Thermolysis of Tetra(methyl-d_3)-1,2-dioxetane: β-Deuterium Isotope Effect

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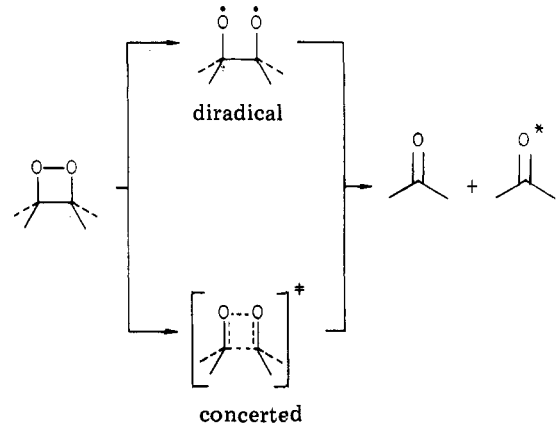
The thermal decomposition of 1,2-dioxetanes has been shown to produce two carbonyl fragments in quantitative yield, one of which may be produced in an excited state.[2] For alkyl-, aryl-, and alkoxy-substituted dioxetanes,[3] two mechanistic extremes were considered[2] to explain the unique process that leads to direct production of high yields of excited triplet carbonyls: (a) diradical (two-step) and (b) concerted (see Scheme I). Most results have been interpreted[2,4] to support a two-step mechanism. No experimental data, to date, have required a concerted interpretation.[2,4] Recent results[5] have shown that substituents can effect the activation parameters of dioxetane thermolysis in unexpected ways. Studies of the effects of 3,4-cyclic substituents on dioxetane properties have shown[5a,c-e] that the activation energies vary with ring size ($6 > 8 > 5 \simeq 7$) while little or no effect was observed in the log A terms. The results for a series of 3,3-dialkyl-1,2-dioxetanes[6] indicated that increased steric interactions produced higher values of activation energies (with little or no effect on ΔS^*). The origin of substituent effects on the thermolysis of dioxetanes is unclear.[6b] We report the synthesis and characterization of tetra(methyl-d_3)-1,2-dioxetane (1), the results of which clearly show an inverse secondary β-deuterium isotope effect on the thermal decomposition.

Results and Discussion

Tetra(methyl-d_3)-1,2-dioxetane (1) was prepared in low yield by the method of Kopecky.[7] Tetra(methyl-d_3)-ethylene was converted to the β-bromo hydroperoxide by the standard procedure.[7] The β-bromo hydroperoxide in CH_2Cl_2 was treated with AgOAc to yield a crude sample of 1 as a yellow oil. Crystallization of 1 from pentane at

Scheme I[a]



[a] An asterisk denotes excited state.

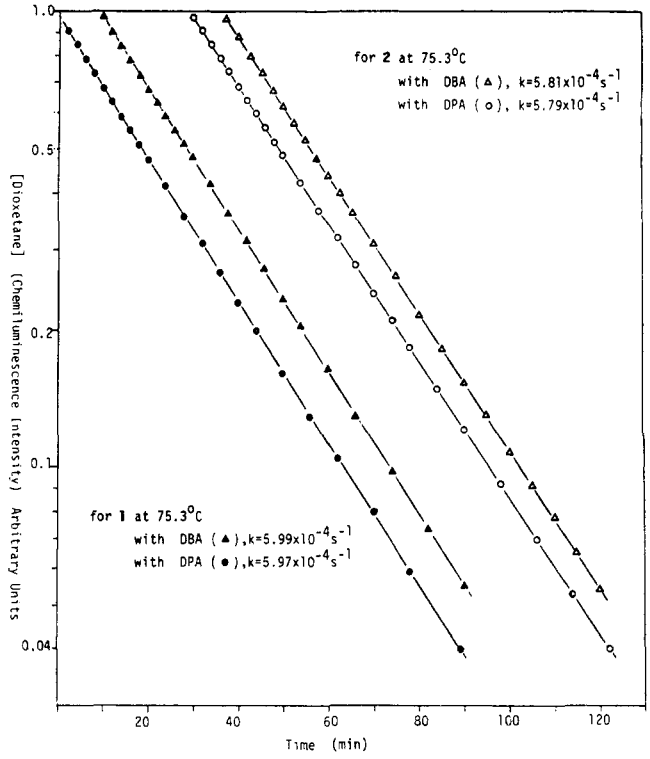
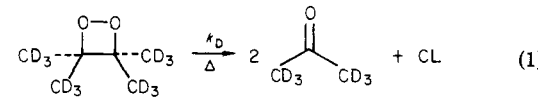


Figure 1. Semilog plots of [dioxetane] vs. time for the thermolysis of 1 (filled symbols) and 2 (open symbols) in xylenes at 75.3 °C with DBA (triangles) or DPA (circles) as added fluorescers (k_H/k_D per molecule = 0.97).

-78 °C yielded analytically pure dioxetane (5%) as yellow needles. Thermal decomposition of 1 in CCl_4 produced acetone-d_6 as the sole observable product (reaction 1).



(1)

1

CL = chemiluminescence

The rates of thermal decomposition of 1, monitored by the chemiluminescence method,[2a] were cleanly first order for at least 4 half-lives and were unaffected by the addition of varying concentrations of fluorescent dyes [9,10-dibromoanthracene (DBA) or 9,10-diphenylanthracene (DPA)] or aqueous Na_2EDTA.[2,4b] Under identical conditions (temperature setting and concentrations), the rate

(1) Fellow of Camille and Henry Dreyfus Foundation, 1981-1986.

(2) For reviews, see: (a) Wilson, T. *Int. Rev. Sci.: Phys. Chem. Ser. Two* **1976**, *9*, 265. (b) Adam, W. *Adv. Heterocycl. Chem.* **1977**, *21*, 437. (c) Horn, K. A.; Koo, J.; Schmidt, S. P.; Schuster, G. B. *Mol. Photochem.* **1978-9**, *9(1)*, 1. (d) Baumstark, A. L. In "Singlet Oxygen" Vol. II; Frimer, A., Ed.; CRC Press: Boca Raton, FL; Uniscience Series, 1984, in press.

(3) The electron-transfer mechanism(s) of chemiluminescent decomposition (high yields of excited singlets) does not occur readily with alkyl-substituted-1,2-dioxetanes.

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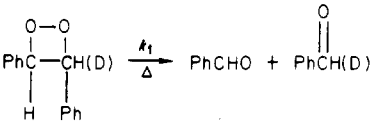
Table I. First-Order Rate Constants for the Thermal Decomposition of 1 and 2 in Xylenes[a]

T,[b] °C	10^4k_D, s^{-1}	10^4k_H, s^{-1}	k_H/k_D[c]
60.5	1.12[d]	1.09[d]	0.97[d]
61.8	1.38 ± 0.03	1.32 ± 0.01	0.96
65.3	2.00	1.91	0.96
66.5	2.37 ± 0.01	2.26 ± 0.01	0.95
69.7	3.31	3.15	0.95
70.1	3.36 ± 0.06	3.26 ± 0.05	0.97
71.0	4.27	4.14	0.97
72.8	4.55 ± 0.02	4.44 ± 0.02	0.98
74.1	5.02 ± 0.02	4.89 ± 0.01	0.97
74.2	5.02	4.92	0.98
74.2	5.06[d]	4.90[d]	0.97[d]
75.3	5.99	5.81	0.97
75.3	5.97[d]	5.79[d]	0.97[d]
75.5	6.06 ± 0.01[d]	5.92 ± 0.01[d]	0.98[d]
75.6	6.21 ± 0.06	5.98 ± 0.01	0.96
79.0	8.68	8.54	0.98
79.7	9.57	9.38	0.98
82.1	12.2 ± 0.1	12.0 ± 0.1	0.98
84.7	15.7	15.3	0.97
86.0	17.1 ± 0.1[e]	16.8 ± 0.1[e]	0.98[e]
87.5	20.8 ± 0.3	20.4 ● 0.3	0.98
90.0	27.8[d]	27.1[d]	0.98[d]

[a] $[dioxetane]_0 \simeq 10^{-4}$, $[DBA] \lesssim 5 \times 10^{-3}$ M. All errors are standard deviations. [b] ±0.3 °C. Experiments with 1 and 2 were carried out without altering the temperature bath settings for each set of conditions. [c] Per molecule. [d] DPA (5×10^{-3} M) as added fluorescer. [e] No added fluorescer (DBA or DPA).

Scheme II[4d]



3

$k_H/k_D = 1.01 \pm 0.02$

of thermolysis of 1 was always greater than that of tetramethyl-1,2-dioxetane, 2 (see Figure 1). A β-deuterium isotope effect (k_H/k_D) of 0.96 ± 0.01 to 0.98 ± 0.01 was observed for the thermolysis of 1 from ~60 °C to 90 °C. The magnitude of the observed β-deuterium isotope effect is not large. However, the data are reproducible and observable over a reasonable temperature range and clearly show an inverse isotope effect on the thermolysis of 1. The data are summarized in Table I.

The yields and types of excited states were measured by the DBA/DPA method.[2] The yield of excited triplet acetone-d_6, directly produced during the thermal decomposition of 1, was found to be 21 ± 10% while the yield of singlet excited acetone-d_6 was found to be ≤0.2%. The results are indistinguishable from those reported[2,4e] for 2.

The present study is the first example of a measurable deuterium isotope effect on dioxetane thermolysis. Previously, Schuster had shown[4d] that there were no measurable[2c] kinetic or product isotope effects on the thermal decomposition of *trans*-3,4-diphenyl-1,2-dioxetane (3) for the substitution of a deuterium for a dioxetane ring proton (Scheme II). The results of Schuster were taken as consistent[2c,4d] only with a biradical mechanism of thermolysis.

The diradical (two-step) mechanism of alkyl dioxetane thermolysis seems well-established.[2,4] Since O–O bond cleavage is rate determining for the diradical process, the present results may be viewed as "formal" γ-deuterium isotope effects and should provide insights into the nature of the transition state for diradical formation. Secondary deuterium isotope effects can be difficult to interpret,[10] but the observed data can be considered in terms of steric effects on the CD_3 groups. Inductive effect arguments appear not applicable since previous studies have shown that formal substitution of alkyl by aryl or alkoxy groups produced[2] no measurable effects. Inverse secondary deuterium isotope effects (based on a steric explanation)[10a] are indicative of a reaction that goes through a transition state which is sterically more strained than the reactant. This approach would suggest that there are increased steric interactions on the methyl groups in the transition state for dioxetane thermolysis. Restated in terms of force constant change terminology, there is an increased force field (bending force constants) in the transition state of dioxetane thermolysis caused by steric compression.[10]

Another aspect that must be considered is steric energy differences. Calculations have shown[11] that the steric energy of 1 is ~1 kcal/mol less than that of 2. However, these differences would have been expected to produce a normal secondary deuterium isotope effect rather than the observed inverse effect. Consistent with the results[6b] on 3,3-dialkyl-1,2-dioxetanes, the present study indicates that there is steric compression in the transition state for dioxetane thermolysis.

Experimental Section

All solvents were of reagent grade. ^1H NMR spectra were recorded on a Varian 360L spectrometer. Gas chromatographic studies were carried out with a Varian Model 920 GC with a 6 ft × 0.25 in. SE-30 on Chromosorb W column. 9,10-Diphenylanthracene (DPA, Aldrich) was used without further purification. 9,10-Dibromoanthracene (DBA, Aldrich) was recrystallized from xylenes before use. Tetra(methyl-d_3)ethylene was prepared by reductive coupling of acetone-d_6 (99.5% D) by the procedure of Tyrlik and Wolochowicz.[8] Combustion analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA 30303.

Dioxetane Synthesis. Tetra(methyl-d_3)-1,2-dioxetane (99+% D, 1) was prepared according to the published procedure[7] for tetramethyl-1,2-dioxetane as follows: 1.4 g (~0.065 mmol) of the β-bromo hydroperoxide of tetra(methyl-d_3)ethylene, prepared in 72% yield by standard procedure,[7] in CH_2Cl_2 was treated with 1.0 g (~0.065 mmol) of freshly prepared silver acetate for 15 min in the dark. The solution was filtered and the solvent removed under reduced pressure. The resulting yellow oil was crystallized from pentane at −78 °C to yield 44 mg (5%) of analytically pure dioxetane 1 as yellow needles: [mp 74–76 °C dec, sealed capillary tube, preheated oil bath; anal. ($C_6D_{12}O_2$) C, D; IR (CCl_4) 2260 w, 2245 w, 1298 w, 1210 w, 1160 w, 1135 m, 1070 w, 1160 m, 1050 w; mass spectrum EI, m/e (relative intensity) 130 (M + 2, 0.15), 129 (M + 1, 1.72), 128 (M, 28.9), 96 (99.8), 78 (99.9), 64 (32.1), 46 (base)]. Samples of 1 were stored as the solid at −30 °C in the dark for months with no detectable decomposition.

Decomposition Studies. A 0.2 M solution of 1 in CCl_4 was heated until the yellow color disappeared. Acetone-d_6 was the sole thermolysis product detected by VPC analysis. Acetone-d_6 was identified by comparison of the IR spectrum with that of an authentic sample.

Kinetic Studies. The chemiluminescence monitoring system is essentially identical to that described previously.[9] The temperature (±0.3 °C) of the reaction mixture was monitored by using a YSI Probe Model 42SC with a no. 423 probe. The cell was pretreated with a concentrated aqueous Na_2EDTA solution. All runs were carried out in xylenes (Aldrich) as the solvent. The initial dioxetane concentrations of all runs were ~10^{-4} M or less in order to avoid complications due to induced decomposition of the dioxetanes. Experiments were monitored for over 4 half-lives. First-order plots of light intensity (dioxetane concentration) vs.

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(11) The steric energy of 1 = 32.81 kcal/mol and that of 2 = 33.75 kcal/mol were calculated (MM2) by Graham Whitesell of Prof. F. M. Menger's group at Emory University, Atlanta, Ga.

time showed no curvature over 4 half-lives. Rate constants were determined by least-squares analysis. Correlation coefficients were greater than 0.999 for all runs. At a given temperature setting, the rate constants were reproducible (see Table I). The error in measurement (±0.3 °C) of the reaction mixture temperature was greater than the thermal stability (±0.1 °C) of the system. Therefore, experiments with 1 and 2 were always carried out without altering the temperature bath settings for each set of runs. Runs with 5.0×10^{-4} M DPA or no added fluorescer yielded results identical with those with DBA (concentration = 5.0×10^{-4} M or less).

Yields of Excited States. The apparatus was calibrated by taking the yield of triplet acetone from **2**, determined by the DBA method, as 0.30 at 60 °C. All experiments were carried out at 60 °C with a constant concentration (initial) of dioxetane. The concentrations of DBA or DPA were varied. The method of calculation of singlet and triplet carbonyl yields by the DBA/DPA method has been discussed in detail.[2] Acetone-d_6 was assumed to have identical properties with those of acetone.

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Registry No. 1, 88635-83-0; 2, 35856-82-7; AgOAc, 563-63-3; D_2, 7782-39-0; Na_2EDTA, 139-33-3; β-bromotetra(methyl-d_3)-ethane hydroperoxide, 90531-19-4; 9,10-dibromoanthracene, 523-27-3; 9,10-diphenylanthracene, 1499-10-1.

Lead Tetraacetate Oxidation of Oxyprotoberberines. A Convenient Synthesis of 13-Oxygenated Berbines and Oxyprotoberberines

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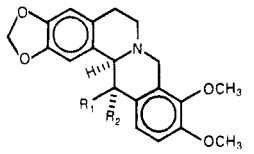
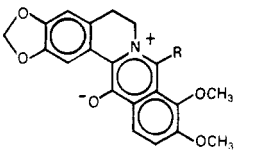
Ophiocarpine (1) is a member of a small subgroup of berbine alkaloids characterized by a hydroxyl group in ring C.[1] Stereochemically, the 13,13a hydrogens in the naturally occurring alkaloids possess a cis relationship. The relationship of **1** to the catecholamines (e.g., epinephrine)



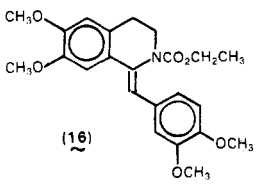
(1) R_1 = OH, R_2 = H

(2) R_1 = H, R_2 = OH



(3) R = H

(4) R = OMe

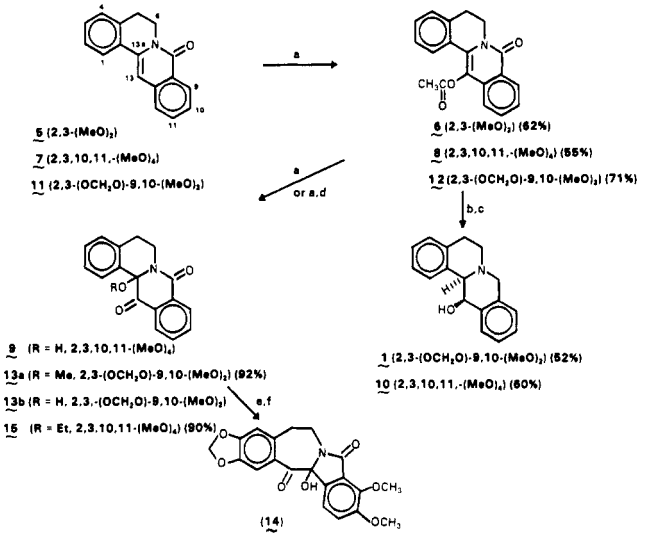


(16)

and its intermediacy in the biosynthesis of the phthalide–isoquinoline and rhoeadine alkaloids[2] has resulted in a variety of synthetic approaches to these compounds. The initial synthesis proceeded from the naturally occurring phthalide–isoquinoline alkaloid, hydrastine, to generate the correct stereochemistry.[3] These syntheses were, in a sense, a reverse biomimetic synthesis. Subsequent approaches, starting from a benzylisoquinoline, have yielded the epimeric epiophiocarpine (**2**), which is not naturally occurring, as the predominant or exclusive product.[4] A solution to the stereoselective reduction of protoberberine derivatives was found when it was observed that borohydride reduction of berberinephenol betaine (**3**),[5] or its 8-methoxy derivative,[6] gave predominantly ophiocarpine (**1**). Presumably, the amine, resulting from the initial reduction, controls the subsequent reduction of the 13-ketone or its enolate to form **1** in preference to **2**. Both **3** and **4** were ultimately derived from the commercially available protoberberine alkaloid berberine chloride.

Since the generality and synthetic limitations for the preparation of compounds **3** and **4** are not known, we decided to approach the synthesis of 13-hydroxyberbines, possessing the correct natural stereochemistry, by using a class of compounds which were readily accessible by a variety of synthetic methods. Additionally oxygen had to be introduced at what ultimately becomes the C13 hydroxyl group and the amino function had to be generated first to control the stereochemistry of the C13 alcohol. To meet these requirements, we selected the oxyprotoberberines because they are synthetically readily available[7]

Scheme I[a]



[a] Reagents: (a) lead tetraacetate, (b) lithium aluminum hydride, (c) sodium borohydride, (d) alcohol, *p*-toluenesulfonic acid, (e) HCl, (f) aqueous ammonia.

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