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ISOTOPE EFFECTS AND HYPERCONJUGATION

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SEVERAL years ago the observation of an isotope effect in the decomposition of 2-pentyl chlorosulfite led to the suggestion that the isotope effect measured the increase in hyperconjugation accompanying the activation.[1] This paper examines the suggestion in the light of subsequent work with the aim of establishing the extent of connection between these isotope effects and hyperconjugation. There will be no attempt to use isotope effects to study the nature of hyperconjugation.

For the purposes of this paper, hyperconjugation is considered to be a contribution to the usual hybrid of valence-bond structures of reasonable further structures with no bond to some atom in place of the single bond of the conventional structures. The partial withdrawal of the electrons of a single bond to another part of the molecule where they can be accommodated is the important feature of this definition, the valence-bond language is not essential for the present purpose. We shall here be only concerned with hyperconjugation involving withdrawal of electrons from a bond to hydrogen, nothing can be said from this work about the so called C–C hyperconjugation.

It was suggested that, when electrons are withdrawn from a C–H bond by hyperconjugation, the force constants for the vibration of the hydrogen are reduced. A reaction with a change in hyperconjugation on activation would then be a process with different force constants of the C–H bond in the starting material and in the activated complex. Thus substitution of deuterium for hydrogen will produce a difference in the change of zero-point vibrational energies on activation for the deuterium and the protium compounds. This difference will in turn be reflected in different activation energies and different rates for the two compounds. When a reaction results in an increase in hyperconjugation on activation, it will be expected to involve a loss in zero-point vibrational energy which will be greater for the protium compound than the deuterium compound, hence the protium compound will react more rapidly.* On this basis it was proposed that the extent of retardation by appropriate deuterium substitution was a measure of the increase in hyperconjugation and hence the increase in electron deficiency on activation.

The initial experiments which led to these ideas were on the decomposition of 2-pentyl chlorosulfite in dioxan solution to a mixture of pentenes and 2-chloropentane. Nearly complete deuteration in the 1 and 3 positions produced a diminution in the

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* This simple treatment makes a number of assumptions about the sources of isotope effects which are only approximate. It can be shown for the cases mentioned here that errors resulting from these assumptions are not serious except when the isotope effect is small, but with $k_H/k_D < 1{\cdot}1$ a more complete treatment would be better if it could be applied.

[1] E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.* 74, 6306 (1952); *Ibid.* 76, 795 (1954).

rate of both reactions with k_H/k_D = ca. 1·4. Both processes were believed to proceed through the rate-determining formation of an ion-pair:

$$ROSOCl \rightarrow R^+ \; OSOCl^-$$

It was desirable to determine an isotope effect on a reaction of well-established mechanism, so the solvolysis of 2-pentyl *p*-toluenesulfonate, in which a transition state closely resembling a carbonium ion is accepted, was chosen.[2] Before this was complete, a very important and pertinent paper by Shiner[3] appeared describing a corresponding diminution in solvolysis rate of *tert*.-amyl chloride produced by β-deuterium substitution. Table 1 shows some of the results of our work and confirms the ideas that this isotope effect occurs in reactions leading to carbonium ions. The rate retardations are expressed at times in this paper as k_H/k_D and elsewhere as $(RT/n) \ln k_H/k_D$, where n is the number of deuteriums per molecule in positions suitable for hyperconjugation. The latter mode of expression is useful for comparing isotope effects at different temperatures and with different numbers of deuterium atoms. In the case of the first two entries in the table it was shown that the free energy of activation difference was indeed temperature independent, showing that the difference occurred exclusively in the heat of activation term. The justification for expressing the effect on the basis of the $\Delta\Delta F^{\ddagger}$ per deuterium is found in the work of Shiner[3] and that of Streitwieser *et al.*,[4] both of whom have shown that the effect of deuterium substitution on the rate is nearly independent of the presence of other deuterium atoms in the molecule. There are, however, well established cases where the effect of deuterium depends on the extent of substitution of the carbon to which it is attached,[3, 5] and where deuterium substitution produces changes in the Arrhenius pre-exponential factor.[5, 6]

TABLE 1. ISOTOPE EFFECTS IN SOLVOLYSIS OF 2-PENTYL COMPOUNDS

Substance	Solvent	$(RT/n)\ln k_H/k_D$ (cal/mole)
ROTs	HCOOH	76
ROTs	CH_3COOH	75
ROTs	80% EtOH	51
RBr	HCOOH	56

Table 1 shows the fall in isotope effect as the solvent or leaving group becomes more nucleophilic, hence supporting the suggestion that the less electron-deficient transition state leads to a smaller isotope effect. Table 2 shows the decrease in isotope effect as we proceed from the limiting tertiary halide, which does not need solvent participation, through the intermediate secondary compound to the primary ethyl compound, where the electron-deficient carbonium ion is a very poor description of the transition

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[2] E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.* 76, 791 (1954).

[3] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* 75, 2925 (1953).

[4] A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Amer. Chem. Soc.* 80, 2326 (1958).

[5] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* 76, 1603 (1954).

[6] E. S. Lewis and G. M. Coppinger, *J. Amer. Chem. Soc.* 76, 4495 (1954).

state. The parenthesized value for the 2-pentyl bromide in 80 per cent ethanol is estimated from Table 1.

TABLE 2. STRUCTURAL INFLUENCE ON ISOTOPE EFFECT WITH NEARLY COMPLETE β-DEUTERIUM SUBSTITUTION

Compound	Solvent	$(RT/n)\ln k_H/k_D$ (cal/mole)
tert.-Amyl chloride	80% EtOH	55[3]
2-Pentyl bromide	80% EtOH	(37)
2-Pentyl *p*-toluenesulfonate	CH_3COOH	75
Ethyl *p*-bromobenzenesulfonate	CH_3COOH	6[7]

A simple extension of these ideas requires that the isotope effect in the ordinary S_N2 reaction should be very small, since the contribution of hyperconjugating electron-deficient structures is minor. Two examples have been studied. The reaction (1) with

$$OEt^- + RBr \longrightarrow EtOR + Br^- \qquad (1)$$

R = *iso*propyl was studied by Shiner [8] and shows a very small and possibly experimentally insignificant isotope effect, with $(RT/n)\ln k_H/k_D$ 12 cal/mole. The reaction of 2-pentyl chlorosulfite in the presence of tertiary amines is an inverting chloride ion substitution represented by (2), it has $(RT/n)\ln k_H/k_D = 35$ cal/mole.[9] Both numbers are substantially smaller than those for any analogous S_N1 reactions.

$$Cl^- + ROSOCl \longrightarrow ClR + SO_2 + Cl^- \qquad (2)$$

The connection between retardation by β deuterium and the carbonium-ion character of the transition state is now reasonably well established, but the results described above do not necessarily identify hyperconjugation as the mechanism of this connection. Most alternative explanations, not involving conjugation, would not predict transmission of the effect through an unsaturated system, so the solvolysis of methyltolylcarbinyl chlorides were studied. Table 3 shows the effects of deuterium substitution in various positions on the solvolysis rates of methyl-*p*-tolylcarbinyl chloride in acetic acid[6] and of this substance and the *meta* isomer in aqueous acetone.[10] Variations of isotope effect with temperature and with the composition of aqueous acetone are not shown. Since the effects are small, the significance of these variations is questionable.

Four features are evident from these data. First, deuterium in the *para*-methyl group does cause some retardation; second, this isotope effect is subject to large changes with solvent; third, deuterium in the *meta*-methyl group does not cause a retardation, and indeed appears to lead to an increased rate; fourth, deuterium in the α position produces a large retardation.

The first of these, retardation by deuterium in the *para*-methyl group, lends support to an explanation in terms of hyperconjugation, especially when the retardation

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[7] E. S. Lewis and W. C. Herndon, unpublished work.

[8] V. J. Shiner, Jr. *J. Amer. Chem. Soc.* 74, 5285 (1952).

[9] E. S. Lewis and G. M. Coppinger, *J. Amer. Chem. Soc.* 76, 796 (1954).

[10] R. R. Johnson, Thesis, the Rice Institute, Houston, Texas (1958).

TABLE 3. ISOTOPE EFFECTS IN THE SOLVOLYSIS OF METHYLTOLYLCARBINYL CHLORIDES

Position of D	Tolyl isomer	Solvent	k_H/k_D
p-CH_3	*para*	CH_3COOH	1·08
ω-CH_3	*para*	CH_3COOH	1·2
p-CH_3	*para*	Me_2CO-H_2O	1·01
ω-CH_3	*para*	Me_2CO-H_2O	1·13
α-CH	*para*	Me_2CO-H_2O	1·11
m-CH_3	*meta*	Me_2CO-H_2O	0·99

is not found with the *meta* isomer. A difference in direction of effect in the *meta* and *para* position is always difficult to explain without recourse to a resonance, or in this case hyperconjugation, effect. The effect in aqueous acetone is very small, but, since the precision of the rate constants was good, it is significant. Shiner and Verbanic[11] have observed a similar effect with *p*-methylbenzhydryl chloride.

The second point, the solvent dependence, is quite interesting. The solvent change shown in Table 3 is in the direction predicted by the considerations of solvent participation mentioned before, but the large change in isotope effect due to the deuterium in the *para*-methyl group is not compatible with the relatively minor change in isotope effect due to substitution in the other methyl group, marked ω in the table. Shiner and Verbanic[11] also observed substantial solvent effects over a small solvent variation. Both results are consistent with solvent participation at some other point than at the electron-deficient carbon, but the details are not clear.

The acceleration by deuterium in the *meta*-methyl group is quite unprecedented. An explanation in terms of an inductive effect can be offered and will be discussed in more detail later.

The effect of α deuterium is clearly not related to hyperconjugation. It is included to demonstrate that there are other sources of secondary isotope effects. The first example was found by Streitwieser *et al.*,[4] who have offered a reasonable explanation.

An interesting extension of these experiments on the aromatic systems is found in the decomposition in water of the *p*-toluenediazonium ion. This substance is stabilized by important hyperconjugation, but the immediate product of the reaction, the *p*-tolyl cation, is not so stabilized. This is deduced from the observation that a *para*-methyl group stabilizes the diazonium ion with respect to this reaction, but the *meta*-methyl group reduces its stability. Thus the inductive effect of the methyl group favors the reaction, and the diminished reactivity of the *para*-methyl substituted compound must be attributed to a resonance effect.[12] One therefore predicts that the C–H bonds of the CH_3 group will be stronger in the transition state than in the initial state, hence substitution of deuterium will lead to an acceleration. The observation[13] that $k_H/k_D = 0·99$ is positive, if not convincing, confirmation of this prediction.

Inductive differences between hydrogen and deuterium have been proposed by Halevi[14] in the direction of greater electron release by deuterium than by hydrogen.

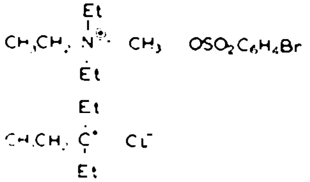
[11] V. J. Shiner, Jr. and C. J. Verbanic, *J. Amer. Chem. Soc.* **79**, 373 (1957).

[12] E. S. Lewis and E. B. Miller, *J. Amer. Chem. Soc.* **75**, 429 (1953).

[13] E. S. Lewis, J. L. Kinsey and R. R. Johnson, *J. Amer. Chem. Soc.* **78**, 4294 (1956).

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

He arrived at this conclusion from considerations of differences in acid strength between phenylacetic acid and its α-dideutero analogue. Benzylamine and its α-dideutero analogue similarly differed in base strength. The source of this difference was attributed to the difference in CH and CD bond distances; the smaller distance for the latter arises in a straightforward way from considerations of zero-point vibration of the anharmonic system. Independent confirmation is found in the shielding of the fluorine nuclei in the CF_2H group of n-C_3F_7H,[15] which by nuclear magnetic resonance methods is less than the shielding by valence electrons of the corresponding nuclei in n-C_3F_7D. This inductive effect best explains the previously quoted results on the increase in rate on substitution of deuterium for hydrogen in methyl-*m*-tolylcarbinyl chloride, and (as suggested by Halevi) may also explain the reverse isotope effect in the reaction of *p*-toluene-diazonium ion. There is now additional evidence on this point from kinetic work. The reaction of methyl *p*-bromobenzenesulfonate with triethylamine has a transition state as shown below resembling that for the solvolysis of triethylcarbinyl chloride electrostatically, although in the solvolysis the atom developing the positive charge is electron deficient, and in the quarternization reaction there is no significant electron deficiency at the nitrogen. The effect of deuterium in one methylene group of the triethylamine was to accelerate the reaction, with $k_H/k_D = 0{\cdot}93$.[16] Not only is the result most easily explained on the basis of an inductive difference, but one can also conclude that the more usual isotope effect in solvolysis is not derived from an electrostatic effect alone, since one might expect isotope effects in the same direction for the quaternization and the solvolysis if the charge near the point of isotopic substitution were the important factor.



$$CH_3CH_2 \cdots \overset{Et}{\underset{Et}{N^{\odot}}} \cdots CH_3 \quad OSO_2C_6H_4Br$$

$$CH_3CH_2 \cdots \overset{Et}{\underset{Et}{C^{\bullet}}} \quad Cl^{-}$$

In addition to work on solvolytic reactions, evidence relating isotope effect and hyperconjugation has come from other sources. Shiner and Cross[17] have found similar but smaller effects in the hydrolysis of acetals, where hyperconjugation had been considered important from other evidence. Swain *et al.*[18] studied the effect of tritium in the methyl group of toluene on the rate of bromination in aqueous acetic acid, and on the rates of some other electrophilic substitutions. Since the transition state for bromination was believed to be highly electron deficient, they estimated that the isotope effect should be larger than in the solvolysis reaction. The observed ($k_H/k_T = 1{\cdot}046 \pm 0{\cdot}009$) isotope effect was smaller than that reported for a solvolysis reaction,[6] so it was concluded that the isotope effect and hyperconjugation were not directly connected. Since the later results, quoted above and in reference 11, show that there is substantial variation in isotope effect with solvent, Swain's result is no longer unexpectedly low, hence his conclusion is no longer necessary. This example does

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

[16] E. S. Lewis and W. J. Farrissey, unpublished observations.

[17] V. J. Shiner, Jr. and S. Cross, *J. Amer. Chem. Soc.* **79**, 3599 (1957).

[18] C. G. Swain, T. E. C. Knee and A. J. Kresge, *J. Amer. Chem. Soc.* **79**, 505 (1957).

illustrate the caution that it is now necessary to use in quantitative interpretation of isotope effects.

In conclusion, it may now be taken as established that hyperconjugation is one of the important sources of secondary isotope effects. There exist other sources of isotope effects, including an inductive difference and an effect from α substitution. Furthermore, the variation of solvent influences the isotope effect is a way that is not well understood, so that the quantitative use of secondary isotope effects is not a reliable tool for studying mechanisms, except when the effects are large.

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