

possible participation of the hydrogen bonding. The fact that dihydrosaxitoxin has less than one-hundredth of the original activity on the excitable membranes¹⁹ has been regarded as important information in this respect. In a way hydrated saxitoxin can be regarded as a concoction of the two isomeric dihydrosaxitoxins. Now that the stereochemistry of dihydrosaxitoxin used in the past was established as the 12 α -isomer, the neurophysiological study of the 12 β -isomer seems to be the next step. Our finding that the absence of 12 β -hydroxyl group drastically changed the sterical environment of the β side of saxitoxin molecule as exemplified

by the change in the side-chain conformation may be significant with regard to the manifestation of toxicity.

Acknowledgment. This work was supported by the PHS Grants FD00619 and GM28754. We wish to acknowledge the support of the Southern New England High Field NMR Facility at Yale University made possible by a grant from Biotechnology Resources Program of the National Institutes of Health (No. RR-798) and NSF Grant CHE-7916210. We also wish to acknowledge Professor Clair Cheer for the Newman projection of X-ray data.

Kinetic Applications of Electron Paramagnetic Resonance Spectroscopy. 36. Stereoelectronic Effects in Hydrogen Atom Abstraction from Ethers¹

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Abstract: Relative rates of hydrogen atom abstraction by photogenerated *tert*-butoxyl from a variety of cyclic and acyclic ethers, acetals, and orthoformates have been measured at -60 °C by an EPR spectroscopic technique. There is a pronounced stereoelectronic effect which produces high rates of abstraction from those C-H bonds adjacent to oxygen which have a relatively small dihedral angle (ca. 30°) with respect to the p-type orbital(s) on the oxygen(s). For C-H bonds which have a large dihedral angle (ca. 90°) abstraction is very much slower. The barrier to inversion of the 2-methoxy-1,3-dioxolan-2-yl radical is ≥ 10 kcal/mol.

In an outstanding series of papers Deslongchamps et al. have shown that molecular reactivities in many areas of heterolytic chemistry are determined by the relative orientation of the bond being broken or made and lone pairs on heteroatoms attached to the reaction center, i.e., by stereoelectronic factors.³⁻⁶ In contrast, in homolytic chemistry the role that adjacent lone pairs play in determining reactivity has received very little experimental attention, particularly insofar as C-H bond homolysis is concerned.⁷ In fact, the only published experimental study is that of Hayday and McKelvey,¹⁰ who found that at ambient temperatures triplet benzophenone abstracted the axial 2-H from *cis*-2-methoxy-4-methyltetrahydropyran at least 8 times faster than it abstracted the equatorial 2-H from the *trans* isomer. Since both compounds gave the same product distribution, it was concluded that a common free radical was formed. This was subsequently con-

firmed by Malatesta et al.¹¹ by using EPR spectroscopy to identify common 2-alkoxytetrahydropyran-2-yl radicals generated from conformationally biased *cis* and *trans* precursors. The *tert*-butoxyl radical also exhibits a strong preference (ca. 12-fold at ambient temperatures) for the axial 2-H over the equatorial 2-H in its reactions with conformationally biased pairs of 2-methoxy-1,3-dioxanes and 2-methyl-1,3-dioxanes.¹²

Despite, or perhaps because of, the dearth of experimental data regarding the role of stereoelectronic effects on the strength of C-H bonds adjacent to heteroatoms, the subject has received considerable theoretical attention, particularly by Wolfe et al.¹³⁻¹⁶ Thus, for example,¹⁴ in methanol the strengths of the C-H bonds *anti* and *gauche* with respect to the O-H bond have been calculated to be ca. 100 and ca. 95 kcal/mol, respectively, a stereoelectronically induced difference of 5 kcal/mol. Wolfe¹⁷ has also emphasized that certain physical properties of C-H bonds which can be related to C-H bond strengths show a strong dependence on orientation when the C-H bond is adjacent to a heteroatom. Examples include C-H bond stretching frequencies in the IR spectra of amines (the Bohlmann bands)¹⁸ and other heterocompounds^{13,16} and ¹³C-¹H coupling constants¹⁹ in the NMR spectra of carbohydrates.²⁰

We have been interested in studying the structure, conformation,

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(2) NRCC Research Associate, 1977-1979.

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(8) Livant, P.; Lawler, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 6044. Beckwith, A. L. J.; Easton, C. *Ibid.* **1978**, *100*, 2913. Agosta, W. C.; Wolff, S. *Ibid.* **1976**, *98*, 4316; **1977**, *99*, 3355.

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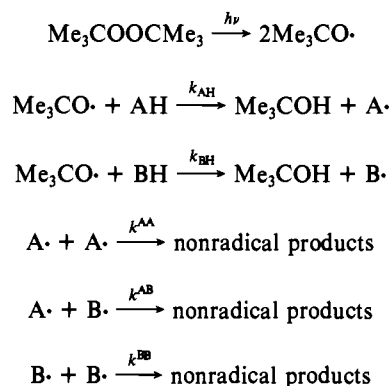
(17) Wolfe, S., private communication.

(18) Bohlmann, F. *Angew. Chem.* **1957**, *69*, 641; *Chem. Ber.* **1958**, *91*, 2157.

(19) The degree of s character in the C-H bond affects both J_{13C-H} and the bond strength.

(20) Perlin, A. S.; Cosu, B. *Tetrahedron Lett.* **1969**, 2921. Schwarcz, J. A.; Perlin, A. S. *Can. J. Chem.* **1972**, *50*, 3667. Bock, K.; Lundt, I.; Pedersen, C. *Tetrahedron Lett.* **1973**, 1037. Perlin, A. S. *Pure Appl. Chem.* **1978**, *50*, 1401. Cyr, N.; Perlin, A. S. *Can. J. Chem.* **1979**, *57*, 2504.

and configuration of radicals derived from ethers by EPR spectroscopy for some time.^{11,21,22} The radicals can be readily generated and identified by photolyzing a mixture of di-*tert*-butyl peroxide and the ether in a hydrocarbon solvent. The present work was undertaken to examine stereoelectronic effects in hydrogen abstraction from ethers by *tert*-butoxyl. Our technique involved competitive hydrogen atom abstraction at -60°C in cyclopropane and/or methylene chloride. This temperature was chosen because optimal EPR spectra were obtained with most radicals. Our kinetic analysis relies on the fact that all radicals derived from the ethers studied are transient, are of relatively low molecular weight, and are sterically unhindered. Radical decay can therefore be assumed to occur by radical-radical reactions at the diffusion-controlled limit.^{23,24} The reaction scheme can be represented by



Under steady photolysis

$$k_{\text{AH}}[\text{Me}_3\text{CO}\cdot][\text{AH}] = 2k^{\text{AA}}[\text{A}\cdot]^2 + 2k^{\text{AB}}[\text{A}\cdot][\text{B}\cdot]$$

$$k_{\text{BH}}[\text{Me}_3\text{CO}\cdot][\text{BH}] = 2k^{\text{BB}}[\text{B}\cdot]^2 + 2k^{\text{AB}}[\text{A}\cdot][\text{B}\cdot]$$

and, on the assumption that $k^{\text{AA}} \approx k^{\text{AB}} \approx k^{\text{BB}}$

$$\frac{k_{\text{AH}}}{k_{\text{BH}}} = \frac{[\text{A}\cdot][\text{BH}]}{[\text{B}\cdot][\text{AH}]}$$

The relative rates of hydrogen abstraction from AH and BH can, therefore, be quite simply obtained by measuring the relative concentrations of A· and B·. The results should, we believe, be reliable to within a factor of about 2 or 3 considering the general similarity in the radicals examined. This degree of reliability is quite adequate to demonstrate the importance of stereoelectronic effects in the homolytic chemistry of ethers. More accurate, but time consuming, kinetic procedures seemed unwarranted for a broad preliminary survey of a large field.

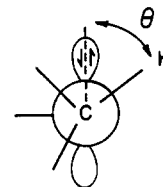
It appears to have been established by photoelectron spectroscopy that the two lone pairs of electrons on oxygen are not equivalent.^{25,26} One lone pair is essentially a pure p-type orbital, and the second lone pair is roughly an s-type orbital.²⁵ The p-type lone pair is of higher energy (lower IP) than the s-type,²⁷ and its

Table I. EPR Parameters for Oxyalkyl Radicals Previously Unreported^a

radical ^b	<i>g</i>	<i>a</i> ^{Hα}	<i>a</i> ^{Hβ}	<i>a</i> ^{Hothers}
5a	2.0029			1.77 (2) ^c 0.26 (3)
5b	2.0031	11.5 (1) ^d	29.8 (1) ^d 28.4 (1) ^d	0.7 (1) ^d
5c	2.0029	18.2 (2)		1.6 (1)
6a	2.0032	10.5 (1) ^e	11.1 (1) ^e	4.0 (1) 0.9 (1) 0.6 (1)
13a ^f	2.0032		25.8 (1)	
14a ^f	2.0032		22.5 (1)	
15a	2.0029			
15b	2.0029		39.5 (1) 19.2 (3) 6.7 (1)	
16a	2.0029			
16b	2.0029		39.0 (1) 18.9 (3) 6.8 (1)	
17b ^f	2.0029	20.2 (1)	6.1 (1) 0.7 (4)	
20a ^g	2.0030	11.1 (1)		0.87 (4)
20b ^g	2.0030	15.3 (1)	22.5 (3)	0.82 (2)

^a In cyclopropane at ca. -120°C unless otherwise specified. Hyperfine splittings are given in gauss. Numbers in parentheses refer to the numbers of equivalent hydrogens. The EPR parameters for radicals generated in this work which are not given in this table have been previously reported, as follows: 1a, 3a,b, 4a,b, 7a,³¹ 8a, 11a,³² 9a, 10a,³³ 12a,³³ 19a,³⁴ 21a,b,³⁵ 22a,b,³⁶ 23a,b.³⁴ ^b 5a refers to the radical obtained on removal of H_a from 5 (see Table II) etc. ^c Two ring hydrogens only. ^d At 20°C . At low temperatures this radical exists as two conformers which are present in approximately equal concentration. Their EPR parameters at -120°C are for conformer 1, *a*^{H α} = 11.3 (1), *a*^{H β} = 31.7 (1) and 27.2 (1), and *a*^{H others} = 1.45 (1) G and for conformer 2, *a*^{H α} = 12.5 (1), *a*^{H β} = 34.5 (1) and 25.5 (1), and *a*^{H others} is not resolved. Spectral simulation gives a barrier, ΔH , to interconversion of 4.0 kcal/mol, with $\Delta S = 1.0$ eu. ^e Arbitrary assignment of *a*^{H α} and *a*^{H β} . ^f In CH₂Cl₂ at ca. -60°C . ^g In cyclopropane at ca. -60°C .

orbital energy is of similar magnitude to that of the unpaired electron. In the radical, therefore, the C_α semioccupied orbital should interact (by conjugative electron delocalization) *only* with the p-type lone pair. We would therefore anticipate that any stereoelectronic weakening of a C–H bond adjacent to oxygen in the parent ether,²⁸ and concomitant acceleration of hydrogen atom abstraction, will be at a maximum when the dihedral angle, θ , between the C–H bond and the p-type orbital(s) on the oxygen(s) is 0° ³⁰ and will be at a minimum when this angle is 90° .



Following Deslongchamps,³⁻⁶ we have used cyclic ethers as the principal means for testing this prediction since their controlled geometry serves to define θ . Our expectations have been amply supported by the experimental results. We have also made a limited series of measurements on some acyclic ethers.

(28) There have been few direct measurements of C–H bond strengths in ethers,²⁹ and in none of these studies has the potential importance of stereoelectronic factors been considered.

(29) For leading references see: Cruickshank, F. R.; Benson, S. W. *J. Am. Chem. Soc.* **1969**, *91*, 1289; *Int. J. Chem. Kinet.* **1969**, *1*, 381; Golden, D. M.; Benson, S. W. *Chem. Rev.* **1969**, *69*, 125; O'Neal, H. E.; Benson, S. W. "Free Radicals"; Kochi, J. K.; Ed.; Wiley: New York, 1973; Vol. 2, Chapter 17.

(30) For an interesting alternative suggestion regarding the cause of the weakening of this C–H bond, see ref 13.

(21) Brunton, G.; Ingold, K. U.; Roberts, B. P.; Beckwith, A. L. J.; Krusic, P. J. *J. Am. Chem. Soc.* **1977**, *99*, 3177.

(22) It is perhaps worth pointing out that EPR spectroscopic parameters led to the suggestion that hydrogen abstraction from certain cyclic ethers should be highly stereospecific.²¹

(23) See, e.g.: Ingold, K. U. "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 2; Griller, D.; Ingold, K. U. *Int. J. Chem. Kinet.* **1974**, *6*, 453; Schuh, H.; Fischer, H. *Ibid.* **1976**, *8*, 341; *Helv. Chim. Acta* **1978**, *61*, 2130; Lezni, M.; Schuh, H.; Fischer, H. *Int. J. Chem. Kinet.* **1979**, *11*, 705.

(24) The ether derived radicals will all be too unreactive at -60°C for reactions such as $\text{A}\cdot + \text{BH} \rightarrow \text{AH} + \text{B}\cdot$ to compete with the radical-radical termination step at the rates of radical production used in our experiments.

(25) Sweigart, D. A. *J. Chem. Educ.* **1973**, *50*, 322 and references cited.

(26) In most previous studies of stereoelectronic effects in heterolytic³⁻⁶ and homolytic¹⁰ reactions, it has been assumed that ethereal oxygen is sp³ hybridized with two lone pairs of equal energy. Although this may not be correct,²⁵ it will, with many substrates, lead to more or less the same conclusions as those derived by considering the lone pairs to be nonequivalent.

(27) By ≥ 10 eV.²⁵

Table II. Relative Reactivities per Equivalent Hydrogen Atom (ρ) of Cyclic Ethers toward $\text{Me}_3\text{CO}\cdot$ at -60°C and Approximate θ Values^a

Ether	H ^b	ρ	θ^c	Ether	H ^b	ρ	θ^c
1	H _a (4)	(1.0) ^d	30°	11	H _a (3) ⁱ	1.2	30° 30°
2	H _a (2)	N. D. ^e	90°	12	H _a (1) ⁱ H _b (1)	0.56 N.D. ^e	30° 30° 30°
3	H _a (2) H _b (4)	8.8 0.32	30° 30° 30°	13	H _a (1) H _b (2) ⁱ	0.35 ^j N.D. ^e	30° 90° 30°
4	H _a (1) H _b (4) ^{d,f}	5.2 0.19 ^f	30° 30° 30°	14	H _a (2) H _b (4) ⁱ	0.26 ^j N.D. ^e	30° 90° 30°
5	H _a (1) H _b (4) ^d H _c (3)	0.27 0.58 0.08	30° 30° 1 ^g 30° 1 ^g	15	H _a (1) H _b (2) H _c (3)	0.55 ^j 0.05 ^j N.D. ^e	30° 30° 1 ^g 30° 1 ^g
6	H _a (1) ^h H _b (1) H _c (1)	0.19 N. D. ^e N. D. ^e	30° 70° 50° 70°	16	H _a (1) H _b (2) H _c (3)	0.06 ^j 0.09 ^j N. D. ^e	90° 90° 1 ^g 30° 1 ^g
7	H _a (2) ⁱ	0.11	30°	17	H _a (1) H _b (6)	N. D. ^e 0.18 ^j	90° 90° 90° 30°
8	H _a (4) ⁱ	0.18	30°	18	H _a (1) H _b (3)	N. D. ^e N. D. ^e	90° 90° 90° 90°
9	H _a (1) H _b (1) H _c (3)	0.65 N. D. ^e N. D. ^e	30° 1 ^g 30° 1 ^g				
10	H _a (1) H _b (1) H _c (3)	0.16 N. D. ^e N. D. ^e	90° 1 ^g 30° 1 ^g				

^a In cyclopropane unless otherwise specified. ^b Number of equivalent hydrogens is given in parentheses. ^c From Dreiding models, an angle is given for each adjacent oxygen. ^d Assumed. ^e Not detected. The C-H bond indicated probably has a ρ value <0.15 (see text). ^f The low ρ value suggests that only two hydrogens may actually be readily accessible to $\text{Me}_3\text{CO}\cdot$. ^g Indeterminate. ^h For steric reasons it is assumed that only one of the two hydrogens on this carbon can react. ⁱ It is assumed that only the axial hydrogens can react since $\theta \approx 90^\circ$ for the equatorial hydrogens. ^j In CH_2Cl_2 for reasons of solubility.

Results

The EPR spectral parameters for many of the radicals produced during this work have been previously reported.^{11,31-36} The parameters for "new" radicals are given in Table I.

The results obtained in competitive experiments with 18 cyclic and 5 acyclic ethers are reported in Tables II and III, respectively. In both tables ρ represents the reactivity per equivalent hydrogen relative to tetrahydrofuran **1**. All reactivities have been measured in two or more independent experiments. The solvent was generally cyclopropane, but for solubility reasons methylene chloride was used for some of the multicyclic ethers. The change in solvent had no apparent effect on relative reactivities. The approximate dihedral angle, θ , between the C-H bond of interest and the p-type lone pair on each adjacent ring oxygen is included in Table II. These angles were estimated from Dreiding molecular models. It can be seen that most cyclic ethers have $\theta \approx 30^\circ$ or 90° and

that other well-defined θ values are not readily obtained.

Discussion

Absolute Reactivities. Though comparatively easy to obtain, the relative reactivities of a set of substrates toward a common radical lose much of their value unless it is shown that even the fastest reaction proceeds at a rate well below ($\leq 10\%$) the diffusion-controlled limit. In the reaction system used in the present work this limit can be calculated²³ to be about $3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ in cyclopropane and somewhat less in methylene chloride. The relative reactivity of cyclopentane toward *tert*-butoxyl was therefore determined since the absolute rate constant, $k_{\text{C}_5\text{H}_{10}}$, for this reaction has been measured by two independent techniques. Thus, Scaiano and co-workers³⁷ report that $k_{\text{C}_5\text{H}_{10}}/H = 8.8 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at 21°C , and Wong³⁸ reports a value of $3.4 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ at 20°C with an activation energy of 6.1 kcal/mol and a preexponential factor $A_{\text{C}_5\text{H}_{10}}/H = 1.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.^{38,39} For our purposes the agreement between the two measurements is satisfactory and, taking Wong's data, we obtain, $k_{\text{C}_5\text{H}_{10}}/H = 7 \times 10^2$

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

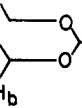
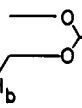
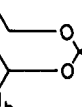
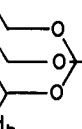
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(38) Wong, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 1235.

(39) Hendry, D. G.; Mill, T.; Piszkiwicz, L.; Howard, J. A.; Eigenmann, H. K. *J. Phys. Chem. Ref. Data* **1974**, *3*, 937.

Table III. Relative Reactivities per Equivalent Hydrogen Atom (ρ) of Acyclic Ethers toward $\text{Me}_3\text{CO}\cdot$ at -60°C in Cyclopropane

Ether	H^a	ρ
1 	H_a (4)	(1.0) ^b
19 	H_a (4)	0.16
20 	H_a (2)	0.29
	H_b (4)	0.11
21 	H_a (2)	0.25
	H_b (6)	0.05
22 	H_a (1)	0.95
	H_b (4)	0.30
23 	H_a (1)	0.53
	H_b (6)	0.10

^a Number of equivalent hydrogens is given in parentheses.^b Assumed.

$\text{M}^{-1}\text{s}^{-1}$ at -60°C . At this temperature the reactivity per hydrogen of cyclopentane relative to tetrahydrofuran was

$$\rho_{\text{C}_5\text{H}_{10}} = \frac{k_{\text{C}_5\text{H}_{10}}/\text{H}}{k_1/\text{H}} = 3.5 \times 10^{-4}$$

and hence, $k_1/\text{H} = 2 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ at -60°C . Diffusion control is therefore not a factor which needs to be considered when examining the reactivity data in Tables II and III.

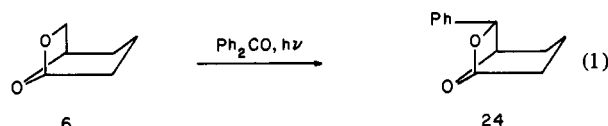
The absolute rate constant, k_1/H , given above can be used to calculate the absolute rate constants for hydrogen abstraction at -60°C from the other ethers listed in the tables. Furthermore, if following Hendry et al.,³⁹ we take the preexponential factor per hydrogen for H abstraction from ethers to be $5 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, then the activation energies for these reactions can also be calculated. For tetrahydrofuran this procedure yields an activation energy of 2.3 kcal/mol.

Relative Reactivities of Cyclic Ethers. Even the most cursory examination of Table II shows that our expectation that appreciable stereoelectronic effects should be observed in hydrogen atom abstractions from cyclic ethers, with a high reactivity when θ is small and low reactivity when θ is large, is fulfilled. However, the effects are not as large as those found in heterolytic reactions.³⁻⁶ This can be attributed to the fact that in the heterolytic processes stabilization arises from interactions between an "empty" orbital and a fully occupied orbital and this should be greater and hence more important than the stabilization which arises from interaction between the developing⁴⁰ semioccupied orbital and a fully occupied orbital in the homolytic processes. In addition, H abstraction by *tert*-butoxyl probably has an early transition state in which radical character in the ether will only be developed to a small extent.⁴⁰

Abstraction from the Carbon Adjacent to One Oxygen. As noted above, the single oxygen in tetrahydrofuran, for which $\theta \approx 30^\circ$, activates the adjacent hydrogens and makes them $1/3.5 \times 10^{-4}$

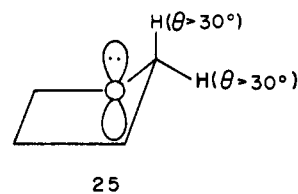
≈ 2860 times as reactive as the hydrogens in cyclopentane. However, no radicals could be detected from **2**, whose two C-H bonds adjacent to the oxygen have $\theta = 90^\circ$.⁴¹ The failure to observe a particular radical implies that the C-H bond in question has a ρ value which is probably less than ca. 0.15 for a radical, giving a many lined EPR spectrum, and probably less than ca. 0.02 for a radical, giving a spectrum of only one or two lines.

The remarkable dependence of ρ on θ for C-H bonds adjacent to one oxygen is further exemplified by **6**. This gave only the radical formed by abstraction of H_a ($\theta = 30^\circ$) with no trace of the radical which would be formed by loss of H_b ($\theta = 70^\circ$), nor even of that which would be formed by loss of H_c though this has two neighboring oxygens ($\theta = 50^\circ$ and 70°). Though rather spectacular, this particular result was not entirely unexpected since Deslongchamps et al.^{3b} have reported that **6**, in contrast to most acetals, was unreactive to ozone. Furthermore, Bernasconi and Descotes⁴² found that only **24** was formed during the photolysis of **6** and benzophenone in benzene (eq 1).



The enhanced reactivity of C-H bonds adjacent to one oxygen with $\theta = 30^\circ$ relative to cyclic alkanes can also be seen in the ρ values found for **7**, **8**, **15** (H_b), **16** (H_b), and **17** (H_b). We attribute our failure to observe the radicals which would be formed by abstraction of H_b from **9**, **10**, **12**, **13**, and **14**, to relatively small ρ values combined in some instances with a relatively large number of EPR spectral lines. Some radicals may also be hard to detect because of line broadening caused by unresolved hyperfine splittings or by dynamic effects.

There can be little doubt that for θ values of ca. 30° ethereal C-H bonds in 6-membered rings are generally less reactive toward *tert*-butoxyl than those in 5-membered rings^{43,44} (cf., for example, **1** or **3** (H_b) with **7** or **8** and **3** (H_a) with **11** or **12** (H_a)). This difference could be due, in part, to the fact that 5-membered rings are conformationally more mobile than 6-membered rings.⁴⁶ If the 5-membered rings are in an envelope conformation with a CH_2 group adjacent to the oxygen out-of-plane, then the θ value for one C-H bond of this CH_2 group will be less than 30° with a consequent increase in its reactivity; see **25**. This increase will, of course, be balanced to some extent by the decreased reactivity of the other C-H bond for which θ becomes greater than 30° .



However, the high conformational mobility of tetrahydrofuran and 1,3-dioxolane may not be the only reason for their high reactivity since we have found that cyclopentane is considerably more reactive toward *tert*-butoxyls than is cyclohexane. Under the same conditions as those used for the ethers in Table II, the relative reactivity per hydrogen of these two hydrocarbons,

(41) The relatively low reactivity of **2** toward radical attack has been noted previously. Gritter, R. J. "The Chemistry of the Ether Linkage"; Patai, S. Ed.; Interscience: New York, 1967; Chapter 9, p 430.

(42) Bernasconi, C.; Descotes, G. C. R. *Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 469.

(43) In the ozonolysis of acetals the C-H bond of a dioxolane is also more reactive than that of a 1,3-dioxane.³

(44) This has been observed even at 130°C .⁴⁵

(45) Zorin, V. V.; Zlotskii, S. S.; Gren, A. I.; Rakhmankulov, D. L. *Zh. Prikl. Khim. (Leningrad)* **1977**, *50*, 1655. Baturbaev, N. A.; Patushenko, E. V.; Zorin, V. V.; Zlotskii, S. S.; Imashev, U. B.; Rakhmankulov, D. L. *Ibid.* **1979**, *52*, 1145.

(46) See, e.g.: Willy, W. E.; Binsch, G.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 5394 and references cited therein.

(40) Pointed out to us by an anonymous referee.

$(k_{C_3H_{10}}/H)/(k_{C_6H_{12}}/H)$, is 3.5–4.0. We attribute the greater reactivity of C–H bonds in cyclopentane and in other 5-membered rings to a rate acceleration induced by the relief of ring strain.⁴⁷ That is, ring strain is greater in 5-membered than in 6-membered rings, e.g., the strain energies of cyclopentane and cyclohexane and of **1** and **7** have been estimated⁴⁹ to be 6.3, 0.2, 6.0, and 1.5 kcal/mol, respectively. Ring strain, from whatever cause,^{40,47} is presumably relieved on forming the radical, and, hence, steric acceleration of C–H bond homolysis will be greater in the 5-membered ring.⁵⁰ The C–H bond strength in cyclopentane has, in fact, been estimated to be ca. 1.3 kcal/mol weaker than that in cyclohexane (viz.,^{50b} 94.2 vs. 95.5 kcal/mol). If half of this difference in bond strengths is reflected in ΔG for hydrogen abstraction, then at -60°C a C–H bond in cyclopentane would be about 4 times as reactive as one in cyclohexane.

Abstraction from the Carbon Adjacent to More Than One Oxygen. Stereoelectronic factors are equally apparent when the reactivities of acetal C–H bonds having well-defined θ values are examined. Thus, when θ is 30° for both oxygens, the reactivity is ca. 5–20 times that found for structurally related cyclic ethers having C–H bonds adjacent to one oxygen with $\theta = 30^\circ$ (cf.: **3** (H_a) and **4** (H_a) vs. **1**, **3**, (H_b), and **4** (H_b); also **11** and **12** (H_a) vs. **7**, **8**, and **17** (H_b)). However, for acetals having θ values of 30 and 90° the C–H bond reactivity decreases (cf. **13** (H_a) and **14** (H_a) vs. **11** and **12** (H_a)) and approaches the values found for ethereal C–H bonds having $\theta = 30^\circ$. The oxygen having $\theta = 90^\circ$ therefore has, at best, no more than a rather weak activating effect on an adjacent C–H bond. As noted above, the acetal hydrogen in **6** is not abstracted to any observable extent.

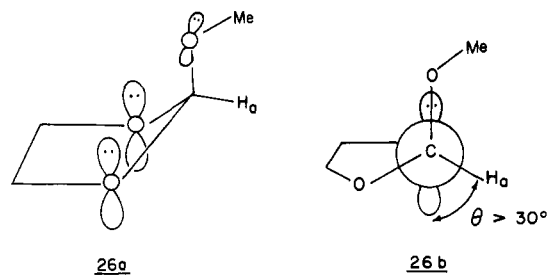
The two orthoformates, **17** and **18**, which have a C–H bond with three well-defined θ values have, unfortunately, all three θ 's equal to 90° . However, our failure to observe either trialkoxyalkyl radical does provide additional proof that whatever effect an oxygen with $\theta = 90^\circ$ has on an adjacent C–H bond, it certainly does not increase the bond reactivity to any great extent. That is, it would appear that even three neighboring oxygens with $\theta = 90^\circ$ do not increase C–H reactivity to anything like the extent that one oxygen with $\theta = 30^\circ$ does.

Of course, bridgehead radicals are notoriously more difficult to form by bond homolysis and, when formed, are more reactive than related acyclic and monocyclic radicals.⁵¹ This is probably due mainly to the fact that bridgehead radicals cannot achieve the planar or nearly planar geometry preferred by unconstrained alkyl radicals.⁵² Nevertheless, this bridgehead effect should not be particularly large for **17** and should be even less for **18** since these molecules are relatively strain free (compared with **2**, for example). An interesting corollary arises from the well-known fact²¹ that unconstrained di- and trialkoxyalkyls are nonplanar at their radical centers. That is, if the hypothesis^{53,54} that the

bending at C_α is due primarily to the electronegativity of the neighboring oxygens is correct, then the radicals from **2**, **17**, and **18** should be *relatively less* strained than the corresponding hydrocarbon-derived radicals. If, on the other hand, bending is due primarily to conjugative electron delocalization,^{32,54,55} then the bridgehead radicals from **2**, **17**, and **18**, in which this cannot occur, should have a similar degree of strain to that found in the hydrocarbon radicals. This suggests that an experimental test⁵⁶ of the two hypotheses regarding the major cause of bending in oxoalkyls may be possible (e.g., by a comparison of the reactivities or α -¹³C hyperfine splittings of 1-adamantyl and **18a**).

Turning now to ring systems having an exocyclic alkoxy substituent, we find two particularly nice examples of the stereoelectronic effect on comparing the reactivities of the axial and equatorial acetal C–H bonds in **9** and **10** and orthoformate C–H bonds in **15** and **16**. Despite the presence of the exocyclic methoxy with its undefined θ value, the axial C–H is more reactive by a factor of 4 for the first pair and 9 for the second pair of substrates at -60°C . For the latter pair, a competitive reaction with *tert*-butoxyls generated thermally from di-*tert*-butyl hyponitrite at $+50^\circ\text{C}$ gave a **15**:**16** reactivity ratio of ca. 6.⁵⁹ This last reaction was carried out in perdeuteriobenzene and was monitored by ¹H NMR. Of course, it is possible that a part of the difference in reactivity between **9** and **10** and between **15** and **16** is due to the anomeric effect^{15,60} which in these isomers stabilizes axial relative to equatorial methoxy groups. That is, **10** and **16** are slightly stabilized with respect to **9** and **15**. However, this probably has relatively little effect on the reactivity of their C(2)–H bonds since, in similar isomeric pairs of molecules having a methyl group in the 2-position rather than methoxy, Beckwith and Easton¹² have shown that the isomer having the axial C(2)–H bond is the more reactive though it is the more stable.

The addition of a third oxygen as an exocyclic methoxy group to the 2-position of a 1,3-dioxane ring has little effect on the reactivity of the C(2)–H bond (cf. **12** (H_a) vs. **15** (H_a)). Presumably the methoxy group orients itself so that θ is ca. 90° . In contrast, in the comparable pair of substrates based on 1,3-dioxolane (viz., **3** (H_a) and **5** (H_a)), the exocyclic methoxy produces a dramatic decrease in C(2)–H reactivity. This cannot reasonably be attributed to steric hindrance (cf., **4** (H_a)). We therefore tentatively suggest that the anomalously low reactivity of **5** (H_a) is a consequence of the anomeric effect^{15,60} which locks the ring in a nonplanar conformation with the methoxy group pseudoaxial (see **26a**).⁶¹ As a result the θ values for the two ring oxygens



(47) Hydrogen abstraction by *tert*-butoxyl from the 4-membered ring (trimethylene oxide) is even faster than abstraction from the 5-membered ring (**1**).^{40,48}

(48) Walling, C.; Mintz, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 1515.

(49) Benson, S. W. "Thermochemical Kinetics"; Wiley: New York, 1978.

(50) For some other homolytic reactions in which cyclohexyl radicals are formed less readily than cyclopentyl radicals, see: (a) Jones, S. H.; Whittle, E. *Int. J. Chem. Kinet.* **1970**, *2*, 479; (b) Ferguson, K. C.; Whittle, E. *Trans. Faraday Soc.* **1971**, *67*, 2618; (c) Hinz, J.; R  chardt, C. *Justus Liebig's Ann. Chem.* **1972**, *765*, 94; (d) Beckhaus, H. D.; Schoch, J.; R  chardt, C. *Chem. Ber.* **1976**, *109*, 1369; (e) Applequist, D. E.; Klug, J. H. *J. Org. Chem.* **1978**, *43*, 1729.

(51) See, e.g.: Applequist, D. E.; Kaplan, L. *J. Am. Chem. Soc.* **1965**, *87*, 2194; Lorand, J. P.; Chodroff, S. D.; Wallace, R. W. *Ibid.* **1968**, *90*, 5266; Fort, R. C., Jr.; Franklin, R. E. *Ibid.* **1968**, *90*, 5267; Humphrey, L. B.; Hodgson, B.; Pincock, R. E. *Can. J. Chem.* **1968**, *46*, 3099; Chick, W. H.; Ong, S. H. *J. Chem. Soc., Chem. Commun.* **1969**, 216; Herwig, K.; R  chardt, C. *Chem. Ber.* **1972**, *105*, 363; Herwig, K.; Lorenz, P.; R  chardt, C. *Ibid.* **1975**, *108*, 1421; Heine, H. G.; Hartmann, W.; Lewis, F. D.; Lauterbach, R. T. *J. Org. Chem.* **1976**, *41*, 1907; Fort, R. C., Jr.; Hiti, J. *Ibid.* **1977**, *42*, 3968; Luh, T. Y.; Stock, L. M. *Ibid.* **1978**, *43*, 3271; Golzke, V.; Groeger, F.; Oberl  nner, A.; R  chardt, C. *Nouv. J. Chem.* **1978**, *2*, 169; Giese, B. *Tetrahedron Lett.* **1979**, 857.

(52) See, e.g.: Griller, D.; Ingold, K. U.; Krusic, P. J.; Fischer, H. *J. Am. Chem. Soc.* **1978**, *100*, 6750; Griller, D.; Preston, K. F. *Ibid.* **1979**, *101*, 1975.

(53) Walsh, A. D. *Discuss. Faraday Soc.* **1947**, *2*, 18. Bent, H. A. *Chem. Rev.* **1961**, *61*, 275. Pauling, L. *J. Chem. Phys.* **1969**, *51*, 2767.

(54) Gregory, A. R.; Malatesta, V. *J. Org. Chem.* **1980**, *45*, 122.

(55) See, e.g.: Bingham, R. C.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1973**, *95*, 7182; Krusic, P. J.; Bingham, R. C. *Ibid.* **1976**, *98*, 230; Bernardi, F.; Epiotis, N. D.; Cherry, W.; Schlegel, H. B.; Whangbo, M. H.; Wolfe, S. *Ibid.* **1976**, *98*, 469.

(56) Earlier experimental tests using 1-substituted cyclopropyl radicals⁵⁷ and alkyl-substituted phosphine cation radicals⁵⁸ favor the Pauling–Walsh model.

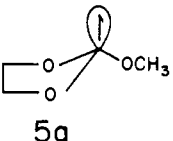
(57) Walborsky, H. M.; Collins, P. C. *J. Org. Chem.* **1976**, *41*, 940.

(58) Iwaizumi, M.; Kishi, T.; Isobe, T. *J. Chem. Soc., Faraday Trans. 2* **1976**, *72*, 113.

(59) Similarly, Beckwith and Easton¹² have found that at ambient temperatures **15** is ca. 10–13 times as reactive as **16** toward *tert*-butoxyls produced photochemically. These workers used both GLC analysis of their reaction mixtures and the ESR method.

(60) For leading reference, see: Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527. Zefirov, N. S.; Shekhtman, N. M. *Russ. Chem. Rev.* **1971**, *40*, 315; Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056; Szarek, W. A.; Horton, D., Eds. *ACS Symp. Ser.* **1979**, No. 87.

Chart I



T (°C)	$a_{\text{ring}}^{\text{H}}$ (2H, G)	a^{H} CH ₃
-120	1.77	0.26
-60	1.70	0.21
0	1.59	0.14

will be dramatically increased (see **26b**) and hence the C(2)-H reactivity will be reduced. This effect will be much less important in the 1,3-dioxane series because of the reduced conformational mobility of 6-membered rings.⁴⁶

Relative Reactivities of Acyclic Ethers. The ether, acetal, and orthoformate C-H bonds in acyclic compounds show a much smaller range of reactivities (see Table III) than was found for their cyclic analogues. The most interesting observation is that the reactivities of the C-H bonds in acyclic compounds are rather similar to those found for *comparable axial* C-H bonds in the 6-membered rings (cf., for example: **19** (H_a), **20** (H_b), **22** (H_b), and **23** (H_b) vs. **7** (H_a) and **8** (H_a); also, **20** (H_a) and **21** (H_a) vs. **11** (H_a) and **12** (H_a); also, **23** (H_a) vs. **15** (H_a)). This suggests that the preferred conformations of the acyclic compounds have θ values which are not dissimilar to those existing in the 6-membered rings.

The Resistance to Inversion of Trialkoxymethyl Radicals. It is well-known that the attachment of electronegative atoms, particularly oxygen and fluorine, directly to C_α of carbon-centered radicals increases bending at the radical center^{21,53-55,62} and the barrier to inversion at this center.^{57,63} We have recently shown that dialkoxyalkyl radicals undergo a very facile inversion.¹¹ Thus, abstraction of H_a from **9** or **10** yields the common *cis*-2-methoxy-6-methyltetrahydropyran-2-yl radical at temperatures as low as -120 °C.¹¹ Similarly, both *cis*- and *trans*-2-ethoxy-4-methyltetrahydropyrans yield a common *cis*-2-ethoxy-4-methyltetrahydropyran-2-yl radical at all temperatures.¹¹ The barriers to the *trans* → *cis* inversion at the radical centers of 2-alkoxytetrahydropyran-2-yls must therefore be fairly low (≤ca. 6 kcal/mol).¹¹

Although inversion is not prevented by two neighboring oxygen atoms, we have now found that in radical **5a**⁶⁴ at least, a third oxygen completely inhibits inversion on the EPR time scale. This radical shows hyperfine splitting (hfs) by *only two* of the four ring protons. The magnitude of the ring hydrogen hfs, and of the methyl hydrogen hfs, does show some temperature dependence, viz., Chart I. However, there is no sign of line broadening even at +20 °C,⁶⁵ which implies that the barrier to inversion is ≥10 kcal/mol for **5a**. With the *possible* exception of a few radicals derived from 3-membered rings,^{48,h} this result represents, to the best of our knowledge, the first example of a pyramidal carbon-centered radical which shows no sign of inversion on the EPR time scale at such relatively high temperatures.⁶⁶

(61) For a related molecular structure see: Müller, K.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1823; Dobler, M.; Dunitz, J. D.; Hawley, D. M. *Ibid.* **1969**, *52*, 1831.

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(64) Only one **5a** radical is detected, but even if both a pseudoaxial and a pseudoequatorial radical were formed initially, the higher energy form could readily isomerize to the lower by a low barrier "envelope-flip".

(65) At higher temperatures **5c** becomes the dominant radical.

Our results with **5a** stand in contrast to the results reported for 1,3-dioxolan-2-yl^{35,67} and 2-methyl-1,3-dioxolan-2-yl.^{35,67,68} In the former radical, the four ring protons are equivalent from -127 °C ($a^{\text{H}} = 1.50$ G) to +24 °C ($a^{\text{H}} = 1.35$ G) which, since the radical center is nonplanar, implies that C_α inversion and ring interconversion are rapid even at low temperatures. In the latter radical, the four ring protons are equivalent at -47 °C ($a^{\text{H}} = 1.20$ G) but do resolve into two pairs at -100 °C ($a^{\text{H}} = 1.0$ and 1.4 G), an effect attributed to the "freezing-out" of the C_α inversion. The enthalpy for activation for inversion was calculated to be ca. 5.7 kcal/mol.

Experimental Section

Materials. 7-Oxabicyclo[2.2.1]heptane⁶⁹ (**2**), 2-methoxy-1,3-dioxolane⁷⁰ (**5**), 6,8-dioxabicyclo[3.2.1]octane⁷¹ (**6**), 1,8-dioxadecalin⁷² (**13**), *cis*-1,4,5,8-tetraoxadecalin⁷³ (**14**), the two 2-methoxy-4,6-dimethyl-1,3-dioxanes⁷⁴ (**15** and **16**), 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane⁷⁵ (**17**), and 2-methoxy-1,3-dioxane⁷⁶ (**27**) were prepared by literature procedures. They were purified by either crystallization or preparative gas chromatography on a 10-ft Carbowax 20M on high performance Chromosorb W column at 95 °C or on a 12-ft 12% O.V. 101 (dimethylsilicone) on high performance Chromosorb W column at 110 °C. These compounds were characterized by elemental analysis, ¹H NMR, and IR spectroscopy. Compounds **9** and **10** were gifts from Dr. R. D. McKelvey and Dr. B. W. Babcock. All other compounds were commercial materials, and, except for 1,3,5-trioxane (**11**) (which was sublimed and then recrystallized from ethanol and ether), they were purified by distillation from LiAlH₄ and were stored over K₂CO₃.

Experimental Procedure. Solutions to be photolyzed contained, typically, di-*tert*-butyl peroxide (purified by passage through alumina), cyclopropane or methylene chloride, and substrate or two substrates in a concentration ratio appropriate for competitive kinetic studies, in a volume ratio of 1:10:1. Solutions were rigorously degassed and sealed under vacuum. Radicals were generated by photolysis directly in the cavity of a Varian E-104 EPR spectrometer using a 500-W high-pressure mercury lamp. Relative radical concentrations were determined in the usual way.²³

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(66) It is worth noting that 2-methoxy-1,3-dioxane gives a rather complex ESR spectrum (which changes little from -120 to -20 °C) which we tentatively interpret in terms of a ca. 2:1 mixture of equatorial (probably $a^{\text{H}}(2\text{H}) = 1.13$ G; $a^{\text{H}}(2\text{H}) = 0.48$ G; $a^{\text{H}}(4\text{H}) = 0.09$ G) and axial (probably $a^{\text{H}}(2\text{H}) = 0.77$ G; $a^{\text{H}}(6\text{H}) = 0.09$ G) 2-methoxy-1,3-dioxan-2-yl radicals having the same *g* values (2.0029). These structural assignments, which are based on Gaze and Gilbert's³³ thorough experimental and theoretical study of 1,3-dioxan-2-yl, seem not unreasonable and so do the probable hyperfine splittings. Unfortunately, however, most of the fine structure (the 0.09-G hfs of the 4 outer lines from the "equatorial" 2-methoxy-1,3-dioxan-2-yl) was lost because of line broadening (see also ref 33). This prevented a precise simulation of the experimental spectrum and rendered an unequivocal assignment of hfs impossible.

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