[CONTRIBUTION FROM THE DIVISION OF PURE CHEMISTRY, NATIONAL RESEARCH COUNCIL, OTTAWA 2, CANADA]

Some Deuterium Isotope Effects. III.[1a] An Inverse γ-Deuterium Isotope Effect

BY K. T. LEFFEK,[1b] J. A. LLEWELLYN[1b] AND R. E. ROBERTSON

RECEIVED JUNE 10, 1960

α-, β- and γ-deuterium isotope effects have been measured for the hydrolysis reactions in water of four *n*-propyl compounds. Interpretation of the α- and β-kinetic isotope effects follows existing theory. The γ-effect is attributed to inhibition of vibrations involving the γ-CH_3 group by increased intramolecular van der Waals forces arising in the transition state of the reaction.

The consequences of replacement of protium hydrogen by deuterium have been investigated for a series of compounds undergoing nucleophilic substitution reactions.[2,3a,b] The effects of isotopic substitution in the α-position have been shown to result from changes in spatial relationships which occur during the activation process,[2,3a,b] and it appears[4,5] that β-substitution provides information concerning hyperconjugative stabilization of the electron-deficient portion of the transition state. Isotopic substitution at more remote sites does not appear to have been investigated, with the exception of certain studies involving conjugated positions in alkyl substituents on the aromatic ring[6-10] so that it is hoped that the present work may provide new information concerning this aspect of deuterium kinetic effects.

A series of hydrolyses in water was examined; the reactions may be symbolized by

$$CH_3CH_2CH_2X + H_2O \longrightarrow CH_3CH_2CH_2OH + H^{(+)} + X^{(-)}$$

Here X, the leaving group, is bromide, iodide, benzenesulfonate or methanesulfonate. The conductimetric methods applied in previous studies were used to measure the pseudo first-order rate constants and have been described in detail elsewhere.[11] Some of the light compounds had already been examined and current measurements are in excellent agreement with the previously published data.[12a,b,c]

Results and Discussion

The consequences of γ-deuterium substitution are detailed in Table I.

The effects of α- and β-isotopic substitution have also been measured and are given in Tables II and III.

TABLE I

γ-ISOTOPE EFFECTS FOR *n*-PROPYL COMPOUNDS

Compound	10^4k_H, sec.$^{-1}$	10^4k_D, sec.$^{-1}$	*T*, °C.	k_H/k_D (± 0.006)
Benzenesulfonate	2.033	2.147	54.183	0.947
Methanesulfonate	1.370	1.453	60.004	.943
Bromide	1.629	1.740	80.009	.921
Iodide	2.230	2.410	90.003	.924

TABLE II

β-ISOTOPE EFFECTS FOR *n*-PROPYL COMPOUNDS

Compound	10^4k_H, sec.$^{-1}$	10^4k_D, sec.$^{-1}$	*T*, °C.	k_H/k_D (± 0.006)
Benzenesulfonate	2.051	1.902	54.251	1.078
Methanesulfonate	1.370	1.276	60.004	1.074
Bromide	1.602	1.520	79.994	1.054
Iodide	2.230	2.094	90.003	1.065

TABLE III

α-ISOTOPE EFFECTS FOR *n*-PROPYL COMPOUNDS

Compound	10^4k_H, sec.$^{-1}$	10^4k_D, sec.$^{-1}$	*T*, °C.	k_H/k_D (± 0.006)
Benzenesulfonate	2.042	1.974	54.192	1.034
Methanesulfonate	1.370	1.322	60.004	1.036
Bromide	1.629	1.663	80.009	0.980
Iodide	2.230	2.217	90.003	1.006

The α-effects follow the pattern outlined in an earlier publication[3a] and it suffices to say that they indicate decreasing crowding in the transition state, about the carbon atom forming the reaction center passing along the series, Br, I, methanesulfonate. The decreased crowding is a consequence of either diminishing nucleophilic interaction, reduced steric hindrance from the leaving group, or more probably both.

The γ-effects were inverse, *i.e.*, the heavy compound reacted more rapidly than the light compound—an unexpected result. It seemed unlikely that electronic effects (inductive, hyperconjugative, etc.) would be transmitted through such a distance along a saturated hydrocarbon chain so that hypotheses of this nature were rejected. The possibility of a "thermodynamic" effect arising from the mass change caused by isotopic substitution was also considered. The effect of increased mass on the translational contribution to the thermodynamic parameters is in a direction which will cause a decreased rate for reactions such as those studied here where two molecules become attached in the transition state.

The rotational effect is more difficult to assess but can be considered as follows: the rotational entropy of a molecule is proportional to log ΠI where ΠI is the product of the moments of inertia about the three axes. In the initial state the total rotational entropy will be dependent on the sum

---

(1) (a) N. R. C. No. 5971. First presented at Spring A.C.S. Meeting, Cleveland, Ohio, April, 1960. (b) Post-doctoral Fellow, N.R.C., 1960.

(2) J. A. Llewellyn, R. E. Robertson and J. M. W. Scott, *Can. J. Chem.*, **38**, 222 (1960).

(3) (a) K. T. Leffek, J. A. Llewellyn and R. E. Robertson, *ibid.*, **38**, 1505 (1960); (b) in press.

(4) E. S. Lewis, Tetrahedron "Hyperconjugation Conference," **5**, 143 (1959).

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

(6) E. S. Lewis and G. M. Coppinger, THIS JOURNAL, **76**, 4495 (1954).

(7) R. R. Johnson, Thesis, The Rice Institute, Houston, Texas, 1958.

(8) E. S. Lewis and E. B. Miller, THIS JOURNAL, **75**, 429 (1953).

(9) E. S. Lewis, J. L. Kinsey and R. R. Johnson, *ibid.*, **78**, 4294 (1956).

(10) V. J. Shiner and C. J. Verbanic, *ibid.*, **79**, 373 (1957).

(11) R. E. Robertson, *Can. J. Chem.*, **33**, 1536 (1955).

(12) (a) R. E. Robertson, *ibid.*, **35**, 613 (1957); (b) P. W. C. Barnard and R. E. Robertson, in preparation; (c) P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **37**, 1491 (1959).

of two such terms: one for the attacking water molecule, the other for the *n*-propyl compound under consideration

$$S_{\text{rot}} \propto (\log \Pi I_{\text{H}_2\text{O}} + \log \Pi I_{\text{RX}})$$

$$S_{\text{rot}} \propto (\log \Pi I_{\text{H}_2\text{O}} \times \Pi I_{\text{RX}})$$

In the transition state we will have a single term $\log \Pi I_{\text{RXH}_2\text{O}}$ which will be greater than $\log \Pi I_{\text{RX}} \Pi I_{\text{H}_2\text{O}}$.[13] Thus there will be an increase in rotational entropy as the system attains the activated state.[14] The magnitude of the increase (which favors reaction) will depend on the proximity of the center of gravity (c.g.) to the point at which the mass increase from reaction occurs (the reaction center). If the c.g. is close to this point, the increase in ΠI will be less so that the rotational activation entropy will be reduced compared with a reaction where the c.g. is remote from the reaction center and the added mass operates through a longer arm. Isotopic substitution will alter the position of the c.g. and considering the above argument it may be seen that substitution close to the reaction center (*e.g.*, α-deuteration) will move the c.g. closer to the reaction center thereby favoring a reduced rate for the heavy compound as a consequence of reduced rotational entropy of activation. Conversely, deuteration at a remote site might produce an increased rate by displacing the c.g. away from the reaction center. Thus an *increased* rate from this source appeared possible and it was necessary to calculate rotational activation entropies in order to settle the issue. The calculations are simple but laborious and will not be described here; it must be noted that an additional complexity appears in the form of the rotational isomers which are possible for *n*-propyl compounds. They have been studied by several groups and their approximate relative proportions are known so that the entropy calculations can contain suitably weighted values for each. The conclusion which was arrived at as a consequence of considering several possible transition state models in turn, in conjunction with each initial state isomer and a mixture of them, was that it was not possible to account for any inverse isotope effect in the *n*-propyl halide systems by this method since effects in excess of unity ($k_{\text{H}}/k_{\text{D}} > 1$) were predicted. The methanesulfonate was not examined. As usual we have neglected vibrational thermodynamic contributions in comparison with the size of zero point changes arising from the same source.

The treatment so far has neglected solvation effects and, as was pointed out by a referee, probably gives maxima for the translational–rotational contributions. The qualitative disagreement with some of the observed effects is important, as is the fact that the isotope effect changes direction with change in substitution site. It is difficult to imagine that any translation–rotation contribution involving the complex[15] solvation shell present in both initial and transition states could be sufficiently sensitive to such small mass and position alterations as to change the direction of the isotope effect (acceleration to deceleration). Additionally, if the system can be regarded as two entities which become united in the transition state, then translational contributions tend to slow reaction for the heavy compound, as would the rotational contribution if we consider that activation produces a large mass increase which is roughly symmetrically disposed. The predicted effects thus have $k_{\text{H}}/k_{\text{D}} > 1$ in agreement with our β-effects but not with the γ- or all of the α-effects. Undoubtedly translation–rotation effects are present but we can only consider their direction and not their magnitude because of difficulties over the model of reaction. Accordingly it seems reasonable to consider that they form a background upon which are superimposed the positional variations in these isotope effects.

The γ-effect is attributed to transition state changes in the zero point energy produced by steric inhibition of vibrations involving the terminal methyl group, probably by the action of the leaving group.

The diagrams show an initial state configuration and a transition state configuration of the type discussed by several other workers.[16–18] If we consider that the $\text{C}\alpha\text{C}\beta\text{H(3)H(4)C}\gamma\text{H}_3$ configuration is unaltered, it is obvious that there is a reduction in the $\text{C}\gamma\text{H}_3\text{–X}$ distance as a consequence of rehybridization of the bonds to $\text{C}\alpha$ and the alteration in $\text{C}\beta\text{C}\alpha\text{X}$ to something approaching 90°. This reduction in intramolecular distance will be reflected as increased non-bonding interatomic forces, and an increase in the steepness of the potential energy curve describing vibrational energetics seems inevitable. It may be that the change in the Me–X distance is greater than that indicated in the above model. The β-effects that have been observed can be considered to be the result of a weak neighboring hydrogen interaction of the type considered by Kreevoy and Eyring[19a] and that applied to β-deuterium isotope effects by Streitwieser.[19b] If this is so and a β-hydrogen atom is interacting to some extent with the $\text{C}\alpha$ p-orbital, then the γ-methyl group may be swung into an even more obstructed position with respect to the X group as in diagram 3. Obviously the β-hydrogen interaction will be weak compared with that involved in a carbonium ion reaction[20] and presumably the total potential energy will be minimized with respect to these two interactions so that the potential energy increase arising from rotation about the $\text{C}\alpha\text{–C}\beta$ bond raising intramolecular van der Waals forces

---

[13] A numerical example from a similar system may assist; $\Pi I_{\text{H}_2\text{O}}$ is about 10^{-120} and ΠI_{MeI} is about 10^{-115}, the product will be 10^{-235}, far less than can possibly be anticipated for any $\text{H}_2\text{O–MeI}$ combination.

[14] The constant terms in the expression for rotational entropy have not been considered, but these cancel when the isotopic comparison is made.

[15] References and discussion in: R. E. Robertson, R. L. Heppolette and J. M. W. Scott, *Can. J. Chem.*, **37**, 803 (1959); R. E. Robertson, *Suomen Kemi.*, **A133**, 63 (1960).

[16] E. D. Hughes, C. K. Ingold and I. Dostrovsky, *J. Chem. Soc.*, 173 (1946).

[17] A. G. Evans, *Trans. Faraday Soc.*, **42**, 719 (1946).

[18] References in J. Hine "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 155 *et seq.*

[19] (a) M. M. Kreevoy and H. Eyring, THIS JOURNAL, **79**, 5121 (1957); (b) A. Streitwieser, Jr., R. H. Jagow, R. S. Fahey and S. Suzuki, *ibid.*, **80**, 2326 (1958).

[20] This is reflected in the small β-isotope effect which is almost of the same order as expected "thermodynamic" effects.

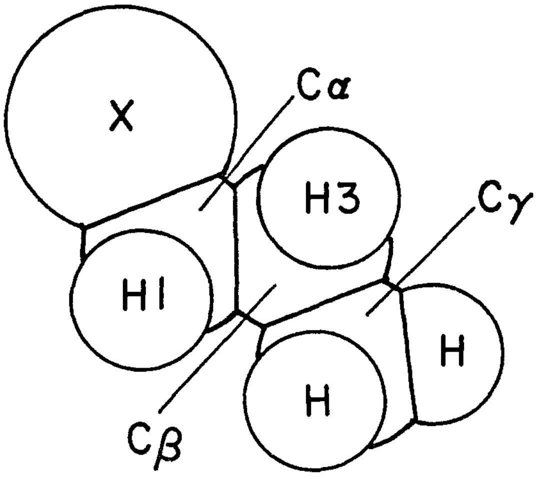

Fig. 1.—An initial state configuration.

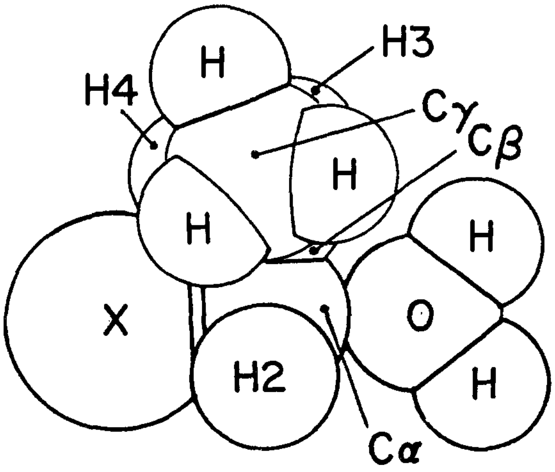

Fig. 2.—Least obstructed transition state configuration.

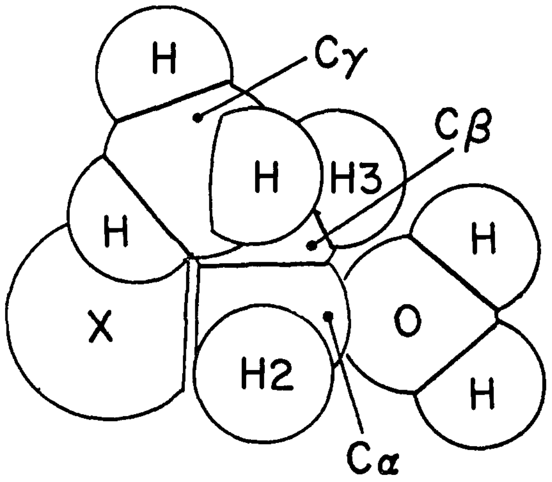

Fig. 3.—Transition state with β-hydrogen interaction.

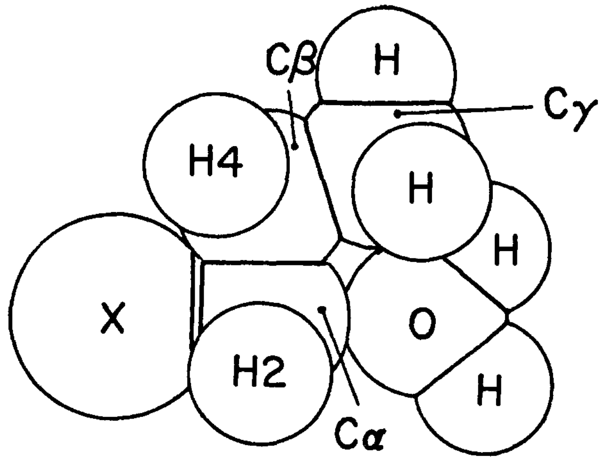

Fig. 4.—Water-obstructed transition state configuration.

cannot be too great. Because β-hydrogen interaction does seem possible we do not consider that the incoming water molecule hinders the internal motion of the terminal CH$_3$ as shown in diagram 4.

It is interesting to note that if the changing β-effects with changing X are interpreted as a consequence of increasing hydrogen interaction produced by more advanced ionization and a more positive α-carbon atom, then the α-isotope effects change in agreement with the idea of a more distant X group in the transition state, and the γ-effect alterations also indicate reduced obstruction.

Experimental

Deuterated n-Propyl Compounds.—Samples of n-propyl-1,1-d_2 bromide, n-propyl-2,2-d_2 bromide and n-propyl-3,3,3-d_3 bromide (minimum isotopic purity 98%) were purchased from Merck & Co. Ltd. The positions of the deuterium atoms were checked by comparing the n.m.r. spectra for the above three compounds with that for an undeuterated sample of n-propyl bromide. The samples were found to be deuterated in the positions specified to the following extent: n-propyl-1,1-d_2 bromide 90%, n-propyl-2,2-d_2 bromide 93% and n-propyl-3,3,3-d_3 bromide 98%.

Each of the n-propyl bromides was converted into the corresponding methanesulfonate and benzenesulfonate by shaking 1 g. of bromide with an equimolar amount of the appropriate silver sulfonate, dissolved in 10 ml. of acetonitrile, for *ca.* 100 hours at room temperature. The precipitated silver bromide was removed by filtration and the remaining solution evaporated to dryness. The residue was extracted with anhydrous ether and, after removal of the ether, the n-propyl sulfonates were purified by distillation under a vacuum. The yields obtained varied between 55 and 75%.

The deuterated n-propyl iodides were prepared by heating 0.5 g. of the appropriate propyl benzenesulfonate with 1.25 g. of dried, powdered potassium iodide and 0.5 ml. of triethylene glycol to 50° under a vacuum. The liberated n-propyl iodide was collected in a liquid nitrogen trap and redistilled at reduced pressure. Yields of 80 to 85% were usually obtained.

It is considered extremely unlikely that any deuterium exchange could take place during the conversion of the n-propyl bromides to sulfonates and the subsequent conversion of the benzenesulfonates to iodides.[21] The kinetic purity of the compounds was verified by the straight line kinetic plots which were obtained in all cases. With the techniques which have been developed in this Laboratory, this test has repeatedly proved to be more sensitive than the normal methods of analysis.

The Kinetic Method.—The conductance method of determining rates of solvolysis as adapted by us has been described in a previous publication.[22] Since the accuracy of rate determinations has such an important bearing on the confidence to be placed in the isotope effects, it will be useful to detail certain changes in technique which have been adopted since the earlier publication. In this period three different bridges of the Shedlovsky type[23] have been used with varying ancillary components without showing any significant differences in the derived rates. Of the various

---

(21) L. Leitch, private communication.

(22) R. E. Robertson, *Can. J. Chem.*, **33**, 1536 (1955).

(23) T. Shedlovsky, THIS JOURNAL, **52**, 1793 (1930).

cell designs tested, the pipet-type cell[24] with capillary filling and overflow tubes appears the most easily adapted to the kinetic requirements that vapor phase above the solution be absent. Shiny platinum electrodes of such size that cell working resistance was in the range 1–50 KΩ proved satisfactory. No particular precaution was required in filling the cells provided the solution had been degassed previously. With high boiling esters this could be done directly just before filling. With the lower boiling halides, it was necessary to freeze the sample in a side arm prior to degassing the backing electrolyte and then to make up the solution under vacuum. Aside from certain rather obvious precautions with respect to the determination of temperature, the chief refinement of technique since the earlier paper is a growing appreciation of the defects of glass as a cell material and the precautions required to ensure highest accuracy in results. In this connection it is wise to regard glass as a sponge which must be thoroughly saturated prior to use in rate determinations with the anion to be produced; *e.g.*, cells in which alkyl iodides are studied must be repeatedly washed with the backing electrolyte solution, the exact number of washes depending on the previous history of the cell.

Temperature Control and Measurement.—The use of a platinum thermometer would seem to be the most satisfactory method of ensuring reliable temperature measurement, other methods being more subject to human frailty. Frequent determinations of the ice point cannot be safely neglected[25] where the thermometer is subject to normal bath vibrations and normal hazards of handling. Adequate stirring of the bath to ensure the same temperature at all cell positions is an obvious requirement. We have found that a large volume sump pump of brass or bronze similar to Eastern Industries model 17-S which drives water through a fan-shaped jet under a perforated false bottom and end baffle creates the required condition.

The necessity for positioning the contact thermometer (Labora) and intermittent heater to ensure feed-back conditions is well known.

Acknowledgment.—It is a pleasure to acknowledge the careful rate determinations made by Mr. S. Sugamori throughout the course of this investigation.

---

[24] G. Jones and G. M. Bollinger, THIS JOURNAL, **53**, 411 (1931).

[25] E. H. McLaren, *Can. J. Phys.*, **35**, 78 (1957).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL.]

Secondary Deuterium Isotope Effects in the Reactions of Carboxylic Acid Derivatives[1a]

BY MYRON L. BENDER[1b] AND MARY S. FENG

RECEIVED JULY 15, 1960

Ethyl acetate-d_3, acetyl chloride-d_3 and acetic anhydride-d_6 have been synthesized. The effect of β-deuterium substitution on the rates of hydrolysis of these carboxylic acid derivatives has been determined. In the basic hydrolysis of ethyl acetate in aqueous solution at 25.0°, $k_H/k_D = 0.90$, a reverse isotope effect. In the hydrolysis of acetyl chloride in 10% and 20% water–acetone (v./v.) at −22°, $k_H/k_D = 1.51$ and 1.62, respectively. The solvolyses of acetyl chloride in cyclohexane containing 0.2665 *M* ethanol and in 5% water–acetone at 25.0° and the solvolysis of acetic anhydride in water at 20.0° showed essentially no secondary deuterium isotope effect. The secondary deuterium isotope effects that occur in the saponification of ethyl acetate and in the hydrolysis of acetyl chloride in 10% and 20% water–acetone can be explained in terms of differences in hyperconjugation in the ground and transition states of these hydrolysis reactions. It is postulated that the transition state of the hydrolysis of acetyl chloride is similar to an acylium ion and that this increase in positive charge leads to an isotope effect in the same direction as that found in SN1 solvolyses. Its magnitude depends on the amount of positive charge developed in the transition state, which in turn is a function of the solvating power and dielectric constant of the medium. It is predicted that the secondary deuterium isotope effect in the hydrolysis of ethyl acetate should be the reverse of that found in SN1 solvolyses, on the basis of the hyperconjugation hypothesis and the known mechanism of the reaction in which the positive charge on the carbonyl carbon atom of the ester in the ground state decreases in the transition state. This prediction is borne out by experiment.

Introduction

A number of kinetic isotope effects of mechanistic consequence involve the substitution of deuterium for hydrogen at a position in the molecule where these atoms cannot be involved in any covalent bond breaking in the chemical reaction under consideration. These so-called secondary (or indirect) isotope effects were first detected in the kinetics of SN1 solvolysis[2,3] of compounds containing β-deuterium atoms and were attributed to differences in hyperconjugative ability between deuterium and hydrogen. It was postulated that the greater reactivity of β-hydrogen compounds compared to β-deuterium compounds resulted from greater stabilization of the electron-deficient transition state by β-hydrogen than by β-deuterium. For instance, in the solvolysis of *t*-amyl chlorides, in which the transition state is believed to resemble the carbonium ion intermediate, it was found that the substitution of deuterium in the methylene group or the methyl groups alpha to the tertiary carbon atom resulted in a lower rate of reaction.[3]

Like the primary deuterium isotope effect which involves the direct cleavage of a carbon–deuterium bond, the secondary deuterium isotope effect has been generally attributed to a mass effect on the frequency of the carbon–hydrogen bond, making the zero-point energy of the carbon–deuterium bond lower than that of the carbon–hydrogen bond. Since the potential energy curve of isotopic molecules is the same, this difference in zero-point energy results in a difference in dissociation energy. Non-bonded structures, important to the resonance hybrid in hyperconjugation would then contribute less in deuterium substituted compounds; an electron-deficient transition state demanding hyperconjugation stabilization would consequently be less stabilized by deuterium and the reaction would thus be slower. These views on the origin of the isotope effect were supported by

---

[1] (a) This research was supported by Contract At(11-1)-295 of the U. S. Atomic Energy Commission. A preliminary communication of some of this work appeared in *Chemistry & Industry*, 1350 (1959). (b) Alfred P. Sloan Foundation Research Fellow; present address: Dept. of Chemistry, Northwestern University, Evanston, Ill.

[2] E. S. Lewis and C. E. Boozer, THIS JOURNAL, **74**, 6306 (1952).

[3] V. J. Shiner, Jr., *ibid.*, **75**, 2925 (1953).