Halogenated Alkylperoxyl Radicals as Oxidants: Effects of Solvents and of Substituents on Rates of Electron Transfer

Zeev B. Alfassi,[†] S. Mosseri, and P. Neta*

Chemical Kinetics Division, Center for Chemical Physics, National Bureau of Standards, Gaithersburg, Maryland 20899 (Received: November 10, 1986; In Final Form: February 13, 1987)

The peroxyl radicals CCl₃O₂, CHCl₂O₂, CH₂ClO₂, CCl₃CCl₂O₂, CFCl₂O₂, CH₃CCl₂O₂, CF₃CHClO₂, and CBr₃O₂ were produced by pulse radiolysis of aerated solutions of the appropriate halogen compound in 2-propanol or 2-propanol-water solutions. Rate constants for one-electron oxidation of chloropromazine by these radicals were determined by kinetic spectrophotometry in various solvent mixtures. The second-order rate constants were found to vary from 1×10^5 to $1 \times$ 10^9 M⁻¹ s⁻¹. They depend very strongly on the solvent polarity and a reasonable correlation is obtained between log k for a certain peroxyl radical and the dielectric constant of the solvent mixture. The rate constants in the same solvent are strongly dependent of the substituents on the methylperoxyl radical and give a good correlation with the polar substituent constants σ*.

Introduction

The reactions of halogenated alkylperoxyl radicals with several substrates, such as phenols, phenothiazines, porphyrins, and fatty acids, have been studied.¹⁻¹³ Most of the kinetic measurements were done in aqueous solutions containing a certain amount of an alcohol. The alcohol enables the dissolution of the halogen compounds or the substrates and also serves as a scavenger for the OH radicals. Recently we have studied the effect of various solvents on the reaction rate constant of CCl₃O₂ radicals with zinc tetraphenylporphyrin (ZnTPP).¹¹ We found that the rate constant for electron transfer from ZnTPP to CCl_3O_2 varies between 3 × 10^7 and 3×10^9 M⁻¹ s⁻¹ for the different solvents. These variations were found to be due to the complexation of ZnTPP with the solvent and the reaction of CCl₃O₂ with the complex was suggested to take place by an inner-sphere electron-transfer mechanism. In this study, the rate constants were generally lower for more polar solvents. This finding is in an apparent contradiction with the general expectation of solvent effects and is obviously due to the strong effect of complexation on the rate of reaction. For an outer-sphere electron-transfer reaction we would expect higher rate constants in solvents with higher dielectric constants because of increased stabilization of polar transition states. In accordance with this expectation, the rate of reaction of CF_3CHClO_2 with 2,2'-azobis(3-ethylbenzthiazoline-6-sulfonate) in water-tert-butyl alcohol solvent was found to decrease by a factor of two when the alcohol content was raised from 2% to 30%.³

This study was undertaken in order to examine the effect of wider variations in solvent polarity and to compare the reactivity of various chlorinated alkylperoxyl radicals. As a substrate we chose chloropromazine because it is known to be readily oxidized by a one-electron transfer process (e.g. reaction 1) to form a radical

$$ClPz + CCl_3\dot{O}_2 \rightarrow ClPz^{*+} + CCl_3O_2^{-}$$
(1)

cation which exhibits intense optical absorption ($\lambda_{max} = 525$ nm, $\epsilon_{max} = 10700 \text{ M}^{-1} \text{ cm}^{-1}$).¹⁴ The rates of reaction of chloropromazine and other phenothiazines with several halogenated peroxyl radicals have been studied in aqueous solutions.^{1,3} Under such conditions, the various phenothiazine radical cations are very long-lived. On the other hand, the lifetime of the chloropromazine radical cation produced by reaction 1 in neat CCl_4 solutions was found to be much shorter.⁷ Therefore, we have carried out most of our experiments in solutions containing at least some water or alcohol.

Experimental Section

Chlorpromazine hydrochloride was obtained from Sigma.¹⁵ Carbon tetrachloride, hexachloroethane, and carbon tetrabromide

were from Eastman, chloroform and methylene chloride were from Mallinckrodt, halothane (CF3CHClBr) was from ICI, and 2propanol was a Baker Analyzed reagent. All the chemicals were of the purest grade available and were used as received. Water was purified by a Millipore Milli-Q system. The pulse radiolysis experiments utilized the apparatus described before.9 Pulses of 2-MeV electrons with a 50-ns duration time were used to deposit 3-10 Gy per pulse in the solution. Kinetic spectrophotometry measurements and computer analysis of the data were done as before. In all experiments the rate of formation of the chlorpromazine radical cation was followed at 525 nm with various (at least four) concentrations of chlorpromazine. The second-order rate constants were derived from plots of k_{obsd} vs. concentration and are accurate to $\pm 20\%$ or better. All experiments were carried out at room temperature, 21 ± 1 °C.

Results and Discussion

The radiolysis of neat CCl4 or of its solutions in 2-propanol or water-alcohol mixtures in the presence of oxygen yields CCl_3O_2 radicals.⁹ Similarly, in the case of chloroform and methylene chloride the $CHCl_2O_2$ and CH_2ClO_2 radicals are formed, respectively. The yields of the various radicals in water-alcohol solutions, however, differ to some extent due to the different reactivities of the halogen compounds with the reducing radicals. All halogenated compounds used in the present study react very rapidly with the solvated electrons¹⁶

$$\mathrm{RCl} + \mathrm{e}_{\mathrm{s}}^{-} \rightarrow \dot{\mathrm{R}} + \mathrm{Cl}^{-} \tag{2}$$

- (1) Packer, J. E.; Willson, R. L.; Bahnemann, D.; Asmus, K. D. J. Chem. Soc., Perkin Trans. 2 1980, 296.
- (2) Monig, J.; Gobl, M.; Asmus, K. D. J. Chem. Soc., Perkin Trans. 2 1981, 805.
- (3) Monig, J.; Asmus, K. D.; Schaeffer, M.; Slater, T. F.; Willson, R. L. J. Chem. Soc., Perkin Trans. 2 1983, 1133.
- (4) Bahnemann, D.; Asmus, K. D.; Willson, R. L. J. Chem. Soc., Perkin Trans. 2 1983, 1661.
- (5) Monig, J.; Bahnemann, D.; Asmus, K. D. Chem. Biol. Interact. 1983, 47, 15.
- (6) Forni, L. G.; Packer, J. E.; Slater, T. F.; Willson, R. L. Chem. Biol. Interact. 1983, 45, 171.
 - (7) Grodkowski, J.; Neta, P. J. Phys. Chem. 1984, 88, 1205.
 - (7) Goldoward, G., H. M. Hubble, P. M. 1997, Oct. 1997, Oct. 1998, 11, 123.
 (8) Neta, P.; Harriman, A. J. Chem. Soc., Faraday Trans. 2 1984, 81, 123.
 (9) Brault, D.; Neta, P. J. Phys. Chem. 1984, 88, 2857.
- (10) Brault, D.; Neta, P.; Patterson, L. K. Chem. Biol. Interact. 1985, 54, 289
- (11) Alfassi, Z. B.; Harriman, A.; Mosseri, S.; Neta, P. Int. J. Chem. Kinet. 1986, 18, 1315.
- (12) Huie, R. E.; Neta, P. Int. J. Chem. Kinet. 1986, 18, 1185. (13) Mosseri, S.; Alfassi, Z. B.; Neta, P. Int. J. Chem. Kinet. 1987, 19,
- 309
- (14) Pelizzetti, E.; Meisel, D.; Mulac, W. A.; Neta, P. J. Am. Chem. Soc. 1979, 101, 6954.

(15) The mention of commercial materials does not imply recognition or endorsement by the National Bureau of Standards not does it imply that the material or equipment identified are necessarily the best available for the purpose.

(16) Anbar, M.; Bambenek, M.; Ross, A. B. Natl. Stand. Ref. Data Ser., Natl. Bur. Stand. 1973, No. 43; 1975, No. 43 Suppl.

[†]Visiting scientist from Ben Gurion University of the Negev, Beer Sheva, Israel.

TABLE I: Bimolecular Rate Constants for the Reactions of Halogenated Alkylperoxyl Radicals with Chlorpromazine (Given in Units of 10⁷ M⁻¹ s⁻¹)

	solvent ^a				
radical	PrOH:RX 1:1	PrOH:RX 9:1	PrOH:H ₂ O:RX 6:3:1	PrOH:H ₂ O:RX 6:12:0.1	PrOH:H ₂ O:RX 1:8:0.01
CCl ₁ O ₂	1.9	2.9	7.2	67	100
CHCI,O,		≤0.2	0.83	11	36
CH ₂ CIO ₂		≤0.2	0.015		2.5
CFCl ₂ O ₂			11.6		
CCl ₃ ČCl ₃ O ₂		2.1 ^b	8.6		
CH ₃ CCl ₂ O ₂			0.23		
CF ₃ CHClO ₂			0.35		
CBr ₃ O ₂		5.7 ^b			

^a Mixtures of 2-propanol (PrOH), water, and the appropriate halogen compound (RX) at the volume ratios stated. ^bPrOH:RX = 50:1.



Figure 1. Linear plots of the rate of reaction (k_{obsd}) of peroxyl radicals with chlorpromazine as a function of CIPz concentration for CHCl₂O₂ in 2-PrOH:H₂O:CHCl₃ = 6:3:1 (\diamond), CCl₃CCl₂O₂ in 2-PrOH:C₂Cl₆ = 50:1 (\square), and CBr₃O₂ in 2-PrOH:CBr₄ = 50:1 (\triangle).

and the resulting radicals react with oxygen to form the peroxyl radical studied.

$$\dot{R} + O_2 \rightarrow R\dot{O}_2$$
 (3)

CCl₄, CBr₄, and other heavily halogenated compounds are reduced also by the radical from 2-propanol relatively rapidly9

$$CCl_4 + (CH_3)_2 \dot{C}OH \rightarrow \dot{C}Cl_3 + Cl^- + (CH_3)_2 CO + H^+ \quad (4)$$

while the less halogenated compounds such as CH_2Cl_2 are not. In the latter cases, the yields of the desired peroxyl radicals are lower. Instead, the radical from 2-propanol forms a peroxyl radical or O_2^{-17} which do not react with chlorpromazine on the time scale on the pulse radiolysis experiments.

Figure 1 shows representative plots of k_{obsd} vs. chlorpromazine concentration. The slopes of the lines give the second-order rate constants for the oxidation of ClPz by the various peroxyl radicals. The intercepts of these lines represent the decay of the peroxyl radical in the absence of ClPz, i.e. by radical-radical reactions or by reactions with other solutes or impurities. Table I summarizes the second-order rate constants derived from the linear plots (such as those shown in Figure 1). For the mixtures of 9:1 2-propanol:RX the relatively short lifetime of the radical cation limits the measurements of k_1 to about 2×10^6 M⁻¹ s⁻¹. When water is added to the solution the lifetime of the chlorpromazine radical cation is greatly extended and thus lower rate constants become measurable. At high concentrations of water, due to the high value of k_1 and the lower solubility of oxygen, k_{obsd} at high CIPz concentrations may become limited by the reaction of R with O₂ (reaction 3). By using high concentrations of ClPz in 8:1 water:2-propanol with 0.1% CCl4 we arrived at a value of kobsd $\sim 4 \times 10^5$ s⁻¹, which leads to $k_3 \sim 2 \times 10^9$ M⁻¹ s⁻¹, in the same range as values reported previously.^{1,3,18}



Figure 2. Correlation between the rate constants for electron transfer from chlorpromazine and the dielectric constant of the solvent mixture for CCl_3O_2 (\square) and $CHCl_2O_2$ (\diamondsuit).

Solvent Effects. Table I shows very clearly that the rate constants for reactions of the three chlorinated methylperoxyl radicals with chlorpromazine increase with increasing solvent polarity. The effect becomes more pronounced for the weaker oxidant among those radicals. Thus, upon changing the solvent from 30% water to 89% water the rate constant for oxidation of CIPz increases by a facor of 14 for CCl_3O_2 , 43 for $CHCl_2O_2$, and 164 for $CH_2Cl\dot{O}_2$.

In many reactions where the transition state is of ionic character, log k is proportional to the polarity of the solvent as given, for example, by the dielectric constant $-\epsilon$.¹⁹ For the mixtures used in the present study we can calculate the dielectric constant by assuming additivity²⁰ of this property, i.e.

$$\epsilon_{\text{mixture}} = \sum X_i \epsilon_i \tag{5}$$

where X_i is the molal volume fraction and ϵ_i the dielectric constant of component i.

Figure 2 shows the dependence of log k_1 for CCl₃O₂ and $CHCl_2O_2$ on the dielectric constant of the solvent mixture (based on $\epsilon(CCl_4) = 2.24$, $\epsilon(2$ -propanol) = 18.3, and $\epsilon(water) = 80.1$.²¹ The data points fit a straight line quite well as expected for a reaction with an ionic transition state. The rate constant for $CCl_3\dot{O}_2$ is described by log $k_1 = 6.9 + 0.030\epsilon$, where ϵ is the dielectric constant of the solvent mixture. For $CHCl_2O_2$ we find $\log k_1 = 5.7 + 0.039\epsilon$. For CH₂ClO₂ we can estimate from the two values in Table I that $\log k_1 = 3.14 + 0.058\epsilon$. Although the error limits for the rate constants impose a considerable uncertainty on the slopes of the lines, it appears that increasing the number

(17) Ilan, Y.; Rabani, J.; Henglein, A. J. Phys. Chem. 1976, 80, 1558.

⁽¹⁸⁾ Emmi, S. S.; Beggiato, G.; Casalbore, G.; Fuochi, P. G. Proc. Tihany Symp. Radiat. Chem., 5th, 1982 1983, 677.
(19) Reichardt, C. Solvent Effects in Organic Chemistry; Verlag Chemie:

Weinheim, 1979.

⁽²⁰⁾ Hildebrand, J. H.; Prausnitz, J. M.; Scott, R. L. Regular and Related Solutions; Van-Nostrand-Reinhold: Princeton, NJ, 1970.

⁽²¹⁾ Dean, J. A. Lange's Handbook of Chemistry, 13th ed; McGraw-Hill: New York, 1985.



Figure 3. Correlation between the rate constant for electron transfer from chlorpromazine and the polar substituent constant σ^* for the reactions of various halogenated peroxyl radicals in 2-PrOH:H₂O:RX = 6:3:1 (\Box , for CH₂ClO₂, CH₃CCl₂O₂, CF₃CHClO₂, CHCl₂O₂, CCl₃O₂, and CFCl₂O₂ in order of increasing k) and 1:8:0.1 (\diamond , for CH₂ClO₂, CHCl₂O₂, and CCl₃O₂).

of halogens, i.e. increasing the redox potential of the radical, results in an increase in the intercept of the line but a decrease in the slope. This means that the effect of the number of chlorine atoms in the methylperoxyl radical on the rate of oxidation depends strongly on the medium. For example, for the solvent consisting water the ratios of reactivities of 89% of $CCl_3\dot{O}_2$:CHCl_2 \dot{O}_2 :CH_2Cl \dot{O}_2 is 1:0.67:0.07, in agreement with the previous conclusion that "introduction of a second chlorine atom increases the reaction rate constant further, but a third atom has little additional effect".² However, this observation is not valid to the same extent for the less polar media. For the mixture containing only 30% water the ratios of reactivities of the same radicals are 1:0.11:0.002. In the absence of water the ratio for CCl_3O_2 :CHCl_2O_2 is greater than 1:0.07.

The increase in rate constant k_1 upon increase in solvent polarity is likely a direct result of an increase in the driving force of the reaction, ΔG° . In going from haloalkane:2-propanol mixtures to predominantly aqueous solutions the driving force for reaction 1 increases since both products are more strongly solvated and hydrogen bonded than the reactants. This increase in ΔG° results in higher rate constants according to the Marcus relation for outer-sphere electron transfer.²² That theory also predicts a decrease in rate constant upon increase in solvent reorganization energy, λ . In the case of haloalkane, 2-propanol, and water, the solvent reorganization energy increases in that order and thus should have an opposing effect to that of the change in ΔG° , but apparently the effect of λ is relatively minor compared with the effect of driving force.

The solvent dependence may provide a partial explanation for the difference in the effect of CCl_4 and halothane in vivo. CCl_4 is known to be quite toxic by causing liver injury due to the formation of the peroxyl radicals which attack biological targets, mainly lipids.^{23,24} In contrast, halothane is widely used as an anaesthetic and is fairly safe. Measurements in aqueous solutions show that the CF₃CHClO₂ radical from halothane is less reactive than CCl₃O₂ by a factor of about 3 for ascorbate^{1,3} and ferric porphyrin,⁹ 6 for linoleic acid,¹⁰ 20 for oleic acid,¹⁰ and 30 for methionine,²⁵ for example. These differences are not dramatically large and cannot explain the difference in toxicity. However, on the basis of our findings, the ratios of the reactivity in the biological lipid media are expected to be very much greater and this may be one of the reasons for the large difference in toxicity. Another reason, which is probably more important, is the difference in the rate of reduction of the two haloalkanes by ferrous cytochrome P450, the reaction that initiates the formation of the peroxyl radicals.

Substituent Effects. Table I also shows the effect of various substituents on the rate of electron transfer from chlorpromazine to substituted methylperoxyl radicals. It is obvious that increasing the number of halogens on the radical raises the rate constant by increasing the driving force of the reaction, i.e. the oxidation potential of the radical. Since the potentials of the radicals are unknown we attempted a correlation with the polar substituent constants $\sigma^{*.26}$ The constants for CCl₃, CHCl₂, and CH₂Cl have been reported.²⁶ Those for CFCl₂, CH₃CCl₂, and CF₃CHCl were derived from comparisons of other values. For example, to derive the value for CFCl₂ we used the difference between the σ^* values for CH₂Cl and CH₂Cl and CH₂CH we calculated the difference between the σ^* for CH₂Cl and CH₂Cl and CH₂CF₃ and added it to σ^* for CHCl₂.

Figure 3 shows the correlation between log k and σ^* . The slope of the main line gives a value of $\rho = 1.7$. A limited plot with the results for the three radicals at higher water content (89%) appears to give a somewhat lower value, $\rho = 1.0$. This effect of solvent on the slope is in accord with the above discussion. The good correlation between log k and σ^* indicates that the substituents increase the rate of reaction by withdrawing electrons from the radical site, as expected for reaction 1 taking place by an electron-transfer mechanism.

The rate constant for oxidation of chlorpromazine by $CBr_3\dot{O}_2$ is about twice as high as that for $CCl_3\dot{O}_2$ in the same solvent. Similar ratios have been found recently for several other substrates in aqueous solutions.²⁷ The higher reactivity of $CBr_3\dot{O}_2$ is unexpected since Br has a lower electron-withdrawing effect than Cl. The reason for this apparent discrepancy is unclear.

Acknowledgment. The research described herein was supported by the Office of Basic Energy Sciences of the U.S. Department of Energy.

⁽²²⁾ Marcus, R. A. J. Chem. Phys. 1956, 24, 966. 1957, 26, 867, 872.

⁽²³⁾ Recknagel, R. O.; Glende, E. A., Jr. CRC Crit. Rev. Toxicol. 1973, 2, 263.

⁽²⁴⁾ Reynolds, E. S.; Moslen, M. T. In *Free Radicals in Biology*, Vol. 4, Pryor, W. A., Ed.; Academic: New York, 1980; p 49.

⁽²⁵⁾ Monig, J.; Gobl, M.; Asmus, K. D. J. Chem. Soc., Perkin Trans. 2 1985, 647.

⁽²⁶⁾ Wiberg, K. B. Physical Organic Chemistry; Wiley: New York, 1964; p 415.

⁽²⁷⁾ Huie, R. E.; Brault, D.; Neta, P. Chem. Biol. Interact., submitted for publication.