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Free-Radical Chemistry of Sulfite

by P. Neta* and Robert E. Huie*

The free-radical chemistry of sulfite oxidation is reviewed. Chemical transformations of organic and biological molecules induced by sulfite oxidation are summarized. The kinetics of the free-radical oxidations of sulfite are discussed, as are the kinetics of the reactions of the sulfite-derived radicals $\dot{S}O_3$ and the peroxy derivative $\dot{S}O_5$ with organic compounds.

Sulfur dioxide is a major air pollutant, formed primarily during the combustion of fossil fuels. Other sources include natural gas scrubbing, the oxidation of naturally emitted reduced sulfur compounds, and smelting of sulfide ores (*1*). Sulfur dioxide is water-soluble, forming bisulfite and sulfite

$$SO_2{\cdot}aq \rightleftarrows H^+ + HSO_3^- \qquad pK_a = 1.86\ (2) \qquad (1)$$

$$HSO_3^- \rightleftarrows H^+ + SO_3^{2-} \qquad pK_a = 7.2\ (3) \qquad (2)$$

and at very high concentration, disulfite.

$$HSO_3^- + SO_2{\cdot}aq \rightleftarrows HS_2O_5^- \qquad pK_a = 1.5\ (4) \qquad (3)$$

At any physiological pH, sulfite and bisulfite will both be important forms of S(IV). We will use primarily the term sulfite to refer to the equilibrium mixture, except when referring specifically to bisulfite. The term S(IV) will be used to include other compounds containing sulfur in the +4 oxidation state.

Sulfur dioxide can produce bronchoconstriction upon inhalation, particularly in asthmatics and during exercise (*5,6*). In addition to inhalation of SO_2, sulfite can enter the body due to its use as a preservative in food, wine, and medications. Finally, sulfite is a likely intermediate in the metabolism of sulfur containing amino acids such as methionine and cysteine.

Both liver and lung tissues contain the enzyme sulfite oxidase which catalyzes the oxidation of sulfite to sulfate. This has led to two contrary views of the possible physiological consequences of ingested sulfite. One point of view is that the body contains sufficient sulfite oxidase to detoxify any reasonably likely dose of sulfite from either inhaled atmospheric SO_2 or from food additives (*7*). The other view is that sulfite reaches the blood and forms *S*-sulfocysteine, $RSSO_3^-$ and, therefore, the subsequent chemistry of S(IV), at least as the *S*-sulfocysteine, must be considered (*8*). Further, epidemiological evidence suggests a relation between SO_2 and lung cancer in workers exposed to arsenic and animal studies on benz(a)pyrene correlate cancer development with SO_2 exposure (*8*).

Sulfite is a strong nucleophile and reacts with many biomolecules by substitution at electrophilic positions. These reactions have been reviewed by Petering (*8*) and will not be discussed here, other than the reaction of bisulfite with cystine [Eq. (4)].

$$RSSR + HSO_3^- \rightleftarrows RSSO_3^- + RSH \qquad (4)$$

This reaction has an equilibrium constant of 0.089 at pH 7.75 and 37°C (*9*). The large concentration of RSSR causes most sulfite in the blood to be bound as *S*-sulfocysteine, $RSSO_3^-$. As Petering points out, the biochemistry of HSO_3^- becomes the biochemistry of $RSSO_3^-$ beyond the lung.

Because of the above equilibrium, however, *S*-sulfocysteine may act as a reservoir for sulfite; when it reaches cells in which RSH is in greater abundance than RSSR, e.g., liver cells, where RSH:RSSR = 10^2–10^3 (*10*), the equilibrium may shift to the left to produce sulfite.

The present review deals exclusively with elements of the radical chemistry of sulfite. In light of the discussion above, it might appear that radical reactions initiated by sulfite are likely to be unimportant. There are, however, two possible sources of radicals from sulfite that can be considered.

First, the lung and the rest of the respiratory system, being rich in oxygen, provide an environment for the autoxidation of sulfite before it can either be removed by sulfite oxidase or converted to S-sulfocysteine. The autoxidation of sulfite may be initiated by trace metal ions or certain enzymes and clearly involves free radicals (*11,12*). The second possible source of radicals is

*Chemical Kinetics Division, National Bureau of Standards, Gaithersburg, MD 20899.

from *S*-sulfocysteine. The one-electron reduction of $RSSO_3^-$ can be written as either

$$RSSO_3^- + e^- \rightarrow RS^- + \dot{S}O_3^- \quad (5a)$$

or

$$RSSO_3^- + e^- \rightarrow R\dot{S} + SO_3^{2-} \quad (5b)$$

Pulse radiolysis experiments in which cysteine radicals were produced in the presence of SO_3^{2-}, or in which $\dot{S}O_3^-$ radicals were produced in the presence of cysteine, showed that RS oxidizes sulfite and that, therefore, the first path is more likely.

Chemical Transformations Induced by Sulfite Oxidation

Much of the interest in the chemistry of radicals derived from sulfite arises from the observations that the reaction of sulfite with several organic compounds requires the presence of an oxidizing agent, usually molecular oxygen. Complementary to these observations are the many studies that show that certain organic compounds inhibit the oxidation of sulfite by oxygen.

The investigation of the effects of organic substances on the rate of oxidation of sulfite solutions by oxygen was initiated by Bigelow (*13*) and carried on actively for several years (*14,15*). In the work involving the oxidation of sulfite catalyzed by trace metal ions, the inhibition could have been caused by the complexation of the metal ion. Therefore, studies were carried out in which sulfite oxidation was inititated by ultraviolet light (*16*). Again, organic substances were found to inhibit the reaction. The photochemical reaction was shown subsequently to be a chain reaction and the inhibition by organic compounds due to breaking the free-radical chains.

Since the inhibition of sulfite oxidation involves, in general, only small total amounts of reaction, products of the chain breaking reaction usually have not been discussed. Also, in some cases the initial reactant might be regenerated in a secondary process. In other cases, however, the chemical transformation of the inhibitor was evident. This was observed initially for quinine sulfate and pyridine, which turned green, and hydroquinone, which became opalescent (*16*). Other work showed that the inhibition of sulfite oxidation by alcohols was accompanied by their oxidation (*17*). In subsequent work, the oxidation of sulfite in the presence of unsaturated compounds was found to result in the addition of sulfite to double bonds (*18*). With pyridine this leads to formation of *N*-pyridinium sulfonate (*19*). The reaction of hydroquinone with sulfite in the presence of oxygen is perhaps the most studied (*20,21*), since sulfite was used as a preservative in hydroquinone-based photographic developers (*22*). In this system two types of reaction appear to take place: (a) oxidation of the hydroquinone by sulfite radicals and by molecular oxygen, and (b) sulfonation of the quinone to form hydroquinone sulfonates (followed by oxidation of the latter to quinone sulfonates) (*21*).

From the point of view of this review, the most important observations have been on the transformation of biological molecules by sulfite in the presence of oxygen. Fridovich and Handler (*23*) have shown that a mixture of horseradish peroxidase, hydrogen peroxide, and a peroxidizible substance initiate sulfite oxidation. Indeed, they used the oxidation of sulfite as a sensitive test for the production of radicals in biological systems (*24*). Klebanoff (*25*) confirmed this finding and further reported that the oxidation of NADH by Mn^{2+}, peroxidase, and O_2 was stimulated by sulfite. Therefore, a biological system can initiate the oxidation of sulfite and the subsequent chain reaction can provide reactive intermediates capable of reacting with biological molecules.

Since this early work, there have been several papers on the oxygen induced reactions of biological molecules with sulfite. It has been found that oxygen is required for the complete sulfonation of protein S-H groups by sulfite (*26*). Sulfite was found to form sulfonates with 4-thiouracil derivatives in the presence of oxygen and this reaction was observed to be inhibited by hydroquinone (*27,28*). Methionine has been shown to be oxidized to the sulfoxide in the presence of sulfite, O_2, and Mn^{2+} (*29*). This reaction appears to be inhibited by superoxide dismutase. Sulfite cleaves DNA in the presence of O_2 and Mn^{2+} (*30*), this reaction is inhibited by hydroquinone. The autoxidation of sulfite can destroy indole-3-acetic acid (*31*) or tryptophan (*32*) and several nucleotides and nucleic acids have been shown to react with sulfite in the presence of oxygen (*33*).

Lipid peroxidation has been induced by sulfite (*34*). This reaction is not only quenched by an antioxidant, 2,6-di-*tert*-butyl-4-hydroxymethylphenol, but also by Mn^{2+}. This supression of lipid peroxidation by Mn^{2+} has also been observed in rat liver homogenate (*35*). Both β-carotene (*36*) and vitamin B1 (*37*) are destroyed during the autoxidation of sulfite. Finally, papain is inactivated during sulfite autoxidation in a reaction which leads to the incorporation of sulfite into the protein (*38*).

In this review, we will discuss the chemistry of the free radicals $\dot{S}O_3^-$ and $\dot{S}O_5^-$, key intermediates formed in the autoxidation of sulfite. In addition, we will discuss briefly the radicals $\dot{S}O_2^-$ and $\dot{S}O_4^-$ and the ion HSO_5^-, due to their possible relationship to the behavior of sulfite in the body.

Formation and Detection of $\dot{S}O_3^-$ Radicals

The sulfite radical is generally produced by the one-electron oxidation of sulfite or bisulfite ions, either chemically or photolytically. The radical is detected either by ESR or by optical absorption spectroscopy. Although the ESR detection is more definitive, kinetic studies on the sulfite radical are more often carried out by absorption spectroscopy, by monitoring either the

absorption of $\dot{S}O_3^-$ itself or more frequently by following the formation of other more strongly absorbing species arising from $\dot{S}O_3^-$ reactions with substrates.

The $\dot{S}O_3^-$ radical has been produced by oxidation of sulfite with Ce^{4+} in acid solution (*39–41*), by reaction of sulfite with radicals produced by Fenton-type reagents, e.g., $\dot{O}H$, $\dot{N}H_2$, and $\dot{S}O_4^-$ (from the reaction of Ti^{3+} with H_2O_2, NH_2OH, $S_2O_8^{2-}$, respectively) (*42*), by reaction with radiolytically produced $\dot{O}H$ radicals or other oxidizing radicals (*43–47*)

$$\dot{O}H + SO_3^{2-} \rightarrow OH^- + \dot{S}O_3^- \quad (6)$$

by photoionization of sulfite directly (*3,48,49*) or through photosensitizers (*49*)

$$SO_3^{2-} + h\nu \rightarrow \dot{S}O_3^- + e^- \quad (7)$$

or by photolysis of dithionate (*50*) or thiosulfate (*51*). The $\dot{S}O_3^-$ single-line ESR spectrum has been detected by using all of the above techniques (*39–42,46,47,49,51*), as well as in biochemical systems such as horseradish peroxidase–hydrogen peroxide (*52*) or prostaglandin hydroperoxidase (*53*). Most of these studies reported a g factor for $\dot{S}O_3^-$ around 2.0030, except experiments with Ce^{4+} in acid solutions, where $g = 2.0022$ has been measured (*39–41*). This difference may suggest a possible complexation of $\dot{S}O_3^-$ with Ce^{3+}.

$$Ce^{4+} + SO_3^{2-} \rightarrow [Ce^{3+}...SO_3^-] \rightleftarrows Ce^{3+} + \dot{S}O_3^- \quad (8)$$

The alternative explanation that the g-factor shift is due to protonation of the radical

$$\dot{S}O_3^- + H^+ \rightleftarrows H\dot{S}O_3^- \quad (9)$$

appears unlikely, since the Ce^{4+} experiments were carried out at pH ≤ 2, while radiolytic and photolytic experiments showed no g-factor shift between pH 0 and pH 12 (*49,54*). The unpaired spin on $\dot{S}O_3^-$ has been calculated to be 62% on the sulfur and 13% on each of the oxygens (*55,56*). $\dot{S}O_3^-$ can be considered, therefore, as a sulfur-centered radical.

The optical absorption of $\dot{S}O_3^-$ exhibits $\lambda_{max} = 255$ nm with $\epsilon_{max} = 1000\ M^{-1}\ cm^{-1}$ (*48*). This relatively weak UV absorption has been used to determine the second-order decay rate constant for this radical

$$2\dot{S}O_3^- \rightarrow S_2O_6^{2-} \text{ or } SO_3 + SO_3^{2-} \quad (10)$$

($2k = 1.1 \times 10^9\ M^{-1}sec^{-1}$) (*3,44,49*) but is not conveniently used for following the kinetics of $\dot{S}O_3^-$ reactions with substrates since many of these substrates or their radical products mask the $\dot{S}O_3^-$ UV absorption. Therefore, in pulse radiolysis experiments often the absorption of the other substrate radical was monitored.

Kinetics of One-Electron Oxidation of Sulfite

As mentioned above, sulfite or bisulfite ions undergo one-electron oxidation by several radicals to produce $\dot{S}O_3^-$. Rate constants for a number of reactions of this type have been determined by pulse radiolysis and are summarized in Table 1. The hydroxyl radical reacts with both sulfite and bisulfite with very high rate constants, near the diffusion-controlled limit. The rate of oxidation by other radicals decreases in an order that appears to reflect the order of expected oxidation potentials of these radicals. Measurements of rate constants over a wide range of pH allows the separate determination of rate constants for the oxidation of sulfite and bisulfite. Whereas the hydroxyl and sulfate radicals react with bisulfite about twice as fast as with sulfite, for every other radical the reaction with sulfite is the faster by far. For Br_2^- the ratio is about 4; for the weaker oxidant I_2^-, the ratio is about 200. For the dimethylaniline radical cation, the reaction with sulfite is very fast ($9.9 \times 10^8\ M^{-1}sec^{-1}$) while the reaction with bisulfite is too slow to measure, ($<8 \times 10^5\ M^{-1}\ sec^{-1}$). Similarly, the aniline radical cation $C_6H_5NH_2^{\cdot+}$ oxidizes SO_3^{2-} with $k = 4 \times 10^9\ M^{-1}sec^{-1}$ and HSO_3^- much more slowly, $k = 4.8 \times 10^6\ M^{-1}\ sec^{-1}$.

$$C_6H_5\dot{N}H_2^+ + SO_3^{2-} \rightarrow C_6H_5NH_2 + \dot{S}O_3^- \quad (11)$$

$$C_6H_5\dot{N}H_2^+ + HSO_3^- \rightarrow C_6H_5NH_2 + H^+ + \dot{S}O_3^- \quad (12)$$

$$C_6H_5\dot{N}H + SO_3^{2-}(HSO_3^-) \rightarrow \text{no reaction} \quad (13)$$

The neutral aniline radical, $C_6H_5\dot{N}H$, on the other hand, does not oxidize sulfite. The cation radicals from promethazine, tryptophan, and tryptamine also oxidize HSO_3^- with moderate rate constants (Table 1) and in these cases the reactions were found to lead to equilibrium. The reverse reactions and equilibrium constants will be discussed below.

Since the autoxidation of sulfite solutions was found to be catalyzed strongly by trace amounts of transition metal ions, the reactions of sulfite with metal ions in their higher oxidation states has been the subject of many studies (*11*). Frequently, these studies are complicated by the ability of sulfite to complex these metal ions. These complexes are often quite stable; mercuric ion (in the presence of chloride) is used to protect sulfite from air oxidation (*67*). Other metal ion-sulfite complexes are more labile, decomposing presumably to the reduced metal ion and the sulfite free radical. For strong oxidants like Mn(III), the reaction is fast and apparently irreversible (*68*). For weaker oxidants like Fe(III), the reaction is much slower and reversible, making the derivation of an elementary rate constant for the oxidation of sulfite difficult.

For substitution-inert metal ion complexes, the situation is somewhat simpler since complex formation by sulfite is not important. Rates have been measured for the reactions of several metal ion complexes and rate

Table 1. Rate constants for reactions of sulfite with radicals.

Reaction	pH	k, M^{-1} sec^{-1}	Reference
$OH + HSO_3^-$	—	9.5×10^9	(57)
$OH + SO_3^{2-}$	—	5.5×10^9	(57)
$O^- + SO_3^{2-}$	14	3×10^8	(43)
$O_2^- + SO_3^{2-}$	9.8	82	(45)
$SO_4^- + HSO_3^-$	—	$\geq 1 \times 10^9$	(3)
$SO_4^- + SO_3^{2-}$	—	$\geq 5 \times 10^8$	(3)
$SO_4^- + HSO_3^-/SO_3^{2-}$	7.8	2.6×10^8	(58)
$SO_5^- + HSO_3^-$	6.8	3×10^6	(59)
$H_2PO_4 + HSO_3^-$	4	2.7×10^8	(59)
$HPO_4^- + SO_3^{2-}$	9	2.7×10^7	(60)
$PO_4^{2-} + SO_3^{2-}$	12	4.1×10^7	(60)
$CO_3^- + SO_3^{2-}$	11	1×10^7	(61)
$Cl_2^- + SO_3^{2-}/HSO_3^-$	7	3.3×10^7	(62)
$Br_2^- + HSO_3^-$	4.2	6.9×10^7	(63)
$Br_2^- + SO_3^{2-}$	10	2.6×10^8	(63)
$I_2^- + HSO_3^-$	3	1.1×10^6	(63)
$I_2^- + HSO_3^-/SO_3^{2-}$	6.7	1×10^7	(63)
$I_2^- + SO_3^{2-}$	11	1.9×10^8	(63)
$NH_2 + SO_3^{2-}$	11	a	(63)
$C_6H_5\dot{O} + SO_3^{2-}$	11	1×10^7	(63)
$1,3\text{-}HOC_6H_4\dot{O} + HSO_3^-/SO_3^{2-}$	7	2.3×10^6	(64)
$1,3,5\text{-}(HO)_2C_6H_3\dot{O} + HSO_3^{2-}/SO_3^{2-}$	7	3.2×10^6	(64)
$C_6H_5\dot{N}H_2 + HSO_3^-$	2.5	4.8×10^6	(63)
$C_6H_5\dot{N}H_2^+ + SO_3^{2-}$	b	4×10^9	(63)
$C_6H_5\dot{N}H + SO_3^{2-}$	13	$<3 \times 10^4$	(63)
$C_6H_5\dot{N}(CH_3)_3^+$	3.6	$<8 \times 10^5$	(63)
$C_6H_5\dot{N}(CH_3)_2^+ + SO_3^{2-}$	10.9	9.9×10^8	(63)
$(chlorpromazine)^{\cdot+} + HSO_3^-$	3.6	$\sim 5 \times 10^5$	(59)
$(promethazine)^{\cdot+} + HSO_3^-$	3.6	6×10^5	(59)
$(promethazine)^{\cdot+} + HSO_3^-/SO_3^{2-}$	6.6	1.2×10^8	(59)
$(tryptophan)^{\cdot+} + HSO_3^-$	3.2	4.2×10^6	(65)
$(tryptamine)^{\cdot+} + HSO_3^-$	3	7.8×10^6	(65)
$(tryptophanamide)^{\cdot+} + HSO_3^-$	3	2.2×10^7	(65)
$(iodole)^{\cdot+} + HSO_3^-$	3	4×10^7	(65)
$(cystine)^{\cdot-} + HSO_3^-, SO_3^{2-}$	7.4	5.4×10^7	(66)

[a] No reaction detected ($k < 10^5 M^{-1} sec^{-1}$). The redox potentials for NH_2 and SO_3^- radicals appear to be very similar, judging from rate constants for their reactions with several reactants.
[b] Calculated from the pH dependence of the rate constant.

constants derived for the primary step, the one electron oxidation of sulfite. Bisulfite and $SO_2 \cdot aq$ are assumed to be unreactive and the reported values depend upon the acid dissociation constants chosen. Some values reported are given in Table 2.

There is no information on the oxidation by free radicals of $SO_2 \cdot aq$, the form of sulfite present in strong acid. Mn(III), a strong oxidant ($E \approx 1.4$ V), does react with S(IV) in 2–6 M $HClO_4$. The very strong inverse dependence of the rate constant on the acid concentration was interpreted as showing that bisulfite was the important reactant, not $SO_2 \cdot aq$ (68).

One-Electron Reduction of S(IV)

Although not of importance in autoxidation, the reduction of S(IV) could be important in some biological systems. The hydrated electron is unreactive toward SO_3^{2-} ($k < 10^6$ $M^{-1}sec^{-1}$) and reacts very slowly with HSO_3^- to produce hydrogen atoms ($k = 2 \times 10^7 M^{-1} sec^{-1}$) (3). On the other hand, SO_2 is reported

Table 2. Rate constants for the oxidation of SO_3^{2-} by complexed metal ions.

Oxidant	k, $M^{-1}sec^{-1}$	Reference
$Fe(CN)_6^{3-}$	0.96	(69)
$Fe(phen)^{3+}$	4.6×10^6	(70)
$Fe(bpy)^{3+}$	2.1×10^8	(71)
$IrCl_6^{2-}$	5.6×10^4	(71)
$IrBr_6^{2-}$	3.2×10^5	(71)
$*Ru(bpy)_3^{2+}$	3×10^5	(72)
$Ru(bpy)_3^{3+}$	2.2×10^9	(72)
$Os(bpy)_3^{3+}$	9×10^3	(72)
$Cu(tetraglycine)^-$	3.7×10^4	(73)
$Mo(CN)_8^{3-}$	6.2×10^3	(74)
$W(CN)_8^{3-}$	22.3	(74)

to be reduced rapidly by $\dot{C}O_2^-$ to produce $\dot{S}O_2^-$, while HSO_3^- and SO_3^{2-} were unreactive (75). $\dot{S}O_2^-$ also is produced by the reduction of bisulfite using methyl viologen radical, flavodoxins, and in a H_2/hydrogenase system (76,77). More recently, enzymatic reduction of bisulfite to $\dot{S}O_2^-$ was demonstrated in hepatic microsomal protein and ascribed to reaction of cytochrome P-450 (78). Also Ti^{3+} was found to react with sulfite in acid solutions (pH 2–6) to produce $\dot{S}O_2^-$ (42). All the above reactions probably occur by electron transfer to SO_2 rather then bisulfite. The radical $\dot{S}O_2^-$ produced in these processes is in equilibrium with dithionite ($S_2O_4^{2-}$) and is known to be a highly reactive one-electron reductant. It reduces metalloporphyrins containing Fe(III), Co(III), and Mn(III) (79–81) and a wide variety of electron-transfer proteins (82). The reactivity of $\dot{S}O_2^-$ appears to follow the same pattern as $\dot{O}_2^-$, with rate constants about 10^3 times higher (83). The potential for the process

$$SO_2(aq) + e^- \rightarrow \dot{S}O_2^- \quad (14)$$

has been estimated as -0.26 V (84).

Reactions of Sulfite Radicals

The $\dot{S}O_3^-$ radical is for the most part a sulfur-centered radical which can act as an oxidant or reductant and like most other radicals may engage in hydrogen abstraction or addition to double bonds. Hydrogen abstraction, e.g., from isopropanol, was found to be unimportant ($k \leq 10^3$ M^{-1} sec^{-1}) (3). This finding is not surprising, since the S-H bond expected to be formed in this process is much weaker than the C-H bond. (Formation of an O-H bond on sulfite is not likely due to the low spin density on the oxygens of this radical) (56).

Addition of sulfite radicals to unsaturated bonds (C=C, C=N, and C≡C) has been demonstrated by ESR (39–42,49,55). These reactions were found to be very sensitive to steric effects by substituents on the unsaturated bond. Because of the steady-state nature of these ESR experiments no kinetic data are available. Attempts to measure addition rate constants by pulse radiolysis using allyl alcohol as an example gave only

an upper limit of 10^6 M^{-1} sec^{-1} (*66*). The ESR results demonstrate, however, the feasibility of sulfite radical addition to unsaturated biological targets.

Extensive kinetic studies were carried out by pulse radiolysis on the oxidation of organic substrates by $\dot{S}O_3^-$. The results are summarized in Table 3. The sulfite radical is found to oxidize ascorbate, trolox (a water-soluble tocopherol derivative), methoxyphenol, hydroquinone, phenylenediamines, and chlorpromazine with moderate rate constants varying in the range of 10^6 to 10^9 $M^{-1}sec^{-1}$, depending on the redox potential of the substrate and on the pH, for example with ascorbate

$$\dot{S}O_3^- + H_2A \rightarrow HSO_3^- + \dot{A}^- + H^+ \quad k<10^6\ M^{-1}sec^{-1} \tag{15}$$

$$\dot{S}O_3^- + HA^- \rightarrow SO_3^{2-} + \dot{A}^- + H^+ \quad k=9\times10^6\ M^{-1}\ sec^{-1} \tag{16}$$

$$\dot{S}O_3^- + A^{2-} \rightarrow SO_3^{2-} + \dot{A}^- \quad k=3\times10^8\ M^{-1}sec^{-1} \tag{17}$$

For hydroquinone, catechol, and several other di- and trihydroxybenzenes, the effect of pH on their reactivity with $\dot{S}O_3^-$ was demonstrated in detail (*64*). All of these compounds were unreactive in neutral solutions but became highly reactive as they deprotonated in basic solutions. Compared to other oxidizing radicals such as Br_2^-, I_2^- (*86*), and phenoxyl (*87*), $\dot{S}O_3^-$ reacts more slowly and appears to be a milder oxidant. From a redox equilibrium established between bisulfite and chlorpromazine at pH 3.6 [Eq.(18)],

$$\dot{S}O_3^- + ClPz + H^+ \rightleftarrows HSO_3^- + ClPz^{+\cdot} \tag{18}$$

the redox potential for the couple $\dot{S}O_3^-/HSO_3^-$ was measured to be 0.84V vs. NHE (*59*). The redox potential for the $\dot{S}O_3^{2-}/SO_3^{2-}$ couple in basic solutions is calculated (from the pK_a of $HSO_3^- \rightleftarrows SO_3^{2-} + H^+$) to be 0.63 V vs. NHE. This change in potential explains why SO_3^{2-} is oxidized by the same oxidant more readily than HSO_3^-, as discussed above (Table 1).

Since the $\dot{S}O_3^-/SO_3^{2-}$ potential is now known, reactions of $\dot{S}O_3^-$ can be used to determine the potential for the one-electron oxidation of other species, in those cases where the electron transfer reaction is fast enough so that the decay of $\dot{S}O_3^-$ due to self-reaction is not important. This was initially carried out for phenol (*59*), leading to a new value of its one-electron redox potential. More recently, equilibrium constants also have been measured for the reactions of $\dot{S}O_3^-$ with tryptophan, tryptamine, and tryptophanamide (*65*), and dimethylaniline (*63*).

Knowing the redox potential for the reduction of $\dot{S}O_3^-$ allows us to calculate its oxidation potential from the known two-electron redox potential for SO_3^{2-} in basic solution:

$$SO_4^{2-} + H_2O + 2e^- \rightarrow SO_3^{2-} + 2OH^- \quad E = -0.92\ V \tag{19}$$

$$\dot{S}O_3^- + e^- \rightarrow SO_3^{2-} \quad E = 0.63\ V \tag{20}$$

Table 3. Rate constants for reactions of $\dot{S}O_3^-$ radicals with various reactants.

Reactant	pH	k, $M^{-1}sec^{-1}$	Reference
Ascorbic acid	<3	$<10^6$	(*85*)
Ascorbate ion	5–10	9×10^6	(*85*)
Ascorbate dianion	>12	3×10^8	(*85*)
Trolox	9	$\sim10^6$	(*85*)
Phenol	11.1	6×10^5[a]	(*59*)
p-Methoxyphenol	9.2	4×10^7	(*59*)
p-Methoxyphenol	12.4	1.2×10^8	(*59*)
Hydroquinone	7	$<10^6$	(*64*)
Hydroquinone	8.9	4.5×10^6	(*64*)
Hydroquinone	10.5	5.4×10^7	(*64*)
Hydroquinone	12.9	3.2×10^8	(*64*)
Resorcinol	12.5	1.5×10^8	(*64*)
p-Phenylenediamine	3.4	$<5\times10^5$	(*63*)
p-Phenylenediamine	5.3	4.2×10^6	(*63*)
p-Phenylenediamine	9.3	5.0×10^7	(*63*)
N,N,N,'N'-Tetramethyl-*p*-phenylenediamine	4.5	8.2×10^6	(*63*)
N,N,N,'N'-Tetramethyl-*p*-phenylenediamine	9.5	5.2×10^8	(*63*)
Tryptophan	3.2	$\sim8\times10^4$[a]	(*65*)
Tryptamine	3	5×10^4[a]	(*65*)
Tryptophanamide	3	4×10^5[a]	(*65*)
Chlorpromazine	3.6	$\sim5\times10^6$[a]	(*59*)
O_2	6.8	1.5×10^9	(*59*)
Lipoic acid	7,12	NR[b]	(*64*)
N-Methylisonicotinic acid	7	NR	(*64*)
Anthraquinone-2-sulfonate	7	NR	(*64*)
Histidine	7	NR	(*64*)
Allyl alcohol	7	NR	(*64*)

[a] Reaction leads to equilibrium; see back reaction in Table 1.
[b] No reaction detected by pulse radiolysis, indicating usually $k<10^5$ $M^{-1}sec^{-1}$.

Subtracting $E(\dot{S}O_3^-)$ = 0.63 V from twice the former value (−0.92 V) leads to

$$SO_4^{2-} + H_2O + e^- \rightarrow SO_3^- + 2OH^- \quad E = -2.47\ V \tag{21}$$

This suggests that $\dot{S}O_3^-$ can act as both a mild oxidant or a strong reductant. It may be difficult to demonstrate the reducing power of $\dot{S}O_3^-$ since many oxidants will react with sulfite ions before the $\dot{S}O_3^-$ radicals are produced in the radiolysis. Moreover, the above calculation of redox potential may not reflect the actual reducing power of $\dot{S}O_3^-$ since the initial product is SO_3, which is subsequently hydrated to SO_4^{2-}, possibly much more slowly than the electron transfer (as argued for the case of $\dot{S}O_2^-$) (*84*). In addition, it has been argued on the basis of spin density on the sulfur, that $\dot{S}O_3^-$ is a much weaker reductant than $\dot{S}O_2^-$ (*55*).

Biological damage by $\dot{S}O_3^-$ may be partly due to oxidation reactions similar to those in Table 3. But the main harmful effects of this radical may lie in the fact that it reacts very rapidly with O_2, $k=1.5\times10^9$ $M^{-1}sec^{-1}$, to form a peroxyl radical which is much more reactive.

$$\dot{S}O_3^- + O_2 \rightarrow S\dot{O}_5^- \tag{22}$$

The alternative reaction path forming $SO_3 + O_2^-$ was

found (*85*) to be unimportant, at least under the experimental conditions of pH 3–12.

Reactions of Peroxysulfate Radical

The $\dot{S}O_5^-$ radical is a stronger oxidant than $\dot{S}O_3^-$; its one-electron redox potential is estimated to be about 1.1 V at pH 7 (*59*). Table 4 indeed shows that $\dot{S}O_5^-$ oxidizes several substrates considerably more rapidly than $\dot{S}O_3^-$, e.g., with ascorbate

$$\dot{S}O_5^- + HA^- \rightarrow HSO_5^- + \dot{A}^- \qquad k = 1.4 \times 10^8\ M^{-1}sec^{-1} \quad (23)$$

Moreover, it can oxidize certain substrates (aniline and dimethylaniline, for example) which are not attacked by SO_3^- at all and which, in fact, can form radicals that oxidize sulfite ions. In such cases, when the redox potential of the substrate is intermediate between those of $\dot{S}O_3^-$ and $\dot{S}O_5^-$, a chain reaction is likely to develop in the presence of O_2 following the general pattern shown in eqs. (24)–(26).

$$\dot{S}O_3^- + O_2 \rightarrow \dot{S}O_5^- \quad (24)$$

$$\dot{S}O_5^- + X \rightarrow SO_5^{2-} + \dot{X}^+ \quad (25)$$

$$\dot{X}^+ + SO_3^{2-} \rightarrow X + \dot{S}O_3^- \quad (26)$$

Although $\dot{S}O_5^-$ can oxidize directly sulfite or bisulfite ions, the intermediacy of a substrate X may enhance the chain process of sulfite oxidation (or peroxidation) by oxygen.

The one-electron reduction of $\dot{S}O_5^-$ yields HSO_5^-, peroxymonosulfate (Caro's acid). This is a strong oxidant, with a standard two-electron reduction potential of 1.82 V (*88*).

$$HSO_5^- + 2H^+ + 2e^- \rightarrow HSO_4^- + H_2O \quad (27)$$

Peroxymonosulfate is known to oxidize many organic compounds (*89*). Of considerable interest is its ability to oxidize sulfides to sulfones (*90*) and primary aryl amines to nitroso compounds (*91*). In addition to these reactions with organic compounds, which might involve oxygen atom transfer, peroxymonosulfate can be reduced by metal ions, possibly producing the highly reactive free radicals, $\dot{S}O_4^-$ or $\dot{O}H$, as it does upon reaction with e_{aq}^- (*92*), e.g.

$$Fe^{2+} + HSO_5^- \rightarrow Fe^{3+} + \dot{O}H + SO_4^{2-} \quad (28)$$

$$Fe^{2+} + HSO_5^- \rightarrow Fe^{3+} + OH^- + \dot{S}O_4^- \quad (29)$$

These radicals, in turn, are capable of rather indiscriminate attack on biological molecules.

The $\dot{S}O_5^-$ radical possibly can also react by atom transfer. This mechanism has been proposed for its reaction with bisulfite (30).

$$\dot{S}O_5^- + HSO_3^- \rightarrow \dot{S}O_4^- + HSO_4^- \quad (30)$$

Table 4. Comparison of some rate constants for reactions of $\dot{S}O_3$, $\dot{S}O_5$ and $\dot{S}O_4$ with organic compounds.

Compound	Rate constants, M^{-1} sec^{-1}		
	SO_3^-	SO_5^-	SO_4^-
Ascorbic	$<10^6$	2×10^{6a}	b
Ascorbate	9×10^6	1.4×10^{8a}	b
Trolox	$\sim 10^6$	1.2×10^{7a}	b
Hydroquinone	$<10^6$	2.7×10^6	b
Hydroquinone-monoanion	5×10^7		b
Catechol	$<10^6$	2.7×10^6	b
Resorcinol	(reverse)	$<1 \times 10^6$	b
Aniline	(reverse)	3×10^{6c}	b
N,N-Dimethylaniline	(reverse)	1×10^{7c}	b
Tyrosine	$<10^6$		$\sim 3 \times 10^{9d}$
Tryptophan	8×10^4		$\sim 2 \times 10^{9d}$
Histidine	NR		$\sim 2.5 \times 10^{9d}$
i-PrOH	$<10^3$		$\sim 8 \times 10^{7d}$
Ethanol		$<10^{3e}$	$\sim 3 \times 10^{7d}$
Fumurate	$<10^5$		$\sim 2 \times 10^{7d}$
Allyl alcohol	NR		1.5×10^{9d}
Glycine	$<10^3$		$\sim 9 \times 10^{6d}$
HSO_3^-	—	3×10^{6f}	$\sim 10^{9d}$

[a] Data of Huie and Neta (*85*).
[b] Was not measured because of thermal reaction of the substrate with $S_2O_8^{2-}$, the precursor of SO_4^-. The reaction, however, is expected to be very fast ($k \geq 10^9\ M^{-1}sec^{-1}$).
[c] Data of Neta and Huie (*63*).
[d] From Ross and Neta (*86*).
[e] Data of Hayon et al. (*3*).
[f] Data of Huie and Neta (*59*).

Other reactions of bisulfite are known to involve oxygen atom transfer (*93–97*).

If $\dot{S}O_5^-$ is capable of transferring an oyxgen atom, the direct oxygenation of organic compounds is feasible, possibly producing the $\dot{S}O_4^-$ radical as a by product. The existence of this type of reaction has not been confirmed.

The mechanism of the self-reaction of $\dot{S}O_5^-$ is not known. It has been proposed that the reaction leads to stable products and serves to terminate the autoxidation of sulfite (*11*). On the other hand, the reaction has been proposed to go to $\dot{S}O_4^-$ or $S_2O_8^{2-}$ (*98*).

$$2\dot{S}O_5^- \rightarrow 2\dot{S}O_4^- + O_2 \quad (31)$$

$$2\dot{S}O_5^- \rightarrow S_2O_8^{2-} + O_2 \quad (32)$$

with the ratio $k(\dot{S}O_4^{2-})/k(S_2O_8^{2-}) = 9$. Although this reaction is not likely to be important in the physiological role of sulfite, it could be important in some of the laboratory studies of the effects of sulfite oxidation on biological systems. The mechanism of this reaction certainly deserves more study.

Reactions of Sulfate Radical

The $\dot{S}O_4^-$ radical, possibly produced by the reactions discussed above, is very reactive toward organic compounds. It can abstract H atoms, add to double bonds,

and oxidize by electron transfer quite rapidly. The rate constants for such reactions with many organic compounds are summarized in a recent compilation (*86*) (see examples in Table 4) and will not be discussed here. It is clear, however, that $\dot{S}O_4^-$ attacks biological targets indiscriminately.

Conclusions

It has been apparent for some time that the effects of SO_2 autoxidation on organic and biological systems are due to reactive intermediates. Since the reactivities of many of these intermediates are now known, the mechanism of these effects can be better understood. For several of the organic compounds, like hydroquinone and other phenolic species, reaction with $\dot{S}O_3^-$ and $\dot{S}O_5^-$ is possible. Indeed, they prove to be the most efficient inhibitors of SO_2 autoxidation. For other organic compounds, like mannitol and methionine, only reactions with $\dot{S}O_4^-$ are likely. Production of HSO_5^- from the reduction of $\dot{S}O_5^-$ opens up additional possibilities, including direct reaction of HSO_5^- and its decomposition to produce $\dot{S}O_4^-$ or $\dot{O}H$.

Within the body, it is apparent that if SO_2 is allowed to undergo autoxidation, cellular damage is inevitable. Whether the presence of S(IV) beyond the region of the lungs can lead to similar damage is not apparent. To a large extent this damage will depend on the equilibrium

$$RSSR + HSO_3^- \rightleftarrows RSSO_3^- + RSH$$

and the probability of forming radicals from $RSSO_3^-$. One-electron reduction of this compound is expected to yield $\dot{S}O_3^-$ radicals. This was recently supported by pulse radiolysis experiments, whereby reduction of $RSSO_3^-$ by e_{aq}^- and $(CH_3)_2\dot{C}OH$ was found to form a radical which oxidized ascorbate with the same rate constant as does $\dot{S}O_3^-$ (*66*). If reduction of $RSSO_3^-$ to $\dot{S}O_3^-$ radical occurs with biological reductants, this could lead to oxidative damage by the $\dot{S}O_3^-$ and the other radicals produced from it. Thus the RS group serves not only as a carrier of sulfite but it also changes the requirements for $\dot{S}O_3^-$ radical formation from oxidation to reduction.

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