hydrazino-1,2,3,4-tetrahydropyrimidine with sodium hydrosulfite in the presence of formic acid and formamide,[4a], m.p. 178–179° (lit.[4a] m.p. 178–179°); $\lambda_{max}^{ethanol}$ 238 mμ (ϵ 18,500); 275 mμ (ϵ 1,600) and 340 mμ (ϵ 4,200); the infrared absorption λ_{max}^{Nujol} (μ); 3.0(w), 3.4(s), 3.8(w), 5.8(s), 6.0(s), 6.4(s), 6.55(s), 6.8(s), 7.0(s), 7.1(m), 7.2(w), 7.4(s), 7.8(s), 8.0(w), 8.25(s), 8.75(w), 9.0(w), 9.2(s), 9.6(s), 10.05(m), 10.4(w), 10.7(m), 11.3(m), 12.2(m), 12.45(w), 13.4(s), 13.55(m), and 13.9(s). The ultraviolet and infrared absorption spectra are identical to those of an authentic sample of fervenulin.[19]

R_f Values of synthetic fervenulin (25°, descending) are: 0.82 (96% water–4% butanol), 0.81 (25% acetic acid–50% butanol–25% water); R_f-values of natural fervenulin: 0.81 (96% water–4% butanol), 0.81 (25% acetic acid–50% butanol–25% water).

Acknowledgment.—The authors wish to express their appreciation to Mr. Wayne H. Nyberg, Miss Phyllis G. Shaul and Mrs. Carol R. Tuttle for their valuable assistance in performing analytical, instrumental and paper chromatographic measurements.

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[19] Kindly provided by Dr T. E. Eble, of the Upjohn Co., Kalamazoo, Mich.

[CONTRIBUTION FROM MELLON INSTITUTE, PITTSBURGH 13, PENNA.]

Solvent Isotope Effects in Catalyzed Hydrolysis of Carboxylic Acid Derivatives

BY S. L. JOHNSON

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Kinetic solvent isotope effects for N-methylimidazole and acetate catalysis of benzoic anhydride hydrolysis, and for N-methylimidazole and 4-methylpyridine catalysis of *p*-nitrophenyl acetate hydrolysis in light and heavy water have been measured. The isotope effects for these reactions fall in the range 1.1 to 1.5, indicating that nucleophilic catalysis is operative. The two mechanistic possibilities for general base catalysis, (1) the general base acting directly on a water molecule in the transition state or (2) prior equilibrium of the ester with hydroxide ion and a general acid-assisted decomposition of the intermediate, are discussed. The latter mechanism is discarded for carboxylic acid derivatives with good leaving groups (phenyl esters and anhydrides).

Solvent isotope effects obtained from rate of reaction in light and heavy water (k_{H_2O}/k_{D_2O}) may in certain cases be used to differentiate between nucleophilic catalysis and true general base catalysis for catalyzed hydrolysis of carboxylic acid derivatives. The reason for this is that general base mechanisms involve a slow proton transfer, therefore, a sizable kinetic isotope effect: small isotope effects (1.0–1.5) will be expected for nucleophilic catalysis by analogy with the small isotope effects for the hydrolysis of alkyl halides and sulfonates, and the acetate-catalyzed enolization of methylacetylacetone.[1,2]

Existing examples of general base catalysis in carboxylic acid derivatives are the hydrolysis of acetylimidazole catalyzed by imidazole,[3a] of 1-acetyl-3-methylimidazolium chloride catalyzed by N-methylimidazole,[3b] of acetic anhydride catalyzed by acetate,[4] of ethyl haloacetates catalyzed by various bases,[5] and of acetylserine derivatives catalyzed by various bases[6]; also, the general base-catalyzed aminolysis of esters.[7] The general base mechanism is enhanced by electron-withdrawing groups on either the alkyl group or the acyl group.

It is possible that carboxylic acid anhydrides could have the properties which make general base catalysis possible even for heterocyclic nitrogen bases, which tend to react by nucleophilic interaction on unsaturated centers. However the general base mechanism in this case is not kinetically distinguishable from nucleophilic catalysis. Therefore in the present work use is made of isotope effects in order to differentiate between these two mechanisms; benzoic anhydride hydrolysis catalyzed by N-methylimidazole in light and heavy water was investigated. In order to compare this result with reactions which in all likelihood react by nucleophilic catalysis, benzoic anhydride hydrolysis catalyzed by acetate and *p*-nitrophenyl acetate hydrolysis catalyzed by N-methylimidazole and 4-methylpyridine were also studied in light and heavy water. The rate of disappearance of both *p*-nitrophenyl acetate and benzoic anhydride can be simply and accurately followed spectrophotometrically allowing increased acccuracy over use of aliphatic anhydrides as substrates. N-Methylimidazole was chosen as the catalytic base instead of imidazole because it was desired to avoid secondary isotope effects due to the NH group of imidazole. In formate-, acetate- and pyridine-catalyzed hydrolysis of acetic anhydride, Gold and Butler have observed solvent isotope effects of 1.1, 1.5–1.7 and 5 ± 1, respectively.[8,9] These results were explained as nucleophilic catalysis by formate,[8] general base catalysis by acetate[8] and a rate-controlling attack of water on the acetylpyridinium ion, the concentration of which is limited by the acetate present in the buffer used.[9]

Experimental

Materials.—*p*-Nitrophenyl acetate was prepared from acetic anhydride and *p*-nitrophenol,[10] and recrystallized several times from petroleum ether; m.p. 77.5–78.0°. Eastman Kodak Co. white label benzoic anhydride was recrystallized three times from benzene–petroleum ether, and

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[1] R. E. Robertson and P. M. Laughton, *Can. J. Chem.*, **34**, 1714 (1956); R. E. Robertson and P. M. Laughton, *ibid.*, **35**, 1319 (1957).

[2] F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958).

[3] (a) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1280 (1959); (b) W. P. Jencks and R. Wolfenden, *J. Am. Chem. Soc.*, **83**, 4390 (1961).

[4] M. Kilpatrick, *ibid.*, **50**, 2891 (1928).

[5] W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961).

[6] W. P. Jencks, E. Cordes and B. Anderson, *J. Biol. Chem.*, **236**, 455 (1961).

[7] J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960); W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 675 (1960).

[8] V. Gold and A. R. Butler, *Proc. Chem. Soc.*, 15 (1960); V. Gold and A. R. Butler, *J. Chem. Soc.*, 2305 (1961).

[9] V. Gold and A. R. Butler, *ibid.*, 4362 (1961).

[10] F. Chattaway, *ibid.*, **134**, 2495 (1931).

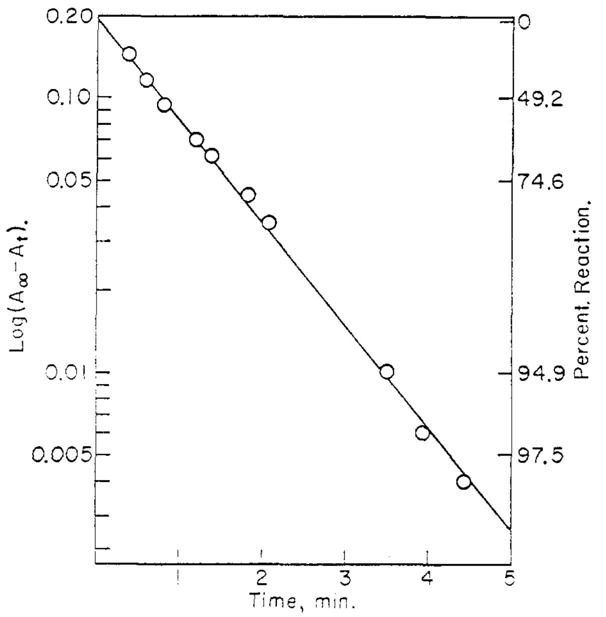

Fig. 1.—First-order rate plot of N-methylimidazole-catalyzed hydrolysis of *p*-nitrophenyl acetate in heavy water.

then sublimed; m.p. 42.0–42.5°. N-Methylimidazole was prepared according to Wallach[11] and fractionated on a Podbielniak column; b.p. 110° (46 mm.).

Anal. Calcd. for $C_4H_6N_2$: C, 58.51; H, 7.36; N, 34.11; neut. equiv., 82.1. Found: C, 58.57; H, 7.26; N, 34.16; neut. equiv., 82.7.

Fisher certified 4-methylpyridine was fractionated on a packed column; b.p. 140.7°, n^{24}_D 1.5041. Allied Chemical reagent grade pyridine was fractionated on a packed column; b.p. 115°. Allied Chemical reagent glacial acetic acid was redistilled. Fisher certified dioxane was redistilled over sodium, and used only when peroxides were absent. C. F. Smith sodium perchlorate was recrystallized from water and dried at 200°. Fisher certified sodium chloride was recrystallized from ethanol–water and dried. Stuart Oxygen Co. 99.5% deuterium oxide and Merck and Co. deuterium chloride (>99.4% isotopic purity) were used in making up the buffers in heavy water.

Buffer Solutions.—The reactions were carried out in solutions made up entirely of the catalytic base, its conjugate acid and inert salts added to keep the ionic strength constant. In the case of acetate catalysis of benzoic anhydride the total ionic strength is 0.17 *M*. In the other reactions the total ionic strength is kept under 0.1 *M*. In all cases the concentration of the catalytic base exceeds that of the substrate by a factor of at least 100. Therefore the products of the reaction cannot interfere with the concentration of the catalytic base. Under these conditions the reactions are pseudo first-order. The buffer solutions containing N-methylimidazole and 4-methylpyridine were prepared by weighing up the desired quantity of base in a volumetric flask and adding volumetrically the appropriate amounts of hydrochloric or deuteriochloric acid, salts, water and dioxane. The acetate buffer solutions were prepared by dissolving acetic acid in either light or heavy water and adding the desired quantities of sodium hydroxide or sodium deuterioxide solutions, salt and water. Sodium deuterioxide was prepared by adding sodium to deuterium oxide under a stream of nitrogen.

Kinetic Measurements.—The reactions were followed spectrophotometrically using a thermostated Beckman DU spectrophotometer. The temperature was accurately controlled at 25.00 ± 0.01°. The rate of appearance of the *p*-nitrophenolate ion or *p*-nitrophenol was followed (400 and 315 mμ, respectively) in those runs using *p*-nitrophenyl acetate as the substrate. The rate of disappearance of the benzoic anhydride was followed at 275 mμ. The fast reactions were started by allowing a premeasured quantity of the buffer solution to come to thermal equilibrium in the cell compartment and adding 0.01 ml. of the substrate dissolved in dioxane. The slow reactions were conveniently studied by adding the aqueous buffer solution, dioxane, and a stock solution of the substrate to a volumetric flask and diluting up to volume. The reactions all followed very accurately pseudo first-order kinetics. Sample rate data are presented in Fig. 1. The rate constant was obtained from a plot of log $(A_\infty - A_t)$ *vs.* time for *p*-nitrophenyl acetate runs and log $(A_t - A_\infty)$ *vs.* time for benzoic anhydride runs where A_∞ is the end-point absorbance and A_t is the absorbance at time *t*. A line originating at time = 0 and log 1.0 is drawn parallel to the plotted line, and the half-life is obtained from the plot at log 0.5. The rate constant is given by $0.693/t_{1/2}$. The catalytic coefficients are obtained by plotting the observed rate constant, k_{obs}, corresponding to each base concentration *vs.* the base concentration (in a series of runs where the buffer ratio is constant); the catalytic coefficient is the slope, and its value and probable error were obtained by using the least squares method. The isotope effect on the catalytic coefficient and its probable error are given by

$$\frac{B \pm b}{A \pm a} = \frac{B}{A} \pm \frac{1}{A}\left(b^2 + \left(\frac{B}{A}\right)^2 a^2\right)^{1/2}$$

where *B* and *b* are the catalytic coefficient in light water and its probable error and *A* and *a* are the catalytic coefficient in heavy water and its probable error.

Results and Discussion

The kinetic results of the hydrolysis of benzoic anhydride in light and heavy water–dioxane mixtures are given in Tables I and II. The N-methyl-

TABLE I

THE KINETICS OF THE HYDROLYSIS OF BENZOIC ANHYDRIDE CATALYZED BY N-METHYLIMIDAZOLES

N-Methyl-imidazole, $M \times 10^3$	N-Methyl-imidazolium ion, $M \times 10^3$	NaCl, $M \times 10^3$	B/BH^+	$k_{obs} \times 10^3$, sec.$^{-1}$
Solvent, 68% dioxane–32% H_2O (v./v.)				
48.82	48.04	0.00	1.016	30.80
48.82	48.04	0.00	1.016	30.80
19.53	19.22	28.82	1.016	12.16
19.53	19.22	28.82	1.016	11.55
19.53	19.22	28.82	1.016	10.50
19.53	19.22	28.82	1.016	11.00
19.53	19.22	0.00	1.016	11.75
19.53	19.22	0.00	1.016	10.66
32.64	28.82	5.50	1.132	20.09
27.20	24.02	10.90	1.132	18.73
38.08	33.63	0.00	1.132	23.49
21.76	19.22	16.3	1.132	13.78
16.32	14.41	21.8	1.132	9.719
27.20	24.02	10.9	1.132	17.08
23.16	23.10	0.00	1.00	
Solvent, 68% dioxane–32% D_2O (v./v.)				
				13.33
23.16	23.10	0.00	1.00	13.59
31.43	36.31	.00	0.866	19.23
31.43	36.31	.00	.866	19.23
41.90	48.42	.00	.866	27.72
41.90	48.42	.00	.866	26.15
41.90	48.42	.00	.866	21.66
41.90	48.42	.00	.866	23.89
31.43	36.31	.00	.866	16.31
20.95	24.21	.00	.866	12.83
20.95	24.21	.00	.866	11.75
31.43	36.31	.00	.866	20.41

[a] At 25°: anhydride concentration, 1×10^{-4} *M*; followed at 275 mμ.

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[11] O. Wallach, *Ber.*, **15**, 645 (1882).

TABLE II

THE KINETICS OF THE HYDROLYSIS OF BENZOIC ANHYDRIDE CATALYZED BY ACETATE ION[a]

Sodium acetate, $M \times 10^2$	Acetic acid, $M \times 10^2$	NaCl, $M \times 10^2$	$OAc^-/HOAc$	k_{obs}, sec.$^{-1}$ $\times 10^4$
Solvent, 14% dioxane–86% H_2O (v./v.)				
16.51	5.31	0.00	3.11	7.404
12.38	3.187	4.128	3.11	5.634
8.256	2.656	8.256	3.11	3.915
8.256	21.50	8.256	0.385	3.598
6.192	16.13	10.32	0.385	2.718
Solvent, 14% dioxane–86% D_2O (v./v.)				
17.89	21.09	0.00	0.848	5.634
11.93	14.06	5.96	.848	4.017
5.965	7.03	11.93	.848	2.222

[a] At 25°; anhydride concentration, 2.03×10^{-4} M; constant ionic strength, 0.1651 M in light water, 0.1739 M in heavy water.

imidazole-catalyzed decomposition of benzoic anhydride was so efficient that it was necessary to employ an aqueous solvent mixture containing at least 68% (v./v.) dioxane. The acetate catalysis was studied in 14% (v./v.) dioxane in order to ensure complete solubility of benzoic anhydride and benzoic acid during the reaction. No significant salt effects could be observed in the case of N-methylimidazole catalysis in light water; therefore, no attempt was made to provide constant ionic strength conditions in heavy water. The two different sodium acetate–acetic acid buffer ratios used did not alter the value for k_{cat} (the slope of a plot of k_{obs} *vs.* sodium acetate concentration), but did alter the k_w (the intercept) value.

Experimental data for N-methylimidazole and 4-methylpyridine catalysis of *p*-nitrophenyl acetate hydrolysis are in Tables III and IV. No attempt was made to maintain constant ionic strength conditions in the case of N-methylimidazole catalysis because the rate effect is small for the additional quantity of salt needed for the constant ionic strength condition.

TABLE III

KINETICS OF N-METHYLIMIDAZOLE CATALYSIS OF *p*-NITROPHENYL ACETATE[a]

N-Methylimidazole, $M \times 10^3$	N-Methylimidazolium ion, $M \times 10^3$	k_{obs} sec.$^{-1}$ $\times 10^3$
Solvent, 0.33% dioxane–99.67% H_2O (v./v.)		
54.40	48.04	18.73
54.40	48.04	21.00
54.40	48.04	19.25
54.40	48.04	19.80
54.40	48.04	17.77
40.80	36.03	15.06
40.80	36.03	14.44
27.20	24.02	9.90
27.20	24.02	10.27
27.20	24.02	10.50
Solvent, 0.33% dioxane–99.67% D_2O (v./v.)		
52.38	60.52	14.74
52.38	60.52	14.44
41.35	41.25	12.17
41.35	41.25	11.18
26.19	30.26	7.70
26.19	30.26	8.153

[a] At 25°; ester concentration, 2.66×10^{-4} M; followed at 400 mμ.

TABLE IV

KINETICS OF 4-METHYLPYRIDINE CATALYSIS OF *p*-NITROPHENYL ACETATE[a]

4-Methylpyridine, $M \times 10^2$	4-Methylpyridinium ion, $M \times 10^2$	$NaClO_4$, $M \times 10^2$	BH^+/B	k_{obs}, sec.$^{-1}$ $\times 10^4$
Solvent, 99.67% H_2O–0.33% dioxane (v./v.)				
6.866	7.974	2.026	1.16	10.04
6.866	7.974	2.026	1.16	10.04
5.150	5.980	4.020	1.16	7.966
2.746	3.190	8.026	1.16	4.780
Solvent, 99.67% D_2O–0.33% dioxane (v./v.)				
9.470	11.85	0.00	1.23	12.79
9.470	11.85	0.00	1.23	12.71
5.682	7.104	4.02	1.23	8.587
5.682	7.104	2.896	1.23	8.375
5.682	7.104	2.896	1.23	8.300

[a] At 25°; ester concentration, 5×10^{-4} M; constant ionic strength, 0.11 M in light water, 0.11–0.12 M in heavy water; followed at 315 mμ.

The catalytic coefficients and the solvent isotope effect on the catalytic coefficients in Tables I-IV are listed in Table V. The outstanding feature of the results in Table V is that there is no large solvent isotope effect for any of the various systems studied. This is not surprising with N-methylimidazole and 4-methylpyridine catalysis of *p*-nitrophenyl acetate and acetate catalysis of benzoic anhydride because these three systems most certainly are not examples of general base catalysis in view of the following facts: (i) During imidazole catalysis of *p*-nitrophenyl acetate hydrolysis, the buildup of acetylimidazole as an unstable intermediate can be observed.[12] N-Methylimidazole does not deviate from the basicity-rate relationship in a series of imidazole derivatives, and therefore should react by the same mechanism as imidazole.[13] (ii) The mechanism of acetate catalysis of benzoic anhydride hydrolysis should be identical with that of formate catalysis of acetic anhydride hydrolysis,[4] which involves nucleophilic attack of formate on the anhydride to form the highly reactive mixed anhydride. The catalytic coefficient for formate catalysis is a factor of 18 higher than that for acetate catalysis. Anions such as propionate and butyrate have no catalytic effect at all, but rather slow the hydrolytic reaction, because the mixed anhydride formed in this case is less reactive than acetic anhydride. Thus, two distinct processes are taking place; nucleophilic catalysis when the mixed anhydride formed is more reactive than the starting anhydride, and a much less efficient true general base catalysis when the nucleophile is identical to the leaving group. Acetate should be a nucleophilic catalyst to benzoic anhydride because acetic benzoic anhydride is 28 times more reactive than benzoic anhydride itself.[14]

For N-methylimidazole-catalyzed hydrolysis of benzoic anhydride the three mechanistic schemes, consistent with the kinetics, are indicated in eq.

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(12) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652 (1957).

(13) T. C. Bruice and G. Schmir, *ibid.*, **80**, 148 (1959).

(14) C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960).

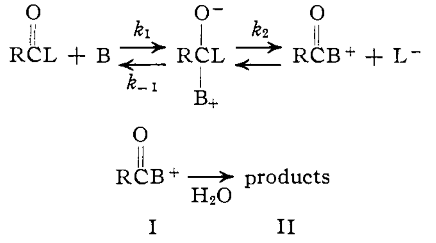
TABLE V

SOLVENT ISOTOPE EFFECTS IN CATALYZED HYDROLYSIS OF CARBOXYLIC ACID DERIVATIVES[a]

Compound	Base	Solvent (v./v.)	k_H, l. M.$^{-1}$ sec.$^{-1}$	k_D, l. M.$^{-1}$ sec.$^{-1}$	k_H/k_D
Benzoic anhydride	N-Methylimidazole	68% dioxane–32% water	0.659 ± 0.014	0.576 ± 0.060	1.14 ± 0.12
Benzoic anhydride	Acetate ion	14% dioxane–86% water	.00423 ± .00002	.00286 ± .00006	1.477 ± .031
p-Nitrophenyl acetate	4-Methylpyridine	0.33% dioxane–99.67% water	.0127 ± .0004	.0114 ± .0002	1.115 ± .043
	N-Methylimidazole		.334 ± .016	.269 ± .017	1.242 ± .099

[a] At 25°.

1–3. Scheme A, eq. 1, is a nucleophilic displacement of the leaving group L by the base B to form a carboxylic acid derivative more reactive than the substrate. Assuming that the point of highest energy may be represented by a structure similar to I or II the solvent isotope effect expected in this case should be in the range 1.0–1.5 due to the change of structure of the solvating water in the transition state from that in the ground state and increased possibilities for hydrogen bonded interactions to the solvent in the transition state compared to the ground state.

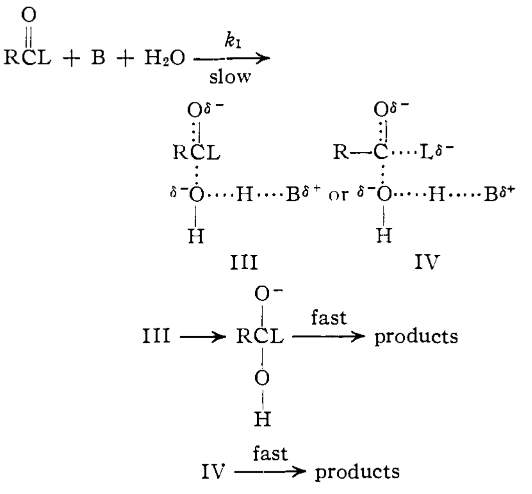


$$\mathrm{RC(=O)L} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{RC(O^-)(B^+)L} \overset{k_2}{\rightleftharpoons} \mathrm{RC(=O)B^+} + \mathrm{L^-} \qquad (1)$$

$$\mathrm{RC(=O)B^+} \xrightarrow[\mathrm{H_2O}]{} \text{products}$$

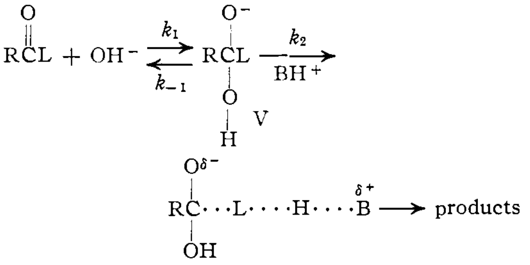
I II

Scheme B, eq. 2, is a base-assisted (by means of partial proton transfer to form an incipient hydroxide ion from a water molecule) carbon–oxygen bond making process either without or with simultaneous bond breaking of the L group (transition states III and IV, respectively). The solvent isotope effect for this mechanism is expected to be sizable (>2), because the catalytic coefficient is given by k_1, the proton transfer step.



(2)

Scheme C, eq. 3, is an alternative mechanism for general base catalysis which involves a prior equilibrium of the ester with hydroxide ion to form the reactive intermediate V, which in a rate-determining acid-assisted step decomposes to products. The rate expression for this scheme is given by eq. 4, where K_w is the ionization constant of water and K_a is the acid dissociation constant for the conjugate acid of the catalytic base. If the k_{-1}/k_2 ratio is much greater than [BH$^+$] (which is the concentration of the acid form of the catalytic base in the buffer. ~0.01 – 0.10 *M*) the kinetic expression becomes eq. 5, where K_1 is k_1/k_{-1}.



(3)

$$k_{\text{obs}} = \frac{k_1k_2(K_w/K_a)[\mathrm{B}]}{k_{-1} + k_2[\mathrm{BH^+}]} = \frac{k_1(K_w/K_a)[\mathrm{B}]}{(k_{-1}/k_2) + [\mathrm{BH^+}]} \qquad (4)$$

$$k_{\text{obs}} = K_1K_wK_2[\mathrm{B}]/K_a \qquad (5)$$

The solvent isotope effect for the catalytic coefficient in eq. 5 (eq. 5 divided by [B]) is given in eq. 6 by the isotope effect on each of the three equilibrium constants as well as on the rate-determining proton transfer step, k_2. The K_1^H/K_1^D ratio should be equal to about 0.5[15].

$$\frac{k_{\text{cat}}^H}{k_{\text{cat}}^D} = \frac{K_1^HK_w^HK_a^Dk_2^H}{K_1^DK_w^DK_a^Hk_2^D} \qquad (6)$$

the K_w^H/K_w^D ratio is equal to 6.5, and the K_a^D/K_a^H value is equal to 0.33–0.25 for acids the strength of acetic acid or N-methylimidazolium ion. Thus the isotope effect will be equal to (1.08–0.81) (k_2^H/k_2^D). Since a sizable (>2) kinetic isotope effect on k_2 is expected, the resulting isotope effect on k_{cat} should be equal to 1.5 or higher. Therefore, isotope effects for scheme C as low as those expected for scheme A are feasible, and the isotope effect criterion cannot be unequivocally used to differentiate between schemes A and C.

If the k_{-1}/k_2 value is much smaller than [BH$^+$], the [BH$^+$] term will dominate the denominator and k_{obs} will be proportional not to the general base concentration [B], but rather to the hydroxide ion concentration [B]/[BH$^+$]. The reaction will therefore be specific base catalyzed and no general base catalysis will be observed. Intermediate values of k_{-1}/k_2 will result in negative curvature in a plot of k_{obs} *vs.* base concentration.

The criterion for the phenomenological observance of general base catalysis *via* scheme C is that the k_{-1}/k_2 value be much greater than 0.01–0.10. The facts do not bear this out for the following reasons: (i) The k_{-1}/k_2 values measured in O^{18} exchange experiments for the reaction of hydroxide with phenyl benzoate is zero,[16a] *i.e.*, bond 2 breaks

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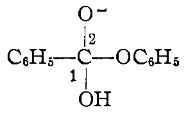
[15] By analogy with the kinetic solvent isotope effect for the benzillic acid rearrangement, J. Hine and H. W. Haworth, *J. Am. Chem. Soc.*, **80**, 2274 (1958).

much faster, acid-unassisted, than bond 1 in the intermediate VI. Since the phenolate ion is a much poorer leaving group than a carboxylate ion,



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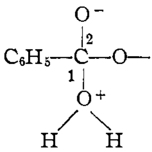


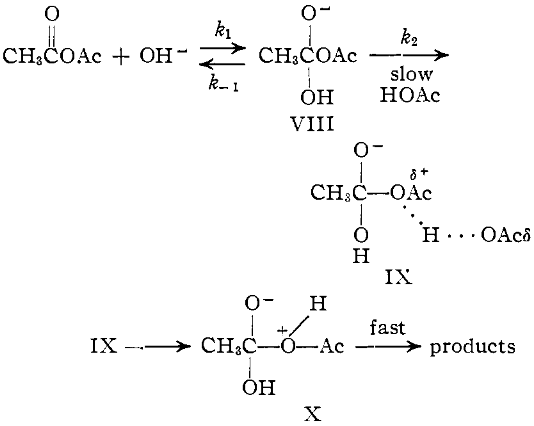
VII

the k_{-1}/k_2 value for the acid-assisted leaving of the carboxylate ion is certain to be zero. (ii) The k_{-1}/k_2 value from O^{18} experiments for the *neutral* hydrolysis of benzoic anhydride is equal to 0.05, *i.e.*, bond 2 in VII breaks 20 times faster,[16b] acid-unassisted, than the fully protonated oxygen bond 1. The value for k_{-1}/k_2 for intermediate III, whose OH group is not fully protonated, would certainly be smaller than 0.05, but even if it were comparable, a plot of k_{obs} *vs.* the base concentration would result in curvature toward the concentration axis. This phenomenon is not observed in this investigation. These two pieces of evidence serve to rule out completely scheme C for carboxylic acid derivatives with good leaving groups.

The solvent isotope effects observed in the present investigation should fall into two groups: isotope effects between 1.0 and 1.5 for nucleophilic catalysis, scheme A; and sizable isotope effects for scheme B. Clearly it can be concluded that N-methylimidazole catalyzes the hydrolysis of benzoic anhydride by nucleophilic catalysis because the solvent isotope effect for this reaction is 1.14, a value in the same range as the other isotope effects studied here for reactions known or inferred to proceed *via* the nucleophilic mechanism. This isotope effect contrasts markedly to the isotope effect of 5 ± 1 found by Gold and Butler for pyridine-catalyzed hydrolysis of acetic anhydride.[8,9] An isotope effect of this size can be rationalized by eq. 1 if the decomposition of the acetylpyridinium ion is rate controlling. This condition has been purportedly achieved[9] because the catalyzed decomposition of acetic anhydride was carried out in an acetic acid–acetate buffer solution (0.015–0.062 *M* in acetate). If, under these conditions the acetylpyridinium ion can selectively react with acetate ion in preference to the water used as solvent, a large solvent isotope effect is not unreasonable because the attacking water molecule will take on a partial positive charge, causing a sizable drop in zero-point energy of the O–H bonds in going from the ground state (3400 cm.$^{-1}$) to the transition state (2900 cm.$^{-1}$ in the limit).[17] However, the selectivity of the acetylpyridinium ion as indicated by Gold and Butler[8,9] is difficult to understand because this compound reacts only to the extent of 65% in 2 *M* hydroxylamine[18] (an extremely effective nucleophile).

The mechanism of acetate catalysis of acetic anhydride hydrolysis must follow mechanism B. The reported[8] isotope effect for the catalytic constant for this reaction is 1.6 ± 0.1 and is closer to 1.7 when corrections are made for salt effects. This isotope effect is smaller than the >2 isotope effect predicted for mechanism B. These measurements[8] were made in a series of runs (six in light water, three in heavy water) in which the concentration of acetic acid was held constant and the concentration of acetate was varied, so that the hydroxide, or deuteroxide concentration increased proportionally with the increase in the acetate concentration. The apparent catalytic coefficients are therefore increased, the increase being larger in heavy water because deuterioxide reacts at a greater rate than does hydroxide due to an increase in zero-point energy in going from the ground state to the transition state.[19] In the present work two buffer ratios were used in studying the acetate-catalyzed hydrolysis of benzoic anhydride (see Table II). When k_{obs} from these results are plotted *vs.* acetate concentration, two lines result with equal slopes, but with different intercepts indicating a significant contribution of hydroxide ion-catalysis at below neutral *p*H's. A similar situation must certainly prevail for acetic anhydride. The isotope effect of 1.6 ± 0.1 resulting from Gold and Butler's[8] measurements may therefore be too low.

Gold and Butler's Mechanism for Acetic Anhydride Hydrolysis Catalyzed by Acetate.—Equation 4 gives Gold and Butler's proposed scheme for the general base mechanism. This mechanism involves prior equilibrium of hydroxide with the anhydride to form the tetrahedral intermediate VIII, which, in a slow proton transfer from oxygen to oxygen (transition state IX), forms the reactive intermediate X which rapidly goes to products. The rationale is that the intermediate VIII



(4)

is present in such low concentration that the k_2 step becomes the rate-limiting step. These authors expressed their rate by eq. 5, where K_1 is the equilibrium constant between VIII and reactants. Equation 5 assumes that the formation of VIII is not kinetically controlled, but rather that its concentration depends only on the reactant concentrations and the value for K_1. The more general

$$k_{obs} = K_1k_2[\mathrm{HOAc}][\mathrm{OH}^-] = K_1k_2(K_w/K_a)[\mathrm{OAc}^-] \quad (5)$$

expression is given by eq. 6; eq. 5 can represent

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[16] (a) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956); (b) C. A. Bunton, T. A. Lewis and D. R. Llewellyn, *Chemistry & Industry*, 1154 (1954).

[17] C. A. Bunton and V. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 3207 (1961).

[18] D. E. Koshland, *ibid.*, **74**, 2286 (1952).

[19] This increase in zero-point energy results from decreased hydrogen-bonded interactions with surrounding water molecules, and from the conversion of a rotational degree of freedom to a bending frequency.

the rate expression only when $k_{-1} >> k_2[\mathrm{HOAc}]$, *i.e.*, when C–O bond breaking is much faster than a proton transfer from O to O. Comparison of rate constants for typical C–O breaking processes and proton transfer processes from O to O is quite convincing evidence that k_{-1} cannot be larger than k_2. When k_2 is larger than k_{-1} eq. 6 becomes a specific base catalytic expression. Gold and Butler's mechanism and scheme C of the previous paragraph are discarded as mechanisms, leaving only scheme B to account for the catalytic effect of acetate toward acetic anhydride.

$$k_{\mathrm{obs}} = \frac{k_1k_2(K_{\mathrm{w}}/K_{\mathrm{a}})[\mathrm{OAc}^-]}{k_{-1} + k_2[\mathrm{HOAc}]} \qquad (6)$$

COMMUNICATIONS TO THE EDITOR

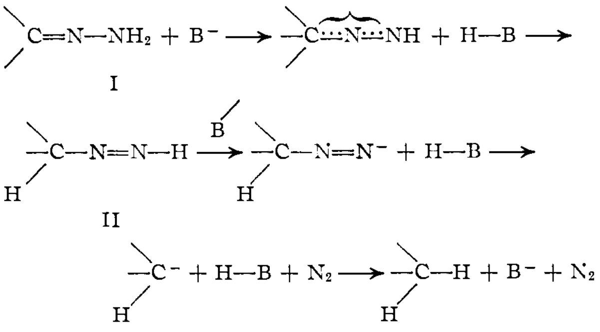
ROOM TEMPERATURE WOLFF-KISHNER REDUCTION AND COPE ELIMINATION REACTIONS[1]

Sir:

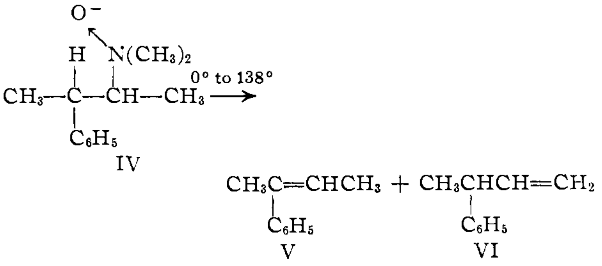
Evidence has accumulated that the reactivity of anions in dimethyl sulfoxide as solvent greatly exceeds that of hydroxylic solvents of comparable dielectric constant.[2] In the present work, we have found that use of dimethyl sulfoxide as solvent allows both the Wolff–Kishner reduction and the Cope elimination reactions to be run at room temperature.

Slow addition of hydrazones of aldehydes and ketones to a solution of sublimed potassium *tert*-butoxide[3] in anhydrous dimethyl sulfoxide[2g] at 25° produced an immediate evolution of nitrogen and formation of hydrocarbon in 60–90% yields.[4] Typical yields of hydrocarbon obtained from the following starting materials are as given: benzophenone hydrazone, 90%; benzaldehyde hydrazone, 67%; camphor hydrazone, 64%; cyclohexanone hydrazone, 80%. The main by-product is azine, whose formation is favored by rapid addition of hydrazone to the reaction mixture.[5] The procedure as applied to benzophenone hydrazone is as follows. To a rapidly stirred mixture of 2 g. of sublimed potassium *tert*-butoxide[3] and 5 ml. of anhydrous dimethyl sulfoxide[2g] was added in very small portions over a 8-hour period 1.96 g. of benzophenone hydrazone. The solution turned deep red and nitrogen was evolved vigorously. The reaction mixture was shaken with a mixture of methylene chloride and water, and the organic layer was washed with water, dried and evaporated. Gross chromatography of the residue on alumina gave 1.5 g. of diphenylmethane and 0.2 g. of benzophenone azine. When an addition time of 0.5 hour was employed, the yield of diphenylmethane decreased to 72% and of azine increased to 22%.

In this reduction reaction, the rate-limiting step is probably a base-catalyzed isomerization of I to II, although proton abstraction from II to give III undoubtedly is base catalyzed also. Apparently the activity of RO^- toward N–H is greatly enhanced in dimethyl sulfoxide for much the same reason that it is enhanced toward C—H.[2d,2g]



In most Cope elimination reactions, *tert*-amine oxides are pyrolyzed without solvent at temperatures of 120–150°.[6] Kinetics of the elimination reaction of *threo*- and *erythro*-N,N-dimethyl-3-phenyl-2-butylamine oxide (IV) to give *cis*- and *trans*-2-phenyl-2-butene (V) and 3-phenyl-1-butene (VI)[7] now have been studied in dimethyl sulfoxide–water mixtures, in tetrahydrofuran–water mixtures, and in the pure solvents. The reactions were followed by vapor phase chromatographic techniques which allowed the amounts of V and VI to be measured within ±1%. Within experimental



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[1] This work was supported by the Office of Ordnance Research, U. S. Army.

[2] (a) R. Fuchs and A. Nisbet, *J. Am. Chem. Soc.*, **81**, 2371 (1959); (b) R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960); (c) L. Friedman and H. Shechter, *ibid.*, **25**, 877 (1960); (d) D. J. Cram, B. Rickborn and G. R. Knox, *J. Am. Chem. Soc.*, **82**, 6412 (1960); (e) J. Miller and A. J. Parker, *ibid.*, **83**, 117 (1961); (f) C. C. Price and W. H. Snyder, *ibid.*, **83**, 1773 (1961); (g) D. J. Cram, B. Rickborn, C. A. Kingsbury and P. Haberfield, *ibid.*, **83**, 3678 (1961).

[3] M. S. A. Research Corporation, Callery, Pa.

[4] With potassium hydroxide in ethylene glycol, this reaction requires 180–200° [D. Todd, "Organic Reactions," John Wiley and Sons, Inc., New York, Vol. 4, p. 378, 1948].

[5] In all cases, physical constants of starting materials, products and by-products check those of the literature.

[6] For example, A. C. Cope, C. L. Baumgardner and E. E. Schweizer, *J. Am. Chem. Soc.*, **79**, 4729 (1957).

[7] D. J. Cram and J. E. McCarty, *ibid.*, **76**, 5740 (1954).