Inorganics) was recrystallized from hexane. Iron pentacarbonyl (Pressure Chemicals) was distilled under nitrogen in the dark. *tert*-Butyl peroxide and hydroperoxide were commercial samples that were purified according to literature procedures.[4] Di-*n*-hexyl peroxide [bp 65 °C (0.23 torr); lit.[5] bp 58 °C (0.5 torr)], di-*sec*-butyl peroxide [bp 43 °C (18 torr); lit.[6] bp 59 °C (50 torr)], *n*-hexyl hydroperoxide [bp 47 °C (2.3 torr); lit.[7] bp 42 °C (2 torr)], and *sec*-butyl hydroperoxide [bp 45 °C (11 torr); lit.[8] bp 41 °C (11 torr)] were all prepared by following literature procedures.

^{1}H NMR spectra were recorded on a Varian T-60 spectrometer, and GLC analyses were performed on a Varian Model 90P instrument equipped with a thermal-conductivity detector and a Hewlett-Packard Model 3380A electronic integrator. Unexceptional internal standard techniques were employed for quantitation. HPLC assays were carried out on a Waters Associates Model 6000A instrument equipped with a refractive index detector. Capillary GC/MS was carried out on a Hewlett-Packard Model 5985B instrument employing 50 m × 0.25 mm fused silica columns of Carbowax 20M or methylsilicone.

Typical Reactions between Alkyl Peroxides and Hydroperoxides and Dicobalt Octacarbonyl and Iron Pentacarbonyl. In an inert-atmosphere drybox dicobalt octacarbonyl (0.342 g, 1.00 mmol) was placed in a 40-mL centrifuge tube equipped with a Teflon-coated stirrer bar. The vessel was capped with a rubber septum and removed to the bench top. Benzene (5 mL) was added by syringe and the vessel cooled in a temperature bath to 6–8 °C. To this solution was subsequently added by syringe, slowly and with vigorous stirring, a solution of *n*-hexyl hydroperoxide (0.591 g, 5.00 mmol) in benzene (5 mL). After an appropriate time (see Table II), the resulting mixture was filtered under nitrogen and analyzed by HPLC on a μ-Bondapak C_{18} column by using methanol–water (30:70).

Reaction of Iron Pentacarbonyl with *sec*-Butyl Hydroperoxide. A solution of *sec*-butyl hydroperoxide (451 mg, 5.00 mmol) in benzene (5 mL) was injected into a 40-mL centrifuge tube equipped with a Teflon-coated stirrer bar and capped with a rubber septum. The vessel was cooled (6–8 °C) before a solution of iron pentacarbonyl (196 mg, 1.00 mmol) in benzene was slowly added, accompanied by vigorous stirring. After a predetermined time, the contents of the vessel were filtered under nitrogen, and the product mixture was analyzed by HPLC on a μ-Bondapak C_{18} column by using a methanol–water (30:70) eluent.

Reaction of *tert*-Butyl Hydroperoxide with Dicobalt Octacarbonyl in *n*-Heptane. To a vigorously stirred solution of dicobalt octacarbonyl (0.171 g, 0.500 mmol) in olefin-free *n*-heptane (5 mL) at 0 °C was added by syringe a solution of *tert*-butyl hydroperoxide (0.901 g, 10.0 mmol) in *n*-heptane. After 1 h the mixture was filtered under nitrogen. Analysis of the resulting solution by GC/MS revealed the presence of a number of solvent-derived products, e.g., 2-heptanone, 4-heptanol, 3-heptanone, and 4-heptanone, identified by a comparison of their respective mass spectra to literature spectra. In addition, an unknown compound with the empirical formula $C_{11}H_{24}O_2$ was observed. On the basis of its characteristic mass spectrum [*m/e* (relative intensity) 189 (M + 1, 0.2), 188 (M^+, 1.7), 131 (0.1), 115 (0.3), 99 (0.2), 98 (9.2), 73 (5.0), 57 (100), 43 (24)], this material is tentatively formulated as the unsymmetrical peroxide *t*-$C_4H_9OOC_7H_{15}$.

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Registry No. Di-*n*-hexyl peroxide, 3903-89-7; di-*sec*-butyl peroxide, 4715-28-0; di-*tert*-butyl peroxide, 110-05-4; *n*-hexyl hydroperoxide, 4312-76-9; *sec*-butyl hydroperoxide, 13020-06-9; *tert*-butyl hydroperoxide, 75-91-2; $Fe(CO)_5$, 13463-40-6; $Co_2(CO)_8$, 10210-68-1.

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Thermolysis of Dioxetanes: Activation Parameters for *cis*-/*trans*-3,4-Dialkyl-1,2-dioxetanes

Alfons L. Baumstark,*[1] Tambra Dunams, Peter C. Roskamp, and Catherine E. Wilson

Laboratory for MBS, Department of Chemistry, Georgia State University, Atlanta, Georgia 30303

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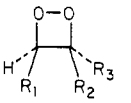
The thermal decomposition of alkyl-substituted 1,2-dioxetanes has been shown[2] to produce two carbonyl fragments, one of which may be produced in an excited state (high yields of excited triplets). Historically, two mechanistic extremes have been proposed[2] to describe the thermal decomposition of alkyldioxetanes:[3] (a) diradical and (b) concerted (Scheme I).

Evidence has accumulated in favor of a diradical mechanism. Group additivity calculations have been employed[4] to predict activation parameters based on the thermochemistry of the dioxetane and the postulated diradical intermediate. Experimental results (lack of solvent effect,[5] insensitivity of E_a to phenyl for methyl substitution,[6] lack of deuterium isotope effect,[7] lack of additional ring-strain effect[8] on E_a) have been interpreted to be consistent with a diradical-like mechanism. Recent results[9] have shown that substituent effects influence the activation parameters of the thermolysis of alkyldioxetanes in unexpected ways. Despite the considerable interest in substituent effects on dioxetane activation parameters, there has been no characterization of cis/trans pairs of dioxetanes (although several pairs have been synthesized).[2,10] We report the characterization of three pairs of *cis*-/*trans*-3,4-dialkyl-1,2-dioxetanes (**1–6**).



1, R_1 = Et; R_2 = Et; R_3 = H
2, R_1 = Et; R_2 = H; R_3 = Et
3, R_1 = *n*-propyl; R_2 = *n*-propyl; R_3 = H
4, R_1 = *n*-propyl; R_2 = H; R_3 = *n*-propyl
5, R_1 = *n*-butyl; R_2 = *n*-butyl; R_3 = H
6, R_1 = *n*-butyl; R_2 = H; R_3 = *n*-butyl

Results and Discussion

Dioxetanes **1–6** were prepared in low yield by closure of the corresponding bromo hydroperoxides with base at

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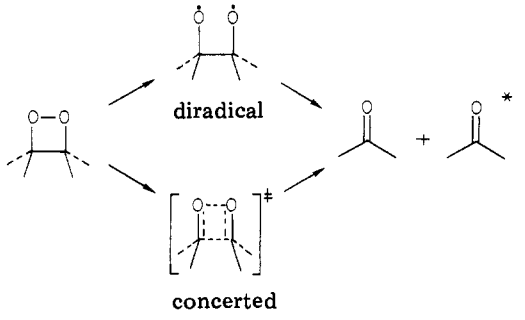
Scheme I[a]



[a] An asterisk denotes an excited state.

Table I. Activation Parameters of the Thermal Decomposition of 1-8 in Xylenes

dioxetane					
cis	trans	E_a, kcal/mol	log A	k(60 °C), s^{-1}	$\Delta S^{\ddagger}$, eu
1[a]		24.5 ± 0.3[b]	13.1	1.15×10^{-3}	−0.7
	2	24.9 ± 0.3	13.1	5.9×10^{-4}	−0.8
3		24.5 ± 0.3	13.1	1.1×10^{-3}	−0.7
	4	25.0 ± 0.3	13.2	6.8×10^{-4}	−0.2
5		24.6 ± 0.3	12.9	5.8×10^{-4}	−1.7
	6	25.1 ± 0.3	13.1	4.6×10^{-4}	−0.6
tetramethyl-1,2-dioxetane[c]		27.3 ± 0.3	13.8	8.0×10^{-5}	2.4

[a] See ref 10. [b] 95% confidence limit. [c] In good agreement with the results reported in ref 8 and 9c.

low temperature. The *cis*-1,2-dioxetanes were prepared (via two steps) from the corresponding *cis*-alkenes while the *trans*-1,2-dioxetanes were prepared from the *trans*-alkenes.[10,11] ^{1}H NMR spectra of the dioxetanes indicated that the cis compounds contained no detectable quantities of the trans compounds and vice versa. NMR spectroscopy showed that the thermolysis of 1–6 produced the expected cleavage products.

The ^{1}H NMR signals for the ring protons for the *cis*-dioxetanes (**1**, **3**, **5**) were observed at $\delta \sim 5.2$ while those for the *trans*-dioxetanes (**2**, **4**, **6**) were observed at $\delta \sim 5.0$ in CCl_4. This is in agreement with the reported data for the ring protons of *cis*-/*trans*-3,4-diethoxy-1,2-dioxetane[10c] (chemical shift difference = 0.3 in $CFCl_3$) and for *cis*-/*trans*-3,4-dimethyl-1,2-dioxetane[10a] (chemical shift difference = 0.4; CCl_4 vs. benzene). The chemical shift for the ring protons of *cis*-3,4-disubstituted 1,2-dioxetanes is downfield from that of the corresponding *trans*-dioxetanes.

The rates of the thermal decomposition of dioxetanes 1–6 were monitored by the decay of chemiluminescence intensity in aerated xylenes or benzene with or without added fluorescers. The rates of thermolysis were cleanly first order for at least 3 half-lives and showed little or no dependence on the type or amount of added fluorescer. For all three pairs, over the temperature range studied, the cis compound decomposed at a rate faster than the trans isomer. The first-order rate constants were determined over at least a 50 °C range. The Arrhenius plot for the thermal decomposition of **3** and **4** is shown in Figure 1. The activation parameter data (determined by the Arrhenius method) for 1–6 are summarized in Table I.

Without the addition of fluorescers (fluorescent dyes), the thermal decomposition of dioxetanes 1–6 were only

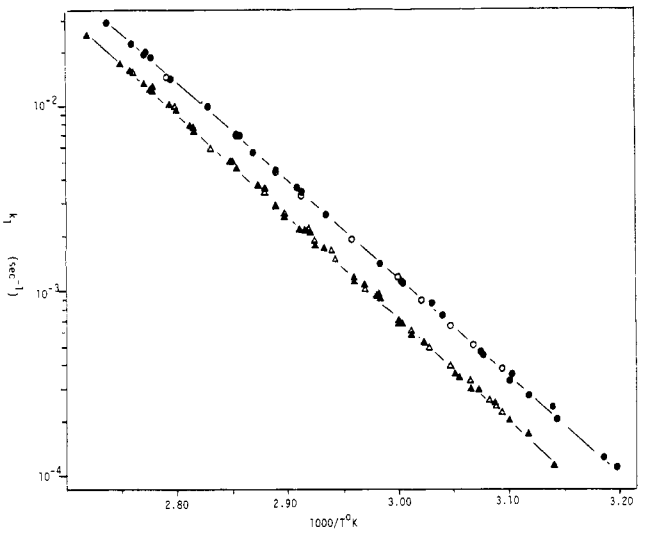


Figure 1. Arrhenius plots for the thermal decomposition of **3** (●, DBA; ○, DPA) and **4** (▲, DBA; △, DPA).

Table II. Variation in E_a for *cis*/*trans*-Dioxetanes

dioxetane pair	k_{cis}/k_{trans} (60 °C)	E_a(trans) − E_a(cis)
1-2	1.9	0.4 ± 0.6[a]
3-4	1.6	0.5 ± 0.6
5-6	1.2	0.5 ± 0.6
cis/*trans*-3,4-diethoxy-1,2-dioxetane	1.4[b]	

[a] 95% confidence limits. [b] At 50 °C; see ref 10c.

weakly chemiluminescent. Addition of low concentrations of dibromoanthracene (DBA) or diphenylanthracene (DPA) greatly increased the intensity of chemiluminescence without increasing the rate of the thermolysis of the dioxetanes. The yields of excited carbonyl products directly produced by the thermal decomposition of the dioxetanes were determined by the DBA/DPA method.[1a,8] The thermal decomposition of dioxetanes 1–6 produced approximately 10% yields of excited triplet carbonyls and very low yields (<0.1%) of excited singlet carbonyls.

The activation energies for the three *cis*-dioxetanes showed little or no variation with substituent chain length. An E_a of ~24.6 kcal/mol seems to be the maximum value for acyclic 3,4-disubstituted 1,2-dioxetanes. Cyclic (cis) substituents have been shown[9b,c] to have a much larger effect on E_a. The activation energies for the *trans*-dioxetanes also showed little or no variation with substituent chain length. The E_a for the series of *trans*-dioxetanes seems to have a limiting value of approximately 25 kcal/mol.

The activation energies for the three *cis*-dioxetanes were approximately 0.5 kcal/mol lower than those of the corresponding *trans*-dioxetanes. However, the ΔE_a for cis/trans pairs is approximately equal to the experimental error (95% confidence limit) in all cases. The $\Delta S^{\ddagger}$ terms showed little or no variation with dioxetane substituents. The ΔE_as for cis/trans pairs as well as the ratios of k_{cis}/k_{trans} at 60 °C are listed in Table II.

The group additivity type calculations employed by Richardson et al. predicted[4] a ΔE_a for *cis*-/*trans*-3,4-dimethyl-1,2-dioxetane of 0.9 kcal/mol. A ΔE_a of approximately 0.9 kcal/mol is also predicted by group additivity calculations for each of the three pairs of *cis*-/*trans*-dioxetanes (1–6) in the present study. The observed ΔE_a for the series of dioxetanes 1–6 was approximately half the predicted value. However, since the magnitude of the error (95% confidence limit) is greater than or equal to ΔE_a, the

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results must be interpreted with caution. The results for the three pairs of dioxetanes agree with one another (despite the size of the error) and *qualitatively* agree with the predicted ΔE_a based on the diradical model.

The data for the *cis*-dioxetanes clearly show that 3,4 steric interactions in *cis*-dialkyl-1,2-dioxetanes are of minor importance. This is not unexpected in view of the results[12] from a study of 3,3-diethyl-1,2-dioxetane (7). The E_a for 7 was found to be 1.5 kcal/mol higher than that of 3,3-dimethyl-1,2-dioxetane with little or no effect on $\Delta S^{\ddagger}$. The ΔE_a for the formal replacement of 3,3-dimethyl groups by 3,3-diethyl groups was large enough to account for the increased E_a of tetraethyl-1,2-dioxetane as compared to that of tetramethyl-1,2-dioxetane. Those results[12] suggested that a major substituent effect on alkyldioxetane thermolysis was due to 3,3 steric interactions as opposed to 3,4 steric interactions.

Experimental Section

All solvents were of reagent grade. ^{1}H NMR spectra were recorded on a Varian 360L spectrometer. GC studies were performed on a Varian 920 gas chromatograph with a 6 ft × 0.25 in. SE-30 on Chromosorb W column (helium flow rate 60 mL/min). 9,10-Diphenylanthracene (Aldrich) was used without further purification. 9,10-Dibromoanthracene (Aldrich) was recrystallized from xylenes (Aldrich) before use. The alkenes were available commercially. *cis*-3,4-Diethyl-1,2-dioxetane (**3**)[9c] has been previously reported.

Dioxetane Synthesis. The following procedure for the synthesis of *trans*-3,4-diethyl-1,2-dioxetane (**2**) was employed for the preparation of all dioxetanes. A 74-mmol sample of *trans*-3-hexene was converted to the bromo hydroperoxide by the standard method of Kopecky.[13] The bromo hydroperoxide, an oil (**Caution!**), was placed in 10 mL of CCl_4 with rapid magnetic stirring (cooled by an ice bath). KOH (5 g) in 20 mL of cold distilled (deionized) H_2O was added dropwise (15 min) to the bromo hydroperoxide solution in the dark. The bright yellow CCl_4 layer was separated, dried over $MgSO_4$, and filtered. The dioxetanes were partially purified by low-temperature vacuum distillation.

Additional purification was accomplished by column chromatography using a jacketed 1-cm-column at −60 °C packed with 20 g of silica gel containing 1% Na_2EDTA (pentane). The dioxetane in CCl_4 was placed on the column and washed with 50 mL of pentane, followed by successive 50-mL portions of a 5% methylene chloride/pentane step gradient. Fractions were assayed for dioxetane by placing a small portion in a concentrated DBA solution in the chemiluminescence apparatus. The solvent from fractions containing dioxetane was removed under reduced pressure and the NMR spectra taken. The ^{1}H NMR spectrum of the dioxetane in CCl_4 showed the dioxetane to be approximately 90% pure. ^{1}H NMR (CCl_4) for **1**: δ 0.9 (t, J = 7 Hz, 6 H), 1.9 (m, 4 H), 5.15 (br t, J = 5 Hz, 2 H). For **2**: δ 0.9 (t, J = 7 Hz, 6 H), 1.9 (m, 4 H), 4.90 (br t, J = 4 Hz, 2 H). For **3**: δ 0.9 (t, J = 7 H, 6 H), 1–2 (br m, 6 H), 5.25 (br t, J = 5 Hz, 2 H). For **4**: δ 0.9 (t, J = 7 Hz, 6 H), 1–2 (br m, 6 H), 5.0 (br t, J = 4 Hz, 2 H). For **5**: δ 0.9 (t, 6 H), 1–2 (br m, 8 H), 5.20 (br t, J = 5 Hz, 2 H). For **6**: δ 0.9 (t, 6 H), 1–2 (br m, 8 H), 5.00 (br t, J = 4 Hz, 2 H). The concentrations of the dioxetane solutions were determined by the method of Wilson and Schaap.[10c] The dioxetane solutions (CCl_4) were stored at −30 °C.

Product Studies. The following general procedure was employed. An approximately 0.2 M solution of the dioxetane in CCl_4 was heated at 60 °C in a sealed NMR tube until the yellow color disappeared. In all cases, the corresponding aldehyde was detected in high yield by NMR spectroscopy. The reaction mixture was also checked by VPC analysis.

Kinetic Studies. The chemiluminescence monitoring system is essentially identical with that described previously by Wilson.[8] The temperature of the cell (±0.2 °C) was monitored by using a YSI Model 42SC with a Series 400 probe before and after each run. The cell was jacketed and the temperature maintained by using a Haake constant-temperature circulating bath. The cell was pretreated with a concentrated aqueous Na_2EDTA solution. Kinetic runs were carried out in benzene or in xylenes (mixture of isomers) as the solvent. The initial dioxetane concentrations were kept low ($\sim 10^{-4}$ M) in order to avoid induced decomposition of the dioxetane. Runs carried out without added fluorescer and with low concentrations ($\sim 10^{-3}$ M) of DPA or DBA were of the first order for at least 3 half-lives and showed essentially no dependence on the type or amount of added fluorescer.

Yields of Excited States. The chemiluminescence monitoring apparatus was calibrated by taking the yield of excited triplet from tetramethyl-1,2-dioxetane, determined by the DBA method,[8] as 0.30 at 45 °C. All experiments were carried out at 45 °C with a constant concentration of dioxetane. The yields of excited carbonyl products were calculated by a method which has been discussed in detail.[2,8]

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Registry No. 1, 73353-62-5; 2, 83929-08-2; 3, 83929-09-3; 4, 83929-10-6; 5, 83929-11-7; 6, 83929-12-8.

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Electrochemical Reduction in the Synthesis of Catechol-Derived Peptides as Potential Metal Chelators and Enzyme Inhibitors

Claudius D'Silva and Kenneth T. Douglas*

Department of Chemistry, University of Essex, Colchester CO4 3SQ, UK

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There has been considerable recent interest in the synthesis[1] of new metal-binding agents, especially catechol based, both as models for related microbial natural products[2] (e.g., the iron-binding enterobactins) and for potential medical use in man.[3] In addition, the catecholamines are important in neurochemistry. Dopamine β-hydroxylase (EC 1.14.2.1) plays an important role in the dynamics of neurotransmission as it catalyses the last step in the biosynthesis of noradrenaline.[4] In view of a recent report of powerful inhibition of this enzyme by bleomycin, a strongly metal-binding glycopeptide antitumor antibiotic,[5] we considered that catechol peptides might bind strongly to dopamine β-hydroxylase by virtue of their extended peptide backbone. We now report a synthetic route to a catechol dipeptide which involves a useful, preparative, electrochemical reduction step, successful where several other reductive procedures failed.

Results and Discussion

N^{α}-Benzoyl-DL-(2,3-dihydroxyphenyl)alanylglycine (**8**) was synthesized by the route shown in Scheme I.

The azlactone **2** was formed by condensation[6] of *N*-benzoylglycine with **1**. Conversion of **2** to the free amino acid **3** followed by N-protection as a variety of derivatives (e.g., Cbz, trifluoroacetyl), even in the presence of borate,

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