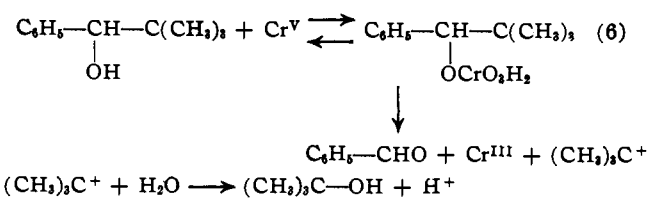
pivalophenone produced is reasonably stable; about 6% of it may be oxidized to the corresponding acid, but the rest survives. Cleavage, then, accompanies the oxidation of the alcohol and is not a subsequent process.

A few oxidations were carried out with deuterioacetic acid and D_2O. The *t*-butyl alcohol produced was analyzed mass-spectrometrically and contained very little, if any, deuterium. When isobutylene was hydrated under these experimental conditions, the ratio of the mass peaks 60/59 was 1.5; in the oxidative experiments it was about 0. Thus the *t*-butyl alcohol found is not formed from isobutylene.

Discussion

t-Butyl alcohol, obtained as the product of the chromic acid oxidation of isotopically labeled phenyl-*t*-butylcarbinol and of anisyl-*t*-butylcarbinol, shows no enrichment in ^{18}O (Table II). Conversely, *t*-butyl alcohol, obtained as the product of oxidation of these carbinols in aqueous solution of acetic acid, initially labeled with oxygen-18 only in the water, shows an isotropic enrichment about equal to that calculated for the solvent. These data are consistent with the following partial mechanism where the cleavage is performed (as explained in the Introduction) by pentavalent chromium.

The argument that reaction scheme 5 is excluded depends on the prior demonstration that the hydrolysis of the di-*t*-butyl acetal of benzaldehyde occurs according



(6)

to eq. 7, without exchange between the solvent and the oxygen atoms originally present in the acetal.[20]

$$C_6H_5CH(OR)_2 + H_2O^* \xrightarrow{H^+} C_6H_5CHO^* + 2ROH \qquad (7)$$

This hydrolysis almost certainly proceeds by way of the same cation, A, $C_6H_5CH{=}\overset{+}{O}{-}C(CH_3)_3$, which is required for the oxidative rearrangement. Therefore, if this intermediate were formed, the oxygen atom originally present in the carbinol would appear in the *t*-butyl alcohol. None does. Therefore the rearrangement does not occur.

On the basis of the present work alone, no distinction can be made between an oxidative process producing a carbonium ion and one producing a radical. The work of Lansbury, *et al.*,[10] coupled with that here reported, makes the carbonium ion sequence of eq. 6 quite probable.

Acknowledgment.—This work was supported in part by a grant from the Petroleum Research Fund of the American Chemical Society.

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[CONTRIBUTION FROM THE JAMES BRYANT CONANT LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE, MASS.]

The Hydrolysis of Methyl Ethylene Phosphate: Steric Hindrance in General Base Catalysis

BY FRANK COVITZ[1a] AND F. H. WESTHEIMER[1b]

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The general base catalysis of the mutarotation of glucose and the general acid catalysis of the inversion of menthone are subject to steric hindrance; 2,6-lutidine is a poorer catalyst than would be expected considering its ionization constant by factors of 25 and about 10, respectively. The hydrolysis of methyl ethylene phosphate is catalyzed by heterocyclic bases with a solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, of about 2; 2,6-lutidine is again a poorer catalyst than anticipated by a factor of ten. These data suggest: (1) that the hydrolysis of methyl ethylene phosphate is subject to general base, rather than to nucleophilic, catalysis; and (2) that general base and general acid catalysis are moderately sensitive to steric hindrance.

One of the criteria which might be considered to characterize nucleophilic, as opposed to general base, catalysis is that the former is subject to steric hindrance. Thus Butler and Gold[2] found that pyridine catalyzes the solvolysis of acetic anhydride, whereas 2-picoline and 2,6-lutidine, which are stronger bases, have no effect on the reaction rate. The pyridine catalysis is diminished by acetate ions, and on this evidence they concluded that, despite the large deuterium solvent isotope effect,[2,3] the reaction proceeds by way of acetylpyridinium ions, *i.e.*, that it represents an example of nucleophilic catalysis.[4] The low rates with 2-picoline and 2,6-lutidine were ascribed to steric hindrance of nucleophilic attack by the bases on the anhydride. Similarly, 2,4-lutidine and 2,6-lutidine (in contrast to pyridine) fail to catalyze the hydrolysis of tetramethylphorphorodiamidic chloride[5]; this reaction presumably occurs by way of nucleophilic attack by the heterocyclic base on the phosphorous atom.

Implicit, however, in the use of steric hindrance as a criterion for nucleophilic attack is the assumption that general base (and general acid) catalysis is not subject to such hindrance. The Brönsted equation[6] connects base strength and catalytic activity

$$k_B = GK_B^x$$

where k_B is the catalytic constant for any base, B, and K_B is its ionization constant; G is a constant for a series of similar bases, and $0 < x < 1$. This relationship might seem already to take into account steric hindrance of the base toward a proton, *i.e.*, such hindrance might already be included in a diminished basicity of B. Recently, however, Gutsche[7] and his co-workers have found that the aldol condensation is promoted by some tertiary amines, including pyridine but that 2,6-lutidine is not very effective. It is here shown that three other reactions which proceed by

(1) (a) National Science Foundation Predoctoral Fellow, 1960–1963; (b) John Simon Guggenheim Fellow, 1962–1963.

(2) A. R. Butler and V. Gold, *J. Chem. Soc.*, 4362 (1961); V. Gold and E. G. Jefferson, *ibid.*, 1409 (1953).

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(6) J. N. Brönsted, *Chem. Rev.*, **5**, 231 (1928).

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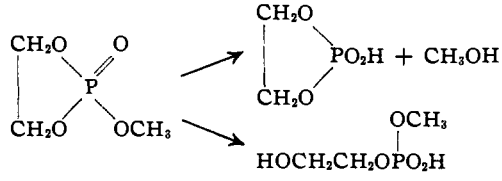
general base and general acid catalysis are subject to steric hindrance. In particular, the hydrolysis of methyl ethylene phosphate is identified as subject to general base catalysis with steric hindrance; the reasoning behind these assignments is covered in the discussion.

Experimental

Materials.—Pyridine, 3-picoline, 4-picoline and 2,4-lutidine were fractionated from calcium hydride. After distillation, each base showed a single peak in vapor phase chromatography over a column of GE silicone on firebrick with an Aerograph model A-100-c V.P.C. apparatus. 2,6-Lutidine (Matheson, Coleman and Bell) was purified by Mr. Robert Blakeley by the procedure of Butler and Gold.[2] β-Glucose, prepared by the method of Hudson and Dale,[8] melted at 148–150°, $[\alpha]^{25}D$ 22.2°. *l*-Menthone was prepared[9] from Eastman Kodak Co. White Label *l*-menthol; the ketone distilled at 92–93° (15 mm.) through a Podbielniak heligrid column. It was pure by vapor phase chromatography, and showed $[\alpha]^{25}D$ −25.9°. Lithium perchlorate was prepared from lithium carbonate (Fisher) by neutralization with aqueous perchloric acid (J. T. Baker, analyzed reagent); the resulting solution gave no precipitate with aqueous silver nitrate. Deuterium oxide (99.7%) was obtained from the Atomic Energy Commission.

Methyl ethylene phosphite[10] was purified by distillation on a Podbielniak spinning band column; the material boiling at 52–52.5° (21 mm.) (reflux ratio, 15:1) was oxidized to methyl ethylene phosphate with nitrogen tetroxide[11] in methylene chloride at −10 to −15°. The product was distilled at about 1 μ pressure in a Hickman still, at a mantle temperature of 40–60° (75% yield from the phosphite) and crystallized when chilled in a Dry Ice–acetone-bath. It melted at −6 to −5° and could be recrystallized in a deep-freeze without change in the m.p. as long white needles from methylene chloride.

Product Analysis.—In alkali, the hydrolysis or methanolysis of methyl ethylene phosphate takes place exclusively with P–O fission and ring opening.[12] However, in acid solution, both ring opening and loss of methoxyl occur. No polymerization



was observed. Since the distribution of products parallels that observed[13] in the acid-catalyzed hydrolysis and exchange of ethylene hydrogen phosphate (and further, since the reaction is extraordinarily fast for C–O cleavage) it has been tentatively assumed that both reactions take place with attack by water on phosphorus.

Methyl ethylene phosphate (600 mg., 4.78 mmoles) was added to a buffer of 673 mg. of pyridine (11.8 mmoles) and 0.50 ml. of 1.00 *M* perchloric acid in 50 ml. of water. The solution was allowed to stand at 30° for an hour. It was then evaporated under reduced pressure to near dryness to remove pyridine and water. During the evaporation, solid barium hydroxide was added to keep the pH of the solution slightly on the basic side (~pH 8). A 50-ml. portion of 95% ethanol was added, and the solution again evaporated. This procedure was repeated several times with absolute ethanol, so that the product precipitated as a white slurry. It was then filtered and washed with ethanol to remove any remaining barium perchlorate. The product was completely soluble in 70% ethanol–water, and therefore was free of barium 2-hydroxyethyl phosphate. The n.m.r. spectrum of the dried product in deuterium oxide solution showed the peaks associated with the barium salt of methyl-2-hydroxyethyl phosphate and (quite well separated from the above) the clean and characteristic doublet for barium ethylene phosphate. (The τ-values for barium methyl-2-hydroxyethyl phosphate are 6.60, 6.44, 6.32, 6.28 and 6.17; those for barium ethylene phosphate are 5.94 and 5.76.) The over-all yield was 91% of a mixture containing 70% of the former and 30% of the latter salt. Attempts to separate the two by crystallization or paper chromatography were unsuccessful. However, the rate constant for the saponification of the cyclic ester probably exceeds that of methyl-2-hydroxyethyl phosphate by at least a factor of 1000. Therefore, the mixed product was subjected to saponification under conditions calculated[14] for 10 half-lives for barium ethylene phosphate. After this treatment (and removal of excess barium hydroxide as the sulfate), the fraction insoluble in 70% ethanol was shown by infrared spectrum to be identical with barium 2-hydroxyethyl phosphate, and the fraction soluble in 70% ethanol similarly was identical with barium methyl-2-hydroxyethyl phosphate.

The same procedure was followed for the imidazole-catalyzed reaction. The yield was 95% of product which consists of 5% barium ethylene phosphate and 95% methyl-2-hydroxyethyl phosphate.

Infrared Spectra.—The infrared spectra of barium salts were taken in potassium bromide disks with a Perkin–Elmer Spectrocord. These spectra, and especially those of a mixture of barium ethylene phosphate with barium methyl-2-hydroxyethyl phosphate, proved sensitive to traces of moisture. Thus, thoroughly dry barium methyl-2-hydroxyethyl phosphate shows a strong absorption at 12.15 μ, whereas in slightly moist KBr (breathing on the ground material is sufficient) the band is shifted to 12.45 μ. Similar sensitivities to moisture in infrared spectra have previously been observed.[15]

Kinetic Methods. (a) Methyl Ethylene Phosphate.—The rate of hydrolysis of methyl ethylene phosphate was determined calorimetrically. Although a few measurements were made at 27° with a crude calorimeter,[16] most of the data have been obtained at 30° with an instrument of moderate precision.[17] This apparatus consists of an inner brass can coated by the American Durafilm Co. with a 0.01-in. layer of Teflon. The inner can is equipped both with a special stirrer to break a bulb containing the sample and with an inlet tube for injection of the sample with a syringe; the calorimeter holds the stirrer, an electrical heater and a Fenwal GA 51 P8 thermistor. The inner chamber is supported from the evacuated outer chamber by a Pyrex collar. A 12-volt storage battery activates a Wheatstone bridge, which is balanced by a decade box on one arm and a fixed resistor on the other. The voltage across the bridge is measured by a Varian chart recorder. The coefficient of thermal leak of the calorimeter is 0.0028 degree per degree minute. Samples of methyl ethylene phosphate, chosen so as to allow a temperature rise of about 0.2°, were sealed in glass bulbs and enclosed in the stirrer assembly. The temperature was raised with the heater to about 0.2° below that of the thermostat. It was then unnecessary to correct for heat leak, since the inner chamber rapidly approached a temperature close to equilibrium. A small, sharp rise in temperature due to heat of solution marked the beginning of reaction, when the bulb was crushed. (Alternatively, a sample was injected from a syringe. The initial temperature of the reaction could then be determined by extrapolation to zero time.) In general, the half-times for the reactions studied were from 10 to 500 seconds. Since the temperature rise was only 0.2°, the increase in rate with increase in temperature was only about 2%; since the rate constants were not determined to better precision than this, no corrections were applied.

(b) **Mutarotation and Inversion.**—The rate of mutarotation of glucose was determined polarimetrically with a jacketed tube maintained at 30° and a Hilger polarimeter, using the standard techniques.[18] The rate of inversion of menthone was also measured polarimetrically.[19] Solutions of buffer and menthone, in 70% ethanol (by volume), were made up at room temperature and transferred to ampoules. These were sealed and heated in a thermostat at 99.0 ± 0.1°. At appropriate intervals the tubes were rapidly cooled to room temperature, opened, and the rotations measured with a Hilger model MKIIA polarimeter, using a sodium vapor lamp as the light source. Upon completion of the measurement, the solution was returned to the ampoule, resealed, rapidly heated to 99° and again placed in the thermostat. The time at room temperature and the cooling and heating times were ignored, since the half-times for the reactions are greater than 10 hours at 100°.

Determination of p*K*'s.—The p*K*'s of the various heterocyclic bases in 70% ethanol by volume were determined by titration of the bases against perchloric acid, with a Radiometer titrator, model TTTlb and scale expander type PHA 630 Ta. The glass electrode, Radiometer type G202C, was standardized against a solution 0.00100 *M* in perchloric acid in 70% ethanol, which was assigned a "pH" in this solvent of 3.00.

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(9) L. T. Sandborn, "Organic Syntheses," Coll. Vol. I, J. Wiley and Sons, Inc., New York, N. Y., 1921, p. 430.

(10) J. R. Cox, Jr., Thesis, Harvard University, 1958.

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(12) R. E. Wall, Thesis, Harvard University, 1960.

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Results

The rates of hydrolysis of methyl ethylene phosphate are assembled in Tables I and II, the rates for the mutarotation of glucose in Table III, and the rates for the inversion of menthone in Table IV. The pK values for the bases in water and in 70% ethanol are presented in Table V, and a summary of the rate constants is given in Table VI. The observed first-order rate constants for the hydrolysis of methyl ethylene phosphate at 27° are plotted against the concentration of buffer at two different buffer ratios in Fig. 1; the data show that the rates are independent of buffer ratio so long as the base concentration is held constant. Further data, for a single buffer ratio, and at 30°, are given in Fig. 2. A similar plot for mutarotation is shown in Fig. 3. Figure 4 presents the data for the inversion of menthone, where the observed first-order rate constants are plotted against the concentration of BH^+ present in the buffer. In Fig. 4, the intercepts on the ordinate axis represent the combined rates for catalysis by water and hydrogen ions. The points for zero buffer concentration are well represented by the equation

$$k_0 \text{ (in min.}^{-1}) = 0.25 \times 10^{-4} + 3.5(H^+)$$

where the hydrogen ion concentration of the 1:1 buffer for each base is calculated from its ionization constant in 70% ethanol. However, since the ionization constants were determined at 25° and the rates at 100°,

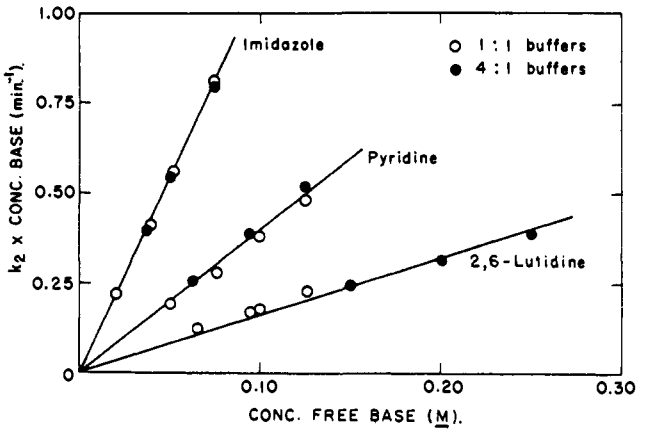

Fig. 1.—Hydrolysis of methyl ethylene phosphate at 27°.

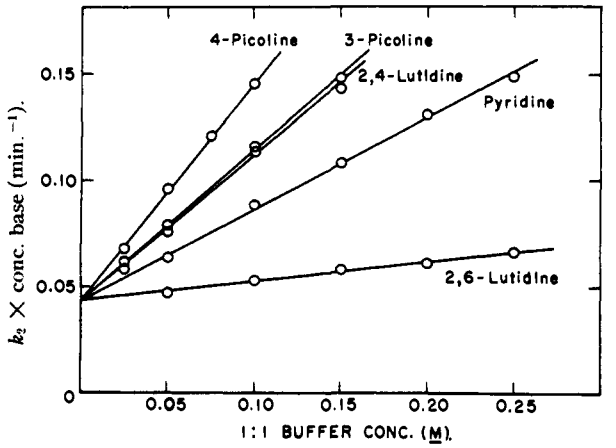

Fig. 2.—Hydrolysis of methyl ethylene phosphate at 30°.

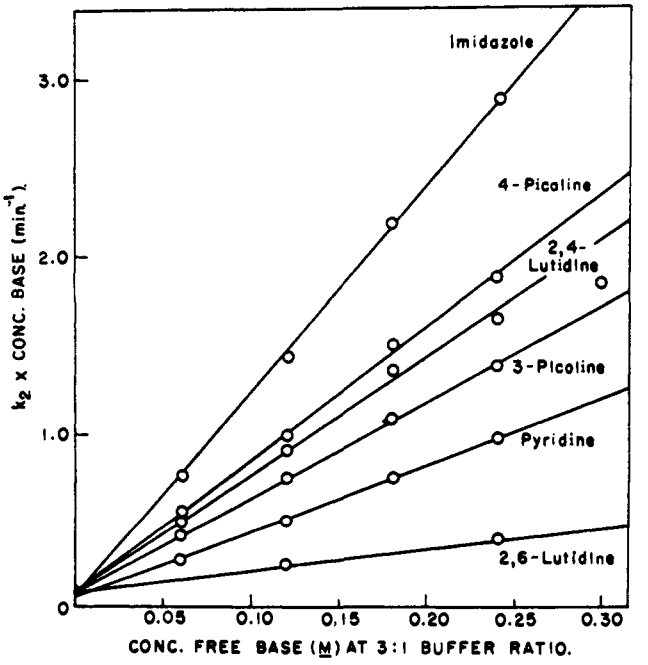

Fig. 3.—Mutarotation of glucose at 30°.

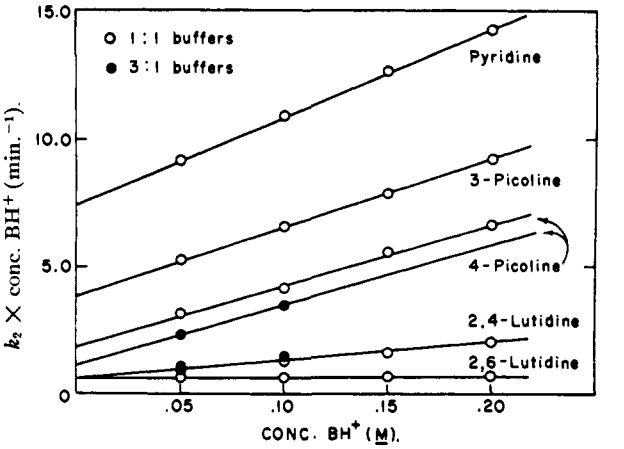

Fig. 4.—Inversion of menthone in 70% ethanol at 99°.

TABLE I

HYDROLYSIS OF METHYL ETHYLENE PHOSPHATE[a]

Base	Concn. free base, M	Buffer ratio (base/acid)	Concn. phosphate, M	k_2 × (B), min.$^{-1}$
Pyridine	0.125	1	0.0231	0.521
	.094	1	.0229	.392
	.063	1	.0219	.262
	.125	4	.0227	.480
	.100	4	.0229	.380
	.075	4	.0218	.280
	.050	4	.0218	.208
	.100[b]	2	.0205	.205
2,4-Lutidine	.070	1	.0188	.420
	.050	1	.0207	.304
	.032	4	.0206	.210
2,6-Lutidine	.125	1	.0220	.239
	.100	1	.0226	.183
	.094	1	.0221	.173
	.063	1	.0220	.141
	.250	4	.0208	.375
	.200	4	.0209	.314
	.150	4	.0208	.247
	.200[b]	4	.0211	.152
Imidazole	.075	1	.0215	8.14
	.050	1	.0213	5.49
	.038	1	.0208	4.16
	.021	1	.0211	2.14
	.075	4	.0207	7.96
	.050	4	.0212	5.52
	.038	4	.0213	4.20
	.050[b]	1	.0212	2.68

[a] At T = 27° and ionic strength = 0.50. [b] Using D_2O as solvent.

TABLE II

HYDROLYSIS OF METHYL ETHYLENE PHOSPHATE[a]

Base	Concn. free base, M[b]	Concn. phosphate, M	$k_2 \times$ (B), min.$^{-1}$
Pyridine	0.240	0.0221	0.985
	.180	.0222	.767
	.120	.0210	.504
	.060	.0200	.274
	.100	.0371	.445
	.100	.0164	.408
	.100	.0120	.396
3-Picoline	.240	.0202	1.37
	.180	.0219	1.10
	.120	.0204	0.753
	.060	.0214	0.421
4-Picoline	.240	.0200	1.87
	.180	.0211	1.51
	.120	.0184	1.04
	.060	.0180	0.545
2,4-Lutidine	.300	.0190	1.85
	.240	.0208	1.65
	.180	.0209	1.35
	.120	.0182	0.895
	.060	.0222	.492
2,6-Lutidine	.240	.0203	.391
	.120	.0210	.244
Imidazole	.240	.0178	2.88
	.180	.0182	2.18
	.120	.0160	1.43
	.060	.0202	0.768

[a] At 30° and ionic strength = 0.50. [b] Buffer ratio = 3:1 using perchloric acid.

TABLE III

MUTAROTATION OF GLUCOSE[a]

Base	Concn. free base, M[b]	k_1, min.$^{-1}$	Base	Concn. free base, M[b]	k_1, min.$^{-1}$
Pyridine	0.250	0.150	2,4-Lutidine	0.150	0.145
	.200	.131		.100	.114
	.150	.109		.050	.0778
	.100	.0879		.025	.0608
	.050	.0625	2,6-Lutidine	.250	.0640
3-Picoline	.150	.148		.200	.0598
	.100	.115		.150	.0572
	.050	.0772		.100	.0519
	.025	.0572		.050	.0451
4-Picoline	.100	.146			
	.075	.121			
	.050	.0954			
	.025	.0671			

[a] At 30° and with glucose concn. = 0.494 M in aqueous solution. [b] Buffer ratio = 1:1 using perchloric acid.

agreement cannot be expected to be perfect. Although the catalysis by hydrogen ions is considerable, general acid catalysis is clearly observed; the slopes of the lines represent the catalytic efficiency of the cationic acids, BH^+.

The catalytic constants for the amines or amine salts (Table VI) are obtained from the relationship

$$k_{obs} = k_0 + k_B(B), \text{ or } k_{obs} = k_0 + k_{BH^+}(BH^+)$$

where k_0 is the rate at a given pH extrapolated to zero concentration of buffer.

Discussion

Although mutarotation[18] is one of the classic examples of general base catalysis[6] where the Brönsted equation has been applied, the new data obviously fail to follow the relationship. 2,6-Lutidine is a much weaker catalyst than 2,4-lutidine, although they are of comparable base strength; similarly, 2,4-lutidine is a poorer catalyst relative to 3-picoline than could have been anticipated from their base strengths. The same

TABLE IV

INVERSION OF MENTHONE[a]

Base	Concn. free base, M[b]	10^4k_1, min.$^{-1}$	10^4k_0, min.$^{-1}$[d]
Pyridine	0.200	14.2	
	.150	12.6	7.45
	.100	10.9	
	.050	9.08	
3-Picoline	.200	9.22	
	.150	7.81	3.80
	.100	6.58	
	.050	5.15	
4-Picoline	.200	6.58	
	.150	5.47	1.95
	.100	4.14	
	.050	3.11	
	.100[c]	3.50	1.05
	.050[c]	2.33	
2,4-Lutidine	.200	2.00	
	.150	1.61	0.59
	.100	1.29	
	.050	0.941	
	.100[c]	1.40	0.59
	.050[c]	0.981	
2,6-Lutidine	.200	.655	
	.150	.628	0.55
	.100	.610	
	.050	.582	

[a] At T = 99°, ionic strength = 0.30 and menthone concn. = 0.582 M. [b] Buffer ratio = 1:1 using perchloric acid. [c] Buffer ratio = 3:1 using perchloric acid. [d] Determined by extrapolation to zero buffer concn.

TABLE V

pK'S OF BASES IN 70% ETHANOL

Base	pK_{H_2O}[a]	p$K_{70\%EtOH}$
Pyridine	5.22	3.64
3-Picoline	5.63	4.02
4-Picoline	5.98	4.34
2,4-Lutidine	6.63	5.06
2,6-Lutidine	6.72	5.13

[a] R. J. L. Andon, J. D. Cox and E. F. G. Herington, *Trans. Faraday Soc.*, **50**, 918 (1954).

TABLE VI

RATE CONSTANTS

Base	Hydrolysis of methyl ethylene phosphate, k_2 (M^{-1} min.$^{-1}$)[a,b]	Mutarotation of glucose, k_2 (M^{-1} min.$^{-1}$)[b]	Inversion of menthone, 10^4k_2 (M^{-1} min.$^{-1}$)[c]
Pyridine	3.6	0.44	34
3-Picoline	5.3	0.69	27
4-Picoline	7.7	1.02	23
2,4-Lutidine	6.7	0.68	7.1
2,6-Lutidine	1.3	0.09	0.5
Imidazole	11.7		
Solvent[d]	0.07	0.04	0.25×10^{-4}

[a] From measurements at 30°. [b] Catalysis by the bases, B. [c] Catalysis by the conjugate acids, BH^+. [d] In min.$^{-1}$; determined by graphical extrapolation.

comparison can be made for the hydrolysis of methyl ethylene phosphate, where again 2,4-lutidine and especially 2,6-lutidine are less powerful catalysts than might have been anticipated, assuming a Brönsted relationship, from consideration of base strength. Inspection of Fig. 4 for the inversion of menthone shows that the catalytic efficiency of the 2,6-lutidinium ion is small and obviously much less than that of the 2,4-lutidinium ion, although the pK's of the two cations are quite similar. The rate for the 2,6-lutidinium ion falls below that anticipated for a Brönsted relationship by

a factor of about 10. However, since the rate constant itself is so small, this estimate may be subject to considerable error, and the catalytic efficiency of the cation may be even less than that here estimated.

The hydrolysis of methyl ethylene phosphate is subject to steric hindrance of moderate size; the effects are comparable to those for mutarotation and for the inversion of menthone. Furthermore, the solvent isotope effect is about 2. Although the latter is somewhat small for general base catalysis, the application of the two criteria—steric effects and solvent isotope effects—combine to indicate that the hydrolysis is subject to general base rather than to nucleophilic catalysis.

The three reactions here studied show steric hindrance, determined kinetically, which exceeds that in the corresponding ionizations.[20] Presumably the ionization constant reflects hindrance which accompanies addition of the proton and solvation of the cation, BH^+, whereas the catalytic constant k_B or k_{BH^+} reflects the interaction of the base with a large organic molecule at the moment when a proton is transferred from one to another. It is not astonishing that these two steric effects are different.

One may tentatively conclude that steric effects for general acid and general base catalysis are of moderate size (perhaps an order of magnitude for 2,6-lutidine), whereas those for nucleophilic attack at carbon[2] or phosphorus[5] are large. Probably the sharpest contrast (and best criterion) rests on the behavior of 2,4-lutidine, which (in the few examples cited) is nearly as active in general acid or general base catalysis as predicted from its pK, but practically without effect as a nucleophilic catalyst.

In addition to the contribution of these kinetic effects to an understanding of general base catalysis, the strong catalytic effect of imidazole in the hydrolysis of methyl ethylene phosphate suggests the role of this base (in histidine residues) in the action of ribonuclease. This aspect of our findings has already been discussed elsewhere.[21,22]

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[CONTRIBUTION FROM THE CENTRAL BASIC RESEARCH LABORATORIES OF ESSO RESEARCH AND ENGINEERING CO., LINDEN, N. J.]

Catalysis by Catechol Monoanion

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Hydrolysis of phenyl chloroacetate has been shown to be strongly catalyzed by the monoanion of catechol. Rate measurements were taken by titrating the acid formed at constant pH, in ~2% dioxane–0.2 M aqueous sodium perchlorate, over a pH range of 6.5 to 9.0 and from 25 to 45°. The catalysis is postulated to proceed by formation of the intermediate ester catechol monochloroacetate, which was shown to hydrolyze about 800 times as fast as phenyl chloroacetate. Participation of the neighboring phenolic hydroxyl group of the catechol anion was indicated by the failure of phenol, guaiacol, resorcinol and hydroquinone to exhibit positive catalysis. The energy of activation for the catalysis by catechol ion is 5.37 ± 0.07 kcal./mole; the entropy of activation −36.3 ± 6 e.u. This is apparently the first reported instance of a difunctional acid–base catalyst for carboxylic ester hydrolysis exclusive of an enzyme system. The similarities to the action of α-chymotrypsin are discussed. The demonstration of catalytic action involving a general acid of $pK_a \geq 12.3$ suggests a similar phenomenon in the enzymatic-active site.

Introduction

Catalysis of ester hydrolysis by nucleophiles has been studied by several workers. Interest in such catalytic species as imidazole[1,2] and *o*-mercaptobenzoic acid[3] has been stimulated by evidence that their functional groups may be responsible for the behavior of enzymatic-active sites.

One reason for the high efficiency of enzyme action may be the participation of more than one functional group on the catalytic site. This investigation concerns the catalysis of ester hydrolysis by non-enzymatic substances which are also polyfunctional. Such a substance is the monoanion of catechol, which has previously been shown to be effective as a nucleophilic agent toward Sarin (isopropyl methylphosphonofluoridate) and toward acid anhydrides and chlorides.[4] Phenyl chloroacetate, with an easily observable hydrolysis rate, was chosen as a substrate.

Experimental

Materials.[5]—Inorganic substances were of reagent grade purity and were not further purified. Imidazole (m.p. 86.6–87.9°) was Eastman Kodak Co. White Label grade. Reagent grade hydroquinone (m.p. 169.8–171.3°) was obtained from Matheson, Coleman, and Bell. Resorcinol and phenol were ACS reagent grade. Catechol and phenyl chloroacetate were recrystallized from commercial products. Commercial guaiacol was redistilled, b.p. 97–99° at 18.9 mm. 1,4-Dioxane was purified by Fieser's[6] procedure. Its purity was checked by vapor-phase chromatography and was better than 99.9%. Catechol monochloroacetate (m.p. 78.5–81.0°; lit.[7] m.p. 81°) was prepared from catechol and chloroacetic anhydride. It was recrystallized from hexane.

Kinetics.—The hydrolysis rates were followed by titrating the acid produced, using a Radiometer pH-Stat apparatus, which included a titrator, titrigraph recorder and a scale expander. Reactions were run in a Teflon-lined stainless-steel vessel of approximately 100-ml. capacity with a water jacket. Temperature of the vessel was maintained within ±0.02° of the desired value by a water-bath. A current of prehumidified nitrogen was passed through the cell during runs.

The reaction medium was 50.0 ml. of 0.2 M sodium perchlorate, with 1.0 ml. of dioxane solution of ester. Where more than one water-insoluble reactant was present, the total amount of dioxane was kept to 1.0 ml. The titrant was 0.2 N sodium hydroxide, delivered from a 0.5-ml. syringe by the titrator through a capillary glass tube (to minimize leakage) to the reaction cell. When it was desirable to introduce an excess of one reactant, the necessary amount was weighed into a polyethylene cup, which fit into the vessel mentioned earlier. Water was put into the space between the cup and the cell wall to allow for rapid temperature equilibration.

pH was measured with a G202B glass electrode and a K401 calomel electrode, manufactured by Radiometer. The calomel

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