Electron-Transfer Processes: Peroxydisulfate, a Useful and Versatile Reagent in Organic Chemistry

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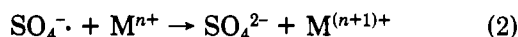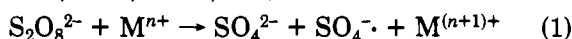
The availability of selective oxidants for organic compounds and of simple sources of radicals to use for selective syntheses are of obvious importance to research in organic chemistry. Peroxydisulfate in several cases fulfills both requirements.

The peroxydisulfate ion, $S_2O_8^{2-}$, is one of the strongest oxidizing agents: the standard redox potential is estimated to be 2.01 V in aqueous solution.[1] Thermal, photochemical, radiolytic, or redox decomposition of $S_2O_8^{2-}$ provides under mild conditions the radical anion $SO_4^-\cdot$, which appears to be a very effective electron-transfer oxidizing agent. We have found that oxidations effected by peroxydisulfate can be developed to become synthetic methods of unique character and value.
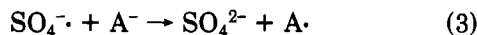
Preparative methods based on oxidations by peroxydisulfate have long been known,[2] but the importance of the electron-transfer nature of many such processes has only recently been recognized. This understanding has permitted interesting new synthetic developments.

Electron-transfer processes are among the most fundamental of simple molecular transformations. When the transfer is exergonic, the reactions occur at or near diffusion-controlled rates.[3] The problem is more complex when slow reactions of large activation energy, for which the transfer would be expected to be endergonic,[4] are involved.

The electron-transfer can concern $S_2O_8^{2-}$ and or $SO_4^-\cdot$; the following main types of interaction can be envisaged: (i) oxidation of metal salts (M^{n+} = Ag^+, Cu^+, Fe^{2+}, Co^{2+}, Ce^{3+}, Mn^{2+}, etc.):

$$S_2O_8^{2-} + M^{n+} \rightarrow SO_4^{2-} + SO_4^-\cdot + M^{(n+1)+} \quad (1)$$

$$SO_4^-\cdot + M^{n+} \rightarrow SO_4^{2-} + M^{(n+1)+} \quad (2)$$

(ii) oxidation of anions (i.e., $RCOO^-$, N_3^-):

$$SO_4^-\cdot + A^- \rightarrow SO_4^{2-} + A\cdot \quad (3)$$

(iii) oxidation of neutral organic molecules with relatively low ionization potentials (aromatics, olefins, amines, amides, etc.):

$$RH + SO_4^-\cdot \rightarrow [RH]^+\cdot + SO_4^{2-} \quad (4)$$
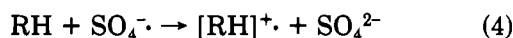
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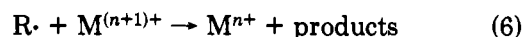
Table I
Standard Reduction Potentials in Aqueous Solution at 25 °C[1]

|	V
$S_2O_8^{2-} + 2e^- \rightleftarrows 2SO_4^{2-}$	2.01
$Ag^{2+} + e^- \rightleftarrows Ag^+$	1.98
$Co^{3+} + e^- \rightleftarrows Co^{2+}$	1.82
$Ce^{4+} + e^- \rightleftarrows Ce^{3+}$	1.61
$Mn^{3+} + e^- \rightleftarrows Mn^{2+}$	1.51
$Fe^{3+} + e^- \rightleftarrows Fe^{2+}$	0.771
$Cu^{2+} + e \rightleftarrows Cu^+$	0.153

(iv) oxidation of nucleophilic radicals $R\cdot$ (α-hydroxyalkyl, α-aminoalkyl, acyl, carbamoyl, cyclohexadienyl, etc.) in induced chain processes:

$$R\cdot + S_2O_8^{2-} \rightarrow R^+ + SO_4^{2-} + SO_4^-\cdot \quad (5)$$
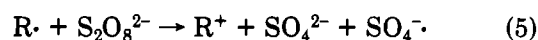
Metal salt catalysis is particularly important in many oxidations because it often governs the overall selectivity. Two types of radical chain mechanisms may be involved. In one, the redox-induced decomposition of peroxydisulfate by M^{n+} according to eq 1 is followed by selective oxidation of the intermediate radicals by $M^{(n+1)+}$ (eq 6); this sets the stage for reaction 1 again

$$R\cdot + M^{(n+1)+} \rightarrow M^{n+} + products \quad (6)$$

to occur, etc. generating a redox chain. The other type of chain mechanism involves mediated electron-transfer (i.e., eqs 7 and 8).

$$Ag^{2+} + RH \rightarrow Ag^+ + [RH]^+\cdot \quad (7)$$

$$2Ag^+ + S_2O_8^{2-} \rightarrow 2Ag^{2+} + 2SO_4^{2-} \quad (8)$$
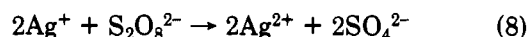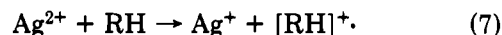
Mediated electron-transfer (eq 7 and 8) is closely dependent on the redox potentials of the salts (Table I), whereas the oxidation of the intermediate radicals by metal salts (eq 6) is largely independent of the redox potentials. In consequence silver, copper, and iron salts show interesting features; Ag^{2+} with its high electrode potential[5] is particularly effective for the electron-transer mediation, Cu^{2+} is very effective in the oxidation of carbon-centered radicals,[6] and Fe^{3+} oxidizes the more nucleophilic radicals (allyl, benzyl, cyclohexadienyl,

(1) W. M. Latimer, "Oxidation States of the Elements and Their Potentials in Aqueous Solution", Prentice-Hall, New York, 1952, p 78.

(2) D. A. House, *Chem. Rev.*, **62**, 185 (1962); G. Sosnovsky in "Organic Peroxides", Vol. II, D. Swern, Ed., Wiley, New York, 1971, p 317.

(3) M. Szwarc and J. Jagur-Grodzinski in "Ions and Ion Pair in Organic Reactions", M. Szwarc, Ed., Wiley, New York, 1974, p 57.

(4) C. Walling, *J. Am. Chem. Soc.*, **102**, 6854 (1980).

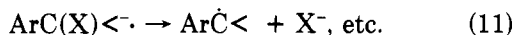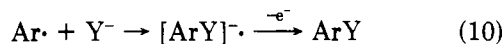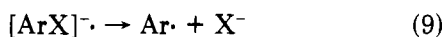(5) J. A. McMillan, *Chem. Rev.*, **62**, 65 (1962).

(6) J. K. Kochi in "Free Radicals", J. K. Kochi, Ed., Wiley, New York, 1973, p 591.

α-hydroxyalkyl, acyl, etc.), but not methyl or primary and secondary alkyl radicals. Mediated electron transfer by Cu^{3+} was also suggested[7] in copper-catalyzed oxidation, but evidence is lacking.
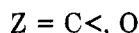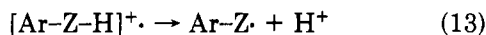
Thus in several cases the results of metal-catalyzed oxidations by peroxydisulfate parallel those of single electron oxidations by high-potential metal salts (Ag^{2+}, Mn^{3+}, Co^{3+}, Ce^{4+}, etc.). Often the only function of $S_2O_8^{2-}$ is to regenerate the metal salt in its higher oxidation form (eq 1 and 2), which is the actual oxidant of the organic compound. In other cases (copper and iron catalysis) the similarity of behavior is caused by the fact that the initial step is always an electron transfer, although it is effected by $SO_4^-\cdot$ (eqs 3 and 4), whereas the subsequent steps are governed by the interactions of the metal salts with the intermediate radicals.

Aromatics

Nuclear[8] and benzylic[9] substitutions of aromatic compounds through radical anions have shown considerable synthetic potentiality (eq 9–11). Somewhat

$$[ArX]^-\cdot \rightarrow Ar\cdot + X^- \qquad (9)$$

$$Ar\cdot + Y^- \rightarrow [ArY]^-\cdot \xrightarrow{-e^-} ArY \qquad (10)$$

$$ArC(X){<}^-\cdot \rightarrow Ar\dot{C}{<} + X^-, \text{ etc.} \qquad (11)$$

analogous functionalizations through aromatic radical cations have also raised much interest (eq 12 and 13).

$$[ArH]^+\cdot + Y^- \rightarrow [ArHY]\cdot \xrightarrow{ox} Ar\text{–}Y \qquad (12)$$

$$[Ar\text{–}Z\text{–}H]^+\cdot \rightarrow Ar\text{–}Z\cdot + H^+ \qquad (13)$$

$$Z = C{<}, O$$

A number of investigators[10–24] have provided evidence

concerning the formation of aromatic radical cations through oxidation by $SO_4^-\cdot$ (eq 14). Most of the evi-

$$ArH + SO_4^-\cdot \rightarrow [ArH]^+\cdot + SO_4^{2-} \qquad (14)$$

dence is circumstantial, but with methoxysubstituted benzenes the resulting species can be detected by ESR spectroscopy.[15]

Absolute rate constants for reactions of $SO_4^-\cdot$ with substituted benzenes have been determined by pulse radiolysis and support the electron-transfer mechanism;[16] the values range from about 5×10^9 M^{-1} s^{-1} for anisole to $<10^6$ M^{-1} s^{-1} for nitrobenzene; Hammett correlation gave $\rho = -2.4$.

The fate of the radical cation is related to the structure of the aromatic compound, the metal salt catalysis, and the reaction medium. Alkyl aromatic and phenol radical cations can behave according to both eq 12 and 13. Thus the oxidation of p-cymene by peroxydisulfate mainly provides p-isopropylbenzyl radical[18,22,23] in a process which parallels the results obtained in oxidation by Co^{3+} salts[25] (eq 15).

$$(15)$$
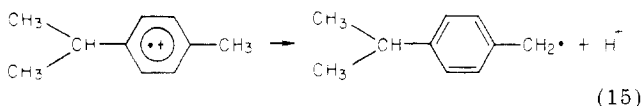
The formation of aldehydes and ketones by oxidation of alkyl aromatics was originally explained by a radical mechanism involving hydrogen abstraction.[20] More recently[21] the reaction has been interpreted to occur via an electron-transfer mechanism and shown to become much cleaner, and therefore of higher synthetic interest, in the presence of catalytic amounts of iron and copper salts (Scheme I).

Scheme I

$$[ArCH_3]^+\cdot \rightarrow Ar\text{–}CH_2\cdot + H^+$$

$$Ar\text{–}CH_2\cdot + Cu^{2+} + H_2O \rightarrow Ar\text{–}CH_2OH + Cu^+ + H^+$$

$$Ar\text{–}CH_2OH \xrightarrow[Fe^{2+}/Cu^{2+}]{S_2O_8^{2-}} Ar\text{–}CHO$$

In aqueous medium it is difficult to selectively stop the oxidation at the alcohol stage either because the reactivity of the benzylic alcohols is comparable to that of the alkyl aromatics or because the alcohols are more soluble in water. An exception is the oxidation of 4,5-dimethylimidazole, which gives with good selectivity 4-(hydroxymethyl)-5-methylimidazole,[26] an important commercial intermediate for 4-methyl-5-[((2-amino-ethyl)methyl)thio]imidazole(cimetidine). It was suggested that an intramolecular hydrogen bond could make the imidazole alcohol less reactive.[26]

The high conversions and yields of aldehydes in the oxidation of methylarenes are consistent with an electron-transfer process because the aldehydes have ionization potentials significantly higher than the corresponding methylarenes (8.8 eV for toluene and 9.6 eV for benzaldehyde). However, the exceptional selectivity observed in the oxidation of mixtures of m- and p-methylanisoles, which affords only p-anisaldehyde,[21] cannot be explained on this basis because the differ-

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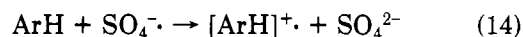(19) C. Walling and D. M. Camaioni, *J. Org. Chem.*, 43, 3266 (1978).

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(22) C. Giordano, A. Belli, A. Citterio, and F. Minisci, *J. Org. Chem.*, 44, 2314 (1979).

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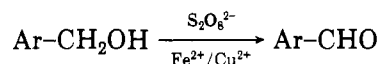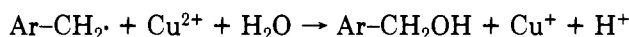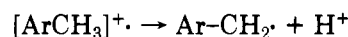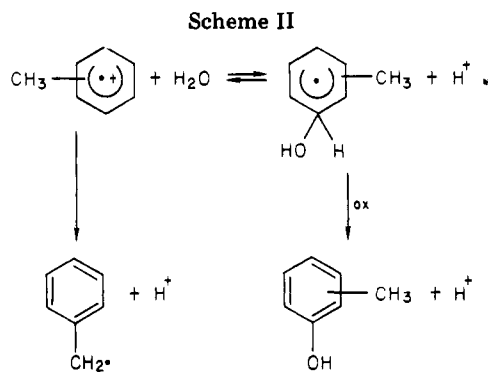(24) C. Giordano, A. Belli, A. Citterio, and F. Minisci, *J. Chem. Soc., Perkin Trans. 1*, 1574 (1981).

(25) A. Onopchenko, J. G. D. Schulz, and R. Seekircher, *J. Org. Chem.*, 37, 1414, 2564 (1972).

(26) A. Citterio and F. Minisci, *Chim. Ind. (Milan)* 64, 320 (1982); Kokai, Tokky Koho 80 127 3575 (1980) (Ital. Appl. 79 20 992 (1979)).

Scheme II

ences of ionization potentials of the two isomers are small. Furthermore, anisole reacts at a diffusion-controlled rate.[16] Probably responsible is an equilibrium between the two aromatic radical cations (eq 16). (It
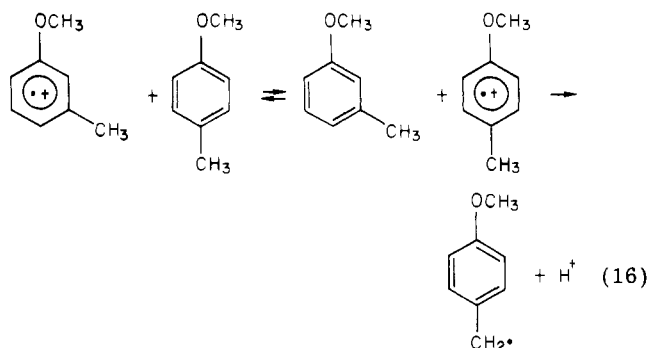
is known that such reactions are very fast when electron transfer is isoergonic.[3]) The equilibrium is shifted to the right by a faster loss of proton from the para isomer.

When the oxidation of alkylbenzenes is carried out in acetic acid, benzylic acetate esters are obtained in good yields (eq 17).[27,28]

$$Ar-CH_3 \xrightarrow[CH_3COOH]{S_2O_8^{2-}/Cu^{2+}} Ar-CH_2OCOCH_3 \qquad (17)$$
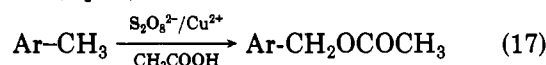
It appears that the acetoxy derivatives, in contrast to the corresponding benzylic alcohols, are significantly less reactive than the starting alkyl aromatics. Polar effects in the initial electron-transfer and in equilibria analogous to that suggested in eq 16 can determine the substrate selectivity.

Reaction with nucleophiles is another fundamental characteristic of radical cations. Thus alkyl aromatic radical cations reversibly react with water, leading to phenols (Scheme II). With toluene the ratio of cresols to benzyl radical derived products depends on the identity of the oxidizing metal salt and the reaction conditions. Owing to the reversibility of the hydration, the slower the rate of oxidation of the cyclohexadienyl radical, the more products derived from benzyl radicals are formed.[14,17]

The hydroxylation of aromatics by peroxydisulfate in aqueous medium generally has only moderate synthetic interest because the phenols formed are more reactive and more soluble in water than the starting aromatic compounds. The direct[22,23,29] or Ag⁺-mediated[30] nuclear acetoxylation by peroxydisulfate is more

Table II
Oxidation Products (%) of Cyclohexene by $S_2O_8^{2-}$ and Metal Salts in Aqueous Medium[33]

metal salt	product yields, %						
	1	2	3	4	5	6	7
Ag⁺	62	20	2.5	5.7	1.2	1.9	6.3
Fe³⁺	49	4.8	3.6	24	10.3	1.2	7.2
Cu²⁺			2	7	4	80	8

useful from a synthetic point of view because the acetoxy derivatives appear to be less reactive than the starting aromatic compounds.

Olefins

The simple olefins have ionization potentials quite close to those of aromatic compounds, for which there is good evidence of electron transfer in the oxidation by peroxydisulfate. It is therefore reasonable also to consider an electron-transfer process for olefin oxidation (eq 18). In aqueous medium the radical cation would

$$>C=C< + SO_4^{-}\cdot \rightarrow >\dot{C}-C<^+ + SO_4^{2-} \qquad (18)$$
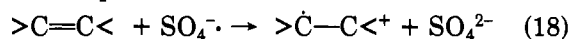
be in equilibrium with the corresponding α-hydroxyalkyl radical[31] (eq 19), analogously to the aromatic

$$>\dot{C}-C<^+ + H_2O \rightleftarrows >\dot{C}-C(OH)< + H^+ \qquad (19)$$
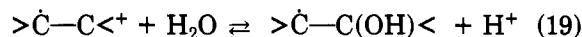
radical cation (Scheme II). Thus with substrates very reactive toward alkyl radicals, such as protonated heteroaromatic bases, α-hydroxyalkylation occurs selectively[32] (eq 20).

90%
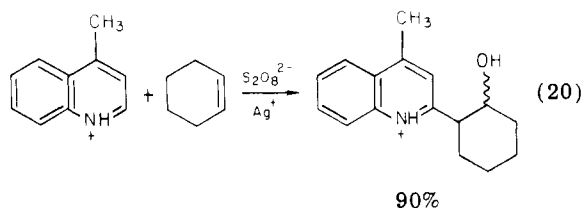
In the absence of radical traps the course of the reaction is governed by the metal salt catalysis.[33] The results with cyclohexene in the presence of Ag⁺, Fe³⁺, and Cu²⁺ in water are summarized in Table II. These results were explained by the further reactions of the α-hydroxyalkyl radical.

It is well-known[34] that, in spite of its high electrode potential, Ag²⁺ is not an effective oxidant of the alkyl radicals when it is generated by the redox system $S_2O_8^{2-}/Ag^+$. It, can, however, compete with $SO_4^{-}\cdot$ in oxidizing the olefinic bond (eq 21). Thus the α-hy-

$$>C=C< + Ag^{2+} \rightarrow >\dot{C}-C<^+ + Ag^+ \qquad (21)$$

droxycyclohexyl radical further reacts with cyclohexene or the solvent (acetonitrile) by hydrogen abstraction, giving cyclohexanol (1) and cyclohexenyl and cyanomethyl radicals (S·) (eq 22). The cyclohexenyl radical

1

mainly dimerizes to bicyclohexenyl 2. To a minor ex-

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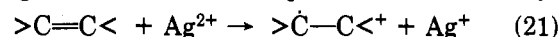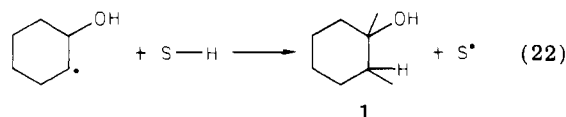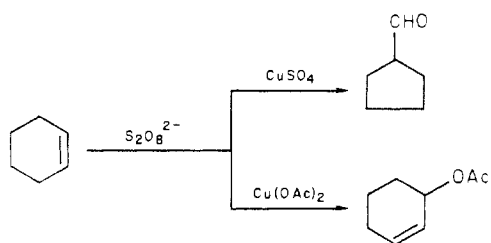(30) K. Nyberg and L. G. Wistrand, *J. Org. Chem.,* 43, 2613 (1978).

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(32) A. Clerici, F. Minisci, K. Ogawa, and J. M. Surzur, *Tetrahedron Lett.,* 1149 (1978).
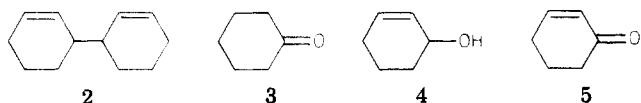
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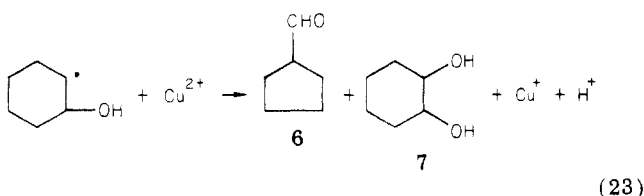
Scheme III

tent it is oxidized to cyclohexenol **4** and cyclohexenone **5**.

Fe^{3+} is a poor oxidant for alkyl radicals, but it oxidizes more effectively the cyclohexenyl radical. In consequence, the main change in comparison with Ag$^+$ catalysis is the decrease of bicyclohexenyl **2** and the increase of cyclohexenol **4** and cyclohexenone **5**. Cyclohexanone **3** is in any case a minor product (2–3%).

CuSO$_4$ is a much more effective oxidant of α-hydroxycyclohexyl radical, and the main reaction products arise from its oxidation (eq 23). When Cu(OAc)$_2$ is,

however, used as catalyst, 2-cyclohexenyl acetate is practically the only reaction product (Scheme III). There is a close analogy with the behaviour of the Hg^{2+} salts[35] (Scheme IV). These results strongly suggest that similar organometallic intermediates are involved in both cases (eq 24 and 25). The high effectiveness of
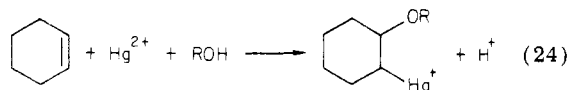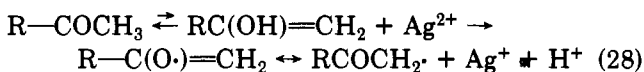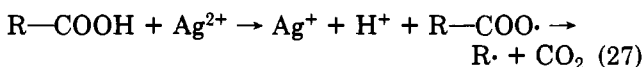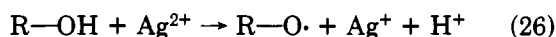

R = H, Ac

the reaction of the alkyl radicals with cupric salts would therefore be related to a specific interaction between paramagnetic species and not to the redox potential of the cupric salt (Table I).

Alcohols, Ketones, and Carboxylic Acids

These three classes of compounds selectively give rise to radicals by a similar initial mechanism, characterized by an Ag$^+$-mediated electron transfer (eq 26–28).[34,36,37]

$$\text{R—OH} + \text{Ag}^{2+} \rightarrow \text{R—O·} + \text{Ag}^+ + \text{H}^+ \quad (26)$$

$$\text{R—COOH} + \text{Ag}^{2+} \rightarrow \text{Ag}^+ + \text{H}^+ + \text{R—COO·} \rightarrow$$
$$\text{R· + CO}_2 \quad (27)$$

$$\text{R—COCH}_3 \rightleftarrows \text{RC(OH)}{=}\text{CH}_2 + \text{Ag}^{2+} \rightarrow$$
$$\text{R—C(O·)}{=}\text{CH}_2 \leftrightarrow \text{RCOCH}_2· + \text{Ag}^+ + \text{H}^+ \quad (28)$$

(35) H. Arzanmanian and J. Metzger, *Synthesis*, 525 (1971).

Among the numerous selective syntheses that have been accomplished by taking advantage of these fundamental interactions, we mention here only the homolytic alkylation of heteroaromatic bases. Thus when 1-hexanol is oxidized by S$_2$O$_8^{2-}$/Ag$^+$ in the presence of protonated quinoline, the 2- and 4-(δ-hydroxylalkyl)-quinolines **8** and **9** are obtained with good yields (90%) and high selectivity in the alkyl moiety.[36]
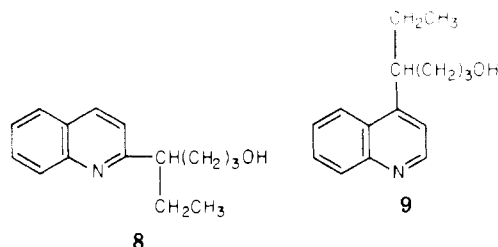

The exclusive formation of δ-hydroxyalkyl radicals can be reasonably explained only by an intramolecular hydrogen abstraction of the intermediate alkoxy radical (eq 29).
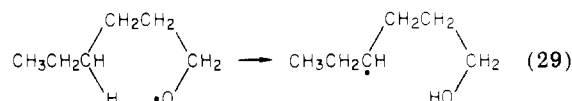
Heteroaromatic bases are very effectively alkylated by silver-catalyzed oxidative decarboxylation of carboxylic acids[38] (eq 30). This is the most convenient
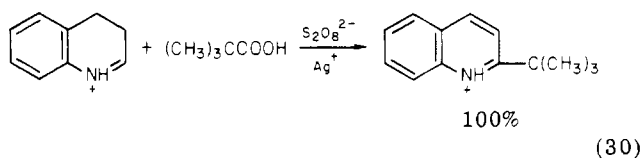
general method of alkylation. Yields are excellent, selectivity is high, experimental conditions are very simple, and the reagents are inexpensive and easily available.[39] Methyl, primary, secondary, and tertiary alkyl, allyl, and benzyl radicals have been successfully used with a large variety of heteroaromatic bases.[39] When acetone is oxidized by peroxydisulfate with silver catalysis in the presence of 1-octene and 4-cyanopyridine, the selective alkylation of the base takes place according to eq 31.[37] The differing polar characters of the radicals
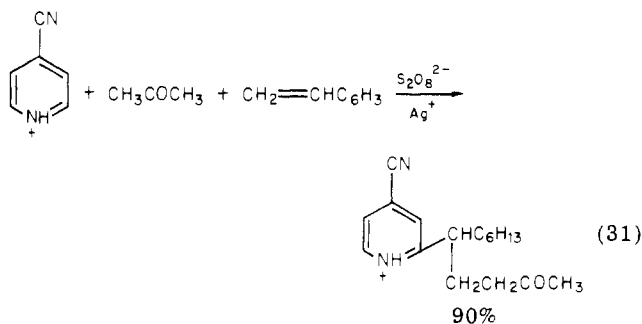
involved is of central significance. The initial radical

(36) T. Caronna, A. Citterio, L. Grossi, F. Minisci, and K. Ogawa, *Tetrahedron*, **32**, 2741 (1976).
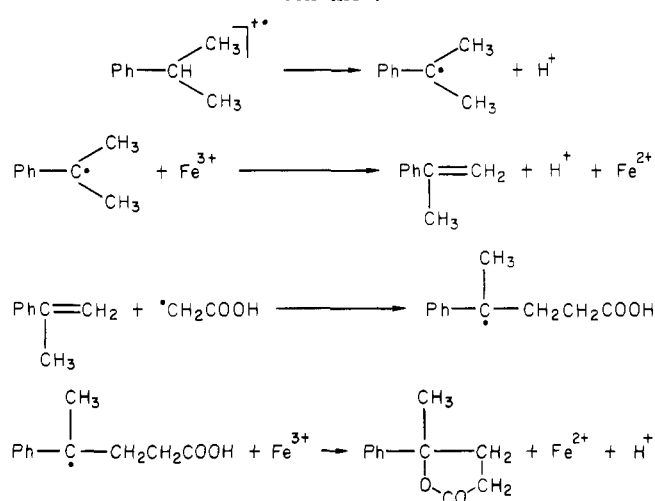(37) A. Citterio, A. Gentile, and F. Minisci, *Tetrahedron Lett.*, in press.
(38) A. Citterio, V. Franchi, and F. Minisci, *J. Org. Chem.*, **45**, 4252 (1980).
(39) F. Minisci, *Synthesis*, 1 (1973); F. Minisci, *Top. Curr. Chem.*, **62**, 1 (1976); F. Minisci and A. Citterio in "Advances in Free-Radical Chemistry", Vol. 6, G. H. Williams, Ed., Heyden, London, 1980, p 105.
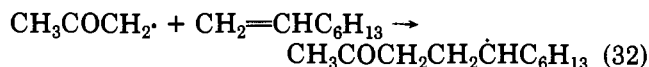
Scheme IV
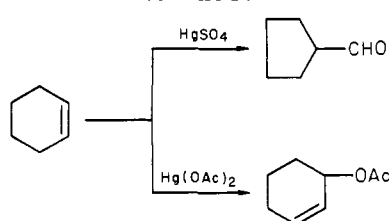
Scheme V

CH_3COCH_2· formed according to eq 28 has electrophilic character; it neither adds to the pyridine ring nor is oxidized. However, it selectively adds to the olefin as shown in eq 32. The radical adduct has nucleophilic

$$CH_3COCH_2· + CH_2{=}CHC_6H_{13} \rightarrow$$
$$CH_3COCH_2CH_2\dot{C}HC_6H_{13} \quad (32)$$

character and selectively alkylates the pyridine ring.[39]

Selectivity of the Oxidation

The facts that peroxydisulfate can oxidize several kinds of organic functions and that rates of oxidation by SO_4^-· are often very high raise a selectivity problem when more than one organic function are present in the reaction medium. Investigation of some such systems has led to interesting synthetic developments.

When an aromatic ring and a carboxyl group are present in a peroxydisulfate oxidation system, there is a problem of positional selectivity if the two groups belong to the same compound or of substrate selectivity if the two groups belong to different compounds. Thus the oxidation of naphthalene by peroxydisulfate in acetic acid[22] leads to acetoxynaphthalenes in the presence of Cu^{2+}, whereas 1-(hydroxymethyl)naphthalene acetate is formed in the presence of Fe^{3+}. The result has been explained[22] with attention to competitive electron-transfer reactions of naphthalene (eq 14) and acetate ion (eq 33). The Cu^{2+} salt has a 2-fold effect:

$$CH_3COO^- + SO_4^-· \rightarrow SO_4^{2-} + CH_3COO· \rightarrow$$
$$CH_3· + CO_2 \quad (33)$$
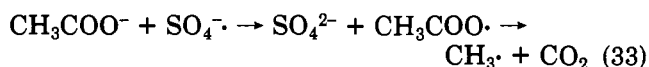
it effectively traps and removes the methyl radical (eq 34) and oxidizes the acetoxynaphthalene radical (eq 35).

$$CH_3· + Cu(OCOCH_3)^+ \rightarrow CH_3OCOCH_3 + Cu^+ \quad (34)$$
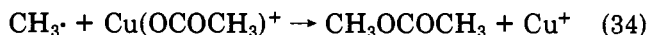
The Fe^{3+} salt is not able either rapidly to oxidize the acetoxynaphthalene radical or to effectively trap the
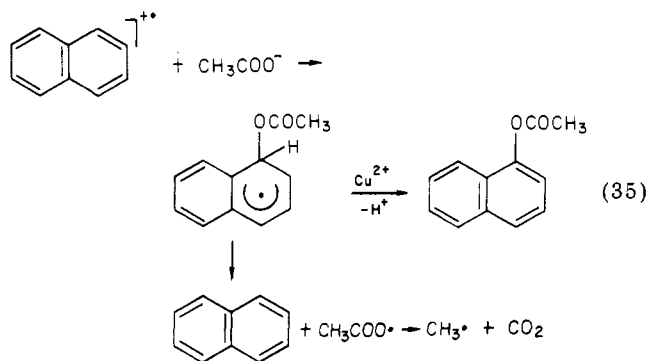
methyl radical. therefore no nuclear acetoxylation occurs. Instead, the methyl radical abstracts a hydrogen atom from acetic acid, leading ultimately to the acetoxymethylnaphthalene according to eq 36 and 37.

$$CH_3· + CH_3COOH \rightarrow CH_4 + ·CH_2COOH \quad (36)$$
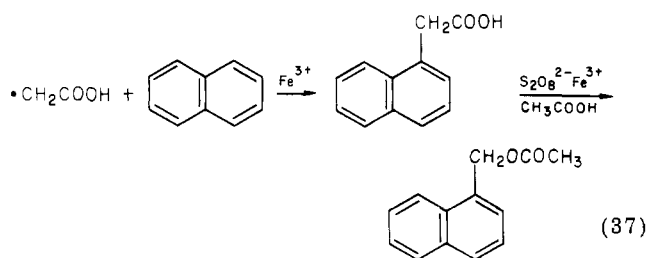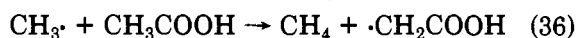
A synthetic development based on simultaneous oxidation of the aromatic ring and the acetate ion utilizes isopropyl aromatics in acetic acid (eq 38).[23] This result
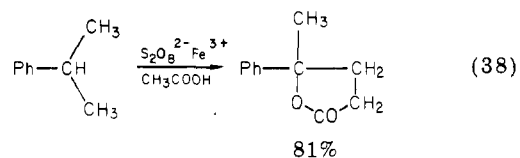

is interpreted[23] as shown in Scheme V.

If this interpretation holds, the same result should be obtained starting from olefins. Actually when α-methylstyrene was subjected to oxidation under the same conditions as for isopropylbenzene, only a small amount of the lactone was obtained; olefin telomerization was the main reaction.[40] When, however, the olefin was slowly added to the reacting mixture, the lactone was obtained in good yield[40] according to Scheme V. That means that α-methylstyrene is more reactive than acetate ion toward SO_4^-· and that Scheme V works effectively only at low concentration of the olefin.

Competition between oxidation of the hydroxyl group or of the olefinic bond by $S_2O_8^{2-}/Ag^+$ characterizes reactions of the olefinic alcohols. Minisci and co-workers[32] have shown that the oxidation of 4-penten-1-ol leads to the radicals 10 and 11. In a preliminary report[32] the formation of 10 and 11 was ascribed to the oxidation of the hydroxyl group (eq 39). However, further research has led the same group[33] to consider probable an electron transfer from the olefin (eq 40) on the grounds that cyclohexene is more reactive than cyclohexanol. Certainly the ionization potential of the olefin plays an important role in determining positional selectivity.

(40) C. Giordano, A. Belli, F. Casagrande, G. Guglielmetti, and A. Citterio, *J. Org. Chem.*, 46, 3149 (1981).

$$(39)$$

$$(40)$$
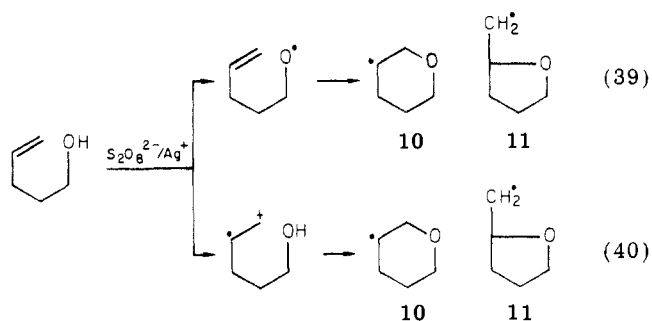
Concluding Remarks

The high redox potential of $SO_4^-\cdot$ enables it to engage in electron-transfer processes with several fundamental classes of organic compounds; the ionization potentials of the substrates play a dominant role in determining their participation in such reactions. Catalysis by metal salts can selectively direct the reaction course in order to achieve selective syntheses. This Account has mainly concerned one area of research with which the authors have been deeply involved. Other research areas, such as the oxidation of ethers, aldehydes, amines, amides, phenols, and organic and inorganic ions, have undoubted interest either for their synthetic utility or for the electron-transfer mechanisms involved. The potentialities of peroxydisulfate oxidation reactions have not yet been completely explored. Many perspectives of further mechanistic and synthetic developments are open.