[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY, CHICAGO 16, ILL., AND NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

Deuterium Oxide Solvent Isotope Effects in the Nucleophilic Reactions of Phenyl Esters[1]

BY MYRON L. BENDER,[2] EDWARD J. POLLOCK AND MAURICE C. NEVEU

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Deuterium oxide solvent isotope effects in two intramolecular and three intermolecular nucleophile-catalyzed hydrolyses of phenyl esters have been determined. Reactions utilizing carboxylate ion as a nucleophile resulted in ratios of k^{H_2O}/k^{D_2O} of 1.8 while reactions utilizing a tertiary amine as a nucleophile gave ratios of 0.9 to 1.0. Values of the isotope effect in the carboxylate ion reactions calculated on the basis of the consideration of the secondary deuterium isotope effects[12] were 1.5 to 1.6 in reasonable agreement with the experimental values. A comparison is made of kinetic isotope effects in general base- and nucleophile-catalyzed hydrolyses, reflecting primary and secondary deuterium isotope effects, respectively. While there is ambiguity in distinguishing between these isotope effects, they may be used in certain restricted situations as an empirical criterion in distinguishing between general base- and nucleophile-catalyzed hydrolyses.

Introduction

Deuterium oxide solvent isotope effects have been extensively studied, in particular for acid (hydronium ion) catalyzed reactions.[3,4] However, the reactions of nucleophiles or bases with substrates such as carboxylic acid derivatives has received relatively little attention until recently. One of the continuing problems associated with the hydrolytic reactions of carboxylic acid derivatives and phosphoric acid derivatives is to distinguish between nucleophilic and general basic catalysis of hydrolysis. The former involves the attack of a nucleophile upon a substrate leading to the formation of an unstable intermediate which spontaneously breaks down to give the product and regenerates the catalytic entity. The latter catalysis involves the attack of a general base on the substrate removing a proton in a rate-determining stage. Either of these two processes may be carried out by a given substance which by definition is at one and the same time both a nucleophile and a general base. The deuterium oxide solvent isotope effect has been used as a criterion to distinguish between these two possibilities. For example, it has been found that catalysis of the solvolysis of tetrabenzylpyrophosphate by lutidine and collidine is only about a third as great in C_3H_7OD as it is in C_3H_7OH; it was therefore proposed that the transfer of a hydrogen atom from the alcohol to the nitrogen base is part of the rate-controlling step of this reaction.[5] A number of general base-catalyzed hydrolyses of carboxylic acid derivatives have been carried out in water and in deuterium oxide and in most cases a factor of two to three has been observed for the ratio k^{H_2O}/k^{D_2O} [6–10] On the other hand, for nucleophile-catalyzed hydrolyses of carboxylic acid derivatives the ratio k^{H_2O}/k^{D_2O} is not far from one.[7,9] Thus the sum total of the experimental observations seems to substantiate the idea that a slow proton transfer should result in a lowering of the rate in deuterium oxide (a primary isotope effect), while a reaction proceeding without such a slow proton transfer should result in no effect of deuterium oxide on the rate.

However, at the same time that the above viewpoint was evolving, it was pointed out that many equilibrium and kinetic isotope effects of deuterium oxide could be explained in a semi-quantitative way solely in terms of solvation differences between H_2O and D_2O, specifically in terms of the differences in hydrogen bonding involved in the two systems (*i.e.*, secondary isotope effects.)[11,12] If in fact differences in solvation between water and deuterium oxide are of sufficient magnitude to result in appreciable kinetic isotope effects then the use of the deuterium isotope effect as a criterion to distinguish between general basic and nucleophilic catalysis is open to criticism. It is the purpose of this paper to explore those deuterium oxide solvent effects which must arise by solvation differences in some nucleophilic reactions of phenyl esters in order to evaluate their importance. Reactions of acetate ion, imidazole and trimethylamine with phenyl esters are reported here. If only primary isotope effects are considered, these reactions would be expected to exhibit no deuterium oxide solvent isotope effect for no proton transfer is involved. This result is found in some but not all cases.

Experimental

Materials.—Sodium acetylsalicylate was an Eastman Kodak Co. white label product. Methyl hydrogen phthalate was prepared as described previously.[13] 2,4-Dinitrophenyl acetate was prepared as described previously.[14] *p*-Nitrophenyl acetate was described previously.[15] Commercial dioxane was purified according to the method of Fieser[16]; b.p. 99–100°, n^{20}_D 1.4218. Acetonitrile was East-

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(3) K. B. Wiberg, *Chem. Revs.*, **55**, 719 (1955).

(4) F. A. Long and J. Bigeleisen, *Trans. Faraday Soc.*, **55**, 2077 (1959).

(5) G. O. Dudek and F. H. Westheimer, *J. Am. Chem. Soc.*, **81**, 2641 (1959).

(6) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 675 (1960).

(7) A. R. Butler and V. Gold, *Proc. Chem. Soc.*, 15 (1960); *Chemistry & Industry*, 1281 (1960).

(8) B. Zerner and M. L. Bender, *J. Am. Chem. Soc.*, **83**, 2267 (1961).

(9) B. M. Anderson, E. H. Cordes and W. P. Jencks, *J. Biol. Chem.*, **236**, 455 (1961)

(10) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961).

(11) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 42 (1961).

(12) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 3207, 3214 (1961).

(13) M. L. Bender, F. Chloupek and M. C. Neveu, *ibid.*, **80**, 5384 (1958).

(14) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1656 (1957).

(15) M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1652 (1957).

(16) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1957, p. 284.

TABLE I

DEUTERIUM OXIDE SOLVENT ISOTOPE EFFECTS IN THE NUCLEOPHILIC REACTIONS OF SOME PHENYL ESTERS

System	Solvent	Temp., °C.	pH(pD)	k^{H_2O}	k^{D_2O}	k^{H_2O}/k^{D_2O}
Aspirin + H_2O	Water	25.0	6.4[i]	3.0×10^{-6}[a,f]	1.7×10^{-6}[a]	1.8
Methyl hydrogen phthalate + H_2O	1% Acetonitrile–water	100	5.8 (pH)[i,e,l] 6.4 (pD)[k,i,l]	1.0×10^{-5}[a]	0.58×10^{-5}[a]	1.8
2,4-Dinitrophenyl acetate + acetate	1% Acetonitrile–water	25.0	4.8[h]	7.3×10^{-4}[b,c]	4.2×10^{-4}[b,c]	1.8
p-Nitrophenyl acetate + imidazole	5% Dioxane–water	25.0	7.0[m]	0.47[b,d,e]	0.47[b,d]	1.0[g]
p-Nitrophenyl acetate + trimethylamine	5% Dioxane–water	13.5	8.35[n]	0.018[b,d]	0.020[b,d]	0.9[j]

[a] Sec.$^{-1}$. [b] L./mole sec. [c] These values are based on one point: acetate ion concentration = 0.053 M. [d] These values are based on five points each; see text. [e] This agrees well with the value of 0.469.[14] [f] This value agrees reasonably with the value of Garrett, 3.6×10^{-6}.[18] [g] This value agrees with value of Anderson, Cordes and Jencks.[9] [h] Sodium acetate buffer; ionic strength 0.14. [i] Phosphate buffer; ionic strength 0.14. [j] This value is subject to greater error than the others because of the small catalytic constant. [k] Both pH 5.8 and pD 6.4 are on the "flat" portion of the methyl hydrogen phthalate pH–rate profile. [l] S. Stene, *Rec. trav. chim.*, **49**, 1133 (1930), showed the pH of phosphate buffers remains constant from 25° to 100°. [m] Imidazole–imidazolium ion buffer. [n] Trimethylamine–trimethylammonium ion buffer.

man Kodak Co. Spectro Grade quality. Imidazole and trimethylammonium chloride were Eastman Kodak Co. white label reagents. Phosphate buffers were prepared from reagent grade potassium dihydrogen phosphate and disodium hydrogen phosphate. Deuterium oxide was obtained from the General Dynamics Corp., San Carlos, Calif., and was greater than 99.5% deuterium oxide.

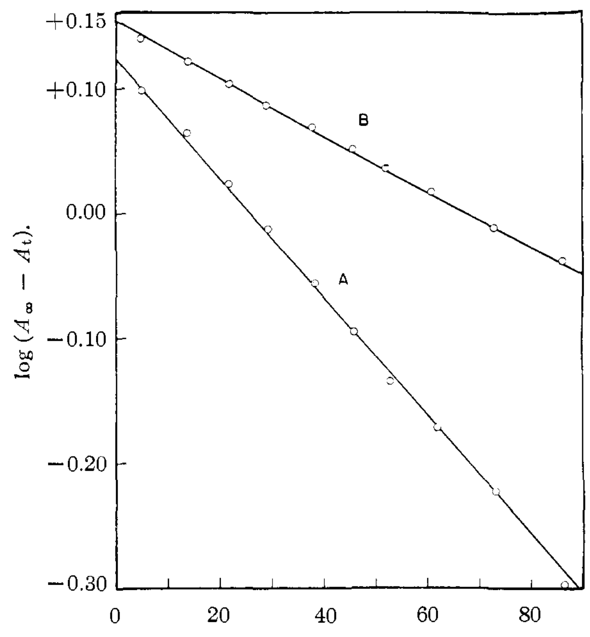

Fig. 1.—The hydrolysis of aspirin in H_2O (A) and D_2O (B) at 25.0°; pH = pD = 6.4.

Kinetics.—The kinetics of hydrolysis of the phenyl esters was followed spectrophotometrically at an appropriate wave length with either a Beckman DK2 recording spectrophotometer or a Beckman DU spectrophotometer, each of which was equipped with a thermostated cell compartment in which the temperature was maintained to within ±0.1° by circulating water from a constant temperature bath. For the methyl hydrogen phthalate hydrolysis a boiling-water thermostat was used.[8] pH measurements were made with a Radiometer model 4c meter equipped with a G 200 B glass electrode and a K130 calomel electrode. A correction of 0.40 pH unit was added to the meter pH readings to obtain pD readings.[8] In all cases the reactions were run under pseudo-first-order conditions in which the concentration of any added nucleophile was in great excess over the concentration of the substrate. First-order kinetic plots were constructed either by the method of Guggenheim[17] or by using conventional first-order kinetics employing an infinity reading of the absorbance. A typical plot, that for the hydrolysis of aspirin in water and deuterium oxide at pH (pD) 6.4, is given in Fig. 1.

Results

Three intermolecular reactions and two intramolecular reactions have been studied. The three intramolecular reactions are the imidazole- and trimethylamine-catalyzed hydrolyses of p-nitrophenyl acetate and the acetate ion-catalyzed hydrolysis of 2,4-dinitrophenyl acetate. The intramolecular reactions include the hydrolysis of aspirin and of methyl hydrogen phthalate, both of which previously have been shown to proceed with o-carboxylate ion participation. The kinetic results of these hydrolyses in water and in deuterium oxide are shown in Table I.

The rate constants in Table I in general have an error of less than 3%. Therefore the ratios, k^{H_2O}/k^{D_2O}, have in general errors of that order associated with them. In the bimolecular reactions it should be noted that the rate constant for the reaction of 2,4-dinitrophenyl acetate with acetate ion is based on one point whereas the rate constants for the reactions of p-nitrophenyl acetate with imidazole and with trimethylamine are based on five points each. A plot of first-order rate constants *versus* concentration of free amine for these latter reactions in both water and deuterium oxide is shown in Fig. 2.

Discussion

All the reactions in Table I appear to follow the same general mechanistic pathway. The aspirin hydrolysis has been shown, on the basic of kinetic and isotopic expeirments, to involve an intramolecular nucleophilic-catalyzed hydrolysis involving an anhydride intermediate.[18,19] The methyl hydrogen phthalate hydrolysis has been shown on the basis of kinetic experiments to involve a similar intramolecular nucleophilic-catalyzed hydrolysis.[19] The reaction of 2,4-dinitrophenyl acetate with acetate ion is an analogous intermolecular nucleophilic-catalyzed hydrolysis involving an anhydride intermediate.[14] Evidence for an anhydride intermediate in this reaction stems from the isotopic experiment involving acetate-^{18}O

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[17] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p. 49.

[18] E. S. Garrett, *J. Am. Chem Soc.*, **79**, 3401 (1957).

[19] M. L. Bender, F. Chloupek and M. C. Neveu, *ibid.*, **80**, 5384 (1958).

ion with 2,4-dinitrophenyl benzoate.[20] The reaction of imidazole with *p*-nitrophenyl acetate is a well-documented example of intermolecular nucleophilic catalysis of hydrolysis involving an N-acetylimidazole intermediate.[14,15,21,22] The reaction of trimethylamine with *p*-nitrophenyl acetate has all the attributes of the imidazole catalysis.[14] These reactions can be formulated as

$$\text{substrate} + \text{nucleophile} \begin{pmatrix}\text{intramolecular or} \\ \text{intermolecular}\end{pmatrix} \xrightarrow{\text{slow}}$$

$$\text{unstable intermediate} \xrightarrow{\text{fast}} \text{products}$$

However, inspection of Table I reveals that the kinetic isotope effects in these mechanistically similar reactions fall into two distinct categories. Those reactions involving a carboxylate ion as a nucleophile exhibit a ratio of k^{H_2O}/k^{D_2O} of 1.8 while those reactions involving a tertiary amine as a nucleophile exhibit a ratio of 0.9 to 1.0. Apparently the change from an intermolecular reaction to an intramolecular reaction makes no difference in the kinetic isotope effect, but a change from an oxy anion to a nitrogen atom as nucleophile does make a difference.

It is of interest at this time to analyze the observed deuterium oxide solvent isotope effects in the nucleophilic reactions of carboxylic acid derivatives. A summary of the present results as well as those in the literature is listed in Table II. These results may be conveniently divided into three parts: (1) general base-catalyzed hydrolysis; (2) nucleophile-catalyzed hydrolysis and (3) hydrolysis by water. Mechanistic division into categories 1 and 2 is fairly well documented by independent evidence. Category 3 is somewhat ambiguous because the reactions listed there could conceivably be either members of category 1 or of category 2. In fact, the work of Jencks and Carriuolo[10] offers convincing evidence that the water reactions of ethyl difluoroacetate and ethyl dichloroacetate are general base-catalyzed hydrolyses. Presumably then the water reaction of methyl trifluoroacetate, and possibly some of the other reactions of category 3, may also be general base-catalyzed reactions.

TABLE II

DEUTERIUM OXIDE SOLVENT ISOTOPE EFFECTS IN THE NUCLEOPHILIC REACTIONS OF CARBOXYLIC ACID DERIVATIVES

	System	k^{H_2O}/k^{D_2O}	Reference
	(1) General base-catalyzed hydrolysis		
1.	Phenyl acetate + glycine (+ glycine)	1.1	6
2.	Phenyl acetate + NH_3 (+ NH_3)	1.5	6
3.	Acetic anhydride + acetate ion	1.65	7
4.	*o*-Carboxyphthalimide	2.5	8
5.	N,O-Diacetylserinamide + imidazole	1.9	9
6.	N,O-Diacetylserinamide + NH_2OH (+ imidazole)	2.4	9
7.	Ethyl difluoroacetate + acetate ion	2.7	10
8.	Ethyl difluoroacetate + imidazole	2.8	10
9.	Ethyl dichloroacetate + acetate ion	2.2	10
10.	Ethyl dichloroacetate + imidazole	3.0	10
11.	Ethyl chloroacetate + imidazole	3.0	10
	(2) Nucleophile-catalyzed hydrolysis		
12.	Phenyl acetate + imidazole	1.07	9
13.	*p*-Nitrophenyl acetate + imidazole	1.0	9[a]
14.	*p*-Nitrophenyl acetate + trimethylamine	0.9	[a]
15.	Acetic anhydride + pyridine	5.7	7
16.	Acetic anhydride + formate ion	1.1	7
17.	2,4-Dinitrophenyl acetate + acetate ion	1.8	[a]
18.	Aspirin	1.8	[a]
19.	Methyl hydrogen phthalate	1.8	[a]
	(3) Hydrolysis by water		
20.	Acetic anhydride + H_2O	2.9, 2.84	7, 23
21.	Benzoyl anhydride + H_2O	3.9, 2.75 (2.45)	7, 23
22.	Benzoyl chloride + H_2O	1.9, 1.7	7, 23
23.	Methyl trifluoroacetate + H_2O	1.8	23
24.	Ethyl difluoroacetate + H_2O	2.1	10
25.	Ethyl dichloroacetate + H_2O	*ca.* 5	10

[a] This research.

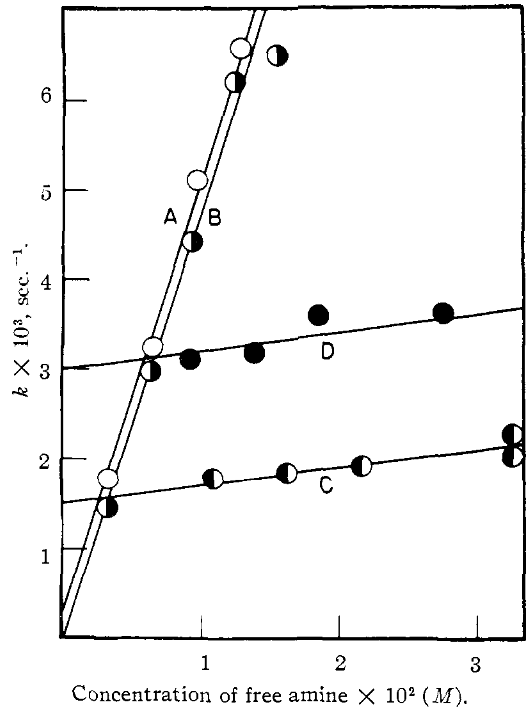

Fig. 2.—Hydrolysis of *p*-nitrophenyl acetate in water and deuterium oxide: A, imidazole catalysis in 5% dioxane-water, μ = 0.0180, 25.0°; B, imidazole catalysis in 5% dioxane-D_2O, μ = 0.0187, 25.0°; C, trimethylamine catalysis in 5% dioxane-water, μ = 0.1700, 13.5°; D, trimethylamine catalysis in 5% dioxane-D_2O, μ = 0.1650, 13.5°.

The kinetic isotope effects in category 1, general base-catalyzed hydrolysis, must involve primary isotope effects since a rate-determining proton (deuteron) transfer must occur at some point in the reaction. The kinetic isotope effects in categories 2 and 3, the nucleophilic reactions, must involve only secondary isotope effects since these reactions involve no rate-determining proton transfers.

Table II does not permit an unambiguous differentiation of primary and secondary deuterium oxide isotope effects, but there are a number of interesting points that may be discerned in Table II.

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(20) M. L. Bender and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5388 (1958).

(21) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957).

(22) C. M. Brouwer, M. J. V. d. Vlugt and E. Havinga, *Konikl. Nederl. Akad. Wetenschappen*, **B60**, 275 (1957).

(23) C. A. Bunton, N. Fuller, S. G. Perry and V. J. Shiner, Jr., *Chemistry & Industry*, 1130 (1960).

Classification 1 involving general base-catalyzed hydrolysis may be conveniently divided into two parts: reactions involving compounds containing good leaving groups such as phenoxide ion and acetate ion (reactions 1–3)[24] and reactions involving compounds containing poor leaving groups such as alkoxide ion and amide ion (reactions 4–11). In the former group a rather low deuterium isotope effect is found. In the latter group a substantial and fairly constant deuterium isotope effect is found, varying between 2 and 3.[25] Whether this division of primary deuterium isotope effects is in fact a real division will depend on the findings of future experiments. At any rate it may be said that for general base-catalyzed hydrolyses involving the loss of an alkoxide ion, a deuterium oxide solvent isotope effect of between 2 and 3 may be confidently expected. These proton (deuteron) transfers in these reactions are from oxygen to oxygen, or nitrogen to oxygen. From simple calculations involving zero point energy differences, the values of these isotope effects would have an upper limit of 10–12. Their magnitude may be compared with many deuterium isotope effects to or from a carbon atom which may attain values of up to 6 or 7.[26]

Classification 2 involving nucleophile-catalyzed hydrolysis may be conveniently divided into two groups, those reactions involving nitrogen nucleophiles (reactions 12–15) and those involving carboxylate ion nucleophiles (reactions 16–19). In the former group three of the four reactions involve essentially no isotope effect. The one reaction of a nitrogen nucleophile exhibiting an isotope effect is the reaction of pyridine with acetic anhydride. This reaction recently has been shown not to conform to eq. 1 since the rate-determining step of the reaction is the decomposition of acetylpyridinium ion to products.[27] Thus it is an exceptional case and can be omitted from general discussion. Apparently nucleophilic reactions of nitrogen bases exhibit no kinetic isotope effect whatsoever.

The nucleophilic reactions involving carboxylate ions do not all have consistent isotope effects. Three of the four reactions (17, 18 and 19) have isotope effects of 1.8[28] while the fourth (reaction 16) has an isotope effect of 1.1. There is no apparent explanation for this discrepancy. The value of the isotope effect in the carboxylate ion reactions may be calculated using the approach of Bunton and Shiner[12] whereas the isotope effect in the nucleophilic reactions involving nitrogen bases cannot, since the necessary hydrogen bonding data are not available in the latter cases. For the calculations of Bunton and Shiner it is necessary to assume a structure of the transition state of the reactions. For the purpose of these calculations it has been assumed that the transition state of the reaction is one in which the carboxylate ion has been added to the carbonyl group of the ester forming a tetrahedral addition intermediate. The formation of this intermediate is in general the slow step in the nucleophilic reactions of carboxylic acid derivatives.[29] The assumption that the transition state of this reaction is similar in structure to the intermediate stems from the considerations of Hammond.[30] Using this assumed transition state it may be calculated readily, using the method of Bunton and Shiner, that the isotope effect, arising from differences in hydrogen bonding in the ground and transition states, is of the order of 1.5 to 1.6 for these reactions. These calculated values agree reasonably well with those found for reactions 17–19, but not with that found for reaction 16. The anomalous position of reaction 16 remains to be explained.[31a,b]

Classification 3, hydrolysis by water, as pointed out earlier, is mechanistically ambiguous. Jencks and Carriuolo[10] have given kinetic evidence that indicates that reactions 24 and 25 are general base-catalyzed reactions and therefore belong in category 1 with reactions of similar isotope effect. Reaction 23 is certainly similar to 24 and 25 and on this basis should also be included in category 1. Whether reactions 20–22 should also be considered to be general base-catalyzed reactions or simply as nucleophilic reactions of water remains to be decided. The isotope effect results could be explained on either basis. Bunton and Shiner[12] have interpreted these effects in terms of secondary deuterium isotope effects, whereas they might equally well be primary isotope effects. This question can be settled by experiments involving criteria other than isotope effects.

Returning to the original question of the differentiation of nucleophilic and general basic catalysis of these reactions by means of the deuterium oxide solvent isotope effect, it is now apparent that there is no unambiguous demarcation between the primary deuterium isotope effect found in general base-catalyzed reactions and the secondary isotope effects found in nucleophilic-catalyzed reactions. However, there are some limited empirical observations that may be made. A comparison of general base- and nucleophile-catalyzed reactions by imidazole and other nitrogen bases reveals that in general the former catalysis will exhibit an isotope effect greater than 2 while the latter will exhibit essentially no isotope effect. Furthermore, in ester reactions catalyzed by car-

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[24] The mechanism of reaction 3 has not been explicitly proved.

[25] The one reaction that shows a ratio of 1.9, the reaction of N,O-diacetylserinamide with imidazole, was carried out at 100°. Extrapolation of this value to 25° would certainly put the isotope effect well over 2.

[26] *Cf.* F. H. Westheimer, *Chem. Revs.*, **61**, 265 (1961), for a discussion of the reason for isotope effects whose values are smaller than those calculated on the assumption of differences only in zero point energies.

[27] C. A. Bunton, N. A. Fuller, S. G. Perry and V. J. Shiner, Jr., *Tetrahedron Letters*, No. 14, 458 (1961).

[28] Reaction 19 was carried out at 100°. Extrapolation to room temperature would give a value greater than 2.

[29] M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

[30] G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

[31] (a) The mechanistic classification of this reaction is somewhat equivocal: see V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1416 (1953). (b) Another possible explanation for the k^{H_2O}/k^{D_2O} of 1.8 in some of the nucleophilic catalyses by carboxylate ions has been suggested by Dr. G. A. Hamilton. In these three reactions (17–19) the attacking reagent is more acidic than the group which is being displaced. Thus in these reactions there may be an equilibrium between the reactants and the tetrahedral intermediate, the rate-determining step being the breakdown of this tetrahedral intermediate. Reaction 16, on the other hand, involves the displacement of carboxylate ion by carboxylate ion, and the rate-determining step may be the usual formation of the tetrahedral intermediate. If this is the case, it is then possible to explain the difference between the kinetic isotope effects in these similar reactions.

boxylate ion, there seems to be a difference in magnitude between the primary deuterium isotope effect (values greater than 2) and the secondary isotope effect (values less than 2). While these are subtle differences, they probably are real. It should be pointed out that part of the observed primary isotope effect may consist of a contribution from a secondary isotope effect. It may be concluded that the use of deuterium oxide solvent isotope effects as a criterion to distinguish between general base- and nucleophile-catalyzed reactions is ambiguous, but when applied in a restricted sense it may be empirically rewarding.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, IND.]

Hydrolysis of Ethylene and Dimethyl Sulfite and the Origin of Strain in Cyclic Esters[1]

BY ROBERT EARL DAVIS

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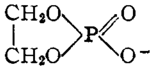
The aqueous alkaline hydrolysis of dimethyl sulfite and of ethylene sulfite has been compared. Ethylene sulfite reacts 360 times as fast at 25° as the dimethyl ester. The heats of hydrolysis have been measured and found to be nearly equal, indicating that there is no thermodynamic strain in the five-membered ring ester. The data have been interpreted with the aid of LCAO-MO calculations on the magnitude of 1,3-non-bonded interactions. The data are discussed in relationship to the behavior of phosphate esters.

Introduction

The mechanisms of reaction of carboxylic esters have received great attention for many years.[2–4] However, only within the past few years have systematic investigations of other types of esters received study. Phosphate esters[5,6] are of great interest as they are metabolites of ribonucleic acids, sugars and other hydroxylic compounds. Derivatives of ethylene phosphate (I) are known as important biological chemicals.[7,8] The tremendous reactivity of I compared to dimethyl phosphate (II) has been described.[9] Compound I hydrolyses about 10^7 times faster than II in alkaline solution. The tremendous kinetic acceleration is present only in the five-membered ring as trimethylene phosphate (III) is much more like II in its behavior.[10] Bunton[11–17] and co-workers have studied the hydrolysis of esters of sulfurous acid in detail as models for understanding phosphate esters. These authors determined the kinetic order and the position of bond cleavage in sulfites using O^{18}. The alkaline hydrolysis of ethylene sulfite was found to be extremely fast[12,14] and only recently has Tillett[17] given approximate values of the second-order rate constant. The authors conclude that 1,3-interelectronic repulsions are responsible for the very fast hydrolysis of the five-membered ring esters.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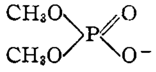
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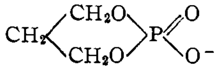
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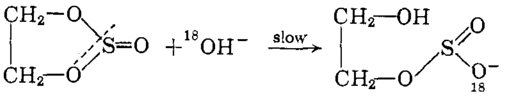
It is the purpose of the present investigation to establish accurate rate constants for the extremely fast hydrolysis reactions and to present thermochemical data. Rather unusual and non-conventional kinetic techniques have been used. The origins of strain in cyclic esters are also discussed.

Results

Kinetic Order.—The data are presented in Tables I–V. The reaction of hydroxide ion with the sulfite esters is strictly first order in hydroxide ion and first order in ester over a very wide variation of concentrations. The rate of production of one mole of sulfur dioxide as either bisulfite or sulfite ion is identical with the rate of consumption of two moles of hydroxide. Differential titration indicates that no monoester is present in greater than 1% concentration. These data are in agreement with those of Bunton[11–17] who also concluded that the reaction was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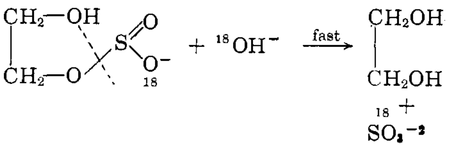
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(1) Paper 11, Esters of Inorganic Acids; paper I, R. E. Davis, *Proc. Indiana Acad. Sci.*, **70**, 106 (1961). Presented in part at the 140th National American Chemical Society Meeting, Chicago, Ill., 1961.

(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 751–782.

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp. 314–353.

(4) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

(5) P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, K. G. Oldham, B. L. Silver and C. A. Vernon, *Chemistry & Industry*, 760 (1955).

(6) Chem. Soc. London Special Publ. No. 8, 1957.

(7) D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 52 (1952).

(8) D. M. Brown, D. I. Magrath and A. R. Todd, *ibid.*, 2708 (1952).

(9) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **78**, 4858 (1956).

(10) L. Kéoy and E. M. Crook, *J. Chem. Soc.*, 710 (1961).

(11) C. A. Bunton, P. B. D. de la Mare, P. M. Greaseley, D. R. Llewellyn, N. H. Pratt and J. G. Tillett, *ibid.*, 4751 (1958).

(12) C. A. Bunton, P. B. D. de la Mare, D. R. Llewellyn, R. B. Pearson and J. G. Pritchard, *Chemistry & Industry*, 490 (1956).

(13) C. A. Bunton, P. B. D. de la Mare and J. G. Tillett, *J. Chem. Soc.*, 4754 (1958).

(14) C. A. Bunton, P. B. D. de la Mare, A. Lennard, D. R. Llewellyn, R. B. Pearson, J. G. Pritchard and J. G. Tillett, *ibid.*, 4761 (1958).

(15) E. D. Davies and J. G. Tillett, *ibid.*, 4766 (1958).

(16) C. A. Bunton, P. B. D. de la Mare and J. G. Tillett, *ibid.*, 1766 (1959).

(17) J. G. Tillett, *ibid.*, 37 (1960).