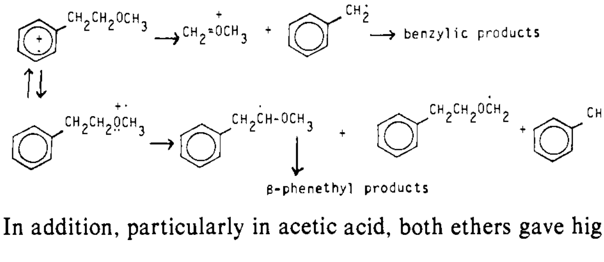
reaction path, despite the insulation of the carboxyl group from the aromatic ring by two CH_2 groups.

Snook and Hamilton have reported that $S_2O_8^{2-}$ oxidations of benzylic ethers in water give products similar to those from the corresponding alcohols.[3] Our own results appear in Tables XI and XII. (1-Phenylpropyl methyl ether in addition behaves quite similarly; a single run in acetic acid gave an 84% yield of propiophenone.) In general the results are consistent with initial benzylic proton loss, but it is noteworthy that, particularly in acetonitrile in the presence of acetate, benzyl methyl ether gives a substantial yield of methyl benzoate, perhaps by fast further oxidation of the intermediate hemiacetal, since benzaldehyde itself is very stable in these systems.



(10)

Data on two more remotely functionalized ethers are given in Tables XIII and XIV. Results here diverge from those with the corresponding alcohols, since the carbon side chains are largely retained and considerable oxidation occurs at the ether function. Gas-phase ionization potentials of alkylbenzenes and alkyl ethers are quite similar, so a plausible formulation is that oxidation actually involves a species with the odd electron on oxygen which then undergoes β-proton loss, or perhaps C–O cleavage.



(11)

In addition, particularly in acetic acid, both ethers gave higher molecular weight products the structures of which were not determined, but mass spectra indicated that the side chains had been retained and OH or acetate functions introduced in the benzylic position.

Table XIV. Oxidation of 3-Phenylpropyl Methyl Ether

conditions[a]	HOAc	HOAc–OAc	AN	AN–OAc
% conversion	60	59	64	61
products				
3-phenylpropyl acetate	12		2	
β-phenylpropionaldehyde	1	15	38	39
β-phenyl-1-propanol	3	11	41	34
M[b]	50	57	1	19
N[b]	27	9	10	5

[a] Cf. Table I. [b] Unidentified high-boiling products, see text.

Amines have even lower ionization potentials, so oxidation of the amino function would be anticipated. Here experiments were carried out in acetonitrile in the presence of acetate, since, in more acid media, the corresponding ammonium ions are quite stable and little oxidation is observed. Under these conditions, β-phenylethylamine is readily oxidized (89% conversion) to give styrene (36%) and β-phenylethyl acetate (60%) plus minor other products. Both products indicate C–N bond scission as the chief decomposition path. Benzylamine, under the same conditions, gives 88–96% benzaldehyde plus benzonitrile. Benzaldehyde is also a major product from *N*-methyl- and *N,N*-dimethylbenzylamine, although a number of minor products are formed as well.

Finally, oxidations of *N*-benzyl- and *N*-(β-phenylethyl)acetamides gave somewhat inconclusive results. Oxidations occurred readily, but major products were high molecular weight materials containing the original amide functions. Anodic oxidations of *N*-alkyl amides are known to give *N*-(α-acetoxyalkyl) amides,[16] and we suggest that the same thing is happening here.

Competitive Oxidation Rates. The reaction scheme of eq 1–5, by itself, implies that the relative rates of oxidation of two substrates should depend simply on their rates of initial oxidation to radical cations. However, electron exchange between aromatics and aromatic radical cations is a rapid process,[17] and we have suggested[8,9] that relative oxidation rates are actually determined by a much more complicated competition

$$\begin{tikzcd}
\mathrm{Ar} + \mathrm{SO_4^{-}\cdot} \arrow[d, "k_a"] & \mathrm{Ar} + \mathrm{SO_4^{-}\cdot} \arrow[d, "k_b"] \\
\mathrm{[Ar]^{+}\cdot} + \mathrm{Ar'} \arrow[r, shift left, "k_c"] \arrow[d, "k_e"] & \mathrm{Ar} + \mathrm{[Ar']^{+}\cdot} \arrow[l, shift left, "k_d"] \arrow[d, "k_f"] \\
\mathrm{Ar'\ products} & \mathrm{Ar'\ products}
\end{tikzcd} \qquad (12)$$

involving not so much the original rates of radical cation formation as the position and completeness of equilibrium between the radical cations and their relative rates of fragmentation. A major argument for this formulation was that benzylic alcohols are selectively oxidized relative to their parent hydrocarbons (for benzyl alcohol–toluene by a factor of ~19 in acetonitrile) in spite of the fact that with an electron-withdrawing group they would be expected to react more slowly with $SO_4^{-}\cdot$.[18] On the other hand, the radical cation of benzyl alcohol undergoes proton loss much more rapidly than does the toluene radical cation,[19] which could account for the difference observed. If the competition in (12)

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(16) Ross, S. D.; Finkelstein, M.; Petersen, P. G. *J. Am. Chem. Soc.* **1964**, *86*, 2745.

(17) Thermoneutral exchanges between aromatics and their radical ions occur at essentially diffusion controlled rates. A similar proposal of radical cation equilibration has been made by Minisci.[5]

(18) Rates of reaction of $SO_4^{-}\cdot$ with aromatics parallel their ease of oxidation, and the gas-phase ionization potentials of toluene and benzyl alcohol are 8.82 and 9.14 eV, respectively.

(19) In water, a difference of ~10^3 has been estimated. Walling, C.; Camaioni, D. M.; Kim, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 4814. Faster proton loss from the benzyl alcohol cation radical is also observed in acetonitrile. Pons, B. S., private communication.

Table XV. Relative Rates of Competitive Oxidations

run	substrates A	substrates B	medium	rel react A:B	source[a]
1	*p*-methoxytoluene	*p*-chlorotoluene	AN	5.4	b
2	*p*-xylene	*p*-chlorotoluene	AN	1.5	b
3	ethylbenzene	toluene	HOAc	1.8	
4	cumene	toluene	HOAc	1.04	
5	*tert*-butylbenzene	toluene	HOAc	0.32	
6	α-methylstyrene	toluene	HOAc	5.06	
7	$Ph_2C{=}CH_2$	toluene	HOAc	8.15	
8	α-methylstyrene	cumene	HOAc	10.5	b
9	α-methylstyrene	cumene	AN	3.1	b
10	β-methylstyrene	allylbenzene	AN	5.33	
11	ethylbenzene	$PhCH_2CH_2$-OAc	AN	7.75	
12	dihydronaphthalene	tetralin	AN	0.9	Table XIII
13	$PhCH_2CHO$	styrene	HOAc	0.04	Table I
14	$PhCH_2CHO$	styrene	AN	0.87	Table I
15	$PhCH_2CHO$	styrene	AN–OAc	40	Table I
16	Ph_2CHCHO	$Ph_2C{=}CH_2$	HOAc	0.21	Table II
17	Ph_2CHCHO	$Ph_2C{=}CH_2$	AN	0.78	Table II
18	Ph_2CHCHO	$Ph_2C{=}CH_2$	AN–OAc	6.6	Table II
19	$PhCH(CH_3)$-CHO	α-methylstyrene	AN	0.59	Table III
20	$PhCH_2COCH_3$	β-methylstyrene	HOAc	0.45	Table IV
21	benzyl alcohol	toluene	AN	19	b

[a] Direct competitions followed by substrate disappearance unless indicated. [b] From ref 8.

is correct, observed relative reactivities are determined by a combination of several rate constants, which cannot be resolved at this time.[20] Nevertheless, they are of empirical interest in predicting the behavior of new substrates and possible yields of intermediate products. Table XV lists a number of values, determined either by direct competitions or from yields of successive products from previous tables,[21] from which several conclusions can be drawn:

1. Oxidation is facilitated by electron-supplying groups and retarded by electron withdrawal (runs 1–3). This is well recognized and consistent with the stability of benzyl acetate and benzaldehyde[8] and the resistance of negatively substituted toluenes to persulfate oxidation.[6] Electron supply should stabilize and favor a radical cation in any equilibrium, and this is apparently more important than any resulting retardation in the rate of proton loss.[22]

2. Alkylbenzenes with benzylic hydrogen show similar reactivities, but *tert*-butylbenzene is relatively unreactive (runs 3–5).[23]

3. Styrenes are genrally oxidized more readily than alkyl aromatics (runs 6–10). The only exception appears to be in fused ring systems; dihydronaphthalene and tetralin show similar reactivities, and indane gives high yields of indene (Table VI). The α-methylstyrene–cumene data indicate that selectivity for olefin is higher in acetic acid (10.5) than in acetonitrile (3.1). Phenylcyclohexane and tetralin data (Tables VII and VIII) suggest similar differences.

4. Competitive rates of oxidation of β-arylcarbonyl compounds and styrenes from which they are derived (runs 12–20) show some variation with structure and a large variation with medium. The carbonyl compounds are rapidly oxidized further in acetonitrile containing acetate but are relatively stable in acetic acid. The reason is not obvious, but, as the tables show, acetic acid is clearly the preferred media if β-carbonyl compounds are the desired products from oxidations of styrenes or alkyl aromatics.

5. As noted earlier[8] and discussed above, benzylic alcohols are preferentially oxidized in the presence of alkyl aromatics (run 21). Although the experimental evidence that this is the consequence of rapid fragmentation of their radical cations is convincing,[22] the reason for this instability is unclear.

Summary

We believe we can now give a reasonably coherent picture of side-chain oxidations in our systems, both in terms of the chemistry of the initial radical cations, and the subsequent oxidation of intermediate radicals:

1. When possible, loss of a proton to yield a benzylic radical is the most characteristic reaction of alkyl aromatic radical cations and occurs with a wide variety of structures.

2. C–C bond cleavage may compete with proton loss when it leads to relatively stable radical and cationic fragments. Benzylic alcohols, ArCHOHR, undergo such cleavage to protonated benzaldehyde and R· when R· is a sufficiently stabilized species.[9] Similarly, β-aryl alcohols and carbonyl compounds are cleaved to benzyl radicals and presumably cationic oxygen-containing fragments.[24]

3. When side chains contain easily oxidized functional groups—ethers, amino groups, etc.—oxidation and cleavage may occur at that point in the molecule even when it is quite remote from the aryl group.

4. Carboxylic acids show unique behavior. Phenylacetic acids are rapidly decarboxylated, γ-phenylbutyric acid undergoes loss of a benzylic proton, but β-phenylpropionic acid reacts by both paths.

5. The radical cations of styrene derivatives behave as though the odd electron was partially delocalized into the double bond and react chiefly by nucleophilic addition of solvent to yield β-hydroxy or acetoxybenzylic radicals, although some minor products may be the consequence of competing proton loss to give an allylic radical. (E.g., β-methylstyrene gives a mixture of allylic acetates, and indene substantial 3-indenol.)

6. Competitive rates of oxidation of different substrates are determined largely by the relative rates of the above reactions and the relative stabilities of the respective radical cations, presumably because of rapid electron-transfer processes between substrate and radical cations.

7. In none of our studies where the above reactions are possible have we observed significant competing ring substitution, although ring substitution in aromatics without side chains is well established.[25] In water, the nature of this competition is well understood in terms of reversible nucleophilic addition of water to the radical cation, e.g.

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[20] Reaction scheme 12 leads to a complex expression, but, if equilibration is fast and essentially complete, it predicts d ln [Ar]/d ln [Ar′] = k_ek_d/k_ck_f, rather than k_a/k_b if equilibration is unimportant. In collaboration with Dr. B. S. Pons, we are currently examining rates of proton loss or other fragmentations of a variety of cation radicals in our media by an electrochemical-spectroscopic technique, cf.: Bewick, A.; Mellor, J. M.; Pons, B. S. *Electrochim.* Acta **1980**, *25*, 931.

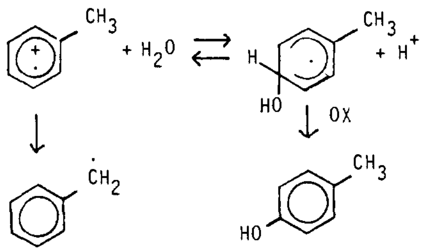
[21] For competitive reactions of A and B, the relation d ln [A]/d ln [B] = k_a/k_b has been asumed. When B is formed from A, reactions were assumed to be first order in A and B and the same order in other reactants. This gives the expression ln (1 + x[B]/[A] = x ln $[A]_o$/[A], where $x = 1 - k_b/k_a$, which must be solved numerically. As noted k_a/k_b is an empirical quantity involving lumped rate constants.

[22] Electron supplying groups decrease the rates of proton loss from toluene cation radicals in water (Sehested, K.; Holcman, J. *J. Phys. Chem.* **1978**, *82*, 651), and the same appears to be true in acetonitrile (Pons, B. S., private communication).

[23] Although we have not investigated the reaction in detail, the major products of *tert*-butylbenzene oxidation in our system in acetic acid appear to be *tert*-butylphenyl acetates.

[24] Although we have observed C–C bond cleavage only when oxygen containing cationic fragments are produced, bicumyl apparently undergoes similar cleavage. Camaioni, D. M., private communication.

[25] Thus, ring acetoxylation of naphthalene is observed under a variety of conditions. With $S_2O_8^{2-}$–Cu^{II} in acetic acid, a 90% yield of 93:7 α- and β-acetoxynaphthalenes is reported. Giordiano, C.; Belli, A.; Citterio, A.; Minisci, F. *J. Org. Chem.* **1979**, *44*, 2314.



(13)

Since the rate of reaction to the left is acid catalyzed, ring substitution is maximized at low acidity in the presence of high concentrations of Cu^{II} or other oxidant.[4] The situation in other media is less clear. Anodic oxidation of toluene in HOAc–NaOAc is reported to give 71% ring acetoxylation, alhough none ocurs when acetate is replaced by perchlorate, and even higher selectivities are observed with more nucleophilic anions such as cyanide.[7] Whether this difference is the consequence of a heterogeneous process or the fact that, in the immediate vicinity of the anode surface, the concentration of acetate is high and any acetoxycyclohexadienyl radicals are immediately oxidized further by electron loss to the anode (thus paralleling the optimum conditions for ring substitution in water cited above) is really not known. Still more puzzling is the report by Jonsson and Wistrand[26] that, while $S_2O_8^{2-}$–Cu^{II} oxidation of mesitylene in strongly acid media (10:1 CH_3COOH/CF_3COOH) gives almost entirely side-chain acetoxylation, 67% ring substitution occurs when Cu is omitted or replaced by Fe or Ag. We can only conclude that, while our conditions are effective in suppressing ring substitution, the factors determining the competition between ring substitution and side-chain fragmentation in nonaqueous media and whether the former here too arises from a reversible nucleophile addition are really not understood. As we have seen, the actual products in our reactions arise from the Cu^{II} oxidation of intermediate radicals, and here results are, in general, consistent with previous observations on such reaction.

8. Simple benzylic radicals are oxidized to acetates or alcohols, or, when β-hydrogens are present, to olefins. From the tables and our previous work, when the latter path is possible it usually predominates. Although acetonitrile is a plausible nucleophile, in none of our reactions in that solvent have we detected *N*-benzylacetamides among our products. This contrasts with the results of anodic oxidations (which generate benzylic cations) and may indicate that the decomposition of benzylic organocopper intermediates in our systems occurs by internal ligand insertion, rather than dissociation to free benzylic cations.

9. Suitably situated nucleophilic substitutents profoundly affect the decomposition of organocopper intermediates. While α-hydroxy radicals are cleanly oxidized to carbonyl compounds, β-hydroxy radicals give final products consistent with the formation of intermediate epoxides, and more remote hydroxyls lead to five-, six-, and seven-membered cyclic ethers. Similarly, remote carboxyl groups can yield five- and six-membered lactone rings.

10. Although all these products depend upon Cu^{II} oxidations, product distributions vary considerably with medium. $S_2O_8^{2-}$ oxidations with other radical oxidants in turn might be expected to yield again quite different product distributions and sequences. It is only by working out these reaction sequences in detail that we can expect to understand the significant differences observed between, for example, $S_2O_8^{2-}$–Cu^{II} reactions and electrolytic oxidations.

Experimental Section

Reagents and solvents were commercial materials or were synthesized by standard methods, with purities checked by GLC or other appropriate means.

Reactions were in general carried out in sealed 15-mL Teflon-capped vials flushed with argon or nitrogen and magnetically stirred in thermostated baths as indicated in the tables and described previously.[8,9]

Analyses were GLC for yields and conversions and by GC-MS (VG Micromass 7070 mass spectrometer) together with retention times for identification, again essentially as previously.[8,9] For runs in acetonitrile it was sometimes possible to analyze reaction mixtures directly. Otherwise reaction mixtures were poured into water and extracted with ether and the ether extracts analyzed. In some cases, e.g., oxidation of carboxylic acids, products were silylated before analysis.

Acknowledgment. Support of this work by a grant from the National Science Foundation is gratefully acknowledged. GC-MS analyses were obtained from our mass spectra laboratory, support of which by NSF Grant CHE-8100424 and the University of Utah Instritutional Funds is also acknowledged, and we thank Dr. Thomas Sharp of that laboratory for his assistance in interpretation of the results.

Registry No. DE, 530-48-3; S, 588-59-0; BM, 637-50-3; AB, 300-57-2; $Cu(OAc)_2$, 142-71-2; Cu^{2+}, 15158-11-9; $S_2O_8^{2-}$, 15092-81-6; $(NH_4)_2S_2O_8$, 7727-54-0; $PhCH_2CH_2OAc$, 103-45-7; $PhCH(CH_3)CHO$, 93-53-8; $PhCH_2COCH_3$, 103-79-7; H_2O, 7732-18-5; PhCHO, 100-52-7; PhCH=CHOAc, 10521-96-7; $PhCH(OH)CH_2OAc$, 10522-41-5; Ph_2CO, 119-61-9; Ph_2CHCHO, 947-91-1; $PhCH_2COPh$, 451-40-1; PhCH(OAc)CH(OH)Ph, 86761-18-4; $PhCOCH_3$, 98-86-2; $H_2C{=}C(Ph)CH_2OAc$, 7534-40-9; $AcOCH{=}C(Ph)CH_3$, 79809-21-5; $H_2C{=}C(Ph)CHO$, 4432-63-7; $PhCOCH_2CH_3$, 93-55-0; $PhCH{=}CHCH_2OAc$, 103-54-8; $PhCH(OAc)CH{=}CH_2$, 7217-71-2; PhPh, 92-52-4; $PhCH{=}CHCH_2CH_2CH_2CHO$, 53847-18-0; $PhCOCH{=}CH_2$, 768-03-6; styrene, 100-42-5; phenylacetaldehyde, 122-78-1; α-methylstyrene, 98-83-9; 1-phenylcyclopentene, 825-54-7; indene, 95-13-6; indane, 496-11-7; 1-phenylcyclohexene, 771-98-2; phenylcyclohexane, 827-52-1; tetralin, 119-64-2; phenylcyclopropane, 873-49-4; β-phenylprpionic acid, 501-52-0; benzyl methyl ether, 538-86-3; 1-phenylethyl methyl ether, 4013-34-7; 2-phenylethyl methyl ether, 3558-60-9; 3-phenylpropyl methyl ether, 2046-33-5; *p*-methoxytoluene, 104-93-8; *p*-chlorotoluene, 106-43-4; *p*-xylene, 106-42-3; ethylbenzene, 100-41-4; toluene, 108-88-3; cumene, 98-82-8; *tert*-butylbenzene, 98-06-6; 1,2-dihydronaphthalene, 447-53-0; benzyl alcohol, 100-51-6; 2-phenylcyclopentanone, 1198-34-1; 2-phenyl-2-cyclopenten-1-one, 39545-99-8; phenylcyclopentadiene, 88243-06-5; 1-indanyl acetate, 26452-98-2; 1-indanone, 83-33-0; 2-indanone, 615-13-4; 3-indenol, 61463-21-6; 2-phenylcyclohexanone, 1444-65-1; 3-acetoxy-2-phenylcyclohexene, 63382-59-2; naphthalene, 91-20-3; 1-acetoxy-1,2,3,4-tetrahydronaphthalene, 21503-12-8; 1,2,3,4-tetrahydronaphthalen-1-one, 529-34-0; 1,2,3,4-tetrahydronaphthalen-2-one, 530-93-8; benzyl acetate, 140-11-4; β-phenylethyl acetate, 103-45-7; 2-chromanone, 119-84-6; methyl benzoate, 93-58-3; 1-phenylethyl acetate, 93-92-5; 1-phenylethanol, 98-85-1; 2-phenylethyl acetate, 103-45-7; 2-phenyl ethanol, 60-12-8; 3-phenylpropyl acetate, 122-72-5; β-phenylpropionaldehyde, 104-53-0; β-phenyl-1-propanol, 1123-85-9.

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(26) Jonsson, L.; Wistrand, L. G. *J. Am. Chem. Soc., Perkin Trans. 1* **1979**, 669.