Tetrahedron Vol. 35, pp. 1471 to 1481
Pergamon Press Ltd., 1979. Printed in Great Britain

TETRAHEDRON REPORT NUMBER 65

THE CHEMISTRY OF SUPEROXIDE ION

DONALD T. SAWYER* and MORTON J. GIBIAN
Department of Chemistry, University of California, Riverside, CA 92521, U.S.A.

(*Received in UK 4 January* 1979)

1. INTRODUCTION

The chemistry and reactivity of superoxide ion ($O_2^{\cdot-}$) have become subjects of considerable interest to chemists and biochemists during the past two decades. Although potassium superoxide (KO_2) is readily formed by burning potassium in air and has been recognized as a source of superoxide ion since 1934,[1] the instability of its aqueous solutions and its limited solubility in organic solvents had precluded studies of the chemistry of $O_2^{\cdot-}$. In 1965–66 electrochemical investigators first established that molecular oxygen in aprotic solvents[2-5] is reduced by a reversible one-electron process to superoxide ion,[6,7]

$$O_2 + e^- \rightleftharpoons O_2^{\cdot-} \qquad E^{\circ\prime} = -0.50\ \text{V vs NHE} \tag{1}$$

which in turn is reduced by a second one-electron process (with involvement of the solvent, dimethyl sulfoxide).[5]

$$O_2^{\cdot-} + e^- \xrightarrow{\text{solvent}} HO_2^- \qquad (E_{pc})_{Me_2SO} = -1.75\ \text{V vs NHE} \tag{2}$$

This discovery provided a convenient means to prepare stable solutions of $O_2^{\cdot-}$ in aprotic solvents with known concentrations by controlled potential coulometry.[3,8] Figure 1 illustrates a cyclic voltammogram for the reduction of O_2 in pyridine with the reversible $O_2/O_2^{\cdot-}$ couple at −0.9 V vs SCE.

The discovery in 1969 that $O_2^{\cdot-}$ is a respiratory intermediate of aerobic organisms[9] has prompted widespread and intense interest in the chemical properties and reactivity of $O_2^{\cdot-}$ with organic functional groups. While many of the thermodynamic data are available,[2-7] unambiguous and quantitative evaluation of the chemical reactivity of $O_2^{\cdot-}$ with various substrates requires substantial concentrations.

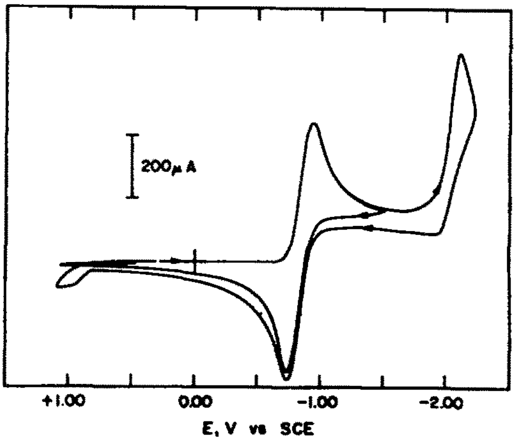


Fig. 1. Cyclic voltammogram for 5 mM molecular oxygen in pyridine (0.1 M tetraporpylammonium perchlorate) at a platinum electrode (area, 0.23 cm^2). Scan rate, 0.1 V s^{-1}. Saturated calomel electrode (SCE) vs NHE, +0.244 V.

Chemical studies of $O_2^{\cdot -}$ have been made much more convenient by the discovery that KO_2 can be solubilized in aprotic media by using crown ethers.[10] However, this approach may yield solutions that are contaminated with varying amounts of K_2O_2 and KOH (the best assays for commercial KO_2 are 96%). Another means to achieve a soluble salt of $O_2^{\cdot -}$ for aprotic solvents is the synthesis of tetramethylammonium superoxide,[11,12] but there have been difficulties with this preparation.[13] KO_2 is soluble to a limited extent in dimethyl sulfoxide[5] and acetonitrile,[14] but both of the last two methods can again result in peroxide and hydroxide impurities. As recently resported,[15] stable $O_2^{\cdot -}$ solutions result from the combination of H_2O_2 and tetraethylammonium hydroxide in pyridine, but there may be various contaminants here as well.

Although $O_2^{\cdot -}$ is unstable in aqueous solutions, transient amounts can be produced by pulse radiolysis of oxygenated solutions of formate ion[16]

$$O_2 + e^-_{aq} \rightarrow O_2^{\cdot -} \tag{3}$$

$$O_2 + H\cdot \rightarrow HO_2\cdot \xrightarrow{OH^-} O_2^{\cdot -} + H_2O \tag{4}$$

$$\cdot OH + HCOO^- \rightarrow CO_2^{\cdot -} + H_2O \tag{5}$$

$$CO_2^{\cdot -} + O_2 \rightarrow O_2^{\cdot -} + CO_2 \tag{6}$$

and by electrolysis of O_2 in alkaline solutions that contain surfactants (quinoline or triphenylphosphine oxide).[17,18]

Before considering the chemical reactivity of $O_2^{\cdot -}$, its physical properties are summarized briefly. In the solid state the O–O bond length of $O_2^{\cdot -}$ is 1.33 Å, which corresponds to a bond order of 1.5.[19] The IR stretching frequency for $O_2^{\cdot -}$ is 1145 cm^{-1} in contrast to 1556 cm^{-1} for O_2 and ~770 cm^{-1} for O_2^{2-}.[20,21] In acetonitrile with 0.1 M tetrapropylammonium perchlorate, $O_2^{\cdot -}$ has a single absorption band with a λ_{max} at 255 nm (ϵ, 1460 $M^{-1}\,cm^{-1}$).[22] Frozen glasses of this same solution at 77°K yield ESR spectra for $O_2^{\cdot -}$ with $g_\perp = 2.008$ and $g_\parallel = 2.083$.[22] In dimethyl sulfoxide, $O_2^{\cdot -}$ from KO_2 plus 18,6-crown ether exhibits an absorption maximum at 250 nm (ϵ, 2686 $M^{-1}\,cm^{-1}$).[23]

In aqueous media (0.1 M sodium formate, 2 m*M* phosphate buffer at pH 7.2) the redox potential, $E^{0\prime}$, for the $O_2/O_2^{\cdot -}$ couple (Reaction 1) is −0.33 V vs NHE on the basis of pulse radiolysis studies.[24] If this value is combined with that for the O_2/H_2O_2 couple at pH 7 ($E^{0\prime} = +0.27$ V vs NHE),[25] then an approximate value can be calculated for the following reaction (at pH 7).[26]

$$O_2^{\cdot -} + 2H^+ + e^- \rightarrow H_2O_2 \quad E^{0\prime} = +0.87\ \text{V vs NHE} \tag{7}$$

The kinetics and thermodynamics for a number of fundamental reactions of $O_2^{\cdot -}$ and $HO_2^{\cdot}$ in water have been evaluated by the pulse radiolysis technique.[27,28]

$$H^+ + O_2^{\cdot -} \rightleftharpoons HO_2^{\cdot} \quad pK_a = 4.88 \tag{8}$$

$$O_2^{\cdot -} + HO_2\cdot \rightarrow O_2 + HO_2^- \quad k_9 = 8.5 \times 10^7\ M^{-1}\,s^{-1} \tag{9}$$

$$HO_2\cdot + HO_2\cdot \rightarrow O_2 + H_2O_2 \quad k_{10} = 7.6 \times 10^5\ M^{-1}\,s^{-1} \tag{10}$$

$$O_2^{\cdot -} + O_2^{\cdot -} \xrightarrow{H_2O} O_2 + HO_2^- \quad k_{11} < 100\ M^{-1}\,s^{-1} \tag{11}$$

$$O_2^{\cdot -} + \cdot OH \rightarrow O_2 + OH^- \quad k_{12} = 1 \times 10^{10}\ M^{-1}\,s^{-1} \tag{12}$$

$$\cdot OH + H_2O_2 \rightarrow HO_2\cdot + H_2O \quad k_{14} = 3 \times 10^7\ M^{-1}\,s^{-1} \tag{13}$$

Recent electrochemical studies indicate that Reaction 11 has a rate constant (k_{11}) of 6 $M^{-1}\,s^{-1}$.[29]

II. CHEMICAL REACTIVITY

Effective basicity. One of the most dominant reaction characteristics of $O_2^{\cdot -}$ solutions is their capacity to effect proton removal from substrates and solvents.[30] Although the pK_a for $HO_2\cdot$ in water has a value of 4.88 (which infers that $O_2^{\cdot-}$ is a weak base),[27] the combination of the reduction half-reaction for $O_2^{\cdot-}$ in water[31]

$$O_2^{\cdot-} + H_2O + e^- \rightarrow HO_2^- + OH^- \quad E^{o\prime} = +0.17 \text{ V vs NHE} \tag{14}$$

with eqn (1) (the redox potential of $O_2/O_2^{\cdot-}$ in water, $E^{o\prime}$, is −0.33 V vs NHE)[24] yields the net expression

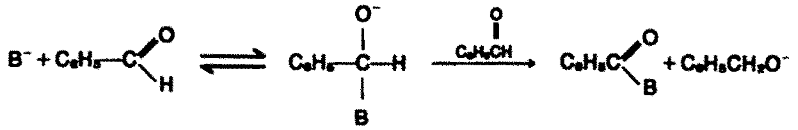
$$2O_2^{\cdot-} + H_2O \rightleftharpoons O_2 + HO_2^- + OH^- \quad k = 2.5 \times 10^8 \tag{15}$$

This equilibrium expression (Reaction 15) is also the result of combining Reactions (8) and (9). The value of the equilibrium constant indicates that superoxide ion solutions can promote proton transfer from substrates (and solvents) to an extent equivalent to that of the conjugate base of an acid with a pK_a value of approximately 23. Reaction (9) is rapid and highly exothermic, which should cause the lifetime of $HO_2^{\cdot}$ generated *via* eqn (8) to be sufficiently short to preclude it as a major reactant with most substrates in solution.[32]

Obviously, even much weaker acids than water will produce an exothermic reaction with $O_2^{\cdot-}$

$$2O_2^{\cdot-} + HB \rightarrow O_2 + HO_2^- + B^- \tag{16}$$

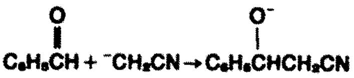
The overall reactions represented by eqn (16) may not be rapid with weak acids (HB), but neither are many of the substrate reactions with $O_2^{\cdot-}$. Indeed, recent studies establish that a number of weakly acidic organic compounds are deprotonated efficiently in the presence of superoxide ion, especially when the organics are solvents or in high concentration.[32,33] For example, under rigorously aprotic conditions $O_2^{\cdot-}$ does ot react with benzaldehyde. However, protic components in impure benzaldehyde cause a rapid loss of $O_2^{\cdot-}$ *via* Reaction (16), which is followed by loss of aldehyde. This reaction of benzaldehyde with $O_2^{\cdot-}$ dismutation products is primarily a Cannizzaro-type process that yields benzyl alcohol and an oxidized benzaldehyde species.[34]



(17)

Whether B^- is HO_2^- or OH^- (from Reaction 16), the final products are benzyl alcohol and benzoic acid. For the former, $C_6H_5CO_3^-$ would be the initial oxidized product, but it reacts rapidly with benzaldehyde to give two benzoic acid molecules.[35]

When benzaldehyde is combined with $O_2^{\cdot-}$ in acetonitrile the bases that result from Reaction (16) apparently are sufficiently strong to generate acetonitrile anion, $^-CH_2CN$, which undergoes a condensation with benzaldehyde.



$$C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}H + {}^-CH_2CN \rightarrow C_6H_5\overset{\overset{\displaystyle O^-}{|}}{C}HCH_2CN \tag{18}$$

Protonation and loss of water leads to $C_6H_5CH{=}CHCN$. This same process occurs efficiently with KOH.[33,36] In the presence of KO_2 an apparent competitive oxidation of $C_6H_5\overset{\overset{\displaystyle O^-}{|}}{C}HCH_2CN$ to $C_6H_5\overset{\overset{\displaystyle O}{\|}}{C}CH_2CN$ occurs. The reaction mixture generates O_2 and peroxide (via Reaction 16), which probably are the actual oxidants.

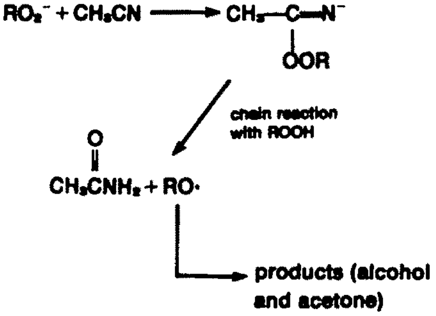
A recent study of t-butyl hydroperoxide in acetonitrile with peroxide concludes that $O_2^{\cdot-}$ attacks alkyl hydroperoxides by a process that involves reduction and cleavage of the O–O bond.[37]

$$O_2^{\cdot-} + ROOH \rightarrow O_2 + OH^- + RO^{\cdot} \tag{19}$$

However, the absence of a primary rapid reaction between $O_2^{\cdot-}$ and dialkyl peroxides,[38] the fact that t-butyl hydroperoxide is not decomposed by $O_2^{\cdot-}$ in several solvents other than acetonitrile, and the observation that $tBuOO^-$ attacks acetonitrile rapidly,[39] raises doubts about the actual occurrence of eqn (19). A more likely reaction sequence is the removal of a proton by $O_2^{\cdot-}$ followed by

$$O_2^{\cdot-} + ROOH \rightarrow HO_2^{\cdot} + ROO^- \qquad (20)$$

dismutation of superoxide via Reaction (9). The RO_2^- attacks acetonitrile via known processes to produce acetamide (eqn 21).



(21)

In toluene and pyridine, the RO_2^- formed in Reaction (20) is stable, but the $O_2^{\cdot-}$ is rapidly destroyed via eqns (20) and (9).

As discussed later under *Non-Oxidizing Properties*, the reaction of superoxide with catechols[14] also involves initial proton transfer, this having been shown by, *inter alia*, the fact that catechol anions and ethers are inert towards $O_2^{\cdot-}$.[32]

Thus, in the presence of water or other proton sources superoxide ion yields strong Bronsted bases via Reaction (15) or (16). These processes also yield O_2 and peroxide, and the combination of base and dismutation products (both effective oxidants) can account for many of the reactivity characteristics that have been attributed to $O_2^{\cdot-}$ as primary processes.[32]

Nucleophilicity

(a) *Alkyl halides.* The first reports of the nucleophilic attack upon alkyl halides by $O_2^{\cdot-}$ in aprotic solvents appeared in 1970.[40,41] Both groups presented electrochemical data that is consistent with a process that is first-order in $O_2^{\cdot-}$ and first-order in RX.[42] The results of subsequent relative kinetic studies that also showed a general process to be operative here confirm that the reaction rates follow the order $1° > 2° \gg 3°$ for alkyl halides and tosylates, and that the attack by $O_2^{\cdot-}$ results in inversion of configuration.[43,44] This provides convincing evidence for the conclusion that the $O_2^{\cdot-}$–RX reaction occurs by an S_N2 mechanism. With 2° and 3° halides, competing elimination reactions that lead to olefins occur.

Reaction of 1° or 2° alkyl halide with $O_2^{\cdot-}$ in benzene, [44] dimethyl formamide,[41] or pyridine[45] leads primarily to dialkyl peroxide with accompanying elimination products (eqns 21–23).[41]

$$RX + O_2^{\cdot-} \rightarrow RO_2\cdot + X^- \qquad (22a)$$

$$RO_2\cdot + O_2^{\cdot-} \rightarrow RO_2^- + O_2 \qquad (22b)$$

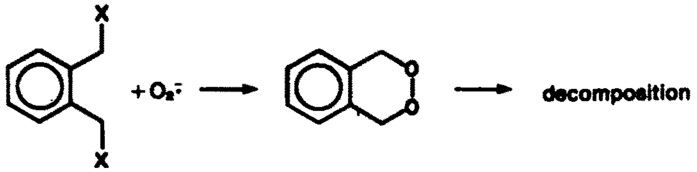
$$RO_2^- + RX \rightarrow ROOR + X^- \qquad (23)$$

The electrochemical stoichiometry is in agreement with this pathway.[41] In dimethylsulfoxide, however, eqn (22b) may be followed by attack on solvent to yield alcohols[43,46] and dimethylsulfone.[47]

$$ROO^- + (CH_3)_2SO \rightarrow RO^- + (CH_3)_2SO_2 \qquad (24)$$

For long reaction times with excess KO_2 (generating, via eqns (9) and (16), strongly basic solutions) or for basic workup (i.e. addition of H_2O rather than acid) of incomplete reactions, the dialkyl peroxide formed in eqn (23) is decomposed by an apparent base-catalyzed process.[48]

A recent study[49] that made use of radical traps has confirmed that ROO· and RO· are intermediates of the nucleophilic attack of $O_2^{\cdot-}$ on alkyl halides in various solvents. The nature of the solvent effects still remains incompletely understood, however. Several synthetic studies also have produced products that support the mechanism given.[46,50] For one of these[50] an endoperoxide was identified, but it was only transiently stable.



(25).

Table 1 summarizes the kinetic data for three studies of the $O_2^{\cdot-}$–RX reaction in two solvents. The results for $(CH_3)_2SO$ were obtained from a chronopotentiometric study in which $O_2^{\cdot-}$ was produced transiently,[40] as well as by stopped-flow reaction of KO_2-crown ether with alkyl bromides.[51] The data for pyridine solvent have been obtained in a recent study in our laboratory in which $O_2^{\cdot-}$ was generated to known concentration levels by controlled potential coulometry prior to the addition of a known concentration of alkyl halide in a sealed cell. The cencentration of $O_2^{\cdot-}$ during the course of the reaction has been monitored by cyclic voltametry. Figure 2 illustrates the $O_2^{\cdot-}$ decay rates for its reaction with the butyl chlorides. The data in Table 1 (and from other studies)[41,43,51] confirm that $O_2^{\cdot-}$ in aprotic solvents acts as a strong nucleophile, and that the relative reactivity of alkyl halides (benzyl > primary > secondary ≫ tertiary, aryl, I > Br > Cl) is consistent with an S_N2 mechanism.

Indeed, the absolute rate constants obtained in these studies indicate that the nucleophilicity of $O_2^{\cdot-}$

Table 1. Second-order rate constants for the reaction of $O_2^{\cdot-}$ and alkyl halides in dimethyl sulfoxide and pyridine

Substrate	Solvent	k_2, $M^{-1}\,s^{-1}$ (25°) *n*	*s*	*i*	*t*
A. Butyl Halides[a]					
BuBr[a]	$(CH_3)_2SO$	3.2	0.6	—	—
BuCl[b]	Pyridine	2.3	0.5	—	< 0.003
BuBr[b]	Pyridine	90	54	35	<0.01
B. Alkyl Bromides[c]					
CH_3Br	$(CH_3)_2SO$	670	—	—	—
CH_3CH_2Br	$(CH_3)_2SO$	350	—	—	—
$CH_3(CH_2)_3Br$	$(CH_3)_2SO$	150	—	—	—
$(CH_3)_2CHBr$	$(CH_3)_2SO$	—	65	—	—

[a] Data from Ref. 40.
[b] Data from Ref. 45.
[c] Data from Ref. 51; stopped-flow reaction of KO_2-crown ether.

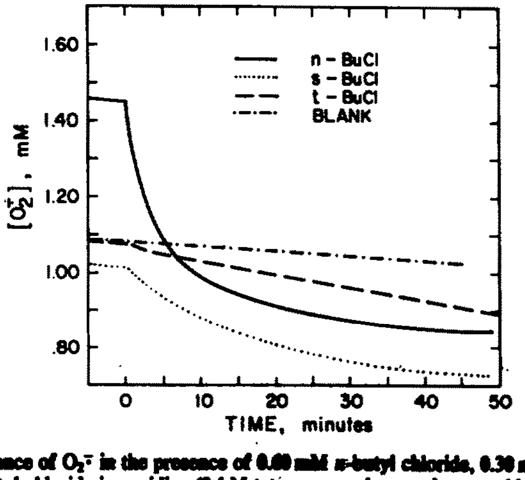


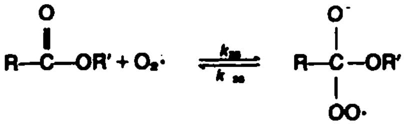
Fig. 2. Rate of disappearance of $O_2^{\cdot-}$ in the presence of 0.60 mM *n*-butyl chloride, 0.30 mM *sec*-butyl chloride and 20 mM *t*-butyl chloride in pyridine (0.1 M tetra-*n*-propylammonium perchlorate) at 25°.

towards typical S_N2 substrates is comparable to that of the highly potent thiophenoxide and thiocyanate, among the best S_N nuclehiles known. Unfortunately, at this time there are not sufficient data in any one solvent to actually fit $O_2^{\cdot -}$ into the established scales of nucleophilicity.[51] One partial explanation for the high nucleophilicity is the fact that $O_2^{\cdot -}$ is an α-effect species, having an electronegative atom adjacent to the attacking atom. However, it is apparently significantly more enhanced in reactivity toward sp^3 carbon than is HOO^- which has the same feature.

(b) *Carbonyl systems*. Reaction of $O_2^{\cdot -}$ with esters yields carboxylic acids and alcohols[52,53] and with acyl halides yields diacylperoxides.[54] It has been shown[52] that acyl oxygen scission occurs for reaction of esters with $O_2^{\cdot -}$ by noting complete retention of configuration in the alcohol moiety from an optically active ester, that the approximate order of reactivity for different n-octanoate esters follows typical acyl-oxygen scission patterns, and that the reaction of diacyl peroxide with KO_2 leads to carboxylic acid.

As part of a study of carbonyl reactions, we recently have examined several aspects of the ester reaction. Figure 3 illustrates the rate of disappearance of $O_2^{\cdot -}$ (as determined by cyclic voltammetry) in the presence of ethyl acetate and phenyl acetate in pyridine as solvent.[33] The rate of reaction with $O_2^{\cdot -}$ also has been determined by cyclic voltammetric reduction of O_2 to $O_2^{\cdot -}$ in the presence of substrate. As illustrated by Figure 4, the peak current for the reoxidation of $O_2^{\cdot -}$ decreases in the presence of the ester and provides a measure of the rate and extent of the reaction.

The second-order rate constants for the reaction of $O_2^{\cdot -}$ with ethyl acetate and with phenyl acetate in pyridine are 0.011 $M^{-1}\,s^{-1}$ and 160 $M^{-1}\,s^{-1}$, respectively.[33] This ratio of 10^4 for the relative rates of reaction of phenyl and ethyl acetates with $O_2^{\cdot -}$ at first seems surprising, but upon closer examination it is consistent with other data for phenyl vs ethyl esters in reactions with effective nucleophiles.[55,56] Initial reaction is proposed to occur via the usual nucleophilic addition-elimination at the carbonyl carbon (eqns 26 and 27).



$$R{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OR' + O_2^{\cdot} \underset{k_{-26}}{\overset{k_{26}}{\rightleftharpoons}} R{-}\underset{\underset{\displaystyle OO\cdot}{|}}{\overset{\overset{\displaystyle O^-}{|}}{C}}{-}OR' \qquad (26)$$

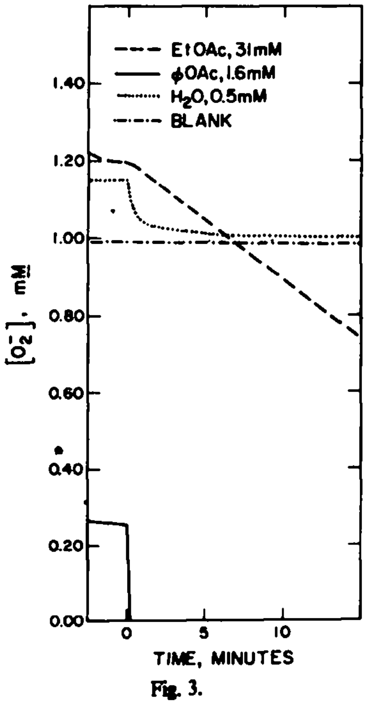


Fig. 3.

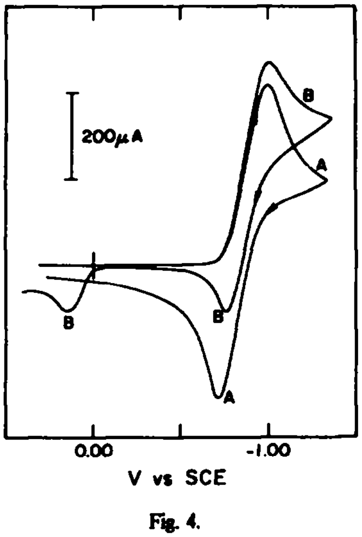
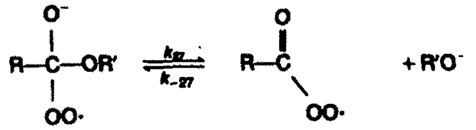


Fig. 4.

Fig. 3. Rate of disappearance of $O_2^{\cdot -}$ in the presence of various substrates in pyridine (0.1 M tetra-*n*-propylammonium perchlorate) at 25°.

Fig. 4. Cyclic voltammograms for (A) O_2 at 1 atm (4.2 mM) and (B) O_2 at 1 atm in the presence of 7.9 mM phenyl acetate in pyridine (0.1 M tetra-*n*-propylammonium perchlorate) at a platinum electrode (area, 0.23 cm^2). Scan rate, 0.1 V s^{-1}.

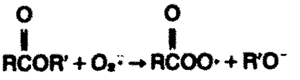


$$R{-}C(O^-)(OO\cdot){-}OR' \underset{k_{-27}}{\overset{k_{27}}{\rightleftharpoons}} R{-}C(=O){-}OO\cdot + R'O^- \qquad (27)$$

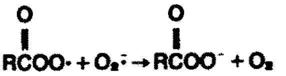
For this situation k_{27} will be highly dependent upon the acidity of R'OH (i.e. the stability of $R'O^-$), and the overall rate depends upon the competition between k_{-26} and k_{27}. For poor leaving groups k_{27} will be slow and rate limiting, but for good leaving groups k_{27} will be much more rapid and make it competitive with k_{-26}. Hence, the loss of $C_6H_5O^-$ in Reaction (27) can compete much more effectively with the loss of $O_2^{-\cdot}$ (k_{-26}) than can the corresponding loss of $C_2H_5O^-$ from the ethyl esters.

The second order constants for $O_2^{-\cdot}$ hydrolysis of $C_6H_5OCOC_6H_5$ and p-$ClC_6H_4OCOC_6H_5$ in dimethylformamide are 3 $M^{-1}\,s^{-1}$ and 25 $M^{-1}\,s^{-1}$, respectively.[52] This ten-fold increase in rate of reaction also is in accord with Reactions (26) and (27) following reasoning similar to that given above.

The overall pathway for ester hydrolysis, then, is given in eqns (28)–(32) (with eqn (28) being the net result of eqns (26) and (27)).

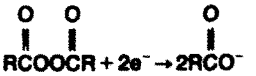


$$RC(=O)OR' + O_2^{-\cdot} \rightarrow RC(=O)OO\cdot + R'O^- \qquad (28)$$

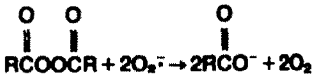


$$RC(=O)OO\cdot + O_2^{-\cdot} \rightarrow RC(=O)OO^- + O_2 \qquad (29)$$

$$RC(=O)OO^- + RC(=O)OR' \rightarrow RC(=O)OOC(=O)R + R'O^- \qquad (30)$$



$$RC(=O)OOC(=O)R + 2e^- \rightarrow 2RC(=O)O^- \qquad (31)$$



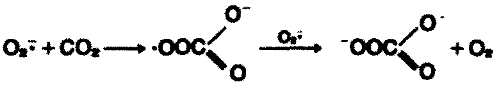
$$RC(=O)OOC(=O)R + 2O_2^{-\cdot} \rightarrow 2RC(=O)O^- + 2O_2 \qquad (32)$$

This is a slightly modified version of the pathway proposed by Magno and Bontempelli[53] in a study of electrochemically generated $O_2^{-\cdot}$ in the presence of esters. Various other possibilities for steps subsequent to Reaction (29) were considered by those authors, but the electrochemical stoichiometry and the observation of an easily reduced transient (diacyl peroxide) led them to favor those steps given above.

α-Keto, α-hydroxy and α-halo carbonyl compounds (acids, esters and ketones) also react with KO_2 by oxidative cleavage to give the carboxylic acid that is derived from the α position.[57] The products probably result from decomposition of an α-hydroperoxy radical or hydroperoxide formed by initial nucleophilic addition.

A recent report[58] indicates that $O_2^{-\cdot}$ oxidizes ascorbic acid by a radical mechanism. That oxidation occurs has been confirmed for ascorbate anion with electrogenerated $O_2^{-\cdot}$ in dimethylformamide.[59] However, in view of the nucleophilicity of $O_2^{-\cdot}$ toward the carbonyl carbon of esters and its poor oxidizing powers, an attractive mechanism involves initial attack on the lactone and subsequent oxidation.

A recent observation by Hill *et al.*[60] is that combination of $O_2^{-\cdot}$ and CO_2 in aprotic media results in CO_4^{2-} formation. This probably occurs by simple addition followed by reduction.



(33)

In a pulse radiolysis study in 1972, Parks proposed $CO_4^{-\cdot}$ from the combination of $O_2^{-\cdot}$ and CO_2.[61]

That aldehydes (i.e. benzaldehyde) do not react with $O_2^{-\cdot}$ probably is due to the reversibility of the addition step (Reaction (26), see Section on *Non-Oxidizing Properties*).

One-electron reductant. A third confirmed reaction characteristic of superoxide ion is its ability to act as a moderate one-electron reducing agent. The redox potential for Reaction (1) indicates that $O_2^{\cdot-}$ has reducing capabilities in aprotic media which are roughly equivalent to those of dithionite ion ($E^{\circ\prime}$, −0.46 V vs NHE).[62] In confirmation of this assessment, a recent study has established that superoxide ion reduces sulfur dioxide to dithionite in dimethylformamide.[63]

$$O_2^{\cdot-} + SO_2 \rightarrow O_2 + SO_2^{\cdot-} \tag{34}$$

$$2SO_2^{\cdot-} \rightarrow S_2O_4^{2-} \tag{35}$$

Not only is this a convenient means to produce standard solutions of dithionite ion in aprotic media, but it also infers that $O_2^{\cdot-}$ may be as effective as dithionite for biochemical reductions.[64] Should this reaction characteristic of $O_2^{\cdot-}$ hold for *in vivo* conditions, it may represent a serious biological hazard of undismutated superoxide.

Superoxide ion reacts rapidly in aprotic media with nitrobenzenes to form the anion radicals, with *p*-benzoquinone to form the semiquinone[65] and it also is an effective reducing agent for copper(II)[66,67] and magnanese(III)[68,69] systems. In aqueous media both iron(III) EDTA and cytochrome *c* are reduced by $O_2^{\cdot-}$.[70]

Interest in the reaction of $O_2^{\cdot-}$ with transition metal ions is the result of the observation that a group of metalloenzymes which contain copper and zinc,[9,71] iron[72] and manganese[73] efficiently catalyze the dismutation of $O_2^{\cdot-}$ to O_2 and H_2O_2.[9b] One step of the catalytic cycle is believed to involve the reduction of the oxidized enzyme by $O_2^{\cdot-}$.

Although the reaction of $O_2^{\cdot-}$ with alkyl hydroperoxides has been cited as an example of a reductive cleavage of the O–O bond,[37,74,75] we believe that ROOH serves primarily as a proton source to bring about the rapid dismutation of $O_2^{\cdot-}$ via Reactions (8) and (9). The reasons for this contention were discussed in the section on *Effective basicity*, and are supported by the fact that alkyl hydroperoxides are in general more acidic than alcohols; the latter rapidly react with $O_2^{\cdot-}$ to give oxygen and alkoxide ions.[75]

Another proposed reduction by $O_2^{\cdot-}$ is the "quenching" of singlet oxygen ($^1O_2$),[76]

$$^1O_2 + O_2^{\cdot-} \rightarrow O_2^{\cdot-} + {}^3O_2 \quad \Delta G = -91\ \text{kJ} \quad k = 1.6 \times 10^9\ M^{-1}\,s^{-1} \tag{36}$$

which in turn brings us to the question of whether singlet state ($^1\Delta_g$) or triplet state ($^3\Sigma_g^-$) molecular oxygen results from oxidation and dismutation of $O_2^{\cdot-}$. Wavefunctions for the ground state of $O_2^{\cdot-}$ have been calculated by use of unrestricted open shell LCAO–SCF functions that are based on the INDO formalism.[77] The calculations indicate that removal of the highest energy electron from $O_2^{\cdot-}$ will produce a triplet state. In particular, the vertical transfer of an electron to form the $^3\Sigma_g^-$ state of O_2 is favored by ~48 kJ relative to the transfer of an electron to form the $^1\Delta_g$ state. The calculations also show that a triplet transition state leads to triplet O_2, while a singlet transition state leads to $^1\Delta_g\ O_2$.

Photon counting has been used to determine the relative yields of dimeric $^1\Delta_g\ O_2$ that result from the oxidation and dismutation of $O_2^{\cdot-}$.[77] The results indicate that the $Fe^{III}(ClO_4)_3$–$O_2^{\cdot-}$, the $HClO_4$–$O_2^{\cdot-}$, and the superoxide dismutase –$O_2^{\cdot-}$ systems involve either adiabatic electron-transfer or a triplet transition state, because they produce directly the $^3\Sigma_g^-$ state of O_2. On the other hand, a singlet transition state which leads to the $^1\Delta_g$ state of O_2 apparently is favored for the ferricenium ion–$O_2^{\cdot-}$ system. If the proton-induced dismutation of $O_2^{\cdot-}$ occurs via a step-wise mechanism, calculations for the transition state of $O_2H\cdot$ plus $O_2^{\cdot-}$ (eqns 8 and 9) give either singlet or triplet, depending upon the trajectory chosen. Because erythrocyctic superoxide dismutase (Cu–Zn SOD) catalyzes the dismutation of $O_2^{\cdot-}$ to ground state $^3O_2$,[78] the enzymatic mechanism may involve a triplet transition state.

Complexation ligand (electron-pair donor). $O_2^{\cdot-}$ is the anion of an acid ($HO_2\cdot$, $pK_a = 4.88$). Some of the earliest electrochemical studies of $O_2^{\cdot-}$ in aprotic media demonstrated that $O_2^{\cdot-}$ acts as an electron-pair donor (Lewis base) to protons, alkali metal ions and alkaline earth ions.[3,5,79] In the case of protons, Reactions (8) and (9) provide a reasonable representation of the donor reaction sequence. Lithium ion appears to form a stable $Li(:O_2\cdot)$ complex.[5] When zinc ion and $O_2^{\cdot-}$ are combined in aprotic solvents a two-step reaction occurs with a bis-coordination complex formed initially.[79]

$$Zn^{2+} + 2O_2^{\cdot-} \rightarrow Zn(:O_2\cdot)_2 \tag{37}$$

This is only transiently stable and decomposes to give oxygen and the peroxide.

$$Zn(:O_2\cdot)_2 \rightarrow O_2 + ZnO_2 \qquad (38)$$

Esr and kinetic measurements have demonstrated that $O_2^{\dot{-}}$ also forms coordination complexes with calcium(II) and barium(II) ions in aqueous media as well as in dimethyl sulfoxide solutions.[80]

A recent report indicates that $O_2^{\dot{-}}$ produced by pulse-radiolysis also forms an electron-pair donor complex with manganese(II).[81] A study in acetonitrile with electro-generated $O_2^{\dot{-}}$ and $Mn^{II}(ClO_4)_2$ yields similar results,[82] but the complex is only transiently stable and decomposes to yield O_2. A reasonable mechanism for the initial steps is one that is analogous to that for the Zn(II)–$O_2^{\dot{-}}$ system.

$$Mn^{2+} + O_2^{\dot{-}} \rightarrow Mn^{II}(:O_2\cdot)^+ \qquad (39)$$

$$Mn^{II}(:O_2\cdot)^+ + O_2^{\dot{-}} \rightarrow [\cdot O_2:Mn^{II}:O_2\cdot] \rightarrow O_2 + Mn^{II}O_2 \qquad (40)$$

Such a process, with Mn(II) acting as a Lewis acid, is analogous to the proton-induced dismutation of $O_2^{\dot{-}}$ and may represent the catalytic mechanism for the Cu–Zn, Mn and Fe superoxide dismutases. By invoking an acid-catalyzed mechanism, the difficult problem of the reduction of $O_2^{\dot{-}}$ by the reduced enzyme is overcome.[83] (The latter has been universally invoked for the enzyme mechanism.)

A recent electrochemical study in these laboratories[79] confirms that $O_2^{\dot{-}}$ forms coordination complexes in aprotic media with Li(I), Ca(II), Zn(II), Cd(II), Mn(II), Fe(II), Co(II), Y(III) and Cr(III). With the exception of the Li(I) system, the complexes are only transiently stable and dismutate to O_2 and the peroxide, probably in a manner analogous to Reactions (39) and (40). Several of the metals also catalyze subsequent dismutation of the peroxide to O_2 and the metal oxide.

Non-oxidizing properties. Although numerous groups[14,64,84–88] have presented evidence that solutions of superoxide ion can cause a net oxidation of substrates, the direct transfer of an electron to $O_2^{\dot{-}}$ is an unreasonable characteristic for solution conditions where $O_2^{\dot{-}}$ is stable, namely aprotic media.[32] Equations (1) and (2) indicate that from a thermodynamic standpoint superoxide ion is a moderate reducing agent, but a pitifully weak oxidizing agent (roughly the equivalent of sodium ion). However, in the presence of proton sources, $O_2^{\dot{-}}$ dismutates rapidly to HO_2^- and O_2 via Reactions (8) and (9) as described earlier. Because all of the reports that discuss the oxidizing properties of $O_2^{\dot{-}}$ have involved systems with proton sources, a reasonable explanation of the observed oxidation reactions is that they actually involve intermediates and products of the proton-induced dismutation reaction ($HO_2\cdot$, O_2, HO_2^- and H_2O_2; in nonaqueous media HO_2^- reacts with H_2O_2 to yield $O_2^{\dot{-}}$ and apparently $\cdot OH$[15]).

The oxidative inertness of $O_2^{\dot{-}}$ is confirmed by its non-reactivity with a wide variety of functional groups, including benzaldehyde, under rigorously aprotic solutions (dry pyridine).[33] Voltammetric studies have established that $O_2^{\dot{-}}$ is thermodynamically unable to oxidize catechols or their anions in acetonitrile by electron transfer.[32] Indeed, the combination of $O_2^{\dot{-}}$ with the anion of 3,5-di-t-butylcatechol in pyridine results in no reaction and neither the monomethyl nor dimethyl ethers of catechol reacts with $O_2^{\dot{-}}$. The initial reaction of superoxide with 3,5-di-t-butylcatechol[14,84] appears to involve a proton transfer from the catechol to $O_2^{\dot{-}}$, followed by further chemistry of the resulting $HO_2\cdot$ species. Presumably, the reported oxidations of hydrazines,[64,86,87] thiols,[41,88] and alcohols[41] also involve an initial proton transfer to $O_2^{\dot{-}}$ (dialkyl sulfides, ethers and alkoxides are inert). A recent report[86] confirms that protons or metal cations are necessary to catalyze the oxidation of hydrazine by superoxide.

There is evidence that in the presence of sufficient water molecules, superoxide solutions can bring about the oxidation of transition metal ions (Mn(II)[69] and Cu(I)[83]). Although this may be the result of an initial proton-induced dismutation of $O_2^{\dot{-}}$ to products that effect the oxidation, an alternative possibility is a direct electron transfer which is promoted by formation of a metal-peroxide intermediate (oxidative addition, eqn 41). This adduct may subsequently be reduced by a second $O_2^{\dot{-}}$ in a process analogous to the generally accepted mechanism for the enzymatic dismutation of $O_2^{\dot{-}}$.[83]

$$M^{n+} + O_2^{\dot{-}} \rightarrow [M^{(n+1)+}(O_2^{2-})] \qquad (41)$$

$$[M^{(n+1)+}(O_2^{2-})] + O_2^{\dot{-}} \xrightarrow{H_2O} M^{n+} + O_2 + H_2O_2 \qquad (42)$$

Acknowledgements—This work was supported by the National Science Foundation under Grant No. 76-24555 (D.T.S.) and Grant No. BMS-03481 (M.J.G.) and by the U.S. Public Health-Service-NIH under Grant No. GM-22761 (D.T.S.) and Grant No. GM-21903 (M.J.G.).

REFERENCES

[1] E. W. Neuman, *J. Chem. Phys.* **2**, 31 (1934).
[2] D. L. Maricle and W. G. Hodgson, *Analyt. Chem.* **37**, 1562 (1965).
[3] D. T. Sawyer and J. L. Roberts, Jr., *J. Electronanal. Chem.* **12**, 90 (1966).
[4] M. E. Peover and B. S. White, *Electrochim. Acta* **11**, 1061 (1966).
[5] E. J. Johnson, K. H. Pool and R. E. Hamm, *Analyt. Chem.* **38**, 183 (1966).
[6] A. D. Goolsby and D. T. Sawyer, *Ibid.* **40**, 83 (1968).
[7] D. Bauer and J. P. Beck, *J. Electroanal. Chem. Interfacial Electrochem.* **40**, 233 (1972).
[8] J. A. Fee and P. G. Hildenbrand, *FEBS Letters* **39**, 79 (1974).
[9a] J. M. McCord and I. Fridovich, *J. Biol. Chem.* **244**, 604 (1969); [b] I. Fridovich, *Acc. Chem. Res.* **5**, 321 (1972).
[10] J. S. Valentine and A. B. Curtis, *J. Am. Chem. Soc.* **97**, 224 (1975).
[11a] A. D. McElroy and J. S. Hashman, *Inorg. Chem.* **3**, 1798 (1964); [b] J. S. Hashman and J. W. Berkstresser, *U.S. Pat*, 3,119,870; *Chem. Abstr.* **60**, 9151f (1964); J. S. Hashman and J. C. Reaforth, *U.S. Pat.* 3,103,140; *Chem. Absts* **60**, 2758c (1964).
[12] E. I. Latysheva, E. N. Cherkasov, S. A. Tokareva, N. G. Velikova and I. I. Volnov, *Izvest. Akad. Nauk, SSR, Ser. Khim* **8**, 1684 (1974). Engl. Transln. **23**, 1610 (1974).
[13] Results from our laboratory.
[14] Y. Moro-oka and C. S. Foote, *J. Am. Chem. Soc.* **98**, 1510 (1976).
[15] J. L. Roberts, Jr., M. M. Morrison and D. T. Sawyer, *Ibid.* **100**, 329 (1978).
[16] I. G. Draganic and Z. D. Draganic, *The Radiation Chemistry of Water.* Academic Press, New York (1971).
[17] J. Chevalet, F. Rouelle, L. Gierst and J. P. Lambert, *J. Electroanal. Chem.* **39**, 201 (1972).
[18] B. Kastening and G. Kazemifard, *Ber. Bunsenges. Phys. Chem.* **74**, 551 (1970).
[19] L. Vaska, *Acc. Chem. Res.* **9**, 175 (1976).
[20] L. Andrews, *J. Am. Chem. Soc.* **90**, 7368 (1968).
[21] J. C. Evans, *J. Chem. Soc.* Chem. Comm. 682 (1969).
[22] T. Ozawa, A. Hanaki and H. Yamamoto, *FEBS Letters* **74**, 99 (1977).
[23] J. San Fillipo, private communication, Rutgers University (1978).
[24] Y. A. Ilan, D. Meisel and G. Czapski, *Israel J. Chem.* **12**, 891 (1974).
[25] P. George, *Oxidases and Related Redox Systems* (Edited by T. E. King, H. S. Mason and M. Morrison), pp. 3–36. Wiley, New York (1965).
[26] J. A. Fee and J. S. Valentine, *Superoxide and Superoxide Dismutase* (Edited by A. M. Michelson, J. M. McCord and I. Fridovich), pp. 19–60. Academic Press, New York (1977).
[27] D. Behar, G. Czapski, J. Rabini, L. M. Dorfman and H. A. Schwartz, *J. Phys. Chem.* **74**, 3209 (1970).
[28] L. M. Dorfman and G. E. Adams, *Reactivity of the Hydroxyl Radical in Aqueous Solutions*, pp. 35, 38, 39. NSRDS-NBS 46 (SD Catalog No. C13.48:46), U.S. Government Printing Office, Washington, D.C. (June 1973).
[29] J. Divisek and B. Kastening, *J. Electroanal. Chem.* **65**, 603 (1975).
[30] M. Tezuka, H. Hamada, Y. Ohkatsu and T. Osa, *Denki Kogaku* **44**, 17 (1976).
[31] Y. A. Ilan, G. Czapski and D. Meisel, *Biochim. Biophys. Acta* **430**, 209 (1976).
[32] D. T. Sawyer, M. J. Gibian, M. M. Morrison and E. T. Seo, *J. Am. Chem. Soc.* **100**, 627 (1978).
[33] M. J. Gibian, D. T. Sawyer, T. Ungermann, R. Tangpoonpholvivat and M. M. Morrison, *Ibid.* **101**, 640 (1979).
[34] G. W. Gokel, H. M. Gerdes and N. W. Rebert, *Tetrahedron Letters* 653 (1976). These authors show that the base-crown ether catalyzed Cannizzaro reaction in organic solvents is rapid and efficient.
[35] D. Swern, *Organic Peroxides*, Vol. I, pp. 328 ff. Wiley-Interscience, New York (1970).
[36] G. W. Gokel, S. A. DiBiase and B. A. Lipisko, *Tetrahedron Letters* 3495 (1976).
[37] J. W. Peters and C. S. Foote, *J. Am. Chem. Soc.* **98**, 873 (1976).
[38] M. J. Gibian, T. Ungermann, M. M. Morrison and D. T. Sawyer, unpublished results.
[39] M. J. Gibian and T. Ungermann, *J. Am. Chem. Soc.* **101**, 1291 (1979).
[40] M. V. Merritt and D. T. Sawyer, *J. Org. Chem.* **35**, 2157 (1970).
[41] R. Dietz, A. E. J. Forno, B. E. Larcombe and M. E. Peover, *J. Chem. Soc.* **B**, 816 (1970).
[42] F. Magno, R. Seeber and S. Valcher, *J. Electroanal. Chem.* **83**, 131 (1977).
[43] J. San Fillipo, Jr., C.-I. Chern and J. S. Valentine, *J. Org. Chem.* **40**, 1678 (1975).
[44] R. A. Johnson and E. G. Nidy, *Ibid.* **40**, 1680 (1975).
[45] M. J. Gibian, R. Tangpoonpholvivat, T. Ungermann, M. M. Morrison and D. T. Sawyer, unpublished data (1978).
[46] E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida and C. S. Shiver, *Tetrahedron Letters* 3183 (1975).
[47] M. J. Gibian and T. Ungermann, *J. Org. Chem.* **41**, 2500 (1976).
[48] C.-I. Chern, R. DiCosimo, R. DeJesus and J. San Filippo, *J. Am. Chem. Soc.* **100**, 7317 (1978).
[49] M. V. Merritt and R. A. Johnson, *Ibid.* **99**, 3713 (1977).
[50] L. H. Dao, A. C. Hopkinson, E. Lee-Ruff and J. Rigaudy, *Can. J. Chem.* **55**, 3791 (1977).
[51] W. C. Danen and R. J. Warner, *Tetrahedron Letters* 989 (1977).
[52] J. San Fillipo, Jr., L. J. Romano, C.-I. Chern and J. S. Valentine, *J. Org. Chem.* **41**, 586 (1976).
[53] F. Magno and G. Bontempelli, *J. Electroanal. Chem.* **68**, 337 (1976).
[54] R. A. Johnson, *Tetrahedron Letters* 331 (1976).
[55] W. P. Jencks, *Catalysis in Chemistry and Enzymology*, pp. 480–487. McGraw-Hill, New York (1969).
[56] M. L. Bender, *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, pp. 176–179. Wiley-Interscience, New York (1971).
[57] J. San Fillipo, Jr., C.-I. Chern and J. S. Valentine, *J. Org. Chem.* **41**, 1077 (1976).
[58] M. Nishikimi, *Biochem. Biophys.* Res. Commun. **63**, 463 (1975).
[59] E. J. Nanni, Jr. and D. T. Sawyer, unpublished results (1978).
[60] H. A. L. Hill, private communication, Oxford University (1978).
[61] D. F. Parkes, *J. Chem. Soc.*, Faraday I **68**, 2103 (1972).
[62] R. P. Martin and D. T. Sawyer, *Inorg. Chem.* **11**, 2644 (1972).
[63] M. D. Stallings and D. T. Sawyer, *J. Chem. Soc.* Chem. Commun. in press (1979).
[64] M. D. Stallings and D. T. Sawyer, unpublished results (1978).
[65] R. Poupko and I. Rosenthal, *J. Phys. Chem.* **77**, 1722 (1973); I. Rosenthal and A. Frimer, *Tetrahedron Letters* 2805, 2809 (1976).
[66] J. S. Valentine and A. B. Curtis, *J. Am. Chem. Soc.* **97**, 224 (1975).
[67] D. Klug-Roth and J. Rabini, *J. Phys. Chem.* **80**, 588 (1976).

[68] J. S. Valentine and A. E. Quinn, *Inorg. Chem.* **15**, 1997 (1976).
[69] J. K. Howie, M. M. Morrison and D. T. Sawyer, *Electrochemical Studies of Biological Systems* (Edited by D. T. Sawyer), *ACS Sym. Ser.* **38**, 97 (1977).
[70] B. Halliwell, *FEBS Lett.* **56**, 34 (1975).
[71] B. B. Keele, Jr., F. J. Yost, Jr. and I. Fridovich, *J. Biol. Chem.* **246**, 2875 (1971).
[72] J. J. Villafranca, F. J. Yost, Jr. and I. Fridovich, *Ibid.* **249**, 3532 (1974).
[73] R. A. Weisiger and I. Fridovich, *Ibid.* **248**, 3582 (1973).
[74] A. LeBerre and Y. Berguer, *C.R. Acad. Sci., Paris* **260**, 1995 (1965).
[75] A. LeBerre and Y. Berguer, *Bull. Soc. Chim. Fr.* 2363 (1966).
[76] H. J. Guiraud and C. A. Foote, *J. Am. Chem. Soc.* **98**, 1984 (1976).
[77] R. R. Birge, L. M. Hubbard, M. M. Morrison and D. T. Sawyer, *Ibid.* **100**, submitted (1978).
[78] R. Zimmermann, L. Flohe, U. Weser and H. Hartmann, *FEBS Lett.* **29**, 117 (1973).
[79] E. J. Johnson, K. H. Pool and R. E. Hamm, *Analyt. Chem.* **39**, 888 (1967).
[80] R. C. Bray, G. N. Mautner, E. M. Fielden and C. I. Carle, *Superoxide and Superoxide Dismutases* (Edited by A. M. Michelson, J. M. McCord and I. Fridovich), pp. 61–75. Academic Press, New York (1977).
[81] B. H. J. Bielski and P. C. Chan, *J. Am. Chem. Soc.* **100**, 1920 (1978).
[82] L. Biesecker and D. T. Sawyer, unpublished results (1978).
[83] J. A. Fee, *Superoxide and Superoxide Dismutases* (Edited by A. M. Michelson, J. M. McCord and I. Fridovich), pp. 173–192. Academic Press, New York (1977).
[84] E. Lee-Ruff, A. B. P. Lever and J. Rigaudy, *Can. J. Chem.* **54**, 1837 (1976).
[85] I. B. Afanas'ev and H. I. Polozova, *Zh. Org. Khim.* **12**, 1833 (1976).
[86] H. P. Misra and I. Fridovich, *Biochemistry* **15**, 681 (1976).
[87] C.-I. Chern and J. San Filippo, Jr., *J. Org. Chem.* **42**, 178 (1977).
[88] K. Asada and S. Kanematsu, *Agric. Biol. Chem.* **40**, 1891 (1976).