Synthesis and Oxygen-Atom Transfer Reactions of 3-Hydroperoxy-3,4,4,5,5-pentasubstituted-1,2-dioxolanes

A. Baumstark,* Y.-X. Chen and A. Rodriguez

Department of Chemistry, Georgia State University
Atlanta, GA 30303-3083 USA
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A series of 3-hydroperoxy-3,4,4,5,5-pentasubstituted-1,2-dioxolanes **2a-d** were synthesized in good yield from the corresponding 3-hydroxy-1,2-dioxolanes by reaction with concentrated hydrogen peroxide in acetonitrile with *p*-toluenesulfonic acid as catalyst. The 3-hydroperoxy-1,2-dioxolanes were effective oxygen-atom transfer reagents for the oxidation of thioanisole, triethylamine and 2,3-dimethyl-2-butene to the sulfoxide, *N*-oxide and epoxide, respectively. The reactions occurred under mild conditions and were found to be of the second order overall. The second order rate constants (k_2) were determined for oxidation of thioanisole by **2a-d** in deuteriochloroform. For **2a**, k_2 values for *N*-oxidation and epoxidation were also measured. The 3-hydroperoxy-1,2-dioxolanes were found to be less reactive than the structurally similar cyclic α-azohydroperoxides but much more reactive than simple hydroperoxides. The mechanism of oxygen-atom transfer is postulated to occur *via* nucleophilic attack of the substrate on the terminal oxygen of the hydroperoxide. Intramolecular hydrogen bonding of the hydroperoxy proton to a dioxolane oxygen appears to account for the reaction order in aprotic media.

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Introduction.

The oxidation of many classes of organic compounds can be carried out by organic hydroperoxides [1]. In addition to radical pathways, organic hydroperoxides can transfer oxygen-atoms under mild conditions *via* concerted, electrophilic pathways (Reaction 1). Mechanistically, these reactions are equivalent to Sn2-type attack of the substrate on the terminal oxygen atom of the

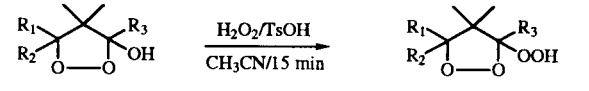
$$ROOH + :X \rightarrow ROH + X=O \quad (1)$$

hydroperoxide. Our work has shown that cyclic α-azohydroperoxides (3-hydroperoxy-4,5-dihydro-3*H*-pyrazoles) are of extremely high reactivity in ionic (electrophilic) oxygen-atom transfer reactions [2]. The reactivity of the system has been shown to be due, in part, to the ability to form an intramolecular hydrogen bond [3] in the transition state. Recently, we have developed a route for the synthesis of 3-substituted-1,2-dioxolanes [4] which show structural similarities to cyclic α-azo compounds. We report here the synthesis and electrophilic oxygen-atom transfer reactions of a series of 3-hydroperoxy-4,4,5,5-tetrasubstituted-1,2-dioxolanes.

Results and Discussion.

3-Hydroperoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane (**2a**), 3-hydroperoxy-3,5-diphenyl-4,4,5-trimethyl-1,2-dioxolane (**2b**), 3-hydroperoxy-3,4,4,5,5-pentamethyl-1,2-dioxolane (**2c**) and 3-hydroperoxy-3,5,5-triphenyl-4,4-dimethyl-1,2-dioxolane (**2d**) were synthesized in moderate to excellent yields by the reaction of the corresponding 3-hydroxy-1,2-dioxolanes **1a-d** with concentrated hydrogen peroxide (*p*-toluenesulfonic acid-catalyst) in acetonitrile (Reaction 2). In addition, compound **2a** was synthesized by treatment of the corresponding 3-methoxy-1,2-dioxolane to the reaction conditions. The 3-hydroperoxy-1,2-dioxolanes **2a,b,d** were purified readily by pentane extraction followed by recrystallization.

Reaction 2



(2)

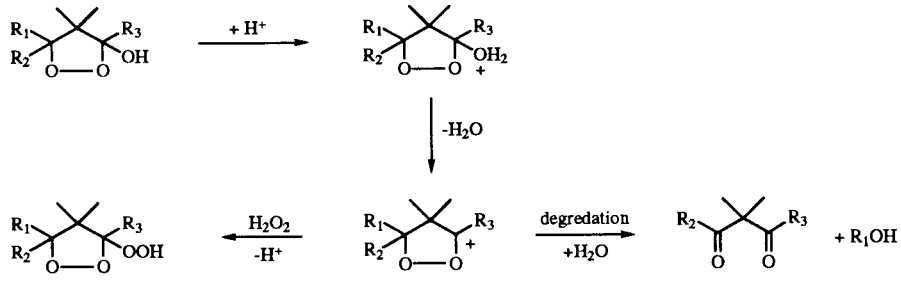
1a-d

2a, $R_1 = R_2 = Me$; $R_3 = Ph$
2b, $R_1 = R_3 = Ph$ $R_2 = Me$
2c, $R_1 = R_2 = R_3 = Me$
2d, $R_1 = R_2 = R_3 = Ph$

Compound **2c**, isolated as an oil, proved difficult to purify since it was water soluble and volatile. The hydroperoxides were characterized by spectral and physical methods. Hydroperoxy compounds **2a-d** appeared to be of greater thermal stability than the 3-hydroxy-1,2-dioxolane analogs. For example, **2a** was found to undergo only 6% decomposition in deuteriochloroform at 34°C in 1 week.

The synthesis of 3-hydroperoxy compounds by substitution under mild, acetic conditions provides new methodology for functionalization of 3-hydroxy-1,2-dioxolanes and related compounds. Adam has reported [5] the synthesis of 3-hydroperoxy-6,6-dimethyl-3-phenyl-1,2-dioxane *via* reaction of the corresponding triflate with hydrogen peroxide (buffered by sodium acetate). Our recent work [6] on the derivatization of 3-hydroxy-1,2-dioxolanes confirmed that harsh acidic conditions resulted in degradation (rearrangement) reactions of the 1,2-dioxolane system to yield 1,3-diketones for our case. However, the 5,5-dimethyl compounds were found to be of sufficient stability to allow substitution (methoxy for hydroxy) to occur at position-3 in methanol in the pres-

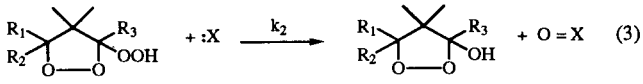
Scheme 1



ence of hydrogen chloride. In addition, we noted that 3-methoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane underwent hydrolysis in moist acetonitrile when traces of acid were present. This led to the development of the mild, acidic conditions for Reaction 2. A likely mechanism involves protonation of the 3-hydroxy group with subsequent loss of water to yield an intermediate carbocation. Trapping of the carbocation by hydrogen peroxide yields the 3-hydroperoxy compounds while rearrangement from position-5 leads to degradation with formation of 1,3-diketones. Surprisingly, the substitution reaction works well even when $R_1 = R_2 = Ph$ if the temperature is controlled. Presumably, lower temperatures favor formation of the 3-hydroperoxy compounds by slowing degradation sufficiently to allow trapping of the carbocation intermediate by hydrogen peroxide. The proposed mechanism is shown in Scheme 1.

The reactions of 3-hydroperoxy-1,2-dioxolane **2a** with thioanisole, triethylamine, benzyldimethylamine and 2,3-dimethyl-2-butene at 34°C yielded 3-hydroxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane and sulfoxide, *N*-oxides and tetramethyloxirane, respectively, in essentially quantitative yields (Reaction 3). Oxidation of thioanisole by one equivalent of compounds **2b-d** resulted in quantitative formation of the sulfoxide. The precursors for the synthesis of the 3-hydroperoxy-1,2-dioxolanes, 3-hydroxy-1,2-dioxolanes, **1a-d**, were formed in quantitative yield in these oxidations (Reaction 3). The oxidation products were isolated by standard procedures and the structures proven by comparison of spectral and physical properties with those of authentic samples.

Reaction 3



2 $X = R_2S, R_3N$, alkene (3)

The electrophilic oxygen-atom transfer capabilities (kinetic behavior) of the 3-hydroperoxy-1,2-dioxolanes were determined at 34°C in several solvents. All kinetic runs showed excellent second order behavior overall; first order in 3-hydroperoxy-1,2-dioxolane and first order in substrate. The rate of disappearance of starting materials was identical to the rate of appearance of products. For *S*-oxidation in deuteriochloroform compounds **2a,b** and **d** were found to be of similar reactivity while **2c** was approximately one order of magnitude less reactive than any of the other dioxolanes. This trend is consistent with the electronic effects of a phenyl group at the 3-position *vs* that of a 3-methyl group. The effect of phenyl substitution at position-5 was much less pronounced. Compounds **2b** and **d** showed a slightly enhanced reactivity as compared to compound **2a** with 5,5-dimethyl groups. The oxidations tended to be roughly 7-times faster in

Table 1

Product Yields and Second Order Rate Constants for Heteroatom Oxidation and Epoxidation by 3-Hydroperoxy-1,2-dioxolanes **2a-d** at 34°C

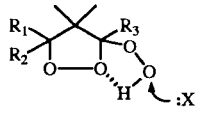
ROOH	Substrate	Product	% Yield [a]	$k_2 M^{-1}s^{-1}$ [b]	Solvent
2a	PhSMe	PhS(O)Me	91	5.3×10^{-3}	$CDCl_3$
2a	PhSMe	PhS(O)Me	96	7.7×10^{-4}	C_6D_6
2a	Et_3N	$Et_3N(O)$	98	2.5×10^{-2}	$CDCl_3$
2a	Et_3N	$Et_3N(O)$	92	3.25x10-3	CD_3CN
2a	$BzNMe_2$	$BzN(O)Me_2$	87	2.1×10^{-3}	$CDCl_3$
2a	$BzNMe_2$	$BzN(O)Me_2$	98	3.85×10^{-4}	CD_3CN
2a	2,3-Dimethyl-2-butene	epoxide	98	9.3×10^{-5}	$CDCl_3$
2b	PhSMe	PhS(O)Me	97	1.0×10^{-2}	$CDCl_3$
2c	PhSMe	PhS(O)Me	96	6.7×10^{-4}	$CDCl_3$
2d	PhSMe	PhS(O)Me	98	7.2×10^{-3}	$CDCl_3$

[a] Determined by ^1H nmr spectroscopy relative to added standard (±2%).
[b] Error ±5% of value.

deuteriochloroform than in either benzene-d_6 or deuterioacetonitrile. The results are listed in Table 1.

The 3-hydroperoxy-1,2-dioxolanes are effective new oxygen-atom transfer reagents. Their reactivity is similar to that of acyclic α-azohydroperoxides and roughly one order of magnitude lower than that of cyclic α-azohydroperoxides [2]. The relative reactivities and kinetics for the electrophilic oxygen-atom transfer reactions of the 3-hydroperoxy-1,2-dioxolanes **2a-d** are indicative of a mechanism similar to that for α-azohydroperoxide oxidations. The process involves ionic attack of the substrate on the terminal oxygen of the hydroperoxide. The relatively high reactivity of hydroperoxide oxygen can be ascribed to electronic effects (electron withdrawing groups) and to intramolecular hydrogen bonding of the hydroperoxy proton to a peroxy oxygen (Scheme 2).

Scheme 2



The lower reactivity of compounds **2a-d** *vs* that of cyclic α-azohydroperoxides [2] is likely to be a function of hydrogen bonding to oxygen in the former *vs* a *syn* azo function in the latter.

In conclusion, a new synthetic method for the synthesis of reactive oxygen-atom transfer reagents has been developed. Since the precursors, 3-hydroxy-1,2-dioxolanes, are formed as products during oxidation, this system has the potential to be a cyclic process. If achieved this would allow use of hydrogen peroxide as the active oxygen source for the regeneration of catalytic quantities of the reactive reagent **2**. New mechanistic insights into the mechanism of the substitution progress have been gained.

EXPERIMENTAL

All solvents were of reagent grade. Acetonitrile was distilled from phosphorus pentoxide and dried over molecular sieves. 2,3-Dimethyl-2-butene, thioanisole, dimethylbenzylamine and triethylamine were available commercially (Aldrich) and were distilled if necessary before use. The 3-hydroxy-3,4,4,5,5-pentasubstituted-1,2-dioxolanes **1a-d** were prepared according to the published procedure [4]. 3-Methoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane has been synthesized in our laboratory [6]. Melting points were taken on a Thomas-Hoover (Uni-melt capillary melting point apparatus) and are uncorrected. The ^{1}H nmr and ^{13}C nmr spectra were recorded on a JEOL GX-270 NMR spectrometer. The ^{1}H nmr kinetic runs were carried out on a Varian EM-360 NMR spectrometer. The ir spectra were recorded on a Bomen-Michelson 100-FT-IR spectrometer. Combustion analysis was performed by Atlantic Microlabs, Atlanta, Georgia.

3-Hydroperoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane (**2a**).

To a solution of 13.0 mg (0.059 mmole) of 3-hydroxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane in 0.6-ml of anhydrous acetonitrile, 40 μl of anhydrous hydrogen peroxide [Caution!] were added. A crystal (~1-2 mg) of *p*-toluenesulfonic acid was introduced to the above mixture (chilled by ice-bath). The reaction mixture was stirred at room temperature for 15 minutes. After rotary evaporation of the solvent (low temperature), the residue was extracted with pentane. Removal of pentane left a solid residue which was dissolved in ether. The ethereal solution was washed with chilled saturated sodium bicarbonate and dried over magnesium sulfate. The excess solvent was removed under reduced pressure to yield 12.9 mg (0.054 mmole) of 3-hydroperoxy-3-phenyl-4,4,5,5-tetramethyl-1,2dioxolane as a colorless solid (93%) which was recrystallized from pentane, mp 90-91°C; ^{1}H nmr (deuteriochloroform) δ 0.64 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 7.38-7.50 (m, 5H, ArH), 8.36 (s, 1H, OOH), ^{13}C nmr (deuteriochloroform) 18.3, 23.5, 23.7, 24.6, 58.8, 88.0, 115.8, 126.8, 128.3, 128.7, 135.5, ir (potassium bromide): 3380 cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; Found: C, 65.47; H, 7.49.

3-Hydroperoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane (**2a**).

This compound also was prepared by substitution of 3-methoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane for 3-hydroxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane in the method described above. Thus, 21.5 mg (0.091 mmole) of 3-methoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane was employed to yield 18.6 mg (0.078 mmole) of 3-hydroperoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane (86%).

cis-3-Hydroperoxy-4,4,5-trimethyl-3,5-diphenyl-1,2-dioxolane (**2b**).

To a chilled (icebath) solution of 15.7 mg (0.0552 mmole) of 3-hydroxy-4,4,5-trimethyl-3,5-diphenyl-1,2-dioxolane in 0.6 ml of anhydrous acetonitrile, 40 μl of anhydrous hydrogen peroxide was added. A crystal of *p*-toluenesulfonic acid was added immediately. The reaction mixture was stirred at room temperature for 20 minutes. The solvent was evaporated under reduced pressure. After removal of the excess hydrogen peroxide, the residue was extracted with pentane. Removal of the solvent, gave 15.8 mg (0.0526 mmole) of an isomeric mixture of *cis*- and *trans*-3-hydroperoxy-4,4,5-trimethyl-3,5-diphenyl-1,2-dioxolane (95%). The less soluble isomer was separated to yield 7.0 mg (0.233 mmole) of *cis*-3-hydroperoxy-4,4,5-trimethyl-3,5-diphenyl-1,2-dioxolane as a colorless solid (42%), mp 105-107°C; ^{1}H nmr (deuteriochloroform) δ 0.22 (s, 3H), 1.31 (s, 3H), 1.83 (s, 3H), 7.21-7.46 (m, 10H), 8.58 (br, 1H); ^{13}C nmr (deuteriochloroform) δ 18.2, 25.0, 27.4, 59.3, 91.4, 116.0, 125.1, 127.1, 128.1, 128.3, 128.9, one signal not resolved, 134.2, 143.5; ir (potassium bromide): cm^{-1} 3386.

Anal. Calcd. for $C_{18}H_{20}O_4 \cdot 0.25H_2O$: C, 70.91; H, 6.78. Found: C, 70.92; H, 6.56.

3-Hydroperoxy-3,4,4,5,5-pentamethyl-1,2-dioxolane (**2c**).

To a chilled (ice-bath) solution of 63.6 mg (0.397 mmole) of 3-hydroxy-3,4,4,5,5-pentamethyl-1,2-dioxolane in 2.0 ml of anhydrous acetonitrile, 140 μl of anhydrous hydrogen peroxide [Caution!] was added. A 5 mg portion of *p*-toluenesulfonic acid were added. The reaction mixture was stirred at room tempera-

ture for 15 minutes and then the solvent was evaporated under reduced pressure (ice-bath). The residue was extracted twice with pentane (5 ml). Removal of the pentane gave 53.4 mg (0.303 mmole) of 3-hydroperoxy-3,4,4,5,5-pentamethyl-1,2-dioxolane as a slightly yellowish oil (76%), ^{1}H nmr (deuteriochloroform) δ 1.02 (s, 3H), 1.09 (s, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 1.49 (s, 3H), 8.57 (br, 1H); ^{13}C nmr (deuteriochloroform) δ 15.1, 18.6, 23.3, 23.5, 24.0, 57.0, 87.5, 114.3; ir (nujol) cm^{-1} 3414. Compound **2c** was found to be volatile and water soluble. Chromatographic methods could not separate **2c** from the starting material **1c**. All batches were found to contain varying quantities of **1c**, usually around 20%. Elemental analysis data were satisfactory when corrected for **1c** content.

3-Hydroperoxy-4,4-dimethyl-3,5,5-triphenyl-1,2-dioxolane (**2d**).

To a chilled (ice-bath) solution of 66.0 mg (0.19 mmole) of 3-hydroxy-4,4-dimethyl-3,5-triphenyl-1,2-dioxolane in 2.0 ml of anhydrous acetonitrile, 100 µl of anhydrous hydrogen peroxide was added. A crystal (1.8 mg) of *p*-toluenesulfonic acid was added. The reaction mixture was stirred at 0-4°C for 30 minutes and then the solvent was evaporated under reduced pressure (1 mm/Hg) at the same temperature. After removing the liquid residue (excess of hydrogen peroxide), the solid residue was extracted with 20 ml of ether. The ethereal solution was washed with chilled saturated sodium bicarbonate and dried by passing through a short pipette filled with magnesium sulfate. Removal of solvent gave a residue which was triturated with pentane to yield 45.7 mg (0.126 mmole) of 3-hydroperoxy-4,4-dimethyl-3,5,5-triphenyl-1,2-dioxolane as a colorless solid (66%), mp 112-114°C; ^{1}H nmr (deuteriochloroform) δ 0.77 (s, 3H), 1.53 (s, 3H), 7.19-7.39, 7.54-7.80 (m, 15H), 7.49 (br, 1H); ^{13}C nmr (deuteriochloroform) δ 19.6, 25.4, 62.3, 92.3, 116.5, 125.6, 126.2, 126.7, 127.1, 127.8, 128.2, 129.0, two signals not resolved, 134.5, 141.5, 143.0; ir (potassium bromide): 3386 cm^{-1}.

Anal. Calcd. for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.04; H, 6.21.

Preparation of Anhydrous Hydrogen Peroxide.

Anhydrous hydrogen peroxide in ether [7] was prepared [Caution!] as follows: 1.0 ml of 70% hydrogen peroxide (FMC) was added to approximately 10 ml of anhydrous ether (Aldrich) followed by the addition of 1.0 g anhydrous sodium sulfate. The mixture was allowed to stand overnight at 4°C. The ether layer was decanted, dried over anhydrous magnesium sulfate and filtered. The ether was removed under reduced pressure (ice-bath) to yield the anhydrous hydrogen peroxide which was used immediately. Commercially available 70% hydrogen peroxide could be used in the synthesis of **2a-d** with a concomitant loss of yield.

Kinetic and Product Studies.

Heteroatom oxidation with 3-hydroperoxy-3,4,4,5,5-pentasubstituted-1,2-dioxolanes **2a-d**. The following general procedure was employed for all kinetic experiments of heteroatom (S,N) oxidation. About 0.040 mmole of hydroperoxide was dissolved in 0.500 ml of deuteriochloroform (or perdeuteriobenzene) containing anisole as internal standard in a new 5 mm nmr sample tube. The desired quantity of thioanisole (or triethylamine) to achieve a ratio of peroxide to substrate of about 1:1.5 was injected and mixed. The solution was maintained at 34°C (Varian EM-360 NMR spectrometer). The ^{1}H nmr spectra were recorded and integrated at various time intervals (every 2-10 minutes). The kinetic data were determined by monitoring the appearance of sulfoxide (or *N*-oxide) and/or the disappearance of hydroperoxide relative to the internal standard, and obtained for at least 2 half lives with excellent correlation coefficients (≥0.99, all cases). The products, sulfoxide (or *N*-oxide) and corresponding 3-hydroxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane, were separated and the structures were proven by comparison of their ^{1}H nmr spectra with those of authentic samples.

Epoxidation by 3-Hydroperoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane.

3-Hydroperoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane (9.4 mg, 0.04 mmole) was dissolved in a 0.500 ml of deuteriochloroform in a new 5 mm nmr sample tube containing 13.2 mg of anisole as the internal standard. Then 5.07 mg (0.0603 mmole) of 2,3-dimethyl-2-butene was injected *via* syringe. The solution was maintained at 34°C (HAAKE bath). The ^{1}H nmr spectra were taken at 1.5 hour intervals. The yield of tetramethyloxirane (98%) was determined relative to the internal standard. Second-order plots for the epoxidation reaction were linear for at least 2 half-lives (correlation coefficient >0.99). The product, 3-hydroxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane **1a**, was found to begin decomposition to pinacolone and benzoic acid under the experimental conditions after one day. Meanwhile, an independent experiment on the thermolysis of 3-hydroperoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane **2a** in deuteriochloroform at 34°C showed only 6% decomposition after a week. The structure of oxirane and 3-hydroxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane was proven by spectral methods.

Acknowledgment.

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