and −78 to 0 °C for 2 h, the reaction mixture was quenched by the addition of water, concentrated in vacuo to remove tetrahydrofuran and extracted with hexane containing a few drops of triethylamine.[16] The crude product was isolated by drying over sodium sulfate and removal of solvent in vacuo and then rapidly chromatographed on basic alumina (activity V) using ether–hexane (2:3) containing a little triethylamine to afford in 35% yield pure epoxy ester **14**, R_f 0.48 (triethylamine-treated silica gel plate with ether–hexane, 1:1): ultraviolet $\lambda_{\max}$ (methanol) 269, 278, 287 nm (ϵ 30 500, 40 000, 34 400). Since the epoxy ester **14** is both air and acid sensitive, it was stored at −78 °C under argon in frozen benzene containing a small amount of triethylamine and 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy free radical[17] as stabilizers.[18] The ^{1}H NMR spectrum of **14** indicates that the synthetic product consists of approximately equal amounts of 5,6-cis and 5,6-trans epoxides. Saponification of **14** with cold aqueous base under argon produced solutions of the salt of **2**, which could be reconverted into **14** with dimethyl sulfate.

The methyl ester **14**, when treated with methanol, undergoes rapid solvolysis to form approximately the same mixture of methyl ethers as are observed to form when the unstable biosynthetic precursor of **1** in neutrophils is quenched with methanol and esterified with diazomethane (comparison by gas chromatography–mass spectrometry).[19] In addition a similar mixture of the methyl esters of **1** and its isomers resulted from nonenzymic, acid-catalyzed hydrolysis of synthetic **14** and the natural unstable intermediate from neutrophils (after treatment with diazomethane).[19]

The ready availability of **2** and its methyl ester **14** by a simple synthesis opens the way for a host of interesting biological experiments. We are currently studying the large-scale synthesis of SRSA and related compounds and, in addition, other synthetic routes to the eicosanoid **14** and its Δ-7,9 stereoisomers.[20] It now appears that proof of the detailed structure of SRSA is most likely to be obtained by a comparison of synthetic and naturally derived compounds.[21]

References and Notes

(1) See: (a) Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2643; *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2148.

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(4) Prior to this time the structure of the unstable intermediate had been tentatively regarded as the 5,12-oxide of 6,10-*trans*,8,14-*cis*-eicosatetraenoic acid, a highly strained but fascinating structure. Studies on the generation of this ring system by Dr. Pierre Lavallee in these laboratories (1977–1978) indicated it to be exceedingly unstable.

(5) This synthesis has been outlined in a lecture presented on May 28, 1979, at the 1979 International Conference on Prostaglandins held at Washington, D.C.

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(9) Borgeat, P.; Hammarström, S.; Samuelsson, B., lecture presented at the 1979 International Conference on Prostaglandins, May 28, 1979, in Washington, D.C. See *Chem. Eng. News* **1979**, *57*, No. 24, 19.

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(13) Satisfactory infrared, ultraviolet, ^{1}H NMR, and mass spectra were obtained using purified, chromatographically homogeneous samples of each synthetic intermediate. All reactions involving air-sensitive components were conducted under argon.

(14) See: (a) Alexakis, A.; Normant, J.; Villiéras, J. *Tetrahedron Lett.* **1976**, 3461. (b) McGuirk, P. R.; Marfat, A.; Helquist, P. *Ibid.* **1978**, 2465.

(15) Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942.

(16) Triethylamine is used as a stabilizer because of the great sensitivity of the epoxide **14** to traces of acid.

(17) This agent is, in our experience, an outstanding antioxidant for readily oxidized polyunsaturated fatty acid derivatives.

(18) The experimental conditions for the conversion of hydroxy tetraene **11** into the sulfonium salt **13** and for the subsequent coupling reaction with methyl 4-formylbutyrate are very critical. Because of the high reactivity of the mesylate **12** and the sulfonium salt **13**, it is preferable that these intermediates not be isolated but used in situ. The formation of the required ylide from sulfonium salt **13** is carried out at low temperatures and short reaction time to avoid conversion into the isomeric methylide which is susceptible to facile [3,2] sigmatropic rearrangement. For the formation of oxiranes from sulfonium ylides see: (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) Corey, E. J.; Oppolzer, W. *Ibid.* **1964**, *86*, 1899.

(19) This comparison which was performed in the laboratory of Professor Samuelsson will be described in detail in a separate publication.

(20) It is convenient to use the term "eicosanoids" to describe the broad group of C_{20} fatty-acid-derived compounds as recently proposed (lecture cited in ref 5). The eicosanoid family thus includes lipoxygenase-derived hydroperoxides or alcohols (e.g., Samulesson's HETE), SRSA, thromboxanes, and prostaglandins. Professor Samuelsson has proposed the names leucotriene A, B, and C for epoxytetraene **2** (or Δ-7,9 stereoisomer), **1**, and SRSA, respectively (see ref 9).

(21) This research was assisted financially by the National Science Foundation.

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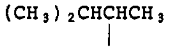
Contribution of Tunneling to Relative Reactivity in an Elimination Reaction[1]

Sir:

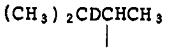
We have found that tunneling can make different contributions to the rates of proton removal from different sites in the same molecule.

The influence of tunneling on the magnitude and the temperature dependence of kinetic hydrogen isotope effects has been explored by numerous workers,[2-4] but the possible contribution of tunneling to relative reactivities has to our knowledge not been discussed. It is evident, however, that two reactions with different tunnel corrections to their isotope effects must also have different tunnel corrections to the reaction rates for the light isotopic species.

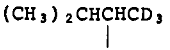
We determined isotope effects as a function of temperature by careful GLC measurement of 1-ene:2-ene ratios for the E2 reaction of **1**–**3** (ONs = *p*-nitrobenzenesulfonate) with sodium ethoxide in ethanol (10–60 °C) and potassium *tert*-butoxide in *tert*-butyl alcohol (20–70 °C). The isotope effect on formation of 1-ene is then given by k_H/k_D = (1-ene:2-ene)$_1$/(1-ene:2-ene)$_3$, and similarly for the isotope effect on formation of 2-ene. The rate of elimination into the undeuterated branch is taken to be unaffected by deuterium in the other branch, an assumption that is probably good to within a few percent. The results are corrected for the small amount of solvolysis that occurs in ethanol and for the incomplete deuteration (2.88 atoms D) of **3**. **2** was >99% deuterated.


$(CH_3)_2CH\underset{\substack{|\\ \mathrm{ONs}}}{C}HCH_3$

1


$(CH_3)_2CD\underset{\substack{|\\ \mathrm{ONs}}}{C}HCH_3$

2


$(CH_3)_2CH\underset{\substack{|\\ \mathrm{ONs}}}{C}HCD_3$

3

Linear regression fits to the Arrhenius equation give the apparent Arrhenius parameters A_{aH}/A_{aD} and $E_{aD} - E_{aH}$ for the reactions yielding 1-ene and 2-ene. From these parameters, the tunnel corrections Q_{tH} and Q_{tD} can be evaluated by means of equations derived on the assumption that the first term of the Bell equation suffices to describe the tunneling behavior of the system.[5] The computer program used for this purpose is described in more detail elsewhere.[6] It is based on essentially the same principles as the program of Caldin and Mateo.[7]

From the tunnel corrections the *semiclassical* values of

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Table I. Arrhenius Parameters and Tunnel Corrections for the Reaction of 3-Methyl-2-butyl *p*-Nitrobenzenesulfonate with Alkoxides in the Corresponding Alcohols

quantity[a]	alkoxide EtONa	 *t*-BuOK
$(A_{aH}/A_{aD})_{1\text{-ene}}$	0.247 ± 0.037	0.174 ± 0.039
$(A_{aH}/A_{aD})_{2\text{-ene}}$	1.053 ± 0.186	0.641 ± 0.191
$(E_{aD} - E_{aH})_{1\text{-ene}}$[c]	1.580 ± 0.102	1.928 ± 0.162
$(E_{aD} - E_{aH})_{2\text{-ene}}$[c]	0.479 ± 0.107	0.801 ± 0.187
$(k_H/k_D)_{\text{obsd, 1-ene}}$[b]	3.39	4.30
$(k_H/k_D)_{\text{obsd, 2-ene}}$[b]	2.33	2.43
$(Q_{tH}/Q_{tD})_{1\text{-ene}}$	2.00	2.44
$(Q_{tH}/Q_{tD})_{2\text{-ene}}$	1.00	1.42
$(k_H/k_D)_{s,1\text{-ene}}$	1.69	1.77
$(k_H/k_D)_{s,2\text{-ene}}$	2.33	1.72
$Q_{tH(1\text{-ene})}$	3.37	4.48
$Q_{tH(2\text{-ene})}$	1.00	1.91
$(k_{2\text{-ene}}/k_{1\text{-ene}})_{\text{obsd}}$[b]	4.6	0.48
$(k_{2\text{-ene}}/k_{1\text{-ene}})_s$	15.5	1.13

[a] Temperature-dependent quantities are for 30 °C in all cases. [b] Calculated from the Arrhenius parameters rather than directly observed, so as to smooth random variations prior to the computer fits. [c] kcal mol^{-1}.

k_H/k_D and $k_{2\text{-ene}}/k_{1\text{-ene}}$—those values that would be observed in the absence of tunneling—can be calculated, since

$$(k_H/k_D)_{\text{obsd}} = (Q_{tH}/Q_{tD})(k_H/k_D)_s$$

and

$$(k_{2\text{-ene}}/k_{1\text{-ene}})_{\text{obsd}} = [Q_{tH(2\text{-ene})}/Q_{tH(1\text{-ene})}](k_{2\text{-ene}}/k_{1\text{-ene}})_s$$

The Arrhenius parameters and the various quantities derived from them are collected in Table I.

It is obvious, both qualitatively from the Arrhenius parameters and quantitatively from the dissection into tunnel corrections and semiclassical values, that tunneling does significantly affect the ratio of Saytzev to Hofmann product in this typical E2 reaction. Discussions of orientation[8] customarily consider the influence of inductive, hyperconjugative, and steric effects on the relative free energies of the respective transition states. Such thermodynamic comparisons necessarily ignore the strictly kinetic phenomenon of tunneling; so we should direct our attention to $(k_{2\text{-ene}}/k_{1\text{-ene}})_s$, *not* $(k_{2\text{-ene}}/k_{1\text{-ene}})_{\text{obsd}}$. When we do so with the present data, a fairly strong observed preference for the Saytzev product (2-ene) with ethoxide-ethanol becomes much stronger, and the modest observed preference for the Hofmann product (1-ene) with *tert*-butoxide-*tert*-butyl alcohol disappears. Substantial differences between orientation in the two media remain, of course, but revisions in our evaluation of the factors determining orientation are certainly in order. We have experiments in progress to delineate further the role of tunneling in orientation in E2 reactions. Until more data are available, it seems pointless to discuss just what changes in theories of orientation may be necessary.

It is interesting to speculate briefly on why tunneling should be more important in formation of the Hofmann than the Saytzev product. At first sight, it goes against the idea that greater steric congestion in the transition state should facilitate tunneling.[3] We suggest that the difference in steric effects between the reactions forming 1-ene and 2-ene may not be great enough to bring this factor into play. It is likely, however, that the transition state leading to the Saytzev product has more double-bond character than that leading to the Hofmann product, which would result in more heavy-atom motion in the reaction coordinate.[6,9] The movement apart of the two β-methyl groups as the β carbon goes from sp^3 to sp^2 should add further to this heavy-atom motion. Both types of heavy-atom motion should tend to decrease the contribution of tunneling.

The semiclassical isotope effects show a distinctly different pattern from the observed ones. The larger observed isotope effects on 1-ene than 2-ene formation result entirely from tunneling, as does the larger isotope effect for 1-ene formation with *tert*-butoxide than with ethoxide. The fact that $(k_H/k_D)_s$ on 2-ene formation is no smaller than that on 1-ene formation (indeed, with ethoxide-ethanol it appears somewhat larger) argues against the suggestion that Saytzev products are formed via more E2C-like transition states than Hofmann products.[10,11] The E2C transition state is postulated to have a base-hydrogen-carbon angle substantially less than the 180° of the E2H transition state,[10] and reactions with nonlinear transition states should have smaller $(k_H/k_D)_s$ values than those with linear transition states.[12]

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(11) Reference 10 reports a $(k_H/k_D)_{1\text{-ene}}$ of 6.3 at 50 °C for the reaction of 3-methyl-2-butyl *tosylate* with ethoxide in ethanol, where k_H and k_D were calculated from the overall rates of elimination + substitution, fractions of elimination, and fractions of 1-ene for the respective isotopic species. Our $(k_H/k_D)_{1\text{-ene}}$ at 50 °C is only 2.9, and it seems unlikely that the change of leaving group would affect k_H/k_D so much. Any secondary isotope effect on elimination into the undeuterated branch of **3** would make our k_H/k_D lower than the strictly intermolecular effect of ref 10, but so large a secondary effect seems even more unlikely. While we cannot explain the discrepancy, we believe our k_H/k_D values are more reliable because they are based on 1-ene:2-ene ratios only, rather than the complex dissection of observed rates of ref 10. In support of this view, our data on 1-ene:2-ene ratios agree fairly well with those reported in ref 10.
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(13) Sherman-Clarke Fellow, 1977-1979; Hooker Fellow, 1978-1979.

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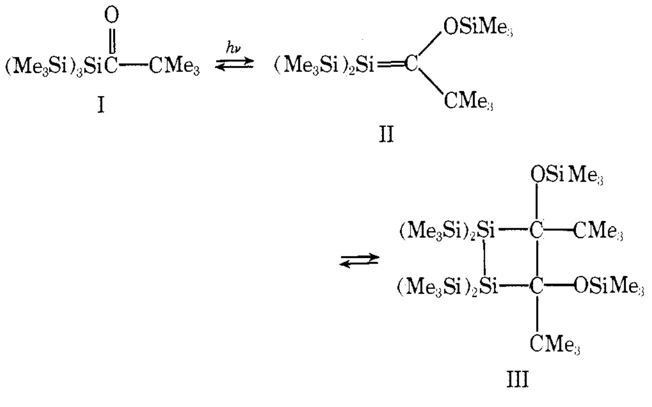
^{29}Si NMR Studies of Relatively Stable Silaethylenes

Sir:

Recently the conversion of pivaloyltris(trimethylsilyl)silane (I) into the isomeric silaethylene II, which exists in solution in equilibrium with its dimer III, was described.[1] Of particular



I

II

III

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