Scandium Ion-accelerated Scavenging Reaction of Cumylperoxyl Radical by a Cyclic Nitroxyl Radical via Electron Transfer

Ikuo Nakanishi,*[1,2] Kumiko Kawaguchi,[1,2,3] Kei Ohkubo,[2] Tomonori Kawashima,[1,2,3] Sushma Manda,[1]
Hideko Kanazawa,[3] Keizo Takeshita,[4] Kazunori Anzai,[1] Toshihiko Ozawa,[1,5]
Shunichi Fukuzumi,*[2] and Nobuo Ikota*[1]
[1]*Redox Regulation Research Group, Research Center for Radiation Safety,*
National Institute of Radiological Sciences (NIRS), Inage-ku, Chiba 263-8555
[2]*Department of Material and Life Science, Graduate School of Engineering, Osaka University, SORST,*
Japan Science and Technology Agency (JST), Suita, Osaka 565-0871
[3]*Department of Physical Pharmaceutical Chemistry, Kyoritsu University of Pharmacy, Minato-ku, Tokyo 105-8512*
[4]*Faculty of Pharmaceutical Sciences, Sojo University, Ikeda, Kumamoto 860-0082*
[5]*New Industry Creation Hatchery Center (NICHe), Tohoku University, Aoba-ku, Sendai, Miyagi 980-8579*

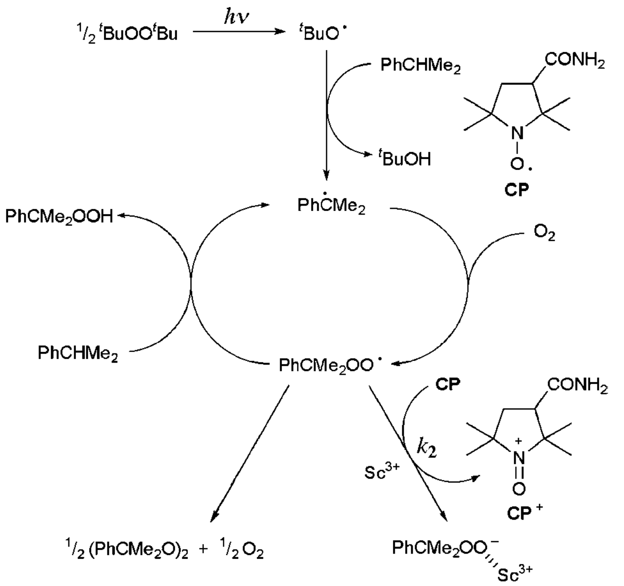
(Received November 13, 2006; CL-061327; E-mail: nakanis@nirs.go.jp)

A cyclic nitroxyl radical used as a spin probe efficiently scavenges cumylperoxyl radical in an aprotic medium via an electron-transfer process, which is significantly accelerated by the presence of scandium ion.

Stable cyclic nitroxyl radicals, extensively used as spin probes for in vivo ESR measurements,[1] are known to act as an efficient protector against radical-induced damage.[2] Extensive efforts have been devoted to elucidate the mechanism of the reactions of nitroxyl radicals with reactive oxygen species (ROS), such as hydroxyl radical ($^{\bullet}$OH)[3,4] and superoxide (HO$_2^{\bullet}$/O$_2^{\bullet-}$),[2a,5] as well as secondary radicals derived from ROS, such as carbon-centered radicals,[6] nitrogen dioxide ($^{\bullet}$NO$_2$),[7] and nitric oxide ($^{\bullet}$NO).[8] Two mechanisms have been proposed for the reaction between nitroxyl radicals and $^{\bullet}$OH based on pulse radiolytic conductivity measurements, i.e., an electron-transfer oxidation of the nitroxyl radical by $^{\bullet}$OH to form an oxoammonium cation or an electrophilic addition of $^{\bullet}$OH to the oxygen atom of the nitroxyl radical.[9] Nitroxyl radicals were also reported to act as an electron donor to scavenge $^{\bullet}$NO$_2$.[7] On the other hand, the oxoammonium cation was reported to play an essential role to scavenge O$_2^{\bullet-}$[5] as well as $^{\bullet}$NO[8] as a one-electron oxidant. Furthermore, Offer and Samuni have recently reported that nitroxyl radicals inhibit peroxyl radical-mediated DNA scission and enzyme inactivation.[10] However, very little is known about the mechanism for the reaction of nitroxyl radicals with peroxyl radicals, which can be generated by the reaction between carbon-centered radicals and O$_2$ with an almost diffusion-controlled rate.[6a,6b]

We report herein the scavenging reaction of cumylperoxyl radical (PhCMe$_2$OO$^{\bullet}$) by 3-carbamoyl-2,2,5,5-tetramethylpyrrolidine-*N*-oxyl (3-carbamoyl-PROXYL; CP), one of cyclic nitroxyl radicals used as a spin probe, in propionitrile (EtCN) at low temperature (193 K). Based on the acceleration effect of scandium ion on the reaction rates,[11] we demonstrate for the first time that the cyclic nitroxyl radical can act as an electron donor to PhCMe$_2$OO$^{\bullet}$.

The rates of scavenging reactions of CP with PhCMe$_2$OO$^{\bullet}$ were measured using ESR. PhCMe$_2$OO$^{\bullet}$ is formed via a photoinduced radical chain process shown in Scheme 1.[12,13] Under photoirradiation of an oxygen-saturated EtCN solution of cumene and di-*t*-butyl peroxide (^{t}BuOO^{t}Bu), the O–O bond of the ^{t}BuOO^{t}Bu is cleaved to produce *t*-butoxy radical,[14] which abstracts a hydrogen atom from cumene to produce cumyl radical. The cumyl radical is readily trapped by O$_2$ to produce PhCMe$_2$OO$^{\bullet}$. PhCMe$_2$OO$^{\bullet}$ can abstract a hydrogen atom from cumene in the propagation step to yield cumene hydroperoxide, accompanied by regeneration of the cumyl radical. In the termination step, PhCMe$_2$OO$^{\bullet}$ decay via a bimolecular reaction to yield the corresponding peroxide and O$_2$ (Scheme 1).[15] When the light is cut off, the ESR signal intensity decays, obeying second-order kinetics according to the bimolecular reaction.[15] In the presence of CP, the decay rate of PhCMe$_2$OO$^{\bullet}$ after cutting off the light becomes much faster than that in the absence of CP (see Supporting Information, Figure S1[16]). The decay rate in the presence of CP obeys pseudo-first-order kinetics. The pseudo-first-order rate constants (k_{obs}) increase with increasing the CP concentration ([CP]) to exhibit first-order dependence on [CP] (Figure 1a). This indicates that CP can efficiently scavenge PhCMe$_2$OO$^{\bullet}$ in EtCN at 193 K. From the slope of the linear plot of k_{obs} vs the concentration of CP is determined the second-order rate constant (k_2) for the scavenging reaction



Scheme 1. Generation of cumylperoxyl radical and the reaction with CP.

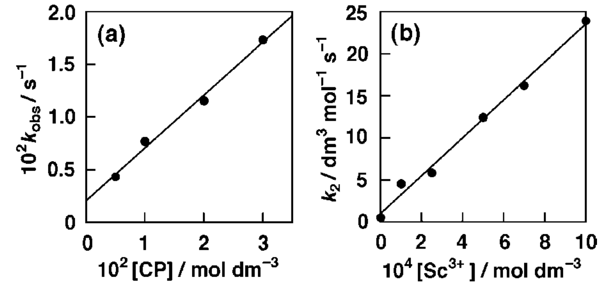


Figure 1. (a) Plot of k_{obs} vs [CP] in the reaction of CP with $\mathrm{PhCMe_2OO^{\bullet}}$ in EtCN at 193 K. (b) Plot of k_2 vs [$\mathrm{Sc^{3+}}$] in the reaction of CP with $\mathrm{PhCMe_2OO^{\bullet}}$ in the presence of $\mathrm{Sc(OSO_2CF_3)_3}$ in EtCN at 193 K.

of $\mathrm{PhCMe_2OO^{\bullet}}$ by CP as 5.0×10^{-1} dm^3 mol^{-1} s^{-1} in EtCN at 193 K.

When $\mathrm{Sc(OSO_2CF_3)_3}$ is added to the EtCN solution of CP and $\mathrm{PhCMe_2OO^{\bullet}}$, the decay rate of $\mathrm{PhCMe_2OO^{\bullet}}$ was significantly accelerated as shown in Figure 1b. Such an acceleration indicates that electron transfer from CP to $\mathrm{PhCMe_2OO^{\bullet}}$ to produce oxoammonium cation ($\mathrm{CP^+}$)[17] and $\mathrm{PhCMe_2OO^-}$ may be involved as shown in Scheme 1. It should be noted that there is no interaction between CP and $\mathrm{Sc^{3+}}$, since the g value as well as the hyperfine coupling constant of the ESR spectrum of CP in the presence of $\mathrm{Sc^{3+}}$ is the same as that in its absence.[18] Thus, CP can act as an electron donor to scavenge $\mathrm{PhCMe_2OO^{\bullet}}$. When $\mathrm{Sc(OSO_2CF_3)_3}$ was replaced by $\mathrm{Mg(ClO_4)_2}$, no acceleration effect on the rate of electron transfer from CP to $\mathrm{PhCMe_2OO^{\bullet}}$ was observed. Thus, the acceleration effect of $\mathrm{Sc^{3+}}$ can be ascribed to the strong binding of $\mathrm{Sc^{3+}}$ to $\mathrm{PhCMe_2OO^-}$, which results in a decrease in the free energy of the electron transfer (Scheme 1).[19] In fact, $\mathrm{Sc^{3+}}$ has recently been reported to be the most effective promoter among various metal ions in metal ion-promoted electron-transfer reactions.[20] The k_2 values at various temperatures in the presence of $\mathrm{Sc^{3+}}$ (1.0×10^{-3} mol dm^{-3}) were also determined in the same manner. From the Arrhenius plot of ln k_2 vs $1/T$ (Figure S2[16]) were determined the activation enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) as 36 kJ mol^{-1} and -39 J K^{-1} mol^{-1}, respectively.

The cyclic voltammogram measured for CP in EtCN (0.1 mol dm^{-3} $\mathrm{Bu_4NClO_4}$) showed a reversible redox wave (Figure S3[16]), from which was determined the one-electron oxidation potential (E^0_{ox}) of CP as 0.69 V vs SCE.[21] On the other hand, the one-electron reduction potential (E^0_{red}) of $\mathrm{PhCMe_2OO^{\bullet}}$ determined directly by the cyclic voltammetry was reported to be 0.65 V vs SCE.[15] Virtually the same E^0_{ox} value of CP as the E^0_{red} value of $\mathrm{PhCMe_2OO^{\bullet}}$ is consistent with the relatively small k_2 value for electron transfer from CP to $\mathrm{PhCMe_2OO^{\bullet}}$.

In conclusion, CP scavenges $\mathrm{PhCMe_2OO^{\bullet}}$ via electron transfer from CP to $\mathrm{PhCMe_2OO^{\bullet}}$, which is significantly accelerated by the presence of $\mathrm{Sc^{3+}}$. The detailed mechanistic information in the scavenging reaction of the peroxyl radical by the nitroxyl radical obtained in this study provides a valuable insight into the development of novel antioxidants effective toward oxidative damage induced by reactive oxygen and nitrogen species.

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16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

17 The formation of $\mathrm{CP^+}$ in the reaction between CP and $\mathrm{PhCMe_2OO^{\bullet}}$ in EtCN was confirmed by the increase in the absorption band at 365 nm, which was observed for $\mathrm{CP^+}$ electrochemically generated at 0.8 V vs SCE in EtCN (0.1 mol dm^{-3} $\mathrm{Bu_4NClO_4}$).

18 Although the absorption band at 231 nm ascribable to CP decays in the presence of $\mathrm{Sc^{3+}}$, obeying second-order kinetics according to an electron-transfer disproportionation, the decay rate was sufficiently slow as compared to the rate of scavenging of $\mathrm{PhCMe_2OO^{\bullet}}$ by CP in the presence of $\mathrm{Sc^{3+}}$.

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21 The E^0_{ox} value of CP in $\mathrm{H_2O}$ (0.08 M $\mathrm{Et_4NClO_4}$) was reported to be 0.62 V vs SCE; see: J. R. Fish, S. G. Swarts, M. D. Sevilla, T. Malinski, *J. Phys. Chem.* **1988**, *92*, 3745.