THERMOLYSIS OF 3-[(TRIMETHYLSILYLOXY)METHYL]-3,4,4-TRIMETHYL-1,2-DIOXETANE: ACTIVATION PARAMETERS, CHEMIEXCITATION YIELDS AND DEPROTECTION

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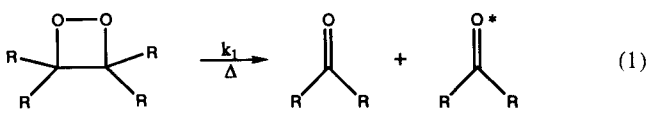
3-[(Trimethylsilyloxy)methyl]-3,4,4-trimethyl-1,2-dioxetane, 1, was prepared in good yield by reaction of 3-hydroxymethyl-3,4,4-trimethyl-1,2-dioxetane, 2, with trimethylsilyl chloride according to the published procedure. Purification was accomplished via low-temperature column chromatography. The activation parameters for the thermolysis of 1 and 2 in xylenes were determined by the isothermal method (for 1: E_a = 26.0 ± 0.6 kcal/mol; $\Delta H^{\ddagger}$ = 25.3 ± 0.6 kcal/mol; $\Delta S^{\ddagger}$ = -2.9 eu; $\Delta G^{\ddagger}$ = 26.2 kcal/mol; $k_{60°}$ = 1.1 x 10^{-4} s^{-1}; for 2: E_a = 25.6 ± 0.7 kcal/mol; $\Delta H^{\ddagger}$ = 24.9 ± 0.7 kcal/mol; $\Delta S^{\ddagger}$ = -3.4 eu; $\Delta G^{\ddagger}$ = 26.1 kcal/mol; $k_{60°}$ = 1.6 x 10^{-4} s^{-1}). The chemiexcitation yields for 1 and 2 were determined by the DPA/DBA method: for 1 ϕ^S = 0.16%; ϕ^T = 17%; for 2 ϕ^S = 0.18%; ϕ^T = 9%. The results for 2 were in reasonable agreement with literature values. Treatment of solutions of 1 with excess tetrabutylammonium fluoride resulted in the removal of the trimethylsilyl protecting group.

Keywords: dioxetane; chemiluminescence; triplet state; trimethylsilyloxydioxetane.

INTRODUCTION

The 1,2-dioxetanes, four-membered cyclic peroxides, have been shown[1] to undergo a characteristic thermal decomposition to two carbonyl fragments one of which may be produced in an excited state resulting in chemiluminescence (reaction 1).



(1)

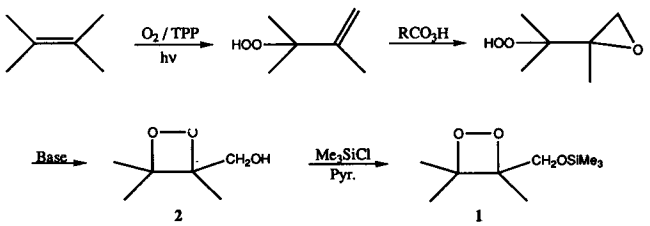
1,2-Dioxetane

* denotes electronically excited carbonyl fragment

Historically, 1,2-dioxetanes and α-peroxylactones (dioxetanones) had been proposed[2] as intermediates in chemiluminescent and bioluminescent processes. The discovery of synthetic methods[3] for the preparation of these unusual strained-ring compounds opened many new, exciting areas of investigation.[1] Thermolysis of alkyl, alkoxy and aryl substituted dioxetanes has been found[1] to lead to direct production of high yields of excited triplet carbonyl fragments. The mechanism of this process is often interpreted in terms of a diradical-like process. "Triplet"-type dioxetanes generally require the presence of added fluorescer to yield strong chemiluminescence. Another type of dioxetane, containing easily oxidized groups,[1] has been noted to be of lower stability and to generate high yields of excited singlet fragments via an electron exchange process to yield directly strong chemiluminescence. The potential roles of dioxetanes in dark biological processes have been examined by Cilento.[4] Recent results have demonstrated[5] that "triplet"-type dioxetanes have photogenotoxic activities. Schaap has shown[6] that oxyaryl groups on dioxetanes can be protected by silylation and that deprotection by fluoride ion results in rapid, chemiluminescent decomposition. We report here the properties of 3-[(trimethylsilyoxy)methyl]-3,4,4-trimethyl-1,2-dioxetane.

RESULTS

3-[(Trimethylsilyloxy)methyl]-3,4,4-trimethyl-1,2-dioxetane, **1**, was prepared in good yield by reaction of 3-hydroxymethyl-3,4,4,-trimethyl-1,2-dioxetane, **2**, with trimethylsilyl chloride according to the published procedures (Scheme 1).[7,8]



Scheme 1[7,8]

The dioxetane **1** was purified by low-temperature column chromatography. Characterization was accomplished by spectroscopy and by analysis of the thermolysis (cleavage) products.

The rates of thermolysis of dioxetanes **1-2** were monitored by the decay of chemiluminescence intensity in aerated xylenes with added fluorescers at constant temperatures. The rates of thermal decomposition were first order for at least three half-lives and showed no dependence on the type or amount of added fluorescer. The first-order rate constants (k_1) were determined over a 50° C temperature range. Correlation coefficients were 0.995 or greater for all cases. The activation parameters, shown in Table 1, were determined by the Arrhenius method.

Table 1. Activation Parameters[a] for the Thermolysis of Dioxetanes **1** and **2** in Xylenes.

Dioxetane	$\Delta H^{\ddagger}$(kcal/mol)	$\Delta S^{\ddagger}$(eu)	$\Delta G^{\ddagger}$(kcal/mol)	$k_1 s^{-1}$(60°C)
1	25.3 ± 0.6	-2.9	26.2 ± 0.6	1.1 x 10^{-4}
2	24.9 ± 0.7	-3.4	26.1 ± 0.7	1.6 x 10^{-4}

[a] calculated for 60° C; errors are 95% confidence limits.

As expected for this type of dioxetane, the thermolyses of **1-2** without the presence of added fluorescers showed only

weak chemiluminescence. Addition of 9,10-dibromoanthracene (DBA) or 9,10-diphenylanthracene (DPA) to solutions of the dioxetanes greatly increased the intensity of chemiluminescence without affecting the kinetics. The yields of chemiexcitation generated during dioxetane thermolysis at 60° C were determined by the chemiluminescence (DBA/DPA) method. Figure 1 shows the data for dioxetane **1**. For both dioxetanes, thermolysis directly produced high yields of excited triplets (ϕ^T), ϕ^T = 0.17 for **1** and 0.09 for **2**, and low yields of excited singlets (ϕ^S) (see Table 2).

Table 2. Chemiexcitation Yields[a] for the Thermolysis of Dioxetanes **1** and **2** in Xylenes at 60° C.

Dioxetane	ϕ^T	intercept/slope[b]	ϕ^S	intercept/slope[b]
1	0.17	471	0.0016	80
2	0.09	467	0.0018	81

[a]Instrument calibrated with tetramethyl-1,2-dioxetane: ϕ^T = 0.30; ϕ^S = 0.0015.
[b]Measure of lifetime of excited species.

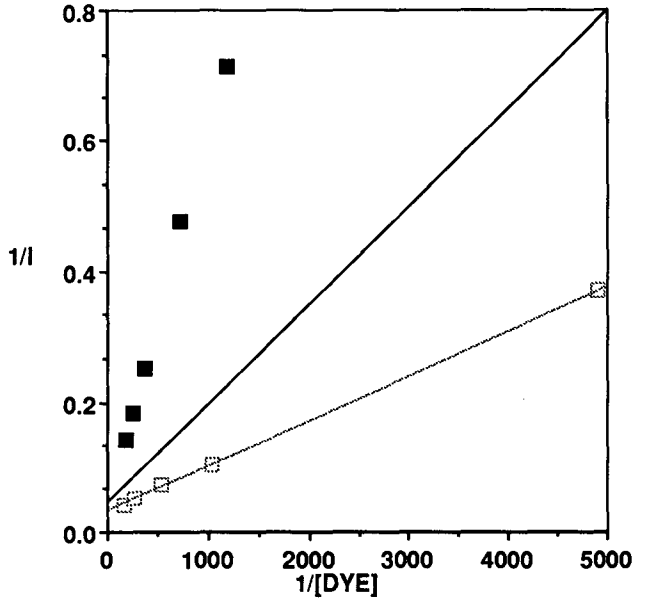
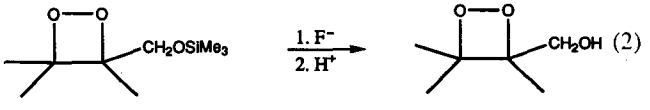


Figure 1. Plot of 1/(intensity) vs 1/[dye] for dioxetane 1 (filled squares - DPA; open squares - DBA) at constant volume, temperature (70° C) and [dioxetane]$_o$ for determination of chemiexcitation yields.

The removal of the silyl group of silyl ethers by fluoride ion is a standard reaction in organic synthesis.[9] Treatment of dioxetane **1** with one equivalent of fluoride ion at ambient temperature resulted in the slow removal of the trimethylsilyl protecting group to regenerate dioxetane **2** in good yield (rxn 2). This reaction was investigated at higher temperatures by the chemiluminescence method. Addition of excess fluoride ion to solutions of **1** in xylenes with DPA as added fluorescer resulted in a change in the kinetic behavior from that of **1** to that of **2** within five minutes. The data from an experiment at 70° C are shown in Fig. 2.



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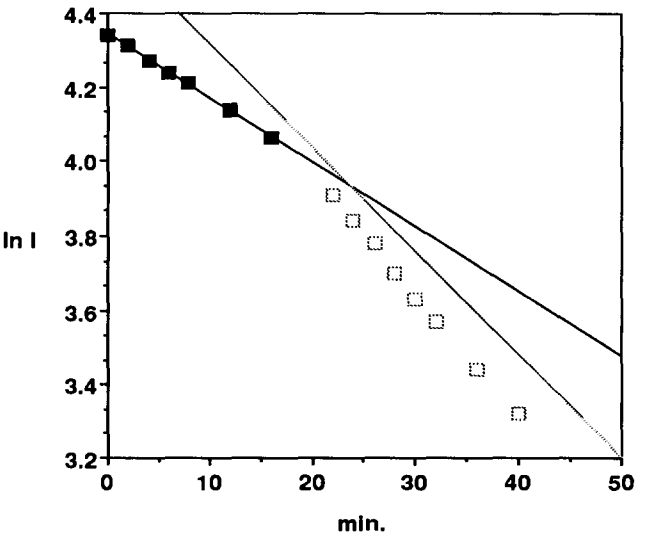

Figure 2. Semi-log plot of chemiluminescence intensity vs time for dioxetane 1 in xylenes (DPA - fluorescer) at 70° C before (filled squares) and after (open squares) addition of fluoride ion.

DISCUSSION

The activation parameter data for the thermolysis of dioxetanes **1** and **2** are similar to those of tetramethyl-1,2-dioxetane and related compounds as expected for normal "alkyl" dioxetanes.[1] The results for **2** are in agreement with literature values obtained[10] by the nonisothermal method. Agreement of activation parameters obtained by the isothermal and nonisothermal methods is indicative of metal-ion free (uncontaminated) solvents.[1] The chemiexcitation yields for the thermolysis of **1** and **2** are as expected[1] for normal "triplet"-type dioxetanes. The values for **2** are in excellent agreement with the published values.[10] The data suggest that these dioxetanes are undergoing thermolysis by the standard process. The results for dioxetanes **1** and **2** are typical[1] of those for "alkyl" dioxetanes.

The desilylation of dioxetane **1** in non-polar solvents was much slower than the desilylation of oxyaryl groups in acetonitrile (seconds) noted[6] by Schaap. Nevertheless, the yield of **2** was moderate which indicates that the tetrasubstituted dioxetane ring is not undergoing nucleophilic attack[11] at the peroxide bond by fluoride ion. Furthermore, the isolation of **2** suggests that the stability of the anion of dioxetane **2** is similar to that of **2**. This conclusion is confirmed by the results of the experiment shown in Figure 2. The value of the rate constant after fluoride ion addition to **1** was within experimental error of that for **2**. Since no proton source other than advantageous water was present, this suggests that the ion of **2** is undergoing thermolysis with a rate similar to that of **2** and with a similar chemiexcitation yield. This indicates that the results for **2** are not affected by intramolecular hydrogen-bonding of the hydroxy group to a dioxetane-ring oxygen.

EXPERIMENTAL

All solvents were of reagent grade. The ^{1}H NMR spectra were recorded on the Varian EM-360L and JEOL GX-270 NMR spectrometers. 9,10-Diphenylanthracene (Aldrich) and 9,10-dibromoanthracene (Aldrich) were recrystallized from xylenes (Aldrich) before use. [*Caution*: all safety procedures[1] for the synthesis, handling and storage of peroxidic materials must be followed.] 2,3-Dimethyl-3-hydroperoxybut-1-ene oxide was prepared[7] according to the published procedure. 2,3-

Dimethyl-2-butene (Aldrich) was used without additional purification. Singlet oxygenation was carried out by use of a 150 watt sodium lamp.

Dioxetane Synthesis

3-[(Trimethylsilyloxy)methyl]-3,4,4-trimethyl-1,2-dioxetane (1)

Dioxetane **1** was prepared according to the published procedure[8]: to 3.79 mmol of trimethylsilyl chloride (Aldrich) dissolved in 7.5 ml of methylene chloride (cooled to 0°C), 300 mg of pyridine was added via a dropping funnel equipped with a $CaCl_2$ drying tube. Within 10 minutes 1.89 mmol of 3-hydroxymethyl-3,4,4-trimethyl-1,2-dioxetane (**2**) in 7.5 ml of methylene chloride was added. After 40 minutes, the solvent was evaporated under reduced pressure at low temperature to give the crude dioxetane as a yellow oil.

The dioxetane was purified by column-chromatography at 0°C using a jacketed 1 cm i.d. column packed with 20 g of silica gel containing 1% Na_2EDTA (pentane). The impure dioxetane was added to the column and washed with 50 ml of pentane followed by successive 50 ml additions of a 10% methylene chloride/pentane (v/v) step gradient. Fractions were assayed for dioxetane content by placing a 25 µl aliquot into a heated DBA solution (1 ml) in the chemiluminescence apparatus. Fractions containing the dioxetane were combined and the solvent removed under reduced pressure. The purified dioxetane **1** was a pale yellow oil. The purity was checked by ^1H NMR spectroscopy. The isolated yield of dioxetane was approximately 50%. The dioxetane was stored in deuteriochloroform at -30°C or lower with little decomposition noted even after several months of storage. Partial hydrolysis of **1** was noted for wet samples after two months of storage. The ^1H NMR data (deuteriochloroform) are: for **1** δ 0.16 (s, 9H), 1.45 (s, 6H), 1.64 (s, 3H), AB system δ_A 3.81, δ_B 4.18 (J_{AB} = 10.2 Hz, 2H).

3-Hydroxymethyl-3,4,4-trimethyl-1,2-dioxetane (2)

Dioxetane **2** was prepared according to the literature procedure[7] as follows: a 25% aqueous solution of tetramethylammonium hydroxide (68.43 mmol) was added to a solution of 2,3-dimethyl-3-hydroperoxybut-1-ene oxide (27.37 mmol) in ether (135 ml) at 10°C. Reaction progress was monitored by measuring increase in chemiluminescence intensity (maximum in 2-4 hours). The organic layer was separated and the aqueous layer was extracted with ether and methylene chloride. The ether layer and the organic extractions were dried over anhydrous magnesium sulfate and the solvents were evaporated under reduced pressure at low temperature. Three recrystallizations from cold pentane yielded the pure yellow crystals (67%) of **2**. ^1H NMR (deuteriochloroform) δ1.35 (s, 3H), 1.45 (s, 3H), 1.65 (s, 3H), 2.30 (s, 1H), AB system δ_A 3.71, δ_B 4.20 (J_{AB} = 12.0 Hz, 2H).

Product Studies

The following general procedure was employed for the thermolysis of dioxetanes **1-2**. A solution of dioxetane (approximately 0.2 M) in carbon tetrachloride was heated at 60° C in a sealed NMR sample tube until the yellow color disappeared. In all cases, the expected carbonyl fragments were the sole products detected by NMR spectroscopy. In addition, the decomposition products were obtained under milder conditions by the metal-ion catalytic route.[1] Traces of Cu^{+2} ions were added to the dioxetane solution by dipping a Cu wire into the solution. The dioxetane was observed to decompose within minutes under those conditions at ambient temperature. The carbonyl products were identified by comparison with authentic samples.

Kinetic Studies

The chemiluminescence monitoring system is essentially identical with that previously described.[1] The reaction cell was jacketed and the temperature maintained by using a constant temperature bath ±0.1°C. The temperature in the cell was monitored by use of a YSI Model 425C apparatus with a series 400 probe (±0.2°C). The cell was pretreated with a concentrated aqueous Na_2EDTA solution and washed with solvent before use. Kinetic experiments were carried out employing 1.0 mL of xylenes (mixture of isomers) as solvent. The initial dioxetane concentration was low (approximately 10^{-4} M) in order to avoid complications from induced decomposition. Experiments carried out without added fluorescer or with low concentrations (~10^{-3} M) of DBA or DPA were of the first order for at least three half-lives and showed no measurable dependence on the type or amount of added fluorescer. The deprotection studies were carried out by addition of 20 µL of a 1.0 M tetrabutylammonium fluoride solution in tetrahydrofuran to the cell (DPA in xylenes). Addition of up to 100 µL of the fluoride solution yielded essentially identical results. The cell had to be cleaned (decontaminated) after several runs to restore the initial rates to the normal values.

Chemiexcitation Yields

The instrument was calibrated[1] with tetramethyl-1,2-dioxetane by taking the triplet yield (ϕ^T determined by the DBA method) as 0.30 and the singlet yield (ϕ^S determined by use of DPA) as 0.15% at 60° C. All measurements were carried out at constant volume with a constant initial concentration of each dioxetane with variation of the fluorescer concentration. The ϕ^T and ϕ^S yields were calculated by a method that has been discussed in detail ($\phi^T = I_{max}\ \phi^{ET}\phi^S_{DBA}/k_1[D]_0$ and $\phi^S = I_{max}/k_1[D]_0$).[1] The concentrations of the dioxetanes were determined by ^1H NMR spectroscopy vs concentration of added standard. The error in the chemiluminescence method is estimated to be ±50% of observed value.

Trimethylsilyl Removal

To 12 mg of dioxetane **1** (0.06 mmol) in 0.5 mL of deuteriochloroform in an NMR sample tube was added 1.1 equivalents of $(n\text{-}Bu)_4$ N F (30 µl of a 1.0 M solution in THF). The progress of the reaction was monitored by ^1H NMR spectroscopy by following the changes in the trimethylsilyl group signal. After ~3 hrs, ^1H NMR spectroscopy showed complete conversion of **1** to dioxetane **2** and Me_3SiF. The deuteriochloroform solution was added to a mixture of 2.0 mL of pentane and 0.1 mL of deionized water. The resulting cloudy organic layer was separated and filtered through anhydrous magnesium sulfate. The clear filtrate was evaporated under reduced pressure (caution: the dioxetane can be lost to evaporation) at 0° C (ice-water bath). The residue was recrystallized (pentane) to yield 6.0 mg (75% yield) of pure dioxetane **2**.

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