KINETIC ISOTOPE EFFECTS AS A VALID MEASURE OF STRUCTURE-REACTIVITY RELATIONSHIPS. ISOTOPE EFFECTS AND NONCLASSICAL THEORY

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Received November 29, 1971 (Revised Manuscript Received February 28, 1972)

Contents

I. Introduction

The measurement of reaction-rate constants and determination of activation parameters as a function of molecular structure is a technique widely utilized in attempts to understand reaction dynamics of organic systems. The potential energy surface for a reaction, even if the mechanism is unaltered, must be modified by change in substitution, *e.g.*, phenyl for methyl. A quantitative prediction of (understanding of) substituent effects requires a quantum-mechanical analysis of shifts in electronic potential energy which must in turn be related to rate constants and their temperature dependence, the most widely used relationship being transition-state theory.[1] Although some semiquantitative and exact analyses of rates and mechanisms have been achieved,[1,2] exact treatment of reaction dynamics for polyatomic systems is at present impossible.

The Hammond postulate[3] and various extensions[4] have been used to make qualitative predictions about transition-state geometry from reactant, intermediate, and/or product geometries and enthalpies of reaction. Thornton[5] has attempted to relate (predict) substituent effects by considering these as linear perturbations of the vibrational potentials for the normal coordinate motions both parallel and perpendicular to the reaction coordinate. Harris and Kurz[6] have considered in detail substituent effects in the SN2 reaction. Orbital symmetry considerations have significantly aided in understanding at least gross details of potential energy surfaces.[7] Implications of neglect of configuration interaction in such treatments have been investigated.[8]

A complementary approach to this problem is measurement and analysis of kinetic isotope effects.[9] Within the limits of the Born–Oppenheimer approximation electronic

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(1) S. Glasstone, K. J. Laidler, and H. Eyring, "Theory of Rate Processes," McGraw-Hill, New York, N. Y., 1941.

(2) (a) K. J. Laidler and J. C. Polanyi, *Progr. React. Kinet.*, **3**, 1 (1965); (b) H. S. Johnson, *Advan. Chem. Phys.*, **3**, 131 (1960); (c) *ibid.*, "Gas Phase Reaction Rate Theory," The Ronald Press Co., New York, N. Y., 1966; (d) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963; (e) M. Karplus and R. N. Porter, *Discuss. Faraday Soc.*, **44**, 164 (1967); (f) R. N. Porter, D. L. Thompson, L. B. Sims, and L. M. Raff, *J. Amer. Chem. Soc.*, **92**, 3208 (1970).

(3) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(4) (a) K. B. Wiberg, *Chem. Rev.*, **55**, 733 (1955); (b) A. Streitwieser, Jr., *ibid.*, **56**, 571 (1956).

(5) (a) E. R. Thornton, *J. Amer. Chem. Soc.*, **89**, 2915 (1967); (b) G. J. Frisone and E. R. Thornton, *ibid.*, **90**, 1211 (1968).

(6) J. C. Harris and J. L. Kurz, *ibid.*, **92**, 349 (1970).

(7) For recent reviews see (a) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968); (b) R. B. Woodward and R. H. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

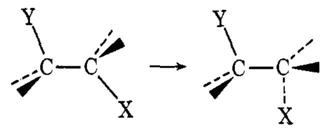
(8) (a) R. N. Porter and L. M. Raff, *J. Chem. Phys.*, **50**, 5216 (1969); (b) L. M. Raff and R. N. Porter, *ibid.*, **51**, 4701 (1969).

(9) For recent reviews and general treatment of isotope effects, see (a) M. Wolfsberg, *Annu. Rev. Phys. Chem.*, **19**, 449 (1968); (b) E. R. Thornton, *ibid.*, **17**, 349 (1966); (c) P. Laszlo and Z. Welvart, *Bull. Soc. Chim. Fr.*, 2412 (1966); (d) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963); (e) J. Bigeleisen and M. Wolfsberg, *Advan. Chem. Phys.*, **1**, 15 (1958); (f) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960; (g) E. R. Thornton, "Solvolysis Mechanisms," Ronald Press, New York, N. Y., 1964, p 258. (h) For a recent excellent discussion of the theory of kinetic isotope effects, see W. A. Van Hook in "Isotope Effects in Chemical Reactions," ACS Monograph 167, C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, New York, N. Y., 1970, Chapter 1. (i) For a discussion of the origins and interpretations of isotope effects, see E. K. Thornton and E. R. Thornton, *ibid.*, Chapter 4.

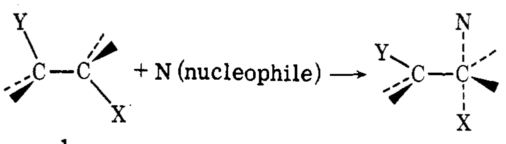
energy is independent of isotopic substitution, and, hence, isotope effects are nuclear mass effects resulting from the motion of different nuclei on the same potential energy surface.[9a,b,h] The variation in the magnitudes of isotope effects with variation in molecular structure can be related *via* absolute reaction rate theory to changes in that part of the potential-energy surface which involves motion of the isotopic atoms. In general, the available information about the surface increases as the "number" of isotope effects available rises. Thus the measurement of a sufficient number of isotope effects permits calculation of transition state force constants (bond orders). For a series of homologous compounds undergoing a given reaction, such information for each reactant would provide a quantitative understanding of the effect of change in reactant structure upon reactivity.

Interest in the ability of neighboring groups to alter the energetics or organic reactions is legend.[10] For reactions proceeding *via* cationic intermediates major controversy has arisen on the interpretation of the experimental data in terms of alteration of reaction energetics and ion structure.[10,11] Interest in rearrangements of free radicals and in elucidation of the ability of neighboring groups to affect the energetics of free radical reactions has flowered.[12] Kinetic isotope effects, especially secondary deuterium effects, have recently been utilized in studying these reactions. This article reviews results and conclusions drawn from a number of these studies. However germane might be a review of the nonisotope effect literature in this field, especially that relating to the "nonclassical ion controversy," such a review is beyond the scope of this article.

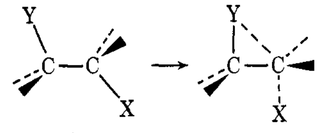
Since the isotope effect studies have principally involved secondary deuterium effects this review addresses itself to the question: Is the "abnormal" secondary deuterium isotope effect a useful criterion for the assessment of participation? A related question is: When is a secondary effect abnormal, and what is the origin of the abnormality? These questions will be considered by analyzing isotope effect data for the following reactions. Consider a hypothetical reactant **1** reacting *via* a unimolecular reaction (eq 1), a bimolecular reaction (eq 2), or a unimolecular reaction involving anchimeric assistance by the neighboring group Y (eq 3). The transition states are **2**, **3**, and **4**, respectively. The points to be considered are: (1) the qualitative response of kinetic isotope effects to a change in molecular structure of the reactants, (2) the general usefulness of any one kind of isotope effect in interpreting (qualitatively) substituent effects upon chemical reactivity, and (3) the utility of kinetic isotope effects as a measure of the variation in transition-state bonding, *i.e.*, the reactant-like:product-like character of the transition state. It is now advantageous to summarize, within the present state of the theory (a) the molecular origins of the various kinetic isotope effects and (b) the variation in these effects to be anticipated upon a change in reaction mechanism.



1 2 (1)



1 3 (2)



1 4 (3)

II. Fundamental Considerations

A. MATHEMATICAL FORMALISM

Equation 4 expresses the isotope effect as the product of the

$$k_1/k_2 = \nu^{\ddagger}{}_{1L}/\nu^{\ddagger}{}_{2L} \times \mathrm{VP} \times \mathrm{EXC} \times \mathrm{ZPE} \qquad (4)$$

classical mechanical ($\nu^{\ddagger}{}_{1L}/\nu^{\ddagger}{}_{2L}$) and quantum mechanical (VP × EXC × ZPE) contributions, where the subscripts 1 and 2 refer to the light and heavy isotopes, respectively.[13] VP represents the vibrational product term, EXC the factor arising from the thermal excitation of vibrations, and ZPE the term arising from zero-point energies. Equation 4 is derivable from eq 5 by the Teller–Redlich product rule[9e]

$$k_1/k_2 = \mathrm{MMI} \times \mathrm{EXC} \times \mathrm{ZPE} \qquad (5)$$

where MMI stands for mass moment of inertia factor.

B. NONANCHIMERICALLY ASSISTED REACTIONS

1. α and β Secondary Deuterium Effects

α-Effects were reported in the 1950's for solvolysis and bimolecular displacement reactions.[14] The α-effect in acetolysis of cyclopentyl tosylate, $k_H/k_D \cong 1.15$, was ascribed to a difference in loss of ZPE between the protio and deuterio compounds in passing from the reactant to the transition state.[14a]

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(10) For general reviews of systems in which neighboring group theory has been at least considered, see (a) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964); (b) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N. Y., 1965; (c) D. Bethell and V. Gold, "Carbonium Ions, an Introduction," Academic Press, New York, N. Y., 1967, Chapter 7; (d) S. Winstein, *Quart. Rev., Chem. Soc.*, **23**, 141 (1969).

(11) For leading references, see (a) H. C. Brown, *Chem. Soc. Spec. Publ.*, **No. 16**, 140 ff (1962); (b) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 111 ff; (c) G. E. Gream, *Rev. Pure Appl. Chem.*, **16**, 25 (1966); (d) H. C. Brown, *Chem. Brit.*, **2**, 199 (1966); (e) G. D. Sargent, *Quart. Rev., Chem. Soc.*, **20**, 301 (1966); (f) H. C. Brown, *Chem. Eng. News*, **45** (7), 87 (1967); (g) D. J. Cram, *J. Amer. Chem. Soc.*, **86**, 3767 (1964); (h) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *ibid.*, **87**, 2137 (1965).

(12) For reviews and leading references see (a) C. Walling in "Molecular Rearrangements," Vol. I, P. De Mayo, Ed., Interscience, New York, N. Y., 1963, pp 407–455; (b) R. Kh. Freidlina in "Advances in Free Radical Chemistry," Vol. I, G. H. Williams, Ed., Academic Press, New York, N. Y., 1965, pp 211–278; (c) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, pp 37–39, Chapters 14 and 17; (d) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 289 (1968); (e) W. G. Bentrude, *Annu. Rev. Phys. Chem.*, **18**, 283 (1967); (f) M. J. Perkins, *Annu. Rep. Progr. Chem.*, **65** (B), 171 (1968); (g) C. Rüchardt, *Fortschr. Chem. Forsch.*, **6**, 251 (1966); (h) A. B. Terent'ev and R. Kh. Freidlina, *Proc. Acad. Sci. USSR*, **158**, 679 (1964); (i) L. K. Montgomery, J. W. Matt, and J. R. Webster, *J. Amer. Chem. Soc.*, **89**, 923 (1967); (j) D. D. Tanner, *ibid.*, **91**, 7535 (1969).

(13) M. Wolfsberg and M. J. Stern, *Pure Appl. Chem.*, **8**, 225 (1964).

(14) (a) A. Streitwieser, R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958); (b) R. R. Johnson and E. S. Lewis, *Proc. Chem. Soc.*, 52 (1958); (c) K. Mislow, S. Borčić, and V. Prelog, *Helv. Chim. Acta*, **40**, 2477 (1957); (d) V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, **74**, 5285 (1952).

Rehybridization of C-α bonds was suggested as the origin of the decrease in ZPE. The absence of an α-effect in the reaction of isopropyl bromide with ethoxide ion[14d] was ascribed[14a] to the presence of both the nucleophile and exiphile in the transition state, **3**, negating a change in ZPE. α-Effects are often discussed in terms of hybridization (geometry) changes occurring along the reaction coordinate. Clearly C-α is undergoing change in geometry in bimolecular reactions typical of eq 2. However, α-effects for SN2 reactions range from inverse to unity to normal. Using the results of elegant "exact" calculations in model chemical systems, Wolfsberg and Stern[13,15] have deduced that for reactions represented by eq 1 the magnitude of the α-effect is dependent upon the reduction in the hydrogen–carbon leaving group bending force constant (HCX), *i.e.*, $f_{\mathrm{HCX}} \rightarrow f^{\ddagger}{}_{\mathrm{HCX}}$[16] in passing from **1** to **2**. The calculated α-effect reflects a lowering of f_{HCX} with the amount of lowering to produce a given effect somewhat dependent upon geometry.[15a] However, to deduce the geometry from a measured α-effect requires an independent method of correlating the HCX bending constant with geometry.[15a] For model reaction 2, *e.g.*, a SN2 reaction, the magnitude of $k_{\mathrm{H}}/k_{\mathrm{D}}$ will depend upon the difference between f_{HCX} and $f^{\ddagger}{}_{\mathrm{HCX}}$ and the magnitude of $f^{\ddagger}{}_{\mathrm{HCN}}$.[15a] In such reactions the α-effect will be a function of the bonding of both the nucleophile and the exiphile to C-α. These investigations together with other experimental[17] and theoretical[17d] studies have confirmed that the difference in loss of ZPE between protio and deuterio compounds in the ground and transition states is principally responsible for the α-effect.[14a]

From empirical evidence, Seltzer[18] suggested that a normal α-effect for a unimolecular reaction should be *ca.* 1.12 per α-D at 105° (1.15 at 25°). The origin of the smaller α-effect in the solvolysis of 1-phenylethyl bromides (*ca.* 1.125) compared to the corresponding chlorides (*ca.* 1.155) was suggested to reflect a smaller reactant-state bending-force constant for HCBr than for HCCl.[19] Calculations[20] indicate, in harmony with this suggestion, that a variation in the leaving group which alters the HCX bending-force constant should produce a variation in the magnitude of $k_{\mathrm{H}}/k_{\mathrm{D}}$.

Hyperconjugation[9d,21] and relief of nonbonded interactions[9b,22] have been supposed to cause the force constant change associated with the β-hydrogens in passing from the reactant to the transition state.[15a] The disagreement between these views cannot be reviewed here. Although steric isotope effects have been observed,[23] the available data[9d,19,21] indicate that hyperconjugation, when possible, is the dominant factor.[19,23f] For an SN1 reaction, the β-effect is a function of the magnitude of the positive charge at C-α[18] and the dihedral angle, φ, between the β-hydrogen and the incipient p orbital on C-α.[21h,i] Thus for tertiary chlorides the β-effect per D varies from 1.31 to 0.99 as φ is varied from 180 (0) to 90°.[21i] In general $k_{\mathrm{H}}/k_{\mathrm{D}}$ for arenesulfonate solvolysis is greater.[14a,21i,24] β-Effects per D for free radical formation are much smaller than those for formation of cations of the same formal structure.[25] These results are consistent with diminished importance of hyperconjugation in free radicals compared to the equivalent cations.[25,26]

2. *Heavy-Atom Effects*

Heavy-atom, and in particular carbon-atom, isotope effects were important in developing the theory of kinetic isotope effects.[9e,f,27] Force constant changes which take place when the transition state is formed from the reactant(s) are important in determining the magnitude of the effect.[9f,13] However, the zero-point energy is no longer so dominant as it is with hydrogen, necessitating consideration of the exact expression or suitable modifications thereof.[9e,f,13,27a] For example, a particular result from model calculations for the reaction of iodomethane-^{13}C with iodide anion yields values of MMI, EXC, and ZPE of 1.2657, 0.8674, and 0.9622 with a k_{12}/k_{13} value of 1.0616.[28] Unimolecular reactions of the type illustrated in eq 1, *e.g.*, SN1 displacements and pyrolysis of azo compounds, involve reduction in the force constants associated with the C-α–X bond. Hence, appreciable isotope effects might be expected for isotopic substitution at C-α and X. Such expectations are not necessarily realized owing apparently to compensating changes in other force constants, (see below). For bimolecular reactions (eq 2) carbon effects at C-α should represent the relative amounts of bond making and bond breaking. Detailed calculations[29] analogous to those for a three-centered hydrogen transfer reaction[29a] confirm the suggestion[29b] that the carbon effect will be maximum

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(15) (a) M. Wolfsberg and M. J. Stern, *Pure Appl. Chem.*, **8**, 325 (1964); (b) M. J. Stern and M. Wolfsberg, *J. Pharm. Sci.*, **54**, 849 (1965); (c) *ibid.*, *J. Chem. Phys.*, **45**, 2618 (1966).

(16) For reasons of clarity force constants are designated by the letter *f*. A superscript ‡ indicates a transition-state force constant. The subscript denotes the nature of the force constant.

(17) (a) S. Seltzer, *J. Amer. Chem. Soc.*, **83**, 1861 (1961); (b) A. A. Zavitsas and S. Seltzer, *ibid.*, **86**, 3836 (1964); (c) C. Y. Wu and P. E. Robertson, *Chem. Ind.* (*London*), 195 (1966); (d) A. V. Willi and C. M. Won, *J. Amer. Chem. Soc.*, **90**, 5999 (1968).

(18) S. Seltzer, *ibid.*, **83**, 2625 (1961).

(19) V. J. Shiner, Jr., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *ibid.*, **90**, 418 (1968).

(20) V. J. Shiner, Jr., M. W. Rapp, E. A. Halevi, and M. Wolfsberg, *ibid.*, **90**, 7171 (1968).

(21) For leading references, see (a) E. S. Lewis and C. E. Boozer, *ibid.*, **74**, 6306 (1952); (b) V. J. Shiner, Jr., *ibid.*, **75**, 2925 (1953); (c) *ibid.*, **74**, 5285 (1952); (d) V. J. Shiner, Jr., and S. Cross, *ibid.*, **79**, 3599 (1957); (e) V. J. Shiner, Jr., and G. S. Kriz, *ibid.*, **86**, 2643 (1964); (f) V. J. Shiner, Jr., *ibid.*, **78**, 2653 (1956); (g) *ibid.*, **83**, 240 (1961); (h) V. J. Shiner, Jr., B. L. Murr, and G. Heineman, *ibid.*, **85**, 2413 (1963); (i) V. J. Shiner, Jr., and J. S. Humphrey, Jr., *ibid.*, **85**, 2416 (1963); (j) V. J. Shiner, Jr., and J. G. Jewett, *ibid.*, **86**, 945 (1964); (k) J. G. Jewett and R. Dunlap, *ibid.*, **90**, 809 (1968).

(22) (a) L. S. Bartell, *J. Chem. Phys.*, **32**, 827 (1960); (b) *ibid.*, *Tetrahedron*, **17**, 177 (1962); (c) *ibid.*, *Tetrahedron Lett.*, 13 (1960); (d) *ibid.*, *J. Amer. Chem. Soc.*, **83**, 3567 (1961).

(23) (a) L. Melander and R. E. Carter, *ibid.*, **86**, 295 (1964); (b) K. Mislow, K. R. Graeve, A. J. Gordon, and G. H. Wahl, Jr., *ibid.*, **86**, 1733 (1964); (c) V. F. Raaen, T. K. Dunham, D. D. Thompson, and C. J. Collins, *ibid.*, **85**, 3497 (1963); (d) H. C. Brown and G. J. McDonald, *ibid.*, **88**, 2514 (1966); (e) H. C. Brown, M. E. Azzaro, J. G. Koelling, and G. J. McDonald, *ibid.*, **88**, 2520 (1966); (f) G. J. Karabatsos, G. C. Sonnichsen, C. G. Papaioannou, S. E. Scheppele, and R. L. Shone, *ibid.*, **89**, 463 (1967); (g) A. J. Kresge and R. J. Preto, *ibid.*, **89**, 5510 (1967); (h) E. D. Kaplan and E. R. Thornton, *ibid.*, **89**, 6644 (1967); (i) G. J. Karabatsos and C. G. Papaioannou, *Tetrahedron Lett.*, 2629 (1968); (j) G. H. Cooper and J. McKenna, *Chem. Commun.*, 734 (1966).

(24) J. O. Stoffer and J. D. Christen, *J. Amer. Chem. Soc.*, **92**, 3190 (1970).

(25) (a) S. Seltzer and E. J. Hamilton, *ibid.*, **88**, 3775 (1966); (b) T. Koenig and W. Brewer, *Tetrahedron Lett.*, 2773 (1965); (c) T. Koenig and R. Wolf, *J. Amer. Chem. Soc.*, **89**, 2948 (1967); (d) S. Rummel, Huebner, and P, Krumbiegel, *Z. Chem.*, **7**, 351 (1967); (e) E. M. Hodnett and P. S. Juneja, *J. Org. Chem.*, **33**, 1233 (1968).

(26) T. Koenig and R. Wolf, *ibid.*, **91**, 2569 (1969).

(27) (a) J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949); *J. Phys. Chem.*, **56**, 823 (1952); (b) J. Bigeleisen and M. Wolfsberg, *J. Chem. Phys.*, **21**, 1972 (1953); **22**, 1264 (1954). (c) For an excellent review of heavy-atom effects, see A. Fry, ref 9h, Chapter 6. I am indebted to Professor Fry for providing a preprint of his chapter.

(28) A. V. Willi, *Can. J. Chem.*, **44**, 1889 (1966).

(29) L. B. Sims, A. Fry, L. T. Netherton, J. C. Wilson, K. D. Reppond, and S. W. Crook, *J. Amer. Chem. Soc.*, **94**, 1364 (1972). I am indebted to Professors Simms and Fry for providing a preprint of the article.

(29a) A. V. Willi and M. Wolfsberg, *Chem. Ind.* (*London*), 2097 (1964).

(29b) A. Fry, *Pure Appl. Chem.*, **8**, 217 (1964).

when the bonding of C-α with X and Y is *ca.* equal. As the transition state shifts toward either the reactants or products, k_{12}/k_{13} systematically decreases.

3. *Summary*

In general the deviation of isotope effects from $\nu^{\ddagger}{}_{1L}/\nu^{\ddagger}{}_{2L}$ is expected to be quite small at room temperature and above if there are no changes in force constants at the isotopic position(s) between reactant and transition states.[15c] The isotope effect thus results from variation in the transition state force fields at the isotopically substituted position.[15] Hence, these effects serve as probes for force constant changes at the isotopic position occurring along the reaction coordinate.

C. ANCHIMERICALLY ASSISTED REACTIONS

Unfortunately this class of reactions has not been scrutinized from the viewpoint of isotope effects theoretically. Consequently, predictions must be made, somewhat intuitively, on the basis of results obtained for the "simpler" reactions. A number of these predictions are contained in the articles to be considered later in this review.

1. *α-Effects*

Participation by the neighboring group Y in reaction 3 involves electronic interaction between Y and C-α. Hence, a bending force constant, $f^{\ddagger}{}_{HCY}$, is introduced into **4** which is not present in **1**. In the simplest approximation, the development of $f^{\ddagger}{}_{HCY}$ compensates to some degree for the reduction in f_{HCX}, *i.e.*, $f_{HCX} \rightarrow f^{\ddagger}{}_{HCX}$, resulting in a decreased k_H/k_D. The variation in the α-effect for model reaction 3 may thus be related to the variation in k_H/k_D for model reaction 2.

2. *β-Effects*

For cationic reactions participation should reasonably reduce the fractional change on C-α in the transition state compared to that for a "simple" SN1 reaction. Consequently, hyperconjugative stabilization of the incipient charge in **4** by the β-hydrogens should be reduced. Deuteration at a β-carbon should result in a reduced isotope effect. The reduced charge and the unfavorable dihedral angle could negate qualitatively a β-effect at the β-carbon bearing the neighboring group. However, conversion of **1** to **4** could affect the C-β–Y bond strength and, hence, alter $f^{\ddagger}{}_{\beta\text{-HCY}}$. Therefore, a β-effect at the β-carbon bearing the neighboring group is a reasonable possibility and might well be termed an α-effect at C-β.

Except for an α-effect at C-β, β-effects would appear to be of no value in studying neighboring group effects in free radical reactions.

3. *Heavy-Atom Effects*

The most obvious changes in bonding in reaction 3 are between C-α and X, C-α and Y, C-β and Y and possibly C-α and C-β. Determination of the heavy-atom effects at C-α, C-β, Y, and X should be most fruitful (a) in ascertaining the presence or absence of anchimeric assistance and (b) in determining for anchimerically assisted reaction of a homologous series of compounds the variation in transition state bonding with change in the neighboring group.

III. Anchimerically Unassisted Reactions

A. THERMALLY INDUCED UNIMOLECULAR REACTIONS

1. *Secondary Deuterium Isotope Effects*

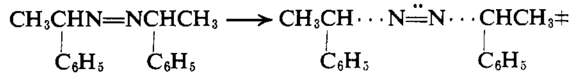
Secondary deuterium isotope effects have been extensively studied in pyrolytic decomposition of azo compounds. α-Effects tabulated in Table I in the series 1,1′-diphenylazoethane[18] (**5**), 1-methyl-1′-phenylazoethane[30] (**6**), and α-phenylethylazomethane[31] (**7**) elegantly demonstrate a change in

Table I

Isotope Effects and Activation Energies for Thermal Decomposition of 5, 6, and 7

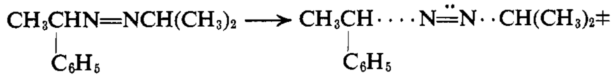
Compd	*Temp, °C*	k_H/k_D *per D*	*Position*	k_{14}/k_{15}	E_a, *kcal/mol*
5	105.28	1.127	Benzyl	1.0229	32.6[a]
6	143.20	1.148	Benzyl	1.0152	36.5[b]
		1.036	Propyl		
7	161.00	1.13	Benzyl		
				1.0132	38.6
		0.97	Methyl		
7	161.00		Methyl	k_{12}/k_{13} = 1.0068	

[a] S. G. Cohen and C. H. Wang, *J. Amer. Chem. Soc.*, **77**, 2457 (1955). [b] C. G. Overberger and A. V. Di Giulio, *ibid.*, **81**, 2154 (1959).



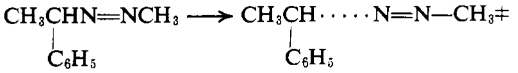
$$\underset{C_6H_5}{CH_3CH}N{=}N\underset{C_6H_5}{CHCH_3} \longrightarrow \underset{C_6H_5}{CH_3CH}\cdots N\overset{\cdot\cdot}{=}N\cdots\underset{C_6H_5}{CHCH_3}{}^{\ddagger}$$

5



$$\underset{C_6H_5}{CH_3CH}N{=}NCH(CH_3)_2 \longrightarrow \underset{C_6H_5}{CH_3CH}\cdots N\overset{\cdot\cdot}{=}N\cdot\cdot CH(CH_3)_2{}^{\ddagger}$$

6



$$\underset{C_6H_5}{CH_3CH}N{=}NCH_3 \longrightarrow \underset{C_6H_5}{CH_3CH}\cdots\cdots N{=}N{-}CH_3{}^{\ddagger}$$

7

mechanism from symmetrical to unsymmetrical one-step cleavage to two-step cleavage. The α-effects indicate that as the molecular dissymmetry is increased the degree of benzylic CN bond breaking increases but the degree of nonbenzylic CN bond breaking decreases. The inverse effect observed upon deuteration of the methyl group in **7** suggests a tightening of the methyl carbon-to-nitrogen bond in the transition state;[31] *i.e.*, at the methyl group $f^{\ddagger}{}_{HCN}$ and $f^{\ddagger}{}_{CN}$ are greater than f_{HCN} and f_{CN}. The activation energies lead to generally equivalent conclusions.[3,4] However, the isotope effects provide both qualitative and quantitative (*vide infra*) structure–reactivity information not directly accessible from the activation energies.

To investigate the influence of molecular structure on reaction dynamics, α-effects were measured in the pyrolysis of *meso-* and *dl*-1,1′,2,2′-tetraphenylazoethane[32] (**8**), 1,1′-di-

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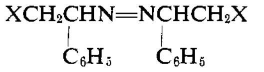
(30) S. Seltzer, *J. Amer. Chem. Soc.*, **85**, 14 (1963).

(31) S. Seltzer and F. T. Dunne, *ibid.*, **87**, 2628 (1965).

(32) S. E. Scheppele and S. Seltzer, *ibid.*, **90**, 358 (1968).

phenylazobutane[33] (**9**), and 2,2′-dimethoxy-1,1′-diphenylazoethane[33] (**10**). Isotope effects and activation energies are tabulated in Table II. In terms of structure–reactivity relationships, a plausible explanation for the reduction in k_H/k_D for *meso*- and *dl*-**8** (1.225 and 1.207) compared to **5** (1.27) is more reactant-like transition states for each of the former than for the latter. This phenomenon assumably results from a more hindered reactant conformation for the diastereoisomers of **8** than for **5**. Both diasteriomeric forms of **8** and **9** are judged to possess comparable strain energy. The very similar α-effects for the diastereoisomers of **8** and **9** thus support the hindered-reactant hypothesis. Interestingly the activation energies for *meso*- and *dl*-**8** and **9** are similar to if not larger than the value for **5**.



$XCH_2CH(C_6H_5)N{=}NCH(C_6H_5)CH_2X$

meso- and *dl*-**8**, X = C_6H_5
9, X = C_2H_5
10, X = CH_3O

Table II

Isotope Effects and Activation Energies for Thermal Decomposition of 8, 9, and 10 at 105.28°

Compd	k_H/k_D[a,b]	k_{14}/k_{15}	E_a, *kcal/mol*
meso-**8**	1.225	1.0158	33.1
dl-**8**	1.207		33.2
9	1.201		33.5
10	1.194		34.0

[a] For two atoms of α-D. [b] Extrapolated from data at other temperatures.

For decomposition of **10** steric and electronic effects of the methoxy substituent, which place opposite demands upon the reactant-like–radical-like character of the transition state, were reasoned approximately to cancel and so yield a value of k_H/k_D similar to the value for **5**. Consequently the fact that the α-effect for **10** is *ca.* 29% lower than the value for **5** is "abnormal." The origin of the abnormality remains obscure. Decomposition might occur *via* a transition state in which each CH_3O group is in a bisected conformation. Such a transition state, if more reactant-like than in the decomposition of **5**, would be consistent with the α-effect, 1.194. Since **10** exhibits a larger E_a than **5** (the rate of decomposition of **10** relative to **5** is 0.23), the transition state for **10** might well be more radical-like. In passing from reactant to transition state the reduction in the α-HCN bending force constant would necessarily be greater for **10** than for **5**. Hence an increase in one or more of the remaining force constants associated with the α-benzylic hydrogen would be required to reduce the α-effect to 1.194.

Interestingly, the α-effect in the gas-phase decomposition of 3,3′-azo-1-propene (**11**) (k_H/k_D = 1.33 per 4 α-D at 161.75°) presents similar problems in interpretation.[34] Two alternatives considered were (a) simultaneous C–N bond rupture with little radical-like character of the transition state or (b) stepwise cleavage with considerable allylic radical character in the transition state.[34] Extrapolation of the data for the hypothetical α,α′-d_2 reactant to 105.28° yields k_H/k_D = 1.18.[33] Thus the magnitudes of the α-effect for **10** and **11** are either unusually small for a simultaneous mechanism or large for a two-step process.[34a]

$CH_2{=}CHCH_2N{=}NCH_2CH{=}CH_2$
11

For a series of homologous compounds undergoing a given reaction, nontransferability of bending force constants associated with the α-hydrogen among the various reactants would produce variations in the α-effect independent of changes in the transition-state bonding. The results of model calculations[33] indicate that a total reduction of 9 to 22% in the α-carbon–hydrogen reactant-state bending force constants would be required to reduce the α-effect from 1.27 for **5** to 1.225 for *meso*-**8** (*ca.* 18% reduction) and to 1.194 for **10**. The nonnegligible change required in the force constants and the maintenance of force constant values in the alkanes[35] argues for the limited importance of force constant nontransferability in producing variations in the α-effect and probably isotope effects in general.

The isotope effect, *i.e.*, k_H/k_D = 1.030 ± 0.007 at 104.57°, in the decomposition of ring-deuterated **5** is nearly, if not completely, classical mechanical in origin.[36] The isotope effect results from a mass effect on the vibration at the saddle point parallel to the reaction coordinate. Quantum mechanical effects arising from differences in steric requirements of protium and deuterium and/or from perturbation of the aromatic C–H force constants in the transition state for **5** are thus negligible. This result may be compared to the stabilization of the transition state when deuterium is substituted for aromatic protium in reactions when positive charge is generated next to a benzene[23g,37] ring and is opposite to the direction of isotope effects when negative charge is produced at a similar position.[37b,38]

α-Effects, tabulated in Table III, have been utilized in probing the pyrolysis mechanism of *tert*-butyl esters of 2-phenylperoxypropanoic acid[39] (**12**), peroxyphenylacetic acid[39]

Table III

α-Effects for Peroxy Ester Decomposition

Compd	*Solvent*	*Temp, °C*	k_H/k_D *per α-D*
12	Isooctane	73.99	1.046
13	Isooctane	84.98	1.066
13	Paraffin oil	84.98	1.060
14	Isooctane	60.46	1.033
14	Paraffin oil	60.46	1.024
15	Paraffin oil	84.98	1.044 ± 0.015

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(33) S. E. Scheppele, W. H. Rapp, D. W. Miller, D. Wright, and T. Marriott, *J. Amer. Chem. Soc.*, **94**, 539 (1972).

(34) B. H. Al-Sader and R. J. Crawford, *Can. J. Chem.*, **48**, 2745 (1970).

(34a) Recent evidence appears to favor the stepwise cleavage mechanism; see K. Takagi and R. J. Crawford, *J. Amer. Chem. Soc.*, **93**, 5910 (1971).

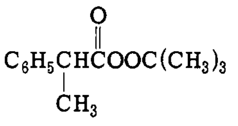
(35) J. H. Schachtschneider and R. G. Snyder, *Spectrochim. Acta*, **19**, 117 (1963).

(36) S. E. Scheppele, D. W. Miller, P. L. Grizzle, and F. A. Mauceri, *J. Amer. Chem. Soc.*, **93**, 2549 (1971).

(37) (a) A. J. Kresge, K. N. Rao, and N. N. Lichtin, *Chem. Ind.* (*London*), 53 (1961); (b) A. Streitweiser, Jr., and H. S. Klein, *ibid.*, 180 (1961); (c) *ibid.*, *J. Amer. Chem. Soc.*, **86**, 5170 (1964); (d) C. Bernasioni, W. Koch, and H. Zollinger, *Helv. Chim. Acta*, **46**, 1184 (1963).

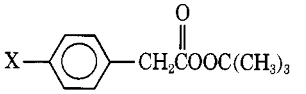
(38) (a) A. Streitwieser, Jr., and H, S. Klein, *J. Amer. Chem. Soc.*, **85**, 2759 (1963); (b) A. Streitwieser, Jr., and J. S. Humphrey, Jr., *ibid.*, **89**, 3767 (1967).

(39) T. Koenig and R. Wolf, *ibid.*, **91**, 2574 (1969).



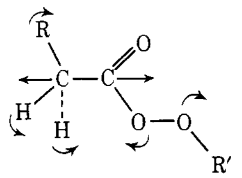
$C_6H_5CH(CH_3)COOC(CH_3)_3$

12



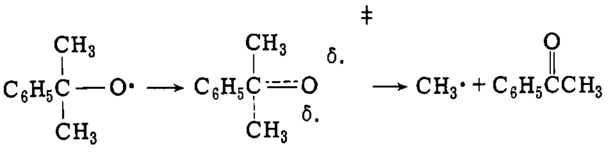
13, X = H
14, X = CH_3O
15, X = NO_2

(**13**), and the *p*-methoxy[40] (**14**) and *p*-nitro[40] (**15**) analogs of **13**. These and related data support a concerted mechanism for **12**, **13**, and **14**.[39,40] Partial nonconcerted decomposition may be indicated for **15**.[40] Although the values of k_H/k_D are not negligible, they are quite small. These low isotope effects have been rationalized by postulating a transition state (**16**) in which the change in bending motion of the α-hydrogen atoms is reduced because of the developing carbon dioxide molecule in close proximity to the incipient radical pair.[39,40] This explanation lacks definiteness in terms of the force constant changes occurring along the reaction coordinate. Clearly the total change in the force field associated with the α-hydrogens in passing from the reactants to the transition states is small. The above explanation might be viewed as necessitating an appreciable transition state force constant describing the α-hydrogen–oxygen interaction which would in effect partially compensate for the reduction in the α-hydrogen–carbon—carbonyl-carbon bending force constant, f_{HCC}, upon passing from reactant to **16**. Although the α-effect then bears no simple relationship to the extent of carbon–carbon bond rupture, this situation would allow for a transition state with considerable C–C bond breaking, *i.e.*, a small stretching force constant for the C–C bond. A low value for f_{HCC} would be an alternative although perhaps remote explanation. For example, assuming $f^{\ddagger}_{HCC}$ in **16** to be comparable in magnitude to $f^{\ddagger}_{HCN}$ for decomposition of **5** would indicate that the magnitude of f_{HCC} is only 50–70% (very approximately) of the value of a normal hydrogen–carbon–carbon bending constant (*ca.* 0.6 mdyn Å[35]). The simplest explanation is that **16** is reactant-like in terms of the carbon–carbon bond; *i.e.*, at the saddle point $f^{\ddagger}_{HCC}$ is not appreciably smaller than f_{HCC}. The trend in k_H/k_D for **12**, **13**, and **14** is consistent with the suggested dipolar character of **16** and the difference in radical stabilities. Unexpectedly k_H/k_D for **15** is very similar to the value for **13**. As previously noted **15** may undergo partial nonconcerted decomposition.



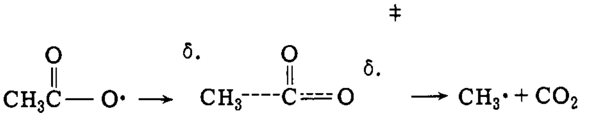
16

The α-effect per D for methyl radical formation from decomposition of the cumyloxyl radical[17b] (**17**) is 1.12 at 75° and from decarboxylation of the acetoxyl radical[41] (**18**) is 1.03 at 74.8°. For decomposition of **17** it has been shown that over half of the vibrational changes accompanying the formation of the methyl radical have occurred in the transition state (**17a**).[17b] This result and the activation energy (*ca.* 8 kcal/mol) demonstrate that **17a** is more reactant-like than product-like.[17b] The α-effect for loss of CO_2 from **18** indicates that the transition state (**18a**) is more reactant-like than product-like. Unless f_{HCC} differs significantly in value between **17** and **18**, $f^{\ddagger}_{HCC}$ is indicated to be smaller for **17a** than for **18a**; *i.e.*, **17a** is more product-like than **18a**.



$C_6H_5C(CH_3)_2{-}O\cdot \longrightarrow [C_6H_5C(CH_3)_2{=}O]^{\ddagger} \longrightarrow CH_3\cdot + C_6H_5COCH_3$

17 **17a**



$CH_3CO{-}O\cdot \longrightarrow [CH_3\text{----}C{=}O(O)]^{\ddagger} \longrightarrow CH_3\cdot + CO_2$

18 **18a**

In the unimolecular decomposition of a series of related compounds it should be remembered that in the first approximation only the variation in the magnitude of the α-hydrogen–carbon—leaving-group bending force constants between the various transition states is directly deducible from the experimental α-effects. Hence, a correlation between bending and stretching force constants is implicitly but apparently reasonably (ref 42 and *vide infra*) assumed when relating changes in α-effect to variation in the reactant-like–product-like character of the transition state.

2. *Heavy-Atom Effects*

The nitrogen effects[43] in the pyrolysis of **5**, **6**, and **7** and the carbon effect[43] at the methyl group in the decomposition of **7** (see Table I) are qualitatively consistent with the conclusions deduced from the α-effects. From the α- and heavy-atom effects Seltzer and Mylonakis[43] were able to calculate consistent transition state force fields for each reactant. For example, assuming almost complete rupture of the benzylic bond in the transition state for **7**, *i.e.*, $f^{\ddagger}_{CN}$ = 0.1 mdyn/Å, requires values of 0.27 and 1.20 in the ratio of the transition-state to reactant-state α-HCN (benzylic) bending and nitrogen–nitrogen stretching force constants, respectively. The methyl CN and HCN stretching and bending force constants were calculated to increase 15% in passing from the reactant to the transition state. In general, a correlation was observed between the reduction in the HCN bending and the CN stretching force constants.

The nitrogen isotope effect is smaller in the decomposition of *meso*-**8**[44] (Table II) than in pyrolysis of **5** (Table I). Although transition-state force constants have not been calculated, both the α and nitrogen effects indicate that the transition state for decomposition of *meso*-**8** is more reactant-like than the one for **5**, *i.e.*, $f^{\ddagger}_{HCN}$ and $f^{\ddagger}_{CH}$ are larger for the former than for the latter.

The ^{13}C effect in the thermal decomposition of ureas into isocyanates and amines is a function of the nitrogen substituents.[45]

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[40] T. Koenig, J. Huntington, and R. Cruthoff, *J. Amer. Chem. Soc.*, **92**, 5413 (1970).

[41] T. Koenig and R. Cruthoff, *ibid.*, **91**, 2562 (1969).

[42] A general correlation between bending and stretching force constants appears to be observed; see ref 35 and G. Herzberg, "Infrared and Raman Spectra," D. Van Nostrand, Princeton, N. J., 1945, p 192 ff.

[43] S. Seltzer and S. G. Mylonakis, *J. Amer. Chem. Soc.*, **89**, 6584 (1967).

[44] S. G. Mylonakis, S. E. Scheppele, and S. Seltzer, unpublished results.

[45] E. M. Magee and F. Daniels, *J. Amer. Chem. Soc.*, **79**, 829 (1957).

B. SOLVOLYTIC UNIMOLECULAR REACTIONS

1. *Secondary Deuterium Effects*[45a]

As mentioned previously, the α-effects but not the reactivity in the limiting solvolysis of 1-phenylethyl chlorides and bromides are different but, within each family, independent of the electronic properties of the ring substituent.[19] For the chlorides the reactivity difference between the *p*-anisyl and unsubstituted compounds is *ca.* 10^6, whereas the α-effects vary only from 1.157 to 1.153. As the electron-releasing ability of the para substituent increases, the β-effect decreases; *e.g.*, $(k_H/k_D)_{\beta\text{-}d_3}$ decreases from 1.224 for *p*-H to 1.113 for *p*-CH_3O. This decrease has been interpreted as reflecting increasing dispersal of the positive charge into the aromatic moiety in the transition state rather than representing a change in the reactant-like character of the transition state. The limiting solvolysis of *p*-methylbenzyl-α-d_2 chloride exhibits nearly the same isotope effect at 25° in 94% and 70% trifluoroethanol–water mixtures[46] (1.146 and 1.140 per D, respectively) as the solvolysis of 1-phenylethyl-*1-d* chloride at 25° in various ethanol–water mixtures (1.146 − 1.153 per D).[19]

The relationship between the magnitude of the HCX bending force constant in the reactant and the α-effect for SN1 reactions has been investigated theoretically.[20] Methyl halides were chosen as model substrates and the transition state force constants were assumed to be independent of the nature of the halogen. The larger α-effect in chloride than in bromide solvolysis was explicable in terms of the larger value of the HCX reactant-state bending force constant for chlorine compared to bromine.

α-Effects in the limiting or near-limiting solvolysis of sulfonates of 2-propanol[47] (**19**), 3-pentyn-2-ol[48] (**20**), and 2-hydroxyadamantane[49] (**21**) are seen in Table IV to be *ca.* 1.22 per α-D. Like the differences in k_H/k_D for **20**-OTs, the β-d_3 and γ-d_3 effects are slightly smaller in 60% aqueous ethanol (1.241 and 1.104) than in 70% aqueous trifluoroethanol (TFE) (1.281 and 1.109).[49b] It has been concluded[49b] that, although solvolysis in the former solvent may have a slight nucleophilic component, solvolysis in aqueous TFE is predominately, if not exclusively, limiting. In harmony with conclusions drawn from other data, the k_H/k_D values for the sulfonates of **21** indicate a solvolysis mechanism having little or no nucleophilic component. A like mechanism is indicated for **19**-OTs.[47] For trifluoroacetolysis (TFA) of **19**-OTs and trifluoroethanolysis of **20**-OTs, the β-effects per CD_3 group are 1.46 and 1.281, respectively. The lower β-d_3 effect for **20**-OTs might result from delocalization of the incipient positive charge in the transition state by the triple bond which reduces hyperconjugative interaction with the hydrogens of the α-methyl. Interestingly, extrapolation of the k_H/k_D values for solvolysis of **21**-OTs in 80 and 60% aqueous ethanol to 25° yields values *ca.* 4 (1.19) and 3% (1.20) lower than the average value for the sulfonates of **19**, **20**, and **21** in TFA and/or TFE, *ca.* 1.22–1.23.

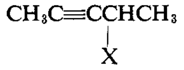
Table IV

α-Effects for Limiting or Near Limiting Solvolysis of Sulfonic Esters

Compd	*Deriv*	*Temp, °C*	*Solvent*	k_H/k_D *per* α-*D*	*Ref*
19	OTs[a]	24.9	CF_3CO_2H	1.22	47
20	OTs[a]		60% aq C_2H_5OH	1.213	48
20	OTs[a]		70% aq CF_3CH_2OH	1.226	48
21	OTs[a]	99.8	80% aq C_2H_5OH	1.149	49a
21	OTs[a]	75.1	60% aq C_2H_5OH	1.168	49a
21	OTs[a]	25	CF_3CO_2H	1.26	49a
21	OtFe[b]	25	50% aq C_2H_5OH	1.225	49b
21	OtFe[b]	25	70% aq CF_3CH_2OH	1.225	49b
21	OtFe[b]	25	97% aq CF_3CH_2OH	1.228	49b

[a] *p*-Toluenesulfonate. [b] 2,2,2-Trifluoroethanesulfonate.

α-Effects in 50% aqueous ethanol and 70% aqueous TFE for 2-bromo-3-pentyne (**22**) and 2-iodo-3-pentyne (**23**) are 1.101 and 1.123 and 1.087 and 1.089, respectively.[48] In aqueous TFE the β-d_3 and γ-d_3 effects for **22** (1.280 and 1.108) are nearly identical with those for **20**-OTs (*vide supra*). The α-effect for **22** (1.123) is smaller than for **20**-OTs but nearly identical with the value for 1-phenylethyl bromide (1.122).[19] The β-d_3 and α-*d* effects (1.200 and 1.101) for **22** in aqueous ethanol indicate a nucleophilic contribution to the solvolysis mechanisms.[48] The β-d_3 effects for **23** in both solvents (1.278 and 1.283) are close to those for **22** and **20**-OTs in 70% aqueous TFE and thus indicate a limiting mechanism for **23**. The α-effects for **23** are then not unusually small but rather in excellent agreement with the theoretically predicted[20] value of 1.09.



$$\underset{\displaystyle X}{CH_3C{\equiv}CCHCH_3}$$

22, X = Br
23, X = I

Maximum α-effects are suggested to accrue for rate-determining conversion of one ion pair to another—presumably an intimate to a solvent-separated ion pair.[46,48,49b] The transition state is suggested to resemble, to a good approximation, ion pairs R^+X^- in which the force constants of R^+ are independent of X^-.[20,48]

That an isotope effect can result from partitioning of ion pairs has been elegantly demonstrated in the benzhydryl benzoate system.[50] Equation 6 represents a general solvolysis mechanism which involves such partitioning of the intimate ion pair **25** between internal return to substrate **24** and dissociation ($k_3 \gg k_{-2}$) to the solvent-separated ion pair **26**. Any difference in the total zero-point energy between the transition states preceding formation of **25** and **26** will result in an isotope effect on the partitioning of **25** between **24** and **26**.[50] It can be shown[50] that the overall α-effect, k_t^H/k_t^D, is a function of the isotope effect on k_1, k_1^H/k_1^D, and the partitioning isotope effect (PIE), $(k_{-1}^D/k_{-1}^H)/(k_2^D/k_2^H)$. For the condition PIE ≥ 1, $k_t^H/k_t^D \geq k_1^H/k_1^D$. The α-tritium effect on the parti-

$$\underset{\mathbf{24}}{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{\mathbf{25}}{R^+X^-} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \underset{\mathbf{26}}{R^+||X^-} \xrightarrow[HOS]{k_3} ROS \qquad (6)$$

(45a) For an extensive discussion of secondary deuterium isotope effects in aliphatic nucleophilic substitution reactions, see V. J. Shiner, Jr., in ref 9h, Chapter 2.

(46) V. J. Shiner, Jr., W. Dowd, R. D. Fisher, S. R, Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *J. Amer. Chem. Soc.*, **91**, 4838 (1969).

(47) A. Streitwieser, Jr., and G. A. Dafforn, *Tetrahedron Lett.*, 1263 (1969).

(48) V. J. Shiner, Jr., and W. Dowd, *J. Amer. Chem. Soc.*, **93**, 1029 (1971).

(49) (a) J. M. Harris, R. E. Hall, and P. v. R. Schleyer, *ibid.*, **93**, 2551 (1971); (b) V. J. Shiner, Jr., and R. D. Fisher, *ibid.*, **93**, 2553 (1971).

(50) B. L. Murr and M. F. Donnelly, *ibid.*, **92**, 6686 (1970).

Table V

Isotope Effects for the Formation of Diarylmethyl Cations at 25° in Aqueous Sulfuric Acid and Spectral Data for the Corresponding Methanols

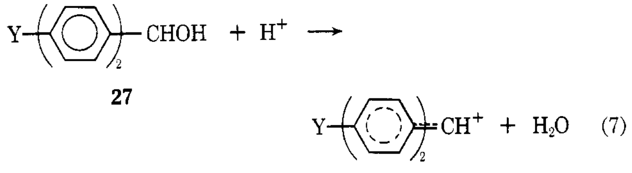
Substituent	K_H/K_D	*Vibrational frequencies in methanol* (cm^{-1})
H	1.29	2130,[a] 998[a]
Cl	1.35	1350,[b] 2140,[a] 1000[a]
CH_3	1.20	1357,[b] 2150,[a] 1002[a]
CH_3O	1.18	1364,[b] 2138,[a] 1004[a]
C_2H_5O	1.17	
$(CH_3)_2N$	1.03[c]	1400[b] 2120,[a] 995[a]

[a] Deuterated methanol. [b] Protiated methanol. [c] Solvent, 99% acetone.

tioning of benzhydryl benzoate ion pairs generated from diphenyldiazomethane and benzoic acid-*O-t* was determined in ethanol-*O-t* and in 90% aqueous acetone.[50] In both solvents a PIE of 1.16 was obtained, indicating the absence of a solvent dependence of PIE and the absence of an isotope effect on partitioning of **26**. Studies in ethanol-*O-d* indicated the absence of an appreciable solvent isotope effect on the ion-pair partitioning. Thus it was concluded[50] that (a) there is either little external ion-pair return or no solvent isotope effect on partitioning of **26** or both and (b) the transition state for product formation is very reactant-like.

From the solvolytic α-tritium effect for benzhydryl benzoate in ethanol at 100°, values of 1.12 and 1.11 were calculated for k_1^H/k_1^D and $(k_{-1}^D/k_{-1}^H)/(k_2^D/k_2^H)$ at 25°.[51] Furthermore, at 25° the value of k_t^H/k_t^D (1.19) calculated from k_t^H/k_t^T at 100° is smaller than the value 1.24 computed for formation of the solvent-separated benzhydryl benzoate ion pair.

For SN1 reactions two phenomena which can influence α-effects are the dependence of the substrate HCX bending force constant on the nature of the leaving group and the partitioning of ion pairs. Variation in the reactant-like–product-like character of the transition state is a third possibility, although an apparently unobserved one for solvolytic reactions in contrast to pyrolytic reactions.



27

(7)

28

However, the data in Table V clearly demonstrate that the equilibrium α-effect for protonation–ionization of 4,4′-disubstituted benzhydrols (eq 7) is dependent upon the substituent.[52] For 4,4′-bis(dimethylamino)benzhydrol nitrogen protonation competes effectively with carbonium ion formation, and thus the value of 1.03 must be regarded as only approximate. The C–H and C–D frequencies listed in Table V suggest that the variation in K_H/K_D results from a dependence of the α-HC force constants (most reasonably the HCC bending force constants) in the cation on the ring substituent. The value of K_H/K_D is observed to increase with electron-withdrawing and decrease with electron-releasing substituents. The results of various α-carbon isotope effect studies (*vide infra*) clearly suggest that bonding to the α-carbon in **27** increases upon ionization. This bond tightening presumably results from delocalization of the positive charge over the π system of the aromatic rings in **28**. As the substituent is varied from electron-releasing to electron-withdrawing, charge delocalization and hence C–C bond tightening in **28** are reasonably expected to decrease. Since the values of f_{HC} and f_{HCC} are indicated to be somewhat larger and smaller respectively for an alkene compared to an alkane,[42] the increase in the C–C bond order upon ionization could effect an increase and decrease respectively in the benzylic HC stretching and HCC bending force constants. As the substituent is varied from electron-releasing to electron-withdrawing, charge delocalization and hence, C–C bond tightening in **28** are reasonably expected to decrease. However, the magnitudes of f_{HC} and f_{HCC} in **28** are expected to be positively correlated with the magnitude of f_{CC}. For example, in the haloethenes an increase (decrease) in the CC stretching force constant is in general paralleled by an increase (decrease) in the HC stretching and HCC bending force constants.[52a] Thus the value of f_{HCC} in **28** should be attenuated as Y is varied from electron releasing to electron withdrawing. Finally, the assumption that the force field associated with the benzylic hydrogen in **27** is independent of Y leads to the conclusion that the decrease in the force field associated with this hydrogen upon ionization and, hence, K_H/K_D should, as observed, become progressively smaller the more electron-releasing the substituent becomes. For the unsubstituted compound the value of K_H/K_D (1.29) is in excess of the value of the ionization isotope effect (1.12) calculated[51] for benzhydryl benzoate in ethanol. Although caution is necessary in view of the differences in solvent, these results suggest that for benzhydryl benzoate the transition states preceding formation of **25** and **26** contain bonding between C-α and oxygen. Furthermore, the value of 1.29 is in excess of Shiner's proposed maximum kinetic α-effect of 1.22.[20,48]

For a given chemical process the value of the equilibrium isotope effect represents a force constant change(s) equal to or greater than the one determining the kinetic effect. The equilibrium isotope effects indicate the occurrence of changes in nonleaving-group bending force constants associated with the α-hydrogen along the reaction coordinate, at least for SN1 reactions. Since changes in these force constants would be reflected in the magnitude of the α-effect, their importance needs to be determined. For example, in passing from the reactant to the transition state an increase in these force constants would tend to compensate for the reduction in the α-HCX bending force constant. Thus in solvolysis of a homologous series of compounds this condition would for a given exiphile diminish the variation in k_H/k_D.

For limiting solvolysis reactions the postulate that the degree of progression of the transition state along the reaction coordinate is essentially invariant to change in substrate is not in harmony with the Hammond postulate[3] or Thornton's rule.[5] For example, the 10^6 rate increase attendant upon replacement of para hydrogen with methoxy in α-phenylethyl chloride reacting in aqueous ethanol seems hardly consistent with no movement of the rate-determining saddle point along the reaction coordinate. The Thornton rule states[5a] that "any

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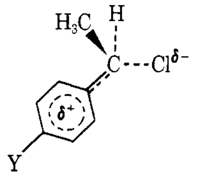
(51) B. L. Murr and M. F. Donnelly, *J. Amer. Chem. Soc.*, **92**, 6688 (1970).

(52) M. M. Mouk and R. Stewart, *Can. J. Chem.*, **41**, 1641 (1963).

(52a) J. R. Scherer and J. Overend, *J. Chem. Phys.*, **32**, 1720 (1960); **33**, 1681 (1960).

substituent change which makes an increase (decrease) in the normal coordinate X of a molecule or transition state more difficult will lead to a perturbed equilibrium geometry in which X is decreased (increased) if the force constant for X motion is positive, but in which X is increased (decreased) if the force constant for X motion is negative." Furthermore, to the extent that substituent effects on reactant bonds are small, which should be true except where the substituent change actually changes one of the atoms of the bond being considered, the effects observed experimentally will be predicted by consideration of substituent effects on the transition state.[5a]

Consider the transition state **29** for solvolysis of ring-substituted α-phenylethyl chlorides in which the reaction coordinate corresponds to stretching of the C–Cl bond. Para substituents that are electron-supplying (-withdrawing) tend to make C-α and Cl more (less) negative but have a larger effect on C-α than on Cl, which makes the C–Cl bond easier (harder) to extend.[5a] Therefore, electron-supplying (-withdrawing) Y should decrease (increase) the product-like character of **29**. Change in Y from H to F to CH_3 to CH_3O results in rate increases of 3, 59, and *ca.* 10^6, and β-d_3 effects of 1.224, 1.211, 1.200, and 1.113.[19] Both the increasing reactivity and decreasing β-effect would appear to be consistent with a progressive reactant-like shift of **29**. The essential constancy of the α-effect[19] could conceivably result from nearly compensating effects of (a) a progressively smaller value of $f^{\ddagger}_{HCCl}$ and (b) a progressively increasing $f^{\ddagger}_{HCAr}$ and/or $f^{\ddagger}_{HCCH_3}$ as Y is changed from CH_3O to CH_3 to F to H. It would seem necessary to assume that the ionic character of **29** decreases as it becomes more reactant-like. If it were to increase[53] rather than decrease, the argument would seem to be invalid. Further studies would seem to be highly desirable.



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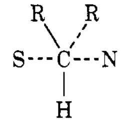
A recent model[5b] for most SN1 transition states (**30**) involving bonding between a specific solvent molecule and carbon leading to an ion pair appears to imply that the α-effect should be a function of substrate structure. The bonds between S and C and X and C in **30** are assumed to be weak but of nearly equal magnitudes. It is argued[5b] that a change in substituent in R will have only a small effect on the antisymmetric motion, *i.e.*, reactant-like–product-like character, but will affect the symmetric motion more. As we understand the argument, the symmetric stretching motion should become less difficult as R becomes more electron-releasing. Qualitatively, for such a change, we reason that the effect should be to decrease the ZPE of the hydrogen-bond bending motion and the symmetric stretching motion leading to larger α- and heavy-atom leaving-group effects.



30

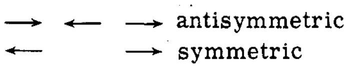


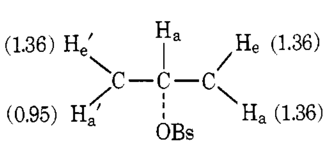
Table VI

Deuterium Isotope Effects for Solvolysis of Cyclopentyl and Cyclohexyl Sulfonates

Compound	*Location of D*	*Solvent*	*Temp, °C*	k_H/k_D	*Ref*
31-OTs	*1-d*	CH_3CO_2H	50	1.15	14a,c
	trans-2-d$_1$			1.16	14a
	cis-2-d$_1$			1.22	14a
31-OBs	*1-d*	70% aq C_2H_5OH	25	1.1869	24
	trans-2-d$_1$			1.1803	24
	cis-2-d$_1$			1.1533	24
32-OBs	*1-d*	50% aq C_2H_5OH	35	1.172	54
	trans-2-d$_1$			1.340	54
	cis-2-d$_1$			1.127	54
33-OTs	*1-d*	CH_3CO_2H	50	1.22	55
	cis-2-d$_1$			1.25	55
	trans-2-d$_1$			1.30	55

It is appropriate to consider α- and β-effects for solvolysis of cyclopentyl[14a,c,24] (**31**), *trans*-4-*tert*-butylcyclohexyl[54] (**32**), and cyclohexyl[55] (**33**) sulfonates (Table VI). Except for **31**-OTs a trans β-deuterium produces a larger k_H/k_D than a cis β-deuterium. It has been suggested[24] that the apparent inversion for **31**-OTs in acetic acid may be an artifact assignable to imprecision in the kinetic measurements. Kinetic data for **31**- and **32**-OBs were obtained by a conductometric method and for **31**- and **33**-OTs by a titrimetric technique. Although the β-effects are not substrate independent, they seem to connote the presence of similar dihedral angles between the cis and trans β-hydrogens and the incipient p orbital at C-α in the transition state within and between the cyclopentyl and cyclohexyl systems.

For **32**-OBs the effect of trans but not cis deuterium was found to be cumulative.[54] The conformation of the transition state is concluded to be that of a twist boat with the calculated positional values of k_H/k_D given in **34**.



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The β-effect for multiple deuterium atoms in **33**-OBs is concluded to be almost but not quite cumulative.[24] It is suggested that solvolysis of **33**-OTs proceeds *via* a twist-boat conformation.[55] Except for **33**-OTs the α-effects are less than the suggested maximum value of 1.22, not constant, and similar to a number of k_H/k_D values for 2-adamantyl tosylate. The explanation could conceivably reside in the product-like character of the transition state and/or partitioning effects. However, the products from aqueous ethanolysis of **32**-OBs-*cis-2-d* are 67% *cis*-4-*tert*-butylcyclohexene, 27% *tert*-butylcyclohexanols of which 94% is the cis isomer, and 6% ethers.[54] The olefin-forming step of the reaction for ethanolysis of **32**-OBs-*cis-2-d* involves loss of an equatorial hydrogen. Solvolysis

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[53] A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 174 ff.

[54] V. J. Shiner, Jr., and J. G. Jewett, *J. Amer. Chem. Soc.*, **87**, 1383 (1965).

[55] W. H. Saunders and K. T. Finley, *ibid.*, **87**, 1384 (1965).

of **31**-OBs-*trans-2-d* yields less olefin than does that of the cis isomer.[54] Thus it is possible that solvent attack on the ion pair[56] leading to substitution or elimination competing kinetically with internal return could account for the α-effects, the increased β-effect for *trans-d*, and other evidence[49a] indicating a nonlimiting solvolysis mechanism. Rate-determining elimination has been proposed[46] to account for the large β-d_9 effect for solvolysis of 2-chloro-2-methylpropane-d_9 in aqueous TFE.

2. *Heavy-Atom Effects*

The carbon-13 isotope effects in the methanolysis and ethanolysis of α-phenylethyl bromide are small, being only 1.0065 at 25° and 1.0064 at 45°, respectively.[57] This small effect was interpreted as reflecting increased bonding to the α-carbon in the transition state from overlap of the incipient p orbital with the π electrons of the phenyl and σ electrons of the C–H bonds of β-methyl.[57,58] The 13-carbon effect could not be used to differentiate between a mechanism involving rate-determining ionization or solvent attack upon an ion pair in equilibrium with substrate. Recently these alcoholysis studies have been extended to the *p*-methyl- and *p*-bromo-α-phenylethyl bromides.[59] The carbon effects for these reactions and for the unsubstituted compound are tabulated below.

α-Carbon-13 Isotope Effects at 0°C

Substituent	*Solvent*	k_{12}/k_{13}	*Ref*
H	CH_3OH	1.0050	58
	C_2H_5OH	1.0018	58
CH_3	CH_3OH	0.9995	59
	C_2H_5OH	1.0005	59
Br	CH_3OH	1.0127	59

Although the limited number of compounds studied precludes definite conclusions, the tendency for k_{12}/k_{13} to decrease (increase) as the substituent becomes more (less) electron donating is consistent with either a reactant-like (product-like) shift of the rate-determining transition state or, if the transition state for each compound is ion-pair-like, an increase (decrease) in the bonding to C-α.

The small k_{12}/k_{14} effect,[60] 1.027, in the hydrolysis of 2-chloro-2-methylpropane-*2*-^{14}C is indicative of hyperconjugative stabilization of the incipient cation in the transition state. It is not clear (*vide supra*) what magnitudes of force constants would be necessary in the Frisone–Thornton model,[5b] **30**, to produce such small carbon effects. Increase in bonding at the central carbon as an important contributor to small carbon effects in SN1 reactions appears demonstrated by detailed experimental and theoretical study of formation of the triphenylmethyl cation from chlorotriphenylmethane-*1*-^{13}C, which gives an inverse carbon isotope effect.[61]

The chlorine isotope effect for ethanolysis of *tert*-butyl chloride is only 1.008.[62] Comparison of the carbon and chlorine isotope effects, with some caution in view of the different Y values for 60% aqueous dioxane and ethanol,[2d] suggests that in the transition state either C–Cl bond breaking is not extensive or extensive solvation of the incipient chloride anion produces considerable ZPE. Evidence favoring the latter explanation is adduced from the fact that the β-effect is nearly independent of solvent[5b,46] and the close agreement between the kinetic β-effect and the β-effect calculated for equilibrium between *tert*-butyl chloride and the *tert*-butyl cation from infrared and Raman spectra.[63]

The chlorine isotope effects in the hydrolysis of benzyl chlorides in aqueous dioxane are insensitive to the electronic nature of the para substituent; *i.e.*, values of k_{35}/k_{37} are 1.0078, 1.0075, 1.0078, 1.0078, and 1.0076 for CH_3O, CH_3, H, Cl, and NO_2.[64] The mechanistic problems attending the solvolysis of benzyl halides[53] render an unequivocal interpretation of these results difficult. Interestingly, the α-effects in the solvolysis of para-substituted benzyl derivatives, the mechanism ranging from near limiting to SN2, are strongly dependent upon both the electronic properties of the substituent and the solvent nucleophilicity.[65]

C. NUCLEOPHILIC SUBSTITUTION REACTIONS

1. *α-Effects*

As mentioned previously, in an SN2 reaction the magnitude of the α-effect is to a first approximation determined by the resultant of the decrease in the HCX bending force constant and the development of the HCN bending force constant.[66] For example, α-effects for reaction of water with methyl iodide and bromide are 0.87 and 0.90,[67] but values of 1.03[68] and 1.10[66] are observed for reactions of thiosulfate ion with methyl bromide and iodide ion with methyl iodide, demonstrating the dependence of α-effect on nucleophile and electrophile. Structure of the organic moiety is important since α-effects are generally found to be (a) inverse for methyl compounds,[67] (b) slightly inverse or normal for ethyl compounds,[69] and (c) normal for *n*-propyl derivatives.[69] For the reaction of water with methyl halides α-effects increase from 0.87 to 0.90 to 0.96 as X is varied from I to Br to OTs. These results indicate a progressively more reactant-like transition state, *i.e.*, a progressively smaller decrease in $f^{\ddagger}_{\alpha\text{-HCX}}$ and increase in $f^{\ddagger}_{\alpha\text{-HCO}}$. In harmony with this conclusion are (a) the correlation of α-effects with difference in polarizabilities of the nucleophile (E_n) and electrophile (E_I)[66] and (b) the observed dependence of the rate ratio for displacement by hydroxide and water.[9g,70] α-Effects for reaction of methyl iodide and cyanide ion do not give a good correlation with $E_n - E_I$.[17d] Caution should be exercised in formulating such conclusions since variations in the HCX reactant-state bending force constant should affect the magnitude of the α-effect independent of

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(56) H. Wiener and R. A. Sneen, *J. Amer. Chem. Soc.*, **87**, 292 (1965).

(57) J. B. Stothers and A. N. Bourns, *Can. J. Chem.*, **38**, 923 (1960).

(58) J. Bron and J. B. Stothers, *ibid.*, **46**, 1435 (1968).

(59) J. Bron and J. B. Stothers, *ibid.*, **47**, 2506 (1969).

(60) M. L. Bender and G. J. Buist, *J. Amer. Chem. Soc.*, **80**, 4304 (1958).

(61) A. J. Kresge, N. N. Lichtin, K. N, Rao, and R. E. Weston, Jr., *ibid.*, **87**, 437 (1965).

(62) R. M. Bartholomew, F. Brown, and M. Lounsbury, *Can. J. Chem.*, **32**, 979 (1954).

(63) (a) J. C. Evans and G. Y. S. Lo, *J. Amer. Chem. Soc.*, **88**, 2118 (1966); (b) G. A. Olah, E. B. Baker, J. C. Evans, W. S. Tolgyesi, J. S. McIntyre, and I. J. Bastun, *ibid.*, **86**, 1360 (1964).

(64) J. W. Hill and A. Fry, *ibid.*, **84**, 2763 (1962).

(65) V. J. Shiner, Jr., M. W. Rapp, and H. R. Pinnick, *ibid.*, **92**, 232 (1970).

(66) For a summary and discussion of α-effects in SN2 reactions, see S. Seltzer and A. A. Zavitsas, *Can. J. Chem.*, **45**, 2023 (1967).

(67) J. A. Llewellyn, R. E. Robertson, and J. M. W. Scott, *ibid.*, **38**, 222 (1960).

(68) K. T. Leffek, *ibid.*, **42**, 851 (1964).

(69) K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, *ibid.*, **38**, 1505 (1960).

(70) S. Hartman and R. E. Robertson, *ibid.*, **38**, 2033 (1960).

transition-state bonding.[20] For example, assume $f^{\ddagger}_{\mathrm{HCO}}$ and $f^{\ddagger}_{\mathrm{HCX}}$ to be invariant to change in X. Then as X is varied from I to Br to OTs an increase in α-effect is to be expected because of increasing reactant-state f_{HCX}. Such conclusions appear to be at least qualitatively justified from the variation in α-effect with change in nucleophile for a given electrophile; see Table III, ref 66. However, the changes are sometimes small. The variation in α-effect with change in electrophile or nucleophile appear to be in agreement with the predictive rules of Thornton[5] and Harris and Kurz.[6]

2. *Heavy-Atom Effects and Quantitative Analysis of Heavy-Atom and α-Effects*

For reactions of methyl iodide with (a) triethylamine, pyridine, and hydroxide ion the ^{14}C isotope effects are 1.102, 1.142, and 1.088,[71] and with (b) hydroxide (hydrolysis)[72] and cyanide[73] the ^{13}C effects are 1.036 and 1.073. Correlation of the temperature-dependent factor for the ^{13}C effects[73] with $E_{\mathrm{n}} - E_{\mathrm{I}}$ was interpreted[66] as suggesting the importance of the variation of bond-making and bond-breaking in determining ^{13}C effects. These changes in carbon effect agree at least superficially with predictions of nucleophile substituent effects on the extent of bond-making and bond-breaking.[5,6]

Exercise of caution is indicated advisable by the results of "exact" calculations for reactions of CH_3I with I^- and with H_2O.[28] For the iodide reaction as $\nu^{\ddagger}_{\mathrm{L}}$ decreases ($\nu^{\ddagger}_{\mathrm{L}} < 0$) the ^{13}C effect increases, demonstrating that the magnitude of the isotope effect is dependent on the curvature of the barrier for motion along the reaction coordinate independent of the nucleophile–carbon–electrophile bonding. Although Harris and Kurz[6] appear to have considered such effects on the ratio of nucleophile–carbon—electrophile–carbon bonding, Thornton[5a] has suggested that this curvature is expected to be much smaller than that for the symmetric motion, with the latter dominating for symmetrical transition states. Coupling of motions of the carbon and hydrogen atoms, alluded to in previous calculations,[71–73] results in an increase in $\nu^{\ddagger}_{1\mathrm{L}}/\nu^{\ddagger}_{2\mathrm{L}}$ for the carbon effects and a decrease in this value for the deuterium effect with increasing curvature.[28] Such coupling would reasonably explain[28] the high α-effect observed by Seltzer and Zavitsas.[66] For the hydrolysis reaction, agreement with the experimental α- and carbon effects is realized with $f^{\ddagger}_{\mathrm{CO}} \geq f^{\ddagger}_{\mathrm{CI}}$ although $f^{\ddagger}_{\mathrm{CO}} > f^{\ddagger}_{\mathrm{CI}}$ seems more probable. In summary, the methyl carbon effect was found to depend principally on (a) the relative degrees of bond making (N···C) and breaking (C···X) in the transition state as measured by $f^{\ddagger}_{\mathrm{CN}}/f^{\ddagger}_{\mathrm{CX}}$, (b) the curvature of the potential barrier as measured by $f^{\ddagger}_{\mathrm{CN}}f^{\ddagger}_{\mathrm{CX}} - f^{2}_{12} = d \leq 0$, and (c) the stiffness of the transition state as measured by $f^{\ddagger}_{\mathrm{HCX}} + f^{\ddagger}_{\mathrm{HCN}}$.[17d,28] The α-effect is dependent on the force constants $f^{\ddagger}_{\mathrm{CH}}$, $f^{\ddagger}_{\mathrm{HCH}}$, $f^{\ddagger}_{\mathrm{CH_3}}$ (out-of-plane bending motion of the CH_3 moiety), and the sum of $f^{\ddagger}_{\mathrm{HCN}} + f^{\ddagger}_{\mathrm{HCX}}$. Extensive calculations have been made for the reaction of CN^- and OH^- with CH_3I.[74] For the cyanide ion reaction, agreement between the experimental Arrhenius parameters for the α-deuterium effect and those calculated for various transition-state models is obtained for only two models for which $f_{\mathrm{CH}} = f^{\ddagger}_{\mathrm{CH}}$, $f^{\ddagger}_{\mathrm{HCC}} > f^{\ddagger}_{\mathrm{HCI}}$ ($f^{\ddagger}_{\mathrm{HCC}}$ values between 0.395 and 0.410 mdyn/Å with $f^{\ddagger}_{\mathrm{HCI}} = 0.300$ mdyn/Å), and $f^{\ddagger}_{\mathrm{CI}}$ and $f^{\ddagger}_{\mathrm{CC}}$ having values of 0.2 and 0.2 and −0.8 and 0.2 mdyn/Å.[17d] The value of $\nu^{\ddagger}_{\mathrm{L}}$ must be imaginary (curvature in the barrier) to obtain agreement between the experimental and calculated carbon-13 effects.[74]

The α-^{13}C effect at 0° for reaction of benzyl bromide with methoxide anion is 1.0531 and for reaction of α-phenylethyl bromide with ethoxide anion is 1.0359.[75] These results are consistent with a transition state which is unsymmetric in the sense that the O–C and C–Br stretching force constants are unequal in magnitude. Neglecting differences between ethoxide and methoxide we reason intuitively that the C–Br bond should be stronger and the C–O bond weaker in the transition state for α-phenylethyl bromide than for benzyl bromide. If the parallel rather than the perpendicular effect is assumed to dominate for unsymmetrical SN2 transition states, the Thornton rule[5a] seems to lead to the same conclusion. The "*k* rule"[6] predicts the same directions of changes in the transition-state bond orders.

Chlorine isotope effects have been reported in bimolecular reactions of *p*-X-substituted benzyl chlorides. For the substituents CH_3O, H, Cl, and NO_2 the isotope effects with cyanide as the nucleophile are 1.0079, 1.0072, 1.0060, and 1.0057.[64] α-^{14}C isotope effects increase from 1.013 to 1.106 as X is varied from CH_3O to Cl.[76] Qualitatively these data are consistent with increasing NC–C and C–Cl transition-state bond orders as the substituent is varied from electron releasing to electron withdrawing. For the substituent change the "*k* rule"[6] would likewise predict an increase in NC–C bond order but would appear to predict a *decrease, not increase*, in C–Cl bond order. However, the assumption that the chlorine effects mirror only changes in the transition-state C–Cl bond order may be erroneous. For this change in substituents a progressive decrease in the C–Cl bond order might be more than offset by increasing energy of solvation of the incipient chloride anion, which would lead to decreasing rather than increasing chlorine effects. The ^{14}C effects are also consistent with such a product-like shift in terms of the transition-state bond orders. Thus the change in these quantities cannot be uniquely defined from the carbon effects. For example, the low carbon effect for *p*-CH_3O could reflect (a) small C–Cl bond breaking or (b) large C–Cl bond breaking compensated for by increased bonding between C-α and C-1 of the aromatic nucleus with little NC–C bond making for both (a) and (b). Therefore, the isotope effects seem to be equally consistent with increasing NC–C and C–Cl transition state bond orders as the substituent is varied from CH_3O to NO_2.

For reaction of *p*-X-substituted benzyl chlorides with the nucleophile thiophenoxide ion, chlorine effects decrease in order 1.0098, 1.0095, 1.0092 as X is varied from CH_3O to H to NO_2.[77]

The reaction of $^{13}CN^-$ with $^{12}CH_3I$ appears to present the only example of a heavy-atom nucleophile effect. The normal carbon effect, $k_{12}/k_{13} = 1.015$ at 11.4°,[72] is an apparent anomaly since the transition state is indicated to be fairly symmetric. The difference between $f^{\ddagger}_{\mathrm{CI}}$ and $f^{\ddagger}_{\mathrm{CC}}$ is calculated to be of the

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[71] M. L. Bender and D. F. Hoeg, *J. Amer. Chem. Soc.*, **79**, 5649 (1957).

[72] K. R. Lynn and P. E. Yankwich, *ibid.*, **83**, 53 (1961).

[73] K. R. Lynn and P. E. Yankwich, *ibid.*, **83**, 790 (1961).

[74] A. V. Willi, *Z. Naturforsch. A*, **21**, 1377, 1385 (1966).

[75] J. Bron and J. B. Stothers, *Can. J. Chem.*, **46**, 1825 (1968).

[76] A. Fry and N. Pearson, Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, No. ORGN-103.

[77] E. P. Grimsrud and J. W. Taylor, *J. Amer. Chem. Soc.*, **92**, 739 (1970).

Table VII

Secondary Deuterium Isotope Effects in Acidolysis of 35, 36, 37, and 38

Compd	*Temp, °C*	*Solvent*	*Atoms of D*	$(k_H/k_D)_\alpha$	$(k_H/k_D)_\beta$
35	75.25	HCO_2H	1.83	1.17	
	25	HCO_2H	2.00	1.21[a,b]	
	75.25	HCO_2H	1.62		1.00
36	50.0	HCO_2H	2.00	1.20	
	25	HCO_2H	2.00	1.22[a]	
	50	HCO_2H			0.97
	75.0	$CH_3CO_2H + LiClO_4$	2.00	1.18	
	25	$CH_3CO_2H + LiClO_4$	2.00	1.21	
	75.0	$CH_3CO_2H + LiClO_4$	1.77		1.00
37	75.0	HCO_2H	2.00	1.21	
	25	HCO_2H	2.00	1.25[a]	
	75.0	HCO_2H	1.00		1.01
	75.0	$CH_3CO_2H + LiClO_4$	2.00	1.21	
	25	$CH_3CO_2H + LiClO_4$	2.00	1.25[a]	
	75.0	$CH_3CO_2H + LiClO_4$	1.00		1.02
38	25.0	HCO_2H	1.92	1.23	
	25	HCO_2H	2.00	1.24[b]	
	60.6	CH_3CO_2H	1.92	1.13	
	25	CH_3CO_2H	2.00	1.15[b]	

[a] Extrapolated from k_H/k_D at other temperatures. [b] Corrected to 2.00 atoms of α-D.

order of 1 mdyn/Å.[74] Furthermore no agreement between experimental and calculated ^{13}C nucleophile effects was obtained.[74]

IV. Kinetic Isotope Effects and the Role of Anchimeric Assistance

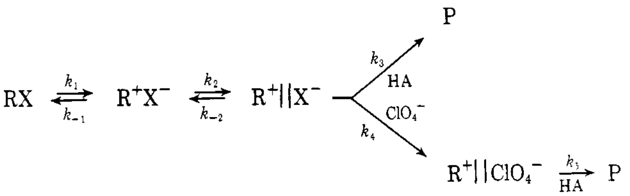
A. CARBONIUM ION REACTIONS[77a]

1. Solvolysis of β-Arylalkyl Derivatives

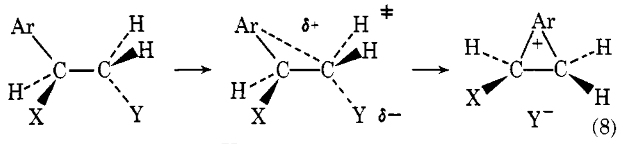
Secondary deuterium isotope effects have been reported for formolysis and acetolysis of 2-phenylethyl[78] (**35**), 2-(4-methoxyphenyl)ethyl[79] (**36**), and 2,2-diphenylethyl[79] (**37**) *p*-toluenesulfonates and for 2-(2,4-dimethoxyphenyl)ethyl[80] (**38**) and 2-(3,5-dimethoxyphenyl)ethyl[80] (**39**) *p*-bromobenzenesulfonate. The acetolysis of **35** and **39** is complicated by internal return and apparently by direct nucleophilic displacement by the solvent. An SN2 pathway is indicated to make a significant contribution to the formolysis mechanism for **39**. An SN1 mechanism is dominant for formolysis of **35** and followed exclusively by acetolysis and formolysis of **36**, **37**, and **38**. Isotope effects for acetolysis of **36** and **37** but not **38** were measured in the presence of lithium perchlorate to suppress ion-pair return. Consequently, α-effects will be considered only for those compounds solvolyzing *via* a limiting mechanism. The values are tabulated in Table VII. Listed in Table VII are values of the α-effects extrapolated to 25° and/or corrected to two atoms of α-D.

Assuming a normal α-effect to be 1.12–1.15 per D a value of k_H/k_D of *ca.* 1.25 to 1.32 per two α-D was anticipated if the mechanism of acidolysis proceeded without anchimeric assistance.[78–80] The observed values of k_H/k_D for formolysis of **35** through **38** and acetolysis of **36**, **37**, and **38** compared to the hypothetical value for unassisted solvolysis were taken to be indicative of β-aryl participation in heterolysis of the C–O bond.[78–80] The modest reduction in these α-effects was interpreted in terms of a transition state C-α-β-aryl bond weak relative to the C-β-β-aryl bond. In harmony with this conclusion was the absence of a β-effect for **35** through **38**. Hence the transition state in eq 8 was indicated not to resemble closely the arylonium ion intermediate.

Scheme I



40 41 42



(8)

X = H or C_6H_5
Y = OTs or OBs

This interpretation of the data needs to be scrutinized. A general mechanism for acidolysis of these esters is presented in Scheme I. Formolysis of **35** is accompanied by return to **40** (R = $C_6H_5CH_2CH_2$) from both intimate (**41**) and solvent-separated (**42**) ion pairs.[81] The amount of phenyl-migrated product rose from 43% in the absence of lithium perchlorate to 50% at 0.5 *M* lithium perchlorate, indicating salt-promoted ionization. The percentage rearrangement in recovered unsolvolyzed **35** was *ca.* 2.7% independent of salt concentration. However, added sodium *p*-toluenesulfonate-^{35}S, which did not affect the percentage of rearranged product, about doubled the percentage rearrangement of unsolvolyzed **35**. It was concluded that internal return is unimportant in formolysis of **36**.[82]

Clearly the α-effects in Table VII cannot be interpreted independently of kinetic considerations. The total α-effect, k_t^H/k_t^D, for Scheme I is given by eq 9 which is derived from an

$$k_t^H/k_t^D = (k_1^H/k_1^D)(F_H^{41}/F_D^{41})$$

$$F_H^{41}/F_D^{41} = [k_2^H/k_{-1}^H + (k_{-1}^D/k_{-1}^H)/(k_2^D/k_2^H)]/[(k_2^H/k_{-1}^H) + 1] \qquad (9)$$

equation of Murr and Donnelly[51] by assuming that $F_H^{42}/F_D^{42} = 1$. This assumption is made (a) because this result was observed for reaction of the solvent-separated benzhydryl benzoate ion pairs[50] and (b) to simplify discussion. Consider the data for formolysis of **35** through **38**. If it is assumed that $k_2 \gg k_{-1}$, then $k_t^H/k_t^D = k_1^H/k_1^D$. An *a priori* estimate of k_1^H/k_1^D

[77a] For a recent discussion of secondary deuterium isotope effects and neighboring group participation, see D. E. Sunko and S. Borčić in ref 9h, Chapter 3.

[78] W. H. Saunders, Jr., S. Asperger, and D. H. Edison, *J. Amer. Chem. Soc.*, **80**, 2421 (1958).

[79] W. H. Saunders, Jr., and R. Glaser, *ibid.*, **82**, 3586 (1960).

[80] C. C. Lee and L. Noszko, *Can. J. Chem.*, **44**, 2491 (1966).

[81] C. C. Lee, R. Tkachuk, and G. P. Slater, *Tetrahedron*, **7**, 206 (1959).

[82] E. F. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958).

for unassisted formolysis of these esters is required. The current status of α-effects for the limiting solvolysis of compounds which are clearly proceeding without anchimeric assistance renders any estimate tenuous. If the transition states for **35** through **38** are assumed to be not appreciably ion-pair-like, *i.e.*, bonding exists between C-α and oxygen, the only published estimate found of k_1^H/k_1^D for unassisted solvolysis is the value 1.12[50] deduced for benzhydryl benzoate. Thus for the β-arylethyl esters a normal value is indicated to be 1.25 at 25°. The values of k_H/k_D for **35** through **38** in formic acid at 25° in Table VII differ insignificantly in value from 1.25, which argues for little or no anchimeric assistance to C–O bond heterolysis. Participation can be viewed as introducing some SN2 character into an SN1 transition state and thus causing an increase in its reactant-like character. In the absence of participation the force field change associated with the α-hydrogens conceivably could be similar to those which produce α-effects of 1.18 to 1.22 per α-D (1.39 to 1.49 per 2 α-D) in SN1 reactions of "simple" substrates. Hence the values of k_H/k_D are significantly "abnormal" and should be interpreted in terms of strong, not weak, bonding between C-α and C-1 of the β-aryl moiety in the transition states.

As a second possibility assume $k_{-1} \gg k_2$. Clearly eq 9 reduces to eq 10. If a PIE value (the term inside the square

$$k_t^H/k_t^D = (k_1^H/k_1^D)[(k_{-1}^D/k_{-1}^H)/(k_2^D/k_2^H)] \qquad (10)$$

brackets in eq 10) of 1.10 per α-D[51] is assumed and an average value of 1.22 is taken for k_t^H/k_t^D (Table VII), the value of k_1^H/k_1^D is calculated to be 1.01. To a first approximation this result would require that $f^{\ddagger}_{\alpha\text{-HCAr}}$ be nearly equal to the decrease in the value of $f_{\alpha\text{-HCO}}$.

However, a mechanism in which $k_{-1} \gg k_2$ may not be correct; see previous discussion relating to internal return. As a third possibility consider the case in which the rate constants for partitioning of **41** between **40** and **42** are not significantly different. Assume $k_2^H = 5k_{-1}^H$ and a PIE value of 1.21, *i.e.*, $(1.10)^2$. Taking k_t^H/k_t^D to be 1.22, eq 9 yields a value of 1.18 for k_1^H/k_1^D. This value is 25% smaller than the value of 1.25 estimated for unassisted solvolysis. For this mechanism the α-effects in Table VII could be consistent with some participation.

In acetolysis of **35** and **36** internal return from **41** seems well demonstrated. The presence of lithium perchlorate during acetolysis of **36** was shown to eliminate a large part of ion-pair return. It was concluded that return from the solvent-separated pair but not from the intimate ion pair was being eliminated. Thus for acetolysis it seems reasonable to assume k_1 to be rate-determining, with $k_{-1} \gg k_2$. This assumption would mean that the α-effects for **36** and **37** are significantly reduced; *i.e.*, a "normal" value is expected to be about 1.49. Thus acetolysis is strongly assisted. If k_1 is rate determining or if no isotope effect exists on partitioning of **41** between **40** and **42** (for a discussion of the effect of anchimeric assistance on the magnitude of PIE see discussion of α-effects in *exo*-bicyclo[2.2.1]hept-2-yl systems), $k_t^H/k_t^D = k_1^H/k_1^D$ and the evidence for bridging in acetolysis as in formolysis is ambiguous. Assuming a PIE > 1 and a value of k_2 not significantly different from k_{-1} would result in a somewhat "abnormal" value for k_1^H/k_1^D. No kinetic evidence is provided to support the idea that the anomalously low value of k_H/k_D for acetolysis of **38** results from ion-pair return that scrambles deuterium between C-1 and C-2.

Thus the α-effects in Table VII provide compelling evidence neither for nor against participation by β-aryl in formic or acetic acid.

When corrected for incomplete deuteration and/or extrapolated to a common temperature, the apparent differences in the α-effects in Table VII, except for acetolysis of **38**, vanish. Nevertheless it is pertinent to examine an interpretation advanced for the apparent differences.[80] Utilizing Hammond's postulate,[3] Streitwieser[53] suggested that as the participatory ability of the neighboring aryl increases, the β-Ar–C-α transition-state distance increases. Following Streitwieser, Lee and Noszko[80] then argued that as the aryl group is changed from phenyl to 4-methoxyphenyl to 2,4-dimethoxyphenyl, the resultant increase in distance between the aryl moiety and C-α in the transition state will cause an increase in the α-effect. Let us expand the argument assuming the C–O bond strength in the transition state to be a function of the strength of bonding between β-aryl and C-α. Isotope effects demand knowledge of force constant changes that occur in passing from the reactant to the transition state. To a first approximation the α- and β-effects for reaction 8 can be discussed in terms of the decrease in the α-hydrogen–carbon–oxygen bending force constant, $\Delta f_{\alpha\text{-HCO}}$, and increase in the α-hydrogen–carbon–β-aryl bending force constant, $\Delta f_{\alpha\text{-HCAr}}$, and alteration in the β-hydrogen–carbon–β-aryl, $\Delta f_{\beta\text{-HCAr}}$, bending constant as the reactant is converted to the transition state. In terms of force constant changes the previous assumptions require that the decrease in the C–O stretching force constant, Δf_{CO}, in passing from the reactant to the transition state will be progressively smaller as the ability of XC_6H_4 to participate increases, *i.e.*, as the magnitude of the β-aryl–C-α stretching force constant in the activated complex decreases. Assuming $\Delta f_{\alpha\text{-HCO}}$ to be a function of Δf_{CO} and momentarily neglecting $\Delta f_{\alpha\text{-HCAr}}$, the prediction is that as the participatory ability of aryl increases, $\Delta f_{\alpha\text{-HCO}}$ and Δf_{CO} decreases (transition state becomes progressively more reactant-like) and the α-effect should *decrease, not increase*. However, the α-effect is determined by the total force field change, *i.e.*, $\Delta f_{\alpha\text{-HCO}} - \Delta f_{\alpha\text{-HCAr}}$. Possibilities are (1) $\Delta f_{\alpha\text{-HCO}} > \Delta f_{\alpha\text{-HCAr}}$, yielding decreasing α-effects; (2) $\Delta f_{\alpha\text{-HCO}}$ essentially equal to $\Delta f_{\alpha\text{-HCAr}}$, resulting in a nearly constant α-effect; or (3) $\Delta f_{\alpha\text{-HCAr}} > \Delta f_{\alpha\text{-HCO}}$, resulting in increasing isotope effects. However, if the extent of C–O bond rupture was nearly or completely independent of the nature of the aromatic system, the value of $\Delta f_{\alpha\text{-HCO}} - \Delta f_{\alpha\text{-HCAr}}$ would increase with increasing participatory ability of neighboring aryl and k_H/k_D would increase. Similarity exists between a reaction involving anchimeric assistance and an SN2 reaction. The reasonable success achieved in relating isotope effects to bonding in the transition state for the latter reactions suggests a similar application in the former. Knowledge of the carbon effects at C-α, C-β, and C-1 in the aromatic ring, of the α- and β-deuterium effects, and of the heavy-atom leaving-group effect as a function of ring substituent coupled with exact calculations would be of immense value in elucidating the bonding (nature of participation) in the solvolytic transition state. An example of this approach is afforded by the ^{14}C effects at C-1 in the aromatic ring reported for solvolysis of 2-phenylethyl (**43a**) and 2-(4-methoxyphenyl)ethyl (**43b**) *p*-nitrobenzenesulfonates.[83] For **43a** k_{12}/k_{14} ratios are 1.022 ± 0.002 at 60° in formic acid, 1.029 ± 0.002 at 45° in trifluoroacetic acid, and 1.034 ± 0.002 at 45° in trifluoroacetic acid

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(83) (a) Y. Yukawa, T. Ando, K. Token, and S. G. Kim, *Tetrahedron Lett.*, 2367 (1969); (b) *ibid.*, 847 (1971).

Table VIII

Isotope Effects in Acidolysis of *threo*-2-Phenyl-1-methylpropyl *p*-Toluenesulfonate and the 4-Methylphenyl Homolog

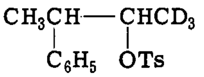
Compd	k_H/k_D CH_3CO_2H	*Temp, °C*	k_H/k_D HCO_2H	*Temp, °C*	k_H/k_D CF_3CO_2H	*Temp, °C*	*Ref*
44-*1-methyl-d*$_3$	1.073	75.1	1.160	25.02	1.170	−7.9	85a
44-*1-d*	1.104	75.1	1.142	25.02	1.133	−7.9	85b
44-*2-d*	1.094	75.1	1.040	25.02	1.009	−7.9	85b
44-*3-d*$_3$	1.065	75.1	1.015	25.02	1.009	−7.9	85a
45-*1-methyl-d*$_3$			1.177	15.00			86
45-*3-d*$_3$			1.006	15.00			86
45-*p-methyl-d*$_3$			1.001	15.00			86

containing sodium trifluoroacetate.[83b] For **43b** the corresponding values are 1.028 ± 0.001 at 60° in acetic acid,[83a] 1.026 ± 0.003 at 30° in formic acid,[83b] and 1.036 ± 0.009 at 0° in trifluoroacetic acid.[83b] The authors point out[83] that these isotope effects provide compelling evidence for participation.

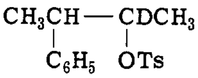
It is instructive to consider what conclusions can be drawn from these isotope effects concerning the relative transition-state bond orders between C-1 of the aromatic ring and C-β and C-α. Participation can be viewed as a three-center displacement, eq 8. It was argued (see section III.B.2) that the isotope effect at the carbon atom of the group being transferred (in this case C-1 of the aromatic ring) should be maximal if the bonds between this carbon and the origin and terminus of the displacement were nearly equal and if $\nu^{\ddagger}{}_L$ had only a very small imaginary value. The carbon effects for **43a** and **43b** are considerably smaller than those for SN2 reactions of methyl iodide (see section III.C.2 and ref 27). Although not exactly analogous a better model might be the ^{14}C effects in the *m*-chloroperoxybenzoic acid oxidation of methyl para-substituted phenyl-*1*-^{14}C ketones.[84] The isotope effect (k_{12}/k_{14}) was observed to increase from 0.998 to 1.084 as the para substituent was varied from CH_3O to NO_2, demonstrating that in the transition state the bonding of C-1 of the aromatic ring to carbon (origin) and to oxygen (terminus) is singularly sensitive to the nature of the para substituent. The isotope effects for **43a** and **43b** seem most reasonably interpreted in terms of transition states in which the C-β–Ar bond strength is in excess of the C-α–Ar bond strength. The contention[11h,78,79] that these transition states do not closely resemble phenonium ions is supported.

The absence of temperature-dependence studies precludes calculation of the ^{14}C effects for **43a** and **43b** at the same temperature. Such data would permit a qualitative assessment of the variation in bonding of C-1 of the aromatic ring to C-α and C-β in the transition state with changes in both the participatory character of the aromatic ring and the ionizing power of the solvent.

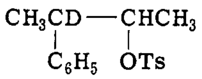
The decrease in the stretching force constant associated with the C-β–Ar bond in passing from the reactant to the transition state implies a decrease in the β-HCAr bending force constant. Consequently, the absence of an "α-effect at C-β" in the limiting solvolysis of **35** and **36** is difficult to comprehend. Insufficient precision in the rate measurements is a possible explanation.


$\underset{C_6H_5}{CH_3CH}-\underset{OTs}{CHCD_3}$

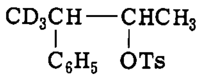
44-*1-methyl-d*$_3$


$\underset{C_6H_5}{CH_3CH}-\underset{OTs}{CDCH_3}$

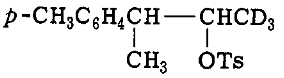
44-*1-d*


$\underset{C_6H_5}{CH_3CD}-\underset{OTs}{CHCH_3}$

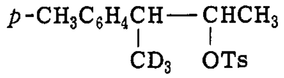
44-*2-d*


$\underset{C_6H_5}{CD_3CH}-\underset{OTs}{CHCH_3}$

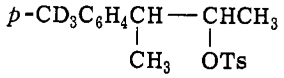
44-*3-d*$_3$


$p\text{-}CH_3C_6H_4\underset{CH_3}{CH}-\underset{OTs}{CHCD_3}$

45-*1-methyl-d*$_3$


$p\text{-}CH_3C_6H_4\underset{CD_3}{CH}-\underset{OTs}{CHCH_3}$

45-*3-d*$_3$


$p\text{-}CD_3C_6H_4\underset{CH_3}{CH}-\underset{OTs}{CHCH_3}$

45-*p-methyl-d*$_3$

Secondary deuterium isotope effects in acetolysis, formolysis, and trifluoroacetolysis of *threo*-2-phenyl-1-methylpropyl *p*-toluenesulfonate[85] (**44**) and in formolysis of *threo*-2-(4-methylphenyl)-1-methylpropyl *p*-toluenesulfonate[86] (**45**) are reproduced in Table VIII. The isotope effects correspond to the ratio of the polarimetric rate constants and, hence, are a direct measure of the isotope effect on ionization. It was argued that if solvolysis of **44** and **45** proceeded without anchimeric assistance the isotope effects to be expected are *ca.* 1.36 for **44**- and **45**-*1-methyl-d*$_3$, *ca.* 1.02 for **44**- and **45**-*3-d*$_3$, 1.12–1.15 for **44**-*1-d*, and 1.08–1.15 for **44**-*2-d*. The last value may be too large since acidolysis would proceed almost necessarily with the phenyl and tosyloxy groups in a trans coplanar configuration in the transition state resulting in a conformation unfavorable for hyperconjugation. The data for acetic acid seem to be most consistent with phenyl participation. Note that (a) the effect for **44**-*1-d* is lower than any value of an α-effect on ionization, (b) in contrast to its consequences in β-arylethyl esters, β-deuteration (**44**-*2-d*) produces an isotope effect nearly equal to that for α-deuteration, and (c) the β-effects at the 1-methyl and C-3 are considerably less than maximal but nearly equal to each other. Consequently these results suggest a transition state in which (a) the bonding between C-1 of the phenyl group and C-2 of the chain is only moderately greater than its bonding to C-1 and (b) the fractional positive charges on C-1 and C-2 are nearly equal.

On the basis of the generally accepted postulate of neighboring-group theory that participation is enhanced as the nucleophilicity decreases and the ionizing power of the solvent increases, it was concluded[85] that a correct trend in the isotope effects for **44** was not observed. Particularly for solvolysis in formic and trifluoroacetic acids the isotope effects were considered to be more in accord with the classical model.

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[84] B. W. Palmer and A. Fry, *J. Amer. Chem. Soc.*, **92**, 2580 (1970).

[85] (a) S. L. Loukas, M. R. Velkow, and G. A. Gregoriou, *Chem. Commun.*, 1199 (1969); (b) *ibid.*, 251 (1970).

[86] S. L. Loukas, F. S. Varveri, M. R. Velkow, and G. A. Gregoriou, *Tetrahedron Lett.*, 1803 (1971).

Table IX

Deuterium Isotope Effects in Solvolysis of *exo*-2-Bicyclo[2.2.1]heptyl Derivatives

Compound	*X*	*Solvent*	*Temp, °C*	k_H/k_D[a]	*Ref*
46-*2-d*	OBs	CH_3CO_2H	24.85	1.11	87a
	OBs	80% aq C_2H_5OH	25	1.124 ± 0.010	87b
	OBs	CH_3CO_2H, CH_3CO_2K	25	1.118 ± 0.013	87b
	OTs	CH_3CO_2H		1.20	87c
46-*6-exo-d*	OBs	CH_3CO_2H, CH_3CO_2K	24.9	1.09 ± 0.03	87d
	OBs	80% aq C_2H_5OH	24.9	1.09 ± 0.01	87d
	OBs	CH_3CO_2H, 1% $(CH_3CO)_2O$	44.4	1.149 ± 0.016	87e
46-*6-endo-d*	OBs	CH_3CO_2H, CH_3CO_2K	24.9	1.11 ± 0.01	87d
	OBs	80% aq C_2H_5OH	24.9	1.11 ± 0.01	87d
	OBs	CH_3CO_2H, 0.7% $(CH_3CO)_2O$	43.3	1.097 ± 0.011	87e
46-*3,3-d*$_2$	Br	Aq CH_3CO_2H	51.25	1.04,[c] 1.02	87f
	OBs	CH_3CO_2H	44.3	1.014 ± 0.018[b]	87g
	OBs	80% aq C_2H_5OH	25.0	1.06, 1.11 ± 0.01[b]	87h
	OBs	CH_3CO_2H, CH_3CO_2K	25.0	1.03, 1.07 ± 0.01[b]	87h
46-*3-exo-d*	OBs	80% aq C_2H_5OH	25.0	1.11 ± 0.01	87h
	OBs	CH_3CO_2H, CH_3CO_2K	25.0	1.07 ± 0.01	87h
46-*3-endo-d*	OBs	80% aq C_2H_5OH	25.0	1.02 ± 0.01	87h
	OBs	CH_3CO_2H, CH_3CO_2K	25.0	1.02 ± 0.01	87h

[a] Per atom of D unless otherwise specified. [b] Per 2 atoms of D. [c] Calculated from polarimetric rate constants.

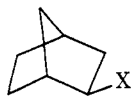
In formic and trifluoroacetic acids k_H/k_D for **44**-*1-d* is similar to if not in excess of the ionization isotope effect for benzhydryl benzoate (1.12) and smaller than the value of 1.22 which supposedly obtains for rate-determining equilibration of ion pairs. Attention should be focused not on this single effect but on the strikingly consistent solvent dependence of each isotope effect; *i.e.*, as the solvent is varied from acetic to formic to trifluoroacetic acid the deuterium effects at the 1-methyl and C-1 become progressively larger and those at C-2 and C-3 become progressively smaller. This solvent dependence could be consistent with nonclassical theory. Conceivably this change in solvent produces a shift in the transition state along the reaction coordinate. As the transition state shifts, the force field associated with C-α and β-phenyl decreases more rapidly than the force field associated with C-α and the tosyloxy group increases. The theory as outlined for the 2-phenylethyl system would then require decreasing charge dispersal from C-1 to C-2, decreasing $\Delta f_{\beta\text{-HCAr}}$, and increasing $\Delta f_{\alpha\text{-HCO}} - \Delta f_{\alpha\text{-HCAr}}$. These considerations would predict isotope effects decreasing at C-2 and C-3 and increasing at C-1 and 1-methyl.

The isotope effects for **45** are taken as evidence against a transition state resembling a symmetrically bridged arylonium ion.[86] In passage from the reactant to the transition state the results argue for little perturbation in the C-2–4-methylphenyl bond strength and for little bond formation between C-1 and the 4-methylphenyl group. It is argued that the intermediate is not an arylonium ion.[86] Although the conclusion may be correct, the isotope effects cannot confirm its validity. It must be remembered that a kinetic isotope effect relates only to the force field change at the isotopically substituted position accompanying conversion of reactant to activated complex. It does not provide information on conversion of activated complex to intermediate.

It is to be hoped that the elegant measurements made for **44** and **45** will be extended to other compounds.

2. *Solvolysis of Bicyclo[2.2.1]heptyl and Related Derivatives*

Tabulated in Tables IX and X respectively are solvolytic deuterium isotope effects for *exo*-(**46**) and *endo*-(**47**) bicyclo[2.2.1]hept-2-yl substrates.[87] Table XI presents deuterium isotope effects for solvolysis of (a) *exo*- and *endo*-2-phenyl- (**48** and **49**) and -2-methyl- (**50** and **51**) bicyclo[2.2.1]hept-2-yl *p*-nitrobenzoates, (b) *exo*- and *endo*-1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl (**52** and **53**) *p*-toluenesulfonates and, (c) *exo*-1,2-dimethylbicyclo[2.2.1]hept-2-yl (**54**) *p*-nitrobenzoate.[88]



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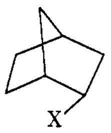

47

For solvolysis of **47**-*2-d*-OBs the value of k_H/k_D at 25° is essentially 1.20 independent of solvent (see Table X). These values are very close to the maximum value of *ca.* 1.22 suggested for limiting solvolysis of simple secondary sulfonates. This correspondence might simply be construed as evidence for a normal solvolytic transition state for **47**-OBs and, hence, for the absence of steric hindrance to ionization. However,

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(87) (a) C. C. Lee and E. W. C. Wong, *J. Amer. Chem. Soc.*, **86**, 2752 (1964); (b) B. L. Murr and J. A. Conkling, *ibid.*, **92**, 3462 (1970); (c) K. Humski, R. Malojčić, S. Borčić, and D. E. Sunko, *ibid.*, **92**, 6534 (1970); see p 6537 and footnote 17; (d) B. L. Murr, A. Nickon, T. D. Swartz, and N. H. Werstiuk, *ibid.*, **89**, 1730 (1967); (e) J. M. Jerkunica, S. Borčić, and D. E. Sunko, *ibid.*, **89**, 1733 (1967); (f) J. P. Schaefer, M. J. Dagani, and D. S. Weinberg, *ibid.*, **89**, 6938 (1967); (g) J. M. Jerkunica, S. Borčić, and D. E. Sunko, *Chem. Commun.*, 1302 (1967); (h) B. L. Murr and J. A. Conkling, *J. Amer. Chem. Soc.*, **92**, 3464 (1970); (i) C. C. Lee and E. W. C. Wong, *Can. J. Chem.*, **43**, 2254 (1965).

(88) (a) J. P. Schaefer, J. P. Foster, M. J. Dagani, and L. M. Honig, *J. Amer. Chem. Soc.*, **90**, 4497 (1968); (b) J. M. Jerkunica, S. Borčić, and D. E. Sunko, *Chem. Commun.*, 1488 (1968); (c) H. L. Goering and K. Humski, *J. Amer. Chem. Soc.*, **91**, 4594 (1969).

Table X

Deuterium Isotope Effects in Solvolysis of *endo*-Bicyclo[2.2.1]hept-2-yl Derivatives

Compound	*X*	*Solvent*	*Temp, °C*	$k_{\mathrm{H}}/k_{\mathrm{D}}{}^{a}$	*Ref*
47-*2-d*	OBs	CH_3CO_2H	50	1.203^{b}	87a
	OBs	Aq dioxane	50.20	1.20^{b}	87i
	OBs	HCO_2H	25	1.22^{b}	87i
	OBs	80% aq C_2H_5OH	25	1.193	87c
	OBs	CH_3CO_2H, CH_3CO_2K	25	1.20	87c
	Br	Aq C_2H_5OH	60.21	1.28	87f
47-*exo-6-d*	OBs	CH_3CO_2H, CH_3CO_2K	70.1	0.98 ± 0.01	87d
	OBs	80% aq C_2H_5OH	49.1	1.00 ± 0.02	87d
	OBs	CH_3CO_2H	65.0	1.021 ± 0.012	87e
47-*endo-6-d*	OBs	CH_3CO_2H, CH_3CO_2K	70.1	0.99 ± 0.02	87d
	OBs	80% aq C_2H_5OH	49.1	0.97 ± 0.01	87d
	OBs	CH_3CO_2H	65.0	0.998 ± 0.009	87e
47-*3,3-d*$_2$	Br	Aq C_2H_5OH	60.21	1.16, 1.30^{c}	89f
	OBs	CH_3CO_2H	65.0	1.26 ± 0.01^{c}	87g
	OBs	80% aq C_2H_5OH	55	1.15, 1.31 ± 0.01^{c}	87h
47-*exo-3-d*	OBs	80% aq C_2H_5OH	55	1.19 ± 0.01	87h
47-*endo-3-d*	OBs	80% aq C_2H_5OH	55	1.12 ± 0.01	87h

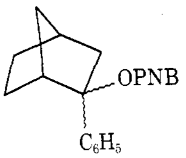
^{a} Per atom of D unless otherwise specified. ^{b} Per 0.94 atom of D. ^{c} Per 2 atoms of D.

Table XI

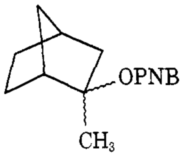
Deuterium Isotope Effects in Solvolysis of Methyl- and Phenyl-Substituted *exo*- and *endo*-Bicyclo[2.2.1]hept-2-yl Derivatives

Compound	*Solvent*	*Temp, °C*	$k_{\mathrm{H}}/k_{\mathrm{D}}{}^{a}$	*Ref*
48-*3,3-d*$_2$	Aq dioxane	39.50	1.18 ± 0.02^{b}	88a
49-*3,3-d*$_2$	Aq dioxane	62.50	1.15 ± 0.02^{b}	88a
50-*3,3-d*$_2$	Aq acetone	95.0	1.334 ± 0.018	88b
51-*3,3-d*$_2$	Aq acetone	120.7	1.306 ± 0.060	88b
52-*2-d*			1.23^{c}	88b
52-*3,3-d*$_2$	CH_3CO_2H	20.10	1.162 ± 0.007	88b
53-*3,3-d*$_2$	CH_3CO_2H	68.2	1.291 ± 0.037	88b
54-*6,6-d*$_2$	Aq acetone	78.47	1.02 ± 0.01	88c

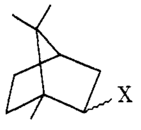
^{a} Per 2 atoms of D unless otherwise specified. ^{b} Per 1.87 atoms of D. ^{c} Per 1 atom of D.



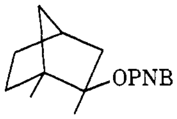
48-*exo*-OPNB
49-*endo*-OPNB



50-*exo*-OPNB
51-*endo*-OPNB



52-*exo*-OTs
53-*endo*-OTs



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the polarimetric and titrimetric rate constants for **47**-OBs in acetic acid, aqueous acetone, and ethanol are identical within the limits of experimental precision.[89] Therefore k_H/k_D may nearly if not completely correspond to the isotope effect on ionization, k_1 of Scheme I. For **47**-OBs Murr and Conkling[87b] have concluded that F_H/F_D (see eq 9) is not greater than 1.02 and $k_H/k_D \cong k_1^H/k_1^D$. The reduction in the α-HCO bending force constant upon passing from the reactant state to the activated complex is indicated to be similiar for **47**-OBs and a "model" secondary sulfonate. However, the transition state for **47**-OBs corresponds to that for ionization (formation of **41** in Scheme I) whereas the activated complex for the model compound corresponds to the transition state for formation of the solvent-separated ion pair (**42**). Therefore, compared to the value for a model sulfonate k_H/k_D for **47**-*2-d*-OBs is abnormally large, indicating a very intermediate-like transition state for C–O bond heterolysis which appears to be evidence for steric hindrance to ionization.

Theory as presently formulated predicts a maximum value of *ca.* 1.125 per D at 25°C for α-effects in limiting solvolysis of secondary bromides. The value of 1.28 for **47**-*2-d*-Br seems impossibly large; a satisfactory explanation for the anomaly is not obvious. The original interpretation[87f] was couched in terms of steric hindrance in solvolysis of the endo bromide. This interpretation would seem to require that the theory of solvolytic α-effects be amiss. Conceivably the value 1.28 is in error. A major problem in qualitative interpretation is the extrapolation of isotope effects from nonbridged compounds to the bicyclo[2.2.1]heptyl substrates. Such extrapolation can lead to erroneous conclusions if the reactant and/or transition state force fields in these molecules are significantly different from those for nonbicyclic systems. Differences between these systems in such factors as coupling of vibronic motions and curvature of the barriers would be hard to recognize at present.

From the temperature dependence the isotope effect for **46**-*2-d*-OBs at 50° was calculated to be 1.07, which is considerably smaller than the value of 1.20 for **47**-*2-d*-OBs.[87a] The reduced α-effect in acetolysis of *exo*-bicyclo[2.2.1]hept-2-yl *p*-bromobenzenesulfonate compared to the endo isomer was ascribed to either anchimeric assistance or to internal return of the classical ion which would scramble deuterium between C-1 and C-2 and result in an artificially reduced α-effect.[87a] The data in Table IX reveal that at 25° the isotope effect for

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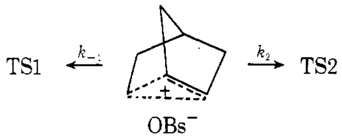
(89) S. Winstein and D. Trifan, *J. Amer. Chem. Soc.*, **74**, 1147 (1952).

46-*2-d*-OBs reported by Lee and Wong[87a] for acetolysis is in good agreement with the values for aqueous ethanolysis and buffered acetolysis reported by Murr and Conkling.[87b] Murr and Conkling[87b] point out that the similarity in α-effects for **46**-*2-d*-OBs tends to exclude scrambling as the cause of the low α-isotope effect. They note that in acetic acid 22% of the ion pairs solvolyze and 78% return with equilibration of C-1 and C-2 whereas the corresponding values are 65 and 35% for ethanolysis. If scrambling were the cause of the low isotope effect on acetolysis, the isotope effect on ethanolysis should be higher. Since k_2/k_{-1} differs considerably between acetic acid and ethanol but $k_\mathrm{H}/k_\mathrm{D}$ is essentially constant, Murr and Conkling[87b] conclude that $F_\mathrm{H}/F_\mathrm{D}$ (eq 9) is not greater than 1.02 in the solvolysis of **46**-*2-d*-OBs and hence $k_\mathrm{H}/k_\mathrm{D}$ must closely approximate $k_{1\mathrm{H}}/k_{1\mathrm{D}}$. In the simplest approximation this result would indicate that $f^{\ddagger}{}_{\mathrm{H-C\text{-}2-O}}$ unexpectedly has the same value in the transition states preceding formation of both the intimate and solvent-separated ion pairs. To consider this apparent anomaly let us analyze the bending force constant changes associated with the C-2 hydrogen accompanying conversion of the intimate ion pair **55** to the transition state preceding formation of **46**-OBs (TS1) and the solvent-separated ion pair (TS2). For the general case assume bonding between C-2 and C-6 in **55**; *i.e.*, TS1 involves anchimeric assistance to bond heterolysis. The changes in the C-2 hydrogen bending force constants in the transformations **55** to TS1 and TS2 are given to a first approximation in eq 11 and 12,



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$$\Delta f_{-1} = f^{55}{}_{\mathrm{H-C\text{-}2-O}} - f^{\mathrm{TS}1}{}_{\mathrm{H-C\text{-}2-O}} + f^{55}{}_{\mathrm{H-C\text{-}2-C\text{-}6}} - f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-C\text{-}6}} \quad (11)$$

$$\Delta f_2 = f^{55}{}_{\mathrm{H-C\text{-}2-O}} - f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-O}} + f^{55}{}_{\mathrm{H-C\text{-}2-C\text{-}6}} - f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-C\text{-}6}} \quad (12)$$

respectively. The magnitude of term $(k_{-1}{}^\mathrm{D}/k_{-1}{}^\mathrm{H})/(k_2{}^\mathrm{D}/k_2{}^\mathrm{H})$ in eq 9, *i.e.*, PIE, is a function of $\Delta f_{-1} - \Delta f_2$ which is given by eq 13. It is eminently reasonable that $f^{\mathrm{TS}1}{}_{\mathrm{H-C\text{-}2-O}} > f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-O}}$.

$$\Delta f_{-1} - \Delta f_2 = f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-O}} - f^{\mathrm{TS}1}{}_{\mathrm{H-C\text{-}2-O}} + f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-C\text{-}6}} - f^{\mathrm{TS}1}{}_{\mathrm{H-C\text{-}2-C\text{-}6}} \quad (13)$$

If the reasonable assumption is made that the increase in the bond order between C-2 and C-6 along the reaction coordinate is correlated with the decrease in the C-2–O bond order, then $f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-C\text{-}6}} > f^{\mathrm{TS}1}{}_{\mathrm{H-C\text{-}2-C\text{-}6}}$. The magnitude of PIE will be determined by the inequality between Δf_{-1} and Δf_2. In the limit as $f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-C\text{-}6}} - f^{\mathrm{TS}1}{}_{\mathrm{H-C\text{-}2-C\text{-}6}}$ approaches $f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-O}} - f^{\mathrm{TS}1}{}_{\mathrm{H-C\text{-}2-O}}$ the value of $(k_{-1}{}^\mathrm{D}/k_2{}^\mathrm{D})/(k_{-1}{}^\mathrm{H}/k_2{}^\mathrm{H})$ approaches unity and $k_\mathrm{t}{}^\mathrm{H}/k_\mathrm{t}{}^\mathrm{D}$ approaches $k_1{}^\mathrm{H}/k_1{}^\mathrm{D}$. Conceivably the negligible PIE for solvolysis of **46**-*2-d*-OBs corresponds to near cancellation of the "individual" PIE's for changes in bonding between (a) C-2 and the brosyloxy group and (b) C-2 and C-6. Although the α-effect for **46**-OBs may be consistent with bridging in TS2 and in the solvent-separated ion pair, *it could but does not necessarily signify anchimeric assistance to ionization.* Let us assume that $f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-O}} \cong 0$, *i.e.*, TS2 is ion-pair-like. As an extreme case assume that the correlation between the C-2–C-6 and C-2–O bond orders is such that $f^{\mathrm{TS}1}{}_{\mathrm{C-H\text{-}2-C\text{-}6}}$ equals zero; *i.e.*, there is no anchimeric assistance to ionization. Then the condition that PIE $\cong$ 1 requires only that $f^{\mathrm{TS}1}{}_{\mathrm{H-C\text{-}2-O}} \cong f^{\mathrm{TS}2}{}_{\mathrm{H-C\text{-}2-C\text{-}6}}$. In general the PIE value for reactions involving anchimeric assistance will depend on the correlation between the increase in the bond order between C-α and the neighboring group and the decrease in the bond order between C-α and the leaving group along the reaction coordinate. Therefore the conclusion that $k_\mathrm{t}{}^\mathrm{H}/k_\mathrm{t}{}^\mathrm{D}$ may closely approximate $k_1{}^\mathrm{H}/k_1{}^\mathrm{D}$ for these reactions is understandable and not an anomaly. Since this argument has omitted a number of factors such as possible changes in the stretching force constant and in the nonreacting bending force constants, *e.g.*, for **46**-OBs $f_{\mathrm{H-C\text{-}2-C\text{-}1}}$ associated with the C-2 hydrogen along the reaction coordinate, the concept needs further attention both theoretically and experimentally. In particular assume that the three-centered bond involving C-1, C-2, and C-6 in TS1 alters the C-1–C-2 bond energy compared to that in the reactant. As the reactant is converted to the transition state $f_{\mathrm{H-C\text{-}2-C\text{-}1}}$ is expected to either increase or decrease. The arguments previously developed that $k_1{}^\mathrm{H}/k_1{}^\mathrm{D}$ should vary with change in neighboring group are not invalidated. Such effects could be important in the acetolysis of 2-arylethylarenesulfonates.

Humski, Malojčić, Borčić, and Sunko[87c] report that the α-effect for acetolysis of **46**-*2-d*-OTs is 1.20 and attribute the low effect to deuterium scrambling due to internal return. It is not clear whether the isotope effect was obtained for **46**-*2-d*-OTs[87c] and/or **46**-*2-d*-OBs.[77a] An initially drifting rate constant was apparently observed for acetolysis of **46**-*2-d*-OBs.[77a] Kinetic data for 3–5% reaction of **46**-*2-d*-OBs yielded a $k_\mathrm{H}/k_\mathrm{D}$ = 1.208.[77a] Unfortunately no discussion of the limits of precision is provided. It has been suggested that participation of the C-1–C-6 bond occurs from a distance which does not allow interference with the CH(CD) bending motions at the reaction center.[77a] The following comment seems appropriate. The α-effect, if it really is as large as 1.21, would seem to favor, within the framework of solvolytic α-effect theory, a normal ion-pair-like transition state for **46**-OBs. It is not clear how such a transition state can approximate a norbornonium ion and yet possess weak bonding between C-1 and C-6. A highly precise determination of the α-effect in the solvolysis of *exo*-norbornyl arenesulfonates is badly needed.

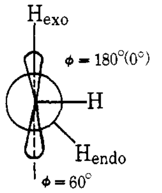
The significant isotope effects at C-6 for both *endo*- and *exo*-deuterium in solvolysis of **46**-OBs is in direct contrast to the absence of such effects in solvolysis of **47**-OBs; see Tables IX and X. Murr, Nickon, Swartz, and Werstiuk[87d] observed nearly identical and solvent-independent isotope effects for **46**-*6-exo-d*-OBs (1.09) and **46**-*6-endo-d*-OBs (1.11). A nearly identical value of 1.097 was reported by Jerkunica, Borčić, and Sunko[87e] for acetolysis of **46**-*6-endo-d*-OBs. However, their value[87e] of 1.149 for **46**-*6-exo-d*-OBs considerably exceeds the value 1.09.[87d] Detailed considerations by Murr and his colleagues rule out scrambling of C-6 deuterium as a significant factor in the large effects for the exo substrates. A calculation indicated that if the isotope effect at C-2 were 1.15 then isotope effects of 1.10 for *endo*- and *exo-6-d* and 1.05 for C-1 must be operative to account for the observed solvolysis results.[87d] It is argued[87d] that the major contribution to the value 1.10 must necessarily be on the ionization of the brosylate. These authors[87d] conclude that the isotope effects at C-6 for **47**-OBs are those typical of a transition state for ionization to a classical cation, whereas the large effects at C-6 for **46**-OBs are not expected on the basis of the classical transition-state hypothesis, at least in its present form. Jerkunica, Borčić, and Sunko[87e] conclude that the effects at C-6 are in perfect agreement with a rate-determining formation of a norbornonium ion in the acetolysis of **46**-OBs. The conclusion that the absence of an isotope effect for solvolysis of **47**-*endo-6-d*-OBs rules out steric hindrance to ionization in solvolysis of **47**-OBs is very possibly fallacious.

The negligible deuterium isotope effect at C-6 in the hydrolysis of 1,2-dimethyl-*exo*-2-norbornyl *p*-nitrobenzoate (see **54**-*6,6-d*$_2$ in Table XI) is in stark contrast to the significant effect at C-6 in the solvolysis of **46**-OBs. The isotope effects at C-6 for **46**-OBs and the absence of corresponding effects for **47**-OBs and **54**-OPNB indicate that in passing from the reactant to the transition state the former but not the latter pair suffers a reduction in the force constants associated with the C-6 hydrogen, implying a reduction in the C-1–C-6 bond order. Let us assume that the decrease in the C-1–C-6 bond order arises from bond formation between C-6 and C-2. To a first approximation as **46**-OBs is converted to TS1 the decrease in $f_{\text{H–C-6–C-1}}$ tends to be compensated by the increase in $f_{\text{H–C-6–C-2}}$. It would thus seem that unless $f_{\text{H–C-6–C-5}}$ also decreases the decrease in the former must be greater than the increase in the latter to make $k_{\text{H}}/k_{\text{D}} > 1$; *i.e.*, C-2–C-6 bond making lags behind C-1–C-6 bond rupture. In our view a norbornonium ion contains equal or nearly equal bonding of C-6 to C-1 and to C-2. Therefore if TS1 is assumed closely to resemble a bridged species $f^{\ddagger}_{\text{H–C-6–C-1}}$ should closely approximate $f^{\ddagger}_{\text{H–C-6–C-2}}$. Assuming the force constant describing the bending of the C-6 hydrogen with respect to C-6 and C-5, $f_{\text{H–C-6–C-5}}$, to have the same value in both the reactant and transition states, nonclassical theory would *a priori* predict a $k_{\text{H}}/k_{\text{D}}$ for C-6 deuterated **46**-OBs of *ca.* 1. The opposite assumption would be that TS1 is quite reactant-like. Although $k_{\text{H}}/k_{\text{D}}$ will depend upon the correlation between the decrease in the C-1–C-6 and the increase in the C-2–C-6 bond orders, $k_{\text{H}}/k_{\text{D}}$ is expected to be less than or equal to unity. For the general case, to realize an isotope effect greater than unity would seem to connote either a lag of C-2–C-6 bond making behind C-6–C-1 bond making or reductions in other C-6 hydrogen force constants not associated with these two bonds along the reaction coordinate. Thus the deuterium isotope effects at C-6 in solvolysis of *exo*-2-norbornyl brosylate are (a) probably inconsistent with classical theory but (b) not clearly consistent with nonclassical theory. The corresponding effects in solvolysis of the endo isomer seem consistent with classical theory.

A similar dilemma arises in predicting the value of $k_{\text{H}}/k_{\text{D}}$ for solvolysis of **46**-OBs deuterated at C-1. Assuming anchimerically assisted ionization for **46**-OBs, the unfavorable dihedral angle between the C-1 hydrogen and the developing p orbital in the transition state prevents an isotope effect.[21i] For anchimerically assisted solvolysis the changes in each of the force constants associated with the C-1 hydrogen taking place as the reactant is converted to the activated complex must be ascertained. Neglecting the C–H stretching force constant leaves the bending force constants $f_{\text{H–C-1–C-6}}$, $f_{\text{H–C-1–C-2}}$, and $f_{\text{H–C-1–C-7}}$. Nonclassical theory predicts that the C-1–C-6 bond order and, hence $f_{\text{H–C-1–C-6}}$, decreases but does not permit an unambiguous estimate of the direction of change, if any, in the C-1–C-2 and C-1–C-7 bond orders and, hence, in $f_{\text{H–C-1–C-2}}$ and $f_{\text{H–C-1–C-7}}$. *A priori* estimating or *a posteriori* rationalizing $k_{\text{H}}/k_{\text{D}}$ even qualitatively would require knowing both the direction and magnitude of change in $f_{\text{H–C-1–C-2}}$ and/or $f_{\text{H–C-1–C-7}}$ unless $f_{\text{H–C-1–C-2}}$ and/or $f_{\text{H–C-1–C-7}}$ like $f_{\text{H–C-1–C-6}}$ decrease in passing from the reactant to transition state. Nonclassical theory, at least in its present state, is not able to make these predictions.

The data in Table IX reveal that dideuteration at C-3 in **46**-Br and -OBs results in a significantly reduced isotope effect. In contrast the β-effect in solvolysis of **47**-*3,3-d*$_2$-Br and -OBs (Table X) is normal. Schaefer, Dagani, and Weinberg[87f] concluded that the small effect for **46**-*3,3-d*$_2$-Br signified delocalization of the C-1–C-6 electrons in the transition state for solvolysis of *exo*-norbornyl derivatives. Similarly a low β-effect was reported for **46**-*3,3-d*$_2$-OBs,[87g] which has been likewise taken as evidence for anchimerically assisted solvolysis.[87b] The isotope effect for the bromide, $k_{\text{H}}/k_{\text{D}} = 1.09$ (polarimetric) and 1.04 (titrimetric) per two β-*d*, compared to the one for the brosylate, $k_{\text{H}}/k_{\text{D}} = 1.014$, is extraordinary since β-effects for secondary bromides are usually smaller than those for the corresponding arenesulfonates.

The $k_{\text{H}}/k_{\text{D}}$ values for **46**-*3-exo-d*- and **46**-*3-endo-d*-OBs demonstrate that the β-effects in the *3,3-d*$_2$ substrates result principally from the *exo-3-d*.[87h] Murr and Conkling[87h] have discussed the individual effects in terms of the geometric dependence of hyperconjugation.[21h,i] Newman projections along the C-2–C-3 bond show a difference in the dihedral angle, ϕ, between the C-3 hydrogens and the vacant p orbital in the nonclassical (**56**) and classical (**57**) ions.[87h] Solvolysis of tertiary chlorides yields β-effects per D of 1.31 and 1.07 for dihedral angles of 180 (0) and 30°. Since arenesulfonate solvolysis generally exhibits larger β-effects than does chloride solvolysis,[21i,87h] a better estimate for $\phi = 30°$ might be the values for solvolysis of cyclopentyl arenesulfonates;[14a,e,24] *e.g.*, for aqueous ethanolysis of **31**-OBs-*cis-2-d* and *-trans-2-d* the values are 1.153 and 1.180, respectively (Table VI). In **56** H$_{\text{exo}}$ is aligned for maximum hyperconjugation whereas H$_{\text{endo}}$ should contribute minimal stabilization. In **57** both dihedral angles are 30° and hyperconjugative stabilization should be about equal for H$_{\text{endo}}$ and H$_{\text{exo}}$. The isotope effect for **46**-*3-exo-d*-OBs, $k_{\text{H}}/k_{\text{D}} = 1.07$ and 1.11, although appreciable, is less than expected for a dihedral angle approaching 180 (0)°; the minimum value predicted would be *ca.* 1.31. The negligible effect for **46**-*3-endo-d*-OBs is consistent with a dihedral angle of *ca.* 60°. The diminished isotope effect resulting from *exo-d* at C-3, the negligible effect for *endo-3-d*, and the results for the *3,3-d*$_2$ compounds have been taken as consistent with delocalization of the C-1–C-6 σ electrons in the transition state reducing the positive charge at C-2 and, hence, hyperconjugation of the C-3 hydrogens.[87f-h,88b] Charge delocalization and the unfavorable stereochemistry inhibit hyperconjugation for the endo H.[87h] Murr and Conkling[87h] suggest two additional factors besides participation which could account for the diminished effect for **46**-*exo-3-d*-OBs: (1) eclipsing of the leaving group that suppresses hyperconjugative electron release, and (2) steric crowding of the exo-3 pro-



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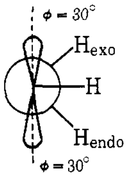

57

ton of **46**-OBs that increases zero-point energy in the transition state.

The data for **47**-*3,3-d*$_2$-Br and -OBs are consistent with solvolysis without participation.[87f–h] In harmony with this conclusion is the similarity between the isotope effects for **47**-*exo-3-d*-OBs and **47**-*endo-3-d*-OBs and those for *cis-2-d* and *trans-2-d* cyclopentyl arenesulfonates. The lower effect for the *endo-3-d* *p*-bromobenzenesulfonate compared to the *exo-3-d* ester has been attributed[87h] to possible hindrance to hyperconjugative electron release and/or steric constraints by the leaving group. Further support for the conclusion that *endo*-norbornyl derivatives solvolyze without participation has been deduced from the β-effects for **48**, **49**, **50**, and **51** (Table XI), which indicate solvolysis for these substrates without participation and charge development at C-2 in the transition state of similar magnitude to that for endo secondary norbornyl derivatives. The 2-phenylnorbornyl cation (**58**) is indicated by nmr analysis to be classical and possess charge dispersal and stabilization similar to that for the 1-phenylcyclopentyl and 1-phenylcyclohexyl cations.[90] The reduced β-effects for **48**-*3,3-d*$_2$ and **49**-*3,3-d*$_2$ are consistent with decreased hyperconjugation resulting from charge dispersal onto the aromatic ring.[19]

The difference between the polarimetrically and the titrimetrically measured isotope effects for **46**-*3,3-d*$_2$-Br may arise from internal return which scrambles the deuterium between C-3 and C-7.[87f] It was deduced that the deuterium effect at C-7 must be vanishingly small.[87f] The lower isotope effect for acetolysis than for aqueous ethanolysis of **46**-*exo-3-d*-OBs and **46**-*3,3-d*$_2$-OBs has been explained by isotopic scrambling to C-7 by internal return.[87h] A range for k_H/k_D of 1.03 to 1.08 has been calculated for *exo*-bicyclo[2.2.1]hept-2-yl-*7,7-d*$_2$ *p*-bromobenzenesulfonate.[87h] The lower isotope effect at C-7 may result from a smaller initial-state zero-point energy of the C-7–H bond or from lack of equivalence of C-3 and C-7 in the transition state.[87h] The isotope effect at C-7 needs to be determined since it cannot be negligible if there is extensive charge dispersal to C-1 in the transition state. Within the framework of nonclassical theory a large effect at C-6 must be shown to be equivalent to the indicated small effect at C-7. On the basis of anchimerically assisted solvolysis the problems attendant in predicting the effect at C-7 are similar to the ones at C-1 and perhaps C-6; *i.e.*, knowledge of changes in that part of the potential function describing the surface involving C-7 is required.

A major inconsistency in the interpretation of the β-effects for **46** through **51** has been recognized.[91] Replacement of the C-2 hydrogen in the nonclassical transition state for *exo*-2-norbornyl derivatives by a 2-methyl or 2-phenyl group provides a sufficient stabilization to significantly reduce or even negate bridging. As we understand the argument, this stabilization of the positive charge results from its delocalization by the methyl *via* hyperconjugation and induction and by the phenyl *via* conjugation with the π electrons. Therefore, to prevent or significantly to reduce bridging in the solvolytic transition states of these tertiary systems would require that charge dispersal from C-2 onto the C-2 substituent be at least as great as delocalization onto C-1 and C-6 in the transition states for these secondary compounds. Assuming anchimerically assisted ionization for **46**, β-effects in the solvolysis of the tertiary substrates *would have been predicted a priori* to be similar to, if not smaller than, those of **46**-Br and -OBs! This prediction is in direct contrast to the experimental results and the previous conclusions drawn from these results. Charge density at C-2 in the transition states of **48** through **51** is indicated as normal and similar to that for **47** (anchimerically unassisted solvolysis). Examination of Dreiding models suggests the absence of steric inhibition of resonance in the 2-phenylnorbornyl cation. An explanation which seems implausible in view of the enormously enhanced solvolysis rates of *endo*-2-methyl- and *endo*-2-phenyl-*exo*-bicyclo[2.2.1]hept-2-yl chlorides ($k_{2\text{-Me}}/k_H$ and $k_{2\text{-Ph}}/k_H$ are *ca.* 10^4 and 10^8, respectively) is that the energies of these tertiary nonclassical cations are greater than those of the corresponding classical ions, which in turn are more energetic than the norbornonium ion. The isotope effects and the nmr data for **58** are qualitatively consistent with "normal" solvolytic transition states for **47** through **51**. Alternatively, the β-effect for **46** does not appear to be explicable by either nonclassical or classical theories.

It has been suggested[92] that elimination from an ion pair competing kinetically with internal return could conceivably account for the large β-effects in solvolysis of **48** and **50**. Unfortunately this effect and other explanations considered by Murr and Conkling[87h] cannot be quantified at the present time.

The available data do indicate a difference in the force constant(s) change associated with the hydrogens at C-2, C-3, and C-6 accompanying conversion of **46** and **47** to their transition states. Such differences are also recognized to exist for the hydrogens at C-6 between **46** and **54** and for the C-3 hydrogens between **46** and **48** through **51**. Unfortunately a precise calculation of these force field changes which would permit deductions about the bonding in the transition states for **46** and **47** and, hence, resolve the vexing problem of the solvolysis mechanism of **46**[11d,93] is presently impossible.

Jerkunica, Borčić, and Sunko[88b] have suggested that anchimerically assisted reactions involve a number of reaction coordinates. At least three different processes are viewed as contributing to neighboring group participation: (1) ionization of the carbon-leaving group bond and development of the positive charge at the reaction center, (2) charge delocalization, and (3) bridging, *i.e.*, bond formation between the neighboring group and the reaction center. For *exo*-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl *p*-toluenesulfonate (**52**-OTs), the fact that the β-effect (k_H/k_D = 1.162 for **52**-*3,3-d*$_2$; see Table XI) is *ca.* half its maximum value was taken to indicate that bridging is not synchronous with C–O bond rupture.[88b] The apparently normal α-effect for **52**-*2-d*-OTs was taken as supporting evidence. For the *exo*-bicyclo[2.2.1]heptyl system bridging was argued[88b] to be more important in diminishing the β-effect than charge delocalization, a conclusion diametrically opposed to that of Schaefer and his coworkers.[87f] Such arguments seem intrinsically unsound. As a solvolytic reaction proceeds the wave function for the reactant state is transformed to the wave function for the product. Hence, the changes in potential energy (electronic, vibrational, and rotational) and kinetic energy must be interrelated and must occur

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(90) D. G. Farnum and G. Mehta, *J. Amer. Chem. Soc.*, **91**, 3256 (1969).

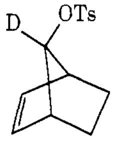
(91) S. E. Scheppele, *Chem. Commun.*, 592 (1971).

(92) I am indebted to Professor Brown Murr for this explanation. This phenomenon is currently under investigation by Professor Murr and his colleagues.

(93) S. Winstein and D. S. Trifan, *J. Amer. Chem. Soc.*, 71, 2953 (1949).

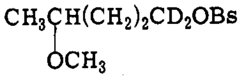
simultaneously. A 1-methyl substituent increases the rate of solvolysis of *exo*-bicyclo[2.2.1]hept-2-yl *p*-toluenesulfonate by a factor of 50.[11d] This rate increase has been taken to indicate participation, the driving force being either formation of a resonance-stabilized nonclassical ion or a Wagner–Meerwein rearrangement producing a tertiary cation.[11d] If in the simplest approximation the α- and β-effects for **52** do not appear to be consistent with such participation, we believe the anomaly should be recognized.

α-Effects have been reported in the solvolysis of *anti*-bicyclo[2.2.1]-5-hepten-7-yl *p*-toluenesulfonate (**59**) and 4-methoxy-1-pentyl *p*-bromobenzensulfonate (**60**).[94] Interpreting the α-effect for acetolysis of **59** is complicated by the uncertainty in predicting the value for solvolysis *via* a "classical" transition state. If a normal value is 1.20–1.22, the *ca.* 40% reduction in the measured effect for **59-7-*d*** is consistent with π-participation as is the enormous rate of solvolysis of **59**.[95] Alternatively the α-effect has been viewed as being only slightly diminished.[94] Again the question needs to be asked: Is the k_H/k_D value for **59-7-*d*** adequately interpreted by considering only the decrease in the HCO bending force constant and increase in the bending force constant which describes the electronic interaction between C-5 and C-6 along the reaction profile? The aqueous ethanolysis of **60** proceeds 99% *via* MeO-5 participation.[96] The α-effect for **60-*2,2-d*₂** supports this conclusion and supports a highly symmetric transition state (see also ref 77a).



59-7-*d*

$k_H/k_D = 1.13$ (HOAc)



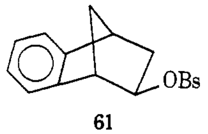
$$\mathrm{CH_3\underset{\displaystyle OCH_3}{C}H(CH_2)_2CD_2OBs}$$

60-*2,2-d*₂

$k_H/k_D = 1.01$ (aqueous C_2H_5OH)

α-Effects have been suggested not to be a sensitive probe for π and σ neighboring group effects[94] and extent of bond cleavage or formation in the rate-controlling step.[87c] A considerable body of data, both experimental and theoretical, would seem to be in disagreement with this latter conclusion; *e.g.*, the opposite conclusion is suggested by the results for azo compound pyrolysis.

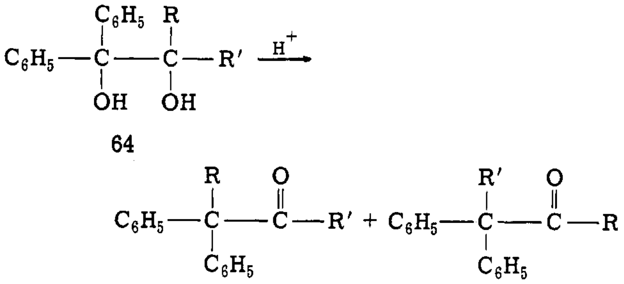
Solvolysis of *exo*-benzobicyclo[2.2.1]hept-2-yl *p*-bromobenzenesulfonate (**61**) proceeds with π-participation.[97] Deuterium isotope effects at C-3 have been reported for **61**, its 7-nitro (**62**), and its 6,7-dinitro (**63**) analogs, and the endo isomers of **61** and **63**.[98] In acetic acid k_H/k_D values per *3,3-d*₂ are 1.05 for **61** at 25°, 1.05 for **62** at 95°, and 1.12 for **63** at 25°. The β-effect for **61** is (a) similar to that for *exo*-norbornyl derivatives and (b) interpreted as evidence of significant π-participation. The increase in the isotope effect with introduction of nitro groups into the aromatic ring has been taken as consistent with diminished π-participation and, hence, increasing hyperconjugative stabilization of the incipient positive charge in the transition state by the exo 3-H. However, in acetolysis of **63** 21% of the product is olefin. That k_H/k_D for **63** may reflect in part elimination either from the substrate or from an intimate ion pair has not apparently been considered by the authors. Interestingly k_H/k_D for *exo-3-d* is *ca.* 1.10 (1.16 after correcting for the SN2 pathway[98]) and *ca.* 1.02–1.03 for the *endo-3-d* compound. It is thus conceivable that the β-effect on ionization is essentially independent of the participatory ability of the aromatic ring; *e.g.*, the rates of acetolysis of **62** and **63** are smaller by *ca.* three and five orders of magnitude than for **61** (see ref 98, Table III). Thus the extent to which an isotope effect on elimination contributes to the overall k_H/k_D needs to be determined.



61

3. *Reactions Involving a 1,2 Migration of Methyl*

Methyl deuterium isotope effects have been reported in the acid-catalyzed rearrangement of 1,1-diphenyl-2-methylpropane-1,2-diol (**64**).[99] The migrational isotope effect was calculated to be 1.195 and 1.214 with CH_3 and CD_3 as the nonmigrating group, respectively. Secondary effects for the nonmigrating methyl are 0.970 and 0.985 with CH_3 and CD_3 as the migrating groups, respectively. The reasonable agreement observed between the two migrational isotope effects and the two nonmigrational isotope effects was taken as good evidence that the rate-controlling and migration steps are identical. The significant migrational isotope effect indicates a loosening of zero-point vibrations in the migrating methyl;[99] *i.e.*, one or more of the force constants associated with the migrating methyl must be smaller in the transition state than in the reactant. The nonmigrational isotope effect indicates that the positive charge in the activated complex is not to be greatly shared with the nonmigrating methyl. As pointed out by Schubert and Le Fevre[99] the isotope effects themselves cannot differentiate between rate-controlling rearrangement of a benzhydryl cation and methyl-assisted heterolysis of the C–OH_2^+ bond.



$R = R' = CH_3$
$R = CH_3; R' = CD_3$
$R = R' = CD_3$

Table XII presents α-, β- and γ-deuterium isotope effects in the solvolysis of 1,2,2-trimethylpropyl *p*-bromobenzenesul-

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[94] R. Eliason, M. Tomič, S. Borčić, and D. E. Sunko, *Chem. Commun.*, 1490 (1968).

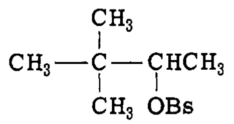
[95] S. Winstein and M. Shatavsky, *J. Amer. Chem. Soc.*, **78**, 592 (1956).

[96] E. L. Allred and S. Winstein, *ibid.*, **89**, 3991 (1967).

[97] For leading references, see (a) P. D. Bartlett and W. P. Giddings, *ibid.*, **82**, 1240 (1960); (b) H. Tanida, *Accounts Chem. Res.*, **1**, 239 (1968); (c) H. C. Brown and G. Tritle, *J. Amer. Chem. Soc.*, **90**, 2689 (1968); (d) H. Tanida, T. Iric, and T. Tsushima, *ibid.*, **92**, 3404 (1970).

[98] H. Tanida and T. Tsushima, *ibid.*, **93**, 3011 (1971).

[99] W. M. Schubert and P. H. Le Fevre, *ibid.*, **91**, 7746 (1969).



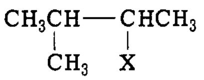
$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OBs}{CH}CH_3$

65

fonate (**65**).[99,100] The two sets of γ-d_9 effects are judged to be essentially equivalent within the limits of experimental precision. The negligible γ-d_9 effect for **65** has been generally[99,100] but not definitively[99] interpreted as evidence against rate-controlling synchronous methyl migration. However, the γ-d_9 effects alone might be insufficient to distinguish between a transition state possessing a strong bond between C-2 and C-3 and a weak bond between C-1 and C-3 and one possessing a strong bond between C-1 and C-3 and a weak bond between C-2 and C-3. However, the latter transition state appears to be ruled out by the α-effect at C-1 and the β-effect at the 1-methyl. Both the α-d and β-d_3 effects for **65** are less than the limiting values of 1.22 and 1.46 and have been taken to indicate some nucleophilic bonding of the leaving group in the transition state.[100]

4. The Role of Hydrogen Participation in Solvolytic Reactions

Kinetic isotope effects have been utilized in probing for hydrogen participation in the solvolysis of the *p*-toluenesulfonic and methanesulfonic esters of 3-methyl-2-butanol. Solvolysis of **66**-*3-d*-OTs at 25° in 80% aqueous ethanol, acetic acid, and



$CH_3\underset{CH_3}{CH}-\underset{X}{CH}CH_3$

66 X = OTs; X = OMs

formic acid yields k_H/k_D ratios of 2.14, 2.26, and 2.25.[101] Hydrolysis of **66**-*3-d*-OMs yields k_H/k_D = 2.25 at 25°.[102] These effects are much larger than ordinary β-effects and, hence, are indicative of hydrogen participation. Acetolysis of **66**-OTs yields 30% acetates and 70% olefins.[101] Hydrolysis of **66**-OMs yields 94% 3-methyl-2-butanol and 6% 2-methyl-2-butene.[102] Shiner[45a] has concluded the 2-methyl-2-butene, 2-methyl-1-butene, and the 1,1-dimethylpropyl acetate are formed from the 1,1-dimethylpropyl cation. This intermediate nicely accounts for the products in hydrolysis of **66**-OMs. Shiner[45a] argues that in the acetolysis of **66**-OTs hydrogen migration is synchronous with ionization rather than occurring from an ion pair. The reduced β-effect for **66**-*1*-d_3-OTs (k_H/k_D = 1.07) is suggestive of participation.[103] Replacement of the six γ-hydrogens by deuteriums yields a k_H/k_D ratio of 1.00 ± 0.01.[103] This result is similar to the one obtained for the nonmigrating methyl group in the acid-catalyzed rearrangement of **64** and indicates that an appreciable orbital vacancy does not develop at C-3 in the transition state. The α-effect, k_H/k_D = 1.178, observed in the trifluoroethanolysis of the *p*-bromobenzenesulfonic ester[104] is not simple to rationalize. Surprisingly, it has been suggested[45a] without any attempt at justification that hydrogen participation increases the α-effect.

Table XII

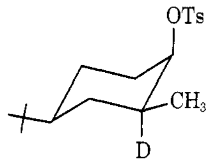
Deuterium Isotope Effects in the Solvolysis of 1,2,2-Trimethylpropyl *p*-Bromobenzenesulfonate

Solvent	*Temp, °C*	*k_H/k_D for* α-d	β-d_3	γ-d_9
97% CF_3CH_2OH	25	1.153[a]	1.188[a]	1.011[a]
70% CF_3CH_2OH	25	1.152[a]	1.205[a]	
50% C_2H_5OH	25	1.159[a]	1.205[a]	1.003[a]
43.32% C_2H_5OH	40			0.979 ± 0.017[b]
95% CF_3CO_2H				0.986 ± 0.014[b]

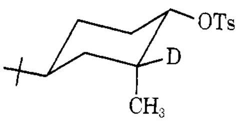
[a] Reference 100. [b] Reference 99.

In the 50% aqueous ethanolysis of *cis*-4-*tert*-butylcyclohexyl *p*-bromobenzenesulfonate (**67**) Shiner and Jewett[105] observed apparent isotope effects of 1.436 and 1.096 for one axial and one equatorial β-deuterium, respectively. For the diaxial monoequatorial deuterated compound **67**-*a,a,e*-d_3 k_H/k_D = 2.565. Clearly k_H/k_D for axial deuterium is hypercumulative since the rate retardation caused by 2,6-diaxial deuterium exceeds the square of that caused by monoaxial deuterium (2.565/1.096 = 2.339 > 2.062 = 1.436^2). It is suggested[105] that neighboring group participation by one axial β-deuterium atom occurs leading to an unsymmetrically bridged intermediate. However, the major product in solvolysis (86%) is 4-*tert*-butylcyclohexene. Contrary to the original report[105] β-tetradeuteration of **67** has been found[106] to reduce the olefin yield to 77%. Interestingly some elimination appears to proceed by loss of the α-hydrogen apparently after β-hydrogen migration.[45a] The large α-effect[105], k_H/k_D = 1.202, is difficult to reconcile with anchimerically assisted ionization. As pointed out[45a] an anchimerically unassisted mechanism involving partitioning of an ion pair between elimination, substitution, return, and possibly a 1,2 hydride shift would also account for the results.

β-Deuterium isotope effects have been reported in the aqueous ethanolysis of isomeric 4-*tert*-butyl-2-methylcyclohexyl *p*-toluenesulfonates at 40°.[107] For **68** through **71** the



68



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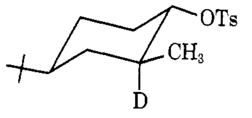

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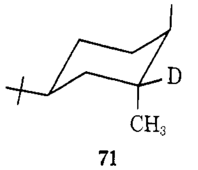

71

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(100) V. J. Shiner, Jr., R. D. Fisher, and W. Dowd, *J. Amer. Chem. Soc.*, **91**, 7748 (1969).

(101) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958).

(102) Y. Inomoto, R. E. Robertson, and G. Sarkis, *Can. J. Chem.*, **47**, 4599 (1969).

(103) Unpublished results of S. Winstein and J. Takahashi cited in ref 45a.

(104) Unpublished results of M. A. Kessick and V. J. Shiner, Jr., cited in ref 45a.

(105) V. J. Shiner, Jr., and J. G. Jewett, *J. Amer. Chem. Soc.*, **87**, 1382 (1965).

(106) Unpublished results of J. G. Jewett and V. J. Shiner, Jr., cited in ref 45a.

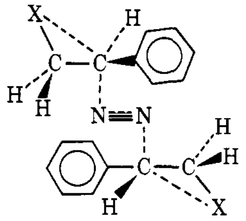
(107) M. Tichý, J. Hapala, and J. Sicher, *Tetrahedron Lett.*, 3739 (1969).

values of k_H/k_D are 2.08, 1.96, 1.19, and 1.15, respectively. For **70** and **71** the isotope effects are similar to the β-effects in solvolysis of cyclopentyl derivatives. For **68** and **69** the isotope effects, which are significantly greater than those normally attributed to hyperconjugative effects, were interpreted[107] along with other evidence[108] as favoring participation by the C-2 hydrogen. For **69** to achieve an anti periplanar arrangement of the C–O and C–D bonds requires reaction *via* a nonchair transition state. In view of the complexity of the products in acetolysis it is disconcerting that the products and their distribution were not determined for aqueous ethanolysis of the unlabeled and labeled esters. In acetic acid a greater proportion of products arises *via* a 1,2-hydrogen rearrangement for **68** and **69** than for **70** and **71**. However, it is not obvious that the product distribution is simply explained in terms of a hydrogen-bridged cation. If ion pairs intervene it would seem that at least in acetic acid all intermediates are not common to the solvolysis mechanism for each ester. Conceivably in ethanolysis of **68** and **69**, but not for some reason from **70** and **71**, k_H/k_D reflects in part hydride transfer in the first formed ion pair. Thus the available data are insufficient to provide a satisfactory interpretation of the isotope effects.

The isotope effects for the "participating" hydrogen are in the range of the primary isotope effects reported for intramolecular 1,2-hydride shifts,[109] *i.e.*, k_H/k_D = 1.5–3.0. In general, these isotope effects are lower than the maximum value expected for equal amounts of bond making and bond breaking[29,110] for a linear three-centered activated complex for hydrogen transfer. Unless the C–H bending rather than stretching force constant is the one principally altered in passing from the reactant to activated complex,[111] it seems questionable that a symmetrical (in the sense of bond orders) activated complex for a 1,2-hydride shift would yield a primary deuterium isotope effect of 2–3. Theoretical studies of the relationship between the magnitude of k_H/k_D and the extent of bond making and bond breaking for 1,2-hydride shifts would be helpful.

B. FREE RADICAL REACTIONS

The only instances where α-effects have been discussed in terms of anchimeric assistance to bond homolysis appear to be in the thermal decompositions of 1,1′,2,2′-tetraphenylazoethane[32] (**8**) and 2,2′-dimethoxy-1,1′-diphenylazoethane (**10**).[33] Anchimerically assisted homolysis of *meso*- and *dl*-**8** and **10** is viewed as proceeding *via* **72** and **73**, respectively. Although consistent with anchimeric assistance the α-effects for *meso*- and *dl*-**8** seem adequately interpreted in terms of a hindered reactant conformation (see section III.A.1). Decomposition *via* **73** is one of several possible interpretations of the low α-effect, k_H/k_D = 1.194, for **10**. However, it is to be emphasized that a choice among possible interpretations is pure speculation at present.



72, $X = C_6H_5$
73, $X = CH_3O$

If anchimeric assistance is assumed for decomposition of **8** and/or **10**, the α-effects indicate that the electronic interaction between the incipient odd electron at C-2 and phenyl in **72** and/or oxygen in **73** is weak.

V. Summary

Since this review is intended to be critical rather than comprehensive, the author wishes to apologize to those investigators whose work has not been cited.

Kinetic isotope effects have generally proven to be useful in elucidating gross details of reaction mechanisms. In a number of cases it has proven possible to develop a qualitatively consistent viewpoint of mechanism from isotope effects for isotopic substitution at various molecular positions. However, for many reactions, not all of which are involved in the nonclassical controversy, it is difficult if not impossible to formulate a decisive interpretation of a single kind or several kinds of isotope effects. Isotope effects confirm the presence of anchimeric assistance in some reactions. In many instances an interpretation of the data based upon an extension of equivalent isotope effects in nonanchimerically assisted reactions is less than satisfactory.

To the extent that absolute reaction rate theory is valid, the problems in interpretation do not reside in an inadequate theory of kinetic isotope effects. Rather organic reactivity theory is insufficient to provide a precise estimate of the quantities in the theory which are required to calculate or even estimate a given isotope effect.

Seltzer and Mylonakis and Willi and Won have elegantly demonstrated that significant and quantitative structure–reactivity (mechanistic) information is accessible upon coupling isotope effects with calculations in the spirit of Wolfsberg and Stern. The intrinsic power of this technique for probing in detail the reaction energetics of large molecules justifies its broad application. If the technique is found to be generally useful, a new frontier in kintic isotope effect research is opened.

Acknowledgment. The author wishes to thank Professor O. C. Dermer for comments pertinent to manuscript preparation and Professors L. M. Raff and J. P. Devlin for stimulating discussions.

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(110) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

(111) M. F. Hawthorne and E. S. Lewis, *J. Amer. Chem. Soc.*, **80**, 4296 (1958).