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The Oxygen Radical-anion $O_2^{\cdot-}$ in Chemical and Biochemical Processes

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The review considers studies of the chemical and biochemical processes with participation of the oxygen radical-anion $O_2^{\cdot-}$ and its principal physicochemical characteristics. Methods for the preparation of $O_2^{\cdot-}$ in aqueous and aprotic media, are examined as are protonation, nucleophilic substitution and oxidation-reduction reactions involving this species, the formation of $O_2^{\cdot-}$ in enzymatic processes and in photosynthesis, the role of $O_2^{\cdot-}$ in the oxygenation of haems, phagocytosis, pathological processes, the toxic effect of oxygen etc.
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I. INTRODUCTION

In 1957-1960 Emanuel' and coworkers[1-3] demonstrated for the first time the importance of the involvement of free radicals in normal and pathological vital processes of organisms. One of the most convincing confirmations of the free-radical hypothesis in biology proved to be the identification in biological systems of the oxygen radical-anion $O_2^{\cdot-}$. The hypothesis of the involvement of $O_2^{\cdot-}$ in enzymatic processes was put forward by Fridovich and Handler in 1958-1962[4-6]. However, as early as 1934 the possible involvement of $O_2^{\cdot-}$ in chemical reactions was pointed out by Haber and Weiss[7,8] in a study of the decomposition of hydrogen peroxide and the oxidation of metal ions by oxygen in aqueous solutions:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\cdot} + HO^{-}, \quad (1)$$

$$HO^{\cdot} + H_2O_2 \rightarrow H_2O + HOO^{\cdot}, \quad (2)$$

$$HOO^{\cdot} \rightleftarrows H^{+} + O_2^{\cdot-}, \quad (3)$$

$$Fe^{2+} + O_2 \rightleftarrows Fe^{3+} + O_2^{\cdot-}. \quad (4)$$

At the present time the formation of $O_2^{\cdot-}$ has been demonstrated in many chemical reactions. Studies on biochemical processes involving $O_2^{\cdot-}$ (enzymatic reactions

catalysed by oxidoreductases, the interaction of haems with oxygen, the mechanism of the protection of the organism from the toxic effect of oxygen, problems of phagocytosis, etc.) have begun to develop, particularly vigorously. A number of reviews devoted to various problems of the chemistry and biochemistry of $O_2^{\cdot-}$ have been published recently[9-19]. In the present review we thought it useful to survey all the principal investigations of the chemical and biochemical properties of $O_2^{\cdot-}$.

II. PHYSICAL PROPERTIES OF $O_2^{\cdot-}$

In the "free" oxygen radical-anion the unpaired electron is delocalised over both oxygen atoms. However, in liquid and solid phases there is a possibility of the formation of ion pairs of $O_2^{\cdot-}$ and counterions—metal or organic cations. The compounds NaO_2 and KO_2 are crystalline substances which are sparingly soluble in organic solvents. In contrast to them, NR_4O_2 (R = alkyl) readily dissolves in dimethylformamide (DMF), dimethyl sulphoxide (DMSO), acetonitrile, etc. The structure of MO_2 (M = metal) was investigated by infrared and Raman spectroscopy[20-24] and EPR[25-34]. The EPR spectrum of $O_2^{\cdot-}$ has been observed only at a low temperature (77 K). It was found[25] that the EPR spectrum of $O_2^{\cdot-}$, obtained by the electrochemical reduction of oxygen in DMF, is characterised by an anisotropic g-factor ($g_1 = 2.006$, $g_2 = 2.009$, and $g_3 = 2.041$). Analogous EPR spectra were obtained when O_2 was reduced in pyridine[26], for MO_2 complexes (M = Ti^{4+}, Hf^{4+}, Tl^{4+}, Sn^{4+}, etc.) in solution[30,31], and for crystalline NaO_2.[29] In addition, using a rapid freezing technique, the EPR spectra of $O_2^{\cdot-}$ and $^{17}O_2^{\cdot-}$ have been obtained[27,28] in the course of the oxidation of xanthene by xanthene oxidase. The observed values of the g-factor can be accounted for by the interaction of $O_2^{\cdot-}$ with the solvent or cations[34]. Apart from the complexes of $O_2^{\cdot-}$ with metal cations, its compounds with cobalt(III)[35-37] and rhodium(III)[38] complexes, which can exist both as monomers and dimers, have been described.

It has been found by the technique of pulse radiolysis that the ultraviolet spectrum of $O_2^{\cdot-}$ in aqueous solutions has a maximum at 250 nm (ϵ = 1800–2000 litre mole^{-1} cm^{-1}).[39-44] λ_{max} = 462 nm for $O_2^{\cdot-}$ in solution in pyridine[45]. The spectrum of $O_2^{\cdot-}$ in acetonitrile, with a maximum at 250 or 255 nm, has been described[46,47]. However, the observation of this maximum may be a consequence of instrumental errors[47], particularly since it is known[48,49] that the absorption maxima of radical-anions in aprotic solvents should be displaced towards longer wavelengths compared with aqueous solutions in consequence of the hydration of the radical-anions in the latter.

The reduction of oxygen in aprotic solvents involves a one-electron mechanism. It has been shown[25] that O_2 is reduced in DMSO and DMF at $E_{1/2}$ = −0.73 and −0.80 V respectively and $O_2^{\cdot-}$ is reduced at −2.40 and −2.8 V. Analogous data were obtained for the reduction of O_2 in DMSO on platinum, gold, and mercury[26,50,51] and in pyridine, dimethylacetamide (DMA), acetonitrile, acetone, methylene chloride, etc. on mercury[26,52-54]. The one-electron reduction of oxygen is quasi-reversible[26], the deviation from reversibility being apparently due to the protonation and dismutation of $O_2^{\cdot-}$.[55] Owing to the rapid reaction of O_2^{2-} with the solvent, the reduction of $O_2^{\cdot-}$ is fully irreversible[56]. When oxygen is reduced in DMF and DMSO in the presence of metal cations, there is an anodic shift of the one-electron wave (owing to the formation of MO_2 ion pairs) and a mixture of the corresponding metal peroxides and superoxides is formed[51,57].

In contrast to aprotic solvents, in aqueous solutions oxygen is reduced electrochemically via a formally two-electron mechanism consisting of two one-electron stages[58]

$$O_2 \xrightarrow{e} O_2^{\cdot-} \xrightarrow{H^+} HOO^{\cdot} \xrightarrow{e} HOO^- . \qquad (5)$$

However, it has been observed recently[59,60] that, in the presence of surface-active substances (quinoline or triphenylphosphine oxide) the protonation of $O_2^{\cdot-}$ on the surface of the cathode is difficult. Under these conditions and at high pH (when the rate of disproportionation of $O_2^{\cdot-}$ is low), $O_2^{\cdot-}$ can be obtained also in aqueous solutions. It has also been suggested that $O_2^{\cdot-}$ be generated by the continuous radiolysis of a formate solution saturated with oxygen[50,51].

Recently much attention has been devoted to a more accurate determination of the O_2 reduction potential in aqueous solution—a parameter which is of great biochemical importance. The initial value $E_0(O_2/O_2^{\cdot-})$ = −0.56 V (relative to the hydrogen electrode)[63] is undoubtedly too low. Thermodynamic calculation yielded $E_0(O_2/O_2^{\cdot-})$ = −0.18 V.[44] Wood examined critically the published values of E_0[60,63,65,66] and concluded that E_0 = −0.33 ± 0.01 V.[64] Then, in a later study[67], a higher value $E_0(O_2/O_2^{\cdot-})$ = 0.07 ± 0.02 V was again obtained. However, this problem can now apparently be regarded as solved: in a number of independent studies on the reduction of O_2 in the presence of surface-active substances[68] and of the equilibria in the reactions of $O_2^{\cdot-}$ with quinones[69-71] and with cytochrome c[72] values in the range $E_0(O_2/O_2^{\cdot-})$ = −0.28 to −0.32 V were obtained. One should bear in mind that these values were calculated for p_{O_2} = 1 atm; adjustment to $[O_2]$ = 1 M leads to $E_0(O_2/O_2^{\cdot-})$ = −0.11 to −0.15 V respectively. The higher O_2 reduction potential in aqueous solutions compared with aprotic solvents can probably be accounted for by the difference between the $O_2^{\cdot-}$ solvation energies[73]. Indeed the energy of solvation of $O_2^{\cdot-}$ by water molecules in the gas phase is higher by 2–3 kcal mole^{-1} then the energy of solvation by acetonitrile molecules[74].

III. CHEMICAL PROPERTIES OF $O_2^{\cdot-}$

1. The Lifetime of $O_2^{\cdot-}$ in Solution

Earlier it was postulated that the lifetime of $O_2^{\cdot-}$ in aqueous solution is very short and that the disproportionation rate constant is high: $k_6 = 2 \times 10^7$ litre mole^{-1} s^{-1}:[75-77]

$$O_2^{\cdot-} + O_2^{\cdot-} \xrightarrow{2H_2O} H_2O_2 + O_2 + 2HO^- . \qquad (6)$$

However, it was later shown that $k_6 < 10$ litre mole^{-1} s^{-1},[42,68,78] so that at pH > 7 $O_2^{\cdot-}$ exists for a relatively long time (the half-life is approximately 1 min at pH 13)[68]. According to the latest data, reaction (6) can be altogether neglected ($k_6 < 0.3$ litre mole^{-1} s^{-1}) and in real aqueous solutions $O_2^{\cdot-}$ disappears as a result of reaction with HOO$^{\cdot}$ or impurities[79].

In aprotic solvents $O_2^{\cdot-}$ exists much longer. Depending on the oxygen reduction conditions and primarily on the possibility of contact between $O_2^{\cdot-}$ and aqueous solutions and the anolyte as well as the $O_2^{\cdot-}$ concentration, the half-life of $O_2^{\cdot-}$ in basic solvents (DMF, DMSO) is 1–20 h[50,73,80-84]. In acetonitrile the stability of $O_2^{\cdot-}$ is much lower[84,85] and one cannot therefore agree with recommendations concerning the use of acetonitrile solutions of $O_2^{\cdot-}$ in biochemical experiments[46,47]. Data[46] showing the instability of $O_2^{\cdot-}$ in DMF can probably be accounted for by the presence of moisture and other impurities in the solvent employed[83].

2. The Reactions of $O_2^{\cdot-}$ in Aqueous Solutions

The oxygen radical-anion can be formed in aqueous solutions in various oxidation-reduction processes, for example in the Haber–Weiss cycle mentioned previously[7,8], and also in the oxidation of hydroquinones[86] and anthranols[87] in an alkaline medium. However, photolysis and radiolysis of oxygen-saturated aqueous solutions, which can contain hydrogen peroxide or formic acid, are nowadays widely used for the generation of $O_2^{\cdot-}$†:

$$H_2O \rightarrow H^{\cdot} + HO^{\cdot} + e(aq) \quad (7)$$

$$e(aq) + O_2 \rightarrow O_2^{\cdot-} \quad (8)$$

$$HO^{\cdot} + HCOO^- \rightarrow H_2O + COO^{\cdot-} \quad (9)$$

$$COO^{\cdot-} + O_2 \rightarrow CO_2 + O_2^{\cdot-} \quad (10)$$

$$H^{\cdot} + O_2 \rightarrow HOO^{\cdot} \quad (11)$$

$$HO^{\cdot} + H_2O_2 \rightarrow H_2O + HOO^{\cdot} \quad (12)$$

$$HOO^{\cdot} \rightleftarrows H^+ + O_2^{\cdot-} \quad (13)$$

Table 1. The rate constants for the formation of $O_2^{\cdot-}$ by reaction (14) in aqueous solutions at 25°C.

A	pH	$10^9 k_{14}$, litre mole^{-1} s^{-1}	References
Benzoquinone*	7	$4.5 \cdot 10^{-5}$	72
2,5-Dimethylbenzoquinone	7	0.0048	71
Duroquinone	7	0.2±0.05	89
Duroquinone	7	0.22	70
Menadione	7	0.2	89
Menadione	7	0.24	70
Indigodisulphonate	7	0.03	70
Anthraquinone-1-sulphonate	—	0.42	90
Anthraquinone-2-sulphonate	—	0.46	90
Acetophenone	12	2.3	91
Adenine	—	3.6	91
Thymine	—	3.5	91
CO_2	6.9	4.6	92
CO_2	—	2.4	93
CO_2	—	4.2±0.4	94
Dimethyl fumarate	—	2.2	95
CH–CO, ‖ >NC$_2$H$_5$, CH–CO	—	2.0	96
Dithiothreitol	—	1.37	97
Nifuroxime	—	1.5	98
SO_2**	—	0.0013	99
Ru(bipy)$_3^{+}$***	6—7	1.8	101
Ru(bipy)$_3^{+}$***	6—7	7.2±0.8	102
Ru(bipy)$_3^{+}$***	—	7.4	103
Pyrazine****	13.6	1.9	100
Quinoxaline****	13.6	0.37	100

*Method of competition kinetics.
**The stopped flow method.
***Flash photolysis; in the remaining cases pulse radiolysis was used to determine the constants.
****Neutral protonated radical.

In addition $O_2^{\cdot-}$ can also be formed in electron transfer processes:

$$A^{\cdot-} + O_2 \rightarrow A + O_2^{\cdot-} \quad (14)$$

†It has recently been suggested that KO_2 be used to investigate the reactions of $O_2^{\cdot-}$ in aqueous solutions[78,88]. However, the accuracy of quantitative calculations in this case is doubtful.

The rate constants for these reactions are listed in Table 1. The formation of $O_2^{\cdot-}$ in the oxidation by oxygen of macrocyclic nickel(I) complexes, on the one hand, and of univalent Ag^+, Cd^+, Co^+, $HgCl^+$, Pb^+, and Zn^+ ions, on the other, has been described by Tait et al.[104] and Sellers and Simic[105] respectively.

Neutral organic radicals as a rule react with oxygen to form peroxy-radicals. However, the final product of the oxidation of α-hydroxyalkyl radicals in an alkaline medium can be $O_2^{\cdot-}$:[106,107]

$$HOCR_2OO^{\cdot} \overset{pH\ 9.8}{\rightleftarrows} H^+ + {}^-OCR_2OO^{\cdot} \rightarrow O_2^{\cdot-} + CR_2O \quad (15)$$

A bimolecular process is also possible:

$$HO^- + HOCR_2OO^{\cdot} \rightarrow H_2O + {}^-OCR_2OO^{\cdot} \rightarrow O_2^{\cdot-} + CR_2O \quad (16)$$

The rate constants have been found for the following radicals:

Radical	k_{15}, s^{-1}	k_{16}, litre mole^{-1} s^{-1}
$HOCH_2OO^{\cdot}$	$< 10^{108}$	$1.5 \cdot 10^{10}$[108]
$HOCH(CH_3)OO^{\cdot}$	52[108]	$8 \cdot 10^{9}$[108]
$(CH_3)_2C(OH)OO^{\cdot}$	550[107], 665[108]	$5 \cdot 10^{9}$[108]
$(HO)_2C_6H_5OO^{\cdot}$	$8 \cdot 10^{3}$[109]	—
$^-OOCCH(NH_2)OO^{\cdot}$	$1.5 \cdot 10^{5}$[110]	—

The most important chemical processes involving $O_2^{\cdot-}$ are protonation and electron transfer reactions. The protonation reaction (13) is reversible. Its equilibrium constant is usually characterised by the pK for the radical $HOO^{\cdot}$. It has been shown[42,44] that the previously published values of pK($HOO^{\cdot}$) are too low and pulse radiolysis gave pK($HOO^{\cdot}$) = 4.9 ± 0.1. The heat of ionisation and hence the heat of reaction (13) are zero[44]. It has been found recently that $k_{-13} = 4.7 \times 10^{10}$ litre mole^{-1} s^{-1} [68] and $(5 \pm 1) \times 10^{10}$ litre mole^{-1} s^{-1};[94] $k_{13} = (7 \pm 2) \times 10^5$ s^{-1}.[94]

The one-electron $O_2^{\cdot-}$ oxidation reactions

$$O_2^{\cdot-} + A \rightarrow O_2 + A^{\cdot-} \quad (17)$$

in aqueous solutions have been studied mainly by pulse radiolysis. The rate constants for reactions (17) are listed in Table 2. The reactions involving the reduction of $O_2^{\cdot-}$ to the dianion of hydrogen peroxide O_2^{2-} in aqueous solutions are unknown. A combination of two processes is energetically more favourable: the protonation of $O_2^{\cdot-}$ and the reduction of the resulting peroxy-radical. Thus it has been found[67] that the rate constants for the reaction

$$QH_2 + O_2^{\cdot-} \rightarrow HOO^- + QH^{\cdot} \quad (18)$$

are $(1.3–1.7) \times 10^7$ litre mole^{-1} s^{-1} (QH_2 is hydroquinone, methylhydroquinone, or 2,5-dichlorohydroquinone).

It has been shown recently that $O_2^{\cdot-}$ can add to cobalt(II)[125] and iron(II)[120,129] complexes as well as Mn^{2+} ions[127,130] in aqueous solutions without a change in the valence of the metals. The reaction products have the structures of superperoxy- or peroxy-complexes. Analogous oxygenated complexes are formed in the reactions of $O_2^{\cdot-}$ with natural cobalt and iron complexes and their analogous (see Section VI).

3. The Reactions of $O_2^{\cdot-}$ in an Aprotic Medium

Solutions of $O_2^{\cdot-}$ in aprotic solvents can be prepared in two ways: using NaO_2, KO_2, and $R_4N^+O_2^{\cdot-}$ formed beforehand or by the electrochemical reduction of oxygen in the presence of tetra-alkylammonium salts ($R_4N^+O_2^{\cdot-}$ can be obtained by mixing K_2O and R_4NOH powders[131,132]). Furthermore $O_2^{\cdot-}$ is formed when various organic compounds (diketones,

hydroquinones, azo- and nitro-compounds, enolates, etc.) are oxidised by oxygen [133-138], for example [136]:

$$PhNO_2^-K^+ + O_2 \rightarrow PhNO_2 + KO_2 \quad . \qquad (19)$$

Table 2. The rate constants for electron transfer reactions [reactions (17)] in aqueous solutions at 25°C*.

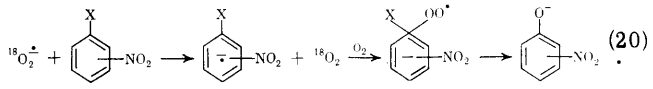
A	pH	$10^{-9}k_{17}$, litre mole^{-1} s^{-1}	References
Benzoquinone	7	1.0	93
Benzoquinone	7	0.98	66
Methylbenzoquinone	7	0.76±0.10	89
Methylbenzoquinone	7	0.80	66
2,3-Dimethylbenzoquinone	7	0.45±0.10	89
2,5-Dimethylbenzoquinone	7	0.36±0.10	89
2,5-Dimethylbenzoquinone	7	0.17; 50±10[a]	71
2,5-Dimethylbenzoquinone	—	0.75	66
2,6-Dimethylbenzoquinone	7	0.58±0.10	89
Duroquinone	7	0.023[a]	89
Duroquinone	7	0.01; 0.046[a]	66
2,5-Dichlorobenzoquinone	7	1.1	66
Menadione	7	0.038; 0.16[a]	66
2,3-Dimethylnaphthoquinone[b]	—	0.02[a]	89
Naphthoquinone-2-sulphonate	7	0.66; 55[a]	66, 71
o-Naphthoquinone	7	0.72	66
o-Naphthoquinone-4-sulphonate	7	0.84	66
Diphenoquinone	7	1.4	66
Dichloroindophenol	7	1.7±0.3	111
Indigodisulphonate	7	$9\cdot10^{-4}$; 0.029[a]	66
Tetranitromethane	5.6—6.2	1.9±0.4	112
Tetranitromethane	—	2.0	113
Tetranitromethane	—	2.0	114
HO$^\cdot$	0.46—6.75	10.1	115
CO_3^-[c]	—	0.4±0.1	43
CO_3^-	—	1.5	116
CO_3^-	—	0.28[e]	117
Br_2^-[j]	—	5.6±0.7	118
HOO$^\cdot$	—	0.085	42
$Fe(CN)_6^{3-}$	9.5—9.7	$(2.7\pm0.9)\cdot10^{-7}$	119
$KFe(CN)_6^{2-}$	9.5—9.7	$(6.2\pm0.6)\cdot10^{-6}$	119
Fe^{3+}(EDTA)	7	0.0018	120
Fe^{2+}(EDTA).OH$^-$	9—10	$(2\pm0.3)\cdot10^{-3}$	120
Cu^{2+}[e,k]	—	1.4	121
Cu^{2+}	—	8.4	122
Cu^{2+}	—	2.7±0.2	123
Cu^{2+}	—	1.9	124
$Cu(HCO_2)^+$	—	1.7	124
$Cu(HCO_2)_2$	—	0.3	124
$Cu(HCO_2)_3^-$	—	0.8	124
$Cu(HCO_2)_4^{2-}$	—	0.4	124
$Cu(NH_3)^{2+}$	5.8—8.5	2.2±0.6	124
$Cu(NH_3)_2^{2+}$	5.8—8.5	2.2±0.8	124
$Cu(NH_3)_3^{2+}$	5.8—8.5	1.0±0.5	124
$Cu(NH_3)_4^{2+}$	5.8—8.5	0.2±0.08	124
Cu(II)-alanine	7.4	$(2.8-3.5)\cdot10^{-3}$	124
Cu(II) glutamate	7.1	$(1-2)\cdot10^{-3}$	124
Cu(II)-glycine	7.9	$2.1\cdot10^{-3}$	124
Cu(II)-hydroxyproline	8.1	0.001	124
Cu(II)-methionine	7.1—7.8	0.006	124
Cu(II)-proline	7.5	$5\cdot10^{-4}$	124
Cu(II)-valine	6.2	0.24	124
Cu(II)-glycylglycine	6.7	0.07	124
Co(II)(4,11-diene-N_4)[f,g]	7—8	1.4	125
Co(II)(1,3,8,10-tetraene-N_4)[f,h]	7—8	1.6	125
Co(II)$(bipy)_2$[f,i]	—	1.9	125
$Mo(CN)_8^{3-}$	8.3—10.4	$(3.0\pm0.5)\cdot10^{-4}$	126
Mn^{2+}[e]	6.7	0.11±0.02	127
Mn^{2+} pyrophosphate	7.8	0.006	128

a Equilibrium constant.
b The reaction was carried out in an isopropyl alcohol–acetone mixture.
c It is suggested that CO_5^- is formed.
d Recalculated by Behar et al.[43]
e It is assumed that the reaction proceeds with formation of MO_2^+.
f It is assumed that oxygenated complexes are formed without change in the valence of the metal.
g 4,11-diene-N_4 = 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradeca-4,11-diene.
h 1,3,8,10-tetraene-N_4 = 2,3,9,10-tetramethyl-1,4,8,11-tetra-azacyclotetradeca-1,3,8,10-tetraene.
i bipy = 2,2-bipyridyl.
j Radiolysis in a flow system.
k Rotating sector method; in the remaining cases pulse radiolysis was used to determine the rate constants.

Similarly $Ru(bipy)_3^+$ reduces O_2 to O_2^- in acetonitrile with $k = 8.5\times10^8$ litre mole^{-1} s^{-1}.[139] It has been observed recently that O_2^- is formed in the decomposition of hydrogen peroxide induced by bases in pyridine[140].

It was shown in an early study[20] that KO_2 and NaO_2 in tetrahydrofuran (THF) and benzene react with acid anhydrides and chlorides via the S_N2 mechanism, forming acyl peroxides. These results have been recently confirmed[141]. It was observed[142] that the solubility of KO_2 in aprotic solvents increases sharply in the presence of crown-ethers. Subsequently it was shown that, under these conditions, KO_2 readily reacts with alkyl halides[143-145], tosylates[143,145], sulphonates[144], and esters[146]. Depending on the solvent, peroxides[144] or alcohols[143,145,147] can be formed. The latter are apparently the products of the transformations of hydroperoxides[145,148]. Using the method of "spin traps", the formation of RO$^\cdot$ radicals in the reaction of KO_2 with RHal was demonstrated; they probably arise as a result of side reactions of ROO$^\cdot$.[149] The rate constants for the reactions of KO_2 with alkyl bromides have been determined by the stopped flow method in DMSO at 25°C: 670 ± 20 litre mole^{-1} s^{-1} for MeBr, 350 ± 20 litre mole^{-1} s^{-1} for EtBr, 150 ± 10 litre mole^{-1} s^{-1} for BuBr, and 65 ± 1 litre mole^{-1} s^{-1} for iso-PrBr.[150] The authors concluded that O_2^- is apparently the most powerful nucleophile in aprotic solvents.

Like alkyl halides, aryl halides react with KO_2 to give a high yield of phenols[151,152]. However, in this case the reaction probably proceeds with electron transfer, because atmospheric oxygen is introduced into the reaction product:



(20)

Similarly, bromo- and chloro-quinolines react with KO_2 to form hydroxyquinolines[153], while bishalogenomethylarenes are converted into cyclic peroxides[154].

Somewhat earlier the nucleophilic reactions of the oxygen radical-anion were investigated using O_2^- prepared electrochemically. It was shown[155,156] that O_2^- reacts with primary alkyl halides in DMF and DMSO, forming alkyl peroxides quantitatively, and the nucleophilic substitution mechanism was proved for the first time:

$$O_2^- + AlkX \rightarrow AlkOO^\cdot + X^- \quad , \qquad (21)$$

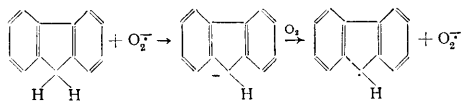
$$AlkOO^\cdot + O_2^- \rightarrow AlkOO^- + O_2 \quad , \qquad (22)$$

$$AlkOO^- + AlkX \rightarrow AlkOOAlk + X^- \quad . \qquad (23)$$

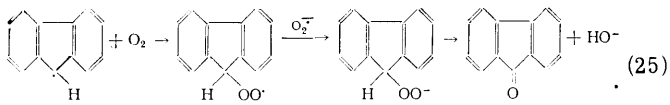
It has been shown recently[157] that reactions of the electrochemically generated O_2^- with phenyl benzoate and *p*-chlorophenyl benzoate result in the formation of aryl peroxides with rate constants of 3 ± 0.3 and 25 ± 5 litre mole^{-1} s^{-1}. $k_{21} = 1.1\times10^4$ litre mole^{-1} s^{-1} for benzyl bromide[158].

The protonation of O_2^- by phenols, carboxylic acids, and alcohols in DMF has been investigated polarographically[159]. The reaction rate constants are in the range 10^2–10^3 litre mole^{-1} and are not correlated with the pK of the proton donors. It has been pointed out[160] that the acid-catalysed disproportionation (6) is responsible for the ability of O_2^- to react with weak acids such as water. It has been suggested in a number of studies that O_2^- can abstract a hydrogen atom from compounds with an active C–H bond.

Thus the following reaction mechanism has been proposed for the chain oxidation of fluorene by the superoxide ion[73]:



(24)



(25)

The current yield of fluorenone is 5000%. Diphenylmethane is oxidised to benzophenone via an analogous mechanism (yield 400%) and 9,10-dihydroanthracene is oxidised to a mixture of anthracene and anthraquinone (yield 2000%). Apart from DMF, pyridine[45] and DMSO[161] can be used as solvents. The nucleophilic addition of O_2^- to activated double bonds has also been described; for example, benzylidenefluorene reacts with O_2^- to form fluorenenone[155] and hexa-1,3-diene and hexa-1,4-diene are converted into benzene[161]. Cyclohex-2-en-1-one forms an epoxide under analogous conditions[155]. According to the latest data, in an aprotic medium O_2^- oxidises hydrazines[162], hydrazones[162], amines[163], benzopyridine derivatives[164], and nitroalkylbenzenes[165], and reduces styrene[166].

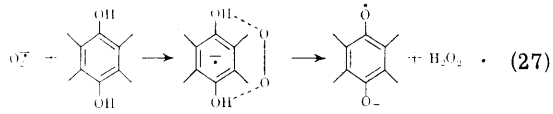
As in aqueous solutions, in aprotic solvents O_2^- readily reduces quinones (whose redox potentials are greater than that of O_2) to semiquinones. The reaction of O_2^- with benzoquinone, trimethylbenzoquinone, menadione, ubiquinones Q_0 and Q_9, tocopherylquinone, and vitamin K_1 in DMF have been investigated[80-82,167,168]. Apart from benzoquinone, the reaction is reversible in all cases. The equilibrium constants have been determined spectrophotometrically for the reactions of O_2^- with the following quinones: trimethylbenzoquinone (7.9 ± 0.6), menadione (1.5 ± 0.1), ubiquinone Q_0 (2.0 ± 0.4), ubiquinone Q_9 (2.9 ± 0.2), tocopherylquinone (1.9 ± 0.2), and vitamin K_1 (5.6 ± 0.4).[168] The closeness of the equilibrium constants to unity suggests that natural quinones can function in biological systems as traps for O_2^- (see below). One-electron reduction of quinones[169] and α-methylacridinone[170] has also been observed in reactions with KO_2; the latter readily reduces copper(II) to copper(I) in phenanthrene complexes[142] and organic copper salts[171]. The reduction of phenoxy-radicals to phenols by the superoxide ion[172] and the reaction of O_2^- with the thianthrene radical-cation[173] have also been described.

It has recently been observed[174,175] that O_2^- is capable of quenching singlet oxygen via an electron transfer reaction:

$$O_2^- + O_2(^1S) \rightarrow O_2 + O_2^- \quad . \qquad (26)$$

According to Guirand and Foote[174], $k_{26} = 1.6 \times 10^9$ litre mole^{-1} s^{-1} in DMSO. An appreciably lower value of k_{26} was found in another study[46], apparently owing to the use of an incorrect extinction coefficient[46] in the calculation of the O_2^- concentration. It is suggested that electron transfer is the first stage in the interaction of KO_2 with the chalcones $RC_6H_4COCH{=}CHC_6H_4R$[176] and tetracyclanes[177].

The possibility of the oxidation of *p*- and *o*-hydroquinones by the superoxide ion in an aprotic medium was first demonstrated in 1976.[178-180] It was observed that the reduction proceeds with the intermediate formation of semiquinone radical-anions; in particular, the semiquinones derived from catechol[178-181], trimethylhydroquinone, dopamine[167,181], adrenaline, and noradrenaline[167] were identified with the aid of electronic and EPR spectroscopy. The absence of oxygen from the reaction mixture indicates a single-stage mechanism of the formation of semiquinones[181]:



(27)

The reduction of O_2^- to O_2^{2-} by aromatic dianions with rate constants of 10^{-3} litre mole^{-1} s^{-1} at 0°C has been described[182].

The reactions of O_2^- accompanied by chemiluminescence are of special interest, primarily for biochemical research. In the initial studies by Stauff and coworkers[183,184] it was pointed out that chemiluminescence due to the formation of singlet oxygen is observed in the reaction of O_2^- with HOO· and on disproportionation of O_2^-:

$$O_2^- + HOO\cdot \rightarrow O_2(^1S) + HOO^- \quad , \qquad (28)$$

$$(O_2 \cdot O_2(^1S)) \rightarrow 2O_2 + h\nu \quad . \qquad (29)$$

According to Khan's data[185], chemiluminescence with the same origin is observed in reactions of KO_2 with anthracene, fluorescein, etc., while Arneson[186] showed that it occurs in reactions catalysed by xanthine oxidase.

Although subsequently doubt was thrown on these results[169,187,188], the formation of $O_2(^1S)$ on protonation of O_2^- was confirmed by experiments involving a specific reagent for singlet oxygen—1,3-diphenylisobenzofuran[189]. Since the formation of $O_2(^1S)$ is possible only when the heat of reaction is greater than the energy of the excitation of O_2 from the ground triplet state to the excited singlet state, the chemiluminescence due to the formation of $O_2(^1S)$ should be observed in the fastest reactions of O_2^-. Indeed, the formation of $O_2(^1S)$ in recombination reactions of O_2^- with radical-cations has been noted[190]. It is noteworthy that, as early as 1970, Dietz et al.[73] suggested that $O_2(^1S)$ is formed in the reaction of O_2^- with diphenylanthracene radical-cations. Khan[191] examined the possibility of the formation of $O_2(^1S)$ as a result of the direct disproportionation of O_2^-, but, Bielski and Allen[79] believe that this process is impossible in real systems. The formation of singlet oxygen has been recently observed in the reaction of O_2^- with diacyl peroxides[192].

Apart from $O_2(^1S)$, the chemiluminescence in the reactions of O_2^- can be due to other compounds. Thus the emission of light has been observed in the reactions of O_2^- with lucigenin[193], *N*-methylacridinone[170], luminol, and luciferin[194]. Some of these reactions were used in biochemical research for the identification of O_2^-.

IV. THE FORMATION OF O_2^- AND ITS INTERACTION WITH BIOLOGICALLY ACTIVE SUBSTRATES

Since O_2^- is present in virtually all components of the living cell, the elucidation of the sources of its formation and the probable mode of its subsequent reactions constitute an urgent problem. This section deals with reactions involving biologically active substrates; enzymatic reactions of O_2^- and interaction with haems are discussed below.

In 1969 Massey et al.[195] noted that O_2^- is formed when reduced flavins are irradiated with visible light under aerobic conditions. The reactions were inhibited by

superoxide dismutase (SOD)—an enzyme which causes the rapid dismutation of $O_2^{\cdot-}$ to O_2 and H_2O_2 (see Section V). Analogous results were obtained in another study[196] where fluorescein, eosin, Methylene Blue, and acridine were used in addition to flavins as one-electron reductants for oxygen. Photolysis resulted in the reduction of nitro blue tetrazolium, which indicated the formation of $O_2^{\cdot-}$.[197-199] The one-electron reduction of oxygen by flavin radicals and reduced flavins was studied by pulse radiolysis and photolysis in water[200-202] and by the stopped flow method in DMF[203]. Fluorescein, tryptophan, and $NADPH_2$ are capable of initiating the formation of compound III of lactoperoxidase (Fe^{3+}-complex of $O_2^{\cdot-}$) on irradiation under aerobic conditions[204]; this reaction is inhibited by SOD. It has been shown[205] that $O_2^{\cdot-}$ is formed in the aerobic oxidation of $NADH_2$ by phenazine methosulphate. The methods described are widely used nowadays for the generation of $O_2^{\cdot-}$ in biochemical experiments.

Other procedures for the generation of $O_2^{\cdot-}$ are also known. It has been shown that $O_2^{\cdot-}$ is formed in the photolysis of water and by its treatment with ultrasound[206,207], in the decomposition of K_3CrO_8 in aqueous solutions[208], and in the photolysis of aqueous CdS suspensions[209]. It has been observed with the aid of SOD that $O_2^{\cdot-}$ is formed in the oxidation of pyrogallol[210], thiols (dithiothreitol, mercaptoethanol, and glutathione)[211], 2-amino-4-hydroxy-6,7-dimethyl-5,6,7,8-tetrahydropteridine and a natural cofactor (tetrahydrobiopterin)[212-214], phenylhydrazine[215], a number of cytotoxic agents (6-hydroxydopamine, 6-aminodopamine, dialuric acid, etc.)[216-218], hydroxylamine[219,220], and dihydroxyfumaric acid[221] and in the photolysis of solutions of tryptophan[222,223], dianisidine[224], and phenoxazine derivatives[225]. The formation of $O_2^{\cdot-}$ in the oxidation of the radical-cation of the herbicide paraquat (1,1-dimethyl-4,4-bispyridinium ion) is biologically important (see Section VII)[226]. Evans et al.[227] questioned the possibility of this reaction but subsequent studies[228,229] confirmed the initial conclusions[226].

The study of reactions of $O_2^{\cdot-}$ with biologically active substrates is of particular importance, because the mechanism of the toxic effects of $O_2^{\cdot-}$ in living organisms and the possibility of combatting them can be discovered in this way. In this connection there has been much interest shown in the reactions of $O_2^{\cdot-}$ with natural hydroquinones, whose mechanism in an aprotic medium was examined previously (see Section III). As early as 1970 Miller observed[198] that *o*-dihydroxybenzenes (catechol, Tiron, and 3,4-dihydroxybenzoic acid) inhibit the reduction of cytochrome *c* by the superoxide ion. It has been shown[230] that $O_2^{\cdot-}$ generated by xanthine oxidase oxidises adrenaline to adrenochrome. This reaction has become an important method for the identification of $O_2^{\cdot-}$ in biological systems. However, one must bear in mind that the oxidation of adrenaline and other catecholamines entails the formation of $O_2^{\cdot-}$.[231,232] Subsequently the reactions of $O_2^{\cdot-}$ with *o*-dihydroxybenzene were investigated by pulse radiolysis[233,234].

α-Tocopherol is not oxidised by the oxygen radical-anion in an aqueous solution[235,236]. However, this is probably due to the low solubility of tocopherol, because $O_2^{\cdot-}$ reacts with its water-soluble analogue in water[235] and with 6-hydroxy-2,2,5,7,8-pentamethylchroman in THF.[237] It has been shown recently[167] that both tocopherol and tocopheryl acetate are capable of reacting with $O_2^{\cdot-}$ in DMF. Ascorbic acid reacts with $O_2^{\cdot-}$ can be formed in the oxidation of ascorbic acid[238]. However, the identification[239] of $O_2^{\cdot-}$ in this process was erroneous[240] and ascorbic acid is therefore an effective "trap" for the superoxide ion. Thiols can also function as traps for $O_2^{\cdot-}$.[236,241] The generally accepted mechanism of these reactions involves two stages with the intermediate formation of a neutral semiquinone:

$$AH_2 + O_2^{\cdot-} + H^+ \rightarrow AH^{\cdot} + H_2O \quad , \qquad (30)$$

$$AH^{\cdot} + O_2^{\cdot-} + H^+ \rightarrow A + H_2O_2 \quad . \qquad (31)$$

However, one must bear in mind the possibility of reactions with the formation of radical-anions, as was shown for analogous processes in an aprotic medium (see Section III).

Yang[242] showed in 1970 that the oxidation of methionine by sodium bisulphite under aerobic conditions is inhibited by SOD, which led him to suggest the involvement of $O_2^{\cdot-}$ in this reaction. (However, according to the latest data[243], $O_2^{\cdot-}$ is capable of reacting with methional to only a slight extent.) The involvement of $O_2^{\cdot-}$ in the sulphoxidation of ethionamide (2-ethyl-4-thioisonicotinamide—an active second-order tuberculostatic agent) by the $NADH_2$–phenazine methosulphate system and in the corresponding enzymatic process has also been suggested[244]. The possibility of the specific interaction of $O_2^{\cdot-}$ with model lipid membranes, due to the attraction of $O_2^{\cdot-}$ to the positively charged side of the membrane, has been demonstrated[245].

Table 3. Rate constants for the reactions of biologically active substrates and enzymes with $O_2^{\cdot-}$ and O_2.

A	k, litre mole^{-1} s^{-1}	Refs.	A	k, litre mole^{-1} s^{-1}	Refs.
$A^{\cdot-} + O_2 \rightarrow A + O_2^{\cdot-}$			$O_2^{\cdot-} + A(AH_2) \rightarrow O_2 + A^{\cdot-}$ and $HOO^- + AH^{\cdot}$		
NAD	$1.9\cdot10^9$	252	Adrenaline[c]	$4.0\cdot10^4$	241
NAD	$2.0\cdot10^9$	253	Adrenaline[c]	$1.7\cdot10^4$	235
Lumiflavin[a]	$1.6\cdot10^8$	200	Tyron	$5\cdot10^8$	233
Riboflavin[a]	$1.38\cdot10^9$	200	Ascorbic acid[c]	$2.7\cdot10^5$	238
FAD[a]	$5\cdot10^7$	200	Ascorbic acid	$1\cdot10^8$	233
FMN[a]	$9\cdot10^7$	200	Ascorbate	$(1.52\pm0.1)\cdot10^5$	259
Cytochrome a_3^{II}[b]	$3.3\cdot10^7$	254	Plastocyanine[c]	$1.1\cdot10^6$	128
Cytochrome oxidase[b]	$3.3\cdot10^7$	255	Cysteine[c]	$2.7\cdot10^6$	241
LDH.NAD	10^9—10^{10}	256	Glutathione (reduced)[c]	$6.7\cdot10^5$	241
Cytochrome c^{II} c	$3\cdot10^{-2}$	72	Homocysteine[c]	$4.6\cdot10^5$	241
Cytochrome b_5^{II} c	23	257	Dithiothreitol[c]	$1.0\cdot10^6$	241
B_{12r}	$5\cdot10^7$	258	Tetrazolium Nitroblue[c]	$5.94\cdot10^4$	259
Paraquat (PQ)[d]	$6.0\cdot10^8$	227	LDH.NAD-H_2	$(1.0\pm0.2)\cdot10^5$	260
			Compound I of horse radish peroxidase	$1.6\cdot10^6$	261
			Horse radish peroxidase[c]	10^7—10^8	262
			Cytochrome c^{III} b	$1.6\cdot10^5$[f]	263
			Cytochrome c^{III}	$1.5\cdot10^6$[e]; $2.5\cdot10^5$[f]	264
			Cytochrome c^{III}	$1.1\cdot10^5$[f]	265
			Cytochrome c^{III}	$1.4\cdot10^6$[e]; $3.0\cdot10^5$[f]	266
			Cytochrome c^{III}	$6.5\cdot10^5$[e]; $2.6\cdot10^5$[f]	267
			Cytochrome c^{III}	$1.1\cdot10^6$[e]	268
			Cytochrome c^{III}	$(2.6\pm0.2)\cdot10^5$	259
			HbO_2[c]	$4\cdot10^3$	269
			metHb[c]	$6\cdot10^3$	269

a,b,cMethods of flash photolysis, stopped flow, and competition kinetics were used to determine k respectively; in the remaining cases pulse radiolysis was used.
d $PQ^{\cdot} + O_2 \rightarrow PQ^{2+} + O_2^{\cdot-}$.
e pH ~ 7.
f pH ~ 8.4.
g pH 9.

The possibility of the interaction of $O_2^{\cdot-}$ with H_2O_2 (the "Haber–Weiss reaction")—a process ensuring the formation of the hydroxy-radical in living cells, i.e.

$$O_2^{\cdot-} + H_2O_2 \rightarrow O_2 + HO^- + HO^{\cdot} \qquad (32)$$

has been studied in a number of investigations. In contrast to the initial hypothesis, the rate of reaction (32) is extremely low according to the latest data[246-248] (although

the reaction between O_2^- and t-BuOOH is possible[249]). However, HO· is apparently formed in the presence of iron or copper complexes[248,250,251]:

$$O_2^- + M^{n+1} \rightarrow O_2 + M^n \quad , \tag{33}$$

$$M^n + H_2O_2 \rightarrow M^{n+1} + HO^- + HO\cdot \quad . \tag{34}$$

The rate constants for reactions of biologically active substrates and enzymes with O_2^- and O_2 are listed in Table 3.

V. THE PARTICIPATION OF O_2^- IN ENZYMATIC OXIDATION-REDUCTION PROCESSES

1. The Participation of O_2^- in Reactions Catalysed by Dehydrogenases, Oxygenases, Hydroxylases, and Peroxidases

In the early studies by Fridovich and Handler[4-6] the hypothesis of the formation of O_2^- in reactions catalysed by milk xanthine oxidase (EC 1.2.3.2)‡—an enzyme under the action of which xanthine is oxidised to uric acid—was based on the ability of the system to initiate the oxidation of sulphite. It was suggested that the O_2^- involved in the reaction is bound to an enzyme. Subsequently a specific enzyme—superoxide dismutase (SOD, EC 1.15.1.1), capable of inducing rapid dismutation of O_2^-—was discovered[271,272]. O_2^- was identified by EPR directly in the reaction of xanthine with xanthine oxidase (XO)[27,28] and also in the oxidation of reduced tetra-acetylriboflavin[263] and ferredoxin[273]. Gray et al.[28] used isotopically substituted oxygen for the final identification of O_2^- in reactions.

The problem of which XO active centres are responsible for the formation of O_2^- was discussed in the literature for a number of years. Massey et al.[195] showed that under aerobic conditions reduced flavins readily reduce cytochrome *c*, the reaction being inhibited by SOD. It has also been shown[273,274] that, after the removal of flavin, XO is incapable of producing O_2^-. On this basis, it was concluded that O_2^- is generated in XO by flavin-adenine dinucleotide (FAD). However, it has been found[275,276] that the rate of generation of O_2^- by ferredoxin is higher by a factor of approximately 12 than the rate of generation by flavins.

A recent careful analysis of the inter-relations between various electron transferring agents in XO showed[277,278] that the oxidation of the reduced enzyme by oxygen consists of two stages; the first, rapid stage, during which five electrons are transferred to oxygen, is due to the interaction of oxygen with a flavin, while the second, slow stage, in which one electron is transferred, is due to the interaction of oxygen with ferredoxin. The authors proposed the following process mechanisms:

$$FADH_2 + O_2 \rightleftarrows FADH_2 \cdot O_2 \, , \tag{35}$$

$$FADH_2 \cdot O_2 \rightarrow FADH \ldots O_2^- + H^+ \, , \tag{36}$$

$$FADH_2 \ldots O_2^- + H^+ + e \xrightarrow{\text{very fast}} FAD\text{-}H_2 \ldots O_2^- \, , \tag{37}$$

$$FADH_2 \ldots O_2^- \xrightarrow{\text{very fast}} FAD\text{-}H\cdot + H_2O_2 \, , \tag{38}$$

$$FADH \ldots O_2^- \rightarrow FADH\cdot + O_2^- \, , \tag{39}$$

$$FADH \ldots O_2^- + H^+ \rightarrow FAD + H_2O_2 \quad . \tag{40}$$

As already stated, the reactions catalysed by XO are accompanied by chemiluminescence[186], which indicates the accumulation of O_2^- in the course of the first three minutes of the reaction[279]. However, the source of the luminescence has not been established[280].

It is natural to suppose that xanthine oxidase cannot be the only enzyme generating O_2^-; the latter should undoubtedly be formed also in other enzyme systems. As early as 1969 it was suggested[281] that O_2 can be reduced to O_2^- in any biological system with strong reducing properties.

Massey et al.[282] postulated that three groups of flavoproteins—dehydrogenases (participating in dehydrogenation processes), oxygenases (under the action of which two oxygen atoms are introduced into the substrate), and hydroxylases (which introduce the hydroxy-group into the substrate)—are capable of reacting with O_2 in their reduced form, forming peroxy-compounds FlOOH, but the latter decompose into a flavosemiquinone and O_2^- only in the case of dehydrogenases. This view concerning the structure of the intermediate compounds of dihydroflavins with oxygen has been generally accepted[283], but later it was suggested that a charge-transfer complex and not a hydroperoxide decomposes into a semiquinone and O_2^-.[284]

The ability of dehydrogenases to generate the superoxide ion has been demonstrated in a number of studies. Massey et al.[195] observed that SOD inhibits the aerobic reduction of cytochrome *c* by the $NADPH_2$ + lipoxidase (EC 1.13.11.12), $NADPH_2$ + glutathione reductase (EC 1.6.4.2), $NADPH_2$ + ferredoxin-NADP reductase (EC 1.6.99.4), and $NADPH_2$ + reduced NADP dehydrogenase (EC 1.6.99.1) systems, i.e., as in the case of XO, electron transfer from these systems to cytochrome *c* is achieved with the aid of the oxygen radical-anion. These data have been confirmed for the $NADPH_2$ + ferredoxin-NADP reductase system[285]. It was shown subsequently that the above enzyme system can produce O_2^- in the oxidation of ferredoxin[276], FMN, or menadione[286]. The ferredoxin–ferredoxin–NADP reductase complex can also generate O_2^-, and, according to the authors[287,288], O_2^- is formed in this case on oxidation of ferredoxin and not the flavin.

It was observed in 1969[289] that, when lactoperoxidase (EC 1.11.1.7) is added to the $NADPH_2$ + reduced NADP-cytochrome *c* reductase (EC 1.6.2.4) system, compound III of peroxidase, which is a complex of O_2^- with the enzyme, is formed. On this basis, it was concluded that reduced NADP-cytochrome *c* reductase can generate O_2^- and this was subsequently confirmed[290-292]. It has been shown[293] that at low temperatures cytochrome oxidase forms the oxygenated complex $Cu(II)Fe(II)O_2^-$.

In contrast to earlier data[195], Nakano et al.[291] showed that at pH > 9, L-aminoacid oxidase (EC 1.4.3.2) is probably capable of generating O_2^-. The involvement of O_2^- (in the form of the active complex $Cu^{2+}O_2^-$) in reactions catalysed by galactose oxidase (EC 1.1.3.9) has been demonstrated[294,295]. Earlier data[296], showing the absence of inhibition of the reaction by SOD, can be accounted for by the presence of peroxidase[295]. The O_2^- ion is formed in the oxidation of 2-nitropropane to acetone, catalysed by 2-nitropropane dioxygenase, which is indicated by the inhibition of the reaction following the addition of SOD and by its acceleration when KO_2 is added[297]. According to some data[298-300], O_2^- is formed in reactions catalysed by mitochondrial enzymes: dihydroorotate dehydrogenase (EC 1.3.3.1) (DOD) and possibly succinate dehydrogenase (EC 1.3.99.1) (SD). DOD contains flavin and non haem iron and its properties should therefore resemble those of xanthine oxidase. Indeed it has been observed[298-300] that

‡ The classification of enzymes is based on the recommendations of the Commission on Biochemical Nomenclature[270].

the reduction of dichlorophenolindophenol in reactions catalysed by DOD is 30% inhibited by the addition of SOD. Although the analogous reaction involving SOD is fully inhibited by SOD, its initial rate is only 3% of the rate of oxidation of succinate to fumarate and in the presence of phenazine methosulphate SOD does not inhibit the reduction of dichlorophenolindophenol by succinate dehydrogenase. It is believed that phenazine methosulphate and oxygen compete in the interaction with the active centre of SD.

The role of lactate dehydrogenase (EC 1.1.2.3) (LDH) in the oxidation of $NADH_2$ by the superoxide ion is very interesting. It is known[301] that in the presence of protons $O_2^{\cdot-}$ can slowly oxidise $NADH_2$:

$$NADH + H^+ + O_2^{\cdot-} \rightarrow NAD + H_2O_2 \quad . \qquad (41)$$

It has been observed[302,303] that the rate of oxidation of $NADH_2$ increases sharply when $NADH_2$ is bound to LDH. The reaction proceeds via a chain mechanism (the chain length at pH 7.35 is 6.2) and is inhibited by SOD. The formation of $NADH_2$ complexes with a non-specifically binding protein (albumin) did not accelerate the oxidation. The following reaction mechanism was proposed[256,260]:

$$LDH + NADH \rightleftarrows LDH.NADH \quad (K = 10^{-6} \text{ litre mole}^{-1}), \qquad (42)$$

$$LDH.NADH + H^+ + O_2^{\cdot-} \rightarrow LDH.NAD^{\cdot} + H_2O_2 \quad [k_{43} = (1.0 \pm 0.2) \cdot 10^4 \text{ litre mole}^{-1}\,s^{-1}], \qquad (43)$$

$$LDH.NAD^{\cdot} + O_2 \rightleftarrows LDH.NAD^+ + O_2^{\cdot-} \quad (k_{44} = 10^9 - 10^{10} \text{ litre mole}^{-1}\,s^{-1}), \qquad (44)$$

$$LDH.NAD^+ \rightleftarrows LDH + NAD^+ \quad (K = 10^{-4} \text{ mole litre}^{-1}). \qquad (45)$$

As already pointed out, according to Massey et al.[282] oxygenases and hydroxylases should generate $O_2^{\cdot-}$ much less effectively than dehydrogenases. However, one must bear in mind that here one is dealing with a comparison of the activities of flavins forming part of the composition of the enzyme; naturally, there exist also other active centres generating $O_2^{\cdot-}$ (for example haems and non-haem iron).

Brady et al.[304] pointed out the possibility of activating tryptophan oxygenase (EC 1.13.11.11) by the oxygen radical-anion, but they thought that such activation was insignificant. However, it has been shown in a number of studies[305-311] that $O_2^{\cdot-}$ is a substrate in reactions catalysed by this enzyme, forming with haemin an oxygenated complex, whose decomposition in the presence of tryptophan leads to the formation of the reaction product—formylkynurenine. It has been observed[312] that luciferin is oxidised by electrolytically produced $O_2^{\cdot-}$ to hydroxyluciferin. It is believed[312] that $O_2^{\cdot-}$ is also involved in the oxidation of luciferin by luciferase from *Pholas dactylus*. However, this reaction is not inhibited by SOD because, according to the authors, $O_2^{\cdot-}$ is bound to the Fe^{3+}-form of the enzyme. The participation of $O_2^{\cdot-}$ in the oxidation of cystamine catalysed by cystamine oxygenase has been demonstrated[313].

There is evidence for the possibility of the involvement of $O_2^{\cdot-}$ or the products of its subsequent reactions, $HOO^{\cdot}$ and $O_2(^1S)$, in the hydroxylation of aromatic compounds[314-317]. As for model systems, SOD inhibits hydroxylation in the presence of a number of enzymes. Thus it has been shown that SOD inhibits the hydroxylation of *n*-hydroxybenzoate and anthranilate by 3-hydroxybenzoate 4-monooxygenase (EC 1.14.93.13) and anthranilate 3-monooxygenase (EC 1.14.16.3),[318] the oxygenation of dopamine to noradrenaline by dopamine β-monooxygenase (EC 1.14.17.1) from the adrenal gland[319], and the hydroxylation of benzphetamine by a set of three microsomal components: cytochrome "P-450", reduced NADP cytochrome "P-450" reductase, and phosphatidylcholine[320,321], i.e. in all these enzyme systems the formation of $O_2^{\cdot-}$ may be expected.

The mechanism of hydroxylation with participation of cytochrome "P-450" was studied in greater detail. Strobel and Coon[320] suggested that, among the three microsomal components mentioned above, hydroxylation is carried out by cytochrome "P-450", while reduced NADP cytochrome "P-450" reductase transfers electrons from $NADPH_2$ to cytochrome *c* and phosphatidylcholine transfers electron from $NADPH_2$ to cytochrome "P-450". However, in 1973 Coon and coworkers[322] observed that $O_2^{\cdot-}$ is formed both in the presence and absence of cytochrome "P-450", i.e. is produced by the reductase; $NADPH_2$ and the reductase can be replaced by other systems generating $O_2^{\cdot-}$, for example the XO + xanthine system. It has been shown[323,324] that, when camphor is hydroxylated by the $NADH_2$ – putidaredoxin oxidoreductase + putidaredoxin (a protein containing two iron atoms and two sulphur atoms) + cytochrome "P-450cam" from *Pseudomonas putidas*, chemiluminescence inhibited by SOD is observed. It is assumed that $O_2^{\cdot-}$ is formed in this system as a result of the oxidation of the oxygenated cytochrome "P-450cam" complex via a side reaction[325].

Earlier it had been suggested[326,327] that $O_2^{\cdot-}$ is not formed in the terminal hydroxylation of alkanes and aliphatic acids by the enzyme system consisting of rubredoxin, reduced NAD rubredoxin oxidoreductase (EC 1.6.99) and ω-hydroxylase (EC 1.14.99) from *Pseudomonas oleovorans*, because the reaction is not accelerated by XO and is not inhibited by SOD. However, May et al.[328] showed that in the presence of $NADH_2$ the above system initiates the oxidation of adrenaline inhibited by SOD, i.e. $O_2^{\cdot-}$ is generated. The hydroxylation of aromatic compounds by hydroxylases, for example, the rat liver benzopyrene 3-monooxygenase (EC 1.14.14.2) containing cytochrome "P-450", is also induced by $O_2^{\cdot-}$.[329,330]

As early as 1963 it was suggested[331] that $O_2^{\cdot-}$ is involved in reactions catalysed by peroxidases (EC 1.11.1.7). Indeed it has been shown[332-335] that the oxygenated form of myeloperoxidase and horse radish peroxidase (compound III) is the product of a reaction of the Fe^{3+}-forms of the enzymes with $O_2^{\cdot-}$. For example, compound III of myeloperoxidase is formed when the enzyme is treated with a solution of $O_2^{\cdot-}$ in DMF.[335] It has also been shown[336] that peroxidase induces the hydroxylation of coumaric acid inhibited by SOD. Compound III of peroxidase can dissociate into the Fe^{3+}-form of the enzyme and $O_2^{\cdot-}$, because it oxidises $NADH_2$ and adrenaline[324,337], both reactions being inhibited by SOD. Bielski and coworkers investigated the reaction of $O_2^{\cdot-}$ with horse radish peroxidase by pulse radiolysis[261,338] (see Table 3).

It has been suggested that $O_2^{\cdot-}$ is involved in the oxidation of $NADH_2$[339-342] and dihydroxyfumaric acid[221] catalysed by peroxidases. $NADH_2$ is apparently oxidised via an analogous mechanism by catalase in the presence of hydrogen peroxide[343]. There is a possibility of the involvement of $O_2^{\cdot-}$ in the biosynthesis of prostaglandins[344] and reactions catalysed by ceruloplasmin[345].

It has been shown that $O_2^{\cdot-}$ is formed in the mitochondria of the liver[346] and heart muscle[347-350] and in liver microsomes[351,352]. It has been stated[347] that $O_2^{\cdot-}$ is generated by a component of the mitochondrial respiratory chain localised between the sites of inhibition by antimycin and rotenone and is then converted under the influence of SOD, which protects enzymes and membranes from its toxic activity, into H_2O_2. However, approximately 20% of the total amount of $O_2^{\cdot-}$ apparently fails to react with SOD and

migrates via membranes causing the peroxidation of lipids[353].

The question of the production of $O_2^{\cdot}$ in microsomes by flavins[354], cytochrome b_{566},[353] mitochondrial ubiquinones[355,356] and microsomal cytochrome "P-450"[357-359] and reduced NADP cytochrome *c* reductase[360,361] needs to be considered. According to the results of Bartoli et al.,[361] $O_2^{\cdot}$ is generated in the liver microsomes of new born rats only by reduced NADP cytochrome *c* reductase, while in adult animals both the reductase and cytochrome "P-450" act with equal efficiency. However, the evidence for the formation of $O_2^{\cdot}$ under the influence of reduced NADP cytochrome *c* reductase was recently questioned[362]. Rich and Bonner[363] believe that the formation of $O_2^{\cdot}$ in mitochondria has no special physiological significance, constituting a "short circuit" in the electron transfer chain.

When studying the ability of mitochondria and microsomes to generate $O_2^{\cdot}$ account must be taken of possible artefacts induced by a change in the concentration of oxygen in the experiments *in vitro*. In particular, it is unlikely that $O_2^{\cdot}$ can be produced by ubiquinones[355,356], because both hydroubiquinones and ubiquinones are effective "traps" for the oxygen radical-anion[167,168].

2. Reactions of Superoxide Dismutase

As already stated, SOD is an enzyme which causes the dismutation of $O_2^{\cdot}$ to H_2O_2 and O_2. Cu-containing SOD has been isolated from bovine blood erythrocytes[272]. Subsequently Mn- and Fe-containing SOD were isolated from the bacteria *E. coli*.[364] The mechanism of the interaction of SOD with $O_2^{\cdot}$ is based on the ability of a variable-valence atom (for example a copper atom) to oxidise and reduce $O_2^{\cdot}$ alternately in the presence of protons:

$$E\text{-}Cu^{2+} + O_2^{\cdot} \rightarrow E\text{-}Cu^{+} + O_2 \quad , \qquad (46)$$

$$E\text{-}Cu^{+} + O_2^{\cdot} + 2H^{+} \rightarrow E\text{-}Cu^{2+} + H_2O_2 \quad . \qquad (47)$$

It is believed[365] that one of the coordination sites of the copper atom is free and that it is the site where $O_2^{\cdot}$ is bound. However, calculation of the redox potential of oxygen based on the thermodynamics of the interaction of SOD with $O_2^{\cdot}$ favours an outer-sphere mechanism[71]. It has been shown that water protons are not involved in reaction (47).[366] According to the latest data[367], the most likely proton donor is the imidazole residue, which binds zinc and copper ions:

$$Zn^{II}\text{—}N\!\!\diagdown\!\!\diagup\!\!N\text{—}Cu^{II}\text{—}OH_2 \underset{O_2^{\cdot}}{\overset{O_2^{\cdot}}{\rightleftarrows}} Zn^{II}\text{—}N\!\!\diagdown\!\!\diagup\!\!NH \cdot Cu^{I}\text{—}OH_2 \quad . \qquad (48)$$

In a study of the optical spectra of the reduced and oxidised forms of Cu-containing SOD, Fielden et al.[368] showed that, after the addition of the $O_2^{\cdot}$ solution, an equilibrium mixture of both forms is formed in both cases. Hodgson and Fridovich[369] demonstrated the reversibility of reactions (46) and (47) using tetranitromethane, a strong electron acceptor, to achieve a leftward shift of the equilibrium. It is believed[370] that at pH > 12 SOD binds hydroxide ions and promotes their oxidation by oxygen with formation of $O_2^{\cdot}$. It has been shown that univalent anions (Cl^-, HO^-, etc.), capable of combining with a copper atom, are competitive inhibitors of SOD[371,372].

The rate constants for reactions catalysed by SOD have been found by pulse radiolysis, polarographically, and by the method of competitive kinetics (Table 4). Table 4 shows that $k_{46} \simeq k_{47} = (1\text{–}3) \times 10^9$ litre mole^{-1} s^{-1} and that the values of k_{46} for Cu-containing SOD are almost independent of pH. For Mn- and Fe-containing SOD, the values of k_{46} decrease with increasing pH. The activation energy for reaction (46) has been found to be 4600 cal mole^{-1}.[376]

Table 4. The rate constants (litre mole^{-1} s^{-1}) for the oxidation-reduction reactions of SOD at 25°C and pH 6–7.

Enzyme	$k_{46}\cdot10^{-9}$	$k_{47}\cdot10^{-9}$	Refs.	Enzyme	$k_{46}\cdot10^{-9}$	Refs
Cu-SOD from bovine blood erythrocytes	2.3	—	373	Mn-SOD from *E. coli***	2.0	378
				Mn-SOD from *E. coli**	0.09 (pH 9.76)	377
				Mn-SOD from chick liver mitochondria**	3.6***	378
Ditto	1.4±0.2	1.9±0.6	374			
»	1.2±0.2	2.2±0.4	375	Mn-SOD from *Bacillus stearothermophilus*	0.56	381
»	2.37±0.18	2.4	376			
»	2.6	—	123	Fe-SOD from *E. coli***	1.9	377
»*	2.3	—	377	Ditto**	0.38 (pH 10.2)	377
»**	1.9	—	378	Fe-SOD from *Photobacterium leognathi*	0.52 (pH 8)	382
»**	0.18	—	202			
»	2.6	—	379	Cu^{2+} $(lys)_2$	0.58±0.10	123
Mn-SOD from *E. coli*	1.3±0.13	1.6±0.6	380	Cu^{2+} $(gly\text{-}his)_2$	0.30±0.02	123
				Cu^{2+} $(gly\text{-}his\text{-}leu)_2$	0.21±0.02	123
				Cu^{2+} $(tyr)_2$	2.6	379

*A polarographic method was used to determine values of *k*.

**Method of competition kinetics (pulse radiolysis used in all the remaining cases).

***The values of k_{46} have been divided by 2, since the enzyme consists of four subunits instead of two.

Two $O_2^{\cdot}$ destruction processes were observed in the reaction of Mn-containing SOD: a rapid process in which the valence of manganese changes from 3 to 2 and a slow process in which Mn^+ is formed[380]. However, it may be that Mn^{2+}- and Mn^{3+}-SOD (and not Mn^+-SOD) are also involved in the slow catalytic process but at a different hydrolytic state.[383] Only rapid reactions apparently occur *in vivo*. A linear relation has been observed[384] between lg k_{46} and $I^{1/2}$ (I is the ionic strength of the solution), whose slope is −1.5 for the ClO_4^-, SO_4^{2-}, and HPO_4^{2-} anions and −2.23 for Cl^-. It is suggested[384] that a slope of −1.50 is consistent with the Brønsted theory. However, this claim is incorrect, because in fact the species reduced in reaction (7) is not $O_2^{\cdot}$ (as assumed in the calculations), but $HOO^{\cdot}$. The influence of electrolytes on the catalytic activity of SOD has also been studied in another investigation[385].

When SOD is used to identify $O_2^{\cdot}$, account must be taken of the fact that Cu-containing SOD is inactivated by hydrogen peroxide[366,386,387], the inactivation being accompanied by luminescence and the reduction of cytochrome *c*. In doubtful cases one must therefore use Mn-containing SOD. The use of Fe-SOD can also lead to errors owing to the presence in it of traces of iron capable of reacting with $O_2^{\cdot}$.[388]

The ability of SOD to induce the rapid dismutation of $O_2^{\cdot}$ was regarded previously as a unique characteristic of this enzyme. However, as early as 1973 Sawada and Yamazaki observed[262] that peroxidase exhibits a dismutase activity. Similarly a non-specific SOD activity has been observed for galactose oxidase[389], catalase, haemoglobin, and methaemoglobin[390]. Weser and coworkers[123,379,391,392] showed that simple copper(II) chelates exhibit dismutase activities. A similar activity is apparently shown by quinoline complexes of manganese[388,393] and iron[394].

The problem of whether or not O_2^- is the sole substrate of SOD or whether the enzyme is capable of suppressing the formation of singlet oxygen has been discussed recently in the literature[395,396]. According to some data[397,398], SOD does not inhibit the reaction of singlet oxygen obtained by traditional methods. However, contrary results have been obtained by Weser and coworkers[397-402], so that the question remains obscure.

3. The Involvement of O_2^- in Photosynthesis

The problem of a possible role of O_2^- in photosynthetic processes has been discussed in a number of studies. It has been observed[403-405] that the aerobic oxidation of sulphite and the reduction of cytochrome *c* by spinach chloroplasts is inhibited by SOD. It has been suggested[403-405] that O_2^- is generated by photosystem I, because the blocking of electron transport by photosystem I led to the inhibition of the photochemical oxidation of adrenaline. Epel and Neumann[406] postulated that O_2^- is formed in the oxidation of electron acceptors with a low redox potential such as Methyl Viologen, which was confirmed by experiments using free radical traps[407]. The primary electron acceptor photosystem I apparently generates O_2^-,[403-405,408] although the involvement of ferredoxin is not ruled out[409,410]. It has been shown[411] that O_2^- is also formed on irradiation of hydrolysed chlorophyll.

The manganese(II) compounds present in chloroplasts exhibit a dismutase activity[128,412]. It has been shown[128] that manganese(II) pyrophosphate undergoes non-catalytic oxidation by the superoxide ion. It has been suggested[413] that O_2^- formed in chloroplasts can be involved in the hydroxylation of *p*-coumaric acid. According to some data[414,415], the reduction of oxygen to O_2^- by chloroplasts is stimulated by ascorbate, which oxidises O_2^- via the mechanism examined previously (see Section IV). It has been suggested[416] that O_2^- is involved in the oxidative cleavage of α,β-dihydroxyethyl(2)thiamine pyrophosphate catalysed by transketolase during photosynthesis.

VI. THE PARTICIPATION OF O_2^- IN THE OXIDATION-REDUCTION REACTIONS OF NATURAL MACROCYCLIC METAL COMPLEXES AND THEIR MODELS

The interaction of natural metal complexes, for example, porphyrin complexes of iron (haems), with oxygen can be represented in a general form by the equation

$$PFe^{II} + O_2 \rightleftarrows \underset{(I)}{PFe^{II}O_2} \rightleftarrows \underset{(II)}{PFe^{III}O_2^-} \rightleftarrows PFe^{III} + O_2^- \quad . \qquad (49)$$

Haemoglobin (Hb) and myoglobin (Mb) are known to form stable oxygenated complexes (HbO_2 and MbO_2), whereas oxygenated forms have not been observed for cytochromes (with the exception of cytochrome "o"[417]). In contrast to Co-analogues of haems, for which it has been established firmly that their oxygenated complexes have the structure of the ion pairs $Co^{III}O_2^-$,[418-432] the structure of the oxygenated complexes of haems continues to be discussed in the literature. There are data supporting both structure (I)[433-437] and structure (II)[306,332,438-443]. In a recent study[444] based on the analysis of the fluorescence spectra of MbO_2 it was concluded that there is an equilibrium between forms (I) and (II), which is displaced towards the former under the usual conditions. It has been shown in recent years that simple iron(II) complexes of porphyrins can form oxygenated structures at a reduced temperature and in the case of sterically hindered complexes at the normal temperature[437,444-450].

Eqn. (49) shows that O_2^- can be formed on decomposition of oxygenated complexes of haems. Indeed the superoxide ion has been observed in the autoxidation of oxyhaemoglobin and oxymyoglobin[451-454]. It has been shown that the oxidation of HbO_2, accompanied by the formation of O_2^-, is accelerated under the influence of phenoxides[455,456], hydroquinone, catechol[457], phenylhydrazine[455,458], menadione[458], etc. Presumably the reaction with electron donors (hydroquinones, phenoxides) involves the reduction of coordinated O_2^- to HOO^- with subsequent dissociation of the complex to methaemoglobin and HOO^-.[456] A similar reaction has been described for oxygenated cobalt complexes[460]. In the presence of electron acceptors (for example, quinones) direct one-electron oxidation of oxyhaemoglobin is possible[459]. In addition, O_2^- is formed in the flash photolysis of HbO_2[461] and in ligand substitution reactions[462,463]:

$$Hb^{II}O_2 + X^- \rightarrow Hb^{III}X^- + O_2^- \quad ; \qquad X^- = CN^-,\ N_3^-\ \text{etc.} \qquad (50)$$

The kinetics of the reaction of O_2^- with cytochrome *c* have been investigated in detail[263-268] (see Table 3):

$$O_2^- + \text{cytochrome } (Fe^{III}) \rightleftarrows O_2 + \text{cytochrome } c\,(Fe^{II}) \quad . \qquad (51)$$

The distinctive features of reaction (51) are a comparatively low rate and the dependence of the rate constant on pH. It is believed[267] that the low rate of this reaction can be accounted for by the involvement of water molecules in the transition state; according to Koppenol et al.,[268] O_2^- attacks the edge of the porphyrin ring. The reaction proceeds without the formation of an intermediate complex[266,267]. The dependence of the rate constant on pH is apparently due to the change in the conformation of cytochrome[266,267], but the result may be distorted by the influence of the ionic strength[268]. Apart from cytochrome *c*, O_2^- is capable of reducing its derivatives, for example, acetylated cytochrome *c*.[464]

The autoxidation of ferrocytochrome *c* is a slow reaction ($k_{-51} = 3 \times 10^{-2}$ litre mole^{-1} s^{-1} [72]). As was to be expected, SOD accelerates autoxidation, causing a rapid dismutation of O_2^-.[465,466] Cytochrome b_5, whose reduction potential is lower by 200 mV than that of cytochrome *c*, is oxidised with formation of O_2^- but at a much lower rate (the rate constant is 23 litre mole^{-1} s^{-1}).[257] In conformity with Eqn. (49), the reaction of O_2^- with metHb results in the formation of HbO_2,[269,467-469] but there is no reaction with metHb$_4$.[469] At the same time O_2^- can oxidise HbO_2 to metHb, evidently via the mechanism examined above[269,467,470,471]. In contrast to normal haemoglobin, the reaction of O_2^- with unstable haemoglobins results in the oxidation of thiol groups and the formation of dimers[467].

The study of the mechanism of the interaction of O_2^- with natural metal complexes and their models in an aprotic medium has begun recently. It is of particular importance, because real biochemical processes involving haems take place in a hydrophobic environment. As early as 1973 Ellis and Pratt[472] showed that O_2^- forms at −50°C an oxygenated complex with hydroxocobalamin (vitamin B_{12a}) in DMF. Analogous observations were made also for the reaction of O_2^- with the dimethyl ether of Fe(III)-protoporphyrin IX.[473] It has been shown recently[474] that at room temperature O_2^- reduces Co(II)-phthalocyanine ($Co^{II}Pc$) to $Co^{I}Pc$, while the reaction of O_2^- with Co(II)-tetraphenylporphyrin ($Co^{II}TPP$) leads to the formation of the dinuclear complex $TPPCo^{II}OOCo^{II}TPP$,[475] although $Co^{I}TPP$ is also formed as an intermediate. In aqueous solutions O_2^- is

apparently incapable of reducing cyanocobalamin[258], but it reacts in DMF at room temperature with both hydroxy- and cyano-cobalamin, the former being reduced to the Co(II)-form (vitamin B_{12r}).[476] The final reaction products are probably dinuclear peroxy-complexes in both cases[475].

Like cyanocobalamin, haemin chloride is not reduced by the oxygen radical-anion in aqueous solutions[477], but the reaction does proceed in DMF, a new oxygenated haem complex, having the structure $PFe^{II}O_2^{\cdot-}$ or $PFe^{II}(O_2^{\cdot-})_2$ being formed in the presence of a large excess of $O_2^{\cdot-}$.[478] The reliability of the identification of the oxygenated complex in the reaction of $O_2^{\cdot-}$ with the dimethyl ether of protoporphyrin IX[473] is questioned in the same investigation[478]. The reduction of Mn(III)-tetraphenylporphyrin by the oxygen radical-anion in DMSO at room temperature[479] and the formation of the oxygenated complex $ZnTPPO_2^{\cdot-}$ in the reaction of KO_2 with ZnTPP[480] have also been described.

VII. THE TOXIC EFFECT OF $O_2^{\cdot-}$ AND ITS INVOLVEMENT IN PATHOLOGICAL PROCESSES AND PHAGOCYTOSIS

Presumably the $O_2^{\cdot-}$ formed in enzymatic reactions is capable of involvement in side reactions with its immediate environment and exerts thereby a toxic effect on the cell structure. As early as 1969, it was suggested[272] that SOD plays a protective role against the toxic effect of $O_2^{\cdot-}$ in the organism. It was shown subsequently[481] that, when the microorganisms *Str. faecalis* and *E. coli* are grown under oxygen pressure up to 20 atm, the content of SOD increases sharply. The suppression of the synthesis of SOD by puromycin led to a decrease of the number of viable cells. The addition of SOD increased the lifetime in an oxygen medium of *E. coli* cells grown anaerobically and also suppressed the toxic effect of streptonigrin on the latter[482,483], which demonstrates, according to the author, the ability of streptonigrin to generate $O_2^{\cdot-}$ under aerobic conditions. Analogous effects were observed in air and in an oxygen medium for the eukaryote *Saccharomyces cerevisiae*, grown under anaerobic conditions[484].

It has been shown that an increase of the activity of SOD in erythrocytes assists the survival of new born babies[485]. The liver of rat embryos does not contain SOD and its formation is induced by respiration[486]. The radioprotective action of SOD has been discovered recently. It was found that oxygen increases the lethal effects of radiation of cells (apparently in consequence of the formation of $O_2^{\cdot-}$), while SOD increases their resistance[487-493].

As already stated, *E. coli* cells contain Mn- and Fe-SOD. It has been found[364] that Mn-SOD is localised in the cell matrix and protects the organism from the action of endogenic $O_2^{\cdot-}$, while Fe-SOD, present in the periplasm, offers protection against exogenic $O_2^{\cdot-}$. It has been shown[494,495] that the pulmonary toxicity of oxygen is due to the formation of $O_2^{\cdot-}$. The damage to lungs due to this cause can occur during the oxidation of the herbicide paraquat[496,497], the ability of which to generate $O_2^{\cdot-}$ has also been demonstrated in other biological objects[498,499] (see also Section IV). In order to reduce the effect on the lungs of the $O_2^{\cdot-}$ generated during smoking, it has been suggested that SOD be used as a medicinal preparation[500]. Furthermore, $O_2^{\cdot-}$ can cause the oxidative degradation of ribonuclease and the autoxidation of lysyl-tRNA synthetase (EC 6.1.1.6)[501], can reduce the level of glutathione in cells with a deficiency of glucose-6-phosphate dehydrogenase[502], and can inactivate DNA[503].

Various mechanisms of the toxic effect of $O_2^{\cdot-}$ have been considered in the literature. In a number of studies it has been suggested that $O_2^{\cdot-}$ or the singlet oxygen formed as a result of its dismutation are involved in the peroxidation of lipids[400,504-512]. However, it may be that $O_2^{\cdot-}$ participates in the peroxidation of lipids only indirectly by reducing the complex Fe^{3+}-ADP to Fe^{2+}-ADP, which then reacts with lipids[513,514]. It has been shown[515] that $O_2^{\cdot-}$ cannot react directly with cholesterol—an important component of lipid membranes. It has been postulated that $O_2^{\cdot-}$, formed in the autoxidation of menadione[459,502], 1,4-naphthoquinone-2-sulphonate[516], phenylhydrazine[455,458,502,517], dialuric acid[217], and dihydroxyfumaric acid[518,519], induces the haemolysis of erythrocytes. However, it is more likely that the true haemolytic agents are $HO^{\cdot}$, $O_2(^1S)$, and H_2O_2,[520-522] formed as a result of secondary reactions of $O_2^{\cdot-}$.

It has been observed that the reactions of $O_2^{\cdot-}$ with catecholamines[167], cobalamins, and their models[125,475] lead to the formation of stable compounds, which are apparently no longer capable of participating in the normal metabolic processes. This has been confirmed in a study[523] where it was observed that the interaction of $O_2^{\cdot-}$ with catecholamines in rat liver microsomes induces the covalent binding of catecholamines to proteins, which may be the cause of hepatitis. The ability to generate $O_2^{\cdot-}$ is probably the cause of the toxic effect of 6-hydroxy- and 6-amino-dopamines[217] and of β-lapachone[524].

It has been shown recently[525] that $O_2^{\cdot-}$ causes a decrease in the viscosity of the synovial fluid as a result of the depolymerisation of hyaluronic acid, which, according to the author, leads to the development of inflammatory arthritis; SOD inhibits this process and can therefore be used in the treatment of such diseases. There is also other evidence for the involvement of $O_2^{\cdot-}$ in inflammatory processes[526-528] and certain anti-inflammatory drugs and their derivatives (copper complexes of salicylic acid[171,529], and penicillamine[530], corticosteroids[527,528], and others) are capable of interacting effectively with $O_2^{\cdot-}$. However, according to some data[351], corticosteroids do not inhibit and actually promote the formation of $O_2^{\cdot-}$. Na_2PtCl_6 exhibits a similar activity[531]. The formation of $O_2^{\cdot-}$ in inflammatory processes can be the cause of the aggregation of thrombocytes and the liberation of serotonin[532].

Tyler observed[533] that $O_2^{\cdot-}$ can inhibit the activity of reduced NAD dehydrogenase. In order to protect the enzymes of the respiratory chain from $O_2^{\cdot-}$ generated in the course of respiration, mitochondria therefore contain SOD located in the immediate vicinity of reduced NAD dehydrogenase[349]. It has been shown[534] that $O_2^{\cdot-}$ generated by xanthine oxidase can induce the mobilisation of iron from ferritin.

The problem of the role of the superoxide ion in cancer is of very great interest. It has been shown[535] that $O_2^{\cdot-}$ can increase the carcinogenic effect of aromatic hydrocarbons. The generation of $O_2^{\cdot-}$ could be the cause of the carcinogenic effect of 4-nitroquinoline *N*-oxide[536]. There are contradictory data concerning the presence and role of SOD in tumour tissues[346,537-543]. The view has been expressed[537] that cancer tissues are more sensitive to the action of $O_2^{\cdot-}$ than normal tissues. It is believed[544] that $O_2^{\cdot-}$ contributes to the inhibiting effect of bleomycin on cancer tissues. The role of $O_2^{\cdot-}$ in the activity of another group of anticancer antibiotics, namely adriamycin, daunomycin, etc., has been discussed in a number of studies. It was observed that these antibiotics promote the formation of free radicals[545] and accelerate the oxidation of $NADPH_2$ in microcomes[546,547] and submitochondrial

particles[548]. The formation of O_2^- has been noted in all cases, which may be the cause of the high cardiotoxicity of the above antibiotics (as a result of the peroxidation of lipids[549]).

However, the hypothesis that adriamycin and daunomycin semiquinones can reduce oxygen to the superoxide ion[546-549] was not confirmed in the study of the interaction of O_2^- with adriamycin in an aprotic medium[550]. On the contrary, it was observed that, when solutions of O_2^- and adriamycin in DMF are mixed, the adriamycin semiquinone is formed quantitatively, i.e. adriamycin behaves as an effective trap for O_2^-. Consequently, adriamycin has a relatively high redox potential, which accounts for its ability to inhibit respiration in mitochondria[551,552]. The formation of O_2^- in the presence of adriamycin is apparently a consequence of unknown side reactions.

The high reactivity of O_2^- can be responsible not only for pathological phenomena but also for the protective response of the organism against external influences. The problem of the possible involvement of O_2^- in phagocytosis is therefore widely discussed in the literature. Thus Babior et al.[553] showed that polymorphonuclear leukocytes reduce cytochrome *c*, the process being inhibited by SOD. According to the data of Johnson et al.,[554] the introduction of SOD on latex particles into phagocytic vacuoles together with the bacteria *E. coli* and *Str. aureus* leads to the complete inhibition of phagocytosis. Subsequently, the formation of O_2^- in phagocytosis was confirmed for both polymorphonuclear and mononuclear leukocytes[555-567], macrophages[568,569], and blood plasma[570]. The generation of O_2^- by human blood thromobocytes has also been observed[571]. O_2^- can be regarded as one of the agents on which the bactericidal activity of leukocytes depends[572,573] although $HO^\cdot$ and H_2O_2 are apparently much more active[573,574].

Phagocytosis is accompanied by a sharply increased absorption of oxygen by granulocytes[555,576]. It is believed that an enzyme system, which employs $NADPH_2$ as the electron donor and generates O_2^-, is responsible for the respiratory burst[576]. It is interesting that increased absorption of oxygen and an increased rate of production of O_2^- in phagocytosis are not observed in patients suffering from chronic granulomatosis (CGM).[577] However, the subcellular fractions of normal and CGM leukocytes generate O_2^- at the same rates[559,578]. It is therefore possible that the cause of CGM is outside the oxygen metabolic system[578].

The mechanism of the involvement of O_2^- in phagocytosis is insufficiently clear. It has been suggested that O_2^- is formed in the phagosome as a result of the enzymatic[579] or Mn^{2+}-catalysed[580] oxidation of $NADPH_2$. The system generating O_2^- is probably associated with the surface of the leukocyte[581]. However, it is not clear how the activity of the enzyme increases sharply during phagocytosis, whether its action is suppressed by virulent bacteria, or whether the latter are specially protected against O_2^-. The generation of O_2^- in phagocytosis is enhanced in the presence of sulphydryl groups, fluoride ions, cytochalasins[582,583], immunoglobulin G[563,584], aliphatic acids[585], and anionic detergents (digitonin, deoxycholate, and zymosan)[584,586-590]. The membrane sialic acid apparently plays an important role in stimulating the formation of O_2^- in phagocytosis[591], while myeloperoxidase[592] and certain local anaesthetics[593] inhibit its formation. Doubts have been expressed also concerning the reliability of certain experiments demonstrating the involvement of O_2^- in phagocytosis[594,595]. Thus the problem of the role of O_2^- in phagocytosis still awaits its final elucidation.

During the preparation of the review for the press, new studies on the chemical and biochemical properties of O_2^- were published. New methods of generating O_2^- were described: by the oxidation of Cu_2O[596] and metal ions[597], by the decomposition of H_2O_2 on metal oxides[598], by the photolysis of aqueous solutions[599], by the photolysis of CdS in non-aqueous media[600], of $Ru(bipy)_3^{2+}$,[601] and of a melamine suspension[602], and also in electrocatalysis in the presence of cobalt chelates[603]. In contrast to earlier data, it was found that O_2^- is not formed in the reaction of $NADH_2$ with phenazine methosulphate[604]. The study of the chemical properties of O_2^- is being continued, namely: nucleophilic substitution reactions with alkyl halides, peroxides[605], and esters[606], electron transfer reactions with copper(II) salicylates[607] and cytochrome *c*[608], and the interaction of O_2^- with ascorbic acid and tocopherol[609-611], hydrogen peroxide (in the presence of iron ions)[612,613], olefins[614] and ketones (in the presence of catalysts of interphase transfer)[615]. The formation of nitroxy-radicals in the reaction of O_2^- with the *N*-oxides of heterocyclic compounds[616,617] and chemiluminescent reactions of O_2^- in the presence of carbonate[618], as well as new compounds of O_2^- with Ba^{2+} and Ca^{2+}[619] and with rhodium(III)[620] and cobalt(III)[621] complexes have been described.

The generation of O_2^- by mitochondria[622,623] and microsomes[624-627] and by reduced FMN[628] and microbial nutrient solutions[629] has been investigated in a number of studies. The study of the properties of SOD and its models has been continued[630-635] and it has been shown that data concerning the involvement in catalysis of only one of the two copper atoms are apparently incorrect[636]. The involvement of O_2^- in reactions catalysed by azoreductase[637], dopamine β-hydroxylase[638], kidney diaminooxidase[639], and 2-nitropropane dioxygenase[640] has been demonstrated. A study has been made also of the participation of O_2^- in reactions of peroxidase[641,642] and *m*-hydroxybenzoate 4-hydroxylase[643], in the vitamin K-dependent carboxylation of the glutamic acid residues of prothrombin[644], in the oxidation of cytochrome oxidase by oxygen at 173 K[645], and in the inactivation of papain[646]. The role of O_2^- in photosynthetic processes was also studied[647,648].

The investigation of the reactions of O_2^- with haems[649,650], the role of O_2^- in cancer[651,652], and the involvement of O_2^- in inflammatory processes[653-657] and in phagocytosis[658-666] have been continued. The involvement of O_2^- in processes associated with the radiation-induced damage of bacteriophages[667], the haemolysis and autoxidation of oxyhaemoglobin[668,669], the damage of the membranes of erythrocytes by copper salts[670], the autoxidation of linoleic acid[671], and the degradation of hyaluronic acid[672] has been demonstrated. It has also been shown that O_2^- is able to pass through erythrocyte membranes via anionic channels[673] and that SOD plays a protective role in the tissues of the crystalline lens of the eye[674,675].

REFERENCES

1. E. B. Burlakova, B. G. Dzantiev, G. B. Sergeev, and N. M. Emanuel', Symposium, "Biokhimicheskie i Fiziko-Khimicheskie Osnovy Biologicheskogo Deistviya Radiatsii" (Biochemical and Physicochemical Principles of the Biological Action of Radiation), Izd. Moskv. Gos. Univ., Moscow, 1957, p. 10.
2. N. M. Emanuel' and L. P. Lipchina, Dokl. Akad. Nauk SSSR, **121**, 141 (1958).
3. E. B. Burlakova and N. M. Emanuel', Dokl. Akad. Nauk SSSR, **135**, 599 (1960).

4. I. Fridovich and P. Handler, J. Biol. Chem., **233**, 1578 (1958).
5. I. Fridovich and P. Handler, J. Biol. Chem., **236**, 1836 (1961).
6. I. Fridovich and P. Handler, J. Biol. Chem., **237**, 916 (1962).
7. F. Haber and J. Weiss, Proc. Roy. Soc., **A142**, 332 (1934).
8. J. Weiss, Naturwiss., **23**, 64 (1935).
9. B. H. J. Bielski and J. M. Gebicki, Adv. Radiat. Chem., **2**, 177 (1970).
10. G. Czapski, Ann. Rev. Phys. Chem., **22**, 171 (1971).
11. I. Fridovich, Accounts Chem. Res., 5, 321 (1972).
12. W. Bors, M. Soran, E. Leugfelder, R. Spoettl, and C. Michel, Current Topics Radiat. Res., 9, 247 (1974).
13. T. E. King, H. S. Mason, and M. Morrison, "Oxidases and Related Redox Systems", Wiley, New York, 1973, Vol. 2, p. 78.
14. I. Fridovich, Adv. Enzymol., **41**, 35 (1974).
15. M. N. Merzlyak and A. S. Sobolev, Biofizika (VINITI, Itogi Nauki), 5, 118 (1975).
16. L. S. Vartanyan, Uspekhi Khim., 44, 1851 (1975) [Russ. Chem. Rev., No. 10 (1975)].
17. V. N. Mishin and V. V. Lyakhovich, Uspekhi Sovr. Biol., **82**, 338 (1976).
18. K. Farhataziz and A. B. Ross, Nat. Stand. Ref. Data Ser., Nat. Bur. Stand., 59, 113 (1977).
19. E. Lee-Ruff, Chem. Soc. Rev., 6, 195 (1977).
20. A. LeBerre and Y. Berguer, Bull. Soc. chim. France, 2363 (1966).
21. L. Andrews, J. Phys. Chem., 73, 3922 (1969).
22. D. E. Milligan and M. E. Jacox, J. Chem. Phys., **55**, 1003 (1971).
23. R. R. Smardzewski and L. Andrews, J. Chem. Phys., 57, 1327 (1972).
24. L. Andrews, J.-T. Hwang, and C. Trindle, J. Phys. Chem., 77, 1065 (1973).
25. D. L. Maricle and W. G. Hodgson, Anal. Chem., 37, 1563 (1965).
26. M. E. Peover and B. S. White, Electrochim. Acta, 11, 1061 (1966).
27. P. F. Knowles, J. F. Gibson, F. M. Pick, and R. C. Bray, Biochem. J., 111, 53 (1969).
28. R. C. Gray, F. M. Pick, and D. Samuel, Europ. J. Biochem., 15, 352 (1970).
29. F. J. Adrian, E. L. Cochran, and V. A. Bowers, J. Chem. Phys., 59, 56 (1973).
30. V. M. Berdnikov, P. V. Schastnev, A. A. Merkulov, A. V. Balaev, N. M. Bazhin, and Yu. V. Gatilov, Zhur. Strukt. Khim., 14, 634 (1973).
31. V. F. Shuvalov, A. P. Moravskii, and Ya. S. Lebedev, Dokl. Akad. Nauk SSSR, **235**, 877 (1977).
32. A. A. Merkulov, V. M. Berdnikov, Yu. V. Gatilov, and N. M. Bazhin, Zhur. Neorg. Khim., 17, 3253 (1973) [Russ. J. Inorg. Chem., No. 12 (1973)].
33. D. M. Lindsay, D. R. Herschbach, and A. L. Kwiran, Chem. Phys., Letters, **25**, 175 (1974).
34. G. W. Eastland and M. C. R. Symons, J. Phys. Chem., 81, 1502 (1977).
35. V. M. Miskowski, J. L. Robins, I. M. Treitel, and H. B. Gray, Inorg. Chem., 14, 2318 (1975).
36. D. A. White, A. S. Solodar, and M. Braizer, Inorg. Chem., 11, 2160 (1972).
37. G. McLendon, S. R. Pickens, and A. E. Martell, Inorg. Chem., 16, 1551 (1977).
38. R. D. Gillard, J. D. P. de Jesus, and L. R. H. Tipping, Chem. Comm., 58 (1977).
39. J. H. Baxendale, Radiat. Res., 17, 312 (1962).
40. J. Rabani and S. O. Nielson, J. Phys. Chem., 73, 3736 (1969).
41. D. Behar and G. Czapski, Isr. J. Chem., 8, 699 (1970).
42. D. Behar, G. Czapski, J. Rabani, L. M. Dorfman, and H. A. Schwarc, J. Phys. Chem., 74, 3209 (1970).
43. D. Behar, G. Czapski, and J. Duchovny, J. Phys. Chem., 74, 2206 (1970).
44. J. H. Baxendale, M. D. Ward, and P. Wardman, Trans. Faraday Soc., 67, 2532 (1971).
45. M. Tezura, Y. Ohkatzu, and T. Osa, Bull. Chem. Soc. Japan, 48, 1471 (1975).
46. J. A. Fee and P. G. Hildenbrand, FEBS Letters, 39, 79 (1974).
47. T. Ozawa, A. Hanaki, and H. Yamamoto, FEBS Letters, 74, 99 (1977).
48. M. Hoshino, S. Arai, and M. Imamura, J. Phys. Chem., 78, 1473 (1974).
49. I. B. Afanas'ev, N. I. Polozova, and G. I. Samokhvalov, Zhur. Org. Khim., 12, 2536 (1976).
50. D. T. Sawyer and J. L. Roberts, J. Electroanal. Chem., 12, 90 (1966).
51. E. L. Johnson, K. H. Pool, and R. E. Hamm, Anal. Chem., 38, 183 (1966).
52. D. C. Luehrs and D. G. Leddy, J. Electroanal. Chem., 41, 113 (1973).
53. T. Fujinaga and S. Sakura, Bull. Chem. Soc. Japan, 47, 2781 (1975).
54. L. P. Vykhodtseva, L. N. Nekrasov, and N. I. Dubrovina, Elektrokhimiya, 13, 1366 (1977).
55. G. Feroci and S. Roffia, J. Electroanal. Chem., 71, 191 (1976).
56. A. D. Goolsby and D. T. Sawyer, Anal. Chem., 40, 83 (1968).
57. E. J. Johnson, K. H. Pool, and R. E. Hamm, Anal. Chem., 39, 888 (1967).
58. D. T. Sawyer and E. T. Seo, Inorg. Chem., 16, 499 (1977).
59. B. Kastening and G. Kazenmifard, Ber. Bunsen Ges. Phys. Chem., 74, 551 (1970).
60. J. Chevalet, F. Roulelle, L. Gierts, and J. P. Lambert, J. Electroanal. Chem., 39, 201 (1972).
61. P. L. Airey and H. C. Sutton, J. Chem. Soc. Faraday Trans. I, 2441 (1976).
62. P. L. Airey and H. C. Sutton, J. Chem. Soc. Faraday Trans. I, 2452 (1976).
63. W. M. Latimer, "Oxidation States of the Elements and Their Potentials in Aqueous Solutions" (Translated into Russian), Inostr. Lit., Moscow, 1954.
64. P. M. Wood, FEBS Letters, 44, 22 (1974).
65. V. M. Berdnikov and O. S. Zhuravleva, Zhur. Fiz. Khim., 46, 2658 (1972) [Russ. J. Phys. Chem., No. 10 (1972)].
66. P. S. Rao and E. Hayon, Biochem. Biophys. Res. Comm., 51, 468 (1973).
67. P. S. Rao and E. Hayon, J. Phys. Chem., 79, 397 (1975).
68. J. Divisek and B. Kastening, J. Electroanal. Chem., 65, 603 (1975).
69. Y. A. Ilan, D. Meisel, and G. Czapski, Isr. J. Chem., 12, 891 (1974).
70. D. Meisel and G. Czapski, J. Phys. Chem., 79, 1503 (1975).
71. Y. A. Ilan, G. Czapski, and D. Meisel, Biochim. Biophys. Acta, 430, 209 (1976).

72. Y.Sawada, T.Iyanagi, and I.Yamazaki, Biochemistry, **14**, 3761 (1975).
73. R.Dietz, M.E.Peover, and P.Rothbaum, Chem. Ing.Techn., **42**, 182 (1970).
74. R.Yamdagni, J.D.Payzand, and P.Kebarle, Canad.J.Chem., **51**, 2507 (1973).
75. G.Czapski and L.D.Dorfman, J.Phys.Chem., 68, 1169 (1964).
76. K.Schmidt, Z.Naturforsch., **16B**, 206 (1961).
77. G.Czapski and B.H.Bielski, J.Phys.Chem., 67, 2180 (1963).
78. S.Marklund, J.Biol.Chem., **251**, 7504 (1976).
79. B.H.J.Bielski and A.O.Allen, J.Phys.Chem., **81**, 1048 (1977).
80. I.B.Afanas'ev, S.V.Prigoda, T.Ya.Mal'tseva, and G.I.Samokhvalov, Dokl.Akad.Nauk SSSR, **209**, 376 (1973).
81. I.B.Afanas'ev, S.V.Prigoda, and G.I.Samokhvalov, Kinetika i Kataliz, **15**, 922 (1974).
82. I.B.Afanas'ev, S.V.Prigoda, T.Ya.Mal'tseva, and G.I.Samokhvalov, Int.J.Chem.Kinet., 6, 643 (1974).
83. I.B.Afanas'ev, S.V.Prigoda, and G.I.Samokhvalov, Zhur.Obshch.Khim., 47, 2507 (1977).
84. M.Tezura, H.Hamada, Y.Ohkatsu, and T.Osa, Denki Kagaku, **44**, 17 (1976).
85. H.J.Guirand and C.S.Foote, J.Amer.Chem.Soc., 98, 1984 (1976).
86. J.A.Pederson, J.Chem.Soc., Perkin Trans.II, 424 (1973).
87. Y.Ogata, K.Nate, and M.Yamashita, Bull.Chem. Soc., Japan, **47**, 174 (1974).
88. G.J.McClune and J.A.Fee, FEBS Letters, 67, 294 (1976).
89. K.B.Patel and R.L.Willson, J.Chem.Soc., Faraday Trans., I, 814 (1973).
90. B.E.Hulme, E.J.Land, and G.O.Phillips, J.Chem. Soc., Faraday Trans., I, 1992 (1972).
91. R.L.Willson, Trans.Faraday Soc., 67, 3008 (1971).
92. M.Simic and E.Hayon, Biochem.Biophys.Res. Comm., **50**, 364 (1973).
93. G.E.Adams and R.L.Willson, Trans.Faraday Soc., 65, 2981 (1969).
94. Y.Ilan and J.Rabani, Int.J.Rad.Phys.Chem., 8, 609 (1976).
95. E.Hayon and M.Simic, J.Amer.Chem.Soc., 95, 2433 (1973).
96. M.Simic and E.Hayon, Int.J.Rad.Biol., **20**, 589 (1971).
97. P.C.Chan and B.H.J.Bielski, J.Amer.Chem.Soc., 95, 5504 (1973).
98. J.E.Biaglow, O.F.Nygaard, and C.L.Greenstock, Biochem.Pharm., **25**, 393 (1975).
99. D.O.Lamberth and G.Palmer, J.Biol.Chem., **248**, 6095 (1973).
100. R.N.Moorthy and E.Hayon, J.Phys.Chem., 78, 2615 (1974).
101. J.H.Baxendale and M.Fiti, J.Chem.Soc., Dalton Trans., 1995 (1972).
102. D.Meisel, M.S.Matheson, W.A.Mulac, and J.Rabani, J.Phys.Chem., 81, 1449 (1977).
103. Q.G.Mulazzani, S.Emmi, P.G.Fuochi, M.Z.Hoffman, and M.Venturi, J.Amer.Chem.Soc., 100, 981 (1978).
104. A.M.Tait, M.Z.Hoffman, and E.Hayon, Inorg. Chem., 15, 934 (1976).
105. R.M.Sellers and M.G.Simic, J.Amer.Chem.Soc., 98, 6145 (1976).
106. J.Rabani, D.Klug-Roth, and A.Henglein, J.Phys. Chem., 78, 2089 (1974).
107. I.Ilan, J.Rabani, and A.Henglein, J.Phys.Chem., 80, 1558 (1976).
108. E.Bothe, G.Behrens, and D.Schulte-Frohlinde, Z.Naturforsch., **32B**, 886 (1977).
109. O.Micic and M.T.Nenadovic, J.Phys.Chem., 80, 940 (1976).
110. S.Abramovitch and J.Rabani, J.Phys.Chem., 80, 1562 (1976).
111. G.L.Greenstock and G.W.Ruddock, Int.J.Rad. Phys.Chem., 8, 367 (1976).
112. J.Rabani, W.A.Mulac, and M.S.Matheson, J.Phys. Chem., 69, 53 (1965).
113. K.D.Asmus, A.Henglein, M.Ebert, and J.P.Keene, Ber.Bunsen Ges.Phys.Chem., 68, 657 (1964).
114. H.C.Sutton, J.Chem.Soc., Faraday Trans.I, 2142 (1975).
115. K.Sehested, O.L.Rasmusson, and H.Fricke, J. Phys.Chem., **72**, 626 (1968).
116. G.E.Adams, J.W.Boag, and B.D.Michael, Proc. Roy.Soc., A**289**, 321 (1965).
117. E.Hayon and J.J.McCarvey, J.Phys.Chem., 71, 1472 (1967).
118. H.C.Sutton and M.T.Downes, J.Chem.Soc., Faraday Trans.I, 1498 (1972).
119. D.Zehavi and J.Rabani, J.Phys.Chem., 76, 3703 (1972).
120. I.A.Ilan and G.Czapski, Biochim.Biophys.Acta, 498, 386 (1977).
121. Yu.N.Kozlov and V.M.Berdnikov, Zhur.Fiz.Khim., 47, 583 (1973) [Russ.J.Phys.Chem., No.3 (1973)].
122. J.Rabani, D.Klug-Roth, and J.Lilie, J.Phys.Chem., 77, 1169 (1973).
123. R.Brigelius, R.Spoettl, W.Bors, E.Lendfelder, M.Sarau, and U.Weser, FEBS Letters, 47, 72 (1974).
124. D.Klug-Roth and J.Rabani, J.Phys.Chem., 80, 588 (1976).
125. M.Simic and M.Z.Hoffman, J.Amer.Chem.Soc., 99, 2370 (1977).
126. M.Faraggi, J.Phys.Chem., 80, 2316 (1976).
127. M.Pick-Kaplan and J.Rabani, J.Phys.Chem., 80, 1840 (1976).
128. Y.Kono, M.A.Takahashi, and K.Asada, Arch. Biochem.Biophys., 174, 454 (1976).
129. G.J.McClune, J.A.Fee, G.A.McClusky, and J.T.Groves, J.Amer.Chem.Soc., 99, 5220 (1977).
130. B.H.J.Bielski and P.C.Chan, J.Amer.Chem.Soc., 100, 1920 (1978).
131. A.D.McElroy and J.S.Hashman, Inorg.Chem., 3, 1798 (1964).
132. E.I.Latysheva, E.N.Cherkasov, S.A.Tokareva, N.G.Velikova, and I.I.Vol'nov, Izv.Akad.Nauk SSSR, Ser.Khim., 1684 (1974).
133. G.A.Rusell, E.G.Janzen, A.G.Bemis, E.J.Geels, A.J.Moye, S.Mak, and E.T.Storm, Adv.Chem. Ser., **51**, 112 (1965).
134. G.A.Russell, A.G.Bemis, E.J.Geels, E.J.Janzen, and A.J.Moye, Adv.Chem.Ser., 75, 174 (1968).
135. G.A.Russell and R.K.Norris, Rev.Reactive Species Chem.React., 1, 65 (1973).
136. G.A.Russell and A.G.Bemis, Inorg.Chem., 6, 403 (1967).
137. M.J.A.Grath, Tetrahedron, **32**, 377 (1976).
138. S.P.Solodovnikov, Izv.Akad.Nauk SSSR, Ser.Khim., 996 (1976).

139. G.P.Anderson, D.J.Salmon, T.J.Meyer, and R.C.Young, J.Amer.Chem.Soc., 99, 1980 (1977).
140. J.A.Roberts, M.M.Morrison, and D.T.Sawyer, J.Amer.Chem.Soc., 100, 329 (1978).
141. R.A.Johnson, Tetrahedron Letters, 331 (1976).
142. J.S.Valentine and A.B.Curtis, J.Amer.Chem.Soc., 97, 224 (1975).
143. J.S.Filippo, C.-I.Chern, and J.S.Valentine, J.Org.Chem., 40, 1678 (1975).
144. R.A.Johnson and E.G.Nidy, J.Org.Chem., 40, 1680 (1975).
145. E.J.Corey, K.C.Nicolaou, M.Shibasaki, Y.Machida, and C.S.Shiner, Tetrahedron Letters, 3183 (1975).
146. J.S.Filippo, L.J.Romano, C.-I.Chen, and J.S.Valentine, J.Org.Chem., 41, 586 (1976).
147. E.J.Corey, K.C.Nicolaou, and M.Shibasaki, Chem.Comm., 658 (1975).
148. M.J.Gibian and T.Ungermann, J.Org.Chem., 41, 2500 (1976).
149. M.V.Merritt and R.A.Johnson, J.Amer.Chem. Soc., 99, 3713 (1977).
150. W.C.Danen and R.J.Warner, Tetrahedron Letters, 989 (1977).
151. P.F.Levonowich, H.P.Tanneubaum, and R.C.Dougherty, Chem.Comm., 597 (1975).
152. A.Frimer and I.Rosenthal, Tetrahedron Letters, 2809 (1976).
153. T.Yamaguchi and H.C.van der Plas, Rec.Trav. chim., 96, 89 (1977).
154. L.H.Dao, A.C.Hopkinson, E.Lee-Ruff, and J.Rigaudy, Canad.J.Chem., 55, 3791 (1977).
155. R.Dietz, A.E.Forno, B.E.Larcombe, and M.E.Peover, J.Chem.Soc.B, 816 (1970).
156. M.V.Merritt and D.T.Sawyer, J.Org.Chem., 35, 2157 (1970).
157. F.Magno and G.Bontempelli, J.Electroanal.Chem., 68, 337 (1976).
158. F.Magno, R.Seeber, and S.Valcher, J.Electroanal. Chem., 83, 131 (1977).
159. H.J.James and R.F.Broman, J.Phys.Chem., 76, 4019 (1972).
160. D.T.Sawyer, M.J.Gibian, M.M.Morrison, and E.T.Seo, J.Amer.Chem.Soc., 100, 627 (1978).
161. Y.Moro-oka, O.J.Chung, H.Arakawa, and T.Ikawa, Chem.Letters, 1293 (1976).
162. C.-I.Chern and J.S.Filippo, J.Org.Chem., 42, 178 (1977).
163. F.E.Scully and R.C.Davis, J.Org.Chem., 43, 1467 (1978).
164. A.Picot, P.Milliet, M.Cherest, and X.Lusiuchi, Tetrahedron Letters, 3811 (1977).
165. H.Sagae, M.Fujihira, T.Osa, and H.Lund, Chem. Letters, 793 (1977).
166. G.Feroci and S.Roffia, J.Electroanal.Chem., 81, 387 (1977).
167. I.B.Afanas'ev and N.I.Polozova, Khim.Farm. Zhur., No.4, 16 (1979).
168. I.B.Afanas'ev and N.I.Polozova, Zhur.Org.Khim. (in the Press).
169. R.Poupko and I.Rosenthal, J.Phys.Chem., 77, 1722 (1973).
170. I.Rosenthal and T.Bercovici, Chem.Comm., 200 (1973).
171. L.R.de Alvare, K.Soda, and T.Kimura, Biochem. Biophys.Res.Comm., 69, 687 (1976).
172. A.Nishinaga, T.Shimizu, and T.Matsuura, Chem. Letters, 547 (1977).
173. T.L.Parker, Diss.Abstr.Int., B37, 3968 (1977).
174. H.J.Guirand and C.S.Foote, J.Amer.Chem.Soc., 98, 1984 (1976).
175. I.Rosenthal, Isr.J.Chem., 13, 86 (1975).
176. I.Rosenthal and A.Frimer, Tetrahedron Letters, 2805 (1976).
177. I.Rosenthal and A.Frimer, Tetrahedron Letters, 3731 (1976).
178. I.B.Afanas'ev and N.I.Polozova, Zhur.Org.Khim. 12, 1833 (1976).
179. Y.Moro-oka and C.S.Foote, J.Amer.Chem.Soc., 98, 1510 (1976).
180. E.Lee-Ruff, A.B.P.Lever, and J.Rigaudy, Canad. J.Chem., 54, 1837 (1976).
181. I.B.Afanas'ev and N.I.Polozova, Zhur.Org.Khim., 14, 1013 (1978).
182. G.Feroci and S.Valcher, Atti Accad.Naz.Lincei, Cl.Sci.Fis.Mat.Natur.Rend., 51, 525 (1971).
183. J.Stauff, H.Schidkeenz, and G.Hartmann, Nature, 198, 281 (1963).
184. U.Sandler and J.Stauff, An.Asoc.Quim.Argentina, 59, 149 (1971).
185. A.U.Khan, Science, 168, 475 (1970).
186. R.M.Arneson, Arch.Biochem.Biophys., 136, 352 (1970).
187. J.Stauff, U.Sandler, and W.Jaeschke, "Chemiluminescence and Bioluminescence", New York, 1973, p.131.
188. R.Nilsson and D.R.Kearns, J.Phys.Chem., 78, 1681 (1974).
189. E.A.Mayeda and A.J.Bard, J.Amer.Chem.Soc., 96, 4023 (1974).
190. E.A.Mayeda and A.J.Bard, J.Amer.Chem.Soc., 95, 6223 (1973).
191. A.U.Khan, J.Amer.Chem.Soc., 99, 370 (1977).
192. W.C.Danen and R.L.Arudi, J.Amer.Chem.Soc., 100, 3944 (1978).
193. K.D.Legg and D.M.Hercules, J.Amer.Chem.Soc. 91, 1902 (1969).
194. A.M.Michelson, Biochemie, 55, 465 (1973).
195. V.Massey, S.Strickland, S.G.Mayhew, L.G.Howell, P.C.Engel, R.G.Matthews, M.Sehuman, and P.A.Sullivan, Biochem.Biophys.Res.Comm., 36, 891 (1969).
196. C.Beauchamp and I.Fridovich, Anal.Chem., 44, 276 (1971).
197. K.V.Rajagopalan and P.Handler, J.Biol.Chem., 239, 2022 (1964).
198. R.W.Miller, Canad.J.Chem.Biochem., 48, 935 (1970).
199. L.E.A.Henry, B.Halliwell, and D.O.Hall, FEBS Letters, 66, 303 (1976).
200. S.P.Vaish and G.Tollin, J.Bioenergetics, 2, 61 (1971).
201. M.Faraggi, P.Hemmerich, and I.Pecht, FEBS Letters, 51, 47 (1975).
202. D.E.Edmonson, F.Rizzuto, and G.Tollin, Photochem.Photobiol., 25, 445 (1977).
203. V.Favaudon, Europ.J.Biochem., 78, 293 (1977).
204. C.Bainy and P.Douzou, Biochem.Biophys.Res. Comm., 56, 386 (1974).
205. M.Nishikimi, N.A.Rao, and K.Yagi, Biochem. Biophys.Res.Comm., 46, 849 (1972).
206. J.M.McGord and I.Fridovich, Photochem.Photobiol., 17, 115 (1973).
207. B.Lippitt, J.M.McCord, and I.Fridovich, J.Biol. Chem., 247, 4688 (1972).

208. E.K.Hodgson and I.Fridovich, Biochemistry, **13**, 3811 (1974).
209. J.R.Harbour and M.L.Hair, J.Phys.Chem., **81**, 1791 (1977).
210. S.Marklund and G.Marklund, Europ.J.Biochem., **47**, 469 (1974).
211. H.P.Misra, J.Biol.Chem., **249**, 2151 (1974).
212. R.E.Heikkila and G.Cohen, Experientia, **31**, 169 (1974).
213. M.Nishikimi, Fed.Proc., **33**, 1256 (1974).
214. M.Nishikimi, Arch.Biochem.Biophys., **166**, 273 (1975).
215. H.P.Misra and I.Fridovich, Biochemistry, **15**, 681 (1976).
216. R.E.Heikkila and G.Cohen, Science, **181**, 456 (1973).
217. G.Cohen and R.E.Heikkila, J.Biol.Chem., **245**, 2447 (1974).
218. R.E.Heikkila and F.S.Cabbat, Res.Comm.Chem. Pathol.Pharm., **17**, 649 (1977).
219. W.Bors, E.Lengfelder, M.Saran, C.Michel, C.Fuchs, and C.Frenzel, Biochem.Biophys.Res. Comm., **75**, 973 (1977).
220. Y.Kono, Arch.Biochem.Biophys., **186**, 189 (1978).
221. B.Halliwell, Biochem.J., **163**, 441 (1977).
222. P.Walrant, R.Santus, and L.J.Grossweiner, Photochem.Photobiol., **22**, 63 (1975).
223. J.P.McCormick and T.Thomason, J.Amer.Chem. Soc., **100**, 312 (1978).
224. H.P.Misra and I.Fridovich, Arch.Biochem.Biophys., **181**, 308 (1977).
225. M.Nishikimi, H.Yamada, and K.Yagi, Photochem. Photobiol., **27**, 269 (1978).
226. J.A.Farrington, M.Ebert, E.J.Land, and K.Fletcher, Biochim.Biophys.Acta, **314**, 372 (1973).
227. A.G.Evans, N.K.Dodson, and N.H.Rees, J.Chem. Soc., Perkin Trans.II, 859 (1976).
228. L.K.Patterson, R.D.Small, and J.C.Scaiano, Radiat.Res., **72**, 218 (1977).
229. J.A.Farrington, M.Ebert, and E.J.Land, J.Chem. Soc., Faraday Trans.I, 665 (1978).
230. H.P.Misra and I.Fridovich, J.Biol.Chem., **247**, 3170 (1972).
231. T.Takabe, M.Miyakawa, and S.Nikai, Bull.Chem. Soc.Japan, **51**, 321 (1978).
232. W.Bors, C.Michel, M.Saran, and E.Lengfelder, Biochim.Biophys.Acta, **540**, 162 (1978).
233. G.L.Greenstock and R.W.Miller, Biochim.Biophys. Acta, **396**, 11 (1975).
234. W.Bors, M.Saran, C.Michel, E.Lengfelder, C.Fuchs, and R.Spoettl, Int.J.Rad.Biol., **28**, 353 (1975).
235. M.Nishikimi and L.J.Machlin, Arch.Biochem. Biophys., **170**, 684 (1975).
236. O.S.Brusov, A.M.Gerasimov, and L.F.Panchenko, Byul.Eksper.Biol.Med., **81**, 33 (1976).
237. S.Matsumoto and M.Matsuo, Tetrahedron Letters, 1999 (1977).
238. M.Nishikimi, Biochem.Biophys.Res.Comm., **63**, 463 (1975).
239. K.Puget and A.M.Michelson, Biochemie, **56**, 1255 (1974).
240. B.Halliwell and C.H.Foyer, Biochem.J., **155**, 697 (1976).
241. K.Asada and S.Kanematsy, Agr.Biol.Chem., **40**, 1891 (1976).
242. S.F.Yang, Biochemistry, **9**, 5008 (1970).
243. W.Bors, E.Lengfelder, M.Saran, C.Fuchs, and C.Michel, Biochem.Biophys.Res.Comm., **70**, 81 (1976).
244. K.Prema and K.P.Gopinathan, Biochem.J., **137**, 119 (1974).
245. A.Petkau, Canad.J.Chem., **49**, 1187 (1971).
246. B.Halliwell, FEBS Letters, **72**, 8 (1977).
247. A.Rigo, R.Stevanato, A.Finazzi-Argo, and G.Rotilio, FEBS Letters, **80**, 130 (1977).
248. J.J.van Hemmen and W.J.A.Meuling, Arch. Biochem.Biophys., **182**, 743 (1977).
249. J.W.Peters and C.S.Fote, J.Amer.Chem.Soc., **98**, 873 (1976).
250. K.-L.Fong, P.B.McCay, J.Poyer, H.R.Misra, and B.B.Keele, Chem.Biol.Interact., **15**, 77 (1977).
251. J.M.McCord and E.D.Day, FEBS Letters, **86**, 139 (1978).
252. R.L.Willson, J.Chem.Soc., Chem.Comm., 1005 (1970).
253. E.J.Land and A.J.Swallow, Biochim.Biophys.Acta, **234**, 34 (1971).
254. B.Chance and M.Erecinska, Arch.Biochem. Biophys., **143**, 675 (1971).
255. B.Chance, Disc.Faraday Soc., **17**, 120 (1954).
256. B.H.Bielski and P.C.Chan, J.Biol., **250**, 318 (1975).
257. M.C.Berman, C.M.Adnams, K.M.Ivanetch, and J.E.Keuch, Biochem.J., **157**, 237 (1976).
258. M.Faraggi and J.G.Leopold, Biochem.Biophys. Res.Comm., **50**, 413 (1973).
259. B.H.J.Bielski and H.W.Richter, J.Amer.Chem. Soc., **99**, 3019 (1977).
260. B.H.J.Bielski and P.C.Chan, J.Biol.Chem., **251**, 3841 (1976).
261. B.H.J.Bielski and J.M.Gebicki, Biochim.Biophys. Acta, **364**, 233 (1974).
262. Y.Sawada and Y.Yamazaki, Biochim.Biophys.Acta, **327**, 257 (1973).
263. D.Ballou, G.Palmer, and V.Massey, Biochem. Biophys.Res.Comm., 36,898 (1969).
264. M.Simic, I.A.Taub, J.Tocci, and P.A.Hurwith, Biochem.Biophys.Res.Comm., **62**, 161 (1975).
265. E.J.Land and A.J.Swallow, Arch.Biochem.Biophys., **145**, 365 (1971).
266. J.Butler, G.G.Jayson, and A.J.Swallow, Biochim. Biophys.Acta, **408**, 215 (1975).
267. H.Seki, Y.A.Ilan, Y.Ilan, and G.Stein, Biochim. Biophys.Acta, **440**, 573 (1976).
268. W.H.Koppenol, K.J.H.van Buuren, J.Butler, and R.Braams, Biochim.Biophys.Acta, **449**, 157 (1976).
269. H.C.Sutton, P.B.Roberts, and C.C.Winterbourn, Biochem.J., **155**, 503 (1976).
270. "Enzyme Nomenclature, Recommendations of IUPAC and IUB", Elsevier, Amsterdam, 1972.
271. J.M.McCord and I.Fridovich, J.Biol.Chem., **243**, 5753 (1968).
272. J.M.McCord and I.Fridovich, J.Biol.Chem., **244**, 6049 (1969).
273. W.H.Orme-Johnson and H.Beinert, Biochem. Biophys.Res.Comm., **36**, 905 (1969).
274. H.Komai, V.Massey, and G.Palmer, J.Biol. Chem., **244**, 1692 (1969).
275. I.Fridovich, J.Biol.Chem., **245**, 4053 (1970).
276. H.P.Misra and I.Fridovich, J.Biol.Chem., **246**, 6886 (1971).

277. J.S.Olson, D.P.Ballou, G.Palmer, and V.Massey, J.Biol.Chem., **249**, 4350 (1974).
278. J.S.Olson, D.P.Ballou, G.Palmer, and V.Massey, J.Biol.Chem., **249**, 4363 (1974).
279. E.K.Hodgson and I.Fridovich, Biochim.Biophys. Acta, **430**, 182 (1976).
280. E.K.Hodgson and I.Fridovich, Arch.Biochem. Biophys., **172**, 202 (1976).
281. R.Nilsson, F.M.Pick, and R.C.Bray, Biochim. Biophys.Acta, **192**, 145 (1969).
282. V.Massey, G.Palmer, and D.Ballou, "Flavins, Flavoproteins, III Int.Symp"., Univ.Park Press, Baltimore, 1971, p.349.
283. P.Hemmerich and A.Wessiak, "Flavins, Flavoproteins, V Int.Symp"., Elsevier, Amsterdam, 1976, p.9.
284. C.Kemal, T.W.Chan, and T.C.Bruce, J.Amer. Chem.Soc., 99, 7272 (1977).
285. J.M.McCord and I.Fridovich, J.Biol.Chem., **245**, 1374 (1970).
286. H.P.Misra and I.Fridovich, J.Biol.Chem., **247**, 188 (1972).
287. S.Nakamura, Biochem.Biophys.Res.Comm., **41**, 177 (1970).
288. S.Nakamura and T.Kimura, J.Biol.Chem., **247**, 6462 (1972).
289. S.Nakamura and I.Yamazaki, Biochim.Biophys. Acta, **189**, 29 (1969).
290. S.D.Aust, D.L.Roerig, and T.C.Pederson, Biochem.Biophys.Res.Comm., **47**, 1133 (1972).
291. M.Nakano, T.Noguchi, Y.Tsutsumi, K.Sugioka, Y.Shimizu, Y.Tsuji, and H.Inaba, Proc.Soc.Exp. Biol.Med., **147**, 140 (1974).
292. I.Ishiguro, R.Shinohara, A.Ishikura, and J.Naito, Cherm.Pharm.Bull., **222**, 2935 (1974).
293. B.Chance and J.S.Leigh, Proc.Nat.Acad.Sci.USA, 74, 4777 (1977).
294. G.A.Hamilton, R.D.Libby, and C.R.Hartzell, Biochem.Biophys.Res.Comm., **55**, 333 (1973).
295. G.A.Hamilton, P.K.Adolf, J.de Jersey, G.C.Du Bois, G.R.Dyrkacz, and R.D.Libby, J.Amer.Chem.Soc., **100**, 1899 (1978).
296. L.D.Kwiatkowski and D.J.Kosman, Biochem. Biophys.Res.Comm., **53**, 715 (1973).
297. T.Kido, K.Asada, and K.Soda, J.Biol.Chem., **253**, 226 (1978).
298. H.J.Forman and J.A.Kennedy, Biochem.Biophys. Res.Comm., 60, 1044 (1974).
299. H.J.Forman and J.A.Kennedy, J.Biol.Chem., **250**, 4332 (1975).
300. H.J.Forman and J.A.Kennedy, Arch.Biochem. Biophys., 173, 219 (1976).
301. E.J.Land and A.J.Swallow, Biochim.Biophys.Acta, **234**, 34 (1971).
302. B.H.J.Bielski and P.C.Chan, Arch.Biochem. Biophys., **159**, 873 (1973).
303. P.C.Chan and B.H.J.Bielski, J.Biol.Chem., **249**, 1317 (1974).
304. F.O.Brady, H.J.Forman, and P.Feigelson, J.Biol.Chem., **246**, 7119 (1971).
305. F.Hirata and O.Hayaishi, J.Biol.Chem., **246**, 7825 (1971).
306. O.Hayaishi, Y.Ishimura, H.Fujisawa, and M.Nozaki, "Oxidases and Related Redox Systems", 1973, Vol.1, p.125.
307. F.Hirata, S.Nomiyama, and O.Hayaishi, Acta Vitaminol., **29**, 288 (1976).
308. T.Taniguchi, F.Hirata, and O.Hayaishi, J.Biol. Chem., **252**, 2774 (1977).
309. O.Hayaishi, F.Hirata, T.Ohnishi, J.-P.Henry, I.Rosenthal, and A.Katoh, J.Biol.Chem., **252**, 3548 (1977).
310. F.Hirata, T.Ohnishi, and O.Hayaishi, J.Biol. Chem., **252**, 4637 (1977).
311. T.Ohnishi, F.Hirata, and O.Hayaishi, J.Biol. Chem., **252**, 4643 (1977).
312. A.Michelson and M.F.Isambert, Biochemie, 55, 619 (1973).
313. S.Dupre, G.Federici, L.Santoro, F.Rossi, and D.Gavallini, Mol.Cell.Biochem., 9, 149 (1975).
314. K.R.Prema, S.D.Rabindranath, C.S.Vaidyanathan, and N.A.Rao, Biochem.Biophys.Res.Comm., 48, 1049 (1972).
315. S.D.Rabindranath, A.A.Kumar, R.P.Kumar, C.S.Vaidyanathan, and N.A.Rao, Arch.Biochem. Biophys., 165, 478 (1974).
316. S.Strickland and V.Massey, "Oxidases and Related Redox Systems", Wiley and Sons, New York, 1973, Vol.1, p.189.
317. S.A.Coscin and I.Fridovich, Arch.Biochem.Biophys., **153**, 778 (1972).
318. K.P.Prema, S.D.Ravindranath, C.S.Vaidyanathan, and N.A.Rao, Biochem.Biophys.Res.Comm., 49, 1422 (1972).
319. T.Z.Lin, J.-T.Shen, and W.F.Ganong, Proc.Soc. Exp.Biol.Med., **146**, 37 (1974).
320. H.W.Strobel and M.J.Coon, J.Biol.Chem., **246**, 7826 (1971).
321. M.J.Coon and T.van der Hoeven, IX Int.Congr. Biochem., Stockholm, 1973, p.7Sc3.
322. M.J.Coon, A.P.Autor, R.F.Boyer, E.T.Lode, and H.W.Strobel, "Oxidases and Related Redox Systems", Wiley, New York, 1973, Vol.2, p.529.
323. S.G.Sligar, J.D.Lipscomb, P.G.Debrunner, and I.C.Gunsalez, Biochem.Biophys.Res.Comm., 61, 290 (1974).
324. S.G.Sligar and P.Debrunner, Fed.Proc., 33, 1256 (1974).
325. J.D.Lipscomb, S.G.Sligar, M.J.Namtvedt, and I.C.Gunsalez, J.Biol.Chem., **251**, 1116 (1976).
326. T.Ueda and M.J.Coon, J.Biol.Chem., **247**, 5010 (1972).
327. S.W.May and B.J.Abbott, J.Biol.Chem., 248, 172 (1973).
328. S.W.May, B.J.Abbott, and A.Felix, Biochem. Biophys.Res.Comm., **54**, 1540 (1973).
329. A.J.Paine and A.E.M.McLean, Biochem.Biophys. Res.Comm., 58, 482 (1974).
330. A.J.Paine and A.E.M.McLean, Biochem.Soc. Trans., **2**, 605 (1974).
331. I.Yamazaki and L.H.Piette, Biochim.Biophys. Acta, 77, 47 (1963).
332. J.Peisach, W.E.Blumberg, B.A.Wittenberg, and J.B.Wittenberg, J.Biol.Chem., **243**, 1871 (1968).
333. T.Odajima and I.Yamazaki, Biochim.Biophys.Acta, **206**, 77 (1970).
334. T.Odajima, Biochim.Biophys.Acta, 235, 52 (1971).
335. T.Odajima and I.Yamazaki, Biochim.Biophys.Acta, **284**, 355 (1972).
336. B.Halliweli and S.Ahluwalia, Biochem.J., **153**, 513 (1976).
337. G.Rotilio, G.Falcioni, E.Fioretti, and M.Brunori, Biochem.J., **145**, 405 (1975).
338. B.H.J.Bielski, D.A.Comstock, A.Haber, and P.C.Chan, Biochim.Biophys.Acta, 350, 113 (1974).

339. I. Yamazaki and K. Yokota, Moll. Cell Biochem., **2**, 39 (1973).
340. K. Yokota and I. Yamazaki, Biochemistry, **16**, 1913 (1977).
341. K. Takayama and M. Nakano, Biochemistry, **16**, 1921 (1977).
342. B. Halliwell, Planta, **140**, 81 (1978).
343. B. Halliwell, FEBS Letters, **80**, 291 (1977).
344. C. Deby, Arch. Int. Physiol. Biochem., **84**, 867 (1976).
345. I. Pecht and M. Goldberg, Fast Proc. Rad. Chem. Biol., 1975, p. 277.
346. O. Dionisi, T. Galeotti, T. Terranova, and A. Azzi, Biochim. Biophys. Acta, **403**, 292 (1975).
347. G. Loschen, A. Azzi, C. Richter, and L. Flohe, FEBS Letters, **42**, 68 (1974).
348. A. Boveris and V. E. Bechis, Rev. Soc. Argent. Biol., **50**, 38 (1974).
349. A. Boveris and E. Cadenas, FEBS Letters, **54**, 311 (1975).
350. D. D. Tyler, Biochim. Biophys. Acta, **396**, 335 (1975).
351. D. N. Nelson and A. Ruhmann-Wehnhold, J. Clin. Invest., **56**, 1062 (1975).
352. V. M. Mishin, A. G. Pokrovskii, and V. V. Lyakhovich, Biokhimiya, **41**, 763 (1976).
353. H. Nohl and D. Hegner, Europ. J. Biochem., **82**, 862 (1978).
354. H. Ninnemann, R. J. Strasser, and W. L. Butler, Photochem. Photobiol., **26**, 41 (1977).
355. A. Boveris, E. Cadenas, and A. O. M. Stoppani, Biochem. J., **156**, 435 (1976).
356. E. Cadenas, A. Boveris, C. I. Ragan, and A. O. M. Stoppani, Arch. Biochem. Biophys., **180**, 248 (1977).
357. H. A. Sasame, J. R. Mitchell, and J. R. Gillette, Fed. Proc., **34**, 729 (1975).
358. C. Richter, A. Azzi, U. Weser, and A. Wendel, J. Biol. Chem., **252**, 5061 (1977).
359. C. Auclair, D. DeProst, and J. Hakim, Biochem. Pharmacol., **27**, 355 (1978).
360. V. V. Lyakhovich, V. M. Mishin, and A. G. Pokrovskii, Biokhimiya, **42**, 1323 (1977).
361. G. M. Bartoli, T. Galeotti, G. Palombini, G. Parisi, and A. Azzi, Arch. Biochem. Biophys., **184**, 276 (1977).
362. C. Auclair, M. Torres, and J. Hakim, FEBS Letters, **89**, 26 (1978).
363. P. R. Rich and W. D. Bonner, Arch. Biochem. Biophys., **188**, 206 (1978).
364. E. M. Gregory, F. J. Yost, and I. Fridovich, J. Bacteriol., **115**, 987 (1973).
365. J. A. Fee and R. L. Ward, Biochem. Biophys. Res. Comm., **71**, 427 (1976).
366. E. K. Hodgson and I. Fridovich, Biochemistry, **14**, 5294 (1975).
367. M. E. Adam, E. M. Fielden, F. Lavelle, L. Calabrese, D. Cocco, and G. Rotilio, Biochem. J., **167**, 271 (1977).
368. E. M. Fielden, P. B. Roberts, R. C. Bray, and G. Rotilio, Biochem. Soc. Trans., **1**, 52 (1973).
369. E. K. Hodgson and I. Fridovich, Biochem. Biophys. Res. Comm., **54**, 270 (1973).
370. M. A. Symonyan and R. M. Nalbandyan, Biochem. Biophys. Res. Comm., **71**, 1131 (1971).
371. A. Rigo, P. Viglino, and G. Rotilio, Biochem. Biophys. Res. Comm., **63**, 1013 (1975).
372. A. Rigo, R. Stevanato, P. Viglino, and G. Rotilio, Biochem. Biophys. Res. Comm., **79**, 776 (1977).
373. D. Klug, J. Rabani, and I. Fridovich, J. Biol. Chem., **247**, 4839 (1972).
374. J. Rabani, D. Klug, and I. Fridovich, Isr. J. Chem., **10**, 1095 (1972).
375. D. Klug-Roth, I. Fridovich, and J. Rabani, J. Amer. Chem. Soc., **95**, 2786 (1973).
376. E. M. Fielden, P. B. Roberts, R. C. Gray, D. J. Lowe, G. N. Mautner, G. Rotilio, and L. Calabrese, Biochem. J., **139**, 49 (1974).
377. A. Rigo, R. Tomat, and G. Rotilio, J. Electroanal. Chem., **57**, 291 (1974).
378. H. J. Forman and I. Fridovich, Arch. Biochem. Biophys., **158**, 396 (1973).
379. R. Brigelius, H. J. Hartmann, W. Bors, M. Saran, E. Lengfelder, and U. Weser, Z. Physiol. Chem., **356**, 739 (1975).
380. M. Pick, J. Rabani, F. Yost, and I. Fridovich, J. Amer. Chem. Soc., **96**, 7329 (1974).
381. M. E. McAdam, R. A. Fox, F. Lavelle, and E. M. Fielden, Biochem. J., **165**, 71 (1977).
382. F. Lavelle, M. E. McAdam, and E. M. Fielden, Biochem. J., **161**, 3 (1977).
383. J. K. Howie, M. M. Morrison, and D. T. Sawyer, ACS Symp. Ser., 97 (1977).
384. A. Rigo, P. Viglino, G. Rotilio, and R. Tomat, FEBS Letters, **50**, 86 (1975).
385. M. E. McAdam, Biochem. J., **161**, 697 (1977).
386. M. A. Symonyan and R. M. Nalbandyan, FEBS Letters, **28**, 22 (1972).
387. E. K. Hodgson and I. Fridovich, Biochemistry, **14**, 5299 (1975).
388. B. Halliwell, FEBS Letters, **56**, 34 (1975).
389. L. Cleveland and L. Davis, Biochim. Biophys. Acta, **341**, 517 (1974).
390. K. Kovacs and B. Matkovitcs, Enzyme, **20**, 1 (1975).
391. K. E. Joester, G. Jung, U. Weber, and U. Weser, FEBS Letters, **25**, 28 (1972).
392. M. Younes and U. Weser, FEBS Letters, **71**, 87 (1976).
393. J. K. Howie and D. T. Sawyer, J. Amer. Chem. Soc., **98**, 6698 (1976).
394. E. T. Seo, T. L. Riechel, and D. T. Sawyer, Inorg. Chem., **16**, 734 (1977).
395. A. F. Argo, C. Grovagnoli, P. DeSole, L. Calabrese, G. Rotilio, and B. Mondoni, FEBS Letters, **21**, 183 (1972).
396. W. Paschen and U. Weser, Biochim. Biophys. Acta, **327**, 217 (1973).
397. K. Goda, T. Kimura, A. L. Thaler, K. Kees, and A. P. Schaap, Biochem. Biophys. Res. Comm., **58**, 660 (1974).
398. A. P. Schaap, A. L. Thaler, G. R. Faler, K. Goda, and T. Kimura, J. Amer. Chem. Soc., **96**, 4025 (1974).
399. U. Weser, W. Paschen, and M. Younes, Biochem. Biophys. Res. Comm., **62**, 769 (1975).
400. C. Richter, A. Wendel, U. Weser, and A. Azzi, FEBS Letters, **51**, 300 (1975).
401. W. Paschen and U. Weser, Z. Physiol. Chem., **356**, 727 (1975).
402. M. Younes and U. Weser, FEBS Letters, **61**, 209 (1976).
403. K. Asada and K. Kiso, Europ. J. Biochem., **33**, 253 (1973).
404. K. Asada, K. Kiso, and K. Yoshikawa, J. Biol. Chem., **249**, 2175 (1974).
405. K. Asada and K. Kiso, Agr. Biol. Chem., **37**, 453 (1973).

406. B.L.Epel and J.Neumann, Biochim.Biophys.Acta, **325**, 520 (1973).
407. J.R.Harbour and J.R.Bolton, Biochem.Biophys. Res.Comm., 64, 803 (1975).
408. F.Boucher and G.Gingras, Biochem.Biophys.Res. Comm., 67, 421 (1975).
409. E.F.Elstner, C.Stoffer, and A.Heupel, Z. Naturforsch., 30c, 53 (1975).
410. J.F.Allen, Biochem.Biophys.Res.Comm., 66, 36 (1975).
411. L.S.Jahnke and A.W.Frenkel, Biochem.Biophys. Res.Comm., 66, 144 (1975).
412. J.Lumsden and D.O.Hall, Biochem.Biophys. Res.Comm., 64, 595 (1975).
413. B.Halliwell, Europ.J.Biochem., 55, 355 (1975).
414. J.F.Allen and D.O.Hall, Biochem.Biophys.Res. Comm., **52**, 856 (1973).
415. J.F.Allen and D.O.Hall, Biochem.Biophys.Res. Comm., 58, 579 (1974).
416. S.Asami and T.Akazawa, Biochemistry, **16**, 2202 (1977).
417. Y.Orii and D.A.Webster, Plant.Cell Physiol., 18, 521 (1977).
418. J.H.Bayston, N.K.King, F.D.Looney, and M.E.Winfield, J.Amer.Chem.Soc., 91, 2775 (1969).
419. B.M.Hoffman, D.L.Diemente, and F.Basolo, J.Amer.Chem.Soc., **92**, 61 (1970).
420. F.A.Walker, J.Amer.Chem.Soc., **92**, 4235 (1970).
421. S.A.Cockle, H.O.Hill, and R.J.P.Williams, Inorg.Nuclear Chem.Letters, 6, 131 (1970).
422. E.Melamud, B.L.Silver, and Z.Dori, J.Amer. Chem.Soc., 96, 4689 (1974).
423. H.C.Stynes and J.A.Ibers, J.Amer.Chem.Soc., 94, 5125 (1972).
424. D.V.Stynes, H.C.Stynes, J.A.Ibers, and B.R.James, J.Amer.Chem.Soc., 95, 1142 (1973).
425. F.A.Walker, J.Amer.Chem.Soc., 95, 1154 (1973).
426. M.J.Carter, D.P.Rillema, and F.Basolo, J.Amer. Chem.Soc., **96**, 392 (1974).
427. J.P.Collman, R.R.Gagne, J.Kouba, and H.Ljusberg-Wahren, J.Amer.Chem.Soc., 96, 6800 (1974).
428. B.M.Hoffman and D.H.Petering, Proc.Nat.Acad. Sci.USA, 67, 637 (1970).
429. J.C.W.Chien and L.C.Dickinson, Proc.Nat.Acad. Sci.USA, 69, 2783 (1972).
430. T.Yonetani, H.Yamamoto, and T.Iizuka, J.Biol. Chem., **249**, 2168 (1974).
431. B.M.Hoffman, T.Szymanski, and F.Basolo, J.Amer.Chem.Soc., 97, 673 (1975).
432. D.Getz, E.Melamud, and B.L.Silver, J.Amer. Chem.Soc., 97, 3846 (1975).
433. L.Pauling and C.D.Coyell, Proc.Nat.Acad.Sci. USA, **22**, 210 (1933).
434. L.Pauling, Nature, **203**, 182 (1964).
435. C.H.Barlow, J.C.Maxwell, W.J.Wallace, and W.S.Caughey, Biochem.Biophys.Res.Comm., 55, 91 (1973).
436. J.C.Maxwell, J.A.Volpe, C.H.Barlow, and W.S.Caughey, Biochem.Biophys.Res.Comm., 58, 166 (1974).
437. J.P.Collman, R.R.Gagne, C.A.Reed, T.R.Halbert, G.Lang, and W.T.Robinson, J.Amer.Chem.Soc., 97, 1427 (1975).
438. J.J.Weiss, Nature, **202**, 83 (1964).
439. J.J.Weiss, Nature, **203**, 183 (1964).
440. J.B.Wittenberg, B.A.Wittenberg, J.Peisach, and W.E.Blumberg, Proc.Nat.Acad.Sci.USA, 67, 1846 (1970).
441. Y.Yshimura, V.Ullrich, and J.A.Peterson, Biochem.Biophys.Res.Comm., **42**, 140 (1971).
442. H.Schleyer, D.Y.Cooper, and O.Rosenthal, "Oxidases and Related Redox Systems" 1973, Vol.1, p.469.
443. J.P.Collman, J.I.Brauman, T.R.Halbert, and K.S.Susliok, Proc.Nat.Acad.Sci.USA, 73, 333 (1976).
444. A.S.Koster, J.Chem.Phys., 63, 3284 (1975).
445. G.C.Wagner and R.J.Kassner, J.Amer.Chem. Soc., 96, 5593 (1974).
446. W.S.Brinigar and C.K.Chang, J.Amer.Chem.Soc., 96, 5595 (1974).
447. W.S.Brinigar, C.K.Chang, J.Geibel, and T.G.Tralor, J.Amer.Chem.Soc., 96, 5597 (1974).
448. D.L.Anderson, C.J.Weschler, and F.Basolo, J.Amer.Chem.Soc., 96, 5599 (1974).
449. J.Almug, J.E.Baldin, R.L.Dyer, J.Huff, and C.J.Wilkerson, J.Amer.Chem.Soc., 96, 5600 (1974).
450. C.K.Chang and T.G.Traylor, Biochem.Biophys. Res.Comm., 62, 729 (1975).
451. H.P.Misra and I.Fridovich, J.Biol.Chem., **247**, 6960 (1972).
452. R.Wever, B.Oudega, and B.F.van Gelder, Biochim.Biophys.Acta, **302**, 475 (1973).
453. M.Brubori, G.Falcioni, E.Fioretti, B.Giardina, and G.Rotilio, Europ.J.Biochem., 53, 99 (1975).
454. T.Cotoh and K.Shikama, J.Biochem., 80, 397 (1976).
455. B.Goldberg and A.Stern, J.Biol.Chem., **250**, 2401 (1975).
456. W.J.Wallace and W.S.Caughey, Biochem.Biophys. Res.Comm., 63, 561 (1975).
457. O.Augusto and G.Cilento, Arch.Biochem.Biophys. 168, 549 (1975).
458. B.Goldberg, A.Stern, and J.Peisach, J.Biol. Chem., **251**, 3045 (1976).
459. B.Goldberg and A.Stern, Biochim.Biophys.Acta, **437**, 628 (1976).
460. E.W.Abell, J.M.Pratt, R.Whelan, and P.J.Wilkinson, J.Amer.Chem.Soc., 96, 7120 (1974).
461. L.S.Demma and J.M.Salhany, J.Biol.Chem., **252**, 1226 (1977).
462. W.J.Wallace, J.C.Maxwell, and W.S.Caughey, Biochem.Biophys.Res.Comm., 57, 1104 (1974).
463. A.E.Myshkin, V.N.Chibrikin, and L.A.Piruzyan, Zhur.Obshch.Khim., 45, 1624 (1975).
464. A.Azzi, C.Montecucco, and C.Richter, Biochem. Biophys.Res.Comm., 65, 597 (1975).
465. K.A.Markossian and R.M.Nalbandyan, Biochem. Biophys.Res.Comm., 67, 870 (1975).
466. R.H.Cassell and I.Fridovich, Biochemistry, 14, 1866 (1975).
467. C.C.Winterbourn, B.M.McGrath, and R.W.Carrell, Biochem.J., 155, 493 (1976).
468. D.Haristoy, Report IPNO-T-76-04 (1976); Chem. Abs., 87, 97671 (1977).
469. Y.A.Ilan, J.Rabani, and G.Czapski, Biochim. Biophys.Acta, 446, 277 (1976).
470. R.E.Lynch, G.R.Lee, and G.E.Cartwright, J.Biol.Chem., **251**, 1015 (1976).
471. R.E.Lynch, J.E.Thomas, and G.R.Lee, Biochemistry, 16, 4563 (1977).

472. J.Ellis and J.M.Pratt, Chem.Comm., 781 (1973).
473. H.A.O.Hill and D.R.Turner, Biochem.Biophys. Res.Comm., 56, 739 (1974).
474. S.V.Prigoda, A.A.Shteinman, and I.B.Afanas'ev, Koord.Khim., 3, 1684 (1977).
475. I.B.Afanas'ev and S.V.Prigoda, Koord.Khim., (in the Press).
476. S.V.Prigoda and I.B.Afanas'ev, Koord.Khim., 4, 1386 (1978).
477. J.Butler, G.G.Jayson, and A.J.Swallow, J.Chem. Soc., Faraday Trans.I, 13 (1976).
478. I.B.Afanas'ev, S.V.Prigoda, A.M.Khenkin, and A.A.Shteinman, Dokl.Akad.Nauk SSSR, **236**, 641 (1977).
479. J.S.Valentine and A.E.Quinn, Inorg.Chem., **15**, 1997 (1976).
480. J.S.Valentine, Y.Tatsuno, and M.Nappa, J.Amer. Chem.Soc., 99, 3522 (1977).
481. E.M.Gregory and I.Fridovich, J.Bacteriol., **114**, 543 (1973).
482. E.M.Gregory and I.Fridovich, J.Bacteriol., **114**, 1193 (1973).
483. H.M.Hassan and I.Fridovich, J.Bacteriol., **129**, 1574 (1977).
484. E.M.Gregory, S.A.Coscin, and I.Fridovich, J.Bacteriol., **117**, 456 (1974).
485. B.W.Bonta, E.R.Gawron, and J.B.Warshaw, Pediatr.Res., 11, 754 (1977).
486. K.Utsumi, T.Yoshioka, N.Yamanaka, and T.Nakazawa, FEBS Letters, 79, 1 (1977).
487. F.J.Yost and I.Fridovich, Arch.Biochem.Biophys., **175**, 514 (1976).
488. H.P.Misra and I.Fridovich, Arch.Biochem. Biophys., **176**, 577 (1976).
489. L.W.Oberley, A.L.Lingren, S.A.Baker, and R.H.Stevens, Radiation Res., 68, 320 (1976).
490. A. Petkau, K.Kelly, W. Schelak, S.D. Plescach, C.Barefoot, and B.E.Meeker, Biochem.Biophys. Res.Comm., 67, 1167 (1975).
491. A. Petkau, K.Kelly, W. Schelak, and C. Barefoot, Biochem.Biophys.Res.Comm., 70, 452 (1976).
492. A. Petkau and W. Schelak, Biochim. Biophys. Acta, **433**, 445 (1976).
493. A. Petkau, W. Schelak, and S. D. Pleskach, Life Sci., **22**, 867 (1978).
494. J.D.Crapo and D.Tierney, Amer.J.Physiol., **226**, 1401 (1974).
495. R.S.Bhatnagar, Biochem.Eff.Environ Pollut., 47 (1977).
496. A.P.Autor, Life Sci., **14**, 1309 (1974).
497. M.R.Montgomery, Res.Comm.Chem.Path.Pharm., 16, 155 (1977).
498. J.A.Farrington, Proc.XIII British Weed Control Conf.ICI Ltd., Bracknell, Berks, 1976, Vol.1, p.225
499. G.N.Giannopolitis and S.K.Ries, Weed Sci., **25**, 298 (1977).
500. M.G.Saifer, L.D.Williams, and W.Huber, US P.4 022 224 (1977); Chem.Abs., 87, 48777 (1977).
501. F.Lavelle, A.M.Michelson, and L.Dimitrijevic, Biochem.Biophys.Res.Comm., **55**, 350 (1973).
502. R.M.Leipzig, G.J.Brewer, and W.C.Kruckeberg, Prog.Clin.Biol.Res., 1, 711 (1975).
503. J.J.van Hemmen and W.J.A.Meuling, Biochim. Biophys.Acta, **402**, 133 (1975).
504. J.A.Fee and H.D.Teitelbaum, Biochem.Biophys. Res.Comm., 49, 150 (1972).
505. T.C.Pederson and S.D.Aust, Biochem.Biophys. Res.Comm., 48, 798 (1972).
506. R.Zimmermann, L.Flohe, U.Weser, and H.J.Hartmann, FEBS Letters, **29**, 1017 (1973).
507. T.C.Pederson and S.D.Aust, Biochem.Biophys. Res.Comm., **52**, 1071 (1973).
508. J.S.Bus, S.D.Aust, and J.E.Gibson, Biochem. Biophys.Res.Comm., 58, 749 (1974).
509. U.Takahama and M.Nishimura, Plant Cell Physiol., 17, 111 (1976).
510. J.M.C.Cutteridge, Biochem.Biophys.Res.Comm., 77, 379 (1977).
511. I.M.Goldstein and G.Weissman, Biochem.Biophys. Res.Comm., 75, 604 (1977).
512. M.N.Merzlyak, S.G.Yuferova, and A.S.Sobolev, Biofizika, **22**, 846 (1977).
513. T.Noguehi and N.Nakano, Biochim.Biophys.Acta, 368, 446 (1974).
514. D.D.Tyler, FEBS Letters, 51, 180 (1975).
515. L.L.Smith, M.J.Kulig, and J.I.Teng, Chem.Phys. Lipids, 20, 211 (1977).
516. B.Goldberg and A.Stern, J.Biol.Chem., **251**, 6468 (1976).
517. A.Valenzuela, H.Rios, and G.Neiman, Experientia, 33, 962 (1977).
518. B.Goldberg and A.Stern, Arch.Biochem.Biophys., 178, 218 (1977).
519. B.Goldberg and A.Stern, Acta Biol.Med.Cer., 36, 731 (1977).
520. A.M.Michelson and P.Durosay, Photochem. Photobiol., **25**, 55 (1977).
521. E.W.Kellogg and I.Fridovich, J.Biol.Chem., **252**, 6721 (1977).
522. R.E.Lynch and I.Fridovich, J.Biol.Chem., **253**, 1838 (1978).
523. E.Dybing, S.D.Nelson, J.R.Mitchell, H.A.Sasame, and J.R.Gillette, Mol.Pharm., 12, 911 (1976).
524. R.Docampo, F.S.Cruz, A.Boveris, R.P.A.Muniz, and D.M.S.Esquivel, Arch.Biochem.Biophys., 186, 292 (1978).
525. J.M.McCord, Science, 185, 529 (1974).
526. Y.Oyanagui, Biochem.Pharm., **25**, 1465 (1976).
527. Y.Oyanagui, Biochem.Pharm., **25**, 1473 (1976).
528. I.M.Goldstein, D.Roos, G.Weissmann, and H.B.Kaplan, Inflammation, 1, 305 (1976).
529. U.Weser, C.Richter, A.Wendel, and M.Younes, Bioinorg.Chem., 8, 201 (1978).
530. M.Younes and U.Weser, Biochem.Biophys.Res. Comm., 78, 1247 (1977).
531. Y.Oyanagui, Biochem.Pharm., **26**, 473 (1977).
532. R.I.Handin, R.Karabin, and G.J.Boxer, J.Clin. Invest., 59, 957 (1977).
533. D.D.Tyler, IX Int.Congress on Biochemistry, Stockholm, 1973, p.231.
534. D.M.Williams, G.R.Lee, and G.E.Cartwright, J.Clin.Invest., 53, 665 (1974).
535. A.M.Michelson and M.E.Buckingham, Biochem. Biophys.Res.Comm., 58, 1079 (1974).
536. J.E.Biaglow, B.E.Jacobson, and O.F.Nugaard, Cancer Res., 37, 3306 (1977).
537. A.V.Peskin, I.B.Zbarskii, and A.A.Konstantinov, Dokl.Akad.Nauk SSSR, **229**, 751 (1976).
538. V.Z.Lankin and S.M.Gurevich, Dokl.Akad.Nauk SSSR, **226**, 705 (1976).
539. R.H.Wickramasinghe, P.R.K.Reddy, L.Klein, and C.A.Villee, Clin.Biochem., 9, 24 (1976).

540. G.M.Bartoli, T.Galeotti, and A.Azzi, Biochim. Biophys.Acta, 497, 622 (1977).
541. A.Petkau, L.G.Monasterski, K.Kelly, and H.G.Friesen, Res.Comm.Chem.Pathol.Pharm., 17, 125 (1977).
542. A.V.Peskin, Ya.M.Koen, I.B.Zbarsky, and A.A.Konstantinov, FEBS Letters, 11 (1977).
543. S.K.Sahu, L.W.Oberley, R.H.Stevens, and E.F.Riley, J.Nat.Cancer Inst., 58, 1125 (1977).
544. R.Ishida and T.Takahashi, Biochem.Biophys.Res. Comm., 66, 1432 (1975).
545. K.Handa and S.Sato, Gann, 66, 47 (1975).
546. S.Sato, M.Iwaizumi, K.Handa, and Y.Tamura, Gann, 68, 603 (1977).
547. N.R.Bachur, S.L.Gordon, and M.V.Gee, Mol. Pharm., 13, 901 (1977).
548. W.S.Thaler, Chem.Biol.Interactions, 19, 265 (1977).
549. J.Goodman and P.Hochstein, Biochem.Biophys.Res. Comm., 77, 797 (1977).
550. I.B.Afanas'ev, N.I.Polozova, and G.I.Samokhvalov, Bioorganic Chemistry (in the Press).
551. M.Gosalvez, M.Blanco, J.Hunter, M.Miko, and B.Chance, Europ.J.Cancer, 10, 567 (1974).
552. Y.Yamamoto, I.L.Hansen, T.H.Porter, and K.Folkers, Biochem.Biophys.Res.Comm., 58, 633 (1974).
553. B.M.Babior, B.S.Kipnes, and J.T.Curnutte, J.Clin.Invest., 52, 741 (1973).
554. R.B.Johnston, B.Keele, L.Webb, D.Kessler, and K.V.Rajagopalan, J.Clin.Invest., 52, 44a (1973).
555. I.Fridovich and N.England, J.Med., 290, 624 (1974).
556. R.C.Allen, S.J.Yevich, R.W.Orth, and R.H.Steele, Biochem.Biophys.Res.Comm., 60, 909 (1974).
557. A.Nakagawara and S.Minakami, Biochem.Biophys. Res.Comm., 64, 760 (1975).
558. D.B.Brath and M.L.Karnovsky, J.Exp.Med., 141, 257 (1975).
559. R.B.Johnston, B.B.Keele, H.P.Misra, J.E.Lehmeyer, L.S.Webb, R.L.Baehner, and K.V.Rajagopalan, J.Clin.Invest., 55, 1357 (1975).
560. R.B.Johnston, B.B.Keele, H.P.Misra, J.E.Lehmeyer, and L.S.Webb, "Phagocytic Cell Host Resistance", New York, 1975, p.61.
561. M.L.Salin and J.M.McCord, J.Clin.Invest., 56, 1319 (1975).
562. R.S.Weening, R.Wever, and D.Loos, J.Lab.Clin. Med., 85, 245 (1975).
563. R.B.Johnston, J.E.Lehmeyer, and L.A.Curthrie, J.Exp.Med., 146, 1551 (1976).
564. S.Weiss, G.Kling, and A.L.Buglio, Clin.Res., 23, 497a (1975).
565. M.-F.Tsan, B.Newman, and P.A.McIntyre, Br.J. Haematol., 33, 189 (1976).
566. L.R.DeChatelet, D.Mulliken, and C.E.McCall, J.Infect.Dis., 131, 443 (1975).
567. L.D.DeChatelet, P.S.Shirley, L.McPhail, C.C.Huntley, H.B.Muss, and D.A.Bass, Blood, 50, 525 (1977).
568. D.B.Drath and M.L.Karnovsky, J.Exp.Med., 141, 257 (1975).
569. M.Rister and R.L.Baehuer, Br.J.Haematol., 36, 241 (1977).
570. F.J.Yost and I.Fridovich, Arch.Biochem.Biophys., 161, 395 (1974).
571. A.J.Marcus, S.T.Silk, L.B.Safier, and H.L.Ullman, J.Clin.Invest., 59, 149 (1977).
572. B.M.Babior, J.T.Curnutte, and R.S.Kipnes, J.Lab.Clin.Med., 85, 235 (1975).
573. W.J.Litchfield and W.W.Wells, Arch.Biochem. Biophys., 188, 26 (1978).
574. L.R.DeChatelet, P.S.Shirley, P.R.Goodman, and C.E.McCall, Antimicrob.Agents Chemother., 8, 146 (1975).
575. J.T.Curnutte and B.M.Babior, J.Clin.Invest., 53, 1662 (1974).
576. B.M.Babior, J.T.Curnutte, and B.J.Murrich, J.Clin.Invest., 58, 989 (1976).
577. J.T.Curnutte, D.M.Whitten, and B.M.Babior, N.England J.Med., 290, 593 (1974).
578. B.M.Babior, J.T.Curnutte, and R.S.Kipnes, J.Clin.Invest., 56, 1035 (1975).
579. P.Patriarca, D.Dri, K.Kakinuma, and F.Rossi, Biochim.Biophys.Acta, 385, 380 (1975).
580. C.Auclair, E.Cramer, J.Hakim, and P.Boivin, Biochemie, 58, 1359 (1976).
581. I.M.Goldstein, M.Cerqueira, S.Lund, and H.B.Kaplan, J.Clin.Invest., 59, 249 (1977).
582. J.T.Curbutte and B.M.Babior, Blood, 45, 851 (1975).
583. A.Nakagawara, K.Kakinuma, H.Shin, S.Miyazaki, and S.Minakami, Clin.Chim.Acta, 70, 133 (1976).
584. D.Roos, I.M.Goldstein, H.B.Kaplan, and G.Weissmann, Agent Act., 6, 256 (1976).
585. K.Kahinuma and S.Minakami, Biochim.Biophys. Acta, 538, 50 (1978).
586. I.M.Goldstein, D.Roos, H.B.Kaplan, and G.Weissmann, J.Clin.Invest., 56, 1155 (1975).
587. C.Auclair, J.Hakim, and P.Bovin, FEBS Letters, 79, 390 (1977).
588. K.Takanaka, Hiroshima Kogyo Daigaku Kenkyu Kiyo, 11, 1 (1977).
589. H.J.Cohen and M.E.Chovaniec, J.Clin.Invest., 61, 1081 (1978).
590. H.J.Cohen and M.E.Chovaniec, J.Clin.Invest., 61, 1088 (1978).
591. M.F.Tsan and P.A.McIntyre, J.Exp.Med., 146, 1308 (1976).
592. H.Rosen and S.J.Klebanoff, J.Clin.Invest., 58, 60 (1976).
593. I.M.Goldstein, S.Lund, S.Hoffstein, and G.Weissmann, J.Exp.Med., 146, 483 (1977).
594. D.Amano, Y.Kagosaki, T.Usui, S.Yamamoto, and O.Hayaishi, Biochem.Biophys.Res.Comm., 66, 272 (1975).
595. D.Klebanoff, J.Biol.Chem., 249, 3724 (1974).
596. H.H.Dollwet, Sci.Biol.J., 4, 29 (1978).
597. A.M.Michelson, "Superoxide and Superoxide Dismutases", Acad.Press, London, 1977, p.19.
598. N.Kitajima, S.Fukuzumi, and Y.Ono, J.Phys. Chem., 82, 1505 (1978).
599. R.A.Holroyd and B.H.J.Bielski, J.Amer.Chem. Soc., 100, 5796 (1978).
600. J.R.Harbour and M.L.Hair, J.Phys.Chem., 82, 1397 (1978).
601. V.S.Srinivasan, D.Podolski, N.J.Westrick, and D.C.Neckers, J.Amer.Chem.Soc., 100, 6513 (1978).
602. C.C.Felix, J.S.Hyde, T.Sarna, and R.C.Sealy, Biochem.Biophys.Res.Comm., 84, 335 (1978).
603. A.Puxeddu, N.Marsich, and G.Costa, Chem. Comm., 339 (1978).
604. B.Halliwell, Biochem.J., 167, 279 (1977).

605. C.-I. Chern, R. DiCosimo, R. DeJesus, and J. SanFillippo, J. Amer. Chem. Soc., 100, 7317 (1978).
606. W. G. Niehaus, Bioorg. Chem., 7, 77 (1978).
607. M. Younes, E. Lengfelder, S. Zienau, and U. Weser, Biochem. Biophys. Res. Comm., 81, 576 (1978).
608. Y. Ilan, Y. A. Ilan, and G. Czapski, Biochim. Biophys. Acta, 503, 399 (1978).
609. M. Nishikimi and K. Yagi, Biochem. Med. Aspects Act. Oxygen, Papers of symposium, University Park Press, Baltimore, 1977, p. 79; Chem. Abs., 89, 55350 (1978).
610. P. B. McCay, K.-L. Fong, E. K. Lai, and M. M. King, Proc. Int. Symp. Tocopherol, Oxygen Biomembr., Elsevier, Amsterdam, 1978, p. 41.
611. K. Yagi, H. Yamada, and M. Nishikimi, Proc. Int. Symp. Tocopherol, Oxygen Biomembr., Elsevier, Amsterdam, 1978, p. 1.
612. G. Cohen, see Ref. 597, p. 317.
613. B. Halliwell, FEBS Letters, 92, 321 (1978).
614. A. A. Frimer, I. Rosenthal, and S. Hoz, Tetrahedron Letters, 4631 (1977).
615. M. Lissel and E. V. Dehmlow, Tetrahedron Letters, 3689 (1978).
616. A. Rigo, E. Argese, R. Stevanato, E. F. Orsega, and P. Viglino, Inorg. Chim. Acta, 24, 471 (1977).
617. G. R. Buettner and L. W. Oberley, Biochem. Biophys. Res. Comm., 83, 69 (1978).
618. J. P. Henry and A. M. Michelson, see Ref. 597, p. 283.
619. R. C. Bray, G. N. Mautner, E. M. Fielden, and C. I. Claire, see Ref. 597, p. 61.
620. H. Caldararu, K. DeArmond, and K. Hanck, Inorg. Chem., 17, 2030 (1978).
621. S. R. Pickens, A. E. Martell, G. McLendon, A. B. P. Lever, and H. B. Gray, Inorg. Chem., 17, 2190 (1978).
622. A. Boveris, R. A. Sanchez, and M. T. Beconi, FEBS Letters, 92, 333 (1978).
623. S. Huq and J. P. Palmer, Plant Sci. Letters, 11, 351 (1978).
624. P. I. O'Brien, Pharm. Therapeutics, A2, 517 (1978).
625. C. Auclair, D. DeProst, and J. Hakim, Biochem. Pharm., 27, 355 (1978).
626. H. Kuthan, H. Tsuji, H. Graf, V. Ullrich, J. Werringloer, and R. W. Estabrook, FEBS Letters, 91, 343 (1978).
627. R. C. Sealy, H. M. Swartz, and R. L. Olive, Biochem. Biophys. Res. Comm., 82, 680 (1978).
628. A. M. Michelson, see Ref. 597, p. 87.
629. J. Carlsson, G. Nyberg, and J. Wrethen, Appl. Environ. Microbiol., 36, 223 (1978).
630. S. Kanematsu and K. Asada, Arch. Biochem. Biophys., 185, 473 (1978).
631. H. P. Misra and I. Fridovich, Arch. Biochem. Biophys., 189, 317 (1978).
632. J. A. Fee and G. J. McClune, Dev. Biochem., 1, 273 (1978); Chem. Abs., 89, 142577 (1978).
633. C. C. Winterbourn, J. K. Freuch, and R. F. C. Claridge, FEBS Letters, 94, 269 (1978).
634. E. Lengfelder and E. F. Elstner, Z. Physiol. Chem., 359, 751 (1978).
635. D. Stone, P. S. Lin, and L. Kwock, Int. J. Radiat. Biol., 33, 393 (1978).
636. S. A. Cockle and R. C. Bray, see Ref. 597, p. 215.
637. R. P. Mason, F. J. Peterson, and J. L. Holtzman, Mol. Pharm., 14, 665 (1978).
638. J.-P. Henry, F. Hirata, and O. Hayaishi, Biochem. Biophys. Res. Comm., 81, 1091 (1978).
639. M. Younes and U. Weser, Biochim. Biophys. Acta, 526, 644 (1978).
640. K. Soda, T. Kido, and K. Asada, see Ref. 609, p. 119.
641. I. Yamazaki, K. Yokota, and R. Nakajima, see Ref. 609, p. 91.
642. J. DeRycker and B. Halliwell, Biochem. J., 175, 601 (1978).
643. A. A. Kumar, C. S. Vaidyanathan, and N. A. Rao, Indian J. Biochem. Biophys., 15, 5 (1978).
644. M. P. Esnouf, M. R. Green, H. A. O. Hill, G. B. Irvine, and S. J. Walter, Biochem. J., 174, 345 (1978).
645. G. M. Clore and E. M. Chance, Biochem. J., 173, 799 (1978).
646. W. S. Lin, D. A. Armstrong, and M. Lal, Int. J. Radiat. Biol., 33, 231 (1978).
647. E. F. Elstner, M. Saran, W. Bors, and F. Lengfelder, Europ. J. Biochem., 89, 61 (1978).
648. P. A. Jursinic, FEBS Letters, 90, 15 (1978).
649. T. Miura, N. Ogawa, and T. Ogiso, Chem. Pharm. Bull., 26, 1261 (1978).
650. V. K. Kol'tover, O. I. Koifman, A. M. Khenkin, and A. A. Shteinman, Izv. Akad. Nauk SSSR, Ser. Khim., 1690 (1978).
651. N. R. Bachur, S. L. Gordon, and M. V. Gee, Cancer Res., 38, 1745 (1978).
652. L. W. Oberley, I. B. Bize, S. K. Sahu, S. W. H. C. Leuthauser, and H. E. Gruber, J. Nat. Cancer Inst., 61, 375 (1978).
653. Y. Oyanagui, Biochem. Pharm., 27, 777 (1978).
654. H. Ohmori, K. Komoriya, A. Azuma, Y. Hashimoto, and S. Kurozumi, Biochem. Pharm., 27, 1397 (1978).
655. R. B. Johnston and J. E. Lehmeyer, see Ref. 597, p. 291.
656. P. Puig-Parellada and J. M. Planas, Biochem. Pharm., 27, 535 (1978).
657. M. Rister, K. Bauermeister, U. Gravert, and E. Gladtke, Lancet, 1094 (1978).
658. R. B. Johnston, C. A. Godzik, and Z. A. Cohn, J. Exp. Med., 148, 115 (1978).
659. S. H. Stokes, W. B. Davis, and W. A. Sorber, J. Reticuloendothelial Soc., 24, 101 (1978).
660. K. Takanaka and T. Usui, Hiroshima J. Med. Sci., 27, 23 (1978).
661. B. M. Babior, see Ref. 597, p. 271.
662. R. L. Salin and J. M. McCord, see Ref. 597, p. 257.
663. R. C. Jandl, J. Andre-Schwartz, L. Borges-DuBois, R. S. Kipnes, B. J. McMurrich, and B. M. Babior, J. Clin. Invest., 61, 1176 (1978).
664. C. Auclair, M. Torres, and J. Hakim, Biochem. Biophys. Res. Comm., 81, 1067 (1978).
665. S. J. Weiss, G. W. King, and A. F. LaBuglio, Amer. J. Hematol., 4, 1 (1978).
666. T. Gabig, R. S. Kipnes, and B. M. Babior, J. Biol. Chem., 253, 6663 (1978).
667. A. Samuni, M. Chevion, Y. S. Halpern, Y. A. Ilan, and G. Czapski, Radiat. Res., 75, 489 (1978).
668. J. K. Freuch, C. C. Winterbourn, and B. W. Carrell, Biochem. J., 173, 19 (1978).
669. G. Rotilio, E. Fioretti, G. Falcioni, and M. Brunori, see Ref. 597, p. 239.
670. K. S. Kumar, C. Rowse, and P. Hochstein, Biochem. Biophys. Res. Comm., 83, 587 (1978).
671. M. J. Thomas, K. S. Mehl, and W. A. Pryor, Biochem. Biophys. Res. Comm., 83, 927 (1978).
672. B. Halliwell, FEBS Letters, 96, 238 (1978).

673. R. E. Lynch and I. Fridovich, J. Biol. Chem., **253**, 4697 (1978).
674. S. D. Varma, T. K. Ets, and R. D. Richards, Ophthalmic Res., 9, 421 (1977).
675. K. C. Bhuyan and D. K. Bhuyan, Biochim. Biophys. Acta, **542**, 28 (1978).

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