Peroxynitrite Reactions with Dimethylsulfide and Dimethylselenide: An Experimental Study

Yurii V. Geletii,* Djamaladdin G. Musaev,* Lyuba Khavrutskii, and Craig L. Hill

Department of Chemistry, and Cherry L. Emerson Center for Scientific Computation, Emory University,
1515 Pierce Drive, Atlanta, Georgia 30322

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The kinetics of the peroxynitrite ($ONOO^-$ and HOONO, PN for both) reaction with $(Me)_2X$ (X = S and Se, dimethyl sulfide (DMS) and dimethylselenide (DMSe)) was studied. The reaction is first order with respect to both PN and $(Me)_2X$ concentrations. $(Me)_2X{=}O$ and NO_2^- were formed with 100% yield based on PN in all cases except in the DMS reaction with HOONO, where the yield was ∼80%. DMSe is much more reactive than DMS toward both $ONOO^-$ and HOONO, while HOONO reacts much faster than $ONOO^-$ with both $(Me)_2X$. The activation entropies (in cal deg^{-1} mol^{-1}) and enthalpies (given in parentheses, in kcal/mol) for the reactions of DMS and DMSe with HOONO were determined to be -23 ± 3 (5.9 ± 0.5) and -20.5 ± 3 (4.6 ± 0.5), respectively. The corresponding values for the reaction with $ONOO^-$ were -29 ± 3 (9.7 ± 0.6) and -28 ± 3 (7.2 ± 0.5). A partial replacement of water with an organic cosolvent resulted in a decrease in the rate of reaction of $ONOO^-$ with both DMS and DMSe, while it had no effect on the rates of reaction with HOONO. The experimental data were analyzed using the reaction mechanism based on our previous computational studies (Musaev, D. G.; Geletii, Yu.V.; Hill, C. L. *J. Phys. Chem. A* **2003**, *170*, 5862). This mechanism includes the formation of a prereaction complex followed by O−O bond cleavage in a rate-limiting step. Strong hydration of $ONOO^-$ decreases the O−O bond cleavage barrier in a transition state, resulting in a lower reaction rate in mixed aqueous−organic solvents. In general, a fairly quantitative agreement between experimental and theoretical data was obtained.

Introduction

Peroxynitrite (PN)[1] has been known for 100 years[2] and has been extensively studied during the past decade due to its potential important role in biology and medicine. PN is quickly formed in a recombination of $O_2^{\bullet -}$ and NO, $k = 1.6 \times 10^{10}$ M^{-1} s^{-1} (see ref 3 and refs therein), and both reactants are generated in cells. Alternatively, peroxynitrous acid also can be formed by the recombination of $HO^\bullet$ and $NO_2^\bullet$ in upper atmosphere layers (see ref 4 and refs therein). However, a possible role of PN in atmospheric chemistry and especially its reactions with volatile organic compounds (e.g., dimethylsufide) have not been thoroughly studied. Independent of its significance in biological and atmospheric chemistry, from the standpoint of its structure and reactivity, PN is a very interesting molecule. During the past decade, several reviews on different aspects of PN chemistry and biochemistry have been published.[5−13]

Peroxynitrite anion, $ONOO^-$, is rather stable and very slowly decomposes to nitrite and dioxygen, while the acid, HOONO, rapidly ($k \sim 1.2$ s^{-1} at 25 °C) isomerizes to nitrate. This quick isomerization is accompanied by formation of highly reactive radical species (see refs 5 and 14−16 and refs therein). The mechanism of this reaction is questionable and presently is hotly debated.[2] PN reactions also can be catalyzed by transition-metal ions[17−23] and by compounds having C=O double bonds (CO_2, ketones, and aldehydes).[24−29]

The fastest PN bimolecular reaction found so far occurs with metalloporphyrins (myeloperoxidase, Fe(III)TMPyP, and Mn(II)TMPyP) and proceeds with $k > 10^7$ M^{-1} s^{-1}.[30−32] A selenoorganic compound ebselen reacts only an order of magnitude slower with $ONOO^-$ (no reaction with HOONO), $k = 2 \times 10^6$ M^{-1} s^{-1} (25 °C, pH >8).[33] Surprisingly, D,L-selenomethionine reacts much faster with HOONO ($k = 2 \times 10^5$ M^{-1} s^{-1} (25 °C, pH > 4.6) than with $ONOO^-$ ($k = 200 \pm 170$ M^{-1} s^{-1}).[34] Similar sulfur compounds are 2 orders of magnitude less reactive; the reaction rate constants for HOONO and $ONOO^-$ with methionine are 1.7×10^3 and 8.6 M^{-1} s^{-1}, respectively.[35] The second-order rate constants for the reactions with other biologically related compounds such as cysteine, glutathione, or ascorbic acid are in the range 2×10^2−6×10^3 M^{-1} s^{-1} (for review, see: refs 6 and 8−13). Carbon dioxide is present in vivo in a relatively high concentration, therefore it is likely to be the most important PN scavenger, $k = 3 \times 10^4$ M^{-1} s^{-1} (with $ONOO^-$, 25 °C).[10,24,36] Ascorbate anion, a major biological antioxidant, reacts with PN relatively slowly ($k = 42$−47 M^{-1} s^{-1} at 25 °C, pH 7.4),[37,38] but this reaction can be catalyzed very efficiently by transition-metal complexes such as Fe and Mn porphyrins[30,39] and particular copper complexes.[40,41] All these reactions are pH dependent and proceed via different mechanisms.

Computational methods are extremely useful in providing highly detailed information on reaction mechanisms. The structure, stability, and reactivity toward different compounds of $ONOO^-$ and HOONO were studied computationally in several papers.[28,42−51] In general, it was demonstrated that the $ONOO^-$ anion has cis and trans isomers, *cis*-$ONOO^-$ being more stable by 2−4 kcal/mol and separated from *trans*-$ONOO^-$ by an energy barrier of about 21−27 kcal/mol. HOONO has two of the energetically lowest isomers, cis−perp and cis−cis, which differ from each other by rotation (about 90−100°) around the O−H bond (ref 52 and refs therein). These two

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* Corresponding authors. E-mail: iguelet@emory.edu and dmusaev@emory.edu.

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TABLE 1: Bimolecular Rate Constants and Activation Parameters of PN Reactions with DMS, DMSe, Methionone (MetS), and Selenomethionine (MetSe)

substrate	pH	k_4 M^{-1} s^{-1} (25 °C)	log A	E_{act} kcal/mol	$\Delta S^{\ddagger}$ cal deg^{-1} mol^{-1}	$\Delta H^{\ddagger}$ kcal/mol	T °C	ref
DMS	4.6[a]	$(2.1 \pm 0.2) \times 10^3$	8.0 ± 0.2	6.5 ± 0.5	-23 ± 3	5.9 ± 0.5	6−45	
	6.8[b]	$(6.7 \pm 0.5) \times 10^2$						
	7.4[b]	$(2.3 \pm 0.2) \times 10^2$						
	~13[c]	0.23 ± 0.02	6.9 ± 0.2	10.3 ± 0.7	-29 ± 3	9.7 ± 0.6	15−55	
	~13[c,d]	0.04 ± 0.004	6.0 ± 0.2	10.2 ± 0.7	-33 ± 3	9.6 ± 0.6	15−55	
MetS	<5	$(1.7 \pm 0.1) \times 10^3$						35
	7.6	$(1.7 \pm 0.1) \times 10^2$						35
	7.4	$(1.8 \pm 0.1) \times 10^2$						58
	>9	8.6 ± 0.2						35
DMSe	4.6[a]	$(2.7 \pm 0.3) \times 10^4$	8.3 ± 0.2	5.2 ± 0.5	-20.5 ± 3	4.6 ± 0.5	6−45	
	6.8[b]	$(9.0 \pm 0.9) \times 10^3$						
	7.4[b]	$(3.2 \pm 0.3) \times 10^3$						
	~13[c]	6.0 ± 0.5	6.4 ± 0.2	7.8 ± 0.6	-28 ± 3	7.2 ± 0.5	15−55	
	~13[c,d]	1.1 ± 0.1	5.3 ± 0.2	7.8 ± 0.7	-31 ± 3	7.2 ± 0.5	15−55	
MetSe	4.6	$(2.05 \pm 0.05) \times 10^5$			-30.5 ± 0.3	2.55 ± 0.08	5−46	34
	7.4	$(1.16 \pm 0.01) \times 10^2$						34
	>10	200 ± 170						34

[a] 100 mM acetate buffer. [b] 75 mM phosphate buffer. [c] 85 mM NaOH. [d] 50% v/v EtOH.

isomers are practically degenerate in energy and easily can rearrange to one another (ref 52 and refs therein).

Recently we performed comprehensive theoretical studies of DMS and DMSe reactions with both $ONOO^-$ and HOONO.[53] The major goal of this paper was to study the same reactions experimentally and thus to compare the experimental and theoretical data.

Experimental Section

Chemicals. Dimethylsufide (DMS) and dimethylselenide (DMSe) were purchased from Aldrich (U.S.A.) and Alfa Aesar (U.S.A.). Both were of highest purity, packed under Ar, and used without further purification. PN was synthesized in a simple flow reactor[54] by mixing acidified hydrogen peroxide and nitrite and then quenching the HOONO formed with aqueous sodium hydroxide solution. The unreacted H_2O_2 was destroyed by treatment with MnO_2. A 0.10−0.12 M solution of PN was obtained and then diluted with 50 mM NaOH to give PN concentrations of ~20 mM, which were then stored at −20 °C. PN concentration was determined by UV−vis spectroscopy, $\epsilon_{302} = 1.7 \times 10^3$ M^{-1} cm^{-1}.[55]

Instrumentation. UV−vis spectra and kinetic data of slow reactions were acquired using diode-array Hewlett-Packard 8452A spectrophotometers equipped with magnetic stirrers and temperature controllers (HP 89090A). Fast reactions were studied using a SF-61 stopped-flow instrument (Hi-Tech Scientific, U.K.). pH measurements were made using an Orion model 250A pH meter.

Buffer Solutions. Phosphate buffers (0.15 M) were prepared in Barnstead Nanopure-quality water from Na_2HPO_4 and $NaH_2PO_4 \cdot H_2O$ (Fisher Scientific, U.S.A.). Control experiments showed that diethylenetriaminepentaacetic acid did not affect the rate of PN decay, therefore no organic chelators were used. Acetate buffer (0.2 M) was prepared from glacial acetic acid (Fisher Scientific, U.S.A.), and its desired pH was achieved by adding NaOH or HCl.

General Procedures. In most kinetic experiments, solutions of all reactants (in buffer or in aqueous NaOH) except PN were mixed in a stopped-flow instrument with an equal volume of PN solution diluted with aqueous NaOH. A variable drive ratio was used to mix 1 part PN solution with 3 parts acetate buffer/EtOH solution to study the effect of EtOH on the reaction at low pH. Thus, the total amount of EtOH could reach 50% (v/v) after mixing. In the case of slower reactions, a cell containing necessary reagents (with total volume ~2 mL) was placed into Hewlett-Packard 8452A spectrophotometers, and after temperature equilibration, a small volume of PN solution (<0.1 mL) was injected. The spectra were collected in an appropriated time interval. A pH value was determined at the end of the reaction after mixing all reagents. The NaOH concentration of PN stock solution and the pH of buffer solutions was adjusted to obtain the desired final pH value. The activation parameters were determined from the dependence of the reaction rate constants on temperature in their ranges (given in Table 1). The activation energies and pre-exponential factors were calculated from the Arrhenius plot, and the activation enthalpies $\Delta H^{\ddagger}$ and entropies $\Delta S^{\ddagger}$ were calculated from the Eyring plot.

Product Studies. The nitrite concentration was measured by Griess reagent (1% w/v sulfanilamide and 0.1% w/v *N*-(1-naphthyl)-ethylenediamine in 8.5% phosphoric acid).[56] The background concentration of nitrite in the PN stock solutions was determined using this reagent as described in Plumb, 1992.[57] Briefly, PN was decomposed at ~0 °C at pH ~2.0 for 20 s, and then the pH was adjusted to neutral. The yield of nitrite in PN decomposition was determined as a difference between nitrite formed in a studied reaction and that formed at pH ~2.0. Both DMS and DMSe were found to interfere considerably with nitrite determination. Therefore, before nitrite measurements were taken, the reaction solutions were carefully purged with Ar for 2−3 min to entirely remove unreacted substrate. DMSe is much less volatile compared to DMS and is more difficult to remove, resulting in greater experimental error. DMSO and DMSeO yields were quantified by ^1H NMR (600 MHz) after 1:1 dilution of the reaction mixture with D_2O with dioxane (solution in D_2O) as an internal standard. Since the reaction at neutral pH is fast, the mixing was performed using a stopped-flow instrument. Under basic conditions the reaction was carried out in carefully sealed vials to avoid loss of $(Me)_2X$. The incubation time was at least 45 min for DMS or 10 min for DMSe (>8 of PN half-lives).

Kinetic Studies. Kinetic studies of PN decay were carried out by measuring the absorbance at 302 nm. $(Me)_2X$ was always in excess of PN. Unless otherwise indicated, initial PN concentrations were never higher than 0.5 mM. The apparent first-order rate constants, k_{obs}, were determined at different concentrations of $(Me)_2X$ from kinetic traces and collected over more than 4−5 half-lives, using standard software (KISS 5.1 for Macintosh in the case of stopped-flow experiments or MS Excel for slower reactions). Bimolecular rate constants were determined from a slope of a k_{obs} − [S] plot.

Results

Reaction Products. Under basic conditions DMS was selectively oxidized by $ONOO^-$ to DMSO, and no dimethyl sulfone was detected. DMSO and nitrite yields based on consumed PN were close to 100%. For example, 0.56 mM of PN (initial concentration) and 40 mM of DMS (in 50 mM NaOH, 25 °C) produced (0.56 ± 0.03) mM of NO_2^- and (0.56 ± 0.03) mM of DMSO. The mass balance with respect to DMS was not 100% due to the very high volatility of DMS. Hence, the following reaction takes place under basic conditions (eq 1)

$$\mathrm{DMS} + \mathrm{ONOO}^- \rightarrow \mathrm{DMSO} + \mathrm{NO_2}^- \quad (1)$$

At pH < 7.0, DMSO was also the major product, but its yield as well the yield of nitrite were always lower than the amount of PN consumed. For example, 0.56 mM of PN and 40 mM of DMS (pH = 5.7 ± 0.3, 0.15 M phosphate buffer, 25 °C) produced (0.46 ± 0.03) mM of NO_2^- and (0.46 ± 0.03) mM of DMSO or (82 ± 10)% based on PN. The missing ∼20% of PN is likely to isomerize to nitrate, but cannot be attributed to HOONO isomerization via its monomolecular decomposition since the contribution of this process did not exceed 2% under our experimental conditions. Thus, the bimolecular oxidation of DMS by HOONO can be described in eq 2

$$\mathrm{DMS} + \mathrm{HOONO} \rightarrow \mathrm{DMSO}\ (\sim 80\%) + \mathrm{NO_2}^-\ (\sim 80\%) + \mathrm{H}^+ \quad (2)$$

Our findings are not unprecedented. In the reaction with methionine at pH 5.7−7.8, sulfoxidation was accompanied by PN isomerization; one nitrate was formed per every two sulfoxides and two nitrites.[35] Ethylene was also observed as a product,[58] but a mechanism of its formation has been questioned.[35] Threonylmethionine oxidation by PN at neutral pH was shown to produce acetaldehyde through a pathway that did not include a discrete hydroxyl radical.[59] It has been suggested that ethylene and acetaldehyde were formed in a bimolecular one-electron oxidation pathway.[58,59]

A quantification of absolute product yields in DMSe oxidation was less accurate than in the case of DMS because of the lower volatility of DMSe relative to DMS. Therefore we compared the yields of nitrite and DMSeO under identical (except pH) conditions ($[PN]_0 = 0.5$ mM, [DMSe] = 3 mM, 25 °C, pH = 5.7 or in 50 mM NaOH). The nitrite yield was only 5−7% lower at pH 5.7 than in 50 mM NaOH, while the DMSeO yield was 5−10% higher. Such a difference is not significant and lies in the range of experimental error (∼10%). Thus, DMSe is selectively oxidized to DMSeO by both $ONOO^-$ and HOONO (eq 3)

$$\mathrm{DMSe} + \mathrm{ONOO}^-\ (\mathrm{HOONO}) \rightarrow \mathrm{DMSeO} + \mathrm{NO_2}^-\ (\mathrm{H}^+) \quad (3)$$

Reaction Kinetics. The kinetics of PN decay were exponential, and the rate increased linearly with $(Me)_2X$ concentrations (Figure 1). Thus, the rate law is in eq 4

$$-\mathrm{d[PN]}/\mathrm{d}t = k_{\mathrm{obs}}[\mathrm{PN}] = k_0[\mathrm{PN}] + k_4[\mathrm{PN}][(\mathrm{Me})_2\mathrm{X}] \quad (4)$$

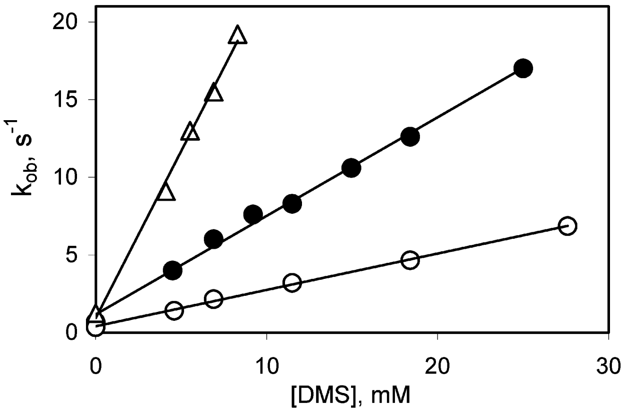

Figure 1. Dependence of apparent reaction rate constants of PN decay on DMS concentration at different pH. (△) pH 4.6, 100 mM acetate buffer, $[PN]_0 \sim 0.9$ mM; (●) pH 6.8, 75 mM phosphate buffer, $[PN]_0 \sim 0.5$ mM; (○) pH 7.4, 75 mM phosphate buffer, $[PN]_0 \sim 0.2$ mM. 25 °C.

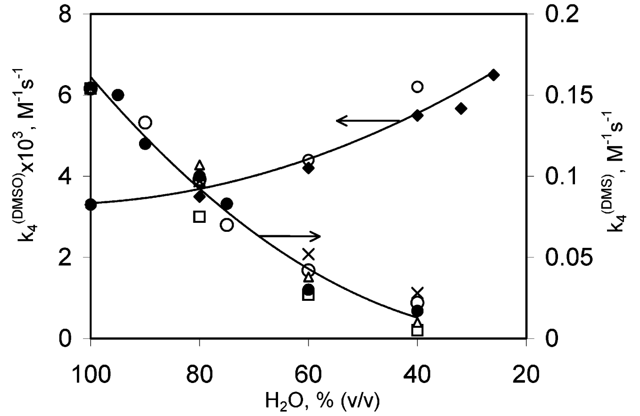

Figure 2. Dependencies of bimolecular reaction rate constants of DMSO ($k_4^{(DMSO)}$) and DMS ($k_4^{(DMS)}$) oxidation by $ONOO^-$ on the amount of water in mixed aqueous/organic solvents. T = 20 °C, 25 mM NaOH. (○) EtOH; (●) and (◆) *t*-BuOH; (△) THF; (□) CH_3CN; (×) $C_4H_8SO_2$ (tetramethylenesulfone).

Some deviations from linearity of k_{obs} − $[(Me)_2X]$ were reported[58] for the reaction with methionine but were not observed in a more recent study.[35] No such deviations were seen in this work for either $(Me)_2X$ employed. The data obtained as well as selected data from the literature are shown in Table 1.

Cu and Co ions and complexes are very efficient catalysts of the reaction between PN and ascorbic acid.[20,40,41] To rule out a similar catalysis in the case of $(Me)_2X$, Cu^{2+} (up to 7 μM as $CuCl_2$) and Co^{2+} (up to 8 μM as $CoCl_2$) were added to the reaction at pH 7.4. No effect was observed.

DMS oxidation by $ONOO^-$ was very weakly dependent on ionic strength; only a 25% rate increase was observed in the presence of ∼2.5 M NaCl (25 °C, 85 mM NaOH). Addition of nitrite anion slightly inhibited the reaction. For example, 90 mM of $NaNO_2$ decreased the rate by 20% (25 °C, 85 mM NaOH). At lower pH, the rate of PN decay (in the absence of DMS) weakly increased with nitrite concentration due to an oxidation of NO_2^- by HOONO.[60] For example, running the reaction in the presence of 100 mM $NaNO_2$ increased the rate constant of HOONO decay from 1.1 to 1.6 s^{-1} (25 °C, pH 4.4, 100 mM acetate buffer). At low nitrite concentrations (<20 mM) the effect was insignificant in the presence as well as in the absence of DMS.

Solvent Effect. At high pH oxidation of DMS to DMSO by $ONOO^-$ (k_4 for DMS oxidation, henceforth $k_4^{(DMS)}$) is inhibited

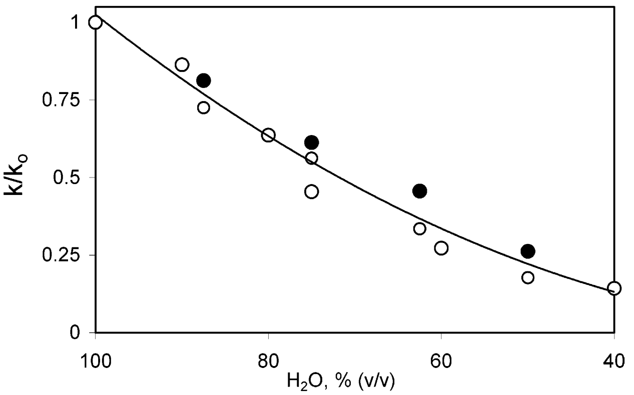

Figure 3. Dependencies of bimolecular reaction rate constants of DMS (○) and DMSe (●) oxidation by $ONOO^-$ on amount of water in EtOH–H_2O. $T = 25$ °C, 85 mM NaOH, $[PN]_0 \sim 0.2-0.6$ mM.

by addition of an organic cosolvent. In contrast, the subsequent oxidation of DMSO (k_4 for DMSO oxidation, henceforth $k_4^{(DMSO)}$) is not (Figure 2). For example, substituting 60% of the water with organic cosolvents decreased the rate of DMS oxidation by almost 1 order of magnitude. Surprisingly, this decrease was independent of the cosolvent used. Moreover, the relative effect of replacing water with EtOH on the reaction rate was the same for the reactions of $ONOO^-$ with both DMS and DMSe (Figure 3). The rate of DMS oxidation by $ONOO^-$ was not affected by polarity or viscosity of such cosolvents (Figure 2) as *tert*-butyl alcohol (2.7), ethanol (24.6), tetrahydrofuran (7.6), acetonitrile (37.5), or tetramethylene sulfone (43.3) with dielectric constants ϵ (given in brackets) varying widely. At pH 4.6, where HOONO is a predominant reaction species, the reaction rate was independent of EtOH content in contrast to the high pH conditions. For example, in an EtOH/H_2O mixture (1:1), the reaction rate constant of DMS with HOONO was $(2.3 \pm 0.2) \times 10^3$ M^{-1} s^{-1} compared with $(2.1 \pm 0.2) \times 10^3$ in water (25 °C, pH 4.6, 100 mM acetate buffer).

Hence, the reactivity of $ONOO^-$ toward DMS and DMSe depends greatly on the amount of water present in the system but not on the nature of cosolvents or on the nature of $(Me)_2X$. This reactivity pattern is likely to support an involvement of an $\{ONOO^-...(H_2O)_n\}$ adduct in the reaction.

Interestingly, DMSO oxidation by $ONOO^-$ ($k_4^{(DMSO)}$) slightly increased in the presence of organic cosolvent (Figure 2). The opposite solvent dependencies of $k_4^{(DMS)}$ and $k_4^{(DMSO)}$ result in different selectivity in water and in mixed aqueous/organic solvents, where $k_4^{(DMS)}/k_4^{(DMSO)}$ drops from ~50 in water to 2–3 when 60% of the water is replaced by organic cosolvent. As a result, DMS oxidation to DMSO proceeds with a higher selectivity in aqueous solutions.

Temperature Effect. The effect of temperature on the reaction rate revealed that DMSe oxidation proceeds with a lower activation energy than DMS oxidation by either HOONO or $ONOO^-$ (Table 1). The reactions with $ONOO^-$ have higher activation enthalpies and more negative activation entropies than with HOONO. Under basic conditions a partial replacement of water with EtOH results in a more negative activation entropy, but does not affect the activation enthalpy (Table 1).

Other Thioethers. Organic cosolvents increase the solubility of thioethers allowing the study of the reactivity of substrates with limited solubility in water. In *tert*-butyl alcohol/water mixture (1:1), the order of reactivity for $ONOO^-$ reactions is DMS > Et_2S ~ THT > $(t\text{-}Bu)_2S$, showing that thioethers with bulky substituents are less reactive.

Discussion

Recently we performed computational studies[53] of the reactions of DMS and DMSe with *cis*-$ONOO^-$ ($ONOO^-$) and *cis*–*cis*-HOONO (HOONO).

Reactions of $ONOO^-$. The computational studies show that reaction of DMS and DMSe with $ONOO^-$ proceeds via the pathway presented in eqs 5–7. In the gas phase, the reaction initiated by the interaction of the negatively charged O^3 end of $ONOO^-$ and the positively charged M center in $(Me)_2X$ results in the formation of a prereaction complex $\{(Me)_2X...^-OONO\}$ (eq 5). The calculated ΔH and ΔG values (here and below given in parentheses) are −6.4 (1.2) and −6.8 (0.8) kcal/mol for X = S and Se, respectively

$$\mathrm{ONOO^- + (Me)_2X \rightleftharpoons \{(Me)_2X...^-OONO\}} \tag{5}$$

$$\mathrm{\{(Me)_2X...^-OONO\} \rightarrow TS1(O{-}O\ activ) \rightarrow \{(Me)_2XO\ (NO_2^-)\}} \tag{6}$$

$$\mathrm{\{(Me)_2XO\ (NO_2^-)\} \rightarrow Me_2XO + NO_2^-} \tag{7}$$

The O–O bond homolysis in the transition state TS1(O–O activ) is a rate-limiting step and results in an intermediate, $\{(Me)_2XO(NO_2^-)\}$, eqs 5–6. The calculated activation barriers ($\Delta H^{\ddagger}$ (ΔG), relative to the reactants) are 15.3 (26.2) for DMS and 8.9 (19.9) kcal/mol for DMSe. The O–O cleavage product $\{(Me)_2XO(NO_2^-)\}$ energy is 51.5 (42.3) and 46.3 (38.0) kcal/mol (X = S and Se, respectively) lower than the reactants. It was shown that the dissociation of $\{(Me)_2XO(NO_2^-)\}$ into DMSO (or DMSeO) and nitrite is barrierless but endothermic by 17.3 (8.6) and 17.6 (9.5) kcal/mol for M = S and Se, respectively. However, the entire reaction of $ONOO^-$ with $(Me)_2X$ to form $(Me)_2XO$ and NO_2^- is found to be exothermic by 34.2 (33.7) and 28.7 (28.5) kcal/mol, for X = S and Se, respectively.[61] The difference in the reaction exothermicity is in good agreement with the S=O and Se =O bond strengths, 124.7 ± 1.0 and 111.1 ± 5.1 kcal/mol, respectively.[62] Thus, despite a higher total exothermicity, the reaction with DMS has a higher activation barrier and therefore proceeds slower than with DMSe.

Hydration of a charged reactant ($ONOO^-$) and products (NO_2^- and/or NO_3^-) may significantly alter the reaction rate and mechanism. Two different theoretical models were used to elucidate the solvent effect. The first of them is the single point polarizable continuum model (PCM), which mostly takes into account the effect of solvent polarity (see references in ref 53). This approach predicted the rate increase in less polar solvent, which is inconsistent with our experimental data; experiments indicate that the rate of this reaction is independent of solvent polarity and decreases with partial replacement of water with organic cosolvent.

The second model was to explicitly include several water molecules into the calculations and reoptimize the geometry of all intermediates and transition states. As a first step, the structures and energetics of $(H_2O)_n(ONOO^-)$ ($n = 1-4$) were studied. These calculations show that two water molecules tightly bind to a terminal O^3 atom of a $ONOO^-$ unit, while the other two are also clustered in the O^3 atom vicinity with slightly lower hydration energies.[53] The sequential enthalpies (and Gibbs free energy) of hydration of these last two water molecules are approximately the same, 11.8 (3.0) and 11.8 (2.6) kcal/mol, respectively, while those of the first and second water molecules are larger, 16.3 (9.0) and 14.2 (4.0) kcal/mol, respectively. Therefore, the reactions of DMS with $(H_2O)_n(ONOO^-)$ were computed only for $n = 1$ and 2 by reoptimizing the geometry of all intermediates and transition states. It was shown that water molecules explicitly included in the calculations destabilize the prereaction complex $\{(Me)_2X...(H_2O)_n(ONOO^-)\}$ relative to the corresponding reactants, ΔH (ΔG) = −4.6 (3.0) and 0.1 (6.2), for $n = 1$ and 2, compared with −6.4 (1.2) kcal/mol for $n = 0$. However, the enthalpies of O−O bond cleavage in the TS1 $(H_2O)_n$(O−O activ) transition states (relative to the reactants) decrease from 15.3 to 14.7 and 13.5 kcal/mol (X = S) for $n =$ 0, 1, and 2, respectively. Extrapolation of these data to $n > 2$ indicates that the activation barrier for $n > 2$ should be even smaller than 13.5 kcal/mol. Thus, *the hydration of ONOO− increases the reaction rate.* Although the calculations for the reaction with DMSe were not performed, the trends should be similar in this case

$$ONOO^- + n(H_2O) \rightleftharpoons (H_2O)_n(ONOO^-) \quad (8)$$

$$(H_2O)_n(ONOO^-)^- + (Me)_2X \rightleftharpoons \{(Me)_2X...(H_2O)_n(ONOO^-)\} \quad (9)$$

$$\{(Me)_2X...(H_2O)_n(ONOO^-)\} \rightarrow \text{TS1 } (H_2O)_n(\text{O−O activ}) \rightarrow \{(Me)_2XO(H_2O)_n(NO_2^-)\} \quad (10)$$

The computational reaction mechanism is in good agreement with our experimental findings. Equations 5−7 result in the reaction rate law in eq 11

$$d[PN]/dt = -K_5k_6[PN][(Me)_2X] = -k_{obs}[PN][(Me)_2X] \quad (11)$$

which is similar to the experimental eq 4, if $k_4 = k_{obs} = K_5k_6$. In general, adding eqs 8−10 into consideration results in a more complex expression for k_{obs}, but the rate remains first order with respect to $ONOO^-$ and $(Me)_2X$ concentrations. The “oxygen atom transfer” was the only pathway predicted computationally and seen experimentally (based on stoichiometry). DMSO (and/or DMSeO) and nitrite were formed with 100% yield based on consumed $ONOO^-$. DMSe is much more reactive compared with DMS, $k_{obs}^{(DMSe)} \gg k_{obs}^{(DMS)}$ and the experimental $\Delta H^{‡}$ values are 9.7 and 7.2 kcal/mol (in 85 mM NaOH) for M = S and Se, respectively (Table 1). The experimental value of activation enthalpy for the DMS reaction is in fairly quantitative agreement with a calculated number (less than 13.5 kcal/mol). Interestingly, the theory predicts that the activation entropies for both $(Me)_2X$ should be the same, which is consistent with the experimental data. When water is partially replaced with organic cosolvent the activation entropy becomes slightly higher, and the reaction rate decreases as a result. Such an increase in activation entropy is consistent with a larger number of water molecules involved in a transition state.

Reactions of HOONO. In the case of HOONO the calculations were performed for M = S and the *cis*−*cis*-HOONO isomer only. In the gas phase, it was shown that the reaction proceeds through an intermediate complex, $\{(Me)_2X...HOONO\}$ (eq 12), in which HOONO coordinates to the sulfur atom via its hydrogen atom. The complexation energy is −10.2 (−1.0) kcal/mol

$$HOONO + (Me)_2X \rightleftharpoons \{(Me)_2X...HOONO\} \quad (12)$$

$$\{(Me)_2X...HOONO\} \rightarrow \text{TS1(O−O activ)} \rightarrow \{(Me)_2XO(HONO)\} \quad (13)$$

$$\{(Me)_2XO(HONO)\} \rightarrow (Me)_2XO + HONO \quad (14)$$

A prereaction complex undergoes further transformation via a concerted transition state TS1 (O−O activ), eq 13. The activation barrier for O−O bond cleavage is 6.1 (7.3) kcal/mol relative to the prereaction complex. The formed $\{(Me)_2XO(HONO)\}$ product, eq 13, dissociates into $(Me)_2XO$ and *cis*-HONO with an energy loss of only 10.9 (1.5) kcal/mol. Alternatively, HOONO may undergo homolysis in a unimolecular rate-limiting reaction to form two discrete radicals, $HO^{\bullet}$ and $NO_2^{\bullet}$, which then oxidize $(Me)_2X$. While the computations predicted the feasibility of both (concerted and homolysis) pathways, under our experimental conditions the latter pathway is very likely not operable ($k_0[PN] \ll k_4[PN][(Me)_2X]$, eq 4).

The inclusion of the solvent effects at the PCM level significantly destabilizes the $\{(Me)_2X...HOONO\}$ complex relative to reactants and only slightly decreases the O−O activation barrier at the TS1 (O−O activ). An explicit inclusion of water molecules into the calculation revealed a much weaker interaction of water with HOONO as compared to $ONOO^-$ and therefore was not studied in detail. In general, in water the equilibrium in eq 12 is likely to be shifted to the left with ΔH_{12} close to zero. A combination of eqs 12−13 results in the reaction rate law similar to eq 11 with $k_{obs} = K_{12}k_{13}$, which is consistent with an experimental eq 4.

The PCM value (which does not include entropy and zero-point energy corrections and therefore can be considered roughly analogous to enthalpy) of the O−O activation barrier is 3.7 kcal/mol in water, calculated relative to the reactants. The inclusion of the zero-point energy and entropy corrections will slightly increase this number. Therefore, this value, 3.7 kcal/mol, should be considered as a lower limit of the activation barrier. Overall, the experimental activation enthalpy, 5.9 kcal/mol (Table 1), is close to the calculated value.

The theoretical study predicts that DMSO and HONO should be the only products. However, the experimental DMSO and HONO yield was ∼80%, suggesting an existence of another oxidation pathway. Such a pathway may include intermediate formation of a $\{((Me)_2XOH)^{\bullet}...^{\bullet}(ONO)\}$ radical pair. This pair was not located in the gas phase, but its existence in solutions cannot be ruled out. The elucidation of this question requires the reoptimization of the geometries of all the intermediates and transition states of reaction 2 in water, applying both the PCM and explicit water approaches. These calculations are in progress.

Conclusions

Both $ONOO^-$ and HOONO react with $(Me)_2X$ through a bimolecular process resulting in NO_2^- and $(Me)_2X{=}O$ with 100% yield in all cases except in the DMS reaction with HOONO (yield ∼ 80%). HOONO is much more reactive than $ONOO^-$, while both are more reactive toward DMSe than DMS. $ONOO^-$ becomes less reactive if water is partly replaced with organic cosolvent. The experimental data are in fair agreement with a reaction mechanism based on our previous computational studies.[53] The reaction proceeds via a prereaction complex followed by O−O bond cleavage in a rate-limiting step. An intermediate formation of a $\{((Me)_2SOH)^{\bullet}...^{\bullet}(ONO)\}$ radical pair may account for a lower yield of $(Me)_2SO$ in $(Me)_2S$ reaction with HOONO.

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References and Notes

(1) IUPAC names: ONOO$^-$ is oxoperoxonitrite(−1), and HOONO is hydrogen oxoperoxonitrite.

(2) Koppenol, W. H. *Redox Rep.* **2001**, *6*, 339.

(3) Nauser, T.; Koppenol, W. H. *J. Phys. Chem. A* **2002**, *106*, 4084.

(4) Matheu, D. M.; Green, W. H. *Int. J. Chem. Kinet.* **2000**, *32*, 245.

(5) Edwards, J. O.; Plumb, R. C. *Prog. Inorg. Chem.* **1994**, *41*, 599.

(6) Halliwell, B.; Zhao, K.; Whiteman, M. *Free Radical Res.* **1999**, *31*, 651.

(7) Pfeiffer, S.; Mayer, B.; Hemmens, B. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1715.

(8) Koppenol, W. H. *Met. Ions Biol. Syst.* **1999**, *36*, 597.

(9) Groves, J. T. *Curr. Opin. Chem. Biol.* **1999**, *3*, 226.

(10) Hurst, J. K.; Lymar, S. V. *Acc. Chem. Res.* **1999**, *32*, 520.

(11) Trujillo, M.; Navillat, M.; Alvarez, M. N.; Peluffo, P.; Radi, R. *Analusis* **2000**, *28*, 518.

(12) Radi, R.; Peluffo, P.; Alvarez, M. N.; Naviliat, M.; Cayota, A. *Free Radical Biol. Med.* **2001**, *30*, 463.

(13) Pryor, W. A.; Squadrito, G. L. *Am. J. Physiol.* **1995**, *268*, L699.

(14) Beckman, J. S.; Beckman, T. W.; Chen, J.; Marshal, P. A.; Freeman, B. A. *Proc. Nat. Acad. Sci., U. S. A.* **1990**, *87*, 1620.

(15) Coddington, J. W.; Hurst, J. K.; Lymar, S. V. *J. Am. Chem. Soc.* **1999**, *121*, 2438.

(16) Richeson, C. E.; Mulder, P.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1998**, *120*, 7211.

(17) Hughes, M. N.; Nicklin, H. G. *J. Chem. Soc. A* **1968**, 450.

(18) Groves, J. T.; Marla, S. S. *J. Am. Chem. Soc.* **1995**, *117*, 9578.

(19) Stern, M. K.; Jensen, M. P.; Kramer, K. *J. Am. Chem. Soc.* **1996**, *118*, 8735.

(20) Geletii, Yu. V.; Bailey, A. J.; Cowan, J. J.; Weinstock, I. A.; Hill, C. L. *Can. J. Chem.* **2001**, *79*, 792.

(21) Al-Ajlouni, A. M.; Paul, P. C.; Gould, E. S. *Inorg. Chem.* **1998**, *37*, 1434.

(22) Zhang, X.; Busch, D. H. *J. Am. Chem. Soc.* **2000**, *122*, 1229.

(23) Babich, O. A.; Gould, E. S. *Res. Chem. Intermed.* **2002**, *28*, 575.

(24) Lymar, S. V.; Hurst, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 8867.

(25) Lymar, S. V.; Hurst, J. K. *Chem. Res. Toxicol.* **1996**, *9*, 845.

(26) Pryor, W. A.; Lemercier, J.-N.; Zhang, H.; Uppu, R. M.; Squadrito, G. L. *Free Radical Biol. Med* **1997**, *23*, 331.

(27) Uppu, R. M.; Winston, G. W.; Pryor, W. A. *Chem. Res. Toxicol.* **1997**, *10*, 1331.

(28) Yang, D.; Tang, Y.-C.; Chen, J.; Wang, X.-C.; Bartberger, M. D.; Houk, K. N.; Olson, L. *J. Am. Chem. Soc.* **1999**, *121*, 11976.

(29) Merenyi, G.; Lind, J.; Goldstein, S. *J. Am. Chem. Soc.* **2002**, *124*, 40.

(30) Ferrer-Sueta, G.; Batinic-Haberle, I.; Spasojevic, I.; Fridovich, I.; Radi, R. *Chem. Res. Toxicol.* **1999**, *12*, 442.

(31) Lee, J.; Hunt, J. A.; Groves, J. T. *J. Am. Chem. Soc.* **1998**, *120*, 7493.

(32) Floris, R.; Piersma, S. R.; Yang, G.; Jones, P.; Wever, R. *Eur. J. Biochem.* **1993**, *215*, 767.

(33) Masumoto, H.; Kissner, R.; Koppenol, W. H.; Sies, H. *FEBS Lett.* **1996**, *398*, 179.

(34) Padmaja, S.; Squadrito, G. L.; Lemercier, J.-N.; Cueto, R.; Pryor, W. A. *Free Radical Biol. Med.* **1997**, *23*, 917.

(35) Perrin, D.; Koppenol, W. H. *Arch. Biochem. Biophys.* **2000**, *377*, 266.

(36) Goldstein, S.; Czapski, G. *Inorg. Chem.* **1997**, *36*, 5113.

(37) Bartlett, D.; Church, D. F.; Bounds, P. L.; Koppenol, W. H. *Free Radical Biol. Med.* **1995**, *18*, 85.

(38) Squadrito, G. L.; Jin, X.; Pryor, W. A. *Arch. Biochem. Biophys.* **1995**, *322*, 53.

(39) Lee, J.; Hunt, J. A.; Groves, J. T. *J. Am. Chem. Soc.* **1998**, *120*, 6053.

(40) Geletii, Yu. V.; Bailey, A. J.; Boring, E.; Hill, C. L. *J. Chem. Soc., Chem. Commun.* **2001**, *2001*, 1484.

(41) Geletii, Yu. V.; Patel, A. D.; Hill, C. L.; Casella, L.; Monzani, E. *React. Kinet. Catal. Lett.* **2002**, *77*, 277.

(42) Tsai, J. H. M.; Harrison, J. G.; Martin, J. C.; Hamilton, T. P.; van der Woerd, M.; Jablonsky, M. J.; Beckman, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 4115.

(43) Tsai, H.-H.; Hamilton, T. P.; Tsai, J.-H. M.; Beckman, J. S. *Struct. Chem.* **1995**, *6*, 323.

(44) Tsai, H. H.; Hamilton, T. P.; Tsai, J. H. M.; van der Woerd, M.; Harrison, J. G.; Jablonsky, M. J.; Beckman, J. S.; Koppenol, W. H. *J. Phys. Chem.* **1996**, *100*, 15087.

(45) Bartberger, M. D.; Olson, L. P.; Houk, K. N. *Chem. Res. Toxicol.* **1998**, *11*, 710.

(46) Houk, K. N.; Condroski, K. R.; Pryor, W. A. *J. Am. Chem. Soc.* **1996**, *118*, 13002.

(47) Bach, R. D.; Glukhovtsev, M. N.; Canepa, C. *J. Am. Chem. Soc.* **1998**, *120*, 775.

(48) Liang, B.; Andrews, L. *J. Am. Chem. Soc.* **2001**, *123*, 9848.

(49) Shustov, G. V.; Spinney, R.; Rauk, A. *J. Am. Chem. Soc.* **2000**, *122*, 1191.

(50) Nagy, P. I. *J. Phys. Chem. A* **2002**, *106*, 2659.

(51) Musaev, D. G.; Geletii, Yu. V.; Hill, C. L.; Hirao, K. *J. Am. Chem. Soc.* **2003**, *125*, 3877.

(52) McGrath, M. P.; Rowland, F. S. *J. Phys. Chem.* **1994**, *98*, 1061.

(53) Musaev, D. G.; Geletii, Yu. V.; Hill, C. L. *J. Phys. Chem. A* **2003**, *170*, 5862.

(54) Koppenol, W. H.; Kissner, R.; Beckman, J. S. *Methods Enzymol.* **1996**, *269*, 296.

(55) Bohle, D. S.; Hansert, B.; Paulson, S. C.; Smith, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 7423.

(56) *Standard Methods for Examination of Water and Wastewater*, 18th ed.; American Public Health Association: New York, 1992.

(57) Plumb, R. C.; Edwards, J. O.; Herman, M. A. *Analyst* **1992**, *117*, 1639.

(58) Pryor, W. A.; Jin, X.; Squadrito, G. L. *Proc. Nat. Acad. Sci., U. S. A.* **1994**, *91*, 11173.

(59) Jensen, J. L.; Miller, B. L.; Zhang, X.; Hug, G. L.; Schoeneich, C. *J. Am. Chem. Soc.* **1997**, *119*, 4749.

(60) Maurer, P.; Thomas, C. F.; Kissner, R.; Rüegger, H.; Greter, O.; Röthlisberger, U.; Koppenol, W. H. *J. Phys. Chem. A* **2003**, *107*, 1763.

(61) {(Me)$_2$XO(NO$_2^-$)} transformation into (Me)$_2$X and NO$_3^-$ (peroxynitrite isomerization) was calculated to proceed with too high activation barrier, therefore is very unlikely to occur.

(62) *CRC Handbook of Chemistry and Physics*, 81st ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 2000.