Acta Chemica Scandinavica B 31 (1977) 173—178

Hydroxylaminolysis of Anilides. IV. α-Effect in the Hydroxylaminolysis of *p*-Nitroanilides. Unexpected Influence of *p*-Nitro Substituent

BARBRO ARIANDER OHLSON and GUNILLA LUNDKVIST

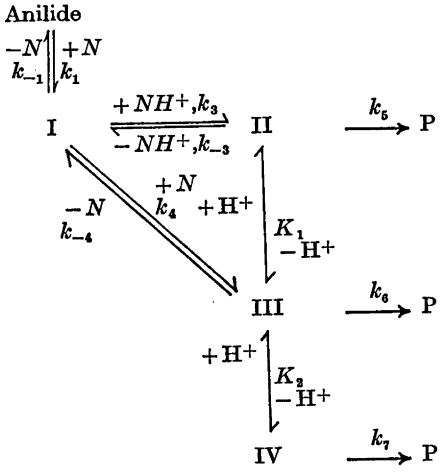
Department of Inorganic and Physical Pharmaceutical Chemistry, Biomedical Centre, University of Uppsala, Box 574, S-751 23 Uppsala, Sweden

The kinetics of the hydroxylaminolysis of *p*-nitroformanilide has been studied in the $[H^+]$ range $10^{-5.37} - 10^{-9.79}$, and of *p*-nitroacetanilide with 10 and 80 % of the hydroxylamine present as free base. The total hydroxylamine concentration varied from 0.2 to 3.0 M, the ionic strength being kept at 3.0 by addition of KCl. The reaction rates are in agreement with a mechanism previously postulated for anilides, where the primary addition intermediate (I, Schemes 1 and 2) is broken down to products *via* three cyclic intermediates (II, III and IV), which are in protolytic equilibrium. At low concentrations of the hydroxylamine system, the breakdown of I also seems to be catalyzed by H^+.

As a consequence of the *p*-nitro substitution, the rate of nucleophilic attack of hydroxylamine on the carbonyl is lowered. This unusual effect is explained by hydrogen bonding of the amide group with the atom in α-position to the nucleophile.

We have earlier postulated [1] that the hydroxylaminolysis of acetanilide follows a mechanism where the breakdown of the initial anilide-hydroxylamine intermediate (I) is assisted by the hydroxylammonium ion (NH^+) as well as by the hydroxylamine molecule (N), (see Scheme 1, where P denotes products). The investigation was later expanded [2] to see if the mechanism was applicable to other anilides as well. These anilides were originally chosen so that both electron donating and electron withdrawing ring substituents were represented. We found that for all the anilides studied, the hydroxylaminolysis reaction could be described by the mechanism postulated for acetanilide.

In the course of the investigation we also found, however, that the electron withdrawing substituent influenced the rate of the nucleophilic attack on the carbonyl carbon in an unusual direction, *i.e.* in the same direction as the electron donating *p*-methoxy group. In alkaline hydrolysis, the rate of the nucleophilic attack on the carbonyl carbon is usually enhanced a hundredfold or more by the introduction of a *p*-nitro group.[3] In the hydroxylaminolysis reaction, however, it is about ten times lower for *p*-nitroformanilide than for formanilide. This is even more surprising as electron donating substituents have been found to behave normally,[2] *i.e.* decrease the rate of the nucleophilic attack.



Scheme 1.

Table 1. Observed pseudo first order rate constants for the formation of *p*-nitroaniline from *p*-nitroformanilide at different concentrations of the hydroxylamine system. The percentages denote the fraction of free hydroxylamine base. The k_{obs} values at 99.9 and 99.97 % have been corrected for alkaline hydrolysis.[3]

	k_{obs}/min^{-1} 10^{-5}										
C	10.00 %	20.00 %	40.00 %	60.00 %	80.00 %	*C*	90.00 %	*C*	99.00 %	99.90 %	99.97 %
0.20	7.8	7.3	6.1	5.5	6.0	0.20	3.9	1.00	80.0	80	80
0.60	18.0	19.0	25.0	33.1	32.0	0.60	29.0	1.78	244	—	—
1.00	39.3	42.6	63.3	79.1	84.2	1.00	83.5	1.80	—	250	250
1.40	59.6	78.4	116	147	159	1.38	167	2.59	293	—	500
1.80	87.9	114	177	238	258	1.79	260	2.60	—	500	—
2.20	115	164	258	347	373	2.16	367				
2.60	144	212	339	454	499	2.57	512				
3.00	177	263	440	568	637	2.83	596				

We now present the rate constants for the hydroxylaminolysis of *p*-nitroformanilide and *p*-nitroacetanilide and offer an explanation for the unexpected behaviour of the *p*-nitrosubstituted anilides.

MATERIALS AND METHODS

p-*Nitroformanilide* was prepared by nitration of formanilide.[4] M.p. 194.5 – 195.5 °C, lit.[5] 194 – 195 °C.

p-*Nitroacetanilide* was prepared analogously. M.p. 214.5 – 215.5 °C, lit.[6] 214 – 216 °C.

All other chemicals used were Merck chemicals, reagent grade.

The kinetic experiments and the assay were performed as in our previous work,[2] with the following modification: To increase the solubility of the *p*-nitroacetanilide the reaction mixtures contained 20 % (v/v) dimethyl sulfoxide (DMSO). In the case of *p*-nitroformanilide no DMSO was needed.

The initial concentration of *p*-nitroacetanilide was 1.6×10^{-3} M and of *p*-nitroformanilide between 8×10^{-5} and 4.4×10^{-4} M. The absorption coefficient for the diazotized and coupled *p*-nitroaniline at 550 nm was 48 700 M^{-1} cm^{-1} in water and 50 000 M^{-1} cm^{-1} in the DMSO-water medium.

The k_{obs} values for *p*-nitroformanilide were determined from plots of log [remaining anilide] against time. Depending on the reaction rate, 20 – 50 % of the reaction was observed during the kinetic runs. In the case of *p*-nitroacetanilide 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. The determination was done graphically or by means of a Hewlett-Packard HP 9810A calculator (least squares regression).

The evaluation of the parameters in the dependence of p on $[H^+]$ was done on an IBM 370/155 computer, using a least squares regression program.

RESULTS

Observed pseudo first order rate constants, k_{obs}, for the formation of *p*-nitroaniline from *p*-nitroformanilide and *p*-nitroacetanilide at constant pH and constant total hydroxylamine concentration (C) are given in Tables 1 and 2. Eqn. (1), which has been derived from Scheme 1, and was introduced in a previous paper [2] from this laboratory, may be used to reproduce the k_{obs} values for *p*-nitroformanilide.

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

In eqn. (1) $[N]$ is the concentration of free hydroxylamine base, and p is a pH-dependent variable.

Table 2. Observed pseudo first order rate constants for the formation of *p*-nitroaniline from *p*-nitroacetanilide at different concentrations of the hydroxylamine system. The percentages denote the fraction of free hydroxylamine base.

	k_{obs}/min^{-1} 10^{-6}	
C	10.00 %	80.00 %
0.60	1.55	2.48
1.00	3.11	7.45
1.40	5.18	13.3
1.80	7.61	24.0
2.20	10.2	36.0
2.60	12.9	51.2
3.00	15.7	68.2

Table 3. Experimental and theoretical p values. The experimental p values are the optimal ones for reproducing the experimental k_{obs} values by means of eqn. (1), using $k_1 = 9.0 \times 10^{-3}$. The theoretical p values have been calculated by means of eqn. (2), using the parameter values listed in Table 4.

% Base	p M^{-1}	p_{theor} M^{-1}	$-\log [H^+]$
10.00	0.61	0.57	5.37
20.00	0.32	0.34	5.72
40.00	0.22	0.22	6.14
60.00	0.18	0.17	6.50
80.00	0.14	0.14	6.92
90.00	0.125	0.126	7.27
99.00	0.103	0.107	8.27
99.90	0.103	0.102	9.27
99.97	0.103	0.101	9.79

The fit is good for all the points except at $C = 0.2$ and for the smaller C values at 10 % base, where the experimental k_{obs} values are higher than those calculated by means of eqn. (1). The optimal k_1 and p values have been determined as described previously,[2] and are listed in Table 3.

Since p-nitroacetanilide has been studied at only two base percentages, k_1 and p values have not been evaluated for this compound. However, it is evident from Table 2 that the dependency of k_{obs} on C is between first and second order at 10 % base and purely second order at 80 % base.

To illustrate the variation of the reaction rate with the pH, k_{obs} has been plotted *vs.* $-\log [H^+]$ for p-nitroformanilide in Fig. 1. The curves are drawn to connect the points and are not calculated. When $[H^+]$ is decreased, the rate increases to reach a maximum at about 90 % base, and then decreases slightly to reach a limiting value, which is very close to the maximum value.

The evaluation of the dependency of p in eqn. (1) on pH was done by means of eqn. (2) as described in Ref. 2. The resulting theoretical p values are listed in Table 3 together with the experimental ones obtained by means of eqn. (1). The optimal parameters of eqn. (2) are listed in Table 4.

The search for the optimal parameters was started from widely differing initial values but the final parameters differed only by less than 1 %. The only parameter that varied to any appreciable extent was K_{VI}, which varied between 1×10^5 and 2×10^5. The reliability of the constants was tested as in Ref. 2. A 3 % change in K_I, K_{III} and K_{IV}, a 5 % change in K_V and a 10 % change in K_{II} resulted in a 3 % change in the calculated p.

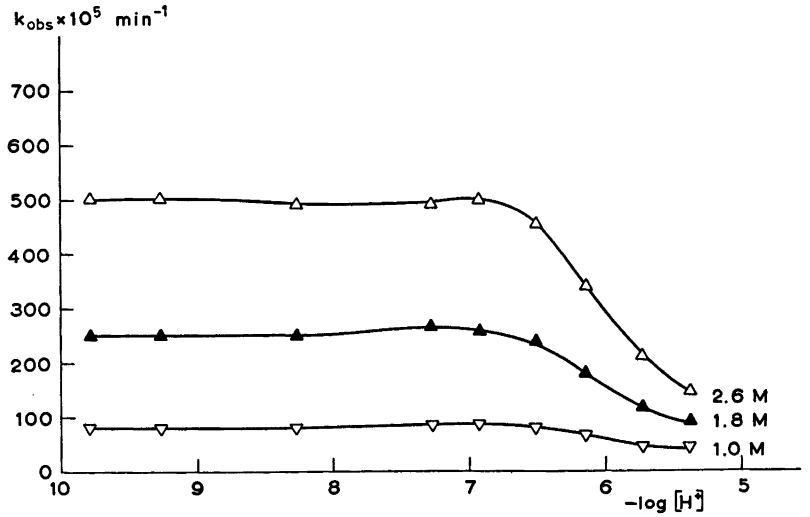


Fig. 1. p-Nitroformanilide. Plot of k_{obs} *vs.* $-\log [H^+]$ at three different C. The dots are experimental. The curves have not been calculated.

Table 4. Values of k_1 and of the parameters in eqn. (2) for four anilides.

	Acetanilide	*p*-Methoxy-acetanilide	Formanilide	*p*-Nitro-formanilide
k_1	7.0×10^{-4}	4.5×10^{-4}	8.0×10^{-2}	9.0×10^{-3}
$K_I = k_4/k_{-1}$ M^{-1}	1.30×10^{-2}	1.00×10^{-2}	1.89×10^{-2}	1.01×10^{-1}
$K_{II} = k_6/k_7K_2$ M^{-1}	2.14×10^{7}	6.30×10^{7}	1.24×10^{7}	3.79×10^{6}
$K_{III} = k_{-4}/k_7K_2$ M^{-1}	1.40×10^{8}	2.01×10^{10}	4.48×10^{7}	9.03×10^{7}
$K_{IV} = k_3/k_{-3}$ M^{-1}	2.30	9.51×10^{1}	9.52×10^{-1}	5.36
$K_V = k_5/k_7K_1K_2$ M^{-2}	8.85×10^{12}	3.81×10^{13}	2.34×10^{12}	1.89×10^{13}
$K_{VI} = k_{-3}/k_7K_1K_2$ M^{-2}	$< 10^{7}$	$< 10^{7}$	$< 10^{7}$	1.5×10^{7}

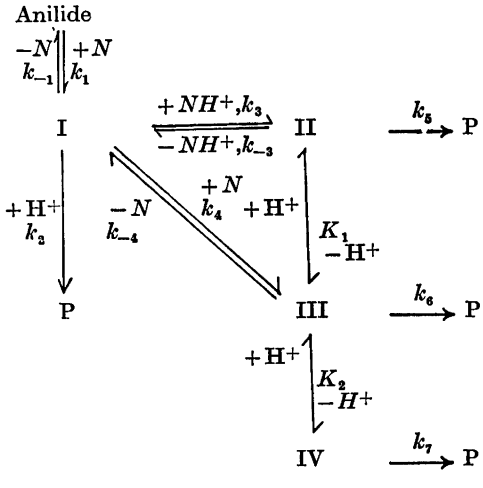
$$p = \frac{K_I + [K_{IV}/K_a + K_IK_{II}][H^+] + [K_{II}K_{IV}/K_a + K_IK_V][H^+]^2 + [K_{IV}K_V/K_a][H^+]^3}{1 + [1/K_a + K_{II} + K_{III}][H^+] + [(K_{II} + K_{III})/K_a + K_V + K_{VI}][H^+]^2 + [(K_V + K_{VI})/K_a][H^+]^3} \quad (2)$$

DISCUSSION

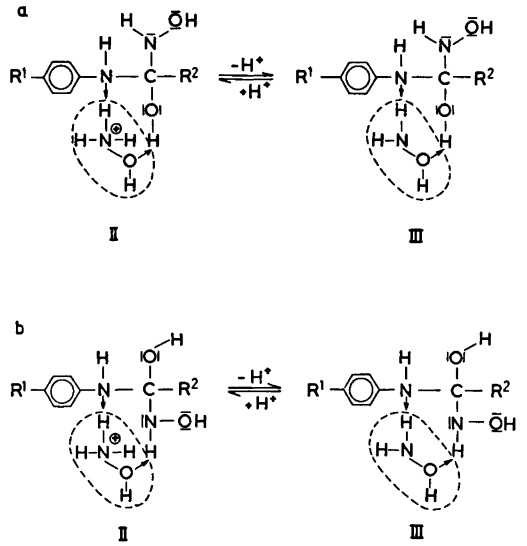
The applicability of eqns. (1) and (2) shows that the hydroxylaminolysis of *p*-nitroformanilide follows the mechanism postulated for the anilides studied previously. At $C = 0.2$ and at the lower part of the 10 % series, however, eqn. (1) fails to give a good fit to the experimental data. This disagreement between experimental and theoretical values cannot be explained by acid hydrolysis. At 10 % base the rate constant for the decomposition of the anilide due to acid hydrolysis can be estimated [7] to be about 9×10^{-7} min^{-1}, *i.e.* about 1 % of the rate of k_{obs} at $C = 0.2$. However, it may be explained by assuming an H^+-catalyzed path from the intermediate I to products in Scheme 1. Such a path has previously been suggested for formanilide [2] (see Scheme 2).

Breakdown of intermediate I. The influence of the *p*-nitro substituent on the steps in Scheme 1 is illustrated in Table 4. In the k_3 and k_4 steps a hydroxylammonium ion (k_3) or a hydroxylamine molecule (k_4) is bound to the intermediate I to form the intermediates II and III. These are shown with the catalyst bonded to the carbonyl hydrogen in Scheme 3a, and to the amine hydrogen in Scheme 3b.

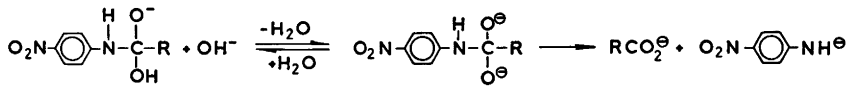
Substitution of an electron-withdrawing group at the *p*-position will lower the electron



Scheme 2.



Scheme 3.



Scheme 4.

density around the carbonyl carbon, which in turn will make the hydrogens at the oxygen or nitrogen more accessible for hydrogen bonding. This results in higher values of K_I and K_{IV}, that reflect the bonding of N and HN to I.

The ratio k_6/k_{-4} obtained by dividing K_{II} by K_{III}, is one seventh of that for formanilide. This may seem strange at first, since the amide bond should be weakened by the *p*-nitro group. However, at the same time the *p*-nitro substituent will decrease the ability of the free electron pair on the amide nitrogen to bind the extra hydrogen, which is necessary to make the aniline moiety a good leaving group.

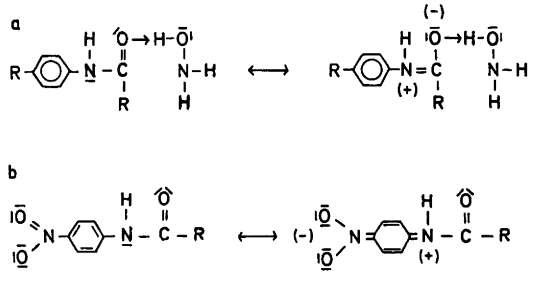
The ion R-ArNH$^-$, the stability of which is increased by the *p*-nitro group, is probably not dissociated from the intermediate III but rather from IV by the k_7 route. This is paralleled by the alkaline hydrolysis mechanism for *p*-nitroformanilide,[3] where this ion was suggested to be dissociated from an intermediate with two negative charges (see Scheme 4).

Formation of intermediate I. The really intriguing part of the hydroxylaminolysis of *p*-nitroformanilide is that the rate of the nucleophilic attack on the carbonyl carbon (k_1) is lowered almost ten times as a consequence of the introduction of the *p*-nitro group. The lowering of k_1 is reflected in the lowering of the total reaction rate by approximately the same factor. This effect has no parallel in the hydrolysis of anilides nor in any other reaction of nucleophiles with carbonyl compounds. In the alkaline hydrolysis,[3] the nucleophilic attack on *p*-nitroacetanilide is about 50 times faster than on acetanilide. Furthermore, in our previous work, the difference in k_1 for the hydroxylaminolysis reactions of different anilides has been well in line with that found in alkaline hydrolysis.

However, the present results are not completely unique. The rate data for *p*-nitroacetanilide in this work show the same decrease in k_{obs} when compared to acetanilide as those for *p*-nitroformanilide when compared to formanilide. Owing to the very low reaction rates and the low solubility of *p*-nitroacetanilide, the reaction was only studied at two pH values. Thus k_1 has not been evaluated, but the relative rates suggest that the decrease in k_1 for *p*-nitroformanilide is indeed a consequence of the *p*-nitro substitution and not due to special properties of the formyl group.

A *p*-nitro group in an anilide ring will decrease the electron density at the carbonyl carbon, thereby facilitating the nucleophilic attack. Since in this case the rate of nucleophilic attack is lowered, it seems that the rate of attack of the hydroxylamine on the anilide is determined not only by the attack of nitrogen on carbon, but also by some other factor. This conclusion is supported by the fact that hydroxylamine is about 1000 times more reactive as a nucleophile than is to be expected from its basicity.[8] A similar enhancement of the reaction rates has been found for other amine derivatives where there is a strongly electronegative element in the α-position to the nucleophile.[8] It has been suggested [9] that the abnormal reactivity is due to hydrogen bonding between the carbonyl oxygen and a hydrogen at the α atom.

There are two possible ways in which hydrogen bonding to the anilide may aid the nucleophilic attack, and by which the observed substituent effect can be accounted for: (1) Formation of a hydrogen bond to the carbonyl oxygen which increases by induction the electron density at the hydroxylamine nitrogen and helps to keep it in position for the nucleophilic attack. For most anilides, the hydrogen bond will be stabilized by the mesomeric structure shown in Scheme 5a (*cf.* Ref.



Scheme 5.

10), and k_1 will depend largely on the degree of electron density at the carbonyl carbon. For anilides with substituents capable of mesomeric interaction with the anilide nitrogen, such as a *p*-nitro group, the resonance structure shown in Scheme 5b will lessen the stabilization of the hydrogen bond. The hydroxylamine nitrogen will be deprived of its usual aid in the nucleophilic attack and k_1 will be smaller than expected. (2) A similar argument may be applied if the anilide nitrogen takes part in the hydrogen bonding. On introduction of a *p*-nitro group, the basicity of this nitrogen will be less reduced than that of the carbonyl oxygen. On the other hand, the geometry at the amide group will change owing to the mesomeric interaction of the *p*-nitro group with the anilide nitrogen. Thus in this case there are steric factors as well as a weaker hydrogen bond to account for the decrease in k_1.

Acknowledgements. We want to thank Miss Britt-Marie Gustafsson and Mrs Barbro Johansson for their skilful technical assistance, and Dr. Sven O. Eriksson for discussing the manuscript.

REFERENCES

1. Eriksson, S. O. and Ohlson, B. A. *Acta Chem. Scand. 26* (1972) 2759.
2. Ohlson, B. A. and Lundkvist, G. *Acta Chem. Scand. B 30* (1976) 915.
3. De Wolfe, R. H. and Newcomb, R. C. *J. Org. Chem. 36* (1971) 3870.
4. Arnall, F. and Lewis, T. *J. Soc. Chem. Ind. 48* (1929) 159.
5. Morgan, G. T. and Michelwait, F. G. M. *J. Chem. Soc. 87* (1905) 931.
6. *The Merck Index*, Merck & Co., Rahway, N. J. 1952, 6th Ed., p. 677.
7. Ohlson, B. A. *Unpublished results.*
8. Jencks, W. P. and Carriuolo, J. *J. Am. Chem. Soc. 82* (1960) 675.
9. Jencks, W. P. *J. Am. Chem. Soc. 80* (1958) 4585.
10. Kaválek, J. and Štěrba, V. *Collect. Czech. Chem. Commun. 40* (1975) 1924.
11. Rysman de Lockerente, S., Nagy, O. B. and Bruylants, A. *Org. Magn. Reson. 2* (1970) 179.

Received August 25, 1976.