Oxidation and Reaction of Trolox c, a Tocopherol Analogue, in Aqueous Solution. A Pulse-Radiolysis Study

Michael J. Thomas*,† and Benon H. J. Bielski‡

Contribution from the Department of Biochemistry, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103, and the Department of Chemistry, Brookhaven National Laboratory, Upton, New York 11973. *Received August 31, 1988*

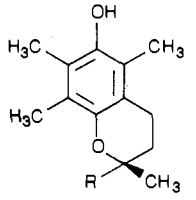
Abstract: Trolox c, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carboxylic acid, **1**, a water-soluble α-tocopherol analogue, was oxidized with Br_2^- to give the phenoxyl radical **2**. These radicals disproportionate by a second-order, pH-dependent process to give **1** and an unstable intermediate **3**, identified as 4,5-dihydro-3,6,8,9-tetramethyl-2*H*-3,9a-epoxy-1-benzoxepin-2,7(3*H*)-dione, which has a strong UV absorption at 235 nm. The disproportionation rate constant decreases with increasing pH, the greatest change occurring between pH 2 and 9, where it decreased by 10^4. The rate constant versus pH plot is consistent with a scheme that involves three reactions of the protonated and the unprotonated forms of **2**. Intermediate **3** undergoes slow pH-dependent decomposition to 2-hydroxy-2-methyl-4-(2,5,6-trimethyl-2,4-dioxo-2,5-cyclohexadienyl)butanoic acid, **4**. The same first-order rate constant was found for the decay of **3** and the appearance of **4**. Simultaneous intramolecular cyclization during disproportionation is unique to **2** and similar derivatives, but would not occur in analogues that have hydrocarbon chains instead of a carboxyl moiety.

Trolox c, **1**, is a water-soluble, phenolic antioxidant in which the polyisoprenoid tail of α-tocopherol (vitamin E), probably the most efficient biologically derived phenolic antioxidant that is known, has been replaced by a carboxyl moiety. Because of the similarity, **1** has been used as a model for the antioxidant behavior of α-tocopherol. However, **1** is generally studied in homogeneous, aqueous solution whereas α-tocopherol is soluble only in organic solvents and membranes. Because the chemistry of sterically hindered phenoxyl radicals of this kind has not been extensively studied in water, we examined the behavior of the phenoxyl radical prepared from **1** to see if it might be a suitable model for the behavior of α-tocopherol.

Earlier work carried out in organic solvents indicated that in the absence of oxygen dimerization would be a major reaction pathway for the phenoxyl radical.[1,2] Phenoxyl radicals that have few steric constraints dimerize by carbon–carbon bond formation while the more hindered phenoxyl radicals form head-to-tail dimers through carbon–oxygen bonds.[2,3] Phenols like α-tocopherol that have methyl moieties attached to the aromatic ring yield a complex mixture of dimeric products with a substantial fraction of coupling occuring between methyl groups.[4-7]

Trolox c was converted to its phenoxyl radical **2** by a mild, one-electron oxidation with Br_2^- (Chart I). This method of oxidizing **1** has been reported by Bisby et al.[8] and by Cabelli and Bielski.[9] However, the present results show, surprisingly, that **2** is converted into a stable product by a process that first involves the disproportionation of **2** to **1** and a cross-conjugated ketone, **3**, that was formed by intramolecular cyclization of the carboxylate to the unsaturated ring. Intermediate **3** undergoes a slow hydrolysis to quinone **4**. This reaction sequence is unusual in that the disproportionation and associated intramolecular cyclization are pH sensitive. The observations made on **2** were confirmed by using the hydroxymethyl analogue of **1**, 3,4-dihydro-6-hydroxy-2-(hydroxymethyl)-2,4,7,8-tetramethyl-2*H*-1-benzopyran, **5**.

Chart I



1: R = CO_2H
5: R = CH_2OH
tocopherol: R = $CH_2(CH_2CH_2CH(CH_3)CH_2)_3H$

Experimental Section

General Remarks. All solutions were prepared with distilled water which had been further treated by a Milli-Q purification system. Trolox c (Aldrich Chemical Co.) was recrystallized twice from methanol–water and dried in vacuo before use, ϵ_{290nm} = 2995 M^{-1} cm^{-1} (methanol) (lit.[10] ϵ_{290nm} = 2920 M^{-1} cm^{-1}). Trolox was always dissolved in water in an inert atmosphere. The pH was adjusted by the addition of either potassium hydroxide (Baker Analyzed) or perchloric acid (G. F. Smith Chemical Co., distilled twice in Vycor). Phosphate buffers were used only where stated (Ultrex grade from Baker). All solutions were saturated with nitrous oxide (Matheson Co.) before pulse radiolysis. Sodium azide and sodium bromide were from Baker Chemical Co. All other chemicals were of the highest grade commercially available. Microanalysis was performed by Atlantic Microlab, Inc.

Ultraviolet spectrophotometric measurements were recorded on either a Cary 210 or a Cary 219 UV/vis spectrophotometer. Infrared spectra were recorded on a Nicolet MX-5 spectrometer using KBr disks. Gas chromatography/mass spectrometry (GC/MS) was carried out on either a Finnigan 4000 or a Delsi-Nermag R10-10C quadrupole mass spectrometer. A DB-1 WCOT column (5-m length, 0.25-mm diameter, 250 μm thick wall coating) was used with a linear oven temperature ramp (10 °C/min) from 150 to 250 °C and with a helium carrier gas flow of 1 cm/s. Proton spectra were recorded on a Bruker AM 300 spectrometer at 300.13 MHz with chemical shifts reported as δ with respect to $(CH_3)_4Si$.

General Procedures. ^{60}Co γ ray irradiations were carried out in a source with a dose rate of 700 rads/min. Pulse-radiolysis experiments were performed as previously described[11] with a 2 MeV van de Graff generator with 80 ns–1 ms puises and doses ranging from 100 to 1600 rads. The reaction cells used in this study had either a 2- or 6.1-cm optical path. The number of free radicals formed per pulse was computed

† Bowman Gray School of Medicine.
‡ Brookhaven National Laboratory.

(1) Joschek, H. I.; Miller, S. I. *J. Am. Chem. Soc.* **1966**, *88*, 3273.
(2) Mahoney, L. R.; Weiner, S. A. *J. Am. Chem. Soc.* **1972**, *94*, 585.
(3) Weiner, S. A.; Mahoney, L. R. *J. Am. Chem. Soc.* **1972**, *94*, 5029.
(4) Schudel, P.; Mayer, H.; Metzger, J.; Ruegg, R.; Isler, O. *Helv. Chim. Acta* **1946**, *46*, 636.
(5) Lars, L.; Nilsson, G.; Daves, G. D.; Folkers, K. *Acta Chem. Scand.* **1968**, *22*, 207.
(6) Skinner, W. A.; Parkhrust, R. M. *J. Org. Chem.* **1966**, *31*, 1248.
(7) Suarna, C.; Craig, D. C.; Cross, K. J.; Southwell-Keely, P. T. *J. Org. Chem.* **1988**, *53*, 1281.
(8) Bisby, R. H.; Ahmed, S.; Cundall, R. B.; Thomas, E. W. *Free Radical Res. Commun.* **1986**, *1*, 251.
(9) Cabelli, D. E.; Bielski, B. H. J. *J. Free Radical Biol. Med.* **1986**, *2*, 71.
(10) Nishikimi, M.; Machlin, L. J. *Arch. Biochem. Biophys.* **1975**, *170*, 684.
(11) Cabelli, D. E.; Bielski, B. H. J. *J. Phys. Chem.* **1983**, *87*, 1809.

0002-7863/89/1511-3315$01.50/0

with the formation of $(SCN)_2^-$ as the calibrant by taking $G((SCN)_2^-) = 6.13$ and the molar absorbance of the radical[12] at 472 nm as 7950 M^{-1} cm^{-1}. Rate constants are the averages of 3–10 runs. All studies were performed at 24 °C. Experiments utilizing stop-flow methods were carried out in aqueous, N_2O-saturated solutions by using reported methods.[13]

2-Hydroxy-2-methyl-4-(2,5,6-trimethyl-2,4-dioxo-2,5-cyclohexadienyl)butanoic Acid, 4. Compound **4** was prepared by alkaline Br_2/KBr oxidation[14] of 2.51 g of **1** in poor yield (0.37 g, 14%), mp 116.5–117.5 °C. This procedure produced a second product that was unstable and not further characterized. The spectral characteristics of **4** are as follows: NMR (1:1 CD_3OD–$CDCl_3$) δ 5.07 (2 H, s), 2.69 (1 H, td [J = 12.08 Hz, 4.88 Hz]), 2.43 (1 H, td [J = 12.08 Hz, 4.88 Hz]), 2.02 (3 H, s), 2.00 (6 H, s), 1.88 (1 H, ddt [J = 5.04 Hz, 11.64 Hz, 13.45 Hz]), 1.71 (1 H, ddt [J = 5.04 Hz, 11.64 Hz, 13.45 Hz]), 1.45 (3 H, s); MS (EI, 42 eV) m/z 266 (M^+), 248 ($M - H_2O$)$^+$, 221 ($M - CO_2H$)$^+$, 203 ($M - (H_2O + CO_2H)$)$^+$; UV λ_{max} (log ϵ) (CH_3OH) 269 nm (4.283); IR (KBr pellet) 3341, 2988, 1742, 1634, 1122 cm^{-1}.

Hydroxymethyl-Trolox c [3,4-Dihydro-6-hydroxy-2-(hydroxymethyl)-2,4,7,8-tetramethyl-2*H*-1-benzopyran], 5. **1** (2.3 g) was dissolved in 100 mL of anhydrous ethanol and treated with 0.25 mL of concentrated H_2SO_4. After 75 mL of ethanol had been distilled, the residue was poured into 80 mL of water and then extracted with three 30-mL portions of diethyl ether. The combined organic layers were washed with water and dried over $MgSO_4$, and after filtering, the solvent was removed in vacuo. The unpurified ethyl ester was taken up in 50 mL of anhydrous diethyl ether, treated with 0.2 g of $LiAlH_4$, and refluxed overnight. The mixture was hydrolyzed with alkaline water and filtered, and the filtrate was dried over $MgSO_4$. After filtering and concentrating, the residue was recrystallized twice from methanol–water, giving colorless crystals (mp 112–112.5 °C): NMR (1:1 CD_3OD–$CDCl_3$) δ 4.82 (2 H, s), 3.57 (1 H, AB q [J = 11.2 Hz]), 3.49 (1 H, AB q [J = 11.2 Hz]), 2.63 (2 H, m), 2.15 (3 H, s), 2.1 (3 H, s), 2.07 (3 H, s), 1.96 (1 H, m), 1.75 (1 H, m), 1.21 (3 H, s); MS (EI, 42 eV) m/z 236 (M^+), 205 ($M - CH_3OH$)$^+$, 203 ($M - (CH_3OH + H)$)$^+$, 165 ($M - C_4H_7O$)$^+$, 164 ($M - C_4H_8O$)$^+$; UV λ_{max} (log ϵ) (CH_3OH) 292 nm (3.559); IR (KBr disk) 3320, 2922, 1647, 1456, 1256, 1045 cm^{-1}.

4,5-Dihydro-3,6,8,9-tetramethyl-2*H*-3,9a-epoxy-1-benzoxepin-2,7-(3*H*)-dione, 3. To 122 mg (488 mmol) of **1** in 40 mL of anhydrous ethanol was added 116 mg (488 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone over a 15-min period. After stirring of the mixture for 10 min, 25 mL of cyclohexane was added followed immediately by 80 mL of water. The cyclohexane layer was separated, washed with dilute $NaHCO_3$ solution and then with water, and then dried over $NaHCO_3$–Na_2SO_4. After filtration and evaporation of the solvent, the colorless, oily residue was chromatographed on alumina TLC plates (Merck) with 1:1 (v:v) benzene–cyclohexane. The crystalline residue (mp 58–59 °C) isolated after extraction has the following properties: NMR ($(CD_3)_2CO$) δ 3.02 (1 H, o [J = 16.06 Hz, 6.58 Hz, 1.34 Hz]), 2.55 (1 H, m), 2.07 (1 H, m), 1.99 (1 H, m), 1.97 (3 H, s), 1.92 (3 H, s), 1.84 (3 H, s), 1.52 (3 H, s); MS (EI, 42 eV) m/z 204 ($M - CO_2$)$^+$, 189 ($M - (CH_3 + CO_2)$)$^+$; UV λ_{max} (log ϵ) (C_6H_{14}) 232.5 (4.185), 276 nm (3.111); IR (KBr disk) 2932, 1802, 1689, 1651, 1647, 1188 cm^{-1}.

2,3,4,5-Tetrahydro-3,6,8,9-tetramethyl-7*H*-3,9a-epoxy-1-benzoxepin-7-one, 6. Forty-six milligrams (204 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone dissolved in 2 mL of acetonitrile was added to 32 mg (137 mmol) of **5** in 4 mL of dry acetonitrile kept at room temperature under argon. After standing for 30 min, the solution was mixed with 8 mL of water and then extracted with five 10-mL aliquots of cyclohexane. The combined cyclohexane extracts were dried over Na_2SO_4. After filtration and removal of the solvent, 24 mg (76% yield) of a white, crystalline solid (mp 100–101 °C) was obtained: NMR (CD_3OD) δ 4.22 (1 H, d [J = 6.9 Hz]), 3.63 (1 H, dd [J = 6.9 Hz, 2.2 Hz]), 2.68 (2 H, m), 1.93 (2 H, m), 1.91 (3 H, s), 1.85 (3 H, s), 1.78 (3 H, s), 1.42 (3 H, s); MS (EI, 42 eV) m/z 234 (M^+), 206 ($M - CO$)$^+$, 204 ($M - CH_2O$)$^+$, 189 ($M - (CH_3 + CH_2O)$)$^+$; UV λ_{max} (log ϵ) (C_6H_{14}) 233 (4.167), 282 nm (3.127), (CH_3OH) 237 (5.158), 291 nm (3.161), (10% aqueous CH_3OH) 239 (4.173), 290 nm (3.228); IR (KBr disk) 2933, 1685, 1639, 1447, 1053, 948 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.67; H, 7.80.

Results

The spectrum and the kinetics for the formation of Br_2^- at neutrality were consistent with earlier reports[15] showing a λ_{max} = 360 nm with ϵ = 10 000 M^{-1} cm^{-1}. However, since it was not known whether the G value for Br_2^-, $G(Br_2^-)$, was independent of pH, the absorption intensity at 360 nm was determined at several different pHs. We assumed that within our experimental error the change in pH did not affect ϵ and therefore that a change in the absorption at a given dose reflects a change of $G(Br_2^-)$ due to competition between H^+ and N_2O for the hydrated electron. As can be seen in the Table I, $G(Br_2^-)$ begins to drop off below pH 4. The rate constant for the second-order decay of Br_2^- was moderately sensitive to changes in acidity below pH 3 (see Table I), undergoing an approximately 3-fold increase between pH 3 and 1. As the increase in k is not proportional to the change in H^+ concentration, we suspect that the increase in k is due to an equilibrium-controlled process in which protonation of a $Br^\bullet$ derivative generates a higher concentration of a more reactive protonated-$Br^\bullet$ species (ref 16 and references therein).

When 50 to 1 mM aqueous solutions of **1** and 100 mM NaBr were irradiated with 2 MeV electrons, the formation of Br_2^- was complete with 50 ns. Following the irradiation pulse, the initial spectrum of Br_2^- was replaced with the absorption spectrum (Figure 1a) of Trolox radical (**2**).[8,9] All parts of the spectrum displayed similar kinetic constants (data not shown). The rate constant for disappearance of Br_2^- (measured at 360 nm) and the rate constant for the formation of **2** (measured at 435 nm) were similar within experimental error from pH 0.2 to 12; $k(Br_2^-$ +

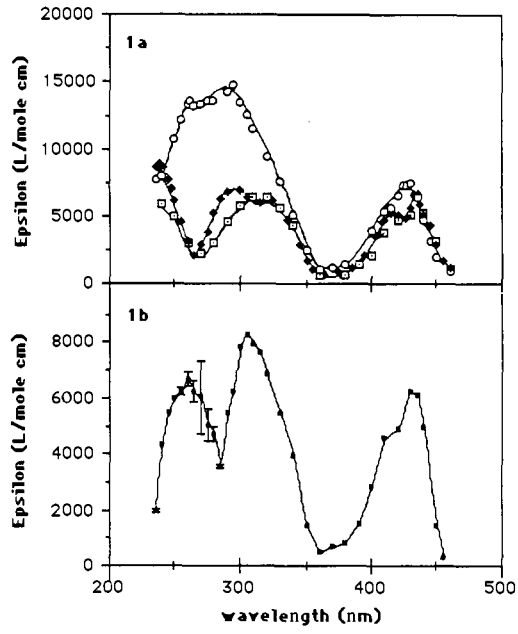


Figure 1. Spectra of various phenoxyl transients in N_2O-saturated water plotted as ϵ versus wavelength (nm): (a) spectrum of **2** at three different pHs; pH 2.37 (open circles), 0.1 M KBr, 52 mM **1**; pH 7.42 (filled diamonds), 0.06 M KBr, 928 mM **1**; and pH 11.08 (open squares) 0.1 M KBr, 52 mM **1** and (b) spectrum of the phenoxyl radical from **5** at pH 4, 0.1 M KBr, 112 mM **5**.

Table I. Changes in $G(Br_2^-)$ for the Formation of Br_2^- and the Second-Order Decay of Br_2^- as a Function of pH

pH	$G(Br_2^-)$	k_{obsd}, M^{-1} s^{-1} × 10^{-9}
0.18	3.11	10.10 ± 3.7
1.03	3.43	8.53 ± 0.42
1.53	4.10	5.36 ± 0.12
2.03	4.90	3.70 ± 0.04
2.49	5.60	2.86 ± 0.06
2.98	5.93	2.65 ± 0.09
3.92	6.10	2.57 ± 0.04
6.40	6.10	2.63 ± 0.07

(12) Schuler, R. H.; Patterson, L. K.; Janata, E. *J. Phys. Chem.* **1980**, *84*, 2089.
(13) Bielski, B. H. J.; Richter, H. W. *J. Am. Chem. Soc.* **1977**, *99*, 3019.
(14) Corey, E. J.; Barcza, S.; Klotmann, G. *J. Am. Chem. Soc.* **1969**, *91*, 4782.
(15) Hug, G. L. In *Optical Spectra of Nonmetallic Inorganic Transients in Aqueous Solutions*; NSRD-NBS, U.S. Department of Commerce, U.S. Government Printing Office: Washington, DC, 1981.
(16) Sutton, H. C.; Downes, M. T. *Trans. Faraday Soc.* **1972**, *68*, 1498.

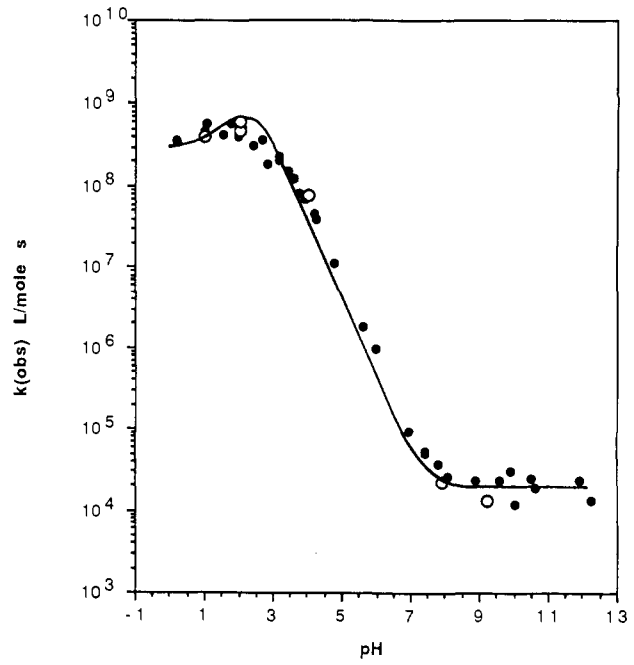


Figure 2. Observed rate constant for the second-order decay of phenoxyl radicals as a function of pH in N_2O-saturated solutions at 24 °C. The filled circles are points for **2** that were determined from solutions that contained from 50 to 1 mM **1** and from 0.05 to 0.1 M KBr. Six points determined for **6** are marked with open circles. These solutions were 0.1 M in KBr and from 52 to 100 mM in **5**. The solid line represents the rate constants calculated with the assumptions stated in the text.

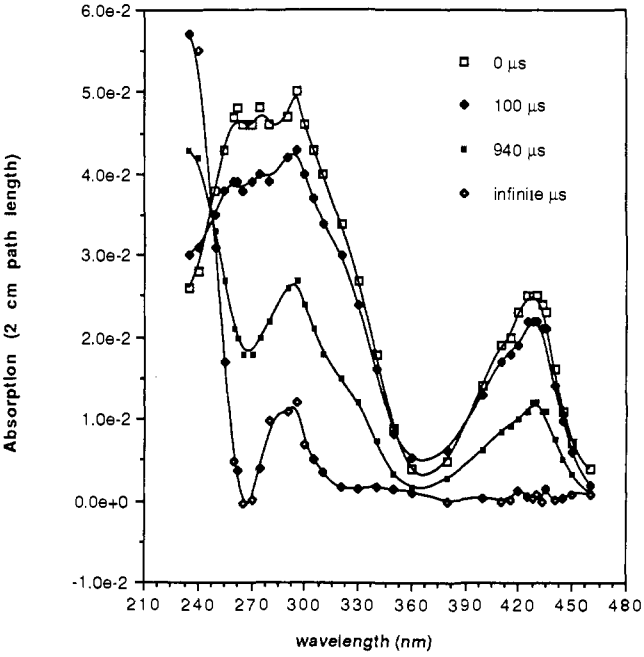


Figure 3. Spectra of irradiated solutions of **1** taken at different times after termination of the irradiation pulse. The data are plotted as absorption versus wavelength (nm) and show the loss of **2** and the concomitant formation of **3**. The N_2O-saturated solution contained 52 mM **1** and 0.1 M KBr at pH 2.4.

1) = (6.01 ± 0.72) × 10^8 M^{-1} s^{-1}.

Intermediate **2** undergoes a pH-dependent second-order decay to **3**. A plot of the observed rate constant versus pH is shown in Figure 2. The spectrum of this intermediate is characterized by the appearance of a strong absorption at 235–240 nm and the appearance of a band at the λ_{max} of **1**, 290 nm (Figure 3). The data were obtained by adding the absorption loss due to the initial consumption of **1** to the measured absorption at each wavelength. However, both of the cross-conjugated ketones, whose syntheses

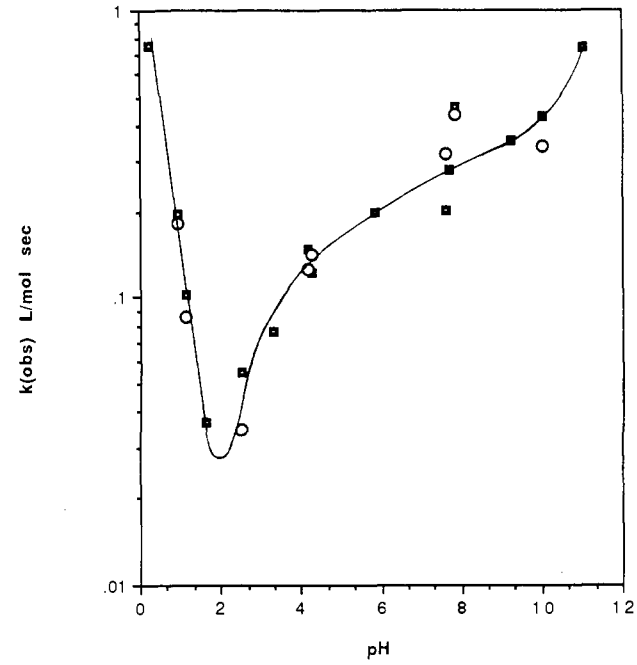


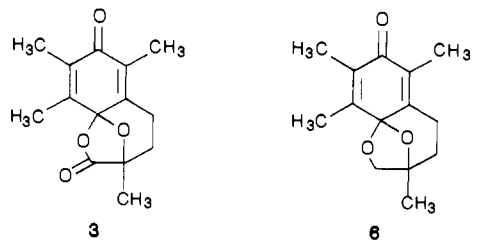
Figure 4. Observed first-order decay of **3** as a function of pH (open circles) and the formation of **4** (filled squares) at 24 °C. These N_2O-saturated solutions contained 44 mM **1** and 0.1 M KBr.

are described in the Experimental Section, have weak bands in the region of 276 (hexane)–291 nm (methanol). The band position appears to be solvent dependent, shifting to longer wavelengths in protic solvents. Calculation of the absorption at 290 nm from the initial irradiation dose, assuming that approximately equal amounts of **1** and **3** are formed, shows that approximately 38% of the absorption intensity is contributed by **3** ($\epsilon \approx 1.53 \times 10^4$ M^{-1} cm^{-1}) and the balance by regenerated **1** ($\epsilon = 2.45 \times 10^4$ M^{-1} cm^{-1} in water). The effect of ionic strength on the decay of **2** was examined by repeating the irradiations with NaBr concentrations ranging from 5 mM to 100 mM at pHs 2.8 and 10.6. The corresponding rate constants for the decay of **2** to **3** were identical within experimental error (data not shown).

Following its formation, **3** undergoes a slow, first-order decay to **4**. The spectrum was identical with that of Trolox quinone, λ_{max} = 260 and 270 nm, prepared by Br_2/KBr oxidation[7] of **1**. The rate of decay of **3** measured at 240 nm is equal to the rate of formation of **4** and shows the same pH dependence (Figure 4). Intermediate **3** was also prepared by short-wavelength irradiation of N_2O-saturated solutions in a stop-flow apparatus at pH 7.8. The first-order decay of **3** measured at 240 nm was identical with the rate of formation of **4** measured at 260 nm (data not shown), confirming the pulse-radiolysis observations. However, the stop-flow experiments yielded rate constants 1.5 times larger than those from pulse-radiolysis experiments. The rate differences are most likely due to the experimental design of the stop-flow study, which allowed us to measure only the last 2–3 half-lives of the reaction.

Irradiation of **1** in a thin-walled quartz cell with either 2 MeV electrons or γ radiation produced a stable product that had an absorption spectrum identical with that of **4**. At 10% conversion, 95% of **1** consumed in the 2 MeV electron irradiation was accounted for by the formation of **4**. When 204 mM **1** (pH 7.1) was irradiated for 10–30-s periods in the γ source, the formation of **4** was linear with time and the quantity of **1** consumed was approximately equal to the amount of **4** formed. Careful measurement of the final spectrum indicated that approximately one-half of the Br_2^- was accounted for by **4**.

The hydroxymethyl analogue **5** was irradiated with 2-MeV electrons under the same conditions as **1**. These solutions gave a transient spectrum which was similar to that of **2** (Figure 1b). Rate constants for the second-order decay of the corresponding phenoxyl radical were within experimental error of those found



3 6

Figure 5. Products produced by the 2,3-dichloro-5,6-dicyanobenzoquinone oxidation of **1** and of **5**.

for **2** at several different pHs (Figure 2). The decay gave a stable product, **6**, that showed a strong absorption between 245 and 250 nm (data not shown). As with **2**, the rate constant was independent of ionic strength.

Solutions of 108 mM **5** dissolved in 5 mM phosphate buffer (pH 8.1) containing 0.1 M NaBr were irradiated in a ^{60}Co source for 9 min. The stable product that formed had a λ_{max} at 240 nm. Approximately 38% of **5** was converted into **6**, calculated with the ϵ ($\approx 1.49 \times 10^4$ M^{-1} cm^{-1}) of 2,3,4,5-tetrahydro-3,6,8,9-tetramethyl-7*H*-3,9a-epoxy-1-benzoxepin-7-one in 10% methanol–water. The increase in absorption at 240 nm was linear with time. In a second experiment 30 mL of 137 mM **5** prepared as above was irradiated for 10 min. The solvent was removed in vacuo and the residue was extracted with 10 mL of cyclohexane. The residue was analyzed by GC/MS and was found to contain **5** and **6**, both identified by their characteristic mass fragments. Integration of the total-ion intensities indicated that the mixture contained approximately 10% **6**.

Because **3** and **6** appeared to contain cross-conjugated keto diene chromophores, we first assumed that dimers were formed and attempted to prepare head-to-tail dimers by various oxidative methods. These procedures did not give head-to-tail dimers, but they instead gave monomers that contained the cross-conjugated keto diene moiety. Oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone using reported methods[17,18] gave the highest yield. Analysis by a number of spectrometric techniques indicates that intramolecular cyclization gives the products shown in Figure 5. 2,3,4,5-Tetrahydro-3,6,8,9-tetramethyl-7*H*-3,9a-epoxy-1-benzoxepin-7-one formed from **5** was found to be stable in aqueous solution.

Discussion

The mechanism for the overall conversion of **2** to **3** must be consistent with the following observations: (1) the products are formed by intramolecular cyclization, (2) the intermediate can readily decompose into **4** by a simple reaction, (3) the amount of **4** isolated is one-half that of **2** formed by Br_2^- oxidation, (4) there is no ionic-strength effect between pH 2.8 and 10.6, and (5) the reaction displays the second-order rate constant versus pH profile shown in Figure 2. A hypothetical reaction path that includes the above points is shown in Scheme I.

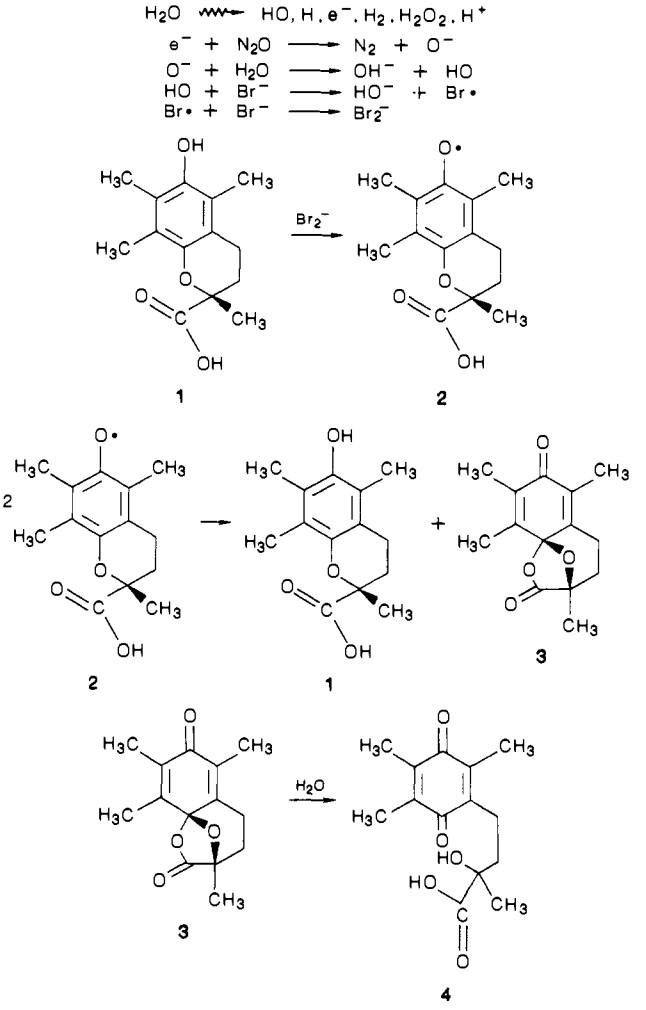
Intramolecular cyclization of **5** was aptly demonstrated by irradiating **5** and recovering cyclized product **6**, which was stable in water. A similar product, **3**, synthesized from **1** by 2,3-dichloro-5,6-dicyanobenzoquinone oxidation was relatively stable only in aprotic solvents, decomposing into **4** in protic solvents. Solutions of **3** prepared by irradiation in water also displayed a slow decomposition to **4**. No absolute proof was obtained that the substance synthesized by 2,3-dichloro-5,6-dicyanobenzoquinone oxidation of **1** is identical with that produced by the irradiation of **1**. However, the similarity of the decay kinetics for **2** and the phenoxyl radical from **5** and the synthesis of cyclized products from **1** and **5** by identical methods make this a reasonable conclusion.

The rate constant profile for disproportionation shown in Figure 2 can be modeled by assuming that **2** and its conjugate acid are involved in three bimolecular reactions: $\mathbf{2} + \mathbf{2} \rightarrow \mathbf{3} + \mathbf{1}^-$, k_1; $\mathbf{2} + (\mathbf{2}\text{–H})^+ \rightarrow \mathbf{3} + \mathbf{1}$, k_2; and $(\mathbf{2}\text{–H})^+ + (\mathbf{2}\text{–H})^+ \rightarrow \mathbf{3} + \mathbf{1} + H^+$, k_3. A curve of similar shape to the experimental line was calculated by assuming $K_a = 0.005$ ($\mathbf{2}\text{–H}^+ \rightleftarrows \mathbf{2} + H^+$), $k_1 = 2 \times 10^4$ M^{-1} s^{-1}, $k_2 = 2 \times 10^9$ M^{-1} s^{-1}, and $k_3 = 3 \times 10^8$ M^{-1} s^{-1} and is shown as a solid line in Figure 2. Calculations based on Scheme I, with the K_a of $(\mathbf{2}\text{–H})^+$ estimated at approximately 0.005, imply that the effect of ionic strength on the second-order rate would only have been detected below pH 1. Therefore, the scheme is consistent with the absenced of an ionic-strength effect on the rate of disproportionation of **2** in the pH range of 2.8–10.6. Interestingly, the ionization of the carboxyl moiety, which has a pK_a between 4 and 5, does not appear to have a rate determining role in the disproportionation of **2**.

Our observations of the formation and decay of **2** agree with previous reports. The spectrum of **2** generated by Br_2^- oxidation of **1** at pH 7.43, 435 nm ($\epsilon = 6.7 \times 10^3$ M^{-1} cm^{-1}) and 320 nm ($\epsilon = 6.5 \times 10^3$ M^{-1} cm^{-1}), is quite similar to that reported by Bisby et al.[8] at pH 7.15, 440 nm ($\epsilon = 5.4 \times 10^3$ M^{-1} cm^{-1}) and 325 nm ($\epsilon = 6.8 \times 10^3$ M^{-1} cm^{-1}), (from their Figure 1[8]) and is identical with the spectra reported by Cabelli and Bielski[9] in more acidic solutions. Our second-order rate constant $k(Br_2^- + \mathbf{1}) = (6.01 \pm 0.72) \times 10^8$ M^{-1} s^{-1} was comparable to the value of 3.8×10^8 M^{-1} s^{-1} found by Bisby[8] and within experimental error of those reported by Cabelli and Bielski.[9]

The spectrum of **2** is typical of phenoxyl radicals in general and it is quite similar to durosemiquinone in the 300–550-nm region.[19] The spectra of both **2** and durosemiquinone are affected by pH; both show a pronounced increase in absorption in the UV region of the spectrum as the pH of the solution decreases. All

Scheme I



(17) Becker, H-D. *J. Org. Chem.* **1965**, *30*, 982.
(18) Durckheimer, W.; Cohen, L. A. *J. Am. Chem. Soc.* **1964**, *86*, 4388.
(19) Bridge, N. K.; Porter, G. *Proc. Roy. Soc. London, A.* **1958**, *244*, 259.

parts of the spectrum of durosemiquinone and **2** decay at similar rates, indicating that they belong to the same species. Like **2**, durosemiquinone undergoes pH-dependent disproportionation in 50% ethanol–water, giving durohydroquinone and duroquinone as the stable products.[19]

The pK_a calculated for $(\mathbf{2}\text{–H})^+ \rightleftharpoons \mathbf{2} + H^+$ implies that $(\mathbf{2}\text{–H})^+$ is not as acidic as other protonated phenoxyl radicals[20] including protonated durosemiquinone,[19] which has a pK_a of -1.1. Methoxy groups, which can be used as a model for the oxymethylene moiety in **2**, are suggested to have approximately the same ability to stabilize phenolic cation radicals as the hydroxyl moiety.[21,22] X-ray studies[23] of α-tocopherol and several analogues, including both **1** and **5**, have shown than the angle between the 2p-type orbital of the para oxygen and the adjacent p-orbital in the aromatic ring is approximately 17°. Motion of the six-membered ring attached to the aromatic ring is constrained and the 2p-type orbital of the oxygen remains in a conformation that facilitates orbital overlap. Therefore, the calculated pK_a of 2.3 is most likely explained by postulating that extended conjugation stabilizes the positive charge, making $(\mathbf{2}\text{–H})^+$ a weaker acid relative to other phenol radical cations.

(20) Land, E. J.; Porter, G.; Strachan, E. *Trans. Faraday Soc.* **1961**, *57*, 1885.
(21) Dixon, W. T.; Murphy, D. *Trans. Faraday Soc.* **1976**, *72*, 1221.
(22) Steenken, S.; Neta, P. *J. Phys. Chem.* **1979**, *83*, 1134.
(23) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053.

Conclusion

Phenoxyl radicals from Trolox c and its analogues disproportionation in aqueous solution, giving starting phenol and a product from intramolecular cyclization. This latter product could not be formed from α-tocopherol radicals and therefore Trolox and its derivatives that have a hydroxymethyl or carboxy moieties at the 2-position are not good models for the behavior of α-tocopherol radicals in the absence of oxygen.

Acknowledgment. The work of M.J.T. was supported in part by Grants RO1 GM 29611-04 and RO1 HL 33532 from the National Institutes of Health. The NMR was purchased in part with funds from NSF Grant PCM-8313203. The research of B.H.J.B. was supported by National Institues of Health Grant RO1 GM23656-10, and it was carried out at Brookhaven National Laboratory, which is operated under contract DE-ACO2-76CH00016 to the U.S. Department of Energy.

Registry No. (±)-**1**, 56305-04-5; (±)-**1** (ethyl ester), 53174-07-5; (±)-**2**, 119681-33-3; (±)-**3**, 119681-34-4; (±)-**4**, 119719-96-9; (±)-**5**, 53101-54-5; (±)-**6**, 119719-97-0; Br_2^-, 12595-70-9.

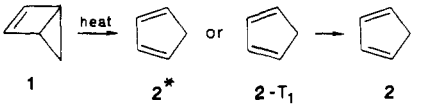
Deuterium and Carbon-13 Kinetic Isotope Effects for the Isomerization of 5,5-Dimethylbicyclo[2.1.0]pent-2-ene to 5,5-Dimethylcyclopentadiene

John E. Baldwin* and Naresh D. Ghatlia

Contribution from the Department of Chemistry, Syracuse University, Syracuse, New York 13244. *Received August 12, 1988*

Abstract: The relative rates of electrocyclic isomerization of 5,5-dimethylbicyclo[2.1.0]pent-2-ene and the 2-^2H, 1,2,4-$^2H_3$, 1,2,3,4-$^2H_4$, and 1,4-$^{13}C_2$ isotopic variants of this system have been determined at 43.6–44.0 °C. There is no detectable carbon-13 effect; deuterium substitution at C(2) is associated with a small k_H/k_D effect, 1.02, and a deuterium at C(1) results in a very large effect, 1.26. The $k_H/k_D(d_3)$ effect between 24.6 and 54.7 °C shows some sensitivity to temperature, ranging from 1.83 to 1.64. The data exclude an important magnetic isotope effect on the isomerization and provide no support for a singlet → triplet intersystem crossing along the reaction coordinate.

The thermal isomerization of bicyclo[2.1.0]pent-2-ene (**1**) with cleavage of the C(1)–C(4) bond to give cyclopentadiene (**2**)[1,2] is geometrically constrained to occur in a disrotatory and thus orbital symmetry forbidden process.[3] Kinetic,[1] thermochemical,[4] and spectroscopic[5,6] studies have delineated the energetic parameters characterizing reactant, transition structure, and S_0 and T_1 states of the product. The overall reaction is exothermic by 47.8 kcal/mol;[4] the $\Delta H^{\ddagger}$ value for the isomerization is 26.3 kcal/mol,[1] and the S_0–T_1 energy gap for cyclopentadiene is 58.0 kcal/mol.[5,6] It follows that the transition structure lies 74.1 kcal/mol above the ground state singlet **2** and 16.1 kcal/mol above **2**-T_1; the



thermochemical facts delineate a relatively rare situation for a thermal isomerization of a hydrocarbon, one where the singlet ground state of the reactant might lead to the triplet state of the final product.

Recent studies have shown that rates of intersystem crossings between singlet and triplet organic radical pairs or diradicals may be influenced by magnetic isotope effects.[7,8] The thermal decomposition of 9,10-diphenylanthracene endoperoxide, for example, gives different proportions of $^3\Sigma$ or $^1\Delta$ dioxygen depending upon whether ^{17}O ($\mu = -1.893$ nuclear magneton, nuclear spin

(1) Brauman, J. I.; Golden, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1920–1921.
(2) Andrews, G. D.; Baldwin, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 4853–4854.
(3) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie-Academic Press: Weinheim, 1971.
(4) Roth, W. R.; Klärner, F.-G.; Lennartz, H.-W. *Chem. Ber.* **1980**, *113*, 1818–1829.
(5) Evans, D. F. *J. Chem. Soc.* **1960**, 1735–1745.
(6) Gorman, A. A.; Gould, I. R.; Hamblett, I. *J. Am. Chem. Soc.* **1981**, *103*, 4553–4558.
(7) Turro, N. J. *Pure Appl. Chem.* **1981**, *53*, 259–286. Turro, N. J.; Kraeutler, B. In *Isotopes in Organic Chemistry, Vol. 6: Isotope Effects: Recent Developments in Theory and Experiment*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1984; p 107–160 and references therein.
(8) Salikhov, K. M.; Molin, Yu. N.; Sagdeev, R. Z.; Buchachenko, A. L. *Spin Polarization and Magnetic Effects in Radical Reactions*; Molin, Yu. N., Ed.; Elsevier: Amsterdam, 1984; Chapter 6.

0002-7863/89/1511-3319$01.50/0