Electron Transfer Reactions of Halothane-derived Peroxyl Free Radicals, $CF_3CHClO_2^{\cdot}$: Measurement of Absolute Rate Constants by Pulse Radiolysis

Jörg Mönig and Klaus-Dieter Asmus *
Hahn-Meitner-Institut für Kernforschung Berlin GmbH, Bereich Strahlenchemie, Postbox 39 0128, D-1000 Berlin 39, Federal Republic of Germany
Michel Schaeffer, Trevor F. Slater, and Robin L. Willson
Department of Biochemistry, Brunel University, Uxbridge, Middlesex UB8 3PH

The halothane-derived peroxyl radical $CF_3CHClO_2^{\cdot}$ has been generated in aqueous solutions by pulse radiolysis. Absolute rate constants for the reduction of halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) by hydrated electrons, hydrogen atoms, and propan-2-ol free radicals have been determined to be k 1.4 × 10^{10} ,3.8 × 10^8, and 7.6 × 10^7 l mol^{-1} s^{-1}, respectively. The predominant product radical $CF_3\dot{C}HCl$ rapidly adds O_2, and an estimate of k 1.3 × 10^9 l mol^{-1} s^{-1}, has been obtained for the absolute rate constant of this reaction. The resulting peroxyl radical $CF_3CHClO_2^{\cdot}$ has been found to react rapidly with a variety of nucleophilic compounds such as 2,2′-azinobis(3-ethylbenzthiazoline-6-sulphonate), the phenothiazines promethazine, chlorpromazine, and metiazinic acid, the vitamins C and E, and propyl gallate. The absolute rate constants for these reactions are found to be generally lower than for corresponding reactions of the carbon tetrachloride-derived radical, $CCl_3O_2^{\cdot}$.

Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) has been widely used for many years as an anaesthetic. Although it has an excellent safety record there have been occasional reports of unexplained liver injury. It has been considered, but so far no firm evidence has been produced, that stable metabolic products *per se* are responsible for such tissue damage. The chemical structure of the drug halothane with its constituent halogen atoms is similar to carbon tetrachloride. It has been suggested that free radical intermediates which are known to initiate liver injury in the case of CCl_4 may be responsible for the corresponding action of halothane.[1-3]

Recent pulse radiolysis studies [4,5] have shown that the free radical formed from CCl_4 by dissociative electron capture reacts rapidly with oxygen to form the halogen-substituted peroxyl radical $CCl_3O_2^{\cdot}$ [reactions (1) and (2)].

$$e^-_{aq} + CCl_4 \longrightarrow \dot{C}Cl_3 + Cl^- \quad (1)$$

$$CCl_3^{\cdot} + O_2 \longrightarrow CCl_3O_2^{\cdot} \quad (2)$$

Unlike $\dot{C}Cl_3$, the peroxyl radical has been shown to react rapidly with several oxidizable compounds including the peroxidase reagent, 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate) (ABTS), with the phenothiazine derivatives promethazine (PZ), chlorpromazine (CZ), and metiazinic acid (MZ), as well as with vitamin E (α-tocopherol), vitamin C (ascorbic acid), and several phenols.[6-9] In this paper we report an analogous investigation on the reactions of the related peroxyl radical formed from halothane. Although dissociative electron capture could, in principle, lead to elimination of Br^-, Cl^-, or F^-, *i.e.* to three different peroxyl radicals, consideration of the bond energies as well as experimental data on biotransformation [10] and products from steady-state radiation [11] clearly show that the predominant pathway is bromide elimination. The peroxyl radical is thus assumed to be the $CF_3CHClO_2^{\cdot}$ radical formed *via* equations (3) and (4).

$$e^-_{aq} + CF_3CHBrCl \longrightarrow CF_3\dot{C}HCl + Br^- \quad (3)$$

$$CF_3\dot{C}HCl + O_2 \longrightarrow CF_3CHClO_2^{\cdot} \quad (4)$$

Experimental

Studies of the electron transfer reactions of the halothane-derived peroxyl radical were undertaken using the 4 MeV, 200 ns electron pulse linear accelerator and associated equipment for pulse radiolysis at Brunel University.[12,13] Studies of the reduction of halothane by the solvated electron, hydrogen atom, and the propan-2-ol radical were carried out using the 1.5 MeV–1μs or 3.8 MeV–5 ns electron pulse Van de Graaff accelerators and associated equipment at the Hahn-Meitner-Institut Berlin.

In all instances the doses per pulse were in the range 2—10 Gy (1 Gy = 1 J kg^{-1} = 100 rad). Solutions were prepared using 'Millipore'-system purified water. Unless otherwise stated all experiments have been undertaken in buffered (10mM-phosphate) solutions at pH 7. Halothane was dissolved in t-butyl alcohol or propan-2-ol before being introduced into aqueous solution.

Halothane (ICI Ltd.) was passed through an alumina column prior to use in order to remove traces of thymol. Promethazine, chlorpromazine, and metiazinic acid were kindly supplied by May and Baker Ltd. Benzoquinone was purified by sublimation before use. ABTS [2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate)] was used as supplied by Boehringer Ltd. Propyl gallate, vitamin E (α-tocopherol), and vitamin C (ascorbic acid) were used as supplied by Sigma Chemicals. All experiments were carried out at room temperature.

Results

(1) *Formation of* $CF_3\dot{C}HCl$ *Radicals*.—The 2-chloro-1,1,1-trifluoroethyl radical can easily be produced in aqueous solution by radiation-chemical induced one-electron reduction. Three well known one-electron reductants have been used in this study, namely the hydrated electron, e^-_{aq}, the hydrogen atom, $H^{\cdot}$, and the propan-2-ol radical, $(CH_3)_2\dot{C}OH$, which are formed either directly in the irradiation of water [equation (5)] or through reaction of $OH^{\cdot}$ and $H^{\cdot}$ with propan-2-ol [equation (6)]. Since halogenated alkyl radicals typically do not

$$H_2O \rightsquigarrow e^-_{aq}, OH^{\cdot}, H^{\cdot}, etc. \quad (5)$$

exhibit significant absorptions in the experimentally accessible wavelength range above 250 nm, the rate constants for the reactions of these species with halothane were measured by either following the absorption of the hydrated electron or by kinetic competition techniques.

$$OH^{\cdot}/H^{\cdot} + (CH_3)_2CHOH \longrightarrow (CH_3)_2\dot{C}OH + H_2O/H_2 \quad (6)$$

On pulse radiolysis of neutral deaerated aqueous solutions containing only t-butyl alcohol (10%), the characteristic and slowly decaying (first half-life *ca.* 10—20 μs) absorption of the hydrated electron was observed immediately after the pulse. In the presence of halothane (0.1—1mM), however, the decay of the e^-_{aq} absorption occurred exponentially and more rapidly with the half-life depending on halothane concentration in agreement with reaction (3).

Kinetic analysis yields the expected linear dependence between the first-order rate constant ($k' = \ln 2/t_{1/2}$) and halothane concentration. From these data the bimolecular rate constant $k_3 = 1.4 \times 10^{10}$ l mol^{-1} s^{-1} is obtained.

In order to determine the rate constant for the reaction of H· with halothane, a competition method was employed using benzoquinone as an absorbing reference compound. The absorption spectrum of the benzsemiquinone radical (BQH·)[14,15] was observed immediately after pulse irradiation of deaerated solutions at pH 1 (adjusted with perchloric acid) containing t-butyl alcohol (10%) and benzoquinone (100μM). Its appearance is attributed to reactions (7) and (8).

$$e^-_{aq} + H_3O^+ \longrightarrow H^{\cdot} + H_2O \quad (7)$$

$$H^{\cdot} + BQ \longrightarrow BQH^{\cdot} \quad (8)$$

In the additional presence of increasing concentrations of halothane (1.25—5mM) the magnitude of the absorption A from the benzsemiquinone radical, BQH·, was progressively reduced. A plot of A^0/A over [halothane]/[BQ], where A^0 refers to the magnitude of the absorption in the absence of halothane, is seen to be linear (Figure 1) in agreement with the occurrence of reaction (9) in competition with reaction (8)

$$H^{\cdot} + CF_3CHBrCl \longrightarrow \text{products} \quad (9)$$

(products: mainly $CF_3\dot{C}HCl + Br^- + H^+$, but possibly also $CF_3\dot{C}HBr + Cl^- + H^+$ and $CF_3\dot{C}BrCl + H_2$) and the competition equation $A^0/A = 1 + k_9[\text{halothane}]/k_8[BQ]$. The slope of the competition plot corresponds to $k_9/k_8 = 0.046$. Since $k_8 = 8.3 \times 10^9$ l mol^{-1} s^{-1},[15] a value of $k_9 = 3.8 \times 10^8$ l mol^{-1} s^{-1} is derived for the reduction of halothane by hydrogen atoms.

A similar competition study was undertaken to determine the rate constant for reaction of the propan-2-ol radical, $(CH_3)_2\dot{C}OH$, with halothane. In this case, *p*-nitroacetophenone (PNAP) was used as a reference in solutions containing propan-2-ol (10%), acetone (10%), and PNAP (100μM). The absorption of the radical anion $PNAP^-$ ($\lambda_{max.}$ 360 and 550 nm) formed *via* reactions (6) and (10)—(12) was monitored at 360 nm.

$$e^-_{aq} + (CH_3)_2CO \longrightarrow (CH_3)_2\dot{C}O^- \quad (10)$$

$$(CH_3)_2\dot{C}O^- + H_2O \rightleftharpoons (CH_3)_2\dot{C}OH + OH^- \quad (11)$$

$$(CH_3)_2\dot{C}OH + PNAP \longrightarrow PNAP^{-\cdot} + H^+ + (CH_3)_2CO \quad (12)$$

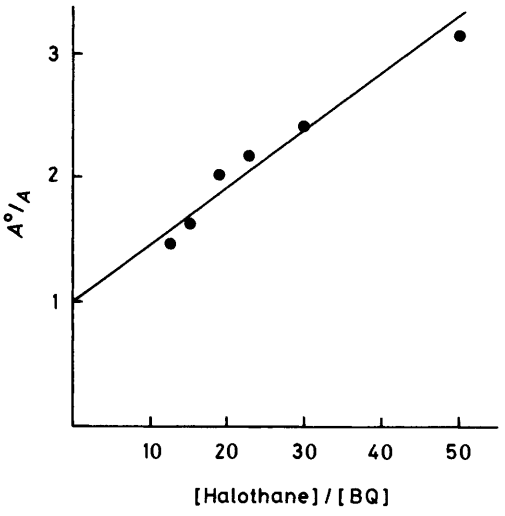

Figure 1. Kinetic competition plot for the effect of halothane on the transient absorption at 410 nm on pulse radiolysis of deaerated solutions containing t-butyl alcohol (10%) at pH 1 and benzoquinone BQ (100μM)

The additional presence of halothane reduced the absorption at 360 nm due to the competing reaction (13).

$$(CH_3)_2\dot{C}OH + CF_3CHBrCl \longrightarrow CF_3\dot{C}HCl + H^+ + Br^- + (CH_3)_2CO \quad (13)$$

From kinetic analysis analogous to that for the H· atom reaction $k_{13}/k_{12} = 0.020$ was determined, and hence with $k_{12} = 3.8 \times 10^9$ l mol^{-1} s^{-1},[16] the rate constant for the reduction of halothane by $(CH_3)_2\dot{C}OH$ radicals is derived to be $k_{13} = 7.6 \times 10^7$ l mol^{-1} s^{-1}.

(2) *Reactions of the* $CF_3\dot{C}HCl$ *Radical.*—It was of considerable interest to study the reactions of the product radical formed by one-electron reduction. The $CF_3\dot{C}HCl$ radical has been implicated as one of the possible toxic intermediates in the metabolism of halothane. One-electron oxidation of biological target molecules by this radical could be one of the early events in tissue damage. It was, therefore, of interest to test the possible oxidizing properties of the $CF_3\dot{C}HCl$ radical by adding various substrates, which are known to produce absorbing one-electron oxidation products, *e.g.* ABTS,[17] ascorbate,[18] propyl gallate,[19] *etc.* However, no absorptions were detected on pulse radiolysis of deaerated neutral 10% t-butyl alcohol solutions containing halothane (10mM) and any of the nucleophiles (X). It is therefore concluded that

$$CF_3\dot{C}HCl + X \longrightarrow CF_3\ddot{C}HCl + X^{+\cdot} \quad (14)$$

reaction (14) occurs, if at all, with absolute rate constants $<10^5$ l mol^{-1} s^{-1}.

When the same experiments were done, however, in air-saturated solutions the absorption spectra of the one-electron oxidation products were observed in all instances. A similar observation had been made in the case of corresponding carbon tetrachloride solutions, where the CCl_3· radical, unlike the CCl_3O_2· radical, was also found to exhibit no oxidizing properties. From our data it is concluded that the oxygen adduct of the halothane radical formed *via* reaction (4) is the oxidizing species which acts *via* reaction (15).

$$CF_3CHClO_2^{\cdot} + X \longrightarrow X^{+\cdot} + \text{products} \quad (15)$$

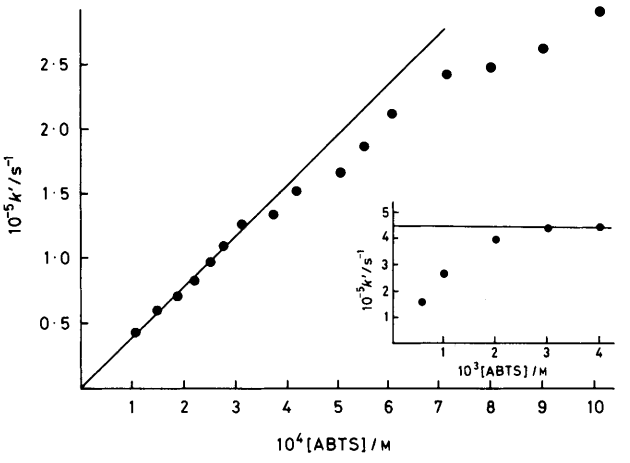

Figure 2. Plot of first-order rate constant for the formation of the $ABTS^{+\cdot}$ absorption at 415 nm *versus* ABTS concentrations on pulse radiolysis of aerated solutions containing t-butyl alcohol (10%) and halothane (10mM). Insert: plot at higher ABTS concentrations

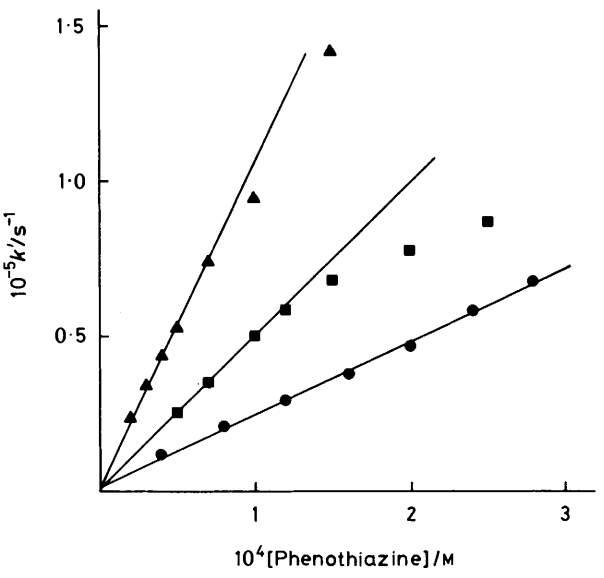

Figure 3. Plot of first-order rate constant for the formation of the phenothiazine radical-cations *versus* phenothiazine concentration on pulse radiolysis of aerated solutions containing t-butyl alcohol (10%), halothane (10mM), and ● promethazine, ■ chlorpromazine, and ▲ metiazinic acid

Absolute rate constants 'k' for the overall reaction of the halothane peroxyl radical with various nucleophiles, the yield of radical product, and absolute rate constant k_{ET} for the electron transfer reactions (assuming absorption to be entirely due to e^--transfer products)

Nucleophile	10^{-9} × k'/ l mol^{-1} s^{-1}	ε/ l mol^{-1} cm^{-1}	Yield (%)	$10^{-9}k_{ET}$/ l mol^{-1} s^{-1}
ABTS	0.39 (10% t-butyl alcohol)	36 000 [a]	70	0.27
	0.5 (2% t-butyl alcohol)			
	0.25 (30% t-butyl alcohol)			
Metiazinic acid	1.1	11 000 [b]	105	1.1 [c]
Chlorpromazine	0.5	12 000 [b]	54	0.27
Promethazine	0.24	9 500 [b]	69	0.17
Ascorbate	0.61 (at pH 7)	3 300 [d]	110	0.61 [c]
	0.2 (at pH 4)			
α-Tocopherol	0.092	3 700 [e]	100 [e]	0.092 [e]
Propyl gallate	0.094	2 900 [e]	100 [e]	0.094 [e]
	0.9 (at pH 8.5)			

[a] At 415 nm.[17] [b] At 530, 510, and 505 nm, respectively.[8] [c] Assuming 100% yield. [d] At 360 nm (M. Schöneshöfer, *Z. Naturforsch.*, 1972, **27***b*, 649). [e] Extinction coefficients ε = 3 700 at 425 and 2 900 l mol^{-1} cm^{-1} at 420 nm for α-tocopherol and propyl gallate, respectively, are derived assuming 100% yield of reaction (15).

The formation of the $ABTS^{+\cdot}$ radical-cation monitored at 415 nm [9,17] in pulse irradiated air-saturated solutions containing t-butyl alcohol (10%), halothane, (10mM), and ABTS (100—300μM), was described by an exponential rate law with half-lives depending on the ABTS concentration. The latter applies, however, only for lower ABTS concentrations, as can be seen from a plot of the experimentally determined first-order rate constant $k' = \ln 2/t_{1/2}$ *versus* [ABTS] in Figure 2. At high ABTS concentrations, this kinetic plot becomes non-linear and a plateau value is obtained (insert in Figure 2). This result suggests that reaction (4) rather than (15) becomes the rate-determining step in the overall reaction at this concentration range. From the plateau the first-order rate constant k' 4.5×10^5 s^{-1} can be derived. Similar studies with ascorbate and propyl gallate at high concentrations gave the same result within the experimental error limit with plateau values of $k' = 3.5 \times 10^5$ and $k' = 3.8 \times 10^5$ s^{-1}, respectively. Assuming $[O_2] = 300\mu M$ in air-saturated solutions at room temperature, the rate constant for the O_2 addition to $CF_3\dot{C}HCl$ is thus evaluated to be $k_4 = (1.3 \pm 0.2) \times 10^9$ l mol^{-1} s^{-1}.

(3) *Reactions of the* $CF_3CHClO_2\cdot$ *Radical.*—The rate constants for the oxidation of the substrates by the halothane peroxyl radical were derived from the low concentration data. Solutions were generally neutral and air-saturated and contained t-butyl alcohol (10%), halothane (10mM), and the substrate (50—300μM). The one-electron oxidation products from reaction (15) were identified by their known absorption spectra. In some cases the electron transfer was found to occur with less than 100% efficiency (see Table) but in no instance could additional absorptions be observed. The percentage yields of electron transfer were calculated using the known extinction coefficients and assuming an initial yield of halothane peroxyl radical of 0.34 μM J^{-1} (equal to the yield of $e^-_{aq} + H^\cdot$).

The actually measured bimolecular rate constants were derived from the initial linear slopes of the respective $k' = \ln 2/t_{1/2}$ *versus* concentration plots, examples for which are shown in Figure 3, and are referred to as 'k'. It has to be kept in mind, however, that if a radical reacts with a substrate molecule by various pathways, the reaction rate is then the sum of all the individual rate constants for every single pathway. The observable build-up kinetics of any of the products, as in our case, is a measure for the overall rate constant and is thus only apparent for the individual process of interest. To obtain the true rate constant k_{ET} of an individual step such as electron transfer, this overall rate constant 'k' has to be multiplied by the relative yield of the respective step. The values of k_{ET} obtained by this calculation are also listed in the

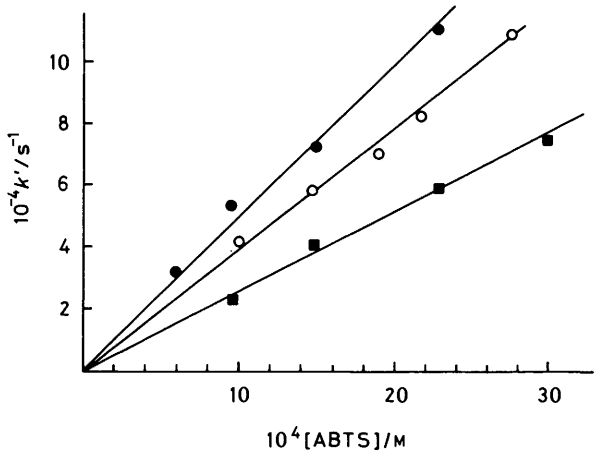

Figure 4. Plot of first-order rate constant for the $ABTS^{+\cdot}$ formation *versus* ABTS concentrations at various t-butyl alcohol concentrations: ●, 2%; ○, 10%; ■, 30%

Table. It is noted that the 100% electron transfer yields are obtained for those substrates with the lowest redox potentials, namely ascorbate and metiazinic acid.

Rate and yield of the electron transfer reactions seem to depend also on the polarity of the solvent. This was seen on pulse radiolysis of aerated aqueous solutions containing halothane (10mM), ABTS (60—300μM), and varying amounts of t-butyl alcohol (2—30%). The results are shown in Figure 4. The rate constants for the overall reaction (16) were found to

$$CF_3CHClO_2^{\cdot} + ABTS \longrightarrow \text{products} \qquad (16)$$

be $k_{16} = 5 \times 10^8$, 3.9×10^8, and 2.5×10^8 l mol^{-1} s^{-1} in 2, 10, and 30% t-butyl alcohol solutions, respectively. The decrease in the overall rate constant with decreasing polarity of the solution was paralleled by a decrease of the $ABTS^{+\cdot}$ radical-cation yield. In 2% t-butyl alcohol solutions the yield of $ABTS^{+\cdot}$ was *ca.* 90% in comparison with 70% in the 30% t-butyl alcohol solutions.

Discussion

The present results show that halothane can readily be reduced. The absolute rate constant for its reduction by e^-_{aq} ($k_3 = 1.4 \times 10^{10}$ l mol^{-1} s^{-1}) is clearly in the range of diffusion controlled processes and is of the same order of magnitude as that for the corresponding reduction of CCl_4 ($k = 3 \times 10^{10}$ l mol^{-1} s^{-1}).[20] Reduction by H· atoms occurs considerably slower and involves an activation energy. The rate constant for this process ($k_9 = 3.8 \times 10^8$ l mol^{-1} s^{-1}) is however considerably larger for halothane than for CCl_4 ($k = 4.8 \times 10^7$ l mol^{-1} s^{-1}).[21] This difference can be explained by the relatively weaker carbon–bromine bond in halothane in comparison with the carbon–chlorine bond in CCl_4 and the fact that these reactions constitute abstraction processes. Other bromine-containing organic compounds such as bromoethanol and bromoacetic acid have also been shown to react more rapidly with hydrogen atoms than only chlorinated or non-halogenated analogues.[22-24]

The reduction of halothane by propan-2-ol radicals ($k_{13} = 7.6 \times 10^7$ l mol^{-1} s^{-1}) which is presumed to be an electron transfer process occurs again with a rate constant similar to the corresponding reduction of CCl_4, for which $k = 1 \times 10^8$ l mol^{-1} s^{-1} was determined by conductivity measurements.[25]

The oxidation of the various substrates on the time scale of our pulse radiolysis experiments clearly depends on the presence of oxygen, *i.e.* the possibility of forming the $CF_3CHClO_2^{\cdot}$ radical. This in turn implies that reduction of the halothane radical, $CF_3\dot{C}HCl$, itself by a reaction (14) which was observed under steady-state γ-radiolysis conditions must be very slow ($k_{14} < 10^5$ l mol^{-1} s^{-1}).[11] Therefore reaction (14) is unlikely to compete effectively with oxygen addition to the halothane radical [reaction (4)] even in the presence of only traces of molecular oxygen.

The oxidations of various substrates by the halothane peroxyl radical are shown to proceed fast with rate constants in the range of 10^8—10^9 l mol^{-1} s^{-1}. It is interesting to note that the absolute rate constants for the $CF_3CHClO_2^{\cdot}$ radical reactions are generally somewhat lower than those previously published for the related $CCl_3O_2^{\cdot}$ radical. The differences in the rate constants for the oxidations of metiazinic acid, chlorpromazine, and promethazine reflect the change in the redox potentials of the respective phenothiazines.

The absolute rate constants for oxidation of the phenol derivatives α-tocopherol and propyl gallate by $CF_3CHClO_2^{\cdot}$ radicals may at first glance be surprisingly low considering the lower redox potentials of these anti-oxidants in comparison with the phenothiazines. These rate data refer, however, to a pH below the pK values of the substrates. At higher pH the rate constants increase, in fact, considerably and $k = 9 \times 10^8$ l mol^{-1} s^{-1} was, for example, measured for the oxidation of propyl gallate at pH 8.5. Our data are therefore clearly in accord with an electron transfer mechanism rather than possible hydrogen-abstraction followed by deprotonation of the halothane peroxide.

It should finally be pointed out that direct comparison of rate constants must still take into account the nature of the solvent system involved. This is apparent from the ABTS oxidation by the halothane peroxyl radical in mixtures of water and t-butyl alcohol.

Our results clearly demonstrate the oxidizing properties of the halothane peroxyl radical. It is therefore quite possible that this radical may initiate lipid peroxidation in a biological environment. Our findings also indicate that the initiation process might be prevented by high local concentrations of antioxidants such as vitamins E and C.

Acknowledgements

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