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Mechanism of Oxidation of Aliphatic Thioethers to Sulfoxides by Hydroxyl Radicals. The Importance of Molecular Oxygen

Christian Schöneich,[†] Ahmed Aced, and Klaus-Dieter Asmus*

Contribution from Hahn-Meitner-Institut Berlin, Bereich S, Abt. Strahlenchemie,
Glienicker Strasse 100, D-14109 Berlin, Germany

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Abstract: The sulfoxide yield in the $^{\bullet}OH$ radical-induced oxidation of dimethylsulfide in aqueous solution is dramatically enhanced by admission of molecular oxygen. Various possible mechanistic pathways leading to sulfoxide can now be eliminated from speculation as a result of a detailed study on the influence of sulfide concentration, pH, isotope effects, radical cation stability and deprotonation kinetics, and electron-transfer reactions from transient radicals to special additives. The major route to sulfoxide is demonstrated to involve a $2\sigma/1\sigma^*$ three-electron-bonded radical cation, $(>S{\therefore}S<)^+$, which, after reaction with OH^- (H_2O), generates a transient neutral sulfuranyl-type radical, $>S(OH)S^{\bullet}<$. The latter is prone to O_2-addition, and the thioperoxyl radical, $>S(OH)S(OO^{\bullet})<$, generated thereby decays intramolecularly into one molecule each of sulfoxide, sulfide, and superoxide. The mechanism may be generalized to the free radical-induced oxidation of any sulfide (at least aliphatic ones) and would thus potentially be of interest, for example, for the stability of sulfide-based drugs or biological material such as methionine-containing peptides and proteins.

Introduction

Oxidation mechanisms by oxygen radicals have been thoroughly investigated over the past years due to their general importance in many biochemical and chemical processes.[1] The strongest oxidant among the various oxygen-centered radicals, from the redox point of view, is the hydroxyl radical ($^{\bullet}OH$) with $E_{^{\bullet}OH/OH^-} = +1.9$ V.[2] Mechanistic studies have revealed, though, that a true "outer-sphere" one-electron transfer by $^{\bullet}OH$ occurs only very rarely. Most reactions rather proceed via addition or addition–elimination reactions ("inner-sphere" electron transfer). Hydroxyl radicals may also typically be engaged in hydrogen atom abstraction reactions.[3]

The intermediary formation of $^{\bullet}OH$ has been suggested, for example, in photochemical processes such as the photooxidation at semiconductor surfaces,[4] metal-catalyzed activation of oxygen,[5] and decomposition of hydrogen peroxide in the presence of metal chelators.[6]

One class of compounds which is readily oxidized by hydroxyl radicals as well as by most other reactive oxygen species is that of organic sulfides. In a recent paper we reported, for example, on the oxidation mechanism of dimethyl sulfide (DMS) by halogenated peroxyl radicals.[7] The key step in this case was found to be the formation of the adduct radical **1** (eq 1). Two different consecutive pathways could be described. An overall 2e-oxidation, proceeding via an intramolecular electron transfer from the sulfuranyl-type radical **1** into the hydroperoxide moiety, leads directly to dimethyl sulfoxide (DMSO) (stoichiometrically indicated in eq 2; the actual mechanism is not an oxygen transfer, though, but involves H^+ and OH^- from the solvent water). Alternatively, the 1e-oxidation intermediate **1** may be stabilized via a proton-catalyzed displacement process (eq 3) which yields the $2\sigma/1\sigma^*$ three-electron-bonded dimer radical cation **2**. The latter was independently and exclusively produced by oxidation of DMS with $^{\bullet}OH$.[8] Interestingly, **2** also degrades into DMSO but only with a rather low efficiency of ≤25–30%, based on the initial concentration of hydroxyl radicals.

$$R(Hal)OO^{\bullet} + S< \rightleftharpoons \underset{\mathbf{1}}{R(Hal)OO-{}^{\bullet}S<} \tag{1}$$

$$\mathbf{1} \xrightarrow{H^+/OH^-} R(Hal)O^{\bullet} + O{=}S< \tag{2}$$

$$\mathbf{1} + S< \longrightarrow R(Hal)OO^- + \underset{\mathbf{2}}{>S\overset{+}{\therefore}S<} \tag{3}$$

Considering the fact that the hydroxyl radical is only a one-electron oxidant, whereas oxidation of sulfides to sulfoxides requires 2e-oxidation, the actual mechanism of sulfoxide formation should include loss of a second electron, namely, the antibonding σ^* electron from the 1e-oxidized dimeric radical cation **2**. Gas-phase experiments using charge-stripping mass spectroscopy have, in fact, indicated the possibility of such a process.[9] In solution, the loss of this second electron could occur, for example, through bimolecular disproportionation of the 1e-oxidation species as proposed for the sulfoxide formation in the electrochemical oxidation of the aromatic sulfide thianthrene.[10] The dication

$$\mathbf{2} \xrightarrow{-e^-} >\overset{+}{S}{-}\overset{+}{S}< \rightarrow >S^{2+} + S< \tag{3a}$$

[†] Present address: Department of Pharmaceutical Chemistry, Mallott Hall, University of Kansas, Lawrence, KS 66045.

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would, in any case, be prone for reaction with water to yield directly 1 equiv of sulfoxide.

$$>S^{2+} + H_2O \rightarrow >S{=}O + 2H^+ \tag{3b}$$

It will emerge from this paper that for aliphatic thioethers, however, such a disproportionation of **2** constitutes only a minor route of sulfoxide formation. Higher yields of sulfoxide are generated, though, in oxygen-containing solutions. In this context, it will be shown and discussed, in particular, that many feasible reaction routes, some of them the subject of previous speculation, must be discarded and that it is essentially an addition of molecular oxygen to a hydroxylated version of **2** which determines the efficiency of sulfoxide formation.

Experimental Section

All chemicals used were of the highest available commercial purity. Dimethyl sulfide (DMS), dimethyl sulfoxide (DMSO), diethyl sulfide (DES), and chloromethyl methyl sulfide (CMMS) were obtained from Aldrich. All these liquids were distilled twice prior to use, and DMS and DES were extracted with water, pH 14, prior to distillation in order to remove traces of methyl mercaptan and ethyl mercaptan. Diethyl sulfoxide (DESO) was synthesized by oxidation of DES with excess hydrogen peroxide according to a procedure described in the literature.[11] The purity was checked by HPLC and NMR. Tetranitromethane (TNM) was supplied by Aldrich and separated from nitroform anion impurities by repeated extraction with water until the aqueous phase became colorless. Benzoquinone (Aldrich) was sublimed, whereas *tert*-butyl alcohol (Merck, p.a.), methylviologen (Aldrich), and *p*-nitroacetophenone (Aldrich) were used without further purification. All solutions were made up immediately before the experiment in deionized water (Millipore Q quality, 18 MΩ). The respective pH's were adjusted with NaOH or $HClO_4$ (Merck, p.a.) and measured with a pH electrode (Ingold) coupled to a Knick digital pH-meter. Saturation with N_2O, N_2O/O_2, or N_2/O_2 mixtures was achieved by bubbling for at least 30 min per 20-mL sample. Mixtures of N_2O and O_2 were calibrated by employing flow meters with defined flow rates of the respective gases.

Steady-state γ-radiolysis experiments were carried out in a field of a 6000-Ci ^{60}Co-γ-source. The dose rate was determined by Fricke dosimetry[12] to be 800 Gy h^{-1}. All radiation chemically derived products were quantified by their respective *G*-values, which represent the number of species generated, consumed, or converted per 100 eV of absorbed energy ($G = 1.0$ equals ca. 1.0×10^{-7} mol J^{-1} absorbed energy).

Pulse radiolysis experiments were performed with a van de Graaff accelerator supplying short pulses of ca. 0.3–0.5-μs duration of 1.55-MeV electrons. Doses per pulse were on the order of 2–3 Gy (1 Gy = 1 J kg^{-1}), corresponding to an average radical concentration of (1.0–1.7) $\times 10^{-6}$ M. Detection of radical species was achieved by optical absorption and conductivity measurements. Further details of this methodology, dosimetry, and data evaluation have been described elsewhere.[13]

Analysis of the respective sulfoxides was done by reversed-phase HPLC, employing a C18 column (Inertsil, 5 μm, 250 × 4.6 mm), and UV detection at 210 nm. The eluents were water/methanol (95:5, v/v) for DMSO (t_R = 4.2 min) and water/methanol (90:10, v/v) for DESO (t_R = 7.1 min). Quantification was based on comparison with authentic standards. At least five different concentrations were employed within the concentration range expected for product formation in the radiolysis experiments.

UV spectra were recorded on a Varian Superscan 3 UV spectrophotometer in the range 200–400 nm.

GC–MS of DMSO was done with a Varian 3700 gas chromatograph equipped with a SE 30 column (30 m) coupled to a Finnigan MAT 44 mass spectrometer. Using He as carrier gas (P = 0.68 bar) under isothermic conditions (T = 170 °C), the DMSO eluted after 3.4 min.

Isotope experiments using $^{18}O_2$ were performed in the following way: Water (4 mL), at appropriate pH, was saturated with N_2O before DMS (separately saturated with N_2O) was added to avoid evaporation of the thioether from the dilute solution. After this procedure 1 mL of $^{18}O_2$-saturated water was added to the solution. In order to maintain the 4:1 (v/v) ratio between N_2O and $^{18}O_2$, the head space of the sample was kept at a minimum.

Results and Discussion

Dependence of DMSO Formation on DMS Concentration, pH, and Oxygen Concentration. Hydroxyl radicals are produced by γ-irradiation of aqueous solutions containing N_2O via reactions 4 and 5 with an overall yield of $G = 6.0$, representing at least 90% of the highly reactive species generated in the radiolysis process.[14]

$$H_2O \rightarrow e_{aq}^-, {}^{\bullet}OH, H^{\bullet}, H_2O_2, H_2, H^+ \tag{4}$$

$$e_{aq}^- + N_2O \rightarrow N_2 + {}^{\bullet}OH + OH^- \tag{5}$$

In their reaction with DMS the •OH radicals produce DMSO with various yields depending on the concentrations of DMS and oxygen, and on pH.

Figure 1a displays the DMSO yields obtained for various concentrations of DMS in the absence and presence of molecular oxygen. Under 1 atm of N_2O/O_2 (80:20, v/v) the majority of hydrated electrons (97%) react with the N_2O according to eq 5. This can be rationalized from the respective concentrations ($[N_2O] \approx 2 \times 10^{-2}$ M and $[O_2] \approx 2.8 \times 10^{-4}$ M) and rate constants ($k_5 = 9.1 \times 10^9$ M^{-1} s^{-1} and $k_6 = 1.9 \times 10^{10}$ M^{-1} s^{-1}).[15]

$$e_{aq}^- + O_2 \rightarrow O_2^{\bullet -} \tag{6}$$

In both systems the DMSO yield increases practically linearly with the DMS concentration over the investigated range. Furthermore, the yields are generally higher by a factor of 3–4 in the oxygen-containing solutions compared to the O_2-free systems, indicating the significance of O_2 for efficient DMSO formation. The curvature and low yields at solute concentrations below 10^{-4} M result from incomplete radical scavenging. (As they have no relevance for the following interpretation of our data, no attempt has been made for a quantitative evaluation.)

Figure 1b displays the DMSO yields obtained for an N_2O/O_2 (80:20, v/v) saturated aqueous solution containing 1×10^{-3} M DMS at various pH's between 3 and 12. The DMSO yields increase practically linearly with increasing pH.

Figure 1c shows the dependence of DMSO formation as a function of oxygen concentration at two different pH's, 5 and 12 ([DMS] = 1×10^{-3} M). These experiments were conducted using N_2/O_2 mixtures instead of N_2O/O_2. These conditions avoid complications caused by an increasing extent of competition between reactions 5 and 6 at higher oxygen concentrations. At higher oxygen contents (≥20 vol %) the DMSO yields are seen to be lower by a factor of about 2 in the N_2/O_2 system as compared to the N_2O/O_2 system. This parallels the yield of hydroxyl radicals in the respective solutions, which, in turn, identifies •OH as the initiating radical species for the sulfoxide formation.

At both employed pH's the yield of DMSO increases, although not linearly, with the concentration of oxygen. The increase observed at pH 12 is, however, considerably steeper than at pH 5.

Possible Reactions and Intermediates. Before mechanistic details of sulfoxide formation are discussed, a scheme of possible reactions (7–15) will be introduced which might lead to or compete against sulfoxide formation. All these reactions either are known to occur (reactions 7–12)[8,16–20] or seem feasible for consideration

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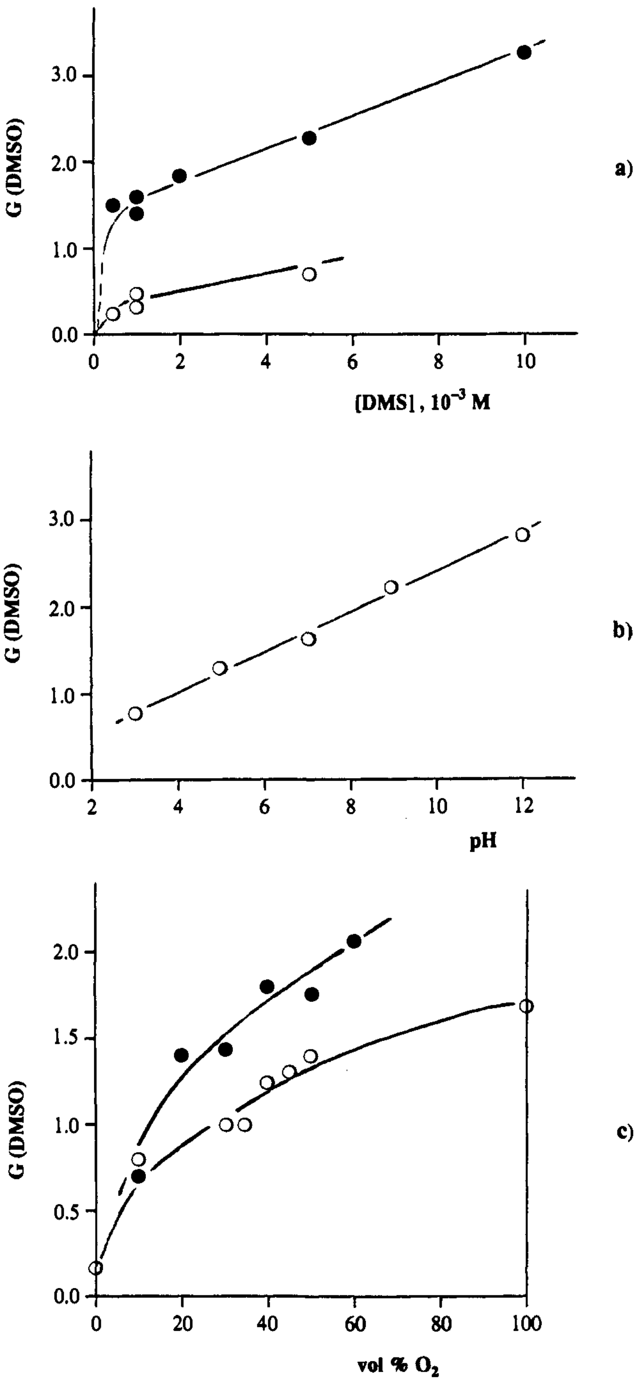

Figure 1. DMSO yield as a function of (a) DMS concentration in N_2O (○) and N_2O/O_2 (4:1 v/v) (●) saturated, aqueous solutions at pH 5.8; (b) pH in N_2O/O_2 (4:1 v/v) saturated, aqueous solutions of 10^{-3} M DMS; (c) oxygen concentration in aqueous, 10^{-3} M solutions of DMS, saturated with mixtures of N_2/O_2 of various ratios, at pH 5 (○) and 12 (●).

(reactions 13–15). According to this scheme, experiments will then be described which have been conducted to prove or disprove participation of particular intermediates and potential reaction routes.

The first step in the reaction of hydroxyl radicals with organic thioethers is generally an addition to the sulfur leading to the intermediate sulfuranyl-type radical **3** (eq 7).[8] This species shows an optical absorption in the 330-nm range[8,16] and was independently suggested to be formed by one-electron reduction of DMSO and subsequent addition of a proton.[17] At high concentrations of sulfide a hydroxide ion is liberated in a proton-catalyzed displacement reaction by a second thioether molecule (eq 8). This process also yields the dimeric radical cation **2**, which can be observed through its strong optical absorption at 465 nm in time-resolved pulse radiolysis experiments.[8,16] This three-electron-bonded species exists in equilibrium with the monomeric radical cation through equilibrium 9 ($K_9 = 2 \times 10^5$ M^{-1}).[16,19]

$$^{\bullet}\mathrm{OH} + \mathrm{S}< \longrightarrow\ >\mathrm{S}^{\bullet}\mathrm{-OH}\ (\mathbf{3}) \tag{7}$$

$$^{\bullet}\mathrm{OH} + >\mathrm{S} \longrightarrow \mathrm{H_2O} + \mathrm{CH_3SCH_2}^{\bullet}\ (\mathbf{4}) \tag{7a}$$

$$\mathbf{3} + \mathrm{S}< \longrightarrow \mathrm{OH}^- +\ >\mathrm{S}\overset{+}{\therefore}\mathrm{S}<\ (\mathbf{2}) \tag{8}$$

$$>\mathrm{S}^{\bullet+} + \mathrm{S}< \rightleftharpoons \mathbf{2} \tag{9}$$

$$\mathbf{3} \longrightarrow \mathrm{H_2O} + \mathbf{4} \tag{10}$$

$$>\mathrm{S}^{\bullet+} \longrightarrow \mathrm{H}^+ + \mathbf{4} \tag{11}$$

$$\mathbf{4} + \mathrm{O_2} \longrightarrow \mathrm{CH_3SCH_2OO}^{\bullet}\ (\mathbf{5}) \tag{12}$$

$$\mathbf{5} + \mathrm{S}< \longrightarrow \mathrm{CH_3SCH_2O}^{\bullet} +\ >\mathrm{S{=}O} \tag{13}$$

$$2\ \mathbf{5} \longrightarrow \mathrm{CH_3SCH_2OH} + \mathrm{CH_3SCHO} \tag{14}$$

$$\mathbf{5} \longrightarrow \mathrm{CH_3SCH_2}^+\ (\mathbf{6}) + \mathrm{O_2}^{\bullet-} \tag{15}$$

At low sulfide concentrations the hydroxyl adduct **3** decays via elimination of water to yield the (methylthio)methyl radical **4** (eq 10).[8] The same species is formed by deprotonation of the monomeric radical cation (eq 11) and possibly also by some direct H-atom abstraction from the alkyl group of the sulfide (eq 7a).[8,19] In contrast, the dimer radical cation **2** deprotonates with much lower rates, if at all.[19] This is indicated by an increase in the lifetime of **2** with increasing DMS concentration.

Species **4** adds oxygen with $k_{12} = 5 \times 10^8$ M^{-1} s^{-1} to form the peroxyl radical **5** (eq 12).[20] In analogy to a mechanism recently shown to occur with peroxyl radicals,[7] species **5** might subsequently oxidize a second thioether molecule to yield sulfoxide via eq 13, in accord with the mechanism indicated in eqs 1–3. A second possibility would be a bimolecular decay, e.g., analogous to the Russell mechanism,[21] under elimination of one molecule of oxygen and yielding a hemithioacetal and methyl thioformate (eq 14). Both organic products are not expected to yield any DMSO, though, but rather to hydrolyze into methyl mercaptan, formaldehyde, and formic acid.[22] However, the peroxyl radical **5** might also eliminate superoxide, in analogy to some mechanisms observed for alcohols and ethers (eq 15).[23] Although reaction 15 is too slow for detection in pulse radiolysis experiments (the mixed first-/second-order decay of **2** is not accelerated by oxygen),[20] it might well occur under γ-radiolysis conditions, where the much lower steady-state concentration slows down any bimolecular radical–radical reaction.

Since the positive charge of **6** formed in reaction 15 should partly be delocalized at the sulfur atom, its reaction with water would provide another possible route to sulfoxide ($CH_3S^+{=}CH_2 + H_2O \rightarrow CH_3S(OH){=}CH_2 + H^+$). (The carbon-centered cation $CH_3SC^+H_2$ as an alternative resonance form is, of course, also susceptible to incorporation of a hydroxyl group to yield CH_3SCH_2OH, decaying further into CH_3SH and HCHO.[22]) The other product generated in reaction 15, namely, the superoxide anion, $O_2^{\bullet-}$ (also formed upon reaction of O_2 with e_{aq}^-), should also be considered as a potential oxidant for the sulfide.

In the following each of the intermediates and reactions which could possibly lead to the formation of sulfoxide will be examined for its actual role in separate experiments.

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Role of Superoxide and H_2O_2. Although the $O_2^{\bullet-}$ ion is only a weak oxidant, it might nevertheless contribute to the formation of DMSO via either oxidation of DMS through an intermediary adduct (eq 16) or subsequent reactions such as dismutation to hydrogen peroxide (eq 17) followed by sulfide oxidation through H_2O_2 (eq 18), a direct oxygen transfer (eq 19), or addition to the dimer radical cation **2** (eq 20). Reaction 20 would lead to a

$$>S + O_2^{\bullet-} \rightarrow [>S\cdots O_2]^{\bullet-} \rightarrow >S^{\bullet+} + O_2^{2-}\ (H_2O_2) \qquad (16)$$

$$2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2 \qquad (17)$$

$$H_2O_2 + >S \rightarrow >S{=}O + H_2O \qquad (18)$$

$$>S + O_2^{\bullet-} \rightarrow >S{=}O + O^{\bullet-}\ ({}^{\bullet}OH) \qquad (19)$$

$$\mathbf{2} + O_2^{\bullet-} \rightarrow >S + >SOO^{\bullet}\ (\mathbf{7}) \qquad (20)$$

thioperoxyl intermediate. Such a species has been suggested to be formed, for example, upon reaction of organic sulfides with singlet oxygen, a process which has been shown to yield sulfoxide quite efficiently (eq 21).[24]

$$\mathbf{7} + >S \rightarrow 2\ >S{=}O \qquad (21)$$

However, none of these processes seems to contribute to the sulfoxide formation in our system, as can be concluded from the following experiments. Superoxide anions are generated, for example, as the exclusive reactant upon radiolysis of N_2O/O_2-saturated aqueous solutions containing 0.1 M $NaHCO_2$ at pH 6.7 via reactions 22 and 23:[25]

$$OH^{\bullet} + HCOO^- \rightarrow H_2O + CO_2^{\bullet-} \qquad (22)$$

$$CO_2^{\bullet-} + O_2 \rightarrow CO_2 + O_2^{\bullet-} \qquad (23)$$

Upon addition of 10^{-3} M DMS to such a system, no formation of DMSO was observed. This finding clearly argues against a contribution of $O_2^{\bullet-}$ to the overall DMSO yield through the $^{\bullet}OH$-initiated process via reactions 18, 19, and 21 (in pursuit of reactions 15, 16, 17, and 20).

Further evidence against an involvement of superoxide in the hydroxyl-iniated sulfoxide formation arises by consideration of the theoretically calculated yield, $G(O_2^{\bullet-})$, available in pH 5–6, 4:1 v/v saturated N_2O/O_2 and N_2/O_2 systems, which amounts to $G(H^{\bullet}) + 0.03G(e_{aq}^-) \approx 0.63$ and $G(H^{\bullet}{+}e_{aq}^-) \approx 3.4$, respectively.[15] In contrast to this ratio of ≈0.2, the experimental DMSO yield ratio is ≈1.6 in the two systems, respectively (see Figure 1a,c). Also, potential scavengers for $O_2^{\bullet-}$ such as tetranitromethane[26] did not decrease the sulfoxide yield. In fact, in N_2O/O_2 solutions of 10^{-3} M DMS, G(DMSO) even slightly increases from 1.55 to 1.70 upon addition of 2.5×10^{-4} M $C(NO_2)_4$ (see also below).

One of the possible molecular substrates known to oxidize organic sulfides to sulfoxides would be H_2O_2. It may be generated through disproportionation of superoxide and is definitely present in any irradiated aqueous solutions as so-called "molecular" product with $G \approx 0.7$.[14] Taking a rate constant of 10^{-2} M^{-1} s^{-1} reported for the H_2O_2-initiated oxidation of methionine[27] and $[H_2O_2] \leq 5 \times 10^{-5}$ M (maximum accumulation in γ-radiolysis experiments), the half-life for the oxidation of 10^{-3} M DMS is estimated to be $t_{1/2} = \ln 2/(10^{-2} \times 10^{-3})$ s ≈ 7×10^4 s ≈ 20 h. This was confirmed by a blind experiment with a solution of 10^{-3} M DMS and 10^{-4} M H_2O_2 which did not yield any appreciable amounts of DMSO within the time period of our experiments (typically ≤2 h). Furthermore, many of the sulfoxide yields measured in our systems clearly exceed the available H_2O_2 yields.

Table I. Yield of Dimeric Radical Cations **2**, $(Me_2S\therefore SMe_2)^+$, as a Function of Oxygen Concentration at Two Different pH's[a]

	G(**2**)	
$[N_2O]/[O_2]$ (v/v)	pH 5.85	pH 8.65
100:0	5.50	5.50
80:20	5.30	5.55
60:40	5.30	5.30

[a] Solutions: 10^{-3} M DMS in water, saturated with N_2O/O_2 mixtures of different ratios. Yields calculated from measured Gε, and ε = 6200 M^{-1} cm^{-1}.[8]

Possible Role of the Sulfuranyl Radical 3 and Its Peroxyl Derivative 8. Since the yield of sulfoxide increases so significantly upon addition of molecular oxygen (see Figure 1a), we must assess the potential role of any peroxyl radical. Addition of O_2 to the sulfuranyl radical **3**, for example, would yield a tetravalent α-hydroxy thioperoxyl radical **8** (eq 24), which could subsequently oxidize a second thioether molecule (eq 25), possibly via a mechanism in analogy to that established for halogenated peroxyl radicals.[7] Interestingly, similarly structured tetravalent sulfur


(**8**) (24)

$$\mathbf{8} + S< \longrightarrow >S{=}O + \text{products} \qquad (25)$$

species have been suggested to be involved in the H_2O_2-mediated oxidation of dialkoxysulfuranes.[28] On the other hand, **8** might eliminate superoxide in analogy to the well-established mechanism for α-hydroxyalkylperoxyl radicals, $R_2C(OH)OO^{\bullet}$.[23] This reaction would directly lead to sulfoxide (eq 26) and would, as it is known to be base catalyzed,[23] further be in accord with the observed pH dependence of the sulfoxide yield.

$$\mathbf{8} \rightarrow >S{=}O + H^+/O_2^{\bullet-} \qquad (26)$$

Convincing evidence against the involvement of **8** can, however, also be deduced from the yields of the dimer radical cation **2** obtained upon pulse radiolysis of aqueous solutions containing 10^{-3} M DMS at pH 5.85 and 8.65, saturated with N_2O/O_2 mixtures of different ratios (listed in Table I). These yields were evaluated from the optical absorptions of **2** recorded at 465 nm immediately after the formation of this species via reactions 7 and 8 was completed. The measured G(**2**) = 5.3 ± 0.2 accounts for almost 90% of the initially generated $^{\bullet}OH$ radicals, well in accord with previous results.[8] Also in agreement with earlier studies, both the lifetime and the yield of **2** remained independent of the oxygen concentration.[20] The latter finding, by the way, clearly shows that a possible reaction of **3** with O_2 to yield **8** could never compete against the formation of **2** via reaction 8 under the employed experimental conditions. This, in turn, eliminates species **8** as a direct precursor of the sulfoxide generated in the present system.

Possible Role of the α-Thioalkyl Radical 4 and Its Peroxyl Derivative 5. Sulfoxide Formation in the Presence of Tetranitromethane and in the Absence of Molecular Oxygen. Radical **4**, $CH_3SCH_2^{\bullet}$, is known to exhibit reducing properties and to react effectively with tetranitromethane (TNM).[29] It may thus contribute to the sulfoxide formation only indirectly, e.g., through

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Table II. Yield of DMSO and Nitroform (NF^-) as a Function of DMS Concentration in the Absence and Presence of Molecular Oxygen[a]

[DMS] (10^{-3} M)	*G*(DMSO)				$G(NF^-)$	
	N_2O		N_2O/O_2			
	without TNM	with TNM	without TNM	with TNM	N_2O	N_2O/O_2
1.0	0.4	0.35	1.55	1.7*	1.8	2.8*
5.0	0.6	0.85	2.3	nd[b]	1.2	nd
10.0	1.0	1.0	3.3	nd	0.9	nd

[a] Solutions: DMS in water, saturated with N_2O or 4:1 (v/v) N_2O/O_2 mixtures, pH 5.8, 2×10^{-4}* or 4×10^{-4} TNM. Error limit: ≤10%. [b] Not determined.

its peroxidized form **5**, $CH_3SCH_2OO^\bullet$. Any such contribution should, however, be suppressed upon addition of suitable electron acceptors such as, for example, tetranitromethane (TNM).

The DMSO yields obtained upon γ-radiolysis of N_2O-saturated solutions, pH 5.8, containing 4×10^{-4} M TNM and various DMS concentrations are listed in Table II. (Under the experimental conditions ≥90% of e_{aq}^- reacts with N_2O rather than with TNM.[26]) It is noted that the DMSO yield is practically not affected by the presence of TNM, although the formation of the yellow-colored, stable nitroform provides ample evidence for a TNM reduction by radical **4**.

Furthermore, the DMSO yield is seen to increase with the DMS concentration, while the overall yield of **4**, generated either directly through reaction 7a or indirectly through the reaction sequence 7–11, should, at best, remain independent of [DMS]. It may actually rather decrease owing to other reaction channels opened by the stabilization of the dimer radical cation **2** at higher DMS concentrations. The latter is, in fact, indicated by a decreasing TNM reduction with increasing [DMS] (see nitroform yields in Table II). Both findings clearly speak against radical **4** being a decisive precursor of DMSO in the anoxic system.

The same arguments basically also discard cation **6**. In the absence of TNM, cation **6** could only be generated via disproportionation of **4**; i.e., the ratio between **6** and **4** would be 1:2. On the other hand, if TNM is present, a 1:1 ratio would be expected; in other words, the sulfoxide yield should have doubled upon the addition of TNM, quite in contrast to the experimental result.

Reaction of Radical 4 with Tetranitromethane. In order to confirm the reaction of **4** with tetranitromethane in an experiment independent from the rather complex DMS scheme, we also generated this radical from a different compound, namely, by reduction of chloromethyl methyl sulfide (CMMS). The experiment conducted was pulse irradiation of an N_2-saturated, aqueous solution, pH 6, containing 1.0 M *tert*-butyl alcohol (to scavenge $^\bullet OH$) and 10^{-3} M CMMS. A strong optical absorption, observable immediately after the 1-μs pulse and displayed in Figure 2a, shows a pronounced maximum at 280 nm and resembles that of the α-thioalkyl-type radical identified in the oxidation of methionine.[30] It is therefore assigned to radical **4** generated in reaction 27.

$$e_{aq}^- + CH_3SCH_2Cl \rightarrow CH_3SCH_2^\bullet\ (4) + Cl^- \qquad (27)$$

The formation of radical **4** was confirmed through its known reaction with tetranitromethane (TNM), which proceeds via a two-step mechanism under formation of an intermediate adduct radical **9** and stable nitroform anions.[29] With $k_{28} = 2.8 \times 10^9$ $M^{-1}\,s^{-1}$ and $k_{29} = 9.0 \times 10^4\ s^{-1}$,[29] reaction 29 becomes the rate-determining step for the formation of nitroform at [TNM] > 3×10^{-5} M.

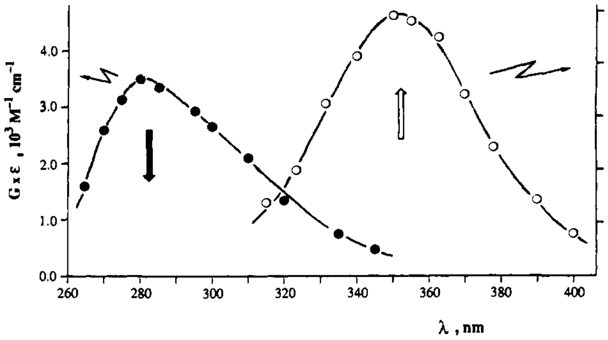

Figure 2. (a) Spectrum of $CH_3SCH_2^\bullet$ radical (**4**) obtained from reduction of CH_3SCH_2Cl by hydrated electrons (●). Aqueous, N_2-saturated solutions of 10^{-3} M CH_3SCH_2Cl, 10% *tert*-butyl alcohol, pH 5–6. (b) Spectrum of nitroform obtained from reaction of $CH_3SCH_2^\bullet$ with tetranitromethane (○). Aqueous, N_2-saturated solutions of 2.4×10^{-2} M CH_3SCH_2Cl, 1.5×10^{-4} M tetranitromethane, 10% *tert*-butyl alcohol, pH 4.

$$4 + C(NO_2)_4 \rightarrow CH_3SCH_2ON^\bullet(O)C(NO_2)_3\ (9) \qquad (28)$$

$$9 \rightarrow CH_3SCH_2^+\ (6) + NO_2 + C(NO_2)_3^- \qquad (29)$$

Figure 2b shows the optical spectrum, recorded ca. 50 μs after pulse irradiation of a similar solution to which TNM had been added ([CMMS] = 2.4×10^{-2} M, [TNM] = 1.4×10^{-4} M, pH 4). The maximum at 350 nm is due to the $C(NO_2)_3^-$ anion formed with a total yield of $(G\epsilon)_{350}$ = 27 500 via the reaction sequence 27–29, but also through some direct reduction of TNM by e_{aq}^- and $H^\bullet$. The contribution through radical **4**, evaluated on the basis of $\epsilon[C(NO_2)_3^-]$ = 15 000 $M^{-1}\,cm^{-1}$ and the known rate constants $k(e_{aq}^- + TNM) = 6 \times 10^{10}\ M^{-1}\,s^{-1}$, $k(H^\bullet + TNM) = 2.6 \times 10^9\ M^{-1}\,s^{-1}$,[26] and an estimated $k_{27} \approx 10^9\ M^{-1}\,s^{-1}$ (average value for reduction of monochloro aliphatics by e_{aq}^-),[31] is estimated to be $G \approx 1.0$ (±0.3). Taking this yield and $(G\epsilon)_{280}$ = 3500 for the total absorptivity generated through radical **4** (Figure 2a), an extinction coefficient of $\epsilon(4)_{280} \approx 3500$ (±1000) $M^{-1}\,cm^{-1}$ is calculated. It is in good agreement with a value of 3000 $M^{-1}\,cm^{-1}$ reported for the corresponding species from methionine.[30]

Our results confirm the high reactivity of radical **4** toward TNM and indicate that **4** can indeed conveniently be generated via 1e-reduction of CMMS, and in such a system it is the only optically absorbing transient. However, the yield of the latter reaction, although almost diffusion controlled, amounts to only about 35% of the yield of initiating hydrated electrons (G = 2.75). The CMMS system is therefore also not free of possible complications, and there must be yet another major reductive pathway for this substrate. In analogy to the well-known fast reaction ($k_{30} \approx 10^{10}\ M^{-1}\,s^{-1}$)[15]

$$e_{aq}^- + RSH \rightarrow R^\bullet + SH^- \qquad (30)$$

we suggest a reductive cleavage of thiolate (reaction 31) to account for the remainder. Due to this uncertainty and the possible involvement of $CH_3OO^\bullet$ and $CH_2(Cl)OO^\bullet$ peroxyl radicals in oxygenated solutions, we therefore did not follow up on the CMMS system but continued to rely solely on the DMS system.

$$e_{aq}^- + CH_3SCH_2Cl \rightarrow CH_3^\bullet + CH_2(Cl)S^-$$
$$\rightarrow CH_2(Cl)^\bullet + CH_3S^- \qquad (31)$$

Sulfoxide Formation in the Presence of Both Tetranitromethane and Molecular Oxygen. Irradiation of N_2O/O_2 (4:1 v/v) saturated aqueous, pH 6, solutions containing 10^{-3} M DMS yields DMSO with G = 1.55 (Table II), i.e., a considerably higher sulfoxide yield than G = 0.4 formed in the absence of oxygen. An even slightly higher yield of G(DMSO) = 1.7 is observed if 2.5×10^{-4}

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(30) Hiller, K.-O.; Asmus, K.-D. *Int. J. Radiat. Biol.* **1981**, *40*, 597.

(31) Lal, M.; Schöneich, Ch.; Mönig, J.; Asmus, K.-D. *Int. J. Radiat. Biol.* **1988**, *54*, 773.

M TNM is added to the oxygen-containing system. In this case TNM is reduced to nitroform with $G = 2.8$.

As reaction 12 occurs with $k_{12} = 5 \times 10^8$ M^{-1} s^{-1},[20] the addition of oxygen to **4** should almost completely be suppressed to $\leq 10\%$ by the tetranitromethane due to the competing reaction of **4** with TNM (eqs 28, 29). The unaffected DMSO yield confirms, therefore, that the sulfoxide formation cannot be the result of a direct reaction of **4** with either TNM or molecular oxygen. This conclusion again discards radical **4** as a precursor of sulfoxide, and considering the results in oxygenated solutions without TNM, it eliminates also the peroxyl radical **5** derived therefrom.

The high yield of TNM reduction (which clearly exceeds that of DMSO formation) indicates that additional reducing species must have been generated in the oxygen-containing system. In the absence of oxygen the yield of TNM reduction ($G = 1.8$; this value and all following data refer to solutions of 10^{-3} M DMS) is considered to be equal to the yield of **4**. Assuming that in oxygenated solutions still $\geq 90\%$ of **4** reacts directly with TNM (see above), this leaves $G = 1.65$. The measured yield of TNM reduction of $G = 2.8$ exceeds this value by $G = 1.15$. At the same time, oxygen enhances the sulfoxide yield by about the same amount (from ≈ 0.4 in N_2O to 1.55 in N_2O/O_2 solutions). It would thus seem that the oxygen-mediated sulfoxide formtion is accompanied by the generation of 1 equiv of reducing species. As will be shown later, the latter is most likely the superoxide anion, $O_2^{\bullet-}$.

Isotope Effects. If H_6-DMS is replaced by its deuterated analogue, D_6-DMS, in the above-mentioned system (without TNM), the sulfoxide yield increases from $G = 1.7$ to 2.5, respectively. (A rationale for this result will be given in the next section in connection with the role of the three-electron-bonded radical cation **2**.)

No product isotope effect was, on the other hand, observed in separate experiments on the oxidation of H_6-DMS and D_6-DMS to the respective sulfoxides by carbon-centered peroxyl radicals such as $CHCl_2COO^\bullet$ [G(DMSO,H)/G(DMSO,D) = 1.02] (Schöneich, Ch.; Aced, A.; Asmus, K.-D. Unpublished results). By extrapolation this is taken as additional evidence against any direct oxidation of the sulfide to its sulfoxide by the peroxyl radical **5**, and it may also speak against involvement of **7** and **8**.

Another isotope experiment was concerned with the origin of the oxygen in the sulfoxide formed. In experiments conducted with $^{18}O_2$ we could not detect any incorporation of this oxygen isotope into the sulfoxide (GC–MS analysis). This suggests that the sulfoxide oxygen does not originate from the molecular oxygen but from the solvent water. (A fast oxygen exchange between DMSO and H_2O can most likely be excluded since even in 60% H_2SO_4 at 30 °C the half-life of oxygen exchange is as long as 9 h,[32] whereas our experiments were completed within 1–2 h. Furthermore, the positive involvement of water in the sulfoxide formation is also indicated in electrochemical oxidations.[33])

Role of the Molecular and the $2\sigma/1\sigma^*$ Three-Electron-Bonded Radical Cations. The considerable isotope effect of about 1.5 observed for DMSO formation in our $^\bullet$OH-induced oxidation of DMS (H_6 vs D_6) parallels an increase in lifetime of the $2\sigma/1\sigma^*$ three-electron-bonded radical cation **2**.[19] This, together with the increase in DMSO yield as **2** becomes more and more stabilized in equilibrium 9 with increasing DMS concentration (Figure 1a, Table II), strongly suggests an active role of just this dimeric species.

Further evidence for the involvement of the three-electron-bonded species is provided by experiments with diethyl sulfide (DES) instead of dimethyl sulfide (DMS). The stability of $(Et_2S\therefore SEt_2)^+$ is considerably lower than that of $(Me_2S\therefore SMe_2)^+$, mainly because of a much faster (more than 10 times)[8] deprotonation of the molecular radical cation $Et_2S^{\bullet+}$, which is in equilibrium with the dimer complex. The DESO yield in N_2O/O_2 (4:1 v/v) 10^{-3} M solutions of diethyl sulfide has indeed dropped to $G \approx 0.5$ (± 0.2) as compared to G(DMSO) ≈ 1.55 in 10^{-3} M DMS solution.

Addition of TNM (2×10^{-4} M), which scavenges the deprotonation product radical $CH_3C^\bullet HSCH_2CH_3$ ($k = 3.3 \times 10^9$ M^{-1} s^{-1}), did not have any effect on the DESO yield, as in the DMS system. The total yield of TNM reduction in this case amounts to $G = 3.9$. Subtracting the likely contribution of $G = 0.5$ by $O_2^{\bullet-}$ (equivalent to the DESO yield in analogy to the DMS discussion), this would leave $G = 3.4$ for direct reduction of TNM by **4**-type radicals in this system ($G \approx 1.3$ of the latter being generated by H-atom abstraction from DES[29] and the remainder resulting from deprotonation of the radical cation).

Since the molecular radical cation, $>S^{\bullet+}$, can clearly be discarded because of the sulfide concentration dependence of the sulfoxide yields (Figure 1a and equilibrium 9), the only remaining species still in the discussion is the $2\sigma/1\sigma^*$ three-electron-bonded, dimer radical cation $(>S\therefore S<)^+$.

Before a detailed mechanism is presented, two possible pathways involving this species can, however, be eliminated right away for the oxygen-containing systems. Since there is almost no change in sulfoxide yield upon a 10-fold increase in the steady-state concentration of radicals ($G = 2.1 \pm 0.3$, staying invariant upon increasing the dose rate from 0.078 to 0.658 Gy s^{-1}), any bimolecular disproportionation according to eq 32 seems negligible.

$$\underset{\mathbf{2}}{>\overset{+}{S}\therefore S<} + H_2O \longrightarrow >S + 2H^+ + >S{=}O \qquad (32)$$

(It may account though for the small sulfoxide yields in O_2-free solutions.) The lack of a dose rate effect also excludes any significant contribution by a possible chain reaction.

Role of Oxygen. Any mechanism describing the formation of sulfoxide via the radical cation **2** must take into account that the presence of molecular oxygen significantly enhances the sulfoxide yield but does not provide the oxygen atom which is incorporated in the sulfoxide function. Furthermore, it must cope with the fact that there is no evidence for any direct reaction of O_2 with **2** (not even with its equilibrated counterpart, the molecular radical cation $>S^{\bullet+}$), as evidenced by pulse radiolysis experiments.[20] Finally, any mechanism must consider that the sulfoxide yield increases with pH (Figure 1b).

The possibility of a slow addition of O_2 to $>S^{\bullet+}$ *en route* to sulfoxide formation has nevertheless been proposed to occur, but only at extremely high partial oxygen pressure in organic solvents.[34] The suggested mechanism involved reactions of intermediary $>S^+{-}OO^\bullet$ and $>S^+{-}OO^-$ with one unoxidized sulfide molecule each, respectively, and would thus be in accord with the sulfide concentration dependence of the sulfoxide yield. However, as this mechanism is based on a direct oxygen atom transfer, this should have shown up to the $^{18}O_2$ experiments. Since this is not the case, we have to discard this possibility in our system.

The formation of sulfoxide via electron transfer in a general reaction of **2** with any suitable electron acceptor, A, other than molecular oxygen is also not consistent with the experimental results. As can be seen from Table III, the yield of DMSO stays rather low (e.g., $G = 0.2$–0.5 for 10^{-3} M DMS solutions) in any oxygen-free system irrespective of the nature of several added electron scavengers (covering quite a range of redox potentials), and the comparatively higher yields are only found for O_2. An outer-sphere electron transfer as formulated in eq 33 is thus ruled

$$\mathbf{2} + A \rightarrow A^{\bullet-} + >S^{2+} + >S \qquad (33)$$

$$>S^{2+} + H_2O \rightarrow >S{=}O + 2H^+ \qquad (3b)$$

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(32) Kunieda, N.; Oae, S. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1324.

(33) Glass, R. S.; Petsom, A.; Hojjatie, M.; Cleman, B. R.; Duchek, J. R.; Klug, J.; Wilson, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 4772.

(34) (a) Riley, D. P.; Smith, M. R.; Correa, P. E. *J. Am. Chem. Soc.* **1988**, *110*, 177. (b) Riley, D. P.; Correa, P. E. *J. Chem. Soc., Chem. Commun.* **1986**, 1097.

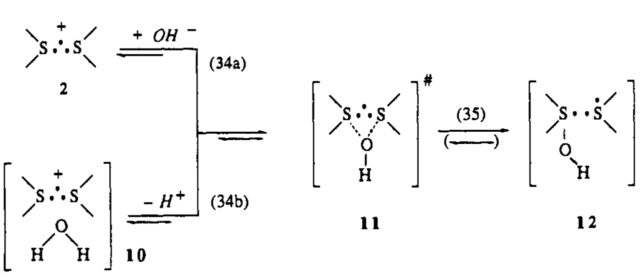
Table III. Yield of DMSO in the Presence of Various Electron Scavengers, A[a]

A	[A] (10^{-4} M)	$E°$ (V)	G(DMSO) (10^{-3} DMS)	(5×10^{-3} M DMS)	(10×10^{-3} M DMS)
methylviologen	2.0	−0.448[b]	0.5	0.75	0.9
p-nitroacetophenone	2.0	−0.356[b]	0.35	0.8	1.0
oxygen (O_2)	2.8	−0.330[b]	1.55	2.3	3.3
benzoquinone	2.0	+0.102[b]	0.35	nd[c]	1.0
tetranitromethane	4.0	+0.310[d]	0.35	0.85	1.0

[a] Solutions: DMS in water, saturated with N_2O, pH 5.8. $E°$: redox potential of $A/A^{\bullet-}$. [b] Reference 2. [c] Not determined. [d] Reference 41.

out. Furthermore, a simple electron transfer or addition/elimination mechanism could not explain the pH dependence of the sulfoxide yields. The results rather call for a particular new mechanism to explain the oxygen-assisted formation of sulfoxide from the dimeric radical cation **2**.

Mechanism. The following mechanism accounts for all experimental results and particularly for the fact that all sulfoxide formation has to start from radical cation **2**. In a first step we propose the formation of radical **11**, which can formally be envisaged to result either from association of the radical cation **2** with OH^- (reaction 34a) or by proton loss from a loose water complex, i.e., a solvated form of this radical cation, namely, **10** (reaction 34b). The hydroxyl adduct **11** is considered only to be a transition state likely to stabilize in a structure with a much tighter sulfur–oxygen bond such as in the sulfuranyl-type radical **12** (reaction 35). The stronger Coulombic attraction between the two constituents in **11**, namely, the sulfur-centered cation, $(>S\therefore S<)^+$, and the hydroxide ion, OH^-, as compared to the much weaker cation interaction of **2** with a water molecule in **10**, certainly contributes to the driving force. Hydroxyl adducts of this kind, although not distinguishing between structures **11** and **12**, have already been discussed as an intermediate in reaction 8[8] and could actually be identified in the •OH-induced oxidation of 1,4-dithiacyclohexane,[35] *cyclo*-methionylmethionine,[36] and methyl 2-(methylthio)acetate.[37]

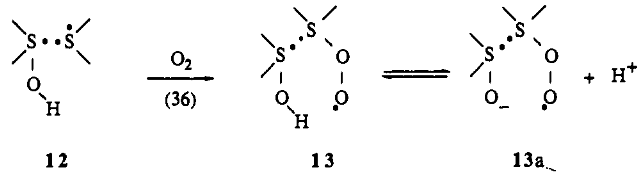


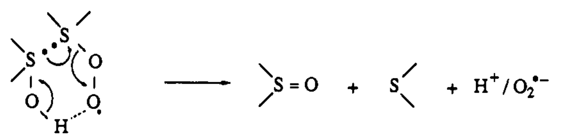
Further support for our mechanism may be drawn from a recent calculation by Guerra,[38] who showed that in an analogous radical, namely, $>C_\alpha(OH)-C_\beta^\bullet<$, the hydroxyl substituent does not transfer to the other carbon atom (yielding $>C_\alpha^\bullet-C_\beta(OH)<$) because the high energy level of the bridged transition state (with •OH loosely attached to both carbon atoms) prevents any effective OH shuttle motion (quite in contrast to the chlorine-substituted analogue). Accordingly, any transitory symmetrical •OH adduct to a C–C bond (to be formed, e.g., in the reaction of •OH with an alkene) will immediately and irreversibly stabilize as the well-known β-hydroxyl radical. Although the electronic situation in this carbo-hydroxylated species is certainly not identical with that in our sulfur-based OH-adduct **11**, the proposed stabilization of the latter to yield the asymmetrical species **12** constitutes, nevertheless, a most interesting analogy.

Both pathways (eqs 34a and 34b) would benefit from an increase in pH. The expected acceleration of the decay of the absorption of **2** upon addition of base has in fact been observed in pulse radiolysis experiments of aqueous DMS solutions[8] and could even be quantified in terms of a rate constant, e.g., $k_{34a} = 2.6 \times 10^9$ M^{-1} s^{-1} for the *cyclo*-methionylmethionine system.[36]

Reactions 34a,b should be reversible, and upon addition of protons, this may perhaps even be true for the structural change outlined in reaction 35. A first-order rate constant of 10^4 s^{-1}, derived by extrapolation to 0 [H^+] in an overall H^+-catalyzed conversion of a hydroxyl adduct into the S∴S-bonded radical cation of *cyclo*-methionylmethionine,[36] may well be attributable to the reverse of reaction 35.

The sulfuranyl radical **12** is considered to have a structure eligible for incorporation of molecular oxygen. Since we cannot expect structure **12** to undergo a direct outer-sphere electron transfer (see results with the other electron acceptors), we have to propose that oxygen addition precedes the electron-transfer steps. Whether structure **13** (or its deprotonated form **13a**) is a thermodynamically stabilized intermediate or just a transition state, though, cannot be decided on the basis of the available results. Electron shift in the cyclic peroxyl structure is then expected to lead to one molecule of sulfoxide, an unoxidized sulfide, and superoxide. This is formulated in eq 37 for the neutral peroxyl radical **13** but should equally, perhaps even better, work with the anionic form **13a**. This mechanism is well in accord with the fact that the sulfoxide oxygen comes from the water and not from the molecular O_2. It also complies with the sulfide concentration dependence as it relies entirely on the dimer radical cation **2**. The formation of superoxide is clearly evidenced by a considerably enhanced reduction of TNM in the oxygenated solutions ($G \approx 2.8$, Table III) as compared to the anoxic system (where TNM was solely reduced by radical **4**; eqs 28 and 29) and as discussed already on a quantitative basis in previous sections. TNM is known to be effectively reduced by $O_2^{\bullet-}$ with $k = 2.0 \times 10^9$ M^{-1} s^{-1}.[26] Our mechanistic considerations are also in agreement with an earlier suggestion by Jones *et al.*[39] on the photochemically initiated sulfoxide formation from 1,5-dithiacyclooctane, a compound which forms a very stable intramolecular S∴S-bonded radical cation.[16,40]





(37)

The pH dependence of the sulfoxide yields probably reflects various independent parameters as indicated by the fact that it does not follow a sigmoidal curve but rather exhibits a more or less linear increase with pH. This may, at least in part, result from the involvement of more than one acid/base equilibrium (e.g., eqs 34a and 36; also the molecular hydroxyl adduct **3** is known to deprotonate[17]). It would, in particular, appear that the formation of **11** and **12**, as well as the deprotonation of **13** into

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(35) Bahnemann, D.; Asmus, K.-D. *J. Chem. Soc., Chem. Commun.* **1975**, 238.

(36) Holcman, J.; Bobrowski, K.; Schöneich, Ch.; Asmus, K.-D. *Radiat. Phys. Chem.* **1991**, *37*, 473.

(37) Bobrowski, K., Schöneich, Ch. *J. Chem. Soc., Chem. Commun.* **1993**, 795.

(38) Guerra, M. *J. Am. Chem. Soc.* **1992**, *114*, 2077.

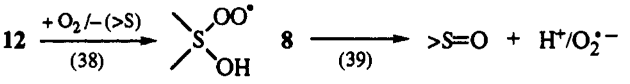
(39) Jones, G., II; Malba, V.; Bergmark, W. R. *J. Am. Chem. Soc.* **1986**, *108*, 4214.

(40) Musker, W. K. *Acc. Chem. Res.* **1980**, *13*, 200.

(41) Rao, P. S.; Hayon, E. *J. Phys. Chem.* **1975**, *79*, 397.

13a, is more effectively accelerated by OH^- than the deprotonation of $>S^{•+}$ and $(>S\therefore S<)^+$.

With respect to reaction 36 one might finally consider a displacement reaction by which O_2 directly substitutes for a sulfide to yield the transient tetravalent α-hydroxy sulfurperoxyl radical **8** *en route* to the sulfoxide. This mechanism differs from the concerted one given above only in that the elimination of the unoxidized sulfide is formulated as a distinct step. Although a directly formed radical **8** (via peroxidation of the primary •OH adduct **3**) could be discarded on kinetic and other grounds, its transient formation during the decay of **12** remains, nevertheless, a possibility.



The origin of the comparatively small yield of sulfoxide generated in the absence of oxygen cannot be revealed unambiguously. In view of the present results and above considerations the previously suggested disproportionation of **4**[8] appears to be less likely, though, than perhaps some disproportionation of **2**.

Conclusion

The •OH radical-induced sulfoxide formation from organic aliphatic sulfides has been shown to be dramatically enhanced in the presence of molecular oxygen as compared to systems lacking O_2. In the present study various possible reaction routes leading to sulfoxide could be eliminated from speculation. It could be demonstrated that the most effective pathway proceeds via the dimeric, three-electron-bonded radical cation, $(>S\therefore S<)^+$. Since this key intermediate can be generated from practically any aliphatic organic sulfide by any suitable oxidizing radical, the results may be generalized. High sulfoxide yields have, for example, been obtained upon oxidation of DMS by $Br_2^{•-}$ in oxygenated solution as well (unpublished result). Our mechanistic findings would then, in turn, help in the understanding of the sulfide oxidation in general, including, for example, the stability of some sulfide-containing (methionine-containing) peptides and proteins, or drugs which are exposed to a free radical-generating environment.

Acknowledgment. The support provided for part of this work by the Association for International Cancer Research (AICR) is gratefully acknowledged.