result. The observed distributions could result either from dynamic tautomerism in individual molecules or a disordered structure containing both tautomers arranged at random, making the mirror planes perpendicular to *c* statistical only. If, in the dynamic model, the interchange were very fast then it would merely add into the true thermal vibrations which should then show an interpretable pattern. An interchange in individual molecules which is slow compared to thermal vibrations and a spatial disordering of different tautomers would be indistinguishable from the X-ray data. Diffuse scattering observed around the intense reflections is consistent with a disordered structure.

The observed bond distances are very well explained by the above model. The bonds C(1)–C(2) and C(2)–C(4) are 1.41 and 1.42 Å, respectively, very close to the average of carbon–carbon single and double bond distances. The C(2)–C(3) distance of 1.47 Å is of the magnitude expected for a carbon–carbon single bond in a conjugated system.[9] The carbon–oxygen distance in the ring (1.36 Å) is very similar to the bond distance of 1.369 Å found for the equivalent bond in 2,6-dimethyl-γ-pyrone.[10] The bond C(4)–O(4) is intermediate between the carbon–oxygen double bond distance and the carbon–hydroxyl distance. The bond C(1)–O(1) is shorter than that expected for a pure carbon–hydroxyl bond, but this could be due to ionic contribution, or to a partial contribution from the symmetrical structure with a central keto group. The bond angles within the ring are normal with the exception of the C(3)–O(3)–C(3) angle which probably opens to accommodate the oxygen atom within the plane of the ring, thus distorting the angles of the carbonyl configuration slightly. This type of angle opening at the oxygen vertex with corresponding narrowing of the adjacent O–C–C angles was also noted in dehydroacetic acid monimide ligands.[11]

It should be noted that the bond distances given above are uncorrected either for thermal motion or corresponding disorder effects. Attempts to correct for thermal motion using the riding model[12] gave less reasonable values than the uncorrected ones, not surprisingly in these circumstances. The simultaneous occurrence of both thermal motion and static disorder of relatively small magnitude creates an indeterminate situation with very high correlation of these variables. The standard deviations computed must therefore be regarded as minimum.

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The Alkaline Hydrolysis of *p*-Nitroacetanilide and *p*-Formylacetanilide[1a]

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Abstract: The hydroxide ion catalyzed hydrolysis of *p*-nitroacetanilide (I) and *p*-formylacetanilide (II) has been investigated at 25.0° at [OH$^-$] ranging from about 10^{-3} to 1 *M*. The rates for both compounds show a very marked dependence on the concentration of hydroxide ion. The kinetic order for I in hydroxide ion varies from 1.8 at low [OH$^-$] to 0.4 at high [OH$^-$]. The order for II is 1.9 throughout the range investigated. At [OH$^-$] below 0.1 *M*, I reacts 25 times faster than II. Both compounds react substantially faster than predicted from a previous study of ring-substituted acetanilides with more electron-donating substituents. These results are interpreted in terms of a mechanism involving nucleophilic attack of hydroxide ion to form a tetrahedral intermediate, followed by ionization to a dianion, and unimolecular breakdown to acetate ion and anilide ion. An inverse solvent isotope effect for *p*-nitroacetanilide ($k_{H_2O}/k_{D_2O} = 0.61$) at [OD$^-$] = 4.60×10^{-3} *M* supports this mechanism. The varying kinetic order in [OH$^-$] for I is explained by a change in the rate-determining step of the reaction at higher concentration of base, in conjunction with ionization of the substrate to give an unreactive anion. The pK_a's of *p*-nitroacetanilide and *p*-formylacetanilide were measured and found to be 13.8 and 14.3, respectively.

In a previous publication from these laboratories,[2] it was proposed that the alkaline hydrolysis of anilides involves a dipolar ion which decomposes to give the carboxylate ion and free amine directly. This proposal was based primarily on the finding that the hydrolysis rates of a series of ring-substituted anilides depend only slightly on substituent, but that the partitioning of the tetrahedral intermediate is markedly influenced by substituent. Subsequent findings of general base catalysis in the hydrolysis of 2,2,2-trifluoroacetanilide,[3] acetanilide,[4] and 2,2,2-trifluoro-*N*-methyl-

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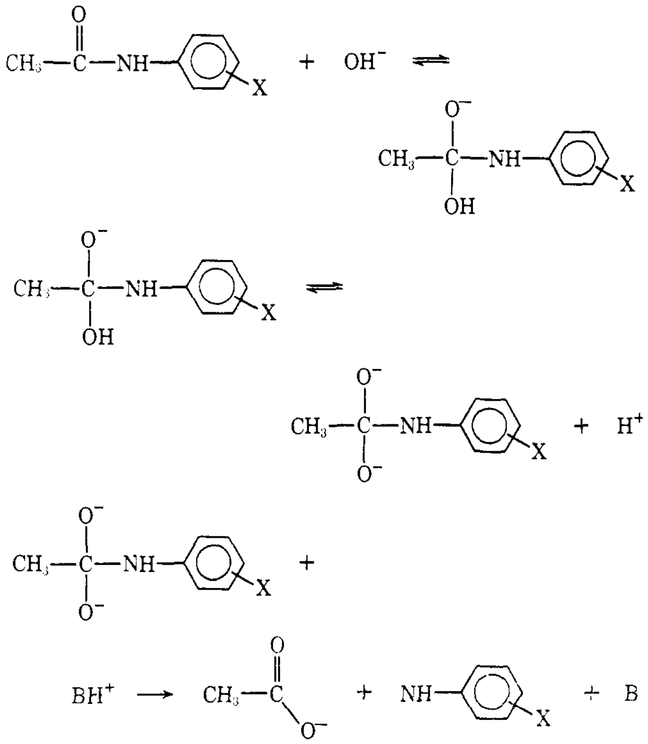
[1] (a) This research was supported by the National Science Foundation; (b) National Institutes of Health Postdoctoral Fellow, 1968–1970; (c) to whom correspondence should be addressed.

[2] M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, 83, 4183 (1961).

acetanilide,[5] as well as the fact that solvent isotope effects of substantially greater than unity have been found for 2,2,2-trifluoro-*N*-methylacetanilide,[6] indicate that a rate-determining proton transfer is occurring. A modification of the original proposal of Bender and Thomas[2] which takes this fact into account is Mechanism I. This mechanism accounts for the observation[2,7] that anilide hydrolysis is dependent on both the first and second powers of the hydroxide concentration, since either H_3O^+ or H_2O may act as the general acid BH^+.

Mechanism I



We have now found that *p*-nitroacetanilide and *p*-formylacetanilide react substantially faster than predicted from previous work[2] on other anilides and, furthermore, the dependence of the rates of hydrolysis of these two compounds on the hydroxide ion concentration is different from that observed with other anilides. These results indicate that a new mechanism is operating for anilides with strongly electron-withdrawing substituents on the phenyl group. This pathway involves the expulsion of a negatively charged anilide ion and not a neutral aniline molecule.

Experimental Section

Materials. *p*-Nitroacetanilide (Aldrich) was recrystallized from 95% ethanol, mp 214–215° (lit.[8] 215–216°). *p*-Formylacetanilide (*p*-acetamidobenzaldehyde, Aldrich) was recrystallized twice from water, mp 156–157° (lit.[9] 153°, lit.[10] 156°). Carbonate-free sodium hydroxide (Baker, reagent) was dissolved in distilled water and standardized against potassium acid phthalate.

Kinetic Measurements. The rates of hydrolysis were measured spectrophotometrically by following the increase in absorbance due to product aniline using a Cary 14PM or Gilford 220 recording spectrophotometer. Wavelengths employed were 380 nm for *p*-nitroacetanilide and 330 nm for *p*-formylacetanilide. Initial concentrations were either 7.27×10^{-5} *M* or 6.19×10^{-4} *M* for I and 8.22×10^{-5} *M* for II. A 0.99% DMSO solution was used in order to facilitate the kinetic measurements. Two runs were also done with I at 0.17% DMSO and $[I] = 1.04 \times 10^{-4}$ *M*.

The initial hydroxide ion concentration varied from 3.8×10^{-3} *M* to 9.7×10^{-1} *M*, and the ionic strength was maintained constant at 0.96 *M*. At the lowest concentrations of hydroxide, the reaction was only monitored to about 2% completion so that the hydroxide ion concentration remained constant during the run. At higher $[OH^-]$, the runs were followed to completion, but since the hydroxide ion was in large excess the reaction exhibited pseudo-first-order kinetics.

The kinetics were analyzed in one of three ways: (1) if the absorbance at $t = \infty$ was determined (after 10 half-lives), a plot of log $(A_\infty - A_t)$ *vs.* t was used; (2) if A_∞ was not determined, the rate constant was determined by the method of Guggenheim;[11] or (3) for very slow reactions, the rate was obtained by following the reaction on the 0.0–0.1 slide wire of the Cary spectrophotometer and dividing the zero-order rate constant for the first 2% reaction by the substrate concentration. The A_∞ used was that determined in the runs which were followed to completion.

For those concentrations of hydroxide at which both the initial rate technique and another method were used, the agreement between the two methods was better than 8%. Agreement was within 3% between the runs in 0.99% DMSO and 0.17% DMSO.

The pK_a of *p*-nitroacetanilide was determined spectrophotometrically at 390 nm by using hydroxide ion concentrations of 2.38×10^{-2} to 1.99 *M* ($\mu = 0.96$ except for $[OH^-] > 1$ *M*). The extinction coefficient of the un-ionized form was determined by using a pH 9.00 buffer. It was impossible to measure the extinction coefficient of the completely ionized form because at higher hydroxide ion concentrations the substrate was salted out. This value was treated as a variable along with the pK_a and a curve was fitted to the experimental points. At the highest $[OH^-]$ used, the substrate was approximately 70% ionized. Since there was appreciable hydrolysis at high $[OH^-]$, the absorbancies were extrapolated to the time of mixing. The pK_a of *p*-formylacetanilide was measured in like manner at 330 nm.

Results

The base-catalyzed hydrolyses of *p*-nitro- and *p*-formylacetanilides may be conveniently followed by observing the increase in absorbance in the visible or ultraviolet spectrum due to product aniline. All reactions were run at 25.0 ± 0.2° with base concentrations ranging from 3.8×10^{-3} *M* to 9.7×10^{-1} *M*. The ionic strength was kept constant at 0.96 with sodium chloride.

Reactions at high $[OH^-]$ were followed to completion, but those at lower hydroxide ion concentrations were analyzed by the method of Guggenheim[11] or by initial rates. All the reactions which were followed to completion gave stable infinity points and excellent pseudo-first-order kinetics. The infinity spectrum in each case was that of the corresponding aniline.

The hydrolysis rates are given in Table I. The possibility of ionization of the starting acetanilide to give an anion which is inert to hydrolysis must be considered. In order to correct for this process, the

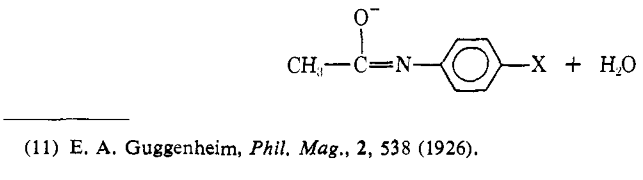


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Table I. Rates of Base-Catalyzed Hydrolysis of *p*-Nitro- and *p*-Formylacetanilides[a]

X	$[OH^-]$, *M*	Log $[OH^-]$	k, sec^{-1}	Log k	Log k_{corr}[b]	Method[c]
NO_2 (I)	3.84×10^{-3}	−2.42	5.81×10^{-7}	−6.24	−6.24	I
	4.60×10^{-3}	−2.34	1.31×10^{-6}	−5.88	−5.88	I[d]
	4.60×10^{-3}	−2.34	1.37×10^{-6}	−5.86	−5.86	I[d]
	9.59×10^{-3}	−2.02	2.67×10^{-8}	−5.57	−5.57	I
	9.59×10^{-3}	−2.02	2.63×10^{-6}	−5.58	−5.58	G
	9.67×10^{-3}	−2.01	2.62×10^{-6}	−5.58	−5.58	I[e]
	1.63×10^{-2}	−1.79	6.83×10^{-6}	−5.17	−5.15	I
	2.88×10^{-2}	−1.54	1.78×10^{-5}	−4.75	−4.72	I
	2.88×10^{-2}	−1.54	1.93×10^{-5}	−4.72	−4.69	C
	5.76×10^{-2}	−1.25	5.90×10^{-5}	−4.23	−4.19	C
	9.59×10^{-2}	−1.02	1.15×10^{-4}	−3.94	−3.89	C
	2.40×10^{-1}	−0.62	3.17×10^{-4}	−3.50	−3.34	C
	4.71×10^{-1}	−0.33	5.31×10^{-4}	−3.27	−3.02	C
	9.59×10^{-1}	−0.02	7.15×10^{-4}	−3.15	−2.73	C
	9.67×10^{-1}	−0.01	6.94×10^{-4}	−3.16	−2.74	C[e]
CHO (II)	2.80×10^{-2}	−1.55	5.11×10^{-7}	−6.29	−6.29	I
	9.27×10^{-2}	−1.03	5.17×10^{-6}	−5.29	−5.27	G
	2.37×10^{-1}	−0.63	2.75×10^{-5}	−4.56	−4.49	G
	4.71×10^{-1}	−0.33	7.03×10^{-5}	−4.15	−4.06	C
	9.40×10^{-1}	−0.03	2.25×10^{-4}	−3.65	−3.52	C

[a] In 0.99% DMSO at 25.0°. [b] Corrected for pK_a of I = 13.8 and pK_a of II = 14.3. [c] C = followed to completion; G = Guggenheim; I = initial rate. [d] D_2O. [e] 0.17% DMSO.

pK_a of both compounds was measured spectrophotometrically. For *p*-nitroacetanilide (I), the pK_a is 13.8 ± 0.2 and for *p*-formylacetanilide (II), it is 14.3 ± 0.3. The hydrolysis rates corrected for ionization, k_{corr} (assuming that the ionized material is totally inactive), are plotted against log $[OH^-]$ in Figure 1.

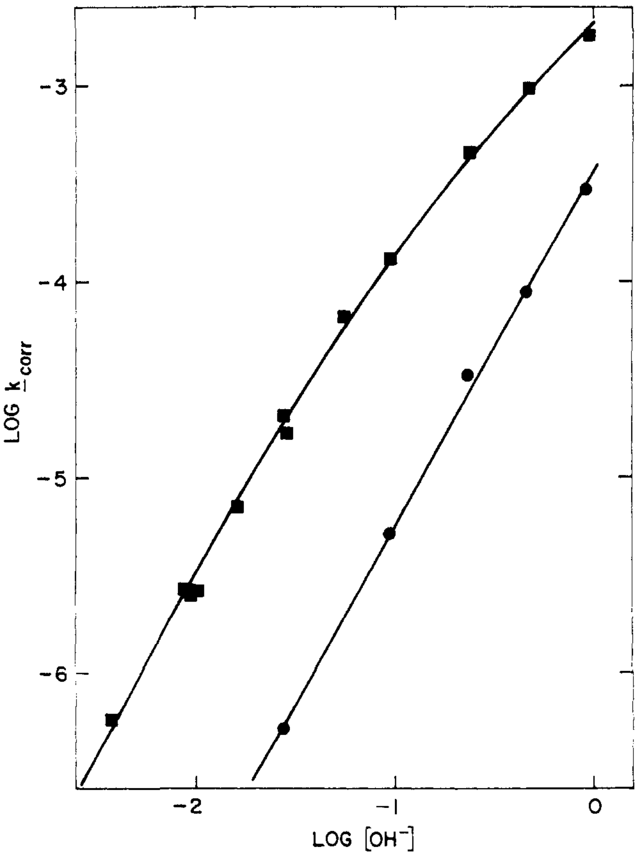

Figure 1. Rate–acidity profile for *p*-nitroacetanilide (■) (I) and *p*-formylacetanilide (●) (II).

Compound I gives a slope of the rate–acidity profile at low $[OH^-]$ of 1.8, whereas at high values of $[OH^-]$, the slope approaches 1.0. A rate–acidity profile of this type may be accounted for by the following rate expression (eq 1). The curve drawn in Figure 1 is

$$k_{corr} = \frac{k_1 k_2 [OH^-]^2}{k_{-1} + k_2 [OH^-]} \tag{1}$$

the theoretical one from eq 1, using values of $k_1 = 2.2 \times 10^{-3}$ and $k_2/k_{-1} = 17$. The value of k_1 was obtained from the rates at high $[OH^-]$ and the ratio k_2/k_{-1} was varied to fit the curve to the experimental points.

In contrast to what was observed for I, the plot of log k_{corr} *vs.* log $[OH^-]$ for II is linear throughout the entire range investigated. The slope of this plot is 1.9, indicating that there are two hydroxide ions required in the transition state at all values of $[OH^-]$. At low $[OH^-]$ the ratio $k_{corr}^{I}/k_{corr}^{II} = 38$, but at higher $[OH^-]$ it is smaller, becoming about 6 at 1 *M* base.

Discussion

The hydrolysis rates for the present compounds are substantially faster than would be predicted from previous work. Bender and Thomas[2] have shown that the rates of substituted acetanilides are virtually independent of the substituent for ring substituents *p*-CH_3O, *p*-CH_3, H, *p*-Cl, and *m*-NO_2 between $[OH^-]$ of 0.24 and 0.96 *M*. Using the value of $\rho = 0.1$ which they obtained and a value of σ^- for *p*-NO_2,[12] a rate constant of 2.5×10^{-6} sec^{-1} can be calculated for *p*-nitroacetanilide at 0.24 *M* hydroxide ion. The observed rate constant is 3.2×10^{-4} sec^{-1} and the rate constant corrected for ionization of the starting material is 4.6×10^{-4} sec^{-1}. Thus, the rate is over one hundred times faster than predicted on the basis of previous work. Similarly, the calculated rate constant for *p*-formylacetanilide at this concentration of hydroxide ion is 2.3×10^{-6} sec^{-1} ($\sigma^- = 1.126$)[12] and the observed value is 2.8×10^{-5} sec^{-1}, about ten

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(12) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, p 211.

times faster than predicted. It is apparent that a new mechanism is operating, different from that for the acetanilides studied previously.

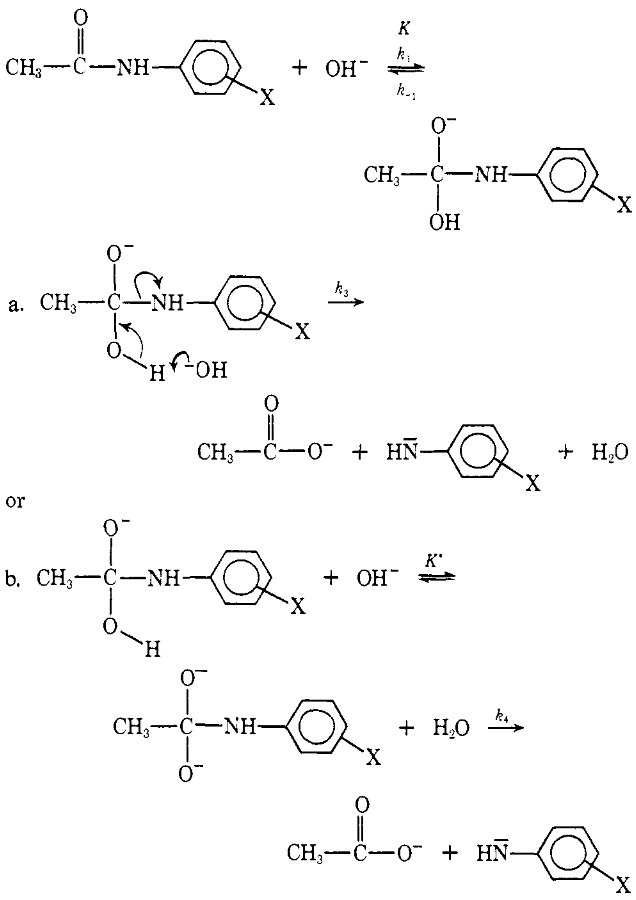
A value of $\rho = 11$ may be calculated from the observed rates of *p*-nitro- and *p*-formylacetanilides at $[OH^-] = 2.8 \times 10^{-2}$ *M*. (This value of $[OH^-]$ is chosen because both compounds exhibit identical pH–rate dependence in this region.) The ρ calculated is, of course, subject to considerable error since it is based on only two points, and these points are very close together. However, the important point is that there is a very large substituent dependence for this mechanism.

Another point of difference between the present results and those obtained previously for ring-substituted acetanilides is the pH dependence. For the other acetanilides the rate is first order in hydroxide ion below pH 13, with a second-order term only becoming apparent above this pH. For *p*-nitroacetanilide, on the other hand, the rate is second order in hydroxide ion at the lower values of pH studied and becomes less than second order at high pH. For *p*-formylacetanilide the rate is second order at all $[OH^-]$ studied. Thus, the predominant process for I and II involves two hydroxide ions rather than one as in the nonactivated anilides.

The requirement for two hydroxide ions demands that a total of two negative charges be accommodated in the transition state. The large rate enhancement with electron-withdrawing substituents suggests that one of these charges is on the amide nitrogen; the other may reasonably be ascribed to the acetate oxygens. Two possible pathways can be envisioned, differing only in the mode of breakdown of the tetrahedral intermediate (see Mechanism II). In pathway a the attack of hydroxide ion is concerted with the loss of anilide ion, whereas in b a preequilibrium ionization is followed by a unimolecular breakdown to products. In Mechanism II, pathway a should be subject to general base catalysis, but pathway b should not. Since general base catalysis at hydroxide ion concentrations used in this work is impossible to detect, solvent isotope effects were examined.

The first step in Mechanism II is the equilibrium addition of hydroxide to the carbonyl. An isotope effect for this equilibrium may be estimated by the following procedure. The only significant change in a hydrogen vibration is the change in the stretching of the hydroxide hydrogen in going from a hydroxide hydrogen to an alcohol hydrogen. (It is being assumed that the hydrogen bonds of the solvent to hydroxide ion and to the product alkoxide ion are equivalent and the isotope effect on them cancels out.) This change in vibration may be approximated by the change in going from hydroxide ion to water. The corresponding stretching frequencies are 3600 and 3400 cm^{-1}.[13] Using the method of Bunton and Shiner[13] the isotope effect on this equilibrium can be calculated to be $K_{H_2O}/K_{D_2O} = 1.13$.

Mechanism II



In pathway a the observed isotope effect will be $k_3(H_2O)/k_3(D_2O)$. Since step k_3 involves a proton transfer in a rate-limiting step, it is expected that it should show an isotope effect greater than unity, although this is not always the case.[14] The isotope effect for this mechanism then should be normal, that is, k_{H_2O}/k_{D_2O} greater than unity.

For mechanism b the observed effect should be $[k_4(H_2O)/k_4(D_2O)][K'(H_2O)/K'(D_2O)][K(H_2O)/K(D_2O)]$. Steps K' and k_4 correspond to a preequilibrium ionization followed by unimolecular breakdown to products. Reactions of this type have been suggested to involve inverse isotope effects.[15] An example is the reaction of 2-chloroethanol in base to give ethylene oxide.[16,17] The observed effect for this reaction is $k_{H_2O}/k_{D_2O} = 0.65$. Combining this value with the value of 1.13 for the equilibrium K gives a predicted value of 0.73. The actual value of the isotope effect for *p*-nitroacetanilide at $[OH^-] = 4.60 \times 10^{-3}$ *M* is 0.61. This number is easily accounted for by pathway b, but in order to explain an isotope effect of this magnitude by pathway a, it is necessary to invoke an inverse isotope effect of about 1.9 in a step involving a rate-determining proton transfer (k_3). Although inverse isotope effects have been observed for reactions in which general catalysis is observed,[18,19] they are quite uncommon, and the authors believe that the isotope effect strongly points to pathway b being the correct one.

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The rate equation given by eq 1 now becomes

$$k_{\text{obsd}} = \frac{k_1k_4K'[\text{OH}^-]^2}{k_{-1} + k_4K'[\text{OH}^-]} \qquad (2)$$

From this equation it is clear that the change from second order in hydroxide to first order for *p*-nitroacetanilide with pH can be explained by a change in the rate-determining step. At low [OH⁻] cleavage of the tetrahedral intermediate to form acetate and *p*-nitroanilide ion (k_4K) is rate determining, whereas at higher [OH⁻] the rate-determining step is the addition of hydroxide to form the tetrahedral intermediate (k_1).

Bender and Thomas[2] have previously obtained values for the addition step (k_1) in the hydrolysis of several acetanilides by ^{18}O exchange work. A value for the addition step for *p*-nitroacetanilide may be calculated from their data and compared with the k_1 obtained here. Since the k_1 step in the present mechanism is hydroxide ion addition to the carbonyl, the results should agree, as the first step is identical in both mechanisms. Extrapolating the data of Bender and Thomas, using $\sigma^- = 1.27$ for *p*-nitro, gives a predicted value of the k_1 step of *p*-nitroacetanilide of 1.5×10^{-3} M^{-1} sec^{-1}. This value compares favorably with the value of 2.2×10^{-3} M^{-1} sec^{-1} obtained here by the use of eq 1.

The rate for *p*-formylacetanilide is second order in hydroxide ion throughout the pH range investigated, in contrast to what was observed for *p*-nitroacetanilide. This implies that k_4 is rate determining at all pH values for *p*-formylacetanilide. From the work of Bender and Thomas, the calculated value of k_1 for this compound is 1.1×10^{-3} M^{-1} sec^{-1}. The maximum value of the observed rate constant is 2.4×10^{-4} M^{-1} sec^{-1} at [OH⁻] = 9.4×10^{-1} M. When this value is corrected for ionization of the substrate, it is 3.2×10^{-4} M^{-1} sec^{-1}. Since the highest observed rate is only about one-third of the calculated k_1, it is expected that there should be only minor curvature in the log k_{corr}–pH plot, in agreement with what is found.

It is to be noted that the proposed mechanism of hydrolysis of both compounds studied involves the cleavage of a dianion to two monoanions. By the law of microscopic reversibility, the lowest energy path for the formation of the anilide from the acid and the amine in basic solution must be the attack of the amide ion on acetate ion. This result is not what one would expect *a priori*, but there is some precedent in the work of Hegarty and Bruice,[20] in which they postulate such an attack in the cyclization of *N*-(*o*-carboxyphenyl)urea.

It is of interest to compare the present results for the hydroxide-catalyzed hydrolysis of anilides to the results for the hydrolysis of *N*-acetyl-L-tyrosine anilides by chymotrypsin.[21,22] It has been found that in the enzymatic reaction, the acylation step for *N*-acetyl-L-tyrosine *p*-nitroanilide is about fifty times faster than predicted from the correlation observed with more electron-donating anilides. It may be that there is a change in mechanism with the *p*-nitroanilide in analogy with the hydroxide ion results. We are presently investigating the enzymatic reaction in order to determine whether this is the cause of the discrepancy observed.

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