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

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Experimental Section

General Considerations. Unless indicated otherwise, reactions were carried out under a nitrogen atmosphere using a Schlenk manifold or in oven-dried glassware in a MBraun glovebox under an atmosphere of purified nitrogen. Anhydrous diethyl ether, THF, toluene, hexanes, and CH_3CN were dried using the Grubbs method on a J.C. Meyer solvent system.[1] Benzene and C_6D_6 was dried over sodium/benzophenone ketyl, then vacuum transferred and stored over molecular sieves. $CDCl_3$ was purchased from Cambridge Isotope Laboratories, dried over CaH_2, and vacuum transferred. Celite was dried under vacuum at 300 °C for 3 days. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument or a Varian 600 MHz instrument (^1H, $\delta = 4.79$ ppm for D_2O. ^1H, $\delta = 7.27$ ppm and ^{13}C, $\delta = 77.16$ ppm for $CDCl_3$. ^1H, $\delta = 7.16$ ppm and ^{13}C, $\delta = 128.06$ ppm for C_6D_6). Spectra were obtained with using recycle delays of 10 seconds.

Electrospray ionization mass spectrometry (ESI-MS) and liquid chromatography-mass spectrometry (LC-MS) were performed at the University of Notre Dame Mass Spectrometry & Proteomics Facility on a Bruker microTOF-Q II instrument. Electronic absorption spectra were taken on an Agilent Cary 60 spectrophotometer in 1 cm quartz cuvettes.

Analytical LC-MS/MS data for the products of *L*-cysteine with elemental sulfur reaction were acquired using Bruker micrOTOF-Q II. Samples were injected onto a Waters ACQUITY UPLC HSS T3 Column, (100 Å pore size, 1.8 μm particle size, 2.1 mm X 150 mm (inner diameter x length)). The solvents used were 0.1 % formic acid in water (solvent A) and 0.1 % formic acid in acetonitrile (solvent B). The flow rate was 0.4 mL min^{-1}. The gradient used with solvent B is as follows: 0 % at 0 min, 0% at 2 min, 75 % at 13 min, 0 % at 13.1 min, 0 % at 15 min.

GC-MS analyses were performed on an Agilent 6890 GC paired with Agilent 5973 Network Mass Selective detector using helium as the carrier gas. A sample volume of 5 uL was injected at a temperature of 220 °C, with a 25:1 split ratio. The gas flow was held at 1.0 mL/min for the duration of the run. The initial oven temperature was held at 60 °C for 4 minutes with the detector off, followed by temperature ramp with the detector on, to 250 °C at 30 °C/min, before holding temperature at 250 °C for 5 min. The total run time was 25 min.

Unless otherwise indicated, all commercial chemicals were used without further purification. Sulfur (S_8) was purchased from Beantown Chemicals and was recrystallized from hot toluene. Methyl iodide (MeI) was purchased from Aldrich and used without further purification. 2-Aminothiophenol was purchased from Acros Organics and stored under nitrogen. 4-Aminothiophenol was purchased from Oakwood Chemical and distilled under vacuum and stored under nitrogen. 4-Methylthiophenol was purchased from Sigma-Aldrich and stored under nitrogen. Cysteamine hydrochloride was purchased from ChemImpex and used without further purification. *L*-cysteine was purchased from Nutritional Biochemical Corporation. 2-Hydroxyethanethiol and acetylthiocholine chloride were purchased from Sigma-Aldrich. Propanethiol was purchased from Oakwood Chemical.

Caution! H_2S is toxic and should be handled in a hood with adequate ventilation and quenched appropriately when used in large amounts.

Buffer Preparation: The pH 7.6 buffer solution (0.1 M) was prepared with sodium dihydrogen phosphate and disodium phosphate. The pH 10.1 buffer (0.1 M) was prepared with sodium bicarbonate and sodium carbonate. The pH 11.5 buffer solution (0.1 M) was prepared with disodium phosphate and sodium hydroxide. A Fisher Scientific Accumet Basic AB15 Plus pH electrode was used to measure the buffer solutions.

Synthesis of 2-Mercaptoethyl-N,N,N-trimethylammonium Chloride ([4^{SH}][Cl])[2]
A 100 mL round bottom flask equipped with a reflux condenser and a stir bar was charged with acetylthiocholine chloride (1.00 g, 5.06 mmol) and HCl (6 M, 10.0 mL). The solution was stirred and heated to 85 ºC for 1 h. The reaction mixture was dried under vacuum overnight to yield the product as a white solid that was used without further purification (0.73 g, 93%).

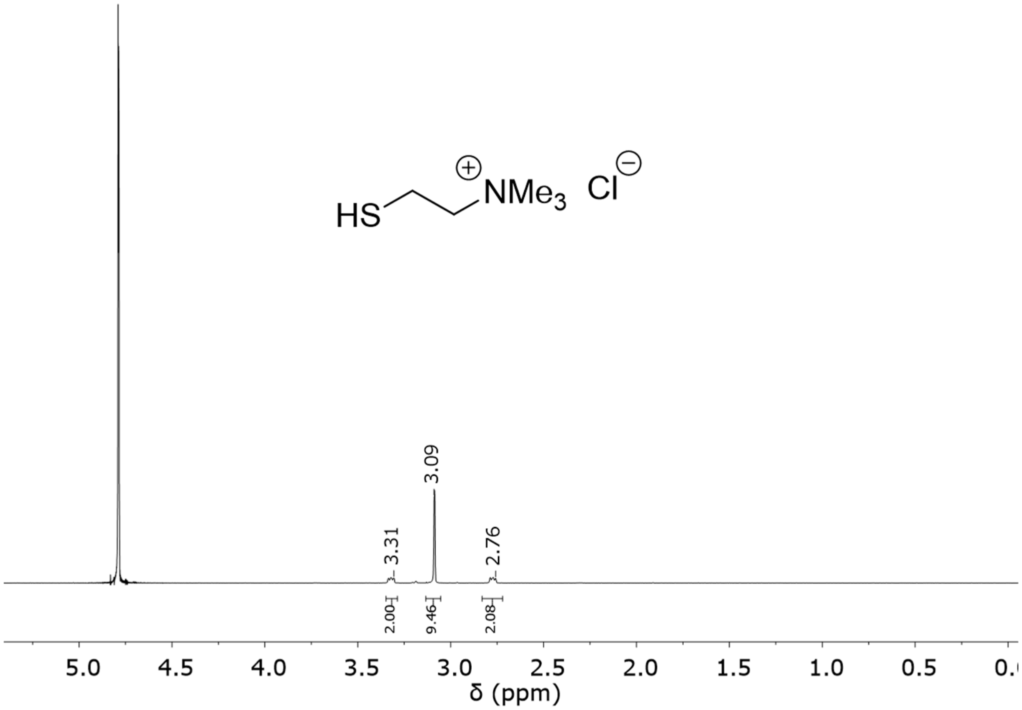


Figure S1. ^{1}H NMR spectrum of [**4^{SH}**][Cl] in D_2O at 25 °C.

Reaction of Cysteamine Hydrochloride (1^{SH}·HCl) with S_8 in Water. In a representative procedure, cysteamine hydrochloride (0.284 g, 2.5 mmol), NaOH (0.100 g, 2.5 mmol, 1 equiv), and S_8 (0.160 g, 5 mmol, 2 equiv) were combined in a scintillation vial equipped with a stir bar under ambient conditions. H_2O (10 mL) was added, and the reaction mixture turned deep yellow within 20 min. at room temperature, and the sulfur was observed to dissolve. For ^{1}H NMR experiments, **1^{SH}**·HCl (0.085 g, 0.75 mmol) was combined with NaOH (0.030 g, 0.75 mmol) and S_8 (0.024 g, 0.75 mmol S atom) in 0.7 mL D_2O.

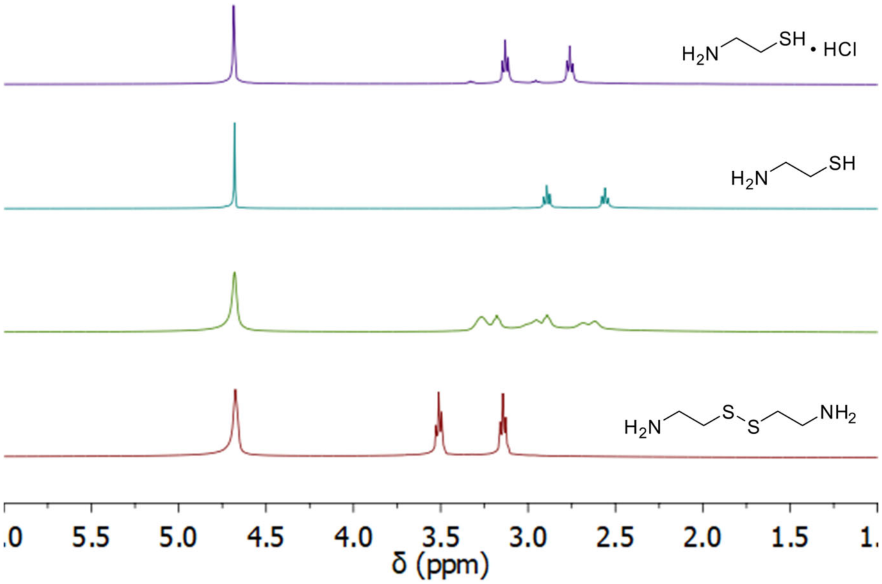


Figure S2. ^{1}H NMR spectra of D_2O solutions of $\mathbf{1}^{\mathbf{SH}}$·HCl (top), $\mathbf{1}^{\mathbf{SH}}$·HCl + NaOH (blue), $\mathbf{1}^{\mathbf{SH}}$·HCl + NaOH + S_8 (green), and $\mathbf{1}^{\mathbf{D}}$ (bottom) at 25 °C.

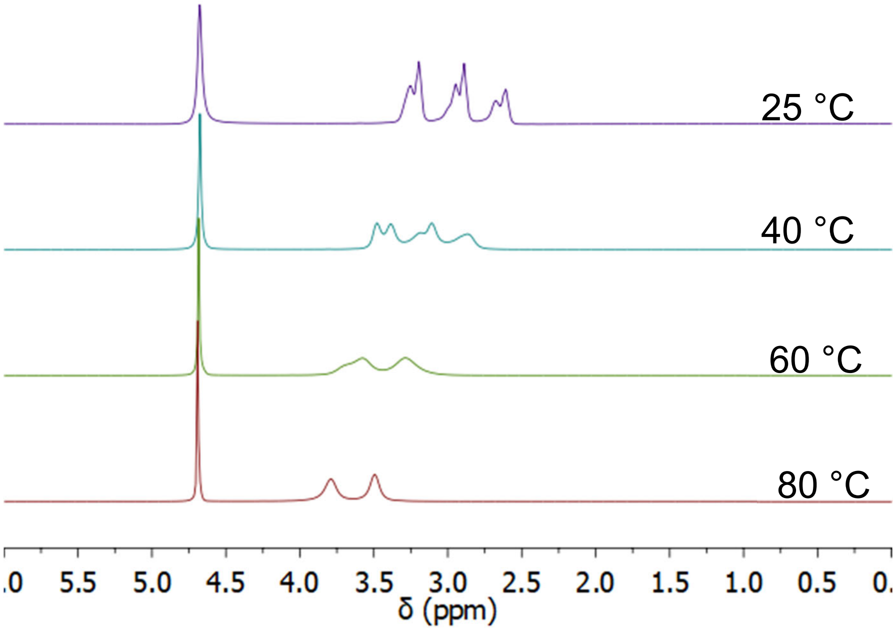


Figure S3. Variable temperature ^{1}H NMR spectra of a D_2O solution of $\mathbf{1}^{\mathbf{SH}}$·HCl + NaOH + S_8.

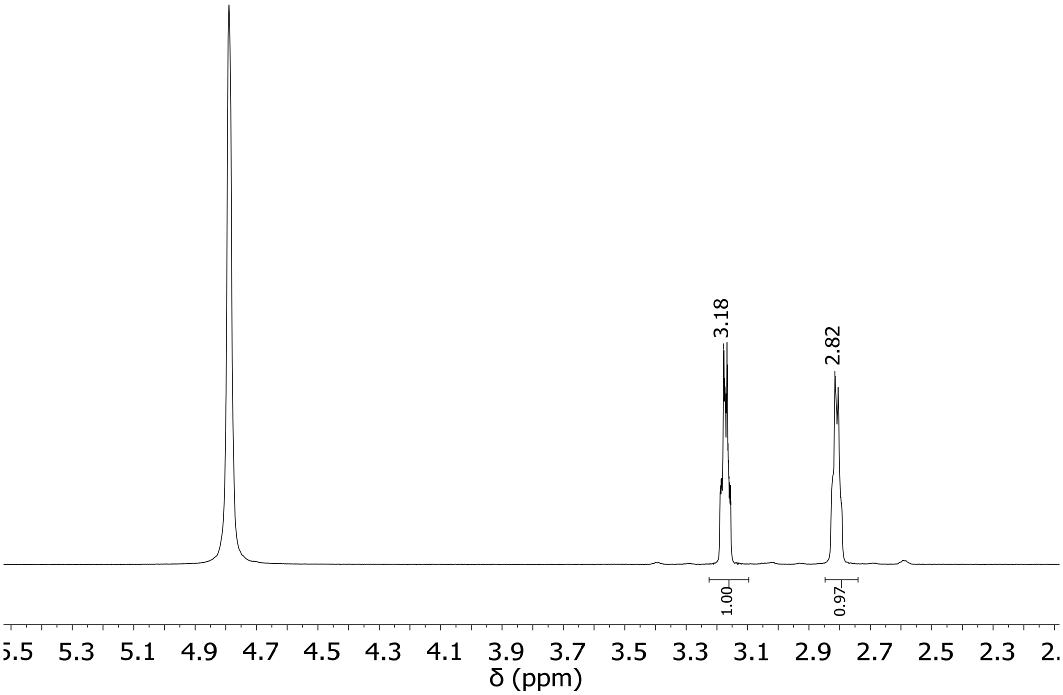


Figure S4. ^{1}H NMR spectrum of $\mathbf{1}^{\mathbf{SH}}$·HCl in buffered D_2O (pH 10) at 25 °C.

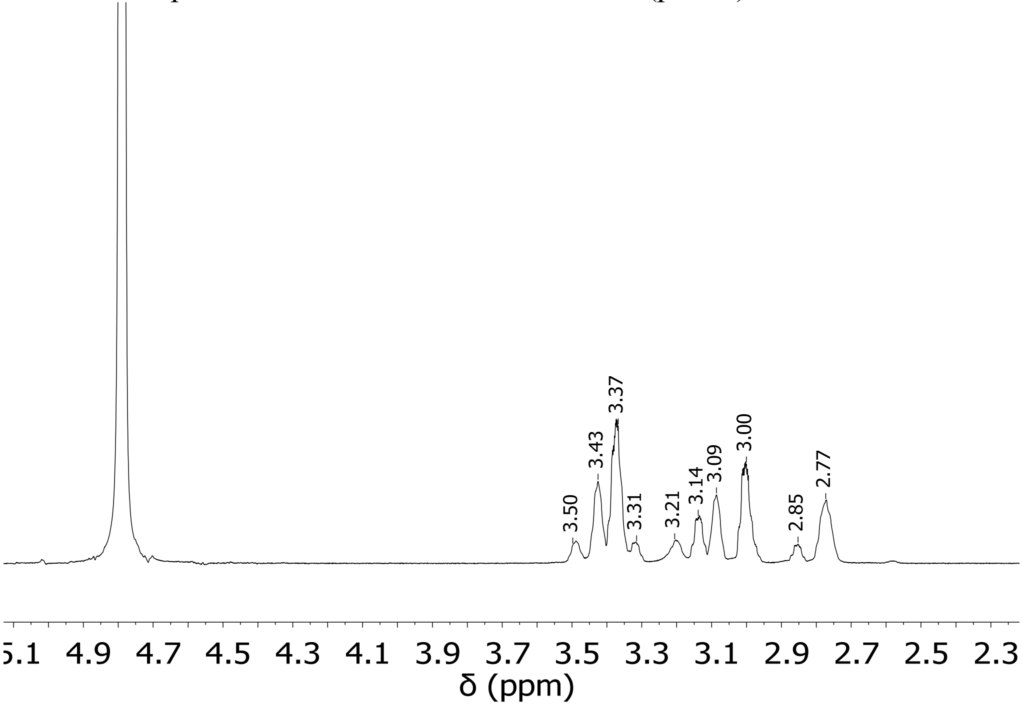


Figure S5. ^{1}H NMR spectrum of $\mathbf{1}^{\mathbf{SH}}$·HCl + S_8 in buffered D_2O (pH 10) at 25 °C.

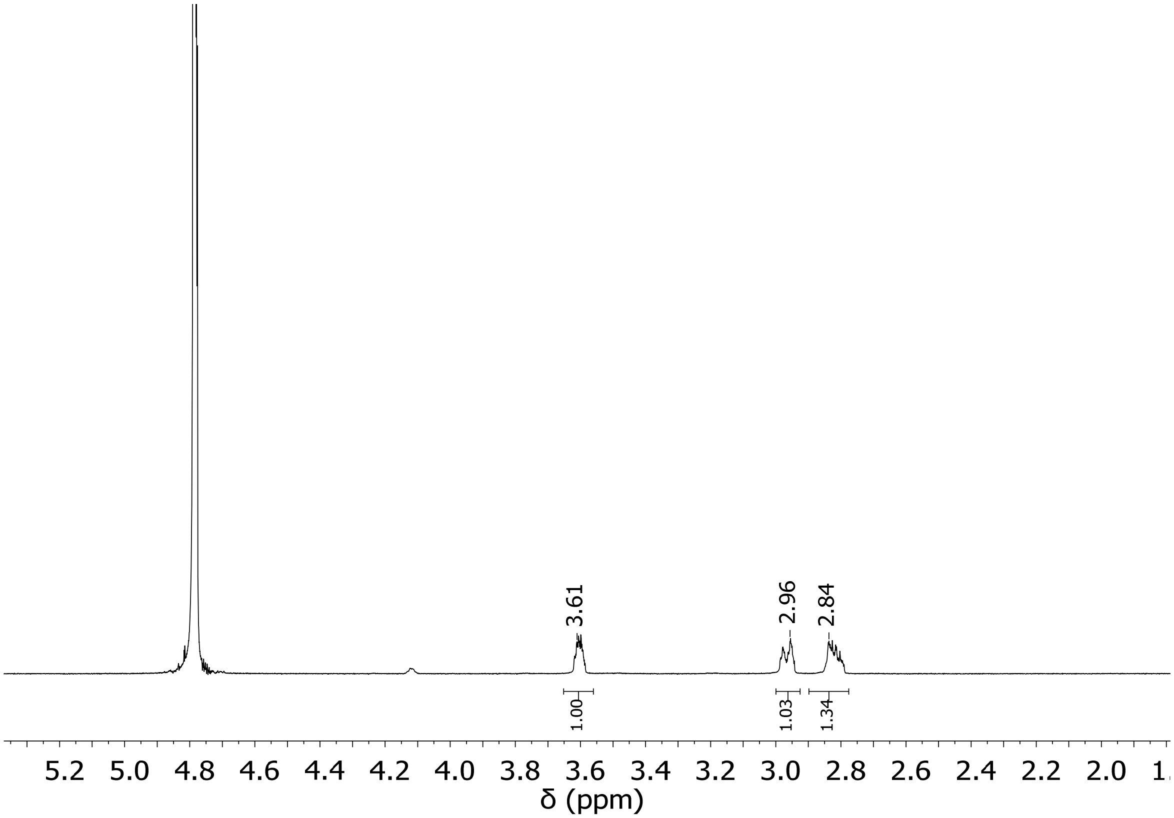


Figure S6. ^{1}H NMR spectrum of $\mathbf{2^{SH}}$ in buffered D_2O (pH 10) at 25 °C.

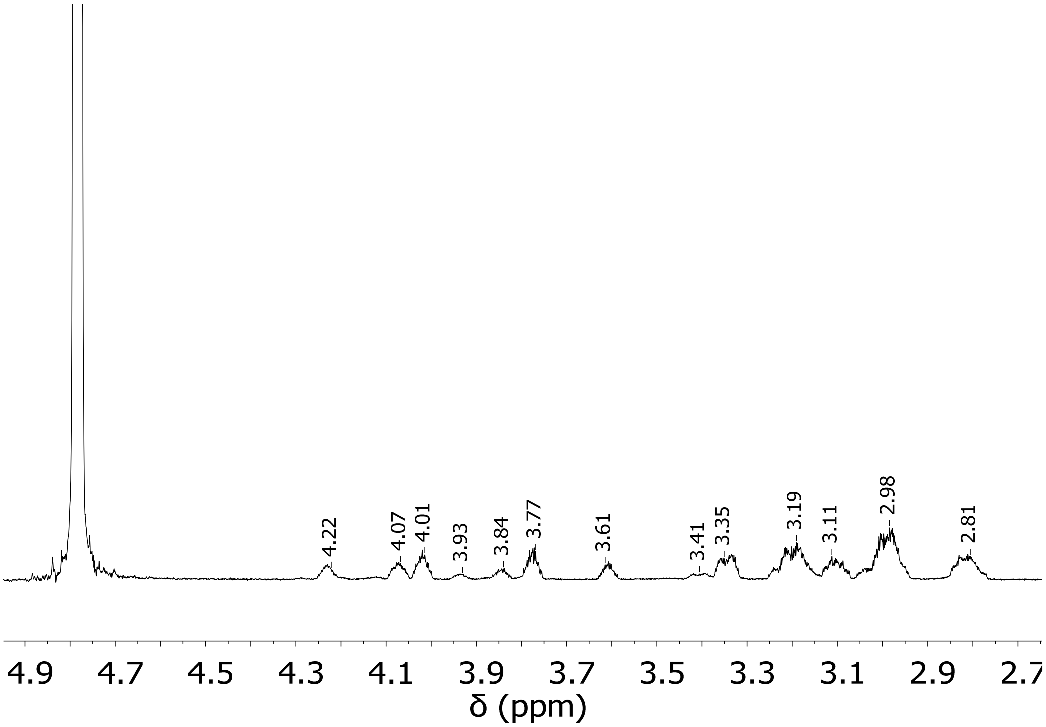


Figure S7. ^{1}H NMR spectrum of $\mathbf{2^{SH}}$ + S_8 in buffered D_2O (pH 10) at 25 °C.

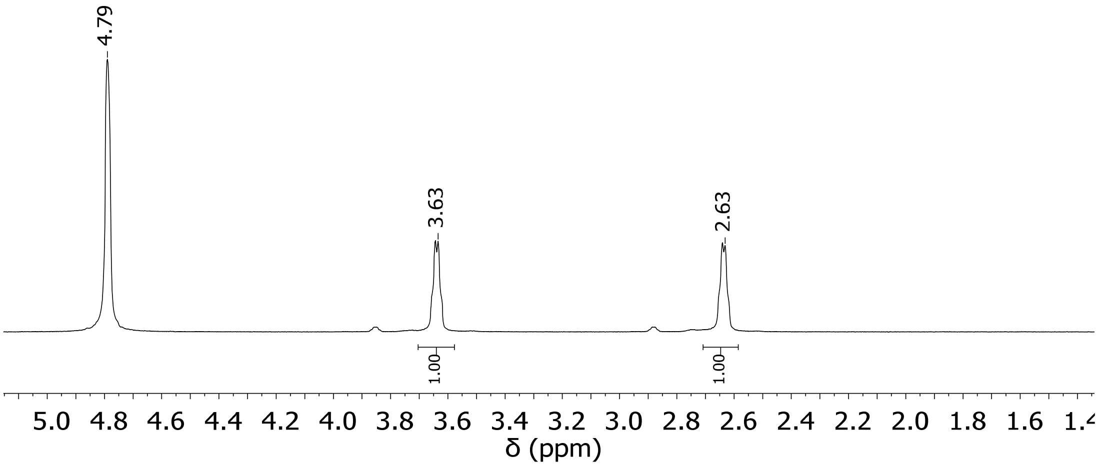


Figure S8. ^{1}H NMR spectrum of $\mathbf{3}^{\mathbf{SH}}$ in buffered D_2O (pH 10) at 25 °C.

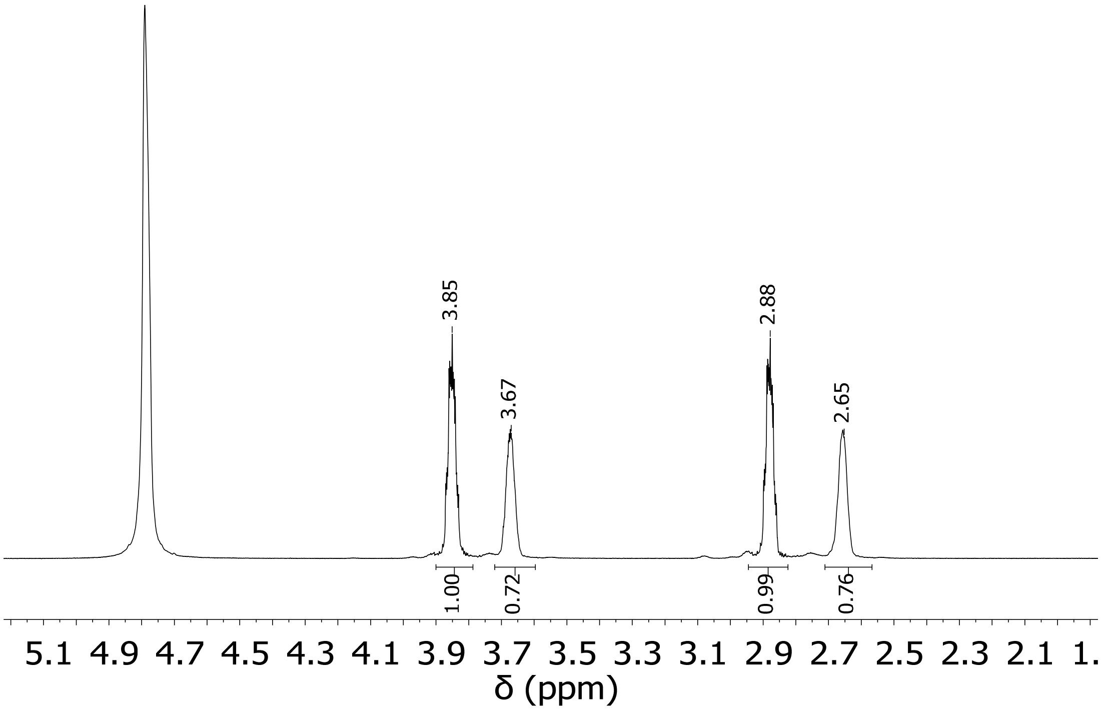


Figure S9. ^{1}H NMR spectrum of $\mathbf{3}^{\mathbf{SH}}$ + S_8 in buffered D_2O (pH 10) at 25 °C.

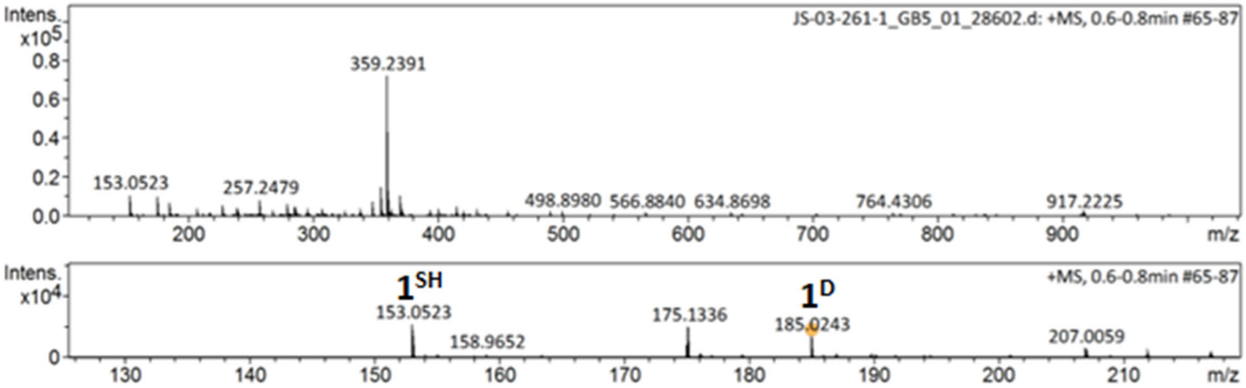


Figure S10. ESI-MS of $\mathbf{1^{SH}}$·HCl + NaOH + S_8 in H_2O.

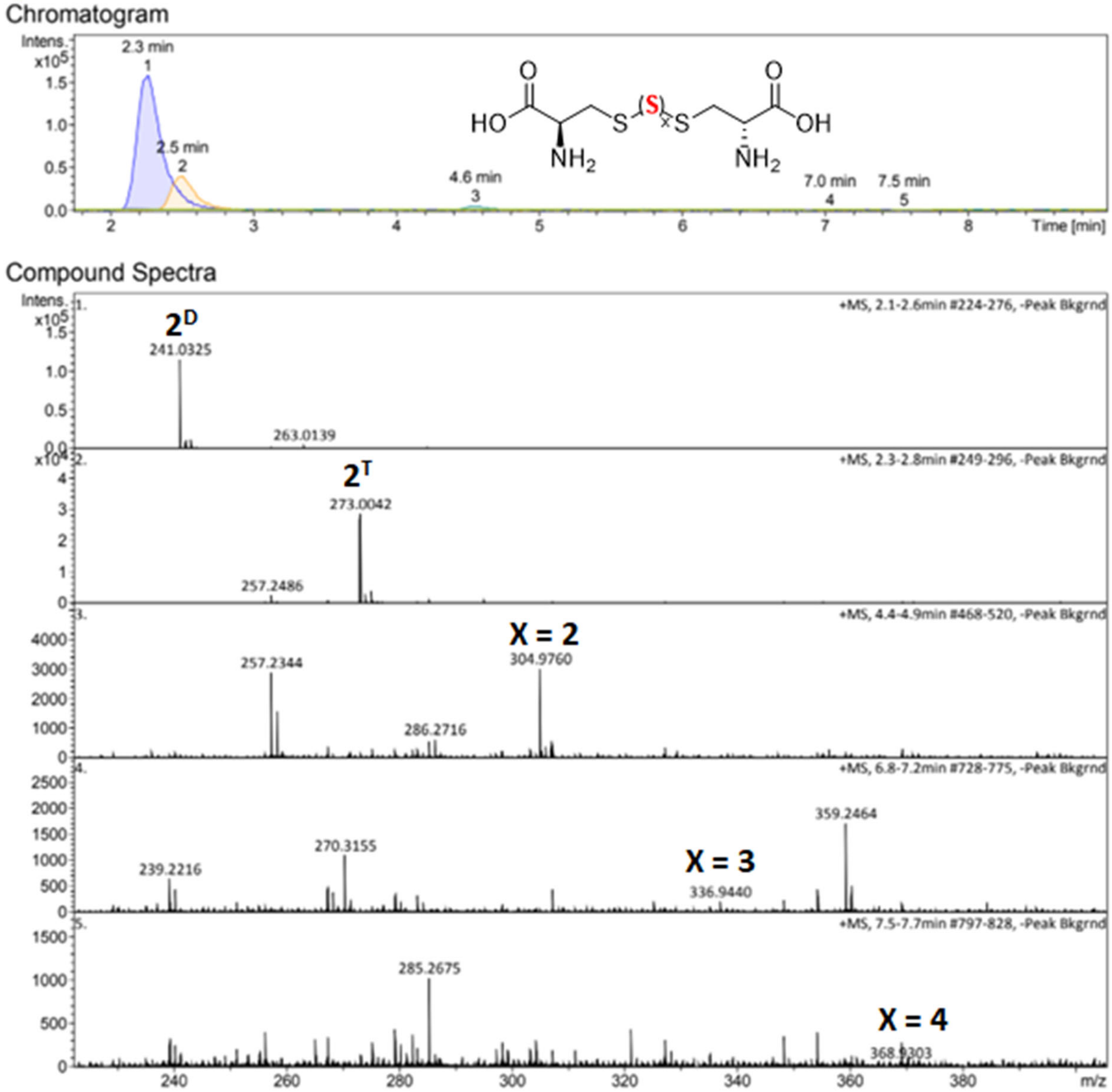


Figure S11. LC-MS chromatogram and MS of *L*-cysteine + S_8 + NaOH in H_2O.

Absorption Spectroscopy Experiments. A 1-cm sealable quartz cuvette equipped with a stir bar was charged with a degassed solution of **1**$^{\mathbf{SH}}$·HCl, **2**$^{\mathbf{SH}}$, or **3**$^{\mathbf{SH}}$ (350 µM, 4.0 mL, buffered at pH 7.6, 10.1, or 11.5). The cuvette was again degassed and refilled with N_2. S_8 (0.005 g, 0.16 mmol) was added under dynamic N_2 flow. Absorption spectra were then taken at different intervals using an Agilent Cary 60 spectrophotometer equipped with a magnetic stirrer.

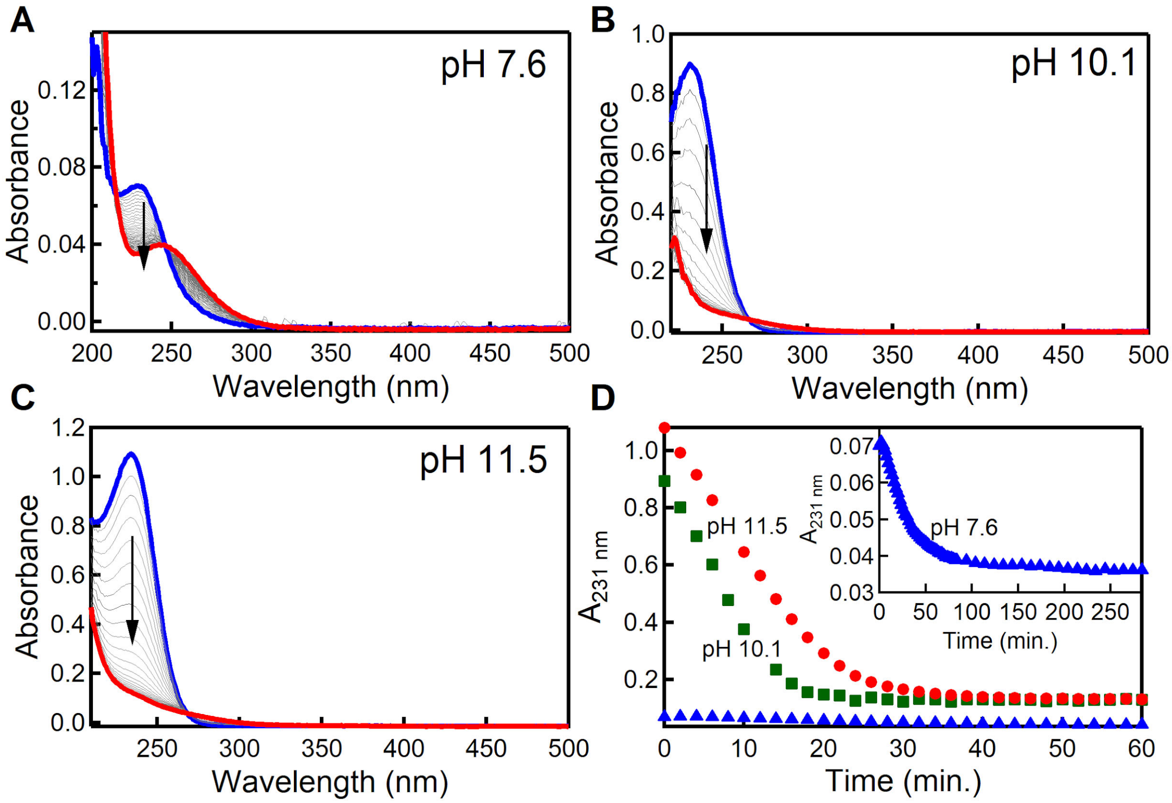


Figure S12. (A-C) Electronic absorption spectra of buffered solutions of **1**$^{\mathbf{SH}}$·HCl (350 µM, blue) with added S_8 over time. (D) Absorbance at 231 nm over time at different pH.

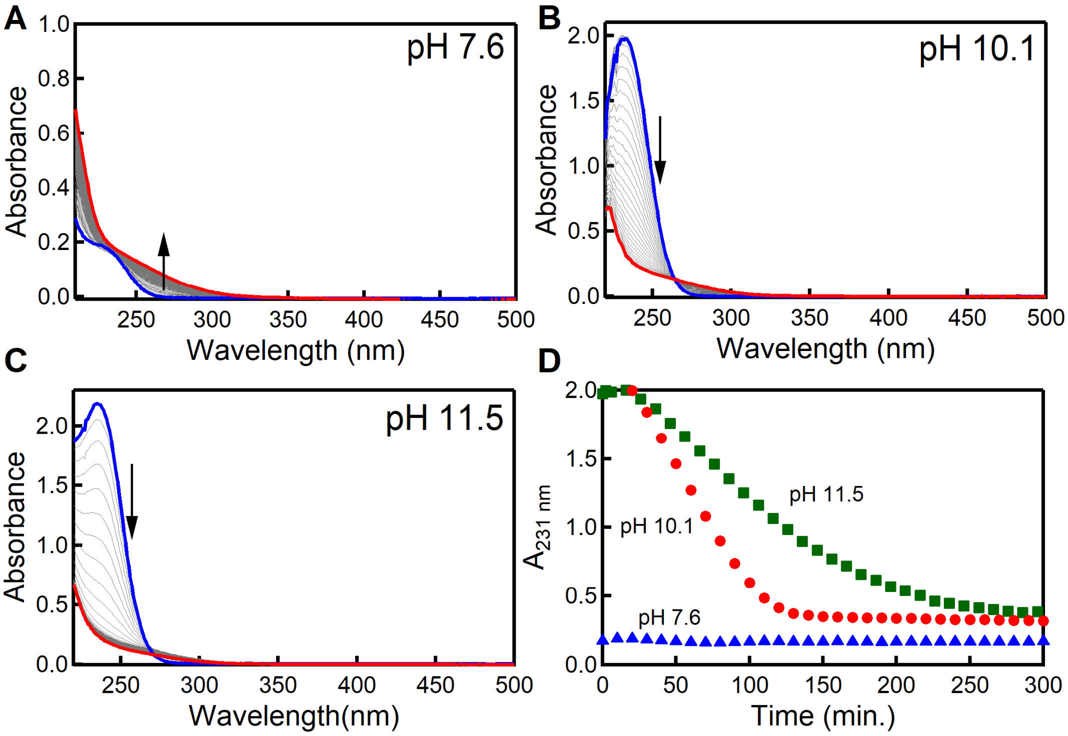


Figure S13. (A-C) Electronic absorption spectra of buffered solutions of $\mathbf{2^{SH}}$ (350 µM, blue) with added S_8 over time. (D) Absorbance at 231 nm over time at different pH.

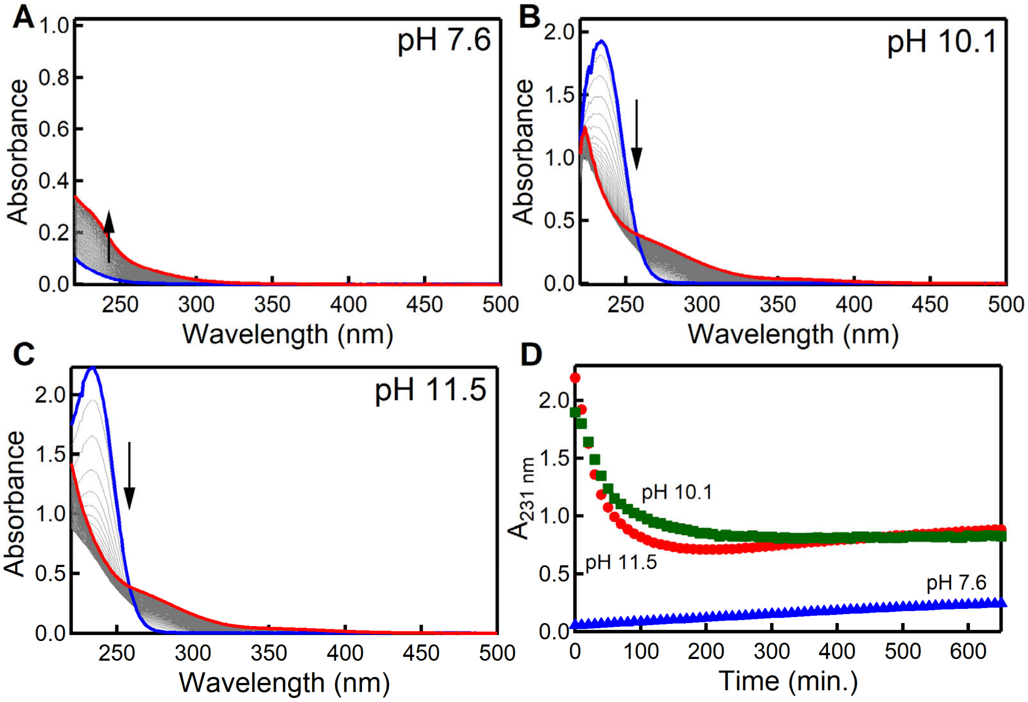


Figure S14. (A-C) Electronic absorption spectra of buffered solutions of $\mathbf{3^{SH}}$ (350 µM, blue) with added S_8 over time. (D) Absorbance at 231 nm over time at different pH.

Preparation of Aqueous Samples for Absorption Spectroscopy. A Schlenk flask equipped with a stir bar was charged with a degassed solution of **1**$^{\mathbf{SH}}$·HCl, **2**$^{\mathbf{SH}}$, **3**$^{\mathbf{SH}}$, or [**4**$^{\mathbf{SH}}$][Cl] (10.0 mL, 0.040 M, pH 10.1) and S_8 (0.050 g, 1.6 mmol, 4 S atom equiv). The reaction mixture was stirred under nitrogen at room temperature until complete. To measure the absorption spectrum, an aliquot of this solution (0.035 mL) was transferred by syringe to a sealable cuvette filled with degassed buffer solution (pH 10, 4.0 mL) under N_2, then quickly measured in an Agilent Cary 60 spectrophotometer to minimize polysulfide hydrolysis.

Calculations for Polysulfide Anion Concentration. The concentration of polysulfide anions was determined by the absorption spectrum of polysulfide anions (Fig. 2D) and previously reported molar absorption coefficient of polysulfide anions (S_5^{2-}, ε = 4700 L mol^{-1} cm^{-1} at 293 nm).[3] In a representative calculation, the $A_{293\ \mathrm{nm}} = 0.75$ for the polysulfide product from reacting **1**$^{\mathbf{SH}}$ with S_8 (Fig. 2D) corresponds to an [S_5^{2-}] ~ 0.16 mM. We note that aqueous polysulfide ions exist in a distribution of S_x^{2-} species that exchange rapidly and that these values are only estimates.

Thiophenol Methylation Competition Experiment: In a representative experiment, an oven-dried screw-cap NMR tube was charged with 2-aminothiophenol (25 µL, 0.24 mmol, 1 equiv), 4-aminothiophenol (30 mg, 0.24 mmol, 1 equiv), triethylamine (66 µL 0.48 mmol, 2 equiv), and 0.7 mL of C_6D_6 in the glovebox. The NMR tube was then sealed with a septum-lined screw cap and taken out of the glovebox. Iodomethane (32 µL, 0.42 mmol, 1.75 equiv) was injected via syringe into the NMR tube, and the tube was inverted several times to mix. The reaction mixture was then filtered through Celite to remove triethylammonium iodide and measured by ^{1}H NMR spectroscopy.

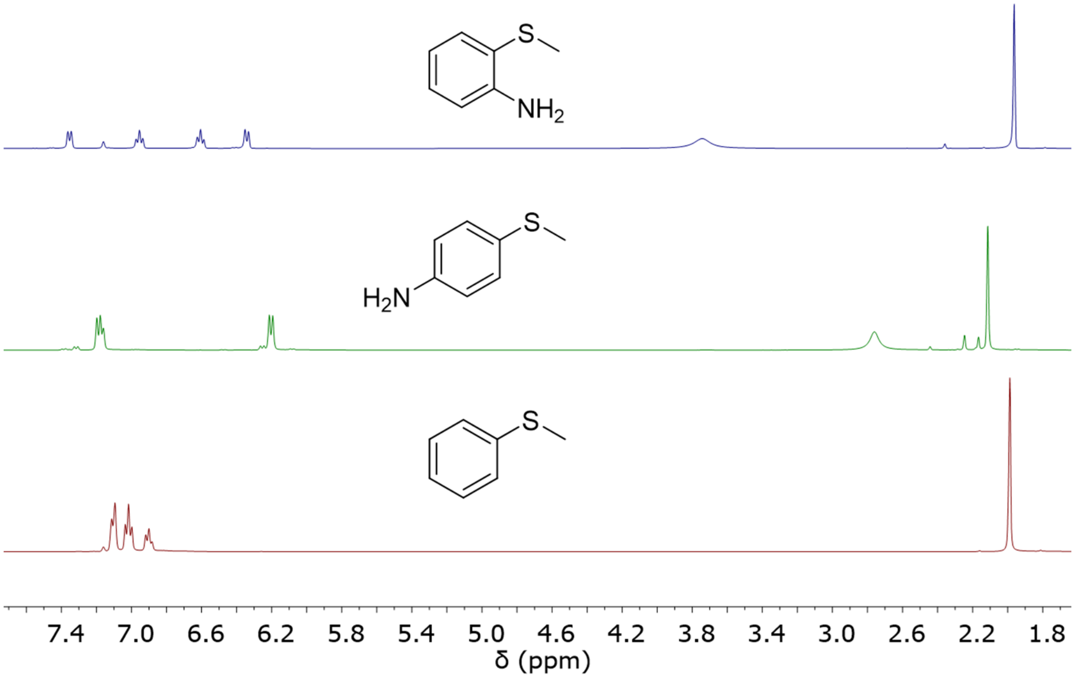


Figure S15. ^{1}H NMR spectrum 2-(methylthio)aniline (top), 4-(methylthio)aniline (middle), and thioanisole (bottom) in C_6D_6 at 25 °C.

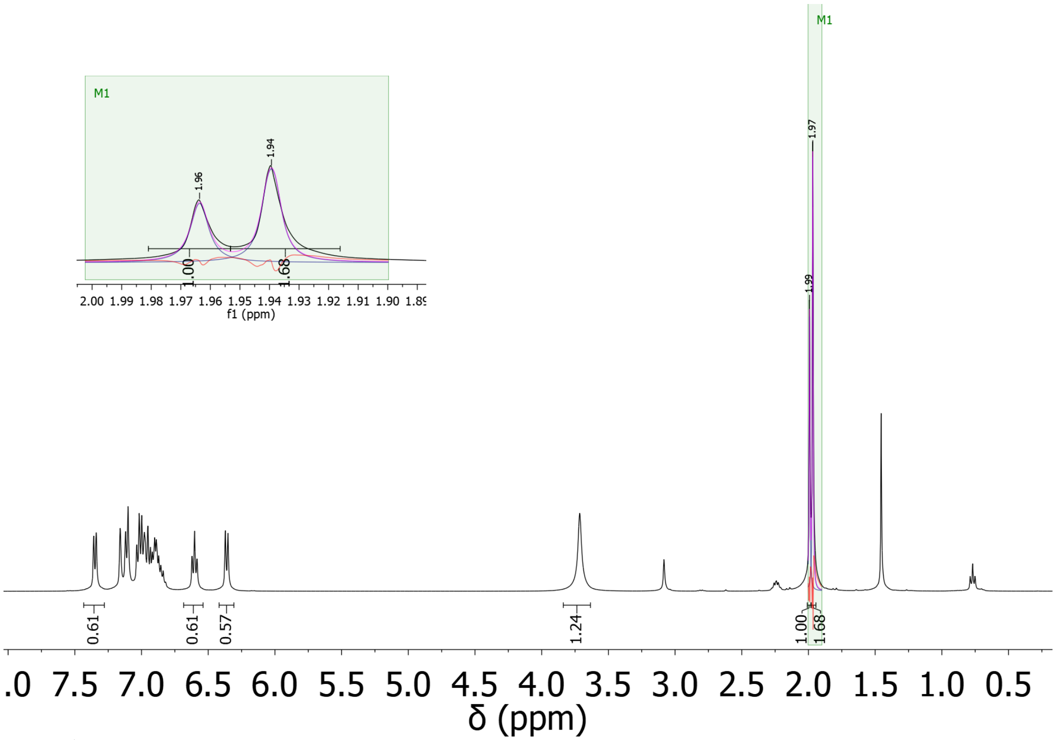


Figure S16. ^{1}H NMR spectrum of C_6D_6 solution of $\mathbf{5^{SH}}$ and thiophenol methylation competition experiment.

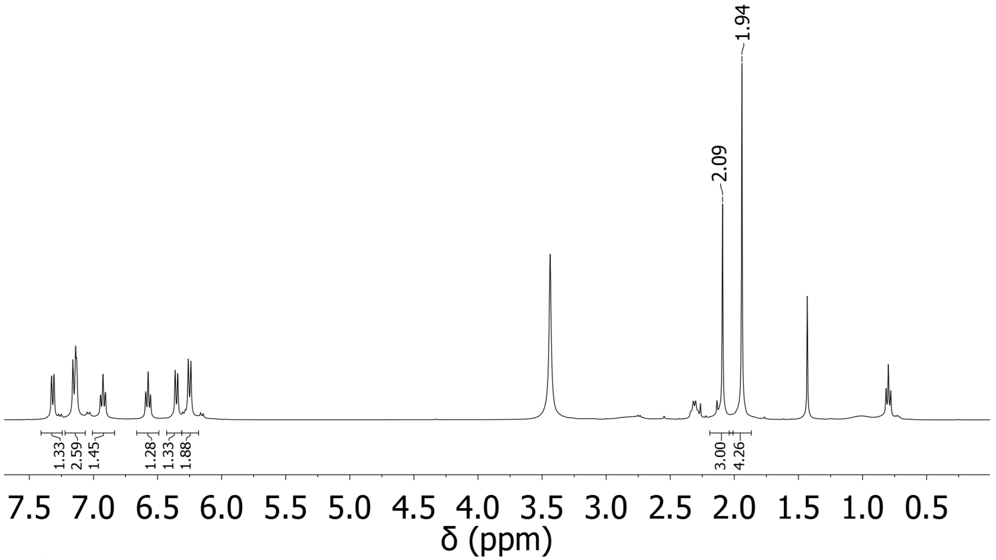


Figure S17. ^{1}H NMR spectrum of C_6D_6 solution of $\mathbf{5^{SH}}$ and $\mathbf{7^{SH}}$ methylation competition experiment.

Reaction of Thiophenols with Sulfur. In the glovebox, an oven-dried J. Young NMR tube was charged with the corresponding thiophenol (**5**$^{\mathbf{SH}}$, **6**$^{\mathbf{SH}}$, **7**$^{\mathrm{SH}}$ or **8**$^{\mathbf{SH}}$, 0.48 mmol, 1 equiv) and C_6D_6 (0.7 mL). S_8 (0.029 g or 0.057 g, 0.96 mmol or 1.9 mmol, 2 or 4 S atom equiv) was added as a solid, and 1,3,5-trimethoxybenzene (0.005 g, 0.030 mol) was added as an internal standard. In some cases, catalytic butylamine (1 µL, 0.012 mmol, 0.025 equiv) or octylamine (47 µL, 0.29 mmol, 0.60 equiv) was added via syringe. The NMR tube was sealed, and the heterogeneous suspension was mixed at room temperature in the dark by inverting the tube by hand or using a motor. The reaction progress was monitored by ^{1}H NMR spectroscopy over time.

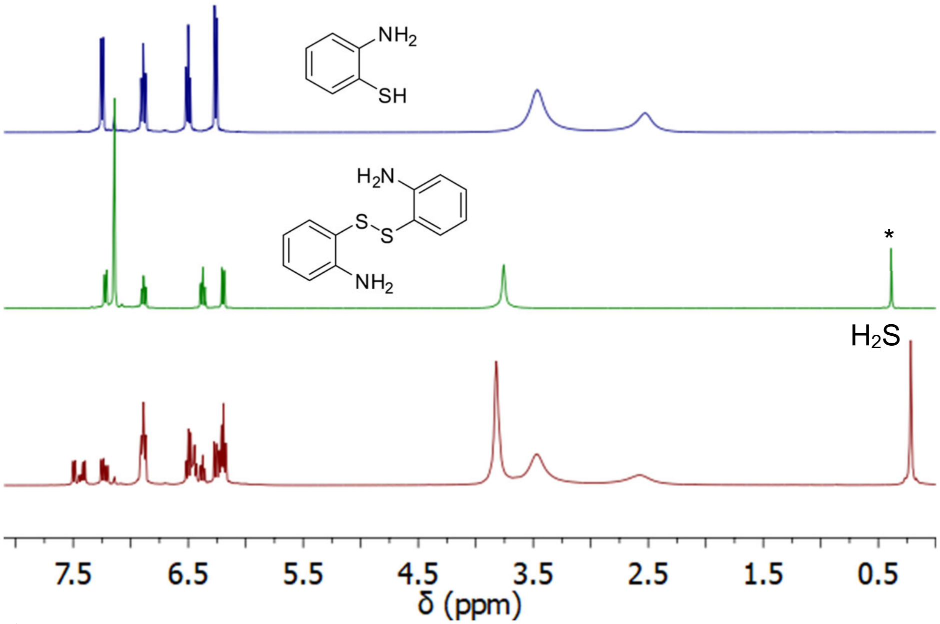
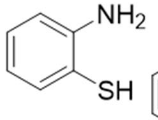
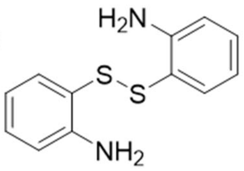


Figure S18. ^{1}H NMR spectra of C_6D_6 solutions of **5**$^{\mathbf{SH}}$, **5**$^{\mathbf{D}}$, and **5**$^{\mathbf{SH}}$ + S_8 at 25 °C. Water (*) is also present.



5$^{\mathbf{SH}}$



5$^{\mathbf{D}}$

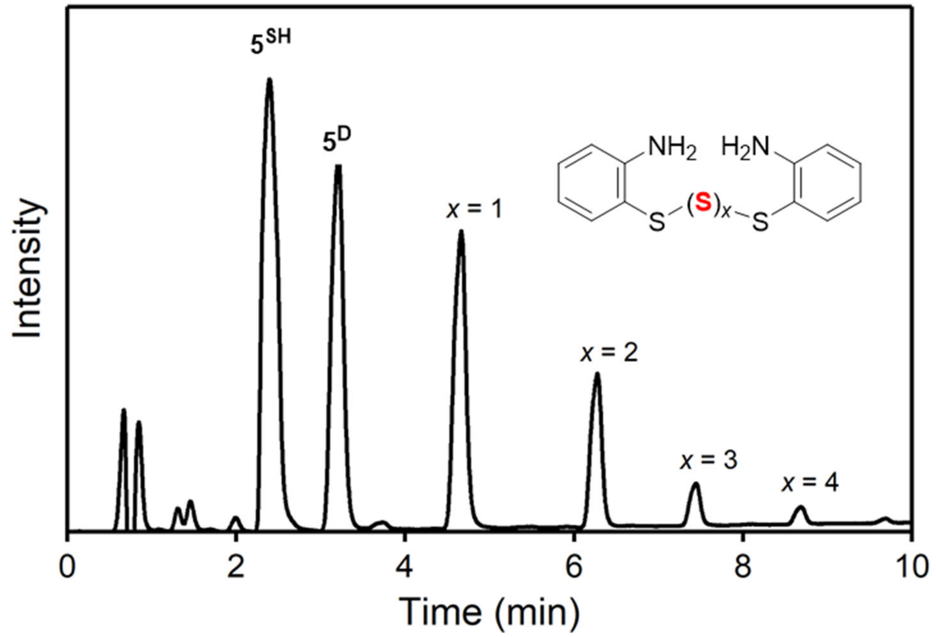


Figure S19. LC-MS chromatogram of **5**$^{\mathbf{SH}}$ + S_8.

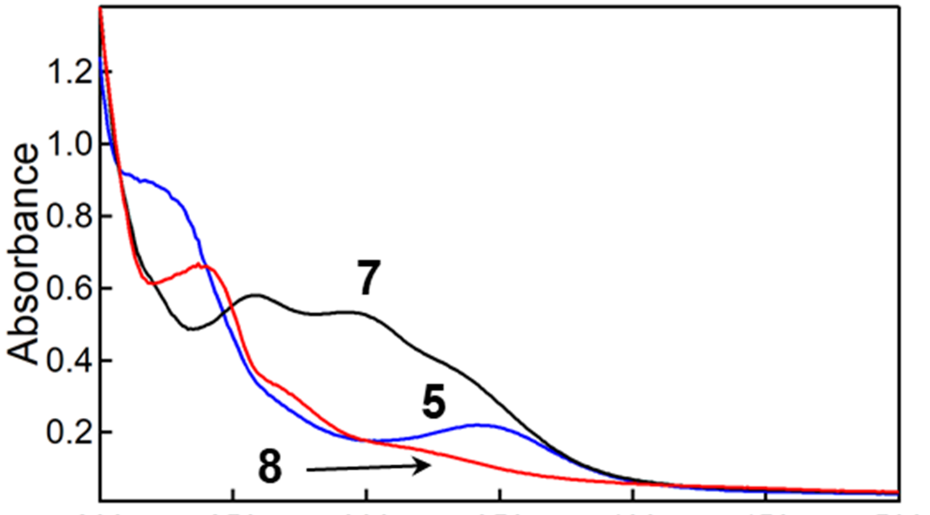


Figure S20. Electronic absorption spectra of products from the addition 2 S atom equivalents to thiophenol (**5**$^{\mathbf{SH}}$, **7**$^{\mathbf{SH}}$, or **8**$^{\mathbf{SH}}$ with catalytic butylamine).

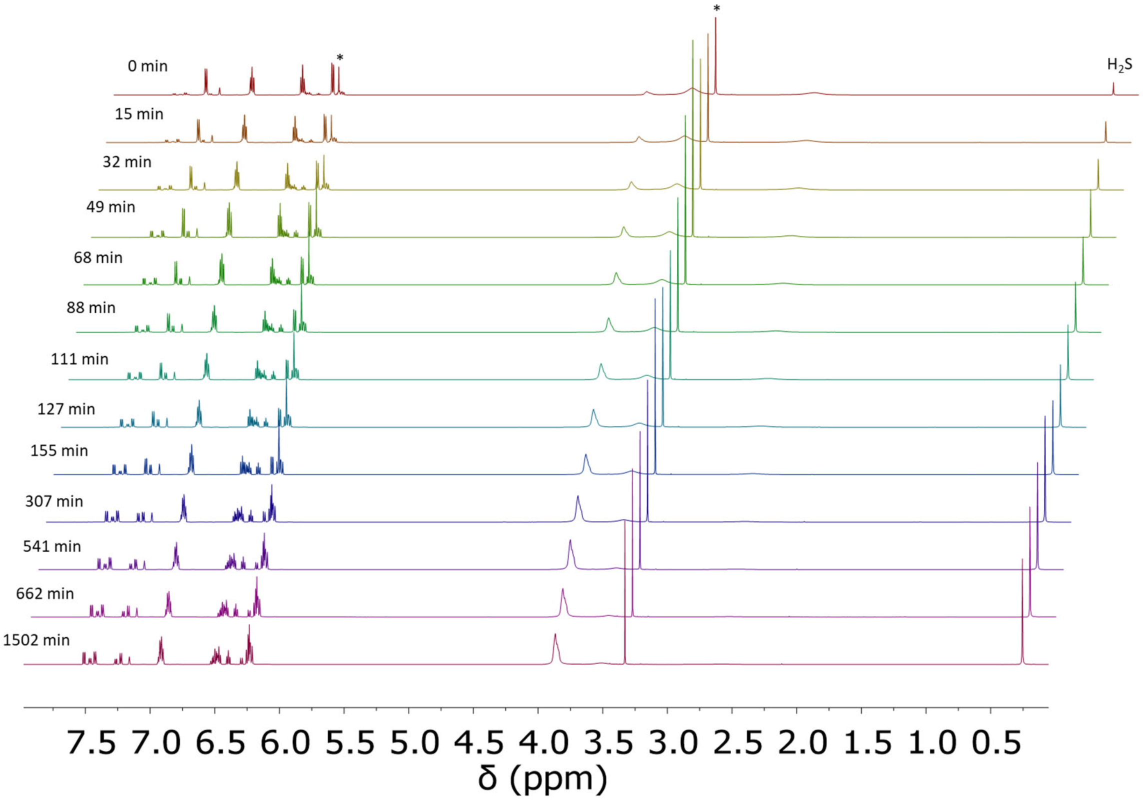


Figure S21. ^{1}H NMR spectra of $\mathbf{5^{SH}}$ + 2 S in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

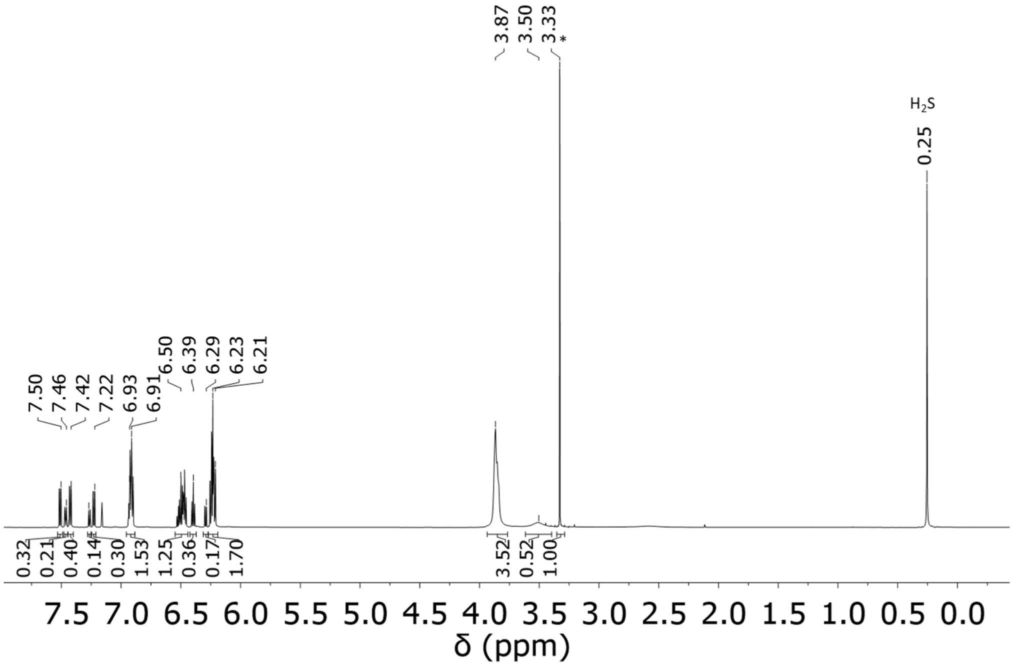


Figure S22. ^{1}H NMR spectrum of $\mathbf{5^{SH}}$ + 2S at 1502 min in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

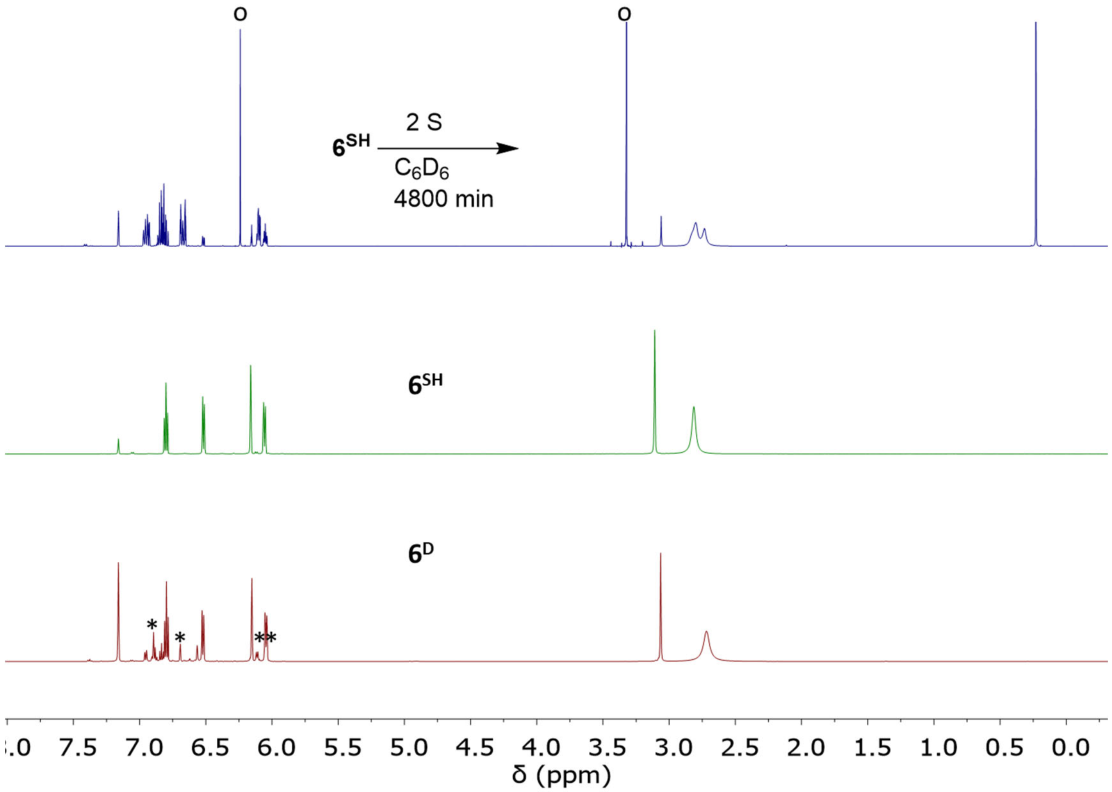


Figure S23. ^{1}H NMR spectra of 6^{SH} + 2S at 4800 min (top), 6^{SH} (middle), and 6^{D} (*) bottom) in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (o) is also present.

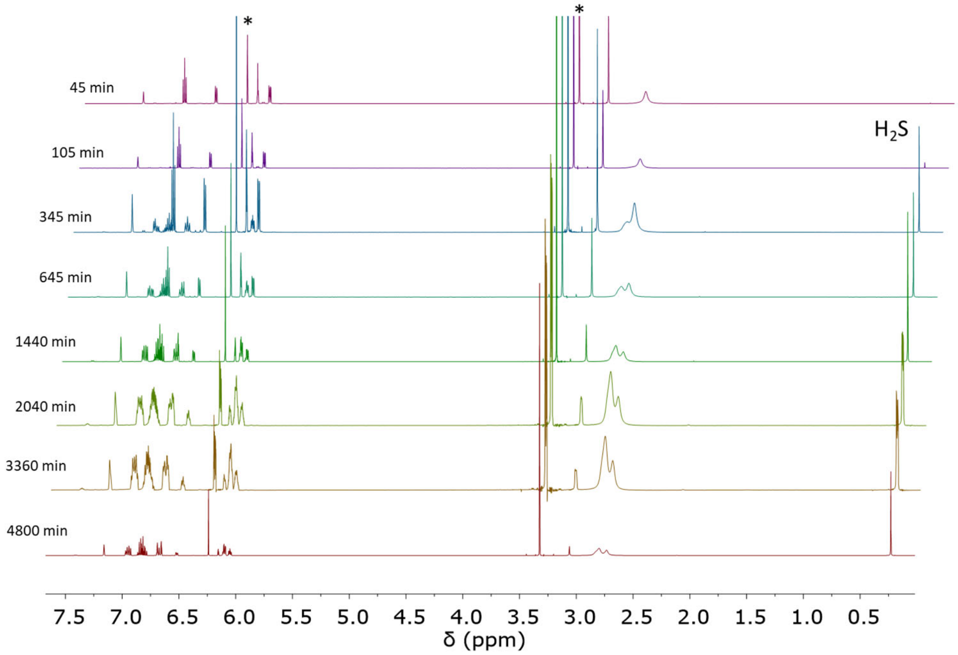


Figure S24. ^{1}H NMR spectra of 6^{SH} + 2S in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

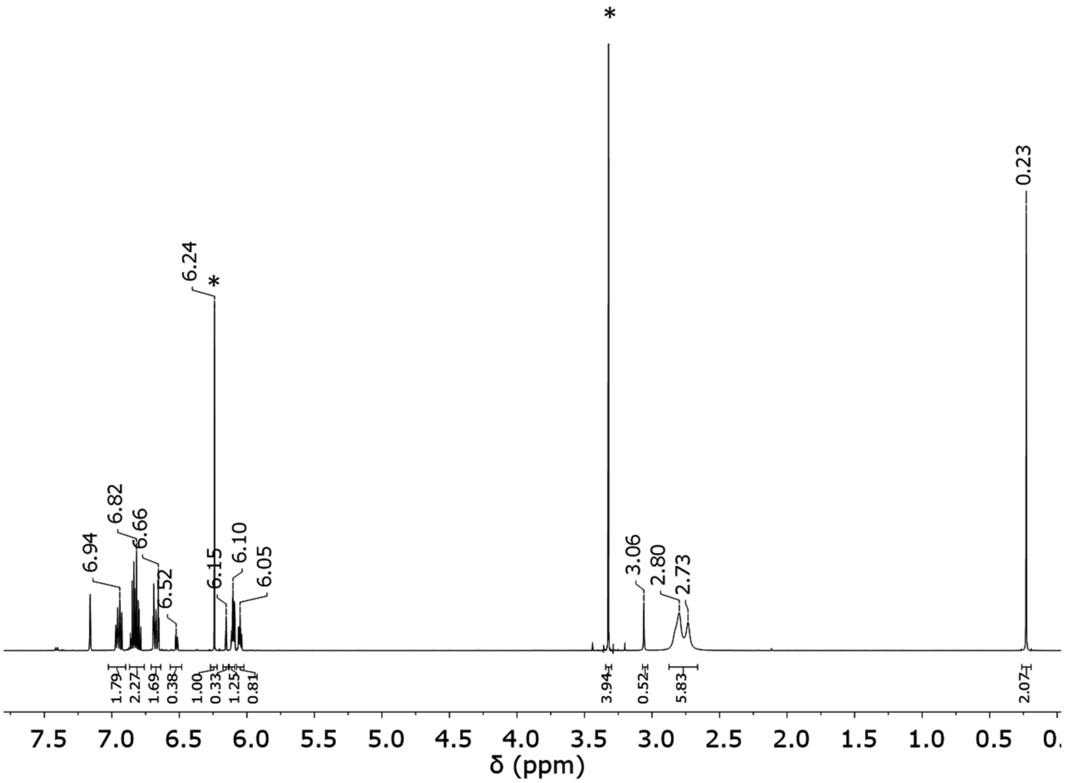


Figure S25. ^{1}H NMR spectrum of $\mathbf{6^{SH}}$ + 2S at 4800 min in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

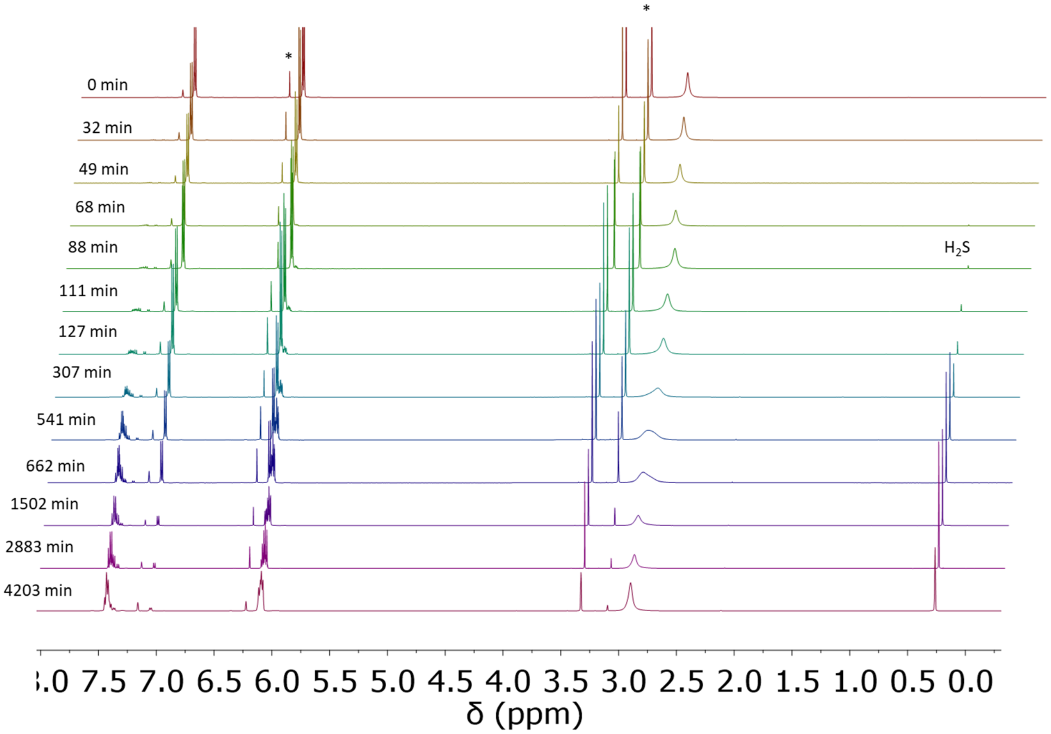


Figure S26. ^{1}H NMR spectra of $\mathbf{7^{SH}}$ + 2S in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

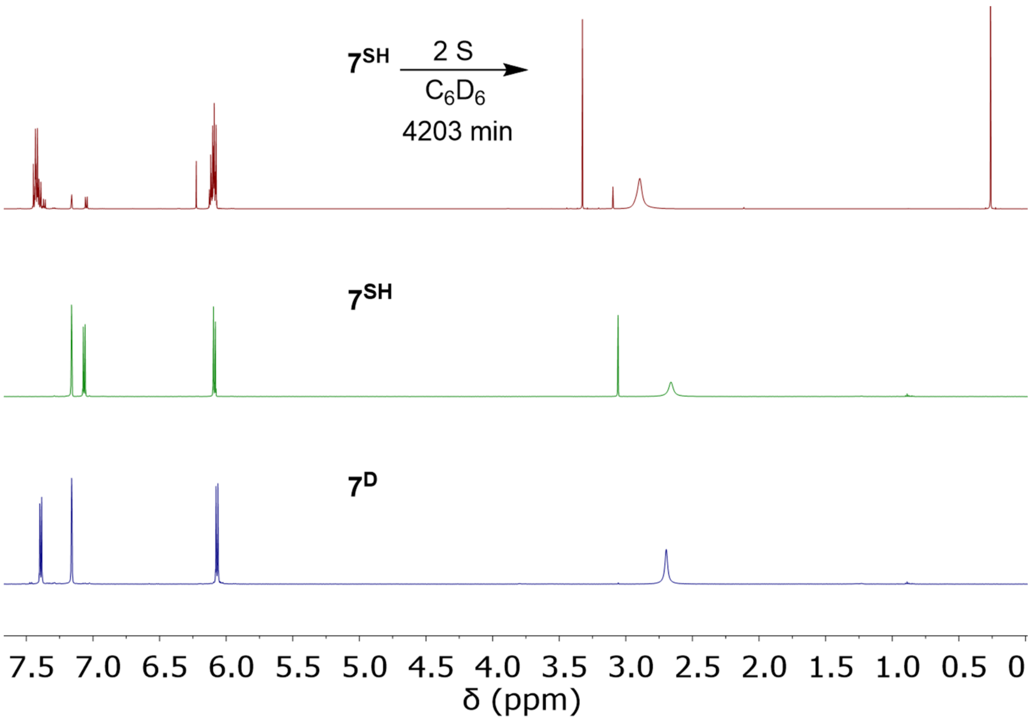


Figure S27. ^{1}H NMR spectra of $\mathbf{7^{SH}}$ + 2S at 4203 min (top), $\mathbf{7^{SH}}$ (middle), and $\mathbf{7^{D}}$ (bottom) in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

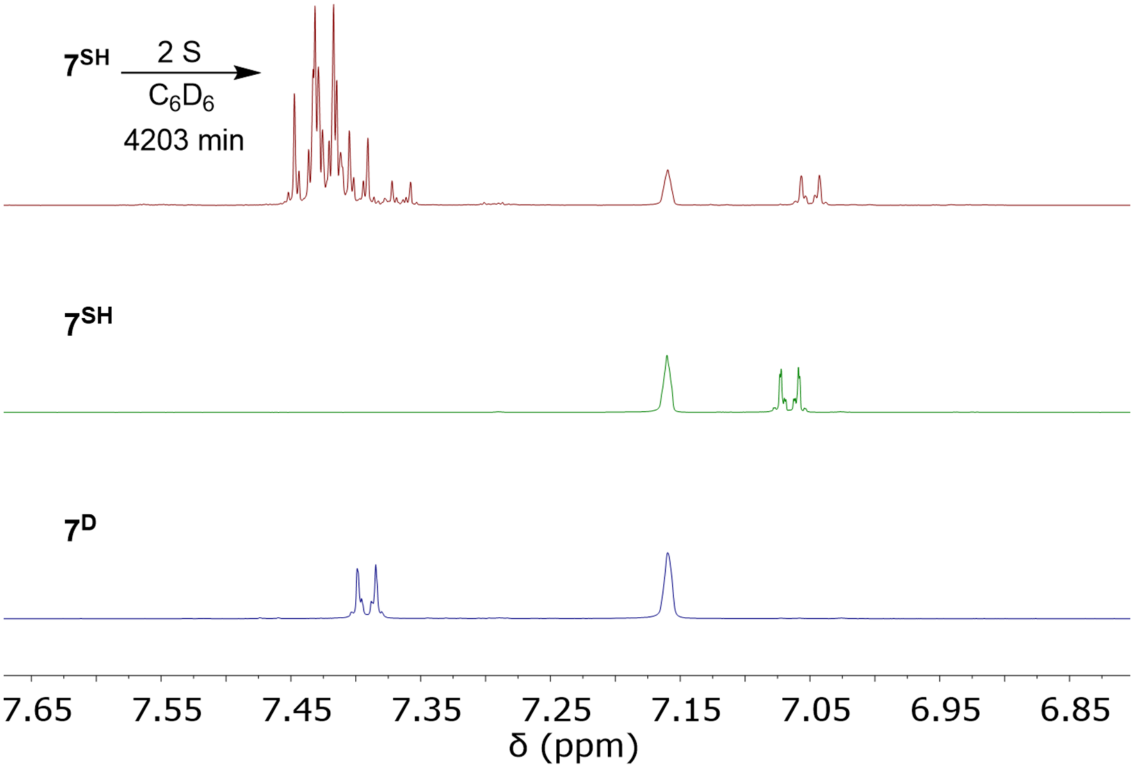


Figure S28. Truncated ^{1}H NMR spectra of $\mathbf{7^{SH}}$ + 2S at 1502 min (top), $\mathbf{7^{SH}}$ (middle) and $\mathbf{7^{D}}$ (bottom) in C_6D_6 at 25 °C.

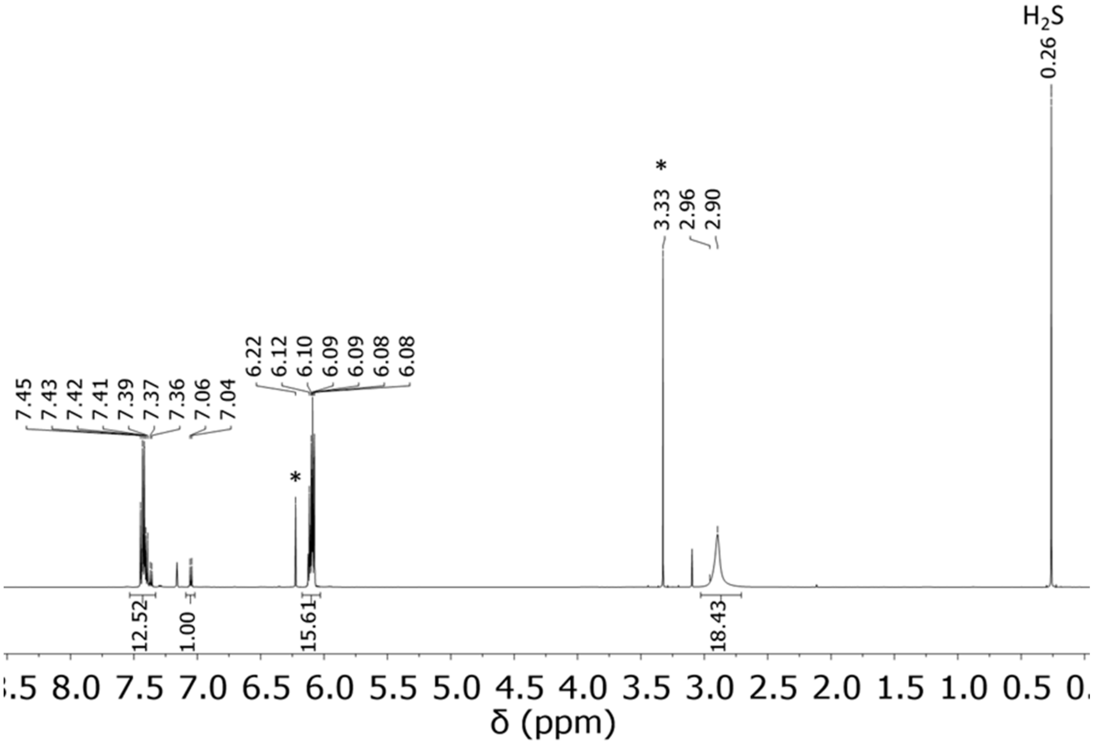


Figure S29. ^{1}H NMR spectrum of $\mathbf{7^{SH}}$ + 2S at 1502 min in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

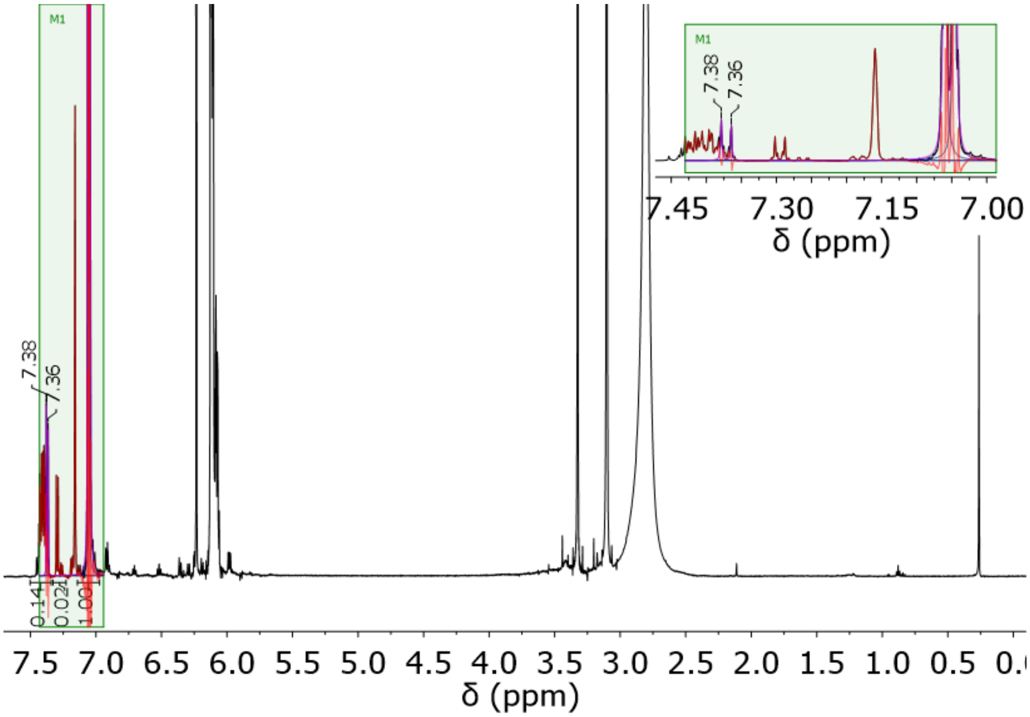


Figure S30. ^{1}H NMR spectrum of $\mathbf{7^{SH}}$ + 2S after 49 min showing fitted $\mathbf{5^{D}}$ (7.38 ppm) and $\mathbf{5^{SH}}$ (7.06 ppm) with MestreNova.

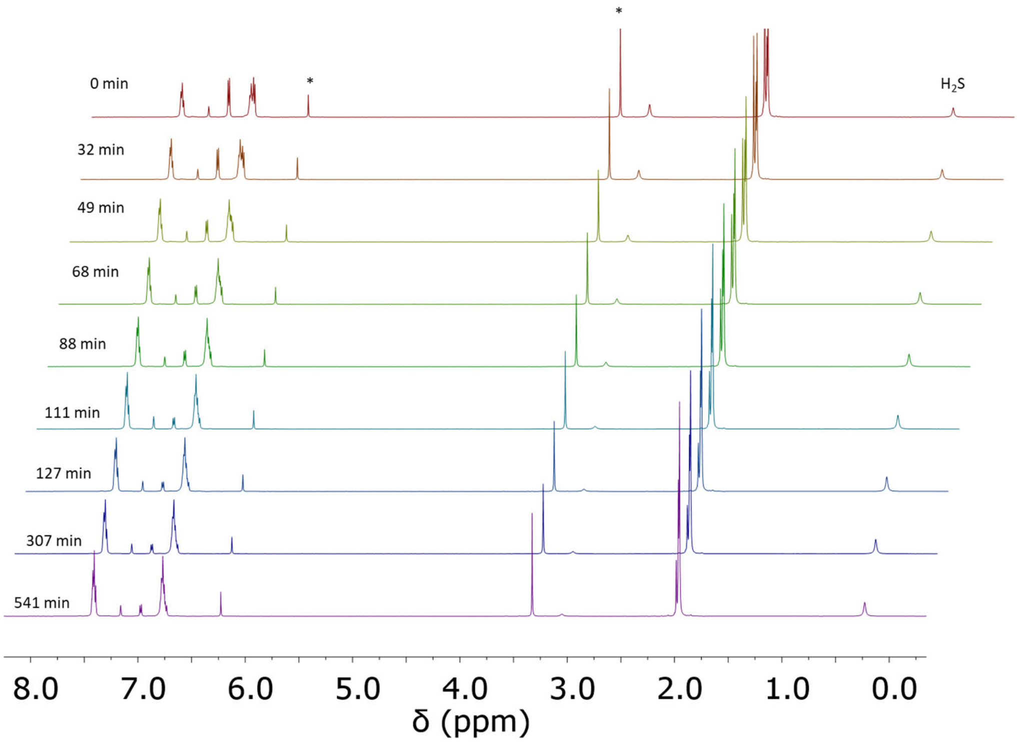


Figure S31. ^{1}H NMR spectra of **8^{SH}** + 2S with 2.5 mol % butylamine monitored over time in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

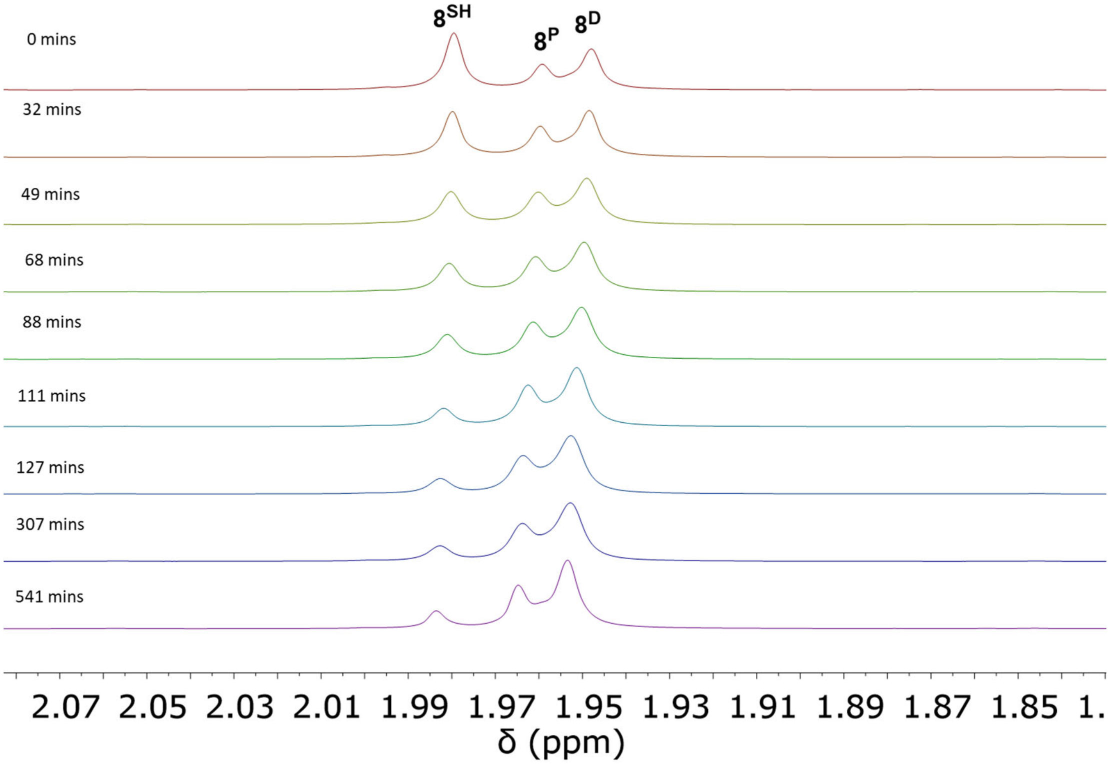


Figure S32. Truncated ^{1}H NMR spectra of **8^{SH}** + 2S with 2.5 mol % butylamine monitored over time in C_6D_6 at 25 °C.

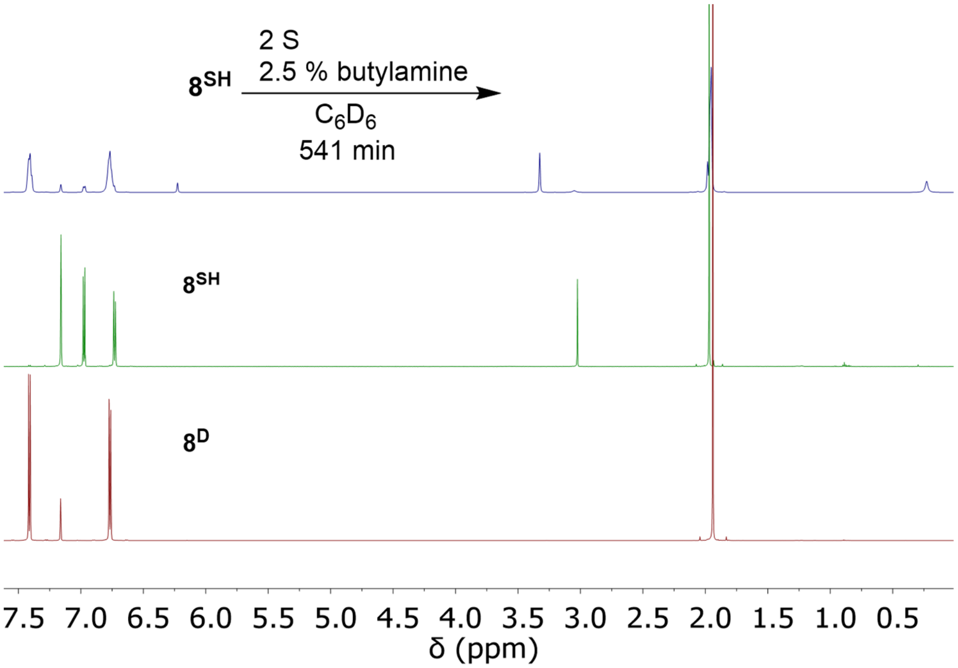


Figure S33. ^{1}H NMR spectra of $\mathbf{8^{SH}}$ + 2S with 2.5 % butylamine at 541 min (top), $\mathbf{8^{SH}}$ (middle) and $\mathbf{8^D}$ (bottom) in C_6D_6 at 25 °C. 1,3,5-Trimethoxybenzene (*) is also present.

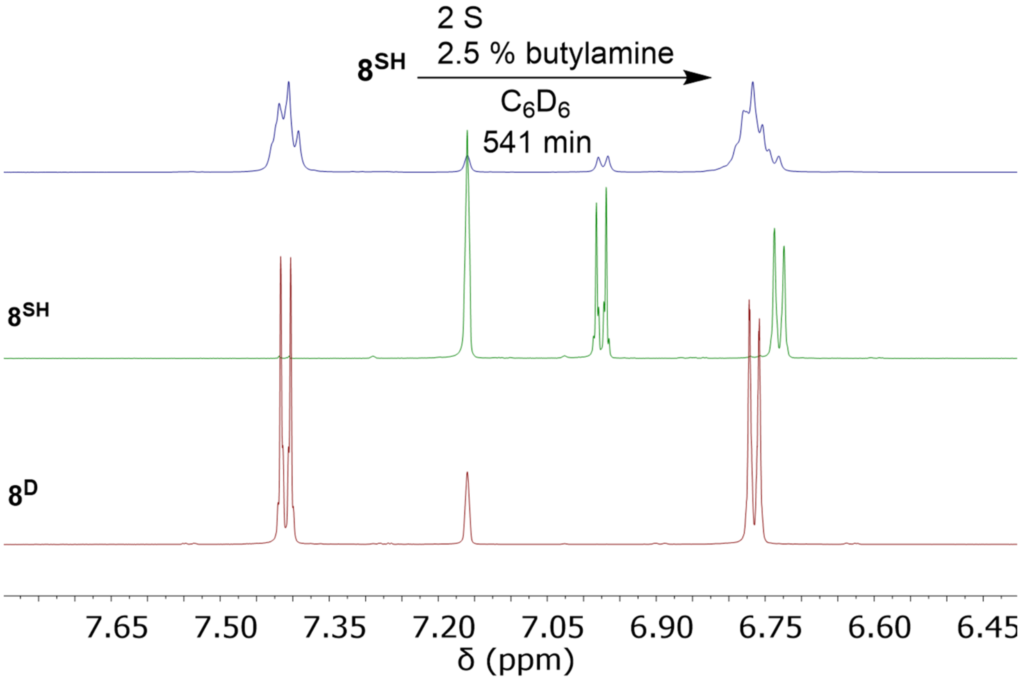


Figure S34. Truncated ^{1}H NMR spectra of $\mathbf{8^{SH}}$ + 2S with 2.5 mol % butylamine at 541 min (top), $\mathbf{8^{SH}}$ (middle) and $\mathbf{8^D}$ (bottom) in C_6D_6 at 25 °C.

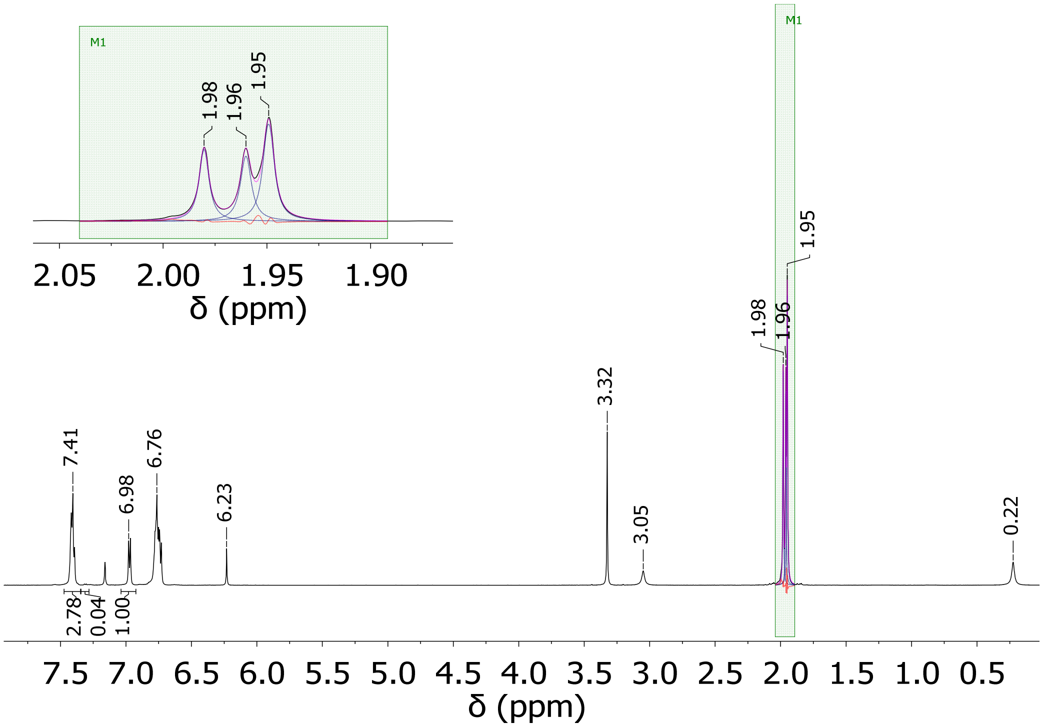


Figure S35. ^{1}H NMR spectrum of **8^{SH}** + 2S with 2.5 mol % butylamine at 49 min showing fitted **8^{T}** (1.98 ppm), **8^{D}** (1.96 ppm) and **8^{SH}** (1.95 ppm) with MestreNova.

Reaction of Thiophenols and Sulfur with Alkenes. In the glovebox, an oven-dried J. Young NMR tube was charged with S_8 (0.087 g, 1.4 mmol, 6 S atom equiv), Alkene (0.48 mmol, 1 equiv) and C_6D_6 (0.7 mL). The corresponding thiophenol (**5^{SH}**, **7^{SH}**, or thiophenol, 0.48 mmol, 1 equiv) was added. The NMR tube was sealed, and, unless otherwise noted, the reaction was heated to 80 °C in a mineral oil bath. The reaction progress was monitored by ^{1}H NMR spectroscopy over time. The **5^{SH}** product was further purified by flash column chromatography (silica gel, n-hexane:ethyl acetate 100:1).

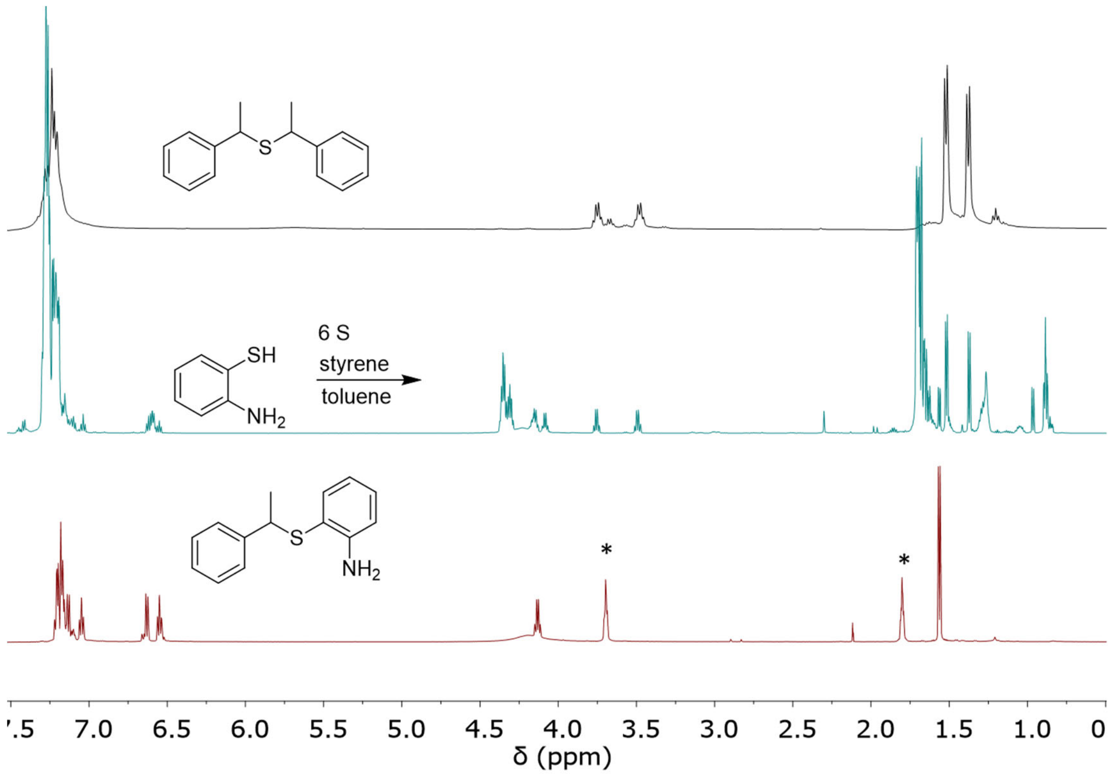


Figure S36. ^{1}H NMR spectra of bis(1-phenylethyl)sulfane (top), the isolated product mixture of $\mathbf{5^{SH}}$, S$_8$, and styrene (middle), and 2-((1-phenylethyl)thio)aniline (bottom) in CDCl$_3$ at 25 °C. THF (*) is also present.

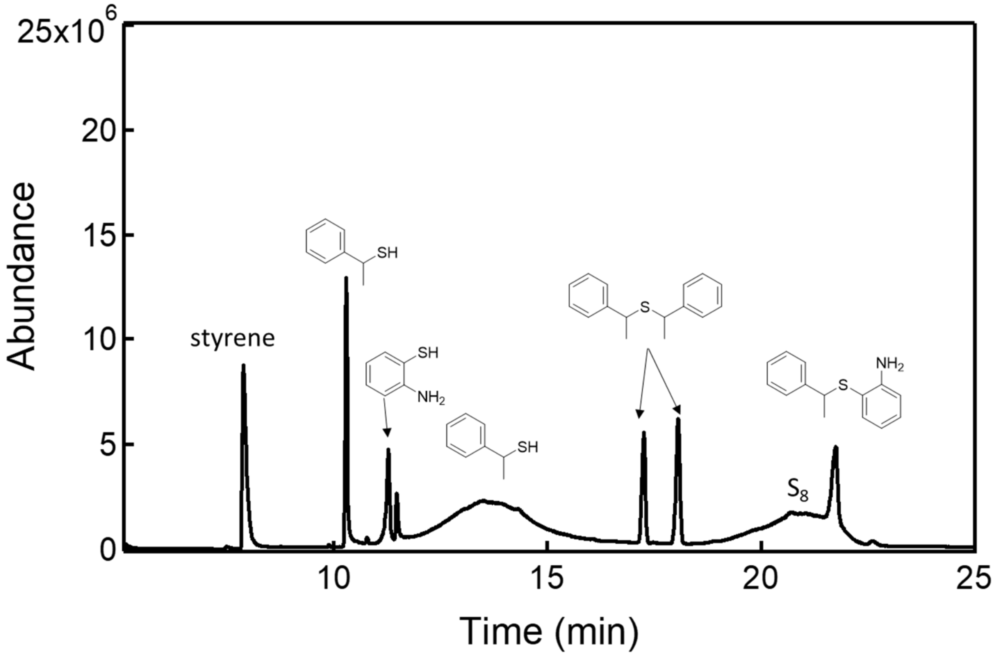


Figure S37. GC-MS chromatogram of isolated product mixture of $\mathbf{5^{SH}}$, S$_8$, and styrene. Styrene, methylbenzylthiol, and 2-aminothiophenol are formed from polysulfide fragmentation at the GC heated inlet.

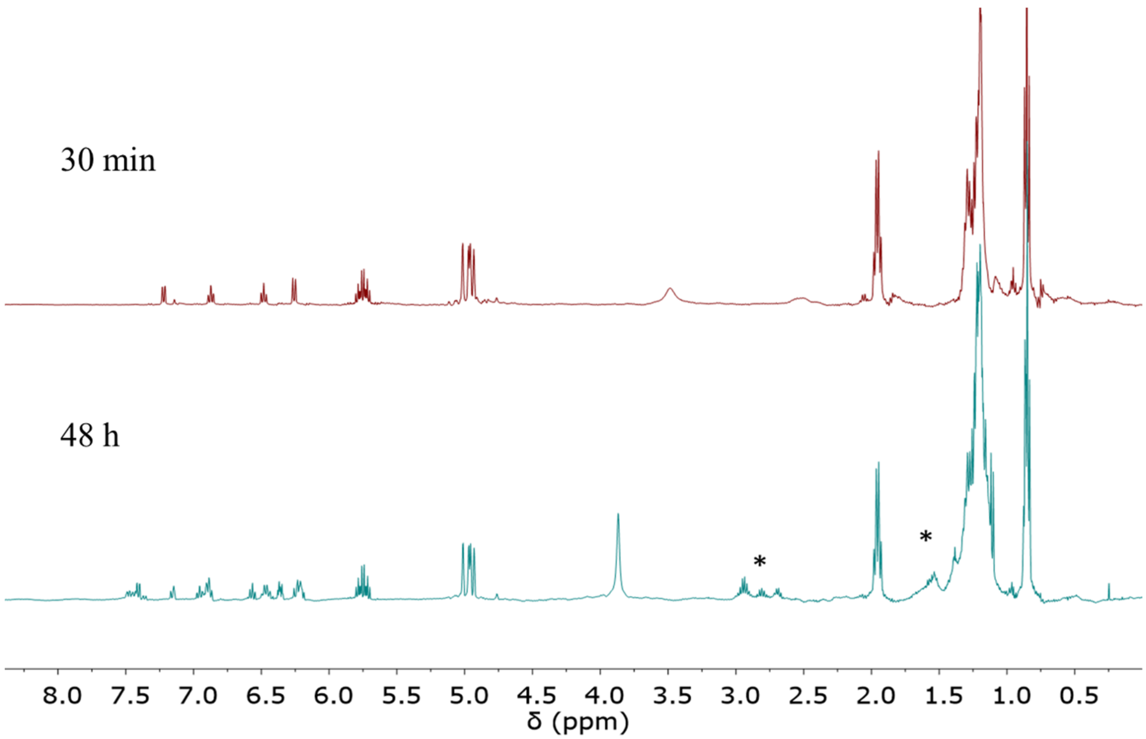


Figure S38. ^{1}H NMR spectra of the reaction mixture of **5**$^{\mathbf{SH}}$, 1-octene and S_8 at 30 min (top) and after 48 h (bottom) in C_6D_6 at 25 °C. Polysulfide product (*).

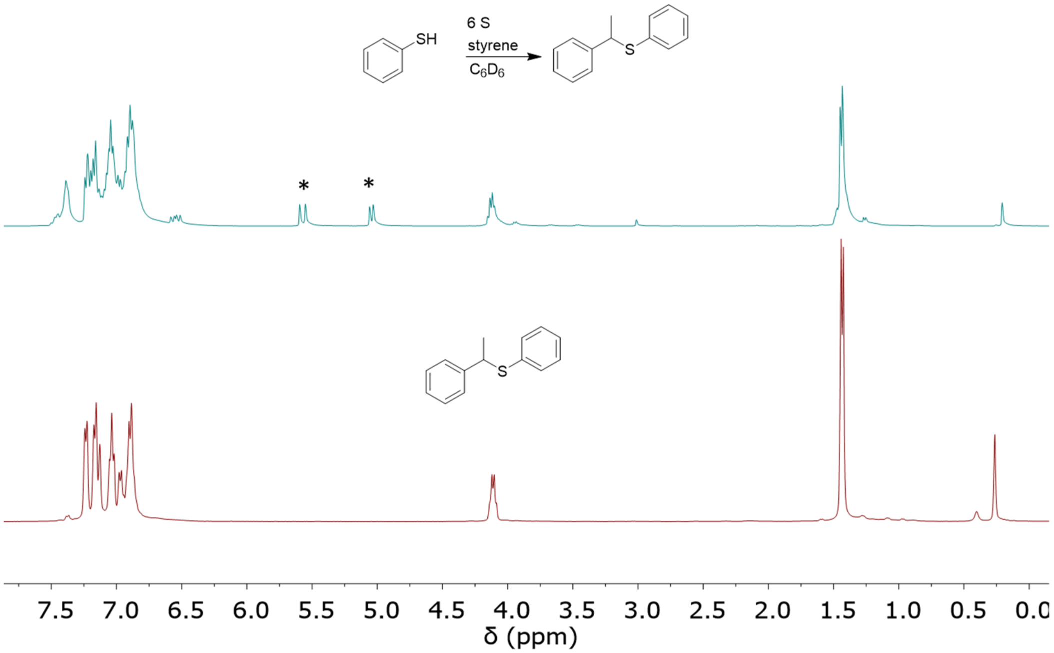


Figure S39. ^{1}H NMR spectra of the reaction mixture of thiophenol, styrene and 6 equiv of S_8 (top), and independently prepared phenyl(1-phenylethyl)sulfane (bottom) in C_6D_6 at 25 °C. Styrene (*) is also present.

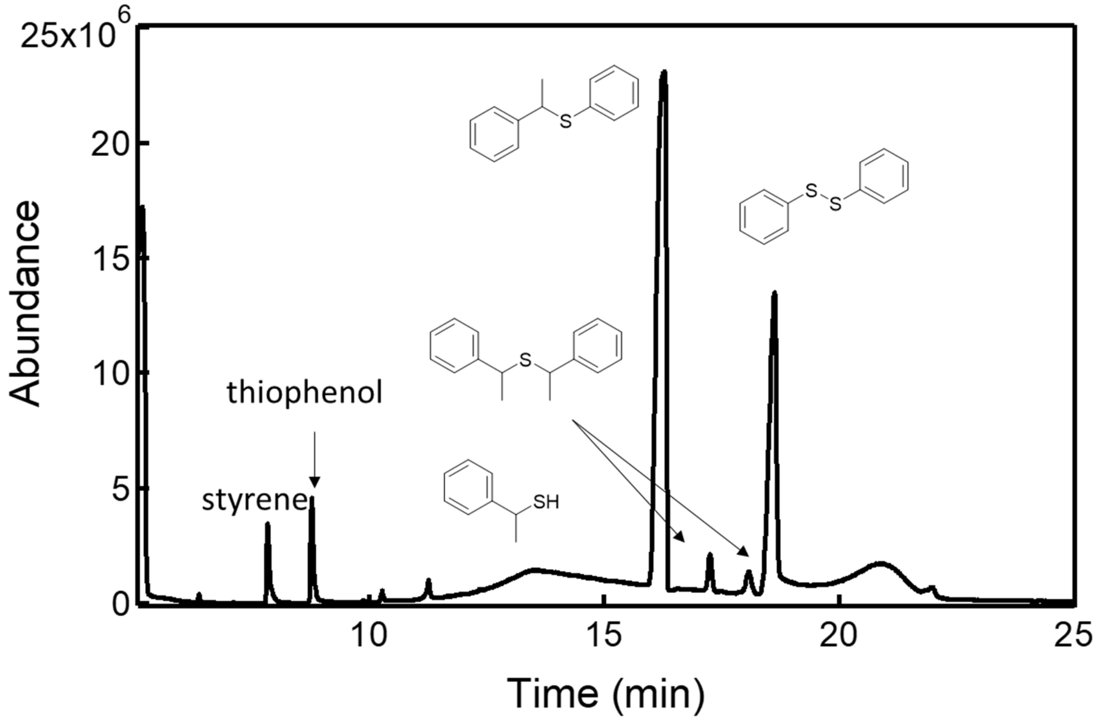


Figure S40. GC-MS chromatogram of reaction mixture of thiophenol, S_8, and styrene. Styrene, methylbenzylthiol, and thiophenol are formed from polysulfide fragmentation at the GC heated inlet. The presence of diphenyl disulfide is formed from the reaction of thiophenol and S_8.

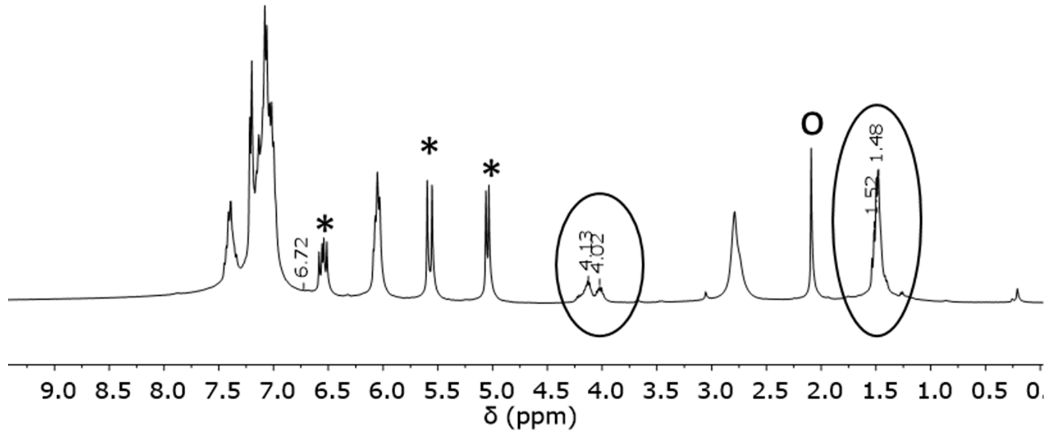


Figure S41. ^{1}H NMR spectrum of the reaction mixture of $\mathbf{7^{SH}}$, styrene and 4 equiv of S_8 after 24 h in C_6D_6 at 25 °C. Circled signals correspond to a mixture of methylbenzyl polysulfide products. Styrene (*) and toluene (O) are also present

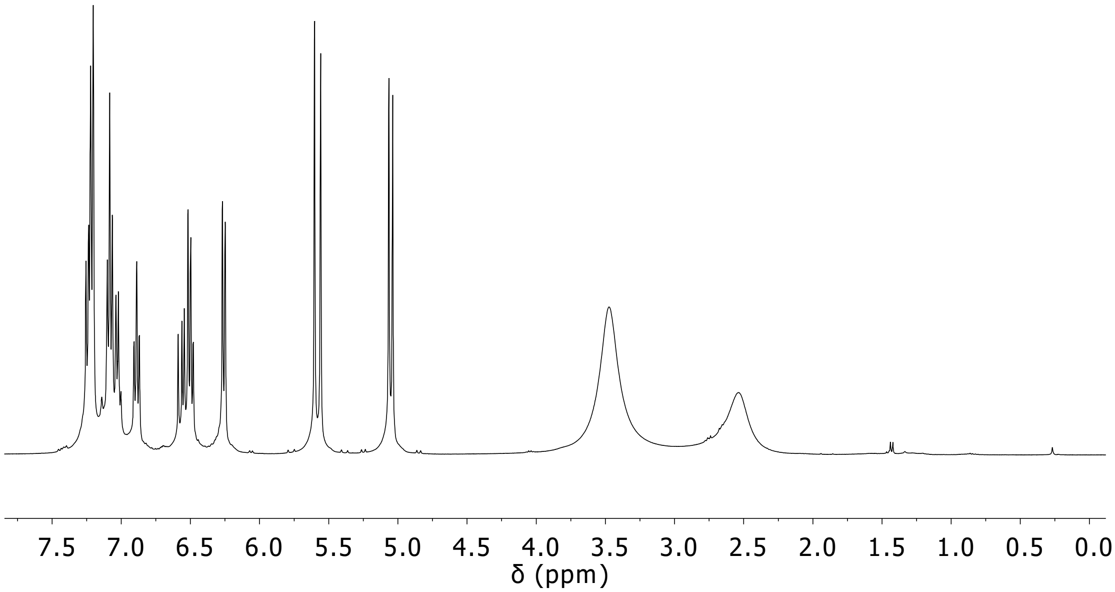


Figure S42. ^{1}H NMR spectrum of the reaction mixture of $\mathbf{5^{SH}}$ and styrene in C_6D_6 at 25 °C showing no reaction in the absence of S_8.

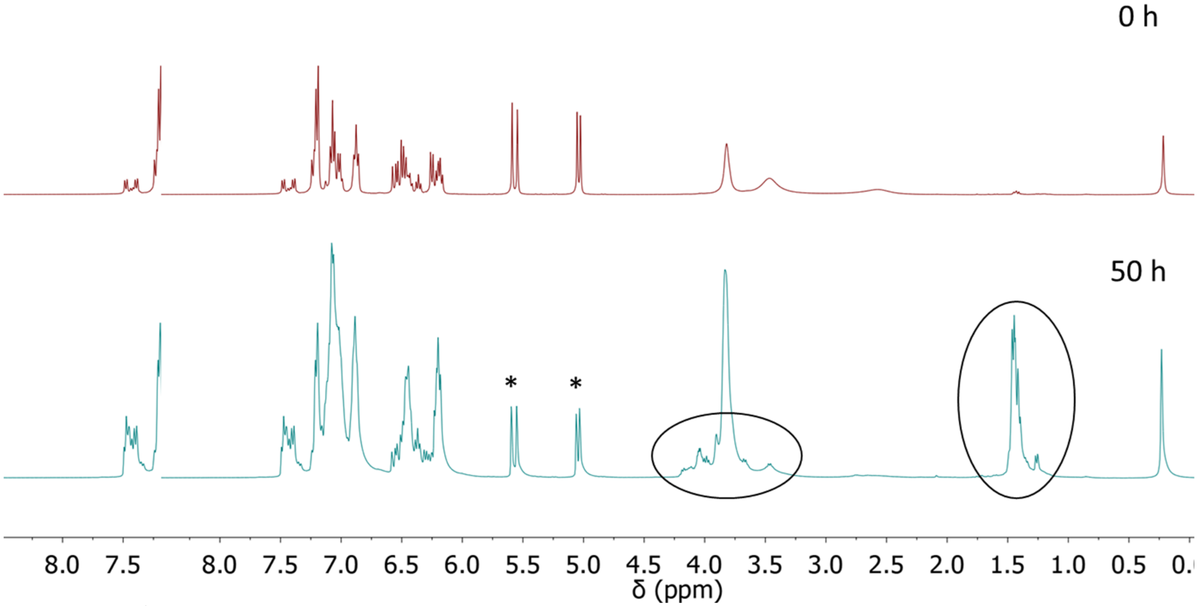


Figure S43. ^{1}H NMR spectra of the reaction mixture of $\mathbf{5^{SH}}$, styrene and S_8 at 0 h (top) and after 50 h (bottom) at 21 °C in C_6D_6. Spectra measured at 25 °C. Circled signals correspond to a mixture of methylbenzyl polysulfide products, identified by a number of overlapping doublets at 1.5 ppm and overlapping quartets at 3.7 ppm. Styrene (*) is also present.

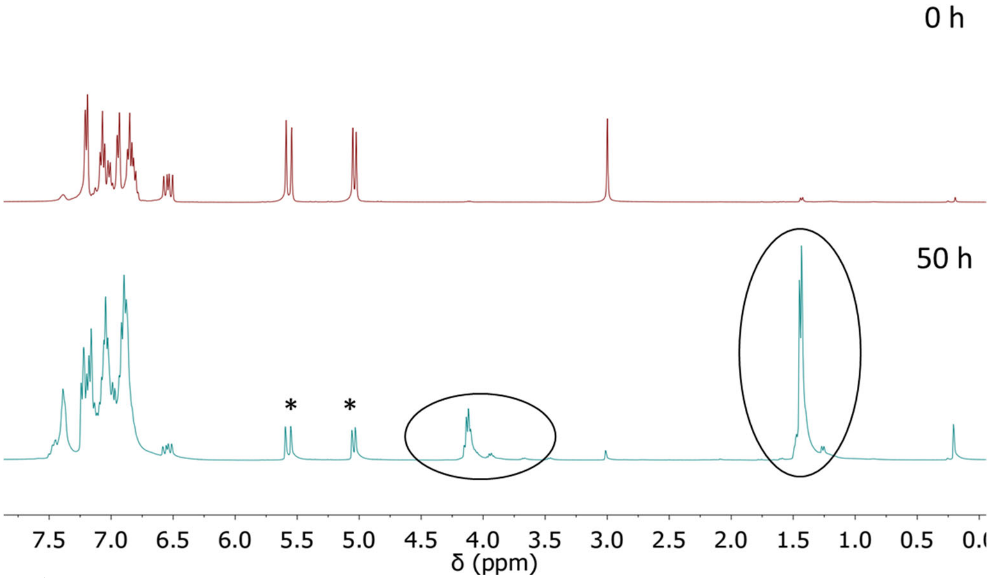


Figure S44. ^{1}H NMR spectra of the reaction mixture of thiophenol, styrene and S_8 at 0 h (top) and after 50 h (bottom) at 21 °C in C_6D_6. Spectra measured at 25 °C. Circled signals correspond primarily to phenyl α-methylbenzyl sulfide, identified by one doublet at 1.5 ppm and a quartet at 4.1 ppm, significantly shifted downfield from the polysulfide products shown in the previous figure. Styrene (*) is also present.

References

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2. J. M. Chalker, L. Lercher, N. R. Rose, C. J. Schofield, B. G. Davis, *Angew. Chem. Int. Ed.*, 2012, **51**, 1835-1839.
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