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How Super Is Superoxide?

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The name "superoxide" has prompted many in recent years to assume an exceptional degree of reactivity for superoxide anion (O_2^-), especially as a strong oxidant and an initiator of radical reactions.[1] The name "superoxide", which was first proposed for the potassium salt of the radical anion O_2^- in 1934,[2] had nothing to do with the chemical reactivity of O_2^-. It was selected because the stoichiometry for KO_2 differed from that for the products of combustion for most metals, e.g., NaOH (hydroxide), Na_2O (oxide), Na_2O_2 (peroxide), NaO_2H (hydroperoxide), and NaO_3 (ozonide).

For many years, superoxide was considered to be little more than an interesting chemical curiosity.[3] Ionic salts of superoxide (yellow to orange solids), which generally were formed from the reaction of dioxygen with metals such as potassium, rubidium, or cesium, were found to be paramagnetic with one unpaired electron per two oxygen atoms. Some of the early interest in the properties of superoxide was caused by the development of a self-contained breathing apparatus in which potassium superoxide, mixed with transition-metal oxide catalysts, was used both to absorb CO_2 and to generate O_2.[4]

In the early sixties several groups reported that KO_2 (suspended in nonpolar solvents) was relatively unreactive and of limited use in organic synthesis.[5-7] (Later work, however, has demonstrated that this lack of reactivity was due to the limited solubility of KO_2 in such solvents.) During the same period investigators of the reactivity of superoxide in aqueous solution (via pulse radiolysis generation) likewise concluded that superoxide was a relatively innocuous species.[8,9]

In 1969 two reports appeared that reopened the question of superoxide reactivity. These were the direct observation of superoxide by ESR during an enzymatic reaction that involved dioxygen[10] and the discovery of metalloproteins that catalyze the disproportionation of superoxide, i.e., "superoxide dismutases" (SOD's) (eq 1). The biological function of the latter was concluded

$$2O_2^- + 2H^+ \xrightarrow{\text{SOD}} O_2 + H_2O_2 \qquad (1)$$

to be the protection of living cells agains the toxic effects of superoxide.[11] The possibility that superoxide might be an important intermediate in aerobic life provided a new impetus to studies of superoxide reactivity.

Our interest in the reactivity of superoxide began with the discoveries that electrochemical reduction of O_2 in dimethyl sulfoxide yields stable solutions of O_2^-[12] and that crown ethers solubilize KO_2 in aprotic solvents and can be used to prepare stable solutions of superoxide for various uses.[13] In this Account, we summarize work from our laboratories on the chemistry of superoxide and our understanding of the inherent reactivity of this species in various chemical environments. Little was known in 1969 about the reactivity of superoxide in any environment. This is no longer the case, however, and we believe our results and those of many others in the superoxide field[14-19] can be used to provide an answer to the question: "How super is superoxide?"

Physical Properties

As a prelude to examining the chemical reactivity of superoxide, its physical properties and those of its conjugate acid, the hydroperoxyl radical ($HO_2\cdot$), are reviewed and summarized in Table I.[2,10,14,20-35] Su-

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(1) Although superoxide ion is frequently symbolized as $O_2^-\cdot$, we use O_2^- because its electronic character is similar to that of NO in that the unpaired electron is in a molecular orbital between the two oxygen atoms and rehybridization must occur before a σ bond can form. The use of the radical *dot* causes many to overemphasize the small degree of radical character observed for O_2^- in its chemical reactions.

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Table I
Physical Properties of Superoxide (O_2^-, KO_2, and $HO_2\cdot$)

	ref
electron structure (O_2^-), paramagnetic (one-unpaired electron)	2
$(1\sigma_s)^2(1\sigma_s^*)^2(2\sigma_s^*)^2(2\sigma_s)^2(\sigma_p)^2(\pi_z)^2(\pi_x)^2(\pi_z^*)^2(\pi_x^*)^1$	20
O-O bond distance (KO_2), 1.28 Å	21
UV absorption spectra	
O_2^- (aqueous), 245 nm (ϵ 2350)	22
$HO_2\cdot$ (aqueous), 225 nm (ϵ 1400)	22
O_2^- (CH_3CN), 255 nm (ϵ 1460)	23
O_2^- (KO_2/18-crown-6/Me_2SO), 250 nm (ϵ 2690)	24
IR absorption spectra, KO_2 (O-O stretch; bond order 1.5), 1145 cm^{-1}	25
EPR spectra (O_2^-)	
aqueous (102 K), $g_\parallel = 2.1$, $g_\perp = 2.00$	10, 26
Me_2SO (77 K), $g_\parallel = 2.11$, $g_\perp = 2.00$	27
CH_3CN (77 K), $g_\parallel = 2.083$, $g_\perp = 2.008$	23
heat of hydration, $-\Delta H \cong 418$ kJ	
$O_2^-\ (\text{gas}) \xrightarrow{H_2O} O_2^-\ (\text{aqueous})$	28
gas-phase basicity, $F^- > O_2^- > Cl^- > Br^-$	29

Redox Potentials in Water and DMF[a]

	$E°$, V, vs. NHE			
	H_2O			
	pH 0	pH 7	pH 14	DMF
$O_2 + e^- \rightarrow O_2^-$		−0.16	−0.16	−0.60
$O_2 + H^+ + e^- \rightarrow HO_2\cdot$	+0.12			+0.12
$O_2^- + H_2O + e^- \rightarrow HO_2^- + OH^-$			+0.20	
$O_2^- + \text{H-sol} + e^- \rightarrow HO_2^- + \text{Sol}^-$				−1.75
$O_2^- + 2H^+ + e^- \rightarrow H_2O_2$		+0.89		
$HO_2\cdot + H^+ + e^- \rightarrow H_2O_2$	+1.44			
$O_2^- + 2H_2O + 2e^- \rightarrow 3\ OH^- + \cdot OH$		+0.9	+0.3	
$HO_2\cdot + 2H^+ + 2e^- \rightarrow H_2O + \cdot OH$	+1.4			
$O_2^- + 2H_2O + 3e^- \rightarrow 4\ OH^-$		+1.20	+0.65	
$HO_2\cdot + 3H^+ + 3e^- \rightarrow 2H_2O$	+1.66			

[a] The values for aqueous media represent the best estimate on the basis of pulse radiolysis, electrochemical, and calorimetric measurements during the past decade.[14, 22, 30-35] The standard state for all reactants and products is unit concentration. If unit pressure is used as the standard state of dioxygen (O_2), the redox potentials for those aqueous reactions in which it is a reactant are shifted by −0.17 V. The values for DMF are from our laboratories.

peroxide is a relatively small univalent anion with an O–O bond distance that is intermediate between that for dioxygen and peroxide. Its aqueous solvation energy indicates that it is almost "fluoride-like" and that it will form exceptionally strong hydrogen bonds with water.

The effect of the strong solvation of O_2^- by water is confirmed by the shift of −0.44 V for the O_2/O_2^- couple on going from H_2O to dimethylformamide (DMF) (Table I). Dimethyl sulfoxide (Me_2SO) ($E°'_{O_2/O_2^-}$ = −0.50 vs. NHE), pyridine ($E°'_{O_2/O_2^-}$ = −0.65 V), and acetonitrile ($E°'_{O_2/O_2^-}$ = −0.80 V) exhibit similar weak solvation of O_2^- relative to aqueous media.

The redox reactivity of superoxide clearly is sensitive to the solvation of O_2^-. But even more important is the stabilization of peroxide by protons. In aprotic media, the peroxide dianion, O_2^{2-} (removed from an ionic lattice, unprotonated, and not coordinated to any metal ion), is a highly unstable species. Thus, the likelihood that superoxide will act as a one-electron oxidant under conditions where an isolated peroxide dianion is the product is nil.[36] On the other hand, when protons or metal ions are available to stabilize the peroxide anion or when an easily abstractable hydrogen atom is available, the thermodynamics are quite different. Some examples of reactions in which superoxide is reduced to peroxide are described in subsequent sections.

Chemical Reactivity

Proton-induced Dismutation and Effective Basicity. The kinetics and thermodynamics for the protonation and disproportionation of superoxide ion (O_2^-) in water (eq 2–5) have been evaluated by the pulse

$$H^+ + O_2^- \rightleftarrows HO_2 \qquad pK_a = 4.69 \qquad (2)$$

$$O_2^- + HO_2\cdot \rightarrow O_2 + HO_2^- \qquad k_3 = 1.0 \times 10^8\ M^{-1}\ s^{-1} \quad (3)$$

$$HO_2\cdot + HO_2\cdot \rightarrow O_2 + H_2O_2 \qquad k_4 = 8.6 \times 10^5\ M^{-1}\ s^{-1} \quad (4)$$

$$O_2^- + O_2^- \xrightarrow{H_2O} O_2 + H_2O_2 \qquad k_5 = <0.3\ M^{-1}\ s^{-1} \quad (5)$$

radiolysis technique[14,22,30,31] and confirm that protons promote a rapid bimolecular process. The equilibrium in aqueous media at neutral pH is far to the right (eq 6), and even at pH 14 disproportionation of O_2^- by H_2O

$$2O_2^- + 2H^+ \rightleftarrows H_2O_2 + O_2 \qquad K_{pH\ 7} = 4 \times 10^{20} \quad (6)$$

is complete.[16]

In aprotic solvents, superoxide is quite stable because disproportionation to give the peroxide dianion O_2^{2-} is highly unfavorable. The effect of adding acidic substrates to stable solutions of O_2^- in aprotic solvents has been determined by stopped-flow spectrophotometry and electrochemical measurements in dimethylformamide (DMF) and in acetonitrile (MeCN). On the basis of the kinetic data, a self-consistent mechanism for the proton-induced disproportion of O_2^- in aprotic media has been proposed for acidic substrates (HA)[37] (eq 7 and 8).

$$HA + O_2^- \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} HO_2\cdot + A^- \qquad (7)$$

$$HO_2\cdot + HO_2\cdot \xrightarrow{k_8} H_2O_2 + O_2 \qquad (8)$$

For strongly acidic substrates ($HClO_4$, HCl, or NH_4ClO_4) in DMF, the rate of proton transfer to O_2^-

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is extremely rapid and the rate-determining step is reaction 8 with $k_8 > 1 \times 10^7$ M^{-1} s^{-1}.[22] In contrast, for moderate or weak acids (e.g., phenol or water), the rate is limited by the transfer of a proton from HA to O_2^- (reaction 7), which is controlled by the K_a of the protic substrate. In DMF the second-order rate constants range from $k_7 = 1 \times 10^4$ M^{-1} s^{-1} for phenol to $k_7 = 1 \times 10^{-3}$ M^{-1} s^{-1} for water.

The tendency of O_2^- to disproportionate via abstraction of protons from substrates and solvents is its most dominant reaction characteristic. Although the pK_a for $HO_2\cdot$ in water has a value of 4.69 (which implies that O_2^- is a weak base),[22] combination of the first and third half-reactions of Table I yields the net expression

$$2O_2^- + H_2O \rightleftarrows O_2 + HO_2^- + OH^- \qquad K = 0.91 \times 10^9 \tag{9}$$

The value of the equilibrium constant indicates that O_2^- 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 24. Thus, addition of O_2^- to an aqueous solution results in the stoichiometric formation of HO_2^- and OH^-, both strong Brønsted bases.[38]

The propensity of O_2^- to remove protons from substrates accounts for its reactivity with acidic reductants and their overall oxidation. Thus, combination of O_2^- with protic substrates (α-tocopherol), hydroquinone, 3,5-di-*tert*-butylcatechol, and L(+)-ascorbic acid) yields products that are consistent with an apparent one-electron oxidation of the substrate and the production of H_2O_2. However, the results of recent electrochemical studies[39] provide clear evidence that these substrates are not oxidized in aprotic media by direct one-electron transfer to O_2^-. The primary step involves abstraction of a proton from the substrate by O_2^- to give substrate anion and the disproportionation products of superoxide (H_2O_2 and O_2). In turn, the substrate anion is oxidized by O_2 in a multistep process to yield oxidation products and H_2O_2. Thus, by continuously purging the O_2 that results from disproportionation of O_2^- when it is combined with α-tocopherol (by vigorous Ar bubbling through the solution), quantitative yields of substrate anion are obtained without significant oxidation.

The reported oxidation of thiols[40,41] and alcohols[40] by O_2^- presumably occurs by the same initial proton-induced dismutation step. However, the facile oxidation of ascorbate by O_2^- in *aqueous media* (buffered at pH 9.9)[42] probably occurs via hydrogen atom transfer. (Such processes are discussed below.)

Nucleophilicity. Although superoxide ion is a powerful nucleophile in aprotic solvents, it does not exhibit such reactivity in water, presumably because of its strong solvation by that medium and its rapid hydrolysis and disproportionation. The reactivity of O_2^- with alkyl halides via nucleophilic substitution was first reported in 1970.[40,43] These and subsequent kinetic studies[44-47] confirm that the reaction is first order in substrate, that the rates follow the order primary > secondary ≫ tertiary for alkyl halides and tosylates, and that the attack by O_2^- results in inversion of configuration.

In aprotic solvents primary and secondary alkyl halides react to yield primarily dialkyl peroxides with accompanying elimination products,[40,46,47] which is consistent with a multistep S_N2 mechanism (eq 10–12).

$$RX + O_2^- \rightarrow RO_2\cdot + X^- \tag{10}$$

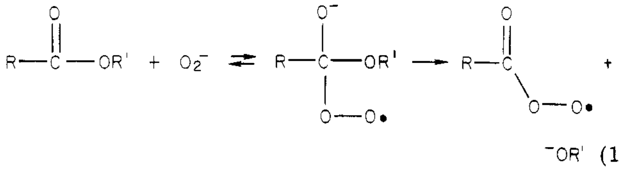
$$RO_2\cdot + O_2^- \rightarrow RO_2^- + O_2 \tag{11}$$

$$RO_2^- + RX \rightarrow ROOR + X^- \tag{12}$$

In dimethyl sulfoxide reaction 11 is followed by attack of the solvent by RO_2^- to give dimethylsulfone and alcohols.[43,45,48] The rate constants for these reactions in dimethyl sulfoxide and in pyridine[16] indicate that the nucleophilicity of O_2^- for such substrates exceeds that of potent nucleophiles such as thiophenoxide and thiocyanate.

Recent work[49] has demonstrated that superoxide ion reacts rapidly with CCl_4, $CHCl_3$, CH_2Cl_2, *p,p′*-DDT, and related polychloro hydrocarbons in aprotic media (DMF and Me_2SO). The overall reactions for the chloromethane substrates are multistep processes that consume one or more O_2^- ions per chloride to yield oxygenated products that are free of chloro groups. The reactions are believed to be initiated via nucleophilic attack by superoxide ion on carbon (or, possibly, on chlorine) with a concerted reductive displacement of chloride ion. Kinetic and electrochemical studies confirm that the initial step is rate limiting and first order with respect to substrate and O_2^-.

Further reactions in which O_2^- acts as a nucleophile include its attack on the carbonyl carbon of esters to yield carboxylic acid anions and alcohols[50-52] and of acyl halides to yield diacyl peroxides.[53] Acyl oxygen scission occurs in the ester reaction on the basis of complete retention of configuration in the alcohol moiety from an optically active ester.[50] The initial reaction is proposed to occur via nucleophilic addition and elimination at the carbonyl carbon[52]



(13)

with subsequent steps to give the net reaction of ester hydrolysis.

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[38] Reference to the data for O_2 reduction in neutral and acidified DMF (Table I) provides an approximate value of the pK_a value for $HO_2\cdot$ in aprotic media [($pK_a \approx 12)_{DMF}$]. Thus, from hydrolytic considerations O_2^- is a stronger base in DMF than in aqueous media because of the much weaker solvation of anions by aprotic solvents. However, the proton-driven disproportionation (eq 9) remains dominant and causes O_2^- to have uniquely strong basicity in aprotic media [e.g., 1-butanol (pK_a = 33)[39] is deprotonated by O_2^- in DMF].[37]

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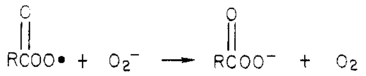
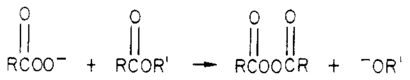
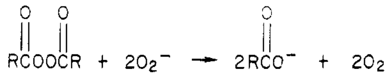

$$\mathrm{R\overset{O}{\overset{\|}{C}}OO\bullet + O_2^- \longrightarrow R\overset{O}{\overset{\|}{C}}OO^- + O_2} \quad (14)$$


$$\mathrm{R\overset{O}{\overset{\|}{C}}OO^- + R\overset{O}{\overset{\|}{C}}R' \longrightarrow R\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}R + {}^-OR'} \quad (15)$$


$$\mathrm{R\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}R + 2O_2^- \longrightarrow 2R\overset{O}{\overset{\|}{C}}O^- + 2O_2} \quad (16)$$

Combination of O_2^- with α-keto, α-hydroxy, and α-halo carbonyl compounds results in nucleophilic addition at the carbonyl carbon followed by oxidative cleavage to give the carboxylic acid that is derived from the α position.[54] An initial reduction by O_2^- of activated α-diketones followed by a radical–radical coupling reaction has been proposed as an alternative mechanism.[55]

One-Electron Reductant. Another characteristic of O_2^- is its ability to act as a moderate one-electron reducing agent. For example, combination of O_2^- with 3,5-di-*tert*-butylquinone (DTBQ) in DMF yields the semiquinone anion radical $DTBSQ^-$ as the major product.[19] The relevent redox potentials in DMF are O_2/O_2^-, $E^{\circ\prime} = 0.60$ V vs. NHE, and DTBQ/$DTBSQ^-$, $E^{\circ\prime} = -0.25$ V vs. NHE, which indicate that the equilibrium constant, K, for the reaction of O_2^- with DTBQ has a value of 0.8×10^6 (eq 17).

$$O_2^- + \mathrm{DTBQ} \rightleftarrows \mathrm{DTBSQ}^- + O_2 \quad (17)$$

Electrochemical studies of sulfur dioxide[56] (SO_2/SO_2^-, $E^{\circ\prime} = -0.58$ V vs. NHE) and of molecular oxygen[39] in dimethylformamide indicate that the equilibrium constant, K, for the reaction of SO_2 with O_2^- (eq 18) has

$$SO_2 + O_2^- \rightarrow O_2 + SO_2^- \quad (18)$$

a value of 1.1. However, the reaction goes to completion because SO_2^- is complexed by SO_2 and also dimerizes to dithionite ion.[57]

The electrochemical, spectroscopic, and chemical evidence confirms that O_2^- is a stronger and more effective reducing agent than dithionite ion in aprotic solvents. In aqueous media the equilibrium constant for the reduction of ferricytochrome *c* by O_2^- has a value of 3.7×10^4.[58]

Superoxide ion also is an effective reducing agent of transition-metal complexes; examples include copper(II),[13,59] manganese(III),[60,61] and iron(III).[62,63] Recent work[64] has demonstrated that O_2^- also reduces ferricenium ion, $Mn^{IV}{}_2O_2(o\text{-phen})_4{}^{4+}$, $Co^{III}(o\text{-phen})_3{}^{3+}$, and $Ir^{IV}Cl_6{}^{2-}$ by one-electron processes.

Oxidation of O_2^- to $^1O_2$. Singlet oxygen ($^1O_2(^1\Delta_g)$) has been reported to result from the oxidation of O_2^- with ferricenium ion[65] and diacyl peroxides[66] and from the disproportionation of O_2^- by proton sources.[67] (However, a later investigation failed to detect $^1O_2$.[68]) Recent studies in our laboratory confirm that substantial amounts of $^1O_2$ are formed by the oxidation of O_2^- with ferricenium ion in DMF[69] but provide little evidence for its formation from the proton-induced disproportionation of O_2^- in DMF.

Conversion of $^3O_2$ to $^1O_2$ is a highly endothermic process[70] (eq 19). From thermodynamic considerations

$$^3O_2 \rightarrow {}^1O_2 \qquad \Delta G = +91 \text{ kJ} \quad (19)$$

the oxidation of O_2^- to $^1O_2$ requires an oxidant with a redox potential of at least +0.34 V vs. NHE. Because the reversible reduction potential for ferricenium ion in DMF occurs at +0.69 V vs. NHE, oxidation of O_2^- to $^1O_2$ is thermodynamically favored.

The results of photon counting experiments indicate that both proton-induced disproportionation ($HClO_4$ + O_2^-) and transition metal ion oxidation ($Fe^{III}(ClO_4)_3$ + O_2^-) of O_2^- yield predominantly triplet oxygen ($^3O_2$).[69] This is believed to be the result of a triplet transition state complex for the disproportionation process, $[(\cdot O_2{:})H({:}O_2\cdot)]_{tr}$, as well as for the redox reaction, $[(\cdot O_2{:})Fe^{III}({:}O_2\cdot)]_{tr}$. Other oxidants which convert O_2^- to $^1O_2$ include $Mn^{III}(O_3terpy)_2{}^{3+}$ and $Mn^{IV}{}_2O_2(o\text{-phen})_4{}^{4+}$.[69]

Oxidant via H-Atom Transfer from Reduced Flavins, Hydrophenazines, and Hydroxylamine. The direct transfer of an electron to O_2^- is an unlikely process in aprotic media because of the extreme instability of the O_2^{2-} species.[14,16] As a result, most of the reported oxidations by O_2^- in such media actually represent an initial proton abstraction to give substrate anion and the species that result from disproportionation, HO_2^- and O_2. The latter oxidize the substrate anion (see above).

Recent studies[71] demonstrate that O_2^- is an effective oxidant of basic reducing substrates with readily transferable hydrogen atoms, e.g., dihydrophenazines, reduced flavins, hydrazines, and hydroxylamine. Dihydrophenazine and N-methylhydrophenazine (both models for reduced flavin) are oxidized to phenazine and N-methylphenazine radical, respectively. The reaction stoichiometry in each case is 1:1, but the net oxidation change is two for dihydrophenazine and one for N-methylhydrophenazine (eq 20, 21). Because O_2^-

$$\mathrm{PhenH_2} + O_2^- \xrightarrow{\mathrm{HSol}} \mathrm{Phen} + (1/n)(\cdot\mathrm{Sol})_n + H_2O + OH^- \quad (20)$$

$$\mathrm{CH_3NPhenH} + O_2^- \rightarrow \mathrm{CH_3NPhen\cdot} + HO_2^- \quad (21)$$

is not a strong enough base in aqueous solution to deprotonate ascorbate anion, the facile oxidation of ascorbate ion at pH 9.9 in aqueous media[42] probably involves a similar hydrogen-atom transfer mechanism. Although O_2^- is not a highly reactive oxidant for organic substrates, these results confirm that it selectively oxidizes those basic substrates that are susceptible to a hydrogen-atom transfer mechanism.

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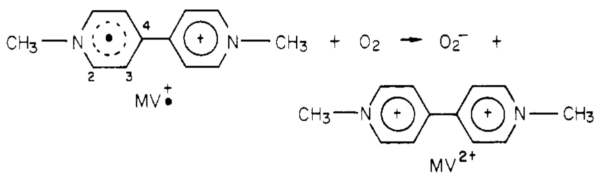
Radical–Radical Coupling with Reduced Methyl Viologen and N^5-Ethyl-3-methyllumiflavin Radical. When reduced methyl viologen ($MV^{+}\cdot$) is combined with O_2 in aqueous media, a stoichiometric yield of O_2^- results (eq 22). However, combination of DMF solutions of $MV^{+}\cdot$ and of O_2^- in 1:1 stoichiometry results in the irreversible formation of a peroxy zwitterion adduct, $[MV^+O_2^-]$, with the -OO^- group at the 2-position.[72] While $MV^{+}\cdot$ and O_2^- are paramagnetic and exhibit characteristic ESR spectra, as well as UV absorption spectra, the adduct is ESR silent and has new absorption bands at 407 and 450 nm in DMF. Not surprisingly, the adduct, $[MV^+O_2^-]$, rapidly decomposes via ring rupture and oxidative reactions to give a multitude of products.



(22)

Although the direct coupling of O_2^- to cation radicals has been proposed previously,[73,74] we believe that this is one of the first observations of a stoichiometric process. The possibility that such a process may also occur in aqueous solution is intriguing considering the toxicity of methyl viologen (paraquat) to aerobic organisms.

Another example of O_2^- acting as a coupling reagent with stable radicals is its combination with N^5-ethyl-3-methyllumiflavin radical (FlEt·), which results in the transient formation of the flavoperoxide anion (4a-FlEtOO⁻).[75] However, in spite of vigorous and persistent research effort,[9,22,30,31] there are no examples of O_2^- acting as an initiator of radical chain reactions. Radical–radical coupling only has been observed for those forcing conditions ($MV^{+}\cdot$ plus O_2^- or FlEt· plus O_2^-) where alternative reactions of O_2^- are not favored.

Reactions with Metal Ions

One-Electron Reductant. Superoxide is a simple one-electron reductant for a large number of metal ions and their complexes. Examples include reductions in aqueous media, e.g., Cu^{2+} hydrate and a large number of other copper complexes,[59,76] $Fe^{III}EDTA$,[77,78] $Fe(CN)_6^{3-}$,[79] $Mn^{III}EDTA$,[80] $Ru^{III}(NH_3)_5(isn)^{3+}$ (isn = isonicotinamide),[81] and $Mo(CN)_8^{3-}$,[82] as well as in aprotic solutions, e.g., $Cu(phen)_2^{2+}$ (phen = 9,10-phenanthroline),[13] Cu^{II}salicylate,[83] $Mn^{III}(TPP)Cl$ (TPP = tetraphenylporphinato),[60] and $Fe^{III}(TPP)Cl$.[63] Some of these complexes are coordinately saturated, and there is no evidence that superoxide must enter the first coordination sphere to reduce these complexes.

Table II
Metal-Catalyzed Voltammetric Reduction of O_2 in Me_2SO (0.1 M TEAP[a]) at a Pt Electrode (0.02 V s⁻¹)

metal[b]	$E_{p,c}$, V vs. SCE	$n(e^-/O_2)$
	−0.80	1
Li^+	−0.79	1
Zn^{2+}	−0.67	2
Cd^{2+}	−0.67	2
Fe^{2+}	−0.52	2
Mn^{2+}	−0.61	4
Co^{2+}	−0.66	4

[a] Tetraethylammonium perchlorate. [b] Concentrations of metal ions are 10 to 30 times those of O_2.

One-Electron Oxidant. Oxidation of metal complexes by superoxide has been much less studied. The best documented examples are oxidation of $Fe^{II}EDTA$ in aqueous solution[77] and of $Fe^{II}(TPP)$ in aprotic media.[63] Both oxidations proceed by oxidative addition of superoxide to form a ferric peroxo complex, $Fe^{III}(O_2^{2-})$. Protonation of the $Fe^{III}EDTA(O_2^{2-})$ complex causes H_2O_2 to dissociate, but the $Fe^{III}(TPP)(O_2^{2-})$ complex is relatively stable in aprotic media.

Most metal ions and complexes are not oxidized by O_2^- in aqueous solution at rates competitive with superoxide disprotonation, even when such oxidations are thermodynamically favored. The probable explanation is that superoxide must be coordinated and reduced in the first coordination sphere of the metal. Oxidations by $HO_2\cdot$, on the other hand, are not limited by the same restriction and $Fe(CN)_6^{4-}$,[79] aqueous Fe^{2+},[84] $Ru^{II}(NH_3)_5(isn)^{2+}$,[81] $Mo(CN)_8^{4-}$,[82] and several other complexes[85] are readily oxidized by the neutral radical.

Ligand. Complexation of metal ions by O_2^- to form a superoxo complex has been observed for Ba^{2+},[86] Ca^{2+},[86] Mn^{2+},[87] and $[Co^{II}(4,11\text{-dieneN}_4]^{2+}$ (4,11-dieneN$_4$ = 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene)[88] in aqueous media and for $Zn^{II}(TPP)$,[89] $Cu^{II}(tet\ b)^{2+}$ (teb b = *rac*-5,7,7,12,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane),[90] vitamin B_{12a},[91] $Mn^{II}(TPP)$,[60] and $Mn(ClO_4)_2$[92] in nonaqueous solutions. Furthermore, complex formation has been observed by EPR upon addition of $HO_2\cdot$ to Ti(IV), Ce(IV), V(V), Th(IV), Mo(VI), Zr(IV), and Hf(IV).[9] The narrow line widths probably indicate that these are O_2^- complexes. Complexation of O_2^- to a metal ion lowers its pK_a. For example, the pK_a of $Ni(O_2)^+$ is 3.2[93] as compared to a pK_a of 4.7 for free O_2^-.

The effect of ligation to metal ions on the properties of O_2^- is illustrated by the potentials and the overall electron stoichiometry for the reduction of O_2 in the presence of $Mn(ClO_4)_2$, $Co(ClO_4)_2$, $Fe(ClO_4)_2$, $Zn(ClO_4)_2$,

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$Cd(ClO_4)_2$, $Ni(ClO_4)_2$, and $LiClO_4$ (Table II).[64] These metal ions appear to act as Lewis acids, and the effect of their presence is to cause the reduction of O_2 to O_2^- to occur at more positive potentials in the order $Fe^{2+} > Mn^{2+} > Zn^{2+} \sim Co^{2+} \sim Cd^{2+} > Li^+ \sim TEA^+$ (where TEA^+ is tetraethylammonium ion, the cation commonly employed as a supporting electrolyte). The overall electron stoichiometry in the presence of Mn^{2+} and Co^{2+} is four electrons per O_2 whereas in the presence of Fe^{2+}, Zn^{2+}, and Cd^{2+} it is two electrons per O_2. When Li^+ is present, only one electron is consumed in the process.

The observations indicate that the thermodynamics of O_2 reduction is dependent upon the presence and nature of the Lewis acid present. Except for Li^+ ion, which appears to form a stable $(Li^+)(O_2^-)$ complex, either two- or four-electron reductions occur in the presence of these metal ions. We believe that the mechanism involves either electrochemical reduction or disproportionation of the metal ion–superoxo complex, e.g.,

$$O_2^- + M^{n+} \rightarrow (M^{n+})(O_2^-) \qquad (23)$$

$$(M^{n+})(O_2^-) \xrightarrow{e^-} (M^{n+})(O_2^{2-}) \qquad (24)$$

or

$$(M^{n+})(O_2^-) + O_2^- \rightarrow (M^{n+})(O_2^{2-}) + O_2 \qquad (25)$$

or

$$2(M^{n+})(O_2^-) \rightarrow (M^{n+})(O_2^{2-}) + M^{n+} + O_2 \qquad (26)$$

The overall electron stoichiometry for Mn(II) and Co(II) (Table II) indicates that the peroxides of these metals are unstable and undergo further reactions, presumably to form oxides or hydroxides.

Reduction of a superoxo complex by another superoxide to give a peroxo complex has been observed by pulse radiolysis for μ-superoxo dicobalt(III) complexes in aqueous solution.[94] Stabilization of peroxide by complexation to metals is evident from a comparison of the reduction potential of O_2^- in Me_2SO ($E°' < -1.7$ V vs. NHE)[95] with the reduction potentials of $(NH_3)_4Co^{III}(O_2^-)(NH_2^-)Co^{III}(NH_3)_4^{4+}$ ($E° = +0.75$ V)[96] and of Cu^{II}(teb b)$(O_2^-)^+$ ($E° = -0.39$ V).[90] Metal ions clearly can stabilize peroxide in a manner similar to that observed for protons.

Natural and Synthetic Superoxide Dismutases. Among the biological systems that involve superoxide, the superoxide dismutases have inspired the most interest. For these enzymes and for metal complexes that catalyze superoxide disproportionation, two mechanism have been proposed (I and II). Mechanism I involves a one-electron reduction of the metal complex followed by reoxidation of the reduced metal complex by another superoxide, presumably through the intermediacy of a metal–peroxo complex. Mechanism II involves complexation of the oxidized metal by superoxide, which is followed by reduction of bound superoxide to peroxide with subsequent protonation to yield hydrogen peroxide. Each step of both mechanisms has an analogue in reactions of superoxide with metal ions and complexes (see above).

Mechanism I

$$M_{ox} + O_2^- \rightarrow M_{red} + O_2 \qquad (27)$$

$$M_{red} + O_2^- \xrightarrow{H_2O} M_{ox} + H_2O_2 \qquad (28)$$

Mechanism II

$$M_{ox} + O_2^- \rightarrow M_{ox}{-}O_2^- \qquad (29)$$

$$M_{ox}{-}O_2^- + O_2^- \xrightarrow{H_2O} M_{ox} + O_2 + H_2O_2 \qquad (30)$$

If a metal complex is reduced by superoxide and its reduced form is reoxidized by superoxide in aqueous solution, both at rates competitive with that for superoxide disproportionation, the complex probably can act as a superoxide dismutase by mechanism I. Because $E°' = -0.16$ V vs. NHE for the reaction $O_2 + e^- \rightarrow O_2^-$ and $E°'_{pH7} = +0.89$ V for the reaction $O_2^- + 2H^+ + e^- \rightarrow H_2O_2$, the complex must have a potential falling between these two values; i.e., $-0.16\ V < E°' < +0.89$ V in order to act as a catalyst of superoxide disproportionation by this mechanism. As pointed out by Stein and Fackler,[80] Mn^{III}EDTA does not function as a SOD, probably because its reduction potential is too high, i.e., +0.82 V vs. NHE. In this regard, the cyanide complex of Cu–Zn–SOD protein has a reduction potential of less than −0.44 V vs. NHE.[97] Hence, cyanide may inhibit the enzyme not by blocking access of superoxide to the copper ion but by making the Cu^{II} form too stable to be reduced by superoxide. The redox potentials of superoxide dismustases that have been measured fall in a narrow range midway between the allowable limits (Cu–Zn–SOD, $E°' = +0.26$ V; Mn–SOD, $E°' = +0.31$ V; Fe–SOD, $E°' = +0.29$ and $+0.23$ V).[97,98]

Mechanism II has been proposed for aqueous Cu^{2+}[99] and for superoxide disproportionation catalyzed by Lewis acid metal ions that are redox inactive (see above). Clearly, mechanism I cannot be operating for superoxide dismutases that can be neither oxidized nor reduced by superoxide, e.g., Zn^{2+}. But in the case of a redox-active metal ion or complex, e.g., Cu^{2+}, to establish the mechanism will require that intermediates be observed.

The bis(8-quinolinato)manganese(II) complex also has been shown to be an effective catalyst for the disproportionation of O_2^- in aprotic media and has been proposed as a model for the manganese–SOD enzymes.[100] The apparent mechanism involves a Mn^{III}–peroxide intermediate, which oxidizes a second O_2^- to yield H_2O_2 and O_2 plus the original Mn^{II} complex.

Superoxide as a Synthetic Reagent for Preparation of New Dioxygen Complexes. The most common route to dioxygen complexes is reaction of O_2 with a low-valent metal ion or complex.[101] But the low-valent metal ion may not be readily accessible in some cases, and direct complexation by O_2^- may be a simpler route, e.g., $[Zn^{II}(TPP)(O_2)]^-$[89] and $[Mn^{II}(TPP)(O_2)]^-$.[60] In other cases, the same dioxygen complex

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can be made either from the reduced metal plus O_2 or the oxidized metal plus O_2^-, e.g., $Fe(TPP)(O_2)$,[63] $[Co^{II}(4,11\text{-dieneN}_4)(O_2)]^{2+}$,[89] and $Co^{III}(O_2^-)$ in vitamin B_{12}.[91] In certain instances a dioxygen complex can be prepared from superoxide ion but not from dioxygen because the low-valent metal ion reacts rapidly with the initially formed complex (eq 31, 32). The use of O_2^- results in the successful synthesis of $[Cu^{II}(\text{tet b})(O_2^-)]^+$[90] and $[Fe^{III}(TPP)(O_2^{2-})]^-$.[63]

$$M_{red} + O_2 \rightleftarrows M_{ox}(O_2^-) \tag{31}$$

$$M_{ox}(O_2^-) + M_{red} \rightarrow M_{ox}(O_2^{2-})M_{ox} \rightarrow \rightarrow \text{products} \tag{32}$$

Three other particularly interesting dioxygen complexes, $(\text{olefin})_2Rh^I(O_2^{2-})Rh^I(\text{olefin})_2$,[102] a related complex of Pd^{II},[103] and $Al_2(CH_3)_6(O_2)$,[104] have also been synthesized by the use of superoxide.

Superoxide Involvement in Metal Autoxidation Reactions. Superoxide frequently has been proposed as a product or intermediate of metal ion catalyzed autoxidation reactions. For example, Ag^0, Hg^0, Cd^+, Co^+, Pb^+, and Zn^+ have been shown to produce O_2^- in aqueous solution.[93] The caged complex $[Co^{II}(\text{sepulchrate})]^{2+}$ is oxidized by O_2 in a reaction whose first step is almost certainly outer sphere oxidation to produce O_2^-.[105] Taube and co-workers have studied the autoxidation of Ru^{II} amine complexes at low pH[106] (eq 33–36). Their proposed mechanism has been tested by the use of O_2^- and $HO_2\cdot$ generated by pulse radiolysis.[81]

$$Ru^{II} + O_2 \rightleftarrows Ru^{III} + O_2^- \tag{33}$$

$$O_2^- + H^+ \rightleftarrows HO_2\cdot \tag{34}$$

$$Ru^{II} + HO_2\cdot \rightarrow Ru^{III} + HO_2^- \tag{35}$$

$$H^+ + Ru^{II} + HO_2\cdot \rightarrow Ru^{III} + H_2O_2 \tag{36}$$

The $Cu^I(\text{phen})_2^+$ complex only reacts with O_2 in Me_2SO in the presence of protons,[13] which suggests that the reaction proceeds either by dissociation of $HO_2\cdot$ from a mononuclear $Cu^{II}(O_2^-)$ complex or of H_2O_2 from a binuclear $Cu^{II}(O_2^{2-})Cu^{II}$ complex. The oxidation of $Mn^{II}(TPP)$ by O_2 in Me_2SO does not yield O_2^-,[60] which suggests that the reaction proceeds through a binuclear peroxo complex. By contrast, the Os^{II} porphyrins are oxidized by O_2 in nonaqueous solution by an outer sphere mechanism to yield O_2^- directly.[107] Likewise, there is evidence for a similar oxidation pathway of low-spin six-coordinate Fe^{II} porphyrins.[108]

Methods of Synthesis

Under biological solution conditions, significant fluxes of O_2^- can be produced from O_2 by reduction with the xanthine/xanthine oxidase system.[109] Reduced flavins (riboflavin, FMN, FAD) also yield O_2^- when combined with O_2 in aqueous media.[11,110] However, because of the inherent instability of O_2^- in aqueous media, neither of these "natural" methods of synthesis is an effective preparative means to O_2^-. Pulse radiolysis can be used to generate significant fluxes of O_2^- in aqueous media.[8,9,22,30,31,42] However, the net yields of products from most O_2^-–substrate reactions are too small for isolation and characterization.

Since 1965, three practical methods for the preparation of solutions of superoxide in aprotic solvents have evolved. The first of these is electrochemical reduction of dioxygen in the presence of a supporting electrolyte.[12,43] The solvents most commonly used are dimethyl sulfoxide (Me_2SO), dimethylformamide, pyridine, and acetonitrile. An advantage of electrochemical preparation of superoxide solutions is the possibility of generating O_2^- in situ in the presence of a substrate. Moreover, one can use electrochemical techniques to monitor O_2^-, reactants, intermediates, and products during the course of the reaction. Such an approach has proven highly successful in several studies of superoxide reactivity.[22,43] The principal disadvantage of the electrochemical method is that it is difficult to produce high concentrations of O_2^-, which makes this method unsuitable for synthetic procedures. Other disadvantages are the inconvenience of the method if electrochemical equipment is not readily available and possible interference from reactions of electrolytes or electrodes.

The second method of preparation[111] makes use of tetramethylammonium superoxide, $(Me_4N)O_2$, an ionic salt of O_2^- which is readily soluble in a number of aprotic solvents and yields stable solutions of superoxide. The main disadvantage is the cumbersome procedure that is required to produce $(Me_4N)O_2$, which, unfortunately, is not commercially available.

The third and most convenient method is solubilization of KO_2 through the use of crown ethers.[13] Both KO_2 and a number of crown ethers are readily available commercially, and relatively concentrated solutions of O_2^- can be prepared in aprotic as well as apolar solvents. Alternatively, reactions can be carried out in two-phase systems by the use of solid KO_2 with the crown ether acting as a phase-transfer catalyst. This latter approach has the advantage that superoxide is never present in the solution at high concentrations and, thus, side reactions with solvent are minimized. The principal disadvantages are the limited purity of KO_2 as purchased (assay, ~96% KO_2, with KOH, K_2O_2, and K_2CO_3 the most likely contaminates; at present there is no method for further purification) and the possibility of a slow decomposition of crown ethers in these solutions.[112]

Superoxide ion also can be prepared in situ by several specific reactions in aprotic media. When tetraalkylammonium hydroxide is added to H_2O_2 in pyridine, a stoichiometric yield of O_2^- results[113] (eq 37, 38). The

$$H_2O_2 + OH^- \rightarrow HO_2^- + H_2O \tag{37}$$

$$HO_2^- + H_2O_2 \xrightarrow{\text{Pyr}} O_2^- + H_2O + (1/n)[\text{Pyr}(\cdot OH)]_n \text{ polymer} \tag{38}$$

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same results are obtained from the controlled-potential reductive electrolysis of H_2O_2 in pyridine.[114] Recent experiments[19] confirm that O_2^- can also be produced in good yield through reduction of O_2 by the dianions of either *p*-hydroquinone (H_2Q) or ascorbic acid in aprotic media (eq 39).

$$Q^{2-} + O_2 \rightarrow O_2^- + Q^{-\cdot} \qquad (39)$$

How Super?

Superoxide clearly is not "superreactive" in the sense that many investigators have assumed. It is not a reactive electron-transfer oxidant of organic or inorganic substrates unless the resulting peroxide anion is somehow stabilized, for example, by coordination to a metal. Superoxide will oxidize certain basic reductants such as reduced flavins by a hydrogen atom transfer mechanism, but such substrates are not common.

Although superoxide contains an odd number of electrons, its reactivity does not resemble that of typical organic radicals. The principal example of such reactivity for superoxide is the formation of a superoxide adduct with reduced methylviologen via a radical–radical coupling mechanism. Under aprotic conditions, O_2^- is a strong nucleophile, but such reactivity is not observed in aqueous solutions. In this property, superoxide resembles small anions such as fluoride, which are powerful nucleophiles only in non-hydrogen-bonding media. Superoxide also can act as a ligand to metal ions and complexes. The most dominant characteristic of O_2^-, by far, is its ability to act as a strong Brønsted base. It readily removes protons from water and weakly acidic substrates such as 1-butanol, and in so doing it rapidly disproportionates to become a source of peroxide and dioxygen. Because these products of the disproportionation of superoxide are strong oxidants, addition of superoxide to a protic substrate frequently results in overall oxidation; however, the true oxidant is H_2O_2 or O_2 rather than O_2^-. Superoxide also is a moderate one-electron reducing agent (about as effective as dithionite). When O_2^- is oxidized by strong one-electron oxidants with closed coordination spheres, singlet oxygen ($^1O_2$) is formed via a singlet transition state.

We conclude that the "super" in superoxide should not be taken to imply exceptional reactivity for that species based on the chemistry that is now known. Nevertheless, superoxide has been and will continue to be an interesting species for study because of the multiplicity of its chemical reactions and because of its importance as an intermediate in reactions that involve dioxygen and hydrogen peroxide.

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Siloxy Dienes in Total Synthesis[†]

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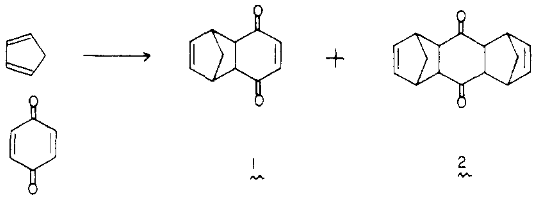
Early research around the turn of this century identified an unusual reaction, whereby certain "conjugated" dienes, upon thermolysis, undergo dimerization.[1] Albrecht[2] described an investigation into the reaction of cyclopentadiene with *p*-benzoquinone and noted the formation of 1:1 as well as 2:1 (diene: quinone) products. A major step forward in this field was achieved in 1928 by Diels and Alder who determined the structures of Albrecht's adducts to be of the type 1 and 2.[3] Moreover, in a classic series of logical and comprehensive investigations, they demonstrated the generality and elucidated the basic regiochemical and stereochemical principles of this reaction which now bears their names. The synthetic applications of the Diels–Alder reaction, as well as the very subtle mechanistic issues which it raises, are of such import that the continuing attention it has received is entirely justified.



Understandably, the Diels–Alder reaction has been extensively discussed in the review literature.[4] Al-

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[†] I am pleased to dedicate this Account to Professor Gilbert Stork on the occasion of his recent receipt of the Roussel, Nichols, and Cope Awards.
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