nm by mixing 10 μL of the stock in 3 mL of solvent. In some runs HCl was added, but this had no effect on the rates. The decarboxylation of the anions was monitored at 230–235 nm by first adding KOH to give 0.02 M KOH prior to addition of the β-keto acid. A nonlinear least-squares analysis of the absorbance data usually gave first order rates with standard deviations of 1% of less for absorbance changes of 0.2–0.4. All runs were done at 25.0 ± 0.1 °C and were followed for 3–6 half-lives.

pK_a measurements were performed in 70% methanol/water (v/v at 25 °C) cooled to 0.0 ± 0.1 to minimize decarboxylation. About 5–10 mg of accurately weighed keto acid (**1a** or **1e**) was dissolved in 6 mL of 70% methanol at 0 °C. The pH electrode (previously cooled to 0 °C) was inserted, 20-μL aliquots of cold 0.30 N KOH in 70% methanol were added, and the pH recorded. The entire procedure took no longer than 10–15 min. The pK_a's were calculated from weighted least-squares analysis of a plot of $1/[H^+]$ vs. [anion]/[acid].

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Registry No. **1a**, 87373-02-2; **1e**, 87373-03-3; **2a**, 42031-70-9; **3a**, 87373-04-4; **3e**, 22249-33-8; **4a**, 87373-05-5; **4e**, 87373-06-6; **5a**, 87373-07-7; **5e**, 87373-08-8; **6**, 87373-09-9; **7**, 87373-10-2; **8**, 87373-11-3; **9**, 87373-12-4; 5-*tert*-butyl-2-oxocyclohexanecarboxylic acid, 42031-70-9.

Bromide Ion Promoted β-Elimination in α-Bromo Ester Substrates. Evidence for an Intermediate in the E2C Reaction

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The TDKIE criteria of transition state geometry in H-transfer reactions have been applied in the title reactions; a bent transition state consistent with the geometry of the E2C reaction has been verified by the results of intramolecular and intermolecular competition modes of determining k_H/k_D as a function of temperature. The extraordinary magnitude measured for the α secondary deuterium isotope effect in the E2C mechanism is reconciled with a very loose transition state and an acute angle of H-abstraction in the course of rearward approach to C_α by the promoter base. The virtual identity of the inter- and intramolecular isotope effects can be correlated by the assumption of a reaction intermediate of trigonal-bipyramid structure surrounding C_α and in which the abstractable H and D atoms are equally available to the action of the promoter base. The properties of this intermediate (**4**), by way of contrast with the transition state of an S_N2 process, are discussed in detail.

Since the earliest observations[1-3] of the remarkable efficiency of certain weak bases (thiolate, halide anions, etc.) in bringing about the biomolecular β-elimination of HX, the mechanism of this reaction has been the subject of vigorous controversy. The credibility of the proposed E2C mechanism[4-7] transition state (TS) (Figure 1a) espoused by Winstein and Parker and their co-workers and opposed by Bunnett[8,9] (Figure 1b) has recently been achieved by application of the temperature dependence of the kinetic isotope effect (TDKIE)[10] criteria of the geometry of an H-transfer TS. Thus, it was shown[11] that, in a conventional example of halide ion-promoted elimination of HX from C_6H_5–CH_2–CH_2X in aprotic media, a temperature-independent k_H/k_D was to be observed ($[\Delta E_a]_D^H \approx 0$) over a long temperature range (~70 °C). Values for A_H/A_D of up to 6.6 depending on the leaving group, X, were determined. These A_H/A_D values were greater than the practical limit for linear H-transfer (i.e., 1.2). Such properties of the isotope parameters have been frequently correlated[10] with a bent TS of H-transfer and, in the present instance, have provided strong support for the E2C mechanism, while distinguishing it from the Bunnett E2 process involving linear H-transfer.

Moreover, the magnitude of A_H/A_D has been shown both theoretically and empirically to correspond directly with the angle of H-transfer.[12] On this basis, also, it was concluded that (so-called) tight transition states with little ionic extension of the C_B–$H^{+\delta}$ bond and little sp^2 development at C_α show the larger values of k_H/k_D (large angles of H-transfer), contrary to earlier interpretations[13] based on single-temperature values of k_H/k_D.

Correlating a bent TS with the magnitude and temperature dependency of the primary deuterium kinetic isotope effect may be conducted by using a quantum mechanical treatment within the framework of transition state theory. The concept that a bent TS gives rise to a small, primary deuterium isotope effect was first put forward by Lewis,[14,15] and has since been adopted by

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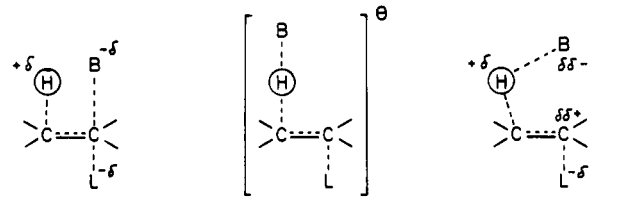

E 2 C — Winstein-Parker — Figure 1a

E 2 (Concerted) — Bunnett Paeneolefinic — Figure 1b

E 2 C (Carbonium) — McLennan model — Figure 1c

Figure 1.

others.[16] The origin of the small effect is thought to lie chiefly in the changing sensitivity to isotopic substitution of the TS's out-of-plane bending vibrations.[17] That is, k_H/k_D is determined principally by the zero-point-energy change in the out-of-plane bending vibrations between the reactant and TS. But this energy difference is offset by the zero-point-energy change in the composite stretching and bending motion, $\nu_R^{\neq}$, on proceeding from the ground state to the TS. Consequently, the isotope effect is much smaller than that of a linear, symmetrical TS. The occurrence of a small, primary deuterium isotope effect may signify the attainment of a bent TS. But this observation alone cannot lead to a distinction between a bent TS and an unsymmetrical TS of linear H-transfer. For such a distinction, the temperature dependency of the isotope effect must be determined.

In two recent communications, kinetic data at several temperatures have been presented on the reaction of *n*-octyllithium with hydrogen and deuterium[18] and on the β-hydride elimination in *n*-octyllithium and the 2-deutero compound.[19] For both of these reactions, $[\Delta E]_D^H$ was of the order of 1.25, and the ratio A_H/A_D was 0.24 and 0.72, respectively. From these values and the premise that both reactions occur via four-center cyclic transitions states, it was concluded that the parameters $[\Delta E]_D^H = 0$ and $A_H/A_D > 2^{1/2}$ are not a valid criterion for a nonlinear hydrogen transfer.

We disagree with this conclusion. In the hydrogenolysis reaction studied by Vitale and San Filippo, the terms k_{H-H} and k_{D-D} have an entirely different relation to each other than do k_{H-X} and k_{D-X}, which express the rates of breaking bonds to a common reaction center, and on which the TDKIE criteria are based. Moreover, both of the *n*-octyllithium reactions take place within an aggregate, probably hexameric. It has been emphasized[20] that in this situation, attribution of a four-center cyclic transition state for the β-elimination may be a gross oversimplification, and that the geometry cannot be specified. It seems possible that the hydrogen transfer in these reactions occurs with a more-or-less linear geometry by cooperation of several octyllithium molecules.

The Carbonium Ion E2C Transition State. A rival E2C mechanism proposed recently by McLennan,[13a] in a closely reasoned disquisition, holds that the C_α seat of reaction develops carbonium ion character in the TS which the approaching nucleophile stabilizes through dipolar interaction accompanying the angular abstraction of hydrogen at C_β (see Figure 1c). However, the fact that C_α in $C_6H_5CH_2$–CH_2–X substrates (undergoing the E2C) is a primary carbon incapable of sustaining carbonium ion properties appears to militate against acceptance of the Figure 1c TS.

Further evidence against this mechanism has been elucidated in the course of studies to be reported here. Thus, the substitution of the electron-withdrawing –COOEt group at C_α in C_6H_5–CH_2CH_2X substrates, i.e., in 2-bromo-3-phenylpropionate esters (1), accelerates the β-elimination induced by weak bases through the McLennan E2C mechanism[13a] anticipates retardation.

Finally, the effect of a methyl substituent at C_α on the base of β-elimination has been evaluated by means of the data listed in Table I. Normally such a substitution should greatly stabilize carbonium ion formation, viz., as it does in going from 2-propyl to *tert*-butyl bromide in the S_N1. However, it will be seen in Table I to have only a minor influence on the rates and activation parameters under E2C reaction conditions; such results cannot be reconciled with the McLennan proposal.

Table I. Arrhenius Parameters in the Second-Order β-Elimination Reactions[a] of Substrates 1 and 3 Promoted by a 10-Fold Excess of Tetraethylammonium Bromide in Acetonitrile Solvent

substrate	ethyl 2-bromo-3-phenylpropionate (1)	methyl 2-bromo-2-methyl-3-phenylpropionate (3)
log *A*	9.9 ± 0.3	11.3 ± 0.7
E_A, kcal/mol	23.6 ± 0.4	25.0 ± 0.1
correl coeff	0.9999	0.9997

[a] Reaction kinetic pursuit, on average, from 3 to 88% elimination.

Results

Application of the TDKIE Criteria.[10] The temperature dependence of k_H/k_D was measured over a 50–70 °C range by using $Et_4N^+Br^-$ as the source of weak base in CH_3CN solvent. Two different approaches were employed for estimation of k_H/k_D by competition methods, which are generally recognized to afford the most reliable, high-precision data.[21] In the intramolecular mode, ethyl 2-bromo-3-phenylpropionate-*3-d* (**1a**) was reacted with $Et_4N^+Br^-$ in CH_3CN solution to form a mixture of undeuterated (**2a**) and monodeuterated (**2b**) ethyl cinnamate, products whose composition was determined by the high-precision mass spectral procedure developed[10] for such purposes. The data obtained are listed in Table II and and the conclusion to be deduced from the computed KIE parameters ($[\Delta E_a]_D^H = 0$; $A_H/A_D = 2.60$) is that a bent TS of H transfer prevails in this reaction.

In the intermolecular competition mode, a 50:50 composition of ethyl 2-bromo-3-phenylpropionate-*3,3-d*$_2$ (**1b**) and its undeuterated analogue (**1**) was reacted under conditions identical with those employed in the intramolecular mode. This, again, yielded a mixture of **2a** and **2b** which was analyzed in the same way and with results compiled in Table III. The values of the KIE parameters in the intermolecular competition computed from these data ($[\Delta E_a]_D^H = 0$; $A_H/A_D = 2.73$) are regarded as identical

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Table II. Intramolecular Isotope Effect in the Bromide[a] Ion Promoted β-Elimination Reaction of $C_6H_5CHDCHBrCOOEt$ (1a)

reaction temp, °C ± 0.05 °C	corrected[b,c] $(M_D/M_H)_{corr}$ (= k_H/k_D)	mean k_H/k_D
78.5	2.553 ± 0.002	
88.1	2.631 ± 0.002	2.606 ± 0.030
100.5	2.620 ± 0.009	
114.0	2.619 ± 0.003	ΔT = 50.1 °C
128.6	2.606 ± 0.002	

[a] A tenfold excess of Et_4NBr in CH_3CN solution, ~0.007 M in substrate. [b] The correction to be applied in determining the measured isotope ratio M_D/M_H = [2b]/[2a] = the ratio of ethyl cinnamate-β-*d* to ethyl cinnamate is based on the finding that M_{H+1}/M_H = 0.1304 ± 0.0001 and M_{D-1}/M_D = 0.1651 ± 0.0002. The $(M_D/M_H)_{corr}$ = $(M_D - M_{H+1})/(M_H - M_{D-1})$, where M_D/M_H = M_{177amu}/M_{176amu}; thus, the $(M_D/M_H)_{corr}$ = $(M_{177} - M_{H+1})/(M_{176} - M_{D-1})$. The deduced equalities give the revised equation $(M_D/M_H)_{corr}$ = 0.134 (7.669 − *I*)/(*I* − 0.165) where $I = M_{176}/M_{177}$. [c] The isotopic ratio, M_D/M_H, was determined by mass spectral analysis on a Hewlett-Packard 5930A mass spectrometer equipped with a 5932A data system. Typical conditions called for a 70 eV ionizing energy, a 25 mA ionizing current, an analyzer-inlet pressure of 5×10^{-7} to 1×10^{-6} Torr, a source temperature of 150 °C and a filter temperature of 100 °C. Sample introduction was effected by means of a direct insertion probe. Under equilibrated conditions, the parent peaks of the labeled and unlabeled compounds were scanned 20 000 times per sample to yield a mean isotopic ratio, M_D/M_H, of high precision (% error ≤ 0.3). This high-precision isotopic ratio measurement procedure was originally devised by Kwart and Stanulonis[46] and has recently been applied by Reimschüssel and Paneth.[47]

with those in the intramolecular, when one corrects for the added (normal) secondary deuterium isotope effects[22] of about 4% inherent in the dideuterated substrate (**1b**) of the intermolecular competition and the sp^2 character developing at C_β in the TS.

The effect of changing the solvent and the source of bromide ion on the KIE parameters was tested with the use of LiBr in DMF in an intramolecular isotope competition. The data gathered in Table IV and the computed KIE parameters ($[\Delta E_a]_D^H$ = 0; A_H/A_D = 2.52) show that the bent TS structure is only slightly sensitive to such changes of reaction conditions.

The effect of substituting an α-methyl into the substrates 1 on the KIE parameters, i.e., through the intramolecular competition reaction of methyl 2-bromo-3-phenylpropionate-3-*d*, **3a**, with LiBr in DMF, is revealed by the data gathered in Table V ($[\Delta E_a]_D^H$ = 0; A_H/A_D = 2.39) compared to A_H/A_D = 2.52. In CH_3CN with Et_4NBr as the source of bromide and in the intermolecular competition mode (Table VI), the α-CH_3 effect is apparently greater; though $[\Delta E_a]_D^H$ is still zero, A_H/A_D = 1.91 represents a somewhat greater decline (from 2.73). Ion pairing effects are apparently more important in the TS in which the C_β–$H^{+\delta}$ bond is more ionized through the α-CH_3 hyperconjugation influence.

Measurements of $(k_H/k_D)_\alpha$, the intermolecular competition in the reaction of a 50:50 mixture of ethyl 2-bromo-3-phenylpropionate-2-*d* (**3c**) and its undeuterated analogue 1 with $Et_4N^+Br^-$ in CH_3CN solvent, yielded the data (Table VII) from which the α-secondary deuterium isotope effect could be determined.

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Discussion

A number of inferences can be readily drawn from the above results, as follows. The failure of an α-methyl substituent to substantially alter the activation parameters (Table I) of the bromide ion promoted E2C is a convincing demonstration of the fact that the TS of this mechanism is far from S_N2-like, as originally conceived by Winstein.[2] Bunnett's objections[9] to the E2C mechanism are based on the assumption that a significant degree of covalent bonding is achieved in the TS between C_α and the rearward-approaching base–nucleophile. The present results constitute another element of evidence that the S_N2-like characteristic attributed to the E2C mechanism is limited only to the direction and not the extent of rearward approach. The absence of any realized steric repulsions arising from substitution at C_α is testimony to the fact that in the E2C the promoting reagent does not penetrate to within detectable covalent bonding distances before the H-abstraction is experienced in the TS. The action of the promoter is more like a nucleophilic trigger.[23,24] a not unprecedented effect in which a nucleophile initiates small electronic displacements (here a partial displacement of the leaving group) that serve to trigger a concert of bond making and breaking in the TS.

In point of fact, the lowering of the A_H/A_D value associated with α-CH_3 substitution is clearly not a steric repulsion effect. It is due to a looser TS, one with more sp^2 character stabilized by methyl hyperconjugation. As previously pointed out, model calculations[25] have shown that A_H/A_D (i.e., k_H/k_D at constant temperature) is a steep, direct function of the angle of H-transfer in the TS. Thus, the slightly greater tolerance of sp^2 character at C_α originating with methyl substitution may permit a slightly closer rearward approach of the advancing promoter base. Moreover, there is a good possibility that α-CH_3 hyperconjugation[26] is enhancing the ionization of the C_β–$H^{+\delta}$ bond in the TS, which brings the transferring H closer to the basic center apically located in the TBP intermediate from which the TS arises, and thus narrows the angle of H-transfer.

The α-Secondary Deuterium Isotope Effect. In view of the experimental results and argument against the McLennan E2C model[13a] stipulating carbonium ion development at C_α, the magnitude of the secondary $(k_H/k_D)_\alpha$ measured by Parker[27] in a number of base catalyzed β-elimination reactions (showing large values of up to 1.13) cannot be associated with any mimicry of the S_N1 process. Moreover, since the E2C does resemble the S_N2 process, at least with respect to the geometry of the promoter reagents approach to C_α, it is of interest to compare the secondary k_H/k_D at C_α in the E2C with the corresponding values discussed in the literature in connection with various types of S_N2 processes.

A maximum value of $(k_H/k_D)_\alpha$ = 1.04 has been predicted[28] for the associative S_N2 TS. However, this has been challenged and, recently, much larger values (k_H/k_D = 1.09) have been found[29] in thiophenoxide displacement reactions in DMF solutions of benzylic substrates. Still larger values of $(k_H/k_D)_\alpha$ have been reported in cases involving groups

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Table III. Intermolecular Primary Deuterium Isotope Effect in the Bromide Ion (Et_4NBr/CH_3CN Solution) Promoted β-Elimination Reaction of a Mixture of $C_6H_5CD_2CHBrCOOEt$ (1b) and $C_6H_5CH_2CHBrCOOEt$ (1)

reaction temp °C ± 0.005 °C	fraction of reaction completed, f	corrected[a] isotopic ratio, R_A	k_H/k_D[b] computed	mean k_H/k_D at each temp	mean k_H/k_D over reaction temp range[c]
66.9	0.090	0.3771 ± 0.0006	2.700 ± 0.005	2.705 ± 0.007	2.73 ± 0.01
66.9	0.132	0.3837 ± 0.0008	2.710 ± 0.006		
101.2	0.130	0.3817 ± 0.0007	2.721 ± 0.005	2.722 ± 0.001	ΔT = 63.1 °C
101.2	0.150	0.3859 ± 0.0001	2.723 ± 0.001		
130.0	0.091	0.3735 ± 0.0.0007	2.728 ± 0.005	2.75 ± 0.003	
130.0	0.113	0.3717 ± 0.0001	2.772 ± 0.001		
130.0	1.00	R_{A_o} = 0.975 ± 0.001			

[a] See Table II, footnote b for correction procedure. [b] For computation of the isotope effect from the product mass ratio after a known amount of reaction, the following equation is employed:

$$\left[\frac{k_D}{k_H} - 1\right] \ln\left[1 - \frac{f(1 + R_{A_o})}{(1 + R_{A_f})}\right] = \ln\left[1 + \frac{(R_{A_o} - R_{A_f})f(1 + R_{A_f})}{R_{A_o}\left(1 - \frac{f(1 + R_{A_o})}{(1 + R_{A_f})}\right)}\right]$$

where f = the fraction of reaction, R_{A_f} equals the isotopic ratio, $(M_D/M_H)_{corr}$, of the product at f, and R_{A_o} equals the initial, corrected isotopic ratio of the substance. [c] A total of 20,000 mass ratio determinations are used at each temperature and each fraction of reaction completed.

Table IV. The Intramolecular Primary Deuterium Isotope Effect in the Weak Base Promoted β-Elimination Reactions of Ethyl 2-Bromo-3-phenylpropionate-3-d_1 with Lithium Bromide in Dimethylformamide

reaction temp °C ± 0.05 °C	corrected[a,b] k_H/k_D	mean k_H/k_D
66.7	2.508 ± 0.003	2.52 ± 0.02,
76.5	2.507 ± 0.002	120 000 determinations,
100.6	2.507 ± 0.004	ΔT = 73.3 °C
114.4	2.520 ± 0.005	
128.6	2.515 ± 0.002	
140.0	2.552 ± 0.002	

[a] See Table II, footnote b, for correction procedure. [b] A total of 20 000 mass ratio determinations are used at each temperature.

Table V. Intramolecular Primary Deuterium Isotope Effect in the Weak Base Promoted β-Elimination Reactions of Methyl 2-Bromo-2-methyl-phenylpropionate-3-d_1 with Lithium Bromide in Dimethylformamide (DMF)

reaction temp °C ± 0.05 °C	corrected[a,b] k_H/k_D	mean k_H/k_D
66.3	2.37 ± 0.01	2.39 ± 0.02,
79.0	2.384 ± 0.003	120 000 determinations,
89.7	2.38 ± 0.02	ΔT = 54.8 °C
101.5	2.38 ± 0.02	
110.7	2.427 ± 0.004	
121.1	2.408 ± 0.003	

[a] Here (compared to the correction in Table II) the measured isotope ratio (M_D/M_H) equals the ratio of methyl α-methylcinnamate-β-d to the undeuterated analogue. The correction here is based on the findings, where $M_D/M_H = M_{177amu}/M_{176amu} = I$ and M_{H+1}/M_H = 0.2070 ± 0.0002; M_{D-1}/M_D = 0.2380 ± 0.0002. Thus, $(M_D/M_H)_{corr} = 0.212\,(4.831 - I)/(I - 0.238)$. [b] A total of 20 000 mass ratio determinations are used at each temperature.

migrating intramolecularly and effecting rearward displacement at the reaction center.[30-32] These S_N2-like processes, characterized by an intermediate endowed with trigonal bipyramid disposition of the groups surrounding the seat of reaction, have somewhat longer apical bonds than are characteristic of the "true associative S_N2 process". Yet they are found to give $(k_H/k_D)_\alpha$ values ranging from 1.098–1.134, considerably larger than the expectation of a typical S_N2.

The value of $(k_H/k_D)_\alpha$ = 1.214 for the bromide ion catalyzed HBr elimination from substrate 1 (see Table VII) is by far the largest value hitherto found for either an S_N2 or a bimolecular HX elimination. One possible explanation for the extraordinary magnitude of this result was that ionization of the α-deuterium could have occurred to a significant extent in the course of the β-elimination reaction of the α-deuterio substrate used in measuring $(k_H/k_D)_\alpha$. However, this was ruled out by showing that at least 99% of the original deuterium in the reaction mixture was present in the product olefin, consistent with the nearly total absence of an α-carbanion intermediate and concomitant deuterium exchange over the entire period of kinetic pursuit of product formation.

As indicated in previous studies, the smaller the value of A_H/A_D in the E2C, the smaller the angle of H-abstraction.[12] In the 2-bromo-3-phenylpropionate (1) β-elimination reaction, the angle of H-transfer (i.e., A_H/A_D is considerably smaller (ca. 100°) than in the corresponding cases of β-phenylethyl substrates, (ca. 150°). Such a result correlates with the looser TS in the reaction of 1. The extraordinarily large value of the secondary $(k_H/k_D)_\alpha$ found for 1 is quite consistent with the interpretation conferred on the magnitude of A_H/A_D in the E2C. It speaks against any significant degree of resemblance of the E2C to an S_N2 process beyond the stipulation of a rearward course of the promoter in its approach to C_α.

Intramolecular vs. Intermolecular Competition Isotope Effects and the Existence of an E2C Intermediate. The virtual identity of the primary k_H/k_D values derived from the intramolecular and intermolecular experiments after correction for secondary deuterium isotope effects[22] provides the necessary assurance that there is not significant difference in the energies of the respective (threo) A and (erythro) B diastereomers (Figure 2) of which the reagent **1a** is comprised. From the methods of synthesis (via the diethyl deuterobenzylmalonate, α-bromination, acid-catalyzed decarboxylation, and reesterification), it can be assumed that the substrate composition consists of a ca. 50:50 mix of A and B. ^2H NMR analysis[33a]

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Table VI. Intermolecular Primary Deuterium Isotope Effect in the Weak Base Promoted β-Elimination of Methyl 2-Bromo-2-methyl-3-phenylpropionate and Its β,β-d_2 Analogue in Reaction with Et_4NBr in CH_3CN

reaction temp °C ± 0.05 °C	fraction of reaction completed, f	corrected[a] isotopic ratio, R_{A_f}	isotope effect,[b] k_H/k_D	mean k_H/k_D	mean k_H/k_D over reaction temp range[c]
66.9	0.091	0.3846 ± 0.0002	1.908 ± 0.001	1.906 ± 0.003	1.908 ± 0.002,
66.9	0.13	0.39035 ± 0.00004	1.9031 ± 0.0002		120 000 determinations,
101.5	0.109	0.3868 ± 0.0009	1.908 ± 0.005	1.907 ± 0.001	ΔT = 65.3 °C
102.0	0.128	0.3896 ± 0.0003	1.906 ± 0.002		
132.2	0.09	0.3839 ± 0.0001	1.9165 ± 0.0008	1.9130 ± 0.0004	
132.2	0.150	0.3917 ± 0.0002	1.910 ± 0.001		
132.2	1.00	R_{A_0} = 0.7131 ± 0.0005			

[a] The value of $(M_D/M_H)_{corr}$ is determined by the procedure given in Table V, footnote *a*. [b] For this computation, see footnote *b* in Table III. [c] A total of 20 000 mass ratio determinations are used at each temperature and each fraction of reaction completed.

Table VII. α-Secondary Deuterium Isotope Effect in the Bromide Ion (Et_4NBr/CH_3CN Solution) Promoted β-Elimination Reaction of a Mixture of $C_6H_5CH_2CDBrCOOEt$ and $C_6H_5CH_2CHBrCOOEt$

reaction temp °C ± 0.05 °C	fraction of reaction completed, f	corrected[a] isotope ratio, R_{A_f}	k_H/k_D[b] computed	mean[c] $(k_H/k_D)_\alpha$
101.2	0.093	0.731 ± 0.002	1.219 ± 0.003	1.214 ± 0.004
101.2	0.133	0.739 ± 0.001	1.210 ± 0.002	
101.2	1.00	R_{A_0} = 0.8826 ± 0.0002		

[a] The correction equation applied here is identical to that described in footnote *a* of Table III. [b] The method of computation is identical to that discussed in footnote *b* of Table III. [c] A total of 40 000 mass ratio determinations were used in deducing this value.

fully supports this assumption.

The corresponding rotamers (Fiugre 2), A′ and B′, cannot be involved in the elimination process in which the antiperiplanar elimination characteristic of the E2C reaction process is known[7] to occur almost exclusively. These statements are based on two lines of evidence: (a) The conformational energies of the A′ and B′ rotamers, compared to A and B, respectively, are greater (>4.0 kcal/mol) than the C–H vs. C–D zero point energy differences (ca. 1.15 kcal/mol), which would ordinarily determine the preferences among the rotamers for undergoing the elimination step. (b) The much more stable *trans*-cinnamate ester is formed exclusively under reaction conditions where the cis is not at all isomerized[33b] to the trans.

Since it is unlikely that the cis ester could have been formed, both because its rotameric precursors (A′ and B′) are energetically improbable and because the product composition of even partly reacted material is found to be devoid of the cis isomer, the origin of the experimental isotope effect in the intramolecular isotope effect experiment (k_H/k_D = 2.6) requires clarification. That is to say, if product is formed in this experiment only from A and B through the established[7] antiperiplanar course of elimination, the intramolecular method of measuring the isotope effect by allowing the reaction of A and B to go to completion and measuring the isotope composition ([**2b**]/[**2a**]) of the product olefins must result in an apparent k_H/k_D = 1.0. The finding of an intermolecular isotope effect in which these diastereomeric preferences are not a factor shows that the actual isotope effect, k_H/k_D, *is* ~2.6. The fact that the corrected intermolecular k_H/k_D is identical with this shows that, at all times in the course of elimination, equal concentrations of competing H and D were equally available for abstraction by Br^-.

This evidence, together with the temperature independence of k_H/k_D, would seem to indicate, despite much data to the contrary,[7] that somehow the E2C process does not conform to the conventional antiperiplanar elimination geometry. The most attractive and reasonable explanation for these results is inspired by Winstein's original suggestion[2] that in the E2C rearward nucleophile attack by the Br^- at C_α gives rise to an actual, short-lived intermediate. A possible candidate structure for this intermediate is **4**.

Since the entering and departing bromide ions appear to be apical and identical in this picture with respect to

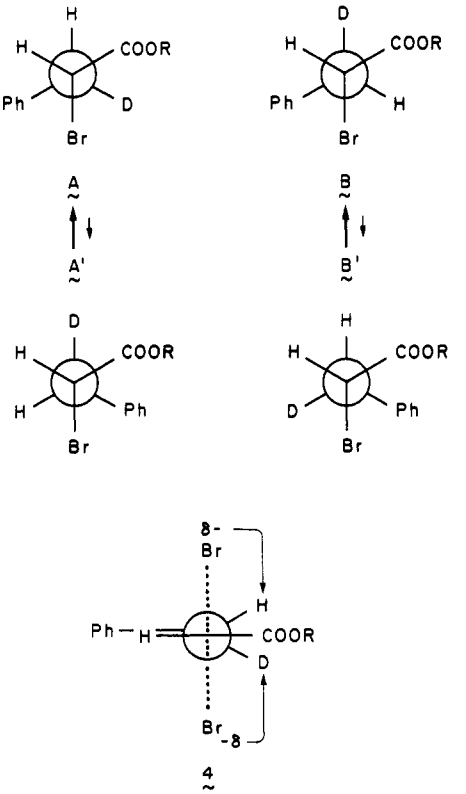

Figure 2. Rotameric forms of the diastereoisomers of ethyl 2-bromo-3-phenylpropionate-3-d_1 (**1a**) in antiperiplanar β-elimination.

(33) (a) Unpublished results with the technique described in Brown, J. M.; Parker, D. *Tetrahedron Lett.* **1981**, *2815*. (b) Results of K. Huss to be reported from these laboratories.

charge character and basicity in this trigonal bipyramid (TBP) structure surrounding C_α, the passage of intermediate 4 to the respective transition states for nonlinear H and D abstraction (indicated by the curved arrows sketched in 4), and subsequently to product formation, is determined only by the usual zero point energy and entropy considerations responsible for an isotope effect. In the present symmetrical case, there apparently is no other preference for H and D abstraction biased by any factors related to steric, basicity or structure–rate effects. However, in an unsymmetrical case, where the apical ligands are very different, several additional factors may enter the determination of k_H/k_D. These will be considered in the following article.[34]

Finally, it should be noted that, in what has been incorrectly called an S_N2-like process,[7,13a,35] at least one and possibly both of the apical bonds, in such a metastable intermediate as 4, are considerably longer and weaker than is required in the TS of a true S_N2 reaction. Evidently, the TS arising from 4 in an E2C reaction, showing evidence of significant double bond development, cannot be related to the TS in an S_N2 process. It has been repeatedly shown[36] that an intermediate does not intervene in the course of an S_N2 process in which considerable covalent bonding has developed in both of the apical positions of its assumed trigonal bipyramid (TBP) transition state structure. The evidence adduced here suggests that an intermediate of TBP structure, possessing long and weak apical bonding to the C_α seat of reaction, appears in the course of the E2C. A pentacoordinate carbon structure with long apical bonds to sulfur has also been characterized as a relatively stable entity by Forbus and Martin.[37] Thus, the intervention of a similarly structured, metastable intermediate like 4 is not an unreasonable assumption for purposes of kinetic interpretation.

Experimental Section

A. Syntheses of Substrates. Reagents and solvents were of commercial grade and were usually purified before use. Gas chromatographic quantitative analyses were performed on a Hewlett–Packard research chromatograph Model 5750 connected to a Hewlett-Packard 3370 A electronic integrator. Preparative gas chromatography was conducted on a F and M dual column gas chromatograph. NMR spectra were obtained on a Perkin Elmer R-12B spectrometer with chemical shifts reported in δ (ppm) with reference to tetramethylsilane (δ 0). Infrared spectra were determined using a Unican-SP-100 spectrometer with reference to polystyrene's frequencies at 1602 and 1583 cm^{-1}. For reactions requiring dry, deoxygenated conditions, the purified reagents and solvents were used in a dry apparatus under nitrogen.

Preparations. Benzyl-α-*d* Alcohol.[38] The reaction of benzaldehyde in ether with lithium aluminum deuteride (99.0% Aldrich) was used. The NMR of the final product indicated >98% monodeuteration of the benzyl alcohol. NMR ($CDCl_3$) δ 7.35 (5 H, s, aromatic protons), 4.55 (1 H, br s, –CHD–), 3.65 (1 H, br s, –OH).

Benzyl-α-*d* Chloride.[39] The reaction of the benzyl-α-*d* alcohol with thionyl chloride in pyridine–benzene solution was used. NMR (CCl_4) δ 7.45 (5 H, singlet, aromatic protons), 4.55 (1 H, br s, –CHD).

Diethyl Benzyl-α-*d*-malonate.[40] The procedure of Adams and Karum was employed in which diethyl sodiomalonate was reacted with the benzyl-α-*d* chloride. Gas chromatographic analysis showed the initial product was 98% pure and contaminated only with 2% of the dibenzylmalonate. Redistillation accomplished the elimination of this impurity, too. NMR (CCl_4) δ 7.30 (5 H, s, aromatic protons), 4.10 (4 H, q, $-OCH_2CH_3$), 3.60 (1 H, br asymmetric d, methine proton), 3.15 (1 H, br asymmetric d, –CHD–), 1.05 (6 H, t, $-OCH_2CH_3$).

2-Bromo-3-phenylpropionic-3-*d* Acid. The procedure outlined below involving commonly employed reaction procedures gave a 60% yield overall based on the starting material of the sequence:

$$C_6H_5CHDCH(COOEt)_2 \xrightarrow[2.\ H_3O^+,\ 20\ °C]{1.\ KOH\text{–}H_2O\text{–room temp}} C_6H_5CHDCH(COOH)_2 \xrightarrow{Br_2,\ Et_2O} C_6H_5CHDCBr(COOH)_2 \xrightarrow[135\ °C]{\Delta(-CO_2)} C_6H_5CHDCHBrCOOH$$

NMR ($CDCl_3$) δ 11.10 (1 H, br s, OH), 7.40 (5 H, s, aromatic protons), 4.50 (1 H, br d, CHBr), 3.35 (1 H, w br m, CHD).

Ethyl 2-Bromo-3-phenylpropionate-3-*d* (1a). The acid precursor (prepared as above) was converted to its ethyl ester in the usual way with 3% w/v sulfuric acid in absolute ethanol. The product obtained in 98% yield, purified by fractional distillation (bp 98.2–99.0 °C at 0.3 mm), showed 100% purity by GC analysis. NMR ($CDCl_3$) δ 7.35 (5 H, s, aromatic protons), 4.45 (1 H, br d, CHBr), 4.25 (2 H, q, OCH_2CH_3), 3.40 (1 H, br m, CHD), 1.20 (3 H, t, OCH_2CH_3).

Benzyl-α,α-d_2 Alcohol. The reaction of ethyl benzoate with lithium aluminum deuteride in ether was used. The product was 99% pure after fractional distillation (bp 68.0–69.0 °C at 5 mm). The NMR indicated >98% dideuteration at C-1. NMR ($CDCl_3$) δ 7.30 (5 H, s, aromatic protons), 3.35 (1 H, br s, OH).

Benzyl-α,α-d_2 Chloride. The procedure used here was analogous to that applied for the preparation of benzyl chloride discussed above. NMR ($CDCl_3$) δ 7.35 (s, aromatic protons).

Diethyl Benzyl-α,α-d_2-malonate. The procedure used here was analogous to that described for the preparation of the diethyl benzyl-α-*d*-malonate described above. NMR ($CDCl_3$) δ 7.20 (5 H, s, aromatic protons), 4.05 (4 H, q, OCH_2CH_3), 3.55 (1 H, br s, methine proton), 1.05 (6 H, t, OCH_2CH_3).

Ethyl 2-Bromo-3-phenylpropionate-3,3-d_2 (1b). Diethyl benzyl-α,α-d_2-malonate was saponified, brominated, decarboxylated, and esterified to the desired product in 57.4% overall yield by methods analogous to those described above for the monodeuterated analogue. The product was isolated in 100% purity by fractional distillation (bp 98.0–98.5 °C at 0.3 mmHg). NMR ($CDCl_3$) δ 7.20 (5 H, s, aromatic protons), 4.40 (1 H, br s, methine proton), 4.15 (2 H, q, OCH_2CH_3), 1.15 (3 H, t, OCH_2CH_3).

Diethyl Benzyl-α-*d*-methylmalonate.[41] The reaction of benzyl-α-d_2 chloride with diethyl sodiomethylmalonate was used. The desired product (90% yield) was collected by fractional distillation (bp 90.0–91.0 °C at 0.2 mm). GC analysis showed the fraction consisted of 98% desired product and 2% unreacted malonic ester. NMR (CCl_4) δ 7.25 (5 H, s, aromatic protons), 4.30 (4 H, q, OCH_2CH_3), 3.30 (1 H, br s, CHD, 1.45 (3 H, s, methyl protons), 1.40 (6 H, t, OCH_2CH_3).

2-Methyl-3-phenylpropionic-3-*d* Acid and Its Methyl Ester. The procedure outlined below involving commonly employed reaction procedures gave high yields (>90%) of intermediates and final product.

$$C_6H_5CHDC(COOEt)_2CH_3 \xrightarrow[2.\ H_3O^+,\ 20\ °C]{1.\ KOH\text{–}H_2O,\ room\ temp} C_6H_5CHDC(COOH)_2CH_3 \xrightarrow[180\ °C\ (-CO_2)]{\Delta} C_6H_5CHDCH(CH_3)COOH \xrightarrow[3\%\ w/v\ H_2SO_4]{CH_3OH} C_6H_5CHDCH(CH_3)COOCH_3$$

NMR ($CDCl_3$) δ 7.20 (5 H, s, aromatic protons), 3.55 (3 H, s,

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OCH_2CH_3), 3.10–2.60 (2 H, m, methine protons at C-2 and C-3), 1.10 (3 H, d, methyl protons).

Methyl 2-Bromo-2-methyl-3-phenylpropionate-*3-d*.[42] The procedure used is outlined below:

$$C_6H_5CHDCH(CH_3)COOCH_3 \xrightarrow[THF,\ -78\ °C]{LiN(i\text{-}Pr)_2} C_6H_5CHDC^-(CH_3)COOCH_3 \xrightarrow[2.\ -78\ °C \rightarrow -10\ °C\ 3.\ H_3O^+,\ 0\ °C]{1.\ CBr_4,\ -78\ °C} C_6H_5CHDCBr(CH_3)COOCH_3$$

The product (81.6% yield) was purified by dry column chromatography for which silica gel and trichloroethylene served as the support and elutant, respectively. GC analysis indicated the collected fraction was 98% α-bromoester and 2% unbrominated ester. NMR (CCl_4) δ 7.25 (5 H, s, aromatic protons), 3.75 (3 H, s, OCH_2CH_3), 3.40 (1 H, br d, CHD), 1.75 (3 H, s, methyl protons).

Diethyl Benzyl-α,α-d_2-methylmalonate.[41] The preparation of benzyl-α,α-d_2 chloride was applied here in procedures identical to those used above for the monodeuterated analogue. NMR ($CDCl_3$) δ 7.20 (5 H, s, aromatic protons), 4.20 (4 H, q, OCH_2CH_3), 1.35 (3 H, s, methyl protons), 1.25 (6 H, t, OCH_2CH_3).

Methyl 2-Bromo-2-methyl-3-phenylpropionate-*3,3-d*$_2$. The sequence of steps used for the preparation of the monodeuterated compound (above) was applied here also for the preparation of the dideutero analogue in overall 70% yield beginning with diethyl benzyl-α,α-d_2-methylmalonate. NMR ($CDCl_3$) δ 7.20 (5 H, s, aromatic protons), 3.75 (3 H, s, OCH_2CH_3), 1.80 (3 H, s, methyl protons).

Hydrobenzoin-*1,2-d*$_2$. The procedure of Wiberg[43] was used to prepare this percursor in the preparation of deuterobenzaldehyde. NMR (acetone-d_6) δ 7.20 (10 H, s, aromatic protons), 4.50 (2 H, br d, OH).

Benzaldehyde-α-*d*. The hydrobenzoin-*1,2*-d_2 was cleaved with lead tetraacetate by the method given by Wiberg.[43]

Ethyl Cinnamate-*3-d* (2b). To a round-bottom flask charged with 13.4 g (0.0681 mol) of dimethyl(carbethoxymethyl)-phosphonate, 7.0 g (0.0649 moles) of benzaldehyde-α-*d*, and 200 mL of *tert*-butanol was slowly added 1.6 g (0.0681 mol) of sodium hydride at 0 °C. Stirring under nitrogen was continued for 30 min., after which time the reaction mixture was refluxed for 2 h. On cooling, the precipitate was filtered off and the *tert*-butanol was distilled from the filtrate. The residual organics were dissolved in ether, washed with water, dried over magnesium sulfate, filtered, and stripped of solvent. On fractional distillation (bp 68.5–69.0 °C at 0.2 mmHg) 6.2 g (0.0349 mol, 53.8% yield) of ethyl cinnamate-*3-d* was obtained. GC analysis of the fraction collected indicated <1% contamination by the unreacted phosphonate ester. NMR ($CDCl_3$) δ 7.50 (1 H, br, s, vinyl proton), 7.30 (5 H, s, aromatic protons), 4.20 (2 H, q, OCH_2CH_3), 1.30 (3 H, t, OCH_2CH_3).

Methyl 2-Methyl-3-hydroxy-3-phenylpropionate-*3-d*. The procedure of Zimmerman and English[44] was followed for carrying out the reaction of methyl 2-bromopropionate with benzaldehyde-α-*d* in a 70% yield of 100% pure product by GC analysis. NMR ($CDCl_3$) δ 7.25 (5 H, s, aromatic protons), 3.75 (3 H, s, OCH_2CH_3), 3.50 (1 H, br s, OH), 2.80 (1 H, br q, methine proton at C-2), 1.10 (3 H, d, methyl protons).

Methyl 2-Methylcinnamate-*3-d*. The procedure of Rinehart and Perkins[45] was used for forming this product from methyl 2-methyl-3-hydroxy-3-phenylpropionate-*3-d*. NMR ($CDCl_3$) δ 7.35 (5 H, s, aromatic protons), 3.70 (3 H, s, OCH_2CH_3), 2.05 (3 H, s, methyl protons).

Preparation of Ethyl 3-Phenylpropionate-2,2-*d*$_2$. A stainless steel bomb charged with 18.2 g (0.1056 mol) of the sodium salt of 3-phenylpropionic, 21.2 g (1.0560 mol) of deuterium oxide and 0.6 g (0.0106 mol) of sodium methylate was heated in a sand bath at 200 °C for 17 h. After cooling to room temperature, the solvents were distilled off, a fresh charge of 21.2 g (1.0560 mol) of deuterium oxide was added, and the procedure was repeated. To a round-bottom flask containing the concentrated reaction mixture was added 21.2 g (1.0560 mol) of deuterium oxide, 20 mL of toluene, 2.0 g (0.0053 mol, 0.05 equiv) of tetra-*n*-butylammonium iodide, and 24.7 g (0.1584 mol, 1.5 equiv) of ethyl iodide. After the reaction mixture was refluxed for 8 h under nitrogen, the excess ethyl iodide was distilled off and the two phase system was extracted with ether. The combined ether extracts were washed with heavy water, dried over magnesium sulfate, filtered, and stripped of solvent. On fractional distillation, 16.4 g (0.0908 mol, 85.9% yield) of ethyl hydrocinnamate-β,β-d_2 was obtained (bp 84.0–84.5 °C at 2 mmHg). The NMR indicated >98% dideuteration at C-2 of the product. NMR (CCl_4) δ 7.25 (5 H, s, aromatic protons), 4.10 (2 H, q, OCH_2CH_3), 2.90 (2 H, br s, methylene protons), and 1.20 (3 H, t, OCH_2CH_3).

Ethyl 2-Bromo-3-phenylpropionate-*2-d* (3c). This product was prepared from ethyl 3-phenylpropionate-2,2-d_2 by the bromination of its enolate with carbon tetrabromide as outlined above.[42] NMR (CCl_4) δ 7.20 (5 H, s, aromatic protons), 4.10 (2 H, q, OCH_2CH_3), 3.30 (2 H, q, methylene protons), 1.15 (3 H, t, OCH_2CH_3).

Kinetic Procedure. A typical kinetic run was performed as follows. The vessel containing the base solution was placed in a well stirred oil bath regulated by a Hallikainen Thermotrol with the actual control temperature measured by a NBS thermometer, constant to within 0.05 °C. Once the base solution had thermally equilibrated at the reaction tempeature, a minimal volume of substrate solution was injected into the vessel; the reaction mixture was vigorously shaken, and the timer was started simultaneously. At well measured times, aliquots were quenched, worked up, and subjected to gas chromatographic quantitative analyses. These analyses were conducted on a F and M 5750 chromatograph connected to a Hewlett-Packard 3370A electronic integrator. The substrate concentration per aliquot was determined by comparing the peak area of the substrate to that of the internal standard. Generally, the kinetic run was performed until the elimination reaction reached greater than two half-lives. For moisture and air sensitive systems requiring extended reaction times, the system was either purged with nitrogen during the course of reaction or its reaction vessel, containing both substrate and base, was evacuated at −78 °C prior to reaction. In all cases, the substrate, base, and solvent were scrupulously purified and dried prior to use.

The kinetic isotope effects were run in both the intramolecular and intermolecular modes by exactly the same procedure used for determining the rates of reaction above. In addtion, the product, isolated from a given run by GC techniques, was condensed in a chilled capillary in the line emerging from the thermal conductivity detector. After the capillary and its contents were sealed from contact with air during subsequent standing, it was subjected to the mass spec procedure for the high precision isotope ratio analysis commonly used in this laboratory.[10]

Registry No. **1**, 39149-82-1; *erythro*-**1a**, 87482-98-2; *threo*-**1a**, 87482-99-3; **1b**, 87482-88-0; **2b**, 87482-94-8; **3**, 18197-77-8; **3c**, 87482-97-1; $C_6H_5CHDCH(COOEt)_2$, 87482-83-5; $C_6H_5CHDCHBrCOOH$, 87482-84-6; $C_6H_5CHDCH(COOH)_2$, 87482-85-7; $C_6H_5CHDCBr(COOH)_2$, 87482-86-8; $C_6H_5CHDC(COOEt)_2CH_3$, 87482-89-1; $C_6H_5CHDC(COOH)_2CH_3$, 87482-90-4; $C_6H_5CHDCH(CH_3)COOH$, 87482-91-5; $C_6H_5CHDCH(CH_3)COOCH_3$, 87482-92-6; $Et_4N^+Br^-$, 71-91-0; Br^-, 24959-67-9; C, 7440-44-0; deuterium, 7782-39-0; diethyl sodiomalonate, 996-82-7; benzyl-α-*d* chloride, 79449-94-8; benzyl-α,α-d_2 alcohol, 21175-64-4; ethyl benzoate, 93-89-0; benzyl-α,α-d_2 chloride, 33712-34-4; diethyl benzyl-α,α-d_2-malonate, 87482-87-9; methyl 2-bromo-2-methyl-3-phenylpropionate-*3,3*-d_2, 87482-93-7; hydrobenzoin-*1,2*-d_2, 36239-19-7; benzaldehyde-α-*d*, 3592-47-0; dimethyl (carbethoxymethyl)-phosphonate, 311-46-6; methyl 2-methyl-3-hydroxy-3-phenylpropionate-*3-d*, 87482-95-9; methyl 2-methylcinnamate-*3-d*, 81254-50-4; ethyl 3-phenylpropionate-*2,2*-d_2, 87482-96-0; 3-phenylpropionic acid sodium salt, 114-84-1.

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