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Electron-Transfer Reactions of Alkyl Peroxy Radicals

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Abstract: One-electron-transfer reactions of alkyl peroxy radicals were studied by pulse radiolysis of aqueous solutions. At pH 13, the methyl peroxy radical was found to rapidly, $k = 1 \times 10^5$–4.9×10^7 M^{-1} s^{-1}, and quantitatively oxidize various organic substrates with $E_{13} = 0.13$–0.76 V vs NHE. On the other hand, this radical was unreactive with compounds with $E_{13} \geq 0.85$ V. Consequently, E_{13} of the methyl peroxy radical is higher than 0.76 V and lower than 0.85 V, which means that E_7 is in the range 1.02–1.11 V. At pH 8, the rate constants of the oxidation of four ferrocene derivatives by the alkyl peroxy radicals ranged from 7.1×10^4 M^{-1} s^{-1} for ferrocenedicarboxylate ($E_8 = 0.66$ V) to 2.3×10^6 M^{-1} s^{-1} for (hydroxymethyl)ferrocene ($E_8 = 0.42$ V). These rate constants were used to evaluate the reduction potential and self-exchange rate of alkyl peroxy radicals in neutral media from the Marcus equation. The calculated $E_7 = 1.05$ V is in excellent agreement with the estimated $E_7 = 1.02$–1.11 V and with one of the previously published values $E_7 = 1.0$ V, but the value is considerably higher than the other $E_7 \sim 0.6$ V. It is suggested that the high reorganization energy, $\lambda = 72$ kcal mol^{-1}, of the peroxide redox couple originates from the requirement for solvent reorganization due to the solvation of hydroperoxide anion in the transition state. In support of this are the activation parameters of the reaction of the methyl peroxy radical with uric acid. The activation entropy is 9 eu lower at pH 7.3 than it is at pH 13.2, whereas the activation enthalpies are unchanged. The importance of entropy control was verified in the reactions of cyclohexyl peroxy radicals with α- and δ-tocopherol in aerated cyclohexane ($\Delta H^{+} \approx 0$ kcal/mol, and $\Delta S^{+} = -25$ and -26 eu). The implications of these findings on the inactivation of alkyl peroxy radicals in general are discussed.

Introduction

Alkyl peroxy radicals, ROO$^\bullet$, are initiators and chain propagators of autoxidation processes in various biological and man-made polymers.[1] Oxidative damage to polyunsaturated fatty acids (PUFA) in living organisms has been shown to lead to deleterious biological consequences, such as inflammation and cancer. In foodstuffs, autoxidation of PUFA causes rancidity. Free radical mediated aging of polyolefins leads to gradual deterioration of their mechanical and physicochemical properties. In contrast to initiation and propagation, which involve H-atom abstraction from the weakest X–H bond, antioxidants may scavenge alkyl peroxy radicals by electron and/or H-atom transfer. Well-known examples of antioxidants–electron donors are natural, ascorbate (vitamin C) and α-tocopherol (vitamin E), and there are man-made antioxidants, butylhydroxytoluene (BHT) and butylhydroxyanisole (BHA), whereas aliphatic and aromatic thiols, such as glutathione, are good H-atom donors.

The redox potential difference between an alkyl peroxy radical and an antioxidant is crucial for the assessment of the ability of antioxidants–electron donors to scavenge and inactivate peroxy radicals. The published values of the reduction potential of alkyl peroxy radicals are $E_7 \sim 0.6$ V[2] and $E_7 = 1.0$ V.[3] To resolve this inconsistency in published data and to determine more accurately the reduction potential of alkyl peroxy radicals, the reactions of peroxy radicals with organic substrates with $E_{13} = 0.13$–0.89 V were studied in alkaline media. The Marcus equation was used for the evaluation of the reduction potential and self-exchange rate of alkyl peroxy radicals from the rate constants of the oxidation of the ferrocenes. Activation parameters of the electron transfer from urate to the methyl peroxy radical were determined in alkaline and neutral media in an attempt to clarify an apparent decrease in the rates of peroxy radical reactions in neutral media. For comparison with neutral aqueous systems, activation parameters of the reaction of cyclohexyl peroxy radical with α- and δ-tocopherol were measured in aerated cyclohexane.

Materials and Methods

(Hydroxymethyl)ferrocene, ferrocenemonocarboxylic acid, 1,1′-ferrocenedicarboxylic acid, *N*,*N*-[(dimethylamino)methyl]ferrocene (Strem), phosphate buffer, 2-methyl-2-propanol, KSCN, KBr, $K_4[Fe(CN)_6]$, cyclohexane (Merck), uric acid, xanthine, guanine, guanosine, hypoxanthine (Sigma), dimethyl sulfoxide (DMSO), cyclohexanol, *N*,*N*,*N′*,*N′*-tetramethyl-*p*-phenylenediamine dihydrochloride (TMPD), and KCl (Fluka), were used as received. Sesamol and 4-methoxyphenol (Sigma) were recrystallized from petroleum ether. α- and δ-tocopherols (99.9% and 95.9%) were the products of Henkel, received as a generous gift from Veris.

Water was purified with a Millipore Milli Q system. All solutions were prepared freshly before each experiment. The pH was adjusted by $HClO_4$ and KOH (Merck) or maintained by the phosphate buffer. Prior to irradiation the solutions were saturated with high-purity gases N_2O (Lek) and O_2 (Tehnogas). The syringe technique was used to prepare N_2O:O_2 (4:1) solutions. In order to minimize rapid thermal oxidation of TMPD in oxygenated solutions, the solution containing TMPD was presaturated with N_2O and mixed with the corresponding oxygen saturated solution without TMPD only 0.5–1 min before each pulse.

A 1.85×10^{14} Bq (nominal activity) ^{60}Co source was used for gamma radiolysis studies. The absorbed doses, which were determined by Fricke dosimetry, were chosen so that free radical induced decomposition of solutes did not exceed 25%, based on G(radicals) = 6.25.

A 2-MeV Febetron 707 pulse radiolysis set up with optical detection[4a] was used for kinetic measurements. Activation parameters were determined using the 3-MeV Van de Graaff pulse radiolysis set up at the Max-Planck-Institut für Strahlenchemie, Mülheim a.d. Ruhr, Germany.[4b] The absorbed doses were measured with reference to the absorbance at 480 nm of the thiocyanate radical ($\epsilon = 7600$ M^{-1} cm^{-1}; $G = 6.0$)[5] generated by the $^\bullet$OH radical oxidation of SCN$^-$ in N_2O-saturated aqueous solutions of 10 mM KSCN.

Reversible redox potentials of ferrocenes at pH 8, E_8, were measured by dropping mercury electrode polarography with 0.1 M KCl as supporting electrolyte.

Peroxy radicals were generated from alkyl radicals by the following $^\bullet$OH radical reactions,[6]

$$^\bullet OH + (CH_3)_2SO \rightarrow {}^\bullet CH_3 + CH_3SO_2^- + H^+$$

$$k = 6.6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$$

$$^\bullet OH + (CH_3)_3COH \rightarrow {}^\bullet CH_2(CH_3)_2COH + H_2O$$

$$k = 6.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$$

$$^\bullet OH + cC_6H_{11}OH \rightarrow c\dot{C}_6H_{10}OH + H_2O$$

$$k \approx 6.1 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$$

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followed by,

$$^{\bullet}R + O_2 \rightarrow ROO^{\bullet}$$

$$k \approx 10^9\ M^{-1}\ s^{-1}$$

where R = $^{\bullet}CH_3$, $^{\bullet}CH_2(CH_3)_2COH$, $c\dot{C}_6H_{10}OH$.

The cyclohexyl peroxy radical, $cC_6H_{11}OO^{\bullet}$, was generated in aerated cyclohexane as described in ref 7.

Results and Discussion

Alkaline Media. The reaction of the methyl peroxy radical with organic substrates at pH 13,

$$CH_3OO^{\bullet} + D^- \rightarrow CH_3OO^- + D^{\bullet} \qquad (1)$$

may be viewed as a simple electron transfer, since no protons are exchanged. (Methyl hydroperoxide is completely deprotonated at pH 13, since $pK_a(CH_3OOH) = 11.5$.[8]) Assuming an outer sphere mechanism, it is expected that the redox potential difference between the peroxy radical and an electron donor, ΔE, determines the rate of the reaction. When ΔE approaches 0 V, the reaction should be effectively slowed down, which enables an estimate of the lower limit of the reduction potential of the peroxy radical.

We measured rate constants of the reactions of the methyl peroxy radical with selected electron donors with E_{13} = 0.13–0.89 V. The results are summarized in Table I.

The methyl peroxy radical oxidizes various organic electron donors rapidly, $k = 1.1 \times 10^5$–$4.9 \times 10^7\ M^{-1}\ s^{-1}$, and quantitatively at pH 13. This was verified in steady-state experiments, where the first-order reactions are favored because of lower radical concentrations (typically $\approx 10^{-9}$ M). The UV–vis spectra of organic substrates were monitored upon gamma irradiation of aqueous solutions at 20 °C. The spectral changes in the $CH_3OO^{\bullet}$ + guanine system were qualitatively and quantitatively similar to those in the $Br_2^{\bullet-}$ system. Since $Br_2^{\bullet-}$ is a strong transient oxidant, E = 1.7 V,[14] capable of oxidizing the purine and pyrimidine derivatives quantitatively,[10] it may be concluded that the reaction of $CH_3OO^{\bullet}$ with guanine is a one-electron oxidation. On the other hand, in $CH_3OO^{\bullet}$ + guanosine and $CH_3OO^{\bullet}$ + hypoxanthine systems, where $k < 10^4\ M^{-1}\ s^{-1}$ was determined by pulse radiolysis, the spectra of purines were unaffected by irradiation. Consequently, $CH_3OO^{\bullet}$ is not capable of oxidizing organic substrates with $E_{13} \geq 0.85$ V. From the reactivities of $CH_3OO^{\bullet}$ with organic electron donors and the steady-state data, it may be concluded that $E_{13}(CH_3OO^{\bullet})$ should be higher than 0.76 V and lower than 0.85 V.

The pH dependence of the reduction potential of the methyl peroxy radical may be evaluated from the formula,

$$E_{pH} = E_0 + 0.059 \log ([H^+] + K_a) \qquad (2)$$

where E_0 is the standard potential (pH = 0), and K_a is the dissociation constant of methyl hydroperoxide, $pK_a = 11.5$.[8] The calculated values are E_0 = 1.43–1.52 and E_7 = 1.02–1.11 V.

Neutral Media. Alkyl peroxy radicals oxidize ferrocene derivatives to the corresponding ferricinium ions at pH 8 (pH = 8 was chosen to avoid complications due to the acid–base equilibria of TMPD and $TMPD^{\bullet+}$),

$$ROO^{\bullet} + (C_5H_4R)_2Fe^{2+} \rightleftarrows ROO^- + (C_5H_4R)_2Fe^{3+} \qquad (3)$$

Table I. Reactivities of Methyl Peroxy Radical with Selected Electron Donors Determined by Pulse Radiolysis at pH 13, 20 °C

substrate, S^-	$E_{13}(S^{\bullet}/S^-)$, V	$k(ROO^{\bullet} + S^-)$,[a] $M^{-1}\ s^{-1}$
isobarbiturate	0.13[b]	4.9×10^7 [c]
urate	0.32[d]	8.8×10^6 [c]
5-hydroxytryptophan	0.33[e]	7.0×10^6 [c]
sesamol	0.45[f]	9.4×10^6
$Fe(CN)_6^{4-}$	0.455[e]	7.2×10^3 [g]
p-methoxyphenol	0.54[e]	9.2×10^5
xanthine	0.73[h]	1.1×10^5
guanine	0.76[h]	1.1×10^5
guanosine	0.85[h]	$<10^4$
hypoxanthine	0.89[h]	$<10^4$

[a] Estimated to be accurate to ±10%. [b] From ref 9. [c] From ref 2. [d] From ref 10. [e] From ref 11 and references cited therein. [f] From ref 12. [g] Due to the relatively slow reaction, the uncertainty is higher, i.e., ±20%. [h] From ref 13.

Table II. Rate Constants of Oxidation of TMPD by Ferricinium Ions Measured by Pulse Radiolysis at pH 8, 20 °C

ferricinium ion, F	$k(F + TMPD)$,[a] $M^{-1}\ s^{-1}$
carboxy-	7.2×10^8
dicarboxy-	9.3×10^8
(hydroxymethyl)-	1.7×10^8
[(dimethylamino)methyl]-	2.2×10^8

[a] Estimated to be accurate to ±10%.

Reaction 3 is followed by the rapid protonation of the peroxide anion,

$$ROO^- + H_2O \rightarrow ROOH + OH^- \qquad (4)$$

$$pK_a = 11.5\text{–}11.9^{8}$$

However, low extinction coefficients of both reactants and products of reaction 3 in the spectral range from 300 to 700 nm preclude accurate determination of the rate constants. To circumvent this difficulty, the consecutive oxidation of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine (TMPD) by incipient ferricinium ion to strongly absorbing ($\epsilon_{565} = 12\,500\ M^{-1}\ cm^{-1}$)[15] and relatively stable $TMPD^{\bullet+}$ was used as a "vehicle". The following procedure was used to determine relevant rate constants.

The ferricinium ions were generated from ferrocenes in the concentration range 1–5 mM in an N_2O-saturated aqueous solution of 0.05–0.2 M KSCN by the $(SCN)_2^{\bullet-}$ oxidation,

$$(SCN)_2^{\bullet-} + (C_5H_4R)_2Fe^{2+} \rightarrow (C_5H_4R)_2Fe^{3+} + 2SCN^- \qquad (5)$$

$$k_5 = 0.57\text{–}8 \times 10^8\ M^{-1}\ s^{-1}\ {}^{16}$$

Various ferricinium ions were found to oxidize TMPD in concentrations from 0.01 to 0.05 mM, quantitatively and rapidly, as may be expected from the relatively low redox potential of TMPD, E_8 = 0.27 V,[9,11] according to

$$(C_5H_4R)_2Fe^{3+} + TMPD \rightarrow (C_5H_4R)_2Fe^{2+} + TMPD^{\bullet+} \qquad (6)$$

The rate constants of reaction 6 are summarized in Table II. The oxidation of TMPD by alkyl peroxy radicals

$$ROO^{\bullet} + TMPD \rightarrow ROO^- + TMPD^{\bullet+} \qquad (7)$$

is in the competition with reaction 3. The rate constant of the oxidation of TMPD in concentrations from 0.01 to 0.1 mM, $k_7 = (8 \pm 1) \times 10^6\ M^{-1}\ s^{-1}$, was determined in $N_2O:O_2$ = 4:1 saturated aqueous solutions at pH 8, at 20 °C. (Our value is considerably lower than the published[17] $k = 4.3 \times 10^7\ M^{-1}\ s^{-1}$. The reason for this discrepancy is not known. However, we believe that our value is more accurate, since it was obtained both directly and from the kinetic treatment (see discussion following reaction 9).)

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Table III. Rate Constants for Reactions of Alkyl Peroxy Radicals with Ferrocenes Measured by Pulse Radiolysis of Aqueous Solutions at pH 8, 20 °C[a]

ferrocene, Fc	E_8,[b] V (Fc)	$k(CH_3OO^\bullet + Fc)$	$k[cC_6H_{10}(OH)OO^\bullet + Fc]$	$k[(CH_3)_2C(OH)OO^\bullet + Fc]$
ferrocenedicarboxylate	0.66	1.1×10^5	9.2×10^4	7.1×10^4
[(dimethylamino)methyl]ferrocene	0.59	2.0×10^5	3.4×10^5	2.0×10^5
ferrocenecarboxylic acid	0.53	2.8×10^5	5.5×10^5	4×10^5
(hydroxymethyl)ferrocene	0.42	1.6×10^6	1.5×10^6	2.3×10^6

[a] In units $M^{-1}\,s^{-1}$, estimated to be accurate to ±20%. [b] Determined by dropping mercury electrode polarography. The same as E_7 given in ref 16.

The concentration of $TMPD^{\bullet+}$ formed in reaction 3 may be calculated from the formula derived by the standard procedure (e.g., ref 18),

$$[TMPD^{\bullet+}] = [TMPD^{\bullet+}]_\infty\{[(k_6' - k_3' - k_7') + k_3' \exp(-k_6't)] - (k_6' - k_7') \exp[-(k_3' + k_7')t]\}/(k_6' - k_3' - k_7') \quad (8)$$

where $k_3' = k_3[(C_5H_4R)_2Fe^{2+}]$, $k_6' = k_6[TMPD]$, and $k_7' = k_7[TMPD]$.

The concentrations of ferrocene and TMPD were adjusted so that $k_6' \gg k_3' + k_7'$, that is, $k_6 \gg k_3[(C_5H_4R)_2Fe^{2+}]$. Therefore, expression 8 reduces to

$$[TMPD^{\bullet+}] = [TMPD^{\bullet+}]_\infty\{1 - \exp[-(k_3' + k_7')t]\} \quad (9)$$

From equation 9, $k_{app} = k_3[(C_5H_4R)_2Fe^{2+}] + k_7[TMPD]$. Therefore, the rate of the oxidation of any ferrocene by alkyl peroxy radicals, k_3, may be obtained from the slope of the plot of $k_{app}/[TMPD]$ vs $[(C_5H_4R)_2Fe^{2+}]/[TMPD]$. The intercept equals the rate constant of the reaction of the peroxy radical with TMPD, reaction 7.

The rate constants determined by the above procedure are summarized in Table III.

The Marcus Equation. The Marcus equation for an outer sphere electron transfer process[19]

$$k_{el} = Z \exp\{-[(\lambda/4)(1 + \Delta G^{\circ\prime}/\lambda)^2/RT]\} \quad (10)$$

where $k_{el} = k_2$ is the rate of electron transfer, $Z = 10^{11}\ s^{-1}$ is the collision frequency in solution, λ is the reorganization energy, and $\Delta G^{\circ\prime}$ is the corrected free energy change in the reaction, may be used to evaluate the unknown redox potential from experimentally determined rates of electron transfer. Providing that[19] (a) the compound of unknown redox potential is reacted with a series of related redox standards, e.g., ferrocenes and (b) $\Delta G^{\circ\prime}$ is in a sufficiently narrow range, the plot of log k_2 vs $-23.06E_8$ may be approximated as a straight line. The slope of this line is equal to that of the tangent to the parabola at the midpoint of the $\Delta G^{\circ\prime}$ range. The slope of the tangent at any point c is given by $0.37[1 + \Delta G^{\circ\prime}(c)/\lambda]$ for the reaction at 20 °C.

The plot of log k_3 vs $-23.06E_8$ (k_3 and E_8 are taken from Table III) is presented in Figure 1. From the slope of the line,

$$\Delta G^{\circ\prime}(c)/\lambda = 0.23/0.37 - 1 = -0.38 \quad (11)$$

For charged reactants, $\Delta G^\circ(c) = -23.06[E_8(ROO^\bullet) - E_8(\text{ferrocenium})]$ is corrected for the electrostatic free energy change due to the change in Z_1Z_2 upon electron transfer, A,

$$\Delta G^{\circ\prime} = \Delta G^\circ + A \quad (12a)$$

$$A = (Z_1 - Z_2 - 1)(e^2f/Dr_{12}) = -2.3\ \text{kcal/mol} \quad (12b)$$

where Z_1 and Z_2 are the formal charges of the reactants (for simplicity, the charges of the ferrocene side chains were neglected in the calculation), $e^2 = 331.2$, $f \approx 1$ (for $\mu \rightarrow 0$), $r_{12} \approx 5.6$ Å,[20] and $D = 78.5$.[21]

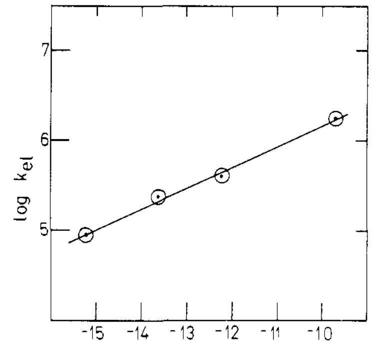

Figure 1. Plot of log k_{el} ($k_{el} = k_3$ is the rate constant of electron transfer from ferrocenes to peroxy radicals) vs the redox potential of ferrocene derivatives at pH 8 (E_8).

The reorganization energy of the reaction is composed of inner sphere, λ_i, and outer sphere, λ_o, terms. The inner sphere reorganization energy originates from the distortions in bond lengths and bond angles of reactants and any specific interactions between them upon electron transfer. In the case of the reaction of the peroxy radical with ferrocenes this term may be neglected, since the changes in the configurations of both reactants are expected to be small. The outer sphere reorganization energy arises mainly from solvation, and can be evaluated from the formula[19]

$$\lambda_o = 3.31 \times 10^2[(1/2r_p) + (1/2r_{Fc}) - (1/d)][(1/n^2) - (1/D)] \quad (13)$$

$$\lambda_o = 33\ \text{kcal/mol}$$

where $r_p \approx 3$ Å[20] and $r_{Fc} \approx 2.6$ Å[20] are the mean radii of the peroxy radical and ferrocene derivative, respectively, approximated as hard spheres, and $d \approx r_p + r_{Fc} = 5.6$ Å. The index of refraction, $n = 1.33$, and dielectric constant, $D = 78.5$, are the values[21] for an aqueous solution at 20 °C. (The correction for the presence of 50 mM (3.5%) dimethylsulfoxide is negligible.)

Substitution of calculated values in eq 11, and taking the midpoint potential $E_8 = (0.66 + 0.42)/2 = 0.54$ V, gives $E_8(ROO^\bullet) = 0.99$ V, i.e., $E_7 = 1.05$ V. Considering the severity of approximations inherent to the above treatment, the calculated $E_7 = 1.05$ V is in an excellent agreement with the determined $E_7 = 1.02$–1.11 V (or $\bar{E}_7 = 1.06$ V).

The self-exchange rate of the peroxide redox couple may be determined from the Marcus cross relation,

$$k_{12} = (k_{11}k_{22}K_{12}f_{12})^{1/2} \quad (14)$$

where k_{12} and K_{12} are the rate and the equilibrium constant of the heteroexchange reaction, k_{11} and k_{22} are the rates of the homoexchange reactions of the peroxide and ferrocene redox couple, respectively, and f_{12} is calculated from[19]

$$\log f_{12} = (\log K_{12})^2/[4 \log (k_{11}k_{22}/Z^2)]$$

The calculated rates of the reactions of peroxy radicals with the ferrocenes and ferrous cyanide are summarized in Table IV.

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Table IV. Rate Constants of Reactions of Peroxy Radicals with Ferrous Complexes

ferrous complex, FeC	E_8(FeC), V	ΔE,[a] V	k_m,[b] M^{-1} s^{-1}	k_c,[c] M^{-1} s^{-1}
ferrocenedicarboxylate	0.66	0.34	9.1×10^4	9.8×10^4
[(dimethylamino)-methyl]ferrocene	0.59	0.41	2.5×10^5	3.0×10^5
ferrocenemono-carboxylate	0.53	0.47	4.1×10^5	7.4×10^5
(hydroxymethyl)-ferrocene	0.42	0.58	1.4×10^6	3.7×10^6
$Fe(CN)_6^{4-}$	0.455	0.545	6×10^3	5.7×10^3

[a] The redox potential difference between the ferrous complex and peroxy radicals, calculated taking $E_8(ROO^\bullet) = 1.00$ V. [b] Measured rate constants (see Table III). The rate of $CH_3OO^\bullet + Fe(CN)_6^{4-}$ was measured directly from the buildup of absorbance at 400 nm, with an accuracy estimated to be ±20%. [c] The rate constants calculated from eq 14 using the following values of the self-exchange rates, k(ferrocenes) = 5×10^6 M^{-1} s^{-1},[19] k(ferrocyanide) = 16 M^{-1} s^{-1},[19] and k(hydroperoxide) = 10^{-2} M^{-1} s^{-1}.

Table V. Activation Parameters of the Reaction of the Methyl Peroxy Radical with Uric Acid Determined by Pulse Radiolysis[a]

pH	k,[b] M^{-1} s^{-1}	ΔH^+, kcal/mol	ΔS^+, cal/mol K
13.2	7.9×10^6	3.3	−13
7.3	1.4×10^5	2.9	−22

[a] Determined from the buildup of the absorbance at 330 nm of the uric acid radical in the aqueous solutions of 1.3 M DMSO, $N_2O:O_2$ = 4:1, 2.7 mM urate at pH 13.2, and 10.5 mM urate at pH 7.3. Temperature was varied from 0 to 60 °C. [b] At 20 °C, estimated to be accurate to ±10%.

The best agreement between the calculated and measured data is obtained for the self-exchange rate of the peroxide redox couple $k = 10^{-2}$ M^{-1} s^{-1}. This value corresponds to an apparent reorganization energy of $\lambda = 72$ kcal/mol. The reorganization energy of the peroxide redox couple is considerably higher than $\lambda = 18$ kcal/mol reported[22] for electron-transfer reactions of nitroaromatic compounds and quinones.

Mechanism of Peroxy Radical Reactions with Electron Donors. The high reorganization energy of the peroxide redox couple in the reactions with ferrocenes in neutral media may be explained by any of the following mechanisms: (1) the formation of a bridged intermediate, i.e., an inner sphere electron transfer, (2) atom-transfer mechanism, with a polar transition state, or (3) high contribution of the solvent reorganization due to the solvation of the incipient peroxide anion (e.g., see reactions 3 and 4).

In an attempt to differentiate between these mechanisms, the activation parameters of the oxidation of uric acid by the methyl peroxy radicals were determined at pH 7.3, where the solvation of the peroxide anion was required, and at pH 13.2, where a simple electron transfer was expected. The results are summarized in Table V.

It may be seen from Table V that while there is no appreciable difference in the enthalpy of activation, ΔS^+ is 9 eu more negative at pH 7.3. This rules out an inner sphere mechanism, since bond formation and breaking required by such a mechanism must result in an increase of the activation enthalpy. In addition, relatively low activation enthalpy, $\Delta H^+ \sim 3$ kcal/mol, and negative activation entropy are characteristic for an electron transfer rather than for an atom transfer, where higher activation enthalpy and positive entropy are expected. It is suggested that entropy control in neutral media originates from the reorganization of water molecules in the transition state to facilitate solvation of incipient peroxide anion. Similar electron transfer concerted with proton transfer from solvent to peroxide anion was postulated[17] to explain the solvent kinetic isotope effect of about 2 in the reactions of peroxy radicals with TMPD. In addition, the reactions of the neutral tryptophan radicals with phenols,[23] which also require solvent participation in the proton exchange between reactants in the transition state, are entropy controlled.

Table VI. Activation Parameters of the Reactions of $cC_6H_{11}OO^\bullet$ with α- and δ-Tocopherol Determined by Pulse Radiolysis in Aerated Cyclohexane[a]

tocopherol	k,[b] M^{-1} s^{-1}	ΔH^+, kcal/mol	ΔS^+, cal/mol/K
α-tocopherol	6.8×10^6	−0.2	−25
δ-tocopherol	2.3×10^6	0.3	−26

[a] Determined from the buildup of the absorbance at 420 nm of the chromanoxyl radical in cyclohexane solution of 4.94 mM δ-tocopherol, or 3.09 mM α-tocopherol. Temperature was varied from 5 to 60 °C. [b] At 20 °C, estimated to be accurate to ±10%.

The activation parameters of the reactions of cyclohexyl peroxy radicals with α- and δ-tocopherol in aerated cyclohexane are summarized in Table VI. Negligible activation enthalpies were measured, $\Delta H^+ \approx 0$ kcal/mol, which indicates an entropy control, $\Delta S^+ = -25$ eu. Obviously, the mechanism of inactivation of cyclohexyl peroxy radicals by both tocopherols is electron transfer, since an H-atom transfer mechanism would be enthalpy controlled with positive entropy.[17,24] It may be suggested that the entropy loss originates from the formation of a hydrogen-bonded transition state, to facilitate a proton transfer from the tocopherol radical cation to the hydroperoxide anion. It is interesting to note that this proton transfer subsequent to electron transfer may occur by tunneling as proposed in another study.[25]

Conclusions

The reduction potential of alkyl peroxy radicals in neutral media, $E_7 = 1.02-1.11$ V, renders them relatively inefficient oxidants of DNA bases and aromatic amino acids, whose oxidation potentials are higher than 1.05 V. However, because of their high ROO–H bond dissociation enthalpy,[26] $\Delta H_{BF} = 88-92$ kcal/mol, they are capable of initiation and propagation of oxidation of PUFA, because ΔH_{BF}(bisallylic C–H) = 75 kcal/mol.[27]

Alkyl peroxy radicals react in neutral aqueous solutions with electron donors by an entropy controlled electron transfer concerted with the proton transfer. The rate of electron transfer should strongly depend on the proton-donating ability of the solvent, which facilitates electron transfer by participation in the hydrogen-bonded transition state. In nonpolar media, such as the hydrophobic interior of the cell membrane, the requirement for the protonation of the incipient hydroperoxide anion may effectively slow down electron transfer, and proton transfer may have a chance. However, in the case of inactivation of the cyclohexyl peroxy radical by α- and δ-tocopherol, the activation parameters indicate that electron transfer may take place even in nonpolar reaction media, providing the possibility of the proton exchange between the reactants.

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(26) Using the method of Koppenol[3] and substituting the reduction potential at pH 0 obtained in this study, $E^\circ = 1.43-1.52$ V, for the standard reduction potential, the dissociative bond enthalpy of ROO–H bond is calculated as,

$$-\Delta H_{BF} = [2.1\ \text{V} + E^\circ(\text{ROO}^\bullet/\text{ROOH})]23.06\ \text{kcal mol}^{-1}\ \text{V}^{-1} + 6.8\ \text{kcal mol}^{-1} = [2.1 + (1.43\ \text{to}\ 1.52)]23.06\ \text{kcal mol}^{-1} + 6.8\ \text{kcal mol}^{-1} = 88\ \text{to}\ 90\ \text{kcal mol}^{-1}$$

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