The E2C Mechanism of Elimination Reactions. 9.[1] Secondary Deuterium Isotope Effects on Rates of Bimolecular Reactions in Alicyclic Systems

David Cook

Research School of Chemistry, The Australian National University, P.O. Box 4, Canberra, A.C.T. 2600, Australia

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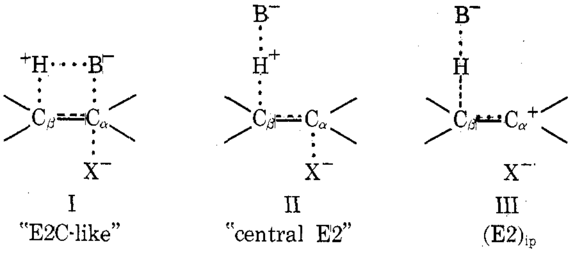
Secondary α-deuterium isotope effects on the rates of NBu$_4$OAc and NBu$_4$Cl promoted bimolecular reactions (E2 and SN2) of cyclohexyl tosylate and cyclohexyl bromide have been studied. The E2 reactions, which we have previously categorized as E2C-like, show α-deuterium isotope effects in the range 1.14–1.22, while the related SN2 reactions give values in the range 1.05–1.08. The discrepancy in the magnitude of the α-deuterium isotope effect for the E2 and SN2 processes is consistent with the view that E2C-like reactions use "looser" transition states than those used in the concurrent SN2 reactions. While the reported α-d isotope effects do not provide positive evidence to support the idea that the base interacts with C$_\alpha$ in the E2 transition states of the reactions studied, neither do they substantiate claims for dismissal of the concept. A comparison of the secondary γ-deuterium and β'-deuterium isotope effects arising in the reaction of cyclohexyl tosylate with NBu$_4$OAc in acetone indicates the two isotope effects to be of equivalent magnitude ($k_{\beta'-d}/k_{\gamma-d} = 0.98$). This observation can only be rationalized for this reaction in terms of a transition state structure in which there is extensive double bond development. It provides compelling evidence against the involvement of any transition state structure which accommodates extensive positive charge development at C$_\alpha$.

The use of secondary deuterium isotope effects as a tool for probing mechanistic detail has been extensively applied in the area of solvolytic processes.[2–4] Drawing from an abundance of available secondary deuterium isotope data, Shiner[3] in particular has been able to present a comprehensive and refined picture of the variation of rate-determining transition state structure in solvolytic reactions resulting from subtle changes in substrate structure and solvent interaction.

In contrast, the application of secondary deuterium isotope effects to studies of base-promoted bimolecular elimination and substitution reactions has been more limited. For E2 reactions, bond-forming and bond-breaking processes take place in a concerted but not necessarily synchronous fashion, between five atomic centers. In consequence, it is generally accepted that E2 reactions are best described as using a broad spectrum of transition states. However, there is some contention as to which of several proposed sets of transition states is most consistent in accounting for all the available reliable data relating to E2 reactions. In view of the above, the isolated use of secondary deuterium isotope effects as a definitive tool for probing E2 mechanism appears to be more limited. In conjunction with other data, however, secondary isotope effects can still provide useful information.

The focus of debate concerning transition state structure in E2 reactions is centered about those elimination reactions catalyzed by weak bases. The E2 transition states for reactions of even strong bases with substrates possessing very good leaving groups but unactivated β-hydrogen atoms also fall within the sphere of controversy. The reactions of secondary alkyl and cycloalkyl tosylates exemplify the latter category. For the above types of reactions, three possible transition state structures for which experimental evidence has been advanced are shown in I–III.



I "E2C-like" II "central E2" III (E2)$_{ip}$

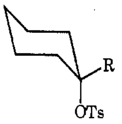
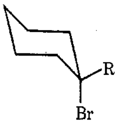
Detailed descriptions of these transition states have been reported elsewhere[5–7] and Ford has reviewed these structures in the light of relevant experimental data.[8,9] The three types of structure differ basically in the nature of the interactions about C$_\alpha$. In contention are (1) whether the base interacts with C$_\alpha$ as in I, or not, as in II or III; (2) whether there is a well-developed double bond between C$_\alpha$ and C$_\beta$ as in I and II, or alternatively a well-developed positive charge at C$_\alpha$ as in III; and (3) whether the covalent C$_\alpha$–X bond is extensively broken as in I or II, or completely ionized as in III.

Evidence has previously been presented indicating that substrates with good leaving groups (e.g., tosylate, bromide) undergoing elimination reactions promoted by relatively weak hydrogen bases but strong carbon nucleophiles (e.g., chloride and acetate anions), respond in much the same way as do SN2 reactions to change of base,[5a,10,11] leaving group,[12] and solvent.[5b,11,13] They also exhibit very similar enthalpies and entropies of activation.[11] These observations form the basis for invoking structures like I involving the interaction of base with C$_\alpha$, to describe the transition states of weak base catalyzed elimination reactions. Parker and co-workers describe such reactions as being "E2C-like", in contrast to those reactions generally involving strong hydrogen bases and poor leaving groups, which are labeled "E2H-like".[14]

To further our understanding of the nature of the interactions around C$_\alpha$, this laboratory has currently been involved in the investigation of secondary deuterium isotope effects on the rates of E2C-like reactions. In a previous report[15a] we noted that α-deuterium isotope effects for the E2 reactions of cyclohexyl tosylate with NBu$_4$OAc/acetone, with EtO$^-$/EtOH, and with t-BuO$^-$/t-BuOH were 1.13, 1.14, and 1.15, respectively. In comparison we were able to report an isolated and approximate value of 1.02 ± 0.05 for the α-deuterium isotope effect on the SN2 reaction of cyclohexyl tosylate with NBu$_4$OAc in acetone. This study has now been expanded, and this paper makes a more extensive comparison of α-deuterium isotope effects arising in concurrent E2 and SN2 reactions. The system studied is shown in reaction 1.

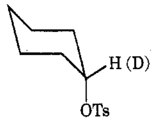
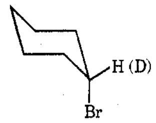
In addition, this paper reports the results of a comparative study of secondary deuterium isotope effects at C$_\gamma$ and C$_{\beta'}$ in the E2 reactions of cyclohexyl tosylate.[15b] In our initial study[15a] of secondary isotope effects in this system, we observed β'-deuterium isotope effects (see reaction 2) in the range

Table I. Kinetic Data for the Reactions of Cyclohexyl and Cyclohexyl-*1-d* Tosylates and Bromides at 75.0 ± 0.1°C with Acetate and Chloride Ions in Acetone Containing 0.015 M 2,6-Lutidine

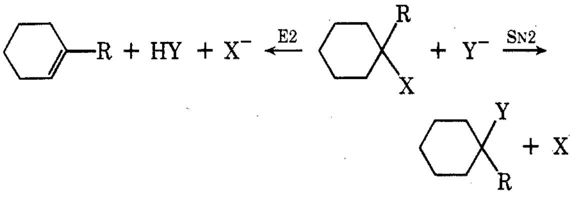
Substrate[a]	Base[b]	R	$10^4 k$,[c] $M^{-1}\,s^{-1}$	$100\,F_E$[d]	$10^4 k_E$,[e,f] $M^{-1}\,s^{-1}$	$10^4 k_S$,[f,g] $M^{-1}\,s^{-1}$	Registry no.
	NBu_4OAc[h]	H	106 ± 1	69.8 ± 0.5	73.6 ± 1.2	31.9 ± 0.5	953-91-3
	NBu_4OAc	D	95.0 ± 1.1	68.0 ± 0.4	64.6 ± 1.1	30.4 ± 0.5	957-27-7
	NBu_4Cl[i]	H	35.1 ± 0.3	70.9 ± 0.4	24.9 ± 0.4	10.2 ± 0.1	
	NBu_4Cl	D	31.5 ± 0.3	69.4 ± 0.3	21.9 ± 0.3	9.6 ± 0.1	
	NBu_4OAc	H	70.2 ± 0.6	90.0 ± 0.5	63.2 ± 0.9	7.00 ± 0.10	108-85-0
	NBu_4OAc	D	58.4 ± 0.1	88.6 ± 0.4	51.7 ± 0.3	6.66 ± 0.04	58692-26-5
	NBu_4Cl	H	8.04 ± 0.01	60.0 ± 0.3	4.82 ± 0.03	3.22 ± 0.02	
	NBu_4Cl	D	7.16 ± 0.06	58.4 ± 0.4	4.18 ± 0.06	2.98 ± 0.04	

[a] [ROTs] or [RBr] ~ 0.01 M. [b] NBu_4^+ is the tetra-*n*-butylammonium cation. Base concentrations ~0.03 M. [c] k is the second-order rate constant for total reaction (E2 + SN2) of substrate. Values are the average of three determinations with mean deviations. [d] F_E is the fraction of the total reaction which is bimolecular elimination, and was determined from the ratio of acid produced to substrate consumed. Values are the mean of at least ten estimations at all stages of reaction in each of two runs per reaction. [e] k_E is the second-order rate constant for the E2 component of the total reaction. [f] Derived from k and F_E: $k_E = F_E k$; $k_S = (1 - F_E)k$. Derived values are shown together with estimated error limits. [g] k_S is the second-order rate constant for the SN2 component of the total reaction. [h] Registry no., 10534-59-5. [i] Registry no., 1112-67-0.

Table II. Secondary α-Deuterium Isotope Effects for the E2 and SN2 Reactions of Cyclohexyl Tosylate and Cyclohexyl Bromide with Bases in Acetone at 75.0°C[a]

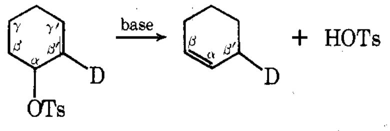
Substrate[a]	Base	k^H/k^D[b]	k_E^H/k_E^D[c]	k_S^H/k_S^D[d]
	NBu_4Cl	1.11 ± 0.02	1.14 ± 0.03	1.06 ± 0.03
	NBu_4OAc	1.11 ± 0.02	1.14 ± 0.04	1.05 ± 0.03
	NBu_4Cl	1.12 ± 0.01	1.15 ± 0.02	1.08 ± 0.02
	NBu_4OAc	1.20 ± 0.01	1.22 ± 0.02	1.05 ± 0.02

[a] All isotope ratios are derived from the rate constants reported in Table I. Estimated error limits are also recorded. [b] k^H/k^D is the α-*d* isotope effect for the total reaction (E2 + SN2). [c] k_E^H/k_E^D is the α-*d* isotope effect for the E2 component of the total reaction. [d] k_S^H/k_S^D is the α-*d* isotope effect for the SN2 component of the total reaction.



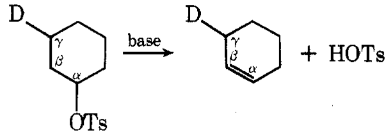
(1)

R = H, D
X = OTs, Br
$Y^- = Cl^-, OAc^-$



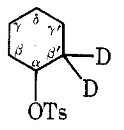
(2)

1.11–1.17. The β'-deuterium isotope effect is now compared with that arising from deuterium labeling at C_γ (see reaction 3).

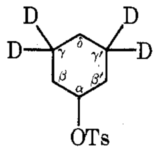


(3)

While the olefin products of reactions 2 and 3 have the deuterium label in equivalent positions (i.e., C_γ and $C_{\beta'}$ are both allylic to the double bond), the labeling of the substrates, relative to C_α, is quite distinct. The substrates selected to make the comparison of C_γ and $C_{\beta'}$ isotope effects were cyclohexyl-*2,2-d*$_2$ tosylate (IV) and cyclohexyl-*3,3,5,5-d*$_4$ tosylate (V).



IV



V

Results

Rate constants at 75.0 °C for the E2 and SN2 pathways of reaction 1 are reported in Table I. Derived secondary α-deuterium isotope effects are shown in Table II. Interference from solvolysis or decomposition of tetra-*n*-butylammonium salts at 75 °C was less than 1% for all reactions studied.[11] The anti nature of the E2 pathways for these reactions has previously been thoroughly established.[5c,11] No allowance has been made for incomplete dissociation of salts. However, rate comparisons between pairs of deuterated and undeuterated substrates were carried out simultaneously under identical reaction conditions (including salt concentrations) so that salt effects upon any reaction are canceled in the derivation of the isotopic rate ratio. The use of 2,6-lutidine to prevent complications from back addition of developed acid to product olefins, and to prevent formation of homoconjugate anion species [i.e., HCl_2^- and $H(OAc)_2^-$], has been described elsewhere.[11,15a,16] No correction for incomplete deuteration of substrates has been applied.

Table III. Kinetic Data for the Reactions of Cyclohexyl-*2,2-d*$_2$ Tosylate (IV) and Cyclohexyl-*3,3,5,5-d*$_4$ Tosylate (V) at 75.0 °C with NBu$_4$OAc in Acetone Containing 0.015 M 2,6-Lutidine

Registry no.	Substrate	$10^3 k$,[a] $M^{-1} s^{-1}$	$100F_E$[b]	$10^3 k_E$,[c] $M^{-1} s^{-1}$	$10^3 k^H_{D2}$,[d] $M^{-1} s^{-1}$	$10^3 k^H_{D4}$,[e] $M^{-1} s^{-1}$	k^H_{D2}/k^H_{D4}[f]
58692-27-6	IV	8.35 ± 0.02	62.8 ± 0.4	5.24 ± 0.05	3.68 ± 0.06[g]		0.98 ± 0.03
58692-28-7	V	11.0 ± 0.1	68.6 ± 0.6	7.55 ± 0.12		3.77 ± 0.06[g]	

[a] k is the second-order rate constant for total reaction (E2 + SN2) of substrate. [ROTs] ~0.01 M; [NBu$_4$OAc] ~0.03 M. Values are the average of three determinations with mean deviations. [b] F_E is the fraction of the total reaction which is bimolecular elimination. [c] k_E is the second-order rate constant for the total E2 component of reaction. [d] k^H_{D2} is the partitioned rate constant for anti elimination of HOTs from IV to yield olefin VI. This value is calculated from k_E ($= k^H_{D2} + k^D_{D2}$) and the intramolecular isotope value (k^H_{D2}/k^D_{D2}) of 2.35 (see text and Experimental Section). [e] k^H_{D4} is the partitioned rate constant for anti elimination into one branch of V to yield olefin VIII, i.e., $0.5k_E$ (see Chart I). [f] k^H_{D2}/k^H_{D4} gives the effect of β'-deuteration relative to γ-deuteration. [g] The reader is cautioned against making comparisons of rate data from this table with rate data reported in Table I, on the grounds that the sets of data in the two tables were *not* determined simultaneously and under identical reaction conditions. In these circumstances, small variations in temperature, base concentrations, solvent purity, etc., may introduce nonisotopic effects into such rate comparisons. A valid comparison of rate data for the reactions of NBu$_4$OAc with cyclohexyl tosylate and with cyclohexyl-*2,2-d*$_2$ tosylate (IV) has been reported previously.[15a]

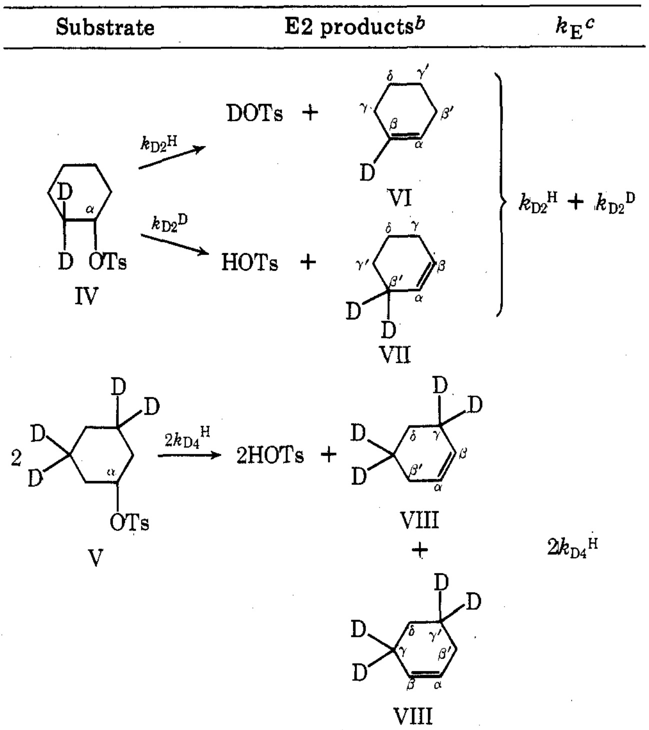
The α-deuterium isotope effect of 1.22 observed for the E2 pathway of the reaction of cyclohexyl bromide with NBu$_4$OAc is rather larger than the other E2 α-isotope effects reported in Table II (cf. 1.14–1.15). Ford and Pietsek[9] have also reported α-deuterium isotope effects in the range 1.13–1.15 for the E2 reactions of 1-bromo-1-arylpropanes with NBu$_4$Br in acetone. On quasi-theoretical grounds[17] the limiting α-deuterium isotope effect for leaving bromide is predicted to be 1.125, and equivalent values have been observed experimentally for solvolyses of substituted α-phenylethyl bromides.[18] While all the above observations tend to cast some doubt on the genuineness of the 1.22 α-*d* value observed in this work for the E2 reaction of cyclohexyl bromide with NBu$_4$OAc, one must be cautious about dismissing the observation as a spurious result. It was noted in part 7,[15a] for instance, that secondary α-*d* isotope effects are strikingly similar in magnitude to β'-*d* isotope effects for the E2 reactions of cyclohexyl tosylate with a variety of bases. We also reported in part 7[15a] a β'-deuterium isotope effect of 1.22 for the E2 reaction of cyclohexyl bromide with NBu$_4$OAc in acetone, and this value therefore gives some credence to the 1.22 α-*d* isotope effect reported in Table II. However, at this time, no suitable explanation is offered for the unusually large secondary isotope effects observed for this reaction.

Elimination from the tosylate IV can proceed by two routes, involving either elimination of HOTs or DOTs, to yield two distinct olefins. Elimination of HOTs from the tosylate V can also proceed by two routes, but in this case the product olefins are identical. The E2 reaction pathways for both these tosylates are shown in Chart I together with the symbolism distinguishing the rate constants for the various elimination routes. The kinetic data for these reactions promoted by NBu$_4$OAc in acetone are reported in Table III. The individual rate constants for the two E2 pathways of IV were calculated by partitioning the total E2 rate constant ($k^H_{D2} + k^D_{D2}$) according to the proportions of the olefin products VI and VII. The olefin ratio [VI]/[VII] ($\equiv k^H_{D2}/k^D_{D2}$) for the reaction of IV with NBu$_4$OAc in acetone at 75.0 °C was determined in a separate experiment, in which the product olefin mixture was isolated by preparative GLC and analyzed by mass spectrometry. k^H_{D2}/k^D_{D2} was found to be 2.35 ± 0.01 at 75.0 °C. The ratio of the rate constants k^H_{D2}/k^H_{D4} then provides a comparison of the γ-*d* and β'-*d* isotope effects. It is assumed that the additional two deuterium atoms in V, located at C_γ in VIII, are too remote to significantly affect the comparison.

Discussion

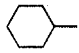
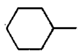
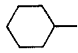
Deuterium Isotope Effects at C_α. The secondary α-*d* isotope effects reported in Table II for the E2 reactions of cyclohexyl tosylate are 1.14 at 75.0 °C. These values are comparable to the values of 1.14 and 1.15 reported by Finley and Saunders[19] for the reactions of cyclohexyl tosylate with lyate ions in ethanol and *tert*-butyl alcohol, respectively, at 49.9 °C. Likewise, the α-*d* isotope effect of 1.15 at 75.0 °C in Table II for the reaction of cyclohexyl bromide with NBu$_4$Cl is comparable to the values of 1.128 and 1.146 observed by Ford and Pietsek[9] for reactions of 1-bromo-1-phenylpropane and 1-bromo-1-(4-tolyl)propane, respectively, with NBu$_4$Br in acetone at 74.6 °C. These α-deuterium isotope effects are indicative of elimination transition states (for rate-limiting processes) in which C_α is significantly rehybridized from sp^3 to sp^2.[2,9,15,19] However they do not tell us whether there is extensive double bond development between C_α and C_β as

Chart I. Reaction Pathways for Bimolecular Anti Elimination from Cyclohexyl-*2,2-d*$_2$ Tosylate and Cyclohexyl-*3,3,5,5-d*$_4$ Tosylate[a]



[a] Symbolism for rate constants: superscript indicates whether H or D is eliminated (as HOTs or DOTs, respectively) in an anti elimination; subscript refers to the extent of deuteration in the substrate. The involvement of base is assumed but omitted for simplicity. [b] The labeling system used in this paper to define the positions where various isotope effects arise is as illustrated in the product olefins (see also ref 15b). [c] k_E represents the sum of the component E2 rate constants for production of cyclohexenes from a given substrate.

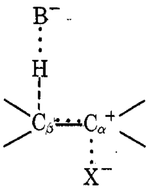
Table IV. α-Deuterium Isotope Effects for Some Reactions of Alkyl and Cycloalkyl Tosylates

Reactants	Reaction mechanism	k^H/k^D [a]	
—OTs/AcOH[b] *i*-PrOTs/TFA[c,d]	Limiting SN1	1.22	↑ Increasing "looseness" of transition states
—OTs/Cl⁻/acetone[e]	E2C (secondary carbon)	1.14	
—OTs/Cl⁻/acetone[e] *i*-PrOTs/H_2O[f,g]	SN2 (secondary carbon)	1.06	
EtOTs/H_2O[g]	SN2 (primary carbon)	1.02	
MeOTs/H_2O[g]	SN2 (primary carbon)	0.98	

[a] k^H/k^D is the secondary α-deuterium isotope effect for the mechanism specified. [b] W. H. Saunders, Jr., and K. T. Finley, *J. Am. Chem. Soc.*, **87**, 1384 (1965). [c] TFA is trifluoroacetic acid. [d] A. Streitweiser, Jr., and G. A. Dafforn, *Tetrahedron Lett.*, 1263 (1969). [e] This work. [f] The SN2 reaction of *i*-PrOTs/H_2O only. For the total reaction (SN1 + SN2) an overall α-*d* isotope value of 1.136 has been reported by Leffek, Llewellyn, and Robertson, *Can. J. Chem.*, **38**, 1505, 2171 (1960). [g] Reference 3, p 128.

proposed in "E2C-like" transition states I or in "central" E2 transition states like II, or, alternatively, whether there is extensive positive charge formation at C_α as in ion-pair transition states such as III.

For an $(E2)_{ip}$ ion-pair mechanism[7] to be operative for reactions such as those mentioned above, the relatively large α-deuterium isotope effects observed for elimination (cf. limiting solvolytic k^H/k^D for tosylates of ~1.22[2] and for bromides of ~1.13[18]) require the reversible ionization process to form a tight ion pair to be substantially the rate-determining step. This apparently rules out rate-determining irreversible capture by base of a preformed ion pair as in III, except when this process marginally competes with the collapse of the ion pair to regenerate starting material. Alternatively, the base could participate in the reversible ionization step as in IX, but



IX

in this case the mechanism becomes virtually indistinguishable from the E1-like (paenecarbonium ion) transition state proposed by Bunnett.[6]

The α-deuterium isotope effects reported in Table II for the SN2 pathways of reaction 1 lie in the range 1.05–1.08. These values are reasonable for SN2 reactions at a secondary carbon atom. Shiner,[3] for example, predicts an α-*d* effect of 1.05–1.07 for the solvolysis of isopropyl brosylate in 90% aqueous ethanol at 25 °C. Shiner's prediction is based upon an observed isotope effect of 1.083,[20] an estimate that solvolysis proceeds by an SN2 mechanism to the extent of 94%, and an allowance for the expected effect of α-methyl substitution (k^H/k^D = 0.98 and 1.02 per D for the hydrolyses of methyl and ethyl brosylate, respectively).[3]

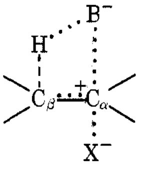
Comparison of the α-*d* isotope effects shown in Table II indicates that in all cases the SN2 isotope effect is smaller than that for the concurrent E2 reaction. The differing isotope effects for the E2 and SN2 processes certainly confirm[21] the extensive stereochemical evidence[5c] proving that competing SN2 and E2 reactions do not use a common transition state as was originally envisaged in the merged mechanism concept.[22] However, the author does not agree with Ford and Pietsek[9] that the discrepancy between E2 and SN2 isotope effects provides grounds for dismissing the concept of "E2C-like" transition states (I) which invoke interaction of the base with C_α.

Seltzer and Zavitsas[23] have studied the influence of nucleophiles and leaving groups upon secondary α-deuterium isotope effects in SN2 reactions. They suggested that larger isotope effects may be expected for those processes where bond breaking becomes more advanced relative to bond formation in the transition state. In other words, the "looser" the SN2 transition state, the larger the α-deuterium isotope effect that can be expected. Extending the argument, it is reasonable to expect that E2C-like reactions will exhibit larger α-*d* isotope effects than those arising in concurrent SN2 processes since the transition states of the former are necessarily "looser" than those of the latter.[5c,24] The observed deuterium isotope effects reported in Table II are consistent with this expectation.

It is interesting to tabulate observed α-deuterium isotope effects for different classifications of mechanism. This is done in Table IV for reactions involving sulfonate leaving groups. Isotope effects increase steadily for the various reactions as bond breaking moves increasingly ahead of bond formation, so that negative charge becomes increasingly localized on the nucleophile and leaving group. Earlier solvation studies[13] of SN2 and E2C transition states led to the same basic conclusion, i.e., that as the carbon atom (C_α) being attacked changes from primary through secondary to tertiary, SN2 and E2C transition states become "looser". The SN1 transition state is a logical extreme, with bond breaking completely ahead of bond forming. It is not intended that Table IV should suggest a continuous spectrum of transition states encompassing SN2, E2C, and SN1 mechanisms, although spectra of transition states for each individual mechanism could be accommodated by such a tabulation. The tabulation of α-deuterium isotope effects is merely used as a guide to estimate the relative "looseness" of particular transition states in much the same way that can be achieved by solvation data.[13] For example, the α-*d* isotope effect for the E2 reaction of cyclohexyl tosylate with NBu_4Cl (k^H/k^D = 1.14) is about midway between the isotope effects observed for the SN2 and SN1 processes for the same substrate (k^H/k^D = 1.06 and 1.22, respectively). The suggestion from this data, that for E2C-like transition states the degree of interaction of base and leaving group with C_α is at some intermediate stage between the extremes existing in the SN2 and SN1 transition states, is entirely consistent with previously published descriptions of E2C transition states.[5b,c,13,25]

Solvation studies[13] have indicated that the transition states of concurrent E2C and SN2 reactions are similarly solvated, suggesting that these transition states have similar negative charge distribution.[26] This is not really at variance with the concept that E2C transition states are "looser" than their SN2 counterparts. The increase in negative charge separation that might intuitively be expected for E2C transition states is probably offset by the partial interaction between the base and the adjacent electropositive β proton. Such an interaction is of course absent in the SN2 transition state.

Deuterium Isotope Effects at C_γ and $C_{\beta'}$. Perhaps the strongest evidence against ion-pair transition states like III or IX, for the class of E2 reaction discussed in this paper, is based upon the lack of response which these reactions display to the electronic effects of substituents at C_α.[8,9,16,27,28] This insensitivity to α substituents can, however, be rationalized in terms of transition state structures like I or II which feature extensive double bond development but little positive charge development at C_α.[8,9,16,27,28] Nevertheless, we have been cautious about dismissing ion-pair transition states solely on the above mentioned grounds. We tentatively suggested[15a,29] the possibility of an alternative structure X in which positive charge at C_α could be accommodated while still falling within the E2C concept. X differs from I because in I there is little or no positive charge at C_α, extensive double bond development, and the β hydrogen is only loosely bound to sp^2-hybridized C_β. In X the β hydrogen is tightly bound to sp^2-hybridized C_β and there is very poor double bond development but extensive positive charge localized at C_α. Both I and X are consistent with the extensive rehybridization at C_α and C_β suggested by secondary deuterium isotope effects at these positions,[15a] and the difference in the extent of C_β–H_β bond breaking in the two structures cannot be distinguished by primary deuterium isotope effects which lie in the range 2.0–4.0.[29] As a rationale for location of positive charge at C_α in X we suggested[29] that because there are two anions loosely bound to C_α in what is effectively an ion triplet, $B^-C^+X^-$, the electronic effects of substituents at C_α may be much less than the requirements in an SN1 transition (which resembles an ion pair, C^+X^-).



X

E2C-like?

However, the present secondary deuterium isotope studies now provide conclusive evidence against transition state structures such as III, IX, or X which accommodate positive charge at C_α. The comparison of secondary deuterium isotope effects at C_γ and $C_{\beta'}$ in Table III for the reaction of cyclohexyl tosylate with NBu$_4$OAc in acetone indicates the two isotope effects are of similar magnitude since $k^{H}_{D2}/k^{H}_{D4} = 0.98$. The inductive effect of the additional two deuteriums in V which are absent in IV probably accounts for the small inverse isotope ratio observed.[30] The equivalence of the C_γ and $C_{\beta'}$, isotope effects in reactions 2 and 3 (or their analogues shown in Chart I) can only be interpreted in terms of transition states like I or II which invoke extensive double bond formation between C_α and C_β. In these circumstances, with C_γ and $C_{\beta'}$, both being allylic to the developing double bond, it is reasonable to expect that hyperconjugative interactions at C_γ and $C_{\beta'}$, (and therefore deuterium isotope effects) would be similar. It is difficult to reconcile equivalent C_γ and $C_{\beta'}$, isotope effects in terms of transition states like III, IX, or X which invoke ion-pair character. Certainly these transition states can explain the observed isotope effects at $C_{\beta'}$ (in the range 1.11–1.17)[15a] in terms of hyperconjugative interactions with the adjacent positively charged C_α, but C_γ is too remote from C_α to explain isotope effects of the same magnitude at C_γ by the same rationale.

Concluding Remarks. The α-, γ-, and β'-deuterium isotope effects reported in this paper provide confirmation for the notion that weak base-catalyzed elimination reactions (and their like) use transition states like I or II which accommodate extensive double bond development between C_α and C_β. The similarity of the γ- and β'-deuterium isotope effects strongly supports the evidence of α-substituent effects[9,16,27] which deny appreciable carbonium ion character at C_α, with the implication that transition states like III, IX, or X are untenable.

Both the "E2C-like" transition state I and the "central E2" transition state II invoke a well-developed double bond, and therefore require that C_α and C_β are considerably sp^2 hybridized, and that the C_β–H and C_α–X bonds are extensively broken. In this respect, a great deal of the evidence presented in support of the E2C mechanism (such as primary[21,29] and secondary[15a] deuterium isotope effects, substituent effects at C_α and C_β,[11,16,24,27,31] and strong tendencies toward Saytzeff rather than Hofmann olefin products[5c,11,16,32]) is also compatible with the "central E2" transition states proposed by Bunnett.[6]

However, I differs from II because it calls for the interaction of the base with C_α. Thus in I, the base B^- and the leaving group X both interact with sp^2-hybridized C_α, with B and X collinear and at opposite corners of a trigonal bipyramid, but anti to each other. It is in this respect that E2C-like transition states resemble SN2 transition states. The similarity in the response to change of base,[5a,10,11] leaving group,[12] and solvent[5b,11,13] for certain E2 and SN2 reactions provides the basis for this concept. In particular, E2C-like transition states satisfactorily account for the fact that certain E2 reactions proceed at rates which correlate quantitatively with the carbon nucleophilicity of the base but which are independent of the hydrogen basicity of the base,[5a,10,11] thus explaining the efficacy of weak hydrogen bases (but strong carbon nucleophiles) to promote elimination in certain systems. These facts are more difficult to reconcile with transition states like II which invoke attack by the base solely at β hydrogen, although Bunnett and Baciocchi[33] have expressed alternative arguments on this question.

Furthermore, the stereochemical restrictions in I require that the electron-rich base B^- and the electropositive β hydrogen (the C_β–H_β bond is well broken in I) are syn to each other so that they can mutually interact. In consequence, the β hydrogen and the leaving group X must be anti to each other. This stereochemical requirement of the E2C-like transition state provides perhaps the most satisfying explanation for the strong preference for anti elimination rather then syn elimination in E2 reactions. The greater the E2C character of an elimination reaction, the stronger will be the preference for anti elimination. It is notable that weak base catalyzed eliminations yield almost exclusively the products of anti elimination.[5c,11,16,25] Once again, these facts cannot be reconciled so convincingly[6] in terms of "central E2" transition states (II) which have less stringent stereochemical requirements.

The major criticism leveled at the E2C concept is that proposed E2C-like reactions do not suffer significant rate retardation when subjected to massive steric hindrance adjacent to C_α.[34–36] The well-known "neopentyl effect" produces rate retardation by as much as 10^4–10^5 for SN2 reactions at a primary carbon atom.[37,38] Bunnett and Eck[35] have therefore argued that ". . . If eliminations . . . occur via "E2C" transition states in which the B–C_α interaction is similar to that in an SN2 transition state, they (E2C reactions) should be subject to steric hindrance of the same magnitude". The fallacy of this argument lies in the assumption that the B–C_α interaction is similar (in bond extension) in E2C-like and SN2 (at primary carbon) transition states. Solvation studies[5b,13] have shown that transition states for SN2 and E2C reactions "loosen" as C_α changes from a primary, to a secondary, to a tertiary alkylated carbon atom. The E2C concept further requires that E2C-like transition states are "looser" than their SN2 counterparts.[16,24] The α-deuterium isotope data listed in Table IV, although limited, are consistent with this view. Cook and Parker[24] have also demonstrated that the magnitude of the "neopentyl steric effect" diminishes rapidly for SN2 reactions as C_α changes from a primary, to a secondary, to a tertiary alkylated carbon atom. Thus, as transition states become "looser", nonbonded interactions decrease markedly and steric effects too fall off dramatically.[37] Therefore it is not surprising to find that E2C-like reactions at secondary and tertiary carbon centers show "neopentyl steric effects" which retard rates by no more than a factor of 10.[24,34-36]

The qualitative correlation that exists between increasing α-deuterium isotope effects (see Table IV) and decreasing neopentylic steric rate retardation appears to be no accident, but rather a definite function of increasing looseness in transition state structure. This interpretation certainly vitiates the arguments proposed by Bunnett and Eck[34-36] and supported by Ford and Pietsek,[9] condemning the E2C concept on the basis of the insensitivity of E2C reactions to steric hindrance.

Finally, Bunnett and Eck[36] have stated that "... Insofar as reaction mechanisms can be defined, they are defined not by direct proof, but by the rejection of possibilities which are found to be incompatible with experimental evidence". Experimental evidence which is seriously incompatible with the E2C mechanism has yet to be presented, and therefore as a mechanistic possibility its credibility continues to increase. By Bunnett and Eck's criterion there is absolutely no justification for its dismissal.

Experimental Section

Kinetics. All reactions were carried out in sealed ampules. Rates for the overall reactions (E2 + SN2) of cyclohexyl bromides with either NBu_4Cl or NBu_4OAc were followed by titration of liberated bromide ion. Rates of the overall reactions of cyclohexyl tosylates with NBu_4Cl and NBu_4OAc were followed by estimation of liberated acid, with the recognition that the extent of acid formation is a constant fraction (F_E) of the total substrate consumed at any time *t*.

The fraction (F_E) of each reaction which was bimolecular elimination was determined from the ratio of acid produced to total substrate consumed at any time *t*. F_E was found to be constant throughout each individual reaction. Total substrate consumed was determined by titration of liberated bromide ion for all the reactions of cyclohexyl bromides, by estimation of acetate ion consumed for reactions of cyclohexyl tosylates with NBu_4OAc, and by the sum of chloride ion consumed and acid produced for the reactions of cyclohexyl tosylates with NBu_4Cl.

Bromide and chloride ions were estimated in acidified aqueous solution by potentiometric titration against silver nitrate. Analysis of bromide ion in the presence of chloride ion was determined similarly but in the presence of added barium nitrate to prevent coprecipitation of silver salts.[39] Acetate ion and developed acid were determined as previously described.[15a] The tendency of the bases NBu_4Cl and NBu_4OAc to form homoconjugate species [HCl_2^- and $H(OAc)_2^-$, respectively] as acid developed in the course of reactions was inhibited by the presence of an excess of 2,6-lutidine in all reaction mixtures.

In all cases where reaction rates are compared, the rates of the relevant reactions were carried out simultaneously, under identical conditions.

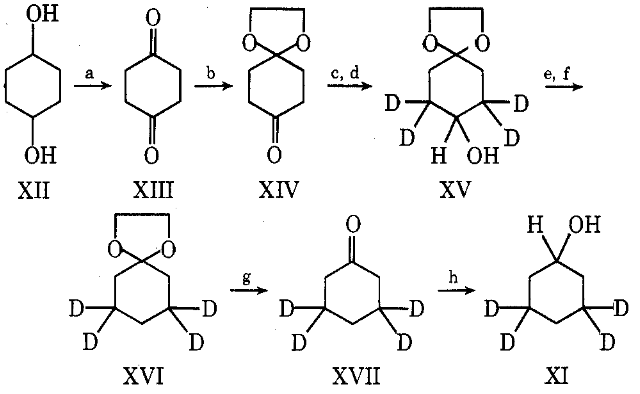
Intramolecular Competition Reaction of Cyclohexyl-*2,2-d*$_2$ Tosylate with NBu_4OAc. The intramolecular isotope value $k^{\rm H}_{\rm D2}/k^{\rm D}_{\rm D2}$ (see Chart I) for this reaction was determined at 75 °C by the method described in part 7.[15a] The value at 75 °C was found to be 2.35 ± 0.01 (cf. 2.90 at 50 °C[15a]).

Materials. Solvent acetone was purified by standard procedure. Tetra-*n*-butylammonium salts were prepared as previously described.[10] Cyclohexyl tosylate, cyclohexyl-*1-d* tosylate (0.8% d_2, 96.3% d_1, 2.9% d_0), and cyclohexyl-*2,2-d*$_2$ tosylate (0.7% d_3, 94.4% d_2, 4.9% d_1, 0% d_0) were prepared as reported in part 7.[15a] Cyclohexyl bromide was purified by distillation, bp 62 °C (25 mm).

Cyclohexyl-*1-d* bromide (1.3% d_2, 95.5% d_1, 3.2% d_0) was obtained from the corresponding alcohol following treatment with constant boiling hydrobromic acid after the method of Vogel.[40]

Cyclohexyl-*3,3,5,5-d*$_4$ tosylate was prepared from cyclohexanol-*3,3,5,5-d*$_4$ (XI) following the procedure of Finley and Saunders.[19] XI was obtained from *cis*-cyclohexane-1,4-diol (XII) by the synthetic sequence shown in Scheme I. Jones oxidation of XII gave the water-soluble dione (XIII), which was isolated by continuous ether extraction of the concentrated aqueous acetone mother liquor. Recrystallization from ether/petroleum ether yielded pure XIII, mp 77–78 °C (lit.[41] 78 °C). XIII was refluxed in dry benzene in a Dean-Stark apparatus with 1 molar equiv of ethane-1,2-diol in the presence of a trace of *p*-toluenesulfonic acid catalyst. After refluxing for 5 h, the reaction mixture was cooled to 25 °C, treated with an excess of barium oxide, and filtered through Celite. The crude monoketal XIV isolated after removal of benzene was contaminated with diketal and unreacted dione XIII. The diketal was effectively removed by precipitation of XIV as the bisulfite-addition compound. Regeneration of XIV from the isolated salt by treatment with aqueous alkali followed by ether extraction conveniently removed the water-soluble dione XIII. Sublimation at 70 °C (0.1 mm) yielded the pure monoketal, mp 72.5–73 °C (lit.[42] 72–73 °C). Conversion of the monoketal XIV to the required alcohol XI was achieved following the procedure outlined by Green et al.,[43] except for the reduction of the tosylate of XV to the hydrocarbon XVI. Instead, removal of the oxygen function was achieved smoothly by stirring the tosylate at 80 °C for 24 h in the presence of a fourfold molar excess of sodium borohydride in hexamethylphosphoramide (HMPT) as solvent. The reaction mixture was quenched with water and extracted with hexane to yield XVI. The use of dipolar aprotic solvents as reaction media for sodium borohydride reductions enhances the nucleophilic reactivity of hydride ion and reduces the yield of unwanted elimination products.[44] Mass spectrometric deuterium analysis[15a] of the ketone XVII (97.5% d_4, 2.5% d_3, 0% d_2) provided an estimate of the deuterium content of the final product cyclohexyl-*3,3,5,5-d*$_4$ tosylate.

Scheme I. Synthetic Route to Cyclohexanol-*3,3,5,5-d*$_4$



a, Jones oxidation; b, ethane-1,2-diol/H$^+$/benzene; c, D_2O/K_2CO_3; d, $LiAlH_4$/ether; e, TsCl/pyridine; f, $NaBH_4$/HMPT; g, H$^+$/aqueous acetone; h, $LiAlH_4$/ether.

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Iodofluorination of Phenyl-Substituted Olefins with Methyliodine(III) Difluoride[1]

Marko Zupan* and Alfred Pollak

Jožef Stefan Institute and Department of Chemistry, University of Ljubljana, 61000 Ljubljana, Yugoslavia

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Methyliodine(III) difluoride reacts with phenyl-substituted olefins, e.g., 1,1-diphenylethylenes and styrenes, to form corresponding vicinal iodofluorides and not the rearranged 1,1-difluorides, obtained in a similar reaction with aryliodine(III) difluoride. Iodofluoride addition undergoes Markownikoff type regioselectivity, forming corresponding 1-phenyl-1-fluoro-2-iodoethanes.

The addition of chlorine to olefinic double bonds using phenyliodine(III) dichlorides has received attention from several groups of workers.[2–4] The corresponding aryliodine(III) difluorides received much more limited attention as fluorinating agents, possibly because of the difficulties involved in their preparation and storage.[5–9] In our recent efforts to develop the polymeric fluorinating agent poly(*p*-iodostyrene difluoride),[10] we have also investigated the fluorination of 1-phenylethylenes with methyliodine(III) difluoride, the only stable representative of the alkyliodine(III) difluorides. The recent reported synthesis of methyliodine(III) difluoride by the reaction of xenon difluoride with an excess of methyl iodide[11] makes this potential fluorinating agent readily available.

Results and Discussion

The preparation of fluoroalkanes represents a different problem from that of the preparation of other haloalkanes and necessitates a specific method of fluorination.[12] Difficulties involve the handling of anhydrous hydrogen fluoride on the laboratory scale, the need for pressure equipment, low temperatures, and the ease of polymerization of alkenes.[12] Iodofluorination with a mixture of hydrogen fluoride–pyridine–*N*-iodosuccinimide avoids some experimental difficulties,[14] e.g., low temperature, high-pressure techniques, and polymerization of olefins.

Following the procedure reported by Gibson,[11] we prepared a solution of methyliodine(III) difluoride by the reaction of xenon difluoride with an excess of methyl iodide. A series of substituted 1-phenylethylenes (**1a–h**) were treated with methyliodine(III) difluoride (Scheme I). The pure product **2a** was isolated in a 55% yield from the crude reaction mixture by preparative TLC. The NMR spectra of the product **2a** showed a triplet signal at −157.5 ppm in ^{19}F NMR spectra and a doublet with coupling constant 23 Hz at 3.75 ppm in ^1H NMR spectra. The structure of 1,1-diphenyl-1-fluoro-2-iodoethanes was established also by chemical transformation. On heating **2a** at 80 °C, 1,1-diphenyl-2-iodoethene (**4**) and