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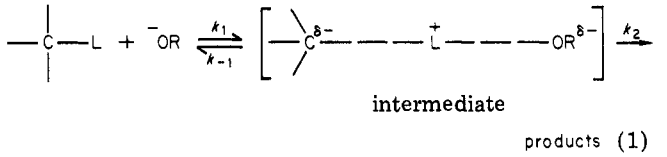
Evidence for Proton Tunneling in Strong Base Promoted (Stepwise) β-Elimination Reactions

Summary: In the case of a single-step, strong base promoted β elimination, tunneling is recognized by a temperature-dependent isotope effect in which $[\Delta E_a]_D^H \gg [\Delta E_0]_D^H$ and $A_H/A_D \ll 0.7$. In a multistep, ElcB-like reaction of methyl 2-methyl-2-bromo-3-phenylpropionate with $NaOCH_3$ it is found that k_H/k_D is temperature independent over a nearly 70 °C range ($[\Delta E_a]_D^H \approx 0$, $A_H/A_D = 1.197$). An appropriate computer program was applied to model the overall mechanism based on a scheme resembling that devised by Streitweiser and further developed by Koch and Dahlberg. The activation parameters computed from the best solution fit to the experimental isotope effect data are consistent with a mechanism of elimination in which the first step is reversible H tunneling through a narrow reaction barrier into the narrow potential well of a hydrogen-bonded intermediate complex. The reaction TS*, arising from this intermediate and having a potential well of nearly the same dimensions as that for the initial complex of base and substrate, accounts for $[\Delta E_a]_D^H \approx 0$. The α secondary deuterium isotope effect measured for the analogous substrate **3** (where CH_3 in **2** has been replaced by deuterium) shows $(k_H/k_D)_\alpha = 1.08$. This result is interpreted to indicate a reactant-like TS*.

Sir: The occurrence of proton tunneling in the course of some E-2 (one step) elimination reactions has been demonstrated by Shiner and Smith.[1] This conclusion stems from their determination of the isotopic activation parameters for the reaction of 1-bromo-2-phenylpropane (**1**): $[\Delta E_0]_D^H \ll [\Delta E_a]_D^H \approx 1.79$ kcal/mol and $A_H/A_D \approx 0.44$; i.e., $k_H/k_D = 0.44 \exp(1790/RT)$, a temperature dependent isotope effect which is the usual means of recognizing tunneling in a single-step, linear H-transfer process.[2] The question to be addressed here is concerned with the identification of tunneling in a *multistep* process in which H transfer is less than fully completed in the transition state (TS*). The KIE values in a somewhat similar processes have been suggested by Streitwieser[3] to be anomalous and attributable to internal return. Recently Koch and Dahlberg[4,5] have discussed a computer-modeling technique for evaluating the various activation parameters involved in such ElcB-like, β-elimination processes promoted by alkoxide bases which can be characterized by the two-step mechanism expressed by eq 1, where L = H or D. We have applied a very similar approach for estimating the isotopic activation parameters prevailing in the methoxide-promoted β-elimination reaction of a substrate, $C_6H_5CHD–C(CH_3)Br–COOCH_3$ (**2**), somewhat analogous to **1** and under reaction conditions for which Shiner[1] has identified tunneling.



(1)

In choosing **2** as the substrate, we reasoned that the $COOCH_3$ substituent would tend to promote an ElcB mechanism, while the benzylic hydrogen would be enhanced compared to that in **1** in its susceptibility to tunneling via strong base abstraction. The $COOCH_3$ was also intended to suppress the possibility for ion-pair development at the α-carbon which might foster a competing $E2_{ip}$ mechanism.[6]

Table I. Primary KIE in the Dehydrobromination of $C_6H_5CHD-(CH_3)Br-COOCH_3$ (2) with $NaOCH_3$ in CH_3OH Solution[a]

temp ± 0.05 °C	exptl[b] k_H/k_D	calcd[c] k_H/k_D	% difference[d]	variance[e] × 10^6
66.3	1.221 ± 0.001	1.226	0.163	4
79.0	1.237 ± 0.003	1.227	0.081	1
89.7	1.225 ± 0.001	1.227	0.081	1
101.5	1.233 ± 0.001	1.227	0.081	1
110.7	1.227 ± 0.004	1.227	0.081	1
121.1	1.229 ± 0.003	1.227	0.081	1
133.5	1.227 ± 0.006	1.227	0.081	1

[a] Sum of variances = 1.0×10^{-5}. The k_H/k_D experimental mean value = 1.228 ± 0.005 for 140 000 determinations. Runs were made by using equimolar (0.01 M) solutions of $NaOCH_3$ and **2** in methanol in serum-capped pressure bottles. The small quantity of pure **2** was rapidly injected under stirring after the base solution had equilibrated in the thermostat to ensure that the temperature of reaction was constant and uniformly maintained throughout the run. The product consisting principally of a mixture of deuterated and undeuterated cinnamate ester was worked up after drowning the reaction in ice-water, extraction with pentane, drying, stripping the solvent, and isolation by a preparative GLC procedure. [b] The D content of each sample was determined by the mass spectroscopic procedure previously described.[11] The parent peaks of the substrates analyzed were scanned 20 000 times per sample to yield a mean value of the M_{176}/M_{177} amu ratio. For methyl α-methylcinnamate the M_{H+1}/M_H amu ratio is 0.207. For methyl β-deuterio-α-methylcinnamate the M_{D-1}/M_D amu ratio is 0.238. The correction made for the measured isotope ratio M_{176}/M_{177} is given by

$$M_D/M_H = 0.212(4.831 - M_{176}/M_{177})/(M_{176}/M_{177} - 0.238)$$

$$k_H/k_D = M_D/M_H$$

[c] A DBASIC program on the B-770 computer was employed to determine the (k_H/k_D) calculated values. Numerous iterations were performed by using the kinetic expressions derived previously[4,5] until the solution with the lowest sum of variances was reached. The parameters listed beneath Figure 1 were arrived at simultaneously. [d] Percent difference = difference/1.197 × 100. [e] Variance = (difference)².

(1) Shiner, V. J., Jr.; Smith, M. L. *J. Am. Chem. Soc.* **1961**, *83*, 593.
(2) (a) Kwart, H.; Nickle, J. H. *J. Am. Chem. Soc.* **1976**, *98*, 2881. (b) Janssen, J. W. A. M.; Kwart, H. *J. Org. Chem.* **1977**, *42*, 1530. (c) Kwart, H.; George, T. J.; Louw, R.; Ultee, W. *J. Am. Chem. Soc.* **1978**, *100*, 3927. (d) Kwart, H.; George, T. J. *J. Org. Chem.* **1979**, *44*, 162. (e) Kwart, H.; Kwart, L. D.; Horgan, A. G. *J. Am. Chem. Soc.* **1981**, *103*, 1232. (f) Kwart, H.; Horgan, A. G.; George, T. J. *J. Org. Chem.* **1981**, *46*, 1970.
(3) Streitwieser, A., Jr.; Hollyhead, W. B.; Sonnichsen, G.; Pudjaatmaka, A. H.; Chang, C. J.; Kruger, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 5096.
(4) Koch, H. F.; Dahlberg, D. B. *J. Am. Chem. Soc.* **1980**, *102*, 6102.
(5) Koch, H. F.; Dahlberg, D. B.; McEntee, M. F.; Klecha, C. J. *J. Am. Chem. Soc.* **1976**, 98, 1060.
(6) For a full discussion, see: Bordwell, F. G. *Acc. Chem. Res.* **1972**, *5*, 374.

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Table II. Secondary α-Deuterium Isotope Effect in the Dehydrobromination of Ethyl α-Bromo-α-L-β-phenylpropionate (3) at 0 °C

fraction of reaction completed[a]	measd isotope ratio,[b] M_{176}/M_{177}	corrected isotope ratio[c] R_{A_0}	corrected isotope ratio[d] R_{A_f}	$(k_H/k_D)_\alpha$
0	1.091 ± 0.001	0.955 ± 0.001		1.080
0.0362	1.154 ± 0.000		0.859 ± 0.000	1.080 ± 0.001
0.0758	1.156 ± 0.003		0.857 ± 0.002	1.085 ± 0.003

[a] The reaction was carried out by using a substrate mixture of 3 with L = deuterium and L = hydrogen. The procedure was quite similar to that described in Table I except the thermostat consisted of a well-stirred ice-water slurry for maintaining the 0 °C temperature in the base solution. The reaction was quenched after a predetermined period of time for which the extent of reaction was known from a previous kinetic study. The base used was NaOEt in EtOH under second-order conditions with stoichiometric amounts of the reagent. [b] Mass spectral analysis was performed as described in Table I. [c] For ethyl cinnamate, the M_{H+1}/M_H amu ratio = 0.1304. For ethyl deuteriocinnamate, the M_{D-1}/M_D amu ratio = 0.1651. The correction made for the measured isotope ratio, M_{176}/M_{177}, is

$$M_D/M_H = 0.134(7.669 - M_{176}/M_{177})/(M_{176}/M_{177} - 0.165)$$

[d] The isotope analysis of product after a known extent of reactions was computed by the procedure discussed by Bigeleisen,[12] where f = extent of reaction, $R_{A_0} = M_{heavy}/M_{light}$ at $f = 0$, and $R_{A_f} = M_{heavy}/M_{light}$ at f.

$$(k_{heavy}/k_{light} - 1) \ln\left[1 - \frac{f(1 + R_{A_0})}{1 + R_{A_f}}\right] = \ln\left[1 + \left(\frac{R_{A_0} - R_{A_f}}{R_{A_0}}\right)\frac{f(1 + R_{A_0})/(1 + R_{A_f})}{1 - f(1 + R_{A_0})/(1 + R_{A_f})}\right]$$

The data gathered through measurements of the primary deuterium isotope effect over a nearly 70 °C range are listed in Table I. They show a completely temperature independent k_H/k_D; thus $\Delta[\Delta E_a]_D^H \approx 0$ and $A_H/A_D \approx 1.2$, the latter being the maximum value expected[7b] for linear H transfer in a single-step process. Koch and Dahlberg[4] have also reported some temperature-independent k_H/k_D values observed in strong base promoted, two-step elimination reactions, but in these cases A_H/A_D was greater than 1.2, usually much greater (i.e., 2.4–4.3).

An appropriate computer program was devised to model the overall mechanism of eq 1, but no assumptions were made as to the magnitudes of the various rate constants and activation parameters.[8] Thus, the four critical activation quantities were found which corresponded to the "best solution", i.e., that having the smallest sum of the variances in computing the values of k_H/k_D at each of the temperatures for comparison with the experimental values (both) listed in Table I. Figure 1 illustrates both the physical significance of the various activation parameters and the various pertinent differences computed from the modeling data. The most relevant quantity, $[\Delta E_1]_D^H = E_1^D - E_1^H = 1.769$ kcal/mol, an estimate of the activation differences for corresponding H and D abstraction steps leading to the electrostatic or H-bonded complex intermediate, is clearly very much greater than the *maximum* activation differences for passage over j, the classical barrier for a C-L bond, determined as $[\Delta E_0]_D^H = 1.15$ kcal/mol. By coincidence, it is nearly identical with the value reported[1] for 1 where tunneling has been concluded to be the course of H abstraction. Moreover, the preexponential function $A_2/A_{-1} = 0.3$ is regarded as a confirmatory indication of tunneling; previous workers[4] have claimed that tunneling is to be recognized whenever A_2/A_{-1} is less than unity.

The reaction profile diagram in Figure 1 depicts the path of H transfer as tunneling below the classical top and through a relatively narrow reaction barrier, meaning that the reaction centers between which H transfer is occurring are very close at this juncture along the reaction coordinate. It then drops into a potential well representing an intermediate in which the proton is held electrostatically between a carbanionic and an alkoxide species, the proton thus serving to diminish the anionic charge density on each. Moreover, this well is narrower than either the ground state or the TS‡ wells because the distance over which the L is vibrating in this intermediate complex is somewhat shorter.[8] The zero-point energy difference, $[\Delta E_0]_D^H$, in this intermediate is consequently slightly greater than in either the ground state or the TS‡. Since $[\Delta E_a]_D^H = 0$ for the reaction of 2, it would appear that the potential wells of the ground state and the TS‡ are very similarly structured; most likely, this is due to the fact that the distance over which the H is vibrating between the two reaction centers is very similar in both the ground state and the TS‡. Furthermore, since no more D exchange in the substrate is found to occur in the course of the reaction of 2 than was found earlier for β-phenylethyl bromide by Skell and Hauser,[9] we see a clear indication that the act of breaking the C–H bond in the intermediate (required to effect exchange in the medium) is equivalent to following the path to the TS‡ and leading irrevocably to product.

Despite the dimensional resemblance of the ground state and the TS‡, the character of the TS‡ (product-like or reactant-like) requires independent evaluation. This has been carried out by measurement of the secondary α-deuterium isotope effect.[10] The data presented in Table II confirm an isotope effect; $k_H/k_D \approx 1.08$. Furthermore, it appears that β elimination in the α-deuterio analogue $C_6H_5CH_2CD(Br)COOCH_3$ (3) occurs more rapidly than enolization and exchange. The D content of the β-elimination product of 3 after >98% completion of reaction

(7) (a) For a discussion and further references regarding temperature-independent isotope effects in a single-step process, see: Kwart, H.; Brechbiel, M.; *J. Am. Chem. Soc.* **1981**, *103*, 4650. (b) Schneider, M. E.; Stern, M. J.; *J. Am. Chem. Soc.*, **1972**, *94*, 1517.

(8) Another way of expressing this is that tunneling occurs where a narrow barrier exists, i.e., when the centers between which H transfer occurs are close together. Thus, when the tunneling proton finds itself on the product side of the barrier, it is trapped in a complex in which it is bonded to the base *but is still within interacting distance of the carbon from which it was transferred.* This complex is the intermediate whose potential well is narrower; i.e., the distance over which it is vibrating with respect to both ^-OR and C_β is shorter than in the ground state.

(9) Skell, P. S.; Hauser, C. R. *J. Am. Chem. Soc.* **1945**, *67*, 1661.

(10) (a) Saunders, W. H.; Jr. *Chem. Scr.* **1975**, *8*, 27. (b) Asperger, S.; Ilskovac, N.; Pavlovic, D. *J. Am. Chem. Soc.* **1961**, *83*, 5032. (c) Cockerill, A. F. *Tetrahedron Lett.*, **1964**, 4913.

(11) Kwart, H.; Stanulonis, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 5249. See also ref 2.

(12) Bigeleisen, J. In "Advances In Chemical Physics"; Pregogine, I., Ed.; Interscience: New York, 1958, Vol. I.

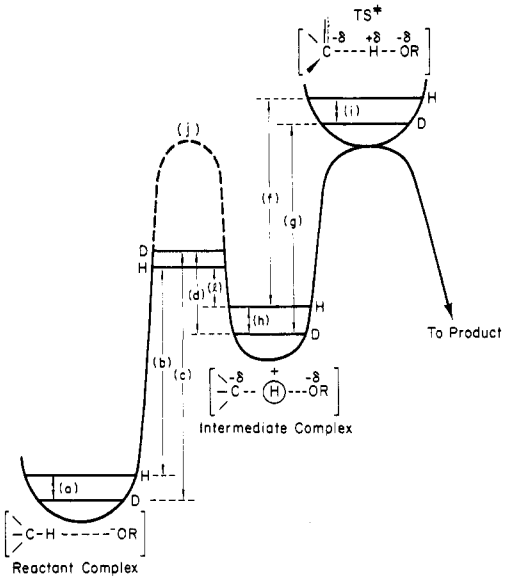

Figure 1. The activation quantities are as follows $a = [\Delta E_0]^H_D$, the ground-state zero-point energy difference for the corresponding C–H and C–D bonds to be ruptured in the TS‡ (=1.15 kcal/mol). $b = E_1^H$ = the energy requirement for reaching the level at which proton tunneling occurs. $c = E_1^D$ = the same energy term (as above) but involving deuteron tunneling. $d = E_{-1}^D$ = the energy required by the deuterated intermediate for tunneling of deuterium in the reverse direction. $e = E_{-1}^H$ = the same energy term (as above) for reverse proton tunneling. $f = E_2^H$ = the energy required by the protonated intermediate to reach the top of the barrier to its decomposition to products in the rate-determining step. $g = E_2^D$ = the corresponding energy term for the deuterated intermediate decomposition. $h = [\Delta E_0]^H_D$ (intermediate) = the zero point energy difference of H and D stretching vibrations in their respective intermediates. $i = [\Delta E_0]^H_D(TS^‡)$ = the zero-point energy difference for the corresponding C–H and C–D bonds in the TS‡ (=1.15 kcal/mol). $[\Delta E_a]^H_D$ (reaction) = $[\Delta E_0]^H_D$ (reactant) – $[\Delta E_0]^H_D(TS^‡)$; i.e., $[\Delta E_a]^H_D = a - i = 0$. j is the classical barrier to proton abstraction. The height of this barrier has been arbitrarily drawn to be approximately equal to that for decomposition of the intermediate to form product. This was done on the (perhaps unjustifiable) assumption that if the width of this barrier had been sufficient to preclude tunneling, the probabilities of the intermediate to proceed in either the forward or reverse direction were similar. The observed $k_H/k_D = 1.228$ was modeled by the internal return mechanism which assumes a significant isotope effect for the second step, i.e., $k_2^H \neq k_2^D$. The kinetic expression used is the following: Parameter values yielding the lowest sum

$$\ln\left[\frac{k^H_{calcd}}{k^D_{calcd}}\right] = \left[\frac{(E_1^D - E_{-1}^D) - (E_1^H - E_{-1}^H) + (E_2^D - E_2^H)}{RT}\right] + \ln\left[\frac{1 + (A_2/A_{-1})\exp[(E_{-1}^D - E_2^D)/RT]}{1 + (A_2/A_{-1})\exp[(E_{-1}^H - E_2^H)/RT]}\right]$$

of variances and percent differences of less than 0.21 on comparing k^H_{obsd}/k^D_{obsd} to k^H_{calcd}/k^D_{calcd} are as follows: (1) $E_2^D - E_2^H = 0.231$ kcal/mol; (2) $E_{-1}^H - E_2^H = -2.000$ kcal/mol; (3) $E_{-1}^D - E_{-1}^H = 2.000$ kcal/mol; (4) $E_1^D - E_1^H = 1.769$ kcal/mol; (5) $A_2/A_{-1} = 0.3$; (6) $E_{-1}^D - E_2^D = -0.231$ kcal/mol. These also result in values for (7) $\Delta H_1^D - \Delta H_1^H = (E_1^D - E_1^H) - (E_{-1}^D - E_{-1}^H) = -0.231$ kcal/mol. The fact that the $E_{-1}^D - E_2^D$ and the $\Delta H_1^D - \Delta H_1^H$ values are identical and opposite in magnitude to the $E_2^D - E_2^H$ value is a fortuitous circumstance that was realized after numerous computer iterations yielded the parameter values 1–5. Likewise, the equivalence of the $E_{-1}^H - E_2^H$ and the $E_{-1}^D - E_{-1}^H$ absolute values is purely the result of arriving at the "best" solution through many computer loops.

differs by less than 1% from that of the initial **3**.

This result is taken to signify that double bond development in the TS‡ has not proceeded more than halfway, i.e., much less than full sp^2 character has developed at C_α, corresponding to considerably less than complete C–Br bond breaking. In point, of fact, the $(k_H/k_D)_\alpha$ per deuterium found for **3** is even less than is reported[10b] for β-phenylethyl bromide **4**, one of the most typical E2 substrates. It can be regarded as evidence of a reactant-like structure of the TS‡. This is a somewhat surprising result, since the additional $COOCH_3$ group at C_α (compared to **4**) would be expected to encourage the development of sp^2 character. Evidently, the conjugation with a COOR group, such as it is, affords very little driving force in the development of an ElcB reaction TS‡. It is the inductive effect of this substituent which is influencing the course of elimination.

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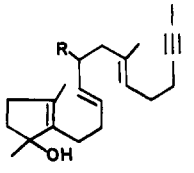
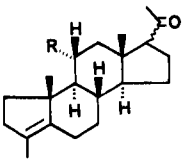
Corticoid Synthesis via Vinylic Fluoride Terminated Biomimetic Polyene Cyclizations[1]

Summary: Acid-catalyzed cyclization of substrate **8**, having a *pro-C(11)*-oxy group and a vinylic fluoride terminator, proceeds with significantly higher regio- and stereoselectively than in the case of the cyclization of the related substrate **3** with the methylacetylenic terminator to give a 58% yield of **5** which is convertible (seven steps) into hydrocortisone acetate.

Sir: By far the most important reaction in the biomimetic polyene cyclization approach to corticoids is the multiring closure step, i.e., the acid-catalyzed transformation of **2** into



1 (R = H)
2 (R = HO)
3 (R = Me_3SiO)



4 (R = H)
5 (R = AcO)

tetracyclic material, consisting mainly (after acetylation) of substance **5**. This latter material is readily converted (two steps) into 11α-hydroxyprogesterone, the key intermediate in the Upjohn method for producing hydrocortisone acetate.[2]

Recently it was disclosed[3] that the vinylic fluoride terminated cyclization **6** → **4** proceeded with exceptionally

(1) For a recent paper in the series on biomimetic polyene cyclizations see: Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512–1513.
(2) (a) Johnson, W. S.; Escher, S.; Metcalf, B. W. *J. Am. Chem. Soc.* **1976**, *98*, 1039–1041. (b) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V.M.; Yarnell, T. M. *Ibid.* **1977**, *99*, 8341–8343.
(3) Johnson, W. S.; Daub, G. W.; Lyle, T.A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800–7802.

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