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Accelerated Reduction and Solubilization of Elemental Sulfur By 1,2-Aminothiols

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Nucleophilic 1,2-aminothiol compounds readily reduce typically-insoluble elemental sulfur to polysulfides in both water and nonpolar organic solvents. The resulting anionic polysulfide species are stabilized through hydrogen-bonding interactions with the proximal amine moieties. These interactions can facilitate sulfur transfer to alkenes.

Despite the insolubility of elemental sulfur (S_8) in water (4.9 μg L^{-1} at 25 °C),[1-2] transfer and reactions of "sulfane" sulfur (S^0) are critical in many biological systems for signalling and redox processes.[3] Although there has been previous work in solubilizing S_8 through the use of surfactants[4] and cyclodextrins,[2] polysulfide anions and organic polysulfides have been proposed as sources of both S^0 and H_2S in biological systems,[5] and many efforts have been made toward quantifying such polysulfide species.[6] In organic solvents, the conversion of S_8 to polysulfide anions or anion radicals is a key step in many reported reactions, including C–S bond formation or metal chalcogenide nanomaterials syntheses.[7-8] As such, understanding the interconversion between S^0, S^{2-} (or H_2S or HS^-), and S_x^{2-} in both aqueous and organic media has been an ongoing area of interest.

Eqns. 1 and 2 show the reaction between thiols (RSH) and S_8 in organic solvents, a typically sluggish reaction that can be catalyzed by alkylamines.[9] First, the S_8 ring undergoes nucleophilic attack by a thiol to ring-open and form a hydropolysulfide (RSS_xH). This step is assisted by amines that can deprotonate the thiol to form the more nucleophilic thiolate. After formation of the hydropolysulfide species, reaction with a second equivalent of the starting thiol compound releases H_2S and forms an organic polysulfide compound (RSS_xSR, x = 0, 1, 2, …). In the absence of thiols, S_8 can be dissolved in neat amine and is reduced to form H_2S and alkylammonium polysulfides (Eq. 3).[10-12] Lastly, thiols and amines can be combined as a solvent for the solubilization of chalcogens and metal chalcogenide materials.[13-14] It should be noted, however, that these last two examples require the use of amines or thiols as solvents, conditions not translatable to biological systems and many synthetic organic reactions.

$$RSH \xrightarrow{x/8\ S_8} RSS_xH \quad (1)$$

$$RSS_xH \underset{}{\overset{RSH}{\rightleftharpoons}} RSS_{x-1}SR + H_2S \quad (2)$$

$$RNH_2 + S_8 \rightleftharpoons [RNH_3]_2[S_x] \quad (3)$$

Aminothiol compounds are an interesting class of molecules that might be expected to combine the sulfur reactivity properties of thiols and amines in a manner that is greater than the sum of their parts. In biological systems, aminothiol compounds are prevalent and include cysteamine (**1**^{SH}) and *L*-cysteine (**2**^{SH}) as common examples (Fig. 1). 1,2-Aminothiols are also common motifs added in post-synthetic modifications of proteins.[15] Although these thiols are well known targets for persulfidation,[6] little is known on the impact of the amine moiety on sulfane reactivity. Other aminothiol compounds such as 2-aminothiophenol (**5**^{SH}) have been primarily targeted for the synthesis of benzothiazoles and related heterocycles.[16-17] Here, we show that an amine moiety in proximity to the thiol group (1) increases the nucleophilicity of the thiol, (2) solubilizes S_8 in the form of polysulfides, and (3) increases H_2S exchange in organic polysulfide compounds. As such, aminothiol compounds present a way to promote sulfane reactivity for both aqueous and organic-phase reactions.

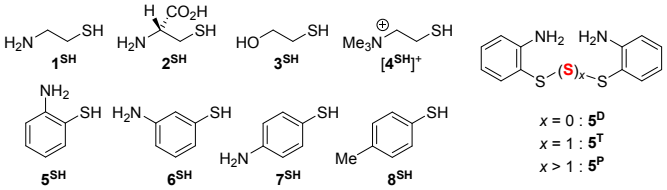

Figure 1. Structures of thiols (***N***^{SH}) studied, along with examples of di(2-aminophenyl) disulfide (**5**^{D}), trisulfide (**5**^{T}), and higher polysulfides (**5**^{P}).

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When a D_2O solution of $\mathbf{1^{SH}}$·HCl (1 M) is treated with NaOH (1 equiv) and excess S_8, the solid S_8 dissolves and the colorless solution turns yellow within minutes at room temperature. In this reaction, S_8 is reduced to polysulfide anions, S_x^{2-} (UV-vis spectroscopy, see ESI),[18-19] and to H_2S, detected by the formation of PbS from the transfer of the reaction headspace to a solution of $Pb(OAc)_2$. ^{1}H NMR spectroscopy of this mixture showed multiple broad new species that coalesce at higher temperatures, indicating exchange, likely between $\mathbf{1^{SH}}$, the corresponding organic disulfide ($\mathbf{1^D}$), and other higher organic polysulfide compounds ($\mathbf{1^T}$, $\mathbf{1^P}$), also confirmed through ESI-MS of the reaction mixture (Eq. 4).

$$\mathbf{1^{SH}} + S_8 \longrightarrow \mathbf{1^{D,T,P}} + H_2S + S_x^{2-} \quad (4)$$

These multiple species can be further distinguished by ^{1}H NMR spectroscopy when dissolved in a pH 10 D_2O buffer. This same reaction with S_8 in water does not occur for the thiol-only compounds propanethiol or 1,2-ethanedithiol, for the amine-only compound ethylenediamine, or with NaOH only.

To deconvolute the effects of amine from electronics-induced changes to the thiol pK_a (for $\mathbf{1^{SH}}$, pK_a 8.6;[20] for $\mathbf{2^{SH}}$, pK_a 8.22;[21] for propanethiol, pK_a ~10.6)[22] we studied the reaction between these thiols and S_8 at different pH under N_2. Figures 2A,B compare the absorption spectra over time of buffered solutions (pH 7.6, NaH_2PO_4/Na_2HPO_4 and pH 10.1, $NaHCO_3/Na_2CO_3$) of $\mathbf{1^{SH}}$·HCl (350 μM) upon treatment with excess S_8 at 21 °C. At pH 10.1, $\mathbf{1^{SH}}$ is primarily zwitterionic in which the thiol is mostly deprotonated while the amine moiety is partly protonated. The distinct absorption band of the thiolate (ca. 231 nm)[23-24] decays within minutes upon addition of S_8. Figure 2C plots the decay of this thiolate absorption over time for pH 10.1 solutions (350 μM) of $\mathbf{1^{SH}}$, $\mathbf{2^{SH}}$, and of 2-mercaptoethanol ($\mathbf{3^{SH}}$, pK_a 9.5)[25-26] after addition of excess S_8. The reaction rates decrease in order of $\mathbf{1^{SH}} >> \mathbf{3^{SH}} > \mathbf{2^{SH}}$, meaning that the ancillary substituent greatly affects its reaction with S_8.

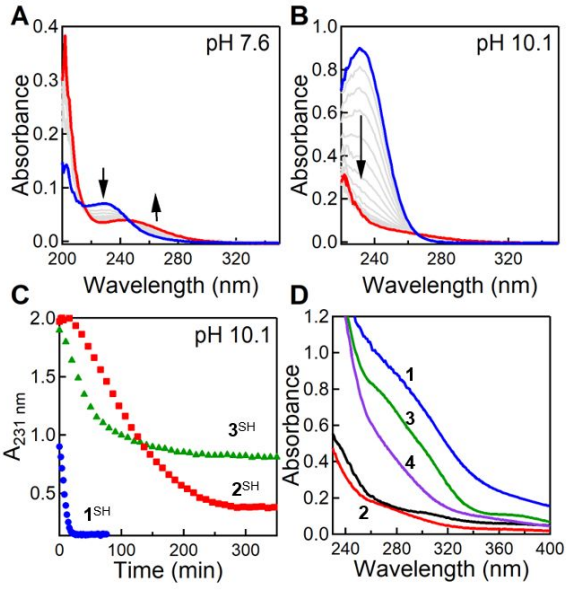

Figure 2. (A) Absorption spectra of a pH 7.6 solution of $\mathbf{1^{SH}}$·HCl (350 μM) with excess S_8 at 21 °C over 280 min. (B) Absorption spectra of a pH 10.1 solution of $\mathbf{1^{SH}}$·HCl (350 μM) with excess S_8 at 21 °C over 80 min. (C) $A_{231\ nm}$ of pH 10.1 solutions of $\mathbf{1^{SH}}$·HCl (blue), $\mathbf{2^{SH}}$ (red), and $\mathbf{3^{SH}}$ (green) (350 μM) with excess S_8 at 21 °C, indicating consumption of thiolate. (D) Absorption spectra of degassed pH 10.1 solutions of $\mathbf{1^{SH}}$·HCl (blue), $\mathbf{2^{SH}}$ (red), $\mathbf{3^{SH}}$ (green), propanethiol (black), and [$\mathbf{4^{SH}}$][Cl] (purple) after reaction with S_8 is complete, indicating different final S_x^{2-} concentrations.

Beyond reaction rates, the aminothiol (or hydroxyethanethiol for $\mathbf{3^{SH}}$) also affects the final sulfur concentrations after the reaction is complete. Dissolved sulfur in the form of polysulfide anions can be quantified using absorption spectroscopy, as higher sulfur content corresponds to more intense absorption at 260 nm.[18] Degassed solutions (pH 10.1, 0.04 M) of $\mathbf{1^{SH}}$·HCl, $\mathbf{2^{SH}}$, $\mathbf{3^{SH}}$, 2-mercaptoethyl-*N*,*N*,*N*-trimethylammonium chloride ([$\mathbf{4^{SH}}$][Cl]), and propanethiol were treated with S_8 (4 S atom equivalents) and stirred at room temperature until completion, i.e. no further change in the absorption spectrum. The solutions were then diluted to 350 μM using degassed pH 10.1 buffer, and the absorption spectra are shown in Figure 2D. In these experiments, the reaction mixtures containing $\mathbf{1^{SH}}$ and $\mathbf{3^{SH}}$ show high sulfur content; approximating all polysulfide species as S_5^{2-}, the polysulfide concentrations were 0.16 and 0.11 mM, respectively, before dilution,[18] corresponding to total *sulfur* concentrations of 0.80 and 0.55 mM. In comparison, the reaction mixtures of $\mathbf{2^{SH}}$, [$\mathbf{4^{SH}}$]$^+$, and propanethiol with S_8 show polysulfide concentrations of 0.020, 0.064, and 0.026 mM, respectively. Taken together, these data suggest that hydrogen-bonding effects from NH_3^+ and OH groups can increase the reaction rate between thiolate and S_8 as well as increase overall sulfane dissolution in the form of polysulfide anions.

We propose that hydrogen-bonding by the amine or hydroxyl groups of $\mathbf{1^{SH}}$ and $\mathbf{3^{SH}}$ can stabilize anionic polysulfides associated with the thiolate group (Fig. 3a). For [$\mathbf{4^{SH}}$]$^+$, which contains a cationic trimethylammonium moiety, some electrostatic stabilization of the polysulfide anion is observed, but as a weaker contribution than hydrogen-bonding (Fig. 3b). The behavior of *L*-cysteine ($\mathbf{2^{SH}}$) is anomalous; despite having an amine moiety close to the thiol group as in $\mathbf{1^{SH}}$, its reaction with S_8 is comparatively slow and a lower concentration of S_x^{2-} is formed. At pH 10.1, the carboxylate of $\mathbf{2^{SH}}$ is deprotonated; we hypothesize that the negatively charged carboxylate group hydrogen bonds with the ammonium group, reducing the effect of the NH_3^+ on thiolate reactivity (Fig. 3c). This result is particularly interesting, as cysteine persulfidation has been proposed as a key intermediate in sulfur signaling.[6, 27] This observed *destabilization* of cysteine-derived polysulfides may therefore increase the reactivity of cysteine persulfide for sulfur transfer during biologically-relevant thiol redox exchange reactions.

Figure 3. (a) Proposed hydrogen-bonding interaction between the ammonium functional group and polysulfide motifs in the product of $\mathbf{1^{SH}}$ and S_8. (b) Proposed electrostatic interaction between the trimethylammonium group and polysulfide in the product of [$\mathbf{4^{SH}}$]$^+$ and S_8. (c) Competing interactions between the deprotonated carboxylate with the ammonium in $\mathbf{2^{SH}}$ are proposed to reduce interactions with the polysulfide group.

As the exchange in water is complicated by polysulfide hydrolysis at low concentrations,[18] we studied aminothiol reactions with S_8 in organic solvents for improved spectroscopic characterization of these polysulfide interactions. The products of the reaction between 2-aminothiophenol (**5^{SH}**) and S_8 in benzene appear to be analogous to the products formed by **1^{SH}** and S_8 in water. Although S_8 is still rather insoluble in benzene (ca. 20 mg S_8/mL C_6H_6 at 25 °C),[28] when a C_6D_6 solution of **5^{SH}** is treated with S_8 (2 S atom equivalents) in a sealed NMR tube, the crystalline S_8 dissolves and the solution turns bright yellow within minutes at room temperature. The ^{1}H NMR spectrum of this mixture shows the formation of H_2S (δ 0.30 ppm)[29] along with di(2-aminophenyl) disulfide (**5^{D}**), di(2-aminophenyl) trisulfide (**5^{T}**) and higher di(2-aminophenyl) polysulfides (**5^{P}**). LC-MS of the final mixture confirms this assignment (see ESI). Similar mixtures have been previously observed as equilibration products upon treatment of **5^{D}** with NaHS in ethanol.[30]

We compared the thiophenol compounds **5^{SH}**, 3-aminothiophenol (**6^{SH}**), 4-aminothiophenol (**7^{SH}**), and 4-methylbenzenethiol (**8^{SH}**) to test the effect of amine proximity to the thiol moiety. Figure 4 plots the concentrations of each thiophenol in C_6D_6 solution after treatment with 2 S atom equivalents of S_8 in a sealed NMR tube under N_2 with the exclusion of light. These plots can be fit well to a first-order rate law, although there is an induction period in the decays of **6^{SH}** and **7^{SH}**, indicating slower solubilization of S_8. Table 1 compares the resulting k_{obs} of these reactions under different conditions, calculated from the first order exponential fit of these data. These results show that the rate of the reaction between thiols and S_8 in benzene is highly dependent on the nucleophilicity of the thiol, which is modulated by nearby amine groups. To support this hypothesis, mixtures of the thiophenols were treated with MeI in a competition experiment. The thiol nucleophilicities were found to decrease in the order **5^{SH}** > **7^{SH}** > **8^{SH}**, consistent with the k_{obs} of the reactions between these thiophenols with S_8 (Table 1, Entries 1, 5, 7). This trend in the reaction rate is proposed to be due to the deprotonation of the thiol moiety by the nearby amine. The 1,2-aminothiol compound, **5^{SH}**, which can exhibit intramolecular thiol activation, reacts faster than the 1,3- and 1,4-substituted compounds **6^{SH}** and **7^{SH}**. The addition of catalytic amine greatly accelerates thiol addition to S_8, however, as previously reported (Table 1, Entries 2, 6).[9, 31]

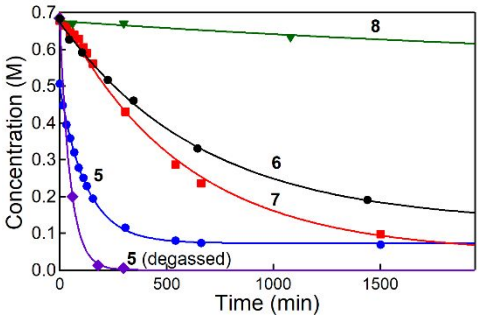

Figure 4. Conversion of thiophenol compounds over time upon addition of 2 S atom equivalents of S_8 in C_6D_6 in sealed NMR tubes.

After nucleophilic attack and ring-opening of S_8 (Eq. 1), H_2S (^{1}H NMR spectroscopy) and inorganic polysulfide ions S_x^{2-} (absorption spectroscopy) or HS_x^- species are formed that can react with the organic polysulfide to form hydropolysulfides (Eq. 2). As a way of evaluating the effects of amine on this exchange, Table 1 compares the final product distributions in the reactions between **5^{SH}**, **6^{SH}**, **7^{SH}**, and **8^{SH}** (0.69 M in C_6D_6) with S_8 (2 S atom equivalents) under different conditions. In these experiments, the thiol is not fully consumed (ca. 10% remaining), consistent with the reversibility of H_2S elimination and reinsertion. For these reactions, the dissolved H_2S concentrations measured by ^{1}H NMR spectroscopy varied, with [H_2S] = 0.30 M for **5**, [H_2S] = 0.42 M for **6,** [H_2S] = 0.32 M for **7**, and [H_2S] = 0.24 M for **8** with 2.5 mol % added butylamine. When a C_6D_6 solution of **5^{SH}** is stirred with S_8 while bubbling N_2 through the mixture to remove H_2S, the mixture reaches equilibrium much faster ($t_{1/2}$ ~ 0.56 h, Table 1, Entry 3), with negligible remaining **5^{SH}**.

Table 1. Distribution of thiophenol-derived products after treatment with S_8 (2 S atom equivalents), determined by ^{1}H NMR spectroscopy. (SH = thiophenol, D = disulfide, T = trisulfide, P = higher polysulfides).

Entry[a]	R	k_{obs} (× 10^{-2} min^{-1})	SH (%)	D (%)	T+P (%)
1	**5**	1.3 ± 0.4	12 ± 1	22.4 ± 0.3	66 ± 2
2	**5**[b]	13 ± 6	16 ± 2	26 ± 2	57 ± 3
3	**5**[c]	2	<1	25	75
4	**6**	0.2 ± 0.1	18.1 ± 0.2	81.9 ± 0.3[e]	
5	**7**	0.29 ± 0.04	9 ± 2	91 ± 2[e]	
6	**8**[b]	2.0 ± 0.2	15 ± 3	52 ± 2	32 ± 2
7	**8**[d]	0.03	82	2	16

[a]Reactions performed in triplicate with standard deviations reported, except for Entries 3 and 7. [b]With 2.5 mol% butylamine. [c]Bubbling N_2. [d]Percentages reported after 100 h. [e]The ^{1}H NMR signals could not be deconvoluted.

Interestingly, while the reaction of **8^{SH}** with S_8 and catalytic butylamine (2.5 mol%, Table 1, Entry 6) is faster, the major product is di(4-methylphenyl) disulfide (**8^{D}**). In contrast, the major product formed between **5^{SH}** and S_8 are di(2-aminophenyl) polysulfides (**5^{T,P}**) (Table 1, Entry 1). We propose that the 2-amino moiety of **5^{SH}** can undergo hydrogen-bonding interactions with H_2S and polysulfide anions (similar to that shown in Fig. 3) to facilitate insertion into the nearby organopolysulfide chains. Because **8^{SH}** has no amine groups near the thiol moiety, less scrambling occurs, resulting in greater selectivity for **8^{D}** over **8^{T}** or **8^{P}**. In contrast, the addition of butylamine does not significantly change the final product distribution of the reaction of **5^{SH}** and S_8.

Having shown accelerated sulfur reduction to polysulfides and H_2S, we hypothesized that 1,2-aminothiol compounds can promote intermolecular sulfane transfer from S_8 to substrates. ^{1}H NMR spectroscopy of a C_6D_6 mixture of S_8 (> 4 S atom equiv), styrene (1 equiv), and **5^{SH}** (1 equiv) shows the formation of styrene-derived polysulfide products at room temperature, along with a mixture of **5^{D}**, **5^{T}**, and **5^{P}** (Fig. 5). Upon heating this reaction mixture to 80 °C, full conversion of styrene is obtained within 24 h. These products were identified as a mixture of the corresponding di(1-phenylethyl) sulfide and diastereomers of di(1-phenylethyl) di-, tri-, and polysulfides, consistent with an overall addition of "H_2S_x" across two molecules of styrene (^{1}H

NMR spectroscopy, GC-MS).[32] Polysulfide products corresponding to the addition of $HS_xC_6H_4NH_2$ to styrene (Fig. 5) were also identified. These products were isolated and purified by column chromatography. These molecular polysulfur products differ significantly from the inverse vulcanization polymers formed from the treatment of styrene with S_8 at higher temperatures.[33] In comparison, the same reaction mixture with **7^{SH}** instead of **5^{SH}** shows only ca. 34% styrene conversion over 24 h. The reaction between PhSH, styrene, and S_8 at room temperature forms primarily phenyl α-methylbenzyl sulfide, the expected product of PhS−H bond addition across the styrene double bond, with no additional incorporation of sulfur.[34] Altogether, these experiments demonstrate that the 1,2-aminothiol moiety of **5^{SH}** facilitates more efficient *polysulfane* transfer to styrene. Similar products are observed in the reaction between **5^{SH}**, S_8, and 1-octene, albeit at much slower rates.

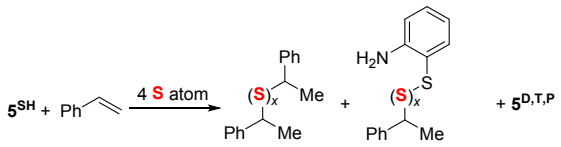

Figure 5. 2-aminothiophenol-mediated addition of sulfur to styrene.

The results above suggest a strategy for increasing polysulfide and hydropolysulfide concentrations at low temperatures in water for biological applications or in organic solvents for the preparation of polysulfur compounds. Ongoing work includes modification of these 1,2-aminothiol compounds for greater selectivity in polysulfide chain length for precision synthesis of new polysulfur-containing products.

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Conflicts of interest

There are no conflicts to declare.

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