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Oxidation of Sulfides by 3-Hydroperoxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane: Effect of Solvent and Sulfide Substituent

Alfons L. Baumstark,* Ya-Xiong Chen, Pedro C. Vasquez, and Yu-Chu Yang†

Department of Chemistry, Georgia State University, Atlanta, GA 30303-3083

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ABSTRACT

The reaction of 3-hydroperoxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane, **1,** *with a series of sulfides (***2a** *= thioanisole,* **2b** *= ethyl phenyl sulfide,* **2c** *= 2-chloroethyl phenyl sulfide, and* **2d** *= 2-chloroethyl methyl sulfide) at 34°C in various solvents yielded the corresponding sulfoxides and 3-hydroxy-1,2-dioxolane* **3** *in quantitative yields. The oxidations showed excellent second-order kinetic behavior overall. In $CDCl_3$, the reactivity order was* **2d** *>* **2b** *>* **2a** *>* **2c**. *For* **2a**, *the relative rate in various solvents was $CDCl_3$ (17); CD_3OD (7); C_6D_6 (~3); CD_3CN (1); $CD_3C(O)CD_3$ (~0.3). Addition of ~1 equivalent of acetic acid to reactions of* **1** *and* **2a** *in $CDCl_3$ and C_6D_6 resulted in small increases in the values of k_2. The results are consistent with an electrophilic oxygen-atom transfer mechanism similar to that proposed for oxidations by α-azohydroperoxides. Since the precursor to* **1,** *3-hydroxy-1,2-dioxolane* **3,** *is regenerated during the oxidation, the system has the potential to be developed as a cyclic process.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem **9:**75–78, 1998

Dedicated to Prof. William E. McEwen on the occasion of his seventy-fifth birthday in recognition of his numerous accomplishments in main group chemistry.

*To whom correspondence should be addressed.

†Research and Technology Directorate, U.S. Army, ERDEC, APG, MD 21010-5423

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INTRODUCTION

Organic hydroperoxides are useful reagents for the oxidation of many classes of organic compounds [1]. In contrast to radical pathways, oxygen-atom transfer can also be accomplished under mild conditions by concerted, electrophilic pathways (Reaction 1) equivalent to an S_N2-type attack of the substrate on the terminal oxygen of the hydroperoxide [1].

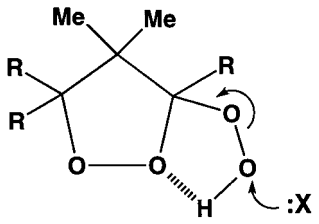
$$ROOH + :X \rightarrow ROH + X = O \qquad (1)$$

We have recently shown [2] that 3-hydroperoxy-3,4,4,5,5-pentasubstituted-1,2-dioxolanes are highly reactive in ionic (electrophilic) oxygen-atom transfer reactions. The reactivity of 3-hydroperoxy-1,2-dioxolanes in heteroatom (N,S) oxidation and epoxidations was found to be substantially greater than that of simple hydroperoxides and comparable to that of α-azohydroperoxides [3]. These reactions occur under mild conditions, do not require the addition of a catalyst, and were found to be of the second order overall in aprotic media. The mechanism of oxygen-atom transfer was postulated to occur via nucleophilic attack of the substrate on the terminal oxygen of the hydroperoxide (intramolecular hydrogen bonded; see Scheme 1) [2,4].

We report here a study of oxidation of selected organic sulfides by 3-hydroperoxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane in varying media.

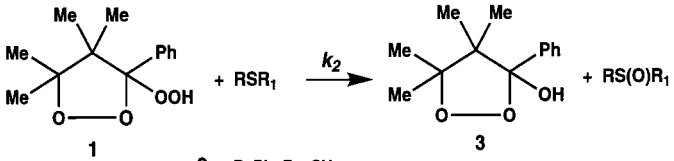
RESULTS AND DISCUSSION

The reaction of 3-hydroperoxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane, **1,** with sulfides (**2a** =



SCHEME 1

thioanisole; **2b** = ethyl phenyl sulfide; **2c** = 2-chloroethyl phenyl sulfide; and **2d** = 2-chloroethyl methyl sulfide) was carried out at 34°C in a series of solvents (Reaction 2). For all cases, the oxidation of the sulfides by 1 equivalent of hydroperoxide **1** resulted in quantitative formation of the corresponding sulfoxides with a concomitant yield of 3-hydroxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane, **3.** No secondary oxidation of the sulfoxides to sulfones was noted. Attempts to oxidize sulfoxides to sulfones by reaction with 3-hydroperoxy-1,2-dioxolane **1** were unsuccessful; instead, **1** slowly underwent thermal decomposition. No thermal decomposition of 3-hydroperoxy-1,2-dioxolane **1** or 3-hydroxy-1,2-dioxolane **3** was observed during the time scale of the sulfide-oxidation experiments. Product **3** was inert to reaction with sulfides. The products were isolated by standard chromatographic procedures and the structures proven by comparison of spectral and physical properties with those of authentic samples.



2 a R=Ph; R_1=CH_3
b R=Ph; R_1=Et
c R=Ph; R_1=CH_2CH_2Cl
d R=CH_3; R_1=CH_2CH_2Cl

(2)

The kinetic behavior of the oxidation of sulfides **2a–d** by **1** was determined. All experiments showed excellent second-order kinetics overall: first order in 3-hydroperoxy-1,2-dioxolane and first order in sulfide. The rate of disappearance of starting materials was identical to the rate of appearance of products (measured versus added anisole as internal standard). For **2a,** the oxidations were faster in deuterochloroform than in either perdeuteromethanol, perdeuterobenzene, or perdeuteroacetonitrile; the reaction was the slowest in perdeuteroacetone. The product studies and kinetic results are summarized in Table 1.

Noting the large relative rate for **2a** in the polar, protic solvent (Table 1), the catalytic effect of added acid was determined. Small amounts of acetic acid were added to the oxidation of thioanisole **2a** by hydroperoxide **1** in aprotic solvents. The results are shown in Table 2. Addition of 1 molar equivalent of acetic acid to a solution of **2a** and hydroperoxide **1** in $CDCl_3$ at 34°C resulted only in a small increase in k_2 value. When C_6D_6 was used as the solvent, the increase in k_2 value for the same quantity of acid was higher (roughly fourfold). The overall effect on S-oxidation was not as pronounced as that noted for the case of acyclic α-azohydroperoxide S-oxidation [5], where addition of 0.5 molar equivalent of perdeuterated acetic acid to the reaction mixture resulted in an almost 10-fold increase in k_2 values.

The rate of oxidation of thioanisole in different solvents proceeds faster in low polarity nonprotic solvents ($CDCl_3$, C_6D_6) than it does in polar nonprotic solvents (CD_3CN, acetone-d_6). Similar results have been observed for acyclic α-azohydroperoxides [5]. For instance, oxidation of benzyl methyl sulfide by p-$MeOC_6H_4CH(OOH)$-N=N–Ph at 34°C is ~2.4 times faster in C_6D_6 than in CD_3CN. In the present case, oxidation of thioanisole **2a** by hydroperoxide **1** takes place ~2.5 times faster in C_6D_6 than it does in CD_3CN. The present results also show that protic solvents like CD_3OD appear to have a catalytic effect, hence, the observed k_2 values. The kinetics results in CD_3OD are in agreement with what was observed for acyclic α-azohydroperoxides. The oxidation of benzyl methyl sulfide by p-$MeOC_6H_4CH(OOH)$-N=N–Ph at 34°C in CD_3OH was found to be six times faster than that in C_6D_6 (k_2 values 4.4×10^{-2} $M^{-1}s^{-1}$ and 7.3×10^{-3} $M^{-1}s^{-1}$, respectively). The present results with hydroperoxide **1** also show a higher k_2 value in CD_3OD (2.0×10^{-3} $M^{-1}s^{-1}$) as compared to C_6D_6 (7.7×10^{-4} $M^{-1}s^{-1}$) with a ratio of ~2.6. This value is smaller than in the acyclic case, perhaps because CD_3OD was used instead of CD_3OH. The increased values of k_2 in protic solvents like CD_3OH may be attributable to hydrogen bonding of the solvent and the "peroxy" oxygen. Evidence of this type of hydrogen bonding has been demonstrated by ^{17}O NMR spectroscopy on α-azohydroperoxides [6]. A similar explanation can be applied to the present results for hydroperoxide **1.**

In deuterochloroform, the reactivity order was found to be **2d** > **2b** ≥ **2a** > **2c.** The rate of oxidation of 2-chloroethyl methyl sulfide **2d** in deuterochloroform at 34°C (1.3×10^{-2} $M^{-1}s^{-1}$) is an order of magnitude faster than the rate of oxidation of 2-chloroethyl phenyl sulfide **2c** (1.2×10^{-3} $M^{-1}s^{-1}$). Sulfide **2c,** an excellent simulant [7,8] for mustard (2,2′-dichlorodiethyl sulfide), has been shown to undergo oxidation in $CDCl_3$ by an N-sulfonyloxaziridine reagent with a k_2 value of ~2×10^{-5} $M^{-1}s^{-1}$ at 18°C

TABLE 1 Sulfoxide Yields and Second-Order Rate Constants for Oxidation of Sulfides **2a**–**d** by 3-Hydroperoxy-1,2-dioxolane, **1,** at 34°C in Varying Solvents

Sulfide	*% Yield Sulfoxide*[a]	k_2 $M^{-1}s^{-1}$[b]	*Solvent*	*Rel. Rate*	k_{rel} ($CDCl_3$)
$PhSCH_3$ **2a**	91	$5.3 \pm 0.1 \times 10^{-3}$	$CDCl_3$	17	4.4
$PhSCH_3$	96	$2.0 \pm 0.1 \times 10^{-3}$	CD_3OD	~7	
$PhSCH_3$	96	$7.7 \pm 0.1 \times 10^{-4}$	C_6D_6	~3	
$PhSCH_3$	91	$3.1 \pm 0.1 \times 10^{-4}$	CD_3CN	1	
$PhSCH_3$	89	$9.4 \pm 0.3 \times 10^{-5}$	$CD_3C(O)CH_3$	~0.3	
PhSEt **2b**	99	$5.7 \pm 0.2 \times 10^{-3}$	$CDCl_3$		4.8
$PhSCH_2CH_2Cl$ **2c**	98	$1.2 \pm 0.1 \times 10^{-3}$	$CDCl_3$		1.0
$PhSCH_2CH_2Cl$	96	$1.2 \pm 0.1 \times 10^{-4}$	CD_3CN		
$CH_3SCH_2CH_2Cl$ **2d**	98	$1.3 \pm 0.1 \times 10^{-2}$	$CDCl_3$		11
$CH_3SCH_2CH_2Cl$	95	$1.2 \pm 0.1 \times 10^{-3}$	CD_3CN		

[a]Isolated yield; yields by NMR spectroscopy quantitative for all cases.
[b]The k_2's are average of two or more experiments; the standard deviations are less than errors shown.

[8]. In addition, sulfide **2c** was found to be 4.6-fold less reactive than **2d** for oxidation by the oxaziridine [8]. Thus, hydroperoxy-1,2-dioxolane **1** appears to be roughly two orders of magnitude more reactive than the N-sulfonyloxaziridine reagent with similar selectivity. The reactivity order is also consistent with the results that have been observed for other reactive organic hydroperoxides like cyclic and acyclic α-azohydroperoxides. For example, k_2 values for the oxidation of benzyl methyl sulfide and benzyl phenyl sulfide with *p*-MeOPhCH(OOH)N=NPh in C_6D_6 at 34°C are 7.3×10^{-3} $M^{-1}s^{-1}$ and 5.4×10^{-4} $M^{-1}s^{-1}$, respectively. As expected, substitution of a methyl group for a phenyl group that decreased sulfide nucleophilicity resulted in decreased k_{rel}.

The rate of oxidation of ethyl phenyl sulfide with 3-hydroperoxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane in deuterochloroform at 34°C (5.5×10^{-3} $M^{-1}s^{-1}$) is 4–5 times faster than the rate of oxidation of 2-chloroethyl phenyl sulfide (1.2×10^{-3} $M^{-1}s^{-1}$). In agreement with the oxaziridine results [8], substitution of a β-hydrogen by a chlorine inductively reduces the sulfide nucleophilicity.

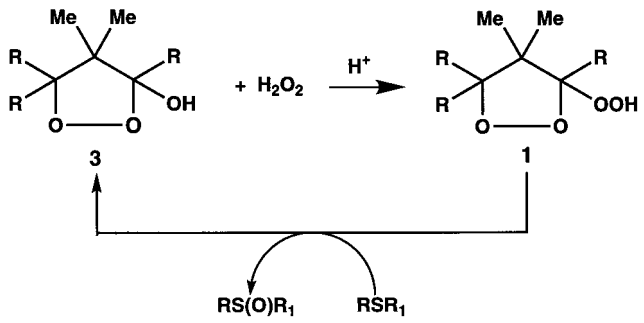
An important observation for the sulfide oxidation by **1** and other 3-hydroperoxy-1,2-dioxolanes is the fact that the hydroperoxide precursor (3-hydroxy-1,2-dioxolane **3**) is regenerated during oxidation of the sulfides. Thus, the system has the potential to be developed as a cyclic process (Scheme 2).

In conclusion, 3-hydroperoxy-1,2-dioxolanes are very selective reagents for S-oxidation that, like perfluorodialkyloxaziridines [9] and cyclic and acyclic α-azohydroperoxides, do not produce sulfide or sulfoxide oxidation to sulfones when 1 equivalent of reagent is employed, thus avoiding unwanted side reactions. In addition, the reactivity of **3** is greater than that of N-sulfonyloxaziridines, similar to that of acyclic α-azohydroperoxides, but less than that of cyclic α-azohydroxides.

TABLE 2 Effect of Added Acetic Acid on the Second-Order Rate Constants for the Reaction of Hydroperoxide **1** with Thioanisole **2a** at 34°C

$[\mathbf{2a}]_0/[\mathbf{1}]_0$[a]	$[CH_3CO_2H]$	*Solvent*	k_2 ($M^{-1}s^{-1}$)
1.4	0	$CDCl_3$	5.3×10^{-3}
1.4	0.040 M	$CDCl_3$	6.3×10^{-3}
1.4	0.072 M	$CDCl_3$	7.6×10^{-3}
1.5	0	C_6D_6	7.7×10^{-4}
1.7	0.080 M	C_6D_6	3.0×10^{-3}

[a]$[\mathbf{1}]_0 = 0.080$ M.



SCHEME 2

EXPERIMENTAL

All solvents were of reagent grade. ^{1}H NMR spectra were recorded on a Varian 360L Spectrometer. GC/MS analyses were performed on a Shimadzu 500 GC/MS. 2-Chloroethyl methyl sulfide, 2-chloroethyl phenyl sulfide, ethyl phenyl sulfide, and methyl phenyl sulfide were commercially available (Aldrich)

and were used without purification. 3-Hydroperoxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane, **1,** was synthesized from 3-hydroxy-1,2-dioxolane **3** according to published procedures [2].

KINETIC STUDIES

The following general procedure was employed for all kinetic experiments of sulfide oxidation. About 0.040 mmole of the hydroperoxide was dissolved in 0.500 mL of perdeuterated solvent ($CDCl_3$, CD_3OD, C_6D_6, CD_3CN, or acetone-d_6) containing anisole as internal standard in a new 5 mm NMR sample tube. The desired quantity of the sulfide to achieve a ratio of peroxide to substrate of about 1:1.5 was added via syringe and mixed. The solution was maintained at 34°C (probe temperature). An ^1H NMR spectrum was recorded and integrated at various time intervals (2–30 min) depending on the speed of the reaction. The kinetic data were determined by monitoring the appearance of sulfoxide and/or disappearance of the hydroperoxide relative to the internal standard, and obtained for at least two half-lives with excellent correlation coefficients (≥0.99, all cases). For the experiments involving acetic acid addition, the procedure was followed as above, except that acetic acid was added via syringe to the peroxide solution before addition of the sulfide [10].

PRODUCT STUDIES

The products, sulfoxides and corresponding 3-hydroxy-pentasubstituted-1,2-dioxolane, were separated from the reaction mixtures by chromatographic techniques (chromatatron) and their structures were proven by comparison of their physical and spectral properties (^1H NMR and GC-MS spectra) with those of authentic samples.

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