Hydroxylaminolysis of Anilides. V. H^+ Catalyzed Hydroxylaminolysis of *p*-Cyanoformanilide and *p*-Chloroformanilide. Differences in Substituent Effects Exerted by Substituents with Mesomeric and Inductive Action

BARBRO ARIANDER OHLSON

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

The kinetics of the hydroxylaminolysis of *p*-cyanoformanilide and *p*-chloroformanilide have been studied at 25 °C in the range $3.62 \leq -\log [H^+] \leq 9.79$. The concentration of hydroxylamine was varied from 0.2 M to 3.0 M ($\mu = 3.0$ by addition of KCl). The kinetics fit the mechanism suggested for the hydroxylaminolysis of *p*-nitroformanilide. With this mechanism, kinetic equations have now been derived for the dependence of k_{obs} on the concentration of the hydroxylamine system and on the pH. The new equations are closely related to those derived for other anilides. The rate constants for the previously studied formanilides are compared and the influence of substituents with and without mesomeric properties are discussed.

It has long been known¹ that nucleophiles showing α -effect, such as hydroxylamine and hydrazine, are unusually active towards amides and esters. Their reactivity far exceeds that expected from their base strength. This has been attributed to the presence of an $-OH$ or $-NH-$ group in the α -position to the amine nitrogen. It was early suggested² that the abnormal reactivity of hydroxylamine is due to hydrogen bonding between the α -group and the carbonyl oxygen. Such a bond should decrease the electron density at the carbonyl carbon and, possibly, hold the nucleophile in a favourable position for attack. Apart from the enhanced rates, until recently nothing unusual had been noted about hydroxylamine as a nucleophile. The relative rates of attack by hydroxylamine on different substrates were comparable with

those shown by HO^- and by ordinary amines. In a recent paper from this Laboratory,³ however, it was noted that the introduction of a *p*-nitro group into an anilide ring, which increases the rate of nucleophilic attack on the carbonyl carbon when the nucleophile is HO^- or an amine, decreases the rate when hydroxylamine was the attacking species. As an explanation for this phenomenon it was pointed out that *p*-nitro substitution lowers the electron density not only at the carbonyl carbon, which makes the nucleophilic attack easier, but also at the oxygen, which reduces the possibility of hydrogen bonding to the α -group. In order to obtain more information about the mechanism of the nucleophilic attack, two more anilides with electron withdrawing substituents have now been studied: *p*-cyanoformanilide, in which the substituent has the same type of electron withdrawing properties as the *p*-nitro group, and *p*-chloroformanilide, in which the substituent lacks $-E$ effect.

MATERIALS AND METHODS

p-Chloroformanilide (m.p. 93–94 °C, lit. 92 °C)⁴ and *p*-cyanoformanilide (m.p. 188–189 °C, lit. 189 °C)⁵ were prepared according to Huffman.⁶ All other chemicals used were Merck reagent grade chemicals.

The hydroxylaminolysis reaction was studied in the range $4.80 \leq -\log [H^+] \leq 9.79$ for *p*-cyanoformanilide and $3.62 \leq -\log [H^+] \leq 9.79$ for *p*-chloroformanilide. $[H^+]$ denotes the

Table 1. Observed pseudo-first order rate constants, $k_{\text{obs}}/\text{min}^{-1} \times 10^{-4}$, for the formation of *p*-aminobenzonitrile from *p*-cyanoformanilide at different concentrations of the hydroxylamine system. The percentages denote the fractions of free hydroxylamine base.

C/M	3.00 %	5.00 %	10.0 %	20.0 %	40.0 %	60.0 %	80.0 %
0.20	0.98	0.84	0.91	0.90	0.99	1.07	0.74
0.60	2.75	2.79	3.09	3.55	4.32	4.98	4.85
1.00	4.67	4.73	5.65	7.05	10.7	13.2	14.0
1.40	6.30	6.82	8.35	10.8	20.1	25.6	28.5
1.80	8.23	8.76	11.5	16.5	30.4	37.9	45.7
2.20	10.7	11.7	15.1	23.2	41.3	57.7	67.8
2.60	12.1	14.2	19.0	29.9	56.5	77.6	91.0
3.00	14.5	16.7	22.7	38.4	73.1	96.4	122

C/M	90.0 %	C/M	99.00 %	99.90 %	99.97 %
0.20	1.25	0.98	—	9.15	—
0.60	4.80	0.99	9.58	—	9.56
0.98	11.9	1.73	—	26.4	—
1.37	24.9	1.78	31.0	—	—
1.74	41.3	1.79	—	—	30.2
2.09	56.2	2.54	—	—	62.3
2.46	78.4	2.58	64.5	—	—
2.94	107	2.59	—	63.8	—

concentration of H^+ . The concentration of the hydroxylamine system was varied between 0.20 and 3.00 M. The kinetic experiments and assays were performed as in a previous work,⁷ with the following modification: To increase the solubility of the *p*-cyanoformanilide, the reaction mixtures contained 1 % dimethyl sulfoxide. This addition allowed a reasonable amount of the anilide to dissolve but was too small to appreciably influence the correlation between

the base percentages and the $[\text{H}^+]$ values. Therefore, these values were taken to be the same as for the water medium.

The molar absorption coefficients for the diazotized and coupled anilines were $\epsilon = 45\,800$ at $\lambda = 540$ nm for *p*-aminobenzonitrile and $\epsilon = 44\,400$ at $\lambda = 555$ nm for *p*-chloroaniline. The initial concentration of *p*-cyanoformanilide was $(0.3 - 0.9) \times 10^{-3}$ M and *p*-chloroformanilide $(0.25 - 2.8) \times 10^{-3}$ M.

Table 2. Observed pseudo-first order rate constants, $k_{\text{obs}}/\text{min}^{-1} \times 10^{-4}$, for the formation of *p*-chloroaniline from *p*-chloroformanilide at different concentrations of the hydroxylamine system. The percentages denote the fractions of free hydroxylamine base. * = corrected for acid hydrolysis.

C/M	0.20 %	1.00 %	5.00 %	10.0 %	20.0 %	40.0 %	60.0 %	80.0 %
0.20	1.04*	1.26	0.96	1.13	1.44	1.58	1.56	1.10
0.60	2.54*	2.75	3.96	4.94	8.92	9.29	10.1	8.60
1.00	4.33	5.37	8.18	10.7	17.7	23.8	28.8	24.2
1.40	6.05	7.72	13.1	18.2	31.8	43.7	62.3	48.1
1.80	8.28	10.8	18.8	27.0	48.9	68.8	103	82.9
2.20	9.91	13.4	24.2	39.1	69.0	102	153	121
2.60	12.0	16.3	30.6	49.1	90.5	141	210	173
3.00	12.9	19.3	37.2	60.4	120	183	286	225

C/M	90.0 %	C/M	95.0 %	C/M	99.00 %	99.90 %	99.97 %
0.20	0.94	0.20	0.67	—	—	—	—
0.60	7.05	0.60	6.22	—	—	—	—
0.98	20.6	1.00	18.3	1.00	15.6	14.8	14.9
1.35	41.0	1.38	34.9	1.78	48.7	—	46.4
1.70	64.8	1.79	58.6	1.79	—	43.7	—
2.14	100	2.17	84.9	2.55	102	—	—
2.53	144	2.56	122	2.57	—	—	87.6
2.79	168	2.95	157	2.60	—	91.8	—

Table 3. Values of p' and q . The q values are obtained from plots of $k_{\text{obs}}/[N]$ vs. C . The p' values are those that give the best fit to the experimental plots of k_{obs} vs. C , when introduced into eqn. (3).

% Base	$-\log [H^+]$ M	<i>p</i> -Cyano- formanilide		<i>p</i> -Chloro- formanilide	
		p' M ⁻¹	q	p' M ⁻¹	q
0.20	3.62	—	—	0.20	0.90
1.00	4.32	—	—	0.025	0.20
3.00	4.81	0.15	0.75	—	—
5.00	5.04	0.12	0.40	0.022	0.045
10.0	5.37	0.10	0.20	0.022	0.021
20.0	5.72	0.11	0.08	0.022	0.015
40.0	6.14	0.115	0.05	0.0205	0.003
60.0	6.50	0.12	0.01	0.022	—
80.0	6.92	0.105	—	0.013	—
90.0	7.27	0.087	—	0.010	—
95.0	7.60	—	—	0.0078	—
99.0	8.27	0.055	—	0.0063	—
99.90	9.27	0.055	—	0.0055	—
99.97	9.79	0.055	—	0.0055	—

Fig. 1. *p*-Chloroformanilide. Plots of k_{obs} vs. C with 10, 60 and 90 % of the hydroxylamine system present as base. The points are experimental. The curves are calculated by means of eqn. (3) using $k_1 = 2.5 \times 10^{-1} \text{ min}^{-1} \text{ M}^{-1}$ and the values of p' and q listed in Table 3.

The k_{obs} values were determined from plots of $\log [\text{remaining anilide}]$ vs. time. Depending on the reaction rate, the hydroxylaminolysis was followed until 10–60 % of the *p*-cyanoformanilide and 4–90 % of the *p*-chloroformanilide had reacted. The rate constants were determined graphically or by means of least squares regression.

RESULTS

The determined pseudo-first order rate constants, k_{obs} , for the formation of *p*-aminobenzonitrile and *p*-chloroaniline from the corresponding anilides are listed in Tables 1 and 2. The tables show the variation of k_{obs} with the concentration of the hydroxylamine system (C) at various base percentages. (In the following, hydroxylamine base will be referred to as N , and the hydroxylammonium ion as HN). Table 3 lists the values of $-\log [H^+]$ corresponding to the different base percentages.

At low base percentages the dependency of k_{obs} on C is slightly more than first order in C as may be calculated from Tables 1 and 2. When the fraction of base is increased, the order of the dependency also increases, and eventually becomes purely second order. This may be seen in Fig. 1, which shows the plots of k_{obs} vs. C at 10, 60 and 90 % base for *p*-chloroformanilide.

Fig. 2. *p*-Cyanoformanilide. Plots of k_{obs} vs. $-\log [\text{H}^+]$ at three different concentrations of the hydroxylamine system. The points are experimental. The curves are not calculated.

The magnitude of the k_{obs} values at a constant C is also pH dependent. At low base percentages the rates are low; they increase with the pH to reach a maximum at about 60–80 % base and then decrease to a limiting value. In Figs. 2 and 3, k_{obs} is plotted vs. $-\log [\text{H}^+]$ for 3 different values of C . In both figures the plots are bell shaped. In the *p*-chloroformanilide plot the maximum at $C=2.6$ M is rather pointed and the limiting values at high pH are comparatively low. The *p*-cyanoformanilide plot, on the other hand, is smooth with high limiting values, resembling the corresponding plot for *p*-nitroformanilide.³ It also reaches the maximum at a somewhat higher pH than *p*-chloroformanilide.

Figs. 4 and 5 show plots of $k_{\text{obs}}/[\text{N}]$ vs. C for *p*-cyano- and *p*-chloroformanilide. They are commented upon in the discussion part of this paper.

Although the investigations cover a pH range of up to 6 units, the only contribution to the reaction rates from acid⁸ or alkaline⁴ hydrolysis was in the *p*-chloroformanilide experiments at 0.2 % base for $C=0.2$ and 0.6 M. In these

runs, about 6 and 3 %, respectively, of the breakdown of the *p*-chloroformanilide can be ascribed to acid hydrolysis. The k_{obs} values given in Table 2 for these points are the corrected ones. In all other cases, the rate of breakdown due to acid or alkaline hydrolysis was calculated to be less than 1 % of the k_{obs} values and no correction was made.

DISCUSSION

A previous paper⁹ presented a mechanism explaining the kinetics of the hydroxylaminolysis of different anilides. This mechanism is the same as the one shown in Scheme 1, except for the part within the dotted line, which has been added later.³ From the mechanism, eqn. (1) was derived for the dependence of k_{obs} on C at constant pH:

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

In this equation, k_1 is the same as in Scheme 1 and p is a pH dependent parameter.⁷

Fig. 3. *p*-Chloroformanilide. Plots of k_{obs} vs. $-\log [\text{H}^+]$ at three different concentrations of the hydroxylamine system. The points are experimental. The curves are not calculated.

Fig. 4. *p*-Cyanoformanilide. Plot of $k_{\text{obs}}/[N]$ vs. C at seven different base percentages.

Fig. 5. *p*-Chloroformanilide. Plot of $k_{\text{obs}}/[N]$ vs. C at four different base percentages.

According to the plots of k_{obs} vs. C and k_{obs} vs. $-\log [\text{H}^+]$, the hydroxylaminolysis reactions of the anilides studied in the present investigation do not differ perceptibly from those of the anilides studied before. The order

of dependency of k_{obs} on C rises from first to second with increasing base percentage and the pH-profiles are bell-shaped. Despite this, it was soon apparent that eqn. (1) did not give an acceptable fit to the experimental values.

Preliminary calculations showed that in the lower pH region the kinetics comprised a term first order in $[N]$ and first order in $[\text{H}^+]$. In a previous paper⁷ the presence of a reaction path was discussed where the breakdown of the initial hydroxylamine-anilide intermediate is catalyzed by H^+ (k_2 in Scheme 1).

To see if this path could quantitatively account for the kinetic deviations from the previously adopted mechanism, an equation corresponding to eqn. (1) was derived from Scheme 1 by the method described earlier⁸ (eqn. 2).

$$k_{\text{obs}} = k_1[N](p'C + q)/(1 + p'C) \quad (2)$$

N, C and k_1 are the same as in eqn. (1), p' is a pH dependent parameter, defined by eqn. (3) and q is defined by eqn. (4).

Scheme 1.

$$p' = \frac{(K_I + K_{IV}[H^+]/K_a)(1 + K_{II}[H^+] + K_V[H^+]^2)}{(1 + [H^+]/K_a)(1 + (K_{II} + K_{III})[H^+] + (K_V + K_{VI})[H^+]^2)(1 + k_2[H^+]/k_{-1})} \quad (3)$$

$$q = \frac{k_2[H^+]/k_{-1}}{1 + k_2[H^+]/k_{-1}} \quad (4)$$

Eqn. (3) is closely related to the equation describing the pH dependence of p' and the constants K_I to K_{VI} denote the same ratios of the separate microconstants in Scheme 1 as in Ref. 7. The constants k_2 and k_{-1} also refer to Scheme 1.

Eqn. (2) may be rewritten as in eqn. (2a).

$$k_{\text{obs}}/[N] = k_1(p'C + q)/(1 + p'C) \quad (2a)$$

There are two important features of this equation. Firstly, when $C = 0$, $k_{\text{obs}}/[N] = k_1q$. Since q is pH-dependent, plots of $k_{\text{obs}}/[N]$ vs. C will have pH-dependent intercepts. Secondly, at very high $[H^+]$, $q = 1$ which renders the equation independent of C ; $k_{\text{obs}}/[N] = k_1$. Thus, if Scheme 1 is valid, k_1 may be evaluated from a plot of $k_{\text{obs}}/[N]$ vs. C , when the plot is parallel to the abscissa, and when k_1 is known q may be calculated from the intercept of the rest of the plots. This was done for *p*-cyano- and *p*-chloroformanilide (see Figs. 4 and 5). The result is listed in Table 4. When q is near to unity, the ratio $(p'C + q)/(1 + p'C)$ changes only little with C . Because of this, the k_1 values estimated as mentioned above may be too low. To compensate for this, the k_1 values have been rounded upwards, and are given in Table 4 with only 1 (2) significant figure (cf. Figs. 4 and 5).

Using the values of k_1 and q estimated from the plots of $k_{\text{obs}}/[N]$ vs. C and p' values found by iterative calculations, eqn. (2) gave good fits to all the plots of k_{obs} vs. C . The best fitting values of p' and q are listed in Table 3.

Since the values of k_1 have been rounded upwards, the values of q listed in Table 3 are all somewhat too small. In Fig. 1, showing the plots of k_{obs} vs. C at 10, 60 and 90 % base for *p*-chloroformanilide, the dots are experimental and the lines are calculated by means of eqn. (2) using the parameter values in Tables 3 and 4. The fit is representative for all the curves from the two substances. Thus, the kinetics of the hydroxylaminolysis reaction of *p*-cyano- and *p*-chloroformanilide may be completely explained by means of the equation derived from the mechanism shown in Scheme 1.

Substituent effects on formation of the intermediate I

Table 4 lists the k_1 values for the four formanilides studied. These values have been calculated by different methods and therefore the errors in the values may be of different relative size. In view of the later findings the method used for formanilide and *p*-nitroformanilide may have yielded k_1 values that are somewhat low but not so low as to influence the relative magnitudes. The effect of the substituents on k_1 will therefore be discussed only qualitatively.

In the case of the *p*-substituted formanilides, all of the substituents are electron-withdrawing. As seen, the *p*-chloro-group, which in this case has inductive effects, increases k_1 by a similar factor to that found in alkaline hydrolysis.⁴ The *p*-cyano and *p*-nitro groups, on the other hand, which have both $-E$ and $-I$ effects reduce k_1 . The different effects of the three substituents support the suggestion that the

Table 4. Values of k_1 , k_2/k_{-1} and k_4/k_{-1} for four formanilides. Both the constants and the ratios are calculated by means of methods, which are commented upon in the text.

	$k_1/\text{min}^{-1} \text{ M}^{-1} \times 10^{-2}$	$k_2(k_{-1})^{-1}/10^4$	$k_4(k_{-1})^{-1}/10^{-2}$
Formanilide	8.0	2	1.9
<i>p</i> -Chloroformanilide	25	0.5	0.55
<i>p</i> -Cyanoformanilide	2	8	5.5
<i>p</i> -Nitroformanilide	0.9	10	10

lowering of k_1 in the *p*-nitro- and *p*-cyano-substituted anilides is due to the mesomeric action of these groups.

In a previous paper³ on *p*-nitrosubstituted anilides, two possible explanations for this phenomenon were presented.

(1) In the nucleophilic attack a hydrogen bond is formed between the hydroxylamine -OH and the carbonyl oxygen. This bond may be stabilized by the mesomeric structure shown in Scheme 2a, except in anilides where the stabilization is hindered by competing mesomeric structures such as that shown in Scheme 2b.

Scheme 2.

The k_1 values of *p*-cyano- and *p*-chloroformanilide are compatible with this explanation.

(2) A hydrogen bond is formed between the hydroxylamine -OH and the anilide nitrogen. The electron density at this nitrogen is lowered by all electron withdrawing substituents, which will result in a weaker hydrogen bond. Furthermore, *p*-substituents with -*E* effects, such as the *p*-nitro group, change the geometry at the nitrogen, which may hinder the hydrogen bonded hydroxylamine in the attack on the carbonyl carbon. In view of the fact that introduction of a *p*-chloro group increases k_1 , this explanation is no longer plausible.

H⁺ catalyzed breakdown of I

According to the plots of $k_{\text{obs}}/[N]$ vs. C , the H⁺ catalyzed breakdown of intermediate

I is detectable (as an intercept) with all the formanilides studied, but in none of the acetanilides. The numerical value of k_2/k_{-1} may be evaluated by means of eqn. (4). This has been done for all the formanilides, and the resulting ratios are listed in Table 4.

When calculating the ratios, the q values given in Table 3 were used for *p*-cyano- and *p*-chloroformanilide; for the other two q was obtained by dividing the estimated intercepts by k_1 . Due to the error in the intercepts, all of the k_2/k_{-1} values should be considered rather rough estimations. They are all of about the same magnitude; possibly the formanilide and *p*-chloroformanilide values can be considered significantly lower than the others. Thus, the significance of the term k_2/k_{-1} in the overall kinetics as described by eqns. (2)–(4) is diminished by the introduction of the acyl -CH₃ group, and possibly increased by substituents with -*E* effects.

This may be due to effects on k_2 or k_{-1} or both. The constant k_{-1} denotes the rate constant for the (spontaneous) breakdown of the anilide-hydroxylamine intermediate to starting materials (see Scheme 3). However, once the intermediate is formed, a -CH₃ group in R² should strengthen rather than weaken the intermolecular C–N bond.

The substituent effect on the ratio k_2/k_{-1} must then be due to changes in k_2 . In other

words, the reaction $I + H^+ \xrightarrow{k_2} P$ is slower when R² is an electron donating group. This is contrary to what would be expected if k_2 denotes the protonation of the anilide nitrogen but in accord with the breakdown of a protonated intermediate IH⁺. Thus, it is suggested that the path within the dotted line in Scheme 1 should be depicted as in Scheme 4.

Hydroxylamine catalyzed breakdown of I

In principle, constants K_I to K_{VI} in eqn. (3), denoting different ratios of the microconstants in Scheme 1, may be evaluated from plots of

Scheme 3.

Scheme 4.

p' vs. $[\text{H}^+]$. In this case, however, the errors in p' are considered too great for the evaluation to give reliable results. The only constant that may be evaluated without computerized mathematical treatment is K_I , which represents the ratio k_4/k_{-1} . This is possible since at low $[\text{H}^+]$ eqn. (4) reduces to $p' = K_I$.

For all other anilides studied, the calculated values of K_I were very close to the p values used at high base percentages, where the reaction rates had reached the limiting values (cf. Figs. 2 and 3). Therefore the limiting values of the experimental p' at high base percentages for p -chloro- and p -cyanoformanilide may be used to discuss the substituent effect on K_I . These values are listed in Table 4 together with the calculated K_I from the formanilides studied earlier.

As seen, there is again a difference between the p -chloro-substituted and the p -cyano- and p -nitro-substituted anilides. In p -cyanoformanilide K_I is higher than in formanilide and half way between the values in formanilide and p -nitroformanilide; the p -chloroformanilide K_I , on the other hand, is lower. It was earlier suggested⁷ that the HN or N which is added in the k_3 and k_4 step is hydrogen bonded to the anilide nitrogen and to a hydrogen in the original nucleophile to form a cyclic intermediate. It was also suggested⁸ that the increase in K_I following p -nitro substitution is due to lowered electron density at the carbonyl carbon, which in turn makes the hydrogens of the original nucleophile more easily accessible for such bonding. In view of the opposite effects exerted by electron withdrawing substituents with and without mesomeric action, it seems more likely that the increasing effect of the p -nitro- and p -cyano substituents is instead due to a change in the geometry at the nitrogen (see Scheme 2b) which facilitates the formation of the cyclic intermediate. The decreasing effect of the p -chloro substituent

should then depend on the decrease in electron density at the nitrogen, which is not compensated for by a change in the geometry and which makes the nitrogen less accessible for hydrogen bonding.

Acknowledgement. I wish to express my sincere thanks to Professor Allan Ågren for discussing the manuscript, and to Mrs Barbro Johansson, Miss Britt-Marie Gustafsson and Miss Anna-Karin Bernhardsson for their skilful assistance.

REFERENCES

1. Jencks, W. P. and Carriuolo, J. J. *Am. Chem. Soc.* 82 (1960) 675.
2. Jencks, W. P. *J. Am. Chem. Soc.* 80 (1958) 4585.
3. Ohlson, B. A. and Lundkvist, G. *Acta Chem. Scand. B* 31 (1977) 173.
4. De Wolfe, R. M. and Newcomb, R. C. *J. Org. Chem.* 36 (1971) 3870.
5. Bogert, M. and Wize, L. *J. Am. Chem. Soc.* 33 (1910) 1494.
6. Huffman, C. W. *J. Org. Chem.* 23 (1958) 727.
7. Ohlson, B. A. and Lundkvist, G. *Acta Chem. Scand. B* 30 (1976) 915.
8. Ohlson, B. A. *Unpublished results*.
9. Eriksson, S. O. and Ohlson, B. A. *Acta Chem. Scand.* 26 (1972) 2759.

Received December 20, 1976.