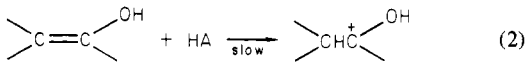
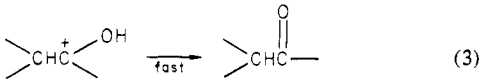
methyl vinyl ethers. As ketonization proceeds, these maxima give way to weaker bands at longer wavelengths, which are characteristic of the carbonyl group, and this change can be used to measure the rates of these reactions. The process follows first-order kinetics with good precision, and observed first-order rate constants measured in dilute mineral acid solution are accurately proportional to hydronium ion concentration. The reaction shows general acid catalysis and gives substantial hydronium ion isotope effects; e.g., $k_{H^+}/k_{D^+} = 2.83 \pm 0.08$ for the enol of isobutyraldehyde. This mechanistic evidence is similar to that obtained for the hydrolysis of simple vinyl ethers,[4] and it suggests that the rate-determining step in the present reaction is the same as that established for vinyl ether hydrolysis, namely rate-determining proton transfer from catalyst to substrate (eq 2); this is then



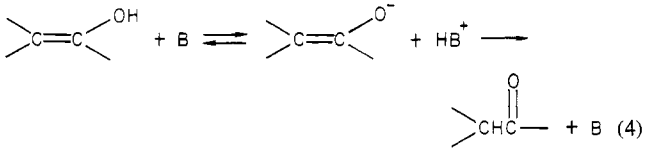
(2)



(3)

followed by proton loss from oxygen to give aldehyde or ketone product (eq 3). Such a two-step reaction scheme is consistent with current opinion on the mechanism of acid-catalyzed enolization of carbonyl compounds,[5] which, by the principle of microscopic reversibility, must occur by the route of the present reaction taken in reverse.

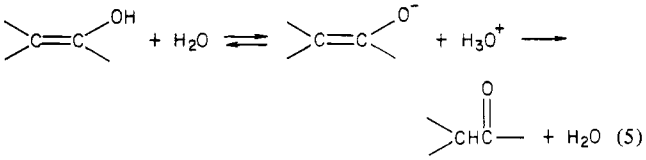
In addition to acid catalysis, the present ketonization reactions show strong catalysis by bases, and the form of this base catalysis indicates a reaction path that involves rate-determining carbon protonation of the enolate anion (eq 4). This scheme is again



(4)

consistent with the accepted mechanism for base-catalyzed enolization of carbonyl compounds. At high pH, this base catalysis becomes saturated, and rate measurements made in the region of saturation can be used to give an estimate of the equilibrium constant for the first step of this base-catalyzed route (eq 4). Measurements made on the enol of isobutyraldehyde lead to the enol acidity constant $K_a = 2.4 \times 10^{-4}$ M, $pK_a = 11.63 \pm 0.03$, which is in good agreement with an approximate estimate, $pK_a = 11.7 \pm 1.0$, derived from free-energy relationships.[6]

The pH–rate profile of these ketonization reactions also shows an uncatalyzed region in which the process occurring may be identified as the reaction of eq 4 with B = H_2O (eq 5). Observed



(5)

rate constants here are therefore products of the acid dissociation constants of the enols and rate constants for carbon protonation of the enolate ions, $k_{obsd} = K_a k'_{H^+}$. Measurements on isobutyraldehyde enol give $k_{obsd} = 4.2 \times 10^{-4}$ s^{-1}, from which, since K_a has been evaluated, $k'_{H^+} = 1.8 \times 10^8$ M^{-1} s^{-1} may be obtained. This result is 8 orders of magnitude greater than the rate constant for carbon protonation of the un-ionized enol of isobutyraldehyde, $k_{H^+} = 0.59$ M^{-1} s^{-1}, which illustrates the very powerful activating influence of a negatively charged oxygen substituent on electrophilic addition to a carbon–carbon double bond.

We have also measured the rate of enolization of isobutyraldehyde, by iodine scavenging, and have found $k_{H^+} = 4.7 \times 10^{-5}$ M^{-1} s^{-1}, in good agreement with an earlier determination.[7] When this value is corrected for aldehyde hydrate formation[8] and is combined with k_{H^+} for ketonization, the keto–enol equilibrium constant $K_E = 1.28 \times 10^{-4}$ and $pK_E = 3.90 \pm 0.01$ is obtained. This result is again consistent with an approximate recent estimate, $pK_E = 2.8 \pm 1.1$.[6,9]

An acidity constant for the ionization of isobutyraldehyde as a carbon acid (eq 6) may be derived by combining the presently

$$(CH_3)_2CHCHO \rightleftharpoons (CH_3)_2CCHO^- + H^+ \qquad (6)$$

determined values of pK_E and pK_a(enol): pK_a(carbon) = pK_E + pK_a(enol). The result, pK_a(carbon) = 15.53 ± 0.03, is to our knowledge the first accurately determined empirically founded acidity constant of a simple carbonyl compound in aqueous solution.

This new method of investigating enol chemistry promises to be of general applicability, and we are in fact currently engaged in applying it to a variety of simple carbonyl compounds.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their financial support of this research.

Registry No. D_2, 7782-39-0; isobutylraldehyde, 78-84-2; isobutyraldehyde enol, 56640-70-1.

(4) Salomaa, P.; Kankaanpera, A.; Lajunen, M. *Acta Chem. Scand.* **1966**, *20*, 1790–1801. Kresge, A. J.; Chiang, Y. *J. Chem. Soc. B* **1967**, 53–57; 58–61. Kresge, A. J.; Chen, H. L.; Chiang, Y.; Murrill, E.; Payne, M. A.; Sagatys, D. S. *J. Am. Chem. Soc.* **1971**, *93*, 413–423. Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *Ibid.* **1977**, *99*, 7228–7233. Okuyama, T.; Fueno, T.; Nakatsuji, H.; Fujimoto, J. *Ibid.* **1967**, *89*, 5826–5831. Kreevoy, M. M.; Eliason, R. E. *J. Phys. Chem.* **1968**, *72*, 1313–1316.

(5) Bell, R. P.; Jones, P. *J. Chem. Soc.* **1953**, 88–92. Lienhard, G. E.; Wang, T.-C. *J. Am. Chem. Soc.* **1969**, *91*, 1146–1153. Toullec, J.; Dubois, J. E. *J. Am. Chem. Soc.* **1974**, *96*, 3524–3532. Hegarty, A. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1975**, *97*, 7188–7189. Albery, W. J.; Gelles, J. S. *J. Chem. Soc., Faraday Trans. 1* **1982**, *78*, 1569–1578. Albery, W. J. *Ibid.* **1982**, *78*, 1579–1590.

(6) Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem.* **1979**, *57*, 240–248. Guthrie, J. P. *Ibid.* **1979**, *57*, 1177–1185.

(7) Talvik, A. J.; Hidmaa, S. O. *Org. React. (NY, Engl. Transl.)* **1968**, *5*, 121–126.

(8) Green, L. R.; Hine, J. *J. Org. Chem.* **1973**, *38*, 2801–2806.

(9) Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 797–802.

Use of the *N*-Oxide of *p*-Cyano-*N*,*N*-dimethylaniline as an "Oxygen" Donor in a Cytochrome P-450 Model System

Michael W. Nee and Thomas C. Bruice*

Department of Chemistry
University of California at Santa Barbara
Santa Barbara, California 93106

Received July 16, 1982

Iodosobenzene, organic peracids, and hydroperoxides have been employed with *meso*-(tetraphenylporphinato)iron(III) chloride [TPPFe^{III}Cl] to model the oxidation reactions of cytochrome P-450.[1] The products formed when peracids or hydroperoxides are employed with either TPPFe^{III}Cl or cytochrome P-450 are similar to those obtained in Fenton-type reactions,[2-4] whereas

(1) (a) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032–1033. (b) Chang, C. K.; Kuo, M.-S. *Ibid.* **1979**, *101*, 3413–3415. (c) Mansuy, D.; Bartoli, J.-F.; Chottard, J.-C.; Lange, M. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 909–910. (d) Mansuy, D.; Dansette, P. M.; Pecquet, F.; Chottard, J.-C. *Biochem. Biophys. Res. Commun.* **1980**, *96*, 433–439. (e) Gold, A.; Ivey, W.; Brown, M. *J. Chem. Soc., Chem. Commun.* **1981**, 293–295. (f) Chang, C. K.; Ebina, F. *Ibid.* **1981**, 778–779. (g) Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884–2886. (h) Lindsay Smith, J. R.; Sleath, P. R. *J. Chem. Soc., Perkin Trans. 2*, **1982**, 1009–1015.

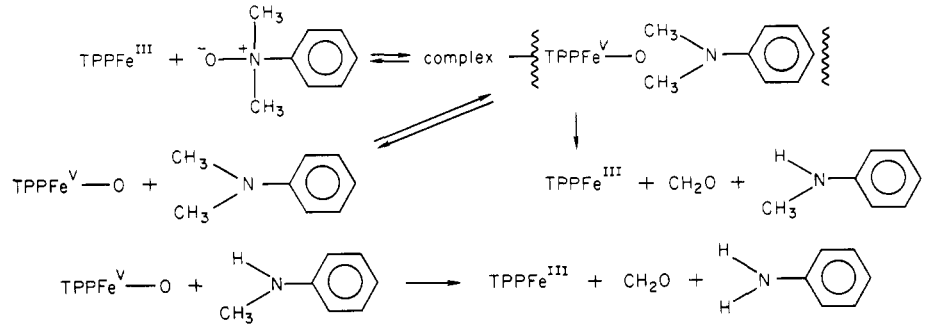
(2) Blake, R. C., II; Coon, M. J. *J. Biol. Chem.* **1981**, *256*, 12127–12133.

(3) (a) Groves, J. T.; McClusky, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 859–861. (b) Groves, J. T.; Van Der Puy, M. *Ibid.* **1976**, *98*, 5280–5297.

(4) But see ref 1g.

0002-7863/82/1504-6123$01.25/0

Scheme I

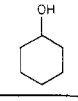


iodosobenzene + TPPFe^{III}Cl models the biologically important two-electron-reduced putidaredoxin + cytochrome P-450 + O_2 system more closely.[1c,e,g] Dynamic investigations of oxygen addition or insertion reactions are not practical with iodosoaromatics because of their polymeric nature,[5] insolubility in organic solvents, and oxidative destruction of the porphyrin ring in the absence of saturation by substrate.[6]

It has been our goal to introduce and study appropriate tertiary amine *N*-oxides as oxidants capable of transferring "oxene" or "oxygen atom" equivalents to metalloporphyrins. *N*,*N*-Dimethylaniline *N*-oxides are soluble in organic solvents and appear to leave porphyrin intact in the absence of added substrate. Our initial publication described a portion of an investigation of the *N*,*N*-dimethylaniline *N*-oxide (DMANO) + TPPFe^{III}Cl system.[6] From kinetic and product studies it was shown that DMANO reacted as both an "oxygen" donor and a substrate. The mechanism of Scheme I was suggested. The kinetic isotope effect, k[DMANO]/k[*N*,*N*-bis(trideuteriomethyl)aniline *N*-oxide], has been shown from initial rates measured from the change in absorbance at 290 nm to equal 1.4.[7] This is probably a secondary isotope effect and is consistent with the isotope effect, k_D/k_H, observed in the reaction of dimethylaniline and *N*,*N*-bis(trideuteriomethyl)aniline with methyl tosylate of 1.13,[8] because the quaternization reaction is essentially the reverse of "oxygen" transfer from DMANO. From GC–MS analysis of products, the discriminatory isotope effect with *N*-methyl-*N*-(trideuteriomethyl)aniline *N*-oxide was established as ~4.5,[7] indicating that this system does not have a high commitment to catalysis. The isotope effects suggest that an intermediate is formed by "oxygen" transfer from DMANO. Although DMANO does epoxidize 2,3-dimethyl-2-butene in the presence of TPPFe^{III}Cl, the yield of epoxide is very low;[7] probably the result of *N*,*N*-dimethylaniline competing with the olefin for the active oxygen species. For the DMANO + TPPFe^{III}Cl system to operate as an "oxygen" donor to various substrates, the rate of "oxygen" transfer from the tertiary amine *N*-oxide must be increased and the rate of oxidation of tertiary amine by TPPFe^{V}O decreased. This should, a priori, be brought about by substitution of electron-withdrawing groups on the phenyl moiety of DMANO. Increasing the electron deficiency of the DMANO phenyl ring destabilizes the *N*-oxide in comparison to the *N*,*N*-dimethylaniline and also decreases the ability of the latter to undergo oxidation by either one-[9] or two-electron transfer.

We report herein preliminary investigations of the *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide (*p*-CN-DMANO) + TPPFe^{III}Cl system in dry CH_2Cl_2 solvent at 30 °C. All solutions were prepared and reactions studied under an oxygen-free nitrogen atmosphere, employing pseudo-first-order conditions: [*p*-CN-DMANO] ≫ [TPPFe^{III}Cl]. In an initial rapid reaction, the absorption bands of TPPFe^{III}Cl (λ_{max} 374, 415, 506, 656, and 688 nm) give way to new spectral bands (λ_{max} 410, 568, and 608 nm). Similar spectral changes have been observed when DMANO[7] and other anionic ligands[10] are added to TPPFe^{III}Cl. As the catalysis of the deoxygenation of *p*-CN-DMANO proceeds, the original spectra of the porphyrin reappears (slightly modified, with somewhat lower extinction). We have observed only minimal loss of porphyrin no matter how large an excess of *p*-CN-DMANO used. GC analysis of the reaction mixture established that approximately 50% demethylation occurred to provide a 70:13:17 ratio of products *p*-cyano-*N*,*N*-dimethylaniline (*p*-CN-DMA):*p*-cyano-*N*-methylaniline (*p*-CN-NMA):*p*-cyanoaniline (*p*-CN-A). The oxidation of alkenes and alkanes by *p*-CN-DMANO with TPPFe^{III}Cl provides the same products as with iodosobenzene and in similar yields (Table I). *p*-Nitro-*N*,*N*-dimethylaniline *N*-oxide is an equally effective oxidant but has the disadvantage of being less stable than *p*-CN-DMANO.[11] The major difference between the *p*-CN-DMANO and the iodosobenzene systems is that while the iodosobenzene system is both stereospecific and kinetically selective for *cis*-alkenes, the *p*-CN-DMANO system is only stereospecific. As would be anticipated, the yield of dealkylation product decreases in the presence of alkene. In the presence of 0.8 M 2,3-dimethyl-2-butene, essentially no dealkylation was observed and 2,3-epoxy-2,3-dimethyl-2-butene was obtained in

Table I. Oxidation of Alkenes and Alkanes by *p*-CN-DMANO and FeTPPCl in Dichloromethane[a]

substrate	product	yield,[b] %
		90 (89[1h])
		45 (48,[1h] 55[1a])
		11 (13,[1h] 15[1a])
		36
	*cis*-stilbene oxide	29 (52,[1h] 82[1a])
	*trans*-stilbene oxide	17 (2,[1h] trace[1a])
		2 (8[1a])

[a] The ratio of substrate to *p*-CN-DMANO to FeTPPCl in the reactions was 100:10:1. The reactions were done at room temperature under a nitrogen atmosphere. [b] GC yields based on *p*-CN-DMANO added. Yields with iodosobenzene and FeTPPCl are given in parentheses.

(5) Buchler, J. W.; Lay, K. L.; Castle, L.; Ullrich, V. *Inorg. Chem.* **1982**, *21*, 842–844.
(6) Shannon, P.; Bruice, T. C. *J. Am. Chem. Soc.* **1981**, *103*, 4580–4582.
(7) Shannon, P.; Nee, M. W.; Bruice, T. C., unpublished results.
(8) Kaplan, E. D.; Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 6644–6651.
(9) Egdell, R.; Green, J. C.; Rao, C. N. R. *Chem. Phys. Lett.* **1975**, *33*, 600–607.
(10) Quinn, R.; Nappa, M.; Valentine, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 2588–2595.
(11) Khuthier, A. H.; Ahmed, T. Y.; Jallo, L. I. *J. Chem. Soc., Chem. Commun.* **1976**, 1001–1002.

90% yield. In the instance of other alkenes of Table I, there is a marked decrease in the percentage yield of didealkylation product, *p*-CN-A, relative to monodealkylated product, *p*-CN-NMA (with norbornane the percentage yields are in an 81:14:5 ratio of *p*-CN-DMA:*p*-CN-NMA:*p*-CN-A). Epoxidation with this system is competitive with dealkylation of *p*-CN-NMA.

In conclusion, the reaction of *p*-CN-DMANO with $TPPFe^{III}Cl$ in CH_2Cl_2, in the absence of O_2, represents a catalysis with rapid turnover in which the "oxygen" moiety is transferred to $TPPFe^{III}$ (Scheme I) and hence employed in N-dealkylations of *N*,*N*-dimethyl- and *N*-methylanilines, epoxidation of alkenes, and hydroxylation of alkanes. The use of *p*-CN-DMANO has distinct advantages over iodosobenzene as an "oxygen" donor to $TPPFe^{III}$, and these advantages should be observable with other metalloporphyrin systems. The reagent *p*-CN-DMANO is soluble in most organic solvents, and in solution it is monomeric. Also, *p*-CN-DMANO does not destroy, by oxidation, the porphyrin ring system. We are continuing work on the kinetics of the *p*-CN-DMANO + $TPPFe^{III}X$ systems, the reaction of *p*-CN-DMANO in the presence of other metalloporphyrins, and the use of other *N*-oxides.

Acknowledgment. This work was supported by grants from the National Institutes of Health and The American Cancer Society. M.W.N. wishes to thank the National Institutes of Health for support as a postdoctoral fellow.

Registry No. $TPPFe^{III}Cl$, 16456-81-8; *P*-CN-DMANO, 62820-00-2; *P*-CN-DMA, 1197-19-9; *P*-CN-NMA, 4714-62-9; 2,3-dimethyl-2-butene, 563-79-1; cyclohexene, 110-83-8; norbornene, 498-66-8; *cis*-stilbene, 645-49-8; *trans*-stilbene, 103-30-0; cyclohexane, 110-82-7; cytochrome P-450, 9035-51-2.

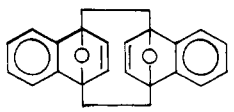
Cyclophanes. 15. Thermolysis of 1,1′,4,4′-Tetrahydro-1,4:1′,4′-diepoxy[2.2](1,4)-naphthalenophane. Intracavity Nonbonded Interaction and Evidence for the Intermediacy of an Isobenzofuranophane

Ann Halverson and Philip M. Keehn*[1]

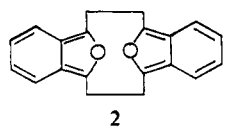
Department of Chemistry, Brandeis University
Waltham, Massachusetts 02254

Received June 7, 1982

Though 1,1′,4,4′-tetrahydro-1,4:1′,4′-diepoxy[2.2](1,4)-naphthalenophane (**1**) has been known for some time,[2-4] little has



1

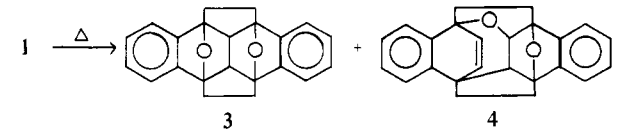


2

been reported on the chemistry of this system. Molecular models of **1** indicate that severe nonbonded interactions exist between the two oxygen atoms within the cavity. We report here on the thermolysis of **1** and present evidence for the intermediacy of isobenzofuranophane **5** and the unusual strain-induced isomerization of **1** to **4**.

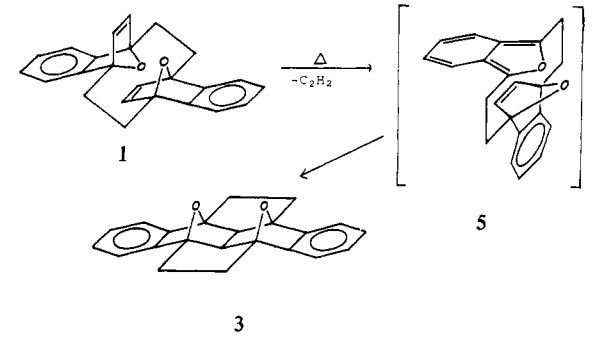
When **1** was heated in DMF or xylene at 150 °C (see Scheme I), a brilliant burgundy color was observed.[5] After dissipation of the color (4 h) the reaction mixture was cooled (0 °C), and a white crystalline material precipitated. Filtration afforded polycyclic diether **3** (26.7%).[6] Evaporation of the solvent from

Scheme I



3 4

Scheme II



1 5

3

the mother liquor and chromatography of the residue (silica gel; 4:1 benzene:ethyl acetate) afforded an unidentifiable oil and polycyclic diether **4** (53.2%) as a foam. Recrystallization from methanol afforded pure **4** (mp 232.5–233.5 °C).

Compound **3** was easily identified by spectral and microanalytical[7] means. The ultraviolet spectrum of **3** ($\lambda_{max}CHCl_3$ (ϵ): 255 mm (981), 262 (1570), 269 (2452), 275 (2845)) indicated the presence of the benzenoid units[8] and the mass spectrum (*m/e* 314 (M^+), 170, 144) showed that its molecular weight was 26 amu (C_2H_2) less than the starting material. The ^1H NMR spectrum was simple ($CDCl_3$; δ 7.13 (AA′BB′, 8 H), 2.75 (AA′BB′, 8 H), 2.06 (s, 2 H)[9]), indicating aromatic and aliphatic protons and the absence of vinyl protons.[10] The highly symmetric nature of **3** was reflected in the ^{13}C NMR spectrum ($CDCl_3$; δ 147.9, 125.6, 117.8, 94.9, 64.3, 28.5) in which only six absorptions were observed.[11] The above data are compatible with the structure assignment for **3**.

Compound **4** was also identified by spectral and microanalytical methods,[12] but the structure elucidation was more complicated. The ultraviolet spectrum of **4** ($\lambda_{max}CHCl_3$ (ϵ) 258 nm (sh) (6484), 268 (9141), 273 (9035), 279 (8928), 292 (4677), 301.5 (1275)) was similar to **1**,[8] but the extinction coefficients were as much as 4 times greater, and an additional two absorptions above 290 nm were observed. Mass spectral analysis (*m/e* = 340 (M^+), 267, 225, 154) indicated that **4** was isomeric with **1**, but the fragmentation pattern was different. The presence of a single olefinic unit was indicated by the absorption of 1 equiv of Br_2,[13] and the ^1H NMR spectrum of **4** confirmed the presence of two nonequivalent vinylic protons ($CDCl_3$; δ 7.17 (m, 8 H), 6.03 (ABq, 2 H, J = 10 Hz) 3.10–2.10 (m, 10 H)). In addition to the presence of eight aromatic protons, the ^1H NMR spectrum indicated that isomer **4** had two more aliphatic protons than **1**.[10] Finally, the ^{13}C NMR spectrum of **4**[14] exhibited 24 distinct absorptions,

(1) Dreyfus Teacher–Scholar 1979–1984.
(2) Keller, L. S. Ph.D. Thesis, Yale University, New Haven, CT, 1970.
(3) Kapicak, L. A.; Battiste, M. A. *J. Chem. Soc., Chem. Commun.* **1973**, 930–931.
(4) Otsubo, T.; Mizogami, S.; Osaka, N.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1841–1849.
(5) This reaction also takes place when solid **1** is heated in a sealed, evacuated tube.
(6) The material did not exhibit a distinct melting point; however, accurate microanalysis was obtained on material recrystallized from EtOAc.[7]
(7) Anal. Calcd for $C_{22}H_{18}O_2$ (**3**): C, 84.05; H, 5.77. Found: C, 83.87; H, 5.94.
(8) Compare with the ultraviolet spectrum of **1**: $\lambda_{max}CHCl_3$ (ϵ) 250 nm (1616), 260 (1722), 268.5 (1824), 275.5 (1875), 282.5 (1773).
(9) These protons must be anti to the two ether bridges if the mechanism described in Scheme II is valid. This stereochemistry is supported by NMR data in the following: Feiser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599–1606.
(10) Compare with the ^1H NMR spectrum of **1** ($CDCl_3$): δ 6.82 (AA′BB′, 8 H), 6.41 (s, 4 H), 2.52 (AA′BB′, 8 H).
(11) Compare with the ^{13}C NMR spectrum of **1** ($CDCl_3$; δ 157.8, 141.7, 122.6, 117.1, 91.5, 27.4) where six absorptions appear for 24 carbon atoms.
(12) Anal. Calcd for $C_{24}H_{29}O_2$ (**4**): C, 84.68; H, 5.92. Found: C, 84.50; H, 5.95.
(13) The dibromide was prepared (77% yield) by treating **4** with 1 equiv of Br_2/CCl_4 and characterized by microanalysis and spectroscopic methods.
(14) ^{13}C NMR ($CDCl_3$) δ 146.2, 145.1, 144.5, 139.1, 134.5, 134.0, 131.2, 127.2, 126.9, 126.3, 126.2, 124.6, 118.3, 118.1, 98.04, 98.00, 97.4, 95.6, 72.9, 71.6, 39.3, 38.0, 34.5, 29.2.

0002-7863/82/1504-6125$01.25/0