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The hydroperoxysulfonium ylide. An aberration or a ubiquitous intermediate?

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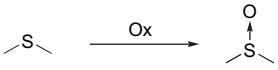
Abstract—An intramolecular isotope effect has been measured for the reaction of singlet oxygen with 2,2,8,8-tetradeuterio-1,5-dithiacyclooctane, **4d$_4$**. The magnitude of the isotope effect, 1.21±0.09, provides verification of removal of an α-hydrogen during the product determining step to form a hydroperoxysulfonium ylide and ultimately the sulfoxide product. The absence of any *special* structural features in **4d$_4$** to enhance the propensity of hydrogen removal is used to suggest that the hydroperoxysulfonium ylide is a ubiquitous intermediate in the reactions of sulfides with singlet oxygen.

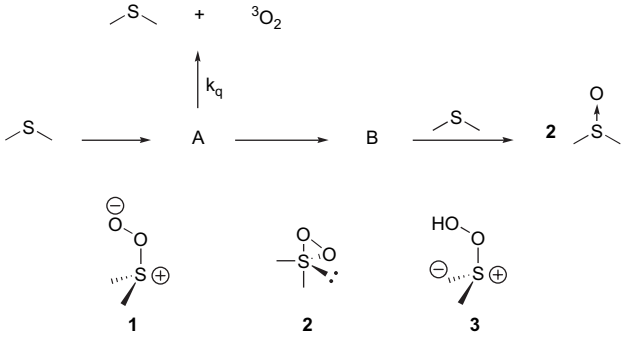
1. Introduction

The oxidation of a sulfide to a sulfoxide despite its apparent simplicity is an extremely important process. A large number of different natural products contain the sulfoxide functional group.[1] It has been reported that oxidation of a single methionine residue in amyloid β-peptide plays a key role in the neurotoxicity responsible for Alzheimer's disease.[2] Although many reagents are available for sulfide oxidation, the oxygenation process with singlet oxygen is perhaps one of the most convenient.



(1)

The ability of singlet oxygen ($^1\Delta_g$) at the time believed to be a sensitizer oxygen complex to perform the transformation shown in Eq. 1 was first demonstrated by Schenck and Krauch in 1962.[3] However, the mechanism of this singlet oxygen reaction has proven to be surprisingly complex. The gross features of the potential energy surface were delineated in, what is now, a classic paper published by Foote and co-workers in 1983.[4] In this manuscript a kinetic study using the 'inert' trapping agents, diphenylsulfide and diphenylsulfoxide, was used to convincingly demonstrate the presence of two intermediates (Scheme 1). Subsequently, the general applicability of this 'two-intermediate' mechanism has been established[5] for a wide range of sulfenyl derivatives including disulfides,[6,7] sulfenamides,[8–10] and sulfenate esters.[11]



Scheme 1.

The first intermediate was characterized as a nucleophilic oxidant capable of transferring an oxygen atom to an exogenous electrophilic acceptor. The structure of this intermediate was reasonably assigned the persulfoxide structure, **1**. A wide variety of selective chemical transformations of this intermediate has served to solidify this assignment.[12] The second intermediate was characterized as an electrophilic oxidant capable of donating a single oxygen atom to nucleophilic acceptors. A thiadioxirane, **2**, structure was assigned to this intermediate. Unfortunately, the meta-stability of these intermediates prevented direct spectroscopic characterization.

In 1998, as a result of a detailed computational study, we suggested that a more viable alternative for the second intermediate was a hydroperoxysulfonium ylide, **3**.[13] This

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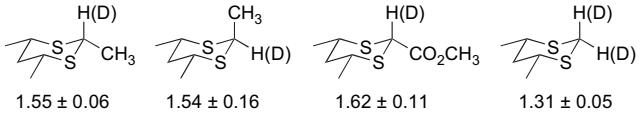
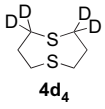
suggestion was based on the computational evidence that revealed that the collapse of the persulfoxide to **3** occurs with a barrier of approximately 6 kcal/mol in comparison to an insurmountable barrier of 20 kcal/mol for its rearrangement to **2**. Experimental data to support this suggestion rapidly following in 1999[14] with the report of substantial kinetic isotope effects for the reactions of singlet oxygen with the series of 1,3-dithianes shown in Scheme 2.[15]



Scheme 2.

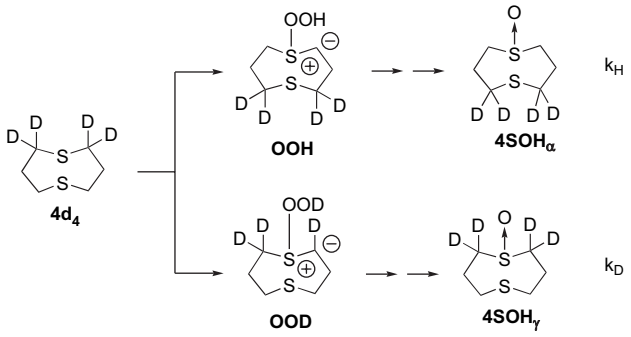
Deprotonations of 1,3-dithianes and their derivatives are well-established procedures for the generation of synthetically useful acyl anion equivalents.[16] In order to alleviate any concern that these 1,3-dithianes are 'unique' singlet oxygen substrates as a result of the acidity of their 2-protons (Scheme 2), we report here a kinetic isotope effect study of the specifically deuterated 1,5-dithiacyclooctane, **4d$_4$**.



2. Results and discussion

The deuterated 1,5-dithiacyclooctane, **4d$_4$**, was synthesized as shown in Scheme 3. A high dilution technique was first used to produce a modest yield of 1,5-dithiacyclooctane, **4**, which was converted to **4SO** with sodium periodate in methanol. Deuterium was washed into this sulfoxide by stirring it at 100 °C in a solution of sodium deuterium oxide in D_2O. Finally, **4SOH$_\gamma$** was reduced with sodium iodide in perchloric acid followed by treatment with $Na_2S_2O_3$ to give a 74% yield of **4d$_4$** with greater than 96% deuterium incorporation.

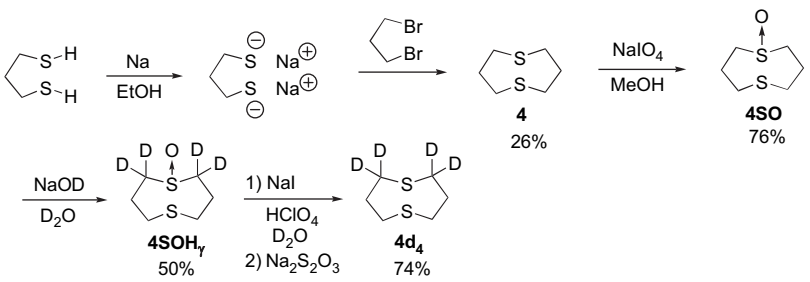
The isotope effect studies with **4d$_4$** were conducted under the high concentration conditions (0.05–0.1 M) known to convert **4** cleanly to the sulfoxide, **4SO**. High conversions (i.e., long irradiation times), which are known to convert **4SO** to a 86:14 mixture of the *cis*- and *trans*-(bis)sulfoxides,[17] and low concentrations,[18] which are known to promote formation of cleavage products, were avoided. Under these carefully controlled conditions, two products, **4SOH$_\alpha$** and **4SOH$_\gamma$**, are exclusively formed in the singlet oxygen reaction. The NMR spectra for the 6-spin system, **4SO**, and the 4-spin system **4SOH$_\gamma$** (Scheme 4), which was available in pure form from the synthesis depicted in Scheme 3, were fit using WINDNMR[19] simulation software. The derived spectral data for **4SO** are given in Table 1. These assignments were subsequently used to assist in the analysis of the isotope effect experiment (vide infra).



Scheme 4.

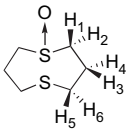
The isotope effect, k_H/k_D, measured in this study is a product isotope effect as depicted in Scheme 4. The isotope effect (i.e., product ratio [**4SOH$_\alpha$**]/[**4SOH$_\gamma$**]) is also equal to [**OOH**]/[**OOD**] since **4SOH$_\alpha$** and **4SOH$_\gamma$** can only form via hydroperoxysulfonium ylides **OOH** and **OOD**, respectively. The most stable conformation of the hydroperoxysulfonium ylide has the hydrogen of the OOH group directly above the negatively charged α-carbon[13] poised for re-delivery back to this carbon upon reaction of the peroxy linkage with a molecule of sulfide substrate to give two sulfoxide products.

The isotope effect k_H/k_D=[**4SOH$_\alpha$**]/[**4SOH$_\gamma$**]=[**OOH**]/[**OOD**]=1.21±0.09 was measured by integration of the α-hydrogen multiplet (H_1 and H_2) between 3.0 and 3.2 ppm and the γ-hydrogen multiplet (H_5 and H_6) between 2.5 and 2.7 ppm from five independent reactions. Figure 1 depicts an example of a typical reaction mixture showing both the multiplet between 2.5 and 2.7 ppm for the γ-hydrogens in **4SOH$_\gamma$** and the multiplet between 3.0 and 3.2 ppm for the α-hydrogens in **4SOH$_\alpha$**. This figure also illustrates the baseline separation between these two multiplets and the large residual peak for **4d$_4$** in these low conversion reaction mixtures.



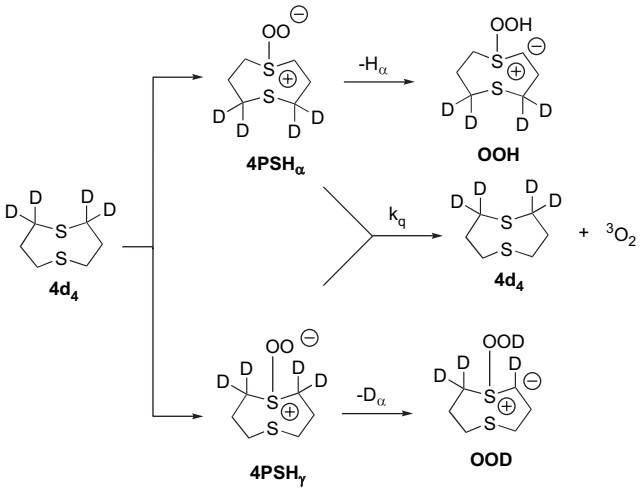
Scheme 3.

Table 1. Spectral Data for **4SO**[a,b]

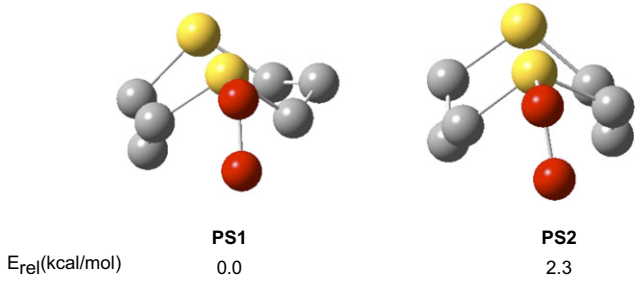


Spin	δ (Hz)	J (Hz)
H_1	1269.17	ddd; J_{12}=−13.08; J_{13}=3.59; J_{14}=7.89
H_2	1246.56	ddd; J_{12}=−13.08; J_{23}=3.85; J_{24}=7.04
H_3	876.18	ddddd; J_{13}=3.59; J_{23}=3.85; J_{34}=−15.77; J_{35}=4.72; J_{36}=7.59
H_4	924.31	ddddd; J_{14}=7.89; J_{24}=7.04; J_{34}=−15.77; J_{45}=8.10; J_{46}=4.13
H_5	1067.41	ddd; J_{35}=4.72; J_{45}=8.10; J_{56}=−14.7
H_6	1031.39	ddd; J_{36}=7.59; J_{46}=4.13; J_{56}=−14.7

[a] The simulation assisted/derived spectral parameters for **4SOH**$_\gamma$ were used as a guide to fit the spectral data for **4SO**.
[b] Data collected at 400 MHz.



Scheme 5.



Scheme 6.

The observation of a significant isotope effect (1.21±0.09) is consistent with formations of hydroperoxysulfonium ylides from persulfoxides **4PSH**$_\alpha$ and **4PSH**$_\gamma$ as shown in Scheme 5. Previous studies with **4** have demonstrated that its diminished efficiency (~70%) in its reactions with singlet oxygen is a result of decomposition of the persulfoxide intermediate to starting material and triplet oxygen (path k_q in Scheme 5).[17] It is the competition between this physical deactivation pathway and formation of the hydroperoxysulfonium ylide, which is responsible for the observed isotope effect. Hydrogen abstraction in **4PSH**$_\alpha$ to form hydroperoxysulfonium ylide **OOH** competes more effectively with physical quenching, k_q, than deuterium abstraction in **4PSH**$_\gamma$ to form **OOD**.

The hydrogen isotopes abstracted in **4PSH**$_\alpha$ and **4PSH**$_\gamma$ to form their corresponding hydroperoxysulfonium ylides, **OOH** and **OOD**, respectively, do not enjoy the electronic environment found in 1,3-dithianes (Scheme 2) that lead to enhanced acidity. An extensive search of persulfoxide, **4PS** conformational space with MP2/6-31G(d) computational method located only two low energy conformations. (i.e., the global minimum and only one conformation within 3 kcal/mol of the global minimum; Scheme 6).[20] The lowest energy persulfoxide, **PS1**, adopts a boat–chair, and the persulfoxide at 2.3 kcal/mol above the global minimum, **PS2**, adopts a boat–boat conformation. Both conformations have α-hydrogens accessible for abstraction (removed for clarity from the structures in Scheme 6) by the persulfoxide terminal oxygen atom. In addition, in both conformations, the remote sulfur, the persulfoxide sulfur, and the oxygen attached to the persulfoxide sulfur are collinear. This suggests that the remote sulfur dissipates the positive charge on the persulfoxide sulfur by donation of lone electron pair density. This was confirmed in a natural bond orbital analysis of

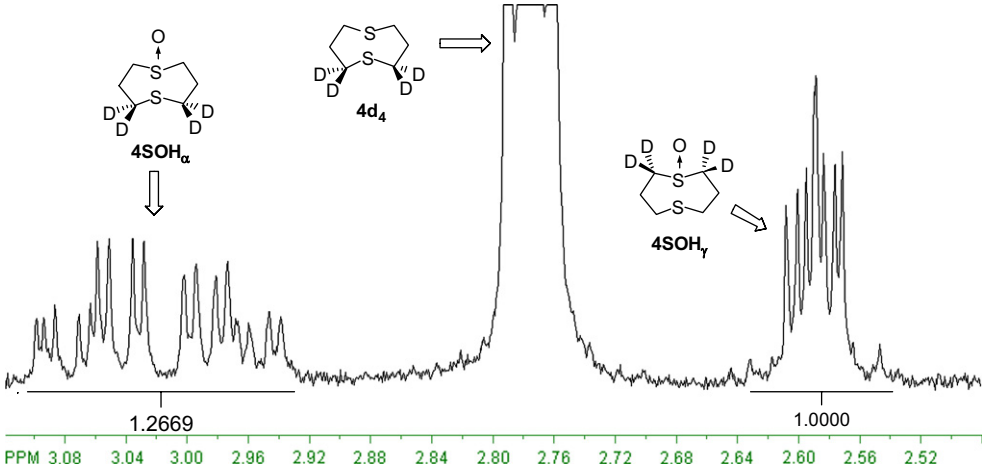


Figure 1. ^{1}H NMR from 2.48 to 3.12 ppm of reaction mixture during photooxygenation of **4d$_4$**.

persulfoxide conformations **PS1** and **PS2** that detected a depletion of the electron density on the remote sulfur consistent with delocalization of the positive charge in the persulfoxide over both sulfur atoms.[21] We argue that this diminished charge on the persulfoxide sulfur should further decrease the acidity of the α-hydrogens in comparison to those found in simple dialkylpersulfoxides.

3. Conclusion

We have demonstrated that 2,2,8,8-tetradeuterio-1,5-dithiacyclooctane, **4d$_4$**, exhibits a significant (20%) isotope effect for the site of product formation in its reaction with singlet oxygen. Consequently, enhanced acidity of the α-hydrogens is not a prerequisite for the observation of an isotope effect and suggests that the hydroperoxysulfonium ylide is a ubiquitous intermediate formed in a wide range of sulfide photooxygenations.

4. Experimental

4.1. General

4.1.1. 1,5-Dithiacyclooctane (4). In a 1000 mL three-necked flask equipped with an overhead stirrer, a condenser, and an adaptor for a syringe pump, 6 g of freshly cut sodium (0.261 mol) was added under nitrogen to 500 mL of rapidly stirred absolute ethanol. After the Na reacted, the solution was heated to 50 °C and 5.3 mL of 1,3-dibromopropane (d=1.989 g/mL, 10.54 g, 52.2 mmol) in 20 mL of absolute ethanol and 5.25 mL of 1,3-propanedithiol (d=1.078 g/mL, 5.66 g, 52.29 mol) in 20 mL of absolute ethanol were simultaneously added by a syringe pump at a rate of 0.17 mL/min over a 2 h period. After addition of the reagents the cloudy white solution was refluxed at 50 °C and then allowed to cool to room temperature. It was then filtered to remove the white precipitate. Excess ethanol was removed at reduced pressure by roto-evaporation that induces the formation of more precipitate. Water (200 mL) was added and the solution was then extracted with 3×150 mL dichloromethane. The dichloromethane extract was dried with anhydrous $MgSO_4$, filtered, and removed slowly under reduced pressure. The crude product was purified by vacuum distillation with freshly cut Na to give a colorless liquid product with a distinctive smell. Yield: 2 g (13.5 mmol, 26%). ^{1}H NMR ($CDCl_3$) δ 2.1 (m, 4H), 2.8 (m, 8H).

4.1.2. 1,5-Dithiacyclooctane-1-oxide (4SO). A solution of 0.35 g (1.77 mmol) of sodium periodate in 7.5 mL of water was added to a solution of 0.26 g (1.76 mmol) of **4** in 20 mL of methanol at room temperature over a 10-min period. This mixture was stirred for 20 h then filtered, and the volatile solvent removed. Water was added to the residue and then extracted three times with chloroform. The combined chloroform extracts were washed with sodium thiosulfate and then dried over anhydrous $MgSO_4$. Purification by column chromatography was accomplished by increasing the eluting solvent polarity from 20% methanol in ethyl acetate (EA) to 45% methanol in EA to give colorless crystals with a low melting point. Yield: 220 mg (1.34 mmol, 76%). ^{1}H NMR ($CDCl_3$) δ 2.1–2.3 (m, 4H), 2.5–2.7 (m, 4H), 3.0–3.2 (m, 4H).

4.1.3. 2,2,8,8-Tetradeuterio-1,5-dithiacyclooctane 1-oxide (4SOH$_\gamma$). A solution of **4SO** (0.41 g, 2.50 mmol) in 2 mL deuterium oxide was added to a ca. 30% solution of sodium deuterium oxide in 8 mL of deuterium oxide (D content 99.8%). After stirring under an N_2 atmosphere at 100 °C for 24 h, the solvent was concentrated under reduced pressure and the mixture was then extracted with chloroform. The combined organic phase was dried over anhydrous $MgSO_4$. After removal of the solvent, the mixture was separated by column chromatography, using a mixture of ethyl acetate and methanol (1:4). Yield: 209.6 mg (1.25 mmol, 49.9%). The content of deuterium was 96% as determined by ^{1}H NMR spectroscopy.^{1}H NMR ($CDCl_3$) δ 3.12–3.16 (m, residual α-hydrogens), 2.55–2.70 (m, 4H), 2.16–2.35 (m, 4H).

4.1.4. 2,2,8,8-Tetradeuterio-1,5-dithiacyclooctane (4d$_4$). A solution of sodium iodide (0.536 g, 3.57 mmol) and 70% perchloric acid (0.239 g, 2.38 mmol) in 10 mL D_2O was added to a solution of **4SOH$_\gamma$** (0.2 g, 1.19 mmol) in 2 mL D_2O. The reaction immediately turned to a cloudy orange color. The reaction was kept at room temperature for 4 h followed by addition of 30% $Na_2S_2O_3$ to reduce the I_3^-. The mixture was extracted three times with chloroform and the combined extracts were washed with $NaHCO_3$. The mixture was dried with anhydrous $MgSO_4$ and then the solvent was removed. The product was purified by column chromatography, ethyl acetate/hexane=1:4. Yield: 134 mg (0.88 mmol, 74%). ^{1}H NMR ($CDCl_3$) δ 2.63–3.00 (m, 4H), 1.87–2.22 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 30.23, 30.78, 29.47 (quintet, J=21 Hz).

4.2. Photooxygenation reactions

The photooxygenation reactions were carried out by irradiation of a CD_3CN solution containing 6.25×10^{-4} M methylene blue and 0.0125 M **4d$_4$**, under continuous oxygen agitation with a 150 W tungsten/halogen lamp through 1 cm of a saturated $NaNO_2$ filter solution for 10 min. The reaction mixtures were analyzed immediately by proton NMR and the isotope effects determined by integration of the appropriate regions.

Acknowledgements

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