Hydroxylaminolysis of Anilides. VI. Kinetic Investigation of the Reaction with Monofluoroacetanilide. Evidence for the Existence of a Reaction Path Involving Three Hydroxylamine Molecules

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The reaction between hydroxylamine and monofluoroacetanilide has been studied by means of kinetic methods in the pH interval $3.62 \leq -\log [H^+] \leq 9.79$. The concentration of the hydroxylamine system (C) varied between 0.2 M and 3.0 M ($\mu = 3.0$ with KCl). In the pH interval studied, the kinetics are mainly in accord with the mechanism previously postulated for formanilides with and without electron withdrawing substituents, from which was derived a mathematical expression for the observed reaction rate which is first order in C at low pH values ($pH \sim 4$) and second order in C at high pH values ($pH > 7$). In addition to this expression the kinetics of the monofluoroacetanilide reaction include a term first order in C at $-\log [H^+] = 9.79$, and a term third order in C in the interval $6.50 \leq -\log [H^+] \leq 7.27$. This is to our knowledge the first reported evidence of an aminolysis reaction which is third order in the amine. Some of the rate constants for the separate steps in the overall mechanism have been evaluated and the influence of the fluoro substitution on these steps is discussed.

In two previous papers ^{1,2} from this Laboratory, the kinetics of the hydroxylaminolysis of acetanilide and of trifluoroacetanilide were studied. The mechanism depicted in Scheme 1 was postulated for the reaction with acetanilide, and eqn. (1) was derived for the relationship between the observed pseudo-first order rate constant, k_{obs} , and the concentration of the hydroxylamine system. ($N = H_2NOH$, $HN = H_2N+OH$, $C = [N] + [HN]$).

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

In eqn. (1), k_1 is the rate constant for the nucleophilic attack by N on the carbonyl carbon, and p is a pH dependent parameter. At high pH values, the product $pC \ll 1$ and $C \sim [N]$. Thus eqn. (1) is reduced to $k_{obs} = k_1p[N]^2 = k[N]^2$. In this pH range, the breakdown of the anilide is thought to proceed entirely *via* the steps k_1 , k_4 , (K_2) and k_7 in Scheme 1.

The kinetics of the trifluoroacetanilide reaction,² on the other hand, could be described simply by eqn. (2).

$$k_{obs} = k_I[N] + k_{II}[N]^2 \quad (2)$$

In the pH range studied, the term first order in $[N]$ was of little importance. According to the second term in the equation, the hydroxylaminolysis reaction is catalyzed by a second hydroxylamine molecule, but the kinetics could not be used as a basis for determination of where and when the catalysis takes place. However, there is nothing in the kinetics to contradict the assumption that the k_{II} path

Scheme 1. A, anilide; P, products.

in the trifluoroacetanilide equation represents the $k_1 - k_4 - K_2 - k_7$ path in the mechanism in Scheme 1.

In an attempt to find a connection between the kinetics of acetanilide and trifluoroacetanilide, we have now investigated the hydroxylaminolysis of monofluoroacetanilide, which may be expected to combine the properties of the other two anilides.

MATERIALS AND METHODS

Monofluoroacetanilide (MFA) was synthesized as described in Ref. 3. All other chemicals used were of analytical grade.

The hydroxylaminolysis reaction was studied in the range $3.82 \leq -\log [H^+] \leq 9.79$. The relation between measured pH values and molar concentration of hydrogen ion, $[H^+]$, in 3 M KCl at 25 °C ($-\log [H^+] = \text{pH} + 0.20$), has been determined previously.^{4,5} Because of the different medium effects in different concentrations of the hydroxylamine system,¹ $-\log [H^+]$ is used instead of pH when a precise denotation is desired.

The kinetic experiments and the assay were performed as in our previous work.⁷ The initial concentration of MFA was $(1-7.5) \times 10^{-3}$ M. The reaction was followed until maximally 40 % of the anilide had reacted.

The k_{obs} values were determined from plots of $\log[\text{remaining anilide}]$ against time, except in a few cases where less than 4 % of the anilide

Table 1. Observed and theoretical pseudo-first order rate constants (k_{obs} and $k_{\text{calc}}/\text{min}^{-1} \times 10^{-5}$) for the formation of aniline from monofluoroacetanilide with different fractions of the hydroxylamine system present as base. The values of k_{calc} have been obtained by means of eqn. (3) using $k_1 = 3 \times 10^{-3} \text{ min}^{-1} \text{ M}^{-1}$ and the values of p' and q listed in Table 2.

C/M	0.2 % k_{obs}	k_{calc}	1.0 % k_{obs}	k_{calc}	3.0 % k_{obs}	k_{calc}	5.0 % k_{obs}	k_{calc}	10.0 % k_{obs}	k_{calc}
0.2	0.087	0.108	0.10	0.10	0.15	0.16	0.17	0.17	0.49	0.25
0.6	0.35	0.33	0.41	0.37	0.62	0.60	0.66	0.70	1.12	1.15
1.0	0.57	0.55	0.69	0.67	1.20	1.19	1.48	1.48	2.49	2.55
1.4	0.82	0.77	1.01	1.02	1.96	1.91	2.40	2.50	4.64	4.42
1.8	0.98	1.00	1.43	1.42	2.81	2.82	3.68	3.73	6.87	6.73
2.2	1.24	1.23	1.89	1.85	3.64	3.71	5.16	5.16	9.62	9.45
2.6	1.47	1.46	2.30	2.32	4.82	4.78	6.87	6.78	12.5	12.6
3.0	1.70	1.69	2.74	2.83	5.96	5.95	8.75	8.58	16.1	16.0

C/M	20.0 % k_{obs}	k_{calc}	40.0 % k_{obs}	k_{calc}	60.0 % k_{obs}	k_{calc}	80.0 % k_{obs}	k_{calc}
0.2	0.37	0.20	0.44	0.49	1.10	0.74	0.93	0.94
0.6	1.72	1.75	3.56	4.27	5.48	6.40	6.50	8.15
1.0	4.56	4.70	11.0	11.4	16.4	17.1	20.0	21.8
1.4	8.80	8.93	21.5	21.5	32.0	32.3	41.4	41.3
1.8	14.3	14.3	36.0	34.3	52.4	51.5	69.8	65.9
2.2	20.3	20.8	52.0	49.5	87.8	74.3	106	95.2
2.6	28.0	28.2	70.2	66.9	122	100	160	129
3.0	37.4	36.6	94.0	86.2	175	129	200	166

C/M	90.0 % k_{obs}	k_{calc}	C/M	99.0 % k_{obs}	k_{calc}	99.9 % k_{obs}	k_{calc}	99.97 % k_{obs}	k_{calc}
0.2	1.46	0.88	0.994	—	—	20.7	21.1	23.9	22.7
0.58	7.20	7.17	0.997	20.7	20.8	—	—	—	—
0.99	19.3	20.3	1.78	60.8	63.0	65.7	64.3	—	—
1.38	39.0	38.3	1.79	—	—	—	—	68.6	69.4
1.78	65.6	61.8	2.54	—	—	125	125	—	—
2.17	102	89.4	2.58	—	—	—	—	139	137
2.55	147	120	2.59	129	126	—	—	—	—
2.95	192	157

Fig. 1. Plots of k_{obs} vs. $-\log [\text{H}^+]$ at three different C values. The points are experimental. The curves are not calculated.

had reacted. In these cases the k_{obs} values were evaluated from plots of concentration of product against time.

RESULTS

Table 1 lists the pseudo-first order rate constants, k_{obs} , for the formation of anilide from MFA at different concentrations of the hydrox-

Fig. 2. Plots of $k_{\text{obs}}/[N]$ vs. C at 0.2, 1.0, 3.0, 5.0 and 10.0 % base.

Fig. 3. Plots of $k_{\text{obs}}/[N]$ vs. C at 20.0, 40.0, 60.0 and 80.0 % base.

ylamine system (*C*) and with different fractions of the system present as base. Fig. 1 shows the variation of k_{obs} with pH at 3 different concentrations of the hydroxylamine system. This kind of pH profile is typical of most anilides, except for the rise at the highest pH value which has not been encountered earlier, and will be commented upon below.

There is no significant contribution to the reaction rate from uncatalyzed or HO^- catalyzed alkaline hydrolysis.⁸ Acid hydrolysis is noticeable only at $C=0.2$ M at 0.2 % base where it has been calculated to amount to about 4 % of k_{obs} .⁸ The value given in Table 1 has been corrected for the acid hydrolysis. In all other cases, the contribution was 1 % or less, and the corresponding k_{obs} values have not been corrected.

Figs. 2–4 show plots of $k_{\text{obs}}/[N]$ vs. C . These plots will be commented upon in the Discussion.

DISCUSSION

The rate data for MFA show the characteristics that we have earlier found^{1,7-9} to be typical of the hydroxylaminolysis of anilides. Also, the pH-dependent intercepts of the plots

Fig. 4. Plots of $k_{\text{obs}}/[N]$ vs. C at 90.0, 99.0, 99.9 and 99.97 % base.

Scheme 2. A, anilide; P, products.

of $k_{\text{obs}}/[N]$ vs. C indicate that the hydroxylaminolysis of MFA involves H^+ catalysis. In that respect MFA differs from acetanilide¹ and trifluoroacetanilide⁸ but is similar to formanilides.⁹ The mechanism proposed for formanilides is shown in Scheme 2. Eqn. (3), which is derived from this mechanism, generally gives a good fit to the experimental data of MFA (Table 1).

$$k_{\text{obs}} = k_1[N](p'C + q)/(1 + p'C) \quad (3)$$

The parameter p' in eqn. (3) is a function of $[\text{H}^+]$ and the microconstants in Scheme 2⁹ and is closely related to p in eqn. (1). The parameter q is also pH-dependent and is defined by eqn. (4).

$$q = \frac{k_{2,\text{dec}}[\text{H}^+]/K_{\text{HI}}k_{-1}}{1 + k_{2,\text{dec}}[\text{H}^+]/K_{\text{HI}}k_{-1}} \quad (4)$$

Eqn. (3) has been fitted to the experimental data by the method described in Ref. 9. The value of k_1 has been estimated from the plot of $k_{\text{obs}}/[N]$ vs. C at 0.2 % base. From the intercepts of the plots of $k_{\text{obs}}/[N]$ vs. C (Fig. 2) approximate values of q have been obtained. Different values of p' and q have then been entered into eqn. (3) and the calculated and experimental k_{obs} values plotted together, until the best fit was obtained. Since the plots of k_{obs} vs. C at 60, 80 and 90 % base are slightly more than second order in C , the uppermost part of these plots ($C > 2$ M) have been disregarded in the search for the optimal p' and q values. A variation of p' by 3–5 % and of q by 10 % gives a less good fit to the experimental k_{obs} values. The optimal p' and q values are listed in Table 2.

Table 2. Values of p' and q in eqn. (3) which give the best fit to the experimental k_{obs} values.

% Base	$-\log [\text{H}^+]$	p'/M^{-1}	q
0.2	3.62	0.20	0.90
1.0	4.52	0.07	0.17
3.0	4.80	0.06	0.08
5.0	5.04	0.06	0.45
10.0	5.27	0.06	0.03
20.0	5.72	0.085	—
40.0	6.14	0.105	—
60.0	6.50	0.105	—
80.0	6.92	0.100	—
90.0	7.27	0.083	—
99.0	8.27	0.076	—
99.9	9.27	0.077	—
99.97	9.79	0.083	—

Formation of Intermediate I

The rate constant k_1 for the formation of the intermediate I may be evaluated directly from a plot of $k_{\text{obs}}/[\text{N}]$ vs. C at low pH if the plot is parallel to the abscissa.⁹ The value of k_1 for monofluoroacetanilide, evaluated by this method from the plot at 0.2 % base, is $3 \times 10^{-3} \text{ min}^{-1} \text{ M}^{-1}$. (For a more detailed comment on the method of evaluation, see Ref. 9). In the hydroxylaminolysis of acetanilide, $k_1 = 7 \times 10^{-4} \text{ min}^{-1} \text{ M}^{-1}$.¹ Thus k_1 is increased fourfold when the fluorine atom is introduced into the acyl group. The effect is small compared to the effect in the corresponding k_1 values in alkaline hydrolysis, where the fluorosubstitution results in a 200-fold increase.^{3,10}

In the nucleophilic attack on the amide group the hydroxylamine molecule is suggested^{7,11} to be hydrogen bonded to the carbonyl oxygen, thus forming a cyclic structure which has two mesomeric forms that help to stabilize the system long enough for the C–N bond to be formed. See Scheme 3. This may explain why hydroxylamine is a far more active nucleophile than is warranted by its basicity.¹² Consequently, if the hydrogen bond is weakened, the rate of formation of the hydroxylamine-

anilide addition intermediate would be lowered. It is known^{13,14} that the hydrogen bond to the carbonyl oxygen is weaker in fluoroacetic acid than in acetic acid. Thus the small increase in k_1 following upon fluoro substitution is the result of two opposed substituent effects: an increase due to lower electron density at the carbonyl carbon and a decrease due to weaker hydrogen bonding to the oxygen.

H⁺ Catalyzed breakdown of I

The value of the ratio $k_{2,\text{dec}}/K_{\text{HI}}k_{-1}$ estimated from the q values in Table 2 is about $6 \times 10^4 \text{ min}^{-1} \text{ M}^{-1}$, which is the same as for *p*-chloro- and *p*-nitroformanilide.⁹

The H⁺ catalyzed path has earlier been found only with formanilides, either unsubstituted or with electron-withdrawing substituents in the *para* position, but not with acetanilides.⁹ The fact that an electron-withdrawing substituent in the acyl part of an acetanilide makes this path kinetically detectable supports the conclusion that the ratio reflects the influence of the substituent on the breaking of the amide bond rather than the influence on the protonation of intermediate I.

Additional catalysis by the hydroxylamine system

At 60–90 % base, the experimental plots of k_{obs} vs. C (not shown here) are slightly more than second order in C . Thus a third *N* or *HN* must be involved in the reaction in this pH range. Since a more than second order dependence on C has not been found with any of the anilides studied earlier in the same C and pH ranges the phenomenon cannot be ascribed to general medium effects but must be due to some specific properties of the MFA structure.

Assuming that Scheme 2 is valid for the hydroxylaminolysis of MFA, the third *N* or *HN* must act as a catalyst in the k_1 step or in one or more of the k_2 , k_3 and k_4 steps, in order to result in a term third order in C , unless it is to be ascribed to a totally different mechanism. However, the relatively small influence of the third order term suggests that a large part of the reaction takes place *via* a path where the additional catalysis is not operating. Thus the possible ways for the additional catalysis are

Scheme 3.

an *N* or *HN* catalyzed nucleophilic attack parallel to the uncatalyzed k_1 path, and an *N* or *HN* catalyzed breakdown of II, III and/or IV parallel to the k_4 , k_5 and k_7 paths. At this stage we cannot distinguish between the two possibilities.

HO⁻ Catalyzed hydroxyl-aminolysis

At high pH (99–99.9 % base) the overall reaction rate reaches a constant value (Fig. 1), which rises as the pH is further increased to give 99.97 % base. According to Ref. 3 this rise cannot be due to alkaline hydrolysis.

The plot of $k_{\text{obs}}/[N]$ vs. *C* at 99.97 % base is parallel to the plots at 99 and 99.9 % base (see Fig. 4), but it has an intercept which makes it lie above the other two. The intercept indicates that at this pH there is a path in the reaction mechanism which involves one *N* and one HO⁻. This path may consist of HO⁻ catalyzed breakdown¹⁵ of I or of hydroxylamine catalyzed breakdown of an anilide-hydroxyl ion addition intermediate.

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