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Method

Chemical trapping and characterization of small oxoacids of sulfur (SOS) generated in aqueous oxidations of H_2S

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ABSTRACT

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, H_2S, in aqueous solution. Unlike their alkyl homologs, there is a little data on their generation and speciation during H_2S 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 H_2S 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 H_2S.

1. Introduction

The chemical biology of hydrogen sulfide, H_2S, 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 H_2S biological functions may in part due to the H_2S derived oxidized products [11,12]. For example, SO_2 has been shown to have protective effects in cardio vascular models akin to H_2S and NO [13–23].

Scheme 1 shows several low valent species formed during oxidation of H_2S in water, which we denote as SOS, small oxoacids of sulfur species. These include sulfenic (HSOH) [24,25], sulfoxylic (H_2SO_2) [26], and thiosulfoxylic acids ($H_2S_2O_2$) [27], all of which have tautomeric forms. The sulfoxylic 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 H_2S oxidation [29–32]. We recently reported trapping of both sulfenyl 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 H_2S may derive from SOS, and thus we investigated their formation in biologically relevant conditions using similar methods, in situ derivatization with nucleophilic sulfenyl trapping reagent dimedone [34,35] and electrophilic reagents iodoacetamide, as well as mono- and di-bromobimane [36]. We will show that the oxidation of H_2S by biologically relevant oxidants using these reagents produces unique products that logically derive from sulfenyl and sulfinyl tautomeric of the SOS.

The generated SOS were derivatized by reaction with nucleophilic traps such as dimedone (DH) and 1-trimethylsiloxycyclohexene [33], as well as electrophilic traps such as iodoacetamide (IA), and mono- or di-bromobimane (BrB and Br_2B). In a standard experiment, 1 mM Na_2S dissolved in pH 7 iP buffer was reacted with 1.2 mM of maleic peroxide, a soft oxidant formed in situ by mixing H_2O_2 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 ion peaks, 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)

2. Sulfenic acid, HSOH

The initial oxoacid produced by H_2S oxidation is sulfenic acid, HSOH. It may exist in two tautomeric forms [38–40], sulfenyl and sulfinyl, **1** and **2**, Scheme 2, which should generate different derivatized products, as were observed in glutathione peroxidations [33]. Upon

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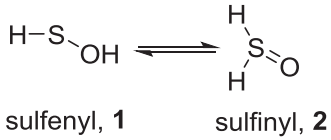
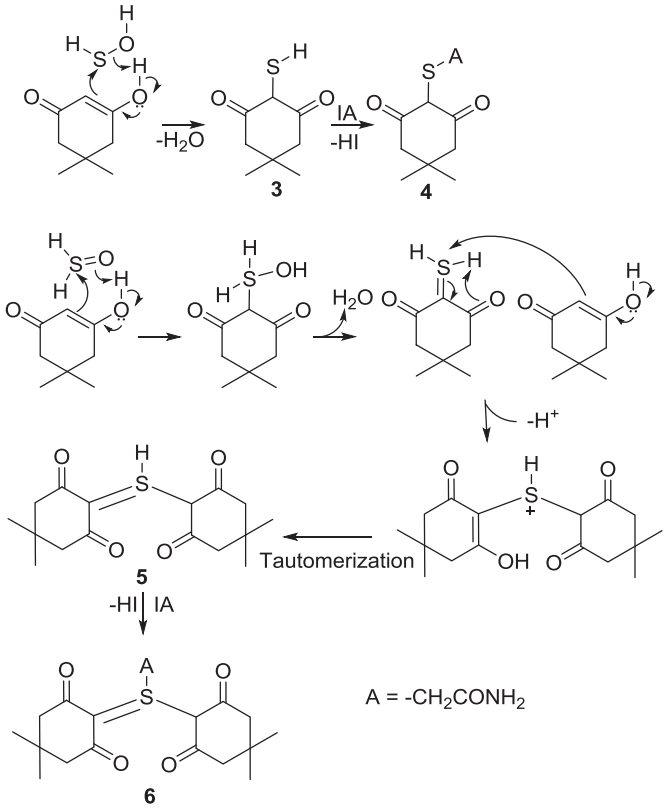
oxoacids

S^0	S^{2+}	S^{4+}
H_2SO	H_2SO_2	HS_2O_2
sulfenic	*sulfoxylic*	*thiosulfoxylic*

Scheme 1. Small oxoacids of sulfur (SOS) species.



Scheme 2. Tautomeric forms of sulfenic acid.



Scheme 3. Sequential reaction mechanism of trapping of sulfenic acid tautomers.

reaction of H_2S 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

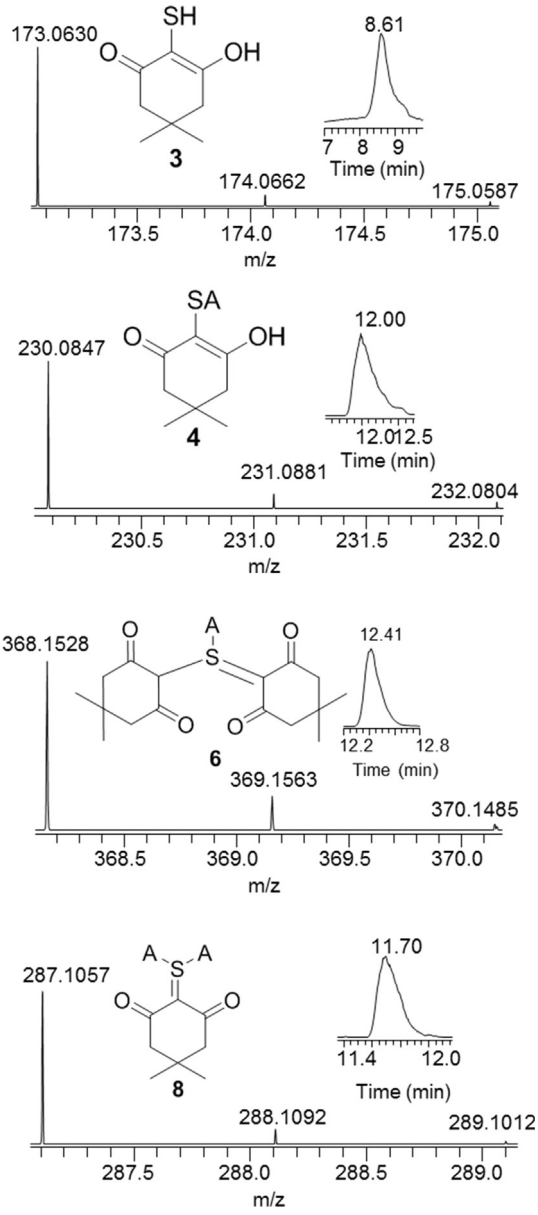
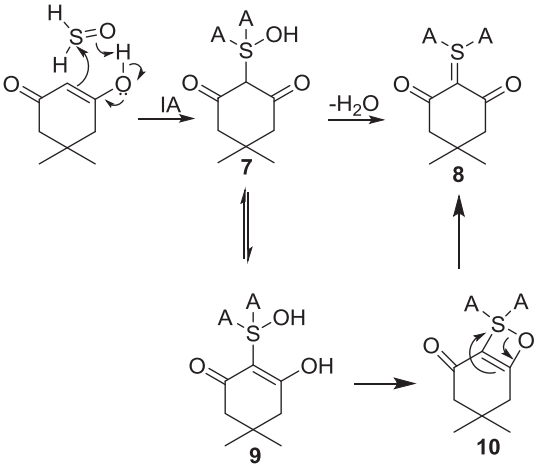
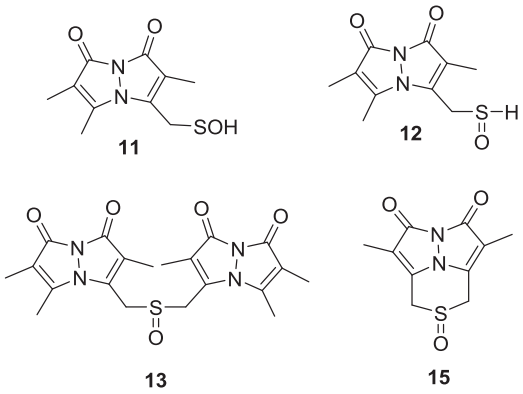


Fig. 1. Selective ion chromatogram and mass spectra of products **3**, **4**, **6** and **8**, obtained in oxidation of H_2S (1 mM) with maleic peroxide (1.2 mM) in pH 7 iP buffer, trapped with a bolus of (5 mM) dimedone and iodoacetamide after 5 mins.



Scheme 4. Reaction mechanism of sulfinyl trapping.



Scheme 5. Derivatized products of **1** and **2**.

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 sulfurane 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 dimedone (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,

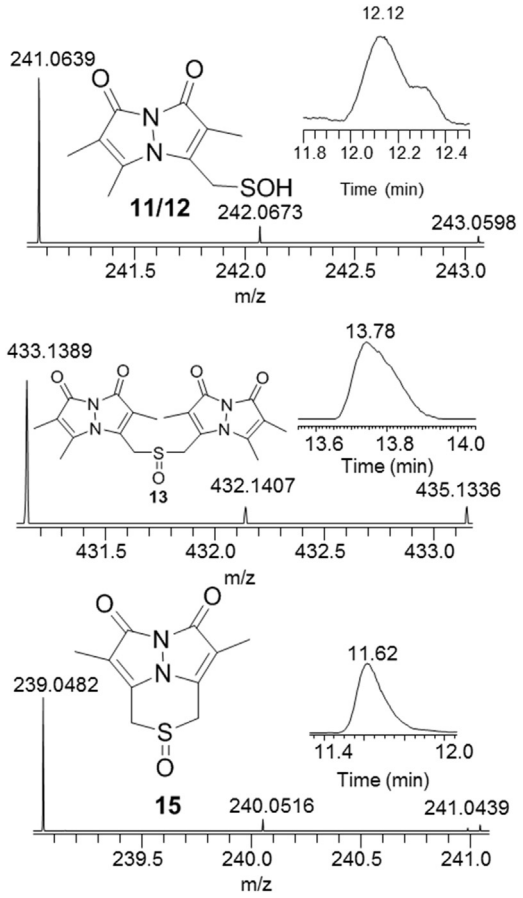
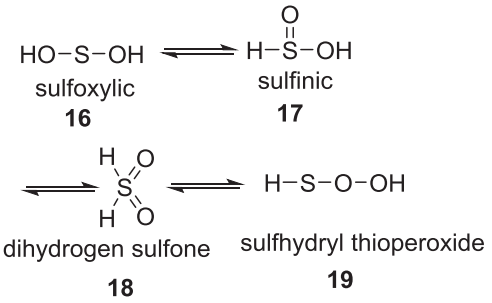


Fig. 2. Selective ion chromatograms and mass spectra of products **11**, **12**, **13** and **15**, obtained in oxidation of H_2S (1 mM) with maleic peroxide (1.2 mM) in presence of mono- and dibromobimane (5 mM) in pH 7 IP buffer.



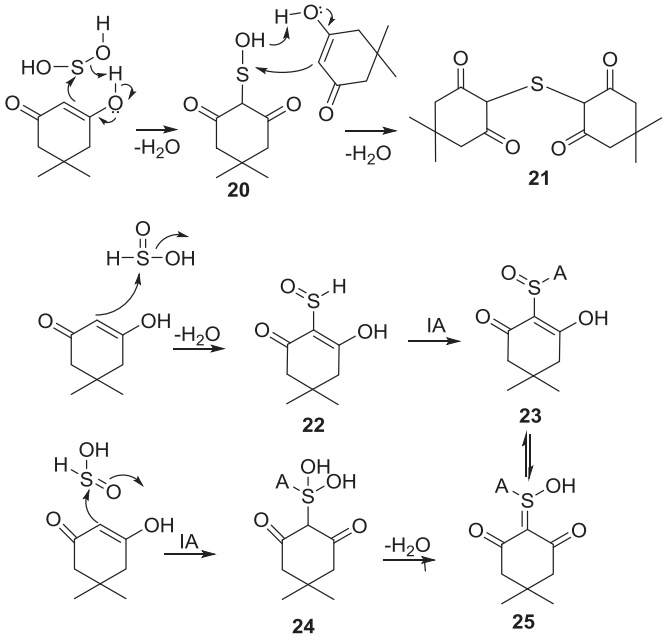
Scheme 6. Sketch of tautomeric forms sulfoxylic acid, H_2SO_2.

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 sulfenyl 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, Br_2B, **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, H_2SO_2

The dioxygenation product of H_2S, H_2SO_2, 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 dimedone, generating thioether **21**, Scheme 7 and Fig. 3. The dimedone 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 7. Sequential reaction mechanism of trapping of sulfoxylic tautomers.

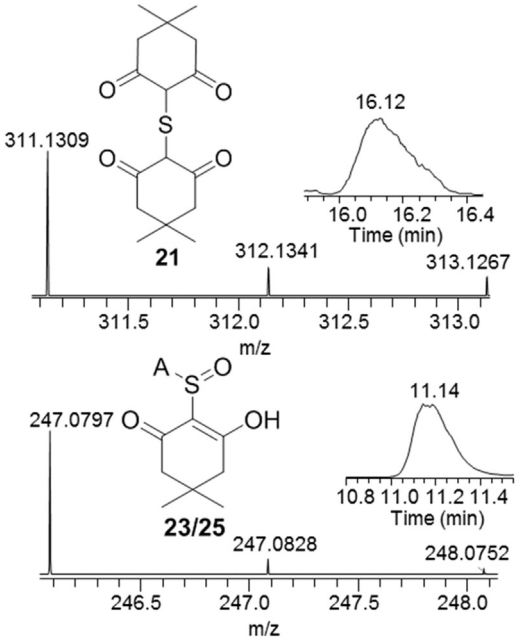


Fig. 3. Selective ion chromatogram and mass spectra of products **21** and **23,** and **25** obtained in oxidation of H_2S (1 mM) with maleic peroxide (1.2 mM) in buffer, pH 7, trapped by a bolus of dimedone and acetamide (5 mM) after 5 min.

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 (H_2O_2) [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 H_2S by outersphere mechanism, effecting a 1 e- oxidation per metal ion Eq. (2), but these may also participate in catalytic reduction of O_2 under the experimental conditions.

$$H_2O_2 + H_2S \rightarrow H_2SO + H_2O \quad (1)$$

$$2\,M^+ + H_2S + H_2O \rightarrow H_2SO + 2\,M \quad (2)$$

Fig. 4 shows the yield of SOS observed in oxidations of H_2S 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 H_2S by equivalent stoichiometries of H_2O_2 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 H_2O_2 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 H_2S.

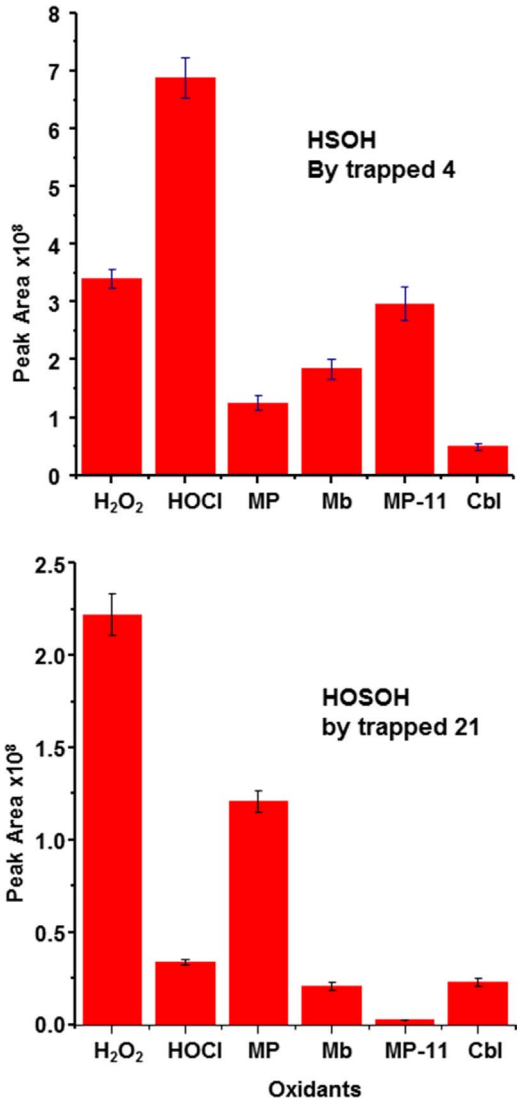


Fig. 4. Relative efficiency of HSOH and HOSOH generation in reactions of H_2S with various oxidants, based on the SIC peak areas for trapped species **4** and **21**. All reactions done in the ratio of 1 mM H_2S, 1.2 mM oxidant in iP buffer pH 7, trapped by addition of 5 mM bolus of iodoacetamide and dimedone after 5 mins. The peak heights and error bars derive from an average of three experiments.

5. Polysulfide oxoacids

Several polysulfide SOS ($H_2S_nO_m$) are also observed in these reaction mixtures, especially in reactions of H_2S with the harder oxidants such as peroxide and hypochlorite, Fig. 5. The simples polysulfide oxide, H_2S_2O, 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-trimethylsiloxycyclohexene, monobimane and dibimane (Supplemental S7).

Similarly, dioxydisulfides of the formula $H_2S_2O_2$, have been reported to be generated in reactions of H_2S with SO_2 in the Wackenroder process [51,52]. Of the seven possible tautomers, only derivatives of two terminal oxides are observed in H_2S oxidations by derivatization, Scheme 9, the diol **30** and mixed tautomer **31** which contains both sulfenyl and sulfinyl functionalities. Nucleophilic trapping of **30** with

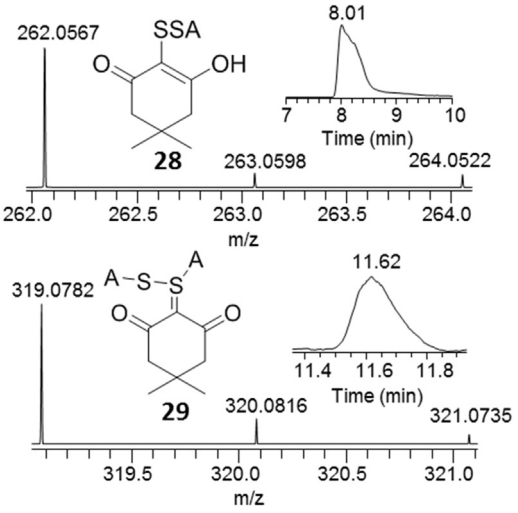
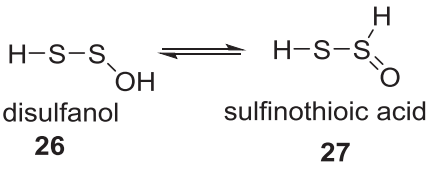
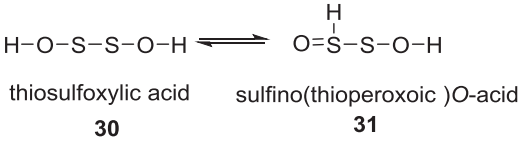


Fig. 5. Selective ion chromatogram and mass spectra of products **28** and **29**, obtained in oxidation of H_2S (1 mM) with hydrogen peroxide-maleic anhydride mixture (1.2 mM) in pH 7 buffer, trapped by a bolus of dimedone and acetamide (5 mM) after 5 min.



Scheme 8. Sketch of tautomeric forms of H_2S_2O.



Scheme 9. Sketch of tautomeric forms of $H_2S_2O_2$.

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).

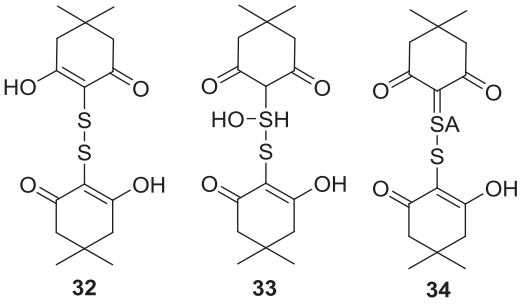
In all reactions, larger polysulfanes mono- and di-oxides HS_xOH and HS_xO_2H are also trapped, as demonstrated by the SICs of polysulfide oxides observed in reactions with H_2O_2 and MP-11, Fig. 7 and S9. As previously mentioned, the harder oxidants generate the more persulfanes; for example, the ranking of observed efficiency of HS_3OH formation is peroxide > hypochlorite > MP > MP-11 > Mb > Cbl. A recent theoretical study found a relatively low energy reaction pathway reaction of H_2S 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 H_2S, Eqs. (3) and (4).

$$HSOH + H_2S \rightarrow HSSH + H_2O \quad (3)$$

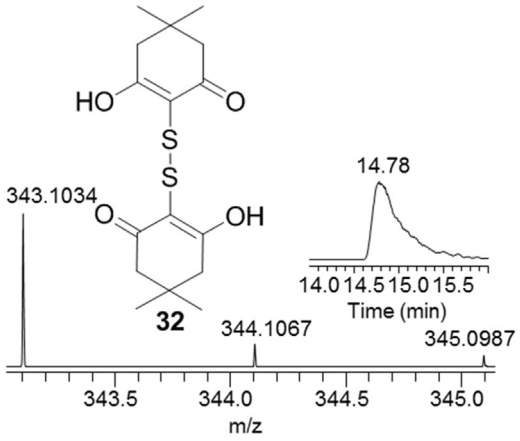
$$HOSOH + H_2S \rightarrow HSSOH + H_2O \quad (4)$$

6. Biological implications

These experiments suggest that SOS are formed readily in aqueous oxidations of H_2S, and are relatively long lived. Like reactive oxygen species, SOS are produced in an evolving flux, i.e., HSOH generation begets HSO_2H, and other species described here. Our results show that SOS may generated from H_2S by endogenous biological oxidants, and



Scheme 10. Derivatized products of **30** and **31**.



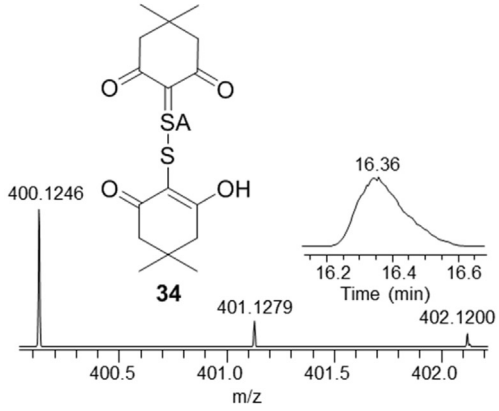


Fig. 6. Selective ion chromatogram and mass spectra of products **31** and **33**, obtained in oxidation of H_2S (1 mM) with hydrogen peroxide-maleic anhydride mixture (1.2 mM) in pH 7 buffer, trapped by a bolus of dimedone and iodoacetamide (5 mM) after 5 min.

thus represent a new class of small reactive molecules which should be considered in the chemical biology of H_2S [54]. For example, many metalloproteins are reduced by H_2S, e.g. metcobalamin is reduced by aerobic reaction with H_2S [55]. Several recent studies report that oxidation of H_2S 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 H_2S oxidation besides SOS generation, i.e., radical coupling that form S–S bonds directly, or the precipitation of elemental sulfur, S^0. But we believe the oxoacids form a unique and long-lived class of biomolecules that may have distinctive activities.

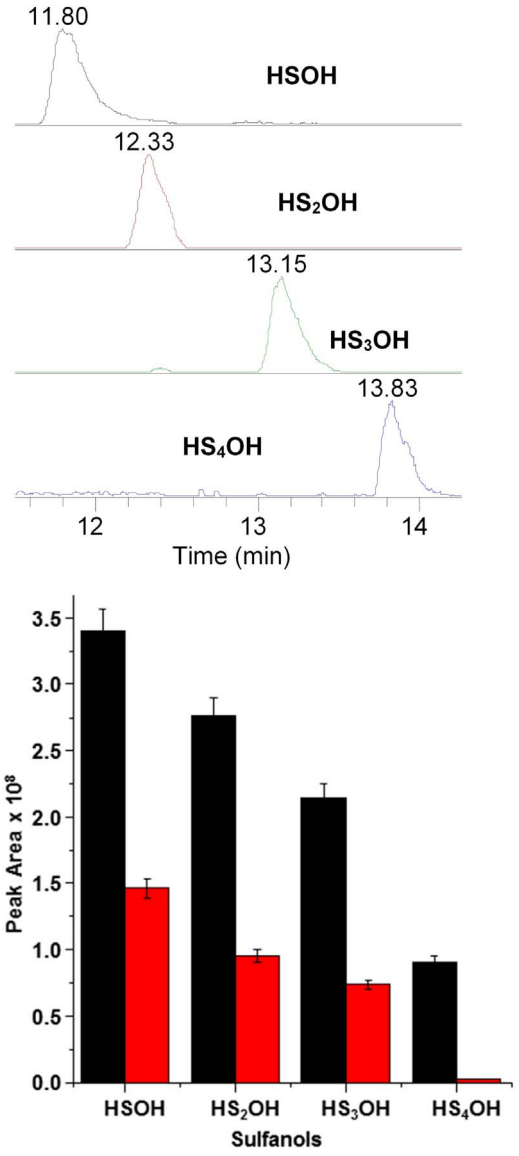


Fig. 7. Selective ion chromatographs (top) and relative peak areas of those SICs (bottom) of HS_nOH generation in reactions of H_2S with H_2O_2 (black) and MP-11 (red). The reactions done in the ratio of 1 mM H_2S and 1.2 mM oxidant in iP buffer pH 7, trapped by a bolus of iodoacetamide and dimedone (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.)

Acknowledgements

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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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