Chemical trapping and characterization of small oxoacids of sulfur (SOS) generated in aqueous oxidations of H₂S

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Small oxoacids of sulfur (SOS) are elusive molecules like sulfenic acid, HSOH, and sulfinic acid, HS(O)OH, generated during the oxidation of hydrogen sulfide, H₂S, in aqueous solution. Unlike their alkyl homologs, there is a little data on their generation and speciation during H₂S oxidation. These SOS may exhibit both nucleophilic and electrophilic reactivity, which we attribute to interconversion between S(II) and S(IV) tautomers. We find that SOS may be trapped in situ by derivatization with nucleophilic and electrophilic trapping agents and then characterized by high resolution LC MS. In this report, we compare SOS formation from H₂S oxidation by a variety of biologically relevant oxidants. These SOS appear relatively long lived in aqueous solution, and thus may be involved in the observed physiological effects of H₂S.

1. Introduction

The chemical biology of hydrogen sulfide, H₂S, has gained much attention with the recent discovery of its endogenous generation [1,2], as well as its implication in a variety of physiological functions such as vasodilation [3–7] and inflammation [8–10]. However, its mechanism of action is still not well understood, and there are reports that implicate H₂S biological functions may in part due to the H₂S derived oxidized products [11,12]. For example, SO₂ has been shown to have protective effects in vascular models akin to H₂S and NO. The initial oxoacid produced by H₂S oxidation is sulfenic acid, HSOH, Scheme 2, which should generate di- and sulfinyl tautomeric forms of the SOS.

Supplemental Materials (S1) Reaction products were identified as [M+H+] singly charged ions as [M+H+] singly charged ions. Reaction products were identified as [M+H+] singly charged ions. Reaction products were identified as [M+H+] singly charged ions. Reaction products were identified as [M+H+] singly charged ions. Single Ion Chromatograms (SICs) are shown to confirm that the observed species are present in the reaction mixture. Further experimental details are given in Supplemental Materials (S1).

2. Sulfenic acid, HSOH

The initial oxoacid produced by H₂S oxidation is sulfenic acid, HSOH. It may exist in two tautomeric forms [38–40], sulfinyl and sulfinyl, 1 and 2, Scheme 2, which should generate different derivatized products, as were observed in glutathione peroxidations [33]. Upon oxidation of H₂S in water, which we denote as SOS, small oxoacids of sulfur (SOS), including sulfenic (HSOH) [24,25], sulfoxyl (H₂SO₂) [26], and thiosulfoxyl acids (H₂S₂O₂) [27], all of which have tautomeric forms. The sulfoxyl acids may dehydrate to sulfur monoxide (SO) [28]. These SOS are highly reactive and notoriously difficult to characterize in biologically relevant conditions, and unlike their alkyl homologs, there is a little data on SOS generation and speciation during H₂S oxidation [29–32]. We recently reported trapping of both sulfinyl and sulfinyl tautomers of oxidized glutathione derivatives using a combination of selective nucleophilic and electrophilic trapping reagents and characterization by high resolution LC MS [33]. We hypothesize that the physiological effect of H₂S may derive from SOS, and thus we investigated their formation in biologically relevant conditions using similar methods, in situ derivatization with nucleophilic sulfinyl trapping reagent dimedone [34,35] and electrophilic reagents iodoacetamide, as well as mono- and di-bromobimane [36]. We will show that the oxidation of H₂S by biologically relevant oxidants using these reagents produces unique products that logically derive from sulfinyl and sulfinyl tautomeric of the SOS.

The generated SOS were derivatized by reaction with nucleophilic traps such as dimedone (DH) and 1-trimethylsiloxybicyclohexene [33], as well as electrophilic traps such as iodoacetamide (IA), and mono- or di-bromobimane (BrB and Br₂B). In a standard experiment, 1 mM Na₂S dissolved in pH 7 IP buffer was reacted with 1.2 mM of maleic peroxide, a soft oxidant formed in situ by mixing H₂O₂ with maleic anhydride; five minutes after reaction initiation, a 5 fold excess of trapping reagents are added [37]. After 1 h, the reaction mixture was injected into an Orbitrap LC HRMS, typically analyzed in the positive ion mode using the gradient elution method with 0.1% formic acid-acetonitrile eluent. Reaction products were identified as [M+H+] singly charged ions, with expected isotope patterns for [34] S and [13] C abundances. Single Ion Chromatograms (SICs) are shown to confirm that the observed species are present in the reaction mixture and separated on the LC column prior to ionization. Further experimental details are given in Supplemental Materials (S1).
reaction of H₂S with peroxymaleic acid, the sulfenyl tautomer is trapped by sequential reaction with dimedone and iodoacetamide yielding the thioether derivative, 4 in Scheme 3 and Fig. 1; an analogous thioether adduct is observed using bromobimane and iodoacetamide traps (S2). In the same reaction mixtures, the sulfinyl tautomer is trapped by consecutive Knoevenagel and Michael additions with dimedone, yielding tetravalent S species, ylide 6 [41,42]. The SICs of these species, along with [M+H⁺] LCMS spectra are shown in Fig. 1. The electrophilic and nucleophilic characteristics of HSOH is also evident in its reaction with 1-trimethylsiloxycyclohexene (S4), which yields unique products analogous to those seen in glutathione peroxidations [33].

The lifetime of HSOH under these experimental conditions was assessed by allowing the reaction mixtures to set for various times before addition of trapping reagents. Using quantification of species 4 gives an approximate half-life for HSOH of 40 mins (S3), much longer than expected for such a reactive species in presence of reactive thiols. By assessing the lifetime of HSOH under these experimental conditions was assessed by allowing the reaction mixtures to set for various times before addition of trapping reagents. Using quantification of species 4 gives an approximate half-life for HSOH of 40 mins (S3), much longer than expected for such a reactive species in presence of reactive thiols. By
comparison, most kinetic studies of S-based radicals suggest sub-second lifetimes, especially in polar solvent such as water [43].

A second ylide 8 is also observed, which we propose derives from dehydration of the intermediate Knovenegal product 7, Scheme 4 [44]. It may possible that this species may be a cyclic sulfuran product 10 derived from 9, the enol tautomer of 7. Further evidence for ylide 8 was obtained in the trapping reactions with BrB, iodoacetamide and dime-done (S5). An analogous ylide is seen in peroxidations of glutathione (S5). These three general derivatization reactions will be used throughout this report to differentiate between sulfenyl and sulfinyl functionalities in the trapped SOS described.

The presence of both tautomers 1 and 2 is affirmed by derivatization with BrB, Scheme 5. The SIC of mass 240.0641 shows two broad peaks, Fig. 2, that we ascribe to tautomeric forms of BSOH, 11, and BS(O)H, 12. The ratio of two, as determined by peak areas, is 100:29 with the sulfinyl tautomer likely the thermodynamically preferred. The presence of the sulfinyl tautomer is clearly shown in production of the bis(bimane) sulfoxide 13. Similarly if the bisbromobimane, Br₂B, 14, is used, a novel bimane sulfoxide 15 is observed. While interconversion between tautomers 11 and 12 is possible, it must be relatively slow as products from both tautomers are observed. A reviewer suggested that S-alkylation of divalent sulfenyl tautomer such as 11 may also generate the sulfinyl 13 after deprotonation and thus provide alternative pathways to species seen.

3. Sulfoxylic acid, H₂SO₂

The dioxygenation product of H₂S, H₂SO₂, may exist as sulfoxylic, 16, sulfinic, 17 dihydrogen sulfone, 18 or the sulfhydryl peroxide, 19, tautomer shown in Scheme 6 [45]. Theoretical calculations suggest that alcohol 16 is the most stable, and peroxide 19 is the least stable tautomer. Using the trapping methodology described, only tautomers 16 and 17 are observed, which suggests these dominate speciation in aqueous solution.

The sulfoxylic tautomer 16 is trapped by sequential addition of dimeredone, generating thioether 21, Scheme 7 and Fig. 3. The dimeredone reacts with sulfinic tautomer 17 attacking SO moiety with elimination of hydroxyl to yield 22 or by Knovenegal type addition yielding 24. Intramolecular dehydration of 24 gives 25 which might exist in equilibrium with 23, but the dehydration is likely kinetically slow. Theory

![Scheme 5. Derivatized products of 1 and 2.](image1)

![Scheme 4. Sketch of tautomeric forms sulfoxylic acid, H₂SO₂.](image2)

![Scheme 6. Sketch of tautomeric forms sulfoxylic acid, H₂SO₂.](image3)

![Scheme 7. Sequential reaction mechanism of trapping of sulfoxylic tautomers.](image4)
predicts sulfoxylic tautomer to be the lowest energy tautomer in the gas phase [45], but the ratio of sulfoxylic and sulfinic acid under our reaction conditions, as by trapped species 21 vs 23/25, is 7:100. Thus the S(IV) oxidation state predominates, perhaps aqueous solvation favors the more acidic sulfinic form.

4. SOS generation from biological oxidants

Utilizing the standard reaction conditions and trapping methods described above, the relative efficiency of SOS generation by a variety of biological oxidants was compared in aerobic, aqueous conditions. The common oxidants hydrogen peroxide (H₂O₂) [46], hypochloric acid (HOCl) [47,48], and maleic peroxide [37], are expected to directly form the SOS by O-atom transfer, Eq. (1). Metalloprotein oxidants such as metmyoglobin (Mb), and microperoxidase (MP-11), hydroxycobalamin (Cbl) are expected to initially oxidize H₂S by outersphere mechanism, effecting a 1 e⁻ oxidation per metal ion Eq. (2), but these may also participate in catalytic reduction of O₂ under the experimental conditions.

\[ \text{H}_2\text{O}_2 + \text{H}_2\text{S} \rightarrow \text{H}_2\text{SO} + \text{H}_2\text{O} \]  
\[ 2\text{M}^+ + \text{H}_2\text{S} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{SO} + 2\text{M} \]  

Fig. 4 shows the yield of SOS observed in oxidations of H₂S by various biologically relevant oxidants, as determined by the summation of SIC peak areas of the derivatized products generated under analogous reaction conditions (peak areas given in Table S6). For example, oxidation of H₂S by equivalent stoichiometries of H₂O₂ and MP-11 formed approximately equivalent amounts of HSOH, by relative amounts yields of derivatized species 4 observed.

As seen in Fig. 4, HOCl was the most selective peroxide at generating HSOH, with H₂O₂ generating 3:2 mixtures of HSOH and HOSOH. As previously mentioned, the milder oxidant maleic peroxide gave lower levels of the primary SOS, but generates best yields of less stable tautomers, perhaps due to a slower rate of reaction. All of the metalloprotein oxidants generated measurable SOS, with MP-11 the more selective for formation of HSOH over HOSOH. Among these metalloproteins, MP-11 has an exposed heme cofactor which perhaps facilitating direct interaction with H₂S.

5. Polysulfide oxoacids

Several polysulfide SOS (H₂SₙOₙ) are also observed in these reaction mixtures, especially in reactions of H₂S with the harder oxidants such as peroxide and hypochlorite, Fig. 5. The simples polysulfide oxide, H₃S₄O₃, has nine possible tautomers [49,50], but only products of the disulfanol, 26 and sulfinothioic acid, 27 are observed under our conditions, Scheme 8. Trapping of 26 with dimedone followed by addition of iodoacetamide yielded disulfide 28 and the product 29 from the Knovenegal intermediate. The ratio of tautomers 26:27 was calculated to be 100:12, in line with theoretical calculations of stability [49]. Additional evidence for 26 and 27 comes from the trapping of this species by 1-trimethylsiloxyxyclohexene, monobimane and dibimane (Supplemental S7).

Similarly, dioxydisulfides of the formula H₂S₂O₂ have been reported to be generated in reactions of H₂S with SO₂ in the Wackenroder process [51,52]. Of the seven possible tautomers, only derivatives of two terminal oxides are observed in H₂S oxidations by derivatization, Scheme 9, the diol 30 and mixed tautomer 31 which contains both sulfenyl and sulfanyl functionalities. Nucleophilic trapping of 30 with
dimedone yields the disulfide 32, Scheme 10 and Fig. 6. Analogous addition of 31 with dimedone, would give intermediate product 33, which undergoes further elimination to yield 34. The observed ratio of products 32 to 34 is 100:11. Additional evidence for 30 comes from trapping of it with 1-trimethylsiloxycyclohexene (S8).

In all reactions, larger polysulfanes mono- and di-oxides HSxOH and HSxO2H are also trapped, as demonstrated by the SICs of polysulfide oxides observed in reactions with H2O2 and MP-11, Fig. 7 and S9. As previously mentioned, the harder oxidants generate the more persulfanes; for example, the ranking of observed efficiency of HSxOH formation is peroxide > hypochlorite > MP > MP-11 > Mb > Cbl. A recent theoretical study found a relatively low energy reaction pathway reaction of H2S with sulfur oxides [53], and suggested that the S-S catenation is catalyzed by hydrogen bonding interactions in water. Thus these polysulfanes oxides may arise from initially formed SOS reacting with H2S, Eqs. (3) and (4).

\[
\begin{align*}
\text{HOSOH} + \text{H}_2\text{S} & \rightarrow \text{HSSH} + \text{H}_2\text{O} \quad (3) \\
\text{HOSOH} + \text{HS}_2\text{O} & \rightarrow \text{HS}_2\text{O}_2\text{H} + \text{H}_2\text{O} \quad (4)
\end{align*}
\]

6. Biological implications

These experiments suggest that SOS are formed readily in aqueous oxidations of H2S, and are relatively long lived. Like reactive oxygen species, SOS are produced in an evolving flux, i.e., HSOH generation begets HSxOH and other species described here. Our results show that SOS may generated from H2S by endogenous biological oxidants, and thus represent a new class of small reactive molecules which should be considered in the chemical biology of H2S [54]. For example, many metalloproteins are reduced by H2S, e.g. metcobalamin is reduced by aerobic reaction with H2S [55]. Several recent studies report that oxidation of H2S by ferric heme proteins metmyoglobin and catalase generate polysulfides [56–58]; we suggest that these products may derive from initial SOS generation. Likewise, persulfide coordinated [2Fe-2S] has been detected during the mechanism of iron-sulfur cluster formation in fumarate and nitrate reduction (FNR), which was explained by cluster sulfur oxidation of unknown sulfur oxygen species [59].

Of course, alternative pathways are possible for H2S oxidation besides SOS generation, i.e., radical coupling that form S–S bonds directly, or the precipitation of elemental sulfur, S0. But we believe the oxoacids form a unique and long-lived class of biomolecules that may have distinctive activities.

Fig. 5. Selective ion chromatogram and mass spectra of products 28 and 29, obtained in oxidation of H2S (1 mM) with hydrogen peroxide-maleic anhydride mixture (1.2 mM) in pH 7 buffer, trapped by a bolus of dimedone and acetamide (5 mM) after 5 min.

Scheme 8. Sketch of tautomeric forms of H2S2O.

Scheme 9. Sketch of tautomeric forms of H2S2O2.

Fig. 6. Selective ion chromatogram and mass spectra of products 31 and 33, obtained in oxidation of H2S (1 mM) with hydrogen peroxide-maleic anhydride mixture (1.2 mM) in pH 7 buffer, trapped by a bolus of dimedone and iodoacetamide (5 mM) after 5 min.
Fig. 7. Selective ion chromatograms (top) and relative peak areas of those SKEs (bottom) of H2O2 generation in reactions of H2S with H2O2 (black) and MP-11 (red). The reactions done in the ratio of 1 mM H2S and 1.2 mM oxidant in iP buffer pH 7, trapped by a bolus of iodoacetamide and dimedone (5 mM) after 5 mins. The peak heights and error bars derive from an average of three experiments. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.redox.2017.10.012.

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