

THE DEUTERIUM ISOTOPE EFFECT

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I. INTRODUCTION

In 1927 Aston (9) determined the atomic weight of hydrogen, using a mass spectrometer, and found the value to be in excellent agreement with the value obtained chemically. However, this agreement was disturbed when Giauque and Johnston (74) found that ordinary oxygen contained appreciable amounts of O^{17} and O^{18} . This indicated that the atomic weight determinations were in error, or that hydrogen also had an isotope (22).

In 1932 Urey, Brickwedde, and Murphy (220) reported spectroscopic evidence for the existence of heavy hydrogen in a sample of ordinary hydrogen which had been concentrated to a small volume by distillation. Shortly thereafter, Washburn and Urey (226) reported the enrichment of heavy hydrogen in water by

electrolysis, and Lewis and MacDonald (132) succeeded in isolating a small amount of pure heavy water. The availability of deuterium quickly led to its application in the study of a variety of problems. In 1934 alone, about two hundred papers appeared dealing with its utilization, isolation, or properties.

After the existence of deuterium had been confirmed experimentally, both Cremer and Polanyi (48) and Eyring and Sherman (63) predicted that hydrogen and deuterium should react at different rates because of the difference in zero-point energy. This prediction has been amply verified, and the deuterium isotope effect has been found to be of great value in the study of the mechanisms of chemical reactions and in the development of the theories of rate processes.

This review represents an attempt to organize and correlate the available data on the deuterium isotope effect and also on the effect noted with tritium. Particular attention has been given to the factors which influence the magnitude of the isotope effect and in many cases the interpretation given is that of this writer. This review is mainly directed toward the interests of those who use the isotope effect in the study of mechanisms of reactions, and thus the conclusions which may be derived regarding the various theories of rate processes have not been included. The effect of deuterium on biological systems has also been omitted unless the results appeared to be of particular interest to chemists.

Most of the references have been obtained from the excellent bibliography of Kimball (121) and from the yearly bibliographies published by the National Bureau of Standards (164). Since in many cases an isotope effect has been determined in the course of another investigation, a number of these data have probably been missed. The writer would appreciate being informed of any such omissions.

II. THEORETICAL BASIS FOR THE DEUTERIUM ISOTOPE EFFECT

Three factors contribute to the generally lower reactivity of bonds to deuterium as compared to the corresponding bonds to hydrogen. These are the difference in free energy, the effect of the difference in mass on the velocity of passage over the potential-energy barrier, and the possibility for non-classical penetration of the energy barrier (21, 77). The major factor which contributes to the free-energy difference is the difference in zero-point energy between a bond to deuterium and the corresponding bond to hydrogen.

The potential-energy curves (Morse curve, figure 1) for a bond to hydrogen and the corresponding bond to deuterium are essentially identical. This can be seen from the fact that the ratio of the infrared stretching frequencies for the two bonds is almost exactly proportional to the ratio of the square roots of the masses of deuterium and hydrogen, or 1.4. The shape of the bottom of the potential-energy curve governs the force constant for the stretching vibration, and this is related to the frequency by the Hooke's law expression (equation 1) where k is the force constant and μ is the reduced mass, which is approximately equal to 1 and 2 for most hydrogen- and deuterium-containing bonds, respectively.

$$\nu = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}} \quad (1)$$

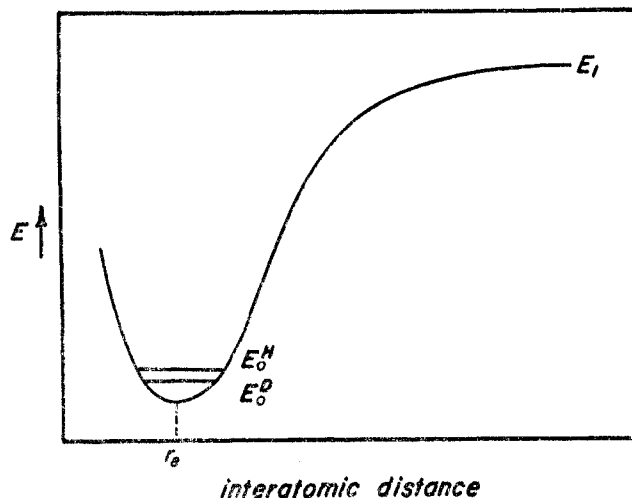


FIG. 1. Morse curves relating potential energy and interatomic distance

The lowest energy level for any bond corresponds to $\frac{1}{2} h\nu$, where h is Planck's constant. This lowest energy level is known as the zero-point energy, and corresponds to the vibrational energy of the bonds of a molecule at absolute zero. Room temperature is close enough to absolute zero so that most (~ 99 per cent) of the bonds are in this vibrational energy level. There is a difference in zero-point energy for a bond to hydrogen and the corresponding bond to deuterium which arises from the effect of the difference in mass on the stretching frequencies. This difference in energy may be calculated if one knows the values of the corresponding frequencies, and is of the order of 1.2–1.5 kcal. per mole.

The difference in zero-point energy has two consequences. The dissociation energy of a compound is the difference between E_1 in figure 1 and the zero-point energy. Since the deuterium compound will have the lower zero-point energy, it will be more stable than the hydrogen analog. Similarly, in a rate process, if one considers the curve relating the potential energy of the system with the distance along the reaction coordinate (figure 2), and if one assumes the bond undergoing reaction to be relatively weak in the activated complex in comparison to the reactants, the effect of zero-point energy on the rate becomes apparent. The weak bond in the activated complex reflects a low force constant, and since the difference in zero-point energy decreases with decreasing force constant, the difference in zero-point energy for this bond in the activated complex will usually be small. Thus, the difference in zero-point energy in the reactants will result in a difference in the height of the potential-energy barrier for reaction, and will result in a higher enthalpy of activation for the deuterium-containing compound. It is of course assumed that the bonds in the molecule which do not participate in the reaction are not affected during the process, and this appears to be a good approximation in most cases.

In the absolute rate theory, the rate of reaction is a function of the concentra-

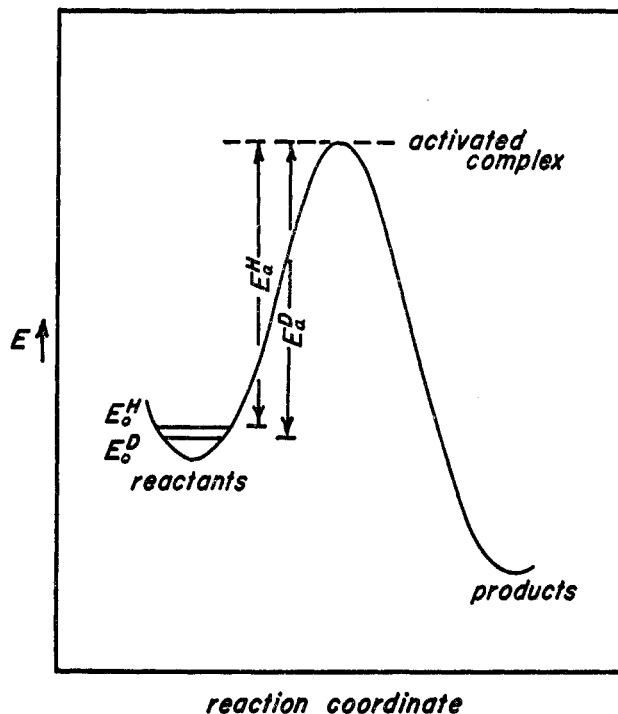


FIG. 2. Potential-energy profile

tion of the activated complex and its rate of passage over the potential-energy barrier, leading to equation 2 (77),

$$k = \kappa \frac{C^\ddagger}{C_A C_B} \left(\frac{kT}{2\pi m^*} \right)^{1/2} \frac{1}{\delta} \quad (2)$$

where k is the rate constant, κ is the transmission coefficient, m^* is the mass of the activated complex in the direction of reaction, δ is the length of the region characterizing the activated complex, C^\ddagger is the concentration of the activated complex, and C_A and C_B are the concentrations of the reactants.

Since the potential-energy surface will be essentially the same for a hydrogen compound and its deuterium analog, δ is about the same for both compounds.¹ Thus the ratio of the rate constants will be given by equation 3, assuming B to be the common reactant.

$$\frac{k_1}{k_2} = \frac{\kappa_1 C_1^\ddagger C_{A2}}{\kappa_2 C_2^\ddagger C_{A1}} \left(\frac{m_2^*}{m_1^*} \right)^{1/2} \quad (3)$$

The concentration terms may be replaced by free-energy terms and the transmission coefficients may be assumed to be the same, giving equation 4.

$$\frac{k_1}{k_2} = \frac{f}{f^\ddagger} \left(\frac{m_2^*}{m_1^*} \right)^{1/2} \quad (4)$$

¹ This is essentially a qualitative description of the method of J. Bigeleisen (21).

The function f is given by

$$f = \frac{s_1}{s_2} \prod_i^{3n-6} \frac{u_i}{u_i + \Delta u_i} e^{\Delta u_i/2} \frac{(1 - e^{-(u_i + \Delta u_i)})}{(1 - e^{-u_i})} \quad (5)$$

where the s 's are the symmetry numbers, $u_i = h\nu/kT$, and $\Delta u_i = h/kT(\nu_{i(1)} - \nu_{i(2)})$. A similar expression may be written for f^\ddagger . At high temperature the first and third terms in the product cancel, leading to $e^{\Delta u_i/2}$, in which $\Delta u_i/2$ is the difference in zero-point energies divided by kT . Since this term approaches unity as the temperature is increased, f also becomes equal to 1 under these conditions. At low temperature the third term becomes negligible.

In order to simplify the calculation, it is usually assumed that the non-reacting bonds in the molecule are not affected during reaction, and thus it is only necessary to consider the stretching frequency of the bond undergoing reactions. Since a detailed knowledge of the potential-energy surface at the energy barrier is usually not available, it is usually possible to determine only the maximum isotope effect which corresponds to no bonding to the hydrogen or deuterium in the activated complex. In this case, f^\ddagger becomes equal to 1 and equation 4 may be rewritten as

$$\frac{k_{\text{H}}}{k_{\text{D}}} = \left(\frac{m_{\text{D}}^*}{m_{\text{H}}^*}\right)^{1/2} \cdot \frac{h\nu_{\text{D}}}{h\nu_{\text{H}}} \cdot e^{(h\nu_{\text{H}} - h\nu_{\text{D}})/2RT} \cdot \frac{1 - e^{-h\nu_{\text{H}}/RT}}{1 - e^{-h\nu_{\text{D}}/RT}} \quad (6)$$

where $h\nu$ is expressed in calories per mole (2.86 times the value in cm.^{-1}).

The last term of equation 6 is equal to 1 up to about 400–500°C. The ratio of the vibrational frequencies for the bond to deuterium and the bond to hydrogen is approximately equal to $1/\sqrt{2}$ in most cases and thus cancels the mass factor, which is approximately equal to $\sqrt{2}$. The equation is then simplified, giving equation 7. At higher temperatures all of the terms in equation 6 except the mass

$$\frac{k_{\text{H}}}{k_{\text{D}}} = e^{(h\nu_{\text{H}} - h\nu_{\text{D}})/2RT} \quad (7)$$

factor will cancel, and the isotope effect will approach $\sqrt{2}$ or 1.4. This has been verified experimentally (164).

Whereas classical statistical mechanics may be used in this treatment for most elements at room temperature or above, hydrogen should properly be treated by quantum statistics to allow for its wave nature. As one of the consequences, with hydrogen there is a possibility for penetration of the potential-energy barrier, or "tunneling." This effect would be predicted to be less probable for deuterium than hydrogen, and would lead to a further difference in the ratio of rates. The tunneling effect has been looked for in many reactions without success. However, recently Bell (17) has found a case in which this effect appears to be important.

In many cases, the observed isotope effect is less than that calculated using the preceding assumptions. This indicates that these reactions should be considered as three-center processes in which the new bond is formed as the old bond is broken. In this case, there will be a difference in zero-point energy in the activated complex which will in part cancel the difference in zero-point energy

TABLE 1

Maximum value of the deuterium isotope effect for one stretching vibration as a function of temperature

Bond	ΔE_0	T	k_H/k_D	Bond	ΔE_0	T	k_H/k_D
	<i>cal.</i>	$^{\circ}\text{C.}$			<i>cal.</i>	$^{\circ}\text{C.}$	
C—H.....	~1150 (1100-1200)	0	8.3	N—H.....	~1270	200	3.9
		25	6.9			300	3.0
		100	4.7			500	2.2
		200	3.4			O—H.....	~1400
		300	2.7	25	10.6		
		500	2.1	100	6.6		
N—H.....	~1270	0	10.3	200	4.4	300	3.4
		25	8.5	500	2.5		
		100	5.5				

in the reactants. If the bonding in the activated complex is as strong as that in the reactants, f and f^\ddagger in equation 4 will be essentially equal, and only the mass factor will remain. Therefore, the minimum isotope effect expected under these conditions would be 1.4.

Hydrogen and deuterium atoms have no zero-point energy. In their reactions one might find a reverse isotope effect if bonding in the activated complex were significant (177).

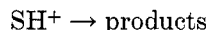
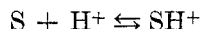
It can be seen from the above equations that the magnitude of the isotope effect is temperature-dependent. For convenience in interpreting the data which will be presented in the following pages, table 1 gives the maximum expected isotope effect for different types of bonds as a function of temperature. The values were calculated assuming tunneling to be relatively unimportant.

III. IONIC REACTIONS IN DEUTERIUM-CONTAINING SOLVENTS

A. Acid catalysis

The study of acid and base catalysis has been of interest to chemists for many years. A comprehensive theory of these reactions was first advanced by Brønsted (35) in 1924 and has been amply verified by many later workers (16). There were, however, a number of unanswered questions, and it is not surprising that many investigations of the effect of deuterium oxide on these reactions were reported from 1935 to 1939.

It has been found that most acid-catalyzed reactions (table 2) proceed more readily in D_2O than in H_2O . This at first appeared surprising, but was soon explained by Moelwyn-Hughes and Bonhoeffer (27, 159). The mechanism of specific acid catalysis is believed to be



where S is the substrate. Since deuterium oxide has a smaller autoprotolysis constant than water by a factor of 5 (239), it is believed to be less basic than water.²

² The apparent lower basicity of deuterium oxide is caused at least in part by the decrease in the H—O stretching force constant in going from water to oxonium ion which is

TABLE 2
Effect of solvent deuterium on the rate of acid- and base-catalyzed reactions

Reaction	T	Catalyst	$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$	$k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$	References
	°C.				
Hydrolysis of ethyl orthoformate.....	25	H ₃ O ⁺		2.35	(30, 31, 32, 96)
Hydrolysis of ethyl formate.....	15	H ₃ O ⁺		1.37	(165)
Hydrolysis of methyl acetate.....	15	H ₃ O ⁺		1.60(1.86)	(95, 96, 165, 197)
Hydrolysis of acetal.....	15	H ₃ O ⁺		2.68	(96, 171)
Hydrolysis of acetonitrile.....	105	H ₃ O ⁺		1.36	(185, 186)
Hydrolysis of acetamide.....	25	H ₃ O ⁺ (0.1 N)		1.45	(185, 186)
	25	H ₃ O ⁺ (4 N)	1.16		
Inversion of sucrose.....	25	H ₃ O ⁺		2.05	(80, 81, 85, 157, 158)
Decomposition of diazoacetic ester.....	25	H ₃ O ⁺		2.86	(78, 79)
Decomposition of dithionic acid.....	60	H ₃ O ⁺		2.48	(205)
Oxidation of bromide by bromate.....		H ₃ O ⁺		2.5	(1, 2)
Oxidation of chloride by bromate.....		H ₃ O ⁺		3.5	
Oxidation of iodide by bromate.....		H ₃ O ⁺		2.4	
Oxidation of bromide by iodate.....		H ₃ O ⁺		4.0-7.0	
Oxidation of iodide by iodate.....		H ₃ O ⁺		~10	
Decomposition of oxalic acid.....	136	H ₃ O ⁺		1.2	(136, 196)
Mutarotation of glucose.....	25	H ₃ O ⁺	1.37		(84)
	25	H ₂ O	3.80 (3.16)		(83, 84, 86, 157, 160, 173, 175)
	25	CH ₃ COOH	2.6		(84)
	25	CH ₃ COO ⁻	2.38		(84)
Alcoholysis of acetamide in methanol..	25	CH ₃ OH ₂ ⁺	2.08		(186)
Bromination (enolization) of acetone...	25	H ₃ O ⁺		2.1	(179, 183, 184)
	25	RCOOH		2	(187)
		CH ₃ COO ⁻	1.15		
Ketonization of enol of methyl acetyl- acetone.....	25	H ₃ O ⁺	1.3		(163)
	25	CH ₃ OH ₂ ⁺	1.3		
Isomerization of aci-nitroethane.....	0		1.00		(142)
Decarbonylation of mesitaldehyde.....	80	H ₂ SO ₄ (100%) (60%)	2.4	1.8	(37)
Decomposition of 1-benzoyl-2-cyano- 1,2-dihydroquinoline to benzalde- hyde.....		H ₂ SO ₄ -t	5.4		(212)
Hydrolysis of ethyl acetate.....		OH ⁻		1.33	(238)
Hydrolysis of acetonitrile.....	35	OH ⁻		1.20	(185, 186)
Hydrolysis of acetamide.....	25	OH ⁻	1.10		(185, 186)
Hydrolysis of monochloroacetate ion...	45	OH ⁻		1.2	(182)
Hydrolysis of diacetone alcohol.....	15	OH ⁻		1.45	(165)
Decomposition of nitramide.....	25	R ₂ COO ⁻	2.0		(125, 134)
	25	H ₂ O	5.21		
Neutralization of nitroethane.....	5	OH ⁻		1.39	(141)
Neutralization of 2-nitropropane.....	5	OH ⁻		1.36	(141)
Bromination of nitromethane.....	25	CH ₃ COO ⁻	1.15		(181, 237)
	25	ClCH ₂ COO ⁻	1.31		
	70	H ₂ O	1.69		
Bromination of methylacetylacetone...	25	CH ₃ OH	1.64		(163)
	25	H ₂ O	1.89		

Thus, the substrate will be able to compete with the solvent for the deuterium in D₂O more effectively than for the proton in H₂O. Since the concentration of the conjugate acid of the substrate will then be higher in D₂O, the rate of the reaction should also be higher in D₂O than in H₂O, provided the second step does not show an isotope effect.

observed in the infrared spectra (20). Thus the zero-point energies of H—O and D—O bonds are closer in the ion than in water, making equilibrium toward the ion less favorable in D₂O than in H₂O.

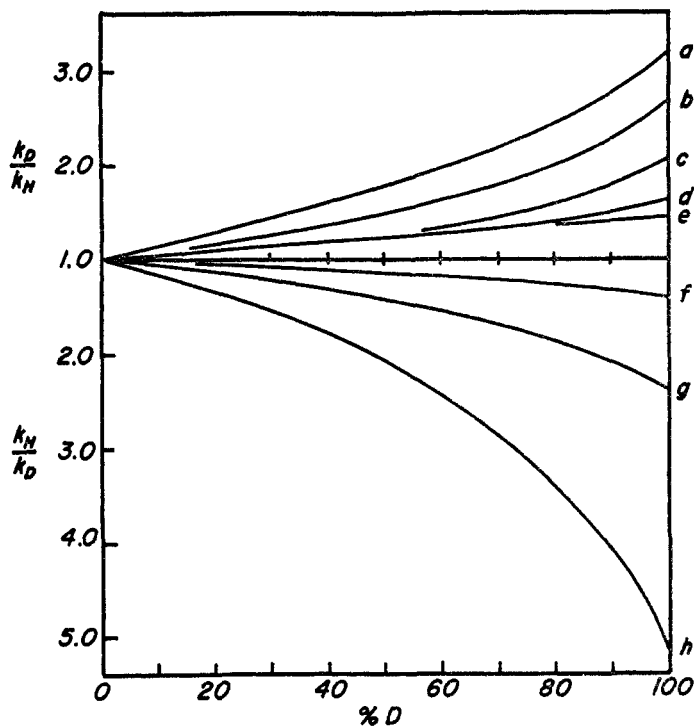
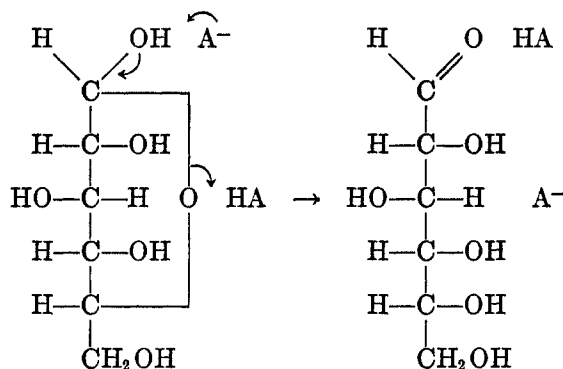


FIG. 3. Effect of deuterium concentration on the rate of some catalyzed reactions. Curve a, decomposition of diazoacetic ester (78); curve b, acid-catalyzed hydrolysis of acetal (171); curve c, inversion of sucrose (81); curve d, acid-catalyzed hydrolysis of methyl acetate (165); curve e, base-catalyzed decomposition of diacetone alcohol (165); curve f, acid-catalyzed mutarotation of glucose (86); curve g, acetate ion-catalyzed mutarotation of glucose (86); curve h, base-catalyzed decomposition of nitramide (125). Other reactions which have been studied are: the acid-catalyzed hydrolysis of ethyl formate (165), the acid-catalyzed hydrolysis of ethyl orthoformate (30), the bromination of acetone (184), and the alcoholic fermentation of glucose and sucrose (180).

It was also noted that the effect of D_2O on the rate was not proportional to the mole fraction of deuterium, but rather increased more rapidly near 100 per cent D_2O (figure 3). Later work has shown that the effect of D_2O on the rate is proportional to its effect on the acidity of acetic acid (41, 124) and formic acid (171), and on the partition of picric acid between water and benzene (82). Since the effect of deuterium on the dissociation of weak acids is of importance, especially when buffer systems are used, it should be mentioned that weak acids are less dissociated in D_2O than in H_2O , in accord with the belief that D_2O is less basic than H_2O . Rule and La Mer (193) have found that the ratio of the dissociation constants in the two solvents is proportional to the acidity of the acid, being essentially unity for H_3O^+ , about 3 for acetic acid, and about 4 for hydroquinone. This result has found confirmation in the work of Martin and Butler (144).

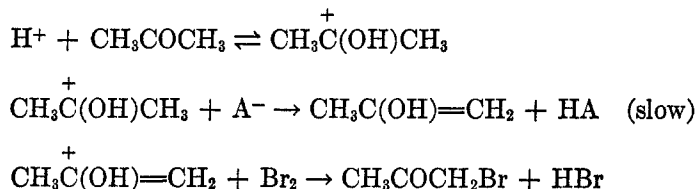
The mutarotation of glucose was one of the first examples of an acid-catalyzed reaction which proceeds more slowly in deuterium oxide than in water. Unlike

the above reactions, this is a case of general acid catalysis and its mechanism is believed to be



in which a proton is transferred from the acid to the substrate and from the substrate to a base in the rate-controlling step. In this case one should obtain a normal isotope effect, since bonds to hydrogen or deuterium are broken in the rate-controlling step. It is interesting to note that in this reaction the magnitude of the isotope effect decreases with increasing strength of the acid. Thus the isotope effects observed using water, acetic acid, and hydronium ion as the acid were 3.8, 2.6, and 1.4, respectively (84), which is the order of decreasing activation energy assuming the entropy of activation to be constant. This correlation of decreasing isotope effect with decreasing activation energy in any series appears to be rather general. The origin of the effect will be discussed in connection with free-radical hydrogen-abstraction reactions.

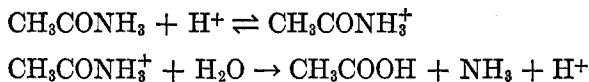
The effect of solvent deuterium was at first thought to provide a method of distinguishing between general and specific acid catalysis, since the former should give reduced rates in D_2O , whereas the latter should give enhanced rates in that solvent (238, 240). However, Reitz (179) found that the bromination of acetone, which is general acid-catalyzed, proceeded more rapidly in D_2O than in H_2O . It has been shown that the rate of enolization of a ketone is equivalent to the rate of bromination (99, 184). The subsequent observation that acetone- d_6 reacts at less than one-seventh the rate of ordinary acetone (183, 184) showed the mechanism to be as follows:



If the forward reaction of the initial equilibrium is much more rapid than the slow step, one would expect the reaction to proceed more rapidly in D_2O than in H_2O because of the effect of deuterium on the first step. The results also show

that there is more than one type of general acid catalysis and illustrate the importance of labeling both the solvent and the substrate with deuterium.

The hydrolysis of acetamide is interesting in that it proceeds more rapidly in D_2O at low acid concentrations and more rapidly in H_2O at high acid concentrations (186). The mechanism is probably



At low acid concentration the initial equilibrium controls the isotope effect, and the reaction is more rapid in D_2O than in H_2O . At higher acid concentrations the acetamide is largely in the form of the conjugate acid in either solvent. The displacement on the conjugate acid would be expected to be slower for D_2O than for H_2O since the former is the weaker base, and thus the isotope effect is reversed under these conditions. The decarbonylation of mesitaldehyde in deuteriosulfuric acid (37) appears to be affected by a similar equilibrium.

In several cases the above criterion for general acid catalysis has proved to be of value. Roberts and Watanabe (191), for example, have found that the acid-catalyzed decomposition of diphenyldiazomethane in ethanol-*d* proceeds more slowly than in ethanol, in contrast to the reaction of diazoacetic ester. Thus, the former is a case of general acid catalysis, whereas the latter is an example of specific acid catalysis.

Most of the accelerations of rate due to the use of D_2O as the solvent are in the order of 1.3–3.0. The halogen-halogenate reaction (1, 2) is unusual, in that values of k_{D_2O}/k_{H_2O} as large as 10 have been observed. This reaction appears to be first order in the halide ion and the halogenate ion and second order in hydrogen ion. It also shows a primary salt effect (198), suggesting that the conjugate acid of the halogenate acid reacts with the halide ion in the rate-determining step. Since two protons would then be involved in the initial equilibrium, one would expect a larger effect than in the cases in which only one proton is involved.

B. Base catalysis

As in the case of specific hydrogen-ion catalysis, specific hydroxyl-ion catalysis usually leads to a faster reaction in D_2O than in H_2O . In one case the effect of deuterium on the rate of reaction was determined over the whole range of H_2O - D_2O mixtures (165) (figure 3). Unlike specific hydrogen-ion catalysis, the effect was linear with deuterium concentration. This suggests that it may be a solvent effect. In two cases, anions other than hydroxyl ion were used, and a small normal isotope effect was noted (181, 187). This has also been attributed to a solvent effect.

In some reactions, such as the decomposition of nitramide, a fairly large normal isotope effect was noted; this undoubtedly arises from an initial rapid exchange of the compound with deuterium in the solvent, followed by a rate-determining removal of a proton or deuteron by the base (18, 125). Here again, the reaction with the lower activation energy (reaction with carboxylate ion) has the lower isotope effect.

TABLE 3
Isotope effects in the neutralization of carbanions

Compound	$k_{\text{CH}_3\text{OH}}/k_{\text{CH}_3\text{OD}}$	Compound	$k_{\text{CH}_3\text{OH}}/k_{\text{CH}_3\text{OD}}$
1-Butylmagnesium bromide.....	0.84	Phenyllithium.....	0.90
1-Butyllithium.....	1.00	Benzylmagnesium chloride.....	0.96
Phenylmagnesium bromide.....	0.97	Methyl sodiopropionate.....	1.16

C. Neutralization of carbanions

The reaction of several carbanions with mixtures of methanol and methanol-*d* has been studied (232). The isotope effect was obtained by comparing the deuterium content of the hydrocarbon formed with that of the methanol, giving the data in table 3. In most cases a small inverse isotope effect was noted, which indicates that there was essentially no change in difference in zero-point energy in going to the activated complex. It is interesting to note that the reaction of methyl Grignard reagent with mixtures of water and deuterium oxide gave methane with the same deuterium content as the solvent, even though only one of the hydrogens in the water reacted (170). The isotope effect must have been small in this case also.

The reaction of diethylzinc with water utilizes both of the available hydrogens. In this case an appreciable isotope effect was noted ($k_{\text{H}}/k_{\text{D}} = 2.5$) (69). It would therefore appear that the use of the Grignard reagent is the more satisfactory method for the determination of the deuterium content of water *via* conversion to a compound which can be analyzed mass spectrometrically.

In a study of the racemization and deuterium exchange of (–) 2-butyl phenyl ketone, the rate of exchange was found to be slightly slower than the rate of racemization in 99 per cent D_2O (99). The difference in rate was attributed to an isotope effect in the neutralization of the anion, and it was concluded that a value of $k_{\text{H}}/k_{\text{D}} = 12$ would accommodate the difference in rate. This value, of course, is subject to a large uncertainty.

The rate of deuterium exchange of acetone has been measured as a function of the deuterium content of the solvent (225). An extrapolation of the data gives $k = 1.55$ in 50 per cent D and $k = 13.8$ in 100 per cent D. Since in the absence of an isotope effect one would expect the rate in 50 per cent D_2O to be one-half of that in 100 per cent D_2O , the isotope effect for the neutralization of the acetone anion may be calculated to be $k_{\text{H}}/k_{\text{D}} = 4.5$. It would be quite reasonable to expect the isotope effect to increase as the basicity of the anion decreases, but there are not sufficient data to indicate whether or not this is correct.

D. Enzyme-catalyzed reactions³

A number of these reactions have been studied in heavy water. Although the data are not completely consistent, Salzer and Bonhoeffer (194) have presented evidence that the magnitude of the isotope effect for the hydrolysis of β -glucosides by emulsin is proportional to the Michaelis constant (table 4). This constant

³ The enzymatic reactions may not be ionic processes, but they are put in this place for convenience.

TABLE 4
Isotope effects in enzyme-catalyzed reactions

Reaction	Enzyme	k_{D_2O}/k_{H_2O}	Michaelis Constant	References
Hydrolysis of salicin.....	Emulsin	0.60	0.017-0.035	(194)
Hydrolysis of phenyl glucoside.....	Emulsin	0.74	0.04-0.065	(194)
Hydrolysis of <i>p</i> -cresyl glucoside.....	Emulsin	0.85	0.14	(194)
Hydrolysis of <i>n</i> -butyl glucoside.....	Emulsin	1.04	0.22	(194)
Hydrolysis of methyl glucoside.....	Emulsin	1.27	0.66-1.12	(194)
Hydrolysis of salicin.....	Emulsin	1.28		(207)
Inversion of sucrose.....		0.76		(206)
Fermentation of glucose.....		0.46		(174, 180)
Fermentation of sucrose.....		0.50		(174, 180)

is inversely proportional to the affinity of the enzyme for the substrate (156). Thus, in the case of substrates which have a strong affinity for the enzyme, and which give a rapid reaction, a normal isotope effect is found. In the case of substrates which have a low affinity for the enzyme, the reaction proceeds more rapidly in D_2O than in H_2O .

A few other isotope effect data are also given in table 4, but these are not necessarily complete.

E. Other reactions

The catalytic decomposition (3, 4) and reduction (40) of hydrogen peroxide by iodide ion and the reduction of diazonium ions by hypophosphorous acid (5, 6) proceed more slowly in D_2O than in H_2O , probably because the reactant undergoes deuterium exchange with the solvent prior to reaction. The uncatalyzed hydrolysis of esters (114, 115), the hydration of chromic chloride (39), the reaction between ascorbic acid and mercuric chloride (102), and the oxidation of pyrogallol in the presence of complex metal ions (241) also proceed more slowly in D_2O than in H_2O . The esterification velocity of benzoic acid was found to be slightly greater in the presence of D_2O than in H_2O (116).

The hydrogen exchange of acetic acid with D_2O is about twice as fast as the exchange between α -deuteroacetic acid and H_2O at 100-200°C. (25). This should correspond roughly to the relative rates of enolization. The exchange of chloroform with D_2O is also about twice as fast as the reaction between chloroform-*d* and H_2O at 25°C. (90). However, the acid-catalyzed exchange of resorcinol-*d*₅ with water is 1-1.4 times as fast as the reaction between resorcinol and D_2O at 65°C. (72).

The solvolysis of *tert*-butyl chloride has been found to proceed more slowly in D_2O than in H_2O by a factor of 1.4. The solvolysis of *tert*-butylsulfonium ion, methyl chloride, and methyl iodide gave the same rate in both solvents (211). Since *tert*-butyl chloride is more dependent on electrophilic solvation in the rate-determining step and is more discriminating between different electrophilic reagents than the methyl halides, this indicates that light water is a better electrophilic reagent than heavy water.

The displacement of halogen from *o*-nitrochlorobenzene by piperidine and

TABLE 5
Effect of β -deuterium on S_N2 and $E2$ reactions

Number of deuterium atoms.....	3.4	5.9	0.98	0.0
Position of deuterium.....	β	β	α	—
k_2 for substitution.....	1.03	0.94	1.06	1.06
k_2 for elimination.....	0.89	0.29	1.68	1.76

piperidine-*d* has been studied in an effort to determine if hydrogen bonding between the amine hydrogen and the *o*-nitro group was a factor in causing *o*-chloronitrobenzene to be more reactive than *p*-chloronitrobenzene. No difference in rate was noted (88). This also suggests that the catalytic constant for piperidine-*d* is the same as that of piperidine in this reaction, whereas it was previously noted that the constant for water is probably greater than that for deuterium oxide.

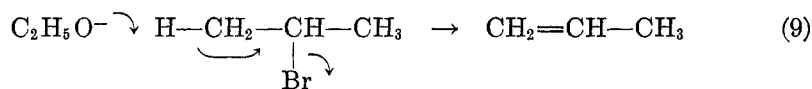
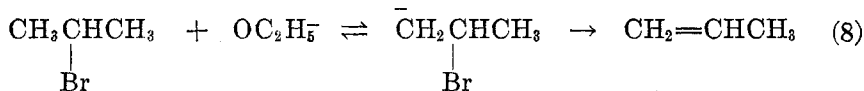
The disproportionation of uranium(V) is about 1.7 times faster in D_2O than in H_2O (56). The mechanism of this reaction is not fully understood.

IV. IONIC REACTIONS OF DEUTERIUM-CONTAINING COMPOUNDS

A. Elimination reactions

The use of deuterium-labeled compounds is particularly valuable in the study of elimination reactions, since in most cases a carbon-hydrogen bond is broken during the reaction. Thus, one should be able to determine to what extent the carbon-hydrogen bond is involved in the rate-determining step.

Shiner has studied the dehydrobromination of 2-bromopropane, using ethoxide ion (199). The rate of the elimination reaction, and also the rate of the competing substitution reaction giving 2-methoxypropane, was determined, giving the data in table 5. It is apparent that the substitution reaction is not markedly affected by deuterium substitution, whereas the elimination reaction is strongly retarded when the deuterium is in the β -position. An isotope effect, k_H/k_D , of 6.7 for reaction with the β -hydrogen may be calculated. This result, coupled with the previous observations that deuterium is not introduced into the olefin formed in base-catalyzed elimination reactions (202), shows that the anion (equation 8) is not a discrete intermediate in the reaction, and that the hydrogen halide may be lost in a concerted process (equation 9).



The $E1$ elimination reaction has also been studied, and in all cases the compound with the β -deuterium was found to react more slowly than the hydrogen analog (table 6). In the cases in which the olefin fraction was measured, it was

TABLE 6
Effect of β -deuterium on rates of S_N1 and $E1$ reactions

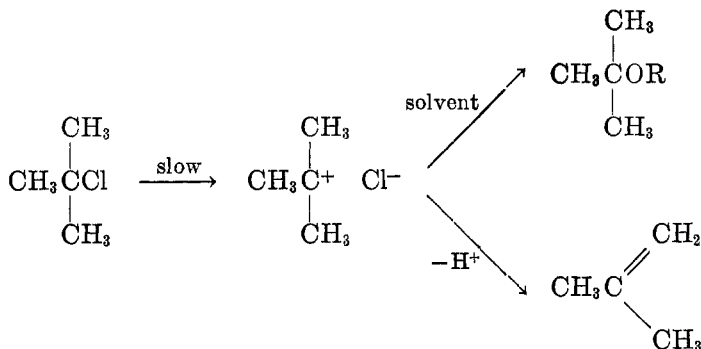
Compound	Solvent	Relative Olefin Fraction*	T	k_H/k_D^\dagger	References
			°C.		
2-Methyl-2-butyl-3- d_3 chloride.....	Aqueous ethanol	0.25/0.36	25	1.40	(200)
2-Methyl- d_3 -2-butyl-1- d_3 chloride.....	Aqueous ethanol	0.37/0.36	25	1.78	(200)
2-Methyl- d_3 -2-butyl-1, 3- d_3 chloride.....	Aqueous ethanol	0.23/0.36	25	2.35	(200)
2, 3-Dimethyl-2-butyl-3- d_1 chloride.....	Aqueous ethanol	0.63/0.66	25	1.28	(201)
2-Pentyl-1, 3- d_2 chlorosulfite.....	Dioxane		77.5	1.41	(29, 129, 130)
	Isooctane		95.5	3.34	(29, 130)
2-Pentyl-1, 3- d_2 bromide.....	HCO ₂ H		98	1.39	(130)
2-Pentyl-1, 3- d_2 tosylate.....	CH ₃ COOH		78.4	1.57	(130)
	HCOOH		39.9	1.69	
	Aqueous ethanol		58.2	1.40	
1-(<i>p</i> -Methyl- d_3 -phenyl)ethyl chloride.....	CH ₃ COOH		50	1.10	(131)
1- <i>p</i> -Tolylethyl-2- d_1 chloride.....	CH ₃ COOH		50	1.28	(131)

* Ratio of olefin fraction in deuterated compound to that of ordinary compound.

† Ratio of overall rate for the ordinary compound and its deuterium analog.

found that deuterium substitution on the β -methylene position decreased the extent of olefin formation.

The mechanism of the S_N1 - $E1$ type reaction is believed to involve the rate-determining formation of a carbonium ion, followed by either bond formation with the solvent or loss of a proton from the β -carbon. The isotope effect has been



attributed to the weakening of the β -carbon-hydrogen bond by either an inductive or a hyperconjugation mechanism (130, 200).

If this bond were weakened in the activated complex, the zero-point energy difference between hydrogen and deuterium would decrease, leading to a higher activation energy and a slower rate of reaction for the deuterium compound. The effect of β -deuterium on the extent of olefin formation is expected, since the rate of loss of a β -deuteron from the intermediate carbonium ion would be decreased, whereas bond formation with the solvent should not be affected.

If one defines hyperconjugation as an effect which operates *via* interaction with the π electrons of the unsaturated system (47) and the inductive effect as one which operates *via* interaction with σ orbitals, it would appear that either mode of electron release will have the same net electrical effect on the β -carbon-

TABLE 7
The deuterium isotope effect of some oxidation and reduction reactions

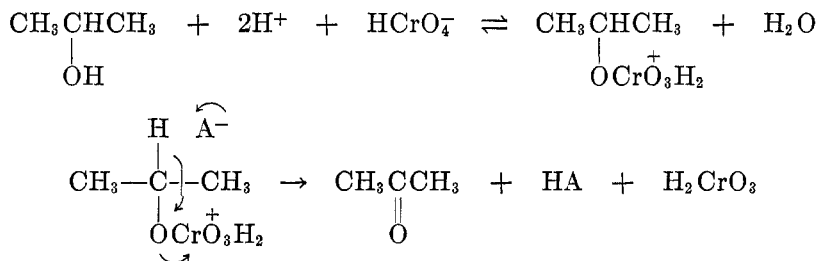
Reaction	Solvent	Reagent	Temperature	k_H/k_D	Reference
			°C.		
Oxidation of 2-propanol-2- <i>d</i> ₁	H ₂ O	HCrO ₄ ⁻	25	6.7	(228)
	Aqueous CH ₃ COOH	HCrO ₄ ⁻	0	8.2	(44)
	Aqueous CH ₃ COOH	ClCrO ₃ ⁻	0	9.6	(44)
Decomposition of diisopropyl- <i>d</i> ₁ chromate.....	Benzene		25	4.6	(128)
Oxidation of ethanol-1- <i>t</i> ₁	H ₂ O	Br ₂	37.5	6.7	(117)
Oxidation of benzyl- <i>α-t</i> ₁ alcohol.....	H ₂ O	HCrO ₄ ⁻	37.5	5	(94)
Oxidation of benzhydrol- <i>α-d</i> ₁	H ₂ O	MnO ₄ ⁻ , OH ⁻	25	6.6	(210)
Oxidation of benzaldehyde- <i>d</i> ₁	Aqueous CH ₃ COOH	HCrO ₄ ⁻	25	4.3	(231)
	H ₂ O	MnO ₄ ⁻ at pH 7	25	7.5	(234)
	H ₂ O	MnO ₄ ⁻ at pH 13	25	2.7	(234)
	H ₂ O	MnO ₄ ⁻ at pH 13	25	2.7	(234)
Oxidation of <i>p</i> -chlorobenzaldehyde- <i>d</i> ₁	H ₂ O	MnO ₄ ⁻ at pH 7	25	7.4	(234)
	H ₂ O	MnO ₄ ⁻ at pH 13	25	1.9	(234)
	H ₂ O	MnO ₄ ⁻ at pH 13	25	1.9	(234)
Oxidation of piperonal- <i>d</i> ₁	H ₂ O	MnO ₄ ⁻ at pH 8	25	4.1	(234)
	H ₂ O	MnO ₄ ⁻ at pH 13	25	3.9	(234)
	H ₂ O	MnO ₄ ⁻ at pH 13	25	3.3	(234)
Oxidation of formate- <i>d</i> ₁ ion.....	H ₂ O	MnO ₄ ⁻	25	7.4	(235)
Cannizzaro reaction of benzaldehyde- <i>d</i> ₁	Aqueous ethanol	OH ⁻	100	1.8	(231)
Cannizzaro reaction of benzaldehyde- <i>t</i> ₁	Aqueous methanol	OH ⁻	98	1.24	(212)
Reduction of <i>o</i> - and <i>m</i> -nitrobenzenediazonium ion:					
By ethanol-1- <i>t</i> ₁	Ethanol			7	(151)
By methanol-1- <i>t</i> ₁	Methanol			7	(151)

hydrogen bonds. Thus it would appear premature to use the observation of an isotope effect in these reactions as evidence for hyperconjugation.

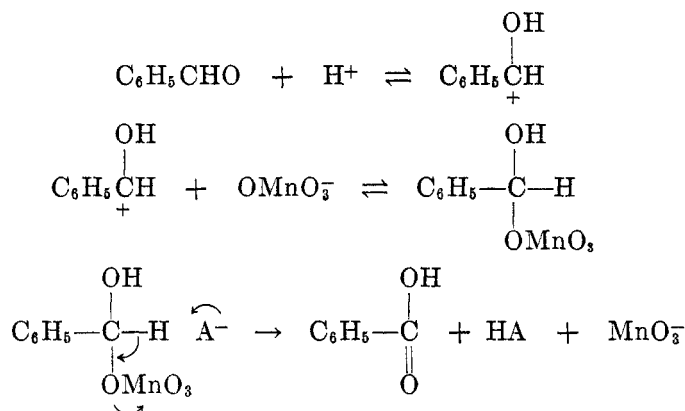
B. Oxidation reactions

Most oxidation reactions of organic compounds involve the cleavage of a carbon-hydrogen bond. The deuterium isotope effect is therefore of particular value in the study of these reactions, since it gives information concerning the nature of the rate-determining step. One of the first uses of this type was reported by Westheimer and Nicolaides (228) as part of a study of the mechanism of the oxidation of isopropyl alcohol by chromic acid. The data obtained in this and later work, as well as other similar data, are shown in table 7.

The large isotope effect noted in this reaction clearly showed that the carbon-hydrogen bond at the α -carbon atom was cleaved in the rate-determining step. This and much other data allowed the formulation of the mechanism as follows (227):

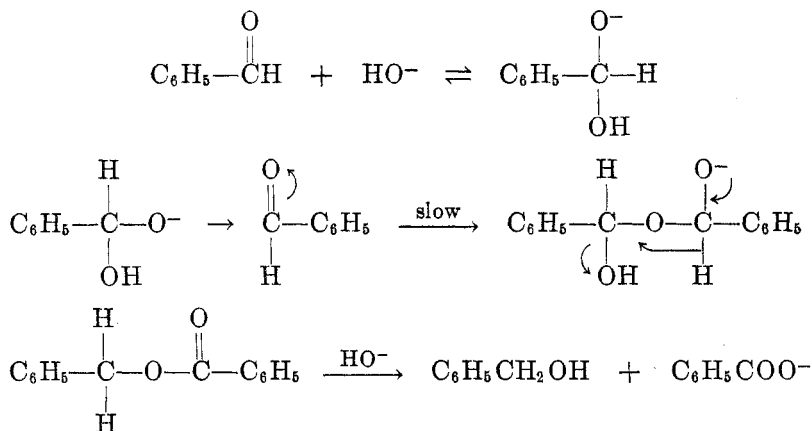


An isotope effect of similar magnitude has been observed in the oxidation of benzaldehyde, *p*-chlorobenzaldehyde, and piperonal by permanganate (234). Here again, the deuterium isotope effect was an important piece of evidence in deducing the mechanism for the acid-catalyzed reaction:



The oxidation of formate ion and benzhydrol by permanganate, the oxidation of benzyl alcohol and acetaldehyde (46) by chromic acid, and the oxidation of ethanol by bromine also gave a similar isotope effect.

The Cannizzaro reaction of benzaldehyde has been found to give a very small isotope effect, using deuterium (231) and tritium (212). As will be shown below, one might expect a fairly large value if the hydride ion were transferred in the rate-determining step. These data suggest that the reaction path may involve the formation of an intermediate ester (57), with the hydride transfer subsequent to the rate-determining step. The small isotope effect may be caused by deuterium substitution on the carbon which is attacked in the rate-determining step.

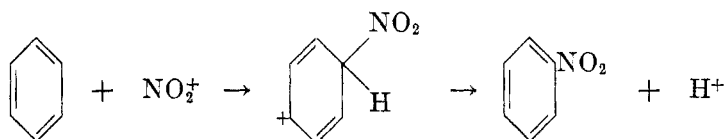


A study of the reduction of diazonium salts by ethanol-1-*t*₁ has shown not only that a carbon-hydrogen bond is broken in the rate-determining step but also that the hydrogen on the α-carbon atom is the one which effects the reduction (151).

This reaction must involve a hydride transfer, and this clearly shows that hydride-ion transfers may give isotope effects of a normal magnitude.

C. Aromatic substitution

It is generally agreed that electrophilic aromatic substitution involves the attack of a positively charged ion, such as NO_2^+ , on the aromatic ring. It is then desirable to determine whether the initial attack or subsequent loss of a proton



is the rate-determining step. Melander (148, 149, 150) has studied this problem using tritium-labeled benzene, nitrobenzene, the three possible mononitritium-substituted toluenes, and naphthalene- α - t_1 . In every case nitration gave no appreciable isotope effect, and a similar result was observed in the case of bromination. The result with benzene has been confirmed using deuterium (28, 126).

These results were interpreted as indicating that the attack by the electrophilic species was the rate-determining step. This view has been criticized by Hammond (87), for the activation energy for the second step would be small, leading to a relatively small extent of rupture of the carbon-hydrogen bond in the activated complex. This in turn might lead to a very small isotope effect, although one might expect that it should not be much less than the theoretical limit of 1.4.

Sulfonation of bromobenzene-4- t_1 , on the other hand, did give an isotope effect ($k_{\text{H}}/k_{\text{T}} = 1.82$) (19). It was suggested that this indicated the second step to be rate-controlling.

D. Enolization

Acid- and base-catalyzed enolization reactions are characterized by the loss of a hydrogen in the rate-controlling step. The isotope effect has been studied for this reaction, and the available data are summarized in table 8. It is evident

TABLE 8
Effect of deuterium substitution on the rate of enolization reactions

Reaction	Solvent	Reagent	T °C.	$k_{\text{H}}/k_{\text{D}}$	References
Bromination of nitromethane- d_3	H_2O	CH_3COO^-	25	6.53	(181)
	H_2O	$\text{ClCH}_2\text{COO}^-$	25	4.28	(181)
	H_2O	H_2O^+	70	3.78	(181)
	D_2O	CH_3COO^-	25	6.92	(181)
	D_2O	$\text{ClCH}_2\text{COO}^-$	25	5.18	(181)
	D_2O	H_2O	70	5.14	(181)
Enolization of nitroethane- d_1	D_2O	HO^-	5	5.5	(141, 143)
Enolization of nitroethane- d_2	D_2O	HO^-	0	10	(237)
Bromination of acetone- d_6	H_2O	H_2O^+	25	7.7	(184, 187)
	D_2O	H_2O^+	25	7.7	(184, 187)
	H_2O	RCOOH	25	~7.7	(187)
	H_2O	CH_3COO^-	25	~7	(187)
Bromination of 2- <i>o</i> -carboxybenzylindan-1-one- d_1	CH_3COOH	CH_3COO^-	25	4.4	(236)
Racemization of phenyl- <i>p</i> -tolylacetic- d_1 acid.....	H_2O	OH^-	100	4.6	(105)

that all these reactions give the normal, expected isotope effect. The results of the bromination of nitromethane are particularly interesting, since a different effect is obtained in water and deuterium oxide. This is of importance, since it indicates the necessity of employing the same solvent for both reactions in order to obtain quantitative data.

E. Enzyme-catalyzed reactions

The enzymatic degradation of *dl*-, (+)-, and (-)-citric- α, α - d_2 acid have been studied (145) in connection with Ogston's theory of three-center enzyme reactions (168). The citric acid recovered from the degradation of *dl*-citric acid had 50 per cent of the original deuterium; that from the (-)-citric acid had nearly all of the original deuterium; and that from the (+)-citric acid had essentially no deuterium. This indicates that the enzyme attaches itself to three centers of the substrate, for otherwise it would not distinguish between the (+) and (-) acids. The enzymatic reduction of acetaldehyde and the oxidation of ethanol- α - d_1 catalyzed by yeast dehydrogenase have also been shown to be stereospecific (135). These results indicate that the specificity of the enzyme is considerably greater than the isotope effect which might be expected in these reactions.

The oxidation of succinic acid (59, 215) and of acetic acid (204) has been found to show an isotope effect; however, the results are not sufficiently definitive to allow the calculation of a value for the isotope effect.

F. Other reactions

The reaction of triphenylsilane with moist piperidine was at first reported to give a large inverse isotope effect (76), but the reaction of this and other silanes was later shown to have a small normal isotope effect (118, 119).

In the conversion of nitroethane- α - d to acetaldehyde- d by the use of the Nef reaction, the product was found to have a higher isotope content than did the starting material. This indicates that the reaction must have a rather large isotope effect (127).

V. FREE-RADICAL REACTIONS IN SOLUTION

A. Hydrogen abstraction by free radicals

A number of these reactions have been studied by Urry (222) and by Wiberg and Slaugh (233). These and other similar data are listed in table 9.

It is first necessary to consider the cause of the inconsistencies in the data. Chlorination always leads to a low isotope effect between 1.4 and 2.2. Wiberg and Slaugh (233) obtained a higher value for the isotope effect in the bromination of toluene than did Urry (222). It has been found that toluene- α - d will exchange deuterium with hydrogen bromide under the conditions of the bromination (233), presumably by abstraction of a hydrogen from hydrogen bromide by a benzyl radical (8), since hydroquinone inhibits the exchange. Thus, a low value for the isotope effect will be obtained if the hydrogen bromide is not removed as it is formed. This probably accounts for the low value obtained by Urry.

TABLE 9
Isotope effects in reactions resulting in the abstraction of a hydrogen atom

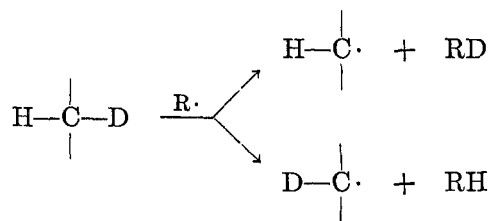
Compound	Radical	T	k_H/k_D	Reference
		°C.		
Toluene- α - d_1	Cl·	80	2.2	(222)
	Cl·	80	2.0	(36)
	Br·	80	3.3	(222)
	Br·	77	4.6	(233)
	N-Succinimidyl	77	4.9	(233)
	CH ₃ COO·	120	9.9	(222)
Toluene- α - d_2	Cl·	77	1.5	(233)
	Br·	77	4.9	(233)
	N-Succinimidyl	77	5.0	(233)
Ethylbenzene- α - d_1	Cl·	80	1.4	(222)
	Br·	80	2.4	(222)
	(CH ₃) ₂ CO·	120	4.1	(222)
	CH ₃ COO·	120	6.5	(222)
	Cl·	80	1.4	(222)
Cyclohexane- d_1	Br·	80	2.4	(222)
	CH ₃ COO·	120	6.9	(222)
	Cl·	80	1.4	(222)
2-Propanol-2- d_1	CH ₃ COO·	120	6.3	(222)
Diphenylmethane- α - d_1	CH ₃ COO·	120	6.7	(222)
Acetic- α - d_1 acid.....	CH ₃ COO·	120	8.3	(222)
Propionic- α - d_1 acid.....	CH ₃ COO·	120	6.8	(222)
Isobutyric- α - d_1 acid.....	CH ₃ COO·	120	5.3	(222)
Isobutyryl- α - d_1 chloride.....	CH ₃ COO·	100	1.2	(178)
2-Methylpropane-2- d_1	Cl·	-15	1.8	(36)

Price and Morita (178) have found that methyl radicals react with isobutyryl chloride at both the α - and the β -position, with the relative rates of 12:1. Since Urry (222) assumed the reaction to occur only at the α -position of the carboxylic acids, his values are probably high in these cases. The isotope effect noted by Price and Morita (178) is unusually low and may be in error, since the value was not measured directly. It might also be mentioned that the rather large isotope effect noted in the reaction of methyl radicals with toluene (222) is considerably above the expected value ($k_H/k_D = 4.5$) at 120°C.

In the case of toluene, the results indicate that the magnitude of the isotope effect is proportional to the reactivity of the free radical. Thus, the reactions with the smallest activation energy gave the smallest isotope effect. Before considering the origin of this effect, it is necessary to consider the type of isotope effects being measured.

The isotope effects previously mentioned usually have been determined by measuring the relative rates of reaction of a deuterium compound and its hydrogen analog. This has been termed an intermolecular isotope effect (133). In the hydrogen-abstraction reactions, the relative rates of reaction of a hydrogen atom and a deuterium atom attached in equivalent places in the same molecule are usually determined. This is commonly known as an intramolecular isotope effect.

In this case, the energy of the reactant is the same for both reactions, and the difference in zero-point energy arises in the activated complex. If a deuterium atom is abstracted,



the resultant radical will still have the zero-point energy of the hydrogen. The removal of a hydrogen atom leads to a radical having a carbon-deuterium bond, with its lower zero-point energy. Thus, an energy diagram for the reaction will correspond to figure 4 rather than figure 2. The activation energy for the removal of a deuterium atom will again be larger than that for the removal of a hydrogen atom, and the magnitude of the isotope effect should be approximately the same for an intramolecular or an intermolecular process.

The curves in figure 5 represent the potential-energy curves for the reactants and the products. The distance between the equilibrium distance for the carbon-hydrogen bond in the reactant and the intersection of the potential-energy curves should be a measure of the strength of bonding of the hydrogen or deuterium in the activated complex. Thus, in the reaction in which the bond has been least affected, the bonding in the activated complex will be the greatest. In the hydrogen-abstraction reaction the reactant has only one energy level, and

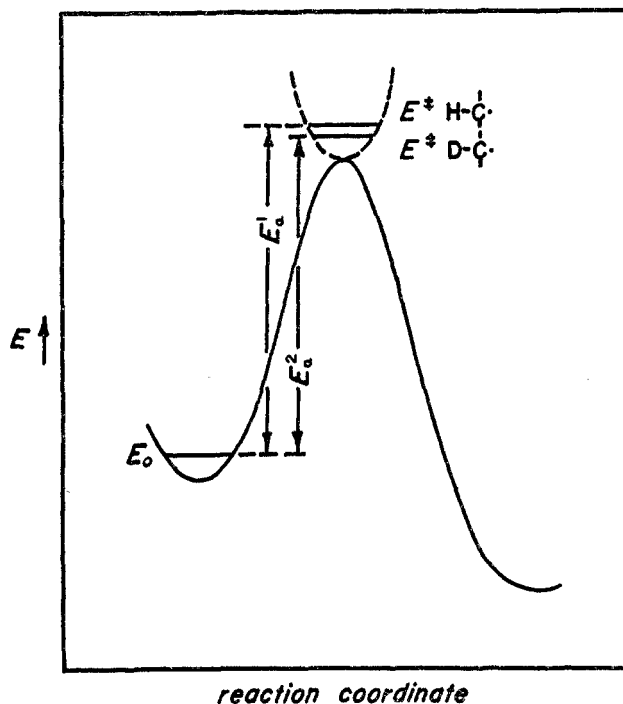


FIG. 4. Potential-energy profile

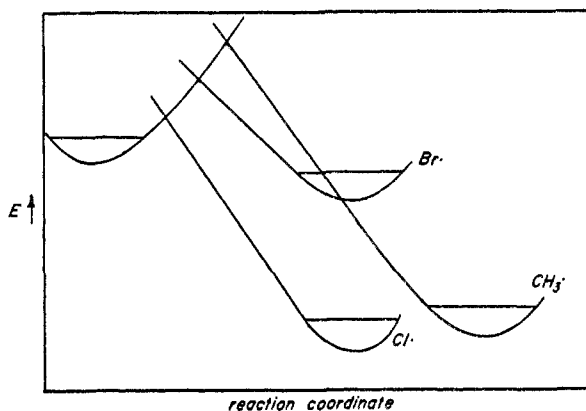


FIG. 5. Potential-energy curves for the reaction of methyl, bromine, and chlorine radicals with toluene.

the difference in energy between hydrogen and deuterium arises in the activated complex. If bonding is strong, there will be little difference in the two activated complexes, whereas, if bonding is weak, the difference will be at its maximum. The reaction with a chlorine radical has the lowest activation energy and consequently the least rupture of the carbon-hydrogen bond, leading to a low isotope effect. The reaction with a methyl radical has a relatively high activation energy, giving extensive rupture of the carbon-hydrogen bond and a large isotope effect. This argument can also be used to explain the differences observed in intermolecular reactions.

The isotope effect has been applied to a study of the optical character of a free radical (48a). The reaction of *N*-bromosuccinimide with optically active ethylbenzene- α - d_1 should effect the replacement of the hydrogen to a greater extent than the deuterium, leading to optically active α -bromoethylbenzene- d_1 if the intermediate radical would support optical activity. The observation that the product was racemic indicated the radical to be planar at some time.

B. Other reactions

Bartlett and Tate (14) have studied the polymerization of allyl acetate and allyl-1- d_2 acetate in order to obtain evidence concerning the nature of the chain-terminating reaction. The rate of polymerization for the labeled compound was 1.93 to 2.89 times as fast as that for the unlabeled compound, indicating that the terminating step was the transfer of an α -hydrogen from the allyl group to the growing chain. An isotope effect, k_H/k_D , for this step was calculated to be 3.3.

The autoxidation of *cis*-9-octadecene-8,8,11,11- d_4 has been found to proceed at about one-fifth the rate for the unlabeled compound (146), indicating that oxidative attack at the α -methylene position was the important chain-propagating reaction. The autoxidation of methyl oleate-9,10- d_2 was found to have a longer induction period than the reaction of methyl oleate, but the reactions proceeded at about the same rate (120).

The homogeneous catalytic hydrogenation of quinone in quinoline solution with dissolved cuprous acetate as the catalyst was found to proceed more slowly with deuterium than with hydrogen (38).

VI. ISOTOPE EFFECTS IN GAS-PHASE REACTIONS

A. Reactions of hydrogen atoms

The reactions of hydrogen and deuterium atoms with hydrogen, deuterium, and deuterium hydride have been studied extensively (66, 223). At 600–750°C. the reaction of hydrogen atoms with hydrogen proceeds about 2.4–2.5 times as fast as the reaction between deuterium atoms and deuterium. The rate of reaction of hydrogen and deuterium atoms with hydrogen chloride has been shown to be in the ratio $k_{\text{H-DCl}}:k_{\text{D-HCl}}:k_{\text{H-HCl}} = 1.3:1:3$ (208). In the above reactions a bond to hydrogen or deuterium is broken in the rate-determining step, and an isotope effect would be expected.

The combination of hydrogen atoms has been found to proceed 1.36 times as fast as the combination of deuterium atoms (7). This is expected, since the hydrogen or deuterium atom has no zero-point energy (177). The reactions of hydrogen and deuterium atoms with oxygen and nitrous oxide were found to have about the same rate (61, 152, 153, 154).

B. Reactions of hydrogen, deuterium, and tritium

The reaction of chlorine with hydrogen was found to be 13.4 times as fast as that with deuterium at 0°C., 9.8 times as fast at 32°C. (192), and 3 times as fast at 30°C. by another worker (68). The reaction of chlorine with tritium hydride was found to give an isotope effect, $k_{\text{H}}/k_{\text{T}}$, of 3.72 at 0°C., and the effect of temperature on the ratio was given by $R = (1.35 \pm 0.03)e^{552 \pm 7/RT}$ (107).

The reaction of bromine with hydrogen has been found to be 3.3 times as fast as the reaction with deuterium at 578°C. (10, 26). The reaction of iodine with hydrogen and deuterium has also been studied. An isotope effect, $k_{\text{H}}/k_{\text{D}}$, of about 2 was noted at 430°C. (23, 33, 73, 213).

The reaction of oxygen with hydrogen was found to be 1.56 times as fast as that with deuterium at 560°C. (42, 71, 92, 93), and the corresponding reaction of nitric oxide gave an isotope effect, $k_{\text{H}}/k_{\text{D}}$, of 1.4 at 800°C. (91).

The homogeneous thermal addition of hydrogen to ethylene at 550°C. has been found to be 2.5 times as fast as the corresponding reaction with deuterium (176, 229).

The reaction of methyl radicals with hydrogen and deuterium gave an isotope effect, $k_{\text{H}}/k_{\text{D}}$, of 5.5 at 130°C. and 2.4 at 290°C. The corresponding reaction of methyl- d_3 radicals gave values of 4.1 at 130°C. and 3.0 at 290°C. (139, 140). These results do not appear to be consistent with the statement (140) that there is little difference in activation energy between the reactions of methyl and methyl- d_3 radicals. The reaction of either methyl or methyl- d_3 radicals with hydrogen deuteride gave an isotope effect, $k_{\text{H}}/k_{\text{D}}$, of 1.7–1.8 at 210°C. (230).

C. Thermal and photochemical decomposition reactions

The decomposition of hydrogen iodide has been found to proceed 1.6 times as fast as the decomposition of deuterium iodide at 430°C. (23, 33, 73, 213). The decomposition of diethyl ether and its fully deuterated derivative gave an isotope effect of 2.14, whereas the fully inhibited reaction had an isotope effect of 1.78 (50). The decomposition of acetaldehyde and acetaldehyde- d_4 gave an isotope effect of 2.5 at 535°C. (190, 203), and the decomposition of ethane and ethane- d_6 gave an isotope effect of 3 at 613°C. (189).

The mercury-photosensitized decomposition of ammonia- d_3 proceeds at one-tenth the rate for ammonia (110). The photochemical decomposition of phosphine- d_3 was found to be 10 per cent faster than the decomposition of phosphine (155). Many of these reactions are complex, and since the measured isotope effects are for the overall reaction, the effect on each individual step is not known.

D. Other reactions

The reaction of sodium atoms with hydrogen and deuterium chlorides at 240°C. gave an isotope effect, k_H/k_D , of 1.20 (15, 60). The reaction of methyl iodide with hydrogen iodide and deuterium iodide gave an isotope effect of 1.4 at 250°C. and 310°C. (166). The relative rates of photochlorination of chloroform and chloroform- d have been measured from -20°C. to 180°C. The ratio of rates is given by $k_H/k_D = (1.4 \pm 0.2)e^{(710 \pm 90)/RT}$ (167).

The reaction of methyl radicals with acetone has been shown to be 3.5 times as fast as the reaction between methyl- d_3 radicals and acetone- d_6 (140). No difference in activation energy was found for the reaction of methyl and methyl- d_3 radicals with acetone. The difference in activation energy for the reaction of methyl radicals with acetone and acetone- d_6 was found to be 1.64 ± 0.08 kcal. for the photochemical reaction between 150°C. and 250°C. (137) and 1.67 ± 0.09 kcal. for the thermal reaction between 466°C. and 525°C. (138, 224).

The mercury-photosensitized polymerization of acetylene was found to be about 30 per cent faster than the polymerization of acetylene- d_2 at 25°C. (112). No isotope effect was noted in the addition of ethyl radicals to ethylene, acetylene, and their deuterium-substituted derivatives (109).

A study of the photooxidation of hydrogen and deuterium iodides led to the following expression for the ratio of rates at 0°C. (45).

$$k_{(D+O_2+M)}/k_{(H+O_2+M)} \times k_{(H+HI)}/k_{(D+DI)} = 1.89$$

E. Mass spectra

The mass spectra of a number of saturated (53, 54, 62, 195, 209, 219) and unsaturated (51, 161, 162) hydrocarbons have been studied. In each case, the probability of removing a deuterium atom was less than the probability of removing a hydrogen atom. A similar effect has been noted with chloroform, which gave a ratio of 3 (52), acetaldehyde (34), isopropyl alcohol (70) and with hydrogen, deuterium, and tritium (55).

TABLE 10
Isotope effects in reactions of metals with water

Metal	Reagent	<i>T</i>	k_H/k_D	References
		°C.		
Li.....	H ₂ O	30	1.85 (1.49)	(100, 101, 106)
	H ₂ SO ₄	40	1.49	(100, 101)
Na.....	H ₂ O	30	2.6 (2.8)	(49, 98, 100, 101, 106)
	H ₂ SO ₄	40	2.9	(65, 100, 101)
K.....	H ₂ O	30	1.44 (1.85)	(100, 101, 106)
Mg.....	H ₂ SO ₄	30	1.65 (2.33)	(100, 101, 106)
Ca.....	H ₂ O	30	1.41	(106)
	H ₂ O	90	1.57	(100, 101)
Zn.....	H ₂ SO ₄	90	1.30	(65, 100, 101)
	H ₂ SO ₄	30	6.1	(65, 106)
Al.....	H ₂ SO ₄	90	5.6	(100, 101)
	H ₂ O	400	1.6	(89)
	H ₂ SO ₄	30	4.5	(65, 106)
	H ₂ SO ₄	90	4.0	(100, 101)
Si.....	NaOH	30	4.9	(106)
	NaOH	90	4.3	(100, 101)
Cr.....	NaOH	90	2.3	(100, 101)
Cr.....	H ₂ SO ₄	90	4.5	(100, 101)
Mn.....	H ₂ SO ₄	90	5.1	(100, 101)
Fe.....	H ₂ SO ₄	30	6.6	(106)
	H ₂ SO ₄	90	4.3	(100, 101)
Co.....	H ₂ SO ₄	90	4.1	(100, 101)
Ce.....	H ₂ SO ₄	90	2.5	(100, 101)

VII. DEUTERIUM ISOTOPE EFFECTS IN HETEROGENEOUS REACTIONS

A. Reaction of metals with water

Some of the first examples of the deuterium isotope effect were observed in the reaction of water vapor with iron at 500°C. (24, 97) and in the reaction of dilute sulfuric acid with zinc, aluminum, calcium, and sodium (65). The results of a large number of similar experiments have been reported; these data are summarized in table 10. The relative rates were measured by comparing the deuterium content of the evolved hydrogen with that of the water.

In one case the rate of reaction of magnesium with water and with deuterium oxide was measured. In acid solution the rates were the same, but in sodium chloride solution the rate was 30 times faster in D₂O than in H₂O (43). This observation does not appear to be in accord with the other results.

B. Reactions of hydrogen

The metal surface catalyzed reaction of hydrogen with deuterium has been found to have one-third the rate of the ortho-para hydrogen conversion at 14°C. (64). This type of reaction has been reviewed by Eley (58).

The hydrogenation of ethylene in the presence of nickel (218), platinum (67), iron (122, 123) and copper (108, 176, 229) catalysts has been studied. In general, deuterium reacts less readily than hydrogen at room temperature, but as the temperature is raised, the rates become identical. When an iron catalyst is used, deuterium is more reactive than hydrogen above 100°C. Taylor and Dibeler recently reported a careful reinvestigation of this type of reaction using mass

spectrometric methods, and they also reviewed the previous work (214). In connection with studies on hydrogenation reactions, the velocity of adsorption of hydrogen and deuterium by various catalysts has been studied (11, 147, 172).

The metal surface catalyzed reaction between hydrogen and oxygen has been found to show an isotope effect, k_H/k_D , of 2.31 at 255°C. on nickel (152), of 2 below 100°C. on lead (216), of 1.5 at 100–200°C. on lead, and of 1.0 above 200°C. on either lead or palladium (217). The reduction of nitrous oxide by hydrogen showed an isotope effect of 2.1 at 192°C. in the presence of a nickel catalyst (152). Under the same conditions the reaction of hydrogen with oxygen showed an isotope effect of about 2 (152).

The reduction of cuprous chloride (104) and silver chloride (103) by hydrogen was found to be more rapid than the reduction by deuterium.

C. Other reactions

The rate of decomposition of ammonia- d_3 on a tungsten wire at 680°C. was slower than the decomposition of ammonia by a factor of 1.6 (13, 111). The catalyzed decomposition of hydrogen peroxide proceeds about five times as fast in H_2O as in D_2O (75, 169).

The reaction of calcium carbide with water has been reported to give isotope effects of 2.3 (106, 188) and 1.5 (100, 101). The reaction of aluminum carbide with water was reported to give an isotope effect of 3.9 at 0°C. (12), 2.44 at 30°C. (106), 2.03 at 40°C. (100) and also 23 (221). The reaction of ferrous sulfide with dilute sulfuric acid gave an isotope effect of 2.46 at 30°C. (106). The reaction of calcium hydride with water showed essentially no isotope effect (100). The reaction of lithium aluminum hydride or deuteride with water gave a small but not consistent isotope effect (118).

VIII. SUMMARY

The deuterium isotope effect arises largely from the difference in zero-point energy between a bond to hydrogen and the corresponding bond to deuterium. The maximum isotope effect will be obtained when the bond to hydrogen or deuterium is essentially completely cleaved in the activated complex, and the isotope effect will decrease with increasing bonding in the activated complex. In general, in any series of related reactions, the reaction with the lowest activation energy will have the lowest isotope effect.

Although the isotope effect is useful in determining whether a bond to hydrogen is cleaved in the rate-determining step, it must be used with caution. An isotope effect of 3.3 has been found in the decomposition of β -deuterium-substituted chlorosulfites (29, 130), in which the bond to hydrogen or deuterium is not cleaved in the rate-determining step, and essentially no isotope effect was noted in the reaction of Grignard reagents with methanol (232) or water (170), a reaction which probably does involve the cleavage of a bond to hydrogen. These reactions, however, are not typical of most reactions which would be studied by the use of this technique.

It has also been observed that there is no apparent difference in magnitude

for the isotope effect in the removal of hydrogen or deuterium as a proton, a hydride ion, or an atom.

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