Hyperconjugation and the Angular Dependence of β-Deuterium Isotope Effects

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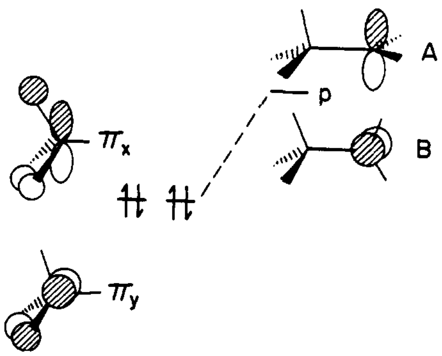
Abstract: A method for the correlation of the magnitude of kinetic secondary β-deuterium isotope effects in solvolytic reactions with the conformation of the reaction transition states is proposed. An empirical angular correlation was developed and several secondary and tertiary carbocation species were analyzed. Good agreement between the observed and calculated isotope effects was found for all cases where the secondary substrate reacts by the same mechanism as the corresponding tertiary α-Me derivative. This makes the described method a convenient probe for the geometry of solvolytic transition states. The possibility of making deductions about the involvement of anchimeric and/or nucleophilic participation in the solvolysis of secondary substrates is discussed. The absence of hyperconjugative stabilization of secondary cations appears to be the major factor responsible for high ($>10^6$) CH_3/H rate ratios.

The identification of the origin of secondary deuterium isotope effects has been of considerable interest.[2] While the α effects are mostly due to changes in the out of plane bending force constant in going from the ground state to the transition state,[3] the β effects seem to be of a more complex nature. The description of these effects has to take into account possible inductive, hyperconjugative, steric, anchimeric, and solvent effects.[2,4] Of these, hyperconjugation seems to be the major cause of the β effects as has been demonstrated in numerous cases.[5] The careful examination of the solvolysis of deuterium-labeled *tert*-butyl chloride and other labeled *tert*-alkyl halides demonstrated conclusively the conformational dependence of these effects as expected on the basis of the hyperconjugative interaction.[6] Shiner and co-workers[5a,6b,c] supplied data on the magnitude of the β effects per atom D depending on the dihedral angle between the C-H(D) bond and the vacant p orbital at the cationic center (Table I). These values were derived from experimentally observed effects in partially deuterated *tert*-butyl-d_1, -d_2, -d_6, and -d_9 chlorides by assuming for the cation an eclipsed conformation of C_{3v} symmetry.

However, the hyperconjugative interaction of a freely rotating methyl group with the adjacent empty p function at the carbocation center should be independent of conformation. This follows from the following arguments.[6b,7] In the language of perturbation molecular orbital theory, hyperconjugative stabilization results from the two-electron interaction between the empty p function at C^+ and one (or a combination of both) of the degenerate pair of π symmetry valence orbitals on the methy group. In conformation A only the π_x function on CH_3 interacts with the vacant p orbital; interaction between π_y and p is zero on symmetry grounds. For conformation B the situation is exactly the reverse, only π_y interacts with p. What is important is that the magnitudes of these two interactions (π_x with p in A, and π_y with p in B) are the same. That is, the two factors on which they depend, energy splitting and overlap, are the same in the two limiting conformations. It is also true that in intermediate conformations, where both π_x and π_y methyl group orbitals overlap with the p function at C^+, the total interaction energy is the same as it is in either of conformations A and B. A necessary consequence of this invariance is that whatever function, $f(\theta)$, is used to describe the conformational dependence of the isotope effect associated with an individual methyl group hydrogen must satisfy the relationship,



$$f(\theta) + f(\theta + 120°) + f(\theta + 240°) = \text{constant}$$

Data from Table I obviously do not meet this requirement (Figure 1).

Since the usefulness of the β effects in conformational analysis of solvolytic transition states rests on the correct evaluation of the conformational dependence, we have undertaken a study of this problem. By analyzing the relationship between β effects in secondary and tertiary systems an empirical angular correlation will be developed and the relevance of β-isotope effects in conformational analysis of cationic transition states will be discussed.

Results and Discussion

1. The α-Methyl/Hydrogen Rate Ratio and the Angular Dependence of β Effects. In 1968 Servis, Borcic, and Sunko[8] established a linear free energy relationship between the CH_3/H rate effect and the CH_3/CD_3 isotope effect.

$$\log k(CH_3/CD_3) = 0.02024 \log k(CH_3/H) \qquad (1)$$

A representative and updated list of compounds for which both effects have been experimentally determined is given in Table II.

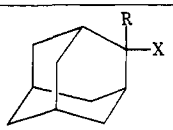
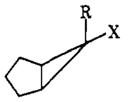
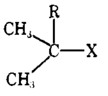
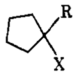
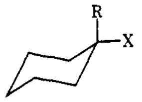
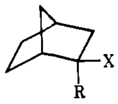
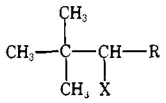
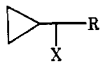
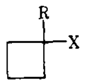
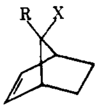
For convenience eq 1 will be referred to as the SBS correlation. This correlation has recently been discussed in detail[9] and it was concluded that it holds for reactions where the formation of the tight ion pair or the formation of the solvent separated ion pair is rate determining for both the hydrogen and the α-methyl compound. This relationship is indicative of a common predominantly *hyperconjugative* origin of both Me rate and β-isotope effects.[11] However, one has to analyze the observed CH_3/CD_3 effects as being due to both a hyperconjugative rate enhancing ($k(H/D) > 1$) effect, $k^x(H/D)$, and an inductive, rate retarding ($k(H/D) < 1$) effect, $k^I(H/D)$. The magnitude of the hyperconjugative effect of the CD_3 group, $k^x(CH_3/CD_3)$, can be calculated from the total effect

Table I[a]

Dihedral angle, deg	0	30	60	90
Isotope effect, $k(H/D)$	1.31	1.07	1.01	0.99

[a] Reference 6c.

Table II

Compd ($R = H, CH_3, CD_3$)	$k(CH_3/H)$	$k(CH_3/CD_3)$	Ref
1. 	$10^{8.12}$	1.48	9
2. 	$10^{7.0}$	1.42	10
3. 	10^{6}	1.33	8
4. 	$10^{4.44}$	1.25	8
5. 	$10^{4.36}$	1.21	8
6. 	$10^{4.27}$	1.22	8
7.  $CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}\underset{X}{CH}{-}R$	10^{2}	1.09	9
8. 	$10^{3.62}$	1.18	8
9. 	$10^{2.11}$	1.09	8
10. 	10^{2}	1.09	9

$k(CH_3/CD_3)$ by correcting it for the inductive effect of 0.985 per atom D.[12]

$$k^x(CH_3/CD_3) = k(CH_3/CD_3)/(0.985)^3 = 1.046k(CH_3/CD_3) \quad (2)$$

As mentioned earlier the total CD_3 isotope effect must be independent of conformation. For the purpose of discussion we can assume that it is composed of the contribution of one hydrogen eclipsing the p orbital of the carbonium ion ($\theta = 0°$) and two hydrogens having their σ C-H(D) bonds at a dihedral angle of $\theta = 60°$ with respect to the vacant p orbital

$$k^x(CH_3/CD_3) = k^x(H/D)_{0°}[k^x(H/D)_{60°}]^2 \quad (3)$$

By assuming that the angular dependence obeys the "$\cos^2 \theta$ rule"[14] the effect of one deuterium atom in the gauche conformation will be $k^x(H/D)_{60°} = [k^x(H/D)_{0°}]^{\cos^2 60°}$ which gives by substitution

$$k^x(H/D)_{0°} = k^x(CH_3/CD_3)^{1/(2\cos^2 60° + 1)} = k^x(CH_3/CD_3)^{1/1.5} \quad (4)$$

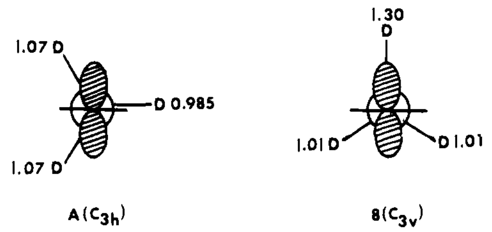


Figure 1. Isotope effects for the bisected (A) and eclipsed (B) conformations of the methyl group calculated from data in Table 1. For conformation A, $k(H/D_3)_{calcd} = 1.128$, and for conformation B, $k(H/D_3)_{calcd} = 1.326$ and $k(H/D_3)_{expt} = 1.3304$ ($(CH_3)_2CClCD_3$ (60% EtOH, 25 °C)).[6b]

Table III

		$k(H/D)_\theta$		
$\log k(CH_3/H)$	$k(CH_3/CD_3)$	0°	30°	60°
8	1.452	1.301	1.214	1.056
7	1.386	1.262	1.186	1.048
6	1.323	1.223	1.159	1.040
5	1.262	1.185	1.131	1.032
4	1.205	1.149	1.106	1.024
3	1.150	1.114	1.080	1.016
2	1.098	1.080	1.055	1.008
1	1.048	1.047	1.031	1.0002

From the value of $k^x(H/D)_{0°}$ the angular dependence of the β effect per atom D can be approximated by the equation

$$\log k(H/D)_\theta = \cos^2 \theta \log[k^x(H/D)_{0°}] + \log k^I(H/D) \quad (5)$$

Since the inductive effect $k^I(H/D) = 0.985$[12] and is independent of the structure of the substrate eq. 5 can be simplified

$$\log k(H/D)_\theta = \cos^2 \theta \log[k^x(H/D)_{0°}] - 0.006\,56 \quad (5a)$$

Combining eq 5a with eq 1, 2, and 4 one obtains

$$\log k(H/D)_\theta = 0.666 \cos^2 \theta \times [0.0195 + \log k(CH_3/CD_3)] - 0.006\,56 \quad (6)$$

and

$$\log k(H/D)_\theta = 0.666 \cos^2 \theta \times [0.0195 + 0.020\,24 \log k(CH_3/H)] - 0.006\,56 \quad (7)$$

Table III gives a list of θ effects as derived from eq 6 and 7.

The values for $k(H/D)_\theta$ (eq 5) which are in this way obtained from CD_3 effects in tertiary substrates will correspond with the values for β effects in secondary substrates if the mechanisms are the same.[16] It is often the case that rates of tertiary chlorides are compared with those for secondary tosylates, but this does not affect the validity of this relation as long as in both cases the same step is rate determining.[17] As is the case with CD_3 effects in tertiary systems, β effects in secondary substrates can be affected by rate determining elimination and/or participation.[18] In such cases the effects will be *larger* than those calculated by eq 6, and corresponding corrections of experimental values have to be made. A detailed analysis of such corrections has been recently published.[18a] It can be assumed that the difference between the observed and calculated effects corresponds to the (primary) effect due to hydrogen (deuterium) migration and/or elimination. Effects *smaller* than calculated are indicative of solvent and/or nucleophilic participation in the rate determining step of the solvolysis of *secondary* substrates. It is understood that nu-

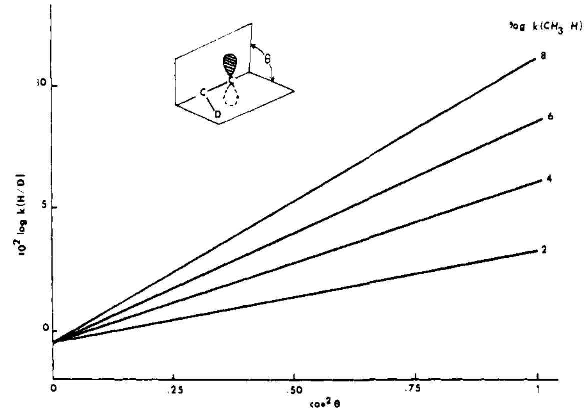


Figure 2. Angular dependence of log k(H/D) for different values of log $k(CH_3/H)$.

cleophilic participation includes also intramolecular neighboring group participation.[19]

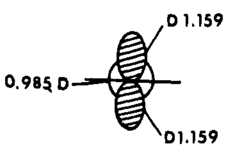
From known CH_3/H rate ratios and the equations given above one can determine the dihedral angle θ in secondary cations, and so obtain valuable information on the geometry of these transient species. In Figure 2, a graphical representation of the angular dependence is given for four different values of $k(CH_3/H)$. If the CH_3/H rate ratios are not known, the corresponding equation

$$\cos^2\theta = \tfrac{3}{2}\left(\frac{0.006\,56 + \log k(\mathrm{H/D})}{0.0195 + \log k(\mathrm{CH_3/CD_3})}\right) \qquad (8)$$

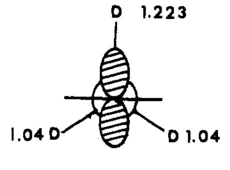
derived from eq 2, 4, and 5 could be used instead. Because of difficulties often encountered in the determination of the CH_3/H rate ratios the $k(CH_3/CD_3)$ value is more reliable, provided 1,2-H(D) shifts or elimination are not occurring in the rate-determining step.

2. Comparison with Experiment. The following carbocations were analyzed by the method described in the preceding paragraph.

***tert*-Butyl.** Using the values from Table III corresponding to a CH_3/H effect of 10^6 (t-Bu vs. i-Pr rate ratio, see Table II) the following breakdown of the effect for the two frozen conformations of the methyl group can be calculated. Obviously, but in contrast with previous results (see Figure 1), both conformers give identical isotope effects for complete deuteration. The IR and Raman spectra of *tert*-butyl cation generated as a stable species in super acid media,[20] have been interpreted as evidence for the C_{3v} symmetry structure B, rather than the propeller shaped, C_{3h} symmetry form A. Ab initio molecular calculations[7,21] using the STO-3G minimal basis set have, however, led to the opposite conclusion.



A

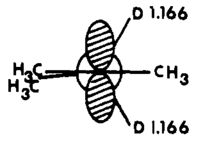


B

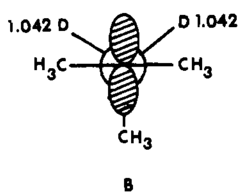
$k(H/D_3)$ 1.32

$k(H/D_9)$ 2.30

***tert*-Amyl.** Recently $^1J_{CH}$ values have been measured for the *tert*-amyl cation and interpreted in terms of a predominance of conformation A (in which all carbons lie in a single plane) over conformation B (in which one methyl is perpendicular to the plane).[15] This experimental result is consistent with the theory's assignment of a C_{3h} rather than a C_{3v} symmetry structure for the *tert*-butyl cation. Ab initio STO-3G level molecular orbital calculations have been carried out on the two possible conformers of the *tert*-amyl cation. Early work, using assumed "standard model" geometries, led to the conclusion that the perpendicular form B was actually some 4 kcal/mol more stable than structure A.[21] STO-3G calculations from our laboratories[22,23] in which the skeletal geometries have been optimized, indicate the two forms to be of equal stability. Further theoretical studies, involving calculations beyond the minimal basis set level, are currently in progress.



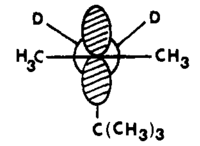
A



B

By solvolyzing the corresponding chlorides in 80% ethanol at 25 °C Shiner has determined both the β-CD_3 and β-CD_2 effects.[24] From the experimentally observed CH_3/CD_3 effect of 1.34, k(H/D) can be calculated for both conformers using eq 6. It follows that the effect for two D atoms in conformation A should be $(1.166)^2 = 1.36$ and in conformation B $(1.042)^2 = 1.086$. The observed d_2 effect of 1.40 supports conformation A in agreement with the NMR data.

2,4,4-Trimethyl-2-pentyl. The solvolysis of the 3,3-d_2 chloride shows a very low value for $k(H/D_2)$ of 1.08. This was interpreted by Shiner as consistent with the gauche conformation.[5a] However, the methyl-d_3 effect of 1.40 was higher than in closely related systems, which was interpreted as being due to internal elimination into the methyl branch from the tight ion pair.[25] If the normal CD_3 effect is similar to CD_3 effects observed in both 2-chloro-2-methylbutane and 2-chloro-2,4-dimethylpentane, i.e., 1.34, the observed CD_2 effect of 1.08 is close to the value calculated using eq 6 for $\theta = 60°$ and $k(CH_3/CD_3) = 1.34$, namely $(1.042)^2 = 1.086$, again in accord with the proposed conformation. STO-3G level calculations have yet to be performed on this system. In view of the predicted closeness in stabilities of the two conformers of the *tert*-amyl cation, it is highly likely that such calculations will indeed show a favoring for the 2,4,4-trimethyl-2-pentyl cation to adopt a conformation in which the bulky terminal *tert*-butyl moiety is as removed from the rest of the molecule as is possible.



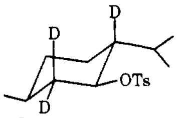
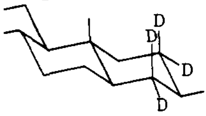
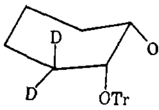
Cyclopentyl. For the solvolysis of cyclopentyl brosylate Humski and Shiner have carefully studied the isotope effects and the stereochemistry of the concurrent elimination reaction.[18a,26] Some of the relevant data are given below.

	cis-β-d_1	*trans*-β-d_1	β-d_4
$k(H/D)_{obsd}$, 40 °C, 100% EtOH	1.10	1.14	1.55
$k(H/D)_{calcd}$ for $\theta = 30°$	1.117	1.117	1.556

The agreement between the experimental and calculated isotope effects is clearly within the limits of accuracy of the method.

Cyclohexyl. The determination of secondary isotope effects in simple cyclohexyl derivatives has been obscured by competitive elimination and hydrogen participation reactions.[27] From the CH_3/H ratio of 22 800 and the SBS correlation[8] the following k(H/D) values can be calculated: $(1.162)_{0°}$; $(1.115)_{30°}$; $(1.027)_{60°}$. We have recently determined the β-isotope effects in a number of cyclohexyl systems[13,28,29] and

Table IV. Isotope Effects in Solvolysis of Substituted Cyclohexyl Derivatives

Compd	$k(CH_3/H)$	$k(H/D_n)$ Obsd (D_n)[a]	$k(H/D_n)$ Calcd $(D_n, \theta°)$
 OTs	10^{6} [b]	1.32 (D_3)[c]	1.32 $(D_2$, 30°; D_1, 90°)
 OBs	10^{6} [b]	1.36 (D_4)[d]	1.30 $(D_2$, 30°; D_2, 90°)
		1.19 $(D_1$, axial)[d]	1.16 $(D_1$, 30°)
 OAc OTr	$10^{4.36}$ [e]	1.23 (D_2)[f]	1.24 $(D_2$, 30°)

[a] Corrected to 100% deuterium content, but not corrected for possible rate determining elimination. [b] Assumed value (see text); [c] reference 28. [d] Reference 13. [e] Reference 8. [f] Reference 29.

the results are summarized in Table IV together with the values calculated for different dihedral angles. Good correspondence is obtained for *cis*-2-acetoxycyclohexyl-*6,6*-d_2 tresylate, a substrate which presumably solvolyzes via a twist boat transition state.[29] The β effects in the menthyl and cholestanyl systems where a chair like transition state is more likely[13,18] are better accommodated by assuming a CH_3/H rate ratio of 10^6. This puts the chair conformer of the cyclohexyl cation in the same relative position with respect to its α-methyl derivative, as the isopropyl cation relative to *tert*-butyl.[7]

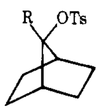
2-Adamantyl. In the completely sp^2 hybridized cation, the angle θ should be 90°, resulting in an effect of 0.985. The observed effect in 70% TFE at 60° [30,31] was 1.029 ± 0.005, which could indicate a distortion of the adamantyl skeleton and a corresponding reduction of the dihedral angle to ~67° (calculated by use of eq 8). Since this distortion is rather large for such a rigid skeleton and the difference in the isotope effect values cannot be due to the contribution of a rate determining 1,2-hydride shift,[32] one could speculate that the cation has essentially retained the sp^3 geometry. This interpretation is in harmony with the observation that secondary adamantyl derivatives solvolyze with retention of configuration.[34]

4-Homoadamantyl. The experimental value for $k(CH_3/H) = 10^{4.62}$ is in slightly better agreement with the observed β-d_2 effect of 1.22 ± 0.02 by assuming an eclipsed conformation for the cation:[35a] $k(H/D_2)$ eclipsed, $(1.171)_{0°} \times (1.029)_{60°} = 1.205$; $k(H/D)$ staggered, $(1.122)_{30°}{}^2 = 1.258$. In a recent paper Nordlander et al.[35b] showed that the observed degenerate 1,2-hydrogen shift[35c] occurs after the ionization step.

***endo*-2-Norbornyl.** From the estimated CH_3/H effect of $10^{5.21}$ [36] the calculated β-d_2 effect for $\theta = 30°$ is 1.29 in agreement with the value observed in the ethanolysis of the *endo*-d_2 brosylate (1.31). The β-d_1 effects are reported to be 1.19 (*exo*-d_1) and 1.12 (*endo*-d_1)[39]. The calculated isotope effect for d_1 (30°) is 1.137. Data on the degree of elimination in the solvolysis of *endo*-2-norbornyl brosylate are not available. Recently, Maskill[40] determined the β-isotope effect in solvolysis of 2-*endo*-norbornyl-*1*-d_1 brosylate. In the classical cation the dihedral angle between the bridgehead C(1)-D bond and the p orbital at C(2) is 80°. This corresponds to a calculated effect of 0.991. The experimentally obtained value was 0.996 ± 0.005 (acetolysis, 54.5°) and 1.000 ± 0.011 (80% aqueous ethanol at 54.5°), respectively.

***exo*-2-Norbornyl.** Both CH_3/H and CH_3/CD_3 rate ratios were determined experimentally (Table II). The β-d_2 effect in 2-norbornyl brosylate was found to be 1.113 (EtOH, 25 °C.[39] Murr also determined the separate effects for *exo*-β-d_1 and *endo*-β-d_1 brosylate.[39] Practically the whole effect resides in the exo deuterium (1.11) with only a small contribution from the *endo*-D (1.02). The calculated effect, assuming a dihedral angle of 30°, is 1.113 per atom D or 1.239 for D_2. This together with the results obtained for the *endo*-2-norbornyl system indicates that the geometry of the transition state for the solvolysis of the exo derivative is different from the transition state of the endo derivative, and that the secondary exo derivative solvolyzes by a different mechanism than the tertiary. If a partial bond formation between C(2) and C(6) occurs in the transition state as implied by the nonclassical structure, the *endo*-C-D bond at C(3) will almost eclipse the C-H bond at C(2) bringing the *exo*-C(2)-D bond in a favorable position for hyperconjugation.[19] The observed effects of 1.11 and 1.02 are perfectly correlated by the $\cos^2 \theta$ rule (eq 5) if $\theta_{exo} = 0°$ $[k(H/D)_{0°} = 1.11]$ and $\theta_{endo} = 60°$ [39] $[k(H/D)_{60°} = 1.011]$.

Table V.[a] Isotope Effects in Solvolysis of 7-Methyl-d_3- and 7-Methyl-d_1-norbornyl Tosylates[b]

Compd	Solvent[c]	Temp, °C	$k_H \times 10^4$ s^{-1}	$k(H/D)$ R = CD_3	$k(H/D)$ R = CH_2D Obsd	$k(H/D)$ R = CH_2D Calcd[d]
 R OTs	97 T	20	4.66 (3)	2.10 (3)	1.26 (2)	1.256
	80 T	20	4.89 (6)	2.00 (7)	1.18 (2)	1.244
	80 E	40	1.21 (1)	1.84 (4)	1.17 (1)	1.207
	97 HFIP	5	23.4 (2)	2.33 (3)		
	70 HFIP	5	2.50 (3)	2.22 (2)		

[a] This work; see also ref 44. [b] The errors are given as standard errors, e.g., 4.66 (3) = 4.66 ± 0.03. [c] T = 2,2,2-trifluoroethanol (w/w); E = ethanol (w/v); HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol (w/w). [d] Reference 45.

Cyclobutyl. This system still presents a puzzle and doubts have been expressed regarding the existence of the unsubstituted cyclobutyl cation in solution.[41] Although the CH_3/H and CH_3/CD_3 rate ratios are well behaved, though small (see Table II), the β effects in the solvolysis of cyclobutyl mesylate-*2,2,4,4*-d_4 are inverse; $k(H/D_4) = 0.928$.[42] Based on preliminary force field calculations for the symmetrical, nonclassical, cyclobutyl cation, the inverse β effect is due to an MMI factor of less than unity.[42b] The ZPE contribution is small but "normal" (1.046). This reveals that caution should be exercised when interpreting isotope effects observed in reactions of heavily deuterated *small* molecules.

7-Norbornyl. This conformationally unambiguous system is of special interest because it shows for reactions in solutions the highest recorded CH_3/H effect of $10^{8.6}$,[43] which corresponds to a CH_3/CD_3 effect of 1.49.[9,44] The actually observed effect was much higher and strongly solvent dependent (Table V). This was taken as an indication of a concurrent solvent promoted rate determining elimination.[9] Some small preference for hydrogen elimination was found when 7-methyl-d_1-norbornyl tosylate was solvolyzed, which duplicates the trend observed in solvolyses of partially deuterated *tert*-butyl chlorides.[6b,45] Taking 1.49 as the limiting value for a CD_3 effect in solvolytic reactions the calculated effect of 1.325 should correspond to one deuterium eclipsing the p orbital at $C_\alpha{}^+$ ($\theta = 0$). An effect of this magnitude ($k(H/D) = 1.34$) was actually observed in the trifluoroethanolysis of *cis*-2-acetoxycyclohexyl-*2*-d_1 tresylate, a system where competing rate determining participation (or elimination) of the eclipsed deuterium is apparently prevented.[29] The extraordinary high electron demand of the 7-norbornyl cation was explained in terms of noninteraction of the cationic center with the ribbon orbitals of the underlying cyclohexane skeleton.[46] Since a similarly high CH_3/H effect was observed in 2-adamantyl derivatives[47] where the noninteracting orbital argument does not hold, a greatly reduced solvation and the absence of hyperconjugative stabilization of the respective *secondary* cation should also be considered as the cause for these high CH_3/H effects.[47,48] It remains to be seen how isotope effects determined in solvents of high ionizing power and low nucleophilicities correlate with effects determined in the gas phase. Work in this direction is in progress.

Conclusions

Based on the well established linear relationship of CH_3/H and CH_3/CD_3 rate effects an empirical method has been developed which allows the estimation of the magnitude of secondary β-deuterium isotope effects in secondary substrates as a function of the dihedral angle between the β-C-D bond and the empty p orbital. From this angular dependence deductions can be made regarding the geometry of the solvolytic transition states if kinetic β-secondary deuterium isotope effects are known. For all cited examples where the secondary substrate reacted by the same mechanism as the tertiary α-Me derivative, good agreement between observed and calculated isotope effects was found. This also suggests that the differences in solvation effects, i.e., the differences in nucleophilic participation by solvent molecules between secondary and tertiary substrates are rather small.[51] If so, then the broad range of observed CH_3/H rate ratios can be attributed to differences in hyperconjugative stabilization of the respective secondary cation.

Better knowledge of all the factors involved is required before an exact quantitative relationship can be worked out, but we think that the described method might, as an approximation, be useful not only for conformational studies but also for determining anchimeric and/or nucleophilic participation[53] in solvolytic reactions of secondary substrates.

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Stereochemical Consequences of Hydrogen Exchange as a Result of Tritium Atom Reactions on Solid Aliphatic Amino Acids[1]

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Abstract: The products and stereochemistry resulting from radicals generated by the interaction of tritium atoms with L-isoleucine and L-alloisoleucine in the solid phase were determined. Among the four possible tritiated stereoisomers for each amino acid the major product was the parent L-amino acid (approximately 70% in each case) with the major fraction of the labeling being in positions other than the α position. Approximately 30% of the labeling resulted in the diastereomeric product by reaction at either the α or β position, with the major pathway being β-inversion. The yield of products from α-carbon attack of L-isoleucine was minor (7.9%) and occurred with net retention. Labeling at the α-carbon of alloisoleucine was <1%. Tritiated glycine was formed from both amino acids by cleavage of the alkyl side chain. This may result from the excitation decomposition of the intermediates formed from recombination of α (or β) amino acid radicals with tritium. Determination of the stereochemical and chemical consequences of radical formation at chiral centers provides a sensitive probe for studying the consequences of tritium (hydrogen or deuterium) atom reactions.

The nature (structure) and fate (i.e., chemistry and stereochemistry) of the highly reactive radicals formed by the reaction of hydrogen atoms with biologically important molecules is not well understood. Its delineation is necessary for understanding solid state atom replacement reactions and in the development of a model for in vivo radiation effects.[2-7]

Previous studies on the interaction of hydrogen atoms generated by microwave discharge or γ irradiation with amino acids,[8-11] polyamino acids,[12-15] and proteins[13,16,17] have used electron spin resonance (ESR) as a qualitative measure mainly of the chemically stable radicals produced in the solid phase by such bombardment. However, the fate of the intermediate radicals, i.e., those important in terms of product formation and stereochemistry, cannot be determined under these conditions. Likewise, in solution Neta et al.[18-21] have measured (by ESR) the kinetics of such reactions by following the disappearance of hydrogen atoms, and Volkert[22] by competition of H-atom donor (amino acids) and scavenger species (allyl alcohol) for radiolytic hydrogen atoms. However, in no case, either in solution or solid phase, has a detailed product analysis been performed or the stereochemistry investigated.

In this study the reaction of hydrogen atoms, by the use of tritium atom reactions with L-isoleucine and L-alloisoleucine, is described. The diastereomeric relationship of these two amino acids gives one a sensitive probe, both as to the position of tritium (hydrogen or deuterium) atom attack as well as the stereochemical consequences of intermediate radicals. The dynamic reaction conditions employed make it probable that the observed products result predominantly from the highly reactive radicals formed, and not from the chemically stable species previously investigated by ESR.[8-17]

The formation of glycine by side chain cleavage of the parent amino acid was also investigated.

Results

A. Stereochemical Result. The major product among the four possible stereoisomers in the tritium labeling of L-isoleucine and L-alloisoleucine using the microwave discharge activation of tritium gas was the production of the labeled parent amino acid with little tritium on the α position. The labeled diastereomeric amino acids were formed predominantly by inversion of the C(3) carbon at the β (tertiary) position and not by inversion at the α-amino carbon (Tables I and II). The labeling of L-isoleucine produced 26.7% alloisoleucine, 87.2% of which resulted from inversion at the β carbon. Similarly the labeling of L-alloisoleucine resulted in the formation of 29.4% of its diastereomer (isoleucine), 99% coming from inversion at the β carbon.

The amount of each diastereomer was determined directly by isolation of the pure material using Dowex 50W-X8 chromatography. The enantiomeric composition of each diastereomer was determined by GLC of the *N*-(L-2-chloropropionyl)amino acid methyl ester (Table II).

Base exchange of each member of the diastereomeric pair (isoleucine, alloisoleucine) which resulted from the labeling of L-isoleucine resulted in a 7.9% loss of the total activity in the sum of the two diastereomers. Most of the loss (5.4%) was from the parent L-isoleucine, indicating that labeling at the α-amino carbon favors retention of configuration by more than a factor of 2. However, base exchange of alloisoleucine and isoleucine generated from L-alloisoleucine resulted in little or no loss of tritium from either diastereomer. In both cases labeling at the C(2) α-amino carbon was shown to be a minor process.

The amount of exchangeable tritium (α-amino carbon tritium) was determined as the percent of decrease in specific activity after base exchange with 4 N $Ba(OH)_2$ at 110 °C (Table III).

These data can also be used as a check on the GLC determination of the amount of D-amino acid formed in the carrier-free diastereomer. The decrease in specific activity in each enantiomeric pair should be equal to the percent D-amino acid formed. Although there is some variation (Table IV), the agreement is good.

B. Glycine Formation. The fragmentation of the alkyl side

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