Acta Chemica Scandinavica B 30 (1976) 915—924

Hydroxylaminolysis of Anilides. III. Hydroxylaminolysis of Formanilide and *p*-Methoxyacetanilide. A Comparison with Acetanilide

BARBRO ARIANDER OHLSON and GUNILLA LUNDKVIST

Department of Inorganic and Physical Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, Box 574, S-751 23 Uppsala, Sweden

The kinetics of the hydroxylaminolysis of formanilide and *p*-methoxyacetanilide have been studied in the pH range 4.8 – 9.6 at a total hydroxylamine concentration varying from 0.1 to 3.0 M. Under the different conditions the reaction rates are in agreement with a mechanism previously suggested for acetanilide, where the tetrahedral addition intermediate is broken down to products *via* three intermediates which are in protolytic equilibrium. A mechanistically preferable form of the mathematically derived rate expression has now been developed. Using this expression, the kinetic parameters for acetanilide have been recalculated and are compared with the corresponding parameters for formanilide and *p*-methoxyacetanilide. The substituent effects support the suggestion that the three equilibrium intermediates are cyclic.

Previous work [1] from this Laboratory has suggested that the hydroxylaminolysis of acetanilide follows a mechanism involving a complex general acid or general base catalysis of the breakdown of a tetrahedral substrate-hydroxylamine intermediate. In contrast to what was found in the hydroxylaminolysis of thiol esters and thiolactones,[2] the kinetics did not indicate catalysis of the formation of the tetrahedral intermediate. In another paper the hydroxylaminolysis of formamide was studied, but the authors [3] were not able to explain satisfactorily the results obtained at "extreme" pH values. Our recalculation of the data for formamide showed that the mechanism proposed for acetanilide was applicable to formamide over the whole pH range studied, whereas the thiol ester mechanism could not be applied.

The hydroxylaminolysis of trifluoroacetanilide has been reported [4] to be a pure second order reaction in hydroxylamine at pH values higher than approximately 5. This suggests that the strongly activated trifluoroacetanilide might follow the thiol ester mechanism rather than the acetanilide one. It is somewhat unexpected that highly reactive carbonyl compounds such as thiol esters and trifluoroacetanilide should require catalysis of the nucleophilic attack if moderately reactive, nonactivated amide compounds like acetanilide and formamide do not. In order to obtain more detailed information about the nature of the intermediates in the acetanilide mechanism we have now studied the hydroxylaminolysis of formanilide and *p*-methoxyacetanilide.

MATERIALS AND METHODS

Materials

Formanilide. Commercially available formanilide (BDH laboratory reagent) was recrystallized from ligroin + xylene (1 + 9). The resulting white needles were washed with light petroleum, b.p. 30 – 60 °C. The melting point was 47 – 48 °C (lit. 47.5 °C).[5]

p-*Methoxyacetanilide* was prepared from *p*-anisidine and acetic anhydride using the Schotten-Baumann procedure. It was recrystallized, first from water and then twice from benzene, yielding white flakes with a melting point of 130 °C (lit. 129 – 131 °C).[6]

All other chemicals used in the kinetic runs and in the assay were Merck chemicals reagent grade.

Acidity constants

The stoichiometric pK_w at 25 °C in 3.0 M KCl (14.13 ± 0.01) and the pK_a for the hydroxyl-

ammonium ion at 25 °C in 3.0 M KCl (6.32 ± 0.01) had been determined previously.[7,8] The stoichiometric pK_w at 25 °C in 5 % (v/v) dimethyl sulfoxide (DMSO) and 3.0 M KCl and the pK_a for the hydroxylammonium ion in the same medium were determined by potentiometric titration and found to be 14.32 ± 0.01 and 6.40 ± 0.01, respectively.

Kinetic experiments

In the kinetic experiments the medium was water, and the ionic strength was adjusted to 3.0 by addition of KCl. In the case of *p*-methoxyacetanilide the medium contained 5 % DMSO to increase the solubility of the anilide. The concentration of *p*-methoxyacetanilide was about 10^{-2} M, and that of formanilide varied between 4.3×10^{-3} and 4.3×10^{-4} M. The hydroxylaminolysis reaction was studied in the concentration range of 0.1 – 3.0 M hydroxylamine. The H^+ concentration varied from $10^{-5.04}$ to $10^{-9.79}$, corresponding to 5.0 – 99.97 % of the hydroxylamine system as base.

The experiments were performed at 25.00 ± 0.05 °C. The volume of the reaction mixtures was 100.00 ml. The hydroxylamine system was added as hydroxylammonium chloride and the desired percentage of hydroxylamine was obtained by neutralizing the hydroxylammonium ion with a calculated volume of a potassium hydroxide solution of known concentration. At the smallest concentration of the hydroxylamine system in the range of 5 – 80 % free base and for all concentrations at 70 % free base, the obtained pH values agreed very well with the calculated ones. In all other cases, however, medium effects became apparent as the concentration of the hydroxylamine system was increased. At base concentrations below 70 %, the measured pH values were lower than the calculated ones. At 5 % base and 3.0 M total hydroxylamine concentration, the pH was 0.4 units lower than the calculated value. This was the greatest deviation found. At 80 % base and 3.0 M total hydroxylamine concentration the measured pH was 0.1 unit higher than the calculated one. At 90 % base and higher, the pH was adjusted to the calculated values; this was done because of the difficulty in achieving an accurate degree of neutralization by adding measured volumes of the highly concentrated KOH solution.

A Radiometer model pHM 4 equipped with a glass electrode and a saturated calomel electrode was used for the pH control.

At high pH and in the presence of air, hydroxylamine is unstable. However, by excluding air and working under nitrogen,[1] kinetic runs can be performed with a negligible loss of hydroxylamine during the experiment.

Assay

The withdrawn samples were analyzed by means of the so-called aniline method.[7] Since this method was first introduced, it has been successively modified by many authors. The method involves diazotization and coupling of the aniline formed, and will be described in full below.

An aliquot of 1.00 – 5.00 ml was withdrawn and added to a given volume of hydrochloric acid of a given concentration in a volumetric flask. After addition of the aliquot, the volume was 10.00 ml and $[H^+]$ was 0.05 M. The diazotization was started immediately by adding 1.00 ml of 1 M $NaNO_2$ and after 3 min the excess nitrite was destroyed with 5.00 ml of a 5 % ammonium sulfamate solution. After another 3 min 5.00 ml of a 1 % solution of the coupling reagent was added, *N*-(1-naphthyl)-ethylene diammonium dichloride. After 10 min (with aniline as the reaction product) or 2 h (with *p*-methoxyaniline as the reaction product) 1 M HCl was added to give a volume of 25.00 ml and the absorbance was measured at the absorbance maximum; 550 nm for aniline and 580 nm for *p*-methoxyaniline. The molar absorption coefficients were 47 900 for aniline and 48 700 for *p*-methoxyaniline. The spectrophotometer used was a Zeiss spectrophotometer model PMQII.

At least 6 samples were analyzed for each determination of a k_{obs} value. The time during which the reactions were followed varied from 50 min to 48 h for formanilide and from 150 min to 100 h for *p*-methoxyacetanilide.

The k_{obs} values for formanilide were determined from plots of log (remaining anilide) against time, except in a few cases where less than 4 % of the anilide had reacted. Depending on the reaction rate, up to 85 % of the reaction was observed during the kinetic runs. In the case of *p*-methoxyacetanilide the reaction was observed only initially (less than 4 % reacted) and the k_{obs} values were evaluated from plots of concentration of product against time.

Theoretical calculations

The evaluation of k_1 and p values and the preliminary estimation of the constants in eqns. (2a) and (2b) were made by means of a Hewlett-Packard HP 9810A calculator. The final determination of the constants was made on an IBM 370/155 computer. The computer programs used were BMD07R, Biomedical computer programs, University of California and VB01A, Harwell Subroutine Library, AERE, England. Both are nonlinear least squares regression programs for curve fitting.

RESULTS

Observed pseudo first order rate constants, k_{obs}, for the formation of the respective anilines at constant pH and constant total hydroxylamine concentration (C), are given in Figs. 1 and 2 for formanilide and in Figs. 3 and 4 for *p*-methoxyacetanilide. Under most of the experimental conditions, the dependence of k_{obs} on C is close to second order but at high C and low pH the dependence approaches first order.

All the determined k_{obs} values are given in Figs. 1–4 as a function of C at given base %. The figures show that the rate increases with rising base % up to a base content of 60–70 % for formanilide and 50–60 % for *p*-methoxyacetanilide and then decreases continuously until at 99.9 % base no further decrease is apparent.

The curves in Figs. 1–4 have been calculated by means of eqn. (1).

$$k_{obs} = k_1[H_2NOH]pC/(1+pC) \quad (1)$$

In eqn. (1) C is the sum of hydroxylamine (N) and hydroxylammonium ion (NH^+) concentrations, k_1 is a constant and p is a pH-dependent variable, *i.e.* a different p value has been used for each base/acid ratio. The significance of p and its variation with pH has been discussed in a previous paper [1] and will be further commented upon in the discussion below. The values of p and k_1 used to calculate the curves in Figs. 1–4 are given in Table 1.

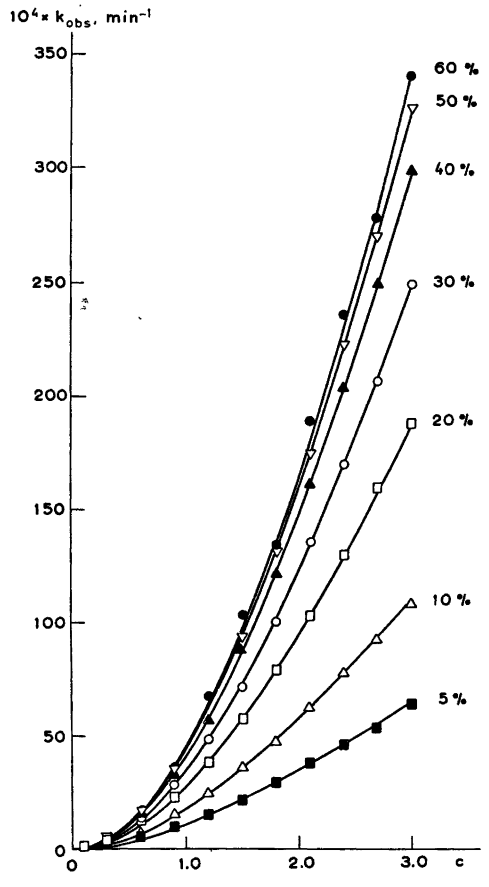


Fig. 1. Formanilide. Plot of k_{obs} *vs.* C at different base percentages. The curves have been calculated from eqn. (1) using the values of k_1 and p listed in Table 1.

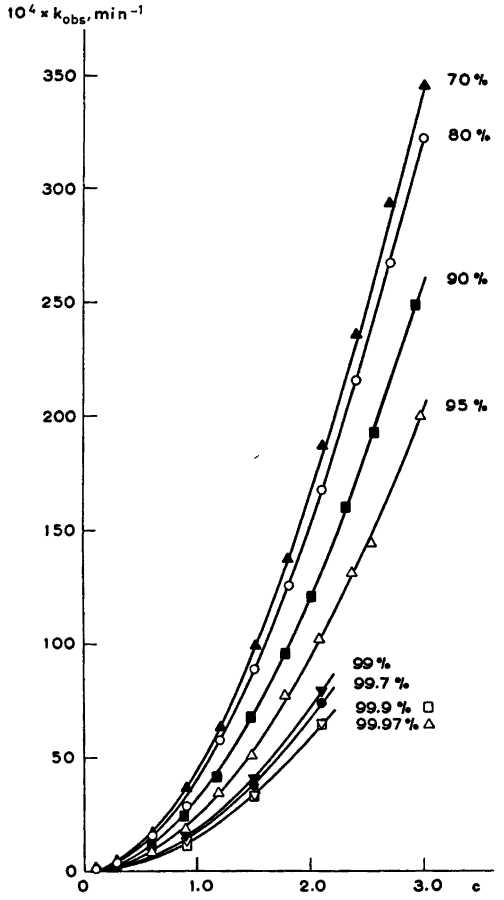


Fig. 2. Formanilide. Plot of k_{obs} *vs.* C at different base percentages. The curves have been calculated from eqn. (1) using the values of k_1 and p listed in Table 1.

Table 1. Values of p used in the calculation of the curves in Figs. 1–4. The values of $k_1 = 8.0 \times 10^{-3}$ M^{-1} min^{-1} for formanilide and $k_1 = 4.5 \times 10^{-4}$ M^{-1} min^{-1} for p-methoxyacetanilide have been used in all calculations. The theoretical p values have been calculated by means of eqn. (2b) using the parameter values given in Table 2.

Formanilide				p-Methoxyacetanilide			
% Base	$-\log [H^+]$	p M^{-1}	p_{theor} M^{-1}	% Base	$-\log [H^+]$	p M^{-1}	p_{theor} M^{-1}
5.00	5.04	0.390	0.390	5.00	5.12	1.55	1.55
10.00	5.37	0.290	0.288	10.00	5.45	0.815	0.833
20.00	5.72	0.210	0.214	20.00	5.80	0.450	0.465
30.00	5.95	0.175	0.176	40.00	6.22	0.244	0.245
40.00	6.14	0.150	0.149	50.00	6.40	0.194	0.190
50.00	6.32	0.125	0.125	60.00	6.58	0.148	0.144
60.00	6.50	0.104	0.104	80.00	7.00	0.079	0.073
70.00	6.69	0.087	0.085	90.00	7.27	0.053	0.047
80.00	6.92	0.068	0.066	99.00	8.27	0.017	0.016
90.00	7.27	0.046	0.046	99.90	9.27	0.012	0.012
95.00	7.60	0.033	0.035	99.97	9.79	0.012	0.012
99.00	8.27	0.024	0.024				
99.70	8.79	0.022	0.021				
99.90	9.27	0.019	0.020				
99.97	9.79	0.019	0.019				

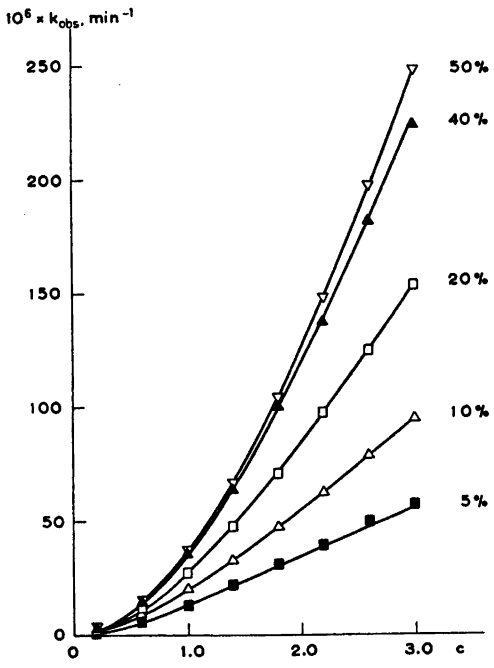


Fig. 3. p-Methoxyacetanilide. Plot of k_{obs} *vs.* C at different base percentages. The curves have been calculated from eqn. (1) using the values of k_1 and p listed in Table 1.

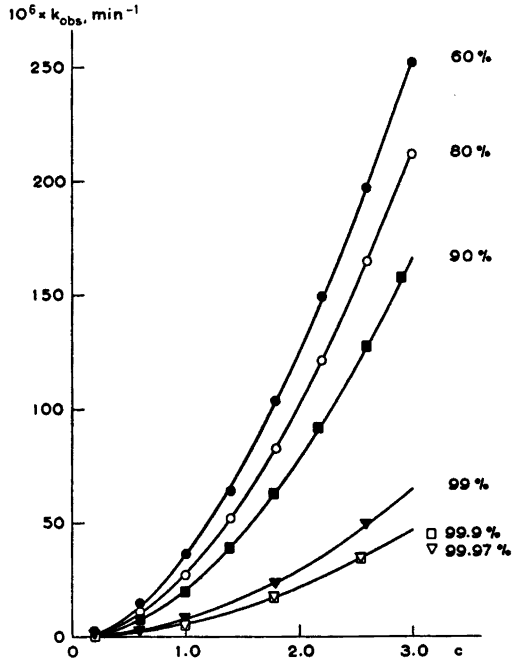


Fig. 4. p-Methoxyacetanilide. Plot of k_{obs} *vs.* C at different base percentages. The curves have been calculated from eqn. (1) using the values of k_1 and p listed in Table 1.

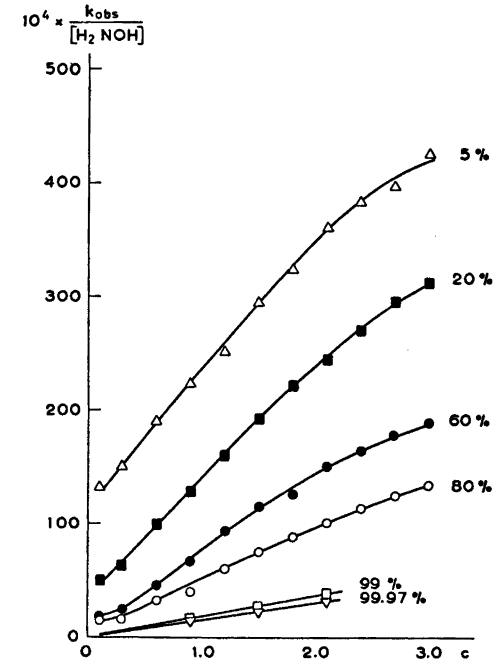


Fig. 5. Formanilide. Plot of $k_{obs}/[H_2NOH]$ *vs.* C at 6 different base percentages. The dots are experimental. The curves have not been calculated.

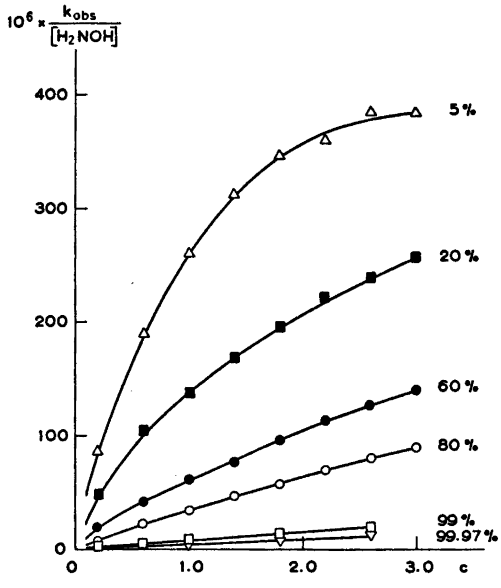


Fig. 6. *p*-Methoxyacetanilide. Plot of $k_{obs}/[H_2NOH]$ *vs.* C at 6 different base percentages. The dots are experimental. The curves have not been calculated.

In the mechanism leading to eqn. (1), k_1 is the rate constant for the nucleophilic attack of hydroxylamine on the carbonylic carbon. The k_{obs} values at high total concentrations at the lowest base percentages are the most useful ones in evaluating k_1. As seen from Figs. 1 and 3 these parts of the plots are almost linear, which indicates that pC in eqn. (1) is considerably larger than 1. A preliminary value of k_1 has been estimated from these plots and then used to calculate the theoretical curves. The value of k_1 first used invariably had to be changed somewhat to give the best possible fit for all base/acid ratios. Too high a k_1 will generally give a bad fit at low base percentages, and too low a k_1 will give a bad fit at high base percentages. These disagreements cannot be compensated for by choosing a suitable value of p. The final k_1 and p values were calculated simultaneously by means of a computer.

The sets of k_1 and p finally chosen were the ones that gave equally good fits to all the plots of k_{obs} *vs.* C, regardless of base percentages.

Generally, values of p deviating from those in Table 1 by approximately 5 % gave a less good fit to the experimental values.

Figs. 5 and 6 show plots of $k_{obs}/[H_2NOH]$ as a function of C; these values have been obtained from some of the curves presented in Figs. 1 – 4. They show how the reaction rate is influenced by a second hydroxylamine molecule or hydroxylammonium ion. The curves in these figures have not been calculated but have been drawn to connect the points as well as possible.

In Fig. 6, which refers to *p*-methoxyacetanilide, the curves have no obvious intercepts. At 5 % base it is quite apparent that the curve approaches a limiting value at the highest C. As the base percentage increases the curves bend less, and at a high pH they show a first order dependency with respect to $[H_2NOH]$.

In Fig. 5, referring to formanilide, the curves have definite intercepts. Owing to smaller p values the curvatures are less marked than in Fig. 6.

In Figs. 7 and 8, k_{obs} values for 4 different C values have been plotted as a function of log $[H^+]$. These figures also show that formanilide reaches its rate maximum at a somewhat smaller $[H^+]$ value than *p*-methoxyacetanilide does, and that a rate limit is reached at small values of $[H^+]$.

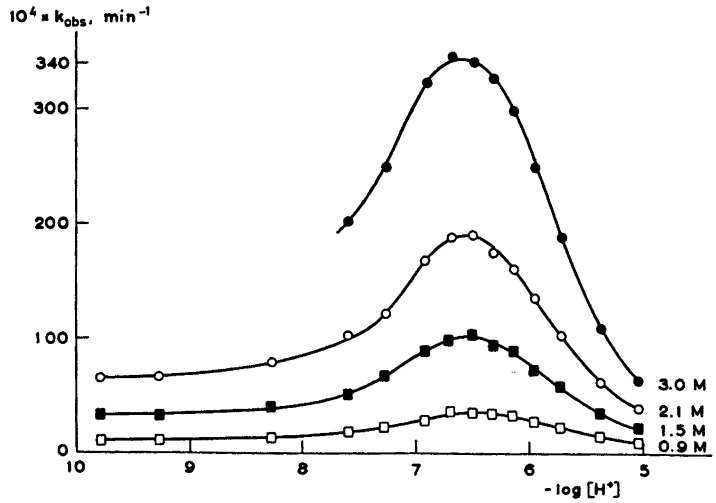


Fig. 7. Formanilide. Plot of k_{obs} *vs.* $-\log [H^+]$ for 4 different C. The dots are experimental. The curves have not been calculated.

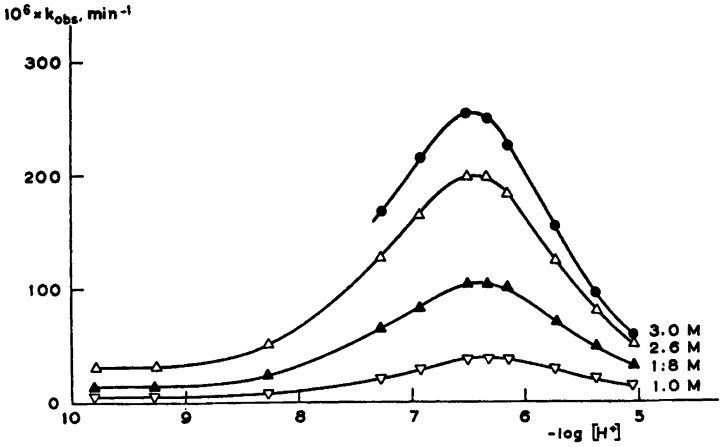


Fig. 8. *p*-Methoxyacetanilide. Plot of k_{obs} *vs.* $-\log [H^+]$ for 4 different C. The dots are experimental. The curves have not been calculated.

The curves in Figs. 7 and 8 have been drawn to connect the points at a given C and have not been calculated.

DISCUSSION

Variation of k_{obs} with C and pH

In the hydroxylaminolysis of acetanilide,[1] plots of k_{obs} *vs.* C were found to be completely described by eqn. (1). This equation may be derived from any mechanism consisting of an uncatalyzed nucleophilic attack on the carbonyl carbon to give an addition intermediate (I, see Scheme 1), followed by a breakdown of the intermediate in which the presence of a second molecule of the nucleophile or its corresponding acid is necessary for the reaction to result in products. By using the steady state approximation, an equation can be derived where all the constants pertaining to the breakdown of the intermediate – be it to starting

materials or products – can be gathered in one complex expression. This expression is here symbolized by p [see eqn. (1)]. A change in the mechanism for the breakdown of the intermediate will give a change in p, but it will not change eqn. (1) as such, as long as the conditions mentioned above are fulfilled.

In the present investigation of the hydroxylaminolysis of formanilide and p-methoxyacetanilide, the plots of k_{obs} *vs.* C are well described by eqn. (1) (see Figs. 1–4).

This is further confirmed for p-methoxyacetanilide in Fig. 6 where k_{obs}/N has been plotted *vs.* C. Eqn. (1) may be rewritten as in eqn. (1a).

$$k_{obs}/N = k_1 pC/(1+pC) \qquad (1a)$$

According to eqn. (1a), the plot of k_{obs}/N *vs.* C should go through the origin. This is indeed the case with p-methoxyacetanilide, as it was with acetanilide.[1] Fig. 5, on the other hand, shows positive intercepts, and a close examination of the plot of k_{obs} *vs.* C in Figs. 1 and 2 shows that the experimental values are indeed higher than the theoretical curve at $C \leq 0.6$ M, whereas at higher concentrations there is good agreement between the theoretical and experimental values.

At 5 % base and the lowest C about 1 % of the total rate can be explained by ordinary acid-catalyzed hydrolysis,[9] but this is far from enough to account for the intercept. At higher C and at a higher pH, the contribution from the acid-catalyzed hydrolysis reaction is negligible.

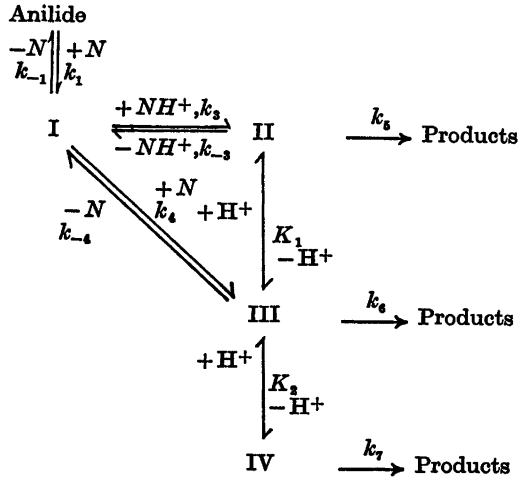
Thus the simplest way to explain the intercepts is by a hydroxylaminolysis reaction where the breakdown of the tetrahedral intermediate to products is spontaneous (catalyzed by water) or catalyzed by H^+ or HO^-. A spontaneous breakdown would give a pH independent intercept. Fig. 5 shows that the intercept increases with rising H^+ concentration, which suggests an acid catalyzed breakdown. No detailed interpretation of the intercepts will, however, be attempted here, since these have been determined by extrapolation and the points at 0.1 M are somewhat uncertain due to experimental difficulties (very low reaction rates).

From the plots of k_{obs} *vs.* $-\log [H^+]$ in Figs. 7 and 8, it is obvious that both N and NH^+ are active in the hydroxylaminolysis reaction, since there is a rate maximum near pK_a for the hydroxylammonium ion. The simplest way to explain this is by a nucleophilic attack by N to form an intermediate, the breakdown of which is assisted by NH^+. Although NH^+ is a potent catalyst, its presence is not absolutely necessary for the breakdown. If it were, the rate should approach zero when the concentration of NH^+ is lowered. Instead, a limiting value is reached at about 99 % base, *i.e.* at a point where an increase of pH will result in a drastic decrease of $[NH^+]$ but in no noticeable increase of $[N]$. Obviously, at high pH, N will act both as nucleophile and catalyst. At low pH no limiting value is to be expected since at least one N must be involved in the nucleophilic reaction.

Interpretation of p

Since in eqn. (1) the second molecule of the nucleophile N and/or its corresponding acid NH^+ is represented by C ($C = N + NH^+$), p will always be dependent on the pH, except in the case where the catalytic effects of the nucleophile and the acid are equal. Thus an investigation of the dependency of p on pH will throw light on the breakdown of the intermediate I to products.

In a previous paper[1] we suggested that the hydroxylaminolysis of acetanilide follows the mechanism presented in Scheme 1.



Scheme 1.

From this mechanism we derived an equation for the dependence of p on [H$^+$] [eqn. (2a)].

$$p = \frac{a + b[H^+] + c[H^+]^2 + d[H^+]^3}{1 + e[H^+] + (fK_a + e/K_a - 1/K_a^2)[H^+]^2 + f[H^+]^3} \quad (2a)$$

Eqn. (2a), where a through f denote big clusters of constants, has two disadvantages. Firstly, a through f have no easily interpretable kinetic meaning. Secondly, they are very complex, and logical errors, such as ascribing two or more different numerical values to the same microconstant (k_3, k_4 *etc.*), may pass unnoticed.

This induced us to rearrange eqn. (2a) into eqn. (2b), see below.

K_I through K_{VI} have distinct kinetic significance. They denote the ratios between the rate constants for the different routes of degradation of the intermediates, as defined in Table 2.

The advantage of eqn. (2a) over (2b) is that it is rather easy to make a first estimate of the parameters a through f. Eqn. (2b) does not involve a larger number of parameters, but it is so complex that it is extremely difficult to make a reasonable guess at where to start the search for the best parameter values. However, from the parameters a through f of eqn. (2a) for acetanilide a fairly good first estimate can be made of the parameters K_I through K_{VI} of eqn. (2b).

The relative simplicity of K_I *etc.* makes it possible to compare the importance of the different paths of decomposition of the intermediates for a certain substrate and to discuss the influence of substituents on the reaction. For this reason, the data for acetanilide have been recalculated using eqn. (2b) instead of eqn. (2a). The result is given in Table 2. By using eqn. (2b) we obtained a slightly better fit to the experimental values of acetanilide than by means of eqn. (2a). Theoretically, the two equations should give the same fit. The difference is probably due to the greater flexibility of eqn. (2b) as well as to a better curve fitting method.

Eqn. (2b) was then used to reproduce the experimental p values of formanilide and p-methoxyacetanilide. The calculated p values are listed in Table 1 and the optimal K_I through K_{VI} values are shown in Table 2.

Formation of intermediate I

On the introduction of a methoxy group into the *para* position of the aniline ring, k_1 decreases from 7.0×10^{-4} to 4.5×10^{-4} M^{-1} min^{-1}. This is in good agreement with the trends of the rate constants for the nucleophilic attack of hydroxide ion on the same substrates: 7.85×10^{-5} M^{-1} s^{-1} for acetanilide [10,11] and 4.20×10^{-5} M^{-1} s^{-1} for p-methoxyacetanilide.[12] The decrease in the rate constants is expected since p-methoxy substitution gives a somewhat higher electron density at the carbonyl carbon.

For formanilide, k_1 of the hydroxylaminolysis increases a hundredfold (see Table 1). This is expected, considering the absence of steric hindrance and the lower electron density at the formyl carbon as compared with the acetyl carbon, and is comparable to the 500-fold increase in k_1 in the hydrolysis of p-nitroacetanilide and p-nitroformanilide [11] and to

Table 2. The parameter values of eqn. (2b) used when calculating the theoretical p values in Table 1.

	$K_I = \frac{k_4}{k_{-1}}$ M^{-1}	$K_{II} = \frac{k_6}{k_7 K_2}$ M^{-1}	$K_{III} = \frac{k_{-4}}{k_7 K_2}$ M^{-1}	$K_{IV} = \frac{k_3}{k_{-1}}$ M^{-1}	$K_V = \frac{k_5}{k_7 K_1 K_2}$ M^{-2}	$K_{VI} = \frac{k_{-3}}{k_7 K_1 K_2}$ M^{-2}
Formanilide	1.89×10^{-2}	1.24×10^{7}	4.48×10^{7}	9.52×10^{-1}	2.34×10^{12}	1×10^{7}
p-Methoxyacetanilide	1.00×10^{-2}	6.30×10^{7}	2.01×10^{10}	9.51×10	3.81×10^{13}	or
Acetanilide	1.30×10^{-2}	2.14×10^{7}	1.40×10^{8}	2.30	8.85×10^{12}	less

$$p = \frac{K_I + [K_{IV}/K_a + K_I K_{II}][H^+] + [K_{II}K_{IV}/K_a + K_I K_V][H^+]^2 + K_{IV}K_V/K_a[H^+]^3}{1 + [1/K_a + K_{II} + K_{III}][H^+] + [(K_{II} + K_{III})/K_a + K_V + K_{VI}][H^+]^2 + (K_V + K_{VI})/K_a[H^+]^3} \quad (2b)$$

the 200-fold difference between acetanilide and formanilide [11] in the total rate of alkaline hydrolysis.

Breakdown of intermediate I

In Table 2 are listed the group constants K_I through K_{VI}. No standard deviations are listed in Table 2, since the two computer programs used in the calculations gave different standard deviations for the same numerical value of a certain constant. In order to test the validity of the constants, we varied them one at a time by ± 1, ± 5, and ± 10 % to see what effect a change in the constants would have on the calculated p values. A variation of K_{III} and K_{IV} by 1 %, of K_{II} and K_V by 5 %, and of K_I by 10 % gave a less good fit to the experimental p values, whereas K_{VI} could be varied by a couple of powers of ten without giving any change at all in the calculated p. K_{VI}, representing the ratio $k_{-3}/k_7K_1K_3$, is evidently too small to be of any significance in the studied pH range; this indicates that the direct breakdown of intermediate II to intermediate I is negligible for all three substances. It seems reasonable to assume that a low variability indicates that a substantial part of the total reaction proceeds via the steps represented in the ratio in question.

At high pH ([H^+] less than 10^{-9}) the experimental p values reach a limiting value. Since at low H^+ concentrations eqn. (2b) is reduced to $p = K_I$, the experimental limiting values were used as the starting values of K_I. These values were not altered in the computerization, but were accepted as the best possible ones.

It has been concluded [12] that the tetrahedral intermediates of the hydrolysis of acetanilide and p-methoxyacetanilide exist long enough for the proton of the $-OH$ group to be exchanged (Fig. 9a). It seems reasonable to assume that the primary tetrahedral intermediate ($I^{\pm}$) in the hydroxylaminolysis reaction, too, should be stable enough to permit proton exchange (Fig. 9b).

Considering the rather large variability of K_I, it is difficult to state positively if this constant, representing k_4/k_{-1}, is significantly altered by the introduction of the p-methoxy group. However, it increases slightly by the abstraction of the methyl group from acetanilide. This suggests that the second hydroxylamine molecule acts as a general base on the hydroxyl group of the acyl carbon or on the amino or hydroxyl group of the nucleophile (Fig. 10). The p-methoxy group is probably too far away to influence significantly the acidity of these protons; the methyl group is sufficiently near to increase the electron densities of the oxygen and the nitrogen at the acyl carbon, thus making the protons less mobile. The hydroxyl group of the original nucleophile is one step further off, but might still be affected.

When [NH^+] = 1.0 M, K_{IV}, representing k_3/k_{-1}, shows that with acetanilide as a substrate, intermediate I will be transformed into intermediate II twice as often as it will decompose into starting materials. This ratio increases fortyfold when a p-methoxy group is introduced and decreases to half the value when the methyl group is abstracted. Since both the p-methoxy group and the methyl group are electron donating, these effects suggest that in the k_3 step a bond is being formed between the hydroxylammonium ion and the free electron pair of the anilide nitrogen.

Combining the substituent effects on K_I and K_{IV} with the mathematical demand from eqns. (2a) and (2b) and Scheme 1 that the intermediates II and III should be interconvertible by the addition or abstraction of a proton only, we come to the conclusion that the hydroxyl-

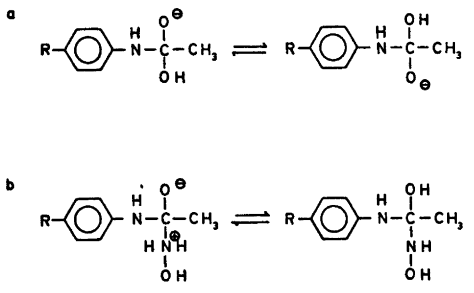


Fig. 9.

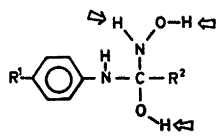


Fig. 10.

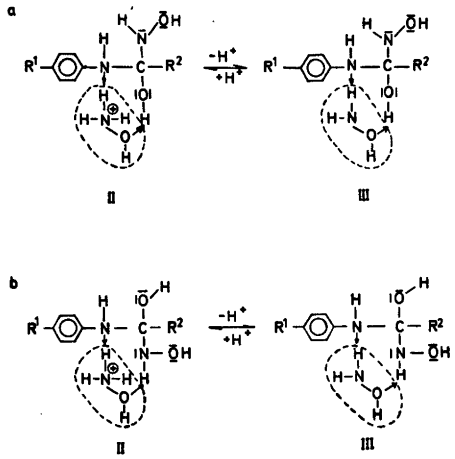


Fig. 11.

amine and the hydroxylammonium ion are bonded to I in a ring structure, the binding sites being the anilide nitrogen and the amino or hydroxyl group (see Fig. 11).

Fig. 11 shows possible structures of the intermediates II and III, the bonding moiety of the acyl part being the hydroxyl group in Fig. 11a and the amino group in Fig. 11b.

It has been suggested [3] that protolytic equilibria between the tetrahedral intermediates in aminolysis reactions will be detectable only when the protolytic constants of the intermediates have the same order of magnitude as that of the nucleophile. From this and from Fig. 10 we may assume the protolytic constants for the conversion of II to III (K_1) to be near to that of the hydroxylammonium ion itself, somewhere around 10^{-6}, but since the K_1 and K_2 values will be influenced by the substituents to an unknown extent, the terms containing these constants, K_{II}, K_{III}, K_V, and K_{VI}, cannot be discussed as they are.

In order to be able to discuss the k_6 and k_{-4} steps, K_{II} is divided by K_{III} to eliminate the k_7K_2 terms. In this way we obtain the following ratios of k_6/k_{-4}: Formanilide 0.28, acetanilide 0.15, *p*-methoxyacetanilide 0.0031. Considering the uncertainty of K_{II} and K_{III}, the slight decrease in the ratio when formyl is replaced by acetyl may not be significant, but there is still a considerable decrease in the ratio when the *p*-methoxy group is introduced. The greater part of the decrease in the k_6/k_{-4} ratio is probably due to a decrease in k_6, since the strength of the amide bond of an anilide is influenced by electron donating or withdrawing substituents in the *para* position of the anilide ring.[11] Electron donating substituents in the acyl part will also strengthen the amide bond but to a smaller extent.

Since all that is known about K_{VI} is that it is too small to be of any significance, there is no possibility of discussing the ratio of k_5/k_{-3} by the same procedure. However, the magnitude of the ratio is worth noticing, since it shows that independent of the substituents the k_5 step is at least a million times larger than the k_{-3} step.

Acknowledgements. We want to thank Dr. Sven O. Eriksson, who initiated this work, for interesting discussions. We also want to express our gratitude to Miss Lillemor Berglund, who carried out most of the experimental work on formanilide, and Miss Anna-Karin Bernhardsson and Mrs Barbro Johansson, who did some additional work on *p*-methoxyacetanilide. The final computer work was carried out in co-operation with Mr. Jan Johansson from the Department of Computer Science of Uppsala University. His ability and never-failing interest gave us new faith in times of mathematical despair.

This work has partly been supported by a grant from the Swedish Natural Science Research Council.

REFERENCES

1. Eriksson, S. O. and Ohlson, B. A. *Acta Chem. Scand. 26* (1972) 2759.
2. Bruice, T. C. and Fedor, L. R. *J. Am. Chem. Soc. 86* (1964) 4886.
3. Jencks, W. P. and Gilchrist, M. *J. Am. Chem. Soc. 86* (1964) 5616.
4. Eriksson, S. O. *Acta Chem. Scand. 22* (1968) 892.
5. *Handbook of Chemistry and Physics*, Chemical Rubber Publishing Co., Cleveland, Ohio 1955, Ed. 37, p. 930.
6. *The Merck Index*, Merck & Co., Inc., Rahway, N. J. 1952, 6th Ed., p. 80.
7. Eriksson, S. O. and Omdal, J.-O. *Acta Pharm. Suec. 1* (1964) 77.
8. Eriksson, S. O., Meresaar, U. and Wahlberg, U. *Acta Chem. Scand. 22* (1968) 2773.
9. Ohlson, B. A. *Unpublished results.*
10. Eriksson, S. O. *Acta Pharm. Suec. 6* (1969) 121.
11. De Wolfe, R. H. and Newcomb, R. C. *J. Org. Chem. 36* (1971) 3870.
12. Bender, M. L. and Thomas, R. J. *J. Am. Chem. Soc. 83* (1961) 4183.

Received May 3, 1976.