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Mechanism of the Reaction of Imido Esters with Amines

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The rates and products of the reactions of ethyl benzimidate and ethyl *m*-nitrobenzimidate with a number of amines have been examined as a function of *p*H. The following evidence strongly supports a mechanism involving rate-determining decomposition of a tetrahedral addition intermediate at low *p*H and a change in rate-determining step to rate-determining formation of such an intermediate from free amine and protonated imido ester at high *p*H: (1) The reactions exhibit sharp *p*H-rate maxima which can only be explained by a change in rate-determining step of the reaction; (2) at low *p*H the existence of a pre-equilibrium involving an addition intermediate is indicated by the formation of $\overset{NHR'}{ArC}{=}NR'$ from $\overset{OEt}{ArC}{=}NH$ and $R'NH_2$, while at high *p*H the addition step is irreversible and $\underset{NHR'}{ArC}{=}NH$ is the only product; (3) at low, but not at high *p*H, the existence of a pre-equilibrium is shown by an exchange of $R'NH_2$ into $\overset{OEt}{ArC}{=}NR$ to give $\overset{OEt}{ArC}{=}NR'$ (analogous to ^{18}O exchange in ester hydrolysis) before appreciable amidine is formed; (4) only the second step, at low *p*H, of the reaction with hydroxylamine, methoxyamine or semicarbazide is subject to general acid-base catalysis.

Introduction

Although the existence of tetrahedral addition intermediates in reactions of aldehydes and ketones has been demonstrated repeatedly, the unequivocal demonstration of such kinetically significant intermediates in transfer and hydrolysis reactions at the carboxyl level of oxidation has been difficult, because of their low stability. Bender has shown that such tetrahedral addition compounds are formed from fluoroacetate esters and alkoxide ions in alcohol solution,[1] and the exchange of labeled oxygen between water and the carbonyl group in ester and amide hydrolysis provides further evidence for the existence of such compounds as intermediates in these reactions.[2] Kinetic data, *i.e.*, the existence of breaks or maxima in *p*H–rate profiles which cannot be explained without postulating a change in rate-determining step from rate-determining formation to rate-determining decomposition of an addition intermediate, provide strong evidence for a tetrahedral addition intermediate in several carbonyl and intramolecular acyl group reactions.[3–6]

The experiments reported here were carried out to study the mechanism of the reaction of imido esters with amines, in the hope of obtaining information on the role of tetrahedral intermediates in this reaction at the carboxyl level of oxidation. It is known from synthetic work that this reaction can give asymmetrical amidines, symmetrical amidines or new imido esters, depending on the reaction conditions,[7–10] but the factors which determine the nature of the product have not been clearly defined. The rate of amidine formation is known to be increased if one of the reactants is present as the conjugate acid[7,10–12] and, after the suggestion of Stieglitz,[13] the reaction has generally been formulated as proceeding through an addition of free amine to the imido ester hydrochloride. The recent studies of Hunter and Ludwig have shown that amidine formation from amino acids proceeds with sharp *p*H–rate maxima, which are different for different amino acids, so that it is possible to obtain a considerable degree of control of product formation in reactions with proteins or mixtures of amino acids, by suitable control of the *p*H.[14] The experiments reported here provide evidence, based on kinetic data and the results of amine exchange experiments, for a kinetically significant tetrahedral addition intermediate in the aminolysis of imido esters.

Experimental

Materials.—Amines and amine hydrochlorides were redistilled or recrystallized before use. Solutions at the desired *p*H were generally prepared just before use by the addition of potassium hydroxide to stock solutions of the hydrochlorides. The previously recrystallized methoxyamine hydrochloride was found by titration to contain approximately 5% ammonium chloride after the kinetic experiments were completed; this should not affect the results, because ammonium chloride was shown not to affect the rate of imido ester disappearance under the conditions used for the methoxyamine experiments. Inorganic compounds were reagent grade. Glass-distilled water was used in all experiments at alkaline *p*H. Ethyl benzimidate hydrochloride[15,16] (m.p. 121–122° dec., lit. 118–120°; infrared bands of free base (neat) at 3.03(w), 6.11(s), 6.23(w) and 6.33(m) μ) and ethyl *m*-nitrobenzimidate hydrochloride[17] (m.p. 140° dec.) were prepared from ethanol and the appropriate nitrile by published procedures and were stored in the dark over phosphorus pentoxide. Ethyl N-methylbenzimidate was prepared by the following modified procedure.[18,19] A mixture of phosphorus pentachloride

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(1) M. L. Bender, *J. Am. Chem. Soc.*, **75**, 5986 (1953).

(2) (a) M. L. Bender, *ibid.*, **73**, 1626 (1951); (b) *Chem. Revs.*, **60**, 53 (1960).

(3) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).

(4) (a) A. V. Willi, *Helv. Chim. Acta*, **39**, 1193 (1956); (b) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 832 (1962).

(5) (a) R. B. Martin, S. Lowey, E. L. Elson and J. T. Edsall, *ibid.*, **81**, 5089 (1959); (b) R. B. Martin and A. Parcell, *ibid.*, **83**, 4830 (1961); (c) R. B. Martin and R. I. Hedrick, *ibid.*, **84**, 106 (1962); (d) H. A. Smith and G. Gorin, *J. Org. Chem.*, **26**, 820 (1961).

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

(7) A. Pinner, "Die Imidoäther und ihre Derivate." Berlin, Germany (1892); *cf. Chem. Revs.*, **35**, 424, ref. 109 (1944).

(8) E. Schmidt, *Ber.*, **47**, 2545 (1914).

(9) (a) R. M. Roberts, *J. Am. Chem. Soc.*, **72**, 3603 (1950); (b) R. M. Roberts and R. H. DeWolfe, *ibid.*, **76**, 2411 (1954).

(10) R. Roger and D. G. Neilson, *Chem. Revs.*, **61**, 179 (1961).

(11) A. Knorr, *Ber.*, **50**, 229 (1917).

(12) F. E. King and R. M. Acheson, *J. Chem. Soc.*, 1396 (1949).

(13) J. Stieglitz, *J. Am. Chem. Soc.*, **35**, 1774 (1913); Blunt, Dissertation, University of Chicago, 1907.

(14) M. J. Hunter and M. L. Ludwig, *J. Am. Chem. Soc.*, **84**, 3491 (1962).

(15) A. W. Dox, in "Organic Syntheses," Coll. Vol. I, H. Gilman and A. H. Blatt, ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 6.

(16) A. Pinner, *Ber.*, **16**, 1655 (1883).

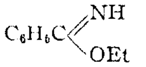
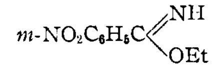
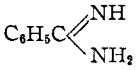
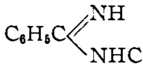
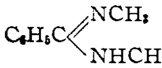
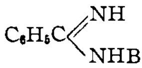
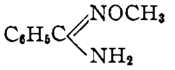
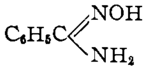
(17) M. Neubert, *Ann.*, **265**, 144 (1891).

(18) H. v. Pechmann, *Ber.*, **28**, 2362 (1895).

(19) G. D. Lander, *J. Chem. Soc.*, **83**, 320 (1903).

TABLE I

ULTRAVIOLET SPECTRAL DATA IN AQUEOUS SOLUTION

Compound		λmax, mμ (ε)	λmax, mμ (ε)	λmin, mμ (ε)
 $C_6H_5C(=NH)OEt$	Neutral	230 (9,500)	270 (620)	262 (510)
	Acid	243 (12,800)	275 infl. (1400)	
 $m\text{-}NO_2C_6H_5C(=NH)OEt$	Neutral	219 (19,300)	264 (7100)	251 (6250)
	Acid	225 (22,700)	260 infl. (6750)	
 $C_6H_5C(=NH)NH_2$	Neutral	226 (9,300)		
	Acid	229 (11,300)	270 (900)	262 (800)
 $C_6H_5C(=NH)NHCH_3$	Acid	227 (12,000)	265 infl. (780)	
 $C_6H_5C(=NCH_3)NHCH_3$	Acid	222 (12,700)	260 infl. (830)	
 $C_6H_5C(=NH)NHBu$	Acid	227 (14,000)	268 infl. (870)	
 $C_6H_5C(=NOCH_3)NH_2$	Neutral		254 (5350)	237 (4300)
	Acid	229 (12,000)	270 infl. (1100)	
 $C_6H_5C(=NOH)NH_2$	Neutral		251 (5000)	240 (4750)
	Acid	227 (12,000)	272 infl. (1000)	
	Base		274 (5500)	245 (4070)

(10.5 g., 51 mmoles), N-methylbenzamide (7.0 g., 52 mmoles) and dry benzene (30 ml.) was refluxed for 25 minutes. Solvent and phosphorus oxychloride were removed under reduced pressure. The crude product was treated with benzene, cooled in ice, and an excess of 0.5 *M* sodium ethoxide in absolute ethanol was added dropwise (*ca.* 110 ml.). The solvents were removed under reduced pressure and the residue was treated with ice-water and extracted three times with ether. The ether layer was dried over sodium sulfate and the solvent was evaporated. Vacuum distillation of the residue gave the imido ester as a colorless liquid (b.p. 70–75°, 1.3–1.4 mm.). Contaminating ethyl benzoate was removed by rapidly extracting an aqueous solution of the compound in dilute hydrochloric acid with chloroform. The aqueous layer was immediately made alkaline and extracted with chloroform. The extract was dried over sodium sulfate and the solvent was evaporated. The product (infrared bands (CCl_4) at 5.97(s) and 6.24 μ) was stored over phosphorus pentoxide.

Ultraviolet absorption maxima and approximate extinction coefficients are summarized in Table I.

Kinetic Measurements.—Rates were generally followed spectrophotometrically at 25.0 ± 0.1° in aqueous solution brought to an ionic strength of 1.0 with potassium chloride (except for the reactions with butylamine and hydroxide ion, which were carried out at an ionic strength of 2.0) with a Zeiss PMQ II spectrophotometer equipped with a thermostated cell compartment. Reactions were carried out with a large excess of amine and were found to follow (pseudo) first-order kinetics, unless otherwise noted. Small corrections were made where appropriate for the rates of acid- and base-catalyzed decomposition of imido ester, measured in separate experiments in the absence of amine. Solutions of imido ester were prepared by neutralization to *p*H 8.5–9.5 of freshly prepared solutions of the hydrochloride and were used within a few hours. The change in absorption at an appropriate wave length (Tables I and II) was followed for at least 2 half-times and the pseudo first-order rate constants were obtained from linear plots of $A_\infty - A_t$ (or $A_t - A_\infty$) against time on semi-logarithmic graph paper and the equation $k_1 = \ln 2/(\text{half-time})$. Measurements of *p*H were obtained with a glass electrode and a Radiometer PHM-4b *p*H meter, at the completion of each experiment. No sodium salts were used. The reaction of *m*-nitrobenzimidate with methylamine could not be followed by this method and was, therefore, followed by measurement of the absorbance of aliquots which were quenched in 0.33 *M* hydrochloric acid and read within 20 seconds, before appreciable hydrolysis of the imido ester had occurred. Acid dissociation constants were determined spectrophotometrically at ionic strength 1.0 from the difference in absorption of the imido ester and its hydrochloride in a series of acetate, phosphate, imidazole and tris-(hydroxymethyl)-aminomethane buffers; the absorption of the hydrochloride and the free base were determined in dilute hydrochloric acid and sodium hydroxide solutions, respectively. Readings were taken immediately after mixing the solutions to avoid absorption changes due to hydrolysis. The pK'_a values of ethyl benzimidate, ethyl *m*-nitrobenzimidate and ethyl N-methylbenzimidate were found to be 6.37, 5.30 and 6.52, respectively.

Isolation of Products. N-Methylbenzamidine from Ethyl Benzimidate and Methylamine.—A solution of imido ester hydrochloride (0.50 g., 2.7 mmoles), methylamine hydrochloride (1.82 g., 27 mmoles) and potassium hydroxide (2.02 ml. of 8 *M*, 16.2 mmoles; calcd. *p*H 11) in water–ethanol (2:1, 30 ml.) was allowed to stand for 5 hours. It was then evaporated under reduced pressure, the residue treated with base (6.5 ml. of 2 *M* sodium hydroxide) and the mixture evaporated to near-dryness. The residue was extracted two times with ether, and the ethereal solution then was treated with gaseous hydrochloric acid. The crude hydrochloride (0.40 g., 87%, m.p. 218–221°) was recrystallized from ethanol–benzene (m.p. 222–223°, lit.[20] 222–223°). *Anal.* Calcd. for $C_8H_{11}N_2Cl$: C, 56.33; H, 6.49; N, 16.42; Cl, 20.77. Found: C, 55.95; H, 6.49; N, 16.12; Cl, 21.03. The same product was isolated from a similar reaction at *p*H 9.2.

N,N′-Dimethylbenzamidine from Ethyl Benzimidate and Methylamine.—A solution of imido ester hydrochloride (0.25 g., 1.35 mmoles) and methylamine hydrochloride (1.82 g., 27 mmoles) in ethanol-water was brought to *p*H 7.2 with potassium hydroxide. After 2 days the *p*H was adjusted to 8.5 and the solution was extracted with ether. The aqueous layer was made strongly basic and evaporated to near-dryness. The residue was extracted with ether and the extract was evaporated to give an oil. The picrate (0.12 g., 24%, m.p. 165–168°) was obtained from ethanol–water and was recrystallized (m.p. 170–172°, lit.[20] 171–172°). *Anal.* Calcd. for $C_{15}H_{15}N_5O_7$: C, 47.74; H, 4.01; N, 18.56. Found: C, 47.64; H, 4.14; N, 18.53. From the mother liquors a second crop of crystals, m.p. 75–115°, was obtained (reported[20] m.p. 130–132° for N-methylbenzamidine picrate).

N-*n*-Butylbenzamidine from Ethyl Benzimidate and *n*-Butylamine.—This compound was prepared in both ethanolic and aqueous (heterogeneous) media. (i) A solution of ethyl benzimidate hydrochloride (0.20 g., 1.08 mmoles) and *n*-butylamine (1.1 ml., 15 mmoles) in absolute ethanol (5 ml.) was allowed to stand at room temperature for 20 hours. Most of the excess amine and solvent was evaporated on the steam-bath and then under reduced pressure.

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(20) F. L. Pyman, *J. Chem. Soc.*, 123, 3359 (1923).

TABLE II

REACTION CONDITIONS FOR RATE MEASUREMENTS AT 25.0°[a]

Imido ester[b]	Amine	Amine, M	pK_a'[c]	pH-rate maximum	Buffer	pH region	mμ
EB	n-$C_4H_9NH_2$	0.50	11.01	9.9	0.2 M Tris[d]	8.1– 9.2	250
					n-Butylamine	9.7–11.9	
EB	CH_3NH_2	.50	10.85	9.8	0.2 M Tris[g]	8.0– 9.0	265
					Methylamine	9.7–12.0	
ENB	CH_3NH_2	.50		9.5	0.2 M Tris[g]	7.3– 9.0	240[e]
					0.2 M H_3BO_3	8.9– 9.5	
					Methylamine	10.1–11.7	
EB	NH_3	.50	9.49	8.8	0.2 M imidazole[g]	6.6– 7.9	255, 270
					0.2 M Tris	8.4– 9.5	270
					Ammonia	8.6–10.5	270
EB	NH_2OH[f]	.10	6.09	7.2	Hydroxylamine	5.1– 6.9	245–235
					0.2 M imidazole[h]	6.9– 8.4	265
					0.31 M Tris[g]	8.1– 9.3	265
ENB	NH_2OH[f]	.10		7.0	Hydroxylamine	5.2– 7.1	260
					0.15 M Tris	7.3– 9.2	
EB	CH_3ONH_2[f]	.10	4.80	7.0	Methoxyamine	3.8– 6.0	245
					0.1 M imidazole[h]	6.6– 7.5	265
					0.1 M Tris[g]	7.8– 9.3	
EB	$H_2NNHCONH_2$[i]	.50	3.83	6.2	Semicarbazide	2.8– 4.8	290
					0.2 M acetate[h]	5.0– 5.8	
					0.2 M imidazole	6.3– 8.1	

[a] The ionic strength was adjusted to 1.0 with KCl (ionic strength = 2.0 for butylamine reactions). [b] EB = ethyl benzimidate; ENB = ethyl *m*-nitrobenzimidate. [c] The pK_a is the pH of the reaction solution at 50% neutralization of the amine. [d] Tris-(hydroxymethyl)-aminomethane. [e] In this reaction aliquots were pipetted into acid and the optical density was recorded within 20 seconds. [f] 4×10^{-5} M ethylenediaminetetraacetic acid was added to the reaction mixtures. [g] Rate independent of buffer concentration. [h] Catalysis by the buffer was observed. [i] Product not isolated. A slower secondary reaction was observed at low pH.

The addition of a little anhydrous ether to the residue and scratching induced crystallization of a colorless solid which was triturated with a small volume of ether. The product, m.p. 193.5–194°, was recrystallized from absolute ethanol (1.5 ml.). (ii) Imido ester hydrochloride (0.204 g., 1.1 mmoles) was treated with water (4 ml.), sodium hydroxide (0.25 ml. of 1 N) and n-butylamine (0.10 ml., 1.4 mmoles) and the mixture was stirred for 4 hours. Dilute aqueous hydrochloric acid was added to pH 8 and the solution was extracted with ether. The aqueous layer was evaporated under reduced pressure to *ca.* 1 ml. and the product was filtered (0.14 g., 63%, m.p. 191–194°) and recrystallized from absolute ethanol (m.p. 193–194°; m.p. on admixture with above compound, 193–194°). *Anal.* Calcd. for $C_{11}H_{17}N_2Cl$: C, 62.10; H, 8.06; N, 13.17; Cl, 16.67. Found: C, 62.15; H, 8.00; N, 13.12; Cl, 16.81.

O-Methylbenzamidoxime from Ethyl Benzimidate and Methoxyamine.—Methoxyamine hydrochloride (0.835 g., 10.0 mmoles) was dissolved in 15 ml. of water and 10% potassium hydroxide was added to pH 6.0. An aqueous solution of ethyl benzimidate hydrochloride (0.464 g., 2.5 mmoles) was added all at once, with good stirring. A liquid separated. The pH was maintained between 5.9 and 6.1 by the addition of potassium hydroxide solution. After 35 minutes the mixture was extracted twice with ether, the extract was dried over sodium sulfate, and the solvent was evaporated. The residual oil (0.35 g., 90%, m.p. 55–58°) solidified on standing. It was recrystallized from ether–petroleum ether (m.p. 57–58°, lit.[21] 57°; infrared bands (Nujol): 6.12(s), 6.25(w) μ). *Anal.* Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66. Found: C, 64.18; H, 6.68; N, 18.38.

Similar experiments in which the pH was maintained at 3.65–3.72, 4.36–4.40 and 4.97–5.01 gave liquids consisting of ethyl benzoate, O-methylbenzamidoxime and ethyl N-methoxybenzimidate.[22] The last was formed in largest amount at the lowest pH, as shown by comparison of infrared spectra. It was separated by chromatography on Florisil with pentane as eluent (infrared bands (neat): 6.20(s), 6.35(w) μ; ultraviolet (neutral): λ_{max} 236 mμ (infl.)). In dilute sulfuric acid it hydrolyzed rapidly to a product with λ_{max} 230 and 274, λ_{min} 259 mμ, presumably ethyl benzoate.[23]

Benzamidoxime from Ethyl Benzimidate and Hydroxylamine.—This compound was prepared in an analogous manner with a 10-fold excess of amine at pH 6.05. The product was obtained on addition of petroleum ether to the benzene extract (70%; m.p. 76–77°, lit.[24] 79–80°). *Anal.* Calcd. for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.93; H, 5.99; N, 20.62.

The same compound was prepared from benzonitrile and hydroxylamine[24] and recrystallized from benzene (m.p. 76–77.5°). Preliminary experiments indicated that at low pH ethyl benzimidate and hydroxylamine give a poor yield of ethyl N-hydroxybenzimidate,[23] which does not readily react further with either hydroxylamine (pH 6.0–8.6) or ammonia (pH 7.5–10).

Reactions of Ethyl N-Methylbenzimidate with Ammonia. (i) **Ethyl Benzimidate.**—Ammonium chloride (2.3 g., 43 mmoles) and ethyl N-methylbenzimidate (0.4 g., 2.5 mmoles) in water–ethanol (2:1, 40 ml.) were brought to an apparent pH of 7.55 with potassium hydroxide. The solution was stirred for 20 minutes, the pH was adjusted to 8.45, and the solution was extracted three times with chloroform. The chloroform extracts were dried over sodium sulfate, the solvent was evaporated under reduced pressure, the residue was taken up in anhydrous ether, a small amount of insoluble material was filtered, and the filtrate was treated with dry hydrochloric acid. The hydrochloride salt of ethyl benzimidate was collected and rinsed with ether (0.15 g., 33%, m.p. 121–122° dec.; on admixture with an authentic sample, m.p. 121–123° dec.).

(ii) **Benzamidine.**—Ammonium chloride (8.1 g., 150 mmoles) was dissolved in water (50 ml.) and sufficient 4 M potassium hydroxide was added to bring the pH to 7.98. Ethyl N-methylbenzimidate (0.50 g., 3.06 mmoles) was dissolved in a little ethanol and added to the ammonia solution. A liquid separated. The mixture was shaken in a stoppered flask for an hour until most of the liquid had gone into solution. The pH then was 7.88. The mixture was extracted three times with ether. The aqueous layer was treated with 5 M sodium hydroxide (30 ml.) and

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[21] F. Tiemann and P. Krüger, *Ber.*, **17**, 1685 (1884).

[22] W. Lossen and J. Zanni, *Ann.*, **182**, 220 (1876).

[23] W. Lossen, *ibid.*, **252**, 170 (1889).

[24] F. Tiemann and P. Krüger, *Ber.*, **17**, 126 and 1685 (1884).

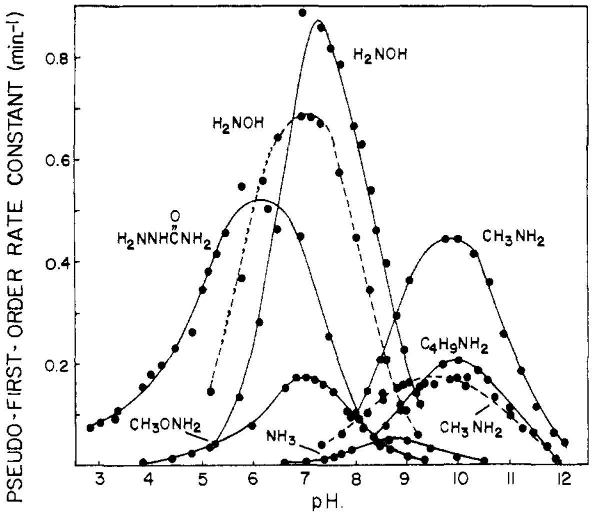

Fig. 1.—Dependence on *p*H of the reactions of ethyl benzimidate (solid line) and ethyl *m*-nitrobenzimidate (dashed line) with amines at 25° and ionic strength 1.0 (*n*-butylamine at ionic strength 2.0).

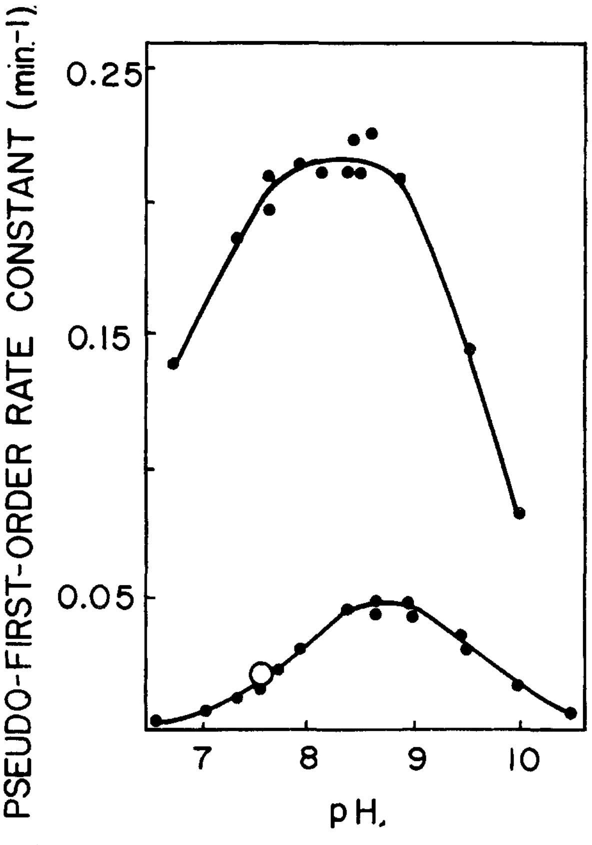

Fig. 2.—Dependence on *p*H of the reactions of ethyl N-methylbenzimidate (upper curve) and of ethyl benzimidate (lower curve) with 0.5 *M* ammonia at 25° and ionic strength 1.0. The open circle is the rate of the second phase of the reaction of ethyl N-methylbenzimidate with ammonia.

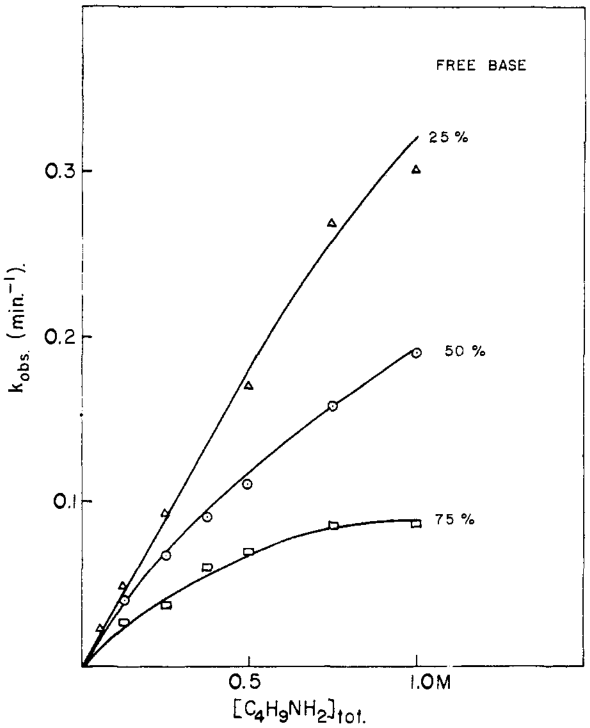

Fig. 3.—The rate of the reaction of ethyl benzimidate with *n*-butylamine as a function of *n*-butylamine concentration at several *p*H values at 25° and ionic strength 2.0.

then partially evaporated under reduced pressure at room temperature. A further portion of sodium hydroxide solution was added (10 ml.) and the solution was then extracted three times with chloroform. The extracts were dried over anhydrous sodium sulfate and the solvent was evaporated. The product was dissolved in a small amount of hot ethanol, and an ethanolic solution of picric acid (0.60 g., 2.6 mmoles) was added. Benzamidine picrate was obtained from ethanol as long, fine yellow needles (0.56 g., 73% on basis of maximum yield of basic products, m.p. 236–237°, lit[25,26] m.p. 233°, 235°).

A similar experiment was carried out at *p*H 8.85. The solution of picric acid and products (*ca.* 10 ml.) deposited a first crop (0.32 g., 36%) with m.p. 234–236°. Concentration of the mother liquor to *ca.* 5 ml. afforded a second crop (0.40 g.) with m.p. 121–175°, which after recrystallization from ethanol–benzene had m.p. 127–163°. A third crop (0.02 g.) had m.p. 127–128°.

(iii) **N-Methylbenzamidine.**—A similar experiment at *p*H 9.80 gave a picrate (0.83 g., 98%, m.p. 123–127°) which was recrystallized from ethanol-benzene (m.p. 128–130°, lit.[20] m.p. 130–132° for N-methylbenzamidine picrate).

Results

The rates of the reactions of ethyl benzimidate and ethyl *m*-nitrobenzimidate with amines show sharp *p*H-rate maxima for all of the amines examined (Fig. 1, Table II). Although there is a general tendency for the maxima to occur at lower *p*H values with the less basic amines, the curves do not agree with the ionization curves of the amines and the imido esters, and the rate maxima do not occur at a *p*H value midway between the *pK*'s of the reactants. Ammonia reacts comparatively slowly, probably because of its "abnormally" high basicity, due to hydrogen-bonding stabilization of the ammonium ion in aqueous solution.[27] At a given *p*H value above neutrality there is less of the protonated form of *m*-nitrobenzimidate (pK_a' 5.30) than of benzimidate (pK_a'

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(25) H. H. Strain, *J. Am. Chem. Soc.*, **49**, 1558 (1927).

(26) G. Ponzio and B. Zanardi-Lamberti, *Gazz. chim. ital.*, **53**, 818 (1923).

(27) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949).

6.37) in solution and the reactions of the former compound with a given amine are slower. Similarly (Fig. 2), the more basic N-methylbenzimidate (pK_a' 6.52) reacts more rapidly with ammonia than benzimidate; it is likely that relief of steric strain also facilitates the reaction of the N-methyl compound.

On the *alkaline* side of the *p*H–rate maxima, the rates may be described by the rate law

$$v = k_1'[\mathrm{RNH_2}][\mathrm{IEH^+}] \qquad (1)$$

In the reaction of ethyl benzimidate with ammonia, for example, the observed rate constants were found to be linear with respect to total ammonia concentration (0.25–1.0 *M*, *p*H 9.49 and 9.85) and to follow eq. 1 with $k_1' = 185\ M^{-1}\ \mathrm{min.}^{-1}$. Corresponding rate constants for other reactions are summarized in Table III. Hydroxylamine and methoxyamine react very rapidly in spite of their low basicity.

TABLE III

RATE CONSTANTS FOR REACTIONS OF ETHYL BENZIMIDATE (EB) AND ETHYL *m*-NITROBENZIMIDATE (ENB) WITH AMINES AT 25° AND IONIC STRENGTH 1.0[a]

RNH₂		k_1', M^{-1} min.$^{-1}$	k_2', M^{-1} min.$^{-1}$	k_3', M^{-1} min.$^{-1}$	k_B', M^{-2} min.$^{-1}$	
					Imidazole	RNH₂
NH_3	EB	185	3.7	11.8		
CH_3NH_2	EB	35,000	91	2,570		
	ENB	145,000	130	12,400		
CH_3ONH_2	EB	79	2.3	0.40	48	0.67
H_2NOH	EB	1,000	7.5	2.1	290	58
	ENB	4,500	6.5	18	[b]	220

[a] Rate constants are defined in eq. 1 and 2. [b] Catalysis observed, but rate constant not determined.

The observed rate constants for the reaction with *n*-butylamine show a leveling off at high butylamine concentrations (Fig. 3); this behavior is more marked at alkaline *p*H values, at which a larger fraction of the butylamine is present as the free base. This effect is similar to that found with amines in the base-catalyzed decomposition reaction (see below).

On the *acidic* side of the *p*H–rate profiles, the rates may be formally described by the rate law

$$v = k_2'[\mathrm{IE}][\mathrm{RNH_2}] + k_3'[\mathrm{IEH^+}][\mathrm{RNH_2}] + \sum_i k_{\mathrm{B}i}'[\mathrm{IEH^+}][\mathrm{RNH_2}][\mathrm{B}i] \qquad (2)$$

As discussed below, these rate terms do not describe the *mechanism* of the reaction but they are useful to provide an empirical description of the experimentally observed rate constants.

For strongly basic amines, the reaction proceeds principally according to the k_2' term, with a small contribution of the k_3' term and no detectable general base catalysis. For the reaction of ethyl benzimidate with ammonia, for example, the rate was found to be linear in respect to total ammonia concentration (0.25–0.90 *M*) at *p*H 7.65 and is not changed by increasing imidazole buffer concentration (0.2–0.6 *M*) at *p*H 7.66 ($k_{\mathrm{obs}} = 0.0176 \pm 0.0002\ \mathrm{min.}^{-1}$ at 0.5 *M* NH_4Cl). The values of k_2' and k_3' for the reactions with ammonia and methylamine are given in Table III.

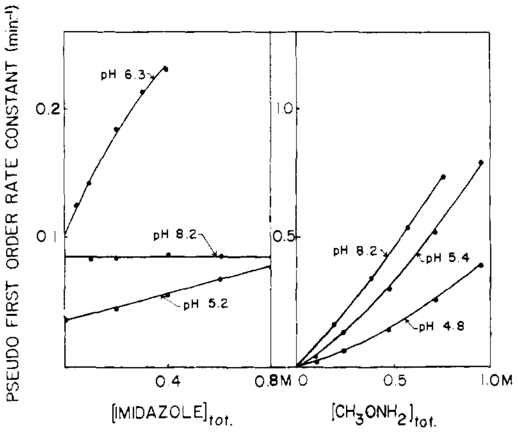

Fig. 4.—The rate of the reaction of ethyl benzimidate with methoxyamine as a function of imidazole buffer and methoxyamine concentrations at several *p*H values at 25° and ionic strength 1.0. The concentration of methoxyamine in the imidazole experiments is 0.095 *M*.

For the weaker bases, hydroxylamine, methoxyamine and semicarbazide, the k_3' term is relatively more important and the reaction on the *acidic* side of the *p*H profile is subject to general base catalysis. Rate data for the reaction of ethyl benzimidate with methoxyamine as a function of imidazole buffer and methoxyamine concentration are shown in Fig. 4. On the acidic side of the *p*H profile the reaction shows catalysis by increasing concentrations of imidazole buffer, which is greater at *p*H 6.3 than at *p*H 5.2, but on the alkaline side of the *p*H profile no catalysis by imidazole is observed. At *p*H 4.8 and 5.4 the rates are proportional to more than the first power of the methoxyamine concentration, which indicates a somewhat less effective catalysis of the reaction by methoxyamine itself.[28] This catalysis is reduced or absent at *p*H 8.2, on the alkaline side of the *p*H profile. Similar catalysis by imidazole and by hydroxylamine was observed for the reactions of ethyl benzimidate and *m*-nitrobenzimidate with hydroxylamine below *p*H 7.0. The rate constants for these reactions are summarized in Table III. No catalysis by imidazole (0.06–0.25 *M*, *p*H 8.33), tris-(hydroxymethyl)-aminomethane (0.1–0.6 *M*, *p*H 8.27) or hydroxylamine (0.025–0.20 *M*, *p*H 8.37) was observed for the reaction of ethyl benzimidate with hydroxylamine on the alkaline side of the *p*H profile.

The isolation and identification of the products of these reactions is described in the Experimental section.

The rate of disappearance of ethyl benzimidate in 0.8 *M* phosphate buffer (1:1 KH_2PO_4–K_2HPO_4) was not altered by the presence of 0.1 *M* trimethylamine, imidazole or *t*-butylamine; only ethyl benzoate was detected as a reaction product by ultraviolet spectrophotometry. A reaction of ethyl benzimidate with the following amines was noted, but was not studied in detail: Ethylenediamine (0.5 *M*, *p*H 10.25) does not give first-order kinetics, presumably because of cyclization to 2-phenyl-

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

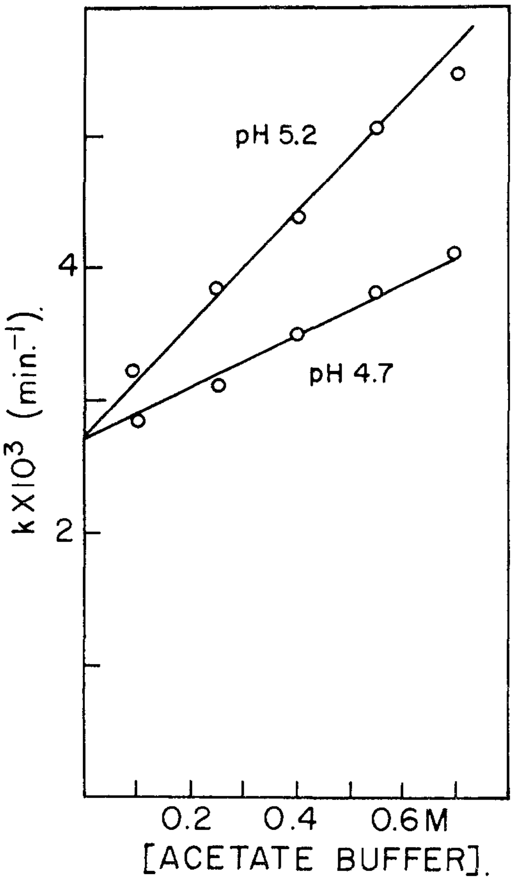

Fig. 5.—Catalysis of ethyl benzimidate hydrolysis by acetate buffers at 25° and ionic strength 1.0; followed at 265 mμ.

4,5-dihydroimidazole[29]; similar behavior, presumably resulting in phenylimidazolone formation,[30] was observed with glycine ethyl ester (0.5 M, pH 6.9; 0.9 M, pH 8.15). Hydrazine reacts rapidly (0.1 M, pH 6.01 and 8.45) to give a product which undergoes a second, slower reaction. Cyclohexylamine (1.0 M, pH 9.0) reacts, presumably to give the amidine.

Acid- and Base-catalyzed Decomposition.—Imido ester hydrochlorides in water undergo hydrolysis to the corresponding oxygen ester and imido esters undergo base-catalyzed decomposition to the corresponding nitrile; the uncatalyzed decomposition of the neutral molecule occurs very much more slowly.[7,31]

The hydrolysis of ethyl benzimidate hydrochloride is catalyzed by acetate buffers at constant pH and ionic strength (Fig. 5). The catalysis is greater at pH 5.2 than at pH 4.7, indicating that the catalysis is proportional to the concentration of acetate ion rather than acetic acid, and the observed rates follow the rate law

$$v = k_0[\mathrm{IEH}^+] + k_c[\mathrm{IEH}^+][\mathrm{AcO}^-]$$

with k_0 = 0.0028 min.$^{-1}$ and k_c = 0.0048 M^{-1} min.$^{-1}$. Stieglitz and co-workers[31] reported several values of k_0 near 0.0030 min.$^{-1}$. Similar catalysis was observed for ethyl m-nitrobenzimidate in the presence of acetate and formate buffers. As has been reported previously, the rates of imido ester hydrolysis are decreased by concentrated salts and acids.[31,32]

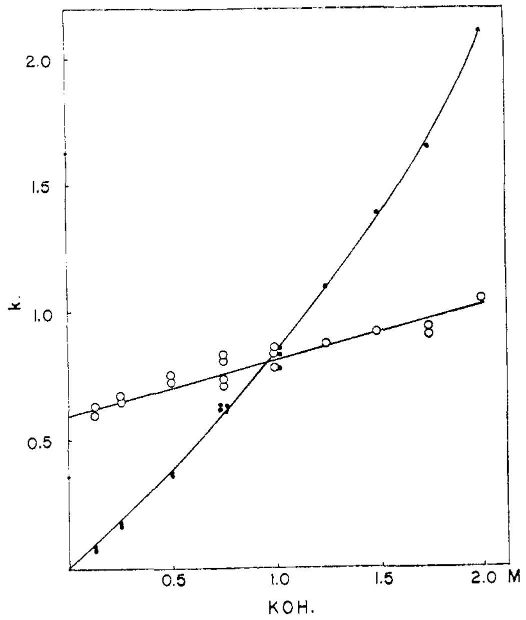

Fig. 6.—The base-catalyzed decomposition of ethyl benzimidate to benzonitrile as a function of hydroxide ion concentration at 25° and ionic strength 2.0: solid points, observed pseudo-first-order rate constants (min.$^{-1}$); open circles, second-order rate constants (M^{-1}min.$^{-1}$) = k_{obs}/[OH$^-$].

The rate of the base-catalyzed decomposition of ethyl benzimidate to benzonitrile at a constant ionic strength of 2.0 increases more rapidly than the first power of the hydroxide ion concentration (Fig. 6). The reaction follows the rate law

$$v = k_1[\mathrm{IE}][\mathrm{OH}^-] + k_2[\mathrm{IE}][\mathrm{OH}^-]^2 \qquad (3)$$

with k_1 = 0.59 M^{-1} min.$^{-1}$ and k_2 = 0.22 M^{-2} min.$^{-1}$. Schlesinger reported a value of 0.69 M^{-1} min.$^{-1}$ for k_1.[31d] Ultraviolet spectroscopy of the reaction products at 0.1 and 2.0 M KOH indicated that the ultraviolet-absorbing reaction product is exclusively benzonitrile. Terms second order in respect to hydroxide ion have been observed for the hydrolysis of anilides,[33] the Cannizzaro reaction,[34] the hydrolysis of phosphonium salts,[35] and the cleavage of acetylacetone,[36] but the explanation suggested for these reactions, involving, a pre-equilibrium addition of hydroxide ion, does not appear to be applicable to the imido ester reaction. The possibility that the second-order

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[29] N. W. Bristow, *J. Chem. Soc.*, 513 (1957).

[30] A. Kjaer, *Acta Chem. Scand.*, **7**, 1030 (1953).

[31] (a) J. Stieglitz, *Am. Chem. J.*, **39**, 29 (1908); (b) I. H. Derby, *ibid.*, **39**, 437 (1908); (c) W. McCracken, *ibid.*, **39**, 586 (1908) (d;) H. I. Schlesinger, *ibid.*, **39**, 719 (1908).

[32] J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2009 (1957).

[33] S. S. Biechler and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4927 (1957).

[34] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 350.

[35] M. Zanger, C. A. VanderWerf and W. E. McEwen, *J. Am. Chem. Soc.*, **81**, 3806 (1959).

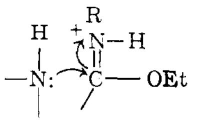
[36] R. G. Pearson and E. A. Mayerle, *ibid.*, **73**, 926 (1951).

term represents a specific salt effect has not been excluded.

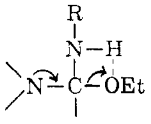
With increasing concentration of amines at constant hydroxide ion concentration, the rate of the decomposition reaction is *decreased* (Fig. 7). The product was shown by ultraviolet spectroscopy to be at least 90% benzonitrile at all concentrations of amine examined. The rate decrease cannot be due to amidine formation, because N-*n*-butylbenzamidine was shown not to react with base under these reaction conditions. This behavior suggests the formation of an unreactive complex between amine and imido ester and is analogous to the decrease in the rate of the reaction of imido ester with butylamine observed at high concentrations of butylamine. However, no definite spectroscopic evidence for the formation of such a complex could be obtained. A similar unreactive complex has been proposed by Higuchi to account for the marked inhibition of benzocaine hydrolysis caused by caffeine.[37]

Discussion

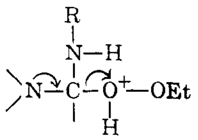
The following considerations provide strong support for a mechanism of imido ester aminolysis in which the condensation of amine and protonated imido ester to form a tetrahedral addition intermediate is rate determining on the alkaline side of the *p*H-rate profile and decomposition of the tetrahedral intermediate is rate determining on the acid side of the *p*H-rate profile. Possible transition states for these reactions are I and II, respectively. The decomposition reaction occurs predominantly through a transition state with no net charge (*e.g.*, IIa), and to a minor extent, also, through a positively-charged transition state (*e.g.*, IIb). Proton transfer occurs in the decomposition reaction, as shown by the presence of general acid-base catalysis.



I



IIa



IIb

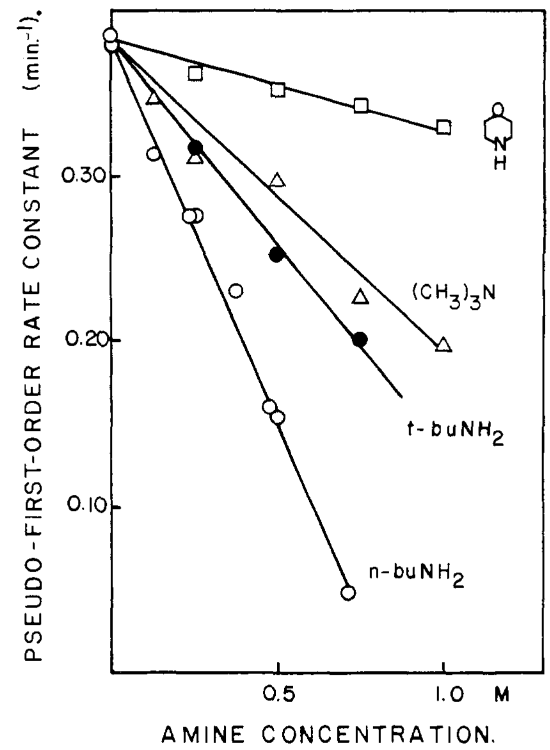


Fig. 7.—The effect of amines on the rate of benzonitrile formation from ethyl benzimidate in 0.5 *M* KOH at 25° and ionic strength 2.0.

All of the reactions examined exhibit sharp *p*H-rate maxima. In no case can these *p*H-rate maxima be accounted for, even approximately, by a simple rate law involving either only rate-determining amine attack or only rate-determining addition compound decomposition on both sides of the *p*H-rate curve.[38] In terms of the rate constants of Table III, this is evident from the fact that k_1' (from the alkaline side of the curve) is at least tenfold larger than k_2' (from the acid side of the curve), although both of these rate constants refer to terms in the rate law of the same kinetic form: $v = k[\mathrm{IEH}^+][\mathrm{RNH_2}]$. Therefore, the rate-determining step must be different on the two sides of the *p*H-rate profile. If the reaction involves rate-determining attack of free amine on protonated imido ester on the alkaline side of the curve (see below), it is necessary to account for a decrease in the observed rate below that calculated for rate-determining amine attack as the *p*H is lowered; this decrease occurs 1 or more *p*H units removed from the point at which it could be accounted for by ionization of one of the reactants. If addition compound formation is rate determining on the basic side, then decomposition of the addition compound must be rate determining on the acid side of the *p*H-rate profile. The same phenomenon occurs in the reactions of aldehydes and ketones with nitrogen bases, in which case the rapid formation of the addition intermediate on one side of the *p*H-rate maximum may be directly shown by infrared and ultraviolet spectrophotometry,[3] and in Schiff base hydrolysis,[4] Schiff base formation,[4b] thiazoline hydrolysis[5] and *o*-carboxyphthalimide hydrolysis.[6] In all of these cases one side of the *p*H-rate curve reflects a series of rate constants rather than the pK_a of a dissociating group. Martin and Parcell have suggested a similar explanation for the decrease in the rate of oxazoline hydrolysis with increasing acid concentration,[39] but in this reaction the possibility that the rate decrease is due to changes in the availability of water and in activity coefficients in acid solutions does not appear to have been ruled out.

Unless direct observation of the formation of addition compound is possible, so that the equi-

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[37] T. Higuchi and L. Lachman, *J. Am. Pharm. Assoc.*, **44**, 521 (1955).

[38] A reaction in which the substrate is *completely* converted to addition compound in an initial fast step might show such a *p*H-rate maximum with rate-determining decomposition on both sides of the *p*H-rate maximum, but a number of spectrophotometric experiments failed to show any detectable amount of such a conversion in the reaction of ethyl benzimidate with amines.

[39] R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, **83**, 4835 (1961).

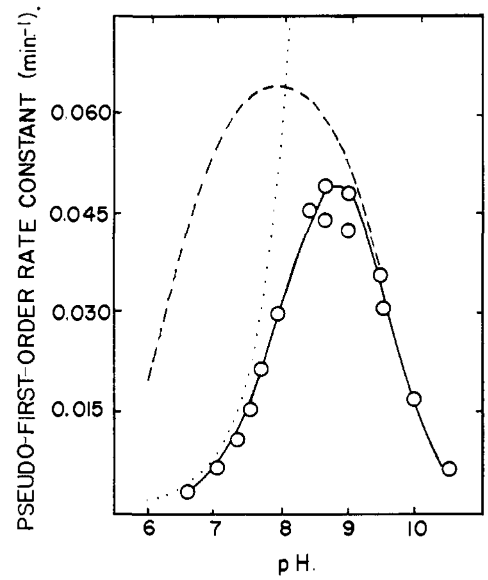


Fig. 8.—The reaction of ammonia with ethyl benzimidate at 25°: dashed line, calculated for rate-determining amine attack; dotted line, calculated for rate-determining addition compound decomposition; solid line, calculated from steady-state rate equation.

librium constant for addition compound formation may be determined, it is not possible to obtain all of the rate constants for a reaction of this type. However, it is possible to determine enough rate constants to establish the shape of the *p*H-rate curve either by calculation from the two extremes of the curve, where the observed reaction involves exclusively rate-determining addition or rate-determining decomposition, or by a steady-state kinetic treatment. The calculations are simplified in the case of the reaction of ethyl benzimidate with ammonia, since only a single imido ester and amidine are involved in this reaction. For the scheme

$$\begin{tikzcd}
\mathrm{IEH^+} \arrow[d, shift left, "K_{\mathrm{IEH^+}}"] & + & \mathrm{B} \arrow[d, shift left, "+\mathrm{H^+}\; K_{\mathrm{BH^+}}"] \arrow[r, shift left, "k_1"] & \mathrm{TH^+} \arrow[l, shift left, "k_{-1}"] \arrow[r, shift left, "K_{\mathrm{TH^+}}"] \arrow[d, "k_3"] & \mathrm{T + H^+} \arrow[l, shift left] \arrow[d, "k_2"] & \\
\mathrm{IE + H^+} \arrow[u, shift left] & & \mathrm{BH^+} \arrow[u, shift left] & \mathrm{PH^+} & \mathrm{P} & (4)
\end{tikzcd}$$

in which IE and IEH$^+$ refer to imido ester, B and BH$^+$ to ammonia, T and TH$^+$ to the tetrahedral addition intermediate and P and PH$^+$ to amidine, as the free base and conjugate acid in each case, the rate of product formation is given by

$$\mathrm{d}[\mathrm{P} + \mathrm{PH^+}]/\mathrm{d}t = k_3[\mathrm{TH^+}] + k_2[\mathrm{T}] \qquad (5)$$

Application of the steady state treatment gives

$$\frac{\mathrm{d}[\mathrm{P} + \mathrm{PH^+}]}{\mathrm{d}t} = \left[k_3 + \frac{k_2K_{\mathrm{TH^+}}}{[\mathrm{H^+}]}\right]\left[\frac{k_1[\mathrm{IEH^+}][\mathrm{B}]}{k_{-1} + k_3 + k_2K_{\mathrm{TH^+}}/[\mathrm{H^+}]}\right] \qquad (6)$$

The observed rate in any given experiment is defined by eq. 7, in which the apparent second-order rate constant, $k_{\mathrm{app}} = k_{\mathrm{obs}}/[\mathrm{B}]_{\mathrm{total}}$, and eq. 6 and 7 may be reduced to eq. 8

$$\frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = k_{\mathrm{obs}}\,[\mathrm{IE} + \mathrm{IEH^+}] = k_{\mathrm{app}}\,[\mathrm{IE} + \mathrm{IEH^+}][\mathrm{B} + \mathrm{BH^+}] \qquad (7)$$

$$\frac{1}{k_{\mathrm{app}}\left[1 + \frac{K_{\mathrm{IEH^+}}}{[\mathrm{H^+}]}\right]\left[1 + \frac{[\mathrm{H^+}]}{K_{\mathrm{BH^+}}}\right]} = \frac{k_{-1}\,[\mathrm{H^+}]}{k_1k_3[\mathrm{H^+}] + k_2k_1K_{\mathrm{TH^+}}} + \frac{1}{k_1} \qquad (8)$$

Thus, if the postulated mechanism is correct, a plot of the quantity on the left side of the equation *vs.* [H$^+$] should give an initially straight line, with intercept $1/k_1$ at $[\mathrm{H^+}] = 0$ and slope $k_{-1}/k_2k_1K_{\mathrm{TH^+}}$, which tapers off at large [H$^+$], where $k_2k_1K_{\mathrm{TH^+}} << k_1k_3[\mathrm{H^+}]$, to the constant value, $k_{-1}/k_1k_3 + 1/k_1$. When such a plot was made, the expected behavior was observed, and the various quantities obtained from the plot (Table IV) were used in the calculation of the theoretical *p*H profile according to eq. 9.

Table IV

Rate Constants for the Reaction of Ethyl Benzimidate with Ammonia at 25° (Eq. 4)

k_1	185	$k_2k_1K_{\mathrm{TH^+}}/k_{-1}K_{\mathrm{IEH^+}}$	3.73
k_3k_1/k_{-1}	11.8	$k_2K_{\mathrm{TH^+}}/k_{-1}$	8.6×10^{-9}
k_3k_{-1}	0.064		

$$k_{\mathrm{calc}} = \frac{k_1\left[1 + \frac{k_2K_{\mathrm{TH^+}}}{k_3[\mathrm{H^+}]}\right][\mathrm{NH_3} + \mathrm{NH_4^+}]}{\left[1 + \frac{K_{\mathrm{IEH^+}}}{[\mathrm{H^+}]}\right]\left[1 + \frac{[\mathrm{H^+}]}{K_{\mathrm{BH^+}}}\right]\left[1 + \frac{k_{-1}}{k_3} + \frac{k_2K_{\mathrm{TH^+}}}{k_3[\mathrm{H^+}]}\right]}\ \mathrm{min.}^{-1} \qquad (9)$$

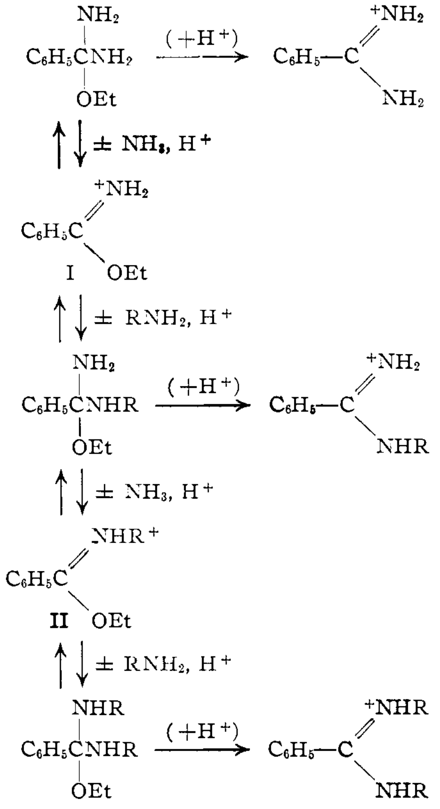
The results are summarized in Fig. 8: the open circles are the experimentally determined first-order rate constants, the solid line represents the calculated *p*H profile, the broken line is the profile expected if the attack of ammonia on protonated imido ester were rate limiting over the whole *p*H range, and the dotted line is the profile expected for a simple rate-limiting decomposition of the intermediate. From the latter two curves it is apparent that even at the low *p*H of 6.25 the loss of ethanol is only *ca.* one tenth as fast as the attack of amine. It is evident that the steady state treatment of the change in rate-determining step provides a satisfactory description of the rate over the whole *p*H range, and that the rates of amine attack and of addition compound decomposition describe the rates at the extremes of the *p*H-rate profile. The experimental rate constant k_1', which describes the rate in the most alkaline region of the *p*H-rate profile, is identical with k_1, whereas the experimental rate constants at the acid extreme of the curve are complex constants: $k_2' = k_1k_2K_{\mathrm{TH^+}}/k_{-1}K_{\mathrm{IEH^+}}$ and $k_3' = k_1k_3/k_{-1}$. It may be noted that the only path for formation of addition compound that was detected involves the reaction of free amine with protonated imido ester. The decomposition reaction proceeds principally through a neutral transition state (*e.g.*, IIa) and to a minor extent through a protonated transition state (*e.g.*, IIb).

The observation that general base catalysis is significant only on the acid side of the *p*H-rate profile (Fig. 4) is further evidence that the rate-determining steps of the reaction are different at alkaline and acid *p*H. Since the rate laws corresponding to a reaction of protonated intermediate with a general base catalyst and of neutral intermediate with the corresponding acid are kinetically indistinguishable (eq. 10), this catalysis

$$v = k[\text{Int. H}^+][\text{B}] = k'[\text{Int.}][\text{HB}^+] \qquad (10)$$

could involve either the removal of a proton from the nitrogen atom of a protonated intermediate, to aid the expulsion of a (solvated) alkoxide ion, or the addition of a proton to the leaving alcohol of a neutral intermediate; cyclic mechanisms involving both types of proton transfer (but only a single molecule of catalyst) are also possible. Such catalysis is significant only for weakly basic amines, which can bring about the unaided expulsion of alcohol less readily than more basic amines. The results imply that the reverse reactions, the alcoholysis and, by analogy, the alkaline hydrolysis of certain amidines are subject to general acid–base catalysis.

If addition compound formation is rate determining on one side of the *p*H–rate curve and its decomposition is rate determining on the other side, then on the latter side the intermediate must be in equilibrium with the reactants (provided that the addition compound does not accumulate; *cf.* ref. 38). If the reacting amine is different from the amine moiety of the imido ester, such an equilibrium must result in the formation of a new imido ester, since the addition compound may be expected to sometimes break down to expel the original amine, rather than alcohol or the attacking amine. Reaction of this new imido ester with amine will eventually give rise to a disubstituted amidine. These reactions are summarized in eq. 11. This amine exchange is analogous to the exchange of $H_2{}^{18}O$ into the carbonyl group of esters and amides during their hydrolysis. However, in the present case, exchange is expected to occur only on the side of the *p*H–rate curve in which a pre-equilibrium formation of addition compound occurs and the loss of alcohol is rate determining.



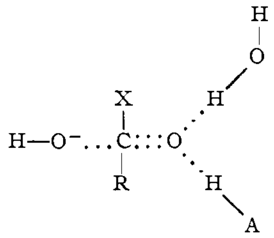
(11)

The situation is best illustrated by the reaction of ethyl N-methylbenzimidate (R = CH_3 in eq. 11) with ammonia (Fig. 2, upper curve). At *p*H 9.8 the only product of this reaction is N-methylbenzamidine, indicating that on the alkaline side of the *p*H–rate profile the attack of amine is rate determining and that the addition compound, once formed, rapidly loses ethanol to give the monosubstituted amidine. At *p*H 8.9, the *p*H maximum, a mixture of products is obtained. At *p*H 7.9 the product of the reaction is unsubstituted benzamidine, indicating that, on the acid side of the curve, the intermediate equilibrates with the large excess of ammonia present in solution before the rate-determining loss of ethanol. Benzamidine is not formed from N-methylbenzamidine and ammonia under the same experimental conditions. The two separate steps of the reaction were observed by following the reaction at two different wave lengths. At *p*H 7.57 in 0.5 *M* ammonium chloride the first step (amine exchange to give ethyl benzimidate) was followed at 235 mμ and was found to proceed with a rate constant of 0.21 min.$^{-1}$. This was followed by a slower reaction which could be followed at 250 mμ. The rate constant for this reaction, 0.020 min.$^{-1}$ (open circle in Fig. 2), is the same as that measured independently for the reaction of ethyl benzimidate with ammonia (lower line, Fig. 2). The presence of ethyl benzimidate in the reaction mixture at the end of the first reaction (but not in experiments at alkaline *p*H) was confirmed spectrophotometrically. Finally, the rapid pre-equilibrium formation of the unsubstituted imido ester was demonstrated by isolation of ethyl benzimidate from a preparative scale experiment at *p*H 7.55, on the acid side of the curve. These results confirm the change in rate-determining step as a function of *p*H which was inferred from the kinetic results and further demonstrate that amine attack is rate determining on the alkaline side and that alcohol elimination is rate determining on the acid side of the *p*H–rate profile.

Similarly, the reaction of ethyl benzimidate with methylamine gives N-methylbenzamidine on the alkaline side and N,N′-dimethylbenzamidine on the acid side of the *p*H–rate profile. Control experiments showed that methylamine does not react with N-methylbenzamidine under the experimental conditions employed. Except at quite acidic *p*H, however, the reaction of benzimidate with alkyl-substituted amines gives principally the monosubstituted product, presumably because the intermediate addition product loses the substituted amine more readily than ammonia because of the greater size and basicity of substituted amines. Thus, unless the rate of alcohol loss is much smaller than the rate of amine attack, the formation of monosubstituted amidine will be favored, even in the presence of excess substituted amine.

An analogous situation exists in the reaction of toluidine with ethyl N-phenylformimidate, which gives only N-phenyl-N′-*p*-tolylformamidine in the absence of acid, but also gives N,N′-di-(*p*-tolyl)-formamidine in the presence of traces of acid.[9] Roberts originally suggested[9a] that this reaction, in the presence of acid, proceeds by a mechanism similar to that of eq. 11, but later it was concluded that the reaction occurred by a back reaction of initially formed N-phenyl-N′-*p*-tolylformamidine.[9b] The synthesis of substituted imido esters by exchange reactions is generally carried out under slightly acidic conditions, and the use of ether–water mixtures of the base of one component and the hydrochloride of the other is presumably effective because the exchange reaction can take place in the slightly acidic aqueous phase. The over-all equilibrium will favor the products in which the hydrochloride of the strongest base is left in the aqueous phase; *i.e.*, the weaker base is incorporated into the imido ester.[7,8,10]

Carbonyl groups in hydroxylic solvents are certainly hydrogen-bonded to one or more molecules of solvent through the lone pair electrons of the oxygen atom and it is conceivable, although perhaps not likely, that the $H_2{}^{18}O$ exchange observed in ester and amide hydrolysis occurs by a displacement reaction with concerted proton transfer to the leaving oxygen atom, without passing through a discrete addition intermediate.[40] Such a concerted reaction is virtually impossible for the amine exchange reactions with imido esters, since the leaving nitrogen atom does not have the necessary available lone pair electrons for proton transfer until the double bond to carbon has been broken, *i.e.*, until an addition intermediate has been formed.



It should be noted that it is very difficult to formulate mechanisms for a number of known reactions involving displacement of the =NR group, such as the hydrolysis of imido ester hydrochlorides and the oxazoline reaction recently described by Rosnati and Misite,[41] without invoking a tetrahedral addition intermediate. Several new examples of compounds analogous to such intermediates, containing three electronegative atoms bound to a carbon atom, have recently been synthesized.[42–44]

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Azo-Hydrazone Conversion. I. The Japp–Klingemann Reaction

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Intermediate azo compounds have been isolated from the Japp–Klingemann reaction. The conditions employed for the isolation of these compounds seems to be general and excellent yields of the azo compounds may be obtained. The cleavage of these compounds with water, ethanol, phenol, aniline and acetic acid was studied. The results indicate that these reactions involve an acyl cleavage and an azo to hydrazone conversion.

An intensive review of the Japp–Klingemann reaction has been published by Phillips.[2] The reaction between a diazonium salt and an active methinyl carbon is assumed to involve formation of an unstable azo compound followed by hydrolytic cleavage of the azo compound. The isolation of these intermediates hitherto has not been accomplished.[3]

Although the cleavage products of the Japp–Klingemann reaction are considered to be hydrazones,[2] it has been difficult to establish this structure. Azo, hydrazone and ene–hydrazine[4] tautomeric forms are also possible.

The coupling of a diazonium salt to a methinyl carbon gives an unstable azo compound which cleaves to give a hydrazone, whereas the coupling product of the same diazonium salt to a methylene carbon is relatively stable. In the latter case, the coupling product is not an azo compound but a hydrazone.[5] Apparently, an azo to hydrazone

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