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# The Redox Chemistry of Sulfenic Acids

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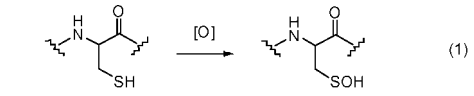
***Abstract:*** A persistent triptycenyl sulfenic acid is used as a model for cysteine-derived and other biologically relevant sulfenic acids in experiments which define their redox chemistry. EPR spectroscopy reveals that sulfinyl radicals are persistent and unreactive toward $O_2$, allowing the O−H bonding dissociation enthalpy (BDE) of the sulfenic acid to be readily determined by equilibration with TEMPO as 71.9 kcal/mol. The $E°$ (RSO•/RSO$^-$) and p$K_a$ of this sulfenic acid are also reported.

Sulfenic acids figure prominently in biological and natural product chemistry. For example, cysteine-derived sulfenic acids (**1**) are key intermediates in signal transduction, responding to the redox state of the cell and modulating gene transcription accordingly,[1] and have also been shown to play both catalytic and structural roles in enzymes,[2] as well as nonenzymatic protein folding.[7] Sulfenic acids are proposed to be key intermediates in the metabolic activation of antithrombotic agents, such as ticlopedine and prasugrel,[8] and, most tangibly, in the biosynthesis of the odorous thiosulfinates in *allium* species, such as garlic, onions, leeks, and shallots.[9] Recently, we have shown that 2-propenesulfenic acid (**2**) derived from allicin, the primary thiosulfinate giving garlic its characteristic odor and flavor, is responsible for garlic's potent antioxidant activity.[10]




(1)

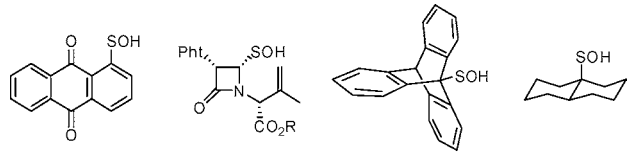
**1**

(2)

**2**

The potential for cysteine-derived sulfenic acids to be ubiquitous in cell signaling processes has prompted the development of numerous approaches for their detection and quantitation.[11] Despite the flurry of research that has ensued, revealing cysteine sulfenic acid involvement in an ever increasing number of pathways, the mechanisms responsible for the formation and reactions of these intermediates remain unclear.[2,4−10,12] This is compounded by the fact that surprisingly little is known of the physicochemical properties of this functional group—largely because the preparation, isolation, and purification of sulfenic acids is not a trivial endeavor.[13]

The first report of the preparation of a sulfenic acid was made by Fries in 1913[14]—an anthraquinone-derived sulfenic acid (**3**) stabilized by an intramolecular hydrogen bond—and few other examples have appeared since.[15] The preparation, isolation, and purification of three types of alkyl sulfenic acids have been reported—ones derived from penicillins (**4**),[16] and ones bearing triptycene (**5**)[17] and (*E*)-decalin (**6**)[18] substitution. Since alkyl sulfenic acids are most appropriate models for **1**, **2**, and other biologically relevant sulfenic acids, we sought to prepare them and determine their redox properties. The preparation of **5**, modified from the literature procedure[17] as detailed in the Supporting Information, was the most straightforward, and we describe our investigations with this compound here.




**3** **4** **5** **6**

When a deoxygenated solution of **5** in benzene containing 5−10% (v/v) di-*tert*-butylperoxide was placed in the cavity of an EPR spectrometer and irradiated for 10 s with UV light, an intense single-line spectrum was obtained with the field center at $g = 2.0114$ (black line, Figure 1).[19] The radical was persistent under these conditions—in contrast with other spectroscopically characterized small-molecule-derived sulfinyl radicals (i.e., MeSO•[20] and *t*-BuSO•[21]),[22] the latter of which was found to undergo a rapid bimolecular self-reaction ($2k = 6 \times 10^7$ M$^{-1}$ s$^{-1}$) at −100 °C.[23] In fact, the same spectrum was obtained days after the initial photolysis. More interestingly, the radical was found to be stable to $O_2$; introduction of air into the sample lead to significant broadening of the signal (Figure 1, red line)—from a line width of less than 0.4 G to close to 1.8 G—owing to the paramagnetism of $O_2$. The original spectrum could be restored by sparging with $N_2$.[24]

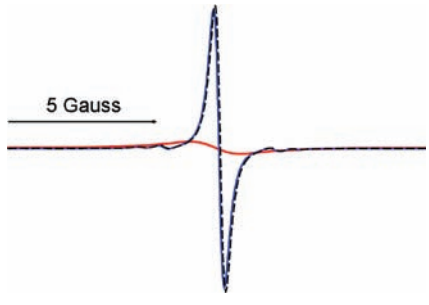



***Figure 1.*** EPR spectrum of **5**• from irradiation of **5** in benzene and 5−10 mol % di-*tert*-butylperoxide in the absence of $O_2$ (---), following exposure to air (red line) and after being sparged with $N_2$ to remove $O_2$ (blue line).

The persistence of **5**• allowed the determination of the O−H bond dissociation enthalpy (BDE) of **5** by EPR using the radical

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equilibration approach.[25] Thus, **5** and TEMPO-H (*N*-hydroxy-2,2,6,6-tetramethylpiperidine) were combined in a deoxygenated benzene solution containing 5% (v/v) di-*tert*-butylperoxide and irradiated in the cavity of an EPR spectrometer. The equilibrium constant for exchange of an H-atom between **5**• and TEMPO was then obtained by integration of the spectral signals corresponding to the two radicals. Since the O−H BDE of TEMPO-H is known (69.6 kcal/mol),[26] and assuming that the entropy change for the equilibrium is negligible, the O−H BDE of **5** could be determined to be 71.9 ± 0.3 kcal/mol. This value is in good agreement with the value predicted by high-level theoretical calculations on smaller alkyl sulfenic acids (∼69 kcal/mol) in some of our recent work.[10] The substantially lower O−H BDE in sulfenic acids compared to the (valence) isoelectronic hydroperoxides (∼88 kcal/mol) can be ascribed to greater spin delocalization onto the S atom in the sulfinyl radical (∼50%) compared to the internal O atom in the peroxyl radical (∼30%).[10,27]

Cyclic voltammetry of $CH_3CN$ solutions of **5** revealed a broad, irreversible anodic (oxidation) peak at 1.46 V versus NHE (Figure 2).[28] Addition of $CF_3SO_3H$ sharpened this peak and shifted it to more oxidizing potentials, eventually becoming constant at 1.57 V, but still exhibiting irreversible behavior.[29] Conversely, the addition of 1 equiv of $Bu_4NOH$ shifted the anodic peak to ∼0.79 V and yielded quasi-reversible behavior, thereby allowing us to estimate a standard potential of $E^\circ = E_{1/2} = 0.74$ V versus NHE for the RSO•/$RSO^-$ couple. For comparison, $E^\circ$ for the ROO•/$ROO^-$ couple in neutral media is estimated to be 1.05 V vs NHE.[30]

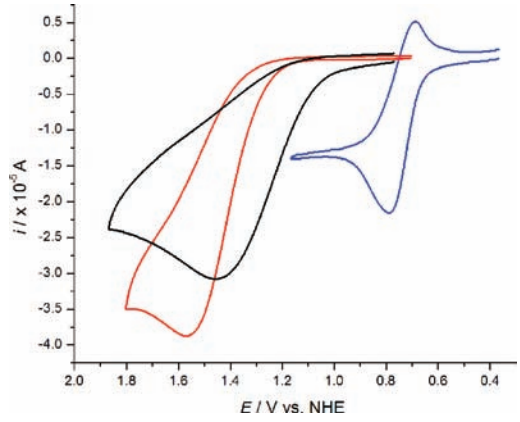


***Figure 2.*** Cyclic voltammagrams corresponding to the oxidation of 5 mM **5** in $CH_3CN$ containing 0.1 M $Bu_4NPF_6$ as supporting electrolyte and no additive (black), (b) 30 mM $CF_3SO_3H$ (red), or (c) 5 mM $Bu_4NOH$ (blue) at a scan rate of 100 mV/s.

To complete our physicochemical studies of **5**, we also determined its p$K_a$. These measurements were carried out in 4:1 (v:v) $CH_3CN/H_2O$, from which we obtained a value of 12.5.[31] The p$K_a$ of *tert*-butyl hydroperoxide under the exact same conditions was ≥14,[32] indicating that sulfenic acids are indeed more acidic than the isoelectronic hydroperoxides. Given that the p$K_a$ difference is small relative to the difference in $E^\circ$, the lability of the O−H bonds in sulfenic acids can be said to derive more from the stability of the sulfinyl radical than the sulfenate anion.

Owing to the very low O−H BDE, moderate acidity, and relatively high oxidation potential of the undissociated form, our data suggest that the redox chemistry of sulfenic acids is dominated by formal H-atom transfer reactions. Alternatively, the proximity of a metal ion or basic amino acid side chain to cysteine sulfenic acids can promote electron transfer chemistry via the sulfenate anion and should be considered when developing mechanistic proposals in this context. The persistence of the 9-triptycenesulfenic acid, and sulfinyl radical derived therefrom, should prove useful for carrying out model reactions of protein-bound cysteine sulfenic acids; further, the physicochemical properties reported here should be valuable to the interpretation of results obtained with them, as well as with the actual biological systems, for which obtaining these data is practically impossible.

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**Supporting Information Available:** Complete experimental details for synthesis, EPR, electrochemical, and p$K_a$ studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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