

1703), and methylenecyclopropane (1780, 1781).

Interactive molecular modeling was performed on a COMTEC DS 300 3-D graphic terminal by using a MOL-GRAPH program package (both obtained from Daikin Kogyo Co.). ORTEP drawings were made by using Johnson's program.³⁰

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(30) Johnson, C. K. ORTEP-II. Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.

for his having made a VAX workstation available for this study.

Supplementary Material Available: Figure 7 (changes in relative MM2-derived steric energies, $\Delta E = E_{2a} - E_{2b}$ (kcal/mol), with decreasing Br^+ -substrate distance, R), Table III (MM2-derived steric energies of **2a** and **2b**), Table IV (net atomic charges on **2a** and **2b** calculated by AM1), Table V (MM2-derived out-of-plane deformation and twist angle in **2a** and **2b** caused by the approach of the model solvated proton to the C=C double bond); Tables VI-X, XII-XVI, XVIII-XXII, and XXIV-XXVIII (tables of atomic coordinates and isotropic thermal parameters, bond lengths, bond angles, anisotropic thermal parameters, H-atom coordinates and isotropic thermal parameters for **2a**, **2b**, **5**, and **9**) (19 pages); observed and calculated structure factors for **2a**, **2b**, **5**, and **9** (Tables XI, XVII, XXIII, and XXIX, respectively) (49 pages). Ordering information is given on any current masthead page.

Cooxidation Reactions during Oxidations of Superoxide with Polyhalides, CO_2 , Phosphates, and Acyl Halides

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Abstract: Superoxide ($\text{O}_2^{\cdot-}$) reacted with polyhalides, CO_2 , phosphates, and acyl halides to form the corresponding peroxy intermediates, which could be used as reactive oxidants. Polyhalides reacted with $\text{O}_2^{\cdot-}$ to cause cooxidation of olefins to the corresponding oxides in good yields. The yields of the oxides correlated well with the reactivities of polyhalides with $\text{O}_2^{\cdot-}$. The reactions of CO_2 and phosphates with $\text{O}_2^{\cdot-}$ caused cooxidation of sulfides to the sulfoxides and that of sulfoxides to the sulfones, respectively, in high yields. The mechanisms of these reactions were examined with the use of K^{18}O_2 . Acyl halides were found to have nucleophilic attack of $\text{O}_2^{\cdot-}$ to generate acylperoxy radicals and anions. On the other hand, CCl_4 as a polyhalide, CO_2 , and phosphates in the reaction with $\text{O}_2^{\cdot-}$ seemed to form CCl_3^{\cdot} , $\text{CO}_2^{\cdot-}$, and phosphate anion radicals, respectively, which were followed by addition of O_2 to form the corresponding hydroperoxides or peroxy anions as potent oxidants. These results seem to indicate that $\text{O}_2^{\cdot-}$ acts as a nucleophile and a one-electron reductant. Also, the relative rate constants were measured by the rotating ring-disk voltammetric method. The orders of magnitude for pseudo-first-order rate constants $k_1/[s]$, were 10^4 , 10^3 , and 10^1 in the reactions of $\text{O}_2^{\cdot-}$ with acyl halides, CCl_4 , and phosphates, respectively. There was a good correlation between $k_1/[s]$ and product yields in the cooxidation of *trans*-stilbene by systems of $\text{O}_2^{\cdot-}$ and acyl halides or anhydrides.

Superoxide ($\text{O}_2^{\cdot-}$), an active oxygen species, is generated universally in biological systems. It plays important roles in various diseases caused by oxygen toxicity such as ischemia,¹ carcinogenesis,² inflammation,³ diabetes,⁴ and aging.⁵ During the past two decades, considerable interest has been focused on the chemistry and the reactivity of $\text{O}_2^{\cdot-}$ by many chemists and biochemists. $\text{O}_2^{\cdot-}$ has diverse reactivities;⁶ in aqueous media, it is a Brønsted base⁷ and dismutates to H_2O_2 and O_2 ,⁸ while in aprotic media, $\text{O}_2^{\cdot-}$ acts as an effective nucleophile^{6,9} or causes labile hydrogen abstraction in addition to dismutation.¹⁰ Moreover, $\text{O}_2^{\cdot-}$ can act as a one-electron reductant^{9,11} or a one-electron oxidant.¹² There are many reports of $\text{O}_2^{\cdot-}$ being very toxic to living cells,¹³ but the reactivity of $\text{O}_2^{\cdot-}$ alone is not as vigorous in vitro as those of other active oxygen species, e.g., $\cdot\text{OH}$, $^1\text{O}_2$.⁶

We have reported that the acylperoxy radical [$\text{RC}(\text{O})\text{OO}^{\cdot}$] or acylperoxy anion [$\text{RC}(\text{O})\text{OO}^-$], generated in situ by treatment of acyl halide with $\text{O}_2^{\cdot-}$, is much more reactive than $\text{O}_2^{\cdot-}$ alone.¹⁴ Sawyer et al. have reported that, in aprotic solvents, $\text{O}_2^{\cdot-}$ can oxygenate CCl_4 or CO_2 to yield peroxy intermediates ($\text{CCl}_3\text{OO}^{\cdot}$ and CCl_3OO^- , $\text{CO}_4^{\cdot-}$ and $\text{C}_2\text{O}_6^{\cdot-}$).^{10,15,16} We have found that $\text{O}_2^{\cdot-}$ oxidizes various substrates in the presence of polyhalides or CO_2 ¹⁷ and also causes serious damage to biological systems in the presence of CCl_4 .¹⁸ Thus, the peroxy intermediates were revealed to be more reactive than $\text{O}_2^{\cdot-}$ alone. Furthermore, we have re-

ported that the phosphate moiety of nucleotides enhances the reactivity of $\text{O}_2^{\cdot-}$ in the nucleobase release reaction of nucleotides.¹⁹

(1) (a) Nishida, T.; Sibata, H.; Koseki, M.; Kawashima, Y.; Yoshida, Y.; Tagawa, K. *Biochim. Biophys. Acta* **1987**, *890*, 82-88. (b) Hess, M. L.; Okabe, E.; Philip, A.; Kontos, H. A. *Cardiovasc. Res.* **1984**, *18*, 149-157. (c) Hess, M. L.; Okabe, E.; Kontos, H. A. *J. Mol. Cell Cardiol.* **1981**, *13*, 767-772. (d) Feher, J. J.; Briggs, F. N.; Hess, M. L. *J. Mol. Cell Cardiol.* **1980**, *12*, 427-432. (e) Aishia, H.; Morimura, T.; Obata, T.; Miura, Y.; Miyamoto, T.; Tsuboshima, M.; Mizushima, Y. *Arch. Int. Pharmacodyn. Ther.* **1983**, *261*, 316-326.

(2) (a) Cerutti, P. A. *Science* **1985**, *227*, 375-381. (b) Miller, R. C.; Osmak, R.; Zimmerman, M.; Hall, E. J. *Int. J. Rad. Oncol., Biol., Phys.* **1982**, *8*, 771-775. (c) Schwarz, M.; Peres, G.; Kunz, W.; Furstenberger, G.; Kittstein, W.; Marks, F. *Carcinogenesis* **1984**, *5*, 1663-1670. (d) Weitzman, S. A.; Weitberg, A. B.; Clark, E. P.; Stossel, T. P. *Science* **1985**, *227*, 1231-1233.

(3) (a) McCord, J. M. *Agent Actions* **1980**, *10*, 522-527. (b) McCord, J. M.; Wong, K.; Stokes, S. H.; Petrone, W. F.; English, D. In *Pathology of Oxygen*; Autor, A. P., Ed.; Academic Press: New York, 1982; pp 75-81. (c) McCord, J. M.; Stokes, S. H.; Wong, K. *Adv. Inflammation Res.* **1979**, *1*, 273-278.

(4) (a) Fischer, L. J.; Hamburger, S. A. *Diabetes* **1980**, *29*, 213-216. (b) Robbins, M. J.; Sharp, R. A.; Slonim, A. E.; Burr, I. M. *Diabetologia* **1980**, *18*, 55-58. (c) Slonim, A. E.; Surbur, M. L.; Page, D. L.; Sharp, R. A.; Burr, I. M. *J. Clin. Invest.* **1983**, *71*, 1282-1288. (d) Asayama, K.; English, D.; Slonim, A. E.; Burr, I. M. *Diabetes* **1984**, *33*, 160-163. (e) Malaise, W. J.; Malaise-Lagae, F.; Sener, A.; Pipeless, D. G. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 927-930.

(5) (a) Bartosz, G.; Leyko, W.; Fried, R. *Experientia* **1979**, *35*, 1193. (b) Kellogg, E. W., III; Fridovich, I. *J. Gerontol.* **1976**, *31*, 405-408.

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Table I. Cooxidation of Substrates during Oxidation of CCl_4 with O_2^{2-} ^a

run	substrate	product(s), %	recovery, %
1	<i>trans</i> -stilbene	<i>trans</i> -stilbene oxide, 62 (0); ^b benzaldehyde, 11 (0); benzoic acid, 11 (0)	3 (89)
2	<i>cis</i> -stilbene	<i>trans</i> -stilbene oxide, 31; <i>cis</i> -stilbene oxide, 2; benzaldehyde, 7; benzoic acid, 6	41
3	styrene	styrene oxide, 56 (0); benzaldehyde, 9 (0); benzoic acid, 8 (0)	11 (91)
4	α -methylstyrene	α -methylstyrene oxide, 79; acetophenone, 19	0
5	β -methylstyrene	β -methylstyrene oxide, 83 (2); benzaldehyde, 7 (2); benzoic acid, 9 (<1)	0 (93)
6	cyclohexene	1,2-epoxycyclohexane, 73; 2-cyclohexene-1-one, 9	nd ^c
7	1-methylcyclohexene	1,2-epoxy-1-methylcyclohexane, 88 (<1)	nd
8	2-cyclohexen-1-one	2,3-epoxycyclohexanone, 4 (0)	80 (0)
9	1-octene	1,2-epoxyoctane, 9 (0); octanoic acid, <1 (0)	nd
10	phenanthrene	phenanthrene oxide, 11 (0)	86 (98)
11	pyrene	pyrene oxide, 4 (0)	58 (98)
12	tetralin	α -tetralone, 22 (0)	71 (96)
13	benzylamine	benzaldehyde, 33 (0); benzoic acid, 4 (0); benzalbenzylamine, 5 (1)	0 (95)
14	<i>N</i> -ethylaniline	aniline, 14 (0)	33 (90)
15	benzamide	benzoic acid, 41 (2)	1 (88)
16	<i>N</i> - <i>n</i> -butylbenzamide	benzoic acid, 56 (8)	27 (77)
17	<i>N</i> -benzylbenzamide	benzoic acid, 60; dibenzamide, 3	4
18	dibenzamide	benzoic acid, 58	40
19	dibenzyl ether	benzoic acid, 27	nd
20	dibenzyl sulfide	dibenzyl sulfoxide, 40 (0); dibenzyl sulfone, 6 (0); benzaldehyde, 48 (<1); benzoic acid, 6 (1)	10 (86)
21	ethyl methyl sulfide	ethyl methyl sulfoxide, 54 (0); ethyl methyl sulfone, 20 (0)	0 (99)

^aThe reaction mixtures contained 0.3 mmol of substrates, 15 mmol of CCl_4 , 3.0 mmol of KO_2 , and 0.3 mmol of 18-crown-6-ether in $\text{CH}_3\text{-CN}$ solution. Reactions were allowed to proceed for 4–24 h at 10–15 °C. ^bValues in parentheses indicate yields in the absence of CCl_4 . ^cnd = not determined.

Such results also indicate that O_2^{2-} becomes reactive in the presence but not in the absence of the phosphate moiety.

- (6) (a) Sawyer, D. T.; Valentine, J. S. *Acc. Chem. Res.* **1981**, *14*, 393–400. (b) Sawyer, D. T.; Gibian, M. J. *Tetrahedron* **1979**, *35*, 1471–1481. (c) Fridovich, I. *Acc. Chem. Res.* **1982**, *15*, 200.
(7) (a) Sawyer, D. T.; Gibian, M. J.; Morrison, M. M.; Seo, E. T. *J. Am. Chem. Soc.* **1978**, *100*, 627–628. (b) Gibian, M. J.; Sawyer, D. T.; Ungermann, T.; Tangpoonpholivat, R.; Morrison, M. M. *J. Am. Chem. Soc.* **1979**, *101*, 640–644. (c) Chern, C.-I.; DiCosimo, R.; Jesus, R. D.; Fillipo, J. S., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 7317–7327.
(8) (a) Bielski, B. H. J. *Photochem. Photobiol.* **1978**, *28*, 645–649. (b) Chin, D.-H.; Chiericato, G., Jr.; Nanni, E. J., Jr.; Sawyer, D. T. *J. Am. Chem. Soc.* **1982**, *104*, 1296–1299.
(9) Danen, W. C.; Warner, R. J. *Tetrahedron Lett.* **1977**, *18*, 989–992.
(10) (a) Roberts, J. L., Jr.; Sawyer, D. T. *J. Am. Chem. Soc.* **1981**, *103*, 712–714. (b) Purrington, S. T.; Kenion, G. B. *J. Chem. Soc., Chem. Commun.* **1982**, 731–732.
(11) Boujlel, K.; Simonet, J. *Tetrahedron Lett.* **1979**, *20*, 1063–1066.
(12) Gebicki, J. M.; Bielski, B. H. J. *J. Am. Chem. Soc.* **1984**, *103*, 7020–7022.
(13) (a) Brawn, K.; Fridovich, I. *Acta Physiol. Scand., Suppl.* **1980**, No. 492, 9–18. (b) Diguseppi, J.; Fridovich, I. *CRC Crit. Rev. Toxicol.* **1983**, *12*, 315–342. (c) Turrens, J. F.; Freeman, B. A.; Levitt, J. G.; Crapo, J. D. *Arch. Biochem. Biophys.* **1982**, *217*, 401–410.
(14) (a) Nagano, T.; Arakane, K.; Hirobe, M. *Chem. Pharm. Bull.* **1980**, *28*, 3719–3721. (b) Nagano, T.; Yokooji, K.; Hirobe, M. *Tetrahedron Lett.* **1983**, *24*, 3481–3483. (c) Nagano, T.; Yokooji, K.; Hirobe, M. *Tetrahedron Lett.* **1984**, *25*, 965–968.

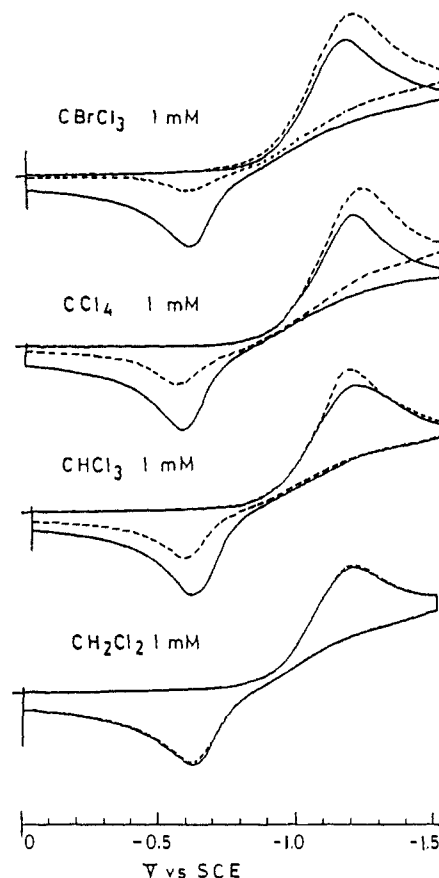


Figure 1. Cyclic voltammograms of O_2 (solid curve) and O_2 plus 1.0 mM polyhalides (dotted curve) in dimethylformamide containing 0.1 M tetraethylammonium perchlorate as a supporting electrolyte. Measurements were done with a platinum electrode at a scan rate of 0.15 V s^{-1} .

In this paper, we report in detail on the oxidation reactions of O_2^{2-} with polyhalides, CO_2 , phosphates, and acyl halides.

Results

Cooxidation of Various Substrates during the Oxidation of Polyhalides with Superoxide. In a heterogeneous CH_3CN solution of potassium superoxide (KO_2) and polyhalides, various substrates were oxidized as shown in Table I with CCl_4 as the polyhalide. In the presence of KO_2 and CCl_4 , styrene and its derivatives afforded their corresponding oxides in good yields with minor products such as benzaldehyde and benzoic acid, formed by oxidative cleavage of the double bonds (Table I). α - and β -methylstyrenes, which are more electron-rich olefins than styrene, were oxidized in higher yield than styrene (runs 4 and 5 in Table I). The results suggest that the ultimate species is an electrophilic oxidant. When *cis*-stilbene was used as a substrate, the major product was not *cis*-stilbene oxide, but *trans*-stilbene oxide. We have examined the time course of product yields in the oxidation of α -methylstyrene. The maximal yield of acetophenone (19%)

- (15) Roberts, J. L., Jr.; Calderwood, T. S.; Sawyer, D. T. *J. Am. Chem. Soc.* **1983**, *105*, 7691–7696.
(16) Roberts, J. L., Jr.; Calderwood, T. S.; Sawyer, D. T. *J. Am. Chem. Soc.* **1984**, *106*, 4667–4670.
(17) (a) Yamamoto, H.; Mashino, T.; Nagano, T.; Hirobe, M. *J. Am. Chem. Soc.* **1986**, *108*, 539–541. (b) Nagano, T.; Yamamoto, H.; Hirobe, M. In *The Biological Role of Reactive Oxygen Species in Skin*; Hayaishi, O., Imamura, S., Miyachi, Y., Eds.; University of Tokyo Press: Tokyo, 1987, pp 241–251. (c) Yamamoto, H.; Mashino, T.; Nagano, T.; Hirobe, M. *Tetrahedron Lett.* in press.
(18) Yamamoto, H.; Nagano, T.; Hirobe, M. *J. Biol. Chem.* **1988**, *263*, 12224–12227.
(19) (a) Yamane, H.; Yada, N.; Katori, E.; Mashino, T.; Nagano, T.; Hirobe, M. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 1104–1110. (b) Nagano, T.; Yamane, H.; Yada, N.; Hirobe, M. In *The Role of Oxygen in Chemistry and Biochemistry*; Ando, W., Moro-oka, Y., Eds.; Elsevier: Amsterdam, **1988**, pp 449–454.

was obtained within 3 h, while the formation of the epoxide (79%) required longer to reach the maximal yield. When the epoxide was used as a substrate, 96% of the starting material was recovered. These data show that the epoxide is stable in the reaction system and acetophenone is not formed via the epoxide.

Cyclic olefins such as cyclohexene and 1-methylcyclohexene also afforded their corresponding epoxides in high yields (runs 6 and 7), while acyclic olefin was epoxidized in low yields of 9% (run 9). Cyclohexenone, which is an electron-poor olefin, was hardly oxidized to its epoxide (run 8). Polycyclic aromatic compounds, such as phenanthrene and pyrene, were cooxidized in one step in this system (runs 10 and 11). Tetralin and benzylamine, which have labile hydrogens, could be oxidized (runs 12 and 13), and substrates such as sulfides, ethers, and amido compounds were also oxidized under similar conditions (runs 15–21). In the absence of CCl_4 , these reactions did not proceed, which shows that both KO_2 and CCl_4 are essential for the oxidation reactions. Peroxide ion (O_2^{2-}) cannot be an actual species, because O_2^{2-} will not disproportionate to give O_2^{2-} in aprotic media.

In the presence of other polyhalides, O_2^{2-} oxidized *trans*-stilbene to the oxide in the following yields: 72% [CBrCl_3], 62% [CCl_4], 27% [CHCl_3], 0% [CH_2Cl_2], 63% [CCl_3CCl_3], 50% [$\text{CCl}_2=\text{CCl}_2$], 43% [$\text{CCl}_2=\text{CHCl}$], 42% [CF_3CHBrCl], 53% [CF_3CCl_3], 26% [PhCCl_3], 2% [*p,p'*-DDT]. The oxidation yields in the presence of the polyhalides correlated well with their order of hepatotoxicity: $\text{CBrCl}_3 > \text{CCl}_4 > \text{CHCl}_3 > \text{CH}_2\text{Cl}_2$.²⁰ We measured the cyclic voltammograms of O_2 in the presence of these polyhalides to determine the reactivities with O_2^{2-} (Figure 1). The cyclic voltammogram for the superoxide- CCl_4 reaction confirmed earlier work reported by Roberts and Sawyer.¹⁰ The solid curves show the cyclic voltammetric reduction of O_2 to O_2^{2-} and the reoxidation of the latter in the absence of polyhalides. The dotted curves illustrate the effects of polyhalides at 1.0 mM. The oxidation peaks for the reverse scan were diminished, which indicates that O_2^{2-} was being scavenged by the reaction with polyhalides. All polyhalides except CH_2Cl_2 exhibited similar effects on the $\text{O}_2/\text{O}_2^{2-}$ electrochemistry and the diminution of the oxidation peaks, which shows that the relative reactivities of these polyhalides with O_2^{2-} also agreed with the order given above. These results show that the oxidation yields of *trans*-stilbene depended upon the reactivities of polyhalides with O_2^{2-} .

These findings suggest that the KO_2 -polyhalide system yields reactive peroxy intermediates, such as CCl_3OOH , which have electrophilic reactivities due to the presence of the electron-withdrawing trichloromethyl group and are markedly more potent oxidizing agents than O_2^{2-} alone.

Cooxidation of Sulfides and Olefins during the Oxidation of CO_2 with Superoxide. After bubbling CO_2 gas for 5 min into a dimethylformamide solution of substrate and 18-crown-6-ether, KO_2 was added, and the reaction mixture was vigorously stirred under a CO_2 atmosphere. When ethyl methyl sulfide was used as a substrate, ethyl methyl sulfoxide was obtained in an excellent yield of 84% (run 1 in Table II). From benzyl methyl sulfide and dibenzyl sulfide, the corresponding sulfoxides were obtained in 78% and 39% yield, respectively, with the minor products of benzaldehyde and benzoic acid (runs 2 and 3). No sulfone was obtained from any sulfides. These results suggest that reactive and electrophilic species different from O_2^{2-} itself are formed from O_2^{2-} and CO_2 .

When *trans*-stilbene was used as a substrate, the major product was *trans*-stilbene oxide (run 4). With use of dry ice as the CO_2 source, this reaction proceeded with the same yield as that shown in run 4. Also in this system, electron-rich olefins such as α - and β -methylstyrenes were oxidized in better yields than electron-poor olefin such as *p*-chlorostyrene (runs 5–8). In the absence of CO_2 , these reactions did not proceed and the starting materials were mainly recovered. These results suggest that electrophilic peroxy intermediates (OC(O)OOH and OC(O)OC(O)OOH) generated

Table II. Cooxidation of Sulfides and Olefins during Oxidation of CO_2 with O_2^{2-} ^a

run	substrate	product(s), %	recovery, %
1	ethyl methyl sulfide	ethyl methyl sulfoxide, 84 (0) ^b	6 (98)
2	benzyl methyl sulfide	benzyl methyl sulfoxide, 78 (0); benzaldehyde, 2 (0); benzoic acid, 2 (44)	20 (41)
3	dibenzyl sulfide	dibenzyl sulfoxide, 39 (0); benzaldehyde, 1 (0); benzoic acid, 2 (44)	47 (15)
4	<i>trans</i> -stilbene	<i>trans</i> -stilbene oxide, 12 (0); benzaldehyde, 1 (0); benzoic acid, 1 (0)	63 (94)
5	styrene	styrene oxide, 10 (0); benzaldehyde, 1 (0); benzoic acid, 1 (0)	88 (95)
6	α -methylstyrene	α -methylstyrene oxide, 23 (0); acetophenone, 14 (0)	57 (95)
7	β -methylstyrene	β -methylstyrene oxide, 34 (0); benzaldehyde, 3 (0); benzoic acid, 1 (11); propionophenone, 1 (0)	55 (83)
8	<i>p</i> -chlorostyrene	<i>p</i> -chlorostyrene oxide, 4 (0); <i>p</i> -chlorobenzoic acid, 4 (8)	92 (84)

^aThe reaction mixture contained 0.3 mmol of substrate, 3.0 mmol of KO_2 , and 0.3 mmol of 18-crown-6-ether in dimethylformamide solution. Reactions were allowed to proceed for 20 h at 15–20 °C under a CO_2 atmosphere. ^bValues in parentheses indicate yields in the absence of CO_2 .

Table III. Cooxidation of Substrates during Oxidation of 5'-GMP with O_2^{2-} ^a

run	substrate	product(s), %	recovery, %
1	ethyl methyl sulfide	ethyl methyl sulfoxide, 5 (0); ^b ethyl methyl sulfone, 5 (0)	85 (94)
2	ethyl methyl sulfoxide	ethyl methyl sulfone, 98 (3)	1 (94)
3	benzalacetophenone	benzalacetophenone oxide, 52 (3); benzaldehyde, 22 (13); benzoic acid, 23 (58)	0 (15)
4	2-cyclohexen-1-one	2,3-epoxycyclohexanone, 77 (0)	4 (0)

^aThe reaction mixture contained 0.3 mmol of substrate, 0.45 mmol of 5'-GMP, 3.0 mmol of KO_2 , and 0.3 mmol of 18-crown-6-ether in dimethylformamide solution. Reactions were allowed to proceed for 1–5 h at 15–20 °C. ^bValues in parentheses indicate yields in the absence of 5'-GMP.

from O_2^{2-} and CO_2 oxidize the substrates.

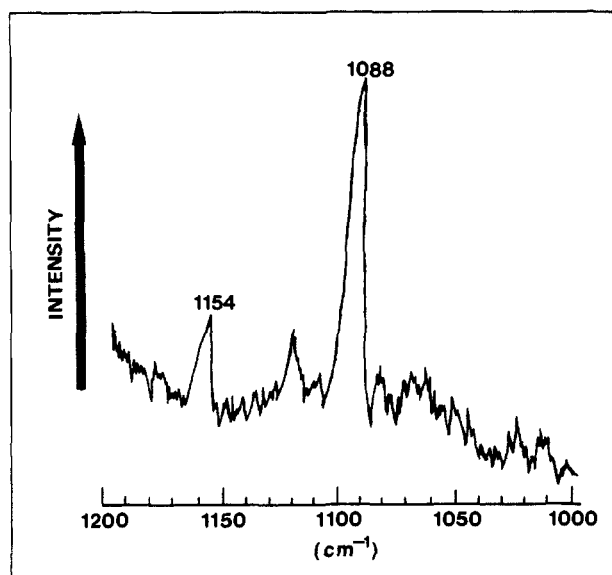
Cooxidation of Various Substrates during the Oxidation of Phosphates with Superoxide. We have reported that the phosphate moiety of nucleotides reacts with O_2^{2-} to form a peroxy intermediate which leads to the nucleobase release reaction of nucleotides.¹⁹ The peroxy intermediate was found to oxidize other substrates (Table III). In a dimethylformamide solution containing KO_2 and 5'-GMP, ethyl methyl sulfide was oxidized to the corresponding sulfoxide in a low yield (run 1). However, when ethyl methyl sulfoxide was used as a substrate, the corresponding sulfone was obtained in excellent yield (run 2). α,β -Unsaturated ketone was also oxidized to the corresponding oxides in good yields (runs 3 and 4). These reactions did not proceed in the absence of 5'-GMP.

Other phosphates were found to be effective for oxidizing ethyl methyl sulfoxide to the sulfone with the following yields: 78% [5'-AMP], 83% [*O*-phosphorylethanolamine], 17% [glucose 6-phosphate], 12% [β -glycerophosphoric acid]. All of these phosphates have been reported to enhance the nucleobase release reaction of nucleotides.¹⁹ When guanosine was added in place of 5'-GMP, ethyl methyl sulfoxide was not oxidized at all.

These results suggest that reactive peroxy intermediate is formed by the reaction of O_2^{2-} with phosphate group and has nucleophilic reactivities.

¹⁸O Incorporation into Substrates in Systems of K^{18}O_2 and Additives. We examined the incorporation of ¹⁸O into substrates

(20) (a) Koch, R. R.; Glende, E. A., Jr.; Recknagel, R. O. *Biochem. Pharmacol.* **1974**, *23*, 2907–2915. (b) Sagai, M.; Tappel, A. L. *Toxicol. Appl. Pharmacol.* **1979**, *49*, 283–291.

Figure 2. Raman spectrum of $K^{18}O_2$ and $K^{16}O_2$.Table IV. Percentage of Incorporation of ^{18}O into Various Substrates in the KO_2 and $PhCOCl$ System

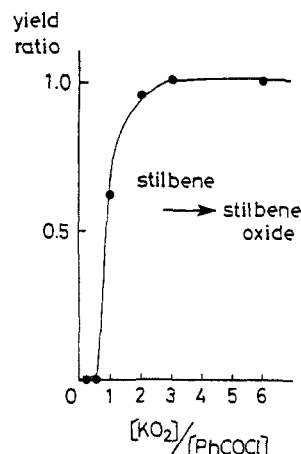
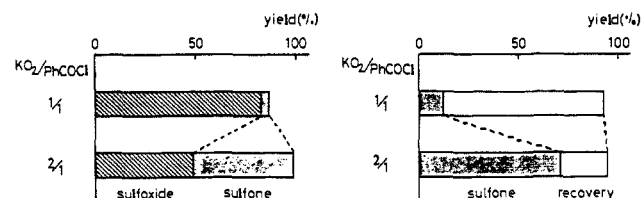
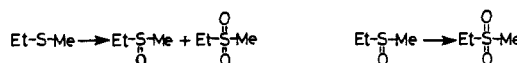
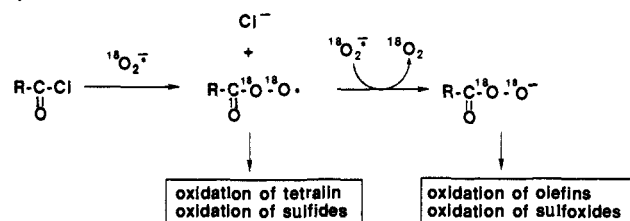
run	substrate	product	% incorporation of ^{18}O into substrate ^a		
			under Ar	under air	under $^{16}O_2$
1	styrene	styrene oxide	100	98	95
2	tetralin	α -tetralone	99	63	15
3	ethyl methyl sulfide	ethyl methyl sulfoxide	100	36	7
4	ethyl methyl sulfoxide	ethyl methyl sulfone	99	97	73

^a Percentage of incorporation was corrected with the $K^{18}O_2$ % content (78%) of KO_2 .

in systems of $K^{18}O_2$ and additives (polyhalides, CO_2 , phosphates, and acyl halides) in order to clarify the oxidation mechanisms. $K^{18}O_2$ was prepared by bubbling $^{18}O_2$ into benzene with dissolved benzhydrol and potassium *tert*-butoxide according to the method of Rosenthal.²¹ The KO_2 powder obtained contained a small amount of $K^{16}O_2$ with large amounts of $K^{18}O_2$. We determined the $K^{18}O_2$ content of the prepared KO_2 powder by using Raman spectroscopy. As shown in Figure 2, the KO_2 powder showed a strong Raman line at 1088 cm^{-1} , which could be assigned to an ^{18}O - ^{18}O stretching vibration, with a weak line at 1154 cm^{-1} assigned to an ^{16}O - ^{16}O stretching vibration. The $K^{16}O_2$ powder showed only an intense Raman line at 1154 cm^{-1} , and the line at 1088 cm^{-1} could be assigned to the ^{18}O - ^{18}O stretching vibration because the $\nu = 2\pi(k/m)^{1/2}$ expression led to an estimation of 1087.8 cm^{-1} as the Raman line of the $K^{18}O_2$. From the intensity ratio of two lines, the content of $K^{18}O_2$ was determined to be 78%.

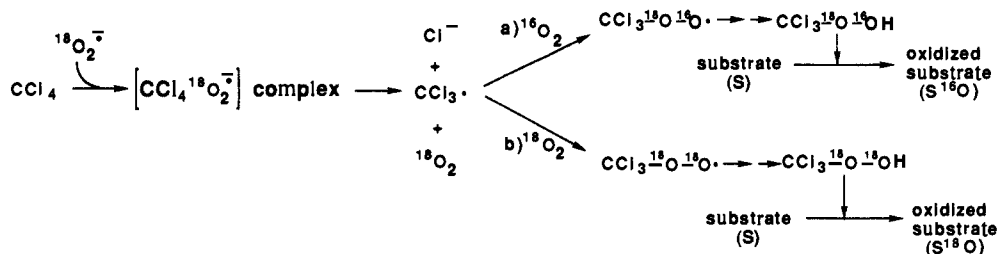
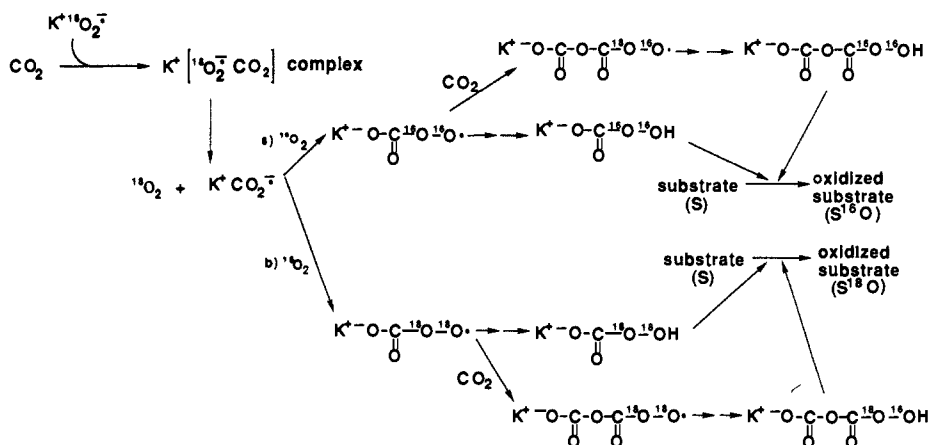
Before the reactions were started, Ar, air, or $^{16}O_2$ gas was bubbled for 30 min into the reaction mixtures, and the bubbling was continued during the reactions in order to examine the source of the oxygen atom incorporated into the reaction products under various $^{16}O_2$ concentrations in each system.

In the $K^{18}O_2$ and $PhCOCl$ system, we examined ^{18}O incorporations into substrates in four oxidation reactions (Table IV). In the oxidations of styrene to styrene oxide and the oxidation of ethyl methyl sulfoxide to sulfone, ^{18}O was incorporated into these substrates almost independent of the concentration of $^{16}O_2$ dissolved in the reaction solution. On the other hand, in the oxidations of tetralin to α -tetralone and the oxidation of ethyl methyl sulfide to sulfoxide, the percentage of incorporation of ^{18}O decreased with an increase in the dissolved $^{16}O_2$ concentration.

Figure 3. Correlation between the ratio of $KO_2/PhCOCl$ and yields of *trans*-stilbene oxide in the KO_2 and $PhCOCl$ system.Figure 4. Effect of $KO_2/PhCOCl$ ratio on the product yields in the oxidation of ethyl methyl sulfide and ethyl methyl sulfoxide.Scheme I. Proposed Oxidation Mechanism of the KO_2 and $PhCOCl$ System

We examined the correlation between the ratio of $KO_2/PhCOCl$ and the yields of the products. As shown in Figure 3, when the amount of KO_2 was equimolar to that of $PhCOCl$, only about a half-maximum epoxidation yield of *trans*-stilbene was obtained, but when the amount of KO_2 was double the molar quantity of $PhCOCl$, the maximum epoxidation yield was obtained. We also examined the effect of the $KO_2/PhCOCl$ ratio on the product yields in the oxidation of ethyl methyl sulfide and ethyl methyl sulfoxide (Figure 4). When KO_2 was used in an amount equimolar with $PhCOCl$, sulfoxide was mainly obtained from sulfide with sulfone as a minor product. When sulfoxide was used as a substrate, the oxidation reaction hardly proceeded. However, when the amount of KO_2 was double the molar quantity of $PhCOCl$, almost the same amounts of sulfoxide and sulfone were obtained from sulfide, and furthermore, the oxidation of sulfoxide to sulfone proceeded with a good yield. Thus, the mechanism shown in Scheme I was proposed for this oxidation system. $^{18}O_2^-$ first reacts by nucleophilic substitution with $PhCOCl$ to form the benzoyl peroxy radical [$PhC(O)^{18}O^{18}O\cdot$], which abstracts one electron from tetralin or sulfides. Next, $^{18}O_2$ derived from $^{18}O_2^-$ or dissolved $^{16}O_2$ attacks the cation radicals formed from these substrates, and in so doing, the oxidation reaction proceeds. On the other hand, in the absence of tetralin or sulfides, $PhC(O)^{18}O^{18}O\cdot$ can be readily reduced by O_2^- to form the benzoyl peroxy anion $PhC(O)^{18}O^{18}O^-$, which attacks olefins and sulfoxides directly to cause oxidation reactions.

(21) Rosenthal, I. *J. Labelled Compd. Radiopharm.* **1976**, *12*, 317-318.
 (22) Koppenol, W. H.; Rush, J. D. *J. Phys. Chem.* **1987**, *91*, 4430-4431.

Scheme II. Proposed Oxidation Mechanism of the KO_2 and CCl_4 SystemScheme III. Proposed Oxidation Mechanism of the KO_2 and CO_2 SystemTable V. Percentage of Incorporation of ^{18}O into Various Substrates in the KO_2 and CCl_4 System

run	substrate	product	% incorporation of ^{18}O into substrate ^a		
			under Ar	under air	under $^{16}\text{O}_2$
1	styrene	styrene oxide	100	59	11
2	tetralin	α -tetralone	98	66	16
3	ethyl methyl sulfide	ethyl methyl sulfoxide	100	46	9
4	ethyl methyl sulfoxide	ethyl methyl sulfone	100	70	20

^aPercentage of incorporation was corrected with the K^{18}O_2 % content (78%) of KO_2 .

In the K^{18}O_2 and CCl_4 system, the percentage of incorporation of ^{18}O decreased with an increase of the dissolved $^{16}\text{O}_2$ concentration in the oxidations of four substrates (Table V). We proposed the reaction mechanism shown in Scheme II. The reaction of $\text{O}_2^{\cdot-}$ with CCl_4 is thought to be initiated by a single electron transfer (SET) from $\text{O}_2^{\cdot-}$ to CCl_4 as reported by Sawyer.¹⁵ The initial step may be the formation of the $[\text{CCl}_4 \text{O}_2^{\cdot-}]$ complex by interaction between $\text{O}_2^{\cdot-}$ and CCl_4 . The resulting activated complex can then dissociate to give $\text{CCl}_3\cdot$, Cl^- , and O_2 . Under aerobic conditions, $^{18}\text{O}_2$ derived from $^{18}\text{O}_2^{\cdot-}$ or $^{16}\text{O}_2$ dissolved in the reaction solution attacks $\text{CCl}_3\cdot$ to form $\text{CCl}_3\text{OO}\cdot$ (path a or path b in Scheme II), which can become CCl_3OOH as an ultimate oxidant.

Under Ar atmosphere, CCl_3OOH can be produced only via path b, which would result in 100% incorporation of ^{18}O into the substrate.

The results obtained by the K^{18}O_2 and CO_2 system are shown in Table VI. In this system, no sulfone was obtained from sulfoxide. The percentage of incorporation of ^{18}O decreased with an increase in the dissolved $^{16}\text{O}_2$ concentration in the oxidation of substrates. The proposed mechanism is shown in Scheme III. The initial step may be the formation of the $[\text{O}_2^{\cdot-} \text{CO}_2]$ complex by interaction between $\text{O}_2^{\cdot-}$ and CO_2 . The resulting complex can then dissociate to give $\text{CO}_2^{\cdot-}$ and O_2 . Under aerobic conditions, $\text{CO}_2^{\cdot-}$ is attacked by $^{18}\text{O}_2$ or $^{16}\text{O}_2$ to form $\text{CO}_4^{\cdot-}$, followed with the formation of $\text{C}_2\text{O}_6^{\cdot-}$ by addition of another molecule of CO_2

Table VI. Percentage of Incorporation of ^{18}O into Various Substrates in the KO_2 and CO_2 System

run	substrate	product	% incorporation of ^{18}O into substrate ^a		
			under Ar	under air	under $^{16}\text{O}_2$
1	styrene	styrene oxide	100	54	14
2	tetralin	α -tetralone	96	61	17
3	ethyl methyl sulfide	ethyl methyl sulfoxide	100	41	10

^aPercentage of incorporation was corrected with the K^{18}O_2 % content (78%) of KO_2 .

Table VII. Percentage of Incorporation of ^{18}O into Various Substrates in the KO_2 and 5'-GMP System

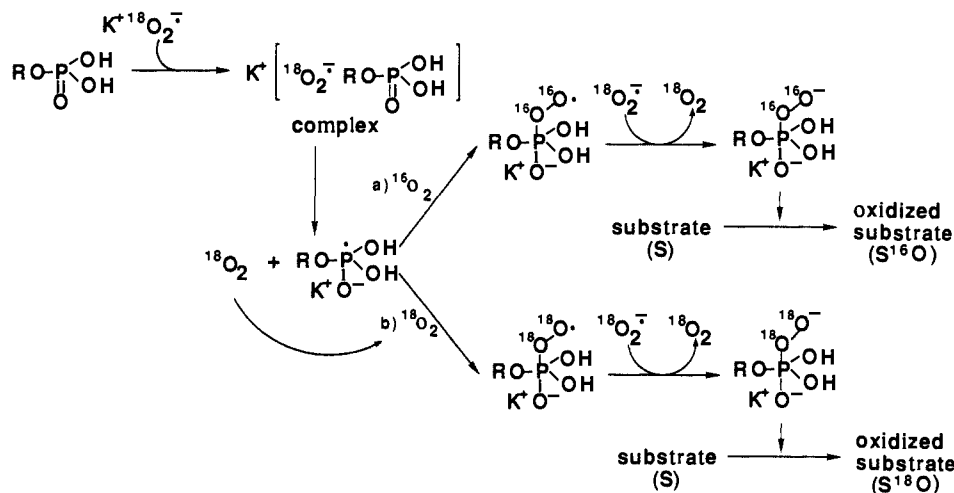
run	substrate	product	% incorporation of ^{18}O into substrate ^a		
			under Ar	under air	under $^{16}\text{O}_2$
1	ethyl methyl sulfide	ethyl methyl sulfoxide	100	38	6
2	ethyl methyl sulfoxide	ethyl methyl sulfone	99	43	7

^aPercentage of incorporation was corrected with the K^{18}O_2 % content (78%) of KO_2 .

(path a or path b in Scheme III). Under Ar atmosphere, $\text{CO}_4^{\cdot-}$ and $\text{C}_2\text{O}_6^{\cdot-}$ can be formed only via path b. The ultimate oxidant $^-\text{OC}(\text{O})\text{OOH}$ and $^-\text{OC}(\text{O})\text{OC}(\text{O})\text{OOH}$ have electrophilic reactivity and oxidize sulfides and olefins.

In the K^{18}O_2 and 5'-GMP system, ^{18}O incorporation was examined in the oxidations of sulfide and sulfoxide. The percentage of incorporation decreased with an increase of the dissolved $^{16}\text{O}_2$ concentration in this system as well (Table VII). A mechanism similar to those of the systems of CCl_4 and of CO_2 can be supposed for this system (Scheme IV). The ultimate peroxy anion which has nucleophilic reactivity is thought to oxidize substrates.

Kinetics of the Reaction of Superoxide with Additives. We have measured pseudo-first-order rate constants, k_1 for the reactions of $\text{O}_2^{\cdot-}$ with acyl halides, acid anhydrides, phosphates, and some

Scheme IV. Proposed Oxidation Mechanism of the KO_2 and Phosphate SystemTable VIII. Kinetics Constants for the Reactions of Superoxide with Additives in Dimethylformamide (0.1 M Tetraethylammonium Perchlorate) at 25 °C^a

run	additive, [s]	$k_1/[s]$, M ⁻¹ s ⁻¹
1	benzoyl chloride	$(2.6 \pm 0.3) \times 10^4$
2	3,5-dinitrobenzoyl chloride	$(2.6 \pm 0.2) \times 10^4$
3	acetyl chloride	$(2.5 \pm 0.2) \times 10^4$
4	phenylacetyl chloride	$(2.5 \pm 0.2) \times 10^4$
5	tosyl chloride	$(3.0 \pm 0.3) \times 10^4$
6	diethylcarbonyl chloride	$(1.3 \pm 0.1) \times 10^4$
7	acetic anhydride	$(2.3 \pm 0.5) \times 10^4$
8	trifluoroacetic anhydride	$(2.3 \pm 0.3) \times 10^4$
9	succinic anhydride	$(1.1 \pm 0.1) \times 10^4$
10	<i>N</i> -bromosuccinimide	$(2.2 \pm 0.1) \times 10^4$
11	carbon tetrachloride	$(3.7 \pm 1.0) \times 10^3$
12	<i>n</i> -propyl bromide	$(1.5 \pm 0.1) \times 10^3$
13	phosphoric acid triphenyl ester	$(7.9 \pm 1.0) \times 10$
14	phosphoric acid trimethyl ester	$(1.2 \pm 0.2) \times 10$
15	phosphoric acid triethyl ester	$(1.1 \pm 0.1) \times 10$
16	phosphoric acid tri- <i>n</i> -butyl ester	$(1.0 \pm 0.1) \times 10$

^aPseudo-first-order rate constants, k_1 (normalized to unit additive concentration [s]) were determined from measurements with use of a platinum-glassy carbon ring-disk electrode that was rotated at 900 rpm.

other compounds by the voltammetric rotating ring-disk method. As shown in Table VIII, $k_1/[s]$ for the reactions of $\text{O}_2^{\cdot-}$ with various acyl halides and acid anhydrides were approximately 10^4 . In case of CCl_4 , $k_1/[s]$ was about 10^3 , which agreed with the value reported by Sawyer.¹⁵ *n*-PrBr and the phosphates reacted with $\text{O}_2^{\cdot-}$ at a $k_1/[s]$ of about 10^3 and 10^1 , respectively.

In the presence of acyl halides or anhydrides, *trans*-stilbene was oxidized to its oxide by $\text{O}_2^{\cdot-}$.^{14b} We investigated the correlation between $k_1/[s]$ for the reactions of benzoyl and acetyl compounds with $\text{O}_2^{\cdot-}$ and the yields of *trans*-stilbene oxide in systems of KO_2 and additives (Table IX). In the case of acyl halides or anhydrides, which can react comparatively quickly with $\text{O}_2^{\cdot-}$ ($k_1/[s]$: $\sim 10^4$, runs 1, 2, 5, and 6 in Table IX), *trans*-stilbene oxide was obtained in good yields. However, esters of thioester reacted too slowly with $\text{O}_2^{\cdot-}$ to afford *trans*-stilbene oxide (runs 3, 4, and 7). In the epoxidations of olefins, high reactivities of additives with $\text{O}_2^{\cdot-}$ are necessary to oxidize substrates.

Discussion

$\text{O}_2^{\cdot-}$ reacts with compounds such as polyhalides, CO_2 , phosphates, and acyl halides to form peroxy intermediates which are potent oxidants. The results of ¹⁸O-incorporating experiments indicate two types of mechanisms in the formation of the ultimate species as shown in Scheme I-IV. One mechanism is that in which $\text{O}_2^{\cdot-}$ causes nucleophilic substitution to acyl halides to form peroxy radicals and peroxy anions. The other is that in which the peroxy intermediates are formed via the addition of O_2 dissolved in the reaction solution to the corresponding radicals, CCl_3^{\cdot} , $\text{CO}_2^{\cdot-}$, and

Table IX. Correlation between $k_1/[s]$ ^a and Epoxidation Yield of *trans*-Stilbene in the KO_2 and Additive System

run	additive, [s]	$k_1/[s]$, M ⁻¹ s ⁻¹	epoxidation yield, ^b %
1	benzoyl chloride	$(2.6 \pm 0.3) \times 10^4$	62
2	benzoic anhydride	$(2.8 \pm 0.3) \times 10^4$	79
3	ethyl benzoate	$(4.3 \pm 0.4) \times 10^{-1}$	<1
4	thiobenzoic acid <i>S</i> - <i>n</i> -butyl ester	$(1.5 \pm 0.2) \times 10^2$	0
5	acetyl chloride	$(2.5 \pm 0.2) \times 10^4$	12
6	acetic anhydride	$(2.3 \pm 0.5) \times 10^4$	52
7	ethyl acetate	$(3.1 \pm 0.3) \times 10^{-1}$	<1

^aPseudo-first-order rate constants, k_1 (normalized to unit additive concentration [s]), were determined from measurements with a platinum-glassy carbon ring-disk electrode that was rotated at 900 rpm. ^bYield of *trans*-stilbene oxide was obtained in the KO_2 and additive system.

$\text{H}_2\text{RPO}_4^{\cdot-}$, as observed for CCl_4 , CO_2 , and phosphates. We found that the dissolved O_2 concentration has no effect on epoxidation yields in the oxidation of *trans*-stilbene in the KO_2 and CCl_4 system. (Epoxidation yield of *trans*-stilbene: 42% (under Ar atmosphere), 46% (under air), 47% (under 100% O_2)).¹⁷ Furthermore, in Tables VI-VIII, the percentage of incorporation of ¹⁸O was considerably high under air. These results suggest that ¹⁸ O_2 produced by the reactions of ¹⁸ $\text{O}_2^{\cdot-}$ with CCl_4 , CO_2 , and phosphates can attack the CCl_3^{\cdot} , $\text{CO}_2^{\cdot-}$, and phosphate anion radical more easily than ¹⁶ O_2 dissolved in the reaction solution by the solvent cage effect. Sawyer et al. have reported that there is a good correlation between the logarithm of $k_1/[s]$ for the reaction of $\text{O}_2^{\cdot-}$ with polyhalides having a trichloromethyl group and the reduction potentials of polyhalides.¹⁵ The result suggests that the SET step is the rate-determining one for the reaction of $\text{O}_2^{\cdot-}$ with polyhalides.

The reactivities of these peroxy intermediates are either electrophilic or nucleophilic, depending upon the added compound. In the cases of CCl_4 and CO_2 , the peroxy intermediates have electrophilic reactivities, while with phosphates, the peroxy intermediate has nucleophilic reactivity.

The peroxy intermediates formed by $\text{O}_2^{\cdot-}$ and various compounds are thought to play important roles in biological systems. CCl_3OOH may be the ultimate species in the hepatotoxic effect of CCl_4 .²³ We have reported that the reaction of CCl_4 with $\text{O}_2^{\cdot-}$ caused serious damages in biological systems in vivo.¹⁸ It may be noteworthy that the reactivities of polyhalides with $\text{O}_2^{\cdot-}$ and epoxidation yields correlate well with the hepatotoxic activities of polyhalides. The activated carbon dioxide species ($^-\text{OC}(\text{O})\text{OOH}$, $^-\text{OC}(\text{O})\text{OC}(\text{O})\text{OOH}$, etc.) are reported to be produced in

(23) (a) Slater, T. F. *Ciba Found. Symp.* 1979, 65, 143-163. (b) Mico, B. A.; Pohl, L. R. *Arch. Biochem. Biophys.* 1983, 220, 596-609.

the vitamin K-dependent carboxylation of glutamic acid residues of prothrombin.²⁴ Furthermore, the reaction of $O_2^{\cdot-}$ with phosphates offer some suggestion about the mechanism of nucleic acid damage by active oxygen species. The biological roles of these peroxy species are under investigation.

Experimental Section

Equipment. The Shimadzu 6-AM PEG 6000 GC system and the Shimadzu LC-3A Nucleosil μC_{18} system were used to separate and identify reaction products. A Yanaco Model P-1000 voltammetric analyzer and Model FG-121B, N F Circuit Design Block Co., Ltd., were used to measure cyclic voltammograms. Raman Spectra were obtained with a Jasco R-800 laser raman spectrophotometer. A JEOL DX-300 GC-MS system was used to determine the incorporation ratio of ^{18}O into reaction products. A Nikko Keisoku potential sweeper NPS-2, dual potentiogalvanostat DGPS-1, motor speed controller SC-5, rotating ring-disk electrodes RRDE-1 rotator, and glassy carbon or platinum ring-disk electrodes were used for the kinetic measurements.

Chemicals and Reagents. Potassium superoxide (KO_2) was prepared according to the method of Rosenthal,²¹ and 18-crown-6-ether was purchased from Tokyo Kasei. Tetraethylammonium perchlorate (TEAP) was purchased from Wako Pure Chemical Industries, Ltd. Carbon dioxide (CO_2) gas was obtained from Suzuki Shokan Inc. Other reagents and substrates were of analytical grade or of the highest purity available and generally were used without further purification.

Methods. Oxidation of Various Substrates in the System of KO_2 and Polyhalides. Finely powdered KO_2 (3.0 mmol) was added to an acetonitrile solution (18 mL) containing the substrates (0.3 mmol) and 18-crown-6-ether (0.3 mmol). Then polyhalide (15 mmol) was added dropwise to the solution. The resulting heterogeneous mixture was vigorously stirred at 10–15 °C for 4–24 h with protection from moisture. After the reaction was finished, the mixture was filtered to remove unreacted KO_2 . The product yields were determined by HPLC and GC.

Cyclic Voltammetry of O_2 in the Absence or Presence of Polyhalides. The reactivities of polyhalides with $O_2^{\cdot-}$ were monitored by measurement of cyclic voltammetry of dioxygen in the absence or presence of polyhalides using platinum for the electrode and dimethylformamide as the

solvent. All the solutions were prepared at 1.0 mM and contained 0.1 M tetraethylammonium perchlorate (TEAP) as a supporting electrolyte.

Oxidation of Substrates in the System of KO_2 and CO_2 . The substrate (0.3 mmol) and 18-crown-6-ether (0.3 mmol) were dissolved in dimethylformamide (18 mL) with bubbling of CO_2 gas for 5 min, followed by addition of finely powdered KO_2 (3.0 mmol). The reaction mixture was vigorously stirred at 15–20 °C under a CO_2 atmosphere for 20 h. The reaction mixture was filtered and the product yield was determined by HPLC and GC.

Oxidation of Substrates in the System of KO_2 and Phosphates. Finely powdered KO_2 (3.0 mmol) was added to a dimethylformamide solution (18 mL) containing the substrates (0.3 mmol), 18-crown-6-ether (0.3 mmol), and phosphate (0.45 mmol). The reaction mixture was vigorously stirred at 15–20 °C for 1–5 h with protection from moisture. The reaction mixture was filtered and the product yields were determined by HPLC or GC.

Experiments Incorporating ^{18}O into Reaction Products. Ar, air, or $^{16}O_2$ gas was bubbled into the reaction mixture of substrate, 18-crown-6-ether and $K^{18}O_2$ for 30 min before the reaction was started in a flask with a serum rubber stopper. This was done to examine the oxygen atom source incorporated into the reaction products under various $^{16}O_2$ concentration conditions. Next, the additive compound in a solvent prebubbled with the same gas was added to the reaction mixture via a gas-tight syringe. The resulting reaction mixture was vigorously stirred with bubbling of the same gas. The reaction was quenched by the addition of prebubbled H_2O . The incorporation ratio of $^{18}O_2$ into the reaction products was determined by GC-MS.

Kinetic Measurements by Ring-Disk Voltammetry. The rate of reactions of various additive compounds with $O_2^{\cdot-}$ was measured with a rotating ring-disk electrode under pseudo-first-order conditions. A rotating (900 rpm) platinum ring-glassy carbon disk was used for the measurement in air-saturated 0.1 M tetraethylammonium perchlorate (TEAP) in dimethylformamide. The bulk O_2 concentration was ca. 1 mM. The data were analyzed by the procedures described by Albery and Hitchman to obtain the pseudo-first-order rate constant, k_1 .²⁵

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(24) (a) Stah, D. V.; Suttie, J. W. *Biochem. Biophys. Res. Commun.* **1974**, *60*, 1397–1402. (b) Esnouf, M. P.; Green, M. R.; Hill, H. A. O.; Irvine, G. B.; Walter, S. J. *Biochem. J.* **1978**, *174*, 345–348. (c) Esnouf, M. P.; Fainey, A. I.; Green, M. R.; Hill, H. A. O.; Okolow-Zubkouska, M. J.; Walter, S. J. In *Biological and Clinical Aspects of Superoxide and Superoxide Dismutase*; Bannister, W. H., Bannister, J. V., Eds.; Elsevier/North-Holland: New York, 1980, pp 72–83.

(25) Albery, W. J.; Hitchman, M. L. In *Ring-Disk Electrodes*; Clarendon Press: Oxford, 1971.

1-Oxabicyclobutonium Ions Can Intervene in Epoxycarbonyl and 3-Oxetanyl Solvolyses

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Abstract: The solvolytic reactions of **9** and **12** have been investigated with a view toward probing the possible stereospecific involvement of 1-oxabicyclobutonium ions **4** and **5**, respectively. Solvolysis of **9** in aqueous acetone led to the detection of **10** and **11** as products. A similar experiment on **12** led to **13** and **14** identified by independent synthesis from **15**. Oxetanyl ester **13** was demonstrated to lead to **14** under the solvolytic conditions employed. These results are compatible only with mechanisms requiring the stereospecific, rate-determining, and anchimerically assisted formation of **4** in the reactions of **9** and **10**, and of **5** in the reactions of **12** and **13**. Ions **6** and **7** are not intermediates. Ab initio molecular orbital theory calculations at the MP2/6-31G*//HF/6-31G* level confirmed that of ions **4**–**7** likely to intervene, **4** and **5** are least energetic. This is the first unequivocal demonstration of the involvement of 1-oxabicyclobutonium ions in epoxycarbonyl and 3-oxetanyl solvolytic processes and of the ability of epoxides to act as conventional neighboring group participants toward adjacent electrophilic sites.

Although the solvolytic chemistry of epoxycarbonyl systems has been investigated repeatedly over the last 20 years, consistent and compelling evidence that the epoxide substructure can play a

participatory role in the ionization step and that 1-oxabicyclobutonium ions can mediate these and related reactions remains lacking. Thus while Richey's¹ epoxycarbonyl solvolytic rear-