Hydrolysis of Formanilides in Alkaline Solutions

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The rates of alkaline hydrolysis of several meta- and para-substituted formanilides are nearly independent of the nature of the substituent. pH–reaction rate profiles and entropies of activation are consistent with a mechanism involving rate-limiting general acid–general base catalyzed elimination of arylamine from the tetrahedral adduct of hydroxide ion and the anilide. *p*-Nitro- and *p*-cyanoformanilides, which are partially dissociated to unreactive conjugate bases at high pH, are anomalously reactive toward alkaline hydrolysis. The enhanced reactivity of these compounds is attributed to their hydrolysis by a mechanism involving dissociation of a dinegatively charged tetrahedral intermediate into formate ion and arylamide ion. *p*-Nitroacetanilide and *N*-methyl-*p*-nitroformanilide are also anomalously reactive, probably for the same reason. Carbonyl-^{18}O isotope exchange experiments and pH–rate profiles reveal that *p*-nitroacetanilide hydrolyzes by two processes, one first order in hydroxide ion and the other second order in hydroxide ion. The kinetics of hydrolysis of several *N*-methylformanilides suggest that these reactions are mechanistically similar to hydrolyses of the corresponding formanilides.

Prior to 1950, little was known about the kinetics of carboxamide saponification; Reid[2,3] had investigated the effects of aryl substituents on the rate of alkaline hydrolysis of benzamides, and Crocker[4] and Calvet[5] had studied the influence of acyl substituents on alkaline hydrolytic reactivity of aliphatic amides.

More recently, the effects of amide structure, hydroxide ion concentration, weak acids and bases, solvent composition, temperature, and other variables on the kinetics of alkaline hydrolysis of amides have been the subjects of a number of investigations. These include studies of hydrolyses of aliphatic amides,[6–9] chloroacetamides,[10] aliphatic and aromatic diamides,[11–15] benzamides,[9,16–18] glycinamide,[19] and urea.[20] Kinetic studies of alkaline hydrolysis of a number of N-substituted amides have also been reported. Most of these investigations concerned acetanilides,[21–23] acyl-substituted acetanilides,[23–32] and *N*-methylanilides.[24,29,33–35] Saponifications of glycylglycine,[36] α-propylamino-2′-methylpropionanilide,[37] and several heterocyclic amides[38–42] have also been studied.

The products of amide hydrolysis in alkaline solutions are carboxylate ions and ammonia or amines (eq 1).

$$\mathrm{RCONR'R''} + \mathrm{OH^-} \longrightarrow \mathrm{RCO_2^-} + \mathrm{R'R''NH} \qquad (1)$$

Saponification of simple aliphatic amides,[4–7] benzamides,[2,3,16,17] and a number of diamides[11–15] are first order in hydroxide ion, as would be expected if these reactions occur by the $B_{Ac}2$ mechanism of Ingold.[43]

Amide saponification is sensitive to both polar and steric effects of acyl substituents. Reactivity of aliphatic amides is decreased by alkyl substitution in the acyl substituent R (eq 1), with β-alkyl substituents retarding saponification more than α-alkyl substituents.[4–7,9] Electron-attracting acyl substituents accelerate alkaline hydrolysis of amides, with the result that mono-, di- and trichloroacetamides,[5,10] nitro- and halobenzamides,[2,3,17–19] and halo- and ammonio-substituted acetanilides[24–32] are more reactive than their unsubstituted analogs. In general, acyl substituent effects on alkaline hydrolysis are reflected more in the energy than in the entropy of activation.[6,7,9,17]

It has recently become apparent that carboxamide hydrolysis is mechanistically more complex than previously supposed. Bender and coworkers demonstrated that alkaline hydrolysis of carbonyl-^{18}O-labeled benzamide[16] and several carbonyl-^{18}O-labeled acetanilides[21] is accompanied by partial exchange of solvent oxygen for carbonyl oxygen. This observation indicates that the complexes formed by reaction of hydroxide ion with these amides are neither transition states (in which case no exchange would occur) nor intermediates in equilibrium with the starting materials (in which case complete

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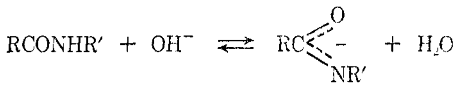
exchange should occur). In addition, rates of hydrolysis of a number of amides exhibit a greater than first-order dependence on hydroxide ion concentration in certain pH ranges. This is true of chloroacetamide,[10] glycinamide,[20] glycylglycine,[36] a number of anilides[22–29,31,32] and *N*-methylanilides,[21,24,33–35] urea,[20] 5,5-dialkylbarbituric acids,[38–40] dihydropyrimidine,[41] and dihydrouracil.[42] The kinetics of many amide hydrolyses are complicated by the fact that the amides exist in equilibrium with unreactive conjugate bases (eq 2). Amides which are sufficiently acidic to form

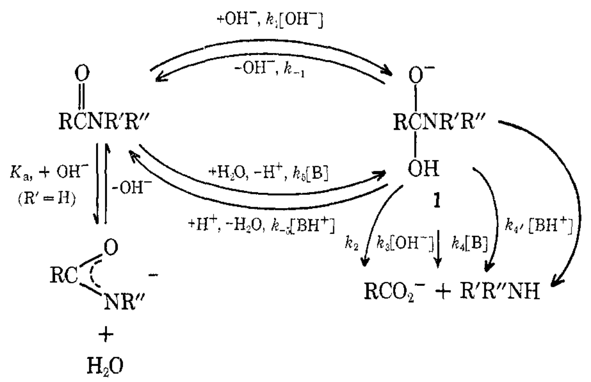


$$\mathrm{RCONHR'} + \mathrm{OH^-} \rightleftharpoons \mathrm{RC}\overset{\mathrm{O}}{\underset{\mathrm{NR'}}{\lessdot}}{}^{-} + \mathrm{H_2O} \tag{2}$$

appreciable amounts of unreactive conjugate bases at high pH include dichloro- and trichloroacetamide,[10] trichloro- and trifluoroacetanilide,[24–27,31] fluoroacetanilide,[28] trimethylammonioacetanilide,[29] *p*-nitroacetanilide,[23] 5,5-dialkylbarbituric acids,[38–40] dihydropyrimidines,[41] and dihydrouracil.[42] Further, the alkaline hydrolyses of a number of amides (acetanilide,[22] acyl-substituted acetanilides,[25–29,31,32,34,35] and chloramphenicol[30]) are subject to catalysis by general acids and bases.

The work of Eriksson,[22,25–29,38–40] Schowen,[33–35] Mader,[31] Pratt,[32] and Bender[16,21] suggests a mechanism of amide hydrolysis which rationalizes all of the experimental results described above (Scheme I).

Scheme I



According to this mechanism, amide hydrolysis involves reversible, general base catalyzed formation of an anionic tetrahedral intermediate, followed by general acid–general base catalyzed elimination of ammonia or amine from the intermediate. At sufficiently high pH, some amides dissociate to unreactive conjugate bases in a parasitic side equilibrium.

Assuming validity of the steady-state approximation for the concentration of the tetrahedral intermediate, this mechanism leads to the expression for the observed first-order rate constant, k_{obsd}, for amide hydrolysis in buffer solutions (eq 3).[32] In eq 3, B represents any Brønsted base and $\mathrm{BH^+}$ its conjugate acid.

$$k_{\mathrm{obsd}} = \frac{1}{1 + K_{\mathrm{a}}[\mathrm{OH^-}]/K_{\mathrm{w}}} \times \left\{ \frac{(k_1[\mathrm{OH^-}] + k_5[\mathrm{B}])(k_2 + k_3[\mathrm{OH^-}] + k_4[\mathrm{B}] + k_{4'}[\mathrm{BH^+}])}{k_{-1} + k_2 + k_3[\mathrm{OH^-}] + k_4[\mathrm{B}] + (k_4 + k_{-5})[\mathrm{BH^+}]} \right\} \tag{3}$$

Since experimental evidence supporting the mechanism of Scheme I is convincing in the case of certain acyl-activated anilides, it is reasonable to suppose that this mechanism is also applicable to other anilide hydrolyses. The relative importance of the various terms of eq 3 depends on the structure of the amide and the composition of the reaction medium. In unbuffered solutions eq 3 simplifies to eq 4. If the amide is so weakly

$$k_{\mathrm{obsd}} = \frac{k_1[\mathrm{OH^-}]}{1 + K_{\mathrm{a}}[\mathrm{OH^-}]/K_{\mathrm{w}}} \, \frac{k_2 + k_3[\mathrm{OH^-}]}{k_{-1} + k_2 + k_3[\mathrm{OH^-}]} \tag{4}$$

acidic that it is not appreciably dissociated in such solutions, $K_{\mathrm{a}}[\mathrm{OH^-}]/K_{\mathrm{w}} \ll 1$, and eq 4 is further simplified to eq 5. The evidence supporting the mechanism of

$$k_{\mathrm{obsd}} = k_1[\mathrm{OH^-}] \, \frac{k_2 + k_3[\mathrm{OH^-}]}{k_{-1} + k_2 + k_3[\mathrm{OH^-}]} \tag{5}$$

Scheme I (or one very similar to it) is discussed by Eriksson[39] and Pratt.[32]

While acyl substituent effects on alkaline hydrolytic reactivity of carboxamides have been studied extensively, little is known concerning the effects of amide *N* substituents on reactivity. Our interest in aryl substituent effects on anilide hydrolysis stems from the observation, made in the course of a kinetic study of alkaline *N*,*N*′-diarylformamidine hydrolysis,[44] that *p*-nitroformanilide hydrolyzes much faster than *m*-chloroformanilide in alkaline aqueous dioxane solutions. Bender and Thomas had previously reported that rates of alkaline hydrolysis of substituted acetanilides $\mathrm{CH_3CONHC_6H_4X}$ (X = *p*-$\mathrm{CH_3O}$, *p*-$\mathrm{CH_3}$, H, *p*-Cl, and *m*-$\mathrm{NO_2}$) are almost independent of the nature of the aryl group.[21] Our observation suggested either that aryl substituent effects are quite different for formanilide and acetanilide saponifications or that *p*-nitroformanilide is anomalously reactive.

In order to resolve this discrepancy and obtain additional information relevant to the mechanism of anilide saponification, we studied the effects of substituents on the phenyl group, hydroxide ion concentration, and temperature on the kinetics of alkaline hydrolysis of formanilide, *N*-methylformanilide, and a number of substituted formanilides and *N*-methylformanilides. We also studied the alkaline hydrolysis and concurrent carbonyl–oxygen exchange of *p*-nitroacetanilide. These studies confirmed that *p*-nitroanilides are anomalously reactive.

Experimental Section

Materials.—*p*-Aminobenzonitrile [mp 77–81° (lit.[45] mp 86°)] was prepared by reducing *p*-nitrobenzonitrile according to the procedure of Bogert and Hand.[46] The *p*-nitrobenzonitrile [mp 143–146° (lit.[47] mp 147°)] was obtained by a Sandmeyer reaction of *p*-nitroaniline, carried out according to the procedure of Clarke and Read.[48]

p-Hydroxyformanilide was reduced to *N*-methyl-*p*-aminophenol by the procedure of Ehrlich[49] [mp 85° (lit.[50] mp 85°)]. Other arylamines and *N*-methylarylamines were obtained from Matheson Coleman and Bell, Eastman Organic Chemicals, and Aldrich Chemical Co.

Formanilide and *N*-methylformanilide were used as received from Matheson Coleman and Bell. Other formanilides and *N*-methylformanilides were prepared from arylamines or *N*-methylarylamines and acetic formic anhydride, by the procedure

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of Huffman,[51] with the exception of *N*-methyl-*p*-nitroformanilide and *N*-methyl-*p*-chloroformanilide, which were prepared by reaction of the primary arylamines with triethyl orthoformate in the presence of concentrated sulfuric acid at elevated temperatures.[52] Properties of the formanilides and *N*-methylformanilides are listed in Table I.

Table I

Properties of Formanilides, XC_6H_4NRCHO

	R = H		R = CH_3	
X	Mp or bp (mm), °C	Lit. mp	Mp, °C	Lit. mp
p-NO_2	192–194	194–195[a]	116	118–120[m]
m-NO_2	134	134[b]	68–69	70–71[b]
m-Cl	56–57	57–58[c]		
p-Cl	92	102[d]	48–50	51[n]
p-Br	117	119[e]		
p-CH_3	47–51	52[f]		
m-CH_3	137 (1)	18[g]		
p-CH_3O	78–80	80–81[h]		
m-CH_3O	55–57	57[i]		
p-$(CH_3)_2N$	108	108[j]		
p-CN	189	188–189[k]		
p-OH	138–139	139–140[l]	106	108–109[o]

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p-Nitroacetanilide-*carbonyl*-^{18}O (mp 212.5–213°) was prepared by acetylation of *p*-nitroaniline with carbonyl-^{18}O enriched acetyl chloride. The labeled acetyl chloride was obtained by hydrolyzing acetyl chloride in water enriched with ^{18}O (1.6 atom % ^{18}O, Bio-Rad Laboratories), allowing the hydrolysis mixture to equilibrate for 1 week, and converting the recovered ^{18}O-labeled acetic acid to acetyl chloride with PCl_3.

Rate Measurements.—The hydrolysis reactions, which are first order under the conditions used, were followed spectrophotometrically with a Gilford Model 2000 recording spectrophotometer equipped with a thermostated cell compartment. Temperature control was to within 0.01°. Reactions were followed by recording the change in absorbance at the wavelength of maximum difference in absorbance between the anilide and the arylamine product. Spectra of reaction solutions made after complete hydrolysis showed that the arylamines were the only aromatic products. Reaction solutions were prepared by adding enough of a 0.01 *M* solution of the anilide in absolute ethanol to a carbonate-free aqueous sodium hydroxide solution to give a solution which contained 1.00% ethanol and was 10^{-4} *M* in anilide. Except where noted, the ionic strength of the reaction solutions was adjusted to 1.00 by use of sodium chloride. First-order rate constants were calculated graphically from plots of $\ln (A_\infty - A_t)$ *vs.* time (in seconds) or by means of a computer program which calculated the first-order rate constant which best fits the experimental data. Reactions were followed for at least 3 half-lives and usually for 10 half-lives. 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.[53]

Determination of pK_a Values of Anilides.—The pK_a's of *p*-nitroformanilide and *p*-nitroacetanilide were determined spectrophotometrically. Since these compounds hydrolyze rapidly in alkaline solutions, it was necessary to extrapolate to zero time to determine the absorbance of the anilide at each hydroxide ion concentration. Ionic strength was 1.0 for all solutions except those for which $[OH^-]$ was more than 1.0. Since neither of the anilides is completely dissociated at the highest hydroxide ion concentrations used, pK_a values were calculated using the method of Hine and Hine.[54] The pK_a of *p*-nitroformanilide, calculated from absorbance values from $[OH^-] = 0.010$–1.000 *M*, is 12.5 at 30° and 12.8 at 15°. The pK_a of *p*-nitroacetanilide, calculated from absorbance values from $[OH^-] = 0.010$–4.00 *M*, is 13.6 at 30°.

pH–absorbance profiles for *p*-hydroxyformanilide and *N*-methyl-*p*-hydroxyformanilide show that the pK_a values for dissociation of the phenolic proton of these compounds at 30° are 9.2 and 9.0, respectively. These compounds were therefore present as phenoxide ions under the conditions of the kinetic experiments.

Oxygen Exchange of *p*-Nitroacetanilide.—Samples of *p*-nitroacetanilide-*carbonyl*-^{18}O were partially hydrolyzed under the conditions used in the kinetic runs. Sample size was such as to permit recovery of 0.1 mmol of unhydrolyzed anilide. Samples were quenched by addition of sufficient HCl to neutralize the NaOH and immediately extracted 6–8 times with ethyl ether. Evaporation of the ether yielded mixtures and *p*-nitroacetanilide and *p*-nitroaniline, which were separated by thick layer chromatography on silica gel GF 254 (Brinkman Instruments, Inc.). The recovered anilide was recrystallized from benzene and degraded by the procedure of Rittenberg and Pontecorvo,[55] and the resulting CO_2 was analyzed by means of a Consolidated Electrodynamics Model 21-620 mass spectrograph to determine the ratios of the mass 44 and mass 46 peaks. The atom fraction of ^{18}O in the CO_2 was calculated according to Roberts and Urey,[56] and rates of ^{18}O exchange were calculated as described by Bender.[57]

Results

Rate constants for alkaline hydrolysis of a number of formanilides and *p*-nitroacetanilide are collected in Table II, and rate constants for alkaline hydrolysis of several *N*-methylformanilides appear in Table III.

With the exception of *p*-nitroformanilide and *p*-cyanoformanilide, the rate of alkaline hydrolysis of formanilides is independent of substituents on the aryl group, regardless of the temperature and hydroxide ion concentration (Figures 1 and 2). (In Figures 1–3, σ^- values[58] are used for *p*-CN and *p*-NO_2.) Calculated ρ values and standard errors of fit of the log k values to the least-squares regression lines follow: at 15°, 0.200 *N* NaOH, $\rho = +0.046$, $S_y = 0.054$; at 29.9°, 0.200 *N* NaOH, $\rho = -0.057$, $S_y = 0.083$; at 44.2°, 0.50 *N* NaOH, $\rho = +0.019$, $S_y = 0.062$; at 44.2°, 0.100 *N* NaOH, $\rho = -0.015$, $S_y = 0.062$; at 44.2°, 0.500 *N* NaOH, $\rho = -0.080$, $S_y = 0.078$. Under a given set of experimental conditions, *p*-cyanoformanilide is several times more reactive, and *p*-nitroformanilide is several hundred times more reactive, than the other formanilides.

In contrast to the formanilides, *N*-methylformanilide hydrolysis is accelerated by electron-withdrawing aryl substituents in 1.00 *N* NaOH solutions at 29.9° (Figure 3). The Hammett plot of these data is concave upward.

As shown in the pH–hydrolysis rate profiles of Figures 4–6, anilide hydrolysis rates are complex functions

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TABLE II

HYDROLYSIS OF ANILIDES IN AQUEOUS 1% ETHANOL–SODIUM HYDROXIDE SOLUTIONS

$[OH^-]$	10^4k_{exp}, sec^{-1}, at T, °C			
	1.2°	15.0°	29.9°	44.2°
p-Nitroformanilide				
0.010	2.4[a]		21.2[b]	33[b]
0.020	6.6	21.4	51	94
0.050	17.7		160	330
0.067			200	450
0.100	29.5	110	300	620
0.200	46	130	430	930
0.333		180	470	
0.500	50	170	510	1300
0.667		170	510	1400
1.00		220	510	1300
p-Cyanoformanilide				
0.010			0.12[b]	0.30[b]
0.020			0.34	0.93
0.033				2.0
0.050			1.42	4.2
0.067			2.23	6.2
0.100			4.1	11.0
0.200			(9.1)[c]	25
0.333			16.4	36
0.500			24	67
0.667			33	91
1.00			52	138
m-Nitroformanilide				
0.0050			0.021[a]	
0.010			0.059	
0.050			0.49	
0.100			1.0	2.04[a]
0.200			(1.8)[d]	
m-Chloroformanilide				
0.050		0.087		0.59[a]
0.100		0.22		1.24
0.200		0.63	1.30[a]	3.0
0.500		1.7	3.30	8.6
p-Bromoformanilide				
0.050		0.087[a]		0.57[a]
0.100		0.23		1.25
0.200		0.61	1.38[a]	2.6
0.500		2.2		9.6
p-Chloroformanilide				
0.067				0.88[b]
0.100				1.51
0.200		0.75[b]	1.7[b]	3.5
0.333		1.59	2.9	6.7
0.500		3.0	5.6	10.2
0.600			6.8	
0.667		3.8		15.2
0.800		6.8	9.6	
Formanilide				
0.067			0.38[b]	
0.100			0.66	1.45[a]
0.200			1.75	3.3
0.333			3.6	
0.500		2.6[a]	6.4	11.1
0.667			10.1	
1.00			15.6	
m-Formtoluidide				
0.050				0.54[a]
0.100		0.19[a]		1.18
0.200		0.55	1.24[a]	1.74
0.500		2.1		10.7
p-Formtoluidide				
0.050				0.47[a]
0.100		0.22[a]		1.01
0.200		0.53	1.21[a]	2.63
0.500		3.2		6.8
p-Methoxyformanilide				
0.050		0.091[a]		0.56[a]
0.100		0.25	0.59[a]	1.14
0.200		0.72	1.6	2.6
0.500		3.0	5.5	8.5
p-Dimethylaminoformanilide				
0.010			0.027[b]	0.097[b]
0.020			0.073	0.20
0.050			0.23	0.58
0.067			0.35	
0.100			0.57	1.57
0.200			2.3	3.8
0.333			3.4	7.3
0.500			6.5	13.1
0.667			10.2	20.2
1.00			16.9	34
p-Formylphenoxide Ion				
1.00			16.5[b]	
p-Nitroacetanilide				
0.010			0.051[b]	0.148[b]
0.020			0.150	0.44
0.033			0.34	0.97
0.050			0.65	1.82
0.067			0.98	2.8
0.100			1.74	5.0
0.200			3.8	11.3
0.333			5.6	16
0.500			8.2	26
0.677			9.7	31
1.00			11.8	37

[a] Ionic strength = 0.500. [b] Ionic strength = 1.00. [c] Interpolated value. [d] Extrapolated value.

of hydroxide ion concentration. The pH–log rate plots are curved for most of the anilides studied. Apparent kinetic orders with respect to hydroxide ion in 0.01 *N* NaOH solutions range from 1.4 to 1.6 for all of the formanilides except *p*-dimethylaminoformanilide at 44.2°, whose hydrolysis is about 1.1 order in hydroxide ion at pH 12, increasing to 1.4 order at pH 14. The pH–log rate curves for *m*- and *p*-nitroformanilides, *p*-cyanoformailide, and *p*-nitroacetanilide all exhibit downward curvature due to partial dissociation of the anilides to unreactive conjugate bases in the more concentrated sodium hydroxide solutions.

The apparent kinetic order in hydroxide ion for hydrolysis of *N*-methylformanilide and its *m*-nitro and *p*-chloro derivatives is 2.0 at pH 14 and decreases with decreasing pH. The apparent kinetic order with respect to hydroxide ion for hydrolysis of *N*-methyl-*p*-nitroformanilide is about 1.5 at pH 14 and 1.0 at pH 12.5.

Arrhenius activation energies and entropies of activation for hydrolysis of several formanilides in 0.200 *N* NaOH are recorded in Table IV. For all of the formanilides except the *p*-cyano and *p*-nitro derivatives, the energies of activation cluster around 9 kcal/mol and the entropies of activation cluster around −46 eu. The differences between E_a and $\Delta S^{\ddagger}$ values for hydrolysis of these anilides are no greater than the probable errors of the calculated values. For *p*-cyano- and *p*-nitroformanilides, the energies of activation are somewhat

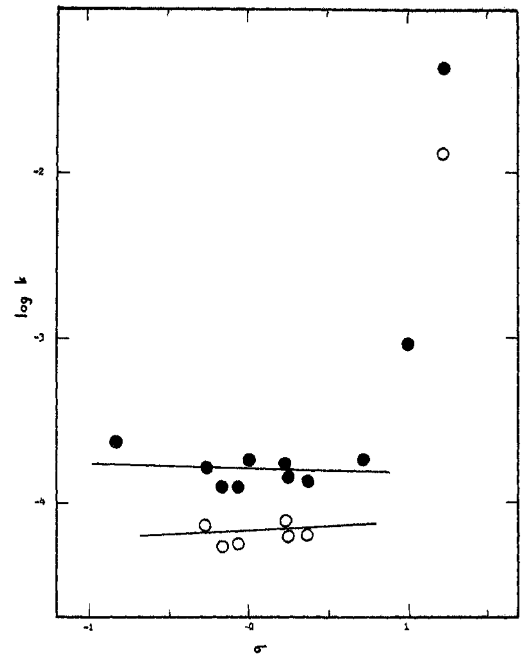


Figure 1.—Hammett plots for hydrolysis of formanilides in 0.200 *N* NaOH at 15.0 and 29.9°: ●, 29.9°; ○, 15.0°.

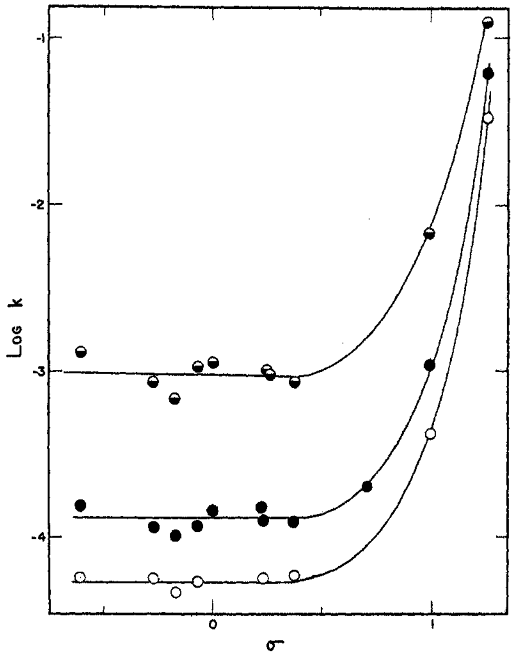


Figure 2.—Hammett plots for hydrolysis of formanilides at 44.2°: ○, in 0.050 *N* NaOH; ●, in 0.100 *N* NaOH; ◒, in 0.500 *N* NaOH.

larger , and the entropies of activation are more than 12 eu less negative, than for the other formanilides.

Hydrolysis experiments with carbonyl-^{18}O-labeled *p*-nitroacetanilide demonstrated that this acetanilide, like acetanilide and its *m*-nitro, *p*-chloro, *p*-methyl, and *p*-methoxy derivatives (previously studied by Bender and Thomas[21]), undergoes concurrent hydrolysis and carbonyl oxygen exchange in alkaline solutions. The results of these experiments, summarized in Table V, show that the rate of hydrolysis is more sensitive to hydroxide ion concentration than is the rate of oxygen exchange. In this respect *p*-nitroacetanilide resembles the acetanilides studied previously.[21]

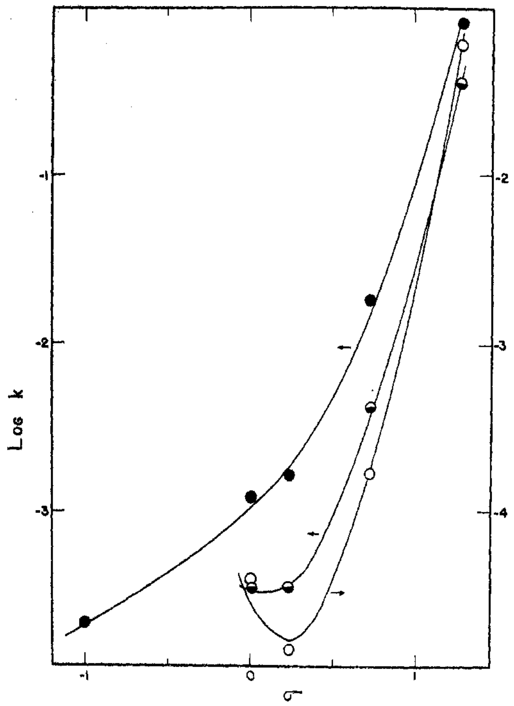


Figure 3.—Hammett plots for hydrolysis of *N*-methylformanilides at 29.9°: ●, in 1.00 *N* NaOH; ◒, in 0.500 *N* NaOH; ○, in 0.100 *N* NaOH.

TABLE III

HYDROLYSIS OF *N*-METHYLFORMANILIDES, $XC_6H_4N(CH_3)CHO$, IN AQUEOUS 1% ETHANOL–SODIUM HYDROXIDE SOLUTIONS AT 29.9°

	10^4k_{exp}, sec^{-1} [a]				
[OH⁻]	X = *p*-NO$_2$[b]	X = *m*-NO$_2$[c]	X = *p*-Cl[d]	X = H[e]	X = *p*-O$^-$[f]
0.010		0.077	0.0058		
0.020	105		0.0116		
0.050	295	0.68	0.043		
0.100	610	1.70	0.151	0.40	
0.200	1200		0.58	0.95	
0.250		8.7			
0.300			1.27		
0.333				1.82	
0.500	3600	42	3.60	3.7	
0.600			5.4		
0.667				6.2	
0.700			7.5		
0.800			9.8		
0.900			12.6		
1.00	8200	187	16.4	12.7	2.18

[a] Ionic strength = 1.00. [b–f] Registry no. are as follows: [b] 5279-61-8; [c] 31947-47-4; [d] 26772-93-0; [e] 93-61-8; [f] 31947-49-6.

TABLE IV

ENERGIES AND ENTROPIES OF ACTIVATION FOR HYDROLYSIS OF FORMANILIDES, XC_6H_4NHCHO, IN 0.2 *N* NaOH

X	Registry no.	$10^{-3}E_a$, cal/mol	$\Delta S^{\ddagger a}$, eu
p-NO$_2$	16135-31-2	12.4	−31
p-CN	6321-94-4	13.5	−33
m-Cl	139-71-9	9.7	−46
p-Br	2617-78-9	9.0	−48
p-Cl	2617-79-0	9.6	−46
m-CH$_3$	3085-53-8	10.1	−45
p-CH$_3$	3085-54-9	10.0	−46
p-CH$_3$O	5470-34-8	8.0	−49

[a] Calculated for 25°.

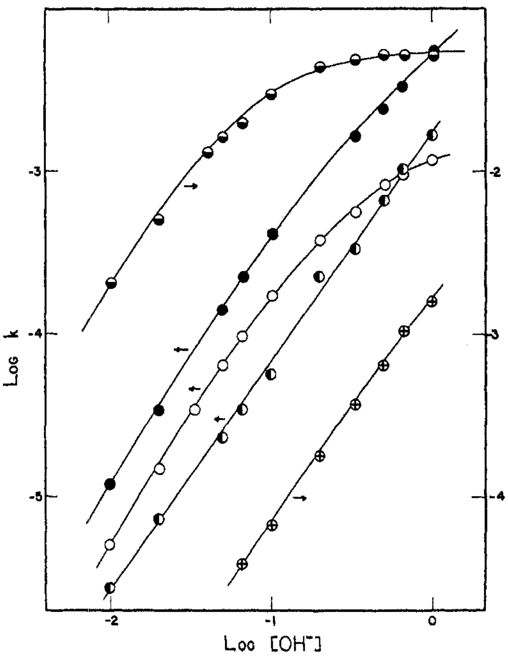


Figure 4.—Representative rate-pH profiles for hydrolysis of anilides at 29.9°: ◒, *p*-nitroformanilide; ●, *p*-cyanoformanilide; ○, *p*-nitroacetanilide; ◐, *p*-dimethylaminoformanilide; ⊕, formanilide.

TABLE V

OXYGEN EXCHANGE DATA FOR *p*-NITROACETANILIDE-^{18}O IN AQUEOUS 1% ETHANOL AT 30°, μ = 1.00

[OH⁻]	10^6k_h, sec⁻¹	10^6k_{ex}, sec⁻¹	k_h/k_{ex}
0.02	1.50	2.56	0.625
0.05	6.52	5.41	1.20
0.10	17.4	7.64	2.28
0.24			~6[a]

[a] Extrapolated value.

We observed small positive salt effects on alkaline formanilide hydrolysis. Typically, hydrolysis rate increases 10–15% when the ionic strength is increased from 0.5 to 1.0.

Discussion

If the *p*-cyano and *p*-nitro derivatives are omitted, Hammett ρ values for formanilide saponification are approximately 0 in the temperature range 15–45° and in the hydroxide concentration range 0.05–0.50 *N*. Bender and Thomas observed similarly small substituent effects on acetanilide hydrolysis[21] and showed that the approximately 0 ρ value for acetanilide saponification is due to the fact that the positive ρ value for formation of tetrahedral intermediate **1** (Scheme I) from hydroxide ion and the anilide is numerically equal to the negative ρ value for partitioning of **1** between products and starting materials. It is quite probable that a similar explanation accounts for the 0 ρ value for formanilide hydrolysis.

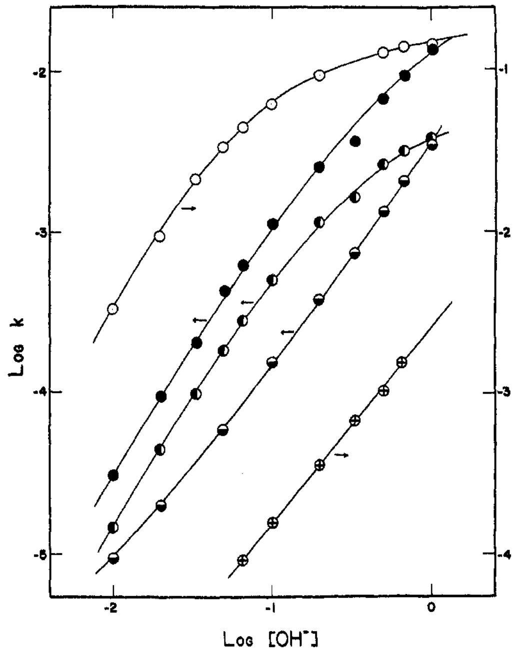


Figure 5.—Representative rate-pH profiles for hydrolysis of anilides at 44.2°: ○, *p*-nitroformanilide; ●, *p*-cyanoformanilide; ◐, *p*,nitroacetanilide; ◒, *p*-dimethylaminoformanilide; ⊕, *p*-chloroformanilide.

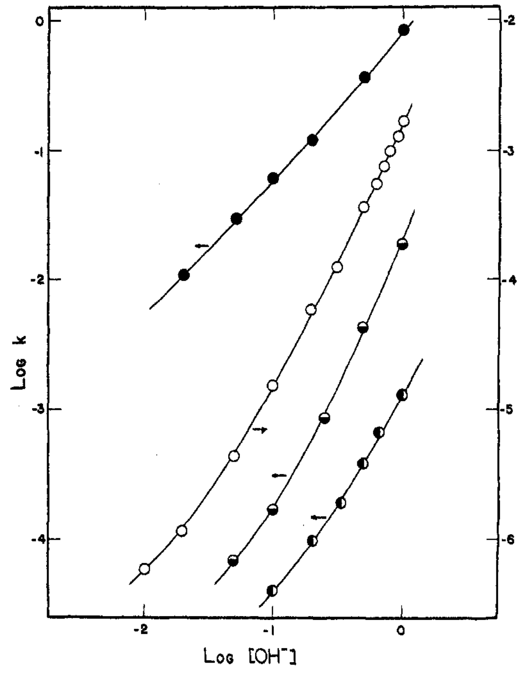


Figure 6.—Rate-pH profiles for hydrolysis of *N*-methylformanilides at 29.9°: ●, *N*-methyl-*p*-nitroformanilide; ○, *N*-methyl-*p*-chloroformanilide; ◒, *N*-methyl-*m*-nitroformanilide; ◐, *N*-methylformanilide.

The complete Hammett plots for formanilide hydrolysis (Figure 1 and 2) curve upward sharply for substituents having large positive σ values. *p*-Cyanoformanilide is about ten times as reactive, and *p*-nitroformanilide is about 100 times as reactive, as other formanilides. In order to eliminate the possibility that the anamolous reactivity of *p*-nitroformanilide might be due to incursion of a mechanism of hydrolysis involving preliminary formyl proton abstraction, we studied the kinetics of alkaline hydrolysis of *p*-nitroacetanilide (see Table II). This anilide also is more than 100 times as reactive as other acetanilides.

According to the mechanism of Scheme I, hydrolysis products in unbuffered alkaline solutions are formed from anionic tetrahedral intermediate **1** by competing reactions which are zero order and first order in hydroxide ion. The influence of aryl and acyl substituents on values of k_1 and the partitioning ratios k_2/k_{-1} and k_3/k_{-1} illuminates the mechanism of anilide hydrolysis. These values, which can be calculated from rates of isotope exchange, rates of hydrolysis, and pK_a values of various aryl- and acyl-substituted acetanilides, are summarized in Table VI.

Table VI

Values of k_1 and Partitioning Ratios for Alkaline Hydrolysis of $YCONHC_6H_4X$

Y	X	10^5k_1, M^{-1} sec^{-1}	k_2/k_{-1}	k_3/k_{-1}, M^{-1}	k_3/k_2, M^{-1}
CH_3	p-CH_3O[a]	4.20[h]	0.195	0.160	0.82
CH_3	p-CH_3[a]	4.85[h]	0.146	0.084	0.57
CH_3	H[a]	7.85[h]	0.097	0.047	0.49
		7.85[i,j]	0.084	0.053	0.63
CH_3	p-Cl[a]	12.7[h]	0.055	0.051	0.91
CH_3	p-NO_2[b]	368[h]	0.077	10.6	138
		470[i]	0.05	8.0	160
CH_2F	H[c,d]	1370[i]	0.021	0.75	36
$(CH_3)_3\overset{+}{N}CH_2$	H[c,e]	1230[i]	0.0030	0.37	123
CCl_3	H[c,f]	15,500[i]	0.025	34	136
CF_3	H[c,f]	155,500[i]	0.025	93	372
$CHCl_2$	p-NO_2[g]	3,900,000[i]	0.05	6130	

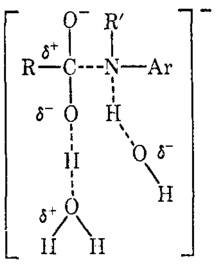
[a] Reference 21, $T = 24.7°$. [b] Present work, $T = 30.0°$. [c] Rates measured in aqueous 9.6% ethanol at 25.0°. [d] Reference 28. [e] Reference 29. [f] Reference 27. [g] Reference 32, $T = 40°$. [h] Data in this row calculated from kinetics of hydrolysis and isotope exchange. [i] Data in this row calculated from kinetics of hydrolysis. [j] Reference 22, $T = 25°$.

The data of Table VI show that electron-attracting substituents on the aryl group increase the rate of formation of the tetrahedral intermediate **1** (k_1 of Scheme I) but are less effective in doing so than electron-attracting acyl substituents. The partitioning ratio k_2/k_{-1} is insensitive to inductive effects of acyl substituents (as expected, since acyl substituents should affect departure of anilide or hydroxide about equally) but is influenced by aryl substituents. Electron-withdrawing substituents on the aryl group decrease k_2/k_{-1}, presumably by diminishing the basicity of anilino nitrogen and so reducing the effectiveness of water as a general acid catalyst in the product-forming step. Values of k_2/k_{-1} show that intermediate **1** reverts to anilide and hydroxide ion 5–40 times faster than it undergoes conversion to products. In contrast, the ratio k_3/k_{-1} is strongly affected by electron-attracting substituents in either the acyl or aryl group of the anilide. For p-nitroacetanilide,trichloro- and trifluoroacetanilides, and p-nitrodichloroacetanilide, k_3/k_{-1} and k_3/k_2 are both much larger than unity. For these anilides, hydroxide ion catalyzed conversion of **1** to products is much faster than reversion of **1** to starting materials at high pH, and formation of **1** becomes rate limiting.

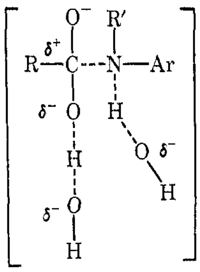
A Hammett plot of log k_1 *vs.* σ is linear with positive slope for all of the acetanilides, including the p-nitro derivative. The Hammett plot of log k_2/k_{-1} *vs.* σ is linear with negative slope for all of the acetanilides except p-nitroacetanilide, whose point is above the line defined by the other points. In contrast, a Hammett plot of log k_3/k_{-1} *vs.* σ is strongly concave upward, passing through a minimum at approximately $\sigma = 0$. This suggests that the mechanism of the third-order hydrolytic pathway changes as the electronic properties of the aryl group changes and that the anomalous reactivity of p-nitroacetanilide is a consequence of its reacting mainly *via* a different mechanism from the other anilides, at least in the pH range 12–14.

p-Cyano- and p-nitroformanilides also appear to hydrolyze by a different mechanism than the other formanilides at high pH. The nonlinear Hammett plots of log k_{obsd} *vs.* σ (Figures 1 and 2) suggest a shift in mechanism, and the fact that the entropies of activation for hydrolysis of the p-nitro- and p-cyanoformanilides are some 15 eu less negative than the entropies of activation for the other formanilides also suggests that formanilides hydrolyze by two different mechanisms. Further, for p-nitroformanilide hydrolysis it is possible to calculate k_1 and k_3/k_{-1} from kinetic data and the pK_a of the anilide. The values of these parameters which best reproduce the experimental data when inserted into eq 4 are $k_1 = 1.9\ M^{-1}$ sec^{-1} and $k_3/k_{-1} = 16\ M^{-1}$ (standard error in log $k = 0.021$ using these values; the fit is not improved by inclusion of a k_2/k_{-1} term, which means that k_3/k_2 is much larger than unity). The value of k_3/k_{-1} is similar to the values calculated for p-nitroacetanilide hydrolysis and is much larger than values calculated for the other acetanilides.

The product-forming step in the hydrolysis of anilides lacking strongly electron-attracting substituents on the aryl group probably involves simultaneous proton removal from the hydroxyl group of intermediate **1** by hydroxide ion or a general base and proton transfer to anilino nitrogen from water or a general acid. This conclusion is supported by the observed general acid–general base catalysis of anilide hydrolysis,[32,35,39] by solvent–deuterium isotope effects,[34] and by the fact that both k_2/k_{-1} and k_3/k_{-1} decrease when the water content of the solvent decreases.[22] The large negative entropies of activation for formanilide hydrolysis in alkaline solutions (Table IV) suggest that transition states for anilide hydrolysis involve considerable bound water. **2** and **3** are possible structures for transition states for second- and third-order hydrolysis of "typical" anilides. Water undergoing covalency change, but not hydrogen-bonded water of solvation, is shown in these structures.



2

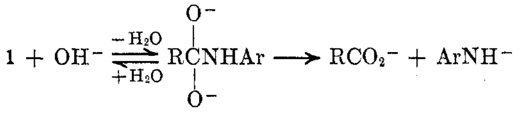


3

Hydrolysis reactions proceeding *via* transition states **2** and **3** involve general acid catalyzed fission of the acyl carbon–anilino nitrogen bond. General base catalyzed dissociation of the tetrahedral intermediate to a carboxylate ion and an arylamide ion would involve cleavage of a strong carbon–nitrogen bond and formation of a strongly basic amide ion. This apparently is energetically unfeasible for most carboxanilides and, in accordance with the dictum that general acid catalysis becomes important when it is most needed, cleavage of the C–N bond is general acid catalyzed.

Hydrolyses of p-nitroanilides (and probabyl p-cyanoformanilide and p-formylacetanilide) probably differ from other anilide hydrolyses in not requiring general acid catalysis for fission of the C–N bond. The acyl carbon–anilino nitrogen bonds in these compounds are weakened by the inductive effect of the aryl substituent, and the arylamide ions formed by C–N bond cleavage are stabilized by resonance interactions between amide nitrogen and the *p*-nitro or *p*-cyano groups.

The large values of k_3/k_2 for *p*-nitroanilide hydrolyses mean that most of the hydrolysis of these compounds at high pH proceeds *via* a process which is second order in hydroxide ion. Thus, the transition state for product formation has two negative charges. Two possible mechanisms which would yield arylamide ions as intermediates from doubly charged transition states are hydroxide ion catalyzed elimination of arylamide ion from **1** and dissociation of a dinegative ion **4**, in equilibrium with **1** (eq 6).



$$1 + OH^- \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} R\overset{O^-}{\underset{O^-}{C}}NHAr \longrightarrow RCO_2^- + ArNH^- \qquad (6)$$

4

4 is more likely to be an intermediate in hydrolyses of anilides having strongly electron-attracting substituents (such as *p*-nitro) than in hydrolyses of other anilides because these substituents increase the acidity of the hydroxyl group of **1**. Pollack and Bender recently reported that the solvent–deuterium isotope effect on hydrolysis of *p*-nitroacetanilide in 0.0046 M OH⁻ at 25° is $k_{H_2O}/k_{D_2O} = 0.61$.[23] This isotope effect is consistent with the mechanism of eq 6.

Pollack and Bender assumed that, at 25° in the pH range 12–14, *p*-nitroacetanilide hydrolyzes exclusively according to eq 6. Actually, a fraction of the reaction at the lower end of the pH range probably yields products from a water-catalyzed reaction of intermediate **1**. In fitting Pollack and Bender's data to eq 4, a better fit results if a k_2/k_{-1} term is included than if it is not. The best fit was obtained using $K_a = 1.6 \times 10^{-14}$, $k_3/k_{-1} = 9.0\ M^{-1}$, $k_2/k_{-1} = 0.015$ and $k_1 = 2.25 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$. The best fit between calculated and observed rate constants for hydrolysis of *p*-nitroacetanilide at 30° (Table II) is obtained by using eq 4 with $K_a = 2.5 \times 10^{-14}$, $k_3/k_{-1} = 8.0\ M^{-1}\ \text{sec}^{-1}$, $k_2/k_{-1} = 0.05$, and $k_1 = 4.7 \times 10^{-3}\ \text{sec}^{-1}$ (standard error in log k using these values is 0.012). We conclude that a small part (about 35% at pH 12; less than 1% at pH 14) of the hydrolysis of *p*-nitroacetanilide proceeds through a singly negatively charged transition state, probably **2**.

The pH profiles for anilide saponification are complex and differ depending on the structure of the aryl group (see Figures 4 and 5). At sufficiently low hydroxide ion cncentration (below pH 12 for all of the anilides of this study), all of the products are formed by the k_2 step of Scheme I, and k_{obsd} is first order in hydroxide ion. As the hydroxide ion concentration increases, a point is reached at which a significant amount of product is formed by the k_3 step, and the kinetic order in hydroxide gradually increases toward 2. If the anilide has electron-withdrawing acyl or aryl substituents, the observed kinetic order in hydroxide ion is unlikely to reach a limiting value of 2 for two reaons: first, the anilide is sufficiently acidic to partly dissociate to an unreactive conjugate base at high pH (eq 2); and, second, k_3/k_{-1} is much larger than unity for these activated anilides, so that formation of tetrahedral intermediate **1** rather than its conversion to products becomes rate limiting at high pH. These two factors combine to cause k_{obsd} to level off to a constant value at sufficiently high pH.

If k_{obsd} is corrected for the protolytic equilibrium of eq 2, it is anticipated that the slope of the rate–pH profile for an activated anilide would increase from 1 to 2 and then diminish to 1 again as the pH is increased over a wide range. Such plots of k_{corr} *vs.* pH [$k_{corr} = k_{obsd}(1 + K_a[OH^-]/K_w)$] for *p*-nitroformanilide and *p*-nitroacetanilide show the expected trends. In the pH range 12–14, the slope of the k_{corr} *vs.* pH plot for hydrolysis of *p*-nitroformanilide at 30° diminishes from 1.65 to 1.0. A similar plot for hydrolysis of *p*-nitroacetanilide at 30° diminishes in slope from 1.7 to 1.1.

Hydrolysis of *N*-methylanilides is not complicated by the parasitic equilibrium of eq 2. Otherwise, the *N*-methylanilides probably hydrolyze by essentially the same mechanisms as ordinary anilides. The hydrolysis reactions are general acid–general base catalyzed,[29,33–35] show mixed and variable kinetic orders with respect to hydroxide ion, and in the case of *N*-methylformanilides yield Hammett plots which are concave upward (Figure 3).

N-Methylformanilides (see Figure 6), *N*-methyltrimethylammonioacetanilide,[29] and a number of other acyl-substituted *N*-methylacetanilides[24] exhibit pH–hydrolysis rate profiles whose slopes increase with increasing pH. The observed pH profiles indicate that product formation *via* the k_3 step of Scheme I becomes important at high pH and further (since slopes of the pH profiles do not decrease at the highest pH) that k_3/k_{-1} and k_2/k_{-1} are both smaller than unity; that is, formation of tetrahedral intermediate **1** does not become rate limiting for these anilides, even at high pH.

The limited data available indicate that *N*-methyl substitution in an anilide increases k_2/k_{-1} (Table VII).

TABLE VII

EFFECT OF *N*-METHYL SUBSTITUTION ON k_2/k_{-1} FOR ANILIDE HYDROLYSIS

	k_2/k_{-1}	
Anilide	R = H	R = CH₃
$CF_3CONRC_6H_5$	0.025[a]	0.2[b]
$CH_3CONRC_6H_4$-*p*-NO_2	0.077[c]	1.1[d]

[a] Reference 27, $T = 25°$. [b] Reference 34, $T = 25°$. [c] Present work, $T = 30°$. [d] R. F. Pratt, Ph.D. Dissertation, University of Melbourne, Australia, 1969.

This may be due in part to the greater release of steric crowding when the tetrahedral intermediate from an *N*-methylanilide is converted to products.

In contrast to alkaline hydrolysis of unactivated formanilides and acetanilides, which give Hammett plots of approximately zero slope at several hydroxide ion concentrations, there is an indication that Hammett plots of hydrolysis of unactivated *N*-methylformanilides have slopes which vary with the hydroxide ion concentration. The limited data available (see Figure 3) indicate that plots of log k_{obsd} *vs.* σ have positive slopes at high hydroxide ion concentration and negative slopes at low hydroxide ion concentration. This indicates that ρ for k_3/k_{-1} is less negative than ρ for k_2/k_{-1}, which is opposite to the situation with acetanilides having no *N*-methyl substituent (Table VI).

The anomalous accelerating effect of electron-attracting substituents on hydrolysis rate is even more striking in the case of *N*-methylformanilides than in the case of formanilides: *N*-methyl-*m*-nitroformanilide is about ten times as reactive, and *N*-methyl-*p*-nitroformanilide is about a thousand times as reactive, as *N*-methylformanilide. The explanation of the enhanced reactivity of nitro-substituted *N*-methylformanilides is probably the same as for other anilides: strongly electron-attracting aryl substituents cause a change in mechanism from that of Scheme I to that of eq 6. This view is supported by the fact that the effect of the *p*-nitro group on the entropy of activation for hydrolysis of *N*-methyl-*p*-nitroformanilide is similar to its effect on the entropy of activation for hydrolysis of *p*-nitroformanilide: the entropy of activation for *N*-methyl-*p*-nitroformanilide hydrolysis in 0.2 *N* NaOH (−18 eu) is more than 20 eu less negative than that for hydrolysis of a more typical anilide, *N*-methyl-*p*-chloroformanilide (−41 eu).

Registry No.—*m*-Nitroformanilide, 102-38-5; formanilide, 103-07-8; *p*-dimethylaminoformanilide, 18606-63-8; *p*-formylphenoxide ion, 18938-17-5; *p*-nitroacetanilide, 104-04-1.

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Reactions of Nitrosobenzene and Azoxybenzene with Benzene, Benzene-d_6, and Cyclohexane at 600°

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Nitrosobenzene reacts with benzene at 200–400° to give mostly azoxybenzene and nitrobenzene. At 500–600° the major products are diphenylamine, biphenyl, phenol, and phenylcarbazoles. Minor products include nitrobenzene, triphenylamine, aminobiphenyl, carbazole, hydroxybiphenyl, diphenyl ether, and aniline. Similar products are formed from azoxybenzene and benzene at 600° with a few exceptions; aniline is a major product and nitrobenzene, triphenylamine, and phenylcarbazoles are not produced. Studies with benzene-d_6 and cyclohexane at 600° showed that in the presence of benzene, nitrosobenzene dissociates to phenyl radical and NO. Disproportionation of nitrosobenzene to azoxybenzene and nitrobenzene occurs in the presence of cyclohexane at 600° but is minor in the presence of benzene.

Although nitrosobenzene and azoxybenzene have been the subject of many investigations, their behavior at elevated temperatures has been relatively unexplored. Bamberger[1] found that nitrosobenzene decomposed at 100° to give mainly azoxybenzene, together with small quantities of nitrobenzene, aniline, *o*-hydroxyazobenzene, and *o*- and *p*-hydroxyazoxybenzene. He proposed that the nitrosobenzene was converted to a mixture of phenylhydroxylamine and nitrobenzene, and the former reacted with nitrosobenzene to give azoxybenzene. Knipscheer[2] pyrolyzed azoxybenzene at 240–250° in the presence of carbon dioxide and obtained 2- and 4-hydroxyazobenzene and azobenzene as products. Dry distillation of azoxybenzene also gave azobenzene along with aniline and nitrosobenzene.[3]

To characterize further the thermal chemistry of nitrosobenzene, we examined its reactions with benzene, benzene-d_6, and cyclohexane. As nitrosobenzene readily gives azoxybenzene, the reactions of azoxybenzene were also studied.

Experimental Section

Experimental procedures and analyses have been described.[4] In a typical experiment, a solution of 19.8 g (0.1 mol) of azoxybenzene and 39 g (0.5 mol) of benzene was pumped into a Vycor tube filled with Vycor chips at 600° under a helium flow of 20 cc/min, with a contact time of 16.1 sec. The vapors were condensed in a flask at 0°; the condensate was distilled to give 32.4 g of benzene and 14.0 g of residue whose analysis is shown in Table II.

Results and Discussion

Nitrosobenzene and Azoxybenzene with Benzene.—The products from the reaction of nitrosobenzene with benzene at 200–600° are listed in Table I. Nitrosobenzene decomposes to nitrobenzene and azoxybenzene at 200–400°, whereas at 500–600° diphenylamine, biphenyl, and carbazoles are the major products. To

TABLE I

REACTION OF NITROSOBENZENE WITH BENZENE[a]

Products	Relative concentration[b] 200°	300°	400°	500°	600°
Nitrobenzene	19.1	19.3	17.5	7.1	5.9
Azoxybenzene	76.1	75.7	62.1		
Azobenzene	3.4	3.9	6.5		
Diphenylamine	Trace	0.6	8.2	33.0	34.3
Aminobiphenyls					0.7
Biphenyl			2.7	37.4	30.2
Phenol	1.2	0.5	1.0	8.4	10.1
Diphenyl ether, hydroxybiphenyls					3.6
Carbazole			1.0	1.4	1.2
Phenylcarbazoles			1.0	11.5	12.0
Triphenylamine				1.0	1.4
Aniline				Trace	0.6

[a] Reaction conditions: contact time, 10–19 sec; mole ratio nitrosobenzene:benzene = 1:5. [b] Determined by gas chromatography.

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[1] E. Bamberger, *Ber.*, **35**, 1606 (1902).

[2] H. M. Knipscheer, *Recl. Trav. Chim. Pays-Bas*, **22**, 1 (1903).

[3] E. Bamberger, *Ber.*, **27**, 1182 (1894).

[4] E. K. Fields and S. Meyerson, *J. Org. Chem.*, **33**, 2315 (1968); **35**, 62 (1970).