Kinetics and Mechanism of Hydrolysis of *N*-Arylimidic Esters

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The influence of aryl substituents, pH, temperature, general acid–base catalysts, and solvent polarity on the kinetics of hydrolysis of ethyl *N*-arylformimidates and ethyl *N*-arylacetimidates was studied in aqueous and aqueous dioxane solutions. The data indicate that hydrolysis of these imidates involves rate-limiting reaction of the conjugate acids of the imidates with water in acidic solutions, and with hydroxide ion in alkaline solutions. Although alkoxyanilinocarbinols are probably intermediates in alkaline solutions, they may not be intermediates in acidic solutions. Hydrolysis at low pH may be a concerted process involving simultaneous C–O bond formation and C–N bond cleavage. The falloff in hydrolysis rate in strongly acidic solutions may be due to the diminished water activity of the solvent, rather than to a change in the rate-limiting step. The two sets of products formed in alkaline imidate hydrolyses may arise from competing reactions of a single intermediate, rather than from reactions of two different intermediates in acid–base equilibrium.

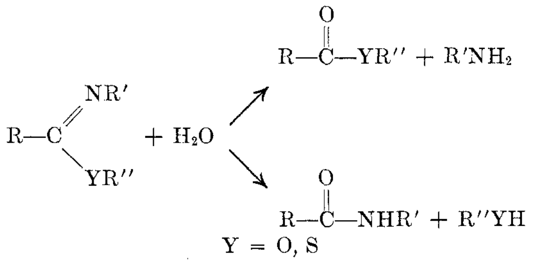
The mechanisms of hydrolysis reactions of imidic esters and related compounds have stimulated much research in the past decade. These reactions are interesting because their kinetics provide direct evidence for the existence of tetrahedral intermediates in nucleophilic displacement reactions at acyl carbon. Moreover, the same tetrahedral intermediates presumably are involved in imidate hydrolysis and ester aminolysis. Information on the mechanisms of formation and breakdown of the tetrahedral intermediates involved in imidate hydrolysis is therefore pertinent to the mechanisms of an important group of acyl transfer reactions.

Reactions whose kinetics have been studied include hydrolyses of alkyl benzimidates,[1-3] alkyl *N*-substituted acetimidates,[4,5] and phenyl *N*-alkylacetimidates.[6,7] Hydrolysis reactions of heterocyclic imidic esters and alkoxyiminium cations such as *N*-(methoxymethylene)morpholinium ion,[8] 2-(*N*-phenylimino)tetrahydrofuran,[9-11] and 2-methyloxazoline[12-14] have also been studied.

Hydrolysis reactions of thioimidates and related compounds, which are mechanistically similar to those of imidates, have also received attention. Reactions studied include hydrolyses of alkyl N-substituted thioimidates,[15,16] alkylthiomidium cations,[15-17] 2-substituted thiazolines,[13,18-20] 2,3-disubstituted thiazolinium ions,[13,19] and 2-methyl-5,6-dihydro-4*H*-1,3-thiazine.[19]

pH rate profiles have been determined for hydrolyses of a number of imidates and thioimidates. The most frequently observed profiles are "bell-shaped," with rate falloffs on either side of a plateau extending from pH 1 or 2 to a pH near that corresponding to the pK_a of the imidate, with a secomd plateau at high pH. Hydrolyses of ethyl *N*-phenylacetimidate,[4] phenyl *N*-methylacetimidate,[6] trifluorethyl *N*-methylacetimidate,[5] 2-(*N*-phenylimino)tetrahydrofuran,[9] Δ^2-oxazolines,[12,14] ethyl *N*-phenylthiobutyrimidate,[15] and Δ^2-thiazolines[18-20] exhibit this type of pH dependence. A few imidate hydrolyses have pH profiles with intermediate pH plateaus which are lower than the high pH plateaus. Examples are hydrolyses of alkyl *N*-alkylacetimidates,[4,5] methyl *N*-ethylthioacetimidate,[16] and 2-methyl-Δ^2-dihydrothiazine.[19] Alkyl thioimidates exhibit bell-shaped pH profiles with a rapidly rising rate at high pH, due to nitrile formation by elimination of thiols.[15] Alkoxyimidium, alkylthioimidium, and related heterocyclic cations, such as alkyl N,N-disubstituted thioimidium cations,[15-17] *N*-(methoxymethylene)morpholinium ion,[8] and 2,3-dimethyl-Δ^2-thiazolinium ion,[19] hydrolyze at rates which are independent of pH at low pH, but which increase with increasing pH at high pH. Several imidate hydrolyses were shown to be subject to general acid–base catalysis.[1,4,6,9,13,15,17]

The products as well as rates of imidate hydrolyses are pH dependent. Typically, an ester and an amine (or an amino ester, in the case of heterocyclic imidates) are the products at low pH, while an amide and an alcohol (or a hydroxyamide) are the products at high pH (eq 1). Usually the pH range at which the reaction



$$\mathrm{R{-}C({=}NR')YR''} + \mathrm{H_2O} \rightarrow \mathrm{R{-}C({=}O){-}YR''} + \mathrm{R'NH_2} \quad \text{or} \quad \mathrm{R{-}C({=}O){-}NHR'} + \mathrm{R''YH} \qquad \mathrm{Y} = \mathrm{O, S} \tag{1}$$

products change differs from that at which reaction rate changes.[4-9,16] Product composition is also influenced by the presence of bifunctional catalysts such as phosphate, bicarbonate, and carboxylate ions, which catalyze the formation of esters and amines.[4,8,10,15]

In acidic solutions, ethyl *m*-toluimidate[3] and 2-methyl-Δ^2-oxazoline[13] hydrolyze about twice as fast in H_2O as in D_2O.

Effects of structure on rate and mechanism of imidate hydrolysis have received less attention than the effects

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of pH and buffer catalysis. In 0.12 *N* HCl, ethyl benzimidate hydrolysis exhibits a Hammett ρ value of $+1.4$.[3] Hydrolysis of 2-aryl-Δ^2-thiazolines has a ρ value of $+2.1$ at pH 0.5, and a ρ value of approximately zero at pH 4. At pH 2.5, the Hammett plot for this reaction was nonlinear.[20] As is usually observed for reactions involving nucleophilic addition to acyl carbon, a formic acid derivative (Δ^2-thiazoline) is considerably more reactive than the analogous acetic acid derivative (2-methyl-Δ^2-thiazoline).[20] Electron-withdrawing alkoxy substituents accelerate the hydrolysis of *N*-methylacetimidates in acidic solutions but are rate retarding in alkaline solutions.[5] The influence of N substituents on hydrolytic reactivity of a series of structurally related imidic esters has not been studied, although it appears that alkyl *N*-alkylacetimidates are less reactive than alkyl *N*-phenylacetimidates at low pH but more reactive at high pH.[4]

The only nonheterocyclic *N*-arylimidic ester whose hydrolysis has been studied in detail is ethyl *N*-phenylacetimidate.[4] In aqueous 10% acetonitrile at 30°, this substance hydrolyzes with a first-order rate constant of about 7×10^{-3} sec^{-1} in the pH range 1–5. Above pH 8 the rate is constant at about 7×10^{-6} sec^{-1}. The inflection point of the sigmoid curve connecting the two rate plateaus is at about pH 6.3. The hydrolysis products also depend on pH. Below pH 6, aniline and ethyl acetate are essentially the only products. Above pH 10, formanilide and ethanol are the products (eq 1, $\text{R} = \text{CH}_3$; $\text{R}' = \text{C}_6\text{H}_5$; $\text{Y} = \text{O}$; and $\text{R}'' = \text{C}_2\text{H}_5$). At intermediate values of pH, aniline and formanilide are both produced. The inflection point of the sigmoid product composition–pH curve falls at pH 7.7. At constant pH, low concentrations of bifunctional catalysts such as phosphate and bicarbonate cause major increases in aniline yield, while monofunctional catalysts have little effect.

More than one mechanism can account for the kinetic and product composition data for imidate hydrolysis.[21] The mechanism proposed by Chaturvedi and Schmir for hydrolysis of ethyl *N*-phenylacetimidate is outlined in Scheme I.[4]

If acid-catalyzed dehydration of the uncharged alkoxyanilinocarbinol II occurs at low pH, this mechanism leads[9] to rate eq 2. The simpler rate equation (3) results if it is assumed that dehydration of II is negligibly slow, *i.e.*, that $k_4 \gg k_{-2}\,[\text{H}^+]$.

$$k_{\text{obsd}} = \frac{[\text{H}^+](k_2 + k_{-5}[\text{OH}^-])(k_4/k_{-2})}{([\text{H}^+] + K_1)([\text{H}^+] + k_4/k_{-2})} \tag{2}$$

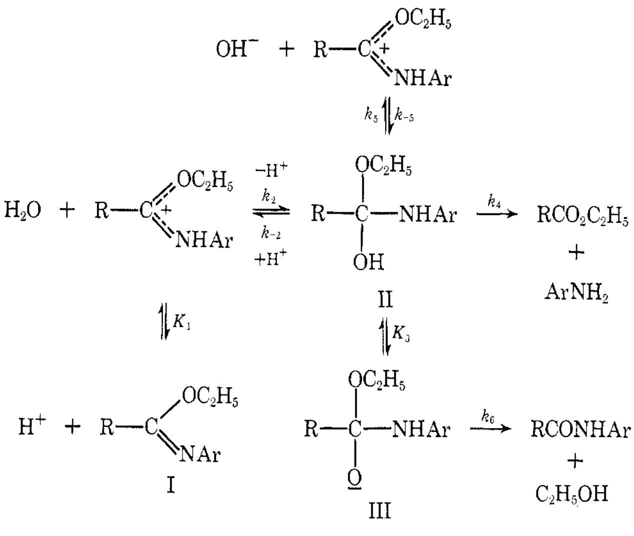
If the reaction follows eq 3, formation of II by reaction of the conjugate acid

$$k_{\text{obsd}} = \frac{[\text{H}^+](k_2 + k_{-5}[\text{OH}^-])}{[\text{H}^+] + K_1} \tag{3}$$

of the imidic ester with water or hydroxide ion is rate limiting over the entire pH range. In the absence of buffer catalysis, the composition of the reaction products depends on the values of K_3, k_4, and k_6, which do not appear in the rate equation.

The principal objective of the work described below was to determine the effect of *N*-aryl substituents on the hydrolytic reactivity of ethyl *N*-arylformimidates and ethyl *N*-arylacetimidates in solutions of low, intermediate, and high pH, and to investigate the effects of solvent polarity, temperature, and solvent acidity on these reactions. The results obtained suggest that the mechanism of Scheme I may require modification.

SCHEME I



Experimental Section

Materials.—The dioxane used in the reaction solutions was purified by the procedure of Fieser,[22] and was distilled from molten sodium shortly before use. Reagent grade chemicals were used in preparing all of the kinetic solutions.

The ethyl *N*-arylformimidates were prepared from triethyl orthoformate and aromatic primary amines by the procedure of Roberts[23,24] and are known compounds.[23-26] The ethyl *N*-arylacetimidates were prepared similarly from triethyl orthoacetate and aromatic primary amines.[27]

Buffer Solutions.—Acetic acid–sodium acetate buffers used in the kinetic experiments had the concentrations, ionic strengths, and buffer ratios shown in Table I.

TABLE I

ACETATE BUFFERS USED IN KINETIC EXPERIMENTS

Buffer	[HOAc]	[HOAc]/[NaOAc]	[NaCl]
A-1	0.00860	0.500	0.0344
A-2	0.01718	0.500	0.0172
A-3	0.0258	0.500	0.00
B-1	0.00860	1.00	0.0430
B-2	0.01718	1.00	0.0344
B-3	0.0258	1.00	0.0258
C-1	0.00860	1.50	0.0458
C-2	0.01718	1.50	0.0402
C-3	0.0258	1.50	0.0344

Rate Measurements.—The hydrolysis reactions, which are first order under the conditions used, were followed spectrophotometrically with a Cary Model 14 recording spectrophotometer equipped with a thermostated cell holder. Reaction solutions were prepared by thoroughly mixing appropriate volumes of the desired aqueous solutions and a very dilute dioxane solution of the imidic ester. Reaction solutions were allowed to come to thermal equilibrium with the cell holder before starting the recorder. Nominally aqueous reaction solutions were prepared by adding 10 λ of a dioxane solution of the imidic ester to 3.00 ml of the aqueous solution in the absorption cell.

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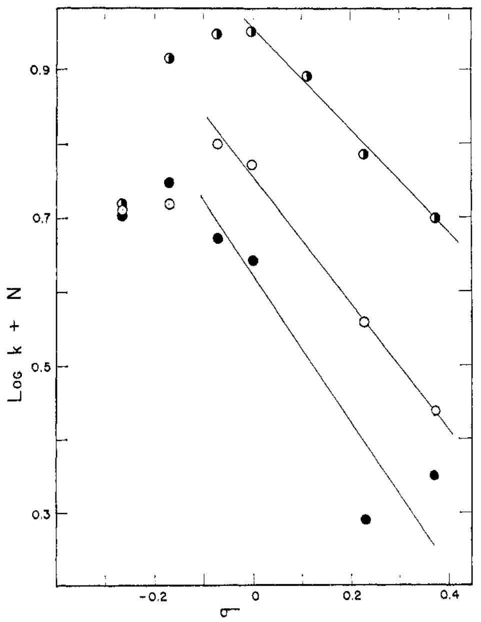

Figure 1.—Hammett plots for hydrolysis of ethyl *N*-arylformimidates: ◑, log k_{H^+} in aqueous 60% dioxane–acetate buffers at 30° ($N = -4$); ○, log k_{HA} in aqueous 60% dioxane-acetate buffers at 30° ($N = +2$); ; ●, log k_0 in alkaline aqueous 20% dioxane at 45° ($N = +4$).

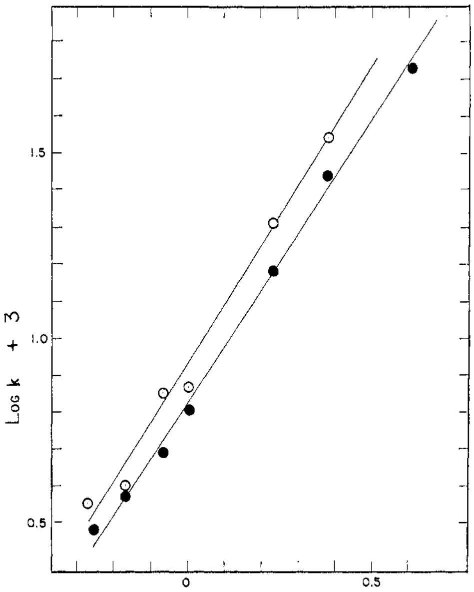

Figure 2.—Hammett plots for hydroxide ion catalyzed hydrolysis of ethyl *N*-arylformimidates in alkaline aqueous 20% dioxane at 45°, ○; for hydrolysis of ethyl *N*-arylacetimidates in aqueous 0.12 *N* HCl at 30°, ●.

Identification of Reaction Products.—Since the arylamines and anilides produced by the hydrolysis reactions have quite different ultraviolet absorption spectra, hydrolysis products were identified spectrophotometrically.

Calculations.—First-order rate constants were calculated graphically from plots of log $(A_\infty - A_t)$ *vs.* t, or by the method of Guggenheim,[28] and are expressed in reciprocal seconds. All rate constants listed in the tables are averages of two or more runs, with agreement between runs usually being within 3%. Energies of activation were calculated from the Arrhenius equation by the least-squares method. Entropies of activation were calculated for 25° as described by Bunnett, using the Arrhenius activation energies and preexponential factors.[29]

Results

The rates of hydrolysis of a series of ethyl *N*-arylformimidates were measured at several temperatures in aqueous dioxane–acetic acid–sodium acetate buffers of three dioxane concentrations. The kinetic data are summarized in Table II. These reactions exhibit buffer catalysis in solutions containing 20, 40, and 60% dioxane, although in 20% dioxane the fraction of the total hydrolysis rate due to buffer catalysis is small. Ultraviolet absorption spectra of the reaction solutions after complete hydrolysis were indistinguishable from those of the primary aromatic amines from which the imidic esters were formed; so it is inferred that ethyl formate and anilines are the products under the conditions used.

Kinetic data for reactions studied in buffers of three different buffer ratios are accurately described by the rate law of eq 4, where k_{obsd} is the experimental first-order rate constant, K_i is the dissociation constant for acetic acid, and k_{H^+} and k_{HA} are the apparent catalytic coefficients of hydronium ion and acetic acid. There

$$k_{obsd} = k_{H^+}K_i([HOAc]/[OAc^-]) + k_{HA}[HOAc] \qquad (4)$$

was no detectable spontaneous (uncatalyzed) reaction, and hydrogen ion catalytic coefficients for hydrolysis reactions studied in buffers were calculated by assuming spontaneous rates of zero. Hydrolysis rate is not markedly affected by changing the salt used to maintain constant ionic strength of the buffers from sodium chloride to sodium nitrate.

Catalytic coefficients of hydronium ion and acetic acid for the various ethyl *N*-arylformimidate hydrolyses, derived from the data of Table II, are collected in Table III. Hammett plots of log k_{H^+} or log k_{HA} *vs.* the substituent constants of the *N*-aryl substituents[30] for reactions in the 60% dioxane buffers are nonlinear, and exhibit downward curvature (Figure 1). Both electron-withdrawing and electron-releasing aryl substituents diminish reactivity in aqueous dioxane-acetate buffers.

Table III also lists Arrhenius activation energies and entropies of activation for the acetic acid catalyzed and hydronium ion catalyzed hydrolysis of ethyl *N*-arylformimidates in aqueous dioxane-acetate buffers. The energies of activation are quite low and are offset by large negative entropies of activation. There is no clear correlation between the nature of the aryl substituents and the values of the activation parameters for either the hydronium ion or the acetic acid catalyzed reactions.

The catalytic coefficients of acetic acid for hydrolysis of ethyl *N*-phenylformimidate in aqueous dioxane buffers at 12° decrease rapidly with increasing dioxane concentration, while the catalytic coefficient of hydronium ion is relatively insensitive to solvent composition.

Ethyl *N*-arylformimidates hydrolyze less than a hundredth as fast in alkaline 20% dioxane solutions as in acetate buffers of the same dioxane concentration. The products of alkaline hydrolysis are formanilides and

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TABLE II

HYDROLYSIS OF X—$C_6H_4N{=}CHOC_2H_5$ IN AQUEOUS DIOXANE–ACETATE BUFFERS

X	Registry no.	Buffer[a]	10^3k_{obsd} at temp, °C		
		60% Dioxane			
			14.8°	30.0°	45.0°
p-CH_3O	26419-17-0	B-1	0.719	1.48	2.86
		B-2	1.00	1.91	3.56
		B-3	1.16	2.36	4.36
p-CH_3	15296-47-6	B-1	1.06	2.08	4.03
		B-2	1.34	2.62	4.83
		B-3	1.54	2.97	5.71
m-CH_3	15296-46-5	B-1	1.21	2.39	4.04
		B-2	1.47	2.89	5.10
		B-3	1.54	2.97	5.71
			11.8°	30.0°	45.0°
H	6780-49-0	A-1	0.656	1.44	2.67
		A-2	0.875	1.95	3.54
		A-3	1.09	2.32	4.50
		B-1	1.07	2.19	4.23
		B-2	1.33	2.73	5.23
		B-3	1.52	3.52	6.15
		C-1	1.60	3.20	6.27
		C-2	1.80	3.78	7.20
		C-3	2.07	4.23	8.04
		C-1[b]		3.49	
			14.8°	30.0°	45.0°
		C-2[b]		4.03	
		C-3[b]		4.43	
p-Cl	13506-16-6	B-1	0.790	1.52	2.75
		B-2	0.955	1.86	3.40
		B-3	1.12	2.14	3.95
m-Cl	15296-49-8	A-1		0.778	
		A-2		1.01	
		A-3		1.26	
		B-1	0.652	1.28	2.32
		B-2	0.770	1.47	2.81
		B-3	0.895	1.72	3.28
		C-1		1.90	
		C-2		2.22	
		C-3		2.38	
		60% Dioxane			
			30.0°	45.0°	60.0°
o-Cl	13506-15-5	B-1	0.326	0.627	1.13
		B-2	0.377	0.736	1.36
		B-3	0.428	0.825	1.5
			45.0°	60.0°	75.0°
o-CH_3	4943-59-3	B-1	0.946	1.71	2.84
		B-2	1.18	2.12	3.58
		B-3	1.44	2.51	4.22
		40% Dioxane			
			12.2°	30.0°	45.0°
H		A-1	8.16	16.2	27.0
		A-2	9.28	18.6	31.5
		A-3	10.8	20.9	36.5
		B-1		30.8	
		B-2		32.6	
		B-3		35.3	
		C-1		43.0	
		C-2		46.3	
		C-3		48.0	
		20% Dioxane			
			−3.8°	12.2°	
H		A-1	20.2	42.5	
		A-2	20.5	45.3	
		A-3	21.0	49.2	
p-CH_3O		A-2		21.4	
p-CH_3		A-2		35.8	
m-CH_3		A-2		48.6	
p-Cl		A-2		33.2	
m-Cl		A-2		31.0	

[a] See Table I for compositions of buffer solutions. [b] $NaNO_3$ was used to maintain constant ionic strength, rather than NaCl.

ethanol. In alkaline dioxane solutions the reaction follows the rate law of eq 5, where k_0 is the rate of the

$$k_{obsd} = k_0 + k_{OH}[OH^-] \qquad (5)$$

pH independent reaction, and k_{OH} is the catalytic coefficient of hydroxide ion. Kinetic data for hydrolysis of ethyl *N*-arylformimidates in alkaline 20% dioxane are collected in Table IV, and catalytic coefficients and activation parameters derived from them appear in Table V. Electron-withdrawing aryl substituents diminish the ratio of uncatalyzed to hydroxide ion catalyzed hydrolysis. The uncatalyzed reaction is retarded by electron-withdrawing aryl substituents ($\rho \cong -0.7$), while the hydroxide ion catalyzed reaction is accelerated by such substituents ($\rho = +1.7$) (see Figures 1 and 2). For the hydroxide ion catalyzed reaction, energies of activation are independent of the nature of the aryl substituent, while both entropies and energies of activation are structure dependent for the uncatalyzed reaction.

The effect of aryl substituents on hydrolytic reactivity of *N*-arylimidic esters at low pH was studied by hydrolyzing a series of ethyl *N*-arylacetimidates in aqueous 0.12 *N* hydrochloric acid. In the vicinity of pH 1 the imidates are essentially completely protonated, and reaction rate is almost independent of acid concentration. Kinetic data and activation parameters for acid hydrolysis of several ethyl *N*-arylacetimidates and ethyl *N*-phenylpropionimidate appear in Table VI.

In acidic solutions log k_{obsd} correlates well with σ, leading to $\rho = +1.5$ for this reaction (see Figure 2). An *o*-chloro substituent increases reactivity, while *o*-methyl and *o*-ethoxy substituents decrease it. Ethyl *N*-phenylpropionimidate hydrolyzes about twice as fast as the corresponding acetimidate.

The effect of solvent acidity and water activity on rates of hydrolysis of three imidates was investigated. Rates of hydrolysis of ethyl *N*-phenylformimidate, ethyl *N*-phenylacetimidate, and ethyl *N*-*m*-chlorophenylacetimidate were measured at 25° in a series of dilute to moderately concentrated aqueous perchloric acid solutions. The hydrolysis of ethyl *N*-*m*-chlorophenylacetimidate was also studied in aqueous hydrochloric acid solutions. The experimental data are tabulated in Tables VII and VIII.

Bunnett plots[31] of log k_{obsd} *vs.* log a_w (a_w is the activity of water in the reaction solution) are curved in the region of low acid concentration, with tangents at log $a_w = 0$ larger than 10, but are nearly linear in the region

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Table III

Catalytic Coefficients and Acivation Parameters for Hydrolysis of X—$C_6H_4N{=}CHOC_2H_5$ in Aqueous Dioxane–Acetate Buffers

X	Temp, °C	10^3k_{HA}[a]	$10^{-4}k_{H^+}$[b]	$10^3E_{a_{HA}}$[c]	$\Delta S^{\ddagger}_{HA}$[d]	$10^3E_{a_{H^+}}$[c]	$\Delta S^{\ddagger}_{H^+}$[d]
			60% Dioxane				
p-CH_3O	14.8	2.56	2.6	7.4	−42	8.6	−10
	30.0	5.12	5.2				
	45.0	8.7	12				
p-CH_3	14.8	2.79	4.2	7.2	−43	8.8	−9
	30.0	5.2	8.4				
	45.0	9.8	18				
m-CH_3	14.8	2.50	5.0	9.6	−34	7.4	−13
	30.0	6.3	8.9				
	45.0	12.3	17				
H	11.8	2.6	4.5	7.7	−41	8.1	−11
	30.0	5.9	9.0				
	45.0	10.9	20				
p-Cl	14.8	1.92	3.1	7.8	−41	8.2	−12
	30.0	3.60	6.1				
	45.0	7.0	12.3				
m-Cl	14.8	1.41	2.6	8.3	−40	8.2	−12
	30.0	2.81	5.0				
	45.0	5.6	10				
o-Cl	30.0	0.59	1.4	10	−38	8.3	−14
	45.0	1.27	2.6				
	60.0	2.61	5.1				
o-CH_3	45.0	2.87	3.5	7.6	−44	10.7	−6
	60.0	4.65	6.5				
	75.0	8.0	15				
			40% Dioxane				
H	12.2	15.3	1.7	7.0	−40	6.6	−20
	30.0	27.3	3.5				
	45.0	55.1	5.5				
			20% Dioxane				
H	−3.8		0.9			6.4	−20
	12.2	39	1.9				

[a] Catalytic coefficients of acetic acid. [b] Catalytic coefficients of hydronium ion, calculated from kinetic data and ionization constants of acetic acid in aqueous dioxane from ref 38. [c] Cal/mol. [d] Cal/(mol degree).

Table IV

Hydrolysis of X—$C_6H_4N{=}CHOC_2H_5$ in Alkaline 20% Dioxane Solutions

X	[NaOH]	10^4k_{obsd} at temp, °C 30.0	45.0	60.0
p-CH_3O	0.0172	1.63	5.65	16.8
	0.0344	1.77	6.31	18.6
	0.0566	2.08	6.88	20.2
p-CH_3	0.0172		6.30	
	0.0344		6.89	
	0.0566		7.68	
m-CH_3	0.0172		5.86	
	0.0344		7.30	
	0.0566		8.30	
H	0.0172	1.90	5.69	15.1
	0.0344	2.46	6.95	20.4
	0.0566	2.96	8.23	24.1
p-Cl	0.0172		5.57	
	0.0344		8.80	
	0.0566		12.6	
m-Cl	0.0172	2.56	8.09	20.2
	0.0344	4.53	14.5	37.3
	0.0566	6.40	20.1	49.3

corresponding to water activities below 0.7. The slopes of the linear portions are about 5. Graphs of log k_{obsd} *vs.* (H_0 + log [H^+]) are nearly linear for all four reactions. The slopes of these lines [the Bunnett–Olsen ϕ values for the reactions[32] have values ranging from 1.07 to 1.2 (Figure 3).

Table V

Catalytic Coefficients and Activation Parameters for Hydrolysis of X—$C_6H_4N{=}CHOC_2H_5$ in Alkaline 20% Dioxane

X	10^4k_0 (45°)	10^3k_{OH} (45°)	$10^3E_{a_0}$[a]	$\Delta S_0^{\ddagger}$[b]	$10^3E_{a_{OH}}$[a]	$\Delta S_{OH}^{\ddagger}$[b]
p-CH_3O	5.05	3.58	16.0	−25	13.5	−29
p-CH_3	5.58	4.01				
m-CH_3	4.70	7.12				
H	4.42	7.38	14.2	−31	13.6	−27
p-Cl	1.96	20.4				
m-Cl	2.24	34.9	15.2	−30	13.6	−25

[a] Cal/mol. [b] Cal/(mol degree).

These data also show that in acidic solutions ethyl *N*-phenylformimidate hydrolyzes about 550 times as fast as ethyl *N*-phenylacetimidate, and that ethyl *N*-*m*-chlorophenylacetimidate hydrolyzes about 4–5 times as fast in moderately concentrated hydrochloric acid solutions as it does in perchloric acid solutions of the same water activity.

Discussion

The pH hydrolysis rate profiles for typical imidic esters exhibit two regions in which rate is independent of pH. It is generally assumed that these rate plateaus correspond to rate-limiting formation of alkoxyaminocarbinol intermediates by reaction of the conjugate acid of the imidate with water and with hydroxide ion. This assumption accounts for the shape of the pH rate pro-

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[32] J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1917 (1966).

TABLE VI

HYDROLYSIS OF $X—C_6H_4N{=}CR—OC_2H_5$ IN AQUEOUS 0.120 *N* HCl

R	Registry no.	X	Temp, °C	10^4k_{obsd}	10^3E_a[a]	$\Delta S^{\ddagger b}$
CH_3	26431-30-1	*p*-C_2H_5O	14.2	6.37		
			30.0	30.5	16.7	−17
			45.2	111		
CH_3	26431-31-2	*p*-CH_3	14.2	8.03		
			30.0	37.1	16.6	−17
			45.2	136		
CH_3	26431-32-3	*m*-CH_3	14.2	11.2		
			30.0	49.6	16.4	−17
			45.2	184		
CH_3	19655-72-2	H	14.2	14.1		
			30.0	64.8	16.4	−16
			45.2	233		
CH_3	26431-34-5	*p*-Cl	4.6	12.1		
			14.2	34.4	16.6	−14
			30.0	152		
CH_3	26431-35-6	*m*-Cl	4.6	22.9		
			14.2	64.0	15.8	−16
			30.0	255		
CH_3	26431-36-7	3,4-Cl_2	4.6	54.1		
			14.2	149	14.9	−17
			30.0	540		
CH_3	26431-37-8	*o*-Cl	4.6	19.1		
			14.2	49	15.9	−15
			30.0	214		
CH_3	26431-38-9	*o*-CH_3	14.2	2.74		
			30.0	13.4	17.0	−18
			45.2	50		
CH_3	26431-39-0	*o*-C_2H_5O	14.2	9.23		
			30.0	39.6	15.8	−19
			45.2	137		
C_2H_5	24433-70-3	H	14.2	27.9		
			30.0	122	16.6	−14
			45.2	480		

[a] Cal/mol. [b] Cal/(mol degree).

TABLE VII

HYDROLYSIS OF $X—C_6H_4N{=}CR—OC_2H_5$ IN AQUEOUS PERCHLORIC ACID AT 25°

		10^5k_{obsd}		
[$HClO_4$]	Log a_w[a]	R = X = H	R = CH_3; X = H	R = CH_3; X = *m*-Cl
0.824	−0.015		174	681
1.648	−0.033		82.9	356
2.472	−0.060		42.7	162
3.296	−0.097		18.2	77.5
4.120	−0.142	4260	7.45	33.8
4.944	−0.210	1610	3.13	
5.768	−0.302	515	0.942	3.92
6.592	−0.418	141	0.26	1.11

[a] a_w = water activity. Values obtained by interpolation of data from ref 31.

files and provides an explanation for the fact that rate and product composition are different functions of pH.

Most discussions of the detailed mechanism of imidate hydrolysis assume that carboxylate ester and amine are formed by breakdown of an uncharged alkoxyaminocarbinol (II of Scheme I), or a zwitterion in equilibrium with it, while amide and alcohol are produced from the conjugate base of the alkoxyaminocarbinol (III of Scheme I). As Schmir and Cunningham point out, however, the kinetic and product data can be accounted for by other reaction schemes (ref 9, footnote 24).

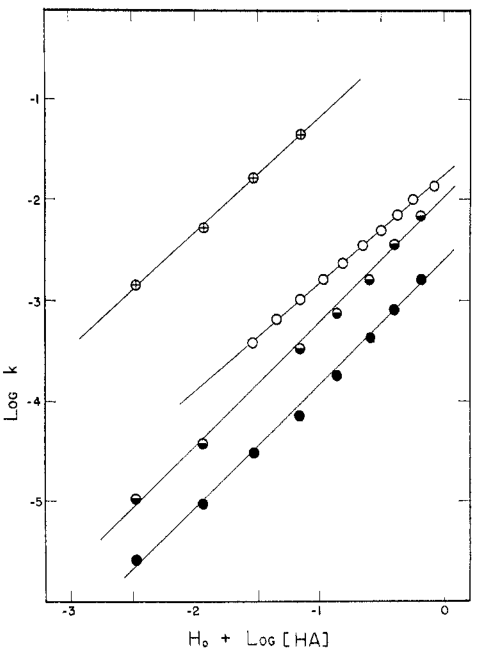

Figure 3.—Bunnett–Olsen plots for hydrolysis of ethyl *N*-arylimidates in moderately concentrated aqueous acid solutions at 25°: ⊕, ethyl *N*-phenylformimidate, perchloric acid; ○, ethyl *N*-*m*-chlorophenylacetimidate, hydrochloric acid; ◓, ethyl *N*-*m*-chlorophenylacetimidate, perchloric acid; and ●, ethyl *N*-phenylacetimidate, perchloric acid.

TABLE VIII

HYDROLYSIS OF *m*-$ClC_6H_4N{=}C(CH_3)OC_2H_5$ IN AQUEOUS HYDROCHLORIC ACID AT 25°

[HCl]	Log a_w[a]	10^4k_{obsd}
0.669	−0.011	137
1.338	−0.023	96.8
2.007	−0.040	72.3
2.676	−0.058	48.6
3.345	−0.082	35.2
4.014	−0.107	22.9
4.683	−0.140	16.3
5.352	−0.164	10.2
6.021	−0.215	6.46
6.690	−0.259	3.90

[a] a_w = water activity. Values obtained by interpolation of data from ref 31.

Alkoxyaminocarbinols are amide hemiacetals, and their hydrolysis reactions may have some features in common with those of amide acetals. Amide acetals hydrolyze in both acidic and alkaline solutions. Due in part to their extremely high reactivity, amide acetals are difficult subjects for kinetic studies. No published kinetic data on hydrolysis of simple amide acetals exist. *N*,*N*-Dimethylbenzamide diethyl acetal hydrolysis is general acid catalyzed in aqueous dioxane buffers and is independent of pH in alkaline solutions.[33] Amide acetals hydrolyze to esters and amines under acidic conditions but yield mostly amides and alcohols under alkaline conditions.[33-35] In other words, the products of amide acetal hydrolysis vary with pH in a manner similar to that observed for imidate hydrolysis, even though the amide acetals cannot be in equilibrium

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[33] W. Doo, M. A. Thesis, University of California, Santa Barbara, Sept 1969.

[34] H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).

[35] T. Taguchi and Y. Kawazoe, *J. Org. Chem.*, **26**, 2699 (1961).

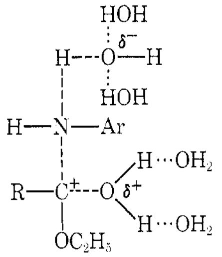
with conjugate bases analogous to III of Scheme I. This, together with the extremely high reactivity of amide acetals under acidic conditions, raises several questions concerning the mechanism of imidic ester hydrolysis. These include the following. Are amide hemiacetals too reactive to be intermediates in imidate hydrolyses in acidic solutions? Is amide hemiacetal dehydration the only plausible explanation for the falloff of imidate hydrolysis rate with increasing acidity in strongly acidic solutions? And finally, is an acid–base equilibrium between two intermediates necessary to account for the pH dependence of imidate hydrolysis product composition?

Hydrolysis of *N*-Arylimidic Esters in Acidic Solutions.—A considerable body of kinetic evidence supports the conclusion that the rate-limiting step of imidate hydrolysis in the region of the low pH plateau involves reaction of water with the conjugate acid of the imidic ester. In addition, substituent effects on rates of hydrolysis of ethyl *N*-arylacetimidic esters in acidic solutions are readily accounted for if the rate-limiting step of the reaction involves attack by water on the acyl carbon of the conjugate acid of the imidic ester. Imidic ester conjugate acids are alkoxyaminocarbonium ions: substituents which stablize carbonium ions should diminish their reactivity with nucleophiles, and *vice versa.* Alkyl groups on the acyl carbon should stabilize the imidate conjugate acids, and a methyl group, with three α hydrogens, should stabilize the conjugate acid of an acetimidate somewhat more effectively than the ethyl group of the conjugate acid of a propionimidate, which has only two α hydrogens. This would account for the fact that ethyl *N*-phenylpropionimidate hydrolyzes about twice as fast as ethyl *N*-phenylacetimidate in dilute hydrochloric acid solutions (Table VI). It would also provide at least a partial explanation for the fact that ethyl *N*-phenylformimidate hydrolyzes more than 500 times as fast as the corresponding acetimidate in acidic solutions, although steric and hydration effects probably also play a role in this case.

Similarly, electron-attracting substituents in the *N*-aryl group should destabilize the conjugate acids of ethyl *N*-arylimidic esters and render them more susceptible to attack by water. This also is supported by the data of Table VI: hydrolysis rates of ethyl *N*-arylacetimidates in dilute hydrochloric acid solutions correlate well with Hammett's σ constants, with a ρ of $+1.5$ (Figure 2). Ortho substituents on the *N*-aryl group appear to influence reactivity primarily by their electronic rather than their steric properties. In ethyl *N*-arylacetimidate hydrolysis, *o*-methyl and *o*-ethoxy substituents decrease reactivity; *o*-chloro increases it.

The observation that differences in hydrolytic reactivity of a series of meta- and para-substituted ethyl *N*-arylacetimidates in dilute hydrochloric acid are due largely to differences in activation energy rather than differences in entropy of activation is also reasonable, if the principal influence of substituents is on the strength of the developing acyl carbon–water oxygen bond in the rate-limiting transition state.

Alkoxyaminocarbinols are usually assumed to be products of the rate-limiting reaction of water with imidate conjugate acids. However, it seems likely that these tetrahedral species have no finite existence in acidic solutions. The large negative entropies of activation for imidate hydrolysis in acidic solutions suggest that assembly of the rate-limiting transition state requires considerable ordering of the solvent. This view is supported by the Bunnett–Olsen ϕ values of 1.1–1.2 for hydrolysis of *N*-arylformimidates and *N*-arylacetimidates in aqueous hydrochloric and perchloric acid solutions (Figure 3), which suggest that the rate-limiting transition state contains about five more water molecules than the species from which it is formed.[32] Such a high degree of hydration can be accounted for by assuming that the rate-limiting step involves concerted general acid–base catalyzed conversion of the imidate conjugate acid to aniline plus the conjugate acid of a carboxylate ester. The transition state structure may resemble IV, in which C–O bond formation is further advanced than C–N bond cleavage.



IV

The treatment of Bunton and Shiner[36] leads to an estimated solvent deuterium isotope effect of $k_{H_2O}/k_{D_2O} \cong 2$ for a transition state having structure IV, in agreement with experimental observation.[3,13]

pH rate profiles for hydrolyses of imidates, thioimidates, oxazolines, and thiazolines exhibit rate decreases at low pH (usually below pH 2). These rate decreases have been attributed to acid-catalyzed dehydration of alkoxyaminocarbinol II, although it has been recognized that a strong dependence of hydrolysis rate on water activity would lead to a similar rate falloff at moderately high acidities.

If, as argued above, the alkoxycarbinolamine is best thought of as a transition state rather than as an intermediate in *N*-arylimidic ester hydrolysis, it follows that the decrease in hydrolysis rate with increasing acidity in moderately concentrated solutions of hydrochloric or perchloric acid (Tables VII and VIII) is a water activity effect. This conclusion is strengthened by the fact that excellent straight lines are obtained in Bunnett–Olsen plots[32] of log k_{exp} *vs.* $(H_0 + \log HX)$ (Figure 3). It should be pointed out, however, that eq 2, derived on the assumption of reversible alkoxycarbinolamine formation, also predicts a strong rate decrease with increasing acid concentration, provided that hydrogen ion activities are substituted for hydrogen ion concentrations.

Hydrolysis of *N*-Arylformimidic Esters in Aqueous Dioxane–Acetate Buffers.—In aqueous dioxane–acetate buffers, ethyl *N*-arylformimidate hydrolyses follow the rate law of eq 4 (Tables II and III). Both the acetic acid and the hydronium ion catalyzed reactions exhibit very low Arrhenius activation energies and large negative entropies of activation. Plots of both k_{H^+} and k_{HA} *vs.* σ are nonlinear, exhibiting downward curvature (Figure 1). Downward curvature in Hammett plots

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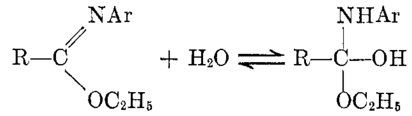
(36) C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, **83**, 42, 3207, 3214 (1961).

may be due to a change in the rate-limiting step of the reaction. In the present instance, however, another cause seems more probable.

The low activation energies of these reactions (6–9 kcal/mol) suggest that the rate-limiting step is preceded by a preequilibrium with a negative temperature coefficient. Preequilibria which might be involved are hydration of the imidate conjugate acid, dissociation of acetic acid, and protonation of the imidate, whose equilibrium constants are designated by K_{hyd}, K_{HA}, and H_{b}, respectively. Imidate hydration (eq 6) is estimated to



$$\mathrm{R{-}C({=}NAr)(OC_2H_5)} + \mathrm{H_2O} \rightleftharpoons \mathrm{R{-}C(NHAr)(OH)(OC_2H_5)} \qquad (6)$$

be endothermic, so that K_{hyd} should increase with increasing temperature. The dissociation constant of acetic acid in aqueous dioxane is relatively insensitive to temperature in the temperature region used in the kinetic measurements.[37] The temperature dependence of K_{b} for imidates is not known, but K_{b} for amines has a negative temperature coefficient,[38,39] and it is reasonable to assume that K_{b} for other nitrogen bases also decreases with increasing temperature.

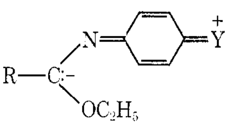
If K_{b} appears in the rate equation, preequilibrium imidate hydration is excluded, since the rate equation for rate-limiting general acid catalyzed hydrolysis of the alkoxyanilinocarbinol is given by eq 7. However, if imidate hydration is rate limiting in acetate buffers, as it appears to be in mineral acid solutions, the rate equation is given by eq 8, where the first term represents water-catalyzed hydration of the alkoxyanilinocarbonium ion, and the second term represents its general acid catalyzed hydration. The first term on the right side of eq 8 corresponds to hydrolysis of the imidate by the same mechanism which operates at low pH in solutions of strong acids. The second term may describe acetate ion catalyzed reaction of water with the acyl carbon of the protonated imidate, or may correspond to proton transfer from acetic acid to imidate nitrogen, concerted with C–N bond fission and water-catalyzed nucleophilic attack by water on the acyl carbon of the imidate. The second process, in which charge is developed on carboxyl oxygen of acetic acid and on oxygen of the water molecule which is functioning as a general base catalyst, seems more likely than the first, in which charge is reduced on both anilino nitrogen and acetate oxygen. Otherwise, it is difficult to account for the fact that the catalytic coefficient of acetic acid increases as the dioxane concentration of the reaction solution decreases (see Table III).

$$k_{\mathrm{exp}} = kK_{\mathrm{hyd}}K_{\mathrm{HA}}[\mathrm{HOAc}]/[\mathrm{OAc}^-] + k'K_{\mathrm{hyd}}[\mathrm{HOAc}] \qquad (7)$$

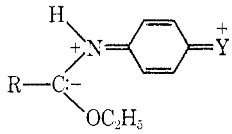
$$k_{\mathrm{exp}} = \mathrm{k}K_{\mathrm{b}}K_{\mathrm{HA}}[\mathrm{HOAc}]/[\mathrm{OAC}^-] + k^1K_{\mathrm{b}}K_{\mathrm{HA}}[\mathrm{HOAc}] \qquad (8)$$

If the points for the *N*-*p*-tolyl- and *N*-*p*-anisylformimidates are excluded, Hammett plots of log k_{H^+} and log k_{HA} for ethyl *N*-arylformimidate hydrolysis in aqueous 60% dioxane–acetate buffers have slopes of approximately −0.6 and −0.9, respectively (Figure 1). The negative ρ values require that the negative ρ for protonation of the imidates (K_{b}) has a larger magnitude than the positive ρ for reaction of the conjugate acids with water (k and k' of eq 8).

It is unlikely that the negative deviations of the points for the *N*-*p*-anisyl- and *N*-*p*-tolylformimidates from the Hammett plots defined by the other imidates are due to stabilization of the alkoxyanilinocarbonium ion conjugate acids of these compounds by the electron-donating para substituents, for if this were the case a similar deviation should have been observed for hydrolysis of *N*-arylacetimidates in dilute hydrochloric acid (Figure 2). The negative deviations of the points for these two compounds suggest that *p*-alkoxy and *p*-methyl substituents may stabilize the imidates relative to their conjugate acids. Canonical structures such as V may make larger contributions to the resonance hybrid of the imidate than structures such as VI make to its conjugate acid, owing to the close proximity of positive charges in the latter.



V



VI

Hydrolysis of *N*-Arylformimidic Esters in Alkaline Solutions.—The fact that hydrolysis rate and product composition are independent functions of pH in alkaline solution leads to the conclusion that alkaline hydrolysis of ethyl *N*-arylimidic esters does not involve a preequilibrium between the imidic ester and alkoxyanilinocarbinol II. Chaturvedi and Schmir[4] found that the high pH plateau of the pH rate profile for ethyl *N*-phenylacetimidate hydrolysis begins at about pH 8, at which the hydrolysis products consist of about 40% aniline and 60% acetanilide. Above pH 10, however, acetanilide is essentially the only product. If the tetrahedral hydrate II is in equilibrium with the imidic ester, the experimental results require that the rate-limiting step involve conversion of II to another intermediate, which yields products *via* two fast processes of different pH dependence. Such a reaction scheme seems unnecessarily complex.

Hydrolysis of ethyl *N*-arylformimidates in dilute 20% dioxane–sodium hydroxide solutions follows the rate law of eq 5. Previously, hydroxide ion catalysis of imidate hydrolysis has been observed only for substrates which exist in cationic form in alkaline solution due to the presence of quaternary nitrogen atoms.[8,15–17] A hydrolytic pathway which is first order in hydroxide ion is not accommodated by the generally accepted mechanisms of *N*-substituted imidic ester hydrolysis (Scheme I, $k_2 \gg k_{-2}$, $k_5 \ll k_{-5}$). Scheme I could be modified to include a hydroxide dependent pathway by assuming that hydroxide ion may react with the unprotonated imidate to form an anilide ion [$\mathrm{HC(OC_2H_5)(OH)(NAr)^-}$] which is in equilibrium with III.

While alkoxyanilinocarbinols (II) may not be intermediates when *N*-arylimidic esters hydrolyze in acidic solutions (see above), they probably are discrete intermediates in the alkaline hydrolysis of these compounds.

Otherwise, it would be difficult to account for the fact that the product forming steps follow the rate-limiting step in alkaline solutions. The pH-indepen-

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[37] H. S. Harned and L. D. Fallon, *J. Amer. Chem. Soc.*, **61**, 2374 (1939).

[38] L. L. Schalager and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 14 (1963).

[39] E. J. King, "Acid-Base Equilibria," Pergamon Press, Macmillan, New York, N. Y., 1965, p 187.

dent process which produces II in alkaline solutions presumably involves reaction of hydroxide ion with the conjugate acid of the imidate.

The usual explanation for the dependence of imidate hydrolysis product composition on pH assumes that amine and ester are formed from a more highly protonated intermediate than that which yields amide and alcohol. A scheme involving an equilibrium between intermediates II and III satisfactorily accounts for the experimental observations (see Scheme I). Alternatively, alkaline imidate hydrolysis may resemble alkaline hydrolysis of amide acetals, in which two sets of products are formed by competing reactions of the amide acetal. The alkoxyanilinocarbinol II may form aniline and carboxylate ester by an S_E2 reaction with hydronium ion, and form anilide and alcohol by dissociation to alcohol and an anilinohydroxycarbonium ion, which is converted to the anilide by loss of a proton. Amide acetals exhibit measurable electrical conductivity in polar aprotic solvents,[34,40] presumably owing to dissociation to alkoxyaminocarbonium and alkoxide ions, and a similar dissociation of alkoxyanilinocarbinol II in water seems reasonable. If this dissociation occurs, both sets of products may be formed from II. The mechanism of the product forming step in alkaline hydrolysis of imidic esters remains open.

If the uncatalyzed alkaline hydrolysis of N-arylimidic esters involves rate-limiting reaction of hydroxide ion with the imidate conjugate acid, it will follow the rate law of eq 9, where K_b is the basicity constant

$$k_o = kK_bK_w \qquad (9)$$

of the imidate and K_w is the autoprotolysis constant of water. The observed activation parameters (Table V) for this reaction are thus complex quantities. From the known enthalpy and entropy of dissociation of water[41] and enthalpies and entropies of protonation of imidates estimated from those of amines (ref 36, p 14), I estimate the enthalpy of activation for the reaction of hydroxide ion with ethyl N-phenylformimidium ion to be about 10 kcal/mol and the entropy of activation to be about −25 eu. These values are reasonable for a bimolecular reaction of this charge type.

k_0 values for alkaline N-arylformimidate hydrolysis were obtained from intercepts of k_{exp} *vs.* [OH$^-$] plots, and are of low precision in the case of imidates having electron-withdrawing aryl substituents. Making allowance for this, the Hammett ρ value obtained for the imidates except the p-methoxy- and p-methyl-substituted compounds (Figure 1) is *ca.* −0.7 for the uncatalyzed reaction. The negative deviation of the points for the p-anisyl and p-tolyl compounds can be rationalized by the same argument used above for the hydrolysis reactions in acetate buffers.

The rate-limiting step of the hydroxide-catalyzed hydrolysis reaction probably involves attack by hydroxide ion on the acyl carbon of the N-arylformimidate. This bimolecular process, which is analogous to that involved in alkaline hydrolysis of amides and esters, should have a substantial negative entropy of activation, as is observed. The Hammett ρ value of +1.7 (Figure 2) for this reaction is of the expected sign and of reasonable magnitude for a nucleophilic addition to a carbon–nitrogen double bond.

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(40) G. Simchen, H. Hofmann, and H. Bredereck, *Chem. Ber.*, **101**, 42 (1968).

(41) E. A. Moelwyn-Hughes, "Physical Chemistry," 2nd ed, Macmillan, New York, N. Y., 1961, p 877.

Mechanism of the Base-Catalyzed Synthesis of Azobenzenes

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The base-catalyzed reaction between aniline and nitrosobenzene to form azobenzene has been investigated kinetically under homogeneous reaction conditions. Energy of activation, entropy of activation, and Hammett ρ values are calculated. The mechanism is postulated as nucleophilic attack of the negatively charged nitrogen atom of aniline on the nitrogen atom of nitrosobenzene. This is the reverse of the mechanism proposed for the same reaction in acid solution.

The base-catalyzed reaction between aniline and nitrosobenzene to form azobenzene was first utilized by Campbell[1] and coworkers. Hot concentrated sodium hydroxide was used with toluene as the solvent with the result that the reaction took place at the interface of a two-phase system. Azoxy compounds are also a minor product of this reaction. In order to investigate the kinetics and to elucidate the mechanism of this reaction, homogeneous reaction conditions are desirable. It was found that a homogeneous reaction mixture could be obtained by using tetramethylammonium hydroxide in a 80% pyridine–20% water, by volume, solution. It was then possible to follow the kinetics of the reaction spectrophotometrically.

Results

In 0.10 M tetramethylammonium hydroxide solutions (80% pyridine–20% water by volume) with the initial concentration of aniline 0.025–0.250 M and that of nitrosobenzene 0.050–0.300 M, the rate of the reaction was found to be proportional to the product of the stoichiometric concentrations of aniline and nitrosobenzene. The pseudo-second-order rate constants, k, were calculated by means of a FORTRAN IV G program on an IBM 360/50 computer. The constants were satisfactory as shown in Table I.

In 80% pyridine–20% water, under the experimental conditions used, the pseudo-second-order rate constant for the formation of azobenzene is linearly related to the tetramethylammonium hydroxide concentration. The linear equation is

$$k = (0.29 + 70.4s) \times 10^{-4}\ \text{l. mol}^{-1}\ \text{sec}^{-1}$$

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* To whom correspondence should be addressed.

(1) N. Campbell, A. W. Henderson, and D. Taylor, *J. Chem. Soc.*, 1281 (1953).