solution volume. For higher Me_2SO proportions (60% and 70%), the reagents were taken first and the final volume was made up with Me_2SO. All pH measurements were performed on an Orion Research 611 digital pH meter (30% and 50% Me_2SO) and on a Metrohm/Brinkman 104 pH meter (60% and 70% Me_2SO). Both meters were equipped with a Corning No. 476022 glass electrode and a Beckman No. 39400 calomel reference electrode. The pH meters were calibrated for Me_2SO–water mixtures with buffers described by Hallé et al.[40]

Kinetic Measurements. A Durrum-Gibson stopped-flow spectrophotometer with computerized data acquisition and analysis[41] was used to monitor all the reactions except those involving the piperidinium ion catalysis. For this purpose, a Durrum multimixing system (Model D-132) was used. In the first stage, T_{OH}^- was generated by mixing the substrate solution with 0.2 M KOH. The hydroxide ion concentration now was 0.1 M. In the second mixing, different amounts of a piperidene buffer were injected (which also contained HCl to neutralize the 0.1 M hydroxide remaining after the first mixing) after aging the first mixture for about 80 ms. This aging time assured that the formation of T_{OH}^- was complete.

Acknowledgment. This research was supported by Grants CHE-8024261 and CHE-8315374 from the National Science Foundation.

Supplementary Material Available: Tables of τ^{-1} values as functions of [KOH] and piperidinium ion concentration in water, Me_2SO solutions, and Me_2SO–water solutions at 20 °C (9 pages). Ordering information given on any current masthead page.

---

[40] Hallé, J.-C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim. Fr.* **1970**, 2047.

[41] Developed by Dr. F. A. Brand.

Temperature-Dependent Stereoselectivity and Hydrogen Deuterium Kinetic Isotope Effect for γ-Hydrogen Transfer to 2-Hexyloxy Radical. The Transition State for the Barton Reaction

Mark M. Green,*[1] Barbara A. Boyle,[1] M. Vairamani,[1] Triptikumar Mukhopadhyay,[1] William H. Saunders, Jr.,[2] Phillip Bowen,[3] and Norman L. Allinger[3]

Contribution from the Departments of Chemistry, Polytechnic University, Brooklyn, New York 11201, University of Rochester, Rochester, New York 14627, and University of Georgia, Athens, Georgia 30602. *Received September 3, 1985*

Abstract: The diastereomers of 5-deuterio-2-hexanol, prepared stereospecifically from acetol and lactic acid by using fermentation procedures, have been subjected to the Barton reaction with Ag_2CO_3/Br_2 in pentane over the temperature range −8.65 to 30.05 °C. The derived 2,5-dimethyltetrahydrofuran deuterium incorporation yields both the C-5 diastereotopic hydrogen stereoselectivity and the isotope effect (k_H/k_D) for the intramolecular hydrogen-transfer step. The isotope effect is classically temperature dependent, 5.82 (±0.07), 30.05; 6.01 (±0.22), 20.55; 6.81 (±0.17), 10.55; 6.90 (±0.08), 1.65; 7.47 (±0.49), −8.65 °C, while the stereoselectivity is small, 1.23 (1.65 °C), and temperature independent. Molecular mechanics calculations show that conformations with linear arrangements of C_5, H, and O show small steric energy differences between the diastereotropic hydrogens at C-5. Calculations of isotope effects and their temperature dependencies for model transition states match the experimental data for only C_5, H, and O angles greater than 150°. The Hofmann–Loeffler–Freitag reaction of the cation radical of 5-deuterio-2-aminohexane exhibits an isotope effect ($k_H/k_D = 1.20$) and stereoselectivity ($k_a/k_b = 1.54/1$), both at 25 °C, for the comparable γ-hydrogen-transfer step suggesting a more acute angle of transfer than for the alkoxy radical.

Intramolecular transfer of carbon bound hydrogen to a heteroatomic radical site defines a set of reactions of long use in synthesis.[4] The fact that little more is known of the hydrogen transfer transition states than their characteristic occurrence via six-membered rings follows from the kinetic difficulty of isolating the hydrogen transfer, which is rapid[5,6] and, therefore, not rate determining, from the various steps in the overall mechanistic picture.[4]

Early discussions of intramolecular hydrogen transfer noted the possible conflict between the expected propensity for a 180° C–H–X angle and more acute transfer angles which might minimize strain.[7] It is known that the hydrogen selectivity of these reactions depends on the angle and distance between the transferred hydrogen and the abstracting atom and that these characteristics change with the state and identity of the abstracting radical.[8-10] Attempts to understand the geometry of these intramolecular hydrogen-transfer reactions have centered on extrapolations from preferences in competitive transfers within a single molecule or observations that transfer does not occur. This

---

[1] Polytechnic University—address correspondence to M. M. Green.

[2] University of Rochester.

[3] University of Georgia.

[4] For an overview and leading references see: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 2nd ed. Part A; Plenum Publishes: New York, 1984; pp 671–676.

[5] Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; DeMayo, P., Ed.; Academic Press: 1980; Vol 1, Essay 4, and particular p 251 ff.

[6] The rate constant for the oxygen radical system has been measured. See: Gilbert, B. C.; Holmes, R. G. G.; Laue, H. A. H.; Norman, R. O. C. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 1047.

[7] Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657. The expectation for linear transfer (see ref 5 above) is based on the linear transfer assumed for intermolecular SH_2 reactions at hydrogen and on the $H_2 + H\cdot$ reaction. See: Siegbahn, P.; Liu, B. *J. Chem. Phys.* **1978**, *68*, 2457. Truhlar, D. G.; Horowitz, C. J. *Ibid.* **1978**, *68*, 2466.

[8] Heusler, K.; Kalvoda, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 525.

[9] Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55.

[10] Carruthers, W. *Some Modern Methods of Organic Synthesis*; Cambridge University Press: London, 1971; Chapter 4.

0002-7863/86/1508-2381$01.50/0

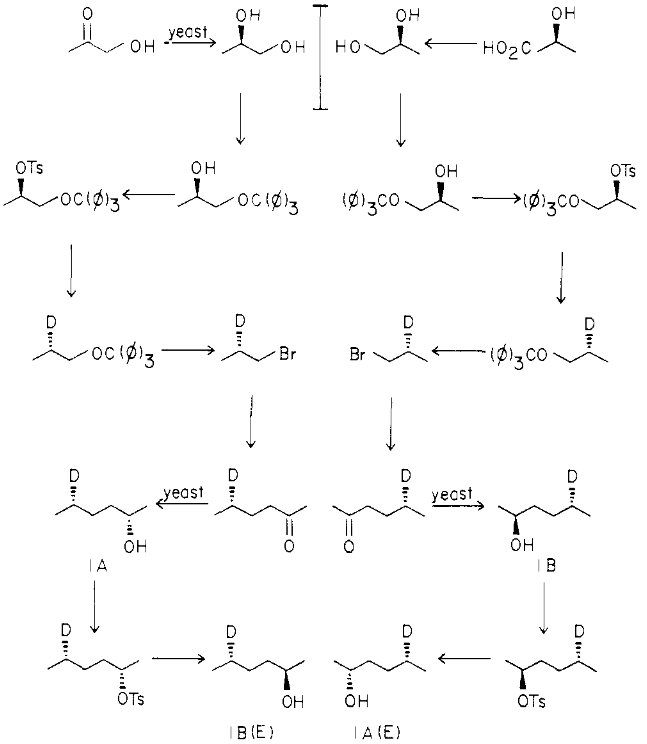
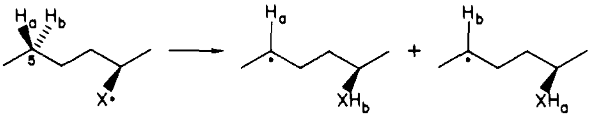


Figure 1.

approach has not generated a consistent view. Recent discussions have simply generally assigned the transition state as approximately linear,[5] without regard to the interplay of spatial parameters which must define the individual characteristics of the various reactions in this class.[4]

It has been shown in stereospecifically C-5 deuterated 2-hexyl systems that selective transfer of the diastereotopic hydrogens at C-5 to a heteroatomic radical site substituent at C-2 (eq 1) allowed correlations between various rearrangements of this type both in solution and in the gas phase.[11] Such experiments yield two independent kinds of information about the γ-hydrogen transfer step: the steric difference between transfer of the diastereotopic hydrogens (k_a/k_b) and the hydrogen deuterium kinetic isotope effect (k_H/k_D). In the present work we have determined the temperature dependency of these kinetic parameters for the transfer of C-5 hydrogen to oxygen in the 2-hexyloxy radical. As discussed below, such quantitative experimental information intersects with calculations in the areas of molecular mechanics[12] and isotope effects.[13] The γ-hydrogen-transfer experiment is thus attractive in that it demands that these calculations[12,13] act as a check on each other. There can only be one transition state in the particular system studied, and both theoretical correlations with the data must lead to the same result.



(1)

In order to utilize the experiment in this manner, one must evaluate the contribution from tunneling and the energy of activation difference between hydrogen and deuterium transfer in

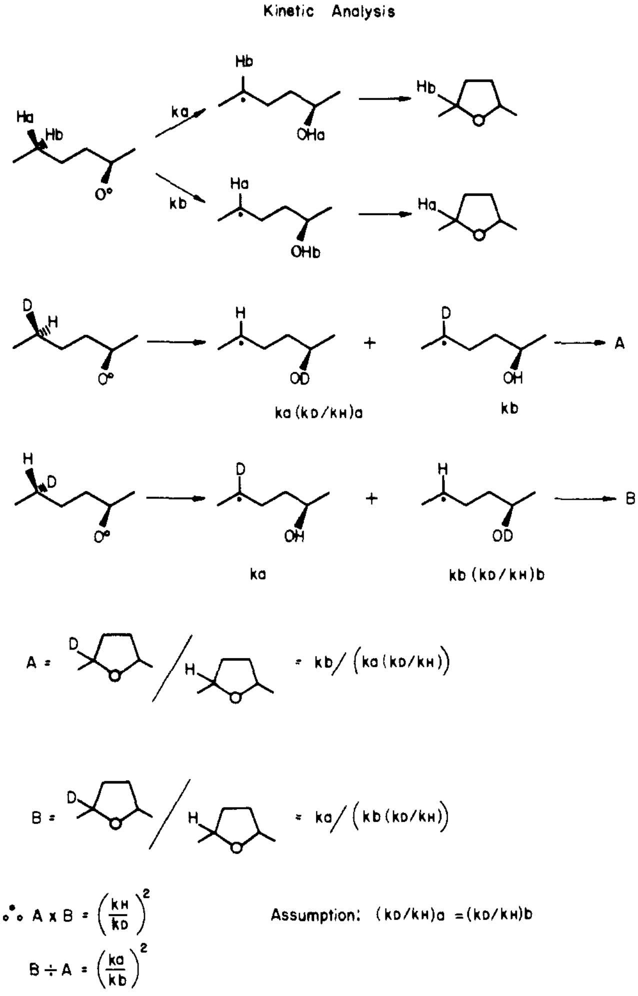


Figure 2.

the isotope effect measurement and must separate the enthalpic and entropic contributions to the observed stereoselectivity. The temperature dependence of the relative rate of hydrogen-deuterium transfer accomplishes these objectives.

Results

Synthesis. Availability of the diastereomers of 5-deuterio-2-hexanol, with known absolute configurations, is the material prerequisite for this work. As exhibited schematically in Figure 1, these materials were made available by the synthetic procedures earlier developed for our investigations on the relationship between γ-hydrogen-transfer reactions in electron-impact mass spectrometers and in solution.[11,14] The synthesis yields both enantiomers of each diastereomer. Since the relationship between **1A** and **1B** must be identical with the relationship between (*E*)-**1A** and (*E*)-**1B**, one can reproduce the experimental data either by the conventional manner of reproducing measurements on the same samples or by using a different set of enantiomeric samples. In addition, in this way both compared diastereomers are produced either from one enantiomer of 1,2-propanediol or from each of the individual enantiomers of 1,2-propanediol (see Figure 1).

Kinetics. In the method utilized (see below) to produce the 2-hexyloxy radicals from 2-hexanol, the final products are the stereoisomers of 2,5-dimethyltetrahydrofuran. In our earlier work[11,14] on 5-deuterio-2-hexanol, we found the deuterium incorporation to be identical in both the *cis*- and *trans*-2,5-dimethyltetrahydrofurans, thus, in this effort we have taken the convenience to use the isomer mixture for our analysis. The identical deuterium content of the cis and trans isomers is consistent with the overall mechanism, since the tetrahydrofuran ring

---

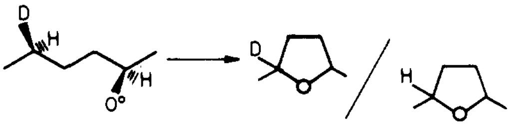
[11] For a review see: Green, M. M. *Tetrahedron* **1986**, *36*, 2687. For related work see: Green, M. M.; Mayotte, G. J.; Meites, L.; Forsyth, D. *J. Am. Chem. Soc.* **1980**, *102* 1464. Green, M. M.; McCluskey, R. J.; Vogt, J. *Ibid.* **1982**, *104*, 2262.

[12] Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1 and section 10 in particular. See also: Boyd, D. B.; Lipkowitz, K. B. *J. Chem. Ed.* **1982**, *59*, 269. Cox, P. J. *Ibid* **1982**, *59*, 275, and references therein pertaining to rate and conformational mapping studies. See also: Osawa, E.; Musso, H. *Angew. Chem. Int., Ed. Engl.* **1983**, *22*, 1.

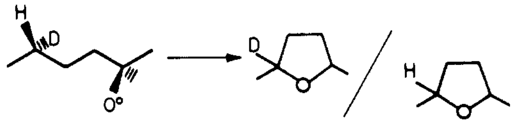
[13] Melander, L.; Saunders, W. H. *Reactions Rates of Isotopic Molecules*; Wiley Publishers: New York, 1980; Chapter 3, p 56 ff.

[14] For a condensed version of this synthetic approach see: Green, M. M.; Moldowan, J. M.; McGrew, J. G., II. *J. Org. Chem.* **1974**, *39*, 2166.

Table I



temp, °C (±0.2)	ratio (λ_{95}; no. exp)
-8.65	6.02 (±0.52, 5)
1.65	5.63 (±0.05, 3)
10.55	5.56 (±0.22, 4)
20.55	4.87 (±0.27, 5)
30.05	4.77 (±0.10, 3)



temp, °C (±0.2)	ratio (λ_{95}; no. exp)
-8.65	9.26 (±0.92, 5)
1.65	8.47 (±0.12, 3)
10.55	8.36 (±0.27, 3)
20.55	7.42 (±0.36, 5)
30.05	7.09 (±0.09, 3)

is closed after the hydrogen(deuterium)-transfer step.[14]

The kinetic analysis to determine the isotope effect k_H/k_D and the stereoselectivity k_a/k_b is presented in Figure 2. This information arises via measurement of the deuterium content of the heterocycle produced from each diastereomer of 5-deuterio-2-hexanol.

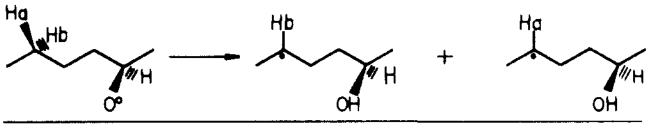
The assumption for equivalence of the diastereotopic primary isotope effects rests on the reasonable expectation that the mechanistic details of the transfer step, i.e., the extent of bond breaking and making and the angle of transfer, are the same independent of whether H_a or H_b is transferred. The forces controlling these parameters, involving the entire energy of activation, are large, compared to the small energy difference between the diastereotopic states. This argument is supported by a parallel study of diastereotopically deuterated-2-butyl acetate pyrolysis[15] in which the k_H/k_D values for the diastereotopic deuteriums (determined by an absolute rate method) did not differ beyond the experimental error.[15]

The deuterium content of the derived 2,5-dimethyltetrahydrofurans was determined by mass spectrometric analysis of the electron impact induced loss of methyl from the molecular ion. The latter peak was complicated by loss of hydrogen ions, which could not be eliminated at any electron voltage that yielded reasonable intensity for the analytical work. The analysis of the deuterium content using the M-15 ion was not variant with various electron voltages; loss of methyl α to an ether function is known to proceed by a simple cleavage mechanism.[16] In the mass spectrum one observes a loss of only 15 units from the deuterated or undeuterated 2,5-dimethyltetrahydrofurans. The deuterium remains entirely with the charged fragment.

The temperature-dependent rate experiments reported here were conducted over an approximately 40 °C range in pentane with Ag_2CO_3 and bromine. The diastereomeric deuterated 2-hexanols were collected by preparative gas chromatography immediately before reaction. Reaction was initiated by dropwise addition of an equivalent of bromine. Control experiments show that exclusion of air does not affect the yield or the deuterium ratios in the resulting furans. The solvent purity and the age of the Ag_2CO_3 are the paramount factors in the yield of this reaction.

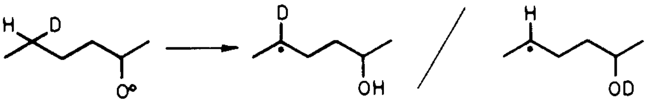
The following experiment was carried out as a control. Deuterated 2-hexanol was recovered by preparative gas chromatograhy after the reaction was stopped by decantation and shown to be identical with the starting deuterated diastereomer by both mass spectrometric deuterium analysis and by using the recovered deuterated 2-hexanol in a new reaction and measuring the ratio of deuterated to undeuterated 2,5-dimethyltetrahydrofurans produced from it. The recovered 2-hexanol shows behavior identical with that of the starting 2-hexanol in both these experiments. This demonstrates that the initially transferred deuterium is not returned to the originating carbon site. If this were the case, even if the deuterium were not exchanged with (and, therefore, lost to) solvent, such an event must cause epimerization at the deuterium-substituted C-5 carbon.

Table II



temp, °C (±0.2)	k_a/k_b ($\pm\lambda_{95}$)
-8.65	1.24 ± 0.08
1.65	1.23 ± 0.03
10.55	1.23 ± 0.03
20.55	1.24 ± 0.05
30.05	1.22 ± 0.02

Table III



temp, °C (±0.2)	k_H/k_D ($\pm\lambda_{95}$)
-8.65	7.47 (± 0.49)
1.65	6.90 (± 0.08)
10.55	6.81 (± 0.17)
20.55	6.01 (± 0.22)
30.05	5.82 (± 0.07)

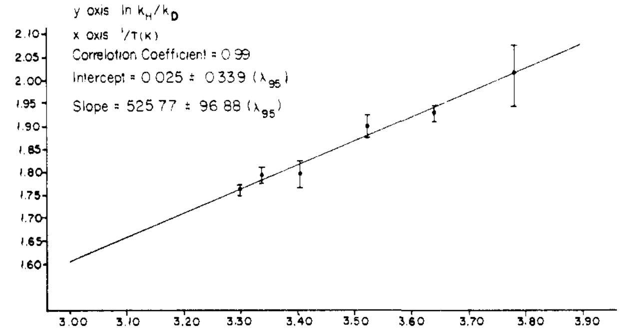


Figure 3.

Table I presents the ratios of deuterated to undeuterated 2,5-dimethyltetrahydrofurans produced from the diastereomeric deuterated 2-hexanols by reaction with Ag_2CO_3/Br_2 in pentane at temperatures varying from -8.65 to 30 °C. In parentheses are found the number of independent experiments and the 95% confidence error limits.[17] Each experiment involved an independent chemical reaction followed by gas chromatograpic collection of the produced 2,5-dimethyltetrahydrofurans and analysis of numerous repeated slow scans over the appropriate region of the mass spectrum.

With reference to Figure 2, it is clear from Table I that when deuterium occupies the H_a site (for the [R] configuration at C-2) it is lost preferentially. Thus the ratio of deuterated to undeuterated 2,5-dimethyltetrahydrofurans is lower from (*E*)-**1A** (or **1A**) compared to (*E*)-**1B** (or **1B**) (refer to Figure 1). The lower ratio corresponds to increased transfer of deuterium from C-5 to

---

(15) Skell, P. S.; Hall, W. L. *J. Am. Chem. Soc.* **1964**, *86*, 1557.

(16) See: McLafferty, F. W. *Interpretation of Mass Spectra*, 3rd ed.; University Science Books: Mill Valley, CA, 1980; pp 209–211, and references therein.

(17) The 95% confidence limts (λ_{95}) were calculated from the data following: Shoemaker, D. P.; Garland, C. W.; Steinfeld, J. I. *Experiments in Physical Chemistry*; McGraw-Hill: New York, pp 32–33. The least-square analysis was adapted from Worthington, A. G.; Geffner, J. Treatment of Experimental Data; Wiley Publishers: New York, pp 249–250.

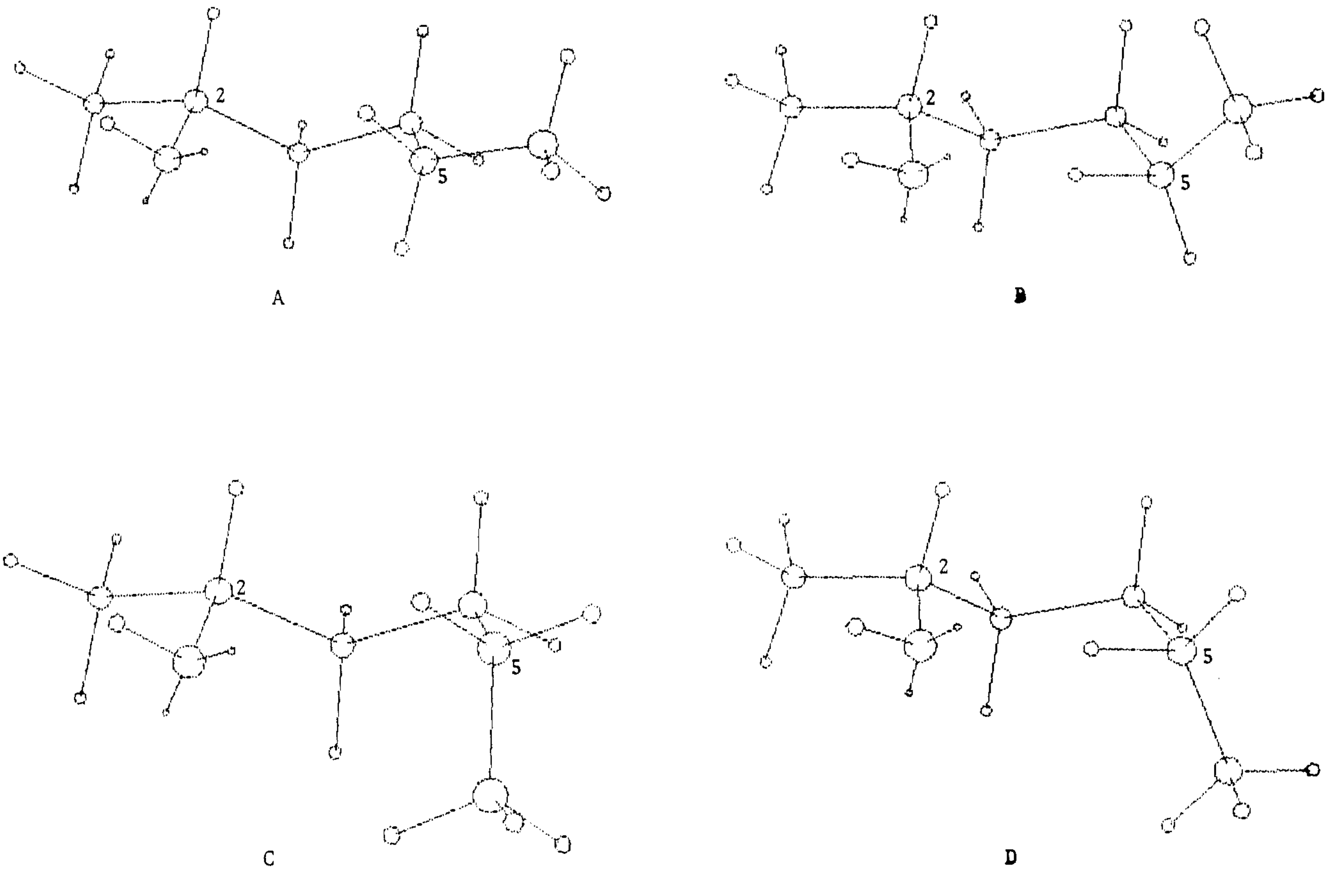


Figure 4.

oxygen since the transferred atom is subsequently lost.

The data in Table I were handled according to the procedure in Figure 2 to yield the stereoselectivity (k_a/k_b) and the isotope effect (k_H/k_D) values at each temperature (Tables II and III). Thus one notes that for either diastereotopic position at C-5, transfer of hydrogen is favored over transfer of deuterium and that this ratio (k_H/k_D) is strongly temperature dependent. Moreover, the rates of transfer of hydrogen from sites H_a and H_b are unequal, and the ratio, surprisingly, shows no temperature dependence.

An Arrhenius plot of the isotope effect data yields an excellent straight line (correlation coefficient of 0.99) (Figure 3) with reasonable slope and intercept values. Thus, the intercept at $T = \infty$ leads to a value of the preexponential A_H/A_D of 1.03 ±0.35 within 95% confidence. The slope reveals the energy difference associated with the isotopic paths, i.e., E_{HD} = 1045 cal/mol (±193 λ_{95}).

The A_H/A_D value is expected for a classical reaction path with little or no contribution from tunneling, while the E_{HD} value almost exactly equals the zero point energy difference for hydrogen or deuterium bound to aliphatic carbon.

An additional check on these data follows from the fact that in the experiments conducted here only the transition state for γ-hydrogen transfer is focused on independent of the complex mechanistic path which may precede or follow this key step. Thus, it must follow that creation of the 2-hexyloxy radical by any route and measurement of the hydrogen transfer in the deuterated molecule will yield the same result. We had previously determined the k_a/k_b and k_H/k_D values for 2,5-dimethyltetrahydrofuran production from 5-deuterio-2-hexanol on reaction with $Pb(OAc)_4$ in cyclooctane, a solvent with similar properties to pentane, at 80 °C and with Ag_2O and Br_2 under the same conditions.[11] The isotope effects under those conditions were 4.6 and 4.7, respectively, while extrapolation of the line in Figure 2 to 80 °C yields 4.52. The stereoselectivities, as predicted by the temperature independent data in Table II, were both 1.2.[11]

Molecular Mechanics Calculations. The slight temperature-independent preference for transfer of the *pro*-[R] C-5 hydrogen in [R]-2-hexyloxy radical (Table II) does not allow a measurable enthalpic difference (see below) between the diastereotopic transition states involving transfer of the *pro*-[R] or *pro*-[S] C-5 hydrogen. In order to quantitatively evaluate transition state models which would meet this demand, we carried out molecular mechanics calculations using the MM2 program[18] (see Experimental Section). This is a reasonable goal because we are evaluating the difference between two states with identical bonding relationships, that is, an energy of activation difference rather than an absolute energy of activation. Four conformations were considered, as exhibited in Figure 4.

Taking into account the possible dependence of the results on the partial breaking of the C_5 to hydrogen bond, certain reasonable adaptions of the force field were undertaken. The stretching parameter $K(s)$ was varied from 3.0–8.0 mdyn/Å for the bond C(5)–H(a or b). The initial bond length here was set equal to 1.30 Å indicating considerable bond stretching. The bending constant $K(B)$ for C(5)–H(a or b)–O(7) was varied from 0.62–1.0 mdyn/deg. The energy difference between H_a and H_b was only slightly sensitive to these large changes in the detailed parameters of the bonds associated with the transfer of these hydrogens from carbon to oxygen. In addition, using $K(s) = 5$ and $K(B) = 0.8$ as average values from above, the lengths of the O–H and C–H bonds were varied from 1.5–1.1 and from 1.2–1.6 Å, corresponding to a wide variation in transition-state development. Again, the energy difference between transfer of H_a and H_b was essentially invariant to these parameters. In every case the bent state (models A and C, Figure 4) differed by 700–1100 cal mol^{-1}, while the linear state (models B and D, Figure 4) differed by close to 300 cal mol^{-1}.

The force field calculations for the bent state yield an energy difference for the stereoselective transfer of the diastereotopic hydrogen (i.e., 700–1100 cal mol^{-1}) which is incompatible with the experimental values (Table II). The lowest value in this range would require a $\Delta\Delta S^{\ddagger}$ value of 1.9 eu to bring the stereoselectivity

---

[18] For a comprehensive account of this field see: Burkert, U.; Allinger, N. L. Molecular Mechanics; American Chemical Society Monograph 177, Washington, DC, 1982.

Table IV. Assumed Force Constants

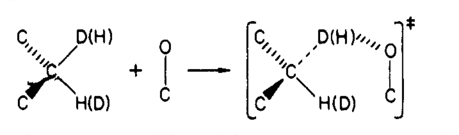
type	value^a, mdyn/Å
C–H str	4.7
C- - -H str	4.7 n_{CH}
C–C str	4.7
O- - -H str	7.8 n_{OH}
C–O str	5.8
C–C–C bd	0.35
H–C–C bd	0.40
H- - -C–C	0.40 n_{CH}
H- - -CH bd	0.46 n_{CH}
H- - -OC bd	0.60 n_{OH}
C- - -H- - -O bd^b	0.40 $n_{CH}n_{OH}$
C- - -H- - -O lin bd^c	0.32 $n_{CH}n_{OH}$
C- - -H- - -OC tors^b	0.02
H–C- - -H- - -O tors^b	0.02
H–C- - -H- - -O–C tors^c	0.02

^{a} Bending and torsional force constants are multiplied by r_1r_2 (equilibrium bond lengths) before the calculations. The bond orders (n) are those appropriate for the particular model. ^{b} For models with nonlinear C- - -H- - -O. ^{c} For models with linear C- - -H- - -O.

to the observed value at 30 °C. This entropy difference is not reasonable,[19] and, in addition for this $\Delta\Delta S^\ddagger$ value, the stereoselectivity at the lowest observed temperature would be predicted as 1.45/1 which is far beyond the error of these observations (Table II).

The linear states B and D (Figure 4) yield a calculated value of $\Delta\Delta H^\ddagger$ (300 cal mol^{-1}) which represents a selectivity (k_a/k_b) of 1.65 if $\Delta\Delta S^\ddagger$ were zero. This is also outside the experimental uncertainty but a $\Delta\Delta S^\ddagger$ of –0.5 eu (i.e., $S_a - S_b$), which is within reason,[19] brings k_a/k_b to 1.24/1 at 30 °C and to 1.31/1 at –9 °C, values near to the experimental ones (Table II). These numbers for k_a/k_b fit more closely, necessitating a smaller $\Delta\Delta S^\ddagger$ as $\Delta\Delta H^\ddagger$ drops. Thus, the linear state is the closest approximation to the actual transition state that the force field calculation can make.

Model Calculations of Isotope Effects. The availability of isotope effects measured over a range of temperature sets more stringent restraints upon possible transition state models than an isotope effect at only one temperature. Qualitatively, the fairly large k_H/k_D values observed in this work suggest a transition state with a linear, or at least not markedly nonlinear, arrangement of the C–H–O system.[20] The normal Arrhenius parameters (Figure 3) suggest that tunneling is not very important.[21] In an effort to set at least semiquantitative limits upon the range of transition states consistent with the experimental results, we undertook model calculations. The cutoff model[22,23] we used is shown in eq 2. An intermolecular rather than intramolecular model was chosen to avoid problems encountered with cyclic transition states in assigning off-diagonal elements in the force-constant matrix and in obtaining a reasonable reaction coordinate.[24] Excision of the carbon atom connecting the two reaction centers should have little influence on the numerical results, as it is three bonds removed from the hydrogen (deuterium) being transferred.



(2)

Standard values of bond lengths were used: 1.54 for C–C, 1.09 for C–H, 0.96 for O–H, and 1.43 Å for C–O. Bond lengths of reacting bonds were adjusted from the standard single-bond values (r_i°) by using the Pauling relation[25,26]

$$r_i = r_i^\circ - 0.3 \ln n_n \qquad (3)$$

Table V. Calculated Deuterium Isotope Effects for $C_2CHD + CO$ (Full Bond Model^a)

C- -H- -O angle	A^b	n_{OH}	k_H/k_D,^{c} 30 °C	ΔE_a,^{d} kcal mol^{-1}	$A_H/A_D{}^d$	Q_{tH}/Q_{tD},^{e} 30 °C
180	1.000	0.3	4.453	0.870	1.049	
		0.5	3.856	0.784	1.048	
150		0.3	3.204	0.720	0.969	
		0.5	3.197	0.667	1.056	
120		0.3	1.988	0.456	0.931	
		0.5	1.969	0.441	0.947	
180	1.025	0.3	5.200	1.017	0.960	1.129
		0.5	4.605	0.924	0.992	1.099
150		0.3	4.002	0.848	0.979	1.086
		0.5	3.735	0.797	0.995	1.088
120		0.3	2.314	0.537	0.948	1.027
		0.5	2.260	0.528	0.941	1.032
180	1.049	0.3	5.956	1.224	0.779	1.331
		0.5	5.343	1.121	0.829	1.277
150		0.3	4.595	1.018	0.846	1.248
		0.5	4.309	1.030	0.782	1.248
120		0.3	2.636	0.637	0.914	1.096
		0.5	2.588	0.638	0.897	1.109
180	1.095	0.3	8.281	2.076	0.261	2.247
		0.5	7.574	1.947	0.296	2.128
150		0.3	6.131	1.650	0.393	1.906
		0.5	5.892	1.659	0.373	1.953
120		0.3	3.291	0.932	0.699	1.372
		0.5	3.288	0.970	0.649	1.430

^{a} Total bond order to H conserved in transition state: $n_{OH} + n_{CH} = 1.0$. ^{b} See text and eq 3. ^{c} Includes tunnel correction. ^{d} From fitting calculated k_H/k_D values at –10, 3, 16, and 30 °C to the Arrhenius equation by using a standard linear least-squares program. ^{e} The tunnel correction to the isotope effect calculated from $|\nu_L^\ddagger|$ values and the first term of the Bell equation (ref 28).

All HCC and CCC bond angles were tetrahedral, and the COH bond angle was kept at 120°. The C–H–O angle was 180, 150, and 120° in three different versions of the model. The force constants and their variation with bond order are given in Table IV. They are obtained from or estimated from values in literature compilations.[27-29]

In one set of calculations, $n_{CH} + n_{OH} = 1.0$ with $n_{CH} = 0.9$, 0.7, 0.5, 0.3, and 0.1 was assumed for the reacting bonds. In another, n_{CH} and n_{OH} were taken, respectively, as 0.8, 0.1; 0.5, 0.2; 0.25, 0.25; 0.2, 0.5; and 0.1, 0.8 in five models ranging from reactant-like to product-like. The motion along the reaction coordinate, a C–H–O asymmetric stretch, was secured by an off-diagonal element $F_{CH,OH}$ ($= F_{OH,CH}$) in the force-constant matrix defined by

$$F_{CH,OH} = A(F_{CH}F_{OH})^{1/2} \qquad (4)$$

When $A = 1.0$, the reaction coordinate frequency $\nu_L^\ddagger = 0$, and there is no tunneling; when $A > 1.0$, $\nu_L^\ddagger$ is imaginary. For the latter case, tunnel corrections were calculated from the $\nu_L^\ddagger$ values by using the first term of the Bell equation.[30] These tunnel corrections are included in the isotope effects listed in Tables V and VI. Calculations were performed by using the BEBOVIB-IV program.[31]

Comparison of the calculated and experimental isotope effects must be done with due regard for the uncertainties in each. While the experimental k_H/k_D at any given temperature is uncertain

---

(19) For entropy differences between dimethylcyclohexane isomers see: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Interscience Publishers: 1965; p 56.

(20) See ref 13 above, pp 44–45, 71, 154–156.

(21) See ref 13 above, pp 15, 144–147.

(22) Wolfsberg, M.; Stern, M. *J. Pure Appl. Chem.* **1964**, *8*, 225.

(23) Stern, M.; Wolfsberg, M. *J. Chem. Phys.* **1966**, *45*, 4105.

(24) Keller, J. H.; Yankwich, P. E. *J. Am. Chem. Soc.* **1974**, *96*, 2303.

(25) Pauling, L. *J. Am. Chem. Soc.* **1947**, *69*, 542.

(26) Burton, G. W.; Sims, L. B.; Wilson, J. C.; Fry, A. *J. Am. Chem. Soc.* **1977**, *99*, 3371.

(27) Wilson, E. B., Jr.; Decius, J. C.; Cross, P. *Molecular Vibrations*; McGraw-Hill Publishers: New York, 1955.

(28) Schachtschneider, J. H.; Snyder, R. G. *Spectrochim. Acta.* **1963**, *19*, 117. Snyder, R. G.; Schachtschneider, J. H. *Ibid.* **1965**, *21*, 169.

(29) Herzberg, G. *Infrared and Raman Spectra*; Van Nostrand: Princeton, N.J., 1945.

(30) Bell, R. P. *The Tunnel Effect in Chemistry*; Chapman and Hall: New York, 1980; pp 60–63.

(31) Sims, L. B.; Burton, G. W.; Lewis, D. E. BEBOVIB-IV, *QCPE*, No. 337; Department of Chemistry, Indiana University, Bloomington, Indiana.

Table VI. Calculated Deuterium Isotope Effects for $C_2CHD + CO$ (Partial Bond Model[a])

C--H--O angle	A[b]	n_{OH}	k_H/k_D,[c] 30 °C	ΔE_a,[d] kcal mol^{-1}	A_H/A_D[d]	Q_{tH}/Q_{tD},[e] 30 °C
180	1.000	0.2	6.031	1.107	0.960	
		0.25	7.043	1.256	0.874	
150		0.2	4.308	0.932	0.917	
		0.25	5.527	1.056	0.956	
120		0.2	2.966	0.734	0.876	
		0.25	3.964	0.920	0.860	
180	1.025	0.2	6.868	1.202	0.933	1.074
		0.25	7.944	1.328	0.875	1.045
150		0.2	5.217	1.017	0.963	1.054
		0.25	6.171	1.123	0.956	1.046
120		0.2	3.412	0.792	0.916	1.020
		0.25	4.462	0.969	0.892	1.021
180	1.049	0.2	7.556	1.319	0.844	1.182
		0.25	8.629	1.411	0.829	1.115
150		0.2	5.783	1.119	0.901	1.148
		0.25	6.678	1.199	0.912	1.115
120		0.2	3.791	0.861	0.907	1.069
		0.25	4.891	1.024	0.893	1.065
180	1.095	0.2	9.190	1.662	0.581	1.526
		0.25	10.053	1.625	0.675	1.321
150		0.2	6.922	1.409	0.666	1.440
		0.25	7.647	1.394	0.754	1.310
120		0.2	4.439	1.033	0.797	1.231
		0.25	5.524	1.155	0.811	1.196

[a] Total bond order to H in transition state not conserved. For n_{OH} = 0.2, $n_{OH} + n_{CH} = 0.7$ and for n_{OH} = 0.25, $n_{OH} + n_{CH} = 0.5$. [b-e] See corresponding footnotes in Table V.

by only a few percent, there is some flexibility in the models used to obtain the calculated values. Reasonable variations in force constants or geometry could change the values significantly. It is difficult to set any specific limits on permissible changes in the models, but we have arbitrarily allowed as possibilities all models with k_H/k_D within 5.8 ± 1.0, the experimental value at 30 °C (Table III). We then apply to each of the acceptable models the further test that they give Arrhenius parameters within the experimental error of the Arrhenius parameters calculated from the observed isotope effects, 0.85–1.24 kcal mol^{-1} for E_a and 0.68–1.38 kcal mol^{-1} for A_H/A_D.

The calculated k_H/k_D values at 30 °C reported in Tables V and VI include only relatively symmetrical transition states, the two on either side of the maximum in k_H/k_D,[32] so as to save space. The more reactant-like or product-like transition states for a given model show smaller k_H/k_D values and more normal Arrhenius parameters (A_H/A_D closer to unity). The models in Table V all require a total bond order to hydrogen of unity, $n_{OH} + n_{CH} = 1.0$. The models in Table VI relax this requirement, letting $n_{OH} + n_{CH}$ = 0.7 and 0.5 when n_{OH} = 0.2 and 0.25, respectively.

If we limit ourselves to the models in Table V, it is clear that only linear transition states fit the experimental results, specifically those for which A = 1.025 and 1.049. Thus, modest tunnel corrections (1.1–1.3) are not only allowed, they are needed to bring k_H/k_D up to the observed value. The 180° model with A = 1.0 (no tunneling) does come fairly close, as does the 150° model with A = 1.049. As long as conservation of total bond order to hydrogen is required, only linear or nearly linear (C–H–O angle > 150°) models fit the experimental fact.

If conservation of total bond order to hydrogen is not required, a wider range of models can fit the facts. For the results in Table VI, models with $n_{CH} + n_{OH} = 0.7$ easily fit the experimental results when A = 1.025 or 1.049, and the C–H–O angle is 150°. They also fit when A = 1.0 or 1.025, and the angle is 180°. Models with $n_{CH} + n_{OH} = 0.5$ actually do not give tabulated k_H/k_D values small enough to fit the observed results when the C–H–O angle is 180°, though more reactant-like or product-like models (not tabulated) could. Models with the C–H–O angle 150° and A = 1.0, 1.025, or 1.049 fit, and even one model with a 120° angle (A = 1.095) also fits.

It seems to us that the models in Table VI are distinctly less plausible than those in Table V. The reaction coordinate for this reaction is a simple one, involving only C–H and O–H as reacting bonds. Any decrease in total bond order to hydrogen then must mean an increase in activation energy. There are no other reacting bonds that could compensate for the loss of bond energy by becoming tighter. We thus believe that the combination of isotope effect calculations and experimental results make a good case for a C–H–O angle in the transition state that is certainly greater than 150° and probably closer to 180°.

Discussion

The correlation between the temperature dependent isotope effect and stereoselectivity of the C-5 hydrogen transfer to 2-hexyloxy radical and the molecular mechanics and isotope effect calculations for model transition states points strongly to a linear or close to linear (>150°) CHO angle of transfer.

Such a geometry could engender some strain in the connecting chain. If this were true it would constitute direct evidence for the general assumption that intermolecular SH_2 reactions at hydrogen by alkoxy radical involve a linear three atom array transition state.[33] In other words, if, in the intramolecular case studied here, a linear course is taken in spite of steric forces which would favor the bent case (refer to Figure 4), one must conclude that the orbital requirements favor linearity over more acute angles of transfer by at least the energy associated with the strain difference between the linear and acute angle conformational states.

We have carried out molecular mechanics calculations to evaluate this strain difference between the isomeric linear and bent conformational states (Figure 4). The steric energies and, therefore, the strain energies[34] of the bent and linear states (Figure 4) vary widely with the distance between C_5, its bound hydrogen and oxygen. The calculations show the steric energies to be sensitive only to the sum of the distance between the three atoms C, H, and O. Moreover as discussed earlier, tthe steric energies are only slightly sensitive to the stretching and bending force constants associated with these atoms. Two typical values are the following: for C_5–H of 1.26 Å and H···O of 1.5 Å, B (and D) differs from A (and C) by 7.2 (and 6.5) kcal mol^{-1}, respectively; for C_5–H of 1.1 Å and H···O of approximately 2 Å, B (and D) differs from A (and C) (Figure 4) by 17.6 (and 17.2) kcal mol^{-1}, respectively.

We, therefore, can draw the qualitative conclusion that the bent states A and C (Figure 4) are of lower energy. Unfortunately, no exact value can be assigned for the energy difference between the bent and linear transition states of interest here because we cannot estimate precisely enough the C, H, and O atomic distances, even though (as discussed earlier) we can assign the angular relationship. This follows since at all atomic distances varying over a wide range, the diastereotopic bent states A and C differ consistently by a steric energy of between 0.8 and 1.1 kcal mol^{-1} while the linear states, B and D, differ by about 0.2–0.3 kcal mol^{-1}. This is consistent with the correlation between the experimental stereoselectivity and the linear transition state, as discussed earlier.

In contrast to the Barton reaction studied and discussed here, the apparently similar γ-hydrogen transfer to amino cation radicals, i.e., the Hofmann–Loeffler–Freitag reaction,[9] in the 2-hexylamine case shows an isotope effect (k_H/k_D) of only 1.20 at 25 °C.[35] This result suggests that even by allowing the widest

---

[32] Since the forming bond (OH) is stronger than the breaking bond (CH), the k_H/k_D maximum, which comes when $F_{CH} = F_{OH}$, will come before the OH bond is half formed. For the $n_{CH} + n_{OH} = 1.0$ models in Table V, the k_H/k_D maximum is at $n_{OH} = 0.38$. For the $n_{OH} + n_{CH} < 1.0$ models in Table VI, the k_H/k_D maximum is at about $n_{OH} = 0.23$.

[33] See ref 5 and as well numerous references to this assumed geometry throughout, *Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol. I and II. Although complex organic radicals have not been treated theoretically, a complete ab initio calculation on the $H_2 + H\cdot$ system shows the potential for small distortions from linearity to be soft, i.e., only about 200 cal mol^{-1} to go to 170°. See: Siegbahn, P.; Liu, B. and Truhlar, D. G., Horowitz, C. J. in ref 7 above. For leading references to the stereochemistry of homolytic substitution see: Green, M. M.; Gigeure, R. J.; Nicholson, J. R. P. *J. Am. Chem. Soc.* **1978**, *100*, 8020.

[34] See ref 18 above, Burkert and Allinger, pp 184 ff for an explanation of these terms.

variation in the symmetry of the transition state, the Barton and Hofmann–Loeffler–Freitag reactions do not occur with the same angle of transfer. This hypothesis would be strongly supported by a substantial energy of activation difference and an attendant temperature dependency for the transfer of the C-5 diastereotopic hydrogens in the 2-hexylamine cation radical. The larger value for k_a/k_b (1.54/1 at 25 °C)[35,36] may be an indication of this. Another indication that the angle of transfer in the amine cation radical may be more acute than for the Barton reaction is the observation of γ-hydrogen abstraction in the cation radical of aminocyclohexane[9] but not in the analogous alkoxy radical of cyclohexanol.[8]

The difference between the alkoxy radical and the amine cation radical[35] raises the question of why the orbital demand for linearity, demonstrated by the results of this work on the oxygen radical, may be lessened in the amine cation radical.[9] One suggestion is that the cation radical abstracts hydrogen over a lower barrier with an earlier, more reactant-like transition state. Such a difference, which is not unlike the difference between SH_2 reaction at hydrogen by bromine or chlorine radical,[37] would engender less bond breaking at the saddle point and, therefore, reasonably less electron delocalization and less orbital demand. Quantum mechanical calculations would be of interest on this point.

A practical point of interest could involve the amine cation radical in place of the alkoxy radical in synthetic situations with large energy barriers. This idea could have been helpful to the Swiss group which attempted to activate the C-9 hydrogen of a 5-β steroid utilizing an oxygen radical at the 3α-position.[38] This reaction, which bears the energetic cost of movement of the A ring into the boat form, and which would be of considerable use for entry into the important C ring functionalized steroids, gave only a tiny yield along the desired path by using the alkoxy radical.[38,39]

Experimental Section

Kinetics. The deuterated stereoisomers of 2-hexanol were prepared for this work by repeating the synthetic procedures previously reported.[14] Mass spectra were taken on a Hitachi RMU-6L instrument. NMR spectra were measured on an FX-90Q or and A-60A spectrometer. All gas chromatography was carried out on a 6-ft 20% SE-30 column on a Varian Model 920. Temperature control for the kinetic runs was achieved with a Tamson TC-45 bath and a Neslab PBC-2 cooler.

The reactions were conducted in pentane which was purified by washing with sulfuric acid until the acid was colorless followed by washing with water to neutrality. The pentane was stirred over $CaCl_2$ at room temperature for many hours, then distilled under nitrogen, and stored over molecular sieves in a desiccator. The Ag_2CO_3 had to be yellow and had to be prepared within 1 day in order to give good yields of the 2,5-dimethyltetrahydrofurans. Ag_2CO_3 was precipitated by the addition of $NaHCO_3$ to a solution of $AgNO_3$ in H_2O. It was dried in a desiccator over P_2O_5 under vacuum. This preparation and storage was done in the dark or under red light.

In a typical kinetic run the appropriate diastereomeric deuterated 2-hexanols were collected by preparative GC at 70 °C at 14 s/10 cm^3 He flow. The diastereomers (ca. 10 mg of each) were placed side-by-side in a 5-mL 14/20 round-bottomed flask wrapped in foil out of direct light already containing ca. 0.5 mL of pentane and 0.06 grams of Ag_2CO_3. The contents were magnetically stirred in the temperature bath, and 4 μL of Br_2 were added to each flask. The flasks were capped. The yield was periodically checked by GC, and at the appropriate time, e.g., several days at −8 °C (at this temperature another 4 μL of bromine was added after 2 days) and a few hours at 30 °C, the resultant 2,5-dimethyltetrahydrofuran was preparatively collected at dry ice temperature by GC at 60 °C column temperature and 14 s/10 cm^3 He flow. These collected materials were analyzed by repeated slow scans in the mass spectrometer over the region m/e 84–86. The unreacted 2-hexanols were also collected by GC and analyzed for deuterium content by mass spectrometry as discussed above in the results section.

Molecular Mechanics Calculations. All the molecular mechanics calculations were performed on the Cyber 750 and 845 by using the MM2 1985 force field.[40] The 2-hexanol was examined in two basic conformations (Figure 4). One conformer has the C–H···O angle roughly tetrahedral, while the other has the three atoms linear.

In order to calculate the energies of the two desired conformers, some manipulations using the MM2 program were necessary and merit description. For the chain-like structure, the driver option was used to rotate the straight chain 2-hexanol structure into a chair-like conformation.

Using the restricted motion option, atoms O(7) and C(5) were fixed in space, i.e., during minimization and these atoms were not allowed to move. The linear conformer was created by the following procedure: (1) the tetrahedral structure, described above, was rotated to place the cartesian coordinate origin at the midpoint of the O(7) and C(5) intramolecular distance, with atoms O(7) and C(5) lying along the X-axis. (2) Next, the H substituent of C(5) was forced to lie on the X-axis by changing its coordinates. (3) Atoms O(7), H, and C(5) were constrained to move only on the X-axis, employing the restricted motion option. The energy of this structure was then minimized.

Acknowledgment. We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, for supporting the work at the Polytechnic University and to the National Science Foundation for support at the Universities of Georgia and Rochester.

Registry No. 2-Hexanol, 626-93-7; deuterium, 7782-39-0.

---

[35] Green, M. M.; Moldowan, J. M.; Armstrong, M. W.; Thompson, T. L.; Sprague, K. J.; Haas, A. J.; Artus, J. J. *J. Am. Chem. Soc.* **1976**, *98*, 849.

[36] Work is in progress by Olivia Haub in this laboratory on the stereoselectivity and isotope effect as a function of temperature for the diastereomers of 5-deuterio-2-hexylamine cation radical.

[37] Huyser, E. S. *Free Radical Chain Reactions*; Wiley-Interscience Publishers: New York, 1970; p 106. Pryor, W. A. *Free Radicals*; McGraw-Hill: New York, 1966; pp 162, 163, and 175.

[38] Immer, H.; Mihailovic, M. L. J.; Schaffner, K.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1962**, *45*, 753.

[39] This approach would be aided by the availability of the 5-β steroids bearing stereospecifically placed 3-amino groups. See: Green, M. M.; Vairamani, M. *J. Org. Chem.* **1981**, *46*, 5037.

[40] The program MM2 is available from the Quantum Chemistry Program Exchange, Department of Chemistry, University of Indiana, Bloomington, IN. Allinger, N. L.; Yuh, Y. *QCPE Newsletter*, **1980**, No. 395, 12 and from Molecular Design, LTD, 47405 Faralon Dr., San Leandra, CA 94577. Newer versions of the program are available from time-to-time. The details of the program are described in ref 41.

[41] Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127 and subsequent papers.