serve similar functions, namely, to keep the ester carbonyl group out of the plane of the ring to which it is attached. This nonplanarity facilitates the intramolecular nucleophilic attack of the neighboring O^- function in two ways: (a) there is a more favorable orientation,[3] and (b) the carbonyl group carbon of the ester is more electrophilic since there is less distribution of positive charge to the aryl ring. The fact that VII hydrolyzes appreciably faster than IV is explained by the greater inductive effect of Cl as compared to CH_3 on both K and k_1, since the steric effect of each should be about the same.[30]

Methyl 2-Acetylbenzoates. In this series the rates for V and VIII are also greater than that for the unsubstituted ester II but the rate ratios for V (1.4) and VII (7.4) as compared to II are appreciably less than the ratios for IV (4.3) and VII (32.2) as compared to I. The steric explanation for the rate increase is similar to that described for the methyl 2-benzoylbenzoates. However, the fact that there is a greater increase in relative rate for the 2-benzoylbenzoates as compared to the 2-acetylbenzoates is difficult to explain. One would expect the equilibrium constants for addition of hydroxide ion to the acetyl groups involved would be greater than those for the benzoyl group (eq 1). The rates (k_1) of cyclization of the intermediates C to intermediates D may be faster for the benzoyl compounds than for the acetyl compounds because of less freedom of rotation of the former due to the greater steric effect of phenyl as compared to methyl. Also, there may be slightly more release of strain in going from C to D in the benzoyl cases. However, in the absence of further experimental data on rates of hydrolysis at different temperatures, further discussion is not warranted. The most important feature as far as the present work is concerned is that there is a steric facilitation of hydrolysis attributable to the 6-methyl and 6-chloro groups in this series.

Methyl 2-Formyl, 2-Acetyl-, and 2-Benzoylbenzoates. In the three unsubstituted esters, methyl *o*-formylbenzoate (III), methyl *o*-acetylbenzoate (II), and methyl *o*-benzoylbenzoate (I), the alkaline hydrolysis may conceivably proceed *via* two mechanisms: (1) attack of hydroxide ion at the carbonyl function as in the case of the 6-substituted esters, and (2) the normal attack of the hydroxide ion at the carbomethoxy function. Since Bender has shown that III hydrolyzes 10^5 faster than methyl *p*-formylbenzoate the main path undoubtedly involves carbonyl attack.[31] With the unsubstituted benzoyl esters the situation is reversed. Methyl *p*-benzoylbenzoate hydrolyzes 1.46 times faster than I. Thus attack of hydroxide ion on the carbomethoxy group may be the rate-controlling step for I.

The rate of hydrolysis of II is intermediate between that of III and I. Since II and III hydrolyze at so much greater rates than does I, the rate-controlling step may be the forward reaction in eq 1. Unfortunately, we have been unable to find a comparative study involving benzophenone, acetopheone, and benzaldehyde in order to estimate the relative rates of such a reaction.

Methyl 2-Formylbenzoates. Although we were unable to prepare pure samples of the normal methyl esters of 6-methyl- and 6-chloro-2-formylbenzoic acids, mixtures of normal and pseudo esters were obtained. Qualitative tests showed that these esters hydrolyzed more rapidly than did methyl 2-formylbenzoate, but the rates were so rapid that further kinetic work on the ester mixtures was not done. Thus, a steric effect to accelerate the hydrolyses is probably present in these cases also but further work is required before a suitable system for measurement can be found.

Acknowledgment. We thank Professor Jack Hine for valuable discussion concerning the kinetic results.

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[30] L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p 260, gives 1.80 and 2.0 Å for the van der Waals radii of Cl and CH_3, respectively.

[31] M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *J. Am. Chem. Soc.*, 87, 4545 (1965).

The Hydrolysis of N-Substituted Acetimidate Esters

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Abstract: The hydrolysis of two acetimidate esters (I and II) derived from aniline and α-methylphenethylamine has been studied at 30° in the pH range 0–12. Hydrolysis yields amines and esters in acid solution and amides at alkaline pH, transition between the two sets of products taking place at pH 7.69 and 8.45 for I and II, respectively. At constant pH, bifunctional catalysts (phosphate, bicarbonate, acetic acid) divert the breakdown of tetrahedral intermediates from the formation of amides to the expulsion of amines. The mechanism previously proposed to account for iminolactone hydrolysis seems to hold generally for the hydrolysis of imidates. This mechanism involves the intermediacy of carbinolamine addition compounds whose breakdown is influenced by pH and by general acid–base catalysts. Implications of this work for the mechanism of ester aminolysis are discussed.

Although the mechanism of hydrolysis of acyclic imidate esters attracted attention as early as 1908,[1] few additional studies appeared in the succeeding six

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[1] (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).

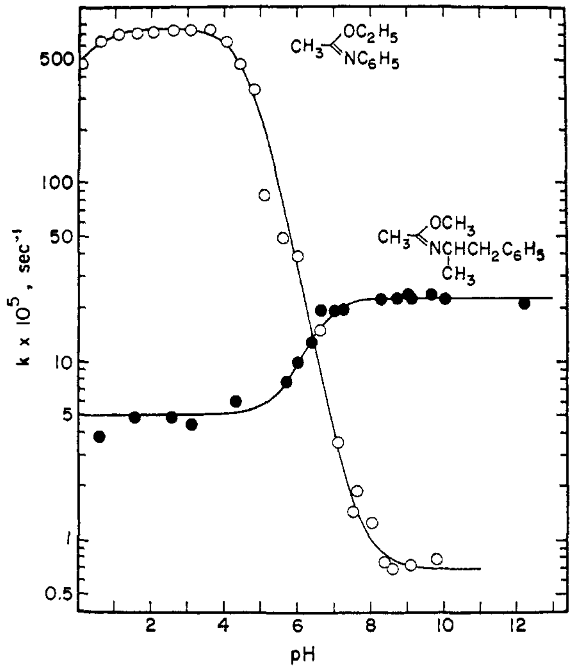


Figure 1. pH–rate profiles for hydrolysis of imidate esters in 10% acetonitrile, 30°. Solid curves are calculated from eq 1 and 2, using constants of Table I.

decades.[2–5] With one exception,[5] kinetic investigation of the hydrolysis of these substances has been limited to acidic media. Recently, it has been shown that the hydrolysis of the cyclic imidate N-phenyliminotetrahydrofuran involves tetrahedral addition intermediates, whose breakdown in neutral or weakly alkaline solution is influenced by pH and by the presence of general acid–base catalysts.[6,7]

It has become evident that information concerning the favored modes of decomposition of tetrahedral intermediates generated from imidate esters contributes to the understanding of certain acyl transfer reactions.[5,8–10] In view of continuing interest in the mechanisms of the aminolysis of esters,[11] we have sought to ascertain the generality of the observations made in iminolactone hydrolysis. The present report describes our studies of the hydrolysis of acyclic imidate esters derived from aliphatic and aromatic amines.

Results

Kinetic Studies. The pH–rate profiles for disappearance of imidate ester in 10% acetonitrile–water,

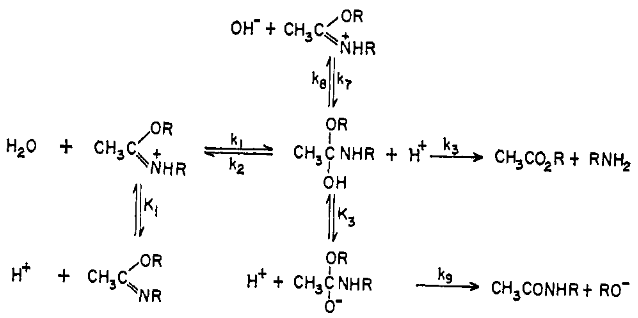
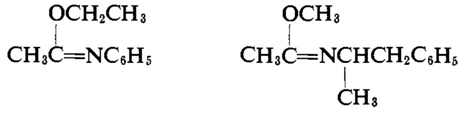


Figure 2. Mechanism of hydrolysis of imidate esters.

μ = 0.5, 30°, were determined for the acetimidate esters I and II (Figure 1). With I, increasing the con-



$CH_3C(OCH_2CH_3)=NC_6H_5$ (I) $\qquad$ $CH_3C(OCH_3)=NCH(CH_3)CH_2C_6H_5$ (II)

I $\qquad$ II

centrations of buffers (0.02–0.10 M, acetate, imidazole, phosphate) at constant pH caused modest rate increases (less than twofold at the highest buffer concentration used), and observed first-order rate constants were extrapolated to zero buffer concentration in the range of pH 4.4–8.0. The rate of disappearance of II was similarly increased in the presence of β-dimethylaminopropionitrile buffer (0.02–0.07 M) at pH 6.4–7.3, and the rate constants recorded in Figure 1 are accordingly corrected for buffer catalysis. In other pH regions, acetate and borate buffers ($<$0.07 M) exerted little catalytic influence on the hydrolysis of II.

The hydrolyses of imines of low and high pK proceed with pH–rate profiles similar in appearance to those of I and II, respectively.[12,13] Ample precedent exists in favor of the proposal that, at pH >1, rate-determining hydration of the protonated imidate ester by water or hydroxide ion yields uncharged tetrahedral intermediates which decompose to products (Figure 2). Further ionization of the intermediates to anionic species may affect the nature of the hydrolysis products, but does not alter the kinetics of imidate disappearance.[7] The small decrease in the rate of hydrolysis of I at pH <1 suggests but does not prove the occurrence of a transition in rate-determining step. As in iminolactone hydrolysis,[6,7] far stronger evidence for the existence of tetrahedral intermediates is found in the examination of the products of hydrolysis (see below).

The kinetic constants (Table I) which define the pH–rate profiles were obtained by fitting the hydrolysis data for I to the rate eq 1 (for pH <3) and 2 (for pH >3).[14]

$$k_0 = \frac{k_1[H^+]k_3/k_2}{([H^+] + K_1)([H^+] + k_3/k_2)} \qquad (1)$$

$$k_0 = \frac{[H^+](k_1 + k_7[OH^-])}{([H^+] + K_1)} \qquad (2)$$

Since the onset of acid inhibition is even more doubtful with II than with I, eq 2 alone was employed to calculate the complete pH–rate profile of II. The acid dissocia-

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[2] (a) J. B. Cloke, E. C. Knowles, and R. J. Anderson, *J. Am. Chem. Soc.*, 58, 2547 (1936); (b) J. B. Cloke and F. A. Keniston, *ibid.*, 60, 129 (1938); (c) R. H. Hartigan and J. B. Cloke, *ibid.*, 67, 709 (1945).

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

[4] (a) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 3505 (1962); (b) R. H. DeWolfe and F. B. Augustine, *J. Org. Chem.*, 30, 699 (1965).

[5] M. Kandel and E. H. Cordes, *ibid.*, 32, 3061 (1967).

[6] G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, 87, 5692 (1965).

[7] B. A. Cunningham and G. L. Schmir, *ibid.*, 88, 551 (1966).

[8] B. A. Cunningham and G. L. Schmir, *ibid.*, 89, 917 (1967).

[9] R. K. Chaturvedi, A. E. McMahon, and G. L. Schmir, *ibid.*, 89, 6984 (1967).

[10] G. L. Schmir, *ibid.*, 90, 3478 (1968).

[11] (a) W. P. Jencks and M. Gilchrist, *ibid.*, 88, 104 (1966); (b) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, 89, 2106 (1967); (c) L. do Amaral, K. Koehler, D. Bartenbach, T. Pletcher, and E. H. Cordes, *ibid.*, 89, 3537 (1967); (d) earlier investigations are thoroughly discussed in T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 66, 134.

[12] W. P. Jencks, *Progr. Phys. Org. Chem.*, 2, 63 (1964).

[13] Reference 6 and earlier studies cited therein.

[14] Equations 1 and 2 are based on the assumption of a steady state in the carbinolamine intermediates and are special cases of the general equation derived earlier.[6]

Table I. Rate and Equilibrium Constants for the Hydrolysis of Imidate Esters at 30° [a,b]

	I	II
pK_1	4.63 ± 0.05[c]	6.44 ± 0.05[c,d]
$k_1 \times 10^5$, sec^{-1}	756	5.1
k_7, M^{-1} sec^{-1}	16,300	8300
k_3/k_2, M	1.3	
pK' [e]	7.69 ± 0.03	8.45 ± 0.05

[a] Constants are defined for the processes shown in Figure 2. [b] In 10% acetonitrile-water, μ = 0.5 M. [c] Calculated from kinetic data. [d] pK_1 determined by potentiometric titration was 6.65. [e] $K' = K_3k_9/k_8$.

tion constant of 6.44 determined from the kinetic data may be compared to that of 6.65 obtained by titration of II under similar conditions. The over-all shape of the pH-rate profile is a function of k_7/k_1 and of pK_1; high values of k_7/k_1 and of pK_1 favor the appearance of profiles such as that of II, *i.e.*, profiles where the pH-independent observed rate constant in alkali (k_7K_w/K_1) is greater than the rate constant k_1 for rate-limiting attack by water. The ratio k_7/k_1 is markedly dependent upon imidate structure and is highest for imidates derived from aliphatic amines; some values which have been found are 2.2 × 10^6 (for I), 3.3 × 10^6 (for an iminolactone derived from aniline),[6] 1 × 10^7 (phenyl N-methylacetimidate),[5] 1.5 × 10^7 (2-methyloxazoline),[15] and 1.6 × 10^8 M (for II). The last value is the highest known to us for imidate esters, although corresponding terms of 1 × 10^8 and 7.6 × 10^7 M have been noted in the hydrolyses of *p*-methoxybenzylidene-1,1-dimethylethylamine[16] and of the 2,3-dimethylthiazolinium ion,[17] respectively.

The Reaction Products. The yield of aniline formed on hydrolysis of I decreases with increasing pH (Table II). At constant pH, low concentrations of phosphate and bicarbonate buffers cause major increases in aniline yield (Table III), while monofunctional buffers have little or no effect (Table II). In particular, the concentrations of phosphate and imidazole buffers required at pH 7.8–7.9 to increase amine yield from 40 to 52% are 0.0001 and 0.02 M, respectively, so that phosphate is at least 200 times more effective than imidazole in this respect.

The catalytic effects of phosphate and bicarbonate buffers on the hydrolysis of II are somewhat less pronounced than with I (Table IV). An interesting difference between the two substrates is that phosphate is only about 12 times more reactive than imidazole in the case of II. With this substance, the increase in amine yield was <2% when borate buffer concentration varied from 0.03 to 0.05 M at pH 8.0–10.4. Methyl phosphate at 0.01 M and pH 8.4 increased amine yield by about 2.5%, an effect equivalent to that produced by phosphate buffer at 4 × 10^{-4} M for the same pH. Since assay for inorganic phosphate[18] indicated that the

Table II. Effect of pH and of Monofunctional Buffers on the Yield of Aniline Obtained from Hydrolysis of Ethyl N-Phenylacetimidate (I)[a]

pH	Buffer	Concn, M	Aniline, %
1.09	HCl		100.2
3.08	Chloroacetate	0.05	100.0
5.10	Acetate	0.05	100.9
7.02	$(C_2H_5)_2NCH_2CH_2CN$	0.02	82.3
7.03		0.04	82.6
7.88	Imidazole[b]	0.0	39.6
7.87		0.005	41.7
7.89		0.01	46.0
7.89		0.02	52.8
8.52	Tris	0.02	15.2
8.53		0.03	14.6
8.53		0.04	16.0
9.05	Borate	0.02	9.4
9.05		0.05	11.3
9.55		0.02	5.9
9.54		0.05	7.1
10.40		0.02	2.1
10.39		0.05	2.8

[a] At 30° in 10% acetonitrile-water, μ = 0.50. [b] In 0.03 M Tris buffer.

Table III. Effect of Bifunctional Buffers on the Yield of Aniline Obtained from Hydrolysis of Ethyl N-Phenylacetimidate (I)[a]

Expt	pH	Buffer,[b] M	Aniline, %	$K_{app} \times 10^8$, M
		a. Phosphate		
1	7.55	. . .	66.0	0.32
	7.54	0.00016	78.2	
	7.53	0.0006	85.8	
	7.52	0.001	94.4	
2[c]	7.85	. . .	41.4	0.44
	7.84	0.0002	61.0	
	7.84	0.001	78.3	
	7.82	0.005	94.7	
3	8.52	. . .	15.7	2.3
	8.58	0.0003	28.7	
	8.59	0.002	53.2	
	8.61	0.01	81.9	
	8.63	0.05	93.4	
4	9.07	. . .	8.3	16.2
	9.08	0.005	30.0	
	9.09	0.02	57.5	
	9.14	0.10	84.2	
		b. Bicarbonate		
5	7.63	. . .	58.3	0.65
	7.65	0.00024	71.2	
	7.66	0.001	84.0	
	7.71	0.01	97.4	
6[c]	8.05	. . .	28.5	0.83
	7.99	0.00036	51.3	
	7.97	0.0072	90.9	
7[c]	9.07	. . .	8.6	8.5
	9.06	0.002	24.0	
	9.04	0.01	57.2	
	9.00	0.05	81.3	
8	9.49	. . .	5.0	38.9
	9.53	0.006	18.7	
	9.54	0.03	41.6	
	9.60	0.10	67.9	
		c. Acetate		
9	7.67	. . .	54.6	15.7
	7.65	0.01	70.1	
	7.65	0.10	87.4	
10	7.94	. . .	31.2	65.7
	7.93	0.05	54.5	
	7.93	0.2	72.2	

[a] At 30° in 10% acetonitrile-water, μ = 0.50. [b] All reaction mixtures contain 0.03 M Tris buffer. [c] Additional data are shown in Figure 4B.

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[15] R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, 41, 1662 (1963).

[16] E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 85, 2843 (1963).

[17] R. B. Martin and A. Parcell, *ibid.*, 83, 4830 (1961).

[18] C. H. Fiske and Y. Subbarow, *J. Biol. Chem.*, 66, 375 (1925).

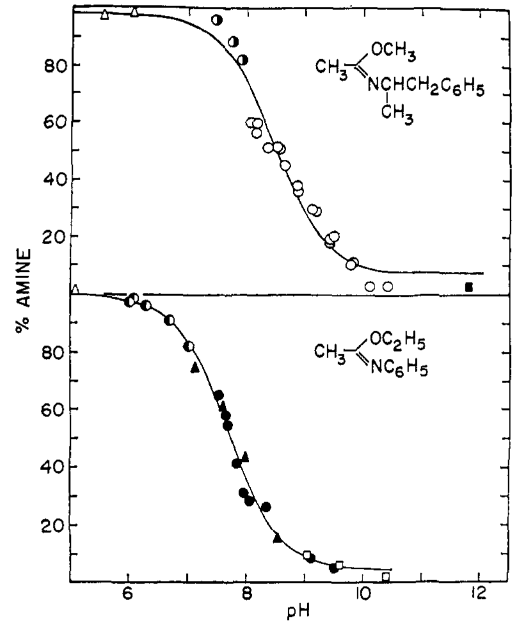

Figure 3. Effect of pH on the yields of amine obtained after hydrolysis of imidate esters I and II. Solid lines are calculated titration curves for monovalent acids of pK' = 7.69 and 8.45, for I and II, respectively: △, acetate, 0.05 *M;* ◐, β-diethylaminopropionitrile, 0.02 *M;* ▲, Tris, 0.02 *M;* ●, Tris, 0.03 *M;* □, borate, 0.02 *M;* ◑, β-dimethylaminopropionitrile, 0.03 *M;* ○, borate, 0.03 *M;* ■, NaOH.

methyl phosphate preparation used contained about 1% phosphate, the catalytic influence of the phosphate monoester is smaller than indicated. Yields of α-methylphenethylamine were based on colorimetric determination of the amine or of methyl acetate, and the identity of the products was confirmed in several cases by examination of the rotatory dispersion spectra of reaction mixtures.

Yields of amine formed from imidate esters in the absence of buffer catalysis are taken to be approximately equal to the yields observed at low concentrations (*ca.* 0.02–0.03 *M*) of β-diethylaminopropionitrile, Tris, and borate buffers (with I) and β-dimethylaminopropionitrile, borate, and sodium hydroxide buffers (with II). With both imidates, amine yield varies with pH as the titration curve characteristic of a univalent acid of dissociation constant pK' = 7.69 ± 0.03 and 8.45 ± 0.05 for I and II, respectively (Figure 3). The computer-calculated curves which best fit the data (least squares) indicate that the yields of amine approach 99–100% asymptotically at low pH and 5 and 8% at high pH, for I and II, respectively. The latter values do not accurately reflect the limiting yields of amine formed at high pH on hydrolysis of the imidates. It is probable that the yields recorded in the pH range 8.5–10.0 are somewhat too high, owing to contamination of reaction mixtures by atmospheric carbon dioxide. With I, the presence of 0.002 *M* adventitious carbonate at pH 9.5 would raise the aniline yield from a negligibly low value to 5%; in the case of II at pH 10, the same concentration of carbonate would result in a 10% amine yield over the true buffer-independent value. The distortion thus induced in the experimental curve is reflected in the poor fit of the least-squares curve at high pH. At pH >10, where the catalytic effectiveness of carbonate buffers drops sharply, yields of amine in the range of 2–3% were obtained from I and II.

Table IV. Effect of Buffers on the Yield of α-Methylphenethylamine Obtained on Hydrolysis of II[a]

Expt	pH	Buffer,[b] *M*	Amine,[c] %	$K_{app} \times 10^3$, *M*
		a. Phosphate		
11	8.18	...	60.0	3.2
	8.18	0.001	69.6	
	8.16	0.008	81.6	
	8.15	0.02	87.7	
12[d]	8.52	...	51.6	6.6
	8.54	0.002	61.7	
	8.55	0.02	85.9	
		b. Bicarbonate		
13	8.56	...	51.2	2.8
	8.59	0.0005	60.6	
	8.60	0.004	76.3	
	8.65	0.02	90.5	
14[d]	9.48	...	20.4	6.6
	9.49	0.003	39.7	
	9.50	0.02	66.8	
		c. Methyl Phosphate		
15	8.42	...	49.5	
	8.42	0.002	51.2	
	8.40	0.01	52.0	
	8.36	0.04	61.0	
		d. Imidazole		
16	8.52	...	48.7	*Ca.* 80
	8.54	0.02	61.5	
	8.53	0.10	72.8	
17	9.42	...	17.9	*Ca.* 1000
	9.44	0.05	22.4	
	9.46	0.10	24.9	
	9.44	0.20	30.5	

[a] At 30° in 10% acetonitrile–water, μ = 0.5. [b] All reaction mixtures contain 0.03 *M* borate buffers, except for experiments 16 and 17 where 0.05 *M* borate was used. [c] In experiments 16 and 17 the product determined was methyl acetate. [d] Additional data are shown in Figure 4A.

At constant pH and in the presence of catalytic buffers, the increase in amine yield formed on imidate hydrolysis is described by a rectangular hyperbola (Figure 4), according to eq 3. (ΔA = increase in amine

$$\Delta A/\Delta A_{max} = [\text{buffer}]/([\text{buffer}] + K_{app}) \qquad (3)$$

yield above that produced in the absence of a reactive buffer; ΔA_{max} = maximum increase possible; K_{app} = concentration of buffer required to produce half the maximum possible increase in yield.)[7,9] For each experiment of the type shown in Figure 4 and Tables III and IV, eight different concentrations of a given buffer were generally used at fixed pH and K_{app} was evaluated by computer fitting of the data to the expression for the two-parameter rectangular hyperbola.[9,19] Maximum yields reached asymptotically at high buffer concentrations were >95% with I and varied in the range 85–100% with II. Resulting values of K_{app} are listed in Tables III and IV, and their dependence on pH is seen in Figure 5 for phosphate and bicarbonate buffer effects on the hydrolysis of I.

The rate of hydrolysis of II was measured at pH 9.5 under conditions where the amine yield was 20% (0.03 *M* borate buffer) and 67% (0.03 *M* borate and 0.02 *M* bicarbonate buffers). Inclusion of bicarbonate buffer

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(19) K. R. Hanson, R. Ling, and E. Havir, *Biochem. Biophys. Res. Commun.*, **29**, 194 (1967).

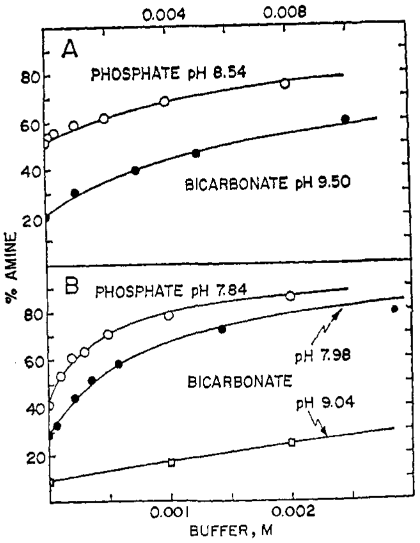

Figure 4. Effect of buffer concentration on yield of amine resulting from hydrolysis of imidate esters. (A) II; abscissa, upper scale. All reaction mixtures contain 0.03 *M* borate buffer. (B) I; abscissa, lower scale. All reaction mixtures contain 0.03 *M* Tris buffer. Solid curves are calculated from eq 3, using values of K_{app} given in Tables III and IV.

caused an increase in rate of no more than 15% of that observed in borate buffer alone.

Discussion

The Mechanism of Hydrolysis of Imidate Esters. The results of the present work suggest that the mechanism proposed[6] to describe the hydrolysis of 2-phenyliminotetrahydrofuran (Figure 2) represents a general mechanism for the hydrolysis of imidate esters. One of its principal features is the occurrence of tetrahedral intermediates in acid–base equilibrium, each species of the intermediate giving rise to different products.

Several lines of evidence support the existence of intermediates in imidate hydrolysis: (1) the nature of the products of hydrolysis varies with pH in a manner which bears no discernible relationship to the effects of pH on the over-all rate of hydrolysis; with II, C=N bond cleavage gradually gives way to almost complete C—O bond cleavage in a pH region (7.5–10.5) where the rate of hydrolysis is essentially independent of pH. It is amusing to note that, with I, transition from the formation of aniline to that of acetanilide occurs at a pH (7.69 ± 0.03) identical with that (7.67) where the rates of water and hydroxide ion addition to the protonated imidate are equal. No such coincidence was found in iminolactone hydrolysis.[6] (2) The presence of low concentrations of certain catalysts produces profound alterations in the nature of the hydrolysis products with little or no concomitant effects on the rate of hydrolysis.[7,9] (3) As in the hydrolysis of iminolactones[6] and thioimidate esters,[9] the extent of C=N bond cleavage (Figure 3) varies with pH as the sigmoid curve expected on the basis of the proposed mechanism.

The Modes of Decomposition of Tetrahedral Intermediates. It is clear now that imidate esters derived from aliphatic alcohols and aliphatic or aromatic amines yield predominantly amines and esters in acid solution and amides and alcohols at alkaline pH, transition occurring near neutrality. That this conclusion was not reached in early studies of imidate hydrolysis is probably the result of the facile hydroxide ion catalyzed conversion of unsubstituted imidates to nitriles and alcohols;[1d,4a] at least two reports, however, exist of the formation of amides on alkaline hydrolysis of imidates derived from amino acids.[20]

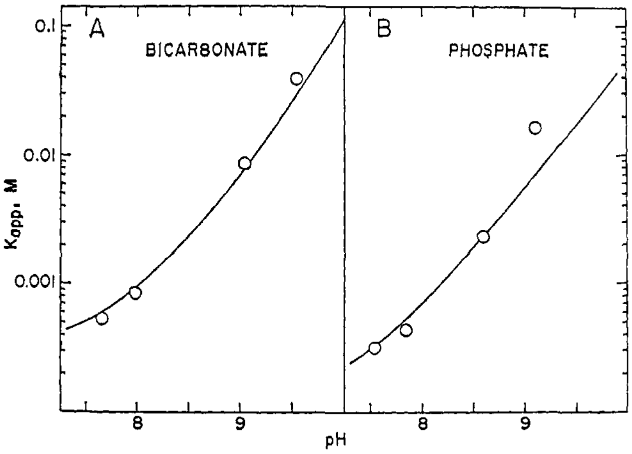

Figure 5. Effect of pH on effectiveness of buffers (given by K_{app}) in increasing the amine yield in imidate hydrolysis. Solid lines are theoretical curves computed as described in the text.

In the terms adopted in the present work (Figure 2), the nature of the products of hydrolysis of a given imidate depends on the relative rates of amine expulsion from the neutral (or most probably zwitterionic) intermediate and of alkoxide expulsion from the anionic intermediate, and on the dissociation constant K_3 of the neutral intermediate. These factors cannot at present be separated, and receive quantitative expression in the constant K'; pK' represents the pH where transition takes place between the possible products.[6,10] It is now possible to begin to define, in quantitative terms, how structural variation in the three groups attached to the central carbon atom of the tetrahedral intermediate is reflected in the favored modes of decomposition of such intermediates, both with respect to pH and general acid–base catalysts. To date, the following pK' values have been found: 7.07 (iminolactone derived from aniline),[6] 7.4 (N-(methoxymethylene)morpholinium methosulfate),[21a] 7.6 (2-methyloxazoline, from a calcu-

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[20] (a) D. F. Elliott, *Biochem. J.*, **45**, 429 (1949); (b) H. Peter, M. Brugger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **46**, 577 (1963).

[21] (a) G. M. Blackburn and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 2638 (1968). (b) Approximate pK_a values are: morpholine, 8.4; ethanolamine, 9.4; α-methylphenethylamine, 9.9 [D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co. (Publishers) Ltd., London, 1965]. (c) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968). (d) In a previous report,[9] we considered but did not favor the possibility that the change in products which takes place in thioimidate hydrolysis at pH 2.7–2.9 is the result of the conversion of a cationic to a neutral intermediate. There is kinetic evidence that cationic and neutral intermediates are involved in the hydrolysis of N-hydroxythioimidate esters,[10] and the same may hold also for acyclic thioimidate esters, at least for the product transition at *ca.* pH 3. At higher pH, a second transition in products has been found with i, suggesting the additional intervention of an anionic carbinolamine (R. K. Chaturvedi, unpublished experiments). The interpretation of the thioimidate data at low pH is complicated by the observation that the hydrolysis of 2-methylthiazoline appears to procede slowly *via* neutral intermediates but with a rate-de-

lation based on the rates of acetyl transfer in O-acetylethanolamine),[10] 7.69 (I), and 8.45 (II). For carbinolamines derived from aliphatic amines, there seems to exist some tendency for amine expulsion to be favored at higher pH as amine basicity[21b] increases. Similar conclusions were reached by Blackburn and Jencks in their study of the aminolysis of methyl formate.[21a] The relatively high pK' value for I remains at present an unexplained anomaly. In contrast to the modest over-all effects of variation in amine basicity on the pathways of tetrahedral intermediate decomposition, increase in the acidity of the alcohol component enhances noticeably the expulsion of alkoxide ion (with phenyl N-methylacetimidate).[5] The behavior of this imidate is more complex than indicated by the present treatment, however, since its hydrolysis appears to involve cationic, neutral, and anionic intermediates, each decomposing to different products.[21c]. In analogous manner, transition from amine to mercaptan expulsion with tetrahedral intermediates generated from thioimidate esters occurs at pH 2.7–2.9 and is largely independent of amine basicity.[9,21d]

A more subtle feature of the problem of the decomposition of tetrahedral intermediates is whether and to what extent each species of the intermediate is capable of giving rise to *both* possible products. Owing to experimental difficulties in analyzing product mixtures containing largely (>95%) one component, it has been possible to answer this question in few instances. An approach to this problem based on the analysis of the kinetics of certain acyl transfer reactions has been suggested;[10] tentatively, it appears that thus far determined partitioning ratios for anionic tetrahedral intermediates, of the type shown in Figure 2, vary between 230 and 1500, in favor of the expulsion of alkoxide ion.[8,10] Clearly, this aspect of the chemistry of tetrahedral intermediates remains to be explored at much greater depth.

The Aminolysis of Esters. The known effects of pH on the nature of the products of imidate hydrolysis, and hence on the favored pathways of breakdown of some tetrahedral intermediates, permit the conclusion that the aminolysis of esters of aliphatic alcohols proceeds with rate-determining breakdown of tetrahedral intermediates at low pH.[10] Transition to rate-determining nucleophilic attack occurs at weakly alkaline pH. Direct experimental evidence for these phenomena has been recently obtained.[21a] An analogous change in rate-determining step has been reported[8] for the reverse reaction (alcoholysis of amides), where rate-determining formation of intermediates at low pH gives way to rate-determining breakdown of intermediates at pH >7. Similar reasoning led Kandel and Cordes[5] to conclude that the aminolysis of phenyl acetate occurs with (mainly) rate-determining amine attack at pH values at least as low as pH 4. The aminolysis of thiolesters parallels that of phenyl acetate.[9]

Bifunctional Acid–Base Catalysis. A remarkable property of the tetrahedral intermediates generated in the hydrolysis of 2-phenyliminotetrahydrofuran was their susceptibility to bifunctional catalysis.[7] Evidence was given that the conversion of the neutral tetrahedral intermediate to aniline and butyrolactone was significantly accelerated in the presence of low concentrations of phosphate, bicarbonate, and acetic acid buffers. The observation that phosphate buffer was a far more effective catalyst than imidazole buffer, in contrast to known relative reactivities of these two catalysts in nucleophilic or general acid–base catalysis,[22] provided support for the proposed bifunctional catalysis.

It is evident from the present work that the hydrolysis of acyclic imidates is affected by bifunctional buffers. In accord with the hypothesis that the conversion of the neutral tetrahedral intermediate (TH) to amine is catalyzed by the conjugate acid (BH) of the bicarbonate–carbonate buffer (eq 4), the curve of Figure 5A was

$$\mathrm{TH} + \mathrm{BH} \xrightarrow{k_3'} \text{amine} \tag{4}$$

constructed from eq 5[7,10] (K_2 is the acid dissociation

$$K_{\text{app}} = \frac{(k_3/k_3')([\mathrm{H}^+] + K')([\mathrm{H}^+] + K_2)}{[\mathrm{H}^+]^2} \tag{5}$$

constant of the buffer; $k_3/k_3' = 3.1 \times 10^{-4}\ M$). To account for the effect of phosphate buffer, it was assumed that both phosphate monoanion and dianion interacted with TH; the modified equation derived earlier[7] was used, with $k_3/k_3' = 0.8 \times 10^{-4}$ and $2.6 \times 10^{-4}\ M$ for $H_2PO_4^-$ and HPO_4^{2-}, respectively (Figure 5B). The term k_3/k_3' is reasonably accurate for HPO_4^{2-} but is much less certain for $H_2PO_4^-$ since the data were obtained in a pH range where the buffer exists largely as the dianion. The relative reactivities arbitrarily chosen for $H_2PO_4^-$ and HPO_4^{2-} were those found to hold in iminolactone hydrolysis.[7] From similar but less extensive data on the hydrolysis of II, it appears that the same equations describe the catalytic effects of buffers in this system.

Monofunctional buffers such as imidazole also catalyze the appearance of amine from I and II, but no thorough study of the mechanism of this effect was done and it is not known with certainty with which carbinolamine species those catalysts interact. The limited data available (Table IV) suggest that imidazolium ion reacts with the anionic carbinolamine, in contrast to the mechanism of action of bifunctional acids. For the present purpose, we note that, both with I (pH 7.9) and with 2-phenyliminotetrahydrofuran (pH 7.3), phosphate buffer is at least 200 times more effective than imidazole buffer. With II, the difference between these two catalysts is much reduced, phosphate being only about 12 times better than imidazole. The latter finding is at least in part the result of a decreased catalytic constant for phosphate (see below). Nevertheless, since phosphate is at least 25 times a better catalyst than methyl phosphate at pH values where both compounds exist predominantly as the dianionic species, it is clear

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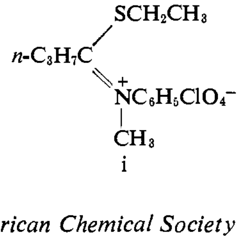
termining proton transfer under some conditions (R. Barnett and W. P. Jencks, personal communication).



$$n\text{-}C_3H_7C(SCH_2CH_3)=\overset{+}{N}(CH_3)C_6H_5\ ClO_4^-$$

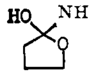
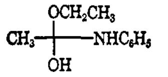
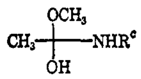
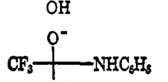
i

[22] See ref 7 and 8 for citation of relevant literature. Another instance of nucleophilic catalysis by phosphate and imidazole is described in ref 23 and additional data have been summarized by Johnson.[24]

[23] M. L. Ernst and G. L. Schmir, *J. Am. Chem. Soc.*, 88, 5001 (1966).

[24] S. L. Johnson, *Advan. Phys. Org. Chem.*, 5, 278 (1967).

Table V. Catalytic Constants for Bifunctional Catalysis of Amine Formation from Carbinolamines[a]

	k_3'/k_3, M^{-1} [b]				
	CH_3COOH	$H_2PO_4^-$	HPO_4^{2-}	HCO_3^-	Ref
	2.5×10^4	6700	2000	4,200	7
 $CH_3C(OCH_2CH_3)(OH)NHC_6H_5$	10^5		3800	3,200	This study
 $CH_3C(OCH_3)(OH)NHR^c$			350[d]	1,700[d]	This study
 $CF_3C(O^-)(OH)NHC_6H_5$		9.2×10^6	2200	16,000	26

[a] All constants determined for 10% acetonitrile–water, 30°, $\mu = 0.5$, except for ref 26, where 9.6% ethanol–water, 25°, $\mu = 1$, was used. [b] Calculated from dependence of K_{app} on pH, using eq 5 (for CH_3COOH and HCO_3^-) and eq 11 of ref 7 (for phosphate); the term K_4k_3/k_{13} of the latter equation is equivalent to k_3/k_3' of the present work. [c] R = α-methylphenethyl. [d] Based on data of Table IV, as well as on additional experiments (not shown).

that special properties must be ascribed to phosphate dianion.[25]

The hydrolysis of trifluoroacetanilide is accelerated by low concentrations of phosphate and bicarbonate buffers.[26] The interpretation originally advanced[26] to explain these findings was similar to that favored in the present work, but has been revised to one involving only general acid catalysis in view of the recent observation that imidazolium ion is one-tenth as effective as phosphate monoanion.[27]

The case for bifunctional catalysis is less well founded with II than with I. It may be that there occurs a gradual merging of bifunctional catalysis into classical general acid–base catalysis as a result of changing amine basicity or steric requirements in the carbinolamine. Possibly more subtle, as yet undefined, factors must be considered in explanations of catalytic effects on tetrahedral intermediates. At present, we limit ourselves to expressing quantitatively the ability of (potential) bifunctional catalysts to promote amine expulsion from carbinolamines in terms of the ratio k_3'/k_3, which compares the rate of the catalyst-induced breakdown to that of the water-catalyzed process (Table V). The susceptibility of carbinolamines to catalytic influences varies widely within the limited series of compounds studied; detailed discussion of these data awaits further examination of these systems.

In view of the findings of this study, it seems probable that the aminolysis of esters in aqueous solution will generally be subject to bifunctional acid–base catalysis by species such as $H_2PO_4^-$, HPO_4^{2-}, HCO_3^-, and carboxylic acids. This catalysis will be observed in the pH region of rate-limiting amine attack on the carbonyl function (pH > pK'), and will lead to a transition in rate-determining step at relatively low catalyst concentration. The quantitative aspects of the relationship of the present findings to the mechanism of ester aminolysis have been discussed elsewhere.[10]

Experimental Section[28]

Ethyl N-phenylacetimidate[29] (I) had bp 42–44° (0.4 mm), n^{25}D 1.5159 (lit.[29] bp 94.5° (12 mm), n^{25}D 1.5167). The ultraviolet spectrum (CH_3CN) showed: no λ_{max} at >220 mμ (ϵ_{240} 5000) (ϵ_{230} 6100); infrared spectrum (thin film): 5.96 μ (C=N–).

Methyl (+)-N-(α-Methylphenethyl)acetimidate (II). A. (−)-N-(α-Methylphenethyl)acetamide[30] had mp 123–124° after recrystallization from ethyl acetate–*n*-hexane (lit.[31] mp 123–125°); ν_{max}^{Nujol} 6.08 μ (lit.[30] 6.08 μ); rotatory dispersion spectrum in methanol (*c* 0.115), 30°: $[\alpha]_{300}$ −165°, $[\alpha]_{270}$ −183°, $[\alpha]_{264}$ −400° (lit.[30] $[\alpha]_{300}$ −163°, $[\alpha]_{270}$ −269° at 25°).[32]

B. The conversion of N-(α-methylphenethyl)acetamide to II was accomplished by the general procedure of Bredereck, *et al.*,[33] for the O-methylation of amides. A mixture of 8.1 g (0.045 mol) of the amide with 5.7 g (0.045 mol) of dimethyl sulfate was maintained at 100–105° for 2 hr, with exclusion of moisture. The cooled reaction mixture was triturated several times with ether. The oily residue which remained after decantation of the supernatant ether was covered with fresh ether and shaken with 30% aqueous sodium carbonate. After drying over $MgSO_4$, the ethereal phase was concentrated *in vacuo*, and the residual oil was dissolved in petroleum ether (bp 30–60°). After filtration to remove a small amount of unreacted amide, the solvent was removed and the residue distilled at reduced pressure. The product (5.8 g, 67% yield) had bp 60° (0.7 mm); n^{25}D 1.4948. *Anal.* Calcd for $C_{12}H_{17}NO$ (191.27): C, 75.33; H, 8.96; N, 7.32. Found: C, 75.38; H, 9.18; N, 7.28. The infrared spectrum (thin film) showed absorption at 5.95 μ (C=N). The proton nmr spectrum (10% in CCl_4, tetramethylsilane as internal standard) showed the following bands, in addition to the aromatic absorption at low field: a doublet at δ 1.09, 3 H, CHCH_3; a singlet at δ 1.46, 3 H, CH_3C=N; an unsymmetrical

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(25) (a) It is uncertain whether methyl phosphate dianion possesses any catalytic properties at all. The observed catalysis may perhaps be entirely accounted for on the basis of the inorganic phosphate contaminant (*ca.* 1%) and the fraction of total methyl phosphate present as the monoanion (*ca.* 1%). (b) The argument might be made that HPO_4^{2-} (pK_a = *ca.* 12.5)[25c] is simply acting as an effective general acid. Since $H_2PO_4^-$ (pK_a = 6.8) is only about three times as reactive as the dianion, the resulting Brønsted α value of 0.09 means that catalysis by general acids other than water should be nearly undetectable. (c) L. G. Sillen and A. E. Martell, "Stability Constants of Metal-Ion Complexes," The Chemical Society, London, 1964, p 180.

(26) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 20, 1892 (1966).

(27) S. O. Eriksson and L. Bratt, *ibid.*, 21, 1812 (1967).

(28) Melting points are uncorrected. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Ultraviolet spectra were determined by means of a Perkin-Elmer Model 350 recording spectrophotometer and optical rotation measurements were recorded with a Cary Model 60 spectropolarimeter.

(29) R. H. DeWolfe, *J. Org. Chem.*, 27, 490 (1962).

(30) N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *J. Am. Chem. Soc.*, 80, 4858 (1958).

(31) S. L. Shapiro, I. M. Rose, and L. Freedman, *ibid.*, 80, 6065 (1958).

(32) The discrepancy between the observed and previously reported[30] rotatory dispersion spectra at 270 mμ probably results from the high resolving power of the Cary Model 60 spectropolarimeter used in the present work. The negative plain curve described by Leonard, *et al.*,[30] is clearly perturbed by aromatic Cotton effects in the region 254–272 mμ. The dispersion curve exhibits a positive excursion, among others, with a maximum at 270–271 mμ, thus explaining the significantly more positive rotation recorded by us at 270 mμ.

(33) H. Bredereck, F. Effenberger, and E. Henseleit, *Ber.*, 98, 2754 (1965).

doublet centered at about δ 2.65, 2 H, $-CH_2-$; a multiplet centered at about δ 3.4, 1 H, $-CH-$; and a singlet, δ 3.55, 3 H, $-OCH_3$; rotatory dispersion spectrum in 10% acetonitrile–0.1 *N* HClat 30° (*c* 0.025), positive plain curve in the region 220–300 mμ, $[\alpha]_{225}$ +7500°.

(+)-N-(α-Methylphenethyl)amine (Aldrich) had $[\alpha]^{30}\text{D}$ +22.5° (*c* 4.8, based on hydrochloride salt) in water containing 1 equiv of HCl (lit.[34] $[\alpha]^{25}\text{D}$ +21.6° (*c* 9)).

Kinetic Measurements. Acetonitrile and imidazole were purified as previously described.[6] β-Dimethylaminopropionitrile was distilled prior to use. Methyl phosphate sodium salt (K and K Laboratories) contained <1% inorganic phosphate.[18] Buffers and inorganic salts were of reagent grade and were used without further purification. Freshly boiled, glass-distilled water was used for all rate determinations and product analyses for reactions at pH >6.

The medium used for the kinetic studies was 10% acetonitrile–water (v/v) at ionic strength 0.5, adjusted with added KCl. The rate of hydrolysis of I was determined spectrophotometrically, by the method previously employed.[9] Buffers used were HCl, chloroacetate, acetate, imidazole, phosphate, Tris, and borate, as appropriate, concentrations varying from 0.02 to 0.1 *M*. Substrate concentration was 1.3–1.6 × 10^{-4} *M*. Selection of wavelengths at which to follow absorbance changes depended on the nature of the reaction products and varied as the absorbing product changed from anilinium ion to aniline to acetanilide as pH increased. The following wavelengths were used to maximize absorbance changes (the pH range and whether absorbance increased or decreased is indicated): 240 mμ (pH 0–4, decrease); 250 mμ (pH 4–5.6, decrease); 230 mμ (pH 6.0–6.5, increase); 235 mμ (pH 7.0–10.0, increase). First-order rate constants were calculated as usual.[9]

The hydrolysis of II was studied in solutions buffered with HCl, cyanoacetate, acetate, β-dimethylaminopropionitrile, borate, and sodium hydroxide, in concentrations of 0.02–0.07 *M*. Tris buffer could not be employed since ORD spectra of the reaction products suggested that II had undergone nucleophilic attack by the buffer. To determine the rate of hydrolysis of II, use was made of the differences in optical rotation at 225 mμ of II, N-(α-methylphenethyl)-acetamide, α-methylphenethylamine, and α-methylphenethylamine hydrochloride; approximate specific rotations at 225 mμ, 30° (*c ca.* 0.02 in 10% acetonitrile-water), were +9000°, −3500°, +2500°, and +1000°, respectively. At pH <5, where the imidate ester was largely in the protonated form, it showed $[\alpha]^{30}_{225}$ +7500°. Owing to the high sensitivity of the Cary Model 60 spectropolarimeter, imidate hydrolysis could readily be studied at 10^{-3} *M* concentration, using water-jacketed cells of 1-cm path length. Rate constants were calculated by means of the Guggenheim[35] method, with $\Delta T >$ three half-lives of reaction.

Product Analysis. The extent of C–N bond cleavage taking place during the hydrolysis of the imidate esters I and II was determined usually by colorimetric assay of the amine produced and occasionally by assay for methyl acetate (with II). Product analyses were performed after eight to ten half-lives of reaction on reaction mixtures identical with those used in the kinetic studies.

A. Aniline was determined colorimetrically by means of a modification of the Bratton–Marshall procedure.[6,7] Control experiments with acetanilide indicated that <0.5% hydrolysis occurred during the time required for complete hydrolysis of I.

B. α-Methylphenethylamine was determined by a modification[9] of the method of Dahlgren.[36] A 1-ml aliquot containing amine at 1 × 10^{-4} *M* gives an absorbance of about 0.6. The concentration of II was 1–5 × 10^{-4} *M*, depending upon the expected yield of amine. N-(α-Methylphenethyl)acetamide does not contribute significantly to the absorbance measured at 540 mμ. Since tertiary amines can also be determined by this procedure,[36] it could not be used in the presence of imidazole or β-dimethylaminopropionitrile buffer. In these cases, methyl acetate, the alternate product of C–N cleavage, was measured.

C. Methyl Acetate. A minor modification of the hydroxamic acid method used by Jencks and Carriuolo[37] for other esters of aliphatic alcohols was used. To a 2-ml aliquot of reaction mixture was added 1 ml of a solution made up from 4 *M* hydroxylamine hydrochloride, 3.5 *M* NaOH, and water (4:5:1), and the mixture was incubated at 30°. After 10 min, 1 ml of 30% $FeCl_3 \cdot 6H_2O$ in 1 *N* HCl was added and the absorbance at 540 mμ read exactly 10 min later. Under these conditions, a 2-ml aliquot containing methyl acetate at 1 × 10^{-3} *M* gives an absorbance of about 0.45 (1-cm light path).

D. Optical rotatory dispersion spectra (220–300 mμ) of reaction mixtures at pH 4.5, 7.7, 8.6, and 9.5 were compared to the ORD spectra of synthetic mixtures whose composition was based on the results of colorimetric assay for α-methylphenethylamine. Agreement between the final spectrum of the reaction mixtures and that of the reconstituted product mixture was good in all cases.

pK_a Determination. A solution of II (2.5 × 10^{-3} *M*) in 10% acetonitrile–water containing enough HCl to bring the initial pH to 3.9 was titrated at 30° with standard NaOH. The ionic strength varied from 0.52 to 0.48 *M* during the course of the titration. The total time which elapsed during titration was <3 min. The titration data were analyzed by the method of Reed and Berkson.[38]

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(34) H. E. Smith and M. E. Warren, *Tetrahedron*, **24**, 1327 (1968).

(35) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(36) G. Dahlgren, *Anal. Chem.*, **36**, 596 (1964).

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

(38) W. M. Clark, "Oxidation-Reduction Potentials of Organic Systems," Williams and Wilkins Co., Baltimore, Md., 1960, p 153.