

radiation (Mo $K\alpha$), $\lambda = 0.71073 \text{ \AA}$; collection range, $4^\circ < 2\theta < 40^\circ$; scan width, $\Delta\theta = 1.4 + (K\alpha_2 - K\alpha_1)^\circ$; scan speed range, $3.0\text{--}15.0^\circ \text{ min}^{-1}$; total data collected, 4426; independent data, $I > 3\sigma(I)$, 3637. The Laue symmetry was determined to be $\bar{1}$, and the space group was shown to be either $P1$ or $P\bar{1}$. Intensities were measured with the ω scan technique as described above. In reducing the data, Lorentz and polarization corrections were applied as well as an empirical absorption correction based on ψ scans of ten reflections having χ values between 70 and 90° . The structure was solved by use of the SHELXTL Patterson interpretation program, which revealed the positions of the two Os atoms in the asymmetric unit, which comprise one full molecule. The remaining non-hydrogen atoms were located in subsequent difference Fourier syntheses. One of the rings (N2) was found to have unusually high thermal motion and was quickly found to be disordered over two sites at roughly 35° to each other about a nearly common pivot. When the thermal parameters involved were constrained to similar values as the other pyridines, the population factors refined to 65%:35% for the N2:N2' rings, respectively. Ideal rigid body phenyl rings with fixed isotropic temperature factors were used for the N2 and N2' rings. All remaining atoms were converted to anisotropic motion, after which all hydrogens were entered in ideal calculated positions. A single nonvariable isotropic temperature factor was used for all of the hydrogen atoms. At this point, four areas of disordered solvent were found and determined to be composed of nine discernable orientations of methylene chloride. The C35 area had only one orientation (80% occupancy), the C36 area had three orientations (40%/30%/30%), the C37 area had two (40%/30%), and the C38 area had three (40%/30%/30%). Thus, there were a total of 3.5 molecules of solvent, statistically, for every solute molecule in the crystal. Due to the low populations rigid bodies were used, based on the geometry of an ordered molecule found in a previous structure. No attempt was made to include solvent hydrogens. After all shift/esd ratios were less than 0.2, convergence was reached at the agreement factors: $R = \sum ||F_o| - |F_c|| / \sum |F_o|$, 0.044; $R_w = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$, 0.046. No unusually high correlations were noted between any of the variables in the last cycle of full-matrix least-squares refinement (except the disordered solvent molecules), and the final difference density map showed a maximum peak of about $1 \text{ e}/\text{\AA}^3$, positioned within one of the solvent groups. The atomic coordinates and equivalent isotropic thermal parameters as well as the observed and calculated structure factors for **B** and **A** are included in the Supplementary Material.

Promoted Thermal Osmylation of 9-Methylanthracene Dimer. 9-Methylanthracene dimer (10.5 mg , $2.73 \times 10^{-5} \text{ mol}$), osmium tetroxide (28 mg , $1.1 \times 10^{-4} \text{ mol}$) and pyridine ($2.2 \times 10^{-4} \text{ mol}$) were dissolved in heptane (3 mL), and the solution was sealed in an ampoule in vacuo. The mixture was heated to 60°C for 18 h and then at 100°C for a further 26 h in the dark. The solvent was removed under reduced pressure. The mixture was analyzed by $^1\text{H NMR}$ (CDCl_3) to give 31% 9-methylanthracene, 40% unreacted dimer, and 29% of the anti-isomer of the adduct **A_m**. To test for the thermal cracking, 9-methylanthracene dimer (10.2 mg , $2.7 \times 10^{-5} \text{ mol}$) and heptane (3 mL) were sealed in an ampoule in vacuo, and the solution was heated to 100°C in the dark for 48 h . Spectrophotometric analysis of the resulting solution indicated the presence of unreacted dimer ($1.2 \times 10^{-5} \text{ mol}$) and 9-methylanthracene ($3.0 \times 10^{-5} \text{ mol}$). We conclude that 56% of the dimer was converted to the monomer. In order to test for the thermal reaction of OsO_4 with pyridine, osmium tetroxide (28 mg , 0.11 mmol) and pyridine (18 L , 0.22 mmol) were dissolved in heptane (3 mL), and the solution was sealed in an ampoule in vacuo. The yellow solution was heated to 100°C in the dark for 48 h . Iodometry of the final pale yellow solution indicated that only 10.2 mg of OsO_4 (36%) remained unreacted.

Acknowledgment. We thank the National Science Foundation and the R. A. Welch Foundation for financial support, J. D. Korp for crystallographic assistance, the Center for Fast Kinetics Research (under the auspices of NIH Grant RR00886 and the University of Texas, Austin) for use of their picosecond laser flash photolysis equipment, and funds from the National Science Foundation to construct our ns- μs laser flash system at Houston.

Supplementary Material Available: Table II containing formation constants of $[\text{Ar}, \text{OsO}_4]$ complexes by the Benesi-Hildebrand method and Tables A-D and F-I containing X-ray crystallographic data consisting of atomic coordinates and equivalent isotropic displacement parameters, bond angles and lengths, and anisotropic displacement parameters for the benzene and anthracene adducts **B** and **A**, respectively (8 pages); Tables E and J containing observed and calculated structure factors (19 pages). Ordering information is given on any current masthead page.

Primary Deuterium Kinetic Isotope Effects for the Thermal [1,7] Sigmatropic Rearrangement of 7-Methylocta-1,3(Z),5(Z)-triene

John E. Baldwin* and V. Prakash Reddy

Contribution from the Department of Chemistry, Syracuse University, Syracuse, New York 13244. Received June 2, 1988

Abstract: 7-Methylocta-1,3(Z),5(Z)-triene isomerizes to 2-methylocta-2,4(Z),6(Z)-triene over the temperature range $60\text{--}115^\circ \text{C}$ through a first-order process characterized kinetically by the activation parameters $\log A^{\text{H}} = 9.8$ and $E_a^{\text{H}} = 21.5 \text{ kcal/mol}$. Parallel kinetic work with the 7-deuterio-7-methyloctatriene establishes the Arrhenius parameters $\log A^{\text{D}} = 10.3$ and $E_a^{\text{D}} = 23.5 \text{ kcal/mol}$. Thus $A^{\text{D}}/A^{\text{H}} = 3.2$ and $(E_a^{\text{D}} - E_a^{\text{H}}) = 2.0 \text{ kcal/mol}$, and a substantial tunneling component for the [1,7] sigmatropic hydrogen migration is evident.

Primary deuterium kinetic isotope effects for sigmatropic migrations of hydrogen have attracted renewed attention in the past few years. The magnitudes $k_{\text{H}}/k_{\text{D}}$ and the possible temperature dependences of these ratios of rate constants continue to attract interest and present substantial challenges to both experimentalists and theoreticians. While most of this attention has been devoted to [1,5] hydrogen shifts,¹⁻⁴ the magnitudes of

several [1,7] hydrogen migrations have been reported. The [1,7] sigmatropic isomerizations leading from 1,3(Z),5(Z)-octatriene to two isomers of 2,4,6-octatriene exhibit $k_{\text{H}}/k_{\text{D}}$ values of $6.4\text{--}7.7$.⁵ For two *cis*-isotachysterol analogues,⁶ [1,7] hydrogen shifts were found to have primary $k_{\text{H}}/k_{\text{D}}$ values of 4.0 and 2.6 at 98.4°C , and two previtamin D analogues gave the corresponding vitamin D analogues at 80.4°C with $k_{\text{H}}/k_{\text{D}}$ values of about 6.⁷ A much

(1) Jensen, F.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3139-3140.

(2) Gajewski, J. J. *Isotopes in Organic Chemistry*; Buncl, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol 7, pp 115-176.

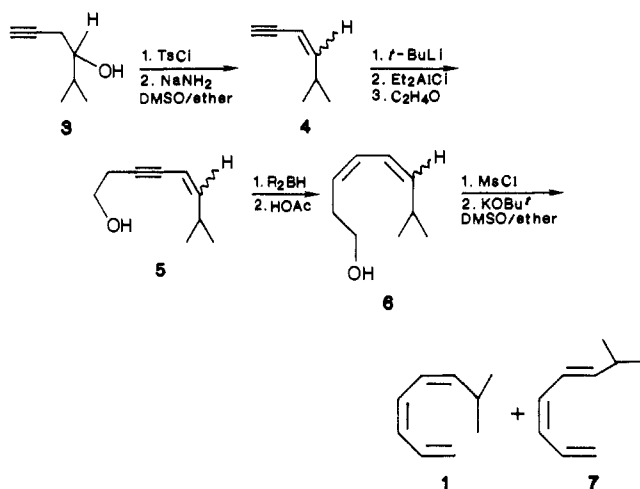
(3) Shen, G.-Y.; Tapia, R.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 7499-7506 and references therein.

(4) Dewar, M. J. S.; Healy, E. F.; Ruiz, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 2666-2667.

(5) Baldwin, J. E.; Reddy, V. P. *J. Am. Chem. Soc.* **1987**, *109*, 8051-8056.

(6) Hoeger, C. A.; Johnson, A. D.; Okamura, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 4690-4698.

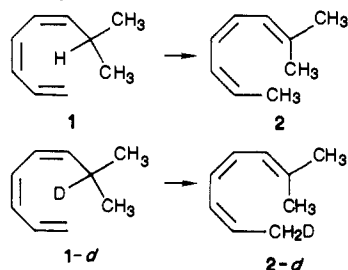
Scheme I



larger primary deuterium isotope effect for the previtamin D₃ to vitamin D₃ transformation reported in 1979⁸ is now recognized to be in error.⁹

None of this recent work, however, has provided reliable information on a possible temperature dependence of k_H/k_D values in [1,7] hydrogen shifts. Okamura and co-workers determined k_H/k_D values at single temperatures.^{6,7} We attempted to measure the primary k_H/k_D ratio for the rearrangements of 1,3(*Z*),5(*Z*)-octatriene to 2,4,6-octatrienes and to include secondary effects explicitly,⁵ but no firm conclusions on the temperature-dependence issue could be drawn: the complexity of the kinetic situation and the ineluctable fact that experimentally accessible rate parameters were functions of both primary and secondary k_H/k_D effects led to uncertainties in the primary k_H/k_D values which were too large for a definitive resolution of the issue.

To answer this question surely, at least for one case, a one-carbon homologue of 1,3(*Z*),5(*Z*)-octatriene, 7-methylocta-1,3-(*Z*),5(*Z*)-triene (**1**), was selected as a suitable substrate: it was expected to show a facile isomerization to but a single isomer, 2-methylocta-2,4(*Z*),6(*Z*)-triene (**2**). The corresponding monodeuteriated hydrocarbon rearrangement **1-d** to **2-d** would show only a primary k_H/k_D effect; there would be no intrusion of any complicating contribution from a concomitant secondary deuterium kinetic isotope effect.

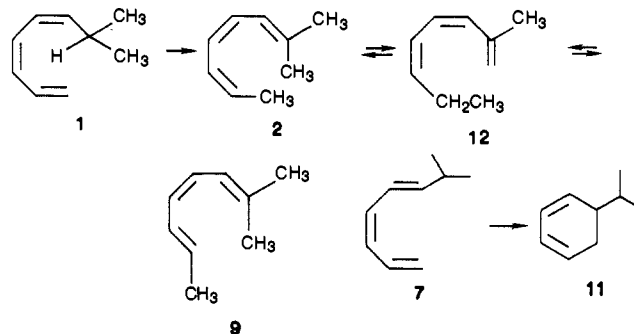


There was the hope that these less complicated [1,7] hydrogen shift reactions could be followed kinetically with sufficient precision as a function of temperature so that whether or not k_H/k_D shows a steep temperature dependence, and thus whether or not there is a significant contribution from a tunnel effect, would be clearly apparent.

Results

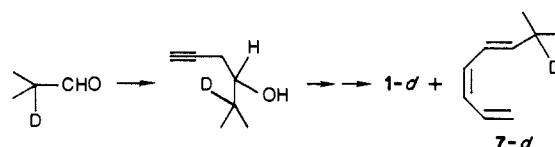
Syntheses. Preparation of triene **1** was accomplished through the sequence of reactions outlined in Scheme I. Condensation of propargylmagnesium bromide with isobutyraldehyde gave alcohol **3**.¹⁰ The corresponding tosylate was prepared and de-

Scheme II



hydroxylated with sodium amide in ether containing some DMSO. The mixture of enynes obtained,¹¹ **Z-4** and **E-4**, could be separated chromatographically, but often the mixture was carried forward directly. The acetylenic diethylaluminum reagent¹² was prepared from **4** and reacted with ethylene oxide to provide alcohol **5**, which could be reduced stereoselectively through reaction with diisobutylborane, followed by protonolysis using acetic acid,^{13,14} to give the 3*Z*,5*Z* and 3*Z*,5*E* isomers of diene **6**. Finally, esterification with methanesulfonyl chloride and treatment of the mesylates with potassium *tert*-butoxide in ether/DMSO gave trienes **1** and **7**, readily distinguishable by ¹H NMR spectroscopy and differences in thermal reactivity.

To secure the desired monodeuterio system **1-d**, the same reaction sequence was followed starting with α -deuterioisobutyraldehyde;¹⁵ the ¹H NMR spectra of all intermediates along this synthetic route had the expected simplifications.



Authentic samples of the four isomers of 2-methylocta-2,4,6-triene, **2**, **8**, **9**, and **10**, were prepared readily through Wittig condensations: the *Z* and *E* isomers of 2-butenal^{16,17} were separately combined with the ylide derived from (3,3-dimethylallyl)triphenylphosphonium bromide to give in each reaction two of the four 2-methylocta-2,4,6-triene isomers.¹⁸

Thermal Isomerization Products. Over the temperature range (60–115 °C) and time intervals used for the kinetic study, **1** and **1-d** rearranged cleanly to **2** and **2-d**, while the corresponding 3*Z*,5*E* trienes **7** and **7-d** proved unreactive. At 185 °C, however, mixtures of **1** and **7** as dilute solutions in 2-methylpentane gave rise to **2** and two additional isolable isomers, identified through chromatographic and spectroscopic means to be 2-methylocta-2,4(*Z*),6-(*E*)-triene (**9**) and 5-isopropylcyclohexa-1,3-diene (**11**).¹⁹ The

(10) von Gutmann, H.; Isler, O.; Ryser, G.; Zeller, P.; Pellmont, B. *Helv. Chim. Acta* **1959**, *42*, 719–728.

(11) Mel'nikov, G. D.; Porfir'eva, Yu. I. *J. Org. Chem. USSR (Engl. Transl.)* **1972**, *8*, 1365–1369.

(12) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014–4020.

(13) Brown, H. C. *Organic Syntheses Via Boranes*; Wiley: New York, 1975; Chapter 3 and references therein.

(14) Mikhailov, B. M.; Bubnov, Yu. N. *Organoboron Compounds in Organic Synthesis*; Harwood Academic Publishers GmbH: Chur, Switzerland, 1984; pp 514–519.

(15) Hine, J.; Houston, J. G.; Jensen, J. H.; Mulders, J. *J. Am. Chem. Soc.* **1965**, *87*, 5050–5059. Varma, K. R.; Caspi, E. *J. Org. Chem.* **1969**, *34*, 2489–2495.

(16) Magid, R. M.; Fruchey, S. O.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359–363. Bergman, R. G. *J. Am. Chem. Soc.* **1969**, *91*, 7405–7411.

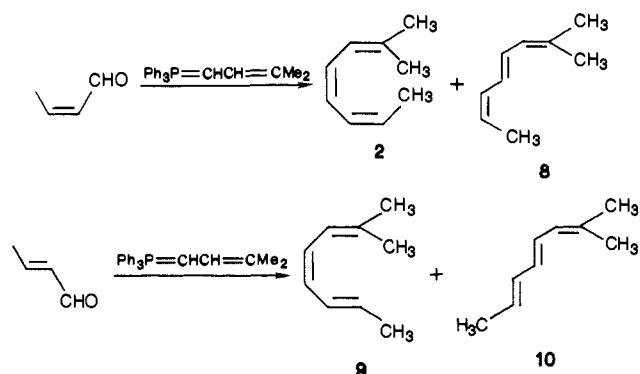
(17) Childs, R. F.; Lund, E. F.; Marshall, A. G.; Morrissey, W. J.; Rogerson, C. V. *J. Am. Chem. Soc.* **1976**, *98*, 5924–5931.

(18) Trienes **8** and **10** have been reported: van Dongen, J. P. C. M.; de Jong, A. J.; Selling, H. A.; Montijn, P. P.; van Boom, J. H.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1077–1081. Josey, A. D. *J. Org. Chem.* **1974**, *39*, 139–145. Josey, A. D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 686–687. Dzhemilev, U. M.; Yakupova, A. Z.; Tolstikov, G. A. *J. Org. Chem. USSR (Engl. Transl.)* **1979**, *15*, 1037–1040.

(7) Okamura, W. H.; Hoeger, C. A.; Miller, K. J.; Reischl, W. *J. Am. Chem. Soc.* **1988**, *110*, 973–974.

(8) Sheves, M.; Berman, E.; Mazur, Y.; Zaretskii, Z. V. I. *J. Am. Chem. Soc.* **1979**, *101*, 1882–1883.

(9) Reference 3, note 9 and Professor Y. Mazur, private communication.



isomerizations providing these products are summarized in Scheme II.

Triene 1 forms 2, as observed at lower temperatures; 2 in turn gives the 4*Z*,6*E* isomer 9 by way of [1,7] hydrogen shifts and the transient reactive intermediate 12, by analogy with the similar and thoroughly studied isomerizations of the corresponding unbranched octatrienes.^{5,20} 5-Isopropylcyclohexa-1,3-diene is the expected ring-closure product from 7.²¹

Kinetics and Kinetic Isotope Effects. Dilute solutions of 1 and of 1-*d* in 2-methylpentane were sealed in glass ampules, heated in a thermostated bath for the appropriate times, and analyzed by analytical gas chromatography on fused silica capillary columns. At long reaction times, small amounts of isomer 9 were detected in some product mixtures (cf. Scheme II). The observed isomerizations 1 to 2 and 1-*d* to 2-*d* followed clean first-order kinetics. Each isomerization was analyzed at 9–11 different reaction times, with each point typically determined in triplicate. A sample kinetic plot, the natural logarithm of the mole fraction of 1-*d* as a function of time at 95 °C, followed through 2 half-lives, is displayed in Figure 1.

The rate constants measured for the isomerizations of 1 and 1-*d* as functions of temperature are summarized in Table I. The Arrhenius plots based on these rate constants are shown in Figure 2; alternatively, one may plot $\ln(k_{\text{H}}/k_{\text{D}})$ against $T(\text{K})^{-1}$ to secure a straight-line correlation with slope $(E_{\text{a}}^{\text{D}} - E_{\text{a}}^{\text{H}})/R$ and intercept $\ln(A^{\text{H}}/A^{\text{D}})$ (Figure 3). From the first treatment of the data, one derives the parameters $E_{\text{a}}^{\text{H}} = 21.5$ and $E_{\text{a}}^{\text{D}} = 23.5$ kcal/mol and $\log_{10} A^{\text{H}} = 9.8$ and $\log_{10} A^{\text{D}} = 10.3$. From the second, $(E_{\text{a}}^{\text{D}} - E_{\text{a}}^{\text{H}}) = 2.1$ kcal/mol and $\ln(A^{\text{H}}/A^{\text{D}}) = -1.15$ or $\log(A^{\text{H}}/A^{\text{D}}) = -0.50$. The two modes of data reduction, then, provide essentially the same results.

While the standard deviation of $(E_{\text{a}}^{\text{D}} - E_{\text{a}}^{\text{H}})$ from the plot of Figure 3 is less than 0.1 kcal/mol, confirming that the data follow the expected pattern in a regular fashion, the 95% confidence interval is more substantial, 1.2–2.9 kcal/mol, a direct consequence of the small number (4) of $[k_{\text{H}}/k_{\text{D}}, T(\text{K})^{-1}]$ data sets and of the relatively small range spanned by T^{-1} .

Discussion

There are three standard hallmarks of hydrogen transfers involving a significant contribution from tunneling:²² $k_{\text{H}}/k_{\text{D}} > (k_{\text{H}}/k_{\text{D}})_{\text{s}}$, an observed primary isotope effect larger than can be calculated from equations based on semiclassical models and transition-state theory; $(E_{\text{a}}^{\text{D}} - E_{\text{a}}^{\text{H}})$ considerably above 1.2 kcal/mol; and $A^{\text{D}}/A^{\text{H}}$ values above unity, with values greater than 2 providing strong evidence that the tunneling correction is considerable.

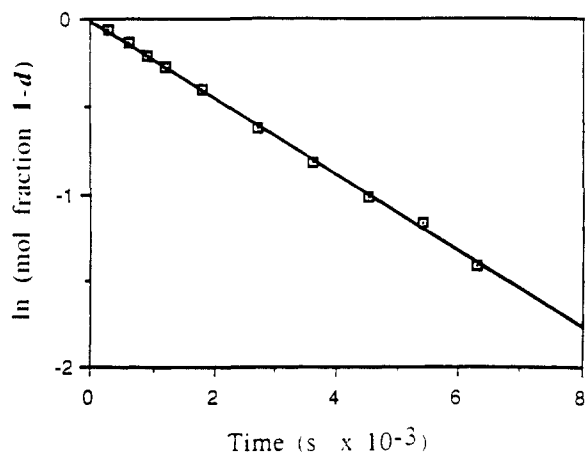


Figure 1. First-order kinetic plot for the isomerization of 1-*d* to 2-*d* at 95 °C.

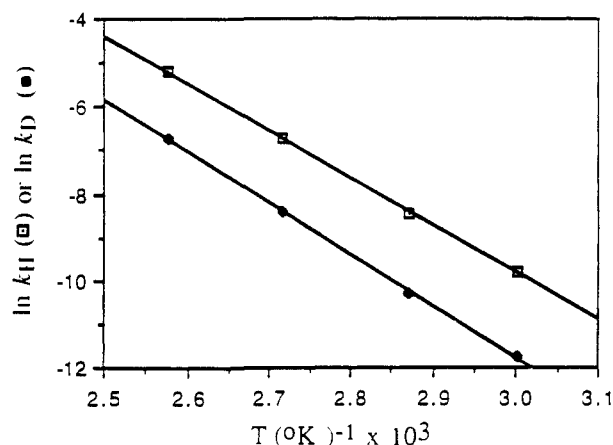


Figure 2. Arrhenius plots for the isomerization 1 to 2 and 1-*d* to 2-*d* between 60 and 115 °C.

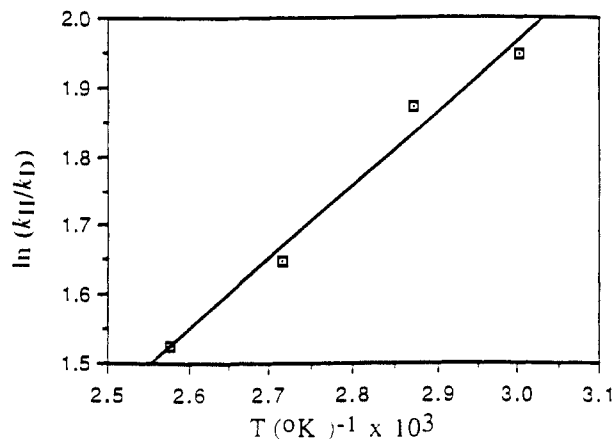


Figure 3. Primary $k_{\text{H}}/k_{\text{D}}$ effect as a function of temperature: $\ln(k_{\text{H}}/k_{\text{D}})$ for 1 to 2 and 1-*d* to 2-*d* against $T(\text{K})^{-1}$.

Table I. Temperature-Dependent First-Order Rate Constants for [1,7] Hydrogen or Deuterium Shifts in 1 and 1-*d*

$T, \text{°C}$	$10^4 k_{\text{H}}, \text{s}^{-1}$	$10^4 k_{\text{D}}, \text{s}^{-1}$	$k_{\text{H}}/k_{\text{D}}$
115.0	55.5	12.1	4.6
95.0	11.6	2.21	5.2
75.0	2.14	0.33	6.5
60.0	0.56	0.080	7.0

The first of these can be recognized as present or not when both an experimentally determined $k_{\text{H}}/k_{\text{D}}$ value and a good theoretical value for $(k_{\text{H}}/k_{\text{D}})_{\text{s}}$ are available. While some effort toward sound $(k_{\text{H}}/k_{\text{D}})_{\text{s}}$ values for the [1,7] antarafacial hydrogen shift in

(19) Walter, H.; Bernhard, G.; Dietrich, M. *Liebigs Ann. Chem.* **1958**, 614, 47–65. Spangler, C. W.; Hennis, R. P. *J. Chem. Soc., Chem. Commun.* **1972**, 24–25.

(20) Baldwin, J. E.; Reddy, V. P. *J. Org. Chem.* **1988**, 53, 1129–1132.

(21) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, 49, 3001–3020 and references therein.

(22) Bell, R. P. *The Proton In Chemistry*, Cornell University Press: Ithaca, NY, 1973; 2nd ed.; pp 270–282. See also: Melander, L.; Saunders, W. H., Jr. *Reactions Rates of Isotopic Molecules*; Wiley: New York, 1980; pp 75, 144–147. McLennan, D. J. *Aust. J. Chem.* **1979**, 32, 1883–1896. Dewar, M. J. S.; Merz, K. M., Jr.; Stewart, J. J. P. *J. Chem. Soc., Chem. Commun.* **1985**, 166–168.

hepta-1,3(*Z*),5(*Z*)-triene is being expended,²³ calculations of similar rigor and thoroughness for the isomerization **1** to **2** have not yet been attempted, and the first criterion therefore cannot be utilized. But the second and third tests are applicable and are both indicative of an important tunneling contribution: ($E_a^D - E_a^H$) is 2.0 kcal/mol, well above the 1.2 kcal/mol value which may be rationalized through semiclassical model calculations, and $A^D/A^H = 3.2$, a value substantially beyond the tunneling/non-tunneling borderline.

We conclude then that the data of Table I and current theory²² indicate that the [1,7] sigmatropic hydrogen shift which converts **1** to **2** occurs with substantial help from the tunnel effect. Other [1,7] sigmatropic hydrogen shifts and [1,5] hydrogen shifts¹⁻⁴ may also be facilitated by tunneling, and whenever the tunnel effect plays an important role in thermal pericyclic reactions involving hydrogen migrations, semiclassical theories applied to these reactions will consistently underestimate k_H/k_D , however large the basis set or sophisticated the computation. Theoretical models which include the tunnel effect adequately will have to be employed before theory and experiment can be brought into accord.

Experimental studies of primary k_H/k_D values for other intramolecular pericyclic hydrogen transfer reactions as functions of temperature, including the degenerate isomerization of hepta-1,3(*Z*),5(*Z*)-triene,²⁴ are in progress.

Experimental Section

Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl immediately before use. Dimethyl sulfoxide was distilled from CaH₂. Pentane and 2-methylpentane (>99% pure) were obtained from Aldrich Chemical Co. All reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Proton NMR spectra were recorded for CDCl₃ solutions on a GE QE 300 spectrometer. Chemical shifts (δ) are expressed relative to internal Me₄Si, and coupling constants (J values) are given in hertz. Chemical shift assignments were confirmed whenever necessary by homonuclear decoupling experiments.

Mass spectral data were secured with Hewlett-Packard (HP) 5890, 5970B, and 9836 instruments and computer. Analytical gas chromatographic analyses were done with a 0.2-mm i.d. 25-m cross-linked 5% phenyl methyl silicone fused silica capillary column and a 0.2-mm i.d. 25-m methyl silicone capillary column, a HP 5780 instrument with flame-ionization detectors, and HP 3390A and 3392A reporting integrators. Preparative gas chromatographic separations were performed with a Varian A-90-P3 instrument using the following columns: A, Carbowax 20M on Chromosorb G 60/80 (0.6 cm \times 3.2 m); B, 10% Carbowax 20M on Chromosorb G 60/80 (0.6 cm \times 60 cm); C, SE-30 on Chromosorb W 60/80 (0.6 cm \times 3.6 m); or D, β,β -oxydipropionitrile (ODPN) on Chromosorb P 60/80 (0.6 cm \times 3 m).

5-Methyl-1-hexyn-4-ol (3), prepared in 75% yield from propargyl-magnesium bromide in ether and 2-methylpropanal (Alfa), had bp 70–72 °C (60 mm) (lit.³ bp 45 °C (12 mm)); ¹H NMR δ 0.92 (d, 3 H, $J = 6.8$ Hz, cis-CH₃), 0.96 (d, 3 H, $J = 6.8$ Hz, trans-CH₃), 1.75–1.83 (m, 1 H, C5-H), 2.01 (d, 1 H, $J = 4.9$ Hz, OH), 2.05 (t, 1 H, $J = 2.7$ Hz, C1-H), 2.30–2.48 (m, 2 H, C3-H), 3.46–3.52 (br m, 1 H, C4-H).

5-Methyl-3-hexen-1-ynes (4). 5-Methyl-1-hexyn-4-ol (10 g, 89 mmol) dissolved in 10 mL of pyridine was treated with *p*-toluenesulfonyl chloride (20 g, 105 mmol). The reaction mixture was stirred for 20 h at room temperature and was then diluted with 100 mL of ether, washed twice with 100-mL portions of 10% HCl, and washed once with 100 mL of saturated sodium bicarbonate solution. The organic extracts were dried (MgSO₄), filtered, and concentrated by rotary evaporation. Analysis of the residue by ¹H NMR spectroscopy did not show absorptions attributable to impurities. **4**: ¹H NMR δ 0.84 (d, 3 H, $J = 6.9$ Hz, cis-CH₃), 0.88 (d, 3 H, $J = 6.8$ Hz, trans-CH₃), 1.93 (t, 1 H, $J = 3$ Hz, C1-H), 2.17 (m, 1 H, C5-H), 2.44 (s, 3 H, benzylic CH₃), 2.56 (dd, 2 H, $J = 2.7, 6$ Hz, C3-H), 4.42 (apparent q, 1 H, $J = 5.9$ Hz, C4-H), 7.34 (d, 2 H, $J = 8.6$ Hz, aromatic), 7.81 (d, 2 H, $J = 8.3$ Hz, aromatic).

The crude tosylates were dissolved in 100 mL of dry ether and were transferred into a 250-mL round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, and a nitrogen inlet. Sodium amide (6.9 g, 178 mmol) was added, the reaction mixture was cooled to 0 °C, and 8 mL of dry dimethyl sulfoxide was added. An exothermic reaction

ensued, and the reaction mixture was stirred another hour, until the evolution of ammonia had ceased. The reaction mixture was then poured into 200 mL of water and was extracted with two 60-mL portions of ether. The combined organic layers were washed with 100 mL of 10% HCl and 100 mL of saturated sodium bicarbonate solution and dried (MgSO₄). Filtration and concentration of the filtrate by careful fractional distillation gave the enynes **4** as a 1:1 mixture of isomers, contaminated by only traces of ether. Analytical samples of the 3*Z* and 3*E* isomers of **4** were separated by preparative GC with column C.

5-Methylhex-3(*Z*)-en-1-yne ((3*Z*)-4): ¹H NMR δ 1.01 (d, 6 H, $J = 6.7$ Hz, CH₃), 2.93 (m, 1 H, C5-H), 3.05 (d, 1 H, $J = 2$ Hz, C1-H), 5.34 (dd, 1 H, $J = 11, 2$ Hz), 5.82 (t, 1 H, $J = 10$ Hz, C4-H).

5-Methylhex-3(*E*)-en-1-yne ((3*E*)-4): ¹H NMR δ 1.01 (d, 6 H, $J = 6.8$ Hz, CH₃), 2.36 (m, 1 H, C5-H), 2.78 (d, 1 H, $J = 2$ Hz, C1-H), 5.41 (d, 1 H, $J = 17$ Hz, C3-H), 6.23 (dd, 1 H, $J = 6.8, 16$ Hz, C4-H).

7-Methyloct-5-en-3-yn-1-ols (5). 5-Methylhex-3-en-1-yne (8.1 g, 86 mmol; a mixture of 3*Z* and 3*E* isomers), dissolved in 50 mL of dry ether, was placed in a 500-mL three-necked round-bottomed flask equipped with a magnetic stirrer, a dry ice condenser, a serum cap, and a nitrogen inlet. The flask was cooled to –78 °C with dry ice–acetone, and 48 mL of 1.7 M *tert*-butyllithium (86 mmol) was slowly injected into the flask. At the end of the addition, the solution turned light yellow. The flask was warmed to 0 °C, and stirring was continued for a further 10 min. Diethylaluminum chloride (48 mL of a 1.8 M solution in toluene, 86 mmol) was then added dropwise through a syringe. A copious white precipitate formed in 5 min. The flask contents were stirred for 30 min at 0 °C, and excess ethylene oxide (7.5 g, 8.6 mL, 0.17 mol, 2 equiv) was then placed in the flask with a Pasteur pipet, while the reaction mixture was cooled at –78 °C. After being stirred for a further 1.5 h at 0 °C, the contents were carefully poured into 200 mL of 10% HCl. The addition was very exothermic and the precipitates dissolved. The mixture was extracted with ether (2 \times 100 mL); the organic layers were combined, washed with 100 mL of saturated NaHCO₃, dried (MgSO₄), filtered, and concentrated by rotary evaporation. Alcohol **5**, 8.5 g (72%), obtained by distillation with a 20-cm Vigreux column, had bp 120–122 °C (30 mm). The cis and trans isomers were separated by preparative GC with column A.

7-Methyloct-5(*Z*)-en-3-yn-1-ol ((5*Z*)-5): ¹H NMR δ 1.00 (d, 6 H, $J = 6.7$ Hz, CH₃), 1.75 (t, 1 H, $J = 6.2$ Hz, OH), 2.61 (dt, 1 H, $J = 2.1$ Hz, 6.3 Hz, C2-H), 2.80–2.92 (m, 1 H, C7-H), 3.74 (apparent quartet, 2 H, $J = 6$ Hz, C1-H), 5.33 (dt, 1 H, $J = 2, 11$ Hz, C5-H), 5.69 (t, 1 H, $J = 10.2$ Hz, C6-H); MS, m/z (relative intensity) 138 (35, M⁺), 91 (100), 79 (97), 77 (79).

7-Methyloct-5(*E*)-en-3-yn-1-ol ((5*E*)-5): ¹H NMR δ 1.00 (d, 6 H, $J = 6.8$ Hz, CH₃), 1.76 (br s, 1 H, OH), 2.28–2.40 (m, 1 H, C7-H), 2.57 (dt, 1 H, $J = 6, 1$ Hz, C2-H), 3.72 (t, 2 H, $J = 6$ Hz, C1-H), 5.42 (d, 1 H, $J = 15.9$ Hz, C5-H), 6.09 (dd, 1 H, $J = 6.8$ Hz, 16 Hz). MS, m/z (relative intensity) 138 (41, M⁺), 91 (100), 79 (95), 77 (74).

7-Methylocta-3(*Z*),5(*Z*)- and -3(*Z*),5(*E*)-dien-1-ols ((3*Z*,5*Z*)-6 and (3*Z*,5*E*)-6). A 250-mL three-necked round-bottomed flask was equipped with a dry ice–acetone condenser, a serum cap, and a nitrogen inlet and was cooled to 0 °C. 2-Methyl-2-butene (18.1 g, 27.3 mL, 0.258 mol) and 50 mL of dry THF were placed in the flask, and borane–dimethyl sulfide complex (12.9 mL of a 10 M solution, 0.129 mol) was injected into the flask. The contents were stirred at 0 °C for 2 h. To the resulting disiamylborane was added with a syringe 6 g (43 mmol) of 7-methyl-5-octen-3-yn-1-ol, and the reaction mixture was stirred for 75 min at 0 °C. Glacial acetic acid (20 mL) was added to the reaction mixture, and the flask contents were stirred at room temperature overnight. The next morning, sodium hydroxide solution (20 g in 20 mL of water) was added, followed by the slow dropwise addition of 20 mL of 30% hydrogen peroxide. After the reaction mixture was stirred for a further 30 min at room temperature, the top layer was separated, and the aqueous layer was extracted with two 100-mL portions of ether. The combined organic layers were washed with 100 mL of 10% HCl and 100 mL of saturated sodium bicarbonate solution, dried (MgSO₄), and filtered. The solvents were removed by rotary evaporation, and the alcohols (3*Z*,5*Z*)-6 and (3*Z*,5*E*)-6 (4.8 g, 80%) were distilled: bp 110–111 °C (40 mm). The same procedure was adapted for small-scale reactions with gas chromatographically purified (5*Z*)-5 and (5*E*)-5 to obtain analytically pure samples of the products, since these alcohols were not easily separated by GC.

7-Methylocta-3(*Z*),5(*Z*)-dien-1-ol ((3*Z*,5*Z*)-6): ¹H NMR δ 0.98 (d, 6 H, $J = 6.6$ Hz, CH₃), 2.46 (apparent quartet, 2 H, $J = 6.6$ Hz, C2-H), 2.79 (m, 1 H, C7-H), 3.68 (t, 2 H, $J = 6.3$ Hz, C1-H), 5.33 (t, 1 H, $J = 10.2$ Hz, C6-H), 5.45 (apparent quartet, 1 H, C3-H), 6.15 (t, 1 H, $J = 11.2$ Hz, C5-H), 6.43 (t, 1 H, $J = 11$ Hz, C4-H); MS, m/z (relative intensity) 140 (31, M⁺), 67 (100), 41 (61).

7-Methylocta-3(*Z*),5(*E*)-dien-1-ol ((3*Z*,5*E*)-6): ¹H NMR δ 1.02 (d, 6 H, $J = 6.8$ Hz, CH₃), 2.37 (apparent septet, 1 H, $J = 6.6$ Hz, C7-H),

(23) Hess, B. A., Jr.; Schaad, L. J.; Pancif, J. *J. Am. Chem. Soc.* **1985**, *107*, 149–154. Professors B. A. Hess, Jr. and L. J. Schaad, private communication.

(24) In conjunction with parallel theoretical work on this isomerization by Professors Hess and Schaad.

2.48 (apparent quartet, 2 H, $J = 6.6$ Hz, C2-H), 3.69 (t, 2 H, $J = 6.2$ Hz, C1-H), 5.32 (q, 1 H, $J = 7.7$ Hz, C3-H), 5.70 (dd, 1 H, $J = 7, 15$ Hz, C6-H), 6.13 (t, 1 H, $J = 11$ Hz, C4-H), 6.30 (dd, 1 H, $J = 11, 15$ Hz, C5-H). MS, m/z (relative intensity) 140 (37, M^+ , 67 (100), 107 (62), 41 (57).

7-Methylocta-1,3(Z),5(Z)- and -1,3(Z),5(E)-trienes (1 and 7). 7-Methylocta-3(Z),5-dien-1-ol (0.5 g, 3.5 mmol; a 1:1 mixture of 5Z and 5E isomers) was allowed to react with methanesulfonyl chloride (0.49 g, 4.2 mmol, 1.2 equiv) in dry ether in the presence of triethylamine at 0 °C for 5 min. The reaction mixture was then poured into 50 mL of water and the hydrolysate was extracted with ether. The organic extracts were washed with 10% HCl (50 mL) and saturated NaHCO_3 (50 mL), dried (MgSO_4), filtered, and concentrated to provide the crude mesylates, pure according to NMR. This mixture of mesylates was redissolved in 3 mL of dry ether and excess potassium *tert*-butoxide (1.2 g, 11 mmol) was added. The reaction mixture was kept at 0 °C, and 3 mL of dry DMSO was added slowly. The reaction mixture was stirred for 5 min and then poured into 100 mL of water and extracted with ether (2 \times 50 mL). The organic layers were washed with 10% HCl (2 \times 50 mL) and saturated sodium bicarbonate (2 \times 50 mL), dried (MgSO_4), and filtered. The filtrate was concentrated by rotary evaporation, and the residue was purified by flash chromatography on a small silica gel column, with pentane as eluant. The resulting mixture of **1** and **7** was used for the thermolysis studies as a dilute solution in 2-methylpentane. Pure samples were obtained from reactions with gas chromatographically purified precursor alcohols.

7-Methylocta-1,3(Z),5(Z)-triene (1): $^1\text{H NMR}$ δ 0.99 (d, 6 H, $J = 6.6$ Hz, CH_3), 2.73–2.88 (m, 1 H, C7-H), 5.13 (d, 1 H, $J = 10$ Hz, C1-cis-H), 5.23 (d, 1 H, $J = 16.8$ Hz, C1-trans-H), 5.35 (t, 1 H, $J = 9.6$ Hz, C6-H), 5.99 (t, 1 H, $J = 10.4$ Hz, C3-H), 6.22–6.36 (pair of overlapping triplets, 2 H, C4-H, C5-H), 6.74–6.89 (m, 1 H, C2-H); MS, m/z (relative intensity) 122 (33, M^+), 79 (100), 91 (54), 107 (35).

7-Methylocta-1,3(Z),5(E)-triene (7): $^1\text{H NMR}$ δ 1.03 (d, 6 H, 6.7 Hz, CH_3), 2.38 (m, 1 H, C7-H), 5.11 (d, 1 H, $J = 10.5$ Hz, C1-trans-H), 5.2 (d, 1 H, $J = 16.6$ Hz, C1-cis-H), 5.72 (dd, 1 H, $J = 15, 7$ Hz, C6-H), 5.86–6.00 (overlapping triplets, 2 H, C3-H, C4-H), 6.46 (dd, 1 H, $J = 11$ and 15 Hz, C5-H), 6.81 (m, 1 H, C2-H); MS, m/z (relative intensity) 122 (32, M^+), 79 (100), 91 (45), 107 (22).

2-Deuterio-2-methylpropanal. According to a published procedure,¹⁵ 2-methylprop-1-enyl acetate²⁵ was reacted with D_2O (99.8 atom %, Aldrich) and a catalytic amount of D_2SO_4 (99.5+%, Aldrich) to provide 2-deuterio-2-methylpropanal. A $^1\text{H NMR}$ spectrum showed no signal for residual methine hydrogen.

Condensation of this deuterium-labeled aldehyde with propargylmagnesium bromide, following the procedure given above for reaction with the analogous unlabeled aldehyde, gave 5-methylhexyn-4-ol-5-*d*: $^1\text{H NMR}$ δ 0.92 (s, 3 H, cis- CH_3), 0.96 (s, 3 H, trans- CH_3), 1.95 (d, 1 H, $J = 4.9$ Hz, OH), 2.04 (t, 1 H, $J = 2.6$ Hz, C1-H), 2.29–2.48 (m, 2 H, C3-H), 3.47–3.52 (br m, 1 H, C4-H). There was no $^1\text{H NMR}$ absorption at 1.75–1.83 ppm, characteristic of C5-H. Further reactions following the sequence shown in Scheme I gave the corresponding mono-deuterio compounds.

5-Methyl-4-[(tolylsulfonyl)oxy]hexyne-5-*d*: $^1\text{H NMR}$ δ 0.83 (s, 3 H, cis- CH_3), 0.87 (s, 3 H, trans- CH_3), 1.93 (t, 1 H, $J = 2.6$ Hz, C1-H), 2.44 (s, 3 H, benzylic CH_3), 2.55 (dd, 2 H, $J = 2.6, 6.0$ Hz, C3-H), 4.41 (t, 1 H, $J = 6.0$ Hz, C4-H), 7.33 (d, 2 H, $J = 8.1$ Hz, aromatic), 7.80 (d, 2 H, $J = 8.2$ Hz, aromatic).

5-Methylhex-3(Z)-en-1-yne-5-*d*: $^1\text{H NMR}$ δ 1.00 (s, 6 H, CH_3), 3.05 (d, 1 H, $J = 2$ Hz, C1-H), 5.33 (dd, 1 H, $J = 2.3, 10.8$ Hz), 5.82 (d, 1 H, $J = 10.4$ Hz, C4-H).

5-Methylhex-3(E)-en-1-yne-5-*d*: $^1\text{H NMR}$ δ 1.00 (s, 6 H, CH_3), 2.78 (d, 1 H, $J = 2.1$ Hz, C1-H), 5.42 (dd, 1 H, $J = 2.1, 16$ Hz, C3-H), 6.23 (d, 1 H, $J = 16$ Hz, C4-H).

7-Methyloct-5-en-3-yn-1-ol-7-*d* was obtained as a mixture of 5Z and 5E isomers: $^1\text{H NMR}$ δ 0.99 (s, 6 H, CH_3), 1.59–1.81 (overlapping triplets, OH), 2.54–2.64 (two overlapping dt, C2-H), 3.69–3.77 (apparent quartet, C1-H), 5.33 (dt, $J = 2, 10.7$ Hz, 5Z-C5-H), 5.42 (dt, $J = 1.4$ Hz, 16 Hz, 5E-C5-H), 5.69 (d, $J = 10.7$ Hz, 5Z-C6-H), 6.08 (d, $J = 15.95$ Hz, 5E-C6-H).

7-Methylocta-3(Z),5(Z)- and 3(Z),5(E)-dien-1-ol-7-*d*: $^1\text{H NMR}$ δ 0.97 (s, CH_3), 1.00 (s, CH_3), 2.42–2.49 (overlapping quartets, C2-H), 3.65–3.70 (overlapping triplets, C1-H), 5.26–5.40 (overlapping signals for 5Z-C6-H and 5Z-C3-H), 5.42–5.49 (apparent quartet, 1 H, 5Z-C3-H), 5.69 (d, 1 H, $J = 15.2$ Hz, 5E-C6-H), 6.07–6.18 (overlapping t for 5Z-C5-H and 5E-C4-H), 6.29 (dd, $J = 11, 15$ Hz, 5E-C5-H), 6.42 (t, $J = 11$ Hz, 5Z-C4-H).

7-Methylocta-1,3(Z),5(Z)- and 1,3(Z),5(E)-triene-7-*d*: $^1\text{H NMR}$

δ 0.98 (s, 5Z- CH_3), 1.02 (s, 5E- CH_3), 5.09–5.26 (overlapping peaks for C1-H), 5.36 (d, $J = 9.4$ Hz, 5Z-C6-H), 5.72 (d, $J = 15.1$ Hz, 5E-C6-H), 5.86–6.03 (overlapping peaks for C3-H, 5E-C4-H), 6.22–6.37 (pair of overlapping t, 5Z-C4-, C5-H), 6.46 (dd, $J = 15, 10.3$ Hz, 5E-C5-H), 6.75–6.88 (m, C2-H).

2(Z)-Butenal. 2(Z)-Buten-1-ol (0.5 g, 6.9 mmol, bp 121 °C), obtained by the Zn/Cu couple reduction of 2-butyne-1-ol,¹⁶ was added to 5 g of activated manganese dioxide (57 mmol, Aldrich) suspended in 50 mL of dichloromethane. Finely powdered 4A molecular sieves (3 g) were then added, and the mixture was magnetically stirred at room temperature. After 3 min, the reaction was 90% complete, as judged by capillary GC. The MnO_2 was immediately filtered, the filtrate was quickly dried (MgSO_4) and filtered, and the filtrate was used directly for the subsequent reaction. An analytical sample was obtained by preparative GC with column C at room temperature. 2(Z)-Butenal: $^1\text{H NMR}$ δ 2.18 (dd, 3 H, $J = 1.6, 7.4$ Hz, CH_3), 5.96–6.02 (br t, 1 H, C2-H), 6.67–6.79 (m, 1 H, C3-H), 10.13 (d, 1 H, $J = 8.1$ Hz, C1-H). The $^1\text{H NMR}$ spectrum also showed the presence of about 5% of 2(E)-butenal.

2-Methylocta-2,4(Z),6(Z)- and -2,4(E),6(Z)-trienes (2 and 8). (3-Methyl-2-butenyl)triphenylphosphonium bromide (3.12 g, 7.60 mmol) was suspended in 100 mL of dry ether at 0 °C. *tert*-Butyllithium (4.5 mL of a 1.7 M solution in pentane, 7.6 mmol) was then syringed into the flask dropwise. An instantaneous orange-red color developed after the addition of the *tert*-butyllithium, and stirring was continued for 5 min at 0 °C. The solution of 2(Z)-butenal in CH_2Cl_2 from the preparation described above was added to the reaction mixture, and stirring was continued at 0 °C for 6 h. The reaction mixture was poured into 150 mL of water, and the hydrolysate was extracted with ether. The organic layers were washed with 100 mL of 10% HCl and 100 mL of saturated sodium bicarbonate, dried (MgSO_4), filtered, and concentrated. The residue was passed through a short silica gel column, and the pentane eluate was concentrated by evaporation to leave **2** and **8** in a 3:2 ratio along with minor amounts of isomers of **9** and **10**, formed from the 2(E)-butenal in the starting aldehyde. The isomers **2** and **8** were obtained in pure form by preparative GC with column D.

2-Methylocta-2,4(Z),6(Z)-triene (2): $^1\text{H NMR}$ δ 1.77 (d, 3 H, $J = 5.7$ Hz, CH_3), 1.78 (s, 3 H, CH_3), 1.83 (s, 3 H, CH_3), 5.56 (m, 1 H, C7-H), 6.16–6.34 (m, 3 H, C3, C4, C5-H), 6.49 (apparent t, 1 H, $J = 10.6$ Hz, C6-H); MS, m/z (relative intensity) 122 (38, M^+), 107 (100), 79 (58), 91 (76), 77 (34).

2-Methylocta-2,4(E),6(Z)-triene (8): $^1\text{H NMR}$ δ 1.76 (d, 3 H, $J = 6.85$ Hz, C8-H), 1.77 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3), 5.39–5.50 (m, 1 H, C7-H), 5.86–5.92 (br d, C3-H), 6.03–6.11 (br t, C6-H), 6.37–6.41 (apparent dd, 2 H, C4, C5-H); MS, m/z (relative intensity) 122 (41, M^+), 107 (100), 79 (59), 91 (82), 77 (37).

2-Methylocta-2,4(Z),6(E)- and 2,4(E),6(E)-trienes (9 and 10). By the procedure detailed above, the ylide from (3-methyl-2-butenyl)triphenylphosphonium bromide (5.87 g, 14 mmol) was reacted with *trans*-crotonaldehyde (1 g, 14 mmol) to afford trienes **9** and **10**. These trienes were subsequently separated by preparative GC with column D at a column temperature of 60 °C.

Triene 9: $^1\text{H NMR}$ δ 1.76 (s, 3 H, CH_3), 1.79 (d, $J = 7.1$ Hz, C8-H), 1.83 (s, 3 H, CH_3), 5.70 (dq, 1 H, $J = 14.8$ Hz, 6.6 Hz, C7-H), 5.86 (t, 1 H, $J = 11$ Hz, C5-H), 6.04 (t, 1 H, $J = 11$ Hz, C4-H), 6.27 (d, 1 H, $J = 11.5$ Hz, C3-H), 6.53 (t, 1 H, $J = 13$ Hz, C6-H); MS, m/z (relative intensity) 122 (39, M^+), 107 (100), 91 (81), 79 (61).

Triene 10: $^1\text{H NMR}$ δ 1.75–1.78 (apparent d, 6 H, CH_3), 5.59–5.7 (m, 1 H, C7-H), 5.83 (d, 1 H, $J = 11$ Hz, C3-H), 6.02–6.20 (m, 2 H, C6-H, C5-H), 6.30 (t, 1 H, $J = 12.4$ Hz, C4-H); MS, m/z (relative intensity) 122 (41, M^+), 107 (100), 91 (80), 79 (58).

Preparative Thermal Isomerization of 7-Methylocta-1,3,5-trienes. A 0.1 M mixture of trienes **1** and **7** was heated in refluxing hexane for 24 h. The 7-deuterated analogues were similarly heated as a dilute solution in hexane for 72 h. Analyses of these reaction mixtures by capillary GC showed that all the 5Z isomers (**1** and **1-d**) had reacted to give 2-methylocta-2,4(Z),6(Z)-triene **2** or **2-d** while the 5E isomers (**7** and **7-d**) remained unchanged. The retention times of the new products **2** and **2-d** were identical with the times found for an authentic, independently prepared sample of **2**. Preparative GC using a Carbowax column at ambient column temperature and a detector temperature of 125 °C furnished pure **2** having a $^1\text{H NMR}$ spectrum identical with a spectrum of the authentic compound, prepared independently as described above, while purified **2-d** had the NMR spectrum reported below.

In another experiment, a sealed-tube thermolysis of a mixture of **1** and **7** in 2-methylpentane was carried out at 185 °C for 16 min; it was found that the 5E isomer (**7**) had reacted to give 5-(2-methylethyl)cyclohexa-1,3-diene (**11**), while the 5Z isomer (**1**) gave an equilibrium mixture of 2-methylocta-2,4(Z),6(Z)- and -2,4(Z),6(E)-octatrienes (**2** and **9**) in a ratio of 1:2.5. These products were separated by preparative GC to secure samples for $^1\text{H NMR}$ spectra, with column B at ambient tem-

(25) Benzra, C.; Barbier, P. *J. Org. Chem.* **1983**, *48*, 2705–2709. Be-doukian, P. Z. *J. Am. Chem. Soc.* **1944**, *66*, 1325–1327.

perature and a detector temperature of 125 °C; the retention times of compounds **11**, **2**, and **9** were 2.6, 10.5, and 11.5 min, respectively. Compounds **2** and **9** showed broad, overlapping peaks, and only 90% pure **9** was isolated. Similar thermal behavior was observed for the 7-deuterated analogues.

5-(2-Methylethyl)cyclohexa-1,3-diene (11): $^1\text{H NMR}$ δ 0.89 (d, 3 H, $J = 3.5$ Hz, CH_3), 0.91 (d, 3 H, $J = 3.5$ Hz, CH_3), 1.59–1.78 (m, 1 H, CHMe_2), 2.04–2.21 (m, 3 H, C5-H, C6-H), 5.67–5.92 (m, 4 H, olefinic H); MS, m/z (relative intensity) 122 (15, M^+), 79 (100), 78 (39), 77 (34).

5-(2-Methylethyl-2-d)cyclohexa-1,3-diene: $^1\text{H NMR}$ δ 0.89 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3), 2.04–2.20 (m, 3 H, C5-H, C6-H), 5.63–5.92 (m, 4 H, olefinic H); MS, m/z (relative intensity) 123 (18, M^+), 79 (100), 78 (42), 77 (33).

2-Methylocta-2,4(Z),6(Z)-triene-8-d (2-d): $^1\text{H NMR}$ δ 1.77 (d, 2 H, $J = 5.8$ Hz, CH_2D), 1.78 (s, 3 H, cis- CH_3), 1.83 (s, 3 H, trans- CH_3), 5.55 (apparent quartet, 1 H, C7-H), 6.12–6.33 (m, 3 H, C3, C4, C5-H), 6.48 (apparent t, 1 H, C6-H). MS, m/z (relative intensity) 123 (52, M^+), 108 (100), 92 (43), 91 (59), 79 (37).

2-Methyl-2,4(Z),6(E)-octatriene-8-d: $^1\text{H NMR}$ δ 1.76 (s, 3 H, CH_3), 1.79 (d, 3 H, $J = 7.1$ Hz, C8-H), 1.83 (s, 3 H, CH_3), 5.70 (dt, 1 H, $J = 6.6$ Hz, 14.3 Hz, C7-H), 5.86 (t, 1 H, $J = 11$ Hz, C5-H), 6.04 (t, 1 H, $J = 11$ Hz, C4-H), 6.27 (d, 1 H, $J = 11.2$ Hz, C3-H), 6.52 (t,

1 H, $J = 13$ Hz, C6-H); MS, m/z (relative intensity) 123 (54, M^+), 108 (100), 92 (42), 91 (58), 79 (37).

Kinetic Measurements. Kinetics of the thermal isomerizations were measured with ca. 1% solutions of trienes in 2-methylpentane. Typically 16 μL of the triene solution was placed in each of a series of 0.5-mm capillary tubes, cooled to -78 °C, and sealed either directly or after establishing an argon atmosphere. These ampules were heated in an oil bath fitted with a mechanical stirrer, heating elements controlled by a Model 253 Bayley precision temperature controller, a metal wire basket for holding the tubes, and a Hewlett-Packard 2802A digital thermometer. The temperature of the bath was maintained to ± 0.02 °C. Samples were withdrawn at appropriate time intervals, cooled in liquid nitrogen or dry ice-acetone, and analyzed by integrating peaks at 4.17 min (1 or 1-d) and at 7.73 min (2 or 2-d) on the phenyl methyl silicone capillary GC column. Each thermolysis reaction mixture was analyzed at least three times. The averaged values are reported in Table I.

Acknowledgment. We are indebted to the National Science Foundation for support of our work on hydrocarbon rearrangements, and to Professors B. A. Hess, Jr., M. M. Kreevoy, Y. Mazur, W. H. Saunders, Jr., and L. J. Schaad for helpful discussions and correspondence.

Communications to the Editor

Biosynthesis of the Unusual Amino Acid 5-Hydroxy-4-oxonorvaline

Robert L. White,* Alphonse C. DeMarco, and
Kevin C. Smith

Department of Chemistry, Acadia University
Wolfville, Nova Scotia, Canada BOP 1X0

Received July 5, 1988

Non-protein amino acids, as a group of natural products, possess a wide array of chemical structures and biological activities, but extensive biosynthetic investigations are limited to a few members of this group of unusual amino acids.¹ The hydroxyketone-containing amino acid, 5-hydroxy-4-oxonorvaline (HON, **3**),² possesses antitubercular³ and antifungal⁴ properties, and we now report results which demonstrate that the initial step in the biosynthetic formation of this unusual amino acid is analogous to the proposed initial step in the biosynthesis of carbapenem antibiotics.⁵

In a typical experiment (Figure 1), an aqueous solution of ^{13}C -labeled substrate (8 mmol) was administered in two equal portions (one at the onset of HON production⁶ and the second 24 h later) to *Streptomyces akiyoshiensis* (ATCC 13480) in 500 mL of medium⁸ containing starch and Pharmamedia. After an additional 24 h of incubation, the cells were removed by centri-

fugation, and HON (ca. 2 mmol) was obtained from the resulting culture broth in one of two ways.² In experiments 1, 2, and 4, HON was isolated directly from the charcoal-treated culture broth by cation exchange chromatography (Amberlite IR-120) and separated from acidic amino acids by anion exchange chromatography (Dowex 1-X8). For further purification and subsequent ^{13}C NMR analysis, HON was converted by NaIO_4 cleavage to aspartate and formaldehyde (isolated as its dimethone derivative).⁹ For experiments 3 and 5, in which doubly labeled precursors were used, NaBH_4 was added to the culture broth to reduce HON to a mixture of two diastereomers of 4,5-dihydroxynorvaline which were isolated by ion-exchange chromatography and converted in concentrated HCl to a corresponding mixture of diastereomeric γ -lactone hydrochloride salts² for purification by recrystallization and ^{13}C NMR analysis.

The results of five separate feeding experiments with sodium [$1\text{-}^{13}\text{C}$]-, [$2\text{-}^{13}\text{C}$]-, and [$1,2\text{-}^{13}\text{C}_2$]acetates¹⁰ and DL-[$4\text{-}^{13}\text{C}$]-¹⁰ and DL-[$2\text{-}^{13},^{15}\text{N}$]aspartates are presented in Figure 1. The pattern of ^{13}C enrichment and ^{13}C - ^{13}C coupling observed in HON, obtained from the three experiments which used labeled acetates as substrates, showed that C-1 to C-4 of HON are derived from a 4-carbon intermediate of the citric acid cycle and that C-5 is derived directly from the methyl carbon of acetate. The nature of the 4-carbon precursor was probed by feeding DL-[$4\text{-}^{13}\text{C}$]aspartate. The principal incorporation of ^{13}C label (3.4 times natural abundance) into C-4 of HON demonstrated that oxaloacetate, malate, or aspartate, and not a symmetrical 4-carbon intermediate of the citric acid cycle, serves as the 4-carbon precursor to HON. The smaller ^{13}C enrichment (1.5 times natural abundance) observed at C-1 of HON would be expected if a portion of the administered DL-[$4\text{-}^{13}\text{C}$]aspartate had been converted to a symmetrical citric acid cycle intermediate (e.g., fumarate) either via oxaloacetate and malate or directly by the action of aspartate ammonia lyase.¹¹ Aspartate, synthesized from fumarate formed

(1) Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; pp 55–138.

(2) Miyake, A. *Chem. Pharm. Bull.* **1960**, *8*, 1071–1073.

(3) Kanazawa, K. I.; Tsuchiya, K.; Araki, T. *Am. Rev. Respirat. Diseases* **1960**, *81*, 924.

(4) Watanabe, S.; Numata, K.; Omura, S.; Yamaguchi, H. *Jpn. Kokai Tokkyo Koho JP 61 243 018* [86 243 018], 1986; *Chem. Abstr.* **1987**, *106*, 72944r.

(5) Williamson, J. M.; Inamine, E.; Wilson, K. E.; Douglas, A. W.; Liesch, J. M.; Albers-Schonberg, G. *J. Biol. Chem.* **1985**, *260*, 4637–4647.

(6) HON production by *S. akiyoshiensis* and the ion-exchange chromatography of amino acids were monitored by using a modified procedure (White, R. L.; DeMarco, A. C., unpublished results) of the *o*-phthalaldehyde precolumn HPLC method.⁷

(7) Jones, B. N.; Gilligan, J. P. *J. Chromatogr.* **1983**, *266*, 471–482.

(8) Miyoshi, T.; Miyairi, N.; Aoki, H.; Kohsaka, M.; Sakai, H.-I.; Imanaka, H. *J. Antibiot.* **1972**, *25*, 569–575.

(9) The four carbons of aspartate correspond to C-1 to C-4 of HON, respectively, and the carbon in formaldehyde corresponds to C-5 of HON. ^{13}C Enrichments were calculated for the carbon derived from HON in formaldehyde dimethone, relative to the natural abundance ^{13}C signals provided by the dimedone reagent, and for the carbons in aspartate, relative to the carboxyl signal of disodium malonate which was added as an internal standard.

(10) Obtained from MSD Isotopes, Montreal, Canada.