In D_2O and D_2O–H_2O solutions, the 0.25, 0.50, and 0.75 neutralization points were determined from each titration. The ionic strength of the solutions was set to 0.04 with KCl. $pK_{A,\alpha}$ values were calculated from the equation

$$pK_{A,\alpha} = pH - \log\frac{[Im]}{[Im^+]} + \log\gamma + \Delta pH_\alpha$$

For example, at $\alpha = 0.398$ the inflection point of the titration curve was at 3.800 ml of added acid; pH meter reading at 0.25 neutralization point, 7.563, at 0.5, 7.085, at 0.75, 6.597; $-\log\gamma = 0.079$; hence $pK_{A,\alpha=0.398} = 7.563 - 0.477 + 0.138 - 0.079 = 7.145$; $= 7.085 + 0.138 - 0.079 = 7.144$; $= 6.597 + 0.477 + 0.138 - 0.079 = 7.133$; av 7.141.

Acknowledgments. The support of the National Science Foundation for purchase of the Perkin-Elmer 202 spectrophotometer (Grant IG-63-9) is gratefully acknowledged. The kindness of M. H. Lietzke[26] in supplying a copy of this source deck, and of W. De Forest, University of Pennsylvania Computer Center, in modifying the program, is also gratefully acknowledged.

Secondary Isotope Effects in the Solvolysis of Norbornyl Bromides

John P. Schaefer, Michael J. Dagani, and David S. Weinberg

Contribution from the Department of Chemistry, University of Arizona, Tucson, Arizona. *Received August 1, 1967*

Abstract: Optically active deuterated norbornyl bromides were prepared and their solvolyses were studied. The following secondary isotope effects (k_H/k_D) per D were observed or calculated: 3,3-d_2-*exo*-norbornyl bromide, 1.04 (polarimetric), 1.02 (titrimetric); 7,7-d_2-*exo*-norbornyl bromide, ~1.0; 3,3-d_2-*endo*-norbornyl bromide, 1.16; 2-*d*-*endo*-norbornyl bromide, 1.28. An analysis of these results suggests that, in the solvolysis of *endo*-norbornyl bromide, the degree of bond breaking which has occurred at the transition state is abnormally large. It is suggested that this is a result of unfavorable steric interactions between the departing halide and the C_6 methylene group. The strikingly low isotope effects observed in the *exo* series are consistent with the proposal that the transition state for the ionization of *exo*-norbornyl derivatives is delocalized and nonclassical. However, the absence of a detectable isotope effect from the 7 position suggests that the geometry of the norbornyl skeleton has not yet undergone a major change at this stage.

The nature of the norbornyl cation and of the transition states that lead to this ion in a spectrum of reactions[1–10] is unquestionably one of the most stimulating problems with which organic chemists have concerned themselves. The extensive literature pertaining to this problem has been critically reviewed[11,12] and the majority of the workers in the field appear to favor giving the existing data interpretations that involve transition states that incorporate σ- or π-bond participation and lead to a nonclassical ion. Brown[13] and his co-workers have vigorously challenged these viewpoints and have precipitated further studies in this area.

The facts on which the postulate that the solvolysis of *exo*-norbornyl derivatives is assisted and leads to a bridged ion is based are high *exo/endo* ratio of ionization rates,[1,2] the stereochemical fate of the cation, namely, racemization,[1,2] a pronounced preference for *exo* addition,[2] and formation of nortricyclene rather than norbornene upon eliminaton.[2,5] Brown,[13] however, has contended that these observations are insufficient to require a nonclassical ion and has suggested that the data can also be accommodated by a pair of rapidly equilibrating ions in which steric factors control the ultimate fate of the ions.

The bulk of recent data[11] that purport to concern the norbornyl cation has been obtained by modifying the norbornyl skeleton and studying the effect of these alterations on the reactivity of the system. Although these data are of interest, their value in resolving the basic problem is obscured by the fact that the drastic changes that are frequently made (*e.g.*, conversion of a secondary to a tertiary center) may upset the delicate balance of factors that exist in the parent system. In addition, new deriving forces that may bear no resemblance to those influencing the reactivity of norbornyl compounds are introduced by these changes. Since isotopic substitutions are the most subtle variations that can be made in a molecule, we have initiated a detailed investigation of the effect of isotopic substitution on the reactivity of norbornyl compounds in an effort to obtain additional data pertaining to the parent system and to the transition state that leads to the norbornyl cation.

If the features of the transition state for the ionization of *exo*-norbornyl tosylate as depicted by Winstein and

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(1) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, 71, 2953 (1949); 74, 1147, 1154 (1952).

(2) S. Winstein, E. Clippinger, R. Howe, and E. Vogelfanger, *ibid.*, 87, 376 (1965).

(3) P. D. Bartlett and S. Bank, *ibid.*, **83**, 2591 (1961).

(4) P. D. Bartlett, S. Bank, R. J. Crawford, and G. H. Schmid, *ibid.*, 87, 1288 (1965).

(5) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2639 (1965).

(6) P. von R. Schleyer, W. E. Watts, R. C. Fort, Jr., M. B. Commisarow, and G. A. Olah, *J. Am. Chem. Soc.*, **86**, 5679 (1964).

(7) M. Saunders, P. von R. Schleyer, and G. A. Olah, *ibid.*, **86**, 5681 (1964).

(8) F. R. Jensen and B. H. Beck, *Tetrahedron Letters*, 4287 (1966).

(9) E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *J. Am. Chem. Soc.*, **85**, 169 (1963).

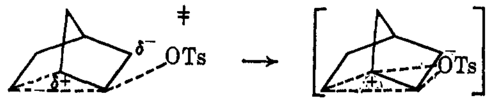
(10) J. A. Berson and A. Remanick, *ibid.*, **86**, 1749 (1964).

(11) G. D. Sargent, *Quart. Rev.* (London), 20, 301 (1966).

(12) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965.

(13) A summary of H. C. Brown's objections, along with numerous references to his papers, can be found in *Chem. Eng. News*, **45**, 86 (Feb 13, 1967).

Trifan[1] are examined in detail, two important factors emerge. The first is that, *in the ionization step, the*



developing positive charge is not localized on C_2 *but is shared by* C_1; the second is that, *when the intimate ion pair has been formed,* C_3 *and* C_7 *have become geometrically equivalent.* These suggestions appeared to be subject to an experimental test through a study of secondary isotope effects, and this paper is concerned with an evaluation of these effects.

Synthetic Studies

From the work of Winstein and Trifan,[1] it was apparent that, if meaningful data on secondary isotope effects were to be obtained, optically active compounds would be needed in the *exo* series to circumvent complications due to internal return. Although it would have been simpler from a synthetic viewpoint to study the reaction of the optically active tosylates, the specific rotation of this derivative is so low that we felt the small changes that we would be trying to detect would probably be obscured by the experimental uncertainties in our rotation measurements. Therefore, preparative methods for the conversion of the norbornanols to norbornyl bromides were investigated.

When optically active *endo*-norbornanol was treated with triphenylphosphine dibromide, optically active *exo*-norbornyl bromide was obtained without any significant racemization.[14] Accordingly, optically active *exo*-norbornanol was prepared by the procedure of Brown[15] and oxidized to norcamphor; the latter was converted into 3,3-d_2-norcamphor by heating with deuteriotrifluoroacetic acid. Reduction of the exchanged ketone with lithium aluminum hydride produced 3,3-d_2-*endo*-norbornan-2-ol which was in turn converted into 3,3-d_2-*exo*-norbornyl bromide.

The preparation of 3,3-d_2-*endo*-norbornyl bromide was much more difficult. Since *exo*-norbornanol is readily accessible, we investigated its reaction with triphenylphosphine dibromide. Although our initial studies[14] in N,N-dimethylformamide indicated that optically active *exo*-norbornanol produced a mixture of which only 1% was *endo*-norbornyl bromide (84% was racemic *exo*-norbornyl bromide and 15% was nortricyclene), this value increased to 12% in the less polar solvent, triglyme. We were, therefore, encouraged to pursue the course of this reaction further, since it appeared that nonpolar solvents might favor the bimolecular displacement path at the expense of carbonium ion formation with concomitant rearrangement. Table I summarizes a cross section of experiments that were carried out in various nonpolar solvents.

These results are significant in that they represent the only known examples of a nucleophilic displacement of an *exo* substituent on the norbornyl framework. More remarkable, however, is the fact that, even in solvents such as benzene, formation of the norbornyl cation is preferred over approach of bromide ion from the *endo* face of the norbornyl framework. While these results are undoubtedly a tribute to the excellence of triphenylphosphine as an exiphile (leaving group) and the ability of the norbornyl cation to exist in unfavorable environments, the departure of this reaction from the norm[14,16] suggests that the C_6 methylene group is capable of exerting a pronounced shielding effect on the *endo* face of C_2.

Table I. Reaction of *exo*-Norbornan-2-ol with Triphenylphosphine Dibromide

Solvent	Reaction time, hr	Temp, °C	Relative yields of norbornyl bromides, % *exo*	*endo*
N,N-Dimethylformamide			∼99	∼1
Triglyme			∼85	∼15
Benzene	18	Reflux	89.5	10.5
Benzene	0	...	91.7	8.3
Benzene	23	Reflux	90.5	9.5
Benzene + Li_2CO_3	3	Reflux	93.6	6.4
Xylene	10	Reflux	92.0	8.0
Xylene–biphenyl	0	...	85.2	14.8
Toluene	20	Reflux	91.0	9.0
Toluene	2	Reflux	84.0	16.0
Toluene–diphenylmethane	0	...	82.3	17.7
Toluene–diphenylmethane	1	Reflux	78.0	22.0
Diphenylmethane	0	...	89.0	11.0
Diphenylmethane	1	25	84.5	15.5

The mechanism of formation of *exo*-norbornyl bromide from *exo*-alcohol must be analogous to that of the decomposition of chlorosulfites; the latter has been shown to proceed through an intimate ion pair.[17–20] Since the normal consequence of the reaction of an optically active alcohol with thionyl chloride is formation of optically active chloride with retention of configuration, our observations provide additional confirmation for the conclusion that the Wagner–Meerwein rearrangement of C_6 from C_1 to C_2 is extraordinarily facile.[9,21] In view of our failure to obtain a greater percentage of displacement reaction, further attempts along these lines were abandoned in favor of a new approach.

Vinyl-d_3 bromide was prepared by the elimination of deuterium bromide from 1,2-dibromoethane-d_4, which is commercially available. Reaction of vinyl-d_3 bromide with cyclopentadiene yielded a mixture of *exo*- and *endo*-2,3,3-d_3-2-norborn-5-enyl bromide which was reduced to a mixture of *exo*- and *endo*-norbornyl bromides using hydrogen in the presence of palladium on charcoal. Deuterium analysis indicated that an average of 2.61 atoms of deuterium per molecule was present. In a similar way, 3,3-d_2-2-norborn-5-enyl bromide was prepared using 2,2-d_2-vinyl bromide as the dienophile; the product possessed an average of 1.44 atoms of deuterium per molecule. Scheme I summarizes the synthetic routes which were used to prepare the labeled intermediates and compounds for solvolysis studies.

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(14) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2635 (1965).

(15) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 486 (1961).

(16) L. Horner, H. Oediger, and H. Hoffmann, *Ann.*, **626**, 26 (1959).

(17) D. J. Cram, *J. Am. Chem. Soc.*, **75**, 332 (1953).

(18) E. S. Lewis and C. E. Boozer, *ibid.*, **74**, 308 (1952).

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(20) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **103**, 687 (1913).

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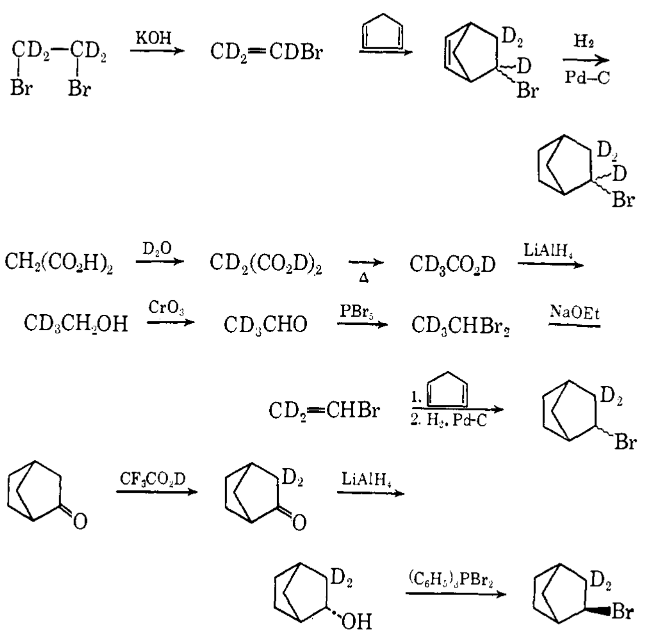
Scheme I. Preparation of Deuterated Norbornyl Bromides



Solvolysis Studies

The solvolysis rates of *endo*-norbornyl bromide (**1**), 3,3-d_2-*endo*-norbornyl bromide (**1**-d_2), and 2,3,3-d_3-*endo*-norbornyl bromide (**1**-d_3) in 50 vol % ethanol were followed conductometrically and were cleanly first order. The rate constants were calculated by a linear least-squares procedure using data evaluated from Guggenheim plots to minimize errors due to uncertainties in the determination of an infinity point; these constants are summarized in Table II.

Table II. Kinetic Data for the Solvolysis of Norbornyl Bromides

Norbornyl bromide	Analytical[d] method	No. of detns	$k \times 10^3$,[e] min^{-1}	t	Solvent[f]
exo	P	2	2.14 (±0.00)	51.25	HOAc-H_2O
exo-3,3-d_2[a]	P	2	1.97 (±0.01)	51.25	HOAc-H_2O
exo	T	2	0.252 (±0.001)	51.25	HOAc-H_2O
exo-3,3-d_2[a]	T	2	0.242 (±0.002)	51.25	HOAc-H_2O
endo	C	4	1.05 (±0.01)	60.21	50% C_2H_5OH
endo-3,3-d_2[b]	C	4	0.850 (±0.003)	60.21	50% C_2H_5OH
endo-2,3,3-d_3[c]	C	4	0.653 (±0.006)	60.21	50% C_2H_5OH

[a] 1.93 D/molecule. [b] 1.44 D/molecule. [c] 2.61 D/molecule. [d] P, T, and C signify polarimetric, titrimetric, and conductometric methods, respectively. [e] The figures in parentheses are the average observed deviations for all of the kinetic runs in that series. [f] Solvents used were acetic acid which was 4 *N* in water and 0.60 *N* in sodium acetate and 50 vol % aqueous ethanol.

Since our synthetic procedures did not afford products that were completely deuterated, it was necessary to correct for this factor to enable us to make a quantitative comparison of the magnitudes of the isotope effect. The observed ratio of rates for **1** and **1**-d_2 was 1.235; since the latter contained 1.44 atoms of deuterium per molecule, the isotope effect per deuterium for the fully deuterated compound is given by

$$(k_H/k_D)_{1\text{-}d_2} = (1.235^{1/1.44}) = 1.16$$

An assumption which is inherent in this calculation is that the β-deuterium isotope effect exerted by the 3-*exo* and 3-*endo* deuteriums is comparable and that the deuterium is equally distributed between these positions. In view of the synthetic procedures that were used and the relative insensitivity of the secondary isotope effect to geometrical factors in the cyclopentane ring,[22] these corrections will not seriously influence any conclusions that can be drawn from the data.[23]

Compound **1**-d_3 contained 2.61 atoms of deuterium per molecule and the combined α- and β-deuterium isotope effects were 1.61. If we assume that the distribution of deuterium between C_2 and C_3 is statistical (*i.e.*, 0.87 deuterium atom per molecule in each position) and that the isotope effects are cumulative, it follows that

$$(k_H/k_D)_\beta = (1.16)^{1.74} = 1.30$$

$$(k_H/k_D)_\alpha(k_H/k_D)_\beta = 1.61$$

$$(k_H/k_D)_\alpha = \frac{1.61}{1.30} = 1.24 \text{ per } 0.87\text{D}$$

$$(k_H/k_D)_\alpha = (1.24)^{1.15} = 1.28 \text{ per D}$$

A similar correction was applied to 2,2-d_2-*exo*-norbornyl bromide and the calculated isotope effect was found to be 1.04 per D (the correction is negligible in this case, since the bromide contained 1.93 atoms of deuterium per mole). The isotope effects which were observed are summarized in Table III.

Two additional factors must be considered before a strict comparison of these data can be made, namely, the effects of solvent changes and temperature differences. Frisone and Thornton[24] have studied the effect of varying the nucleophilicity of the reaction solvent at constant *Y* values and have found that the magnitude of the secondary isotope effect for a limiting solvolysis (*t*-butyl chloride) is independent of this factor. In a related study, Robertson[25] and his co-workers found that the secondary isotope effect observed for *t*-butyl chloride does not vary when the solvent is

Table III. Calculated Secondary Isotope Effects

Norbornyl bromide	k_H/k_D (per D)
exo-3,3-d_2	1.04 (P)
exo-3,3-d_2	1.02 (T)
endo-3,3-d_2	1.16
endo-2-d_1	1.28

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(22) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 2326 (1958).

(23) If no correction is applied, the isotope effect per deuterium atom is 1.11.

(24) G. Frisone and E. R. Thornton, *J. Am. Chem. Soc.*, **86**, 1900 (1964).

(25) K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, *Can. J. Chem.*, **38**, 2171 (1960).

changed from pure water ($Y = 3.5$) to 50% aqueous ethanol ($Y = 1.6$). Thus, it appears that no complication will be introduced by extrapolating the data that we have obtained for the *exo* isomer in aqueous acetic acid to aqueous ethanol. The small differences in temperature (9°) that we employed should likewise have little effect on our conclusions since there are ample data that show that the magnitude of the secondary isotope effect in limiting solvolyses is virtually temperature independent over moderate temperature ranges (25°).[26]

Discussion and Results

Secondary isotope effects that arise from β substitution of deuterium are generally considered[27–29] (see, however, Brown[30]) to have their origin in a hyperconjugative interaction that exists between neighboring alkyl groups and an electron-deficient center. A survey of the literature suggests that the magnitude of this effect is a measure of the electron deficiency at the reaction center in the transition state and is determined by the relative degree of bond making and bond breaking which has occurred. Table IV presents some data that provide a clear illustration of this point.[25]

Table IV. Secondary Isotope Effects in the Solvolysis (Water) of Some Alkyl Compounds

Compound	Temp, °C	k_H/k_D
Ethyl-d_3 *p*-toluenesulfonate	60	1.01
Ethyl-d_3 methanesulfonate	60	1.02
Ethyl-d_3 bromide	80	1.03
Ethyl-d_3 iodide	80	1.03
Isopropyl d_6-bromide	60	1.33
Isopropyl d_6-iodide	60	1.31
Isopropyl d_6-*p*-toluenesulfonate	30	1.55
Isopropyl d_6-methanesulfonate	30	1.54
t-Butyl-d_9 chloride	2	2.56

In the solvolysis reaction, the nucleophilicity of the solvent plays an important role in determining the reactivity of a primary substrate; this factor assumes a minor role as the ability of the reacting compound to stabilize the developing charge internally increases. Since resonance is a variable parameter, the magnitude of which is determined by the electron demand at the reaction center,[31] it is reasonable to expect that hyperconjugation should become an increasingly important factor as a solvolysis becomes more limiting in character. This mechanistic transition is reflected in the variation of the magnitudes of the secondary isotope effects in Table IV.

These observations suggest that, in addition to being useful for detecting external influences on the nature of the transition state in solvolysis reactions, a study of secondary isotope effects should also provide a mirror for internal electronic influences. Although suitable data in this area are scant, the available evidence indicates that this probe will become increasingly important in detailing reaction mechanisms.[32–37]

The isotope effect that we have observed in the solvolysis of 3,3-d_2-*endo*-norbornyl bromide is the largest recorded for a secondary bromide and is more characteristic of those observed for limiting solvolyses. In addition, the α-deuterium isotope effect that we have found is the largest effect of this kind that has been reported. These results indicate that, in the transition state for the solvolysis of *endo*-norbornyl bromide, the positive charge on C_2 is highly developed and the degree of bond breaking that has occurred is abnormally large.

Because approach of a nucleophile from the *endo* face of the norbornyl molecule is apparently unfavorable (*vide supra*), these results are quite reasonable. Departure of a relatively large group like bromide should also be hindered and the transition state will not be reached until a larger-than-normal degree of bond breaking has occurred. These findings are in accord with the suggestion of Brown and his co-workers[38] that the C_6 methylene group retards the solvolysis rate of *endo*-norbornyl derivatives.

Of further interest is the fact that the α-isotope effect that we have estimated for the solvolysis of *endo*-norbornyl bromide is considerably larger than that observed for the corresponding tosylate.[39] Although this difference (1.28 *vs.* 1.20) may in part be due to oversimplifications that we have introduced in our calculations, we regard this difference as being experimentally significant.[40] A survey of the literature,[41] however, indicates that, in all other cases reported, the α-deuterium isotope effect in any particular system is *greater* for tosylates than bromides. In view of the relative sizes of bromine and oxygen, this result is probably a reflection of the more serious interaction between bromine and the C_6 methylene group; this interaction necessitates a greater degree of bond breaking for the bromide than for the tosylate before the transition state is reached.[42]

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(26) L. Hakka, A. Queen, and R. E. Robertson, *J. Am. Chem. Soc.*, **87**, 161 (1965).

(27) E. S. Lewis, *Tetrahedron*, **5**, 143 (1959).

(28) V. J. Shiner, Jr., *ibid.*, **5**, 243 (1959).

(29) V. J. Shiner, Jr., and J. S. Humphrey, Jr., *J. Am. Chem. Soc.*, **85**, 2416 (1963).

(30) H. C. Brown, M. E. Azzaro, J. G. Koelling, and G. J. McDonald, *ibid.*, **88**, 2520 (1966).

(31) See J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3445, 3452 (1953), for a noteworthy example.

(32) W. H. Saunders, Jr., S. Asperger, and D. H. Edison, *ibid.*, **80**, 2421 (1958).

(33) J. P. Schaefer and D. S. Weinberg, *Tetrahedron Letters*, 2491 (1965).

(34) V. J. Shiner, Jr., and J. G. Jewett, *J. Am. Chem. Soc.*, **87**, 1382, 1383 (1965).

(35) S. Borcic, M. Nikoletic, and D. Sunko, *ibid.*, **84**, 1615 (1962).

(36) B. L. Murr, A. Nickon, T. D. Swartz, and N. H. Werstiuk, *ibid.*, **89**, 1730 (1967).

(37) J. M. Jerunica, S. Borcic, and D. E. Sunko, *ibid.*, **89**, 1732 (1967).

(38) H. C. Brown, F. J. Chloupek, and M. Rei, *ibid.*, **86**, 1248 (1964).

(39) C. C. Lee and E. W. C. Wong, *ibid.*, **86**, 2752 (1964).

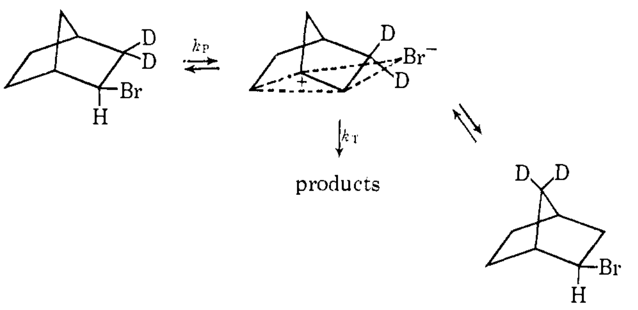
(40) If we assume that in 1-d_3 the 3 position is fully deuterated, this leaves only 0.61 atom of deuterium per mole in the α position. Calculation of the α-deuterium isotope effect under these circumstances gives a value of 1.36. Alternatively, if the α position is assumed to be fully deuterated, the calculated α isotope effect drops to 1.27, which is still significantly greater than the reported value for the tosylate. A second complication could arise from the fact that studies on the tosylate were done in acetic acid whereas we employed 50% aqueous ethanol as the reaction medium. Since 50% aqueous ethanol is a better ionizing solvent and is also more nucleophilic than acetic acid, it would appear that any correction for solvent effects would serve to *increase* rather than decrease the difference in isotope effects.

(41) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 173, tabulates a large number of recent values.

(42) It is interesting to note in this connection that a negligible or slightly inverse isotope effect has been noted in the acetolysis of *endo*-norbornyl-6-*endo-d* brosylate.[36,37] On steric grounds, the smaller size of deuterium should cause this compound to react at a faster rate than the protium analog if repulsion between this position and the leaving group is an important factor influencing the reactivity of *endo*-norbornyl derivatives. However, it seems probable that the difference in size of protium and deuterium is sufficiently small that any kinetic effect due to this difference might be difficult to detect experimentally.

In contrast to these findings, the *exo* isomer exhibits one of the lowest β-secondary isotope effects yet recorded for a compound undergoing a limiting solvolysis. Unless an as of yet unappreciated steric effect can be demonstrated to be responsible for the striking difference in isotope effects that is observed for the two epimers, we are forced to conclude that these results provide compelling support for the suggestion of Winstein and Trifan[1] that the C_1–C_6 σ electrons in the transition state for the solvolysis of *exo*-norbornyl derivatives are delocalized.

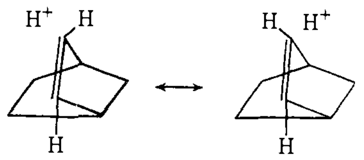
The differences in secondary isotope effects that are observed when polarimetric and titrimetric methods are used to follow the reaction rates are of further interest, the former method giving an isotope effect having about twice the magnitude of that given by the latter. From Table II it will be seen that internal return is quite important in the solvolysis of the *exo* bromide since the polarimetric rate is 8.5 times greater than the titrimetric rate in the solvent systems that we used. Winstein and Trifan[1] noted that the solvolysis of the tosylate behaved in a similar fashion and formulated an intimate ion pair as being the first formed intermediate. Collapse of this ion pair back to *exo*-norbornyl tosylate could occur with equal ease at either C_1 or C_2, a process that would result in conversion of optically active starting material to a racemic mixture, and this process competes effectively with dissociation of the intimate ion pair to the solvated anion on cation.



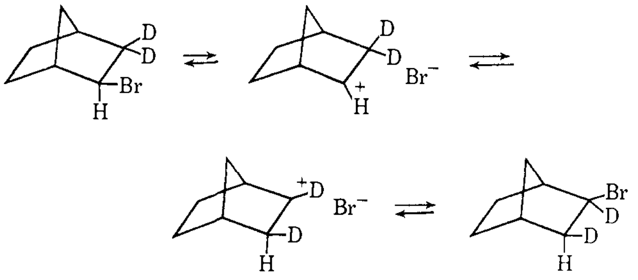
If we accept this interpretation for the bromide and further presume that 2,6-hydride shifts occur to a negligible extent up through the intimate ion pair stage of reaction,[43] it follows that the isotope effect exerted by deuterium located at C_7 must be vanishingly small since within experimental error

$$(k_H/k_D)_P = (k_H/k_D)_T^2$$

In view of our previous conclusion (*vide supra*), this result would require that, although the electrons are delocalized in the transition state, no significant molecular reorganization of the carbon skeleton has yet occurred and the geometry of these nuclei has not changed significantly from that of the parent compound. This presumes that β-secondary isotope effects may be rationalized in accord with hyperconjugative phenomena and the geometrical requirements associated with this effect. In terms of valence bond formulations, the absence of an isotope effect would require that the resonance forms depicted do not contribute significantly to stabilization of the transition state since geometrical factors minimize the degree of orbital overlap that is possible.



The low value for the β-deuterium isotope effect observed for the *exo* compound can also be used to rule out the possibility of 2,3-hydride shifts up through the intimate ion pair stage of the reaction. A 2,3-hydride shift followed by collapse of the ion pair would now place a deuterium atom at C_2. In view of the very large α-isotope effects that have been detected in the norbornyl system,[39] this type of process would contribute to an increase in the measured isotope effect as a function of time. This clearly is not observed.



The results of these studies suggest that secondary isotope effects are a unique and sensitive probe for examining the details of complex reactions and may provide a powerful experimental method for deciding whether or not a cationic transition state should be classified as classical or nonclassical. We are currently pursuing this question in the norbornyl and other bicyclic systems in an attempt to evalute its ultimate usefulness.

Experimental Section[44]

(+)-3,3-d_2-Norcamphor. A solution of deuteriotrifluoroacetic acid was prepared by the cautious addition of trifluoroacetic anhydride (80.0 g, 0.380 mole) to a chilled solution of 98.0 g (4.90 moles) of deuterium oxide in a large heavy-walled glass tube. (+)-Norcamphor (30.8 g, 0.280 mole) was added, the tube was sealed, and the solution was heated at 125–135° for 5 days. The solution was added to a cold solution of 150 ml of water containing 150 g of potassium carbonate and then extracted with 1 l. of pentane. The pentane extract was dried and concentrated. The last traces of solvent were removed by evacuating the sample in a desiccator at 200-mm pressure for brief periods. The exchange was then repeated giving 25.2 g (81.8%) of product, mp 90–93° (lit.[1] mp 91–92°) after sublimation.

Anal. Calcd for $C_7H_8D_2O$: 20.00 atom % excess D. Found: 19.30 atom % excess D (1.93 deuterium atoms per molecule).

3,3-d_2-Norbornyl bromide was prepared by reducing the ketone with lithium aluminum hydride and treating the alcohol with triphenylphosphine dibromide in the manner previously described.[14] The sample used for kinetic studies contained 1.93 atoms of deuterium per molecule.

Reaction of *exo*-Norbornanol with Triphenylphosphine and Bromine. Triphenylphosphine (12.0 g, 0.0457 mole) in 50 ml of solvent was placed in a three-necked, round-bottomed flask fitted with a

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(43) Smith and Petrovitch[21] have demonstrated that this is true for the reaction of the *exo*-thiobenzoate.

(44) Boiling points and melting points (taken in sealed capillary tubes) are uncorrected. Optical rotations were measured with a Rudolph Model 80 high-precision polarimeter. The vapor chromatograms were taken on a Wilkins Instrument and Research, Inc. aerograph or an F & M Scientific Corp. Model 609 flame ionization gas chromatograph. Infrared spectra were recorded with Perkin-Elmer spectrometers, Models 137 and 337, and the nmr spectra on a Varian A-60 spectrometer. Conductivity measurements were performed with an Industrial Instruments, Inc., Model RC 1682 conductivity bridge; a Heathkit Model IN-21 decade condenser was used for phase balance of the bridge circuit. Deuterium analyses were done by J. Nemeth of Urbana, Ill.

condenser, dropping funnel, and mechanical stirrer. Bromine (7.15 g, 0.0447 mole) was added dropwise to the cooled solution (ice–water) over a 20-min period and then the *exo*-alcohol dissolved in 50 ml of solvent was added rapidly with stirring.

The reaction mixture was heated at reflux temperature for varying periods of time while a slow stream of nitrogen gas was admitted to remove the hydrogen bromide evolved. When the reaction was completed, a short Vigreux column was attached to the reaction flask and the solvent and norbornyl bromide were distilled under reduced pressure. The distillate was diluted with pentane; the pentane solution was washed with ice water, aqueous sodium bicarbonate, and ice water again. After drying with magnesium sulfate, the solution was fractionally distilled to give the norbornyl bromides in 50–73% yield. The ratio of *exo* to *endo* isomers was determined by solvolysis in 40% aqueous ethanol at 69° and these results are summarized in Table I.

Vinyl-d_3 Bromide. 1,2-Dibromoethane-d_4 (Isomet Corp., 99 atom % pure, 21.0 g, 0.091 mole) was placed in a three-necked flask fitted with a magnetic stirrer, a dropping funnel, and a condenser with a Claisen head attached. Potassium hydroxide (11.2 g of 85%, 0.17 mole) in 50 ml of 95% ethanol was added dropwise with stirring; potassium bromide precipitated almost immediately. The reaction mixture was heated to reflux until no more deuterated vinyl bromide distilled. The product, bp 16–20° (lit.[45a] bp 16°), weighed 10.6 g (88.3%) and was used without further purification.

2,3,3-d_3-*endo*-2-Norborn-5-enyl Bromide. Vinyl-d_3 bromide (10.6 g, 0.0964 mole) and 6.4 g (0.096 mole) of cyclopentadiene were placed in a sealed tube and heated at 165° for 24 hr. The product was distilled through a 30-cm Vigreux column to give 6.0 g (35% yield) of a colorless liquid, bp 58–59° (11 mm) (lit.[45b] bp 63–65.5° (15.5 mm)). Vpc analysis on a Bentone 34 (10% on Chromosorb W, 60–80 mesh) 0.25 in. × 8 ft copper column at 68° showed that the product was a mixture of *exo* and *endo* isomers (18.7% *exo* and 81.3% *endo*).

The *endo* isomer was separated by preparative vpc on a Bentone 34 column at 78°.

Anal. Calcd for $C_7H_6D_3Br$: 33.33 atom % excess D. Found: 31.70 atom % excess D (2.85 deuterium atoms per molecule).

2,3,3-d_3-2-Norbornyl Bromide. 2,3,3-d_3-2-Norborn-5-enyl bromide (2.0 g, 0.011 mole) was catalytically hydrogenated in ethyl acetate in the presence of 10% palladium on charcoal at atmospheric pressure. After filtration, distillation afforded 1.2 g of 2,3,3-d_3-norbornyl bromide, bp 66–67° (10 mm) (lit.[45b] bp 69–70° (15.5 mm)). Preparative vpc on a Bentone 34 column at 90° gave a mixture of *exo* and *endo* isomers, which could not be separated.

Anal. Calcd for $C_7H_8D_3Br$: 27.27 atom % excess D. Found: 23.70 atom % excess D (2.61 deuterium atoms per molecule).

Acetic Acid-d_4. Malonic acid was exchanged three times with deuterium oxide in dioxane according to the method of Truce and co-workers.[46] Nmr analysis of the exchanged malonic acid indicated that exchange was about 90% complete. Decarboxylation of the deuterated malonic acid at 145° gave the desired product in 85% yield. Analysis by nmr showed that the acid was about 86% deuterated.

2,2,2-d_3-Ethanol. Reduction of acetic acid-d_4 with lithium aluminum hydride in ether[46] afforded 95% ethanol-d_3 in 85% yield. Nmr analysis indicated the presence of 2.5 atoms of deuterium on C_2.

2,2,2-d_3-Acetaldehyde. 2,2,2-d_3-Ethanol (5% water) was oxidized with potassium dichromate in aqueous sulfuric acid.[47] Distillation through a Widmer column afforded 2,2,2-d_3-acetaldehyde, bp 21–25° (lit.[48] bp 20°), in 40% yield. Nmr analysis indicated that 2.3 atoms of deuterium were located on C_2. About 12% of the starting alcohol was recovered and used in subsequent oxidations.

2,2,2-d_3-1,1-Dibromoethane. The procedure which was employed has been described by Wibaut[49] and Burkhardt and Cocker.[50] Phosphorus trichloride (44 ml, 0.50 mole) was placed in a round-bottomed flask and cooled in an ice bath. Bromine (27 ml, 0.50 mole) was added slowly with occasional agitation. This mixture was allowed to stand overnight at room temperature. The contents of the reaction vessel were cooled again in an ice bath and 2,2,2-d_3-acetaldehyde (16.5 g, 0.351 mole) was added dropwise from an addition funnel cooled with circulating ice water through a condenser cooled with ice water. After the reaction mixture had been allowed to stand for 1 hr at 0°, the excess phosphorus pentahalide was decomposed by the slow addition of ice water. The dense 2,2,2-d_3-1,1-dibromoethane was separated from the aqueous layer, which was extracted three times with 100-ml portions of ether. The bromide and the ether solutions were combined and washed several times with water and with aqueous sodium bisulfite. After drying with anhydrous magnesium sulfate, the ether solution was concentrated with a rotary evaporator to give 17.5 g (25.3%) of product.

Vpc analysis on a Reoplex 400 (10% on Firebrick, 60–80 mesh) 0.25 in. × 5 ft copper column at 70° revealed that 5–10% of the product mixture was crotonaldehyde. The deuterated bromide was not purified further. Nmr analysis of the product mixture showed that about 2.4 deuterium atoms were present on C_2.

2,2-d_2-Vinyl Bromide. 2,2-d_2-Vinyl bromide was prepared according to the procedure of Loevenich and co-workers.[51] Sodium (3.3 g, 0.14 g-atom) was added to 110 ml of absolute ethanol in a round-bottomed flask fitted with a condenser and a magnetic stirrer. After the sodium reacted with the ethanol, 2,2,2-d_3-1,1-dibromoethane was added in one portion to the basic solution. A Claisen head was placed on top of the condenser and the reaction mixture was heated to 85° for 2.5 hr. 2,2-d_2-Vinyl bromide, 9.4 g (60%), bp 17–21° (lit.[44] bp 16°), was collected in a receiver cooled with a Dry Ice–acetone bath. Nmr analysis revealed that 1.7 deuterium atoms per molecule were present in the C_2 position.

3,3-d_2-*endo*-2-Norborn-5-enyl Bromide. 2,2-d_2-Vinyl bromide (9.4 g, 0.086 mole) and cyclopentadiene (5.5 g, 0.083 mole) were heated in a sealed tube at 165° according to the procedure of Roberts and co-workers.[45b] After distillation, 4.7 g (32%) of a colorless liquid, bp 55–57° (10 mm) (lit.[45b] bp 63–65.5° (15.5 mm)), was obtained. Preparative vpc on a Bentone 34 column at 90° resulted in pure 3,3-d_2-*endo*-2-norborn-5-enyl bromide.

Anal. Calcd for $C_7H_7D_2Br$: 22.22 atom % excess D. Found: 16.35 atom % excess D (1.47 deuterium atoms per molecule).

3,3-d_2-Norbornyl Bromide. Catalytic hydrogenation of 3,3-d_2-2-norborn-5-enyl bromide (a mixture of *exo* and *endo* isomers) in the presence of 10% palladium on charcoal in ethyl acetate gave a mixture of deuterated *exo*- and *endo*-norbornyl bromide. The product was isolated by preparative vpc on a Bentone 34 column at 90° as the mixture of *exo* and *endo* isomers.

Anal. Calcd for $C_7H_9D_2Br$: 22.22 atom % excess D. Found: 13.10 atom % excess D (1.44 deuterium atoms per molecule).

Kinetic Studies. A stock solution of acetic acid 4.00 *N* in water and 0.60 *N* in sodium acetate at 20° was prepared by adding distilled water (79.8 g, 4.40 mole) and sodium acetate trihydrate (164 g, 1.20 moles of sodium acetate and 3.60 moles of water) to a 2-l. volumetric flask and diluting with glacial acetic acid. All of the polarimetric and titrimetric kinetic samples were prepared within a 2-week period using solvent from this stock solution.

A. Polarimetric Solvolysis of (+)-*exo*-Norbornyl Bromide and (+)-3,3-d_2-*exo*-Norbornyl Bromide. The *exo*-norbornyl bromide (2.50 g, 0.143 mole) was weighed into a 25-ml volumetric flask, solvent was added, and the solution was mixed thoroughly for 10 min. The sample was transferred to a 4-dm polarimeter cell with the aid of a syringe equipped with a Millipore filter assembly to remove any finely divided suspended matter present, and light-weight motor oil from a constant-temperature bath at 51.25 ± 0.02° was circulated through the polarimeter cell jacket. After 15–25 min, readings were begun and were continued until the net optical rotation fell to about one-fourth its initial value. Each data point corresponding to an optical rotation represented the average value of six readings taken over a 2-min interval, except the infinity point, taken after 12 solvolysis half-lives, which represented the average of 36 readings.

B. Titrimetric Solvolysis of *exo*-Norbornyl Bromide and 3,3-d_2-*exo*-Norbornyl Bromide. The *exo*-norbornyl bromide (5.00 g, 0.286 mole) was weighed into a 50-ml volumetric flask and diluted to the mark with solvent; the solution was shaken vigorously for 10 min. Aliquots were transferred to 6-in. test tubes with a 3-ml pipet, the samples were frozen in a Dry Ice–acetone bath, and the tubes were sealed. The samples were placed in a wire cage and submerged in the constant-temperature bath mentioned above.

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A modification of the usual Volhard procedure was required to determine the amount of hydrogen bromide liberated as a function of time, since excess silver ion strongly catalyzes the solvolysis of alkyl halides. Samples were removed periodically from the constant-temperature bath, quenched in a Dry Ice–acetone bath, and opened. The contents were transferred quantitatively to a 250-ml erlenmeyer flask containing a cold solution of 1.000 ml of 0.1752 N potassium thiocyanate (delivered by buret), 20 ml of chloroform, and 20 ml of a solution consisting of 2.5 ml of concentrated nitric acid, 2.0 ml of a saturated aqueous solution of ferric ammonium sulfate, and distilled water. The cold mixture was stirred vigorously with the aid of a magnetic stirring bar and titrated with 0.1783 N silver nitrate to a colorless end point. After two half-lives, the remaining samples were removed from the constant-temperature bath and added to another constant-temperature bath at 94° for an additional 10 half-lives; the infinity point was then determined in triplicate. Control experiments indicated that analysis of a known amount of sodium bromide in the presence of *exo*-norbornyl bromide under the conditions described above could give results accurate to within 0.1%.

C. Conductometric Solvolyses of *endo*-Norbornyl Bromides. The solvent used in all kinetic studies was 50 vol % aqueous ethanol. The constant-temperature bath was maintained at 60.21 ± 0.01°. The conductance cells were of the Freas type with shiny platinum electrodes 1 cm^2 in area and spaced 1 cm apart. Several cells were used for the kinetic studies and rate constants were independent of the cell used. The conductance cells were filled almost to capacity with solvent and equilibrated in the bath before introduction of 4 μl of bromide. After ten solvolysis half-lives for the *exo* isomer (about 700 min), conductivity measurements for the *endo* isomer were begun. Measurements were recorded over a period of five half-lives. No systematic deviations from the first-order rate law were observed and the rate constants were independent of the initial concentration of bromide in the concentration ranges which we employed. Rate constants were reproducible to $\pm\sim 1\%$ and are summarized in Table II.

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The Decarboxylation of *p*-Methoxy-β-methylcinnamic Acid. Solvent Isotope Effects and Acid Catalysis[1]

Donald S. Noyce, Leon M. Gortler, Fred B. Kirby, and Melvyn D. Schiavelli[2]

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received July 24, 1967*

Abstract: In dilute aqueous sulfuric acid, *p*-methoxy-β-methylcinnamic acid undergoes decarboxylation by a reaction which shows strong acid catalysis. In the region of 10–25% sulfuric acid, this reaction is characterized by a rate-determining proton transfer as shown by the fact that the solvent kinetic isotope effect, k_{H_2O}/k_{D_2O}, is 3. In more concentrated sulfuric acid (above 40%), the rate-limiting process changes as shown by the abrupt change in the solvent isotope effect, k_{H_2O}/k_{D_2O} decreasing to 1.7.

Recent studies from these laboratories have examined the complex interrelations among hydration and dehydration reactions, racemization processes, and the synchronous decarboxylation–dehydration reaction of variously substituted cinnamic acids and related β-hydroxy acids. It was shown[3] that β-phenyl-β-hydroxybutyric acid (**1**) undergoes dehydration in moderately concentrated sulfuric acid to give both the conjugated isomer, β-methylcinnamic acid (**2**), and the nonconjugated isomer, 3-phenyl-3-butenoic acid (**3**), at comparable rates. However, the acid-catalyzed hydration of **3** is very rapid and hence little **3** accumulates; the major product of acid-catalyzed dehydration is therefore **2**. Additionally it was shown that racemization of β-hydroxybutyric acids is more rapid than dehydration[4] in 1 M sulfuric acid.

In a related study,[1] of the decarboxylation of β-phenylcinnamic acid in sulfuric acid, a complex rate–acidity profile was observed. It was shown that this complex rate *vs.* acidity profile could be satisfactorily interpreted on the basis of a change in the rate-limiting process. At low mineral acid concentrations the rate-limiting process is acid-catalyzed hydration of β-phenylcinnamic acid and at high mineral acid concentrations the rate-limiting process is the synchronous decarboxylation–dehydration of an equilibrium low concentration of β,β-diphenyl-β-hydroxypropionic acid.

It is the purpose of the present report to examine further predictions from this group of conclusions about the pathways of these reactions.

Experimental Section

Materials. The preparation of β-(*p*-methoxyphenyl)-β-hydroxybutyric acid (**5**) and of β-(*p*-methylphenyl)-β-hydroxybutyric acid (**7**) has been described previously[4] as has the preparation of sulfuric acid-d_2.[5]

Kinetic Methods. Rate measurements were made by following the change in absorbance at 290–300 mμ, a region of the ultraviolet spectrum where the only strongly absorbing species is the substituted cinnamic acid. Solutions were generally 10^{-5} M in organic substrate; at this concentration carbon dioxide (bubble formation) generally caused no difficulty.

For preparation of kinetic solutions a weighed sample of β-(*p*-methoxyphenyl)-β-hydroxybutyric acid was dissolved in a measured small quantity of water. An aliquot of this solution was diluted with sulfuric acid of the requisite strength, rapidly mixed, and

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