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Evidence for Formation of Diphenylphosphinic Peroxy Radical Intermediate: Spin Trapping and Chemical Reactivity of the New Phosphorus Radical Generated from Diphenylphosphinic Chloride and Superoxide

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ABSTRACT

Diphenylphosphinic chloride reacts with the superoxide anion radical in acetonitrile under mild conditions to form a peroxyphosphorus radical intermediate which shows strong oxidizing abilities for the epoxidation of olefins, oxidation of sulfides to sulfoxides, desulfurization of thioamides to amides, and oxidation of triarylphosphines to phosphine oxides. The radical can be trapped using a spin trapping method.

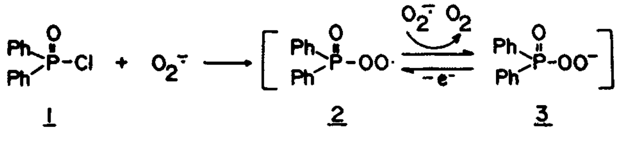
The discovery of $O_2^{\cdot -}$ as a respiratory intermediate of aerobic organisms in 1969 by Fridovich and McCord [1] made it biochemically and chemically important to understand the chemical reactivity of this radical anion. It has been amply demonstrated that $O_2^{\cdot -}$ displays four basic modes of action, including deprotonation, H-atom abstraction, nucleophilic attack, and electron transfer [2]; however, due to its low reactivity in aprotic organic solvents, the superoxide anion radical is relatively inactive and of limited use in organic synthesis [3].

Accumulation of physical and chemical properties of the superoxide anion radical has prompted us to study organic synthesis using this superoxide. There have been arguments as to whether such peroxy heteroatom compounds as the dialkoxyphosphorus peroxy intermediate [4] and the arenesulfur peroxy intermediate [5] are radical or anion species. It has also been postulated that the phosphate peroxy intermediate generated from a nucleotide and superoxide may be involved as a radical species in base liberation reactions [6].

RESULTS AND DISCUSSION

We have now found that diphenylphosphinic chloride reacts with superoxide in acetonitrile under mild conditions to form a peroxyphosphorus radical intermediate (**2**) which was trapped by the use of a spin trapping method and its presence confirmed by various chemical reactions.

SCHEME 1



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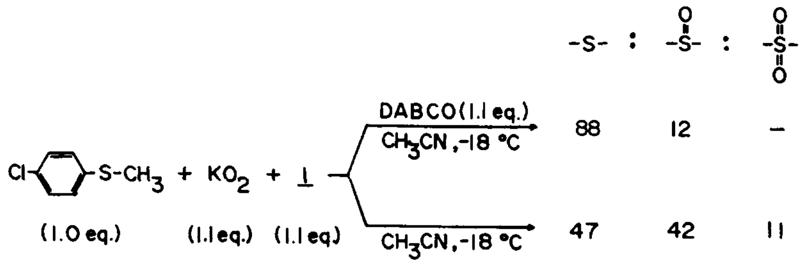


SCHEME 2

A question has been raised whether the real active intermediate involves a radical (**2**) or anionic species (**3**) because a one electron transfer from $O_2^{\cdot -}$ to (**2**) may readily convert (**2**) to (**3**). In this paper, we wish to consider whether the key intermediate behaves like a radical or an anion in this system. Various oxidations of olefins and sulfides have been carried out to analyze the distribution of products, and spin trapping of (**2**) has also been carried out by use of a radical trapping reagent.

It is known that anionic epoxidation of *cis*-stilbene occurs stereospecifically to form *cis*-stilbene oxide, but that electrophilic radical epoxidation results in the formation of *trans*-stilbene oxide [7]. Both *trans*-stilbene and *cis*-stilbene were treated with the peroxyphosphorus intermediate (**2** or **3**) to give only trans-stilbene oxide [8] (from *trans*-stilbene, 28%; from *cis*-stilbene, 12%), which suggests that the peroxyphosphorus intermediate (**2**) is the active species responsible for the oxidations, as in the case of the acylperoxy radical (ArC(O)OO·) [9] and the phenyl nitroso oxide radical (PhNOO·) [10].

It is surprising that the active intermediate (**2**) shows a strong electrophilic character under the basic conditions [11] that prevail in the presence of $O_2^{\cdot -}$, namely, when the oxidation of a mixture of phenyl methyl sulfide and a *p*-substituted phenyl methyl sulfide to sulfoxides by (**2**) (or (**3**)) was carried out in a series of competition reactions, the order of relative reactivities was *p*-methoxyphenyl- > *p*-methylphenyl- > phenyl- > *p*-chlorophenyl methyl sulfide ($\rho = -1.14, \gamma = 0.994$ against Hammett σ_p^+ values)[12]. The value ($\rho = -1.14$) which shows a strong electrophilicity of the attacking reagent is much larger than the value of -0.53 [13] obtained from the oxidation of sulfoxides to sulfones using *m*-chloroperbenzoic acid under acidic conditions. Moreover, in the presence of 1.4-diazabicyclo[2.2.2]octane (DABCO), which is known to reduce a radical to the anion by one electron transfer [14], the oxidation of *p*-chlorophenyl methyl sulfide to the corresponding sulfoxide was inhibited, as shown above.

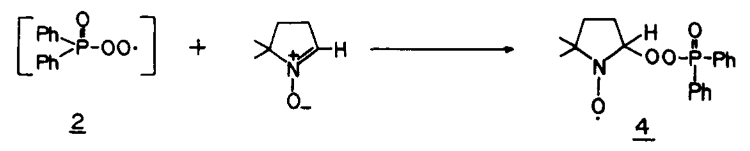
These results provide additional evidence for the formation of the peroxy radical intermediate, $Ph_2P(O)OO\cdot$ (**2**), in the oxidations.

We have further carried out spin trapping studies in order to identify the radical intermediate (by electron spin resonance [ESR] spectroscopy) responsible for the oxidations. The spin trapping method has been proved to be of great use for elucidation of reaction mechanisms involving radical species [15, 16]. Pure 5,5-dimethyl-1-pyrroline-1-oxide (DMPO) was used. The use of DMPO as a spin trapping reagent has the advantage that the α-hydrogen of the DMPO spin adduct exhibits hyperfine coupling which is very sensitive to the nature of the trapping radical [17]. The detailed procedure was referenced in our previous paper [18].

Figure 1 shows the ESR spectrum of the spin adduct formed by the reaction of $O_2^{\cdot -}$ with diphenylphosphinic chloride in the presence of DMPO. Since the values of the ESR spectrum, which has the hyperfine coupling constants, $a_N = 12.5$ G and $a_H = 10.2$ G, are different from those reported for the DMPO spin adducts of $O_2^{\cdot -}$, $HO_2\cdot$, and $HO\cdot$ (17, 19], we conclude that DMPO efficiently traps the radical intermediate (**2**) produced by the reaction of $O_2^{\cdot -}$ with (**1**). The reaction scheme described above is further supported by the following observation. Triphenyl phosphite was used as a quencher of the peroxyphosphorus radical intermediate as shown in scheme 4.

When superoxide solution was added to the mixture of DMPO, triphenyl phosphite and (**1**) in

SCHEME 3



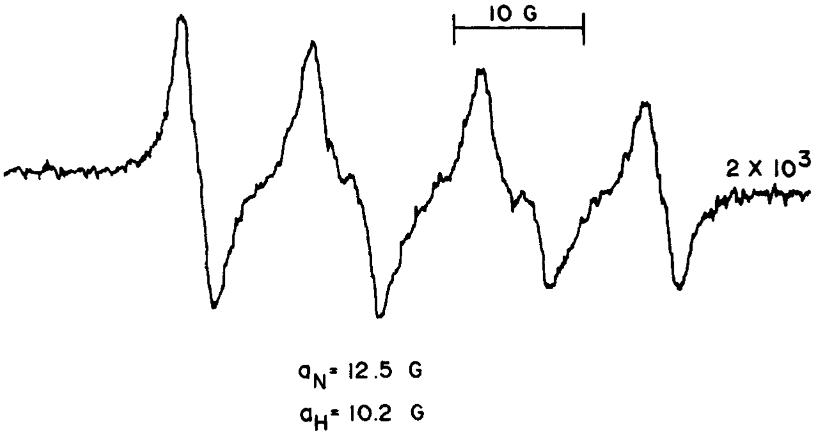


FIGURE 1

CH_3CN, the ESR signal that can be ascribed to the DMPO spin adduct of (**2**) could not be detected. On the other hand, the oxidation product, triphenyl phosphate (**5**) was obtained. Probably, the peroxyphosphorus radical (**2**) preferentially reacted with triphenyl phosphite to give (**5**) instead of (**4**); the reaction rate of (**2**) with DMPO may be much slower than that of (**2**) with triphenyl phosphite.

From the above results obtained by oxidations and direct spin trapping, and quenching of (**2**) with triphenyl phosphite, it can be concluded that the peroxyphosphorus radical (**2**) generated in situ from $O_2^{\overline{\cdot}}$ and (**1**) is the active intermediate responsible for the oxidations. The oxidizing abilities of (**2**) are shown in Table 1. The scope of chemical reactivities of (**2**) is under continuing investigation.

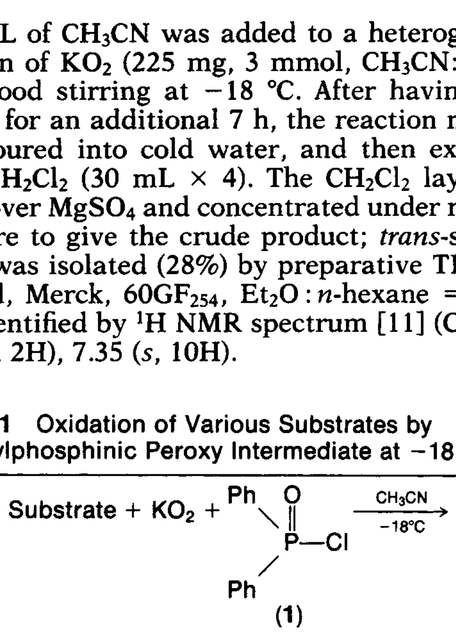
EXPERIMENTAL

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. ^1H nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60A instrument with tetramethylsilane as an internal standard. Infrared spectra were taken on a Bomem MB-100 FT-IR spectrophotometer. ESR spectra were measured on a Jeol JES-FE3AX X-band spectrometer. Acetonitrile was distilled from P_2O_5 before use.

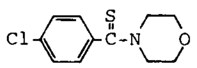
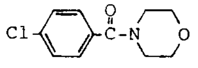
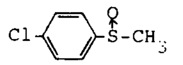
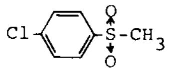
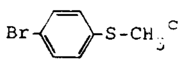
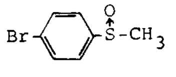
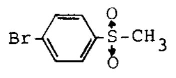
Reaction of trans-*Stilbene with* KO_2 *and* $Ph_2P(O)Cl$

A solution of diphenylphosphinic chloride (114.6 μL, 1.0 mmol) and *trans*-stilbene (93 mg, 0.5 mmol) in 4 mL of CH_3CN was added to a heterogeneous solution of KO_2 (225 mg, 3 mmol, CH_3CN: 2 mL) with good stirring at −18 °C. After having been stirred for an additional 7 h, the reaction mixture was poured into cold water, and then extracted with CH_2Cl_2 (30 mL × 4). The CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product; *trans*-stilbene oxide was isolated (28%) by preparative TLC (Silica Gel, Merck, $60GF_{254}$, Et_2O : *n*-hexane = 1 : 10) and identified by ^1H NMR spectrum [11] ($CDCl_3$) δ 3.75 (*s*, 2H), 7.35 (*s*, 10H).

TABLE 1 Oxidation of Various Substrates by Diphenylphosphinic Peroxy Intermediate at −18 °C

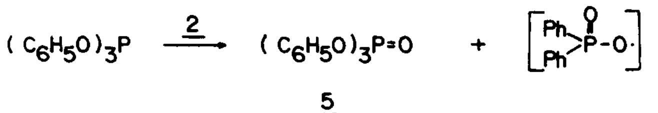


$$\text{Substrate} + KO_2 + Ph_2P(O)Cl\ (\mathbf{1}) \xrightarrow[-18°C]{CH_3CN}$$

Run	*Substrate*[a]	*Time* (*h*)	*Product*	*Yield*[b] (%)
1		6.0		91
2	$(PhO)_3P$	1.5	$(PhO)_3P{=}O$	88
3	Ph_3P	1.0	$(Ph)_3P{=}O$	96
4		6.0		82
5		4.0		12
				88

[a] Molar ratio of KO_2 : $Ph_2P(O)Cl$: Substrate = 6 : 2 : 1.
[b] Isolated yields.
[c] Determined by ^1H NMR.

SCHEME 4



$$(C_6H_5O)_3P \xrightarrow{\mathbf{2}} (C_6H_5O)_3P{=}O + [Ph_2P(O){-}O\cdot]$$

5

Detection of DMPO Spin Adduct (**4**)

To a heterogeneous solution of KO_2 (7.5 mg, 0.1 mmol; CH_3CN, 1 mL) was added a solution 18-crown-6 (32 mg, 0.12 mmol) in 2.5 mL of CH_3CN at −20 °C under N_2. To a solution of diphenylphosphinic chloride (4.5 mg, 0.02 mmol) in 0.6 mL of CH_3CN was added 15 μL (0.13 mmol) of DMPO at −20 °C, and then 0.2 mL of the KO_2 and 18-crown-6 solution was added to the diphenylphosphinic chloride and DMPO solution. Quickly the reaction mixture was transferred to the ESR tube and the ESR spectra were measured at room temperature.

Quenching Experiment for Identification of Peroxy Radical Intermediate

A solution of 18-crown-6 (32 mg, 0.12 mmol), in 2.5 mL of CH_3CN was added to the heterogeneous solution of KO_2 (7.5 mg, 0.1 mmol) in 1 mL of CH_3CN at −20 °C under N_2. To a solution of diphenylphosphinic chloride (4.5 mg, 0.02 mmol) in 0.6 mL of CH_3CN was added 15 μL (0.13 mmol) of DMPO and triphenyl phosphite (64 μL, 0.2 mmol) as a quencher of the peroxyphosphorus radical intermediate, and then 0.2 mL of KO_2 and 18-crown-6 solution was added to the solution of DMPO, triphenyl phosphite, and diphenylphosphinic chloride at −20°C. The reaction mixture was transferred to the ESR tube and the ESR spectra were measured at room temperature.

Reaction of 4-(4-Chlorothiobenzoyl)-morpholine with KO_2 and $Ph_2P(O)Cl$

A solution of diphenylphosphinic chloride (114.6 μL, 1.0 mmol) and 4-(4-chlorothiobenzoyl)-morpholine (120.75 mg, 0.5 mmol) in 4 mL of CH_3CN was added to a heterogeneous solution of KO_2 (225 mg, 3 mmol; CH_3CN, 2 mL) with good stirring at −18 °C. After having been stirred further for 6 h, the reaction mixture was poured into cold water. The aqueous solution was extracted with CH_2Cl_2 (30 mL × 4). The CH_2Cl_2 layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product. The crude product was purified by preparative TLC (Silica Gel, Merck, GF_{254}, $CH_2Cl_2 : MeOH = 25 : 1$) to give 102.6 mg (91%) of pure 4-(4-chlorobenzoyl)morpholine; IR (KBr) 1620, 1440, and 1015 cm^{-1}.

Reaction of Triphenyl phosphite with KO_2 and $Ph_2P(O)Cl$

A solution of triphenyl phosphite (167 mg, 0.52 mmol) and diphenylphosphinic chloride (194.7 μL, 1 mmol) in 3 mL of CH_3CN was added to a solution of KO_2 (225 mg, 3 mmol) in 3 mL of CH_3CN at −18 °C. After having been stirred for 1.5 h, the reaction mixture was filtered and the filtrate concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (Silica Gel, Merck, 70–230 mesh, 1 cm × 20 cm, $Et_2O : n$-hexane = 1 : 1) to give pure triphenyl phosphate (143.3 mg, 88%); IR(KBr) 1591, 1489, 1189, 976 cm^{-1}.

Reaction of Triphenylphosphine with KO_2 and $Ph_2P(O)Cl$

To a solution of KO_2 (225 mg, 3 mmol) in 3 mL of CH_3CN was added a solution of triphenylphosphine (132.4 mg, 0.5 mmol) and diphenylphosphinic chloride (194.7 μL, 1 mmol) in 3 mL of CH_3CN at −18°C. After the mixture had been stirred for 1 h, a 1 N KOH solution (20 mL) was added. The aqueous mixture was extracted with CH_2Cl_2 (30 mL × 4). The combined CH_2Cl_2 layers were washed with brine, dried over $MgSO_4$, filtered, and the filtrate condensed under reduced pressure. The crude product was purified by preparative TLC (Silica Gel, Merck, GF_{254}, Et_2O only) to give 132.8 mg (96%) of triphenylphosphine oxide; mp = 152–154°C (lit. [21] 156°C).

Reaction of p*-Chlorophenyl Methyl Sulfoxide with KO_2 and $Ph_2P(O)Cl$*

To a solution of KO_2 (225 mg, 3 mmol) and *p*-chlorophenyl methyl sulfoxide (87.25 mg, 0.5 mmol) in 4 mL of CH_3CN was added a solution of diphenylphosphinic chloride (194.7 μL, 1 mmol) in 2 mL of CH_3CN at −18 °C. After having been stirred for 6 h, the reaction mixture was poured into a 10% KOH solution, extracted with CH_2Cl_2 (30 mL × 4), dried over $MgSO_4$, filtered, and the filtrate condensed under reduced pressure. The crude product was purified by preparative TLC (Silica Gel, Merck, GF_{254}, $Et_2O : n$-hexane = 3 : 1) to give 78 mg of *p*-chlorophenyl methyl sulfone (82%), which was identified by ^1H NMR ($CDCl_3$) δ 3.07 (s, 3H), 7.34, 7.91 (dd, 4H, J = 9 Hz).

Reaction of p*-Bromophenyl Methyl Sulfide with KO_2 and $Ph_2P(O)Cl$*

To 194.7 μL of diphenylphosphinic chloride (1 mmol) was added a solution of KO_2 (225 mg, 3 mmol) and *p*-bromophenyl methyl sulfide (101.5 mg, 0.5 mmol) in 6 mL of CH_3CN at −18 °C. After having been stirred for 4 h, the reaction mixture was poured into 1 N KOH solution (20 mL), dried over $MgSO_4$, filtered, and the filtrate condensed under reduced pressure to give a mixture of *p*-bromophenyl methyl sulfone (89%) and *p*-bromophenyl methyl sulfoxide (11%), which was determined and identified by ^1H NMR.

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