

Table I. Kinetic Isotope Effects (k_H/k_D) for the 1,5-Hydrogen Shift of 1,3-Pentadiene Using MP2/3-21G Frequencies at 473 K

reactant	calcd	exptl ¹
1,3-pentadiene	2.53	
1,1-dideuterio-1,3-pentadiene	2.54	5.10
5,5-dideuterio-1,3-pentadiene	2.58	5.10

calculations of isotope effects are not expected to be in error by more than the errors in the calculated frequencies of molecular vibrations, which are usually <10%. It therefore seems extremely unlikely that a calculated isotope effect could be in error by a factor of two, due simply to neglect of electron correlation.

Since this problem involved issues of general significance and since it seemed well within the scope of available supercomputers, we decided to calculate the deuterium kinetic isotope effect for the rearrangement of **1** at the MP2/3-21G level. The calculations reported below took 30 h of cpu time on a CRAY X-MP/24 computer.

The *s*-trans conformation of **1** and the transition state geometries were optimized at the MP2/3-21G level by using the GAUSSIAN 82 program.⁸ The transition state was optimized under C_s symmetry, since this corresponds to the lowest saddle point at the MP2 level.⁴ MP2/3-21G force constant matrices were calculated for the optimized geometries by using GAUSSIAN 82. The force constant matrices were mass weighted and converted to frequencies with a program⁹ that inputs the GAUSSIAN 82 archive file. The KIEs were calculated by using the rigid-rotor-harmonic-oscillator approximation.¹⁰

The experimental value¹ for the primary KIE was determined from the 1,1-dideuterio (**3**) and 5,5-dideuterio (**4**) derivatives of **1**, ignoring possible secondary deuterium KIEs. We calculated KIEs for **1**, **3**, and **4** both to compare with experiment and to estimate the secondary isotope effects. Table I contains the results. While none of the calculated KIEs are close to the experimental value, all are close to those from the RHF/3-21G (2.52) and MINDO/3 (2.50) calculations. The KIEs calculated for **3** and **4** differed very little from that for **1**, indicating that the secondary KIEs are small.

These results support the arguments presented by Dewar et al. for the intervention of VAT in this reaction. If VAT is indeed involved, the true activation energy for the reaction must be significantly larger than the experimental one and so larger than the value calculated by Jensen and Houk, the agreement between the latter and experiment being coincidental. For reasons indicated above, this could well be the case.

It should be remembered that *no* current procedure, *ab initio* or semiempirical, can lead by itself to reliable predictions of reaction mechanisms. The best approach is to combine experiment with calculation, including data for as many different properties and for as many different molecules as possible. Isotope effects and entropies of activation are particularly useful in this connection because they are more directly related to the mechanism of a reaction than enthalpies of activation and because it is also easier to calculate them with the requisite accuracy.

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Trajectories of Proton-Transfer Reactions. Experimental Determination of the Magnitude of Primary Deuterium Isotope Effects for Proton Transfers Occurring at Acute Angles

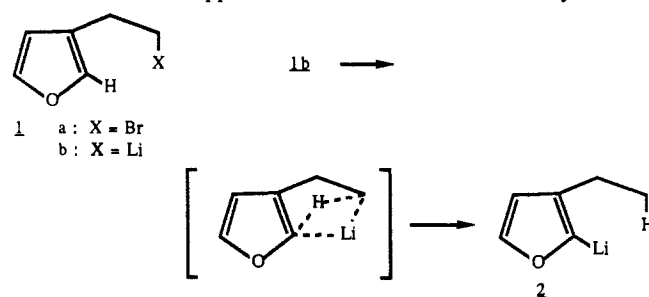
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Proton-transfer reactions represent one of the most fundamental classes of chemical reactions. Although most proton-transfer reactions preferentially occur at or near angles of 180°,^{1,2} some can deviate significantly from a linear trajectory.^{3,4a,b} However, little is known about (a) the energy costs associated with deviations from linearity and (b) correlations between the angle of a proton transfer and the magnitude of its kinetic isotope effect.⁵ This communication attempts to address both of these issues.

The reaction we have utilized to probe these questions is the conversion of 2-(3-furyl)ethylolithium, **1b**, to 3-ethyl-2-lithiofuran, **2**. This reaction appeared to be an ideal case to study for the



following reasons. First, semiempirical calculations on anions **1b** and **2** (with and without lithium) indicated that the proton-transfer process should possess a large thermodynamic driving force (ΔH_{reac} ranged from -15 to -20 kcal/mol).⁶ Second, the calculated index intramolecular proton transfers must occur at angles which are close to 90°.⁷ Third, since this reaction is carried out in an aprotic solvent, problems associated with solvent insertion in the transition state become unimportant.

In our first experiment, lithium alkyl **1b** was generated *in situ* by a lithium-halogen exchange reaction (2 equiv of *t*-BuLi/THF, -78 °C to 0 °C, 2 h) on bromide **1a**. After addition of quinone

(1) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265.

(2) For example, hydrogen bonds (which are considered to be on a reaction coordinate for proton transfer) are often linear. See: (a) Strobusch, F.; Marshall, D. B.; Eyring, E. M. *J. Phys. Chem.* **1978**, *82*, 2447. (b) Scott, R.; Vinogradov, S. *J. Phys. Chem.* **1969**, *73*, 1890. (c) Jones, R. E.; Templeton, D. H. *Acta Crystallogr.* **1958**, *11*, 484.

(3) Maercker et al. have presented strong evidence that the 1,4 proton shift in 4,4-diphenylbutyllithium occurs in an intramolecular fashion. See: Maercker, A.; Passlack, M. *Chem. Ber.* **1983**, *116*, 710.

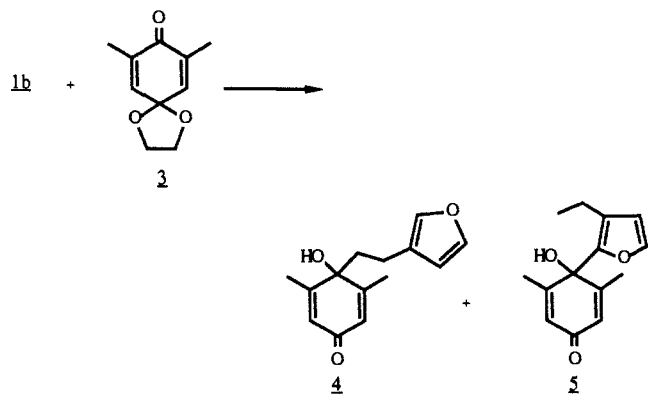
(4) Both Menger^{4a} and Tidwell^{4b} have suggested that certain norbornyl derivatives undergo intramolecular proton abstraction reactions at angles which may be as small as 100°. However, since these proton-transfer reactions were performed in protic solvents, solvent insertion in the transition state cannot be ruled out. Under these conditions it is difficult to determine angular relationships with certainty. See: (a) Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, *105*, 4996. (b) Abad, G. A.; Jindal, S. P.; Tidwell, T. T. *J. Am. Chem. Soc.* **1973**, *95*, 6326.

(5) (a) For some theoretical treatments of the effects of nonlinear proton-transfer transition states on isotope effects, see: More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 785. Anhedo, B.; Bergman, N.-A. *J. Am. Chem. Soc.* **1984**, *106*, 7634. Zhou, P.; Vitale, A. A.; San Filippo, J.; Saunders, W. H. *J. Am. Chem. Soc.* **1985**, *107*, 8049. (b) For an interesting overview on the effects of directionality on chemical reactivity, see: Menger, F. M. *Tetrahedron* **1983**, *39*, 1013.

(6) The calculations use the MNDO method and involve either simple anions or monomeric lithium alkyls which have been fully optimized. However, the energies reported here are only meant to suggest the high exothermicity of this process and not to represent an accurate quantitative measure of ΔH_{reac} .

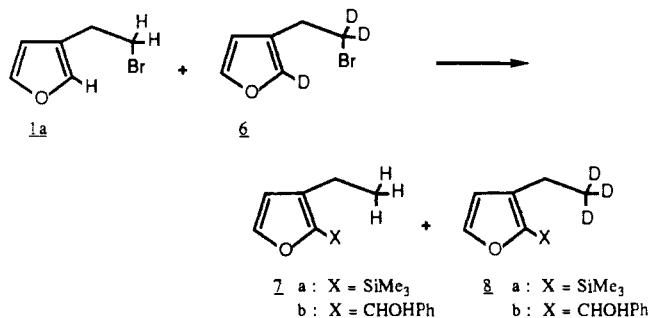
(7) According to these calculations, the pertinent CHC angles are as follows: **1b** (without lithium) = 82°, **2** (without lithium) = 79°, **1b** (with lithium) = 104°, and **2** (with lithium) = 93°.

ketal **3**,⁸ the reaction mixture was allowed to warm to 0 °C over



a period of 2 h. Standard workup, followed by separation of the reaction components by chromatography on silica gel, resulted in the formation of **5** in 70% yield. Small amounts of **4** (1–5%) were also observed.

The above results are compatible with an intramolecular proton transfer since (a) this furan metalation proceeds more rapidly and with higher regioselectivity than do normal intermolecular furan metalations⁹ and (b) addition of variable amounts of tetramethylethylenediamine, a well-known deaggregating agent, did not alter the observed product ratios.¹⁰ In order to determine the molecularity of this process, the following double labeling experiments were performed. Equimolar quantities of **1a** and **6**

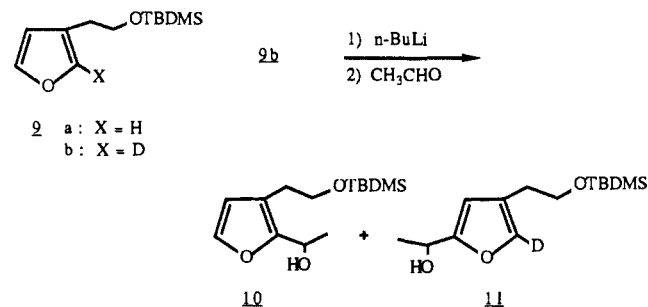


were subjected to lithium–halogen exchange (2 equiv of *t*-BuLi, –78 °C to 0 °C, 2 h, THF), and the resulting reaction mixture was quenched with either benzaldehyde or trimethylsilyl chloride. The furan-containing components were isolated and analyzed for deuterium content with mass spectrometry. Intermolecular reactions should produce equal amounts of d₀, d₁, d₂, and d₃ products, while intramolecular reactions should result in only d₀ and d₃ products. Since only d₀ and d₃ materials were detected, we conclude that this proton transfer is intramolecular.¹¹

Our next task was to determine the effect of the acute angle trajectory on the observed magnitude of the deuterium isotope effect. Insight into the thermodynamics of these processes can be obtained by calculating the heats of formations of furan, ethyllithium, ethane, and α -lithiofuran via the MNDO protocol. By using the data, the calculated ΔH_{react} for this intermolecular proton-transfer is –16.9 kcal/mol. Application of the Hammond postulate suggests a reactant-like transition state, which, in turn, suggests a relatively small $k_{\text{H}}/k_{\text{D}}$.

An experimental measure of the decrease in the isotope effect due to the reactant-like nature of the transition state can be obtained by determining the kinetic isotope effect for a related

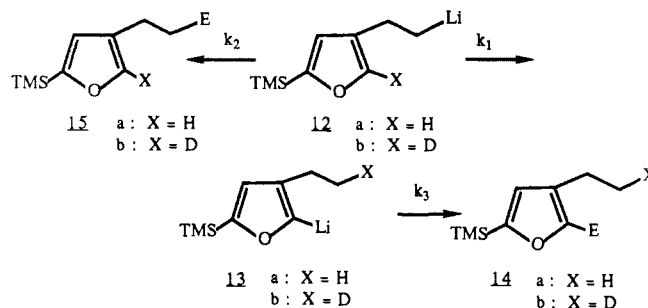
intermolecular furan metalation. In a previous study¹² we had shown that the metalation of furan **9a**, followed by subsequent reaction with an electrophile, resulted in a 1:1 mixture of α - and α' -substituted products. It then follows that the **11/10** ratio (5.6



–45 °C) observed in the metalation of **9b** represents the kinetic isotope effect for the intermolecular metalation.¹³ Since at –45 °C the maximum deuterium isotope effect expected (in the absence of tunneling) is approximately 12, the reactant-like transition state has reduced $k_{\text{H}}/k_{\text{D}}$ by half of its maximum.¹⁴

By using the above result as a base line, we can now assess the additional effects resulting from bending in the transition state. Since the differences in zero-point energies of C–H and C–D stretching frequencies are relatively large, linear transition states exhibit the largest observed isotope effects (in the absence of tunneling). As the nonlinearity increases, bending frequencies become increasingly important and eventually dominate. Since the differences in energies in bending frequencies are relatively small, bent transition states exhibit smaller observed isotope effects.

Measurement of the kinetic isotope effect for the conversion of **1b** to **2** is straightforward as long as one assumes that isotopic substitution which is remote to the reacting center does not alter the rate of the reaction under examination. Thus, for the reactions depicted below the only difference in the rates of reaction of the protio and deuterio derivatives of **12** (derived from its corresponding bromide) should be in k_1 . Since for each of the derivatives, the **14/15** ratio is a measure of k_1 , the ratio of **14a/15a** to **14b/15b** corresponds to the isotope effect for the reaction.¹³ At –45 °C, this value is 1.6. Thus, the acute angle transition state has reduced the magnitude of this primary effect to a value close to that often attributed to secondary effects!



In this article we have provided experimental evidence that (a) acute angle proton transfers compete effectively with intermolecular proton transfers and are therefore energetically feasible processes and (b) the magnitude of the kinetic isotope effects in these reactions is dramatically reduced. These results raise the possibility that some effects which were previously interpreted as secondary isotope effects may actually be primary effects which occur at acute angle trajectories. Further clarification of this issue will be the subject of future reports.

Acknowledgment. Financial support from the National Institutes of Health is gratefully acknowledged.

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(10) (a) Langer, A. W. *N.Y. Acad. Sci.* **1965**, *27*, 741. (b) Schollkopf, U. In *Houben-Weyl Methoden der Organischen Chemie*; Georg Thieme Verlag: Stuttgart, 1970; Vol. 13/1, p 7. (c) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.

(11) While our method of analysis does not permit us to rule out the presence of small amounts (<10%) of d₁ and d₂ products, their presence would still only indicate a small degree of leakage via the intermolecular manifold.

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(13) Product ratios were determined by ¹H NMR analysis.

(14) Since this reaction undoubtedly involves a four-center transition state, the magnitude of $k_{\text{H}}/k_{\text{D}}$ will be also decreased somewhat due to nonlinearity.