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THE REACTIVITY OF SUPEROXIDE: A POTENT OXIDANT GENERATED IN SITU FROM SUPEROXIDE AND CO_2

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Abstract: The reaction of CO_2 with superoxide cooxidized sulfides and olefins to the corresponding sulfoxides and epoxides, respectively, in dimethylformamide. The peroxy intermediates, $CO_4^{\cdot-}$ and $C_2O_6^{\cdot-}$, generated in situ from superoxide and CO_2, were proposed as the ultimate oxidants in the oxidations.

Superoxide ($O_2^{\cdot-}$) appears to play an important role in various biological processes, such as inflammation,[1-3] carcinogenesis,[4-7] radiation-induced damage,[8,9] aging,[10,11] phagocytosis and enzyme reactions.[12] $O_2^{\cdot-}$ has been considered to have diverse but not vigorous reactivities compared with other active oxygen species such as •OH, $^1O_2$, H_2O_2,[13] but has been reported to exert deleterious effects on living cells.[14,15] Thus, the mechanism of the biological effects of $O_2^{\cdot-}$ has been of great interest.[16-19]

We have reported that $O_2^{\cdot-}$ oxidizes olefins and substrates having labile hydrogens in the presence of acyl halides or polyhalides.[20-25] Furthermore, the phosphate moiety of nucleotides enhances the reactivity of $O_2^{\cdot-}$ in the nucleobase release reaction from nucleotides.[26,27] $O_2^{\cdot-}$ reacts with halides or phosphate functional groups to form peroxy intermediates which have more vigorous reactivities than $O_2^{\cdot-}$ alone. These peroxy radical intermediates, generated in situ from $O_2^{\cdot-}$ and some halides or phosphates, have been revealed to be the species responsible for the oxidations.[28-31] Sawyer et al. have reported that in aprotic solvents, $O_2^{\cdot-}$ undergoes nucleophilic addition to carbon dioxide (CO_2) to yield peroxy intermediates ($CO_4^{\cdot-}$ and $C_2O_6^{\cdot-}$).[32] These species may be more reactive than $O_2^{\cdot-}$ alone.

In this communication, we report that peroxy intermediates, derived from $O_2^{\cdot-}$ and CO_2, oxidize sulfides and olefins. In a general procedure, the substrate and 18-crown-6-ether were dissolved in dimethylformamide with bubbling CO_2 for five minutes, followed by addition of freshly prepared potassium superoxide (KO_2).[33] The reaction mixture was vigorously stirred at 15-20 °C under a CO_2 atmosphere for 20 hr. The reaction mixture was filtered and the product yields were determined by HPLC (Table I). When ethyl methyl sulfide was used as the substrate, ethyl methyl sulfoxide was obtained in good yield (84 %). From benzyl methyl

Table I Cooxidation of Sulfides during Oxidation of CO_2 with Superoxide

Substrate	Product %	Recovery %
Ethyl methyl sulfide	Ethyl methyl sulfoxide 84 (0)*	6 (98)
Benzyl methyl sulfide	Benzyl methyl sulfoxide 78 (0), Benzaldehyde 2 (0), Benzoic acid 0 (49)	20 (41)
Dibenzyl sulfide	Dibenzyl sulfoxide 39 (0), Benzalehyde 1 (0), Benzoic acid 2 (44)	47 (15)

The reaction mixture contained 0.4 mmol of substrate, 4 mmol of KO_2 and 0.4 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. * Values in parentheses indicate yields in the absence of CO_2.

Table II Cooxidation of Olefins during Oxidation of CO_2 with Superoxide

Substrate	Product %	Recovery %
trans-Stilbene	trans-Stilbene oxide 12 (0), Benzaldehyde 1 (0)	
	Benzoic acid 1 (0)	63 (94)
Styrene	Styrene oxide 10 (0), Benzaldehyde 1 (0), Benzoic acid 1 (0)	88 (95)
α-Methylstyrene	α-Methylstyrene oxide 23 (0), Acetophenone 14 (0)	57 (95)
β-Methylstyrene	β-Methylstyrene oxide 34 (0), Benzaldehyde 3 (0),	
	Benzoic acid 1 (11), Propiophenone 1 (0),	55 (83)
p-Chlorostyrene	p-Chlorostyrene oxide 4 (0), p-Chlorobenzoic acid 4 (8)	92 (84)

The reaction mixture contained 0.3 mmol of substrate, 3 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. *Values in parentheses indicate yields in the absence of CO_2.

sulfide and dibenzyl sulfide, the corresponding sulfoxides were obtained in 78 % and 39 % yield, respectively, along with the minor products benzaldehyde and benzoic acid. On the other hand, in the absence of CO_2, benzoic acid was mainly obtained (Table I). No sulfone was obtained from any sulfides with treatment of $O_2^{\cdot-}$ and CO_2. When trans-stilbene was used as the substrate, the major product was trans-stilbene oxide (12 %). trans-Stilbene oxide was also obtained in 12 % yield using dry ice as the CO_2 source. From other olefins, the corresponding epoxides were also obtained as shown in Table II. In the absence of CO_2, these reactions did not proceed at all and the starting materials could be recovered. These results suggest that the reactive species generated from $O_2^{\cdot-}$ and CO_2 should be a more potent oxidant than $O_2^{\cdot-}$.

We examined the incorporation of ^{18}O into ethyl methyl sulfoxide and styrene oxide in the $K^{18}O_2$ and CO_2 system in order to clarify the oxidation mechanism. $K^{18}O_2$ was prepared from benzhydrol, potassium tert-butoxide and $^{18}O_2$ according to the method of Rosenthal.[33] Since the resulting KO_2 powder contained a small amount of $K^{16}O_2$, its $K^{18}O_2$ content was determined by Raman spectroscopy. The KO_2 powder showed a strong Raman line at 1088 cm^{-1} with a weak line at 1154 cm^{-1} (Fig. 1). The line at 1154 cm^{-1} could be

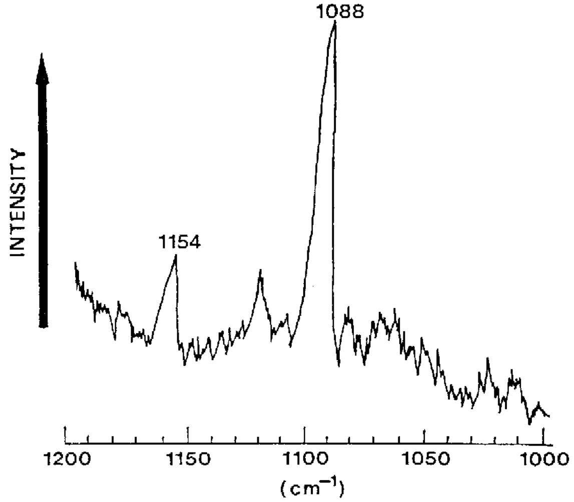
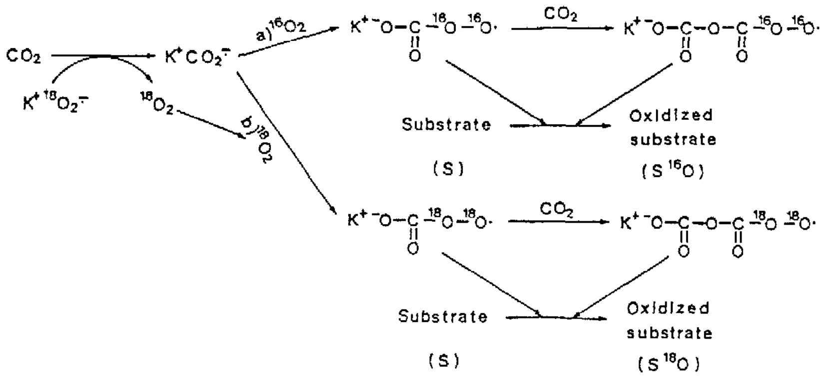


Figure 1. Raman spectrum of $K^{18}O_2$ and $K^{16}O_2$

Scheme I The proposed reaction mechanism



·under Air or $^{16}O_2$ atmosphere ··· path a) or b)
·under Ar atmosphere ··· path b)

assigned to the ^{16}O-^{16}O stretching vibration because Hendra et al. have reported almost the same Raman line (1148 cm^{-1}) of $K^{16}O_2$,[34] while the line at 1088 cm^{-1} could be assigned to ^{18}O-^{18}O stretching vibration because the $v = 2\pi(k/m)^{1/2}$ expression gave an estimation of 1087.8 cm^{-1} as a Raman line of $K^{18}O_2$. From the intensity ratio of the two lines, the content of $K^{18}O_2$ was determined to be 78 %. Ar, air or $^{16}O_2$ gas was bubbled for 30 min into the reaction mixture before starting the reactions in order to examine the oxygen atom source incorporated into the reaction products under various $^{16}O_2$ concentration conditions. With bubbling Ar, 100 % incorporation of oxygen atoms derived from KO_2 into both of sulfoxide and styrene oxide were observed in the oxidations of the sulfide and styrene, based on the $^{18}O_2^{\cdot-}$ content of the KO_2 powder using GC-MS (JEOL DX-300). When air or $^{16}O_2$ gas was bubbled, the incorporation ratio of ^{18}O decreased as the dissolved $^{16}O_2$ concentration increased; that is, the % incorporation ratios of ^{18}O into ethyl methyl sulfoxide were 41 % and 10 % under air and $^{16}O_2$ bubbling, respectively. Incorporation ratios of ^{18}O into styrene oxide were 54 % and 14 % under air and $^{16}O_2$ bubbled conditions, respectively.

The results, that the isotope mixing was observed in the oxidations of styrene and ethyl methyl sulfide under aerobic conditions, not under Ar atmosphere, led us to propose the following reaction mechanism (Scheme I). $O_2^{\cdot-}$ reduces CO_2 to form $CO_2^{\cdot-}$. Under aerobic conditions, $^{18}O_2$ produced from $K^{18}O_2$ or $^{16}O_2$ dissolved in the reaction solution attacks $CO_2^{\cdot-}$ to form $CO_4^{\cdot-}$ (path a or b in Scheme I), which may react with another CO_2 to form $C_2O_6^{\cdot-}$. These radical species can oxidize sulfides and olefins. Under Ar atmosphere, as $CO_4^{\cdot-}$ and $C_2O_6^{\cdot-}$ can be produced only from $^{18}O_2$ (path b), 100 % incorporation of ^{18}O into the reaction products was observed. The active oxidizing species are electrophilic, because electron-rich olefins such as α-methylstyrene and β-methylstyrene were oxidized in better yields than electron-poor olefins such as p-chlorostyrene (Table II) and no sulfones were obtained from the sulfides. When H_2O_2 was used instead of KO_2 in the oxidations, no oxidized products were obtained and the starting materials were recovered in 97 % yield. Furthermore, the peroxide $HOOC(O)O^-$ can not be formed without H_2O in the KO_2-CO_2 system.[32] These results indicate that the peroxy radicals, $CO_4^{\cdot-}$ and $C_2O_6^{\cdot-}$, are the ultimate oxidants.

In conclusion, CO_2 enhances reactivity of $O_2^{\cdot-}$ by forming reactive radicals, which may cause serious damage in biological systems. Further studies on the reaction of $O_2^{\cdot-}$ with CO_2 in the biological systems are in progress.

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