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DEUTERIUM ISOTOPE EFFECTS AND HYPERCONJUGATION

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Abstract– There now exists ample published evidence which indicates that reactions with rate-determining steps which involve carbonium ion or partial carbonium ion formation are slowed by the substitution of a deuterium atom for a hydrogen atom in a hyperconjugating position. In each of the several cases where data are available it seems that the isotope *rate* effect is paralleled by an isotope *activation energy* effect although entropy factors also contribute. It seems fairly clear from theory that the isotope activation energy effects can only arise from (a) changes in vibration frequency of the hydrogen and deuterium atoms on activation, (b) tunnelling of the hydrogen atom or (c) anharmonicity effects. The second effect must be unimportant in these reactions although it might be a major factor in reactions where hydrogen bonds are directly broken. Several lines of evidence indicate that anharmonicity effects although small are present and may confuse the quantitative interpretation of the isotope rate effects. Thus the interpretation of secondary isotope rate effects is complicated but the application of the time-honored classical organic chemical method of comparing the effects in a large number of different compounds indicates that hyperconjugation is the predominant cause of these secondary isotope rate effects. If we further assume that the variations in these effects in closely related compounds are due to variations in hyperconjugation, the following conclusions are tentatively indicated: (1) There are steric effects on hyperconjugation. (2) There are substituent effects on hyperconjugation; conjugating and hyperconjugating substituents increase the extent of hyperconjugation of a single C–H bond. (3) There are solvent effects on hyperconjugation.

IT has been known for several years that the replacement of hydrogen in a hyperconjugating position by a deuterium atom generally leads to a diminution in the rate of carbonium ion-type reactions. The author's studies of these phenomena have been concerned with the solvolysis rates of β-deutero-*tert.*-alkyl chlorides,[1, 2, 3] *p*-(α-deuteroalkyl)diphenylmethyl chlorides[4] and α-deuteroketals.[5]

Similar systems which have been studied by other workers include the solvolysis of (1) β-deutero-2-pentyl chlorosulfite, tosylate and bromide,[6] (2) *cis*- and *trans*-β-deutero*cyclo*pentyl tosylates,[7] (3) β-deutero-β-phenethyl tosylate,[8] (4) 1-chloro-1-(*p*-methylphenyl)ethane-2,2,2-d_3 (methyl-*p*-tolycarbinyl chloride) and its *p*-methyl-d_3 analog.[9]

The present paper will briefly review with deductions from the absolute rate theory the possible origins of these isotope effects; critically examine the rather extensive experimental data now available in order to empirically assess in a qualitative fashion

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[1] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **75**, 2925 (1953).
[2] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **78**, 2653 (1956).
[3] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **76**, 1603 (1954).
[4] V. J. Shiner, Jr. and C. J. Verbanic, *J. Amer. Chem. Soc.* **79**, 373 (1957).
[5] V. J. Shiner, Jr. and Sally Cross, *J. Amer. Chem. Soc.* **79**, 3599 (1957).
[6] E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.* **74**, 6306 (1952); *Ibid.* **76**, 795 (1954).
[7] A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Amer. Chem. Soc.* **80**, 2326 (1958).
[8] W. H. Saunders, Jr., S. Asperger and D. H. Edison, *Chem. & Ind.* 1417 (1957).
[9] E. S. Lewis and G. M. Coppinger, *J. Amer. Chem. Soc.* **76**, 4495 (1954).

the relative importance of the several theoretically possible origins and interpret the meaning of these data with respect to some of the problems of hyperconjugation.

Although several others considered the problem earlier, the most extensive theoretical treatments of the effects of isotopic substitution on reaction rate have been made by Bigeleisen[10] and Melander.[11] Each of these authors examined the effects of changing nuclear mass on the parameters in the equation derived from the "theory of absolute rates" and, although the two treatments differ in some details, the results are equivalent. The equation derived by Bigeleisen for the isotope effect may be expressed as follows, neglecting tunnelling:

$$k_H/k_D = K_H/K_D\left(\frac{m_D^*}{m_H^*}\right)^{\frac{1}{2}} \cdot \frac{s_H/s_D}{s_H^{\ddagger}/s_D^{\ddagger}} \cdot \prod_i \frac{u_i^{\ddagger}{}_H/u_i^{\ddagger}{}_D}{u_{iH}/u_{iD}}$$

$$\prod_i \frac{e^{(u_iH - u_iD)/2}}{e^{(u_i^{\ddagger}H - u_iD^{\ddagger})/2}} \cdot \prod_i \frac{(1 - e^{-u_iH})(1 - e^{-u_iD})^{-1}}{(1 - e^{-u_iH^{\ddagger}})(1 - e^{-u_iD^{\ddagger}})^{-1}}$$

where K represents the transmission coefficient, m^* the effective mass of the molecule along the reaction co-ordinate and s the symmetry numbers. Subscripts H and D refer to values for the hydrogen and deuterium compounds, respectively, and the superscript $\ddagger$ refers to values for the transition state; values with no superscript refer to the initial state. u_i is defined as $h\nu_i/kT$, where h and k are Planck's and Boltzmann's constants, and ν_i is a molecular vibration frequency. The transmission coefficient ratio may be taken as unity and the symmetry number ratio as unity. Since the reactions under discussion in this paper all involve motions of larger atoms, such as halogen or carbon, the effective reaction mass ratio must be very nearly unity as well. Because the vibrations are assumed to be harmonic and the force constants are equal for both hydrogen and deuterium compounds, $u^{\ddagger}{}_{iH}/u^{\ddagger}{}_{iD} = u_{iH}/u_{iD}$ and the ratio of these quantities is unity. The isotope effect is then determined essentially exclusively by the last two product factors. The first of these is the zero-point energy term. The second is due to factors coming into play when vibrational levels higher than the zeroth one are occupied and is relatively unimportant at temperatures at or below room temperatures and frequencies of 1000 cm^{-1} or higher where the higher levels are not utilized. Bigeleisen[10] also derived an equation expressing the activation-energy difference between isotopic molecules which may be written, neglecting the temperature coefficient of the transmission coefficient and tunnelling, as:

$$E_H - E_D = \sum_i \left[\frac{e^{u_i}(u_i - 1) + 1}{(e^{u_i} - 1)^2} - \frac{1}{2}\right] h(\nu_{iH} - \nu_{iD})$$
$$- \sum_i \left[\frac{e^{u_i^{\ddagger}}(u_i^{\ddagger} - 1) + 1}{(e^{u_i^{\ddagger}} - 1)^2} - \frac{1}{2}\right] h(\nu^{\ddagger}{}_{iH} - \nu^{\ddagger}{}_{iD})$$

at reasonably high values for ν and low values for T:

$$E_H - E_D \approx \sum_i \left[\frac{u_i - 1}{e^{u_i}} - \frac{1}{2}\right] h(\nu_{iH} - \nu_{iD}) - \sum_i \left[\frac{u_i^{\ddagger} - 1}{e^{u_i^{\ddagger}}} - \frac{1}{2}\right] h(\nu^{\ddagger}{}_{iH} - \nu^{\ddagger}{}_{iD})$$

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[10] J. Bigeleisen, *J. Chem. Phys.* **17**, 675 (1949).
[11] L. Melander, *Arkiv Kemi* **2**, 211 (1950).

If ν_i is high or T low, the first term in each of the brackets is very nearly zero and the activation-energy difference is due to the difference in the zero-point energy differences in the initial and transition states. If ν_i is low or T high, occupation of the excited vibrational levels becomes significant and the first term in the brackets in each case becomes significant relative to 1/2 and the activation energy is not exactly equal to the difference in the differences in zero-point energies. However, it is important to note that if the frequencies of vibration ν_i do not change on activation ($\nu_i = \nu^{\ddagger}_i$ and $u_i = u^{\ddagger}_i$) then there can be no difference in activation energies between hydrogen and deuterium compounds. Therefore if it is known that deuterium substitution causes a higher activation energy one can be certain that it is due to (1) a lowering of one or more vibration frequencies involving the isotopic atom in the transition state, (2) anharmonicity or tunnelling effects neglected in the above treatment or, much less likely, (3) a temperature coefficient of the transmission coefficient ratio. It also seems impossible that tunnelling effects would be important in those reactions which do not involve C–H bond rupture. Thus an observed isotope activation energy effect means, with the possible exception of anharmonicity effects discussed below, that the vibration frequencies of the isotopic atom change in going to the transition state. This could be due to either bond strength changes or to changes in non-bonding interactions. Bond strength changes may be due either to inductive or hyperconjugative interactions of the isotopic bond with the reaction center. Thus the developing carbonium ion center can withdraw electrons from an adjacent C–H bond, making this bond weaker in the transition state. The bond will therefore have a lower vibration frequency in the transition state and substitution of D for the H will cause the rate to be slower.

Halevi[12] observed that the acid ionization constants of α-dideuterophenylacetic acid and α-dideuterobenzylammonium ion were smaller than those of their protium analogues and suggested that this apparent greater electron release by the C–D bond than the C–H bond is due to anharmonicity and a resulting slight disparity in the mean configurations of the C–H and C–D bonds. These results could be due to the effect suggested or to an inductive effect on the vibration frequencies.[7] More convincing evidence of the role of anharmonicity on the relative ground state electron releasing abilities of C–H and C–D bonds has been given by Tiers,[13] who reports that nuclear magnetic resonance shifts indicate that the fluorine nuclei of the CF_2H group of CF_3–CF_2–CF_2H are less shielded than the corresponding nuclei in CF_3CF_2–CF_2D. Streitwieser[14] has pointed out that the observation of optical activity due solely to differences between D and H, in, for example, CH_3–CH_2–CH_2–CHD–OH,[15] must be due to anharmonicity effects. However, it is difficult to extrapolate from these latter observations and predict what kinetic or equilibrium constant effects should result from such anharmonicity influences. A rather complete theoretical treatment of the isotope effect in the trideuteroacetic acid–trideuteroacetate ion equilibrium, neglecting anharmonicity, should be possible. If this corresponds nearly to the observed values, as Streitwieser[7] suggests is probable, then anharmonicity effects could be judged to be correspondingly small. As Lewis has pointed out in his paper delivered at this Conference, these secondary isotope effects due apparently to inductive interactions are

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[12] E. A. Halevi, *Tetrahedron* 1, 174 (1957).

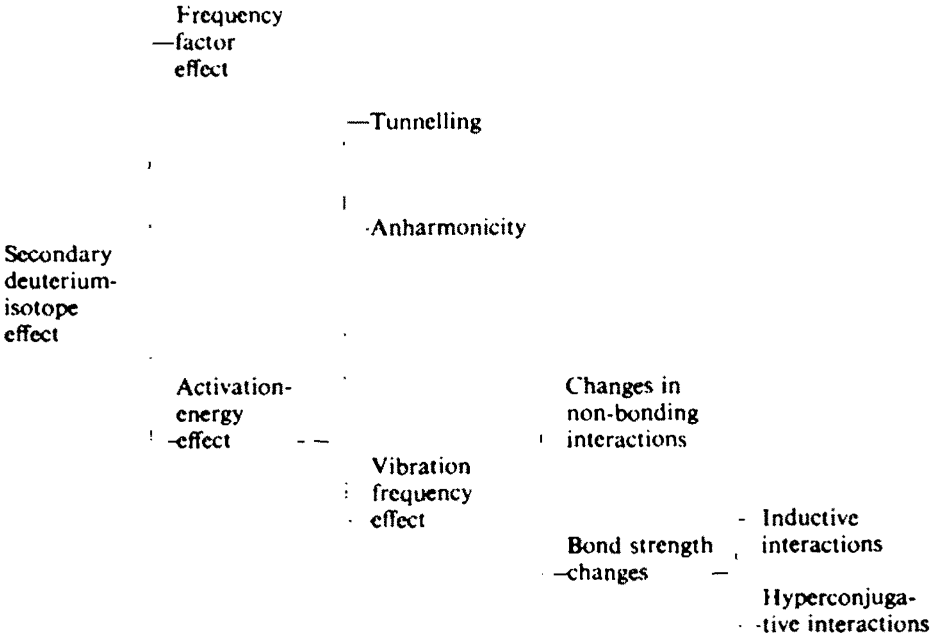
[13] G. V. D. Tiers, *J. Amer. Chem. Soc.* 79, 5585 (1957).

[14] A. Streitwieser, Jr., personal communication.

[15] A. Streitwieser, Jr., *J. Amer. Chem. Soc.* 75, 5014 (1953).

in the direction which make $k_H/k_D < 1$ in the solvolytic reactions and therefore could not alone explain those results.

The origin of the isotope effects as predicted from the theory reviewed in the discussion above are outlined in the following chart:



It can be seen in the above chart that the connection between hyperconjugation and the deuterium-isotope rate effect is a long and complicated one which traces the line along the bottom of the chart from left to right. Isotope activation energy effects due to substitution of deuterium for hydrogen in a hyperconjugating position have been measured for three carbonium ion solvolysis reactions.[3, 4, 9] These values are given in Table 1.

TABLE 1. ISOTOPE ARRHENIUS PARAMETER EFFECTS IN SOLVOLYSIS REACTIONS

Compound	$Ea(D)$-$Ea(H)$	$\log A_D/A_H$
$(CH_3)_2CD$-$CCl(CH_3)_2$*	580	0·32
p-CD_3-C_6H_4-$CHCl$-C_6H_5†	100	0·075
p-CD_3-C_6H_4-$CHCl$-CH_3‡	155	0·084

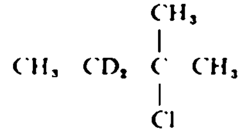
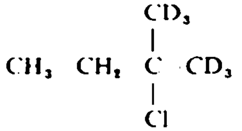
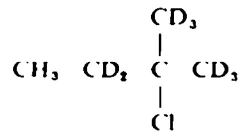
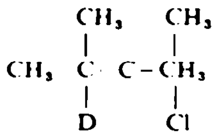
* Ref. 3. † Ref. 4. ‡ Ref. 9.

The results in the first entry in Table 1 are probably more reliable than the other two. Two main conclusions can be reached from the data. First the secondary isotope effects under study are caused in large part by an activation energy effect and secondly the proportion of the total effect due to the activation energy effect seems to be reasonably constant. Thus the comparison available suggests that in a related series of reactions the isotope rate effects are parallelled by isotope activation energy effects.

Tunnelling effects in these reactions must certainly be small. Similarly changes in non-bonding interactions at the β hydrogens must be small because the only nuclei changing their positions appreciably are at least two atoms removed and the hydrogens on the β positions do not appear from models to be crowded.

Thus the only three remaining effects which might influence the activation energy are anharmonicity, inductive interactions and hyperconjugative interactions. From Halevi's and Lewis's results combined anharmonicity and inductive effects seem to be present, but they are apparently considerably smaller than the total effects observed in the solvolysis reactions and in the opposite direction. Lewis, in his paper delivered at this Conference, has examined extensively by comparing examples of observed secondary isotope effects in a wide range of reactions the connection between hyperconjugation and secondary isotope effects and has concluded that hyperconjugation is one of the important sources of isotope effects. In the remainder of this paper the argument will be pushed a step further and some secondary isotope effect results will be used in a tentative exploratory attempt to study hyperconjugation. The important qualifying assumption that will be used is that the relative magnitudes of the secondary isotope rate effects in the closely related reactions being compared reflect the relative degree of hyperconjugative release of electrons from the isotopically substituted bonds. One important point which needs to be emphasized is that, even if this assumption is true, what is obtained is the relative degree of hyperconjugative electron release from the bonds isotopically substituted and not of the entire group. This limitation takes on added significance now that a number of important papers at this Conference have emphasized that C C hyperconjugation may and probably does have an importance comparable to C–H hyperconjugation.

TABLE 2. TERTIARY ALKYL CHLORIDE SOLVOLYSES "80%" AQ. ALCOHOL, 25°

	 $\mathrm{CH_3\ CD_2\ }\underset{\underset{\mathrm{Cl}}{\vert}}{\overset{\overset{\mathrm{CH_3}}{\vert}}{\mathrm{C}}}\mathrm{\ CH_3}$	 $\mathrm{CH_3\ CH_2\ }\underset{\underset{\mathrm{Cl}}{\vert}}{\overset{\overset{\mathrm{CD_3}}{\vert}}{\mathrm{C}}}\mathrm{\ CD_3}$
k_H/k_D	1·40*	1·77*
	 $\mathrm{CH_3\ CD_2\ }\underset{\underset{\mathrm{Cl}}{\vert}}{\overset{\overset{\mathrm{CD_3}}{\vert}}{\mathrm{C}}}\mathrm{\ CD_3}$	 $\mathrm{CH_3\ }\underset{\underset{\mathrm{D}}{\vert}}{\overset{\overset{\mathrm{CH_3}}{\vert}}{\mathrm{C}}}\ \underset{\underset{\mathrm{Cl}}{\vert}}{\overset{\overset{\mathrm{CH_3}}{\vert}}{\mathrm{C}}}\mathrm{-CH_3}$
k_H/k_D	2·35*	1·28†

* Ref. 1. † Ref. 3.

The results summarized in Table 2 show that the β-deuterium rate effect is cumulative as one, two or three of the alkyl groups are deuterated. The results of Streitwieser[7] summarized in Table 3 show in addition that increasing deuteration of a single alkyl group increases the rate effect proportionately. These results are of course consistent with an interpretation based either on inductive or hyperconjugative interactions but more importantly form the basis for dividing the rate effects subsequently quoted into effects per deuterium atom. These are sometimes given as $\Delta\Delta F_a$ per deuterium atom which is $(RT/n)\ \ln\ (k_H/k_D)$, where n is the number of deuterium atoms in the deuterated compound or position. By using this method of presentation, the data given in Table 2 can be re-stated as in Table 4 to indicate that methyl substitution on the β carbon carrying a deuterium atom increases the isotope effect.

TABLE 3. ACETOLYSIS OF *cyclo*PENTYL TOLUENESULFONATES, 50°*

Alkyl toluenesulfonate	k_H/k_D
*trans-cyclo*Pentyl-2-*d*	1·16
*cis-cyclo*Pentyl-2-*d*	1·22
*cyclo*Pentyl-2, 2, 5, 5-d_4	2·06

* Ref. 7.

TABLE 4. TERTIARY ALKYL CHLORIDE SOLVOLYSES "80%" AQ. ALCOHOL, 25°*

Group	$\Delta\Delta F_a$ of deuteration	$\Delta\Delta F_a$ per D
CD_3–	168	56
CH_3–CD_2–	190	95
$(CH_3)_2$–CD–	156	156

* Refs. 1 and 3.

TABLE 5. ACID-CATALYZED HYDROLYSIS OF α-DEUTEROKETALS "90%" AQ. DIOXAN, 25°*

Diethyl ketal of	k_H/k_D	Total obs. $\Delta\Delta F_a$	$\Delta\Delta F$† corr.	$\Delta\Delta F_a$‡ per D	$\Delta\Delta F_a$‡ in group
Acetone-d_6	1·12	67·2	82·5	14	CD_3
Methyl ethyl ketone-α-d_5	1·15	83·0	102·6	30	·CD_2-CH_3
Methyl *iso*propyl ketone-α-d_4	1·11	61·9	93·5	51	$CD(CH_3)_2$
Phenoxyacetone-α-d_5	1·25	132	156·0	57	-CD_2 O-Ø

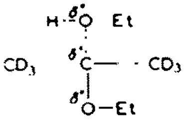
* Ref. 5.

† Corrected to 100% deuteration.

‡ In group other than methyl assuming that the rate effect of deuteration of the methyl group is constant in the series.

Data on the effects of α-deuterium substitution on the rates of hydrolysis of ketals[5] are summarized in Table 5. In the fifth vertical column these data are broken down, assuming that the effect due to deuteration of the methyl group is the same in each compound, into $\Delta\Delta F_a$ values per D atom in each of the different groups.

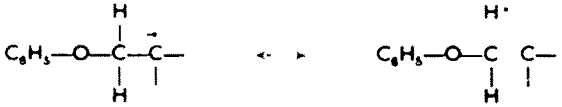
The first conclusion possible is that the isotope effects in these reactions are less than those observed in the solvolysis of β-deutero-*tert*.-alkyl chlorides. This is presumably due to the smaller degree of vacancy at the carbonium ion center in the transition state which is partially reduced by resonance with the attached oxygen. Thus the transition state approaches a carbonium–oxonium ion hybrid represented by the following structure:



Secondly, we see that the rate effect per D atom varies depending on whether the deuterated group is methyl, ethyl or *iso*propyl in the same general way as was observed in the alkyl chloride solvolyses. In addition the rate effect of deuteration of the phenoxymethyl substituent is large. Therefore β substitution of either methyl or phenoxy groups increases the magnitude of the β-deuterium isotope effect. Since the methyl group is an inductive electron releaser while the phenoxy group is an inductive electron attractor, it would seem that the similar effects of the two groups on the isotope rate effect would be related to their conjugative electron-releasing powers, which operate in the same direction for both but to a greater extent in the phenoxy group. If the isotope rate effects are to be attributed to hyperconjugation, it seems reasonable to attribute the substituent influences on the isotope effects as being due to their stabilizing influences on the hyperconjugating resonance contributing forms:

(I) (Ia)

(II) (IIa)



(III) (IIIa)

Thus, owing to the known stabilizing influence of methyl and oxygen substituents on double bonds, (IIIa) should contribute more to the structure of (III) than (IIa) does to (II), and (IIa) to (II) more than (Ia) does to (I). Therefore the extent of β-C-H hyperconjugation would be (III) > (II) > (I). This is just the order observed in the isotope rate effects.

Further substituent influences on the isotope rate effects have been tabulated in Table 6.[3, 16] Here a single β-alkyl substituent in a tertiary alkyl chloride is varied from methyl to ethyl to *iso*propyl to *tert.*-butyl and the effect of deuteration of both the β-methylene group and a β-methyl group on the solvolysis rate is given.

TABLE 6. TERTIARY ALKYL CHLORIDE SOLVOLYSES "80%" AQ. ALCOHOL, 25°*

R	k_H/k_D for $R\text{--}CH_2\text{--}\underset{Cl}{\overset{CH_3}{C}}\text{--}CD_3$	k_H/k_D for $R\text{--}CD_2\text{--}CCl(CH_3)_2$
Me	1·34	1·40
Et	—	1·37
$\mathrm{Pr^i}$	1·34	1·44
$\mathrm{Bu^t}$	1·40	1·08

* Refs. 3 and 16.

The first column of numbers shows the fairly constant rate effect of methyl deuteration as the halide structure is changed. The difference between 1·34 and 1·40 is just on the borderline of the combined experimental error in these rate measurements and may not be significant. Similarly the vertical column of entries on the right shows the constancy of the effect of methylene deuteration on the rate until the last member where the effect is smaller by a factor of about five. This remarkable absence of an isotope rate effect in the solvolysis of 2-chloro-2,4,4-trimethylpentane-3,3-d_2 has been attributed to the operation of severe crowding in this highly branched structure which prevents the β-C-D or β-C-H bonds of the methylene group from adopting a transition state conformation favorable to their hyperconjugation with the carbonium ion center. It is believed that this steric inhibition of the isotope rate effect provides a striking example of the connection between the isotope rate effects and hyperconjugation and simultaneously important evidence for the concept of steric inhibition of hyperconjugation of a given pair of C-H bonds. It should be noted that, if C-C hyperconjugation is important, the C_3-C_4 bond should be in an optimum configuration for the operation of this effect and the *neo*pentyl group might still show appreciable overall hyperconjugative electron-releasing ability. Saunders has recently observed an interesting confirmation of this effect in the absence of a β-deuterium isotope effect in the solvolysis of β-dideutero-β-phenylethyl tosylate.[8] Here the transition state configuration is apparently fixed by participation of the β-phenyl group. This effect leaves the β-C-H or C-D bonds in a poor conformation for hyperconjugation, as shown in the Newman projection formula on the right:

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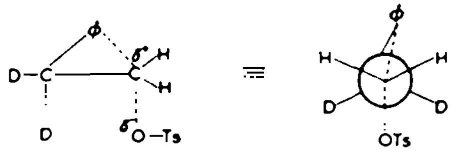
[16] V. J. Shiner, Jr., unpublished results.



The results of a series of experiments on the isotope effects on solvolysis rates of *p*-deuteroalkylbenzhydryl chlorides[4] are summarized in Table 7. These constants were carefully measured and the rate ratios should be accurate to ±1 per cent.

TABLE 7. *p*-DEUTEROALKYLBENZHYDRYL CHLORIDES SOLVOLYSES "80%" AQ. ACETONE, 0°*

p-Alkyl group	k_H/k_D
CD_3–	1·06
CH_3–CD_2–	1·025
$CH_3\text{–}\underset{\displaystyle CH_3}{\underset{\vert}{CH}}\text{–}CD_2\text{–}$	1·020
$(CH_3)_2CD$–	1·006

* Ref. 4.

The first thing that is noticed is that the isotope effects still operate from a spot which is in a position to hyperconjugate through unsaturated linkages with the reaction center. Thus there must be no changes in non-bonding interactions at this remote site on activation and this factor mentioned above is additionally discounted. Lewis[9] has reported similar effects in *p*-tolylmethylcarbinyl chloride and has in addition observed a very small negative isotope effect ($k_H/k_D < 1$) in *m*-tolylmethylcarbinyl chlorides deuterated in the *meta*-methyl position. Thus the absence of the characteristic isotope effect in the *meta* position and its presence in the *para* position argue strongly that hyperconjugation is a dominant factor in promoting such rate effects. It is to be noted additionally that these *p*-deuteroalkyl effects do not show the same relative orders of magnitude characteristic of the β-deuterium effects. Thus the effect per CD is largest in the methyl, next largest in the ethyl and essentially nil in the *iso*propyl group. These results are suggestive of the operation of some steric hindrance to hyperconjugation in the ethyl, *iso*butyl and *iso*propyl groups. This might be expected to be more important when the alkyl groups are attached to a benzene ring than when they are attached to a carbonium ion because the *ortho*-hydrogens are pointing in a fixed direction out in the plane of the benzene ring. In addition there is less energy gained from hyperconjugation from the remote position and less driving force tending to overcome any steric hindrance to the most favorable conformation. It should be pointed out that the isotope effect would be a measure only of the final situation achieved not mitigated by energy expense necessary to achieve it.

Lastly, several sets of experiments indicate that there are important solvent effects on the β-deuterium and related secondary isotope effects. Some results[4] are shown in Table 8.

Lewis has reported to this Conference some similar observations. Although the electron demand from the reaction center will vary from solvent to solvent and cause

TABLE 8. *p*-METHYL-d_3 BENZHYDRYL CHLORIDE SOLVOLYSES, 0°[*]

Solvent	k_H/k_D	Relative ρ[+]	Relative rates
90% aq. alcohol	1·025	0·97	1·0
80% aq. acetone	1·058	0·97	0·14
70% aq. acetone	1·038	0·98	1·0
60% aq. acetone	1·021	1·00	1·9

[*] Ref. 4.

[+] The Hammett ρ constant ratio relative to a value of 1·00 for 67% aq. acetone. Determined from the relative rates of benzhydryl chloride and *m*-methylbenzhydryl chloride in the various solvents.

hyperconjugation to vary likewise, this effect must certainly be small in the experiments cited in Table 8. This is indicated by the values of the Hammett ρ constant relative to 67 per cent aq. acetone calculated from the relative rates of benzhydryl and *m*-methylbenzhydryl chlorides in the various solvents. Thus the relative ρ values change insignificantly while the isotope effects change by a factor of almost three. Therefore, solvent interactions at the isotopic site itself seem to be important in influencing these secondary isotope effects. This much is clearly indicated by the data, but not enough evidence is available to allow one to analyze the situation much further and make any conclusive statements about the nature of such solvent influences. The possibility clearly exists that the solvent effects reflect solvent influences on hyperconjugation.

In conclusion I think that the study of secondary deuterium isotope effects has furnished some of the least controvertible evidence for the existence of hyperconjugation influences in transition states. Since there are clearly other sources of secondary deuterium isotope rate effects, the data must be interpreted with extreme care. However, detailed analyses indicate that hyperconjugation influences account for the major part of the observed β-deuterium and related isotope effects on solvolysis reactions. Assuming that the variations in these effects in closely related reactions are due to variations in hyperconjugation, the following conclusions are tentatively indicated:

(1) There are steric effects on hyperconjugation.

(2) There are substituent effects on hyperconjugation; conjugating and hyperconjugating substituents increase the extent of hyperconjugation by a single C–H bond.

(3) There are solvent effects on hyperconjugation.