compounds. After correcting for this initial 2% hydrogen at the α carbon, the scramblings were obtained and are given in Table IV.

E. 2-Phenyl-1,1-d_2-ethyl Tosylate (15) in Buffered Trifluoroethanol. 2-Phenyl-1,1-d_2-ethyl tosylate (0.02 *M*) was solvolyzed in TFE buffered with sodium acetate (0.03 *M*) at 75° for 67 hr (about 67% reaction assuming $k_H/k_D = 1.21$). Isolation was carried out as described above (B). The acetate and trifluoro ether products were separated by vpc and were in a ratio of 54:46, respectively. The nmr spectra of the recovered tosylate and the recovered ether were identical (except for the relative integrals of the H_2C_α and H_2C_β peaks) with previously obtained spectra.

The scramblings in the recovered tosylate and acetate were obtained from integrations of multiple nmr scans and are 17.1 and 77.4%, respectively. The scrambling in the trifluoro ether was calculated from mass spectral data by two methods, 103 and 100%, respectively.

Hydrolysis of Imidate Esters Derived from Weakly Basic Amines. Influences of Structure and pH on the Partitioning of Tetrahedral Intermediates[1a,b]

Tadashi Okuyama,[1c] Terry C. Pletcher,[1d] David J. Sahn, and Gaston L. Schmir*

Contribution from the Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine, New Haven, Connecticut 06510.
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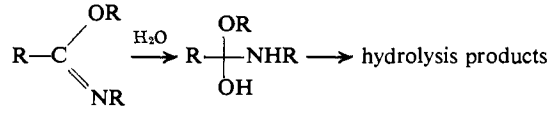
Abstract: A study has been made of the kinetics and products of the hydrolysis of ten imidate esters, derived from amines varying in basicity by more than 15 pK units. The influence of pH on the nature of the hydrolysis products is strongly dependent on the structure of the imidate ester. Ethyl *N*-arylformimidates (I–V) derived from amines of $pK_a > 0$ produce *decreasing* yields of amine as pH is increased. Imidate esters (VIII, X) derived from very weakly basic amines ($pK_a < -6$) produce *increasing* yields of amine as pH is increased. The yield of 2,4-dinitroaniline formed on hydrolysis of VI varies with pH in a complex manner, with a *minimum* in the yield of amine at pH 4.5. The pH dependence of the rates and products of hydrolysis has been interpreted in terms of a mechanism involving cationic, neutral, and anionic tetrahedral intermediates.

The hydrolysis of imidate esters offers a convenient and useful approach to the study of the properties of the unstable tetrahedral addition intermediates



believed to participate in many acyl transfer reactions.[2,3] The important investigation by Martin, *et al.*,[4] of the hydrolysis of 2-methyl-Δ^2-thiazoline was followed by studies of the aminolysis[5] and hydrolysis of imidate esters[6] which revealed that the products of nucleophilic attack at the imidate carbon atom were sensitive functions of pH and general acid–base catalysts. The present state of knowledge of the pathways of breakdown of the tetrahedral addition intermediates generated in the hydrolysis of imidate esters may be summarized as follows. Cyclic and acyclic imidate esters yield amines and esters in acidic solution, and amides (and alcohols) at higher pH.[6a,7–9] The transition in products occurs near neutral pH[6a,7,8] and follows accurately the sigmoid curve characteristic of the ionization of a monovalent acid.[6a,8] Cyclic[10] (Δ^2-thiazolines) and acyclic[11] thioimidate esters, as well as an imidate ester derived from phenol,[9,12] yield decreasing amounts of amine as pH is increased, but the principal product transition takes place at pH 2–3; these compounds (with the exception of Δ^2-thiazolines which could not be studied at sufficiently high pH) also show a second product transition at pH values near neutrality.[11b,12a] In general, the yield of amine formed on hydrolysis of imidates and thioimidates at constant pH increases with increasing buffer concentration, bifunctional buffers (phosphate, bicarbonate) being particularly effective in this regard.[6–8,11]

Little information is available concerning the effect of imidate structure on the behavior of the derived tetrahedral intermediates. Increasing the acidity of the alcohol portion of *N*-methylacetimidate esters resulted in a shift from pH 9.8 (for *O*-ethyl) to pH 6.5 (for *O*-trifluoroethyl) in the midpoint of the product transition.[9] That increasing basicity of the amine tends to facilitate amine expulsion from the tetrahedral intermediate was deduced from the kinetics of the

(1) (a) This work is taken in part from a dissertation presented by D. J. S. in partial fulfillment of the requirements for the M.D. degree, Yale University, 1969. (b) Financial support by the National Institutes of Health and the National Science Foundation is gratefully acknowledged. (c) On leave from the faculty of Engineering Science, Osaka University. (d) Postdoctoral Research Fellow of the National Institutes of Health, 1969–1970.

(2) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 10.

(3) G. L. Schmir, *J. Amer. Chem. Soc.*, **90**, 3478 (1968).

(4) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *ibid.*, **81**, 5089 (1959).

(5) E. S. Hand and W. P. Jencks, *ibid.*, **84**, 3505 (1962).

(6) (a) G. L. Schmir and B. A. Cunningham, *ibid.*, **87**, 5692 (1965); (b) B. A. Cunningham and G. L. Schmir, *ibid.*, **88**, 551 (1966).

(7) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968).

(8) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **90**, 4413 (1968).

(9) T. C. Pletcher, S. Koehler, and E. H. Cordes, *ibid.*, **90**, 7072 (1968).

(10) (a) R. E. Barnett and W. P. Jencks, *ibid.*, **91**, 2358 (1969); (b) C. Cerjan and R. E. Barnett, *J. Phys. Chem.*, **76**, 1192 (1972).

(11) (a) R. K. Chaturvedi, A. E. McMahon, and G. L. Schmir, *J. Amer. Chem. Soc.*, **89**, 6984 (1967); (b) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **91**, 737 (1969).

(12) (a) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968); (b) M. Kandel and E. H. Cordes, *J. Org. Chem.*, **32**, 3061 (1967).

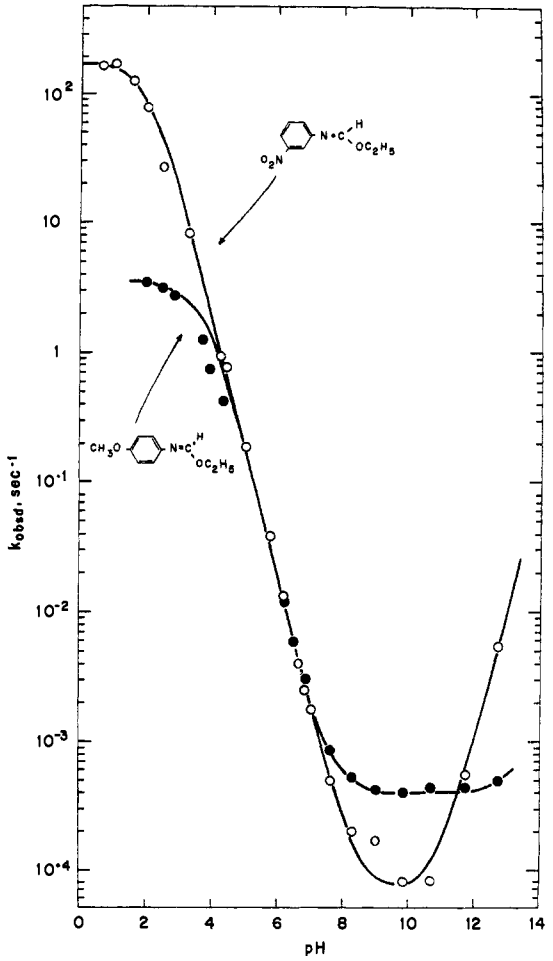


Figure 1. pH-rate profiles for hydrolysis of I and IV in 2% CH_3CN-H_2O, at 30° (μ = 0.5). Curves are calculated from eq 2, using constants of Table I.

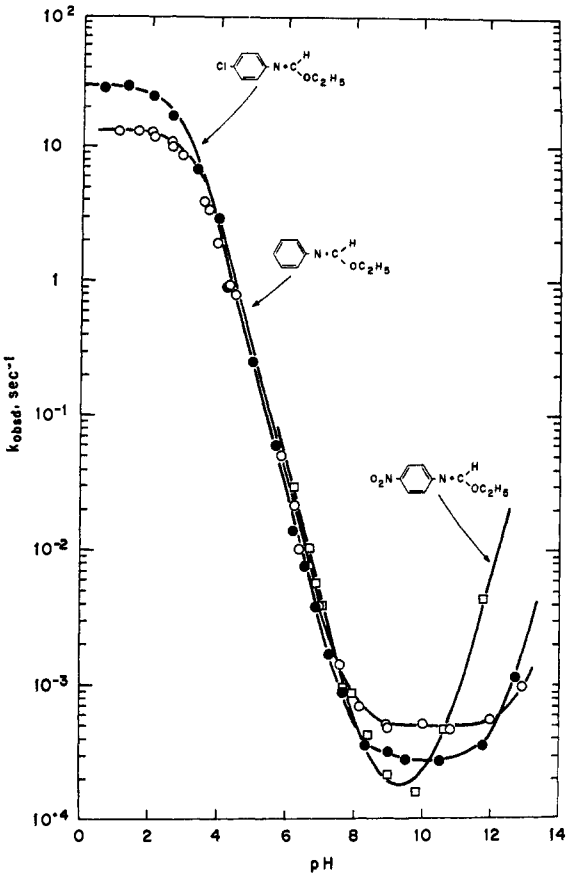


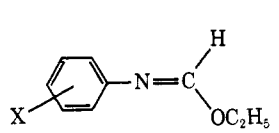
Figure 2. pH-rate profiles for hydrolysis of II, III, and V at 30° (μ = 0.5). Curves are calculated from eq 2, using constants of Table I.

aminolysis of methyl formate;[7] the pH at which the rate of expulsion of amine was equal to that for the alcohol component increased from 6.3 (with glycinamide, $pK_a = 8.4$) to 8.4 (with *n*-propylamine, $pK_a = 10.9$).

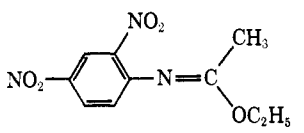
We report herein a study of the hydrolysis of imidate esters derived from aromatic amines of widely varying basicity, our principal objective being the systematic examination of the effects of structural factors on the pathways of breakdown of the tetrahedral intermediates. The unexpected diversity of these effects forms the subject of the present communication.

Results

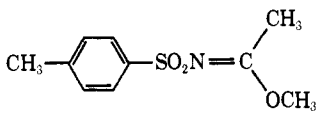
Kinetic Studies. Rapid reaction rates over a wide range of pH[13] as well as the potential for gradual alteration of the basicity of the amine component (without concomitant steric complications) led to the choice of a series of ethyl *N*-arylformimidates (I–V) for detailed study. Although it would have been desirable to limit structural variation to meta and para substitution in *N*-arylformimidates, imidate esters of other structural types were also investigated, thus enabling the range of amine basicity to be considerably extended. These included acyclic derivatives of 2,4-dinitroaniline (VI and VII) and *p*-toluenesulfonamide (VIII), as well as iminolactones based on *p*-nitroaniline (IX) and 2,4,6-trinitroaniline (X).



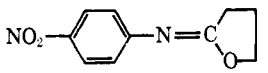
I, X = *p*-OCH_3
II, X = H
III, X = *p*-Cl
IV, X = *m*-NO_2
V, X = *p*-NO_2
VI, X = 2,4-$(NO_2)_2$



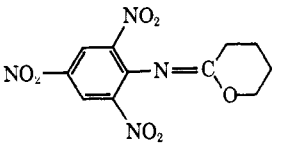
VII



VIII



IX



X

The rate of disappearance of the imidate esters in predominantly aqueous solution at 30° (μ = 0.5) was determined by conventional or rapid (stopped-flow) spectrophotometric methods. Rate constants were extrapolated to zero buffer concentration in all cases

(13) R. H. DeWolfe, *J. Org. Chem.*, 36, 162 (1971).

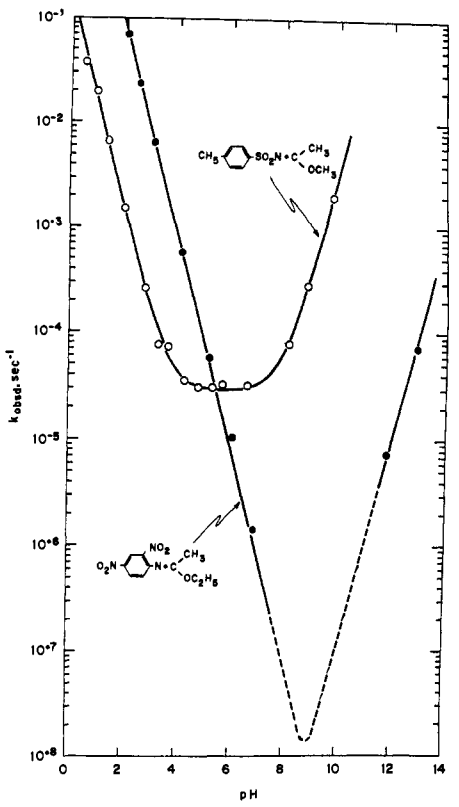


Figure 3. pH–rate profiles for hydrolysis of VII and VIII at 30° (μ = 0.5). VII, 2% CH_3CN–H_2O. VIII, 1% CH_3CN–H_2O. Solid curves are calculated from eq 3 using constants of Table I. Dashed curve is extrapolated rate, assuming acid- and base-catalyzed reactions only.

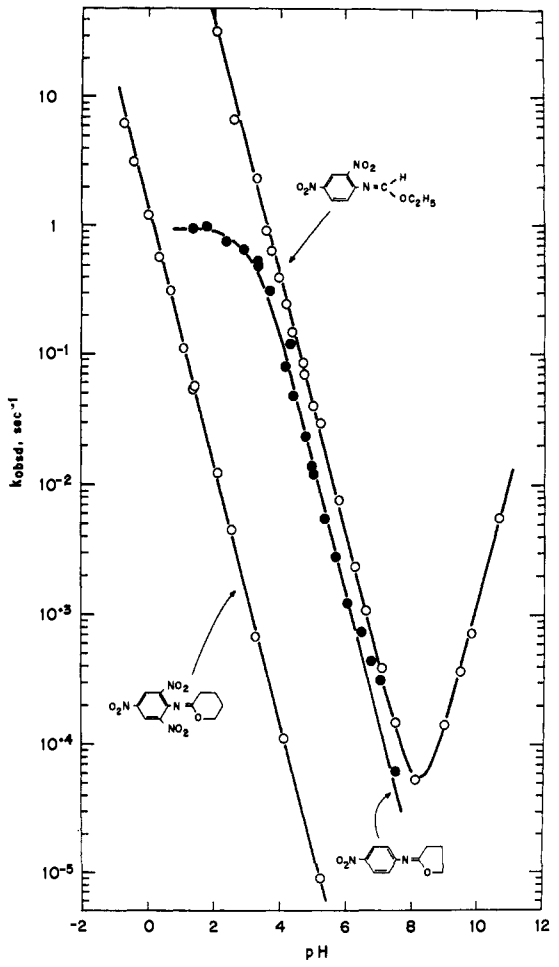


Figure 4. pH–rate profiles for hydrolysis of VI, IX, and X at 30°. VI, 2% CH_3CN–H_2O, μ = 0.5. IX, 10% CH_3CN–H_2O, μ = 0.5. X, 10% CH_3CN–H_2O (see also Table I, footnote *g*). Curves are calculated from eq 2 and 3, using constants of Table I.

except for the iminolactone IX and for the stopped-flow studies; in general, buffers were used in low concentrations (0.02–0.04 *M*) and had little catalytic effect, rate increases at the highest buffer concentration generally amounting to no more than 20% of the extrapolated rate constant.

The pH–rate profiles for I–X (Figures 1–4) exhibit the features previously encountered in the hydrolysis of Schiff bases, imidates, and thioimidates, although not all these features were seen with each substrate.[8,14,15] With the *N*-arylformimidates I–V, there is generally seen a pH-independent rate of hydrolysis at low pH, a rapidly decreasing rate of hydrolysis as the protonated imidate ester is converted to its conjugate base, a new plateau at weakly alkaline pH (where k_{obsd} is much smaller than k_{obsd} for the low pH plateau), and, finally, a base-catalyzed hydrolysis, beginning at pH 10–12. The latter phenomenon, representing most likely nucleophilic addition of hydroxide ion to the imidate free base, had been noted some time ago with Schiff bases derived from aromatic amines,[16] but only recently with analogous imidate esters.[13] As expected, this reaction, barely detectable at pH 13 with the *p*-methoxy imidate I, increases in relative importance with electron withdrawal in the aniline moiety, until it completely overshadows the alkaline plateau with the *p*-nitro imidate V.

(14) W. P. Jencks, *Progr. Phys. Org. Chem.*, 2, 63 (1964).
(15) Reference 6a, and literature cited therein.
(16) (a) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 84, 832 (1962); (b) R. L. Reeves, *J. Org. Chem.*, 30, 3129 (1965); (c) J. Archilar, H. Bull, C. Lagenaur, and E. H. Cordes, *ibid.*, 36, 1345 (1971).

Owing presumably to their much reduced basicity, the imidate esters (VI–VIII, X) derived from the weakest amines show no leveling of rate at acid pH, but on the other hand exhibit very pronounced specific-base catalyzed reactions. Although no data are reported for pH >6 with the trinitrophenyl iminolactone X (Figure 4), this compound reacts rapidly at pH 10–12 (k_{OH} *ca.* 0.14 M^{-1} sec^{-1}) in a complex series of reactions which were not investigated in detail (see Experimental Section).

A mechanism (Scheme I) consistent with these kinetic data and supported by extensive experimentation with related systems[8,14,15] includes the following phenomena: rate-determining attack of water or hydroxide ion on the protonated imidates is replaced at high pH by rate-determining reaction of hydroxide ion with the imidate free base. The products of these nucleophilic additions are tetrahedral adducts in various ionic forms, which undergo (relatively) rapid decomposition to the reaction products. In the sequel, we concern ourselves with the details of the pathways of breakdown of the intermediates.

The kinetic measurements summarized in Figures 1–4 offer no evidence in support of the existence of intermediates on the reaction pathway. The decrease in rate at pH <2 (beyond that caused by complete protonation of the substrate) which is a prominent feature

Scheme I

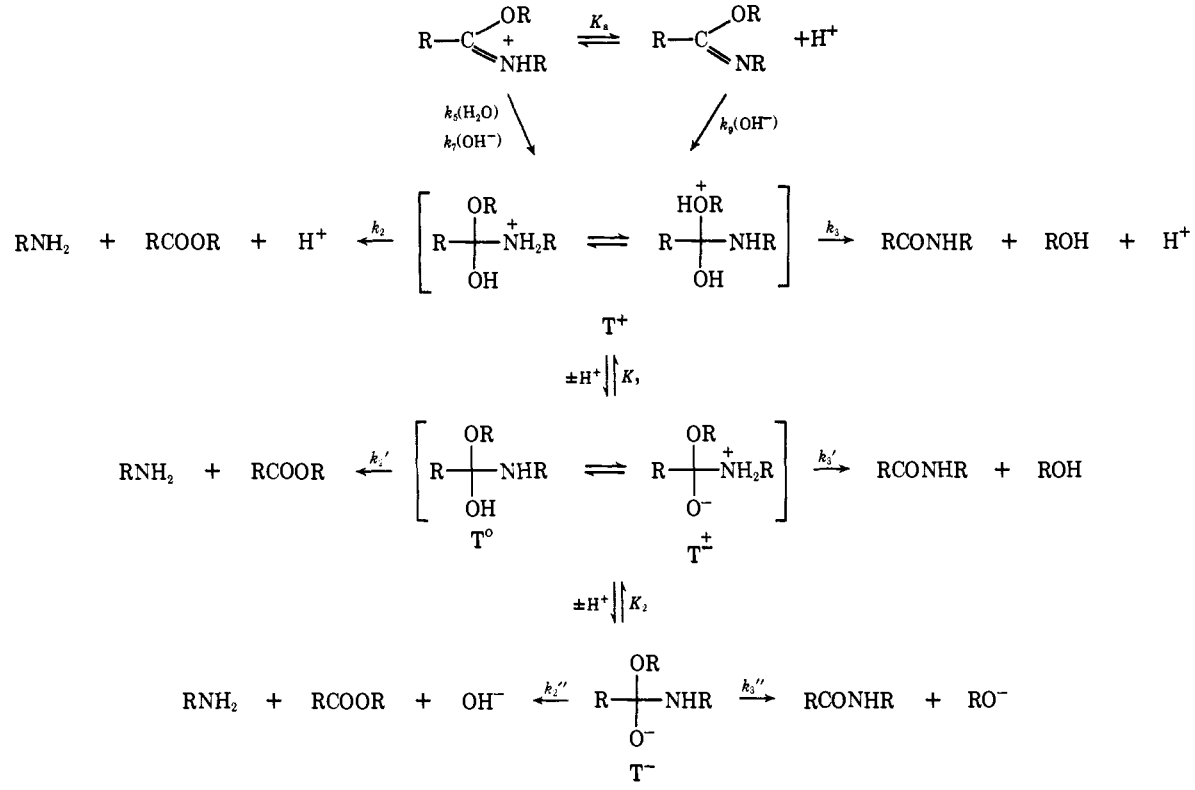


Table I. Rate and Equilibrium Constants for the Hydrolysis of Imidate Esters at 30° (μ = 0.5)

Compd	pK_a[a]	pK_a[b]	k_5, sec^{-1}	10^7k_7, M^{-1} sec^{-1}	k_9, M^{-1} sec^{-1}	$10^4(k_5/K_a)$, M^{-1} sec^{-1}	$10^3(k_7K_w/K_a)$,[c] sec^{-1}
I[d]	5.24[e]	3.74	3.5	0.495	0.001[f]	1.92	0.4
II[g]	4.53[e]	3.40	13.2	1.36	0.004	3.3	0.5
III[h]	3.92[e]	2.94	28.8	2.19	0.012	2.5	0.28
IV[d]	2.41[e]	2.05	175	4.2[i]	0.068	1.96	0.069[i]
V[d]	0.97[e]	(1.1)[j]	(3520)[j]	(76.2)[j]	0.51	4.4	0.14[i]
VI[d]	−4.53[k]				8.2	0.4	(0.01)[l]
VII[d]	−4.53[k]				6×10^{-4}	9×10^{-4}	(0.001)[l]
VIII[m]	−6.39[n]				25.2	1.5×10^{-5}	0.03[o]
IX[p]	0.97[e]	3.20	0.94			0.15	
X[q]	−10.10[k]				(0.14)[r]	1.5×10^{-4}	

[a] pK_a of aniline from which the imidates are derived. [b] pK_a of imidate esters, calculated from kinetic data. [c] pK_w = 13.83: H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 638. [d] 2% CH_3CN–H_2O. [e] At 30°: D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965. [f] Based on one point only. [g] 0.3% CH_3CN–H_2O at pH >4; 2% CH_3CN–H_2O at pH <4. [h] 0.3% CH_3CN–H_2O. [i] Approximate value. [j] Estimated (see text). [k] At 25 ± 3°; see ref 22. [l] Upper limit. [m] 1% CH_3CN–H_2O. [n] At 25°; see ref 21. [o] See Discussion. [p] 10% CH_3CN–H_2O. [q] 10% CH_3CN–H_2O, μ = 0.45, except for measurements in 0.88, 1.76, and 2.63 M HCl. [r] Position of attack by OH^- is not known.

of the hydrolysis of Δ^2-thiazolines[4,17] and Schiff bases[14] and which has been interpreted in terms of the existence of transient intermediates is much less pronounced with imidate esters[6,8,18] at pH 0–2, and its interpretation is equivocal. In the present study, rate measurements were generally not made below pH 1, with the exception of the trinitrophenyl iminolactone X.[19] In what follows, strong evidence will be given for the participation of intermediates in the hydrolysis of I–X, and they are therefore included in Scheme I. Since it is proposed that the formation of the intermediates is rate limiting, the kinetic properties of their decomposition are not reflected in the kinetics of disappearance of the imidate esters.

The theoretical curves which describe the pH–rate profiles were constructed by means of eq 1, the steady-

$$k_{obsd} = \frac{k_5[H^+] + k_7K_w + k_9K_a[OH^-]}{[H^+] + K_a} \quad (1)$$

state rate equation for Scheme I,[20] using the kinetic constants summarized in Table I. Not all the constants of eq 1 could be separately estimated for each compound. In particular, the rate of acid-catalyzed hydrolysis for five of the ten substrates could be ex-

(17) G. L. Schmir, *J. Amer. Chem. Soc.*, 87, 2743 (1965).
(18) R. B. Martin and A. Parcell, *ibid.*, 83, 4835 (1961).
(19) The rate of hydrolysis of X shows small negative deviations from a linear dependence on pH in solutions of 0.5–2.5 M HCl (about 40% in 2.5 M HCl). These could result from (a) the effect of increasing ionic strength, (b) a decrease in water activity, or (c) the inappropriate use of the H_0 function to correlate the rate data with acidity.

(20) The derivation of eq 1 includes the assumption that the rate-determining steps are the formation of the tetrahedral intermediates (present at steady-state concentration) at all pH, thus allowing the reverse reactions to reactants to be neglected.

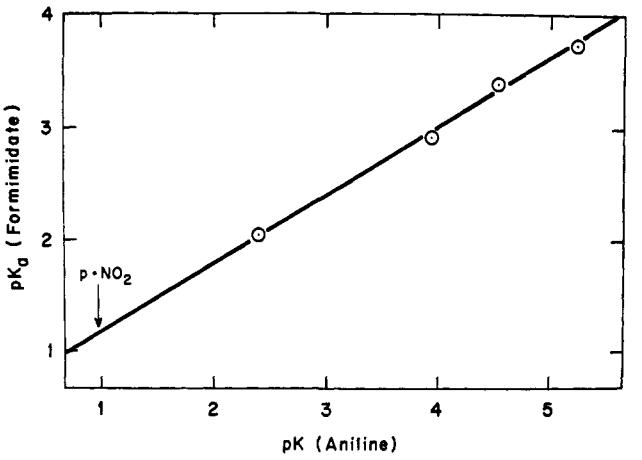


Figure 5. Linear dependence of pK_a of ethyl *N*-arylformimidates on pK_a of component aniline. Arrow indicates estimated pK_a for V.

pressed only as the second-order rate constant k_5/K_a since the value of pK_a was not obtained. In one instance (V), pK_a was estimated by means of a linear free-energy relationship (see below), thus allowing the calculation of k_5 and k_7. For all the substrates, eq 1 reduces to eq 2 since $[H^+] \ll K_a$ in the pH range where

$$k_{obsd} = \frac{k_5[H^+]}{[H^+] + K_a} + \frac{k_7K_w}{K_a} + k_9[OH^-] \qquad (2)$$

the reactions with hydroxide ion are important. From left to right, the terms on the right side of eq 2 represent the three kinetically distinct pathways, which are, respectively, attack of water on protonated imidate, attack of hydroxide ion on protonated imidate (or, less likely, reaction of water with the imidate free base), and reaction of hydroxide ion with imidate free base. With the least basic substrates, $[H^+] \ll K_a$ throughout the entire range of measurement, and eq 3 holds for the

$$k_{obsd} = k_5[H^+]/K_a + k_7K_w/K_a + k_9[OH^-] \qquad (3)$$

complete pH profiles. Reasonable agreement was obtained between calculated curves and experimental data in all cases.

The linear relationship (Figure 5) between pK_a for the formimidates I–IV and pK_a for the corresponding anilines (slope = 0.62) leads to an estimate of pK_a = 1.12 for the *p*-nitrophenylformimidate V. An independent estimate of pK_a = 1.05 for V may be made from the linear dependence (not shown) of pK_a for the formimidates on σ (using σ^- = 1.27 for the *p*-nitro substituent), with ρ = −1.78. Hammett plots for the processes represented by k_5, k_7, and k_9 are reasonably linear, with ρ = +1.77, 1.41, and 1.68, respectively, the estimated constants for the *p*-nitro derivative V falling on or near the straight lines defined by the other substituted formimidates (Figure 6).

The ratio k_7/k_5 varies systematically from 1.4×10^6 M^{-1} (with I) to 0.22×10^6 M^{-1} (with V). These values are among the lowest known for imidate esters[8] and, together with the low values of pK_a, are responsible for the observation that the pH-independent rate of hydrolysis at alkaline pH is so much smaller than the pH-independent rate in acid solution (*e.g.*, by six orders of magnitude with IV).

The Reaction Products. The initial products of hydrolysis of the imidate esters I–X were found to vary with pH, and, at constant pH, with buffer concentration, in complex and unexpected fashion. To establish, with good precision, the dependence of amine yield on pH alone, low concentrations (0.005–0.06 *M*) of buffers were employed, so that lengthy extrapolations to zero buffer concentrations would be avoided. The *N*-arylformimidates I–III were more sensitive to buffer effects than the imidate esters derived from less basic amines. Even with the former compounds, however, buffer effects were relatively small and reasonably accurate extrapolated values could be obtained.

The results of a large number of experiments, extrapolated to zero buffer concentration, are summarized

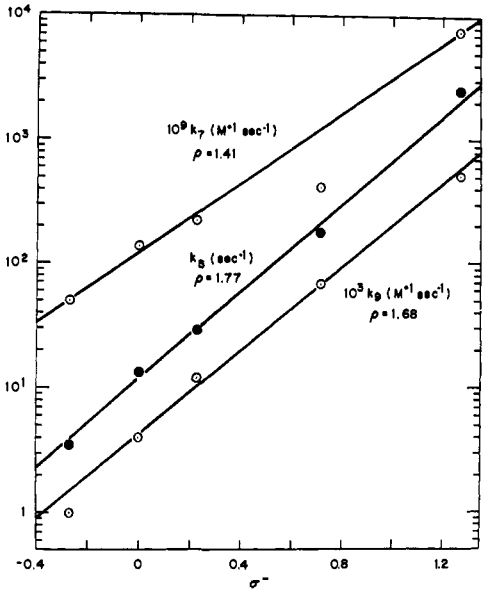


Figure 6. Hammett plots for reactions k_5, k_7, and k_9 (Scheme I).

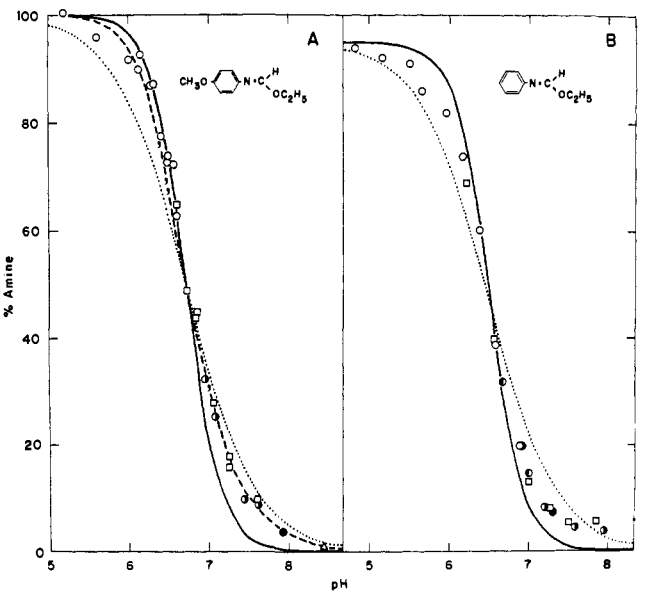


Figure 7. Effect of pH on the yield of amine obtained on hydrolysis of I and II. Buffers used: ○, MES; ◐, imidazole; □, β-dimethylaminopropionitrile; ◑, *N*-methylmorpholine; ●, *N*-ethylmorpholine; △, Tris. Solid and dotted lines are calculated from eq 4 and 5, respectively. Dashed line is calculated from eq 8, using constants given in the text.

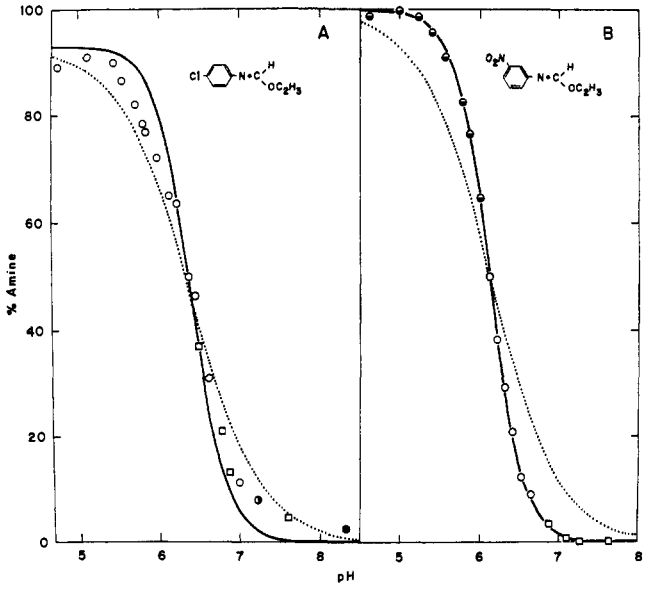


Figure 8. Effect of pH on the yield of amine obtained on hydrolysis of III and IV. Buffers used: ◒, pyridine; ○, MES; □, β-dimethylaminopropionitrile; ◑, *N*-methylmorpholine; ●, *N*-ethylmorpholine. Solid and dotted lines are calculated from eq 4 and 5, respectively.

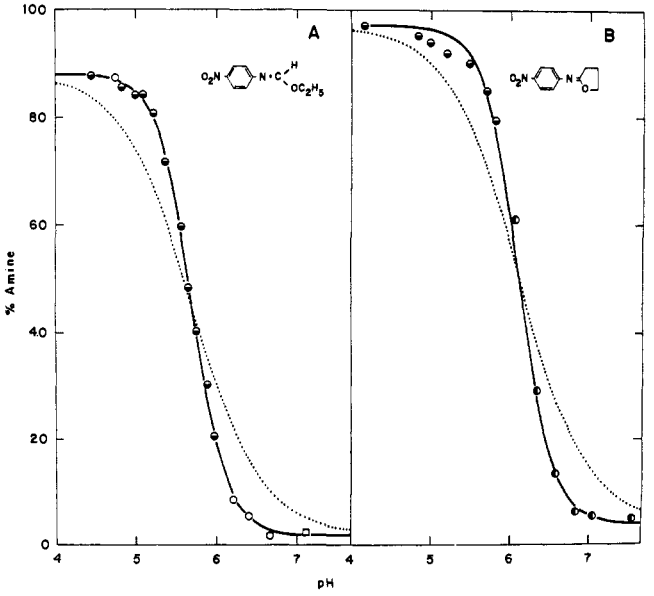


Figure 9. Effect of pH on the yield of amine obtained on hydrolysis of V and IX. Buffers used: ◒, pyridine; ◐, imidazole; ○, MES; □, β-dimethylaminopropionitrile. Solid and dotted lines are calculated from eq 4 and 5, respectively.

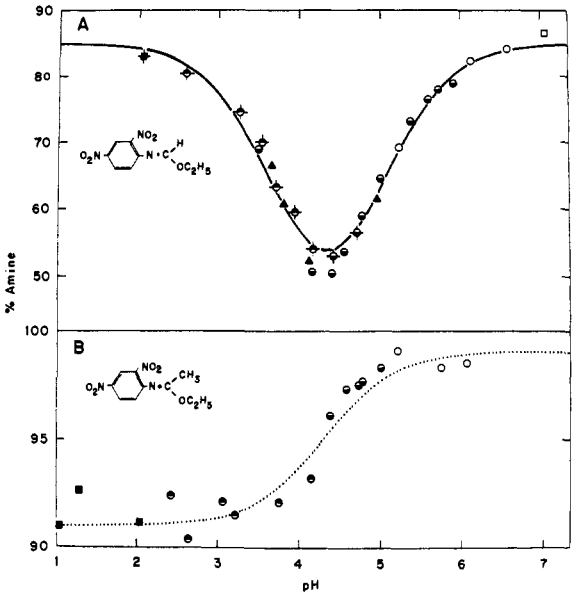


Figure 10. Effect of pH on the yield of amine obtained on hydrolysis of VI and VII. Buffers used: ■, HCl; ◓, triethylenediamine; ▲, acetate; ◒, pyridine; ○, MES; □, β-dimethylaminopropionitrile. With VI, experiments carried out with stopped-flow mixing are indicated by crosses superimposed on buffer symbol. For VI, curve is calculated from eq 8; for VII, curve is calculated ionization curve of monovalent acid. The values of the constants used are given in the text.

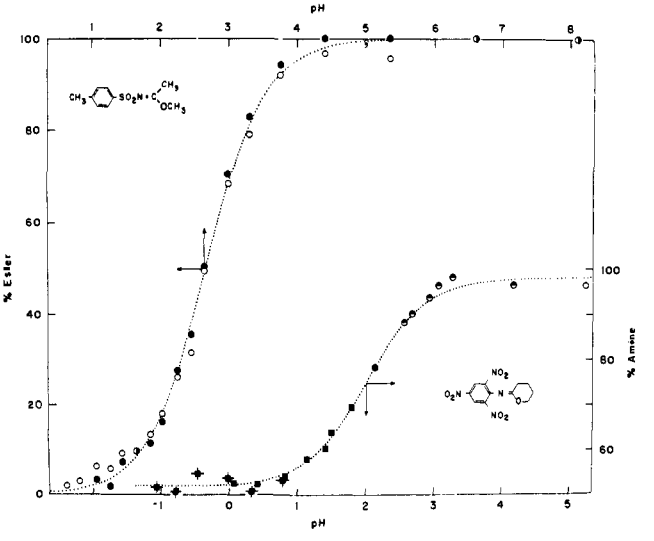


Figure 11. Effect of pH on the yield of amine or ester obtained on hydrolysis of VIII and X. VIII: ●, spectral analysis; ○, hydroxamic acid assay. X: buffers used were HCl (■), triethylenediamine (◓), MES (○). Experiments carried out with stopped-flow mixing are indicated by crosses superimposed on buffer symbol. Curves are calculated ionization curves of monovalent acids, using the constant given in the text.

in Figures 7–11. The effects of pH vary markedly in this series of imidate esters as the basicity of the resident amine is decreased. With imidates derived from moderately basic anilines, of pK_a = 1.0–5.2 (I–V, IX), amine yield *increases with decreasing pH*, in qualitative agreement with general experience of the behavior of imidates and thioimidates formed from aniline[6a,8,11] and more basic amines.[7–9,11] On the other hand, imidate esters (VIII, X) derived from the very weak bases *p*-toluenesulfonamide (pK_a = − 6.4)[21] and 2,4,6-trinitroaniline (pK_a = − 10.1)[22] produce *decreasing yields of amine as pH decreases.* Perhaps the most surprising behavior was noted with the two derivatives of 2,4-dinitroaniline (pK_a = − 4.5), the formimidate VI exhibiting a *minimum* at pH 4.5 in the product–pH profile, while the acetimidate VII showed only a small but apparently real decrease in amine yield from nearly 100 at pH >5 to about 91% at pH <3.

(21) P. O. I. Virtanen and K. Heinämäki, *Suom. Kemistilehti B*, **42**, 142 (1969).

(22) C. M. Rochester, "Acidity Functions," Academic Press, New York, N. Y., 1970, p 25.

With many imidate esters, increasing the concentration of amine buffers at constant pH results in modest increases in the yield of amine formed on hydrolysis of the imidate.[6,8] Similar observations were made here with formimidates I–III. Imidates derived from *p*-nitroaniline (V, IX) or 2,4-dinitroaniline (VI) showed small but definite *decreases in amine yield with increasing amine buffer concentrations.* These unusual buffer effects appear not to have been encountered previously and will be reported in detail in a subsequent publication.

It became apparent early in this investigation that, although formimidates I–V and the iminolactone IX yielded more amine at low pH than at higher pH, the dependence of amine yield on pH could not be satisfactorily correlated with the simple sigmoid function typical of the ionization of a monovalent acid. With the three nitro-substituted imidate esters IV, V, and IX, amine yield varied more rapidly with pH than expected and followed accurately eq 4 where Δ = increase in

$$\Delta/\Delta_{max} = [H^+]^2/([H^+]^2 + K) \quad (4)$$

amine yield over that produced asymptotically at high pH, and Δ_{max} = maximum increase in amine yield in going from high to low pH (Figures 8 and 9). The amine yield from the more basic formimidates I–III (Figures 7 and 8) varied with pH in a manner intermediate between that required by eq 4 and the first-order sigmoid expression (eq 5). An approximate

$$\Delta/\Delta_{max} = [H^+]/([H^+] + K) \quad (5)$$

empirical description of the dependence of amine yield on pH may be given by assuming that amine yield will in general follow the function of eq 6, from which the

$$\Delta/\Delta_{max} = [H^+]^n/([H^+]^n + K) \quad (6)$$

parameter n may be estimated as the slope of a linear plot (eq 7 and Figure 12). Values of $n = 2$ are ob-

$$\log [(\Delta_{max} - \Delta)/\Delta] = n\text{pH} - \text{p}K \quad (7)$$

tained for the *p*- and *m*-nitroimidates IV, V, and IX, the more basic imidates II and III giving $n = 1.4$ and 1.33, respectively. The plot of eq 7 for the *p*-methoxyphenylimidate I is distinctly curved, n varying from about 1.72 to 1.16 as pH is increased. While no precise mechanistic interpretation can be assigned to non-integral values of n, these plots may serve a useful descriptive function for the pH dependence of amine yield from *N*-arylformimidates. The pH values of the midpoint in the product transition (given by pK in eq 7) decrease regularly with decreasing pK_a of the amine portion of the imidates I–V (Table II).

Owing to the necessity of extrapolation to zero buffer concentration, some uncertainty exists in the exact shape of the product–pH profiles for imidates I–III, although it appears certain that a first-order sigmoid curve will not fit the data. Greater confidence may be attached to the experimental results for the nitroimidates IV, V, and IX; in particular, the *m*-nitrophenylimidate IV proved to be almost completely insensitive to buffer effects on amine yield, providing an unequivocal example of a second-order dependence on pH. It is noteworthy that the product transitions in the hydrolyses of the closely related imidate esters ethyl *N*-phenylacetimidate[8] and *N*-phenyliminotetrahydrofuran[6a] follow quite closely the simple sigmoid expression (eq 5).

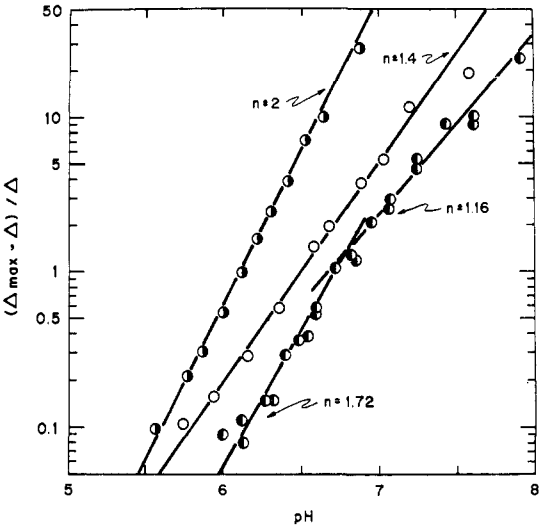


Figure 12. Plot of eq 7 for *N*-arylformimidates: ◐, *p*-methoxy (I); ○, unsubstituted (II); ◑, *m*-nitro (IV).

Table II. pH Values for Product Transitions in Hydrolysis of Imidate Esters

Imidate esters	Amine component	pK_a[a]	pK[b]
I	*p*-Methoxyaniline	5.24	6.72[c]
II	Aniline	4.53	6.50[c]
III	*p*-Chloroaniline	3.92	6.40[c]
IV	*m*-Nitroaniline	2.41	6.12[c]
V	*p*-Nitroaniline	0.97	5.70[c]
IX	*p*-Nitroaniline	0.97	6.10[c]
VI	2,4-Dinitroaniline	−4.53	3.70, 5.00[d]
VII	2,4-Dinitroaniline	−4.53	4.30
VIII	*p*-Toluenesulfonamide	−6.39	2.65
X	2,4,6-Trinitroaniline	−10.10	2.00

[a] pK_a of amine from which the imidate ester is derived; for literature sources, see Table I. [b] pH value for midpoint of product transition. [c] *Cf.* eq 6 and 7. [d] pK' and pK'' (eq 8).

For the least basic imidates VIII and X, the dependence of product yield on pH follows satisfactorily a normal sigmoid curve, with pK = 2.65 and 2.00, respectively; asymptotic values of amine yield, at low and high pH, respectively, are 1 and 100% with VIII, and 52 and 98% with X. The product data for the 2,4-dinitrophenylacetimidate ester VII are tentatively correlated with the same equation, with pK = 4.30, and asymptotes at 91 and 99% for low and high pH, respectively. Owing to the small differences in yields at low and high pH, and the lack of precision of the data, it cannot be excluded that an equation more complex than that for a simple sigmoid curve is required to account for the product data for VII.

The variation of amine yields with pH for the 2,4-dinitrophenylformimidate VI gives an acceptable fit to an equation formally equivalent to that for the ionization curve of a hypothetical divalent acid (eq 8),[11b]

$$\text{amine yield} = \frac{P^+ + (P^0K'/[H^+]) + (P^-K'K''/[H^+]^2)}{1 + (K'/[H^+]) + (K'K''/[H^+]^2)} \quad (8)$$

whose three ionic species form 2,4-dinitroaniline in yields of 85, 40, and 85%, respectively (P^+, P^0, and P^-); transitions between these species occur at pH 3.70

(= pK') and 5.00 (= pK''). It should be noted that a value of 40% must be assigned to the partitioning ratio of the intermediate form of the hypothetical acid, even though the lowest observed yield is 50%. This is the result of overlap between the two limbs of the inverse bell-shaped curve; for the same reason, the estimated values of pK' and pK'' are not identical with the midpoint of the ascending limbs of the experimental curve (Figure 10).

Discussion

Prior to the onset of this study, little information could be obtained from the literature concerning the effects of pH on the nature of the products of hydrolysis of imidate esters derived from amines less basic than aniline. It was known that treatment of the iminolactones IX and X with dilute aqueous sulfuric acid yielded the corresponding amines.[23] Whereas hydrolysis of the ethyl *N*-methyl-*N*-phenylformimidate cation gave only the aniline, a mixture of diphenylamine and of *N*,*N*-diphenylformamide was obtained from hydrolysis of the ethyl *N*,*N*-diphenylformimidate cation under the same conditions.[24] The results of hydrolysis studies on N-sulfonylated imidate esters are difficult to interpret quantitatively and appear to be conflicting; exposure of *N*-tosyl or *N*-nitrobenzenesulfonyl iminolactones to aqueous ethanol or to water was variously reported to yield the corresponding sulfonamide (C–N cleavage)[25] or *N*-acyl-*N*-sulfonylimine (C–O cleavage);[23a] similarly, treatment with sodium or potassium hydroxide in alcohol–water gave either the sulfonamide[23a,26] or the product of C–O cleavage.[27] *N*-Acylated imidate esters are hydrolyzed usually to diacylimines (C–O cleavage) with dilute aqueous or ethanolic acid,[28] or even on exposure to moist air,[29] but heating methyl *N*-ethoxalylbenzimidate in water gives methyl benzoate and ethyl oxamide (C–N cleavage).[28b] Hot water converts several N-phosphorylated formimidates to the corresponding *N*-formylphosphoramidates (C–O cleavage).[30]

The Reaction Mechanism. As in previous studies of the hydrolysis of imidate esters,[6-9,11,12a] the observation that the rates and products of hydrolysis of I–X are independent functions of pH provides compelling evidence for the participation of intermediates on the reaction pathway (Scheme I). The recent suggestion[13] that, although discrete intermediates are probably formed in the hydrolysis of *N*-arylformimidates at alkaline pH, they do not occur in hydrolysis under acidic conditions is incompatible with the present data. For example, with ethyl *p*-chlorophenylformimidate (III), the acid-catalyzed pathway ($k_5[H^+]/K_a$) still contributes 90% of the total rate of reaction at pH 7, but the yield of amine has fallen from 95% at low pH to 10% at pH 7. Similarly, the changes in amine yield with the dinitrophenylimidate VI and the trinitrophenyl iminolactone X occur in pH regions where the rate law for hydrolysis consists solely of the acid-catalyzed term. It thus appears that transient intermediates must be postulated for imidate ester hydrolysis at acidic as well as at alkaline pH.

According to Scheme I, the mechanism of imidate ester hydrolysis at pH >1 involves the rate-determining addition of water or hydroxide ion to yield cationic (T^+), neutral (T^0), and anionic (T^-) carbinolamines in acid–base equilibrium; the different pathways of decomposition of the three species of the intermediates are believed to account for the variation in the nature of the hydrolysis products with changing pH. A similar mechanism has previously been proposed for the hydrolyses of thioimidate esters[11b] and of phenyl *N*-methylacetimidate.[12a] As discussed earlier,[11b] the influence of pH on amine yield could equally well be explained in terms of anionic (T^-) and neutral (T^0) species, with the conversion of the latter to its zwitterionic form ($T^\pm$) requiring acid catalysis. The quantitative relationships between amine yield and pH are identical for the two proposals, and there recently has been obtained evidence that relatively slow proton transfers may play an important part in the interconversion of such unstable intermediates and hence in the mechanism of some acyl transfer reactions.[10,11b,31] Since the present study provides no information on the possible kinetic importance of proton transfer, we prefer to assume that the three intermediates are in equilibrium and that the factors controlling the product distribution are (a) the relative abundance of each of three species at a given pH, and (b) the pathway of breakdown of each species. In what follows, we attempt to rationalize the data of Figures 7–11 in terms of the structures of the imidate esters.

Effect of Structure and pH on the Reaction Products. Application of the steady-state approximation to Scheme I leads to eq 8[11b] for the dependence of amine yield on pH, where the constants are as defined in Table III.

Table III. Definitions of Parameters Used in Analysis of pH–Product Profiles for Imidate Ester Hydrolysis[a]

K'	$= (k_2' + k_3')K_1/(k_2 + k_3)$
K''	$= (k_2'' + k_3'')K_2/(k_2' + k_3')$
P^+	$= k_2/(k_2 + k_3)$
P^0	$= k_2'/(k_2' + k_3')$
P^-	$= k_2''/(k_2'' + k_3'')$

[a] Rate and equilibrium constants refer to steps of Scheme I.

P^+, P^0, and P^- are the partitioning ratios for each species of the intermediate, and pK' and pK'' represent the pH values where product formation undergoes a transition (these pH values in general being not equal to the dissociation constants of the intermediates). Depending upon the choice of values for the five constants, eq 8 may generate two consecutive simple sigmoid transitions,[11b] a bell-shaped curve (with a maxi-

(23) (a) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965); (b) A. S. Bailey and J. J. Merer, *J. Chem. Soc. C*, 1345 (1966).

(24) H. G. Nordmann and F. Kröhnke, *Angew. Chem., Int. Ed. Engl.*, 8, 984 (1969).

(25) (a) D. L. Rector and R. E. Harmon, *J. Org. Chem.*, **31**, 2837 (1966); (b) J. E. Franz, M. W. Dietrich, A. Henshall, and C. Osuch, *ibid.*, **31**, 2847 (1966).

(26) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *ibid.*, **25**, 970 (1960).

(27) P. Diedrich and M. Dohrn, German Patent 833,810 (1952); *Chem. Abstr.*, **47**, 1738 (1953).

(28) (a) H. L. Wheeler and P. T. Walden, *Amer. Chem. J.*, **19**, 129 (1897); (b) H. L. Wheeler, P. T. Malden, and H. F. Metcalf, *ibid.*, 20, 69 (1898); (c) I. Brown and O. E. Edwards, *Can. J. Chem.*, **43**, 1266 (1965).

(29) (a) W. J. Comstock and H. L. Wheeler, *Amer. Chem. J.*, **13**, 520 (1891); (b) H. Bader, *J. Org. Chem.*, **30**, 707 (1965).

(30) K. D. Berlin and M. A. R. Khayat, *Tetrahedron*, **22**, 975 (1966).

(31) (a) J. P. Fox, M. I. Page, A. Satterthwait, and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4729 (1972); (b) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).

mum or a minimum), or steep "sigmoid" transitions approaching the form of eq 4, as well as curves intermediate between eq 4 and the normal sigmoid expression (eq 5).

The amine yield from imidates I–V and IX increases with decreasing pH, but more steeply than predicted by the mechanism (involving neutral and anionic intermediates) first employed to describe the influence of pH on product distribution in imidate ester hydrolysis.[6a,8] Satisfactory theoretical curves can be computed to fit the data for the nitrophenylimidates IV, V, and IX if it is assumed that $P^+ = P^0 \simeq 0.9$–1.0, $P^- < 0.02$, and $pK' > pK''$. The latter requirement is equivalent to stating that alcohol expulsion occurs from the anionic species T^-, but that the release of amine takes place largely or exclusively from a cationic species, rather than from a neutral intermediate, which no longer contributes to product formation. Put another way, the addition or removal of up to two protons is necessary to divert the breakdown of the tetrahedral intermediate from formation of amide to that of amine. If the breakdown of T^0 in fact usually proceeds *via* the zwitterionic species $T^{\pm}$, it would be expected that strong electron withdrawal in the amine would decrease the proportion of neutral intermediate present as $T^{\pm}$, and thus favor product pathways involving T^+ and T^-. Qualitatively, the steepness of the product curves increases in going from the *p*-methoxy imidate I to the *m*- and *p*-nitro imidates IV, V, and IX, in accord with the above reasoning. Owing to the imprecision of the experimental data, it does not seem profitable to attempt exact fitting of the product curves for I–V to eq 8. To illustrate the potential application of eq 8 to such data, however, the dashed line of Figure 7 was computed from eq 8, with $P^+ = P^0 = 1.0$, $P^- = 0$, and $pK' = pK'' = 6.52$.

As the amine component of the formimidates I–V becomes more basic, amine is expelled over a larger range of pH, in preference to the departure of the alcohol fragment (Table II). This observation suggests that amine basicity is an important factor in controlling the pathway of intermediate decomposition with arylformimidates, although the effect is not large, since the midpoint of the product curves shifts by one pH unit only while amine basicity increases by 4.2 units. This trend is similar to that reported in the aminolysis of methyl formate,[7] although in the latter case, the transition pH increased by 2.1 units while amine basicity increased by 2.5 units. It is important to note that, in the present study, the alteration of amine basicity is accompanied by a partial change in mechanism (with respect to the ionic species of intermediate leading to product formation). A similar shift of one pH unit in the product transition occurs when the aniline portion of the iminolactone *N*-phenyliminotetrahydrofuran (product transition at pH 7.1)[6a] is replaced by *p*-nitroaniline (to give IX, product transition at pH 6.1). The aniline yield from the *N*-phenyl iminolactone follows a simple sigmoid curve (implying that amine is expelled from T^0 or $T^{\pm}$), while product formation from IX obeys a second-order dependence on pH (Figure 9). It is not clear why product formation from ethyl *N*-phenylacetimidate[8] conforms well to the first-order sigmoid (eq 4) with a product transition at pH 7.7, while the analogous formimidate (II) requires partial intervention of a cationic species for complete amine formation (Figure 7).

When the basicity of the resident amine is drastically reduced by tosylation, the pattern of product formation is reversed, amine expulsion becoming favored by all mechanisms at pH >3, while at lower pH, departure of methanol prevails, both processes proceeding equally well at pH 2.65. The yield of amine follows accurately a simple sigmoid curve and may be accounted for by a mechanism in which the neutral intermediate (probably in its uncharged form T^0) expels *p*-toluenesulfonamide anion ($pK_a = 10.2$)[32] in preference to methoxide ion ($pK_a = 15.5$),[33] while the protonated carbinolamine T^+ decomposes mainly by expulsion of methanol. As a result of electron withdrawal by the tosyl group, the nitrogen atom of the intermediate is no longer the most basic center of the molecule, its basicity (pK_a for protonation of *p*-toluenesulfonamide $= -6.4$)[21] having become approximately equal to that of ethereal oxygen (pK_a of diethyl ether $= -6.4$).[34] Clearly, leaving ability in an acid-catalyzed reaction is not determined only by the relative proton basicity of the potential leaving groups. This factor appears to be sufficiently important, however, to result in the favored departure of ethanol at low pH.[35]

An analogous explanation appears to hold for the trinitroimidate X. Anionic and neutral species would be expected to expel trinitroaniline anion ($pK_a = 12.2$)[36] rather than the alkoxide ion (pK_a *ca.* $= 16$), while the site of protonation in the cationic intermediate would probably again be oxygen in preference to nitrogen (pK_a for protonation of 2,4,6-trinitroaniline $= -10.1$).[22] Why does the proposed cationic intermediate decompose equally well to both products? Possibly, relief of steric strain induced by the bulky 2,6-substituted aniline enables expulsion of trinitroaniline to compete with that of the alcohol, even in the presence of acid catalysis.

It appears that neutral intermediates are capable of expelling leaving groups whose conjugate acids have pK_a no greater than 10–12 (toluenesulfonamide ion, trinitroaniline anion), without the necessity of the added driving force provided by ionization of T^0 to T^-, which is required for expulsion of the more basic alkoxide ions. This conclusion is supported by the known behavior of thioimidate esters[11b] and phenyl *N*-methylacetimidate,[12a] whose leaving groups of $pK_a = 9$–10 depart readily from neutral intermediates over a wide pH range beginning at pH 2–3.

The leaving ability of the 2,4-dinitrophenylamino group relative to that of the ethoxy group is weakly pH dependent. This might have been anticipated from the relative acidities of 2,4-dinitroaniline ($pK_a = 15.0$)[36] and ethanol ($pK_a = 16$),[33] as well as from their relative basicities ($pK_a = -4.5$ for dissociation of 2,4-dinitroanilinium ion[22] and -6.4 for protonated ethers[34]). With the dinitrophenylformimidate VI, the amine

(32) G. Dauphin and A. Kergomard, *Bull. Soc. Chim. Fr.*, 486 (1961).
(33) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960).
(34) D. G. Lee and R. Cameron, *Can. J. Chem.*, 50, 445 (1972).
(35) The observation (T. C. Pletcher, unpublished experiments) that the hydrolysis of p-$CH_3C_6H_4SO_2NHCOCH_3$ is subject to acid catalysis supports the assignment of the product transition in the hydrolysis of VIII to a cationic–neutral intermediate pair. The hydrolysis of the imide may be considered a model for the alcoholysis of the imide, which should proceed *via* the same intermediates as those formed in the hydrolysis of VIII.
(36) R. Stewart and J. P. O'Donnell, *Can. J. Chem.*, **42**, 1681 (1964).

moiety is somewhat the better leaving group by ratios of 6:1 at high and low pH and is slightly worse than ethanol in departing from a neutral intermediate (presumably in the form of T^0). No ready explanation is apparent for the minimum in the profile: a simplistic argument would suggest that if the amine anion is a better leaving group than ethoxide ion from T^-, then it should also compete favorably with ethoxide ion in the decomposition of T^0; on the other hand, since protonation to T^+ favors expulsion of the amine, breakdown of the neutral intermediate through the (unlikely) zwitterionic species $T^\pm$ should also lead to preferential amine formation. The observed complex influence of pH on product formation with VI suggests that, when the two potential leaving groups are of similar acidity and/or basicity, the delicate balance between their leaving abilities is easily altered by poorly understood factors.

The acetimidate VII exhibits a single transition only (at pH 4.3) which is tentatively assigned to the T^+–T^0 pair.[37] The neutral intermediate expels the amine essentially exclusively (>98%); protonation enhances somewhat the departure of ethanol, reducing the relative advantage of amine over alcohol from >50:1 to about 10:1. The disparity between these results and those for VI is puzzling and remains unexplained at present.

The Hydrolysis of Anilides. The nucleophilic reaction of alcohols with anilides may result in the formation of tetrahedral intermediates identical with or similar to those formed on hydration of imidate esters. If this is the case, it would be expected that the alcoholysis (and, by extension, the hydrolysis) of anilides derived from *p*-nitro and more basic anilines would occur with a change in rate-limiting step at pH 6–7. The rate-determining step at lower pH would be attack of alcohol or water, since expulsion of the aniline from the intermediate is fast relative to return of the intermediate to reactants; at higher pH, expulsion of the amine becomes rate limiting. The expected change in rate-limiting step has already been noted at pH 7 for the intramolecular alcoholysis of 4-hydroxybutyranilide;[38] a recent report describes the occurrence of the similar transition at pH 6 in anilide hydrolysis,[39a] in addition to the well-established second change in rate-limiting step which occurs at higher pH.[39b]

Anilides derived from di- and trinitroanilines would not be expected to exhibit the high pH transition, since the latter has been interpreted to reflect a change from rate-determining breakdown of intermediates (slow release of amine) to rate-limiting attack of hydroxide ion (rapid expulsion of amine). With the polynitro-substituted anilides, conversion of the intermediates to aniline by all mechanisms is fast at pH >6; the added driving force introduced by hydroxide ion catalysis of the breakdown of the monoanionic intermediate[39b] should not be visible in the kinetics of the reaction.[40]

Structure–Reactivity Relationships. The dependence of the reaction rates on substituent for the three kinetically distinct processes k_5, k_7, and k_9 (Scheme I) offers support for the postulated mechanism. The ρ value of +1.77 for attack of water on the protonated imidates is consistent with the destabilizing influence of electron-withdrawing substituents on a potential carbonium ion center and may be compared with ρ values of +1.71, +1.1, +1.99, and +1.5 previously reported for the reaction of water with protonated benzaldehyde[41a] and benzophenone Schiff bases,[41b] 2-phenyl-Δ^2-thiazolines,[17] and ethyl *N*-arylacetimidates, respectively.[13] For the pH-independent process at alkaline pH, the assignment of a mechanism involving reaction of hydroxide ion with protonated substrate (rather than the kinetically equivalent reaction of water with the imidate free base) is analogous to earlier suggestions[14] and is in accord with a ρ value of 1.41 for the process k_7 with formimidates I–V. For the analogous reaction, values of ρ = +1.26, +1.8, and +0.8 have been found with benzaldehyde[41a] and benzophenone[41b] Schiff bases, and Schiff bases derived from aniline.[16b] The reaction of hydroxide ion with the imidate free bases exhibits ρ = 1.68; presumably, electron withdrawal in the aniline portion of the formimidates stabilizes the developing negative charge on the nitrogen atom. This value is in accord with that of +1.7 reported[13] for the same reaction in 20% dioxane–water and may be compared with ρ = +2.6–2.7 for a series of benzaldehyde Schiff bases derived from substituted anilines.[16c,42]

Some interesting comparisons of relative reactivity emerge from the data of Table I. For example, the fully protonated formimidate II reacts with water 1750 times faster than the analogous acetimidate;[8] the same comparison between Δ^2-thiazoline and 2-methyl-Δ^2-thiazoline gave a rate ratio of 320.[17] The dinitrophenylacetimidate VII is 60 times more reactive to acid-catalyzed hydrolysis (comparison of k_5/K_a values) than the *N*-tosylacetimidate VIII; the tosyl compound is, however, 42,000 times more reactive than VII to attack of hydroxide ion on the free base (k_9), reflecting in part the much greater stabilization of the developing negative charge by the tosyl substituent.

The pH-independent reaction of the N-tosylated acetimidate VIII probably represents a rare example of the reaction of water with the neutral imidate, rather than the reaction of hydroxide ion with protonated imidate, favored for other, more basic substrates. Assumption of $pK_a = 0$ for VIII as an upper limit leads to $k_7 = 2 \times 10^9\ M^{-1}\ sec^{-1}$, perilously close to the diffusion-controlled limit. Since the pK_a for VIII is almost certainly lower than 0, k_7 would exceed the rate of diffusion of the reactants. The same calculation for the *p*-nitro imidate V gives $k_7 = 0.76 \times 10^9\ M^{-1}\ sec^{-1}$; since the Hammett plot for k_7 (Figure 6) shows no evidence for curvature at high σ,[43] it is probable that protonated V is still reacting with hydroxide ion. A

(37) The product transition at pH 6.7 in the formimidate II is shifted to 7.7 in the corresponding acetimidate.[8] It thus appears likely that the T^-–T^0 transition at pH 3.70 (in the hydrolysis of the formimidate VI) should be shifted to somewhat higher pH with VII.

(38) B. A. Cunningham and G. L. Schmir, *J. Amer. Chem. Soc.*, **89**, 917 (1967).

(39) (a) S. O. Eriksson and U. Meresaar, *Acta Chem. Scand.*, **25**, 2688 (1971); (b) for a review, see S. O. Eriksson, *Acta Pharm. Suecica*, **6**, 139 (1969).

(40) The same reasoning applies to the hydrolysis of *p*-$CH_3C_6H_4SO_2NHCOCH_3$ at the acyl carbon atom. Rate-limiting expulsion of *p*-toluenesulfonamide at pH <2 should give way to rate-limiting formation of intermediates at all pH above 3. It is therefore expected that the substrate should undergo extensive carbonyl-^{18}O exchange at pH <2.

(41) (a) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **85**, 2843 (1963); (b) K. Koehler, W. Sandstrom, and E. H. Cordes, *ibid.*, **86**, 2413 (1964).

(42) A replot of the rate constants published by Archilar, *et al.*,[16c] using σ^- constants for the *p*-NO_2 substituent (instead of σ) gives ρ = +1.7.

(43) The value of k_7 for the *m*-nitro imidate IV is of low accuracy.

change in mechanism (to reaction of the free base with water) may occur with imidates slightly less basic than V.

Experimental Section[44]

Ethyl *N*-phenylformimidate (II) was prepared by the method of Roberts and Vogt[45] and had bp 118.0–118.5° (40 mm) (lit.[45] bp 117–118° (40 mm)); uv max (CH_3CN) 246 mμ (ε 6400); ir (thin film) 6.10 μ; nmr ($CDCl_3$) δ 1.34 (t, 3, CH_3), 4.30 (q, 2, CH_2), 7.66 (s, 1, formyl). The following imidate esters were also synthesized by this method. **Ethyl *N*-*p*-methoxyphenylformimidate (I)**: bp 164–166° (40 mm); uv max (CH_3CN) 258 mμ (ε 11,000); ir (thin film) 6.08 μ; nmr ($CDCl_3$) δ 1.33 (t, 3, CH_3), 3.75 (s, 3, OCH_3), 4.32 (q, 2, CH_2), 6.85 (s, 4, aromatic H), 7.66 (s, 1, formyl); mass spectrum: molecular ion at *m/e* 179. **Ethyl *N*-*p*-chlorophenylformimidate (III)**: bp 150–153° (40 mm) (lit.[46] bp 112° (4.9 mm)); uv max (CH_3CN) 248 mμ (ε 10,800); ir (thin film) 6.06 μ; nmr ($CDCl_3$) δ 1.33 (t, 3, CH_3), 4.32 (q, 2, CH_2), 7.66 (s, 1, formyl).

Ethyl *N*-2,4-Dinitrophenylformimidate (VI). After removal of ethanol by distillation, the reaction mixture was cooled and the residue was suspended in petroleum ether. Most of the suspended solid went into solution upon careful addition of benzene. The insoluble residue was removed by filtration; on keeping the filtrate in the cold, the crystalline product deposited slowly and was recrystallized from benzene–petroleum ether: mp 37–38°; uv max (CH_3CN) 302 mμ (ε 13,300); ir (thin film) 6.10 μ; nmr ($CDCl_3$) δ 1.40 (t, 3, CH_3), 4.43 (q, 2, CH_2), 7.75 (s, 1, formyl); mass spectrum, molecular ion at *m/e* 239. *Anal.* Calcd for $C_9H_9N_3O_5$ (239.19); C, 45.19; H, 3.79; N, 17.56. Found: C, 44.46; H, 3.77; N, 17.56.

Ethyl *N*-2,4-dinitrophenylacetimidate (VII) was prepared as above with the use of triethyl orthoacetate. After distillation of ethanol, the cooled residue was suspended in benzene and filtered to remove a considerable quantity of 2,4-dinitroaniline. The crystalline product was obtained on addition of petroleum ether to the filtrate and had mp 81–83° after recrystallization from benzene–petroleum ether: uv max (CH_3CN) 306 mμ (ε 13,200); ir (Nujol mull) 5.93; μ; nmr ($CDCl_3$) δ 1.45 (t, 3, CH_2CH_3), 2.10 (s, 3, C–CH_3), 4.52 (q, 2, CH_2); mass spectrum, molecular ion at *m/e* 253. *Anal.* Calcd for $C_{10}H_{11}N_3O_5$ (253.22): C, 47.43; H, 4.36; N, 16.59. Found: C, 47.50; H, 4.36; N, 16.62.

Ethyl *N*-*m*-nitrophenylformimidate (IV) was prepared according to the general procedure of Janiak and Dittrich.[47] A mixture of 13.8 g (0.1 mol) of *m*-nitroaniline and 38 g (0.25 mol) of triethyl orthoformate in 100 ml of acetonitrile containing 0.2 ml of ethanol saturated with gaseous HCl was heated at reflux for 5 hr. After cooling and removing insoluble material by filtration, the product was obtained by vacuum distillation: bp 122–123° (0.4 mm); uv max (CH_3CN) 238 mμ (ε 16,800), shoulder at 315 (2300); ir (thin film) 6.06 μ; nmr ($CDCl_3$) δ 1.37 (t, 3, CH_3), 4.37 (q, 2, CH_2); mass spectrum, molecular ion at *m/e* 194. *Anal.* Calcd for $C_9H_{10}N_2O_3$ (194.19): C, 55.66; H, 5.19; N, 14.43. Found: C, 55.60; H, 5.30; N, 14.27.

Ethyl *N*-*p*-nitrophenylformimidate (V) was obtained by the method used for IV, except that the residue, after removal of solvent *in vacuo*, was taken up in benzene and filtered. Addition of petroleum ether to the filtrate gave the crystalline product, which was recrystallized from benzene–petroleum ether: mp 67–69°; uv max 309 mμ (ε 14,000); nmr ($CDCl_3$) δ 1.37 (t, 3, CH_3), 4.34 (q, 2, CH_2), 7.66 (s, 1, formyl); mass spectrum, molecular ion at *m/e* 194. *Anal.* Calcd for $C_9H_{10}N_2O_3$ (194.19): C, 55.66; H, 5.19; N, 14.43. Found: C, 55.38; H, 5.05; N, 14.73.

This compound is rather unstable, and appears to be easily converted on standing in the solid state, or, more rapidly, in chloroform solution, to *N,N'*-di-*p*-nitrophenylformamidine, mp 249–250° (lit.[48] mp 243°), mass spectrum, molecular ion at *m/e* 286.

Methyl *N*-*p*-toluenesulfonylacetimidate (VIII)[49] had mp 73–74° (lit.[49] mp 74–75°), uv max (CH_3CN) 227 mμ (ε 14,700), ir (Nujol mull) 6.20 μ.

***N*-(Dihydro-2[3*H*]-furylidene)-*p*-nitroaniline (IX). A. 4-Chlorobutyryl-*p*-nitroanilide.** To a solution of 7.2 g (0.05 mol) of 4-chlorobutyryl chloride in 10 ml of tetrahydrofuran kept at 0° was added dropwise a solution of 13.8 g (0.1 mol) of *p*-nitroaniline in 50 ml of tetrahydrofuran. The reaction mixture was stirred for an additional 15 min at 0° and for 1 hr at room temperature. After filtration and removal of the solvent *in vacuo*, the crystalline residue was recrystallized from ethyl acetate–petroleum ether to give 8.1 g (66%) of pale yellow crystals: mp 99°, uv max (CH_3CN) 317 mμ (ε 14,800), ir ($CHCl_3$) 5.85 μ. *Anal.* Calcd for $C_{10}H_{11}ClN_2O_3$ (242.68): C, 49.48; H, 4.56; N, 11.55; Cl, 14.62. Found: C, 49.58; H, 4.75; N, 11.66; Cl, 14.32.

B. The iminolactone IX was prepared in 53% yield by treatment of 4-chlorobutyryl-*p*-nitroanilide with silver tetrafluoroborate as described[6a] for the analogous aniline derivative. After work-up, the oily residue was crystallized from ether–petroleum ether and had mp 67–68° (lit.[23a] mp 62–65°); uv max (CH_3CN) 318 mμ (ε 14,500); ir ($CHCl_3$) 5.92, 6.64, 7.50 μ (lit.[23a] ir (KBr) 5.97, 6.67, 7.48 μ); mass spectrum: molecular ion at *m/e* 206.

2,4,6-Trinitro-*N*-(tetrahydro-2*H*-pyran-2-ylidene)aniline (X),[23b] prepared from picryl azide[50] and 2,3-dihydropyran, had mp 165–166° (lit.[23b] 162–163°); uv max (CH_3CN) 297 mμ (ε 12,400); ir (Nujol mull) 5.92 μ (lit.[23b] 5.93 μ). **2,4,6-Trinitroacetanilide**[51] was prepared from 2,4,6-trinitroaniline.[52] **2,4-Dinitroformanilide**[53] had mp 166–168° (lit.[53] mp 163–164°). **2,4-Dinitroacetanilide,**[54] obtained by heating 2,4-dinitroaniline with acetic anhydride–sulfuric acid, had mp 123–124° (lit.[55] mp 121°). ***N*-Acetyl-*p*-toluenesulfonamide,**[56] recrystallized from ethyl acetate–cyclohexane, had mp 137° (lit.[56] 137°), ir (Nujol mull) 5.80 μ.

4-Hydroxybutyryl-*p*-nitroanilide was prepared by reduction of *N*-*p*-nitrophenylsuccinimide[57] according to the method of Horii, *et al.*[58] To a solution of 5.4 g (0.024 mol) of the succinimide in 45 ml of methanol containing 2 drops of 1 *N* aqueous NaOH was added dropwise, at 0° and with stirring, a solution of 2.3 g (0.06 mol) of sodium borohydride in 45 ml of methanol containing 2 drops of 1 *N* aqueous NaOH. The mixture was stirred for 6 hr at 0–4°, then overnight at room temperature. The reduction sequence was repeated twice more as above with fresh portions of methanolic sodium borohydride solution. Excess reducing agent was destroyed by the dropwise addition of 25 ml of 50% methanolic acetic acid. The solid residue obtained after removal of solvent *in vacuo* was triturated with anhydrous ether. After drying the ethereal phase with $MgSO_4$, addition of petroleum ether yielded pale yellow crystals, which were recrystallized from ether–petroleum ether: mp 110–111°, yield 25%; uv max (CH_3CN) 319 mμ (ε 13,900); ir ($CHCl_3$) 2.9 (OH), 5.90 μ (carbonyl). *Anal.* Calcd for $C_{10}H_{12}N_2O_4$ (224.22): C, 53.56; H, 5.40; N, 12.50. Found: C, 53.75; H, 5.45; N, 12.55.

Kinetic Measurements. Acetonitrile and imidazole were purified as previously described.[6a] Pyridine, β-dimethylaminopropionitrile, *N*-methylmorpholine, and *N*-ethylmorpholine were distilled prior to use. Other 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 kinetic studies was water containing small amounts of acetonitrile, at ionic strength usually 0.5, adjusted with added KCl. Exact solvent compositions are given in Table I. Buffers used were HCl, triethylenediamine, acetate, pyridine, 2-morpholinoethanesulfonate (MES), imidazole, β-dimethylaminopropionitrile, *N*-methyl- and *N*-ethylmorpholine, Tris, borate, carbonate, and sodium hydroxide, as appropriate, concentrations generally varying from 0.02 to 0.04 *M*, except for NaOH solutions. Substrate concentration was usually $0.5–2 \times 10^{-4}$ *M*. Selection of wavelengths at which to follow absorbance changes depended on

(44) Melting points are uncorrected. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. An A.E.I. MS-9 mass spectrometer operating at an ionizing potential of 70 eV was used to obtain mass spectra.

(45) R. M. Roberts and P. J. Vogt, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 464.

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(58) Z. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, **26**, 2273 (1961).

the nature of the reaction products and sometimes varied with pH. With slow reactions, preliminary scans of the ultraviolet spectra of the reaction mixtures were carried out as a function of time to determine wavelength regions where relatively large changes in absorbance occurred. The following wavelengths were used (the pH range and whether absorbance increased or decreased is indicated): I, 260 mμ (pH <6.5, decrease), 265 (pH 6.9, decrease), 235 (pH >7, increase); II, 255 mμ (pH <6.5, decrease), 238 (pH >6.5, increase); III, 240–243 mμ (increase); IV, 238 mμ (increase); V, 360 mμ (increase), 343 (pH >10, increase); VI, 345 mμ (increase; this is the only substrate with which pyridine buffers were used); VII, 400 mμ (increase); VIII, 242 mμ (decrease); IX, 390 mμ (increase); X, 415 mμ (increase). Slow reactions ($t_{1/2}$ > 5 sec) were generally followed in stoppered quartz cuvettes inserted in a water-jacketed cell holder, using a Cary Model 15 spectrophotometer, equipped with automatic sample changer assembly, or with a Zeiss PMQ II spectrophotometer. Faster reaction rates were determined with a Durrum–Gibson stopped-flow spectrophotometer, with a 20-mm light path.

Fast and moderately slow reactions were followed to completion and rate constants were calculated by means of the integrated first-order rate equation. Rate constants for very slow reactions were calculated by means of the Guggenheim procedure[59a] or of a modified Guggenheim treatment.[59b,c]

With the exception of the nitro-substituted imidates, the anilides produced on hydrolysis were essentially stable to further reaction during the time necessary for complete hydrolysis of the imidate esters. *p*-Nitroformanilide is fairly rapidly hydrolyzed at pH >10;[60] to avoid complications resulting from this secondary hydrolysis, the disappearance of V at pH >10 was followed at an isosbestic point for the spectra of *p*-nitroformanilide and *p*-nitroaniline (343 mμ). With the 2,4-dinitrophenylformimidate VI, the rate of hydrolysis of the imidate ester is much greater than that of 2,4-dinitroformanilide at pH <7; at pH >8, the anilide is hydrolyzed at least ten times faster than the imidate, so that the rate of appearance of 2,4-dinitroaniline at 345 mμ is a measure of the rate of hydrolysis of VI. Only at pH 7–8 are the reaction rates of VI and of the anilide of comparable magnitude; since the immediate products of hydrolysis of VI at pH 7–8 consist of at least 85% 2,4-dinitroaniline, the single rate constant determined in that pH range is probably not seriously affected by further hydrolysis of the small amount of anilide produced. In the case of VII, the rate of hydrolysis of the imidate ester is much greater than that of the corresponding anilide at pH <6; at pH 12, the anilide is hydrolyzed 30 times faster than VII, and at pH 13, 4 times faster. In the latter experiments, however, the product of hydrolysis of VII is probably exclusively 2,4-dinitroaniline, and hence competing hydrolysis of 2,4-dinitroacetanilide does not complicate the determination of the rate constants for VII.

At pH >7, the predominant product of hydrolysis of IX is 4-hydroxy-*p*-nitrobutyranilide, whose ultraviolet spectrum is closely similar to that of IX. At pH >7, rate constants for the disappearance of IX were determined by acidifying aliquots of the reaction mixture with 1 *M* phosphate buffer (pH 2.2) and measuring the concentration of *p*-nitroaniline produced by immediate hydrolysis of residual IX.

For experiments using the stopped-flow spectrophotometer, solutions of I–IV in 4% acetonitrile–0.001*M* borate buffer (μ = 0.5, pH 9) were prepared immediately before use and mixed with an equal volume of the desired aqueous buffer solution (0.04 *M*, μ = 0.5) after temperature equilibration for a few minutes at 30°. The half-lives for hydrolysis of I–IV in the borate buffer varied from 20 to 65 min. The stock solution of VI was prepared in 0.001*M* *N*-ethylmorpholine buffer (pH 8), where the half-life for imidate hydrolysis was about 3 hr, the solution of IX was prepared in 0.001 *M* MES buffer (pH 7), and the solutions of X were prepared in β-dimethylaminopropionitrile buffer (0.004 *M*, pH 7), where X is quite stable ($t_{1/2}$ ~ 7 days).

The hydrolysis of X at pH >12 appears to be complex. Spectral scans disclosed that at least two consecutive processes occurred since isosbestic wavelengths shifted gradually during the course of the reaction. Estimates of a second-order rate constant of about 0.14 M^{-1} sec^{-1} were made for the reaction of X with hydroxide ion in the initial, relatively rapid reaction. In 0.1 *N* NaOH, the reaction product(s) undergoes a second reaction, with k_{obsd} ~ 2.3 × 10^{-4} sec^{-1}, about 2.5 times faster than the rate of disappearance of 2,4,6-trinitroaniline under the same conditions (k = 0.9 × 10^{-4} sec^{-1}). The reactions of X, of its initial hydrolysis product, and of trinitroaniline may well represent nucleophilic addition of hydroxide ion to the activated aromatic ring.[61]

Product Analysis. The extent of C–N bond cleavage occurring during the hydrolysis of imidate esters I–X was usually determined by measuring amine yield either by direct spectral examination of the reaction mixture or by colorimetric assay of the amine produced. With VIII, the alternate product of C–N bond fission, methyl acetate, was also determined. Product analysis was performed after 8 to 10 half-lives of reaction on reaction mixtures identical with those used in the kinetic studies. Occasionally, higher substrate concentrations were used, when the yield of the product being measured was low.

A. Aniline was determined colorimetrically by means of a modification of the Bratton–Marshall procedure.[6]

B. *p*-Anisidine was determined by the method used for aniline, except that color development was allowed to proceed for 25 hr at 30°. The absorbance of the resulting blue solution was read at 575 mμ. A 1-ml aliquot of a solution containing *p*-anisidine at 1 × 10^{-4} *M* gave an absorbance of 0.44. Standard curves were based on *p*-anisidine hydrochloride, recrystallized from ethanol, mp 220–222°.

C. *p*-Chloroaniline was determined by the method used for aniline, except that color development was complete in 10–15 min. A 1-ml aliquot (1 × 10^{-4} *M*) gave an absorbance of 0.64 at 546 mμ.

D. Spectral Analysis. 1. Slow Reactions. Standard curves based on mixtures of the aniline and the corresponding anilide were used to determine the concentration of amine formed in imidate hydrolysis. The wavelengths and molar extinction coefficients used were: I, 260 mμ (anisidine, ε 8700; *p*-methoxyformanilide, ε 660); IV, 400 mμ (*m*-nitroaniline, ε 870; *m*-nitroformanilide, ε 34); V, 420 mμ (*p*-nitroaniline, ε 6500; *p*-nitroformanilide, ε 58); VI 420 and 295 mμ (2,4-dinitroaniline, ϵ_{420} 5160, ϵ_{295} 3120; 2,4-dinitroformanilide, ϵ_{420} 88, ϵ_{295} 11,500); VII, 420, 295 mμ (2,4-dinitroacetanilide, ϵ_{420} negligible, ϵ_{295} 9500); VIII, 242 mμ (*N*-acetyl-*p*-toluenesulfonamide, ε 3900; *p*-toluenesulfonamide, ε 670); IX, 390 mμ (*p*-nitroaniline, ε 13,800; 4-hydroxy-*p*-nitrobutyranilide, ε 600); X, 415 mμ (2,4,6-trinitroaniline, ε 8600; 2,4,6-trinitroacetanilide (model for 5-hydroxy-2′,4′,6′-trinitrovaleranilide), ε negligible).

Pyridine buffers (0.02–0.10 *M*) cause no (<1%) detectable change in the molecular extinction coefficient of *p*-nitroaniline, suggesting that the decrease in aniline yield observed with V and IX is not the result of some form of complex formation between *p*-nitroaniline and buffer components.

2. Fast Reactions. With VI (at pH <4.7) and with X (in HCl solution, 0.2–3.5 *M*), amine yield was calculated directly from the oscilloscope trace of the final absorbance of the reaction mixture in the stopped-flow spectrophotometer. Good agreement was obtained in those pH regions where the results of manual mixing could be compared to those of mixing in the Durrum–Gibson apparatus (with half-lives of 0.5–5 sec). The stabilities of VI ($t_{1/2}$ = 3 hr) and X ($t_{1/2}$ = 7 days) in their respective buffered stock solutions were sufficiently high that negligible hydrolysis in the environment of the stock solution took place during the time used for temperature equilibration and the necessary manipulations prior to mixing.

3. Complete Spectra. In several cases, the identity of the reaction products was verified by comparison of the complete ultraviolet spectra of reaction mixtures to those of mixtures containing the expected products at the concentration determined by analysis. With X, 2,4,6-trinitroacetanilide was used to replace the unavailable 5-hydroxy-2′,4′,6′-trinitrovaleranilide. Examples were: IX at pH 2.5 (96% amine), 5.45 (84% amine), 6.10 (35% amine), 7.55 (4.5% amine); X at pH 1.7 (70% amine), 2 *N* HCl (56% amine); IV at pH 6.12 (50% amine); VI at pH 3.8 (60% amine). Good agreement was found in all cases.

E. Methyl acetate was determined by reaction with hydroxylamine.[8] Prior to assay, reaction mixtures in HCl solutions were approximately neutralized by addition of 0.5 *N* NaOH. Acetate and formate buffers at >0.02 *M* interfered with this assay; in such cases, aliquots were diluted 1:5 with water prior to reaction with hydroxylamine. A 2-ml aliquot containing methyl acetate at 1 × 10^{-3} *M* gave an absorbance of about 0.45; under the same conditions, *N*-acetyl-*p*-toluenesulfonamide gave less than 0.01 ab-

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(60) R. H. DeWolfe and R. C. Newcomb, *J. Org. Chem.*, **36**, 3870 (1971).

(61) See C. F. Bernasconi, *J. Amer. Chem. Soc.*, **92**, 4682 (1970), footnote 4, for references to recent reviews of nucleophilic aromatic substitution.

sorbance. To avoid prior neutralization, a modified procedure was also used for reactions at pH 0.6–2.0. To a 2-ml aliquot of reaction mixture was added 1 ml of a solution made up from 4 *M* hydroxylamine hydrochloride and 3.5 *M* NaOH (1:2). After 10 min at 30°, 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. When the yield of methyl acetate was low, cells of 5-cm light path were used.

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Camphene Racemization. III. The *endo*-Methyl Migration Problem[1]

Carl W. David,[2] Bruce W. Everling,[2] Robert J. Kilian,[1] J. B. Stothers,[3] and Wyman R. Vaughan*[2]

Contribution from the Departments of Chemistry of The University of Connecticut, Storrs, Connecticut 06268, and The University of Western Ontario, London, Ontario, Canada. *Received April 7, 1972*

Abstract: By means of ^{13}C labeling at the 8 position of camphene, it has been possible to effect simultaneous analysis by nmr for the amount of the isotope label at each of the possible positions (8, 9, and 10) after partial racemization. With these data it is possible to make full use of integrated rate equations developed earlier and thus obtain a more precise and significant value for the extent of *endo*-methyl migration during racemization. It is also possible to provide reasonably exact rate constants for all of the various processes contributing to racemization, including tricyclene formation. The *endo*-methyl migration appears to be very small: certainly less than 5% (as compared with the previously reported 22%) but very likely not actually zero.

The use of isotopic labeling to help elucidate the mechanism (or mechanisms) of racemization of camphene was first reported simultaneously from the laboratory of J. D. Roberts and that of the senior author of the present paper in 1953. Professor Roberts' study clearly showed that at least two mechanisms were operative: methyl migration (Nametkin rearrangement) and Wagner–Meerwein, 2,6-hydride shift; and the other paper first suggested the cyclical character of the overall racemization process. Then in 1963, the present senior author undertook to examine the individual involvement of each of three processes in the overall racemization:[4] *exo*-methyl migration, *endo*-methyl migration, and Wagner–Meerwein 2,6-hydride shift. To this end, the differential rate equations for the cyclical process were set up and integrated, and by appropriate Taylor's series approximations the integrated equations were solved for the fractional participation of each of the three processes.[4]

In order to obtain numerical values, camphene was labeled with ^{14}C at C-10, and the concentration of the isotope at C-8 was determined as a function of time. But it was also necessary to have corresponding data for camphene initially labeled at C-8, and to this end it seemed permissible to use the earlier data of Roberts[5] for X/X_0 since we[4] wished to avoid extensive repetition of his work. In the event, this proved a poor decision on our part, since the present work has revealed a need for careful solvent–catalyst purification and for lower reaction temperature to avoid demonstrable deterioration of the solvent–catalyst system in periods exceeding 3 hr, even at the lower temperature herein reported. The fortuitous agreement for our calculation of X/X_0 for Roberts' work and the present X/X_0 at 3 hr is just that. We attribute the high value previously reported for α to incompatibility of our original data[4] with Roberts' data[5] assignable to both a real temperature discrepancy and probable inconsistencies in the makeup and stability of the solvent–catalyst system. It was indeed a justifiable objection to using disparate sources of crucial data for the solution of the kinetic equations which in part impelled us to undertake the present investigation, and in part it was the 22% value for α (*endo*-methyl migration) leading to an apparently unique exception to the general absence of such 3,2-*endo*-alkyl migrations as noted by Berson.[6] In addition, at about the same time, Hirsjarvi[7] called attention to the large error inherent in the experimental method and also offered convincing evidence that one should not discount the possibility that racemization could occur *via* tricyclene formation. Thus it was clear that the problem rested in a rather unsatisfactory condition, and particularly because of increasing interest in the exo *vs.* endo migration problem, it seemed highly desirable to reinvestigate the extent of involvement of all logical processes.

Previous work using ^{14}C required starting with the label in two different positions,[4] since analysis for the label was possible only *via* degradation, and only the 8 position was amenable to such a degradative analysis. But the availability of ^{13}C nmr rendered the ^{14}C approach obsolete and provided an elegant method for determining the amount of the isotopic label at all three

(1) This paper also represents part XXVII in the series ^{13}C NMR Studies; part XXVI: J. L. Gough, J. P. Guthrie, and J. B. Stothers, *J. Chem. Soc., Chem. Commun.*, 979 (1972).

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