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The E2C Mechanism in Elimination Reactions. VII.[1a] Secondary Kinetic Hydrogen Isotope Effects in E2 Reactions of Alicyclics

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Secondary kinetic hydrogen isotope effects on the rates of some base-induced dehydrotosylations and dehydrobrominations of cyclohexyl derivatives (E2C-like reactions) have been studied. Secondary hydrogen isotope effects at C_α (13–15%) and at C_β (15–25%) indicate that significant hybridization changes occur at both C_α and C_β in reactions leading to E2C-like transition states. Secondary hydrogen isotope effects (11–22%) at C_ζ (adjacent to C_α and allylic to the site of double-bond development) arise most probably from hyperconjugative interactions and suggest either a well-developed double bond between C_α and C_β, or a well-developed positive charge at C_α in E2C-like transition states. The observed secondary hydrogen isotope effects are *not* consistent with those paene-carbonium E2 transition states in which there is very little change in hybridization taking place at C_β. For the SN2 reactions which accompany E2C-like reactions, secondary β-hydrogen isotope effects are of the same order of magnitude as those for the elimination reactions, whereas, in contrast, it appears that secondary α-hydrogen isotope effects are much smaller for SN2 reactions than they are for E2C-like reactions. The nature of the transition states for E2C-like reactions and their concomitant SN2 reactions are discussed in the light of these findings.

Primary hydrogen isotope effects on the rates of bimolecular β-elimination (E2) reactions have now been studied over the spectrum of transition states available for E2 reactions.[1–6] However, the much smaller secondary hydrogen isotope effects on the rates of E2 reactions have received scant attention. In this paper we examine the kinetic hydrogen isotope effects, primary and secondary, arising in the bimolecular reactions (E2, SN2) of cyclohexyl tosylate and cyclohexyl bromide with selected bases.

There have been studies, which have been well reviewed,[3,6–11] of secondary hydrogen isotope effects in solvolytic processes (E1, SN1 reactions). These arise from hybridization changes, hyperconjugative effects, or nonbonded steric interactions. Secondary kinetic hydrogen isotope effects in solvolytic processes (*i.e.*, those using carbonium ion-like transition states) are by no means negligible, and may run to as much as 10–30% retardation in rate per deuterium atom.[8] In contrast, SN2 reactions usually show much smaller secondary isotope effects[12–14] and in some cases inverse isotope effects have been reported.[15,16]

It is generally accepted that E2 reactions have variable transition states depending upon the particular reaction, but a variety of sets of transition states have been proposed.[5,17–20] As usual, we choose to discuss our results in terms of the E2C–E2H spectrum of transition states,[18–20] but isotope effects tell us nothing about whether the base bonds to C_α in the E2C transition state. The information obtained here does, however, tell us that there are substantial bonding changes at C_α and C_β in the transition states for the reactions of cyclohexyl tosylate with bases. Secondary kinetic hydrogen isotope effects in these systems are not only measurable, but have significant magnitude and cannot be ignored. If they are not recognized, errors in evaluating primary kinetic hydrogen isotope effects occur.[21]

It has been clearly established that the type of reaction studied here is an anti elimination so that one can distinguish between effects due to hydrogen or deuterium cis or trans to the leaving group in cyclohexyl derivatives.[20]

Results

The product ratios of the cyclohexenes from the E2 reactions of *trans*-cyclohexyl-*2-d* tosylate (II-OTs), *trans*-cyclohexyl-*2-d* bromide (II-Br), and cyclohexyl-*2,2-d_2* tosylate (III-OTs) with a variety of bases are shown in Table I. Also shown in Table I for the same series of bases are the cyclohexene product ratios obtained from intermolecular competition experiments during the first 10% of the E2 reactions of an equimolar mixture of cyclohexyl tosylate (I-OTs) and cyclohexyl-*2,2,6,6-d_4* tosylate (V-OTs), as well as of an equimolar mixture of the corresponding bromides (I-Br, V-Br). The product ratios are governed by kinetic hydrogen isotope effects. These reactions, together with the symbolism distinguishing the rate constants for the various elimination routes are shown in Chart I. The data in Table I were derived from mass spectrometric analyses of the olefinic product mixtures arising from the various intramolecular and intermolecular competition experiments.

Rate constants for the total reaction (E2 + SN2) of variously deuterated cyclohexyl tosylates and bromides with NBu_4OAc in acetone containing 2,6-lutidine at 50° are reported in Table II. Specific rate constants for elimination along each pathway illustrated in Chart I were evaluated from the rate constant combinations in Tables I and II, and are collected in Table III. Primary and secondary kinetic hydrogen isotope effects in the reactions of the isotopically substituted cyclohexyl tosylate and cyclohexyl bromide systems are recorded in Table IV. They were evaluated in the following manner.

Primary Isotope Effects (1°). The "true" primary kinetic hydrogen isotope effect for elimination is given by k_H^H/k_D^D in Table IV (*cf.* pathways 1 and 2b in Chart I).

Secondary Isotope Effects. These are of two types which Streitweiser[22] distinguishes as secondary isotope effects of the first and second kind. The criterion for distinction is whether or not the bonds to the isotopic atoms undergo spatial reorientation. In this paper, we use more descriptive terminology for the two sources of secondary isotope effects. Isotope effects of the first kind, *i.e.*, those arising due to hydridization changes at the labeled carbon atom (C_α or C_β), are referred to as hybridization isotope effects. Isotope effects of the second kind arising from isotopic substitution at carbon atoms one removed from those where double-bond formation occurs (*i.e.*, at C_ζ in the cyclohexyl system) are referred to as hyperconjugative isotope effects.

i. Secondary Hybridization Isotope Effects at C_α ($2°C_\alpha$). The secondary isotope effect of a hydrogen atom relative to a deuterium atom at C_α on the leaving tendency of the expelled group X as the hybridization at C_α changes from sp^3 in the ground state to increasing sp^2 character in the transition state, is given by $k_H^H/k_{D_\alpha}^H$ in Table IV (*cf.* pathways 1 and 4 in Chart I).

ii. Secondary Hybridization Isotope Effects at C_β

Table I
Isotope Effects for Elimination from Cyclohexyl Tosylates and Cyclohexyl Bromides with Various Base/Solvent Systems, as Measured by Mass Spectral Analysis of Intra- and Intermolecular Competitive Reactions

Base[a]	Registry no.	Solvent	Temp, °C	II-OTs,[c] k_D^H/k_D^D[d]	III-OTs,[c] $k_{D_2}^H/k_{D_2}^D$[d]	V-OTs,[c] $k_H^H/k_{D_4}^D$[e]	Temp, °C	II-Br,[c] k_D^H/k_D^D[d]	V-Br,[c] $k_H^H/k_{D_4}^D$
NBu_4OPh	16909-23-2	Acetone	50	3.1	3.0	3.8	75	4.0	5.6
NBu_4OAc	10534-59-5	Acetone[b]	50	2.7_4	2.9	3.5[h]	75	3.9 (4.4)[g]	5.1[i]
NBu_4SAr	20627-93-4	Acetone[b]	75	2.4	2.4	3.0	75	3.5	4.7
NBu_4Cl	1112-67-0	Acetone[b]	50	2.6	2.6	4.0[f]	75	3.2	4.6
NBu_4Br	1643-19-2	Acetone[b]	75	2.2	2.4	3.5	75		4.7
NaOEt	141-52-6	EtOH	75	2.3	2.3	2.3	75	3.2	3.9[h]
KO-*t*-Bu	865-47-4	Bu-*t*-OH	75	2.8	2.7	3.2	75	3.8	4.8[h]

[a] NBu_4 is the tetra-*n*-butylammonium cation, OPh is phenoxide, OAc is acetate, and SAr is *p*-nitrothiophenoxide. Base concentrations <0.1 *M*. [b] Solvent contained 0.04–0.10 *M* 2,6-lutidine. [c] Substrate numbers and notation for *k* refer to Chart I. Allowance was made for imperfect deuteration of substrates. [d] This is an intramolecular isotope effect obtained by mass spectral analysis of the proportions of the two possible olefins formed from the single substrate shown (see Chart I and text). [e] This is an intermolecular isotope effect obtained by mass spectral analysis of the ratio of the two olefins formed from the reaction of an equimolar mixture of the substrate shown with its undeuterated analog (see Chart I and text). Analysis was made during the first 10% of reaction. [f] Extrapolated from a value of 3.7 measured at 75°.[23] [g] At 50°. [h] These inter molecular isotope values were also determined from a direct comparison of the measured rate constants for the individual reactions of the tetradeuterated and undeuterated substrates. Isotope values determined by the kinetic method agreed to within 6% with the values shown in the table. [i] A value of 7.1 at 50° was obtained by the kinetic method (see footnote *h*).

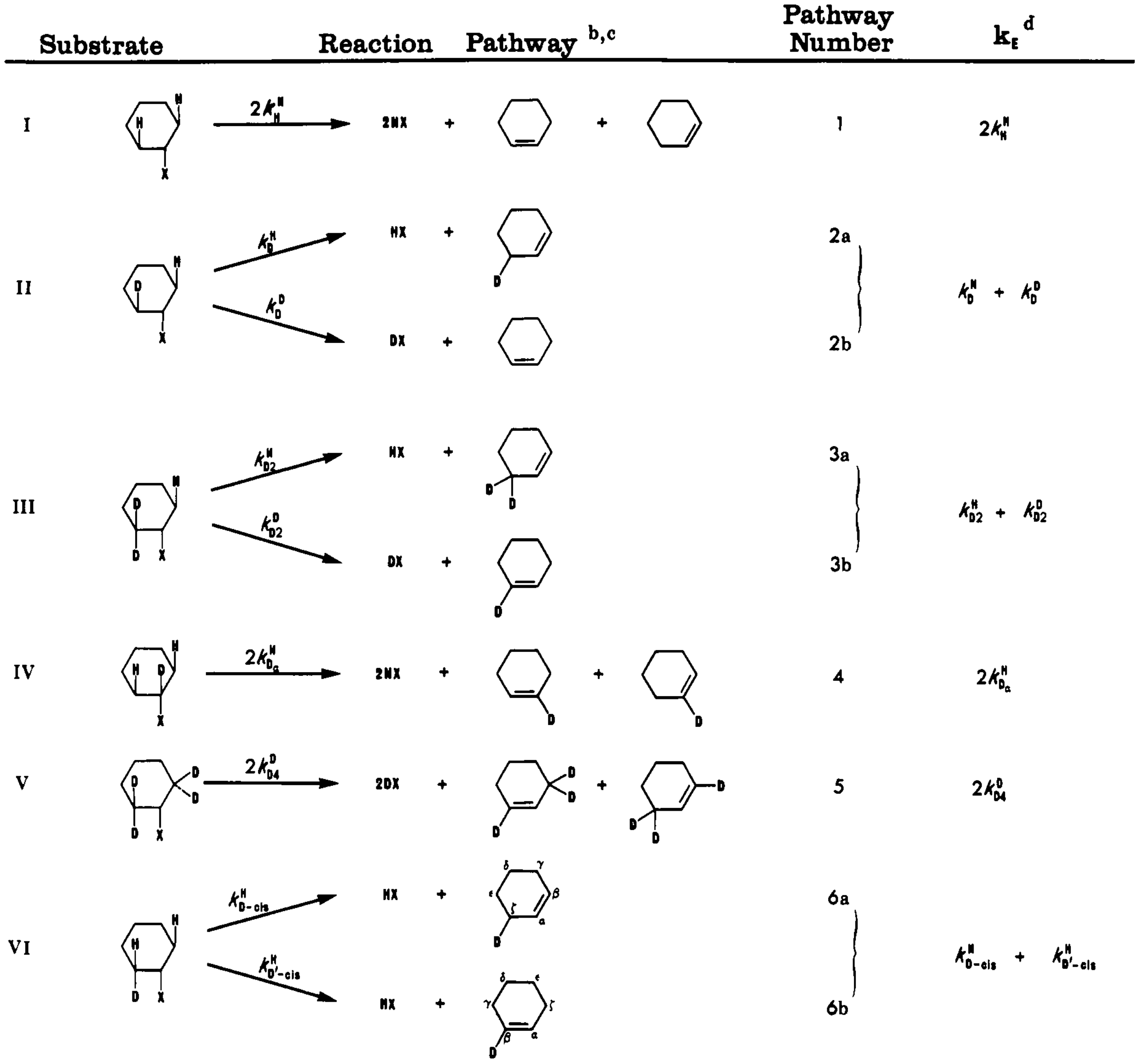
Table II
Kinetic Data for the Reactions of Variously Deuterated Cyclohexyl Tosylates and Bromides at 50° with NBu_4OAc in Acetone Containing 0.15 *M* 2,6-Lutidine

Substrate[a]	Registry no.	10^4k,[b] $dm^3\ mol^{-1}\ sec^{-1}$	F_E[c]	10^4k_S,[d,e] $dm^3\ mol^{-1}\ sec^{-1}$	10^4k_E,[e,f] $dm^3\ mol^{-1}\ sec^{-1}$	E2[g] components
I-OTs	953-91-3	$15.1 \pm 0.1_5$	0.693 ± 0.006	4.6 ± 0.1	10.5 ± 0.2	$2k_H^H$
II-OTs	1085-94-5	10.0 ± 0.12	0.641 ± 0.006	3.6 ± 0.1	6.4 ± 0.1	$k_D^H + k_D^D$
III-OTs	51933-07-4	9.17 ± 0.12	0.621 ± 0.005	3.5 ± 0.1	5.7 ± 0.1	$k_{D_2}^H + k_{D_2}^D$
IV-OTs	957-27-7	13.8 ± 0.1	0.673 ± 0.006	4.5 ± 0.1	$9.3 \pm 0.1_5$	$2k_{D_\alpha}^H$
V-OTs	967-93-1	6.67 ± 0.03	0.434 ± 0.013	3.8 ± 0.1	2.9 ± 0.1	$2k_{D_4}^D$
I-Br	108-85-0	$14.2 \pm 0.1_5$	0.910 ± 0.006	1.3 ± 0.1	12.9 ± 0.2	$2k_H^H$
II-Br	51933-08-5	7.50 ± 0.04	0.870 ± 0.006	0.98 ± 0.05	6.5 ± 0.1	$k_D^H + k_D^D$
V-Br	768-97-8	2.55 ± 0.01	0.711 ± 0.007	0.74 ± 0.02	$1.8 \pm 0.0_5$	$2k_{D_4}^D$

[a] Numbers refer to compounds in Chart I. [b] *k* is the second-order rate constant for total reaction (E2 + S_N2) of substrate. [ROTs] or [RBr] ~ 0.01 *M*; [NBu_4OAc] ~ 0.03 *M* in the presence of 0.015 *M* 2,6-lutidine. Values are the average of two or more determinations with average deviations. [c] F_E is the fraction of the total reaction which is bimolecular elimination. Determined from ratio of acid produced to substrate consumed and found to be constant throughout reaction. Values are the mean of six or more determinations with average deviations. [d] k_S is the second-order rate constant for the S_N2 portion of the total reaction. [e] Derived values are shown together with estimated error limits. [f] k_E is the second-order rate constant for total E2 component of reaction. [g] Indicates the individual E2 rate constants which make up k_E as shown in Chart I.

Chart I

Reaction Pathways for Bimolecular Anti Elimination from Variously Deuterated Cyclohexyl Derivatives[a]



[a] X = *p*-toluenesulphonate or bromide. [b] Symbolism for rate constants: superscript indicates whether H or D is eliminated (as HX or DX, respectively) in an anti elimination; subscript refers to the nature of the deuteration in the substrate. The notation is not intended to be general, but has been simplified as much as possible with reference to the compounds shown in Chart I. The notation for compound VI is necessary to distinguish the two pathways 6a and 6b from each other as well as from pathway 2a of compound II. [c] The labeling system used in this paper to define the positions where various isotope effects arise is as illustrated for the E2 reaction products of substrate VI. The labeling is such that the α carbon (C_α) is always that from which the leaving group X is lost, the β carbon (C_β) is always that from which hydrogen or deuterium is lost, and the ζ carbon (C) is adjacent to C_α but allylic to the developing double bond. The labeling of the carbon atoms clearly depends upon the direction of elimination from the substrate. Double-bond formation always occurs between C_α and C_β. [d] k_E represents the sum of all the E2 rate constants for production of cyclohexenes from a given substrate.

Table III

Partitioned Second-Order Rate Constants ($dm^3\ mol^{-1}\ sec^{-1}$) for the E2 Reactions of Cyclohexyl Tosylates and Cyclohexyl Bromides[a]

X in cyclohexyl X	Base	Solvent	Temp, °C	k^b	$k_H{}^{H c}$	$k_D{}^{H d}$	$k_D{}^{D d}$	$k_{D_2}{}^{H e}$	$k_{D_2}{}^{D e}$	$k_{D_\alpha}{}^{H c}$	$k_{D_4}{}^{D c}$	$k_{D\text{-cis}}{}^{H f}$	$k_{D'\text{-cis}}{}^{H g}$
Br	NBu_4OAc	Me_2CO	50.0	10^4	6.4_5	5.3	1.1				0.9		
OTs	NBu_4OAc	Me_2CO	50.0	10^4	5.2_5	4.7	1.7	4.2	1.4_5	4.6_5	1.4_5		
OTs	NaOEt	EtOH	49.9	$10^{5 h}$	6.7	5.9^i	2.3^i			6.5^j	1.6	5.9	6.0
OTs	KO-*t*-Bu	Bu-*t*-OH	49.9	$10^{5 h}$	4.3_5	$3.7_5{}^i$	1.2^i			3.8	0.7	3.7_5	3.5

[a] Symbolism is defined in Chart I. [b] These values are all derived from rate constants reported in Table II. [c] $k_H{}^H$ and $k_{D(4)}{}^H$ are half the observed E2 rate constants for the reactions of I, IV, and V, respectively, as shown in Chart I. [d] $k_D{}^H$ and $k_D{}^D$ are calculated from the observed E2 rate constants for the reactions of II (see Chart I) and the appropriate intramolecular isotope values ($k_D{}^H/k_D{}^D$) recorded in Table I. [e] $k_{D(2)}{}^H$ and $k_{D(2)}{}^D$ are calculated from the observed E2 rate constant ($k_{D(2)}{}^H + k_{D(2)}{}^D$) for the reaction of III (see Chart I) and the appropriate intramolecular isotope value ($k_{D(2)}{}^H/k_{D(2)}{}^D$) recorded in Table I. [f] $k_{D\text{-cis}}{}^H$ is assumed to be the same as corresponding value of $k_D{}^H$ (see text and Chart I). [g] $k_{D'\text{-cis}}{}^H$ is determined from the observed E2 rate constants ($k_{D\text{-cis}}{}^H + k_{D'\text{-cis}}{}^H$) for the reactions of VI, minus $k_{D\text{-cis}}{}^H$ (see text and Chart I). [h] These values are all derived from rate constants reported by Finley and Saunders.[21] [i] These values were derived using intramolecular isotope values ($k_D{}^H/k_D{}^D$) of 2.6 and 3.1 for the reactions of II-OTs with NaOEt and KO-*t*-Bu, respectively, at 50°. These intramolecular isotope values were extrapolated from the corresponding values recorded in Table I for 75° using temperature data reported by Melander.[23] [j] Measured at 50.0°. The corresponding value of $k_H{}^H$ at 50.0° is $7.4 \times 10^{-5}\ dm^3\ mol^{-1}\ sec^{-1}$ (see footnote *c* and ref 21).

Table IV
Primary and Secondary Kinetic Hydrogen Isotope Effects for E2 Reactions of Cyclohexyl Tosylate and Cyclohexyl Bromide with Bases at 50°

				$k_H^H/k_{D_\alpha}^H$		
			k_H^H/k_D^D,	Secondary[a, b]		
X in cyclohexyl X	Base	Solvent	primary[a]	C_α[c]	C_β[d]	C_ζ[e]
OTs	NBu_4OAc[f]	Me_2CO	$3.0_5 \pm 0.1_5$	1.13 ± 0.04	1.17 ± 0.06	1.11 ± 0.05
	NaOEt	EtOH	2.9 ± 0.1	1.14 ± 0.02[g]	1.15 ± 0.06	1.13 ± 0.03
	KO-*t*-Bu	Bu-*t*-OH	3.6 ± 0.1	1.15 ± 0.01[g]	1.25 ± 0.04	1.17 ± 0.02
Br	NBu_4OAc[f]	Me_2CO	5.4 ± 0.2			1.22 ± 0.04

[a] All isotope effects are calculated from the partitioned second-order rate constants recorded in Table III, as described in the text. Estimated error limits are also recorded. [b] The labeling of carbon atoms is as defined in Chart I. [c] C_α-H hybridization isotope effect. [d] C_β-H hybridization isotope effect. Evaluated as described in the text. [e] C -H hyperconjugative isotope effect. Evaluated as shown in text. [f] In the presence of 0.015 *M* 2,6-lutidine. [g] As reported by Finley and Saunders.[21]

($2°C_\beta$). In the E2 reaction pathways 3b, 5, and 6b shown in Chart I, anti elimination occurs into the branch containing a deuterium atom at C_β cis to the leaving group X. The secondary hydrogen isotope effect arising in this situation, as the hybridization at C_β changes from sp^3 in the ground state to increasing sp^2 character in the transition state, may be evaluated by either of the following ways: (a) from $k_D^D/k_{D_2}^D$ (*cf.* pathways 2b and 3b in Chart I); (b) from $k_H^H/k_{D_2}^D$ (*cf.* pathways 1 and 3b in Chart I) which gives the product of this secondary isotope effect and the primary isotope effect (evaluated as shown above), *i.e.*, $k_H^H/k_{D_2}^D = k_H^H/k_D^D \times k_D^D/k_{D_2}^D \equiv 1° \times 2°C_\beta$ isotope effects (since k_H^H/k_D^D can be found independently, $k_D^D/k_{D_2}^D$ can be calculated); (c) from $k_H^H/k_{D'\text{-cis}}^H$ (*cf.* pathways 1 and 6b in Chart I).

iii. Secondary Hyperconjugative Isotope Effects at C_ζ ($2°C_\zeta$). In the E2 pathways 2a, 3a, 5, and 6a shown in Chart I, anti elimination occurs into the branch away from a site of deuteration at C_ζ. The magnitude of the secondary hydrogen isotope effect arising in this situation due to hyperconjugative interactions (*vide infra*) may be evaluated as follows: (a) from k_H^H/k_D^H (*cf.* pathways 1 and 2a in Chart I) which gives the isotope effect arising when deuteration at C_ζ is initially trans to the leaving group X; (b) from $k_D^H/k_{D_2}^H$ (*cf.* pathways 2a and 3a in Chart I) which gives the isotope effect arising when deuteration at C_ζ is initially cis to the leaving group X; (c) from $k_H^H/k_{D_2}^H$ (*cf.* pathways 1 and 3a in Chart I) which gives the cumulative (*i.e.*, multiplicative) effect arising from dideuteration at C_ζ, cis and trans to the leaving group X.

The magnitude of this hyperconjugative isotope effect was evaluated by all three of the above methods from the reactions of I-OTs, II-OTs and III-OTs with NBu_4OAc in acetone at 50°. The isotope effect was the same, *i.e.*, 11% in magnitude, regardless of the stereochemistry (cis or trans) of the substituent deuterium atom relative to the tosylate leaving group.

In addition to the hydrogen isotope effects evaluated for the reactions of cyclohexyl tosylate and cyclohexyl bromide with NBu_4OAc in acetone, we also include in Table IV for comparison the corresponding primary and secondary isotope effects for the reactions of cyclohexyl tosylate with NaOEt/EtOH and KO-*t*Bu/Bu-*t*-OH. These latter data are derived using the methods outlined above from the partitioned E2 rate constants recorded in Table III. The partitioned E2 rate constants for the NaOEt/EtOH and KO-*t*-Bu/Bu-*t*-OH reactions at 50° were in turn derived from rate constants reported by Finley and Saunders[21] in conjunction with intramolecular data extrapolated[23] from values at 75° reported in Table I (see Table III).

The rate constants for the two E2 reaction routes of *cis*-cyclohexyl-*2-d* tosylate (pathways 6a and 6b in Chart I) could not be separated using intramolecular techniques since the two monodeuterated olefins, which are produced, cannot be distinguished by mass spectrometry. The rate constants can be separated however if it is assumed that $k_{D\text{-cis}}^H = k_D^H$ (*cf.* pathways 6a and 2a). This is not an unreasonable assumption. It has been already shown above, for the reaction of cyclohexyl tosylate with NBu_4OAc, that the stereochemistry (cis or trans) of a substituent deuterium at C_ζ relative to the leaving group at C_α has little or no effect on the magnitude of the secondary hyperconjugative isotope effect when elimination occurs into the branch remote from the site of deuteration.

Discussion

Our first attempts[1] to evaluate primary kinetic hydrogen isotope effects for E2 reactions in alicyclic systems were based in some instances upon the results of intramolecular competition reactions and included effects due to secondary isotope effects. For example, *trans*-cyclohexyl-*2-d* tosylate can undergo anti elimination along two routes (pathways 2a and 2b in Chart I). The olefin product ratio, as determined by mass spectrometry, gives the ratio of the rate constants for the two intramolecular processes, *i.e.*, k_D^H/k_D^D. We had assumed[1] that this "intramolecular" isotope effect was a reflection of the "true" primary hydrogen isotope effect for this system (*i.e.*, $k_D^H/k_D^D = k_H^H/k_D^D$). The "intramolecular" value is lower than the "true" primary value however since it can be expanded to

$$\frac{k_D^H}{k_D^D} = \frac{k_H^H}{k_D^D} \times$$

$$\frac{k_D^H}{k_H^H} \equiv \frac{1° \text{ isotope effect}}{2° \text{ hyperconjugative isotope effect at } C_\zeta}$$

The secondary hydrogen isotope effect involved in this instance is that arising from hyperconjugation and is ~10–20% in magnitude. Like other workers in this area,[21] we initially assumed that secondary hydrogen isotope effects were negligible relative to the magnitude of the associated primary isotope effects. The danger in making such an assumption is clearly demonstrated by the discrepancies between our reported[1] primary hydrogen isotope effects (k_D^H/k_D^D) for the reactions of *trans*-cyclohexyl-*2-d* tosylate with both NaOEt in ethanol and KO-*t*-Bu in *tert*-butyl alcohol *vs.* those reported by Finley and Saunders.[21] Finley and Saunders reported values of 4.47 and 7.53, respectively, at 50°, whereas we found 2.6 and 3.1 at 50°. Professor Saunders[24] has since pointed out to us that the results can be reconciled if it is realized that the Finley and Saunders values are derived from an intermolecular rate comparison [*i.e.*, from $k_H{}^H/(k_D{}^H + k_D{}^D - k_H{}^H)$] whereas our values ($k_D{}^H/k_D{}^D$) are derived from an intramolecular product comparison. We both assumed that sources of secondary isotope effects are negligible (*i.e.*, that $k_D{}^H = k_H{}^H$) but the error arising from this assumption is much more serious when using the Finley and Saunders expression than it is with ours. This can readily be seen by comparison of the two sets of assumed primary isotope effects (2.6 and 3.1 from part VI[1] and 4.5 and 7.5 from Finley and Saunders[21]) with the "true" primary isotope values of 2.9 and 3.6, respectively, for reaction with NaOEt/EtOH and KO-*t*-Bu/Bu-*t*-OH as reported in Table IV.

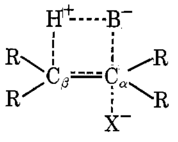
The "intramolecular" isotope effects recorded in Table I for the reactions of *trans*-cyclohexyl-*2-d* tosylate and *trans*-cyclohexyl-*2-d* bromide with a variety of bases have been discussed in part VI.[1] They provide a reasonable reflection of "true" primary hydrogen isotope effects, provided it is realized that these values are probably about 10–20% too low (as judged from the magnitudes of the secondary hyperconjugative isotope effects at C_ζ reported in Table IV).

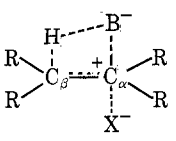
We show in Table I that the "intramolecular" isotope values for the reactions of cyclohexyl-*2,2-d*$_2$ tosylate (*i.e.*, $k_{D_2}{}^H/k_{D_2}{}^D$; see Chart I) with a series of bases is remarkably similar to the corresponding set of values for the reactions of *trans*-cyclohexyl-*2-d* tosylate ($k_D{}^H/k_D{}^D$) and thus close to the true primary isotope effect. The similarity is because the two different types of secondary isotope effect at play in these systems, *i.e.* the hybridization effect at C_β and the hyperconjugative effect at C_ζ, are similar in magnitude. Thus

$$\frac{k_D{}^H/k_D{}^D}{k_{D_2}{}^H/k_{D_2}{}^D} = \frac{k_D{}^H}{k_{D_2}{}^H} \times \frac{k_{D_2}{}^D}{k_D{}^D} = \frac{2^\circ \text{ hyperconjugative isotope effect at } C_\zeta}{2^\circ \text{ hybridization isotope effect at } C_\beta}$$

The sets of intramolecular isotope effects in Table I give little indication that secondary isotope effects are significant. However, compared with the sets of *inter*molecular isotope effects in Table I which show the relative E2 rates for the cyclohexyl and cyclohexyl-*2,2,6,6-d*$_4$ systems, we do get an indication of the distortion produced by the cumulative effect of several secondary isotope effects.

The secondary hydrogen isotope effects for the E2 reactions of cyclohexyl tosylate and cyclohexyl bromide with NBu_4OAc in acetone, NaOEt in ethanol and KO-*t*-Bu in *tert*-butyl alcohol are substantial, *i.e.*, 11–25% (see Table IV). This reflects the fact that a great deal of change has taken place at both C_α and C_β in forming the E2 transition states of these reactions. We have shown elsewhere[18,20,25] that the E2 reactions of cyclohexyl tosylate with a wide range of bases are E2C-like in character; *i.e.*, they may use transition states like VII or VIII.[1] E2 reactions of cyclohexyl bromide are less E2C like, but have considerable E2C character relative to reactions of more acidic substrates with the same bases. These classifications as E2C like are supported by the low primary hydrogen isotope effects exhibited by most eliminations from these two substrates (see Tables I and IV), as discussed elsewhere.[1]


VII


VIII

The E2C–E2H spectrum of transition states has been described in previous publications[18,20] in terms of structure VII. More recently we reported[1] that we cannot reject structures like VIII as being descriptive of E2C-like transition states. With regard to the influence of secondary hydrogen isotope effects, the important feature of transition state structures like VII and VIII is that C_α and C_β are both considerably sp^2 hybridized. In VII there is pπ–pπ orbital overlap to give a well-developed double bond. In VIII there is considerable positive charge formation at C_α, which is stabilized by interaction with the attacking anion and leaving group anion in an ion-triplet arrangement. Despite the rehybridization at C_β in VIII, there is little C_β–H bond breaking, no negative charge at C_β, and as a result a very poorly developed double bond. We prefer VII, but cannot exclude VIII, on existing evidence.

For transition states like VII or VIII, significant secondary hydrogen isotope effects, arising from the extensive hybridization changes at C_α and C_β, are therefore expected. In this work we find that such hybridization isotope effects lie in the range of 13–25% (see Table IV). Is this a large effect? C_α–H isotope effects in solvolysis reactions provide a guide to the magnitude of the secondary hybridization isotope effects that one may expect for reactions using transition states with extensive C_α rehybridization. Streitweiser and Dafforn[26] claim a limiting value of 22% for the α-hydrogen secondary isotope effect arising in the trifluoroacetolysis of isopropyl tosylate. Saunders and Finley[27] have also reported a value of 22% for the α-hydrogen isotope effect in the acetolysis of cyclohexyl tosylate. These values reflect the limiting magnitude of the secondary α-hydrogen isotope effect that one may expect for reactions of secondary tosylates in which carbonium ion character, and consequently the extent of sp^2 hybridization at C_α, is at a maximum, with solvent nucleophilicity at a minimum.[3] The 13–25% secondary hybridization isotope effects observed in this work for the E2 reactions of cyclohexyl tosylate are, we feel, indicative that C_α and C_β have considerable sp^2 character in the transition state, and are consistent with the fact that E2C-like transition states are very product-like.

In other E2 reaction systems, Burton and de la Mare[28] report an α-hydrogen hybridization isotope effect of 12% for the dehydrochlorination of 1,1,2,3,4-pentachlorotetralin with methoxide ion in methanol–acetone. Other evidence suggests that this reaction uses a transition state with a well-developed double bond. In contrast, Cockerill[29] reports low α-hydrogen secondary isotope effects (2–5%) for the reactions of para-X-substituted 2-phenylethyl tosylates (X = MeO, H, and Cl) with KO-*t*-Bu in *tert*-butyl alcohol. The low isotope effects observed in this case are consistent with the E2H-like nature of these reactions in which there is little rehybridization at C_α in the transition state. This contention is supported by the low (<1) tosylate/bromide leaving group tendencies reported for these reactions,[29] a criterion which we have previously shown[1] to be indicative of the E2H-like nature of a reaction.

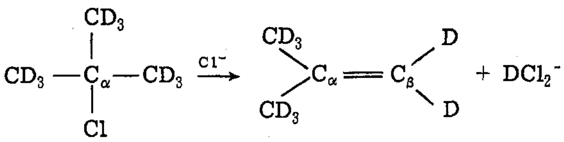
Secondary hyperconjugative hydrogen isotope effects for the reactions studied in this work are 11–22% (see Table IV). Whether these isotope effects arise from the differing hyperconjugative interactions of hydrogen relative to deuterium with sp^2-hybridized C_α, either as a well-developed double bond as in transition states like VII or as a well-developed positive charge at C_α as in VIII, we are unable to decide, but alternatives to either of these are hard to imagine. The magnitudes of the effects however suggest that E2C-like reactions have C_α much changed in the transition state. The concept of a secondary hyperconjugative isotope

Table V
Intermolecular Isotope Effects for the E2 Reactions of Cyclohexyl X and Cyclohexyl-*2,2,6,6,-d*$_4$ X with Bases at 50°

			Total isotope effect		Total secondary isotope effect^c
			Obsd^a	Calcd^b	
X	Base	Solvent	$k_H^H/k_{D_4}^D$	$k_H^H/k_{D_4}^D$	$k_H^H/k_{D_4}^D \times k_D^D/k_H^H$
OTs	NBu$_4$OAc^d	Me$_2$CO	3.6 ± 0.2^e	4.4 ± 0.9	1.2 ± 0.1^e
OTs	NaOEt	EtOH	4.2 ± 0.2^f	4.3 ± 0.6	$1.4_5 \pm 0.1$
OTs	KO-*t*-Bu	Bu-*t*-OH	6.3 ± 0.1^f	6.2 ± 0.6	$1.7_5 \pm 0.0_5$
Br	NBu$_4$OAc^d	Me$_2$CO	7.1 ± 0.2		1.3 ± 0.1

[a] Determined from the observed values of k_H^H and $k_{D(4)}^D$ reported in Table III. [b] Evaluated from the product of the component isotope effects (see Table IV). The total isotope effect is composed of a primary isotope effect, a secondary hybridization isotope effect at C_β, and two secondary hyperconjugative isotope effects at C_ζ. The somewhat large error limits shown here arise from the addition of percentage errors for the four component isotope effects. [c] Determined by dividing the observed total isotope effect ($k_H^H/k_{D(4)}^D$) by the primary isotope effect (k_H^H/k_D^D) found for the system (see Table IV). [d] In the presence of 2,6-lutidine. [e] See ref 36 and text. [f] As reported by Finley and Saunders.[21]

effect in E2C-like reactions seems to be new. Kevill and Dorsey[30,31] have reported some interesting data for the reactions of *tert*-butyl chloride and *tert*-butyl-d_9 chloride in acetonitrile. They observed[30] for the "E1-reaction" a β-deuterium isotope effect of 2.62 at 45°. This corresponds to a secondary hyperconjugative isotope effect of ~11% per deuterium. For the E2 reaction with NEt$_4$Cl Kevill and Dorsey[31] observed a β-deuterium isotope effect of 3.81 at 45°. This latter isotope effect is larger than we would expect for a primary hydrogen isotope effect (*cf.* Table I and part VI) in a reaction which we consider to be very E2C like in nature.[32] The observed value of 3.81 is understandable, however, if it is realized that it represents a primary isotope effect inflated by secondary isotope effects. As the reaction sequence (eq I) shows, the E2 reaction involves eight secondary hydrogen isotope effects (six due to hyperconjugative interactions and two due to hybridization changes at C_β) in addition to the primary isotope effect. If one assumes that the magnitude of the secondary isotope effects for this system is ~10% per deuterium (*cf.* the 11% effect per deuterium in the E1 reaction), the total secondary isotope effect component would amount to 2.1 (*i.e.*, [1.1]^8), yielding a primary isotope effect of 3.81/2.1 = 1.8. This is a much more acceptable value in our view, for a very E2C-like reaction when compared with the less E2C-like reactions of cyclohexyl tosylate which have $k_H^H/k_D^D < 3$.



$$(CD_3)_3C_\alpha Cl \xrightarrow{Cl^-} (CD_3)_2C_\alpha{=}C_\beta D_2 + DCl_2^- \qquad (I)$$

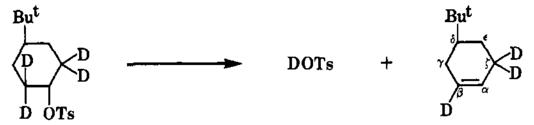
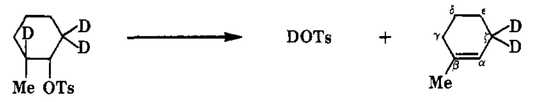
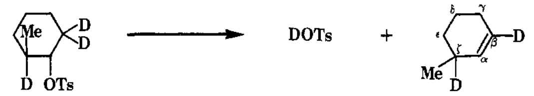
A question arises as to whether one might expect hyperconjugative isotope effects to differ depending upon whether isotopic substitution at C_2 (C_ζ in the product) is cis or trans to the leaving group in the ground state. In the solvolysis of cyclopentyl tosylates, Streitweiser[33] has shown that the effect of cis- and trans-2 deuteration is much the same, with the cis-isotope effect marginally larger than the trans-isotope effect. (*i.e.*, 22 *vs.* 16%, respectively). In this work, for the E2 reactions of cyclohexyl tosylates with NBu$_4$OAc in acetone, the cis- and trans-2-deuterium isotope effects appear to be about the same ($k_D^H/k_{D_2}^H = k_H^H/k_D^H = 1.11$) and the combined effect of cis- and trans-isotope effects gives the expected cumulative effect ($k_H^H/k_{D_2}^H = 1.24 = [1.11]^2$). This suggests that no specific hyperconjugation mechanism is operating in the E2 reactions of the cyclohexyl system, *i.e.*, that a trans-2-hydrogen isotope substituent is in no more favorable position to hyperconjugate with the developing double bond or developing carbonium ion center than is a cis-2-hydrogen isotope substituent (and vice versa). This is consistent with the situation found in many solvolysis reactions studied, particularly in acyclic systems,[34] where conformational restrictions upon hyperconjugating hydrogen isotopes are absent.[35]

Rate constants for the E2 reactions of the tetradeuterated substrates, cyclohexyl-*2,2,6,6*-d_4 tosylate (V-OTs) and bromide (V-Br), should be retarded relative to the rate constants for their undeuterated analogs owing to a combination of several hydrogen isotope effects. These include a secondary isotope effect due to hybridization changes at C_β and two secondary hyperconjugative isotope effects at C_ζ, in addition to the more dominant primary hydrogen isotope effect (see pathway 5 in Chart I). In Table V we compare total isotope effects observed for reactions in these systems with values calculated from the product of all of the component isotope effects. The agreement between observed and calculated total isotope effects is quite good especially for the reactions with NaOEt/EtOH and KO-*t*-Bu/Bu-*t*-OH derived from Finley and Saunders[21] rate data. The observed total isotope effect for the E2 reaction of V-OTs with NBu$_4$OAc in acetone is ~14% lower than the calculated value, but this may be due to the incomplete deuteration of this substrate.[36] In Table V we also show the magnitudes of the total secondary isotope effects for the reactions indicated. These are determined by dividing the total observed isotope effect by the primary isotope effect for the system (see Table IV). Again, the value of the total secondary isotope effect for the reaction of V-OTs with NBu$_4$OAc in acetone is lower (1.2) than the value that can be calculated (1.4) from the component secondary isotope effects. With this in mind it can be seen that the magnitude of the total secondary hydrogen isotope effect for these systems is a rather substantial 30–80%.

In part IV[2] we reported the hydrogen isotope effects observed in the E2 and S$_N$2 reactions of some tri- and tetradeuterated alkyl-substituted cyclohexyl tosylates with NBu$_4$Cl in acetone at 75°. The E2 isotope effects reported were the total observed isotope effects for the specified reactions. In Chart II we re-treat these data and refine from them values for the component isotope effects. Substrates, products, and total E2 isotope effects are shown in Chart II together with an indication of the component isotope effects which are operative in each reaction. If we assume that the magnitudes of the component isotope effects are the same for all three substrates, despite the differing nature of the alkyl substituents, we can set up three equations (1–3) in three unknowns from the information recorded in Chart II. A = primary hydrogen isotope effect, B = secondary C_α–H hyperconjugative isotope effect, and C =

Chart II

Kinetic Hydrogen Isotope Effects on the E2 Reactions of Alkyl-Substituted Cyclohexyl Tosylates with NBu_4Cl in Acetone at 75°[a]

Substrate		$\left(k_E^H/k_E^D\right)$[b]	Component Isotope Effects[c]
IX[d]		3.2	A×B×B×C
X		3.0[e]	A×B×B
XI		2.7	A×B×C

Component Isotope Effects:[f]

A = Primary isotope effect = 1.9

B = Secondary C_ζ–H hyperconjugative isotope effect = 1.19

C = Secondary C_β–H hybridization isotope effect = 1.20

[a] Reactions of 0.035–0.040 *M* NBu_4Cl with 0.015–0.020 *M* alkyl tosylates. [b] k_E^D and k_E^H are the rate constants for elimination from the indicated deuterated substrate and its undeuterated analog. k_E^H/k_E^D represents the total isotope effect observed. [c] Indicates the component isotope effects in each reaction which combine multiplicatively to give the total observed isotope effect. [d] *trans*-4-*tert*-butylcyclohexyl-*2,2,6,6-d*$_4$ tosylate. [e] at 50°. [f] From the data in the chart, three equations in the three unknowns *A*, *B*, and *C* can be set up and readily solved. It is assumed that the magnitudes of the component isotope effects are the same for all three substrates despite the differing nature of the alkyl substituents. Allowance is made for the fact that the datum for the reaction of VIII refers to 50° and not 75° (see text).

$$AB^2C = 3.2 \text{ at } 75° \tag{1}$$

$$AB^2 = 3.0 \text{ at } 50° \tag{2}$$

$$ABC = 2.7 \text{ at } 75° \tag{3}$$

secondary C_β–H hybridization isotope effect. From eq 1 and eq 3 we can derive

$$B = 1.19 \text{ at } 75°$$

We note that eq 2 applies to 50°. However, although primary hydrogen isotope effects are certainly temperature dependent,[23] secondary hyperconjugative isotope effects have been found to vary much less with temperature[37] and in some cases to be actually temperature independent.[38] If we assume that secondary isotope effects are the same at 75 and 50° for the reactions in Chart II we can then substitute our value for *B* into eq 2 and obtain

$$A = 2.14 \text{ at } 50°$$

which can be extrapolated to 75° using Melander's data[23] to give

$$A = 1.90 \text{ at } 75°$$

Substitution of A and B in eq 3 leads to

$$C = 1.20 \text{ at } 75°$$

These derived isotope values are not significantly changed even if secondary isotope effects are slightly temperature dependent to the extent observed by other workers.[37] The component isotope effects thus found for the chloride ion promoted E2 reactions shown in Chart II are consistent with the isotope effects found in this work for reactions of cyclohexyl tosylate with other bases (see Table IV). The primary hydrogen isotope effect (A = 2.1 at 50°) for the NBu_4Cl promoted reactions, for instance, is smaller than the value of 3.0 at 50° observed for NBu_4OAc promoted reactions of cyclohexyl tosylate, as would be expected for more E2C-like reactions.[1] Similarly, the secondary hyperconjugative isotope effect (B = 1.19) and secondary C_β hybridization isotope effect (C = 1.20) for the NBu_4Cl reactions of cyclohexyl tosylate are comparable in magnitude to the secondary isotope effects reported in Table IV for other bases.

Isotope Effects in SN2 Reactions. From the data in Table II, secondary hydrogen isotope effects can be evaluated for the SN2 components of the reactions studied with NBu_4OAc as base. These isotope effects are recorded in Table VI together with available isotope effects for the SN2 reactions of other bases with cyclohexyl derivatives. All of the data in Table VI, with the exception of that for the reaction of NBu_4OAc with cyclohexyl-*1-d* tosylate (IV-OTs), refer to β-hydrogen isotope effects. These β-isotope effects (20–75%) are significantly larger than those reported by Shiner[12] (3–13%) for the SN2 reactions of β-deuterated isopropyl bromides with $EtO^-/EtOH$. This may be due, at least in part, to the fact that SN2 transition states for secondary cyclohexyl tosylates are "looser" and therefore more ionic than the corresponding SN2 transition states for secondary alkyl bromides. That β-hydrogen isotope effects increase in magnitude as the transition state for substitution becomes "looser" has been demonstrated clearly by Leffek and coworkers.[13] They reported small

Table VI
Isotope Effects on the Substitution (SN2) Reactions of Variously Deuterated Cyclohexyl Tosylate and Cyclohexyl Bromides with Bases in Acetone at the Temperatures Shown[a]

	k_S^H/k_S^D[b]				
Substrate[c]	NBu_4OAc,[d,e] 50°	NBu_4Cl,[d] 75°	NBu_4SAr, 75°	NBu_4OPh, 50°	NBu_4N_3, 50°
II-OTs	1.3 ± 0.1				
II-Br	1.3 ± 0.2				
III-OTs	1.3 ± 0.1				
IV-OTs	1.02 ± 0.05				
V-OTs	1.2 ± 0.1[f]	1.3 ± 0.1	1.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1
V-Br	1.7_5 ± 0.2				
IX-OTs[g]		1.4[j]			
X-OTs[h]		1.1[j]			
XI-OTs[i]		1.1[j]			

[a] Base concentrations are 0.03–0.04 *M* with substrates 0.01–0.02 *M*; NBu_4 is the tetra-*n*-butylammonium cation, OAc is acetate, OPh is phenoxide, and SAr is *p*-nitrothiophenoxide. [b] k_S^H/k_S^D is the rate constant for substitution in the undeuterated substrate (k_S^H) relative to the rate constant for substitution in the indicated deuterated substrate (k_S^D). [c] Numbers refer to substrates indicated in Charts I and II. [d] In the presence of 0.015 *M* 2,6-lutidine. [e] Calculated from data recorded in Table II. [f] See text and ref 36. [g] Registry number 51933-09-6. [h] Registry number 52003-55-1. [i] Registry number 52003-56-2. [j] Calculated from rate constants reported in ref 2.

(2–4%) β-isotope effects for hydrolyses at primary carbon in ethyl derivatives, but large (31–55%) β-isotope effects for hydrolyses at secondary carbon in isopropyl derivatives. In this case, of course, the enhancement of the β-isotope effect is due to a shift in mechanism from SN2 (tight) for the primary substrates to borderline or SN1 (loose) for the secondary substrates.

In contrast to the sizable β-hydrogen SN2 isotope effects reported in Table VI, only a 2% α-hydrogen isotope effect was observed for the SN2 reaction of NBu_4OAc with cyclohexyl-*1-d* tosylate (IV-OTs) in acetone. This low value appears to be quite consistent with α-hydrogen isotope effects reported by other workers. No isotope effect at all was observed for the SN2 reaction of 2-bromopropane-*2-d* with $EtO^-/EtOH$,[12,15] and, indeed, small inverse α-hydrogen isotope effects have been reported[15,16] for SN2 reactions at a primary carbon atom.

Concluding Remarks

The hydrogen isotope effects observed in this work for the E2C-like elimination reactions of cyclohexyl tosylate and cyclohexyl bromide with various bases provide additional evidence to support the view that a great deal of change takes place at both C_α and C_β in reactions leading to E2C-like transition states. The following points emerge.

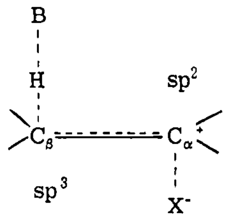
(1) The substantial secondary hybridization hydrogen isotope effects at C_β (15–25%) indicate that there is considerable rehybridization at C_β, from sp^3 in the ground state to sp^2 in the transition state, for E2C-like reactions. This is in agreement with conclusions based on substituent effects, where steric acceleration by bulky β substituents relative to hydrogen, is explicable in terms of changes in bond angles at C_β from tetrahedral to trigonal.[39] In contrast, E2C-like reactions are insensitive to the electronic effects of β substituents,[39,40] which suggests that there is little or no negative charge development at C_β in the transition state.

(2) Secondary hybridization hydrogen isotope effects at C_α (13–15%), as well as secondary hyperconjugative hydrogen isotope effects at C_ζ (11–22%), are both substantial and indicate significant hybridization changes at C_α. This again is in agreement with conclusions based on substituent effects,[39] where steric acceleration by bulky α substituents relative to hydrogen occurs for much the same reason as the rate enhancement observed in SN1 processes, *i.e.*, due to release of steric compression as the hybridization of C_α changes from sp^3 to sp^2 from reactants to transition state.

(3) The extensive changes in hybridization at both C_α and C_β, supported by the observed secondary hydrogen isotope effects discussed above, are consistent with E2C-like transition states like VII or VIII. The low primary hydrogen isotope effects observed for E2C-like reactions, in this work, and previously[1,2] are also consistent with VII or VIII, but do not allow us to decide whether the C_β–H bond is very loose as in VII or only slightly broken as in VIII. The insensitivity of E2C-like reactions to electron-withdrawing and electron-releasing substituents at both C_α[39,41] and C_β,[39,40] suggesting that there is little negative charge at C_β or positive charge at C_α, strongly favors E2C-like transition states like VII in which there is a well-developed double bond. This is supported by the similarity of rates of antidiaxial and anti-diequatorial elimination for E2C-like reactions in alicyclic systems, which is strongly suggestive that very olefin-like transition states are used.[19,20] Similarly, the accelerating effect of α- and β-methyl substituents relative to hydrogen, although explicable in terms of steric effects (*vide supra*), may be due at least in part to stabilizing hyperconjugative interactions with a well-developed double bond as in VII.[20,39]

Transition states like VIII with some positive charge at C_α cannot be ruled out, however. The lack of response which E2C-like reactions exhibit to the inductive effects of substituents at C_α[39,41] may be because there are *two* anions loosely bound to C_α in the transition state, in what is effectively an ion-triplet arrangement.[1] The requirements for positive charge stabilization at C_α by electron-releasing α substituents may therefore be much less than is the case in solvolysis (SN1) transition states[39,41] for instance, which are strongly stabilized by electron-releasing α substituents but which have only one anion (the leaving group) loosely associated with the positive charge center at C_α.

The observed hydrogen isotope effects are not consistent, however, with paene-carbonium transition states like



XII

XII where there is very little change in hybridization taking place at C_β.

We note that, for the SN2 reactions of cyclohexyl tosylates and bromides studies in this work, secondary hydrogen isotope effects at C_β are quite significant. In as much as these β-isotope effects arise from hyperconjugative interactions with C_α, this is consistent with the view that these SN2 reactions use "loose" transition states, and in agreement with the conclusions drawn from solvent effects upon such reactions.[42,43] It is also noteworthy that secondary hydrogen isotope effects at C_β are of the same order of magnitude for both E2C-like reactions and their concomitant SN2 reactions. This is in complete consistency with other observations which have shown that SN2 and E2C-like reactions respond in much the same way to change of leaving group,[25] and of base,[18,44] as well as exhibit very similar enthalpies and entropies of activation.[20]

E2C-like and SN2 reactions differ in two respects as far as isotope effects are concerned. SN2 reactions naturally do not exhibit primary β-hydrogen isotope effects, and any interaction of the base with β hydrogen does not contribute to any stabilization of the SN2 transition state.[45] Also, secondary α-hydrogen isotope effects appear to be much smaller for SN2 reactions than they are for E2C-like reactions. The reaction of NBu_4OAc with cyclohexyl tosylate in acetone for example shows only a 2% hydrogen isotope effect for the SN2 reaction, but a 13% α-hydrogen isotope effect for the E2C reaction. While it is known that increased interaction between a nucleophile and C_α tends to reduce the α-hydrogen isotope effect in solvolysis reactions, as illustrated by the decreasing α-isotope effects observed for hydrolysis of *tert*-butyl, isopropyl, and ethyl derivatives,[13] the discrepancy between loose SN2 and E2C-like reactions is to us a little surprising. However, it does at least emphasize a point we have made before,[19,46] that the bond between the base and C_α in an E2C-like transition state is always looser than that in the concomitant SN2 transition state.

Experimental Section

Mass Spectra. The isotopic compositions of labeled precursors, substrates, and products of the elimination reactions were determined by mass spectrometry. Olefinic products were first isolated by preparative vpc. Compositions of deuterated cyclohexyl tosylates, which could not be determined directly, were equated with those measured for the parent cyclohexanols.

Samples were introduced into an AEI MS9 spectrometer through the heated inlet system, and peak intensities from three slow scans at low ionizing voltage (12–15 eV) in the region of the molecular ion were averaged. Spectra of unlabeled compounds, except cyclohexanol, run under these conditions showed that peaks in the molecular ion region, other than the molecular ion peaks, were negligible. Relative peak intensities of the molecular ions of a partly deuterated compound were therefore a direct measure of the relative amounts of undeuterated, monodeuterated, and polydeuterated compounds, provided that allowance was made for ^{13}C abundance.

The $M - H_2O$ peak from cyclohexanol was isolated and, under conditions of low ionizing voltage, arises principally from 1,3 and 1,4 eliminations.[47] Thus, isotopic compositions of partly deuterated cyclohexanol could be determined. The small amount of 1,2 elimination would cause the deuteration to be underestimated. The isotopic compositions of cyclohexyl-*2,2*-d_2 tosylate and cyclohexyl-*2,2,6,6*-d_4 tosylate, besides being determined using the parent alcohols, were also determined from the mass spectra of the derived bromides. There is minor enrichment of deuterium content accompanying the conversion of tosylate to bromide because of the concurrent elimination, and this would cause the deuteration of the tosylates to be overestimated. Repeated enrichment is unlikely because cyclohexyl tosylate reacts more rapidly with bromide ion than does cyclohexyl bromide. The two types of analysis, from the parent alcohols and the derived bromides, thus place upper and lower limits on the isotopic purity of these two tosylates.

Intramolecular Competition Reactions of II and III. Substrates II and III were individually treated with an excess of base at the temperatures shown in Table I. Product olefin mixtures were isolated by preparative vpc and the ratio of the two olefins was analyzed by mass spectrometry in the vicinity of the molecular ion. Allowance was made for incomplete deuteration of the substrates.

Intermolecular Competition Reactions of I and V. Equimolar mixtures of I and V, 0.1 *M* as bromides or tosylates, were prepared with allowance for the incomplete deuteration of V. They were reacted with 0.1 *M* base for only 10% of reaction and the product olefins were separated by preparative vpc from the reaction mixture. The ratio of the two olefins was analyzed by mass spectrometry in the vicinity of the molecular ion.

Kinetics. Rates for the overall reactions (E2 + SN2) of the variously deuterated cyclohexyl tosylates shown in Table II with NBu_4OAc were measured by following consumed acetate base by titration *vs.* *p*-toluenesulfonic acid in acetone with Bromothymol Blue as indicator. Rates of cyclohexyl bromides were followed by potentiometric titration of liberated bromide ion against silver nitrate after acidification of samples with dilute nitric acid. Rates of all deuterated compounds were measured under identical conditions and simultaneously with undeuterated substrates. All reactions with NBu_4OAc were carried out in the presence excess (0.015 *M*) 2,6-lutidine, to prevent formation of the homoconjugate species $H(OAc)_2^-$ as acid developed in the course of the reaction. The fraction of each reaction (F_E) which was bimolecular elimination was determined from the ratio of acid produced to total substrate consumed, and was found to be constant throughout each individual reaction. Developed acid was estimated by titration *vs.* standard sodium methoxide in methanol using Thymol Blue as indicator. The rate constants reported in Table II are the averages of duplicate or triplicate determinations, with average deviations shown.

Materials. Tetra-*n*-butylammonium salts were prepared as previously described.[40] Sodium ethoxide–ethanol and potassium *tert*-butoxide–*tert*-butyl alcohol solutions were prepared by dissolving the appropriate metal in ethanol or *tert*-butyl alcohol, respectively, under nitrogen. The solvents acetone, ethanol, and *tert*-butyl alcohol were purified by standard procedures. Deuterated and undeuterated cyclohexanols and cyclohexyl bromides were purified by distillation and had bp ~60° (20 mm). They were better than 99% pure as determined by vpc. Cyclohexyl tosylates were prepared as previously described,[20,21] mp 44–46° (lit.[21] 42.5–46.5°).

trans-Cyclohexyl-*2*-*d* bromide (0.8% d_2, 87.3% d_1, 11.9% d_0) and *trans*-cyclohexanol-*2*-*d* (1.2% d_2, 94.2% d_1, 4.6% d_0) were prepared as previously described.[1]

Cyclohexanol-*1*-*d* (1.4% d_2, 91.7% d_1, 6.9% d_0) was prepared by reduction of cyclohexanone with lithium aluminium deuteride in the manner reported by Finley and Saunders.[21]

Cyclohexanol-*2,2,6,6*-d_4 (87 ± 6% d_4, 11.5 ± 4% d_3, 1.5 ± 1.5% d_2, 0% d_1, 0% d_0) was prepared as previously described.[48] The large number of β-deuterium atoms makes the mass spectral analysis of this alcohol slightly unsatisfactory, because of the increased possibility of HOD 1,2 elimination.[47]

Cyclohexyl-*2,2,6,6*-d_4 bromide (92.6% d_4, 7.4% d_3, 0% d_2, etc.) was prepared from the tosylate using 2 equiv of tetra-*n*-butylammonium bromide (0.3 *M*) and 2,6-lutidine in refluxing acetone for 24 hr. The mixture was poured into pentane, extracted with ice-cold dilute hydrochloric acid, and dried (Na_2SO_4), and the remaining starting material was frozen out and recycled. The combined product from two treatments was dried, concentrated, and distilled from unreacted tosylate at below 40° and 5-mm pressure.

Cyclohexanol-*2,2*-d_2 (0.7% d_3, 94. d_2, 4.9% d_1, 0% d_0) was prepared from cyclohexanone-*2,2*-d_2, the reduction being carried out as for the conversion of cyclohexanone-*2,2,6,6*-d_4 to cyclohexanol-*2,2,6,6*-d_4.[48] Cyclohexanone-*2,2*-d_2 was prepared from cyclohexanonecarboxylic acid by deuterium exchange (D_2O) and thermal decarboxylation. A benzene solution of cyclohexanone carboxylic acid (25 g, mainly enol) was briefly shaken with aliquots of D_2O (3 × 5 g). The benzene solution was concentrated at low temperature and twice treated with D_2O in tetrahydrofuran for 7 min at room temperature. After evaporation of solvent at low temperature, the cyclohexanone produced by decarboxylation to this point was removed by pumping at <0.1 mm. The remaining cyclohexanonecarboxylic acid was dissolved in benzene (300 ml) and shaken briefly again with D_2O. The bulk of the D_2O layer was pipetted off, the remainder azeotroped off rapidly, and the solution was refluxed until CO_2 evolution was complete (~1 hr) before washing the benzene solution with ice-cold sodium bicarbonate solution and water. The solution was dried, concentrated, and distilled to give cyclohexanone-*2,2*-d_2. Reduction as described above yielded cyclohexanol-*2,2*-d_2 (41% yield). The low yield was probably the result of too vigorous exchange conditions.

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Reactions of Phosphorus Compounds. 35. Reaction of 4-Salicyloxybutyltriphenylphosphonium Bromide with Alcoholic Alkoxide

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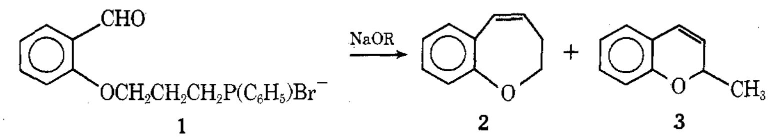
The reaction of 4-salicyloxybutyltriphenylphosphonium bromide (**5**) with alcoholic alkoxide gave 3,4-dihydro-2*H*-1-benzoxocin (**6**), 2-ethyl-2*H*-1-benzopyran (**7**), and 4-(*o*-α,α-diethoxymethylphenoxy)butyldiphenylphosphine oxide (**8a**). Mechanisms are proposed for the formation of **7** and **8**.

In previous papers[1] we have shown that 3-salicyloxypropyltriphenylphosphonium bromide (**1**) with base gives either 2,3-dihydro-1-benzoxepin (**2**) or 2-methyl-2*H*-1-benzopyran (**3**), depending on the nature of the solvent, and we have proposed a mechanism for the formation of **3** from **1**.[1c]



1 2 3

In the present work we wish to report the reactions of 4-salicyloxybutyltriphenylphosphonium bromide (**5**), under the influence of base, to give the expected 3,4-dihydro-2*H*-1-benzoxocin (**6**), 2-ethyl-2*H*-1-benzopyran (**7**), and the unexpected 4-(*o*-α,α-diethoxymethylphenoxy)butyldiphenylphosphine oxide (**8a**) [or 4-(*o*-α,α-dimethoxymethylphenoxy)butyldiphenylphosphine oxide (**8b**)].

The reaction of salicylaldehyde with 1,4-dibromobutane in aqueous NaOH gave a 62% yield of 4-salicyloxybutyl