KINETICS OF ACID-CATALYZED HYDROLYSIS OF SUBSTITUTED FORMANILIDES

J.KAVÁLEK and V.ŠTĚRBA

Organic Chemistry Department,
Institute of Chemical Technology, 532 10 Pardubice

The hydrolysis kinetics of nine *m*- and *p*-substituted formanilides have been studied in diluted sulphuric acid medium at 20°C. Dissociation constants of the protonated formanilides have been measured in the case of four derivatives. The dissociation and rate constants measured have been correlated according to the Hammett equation. At low acidity function values the correlation of the rate constants is non-linear. This finding has been explained by a gradual change in the rate-limiting step from decomposition of the protonated carbinolamine to addition of water to protonated formanilide.

At the present time hydrolysis of amides in solutions of diluted acids is explained by a reaction mechanism involving protonation of the amide molecule and subsequent rate-limiting attack by water[1] (Scheme 1). The reaction rate increases with increasing acid concentration up to a certain value, and then it again decreases. This course is due to that increasing acidity causes a decrease in the water activity and thus also in the rate of the second reaction step (attack of the protonated amide molecule by water). When this influence is greater than that of the increasing acidity on concentration of the protonated amide, the hydrolysis rate decreases. These cases of antagonistic effects of increasing acidity and decreasing water activity can be solved with the use of Eq. (*1*) (ref.[2−5]) or more complex and more general Eq. (*2*) (ref.[6]) proposed by Bunett; here α stands for molar fraction of the protonated substrate, k_2^0 is the second order rate constant in an infinitely diluted solution, ω is the number of water molecules in the activated complex (or more precisely its difference as compared with the protonated amide molecule), and the value of Φ depends also on the difference in hydratation of the complex and that of the protonated substrate. The dependences described by Eqs (*1*) and (*2*) are non-linear in many cases of amide

$$\log k_{\mathrm{exp}} - \log \alpha = \omega \log a_{\mathrm{H_2O}} + \log k_2^0 , \qquad (1)$$

$$\log k_{\mathrm{exp}} + \mathrm{H}_0 = \Phi(\mathrm{H}_0 + \log [\mathrm{H}^+]) + \log k_2^0 \qquad (2)$$

hydrolyses, which was explained in two ways: *a*) the number of water molecules in the activated complex is reduced at higher acidities[7], resp. the activity coefficients ratio $f_{\mathrm{H^+}}/f^+$ does not remain constant[8], or *b*) the reaction can take two simultaneous courses. Besides the hydrolysis going through the activated complex protonated at oxygen (Scheme 1) a second reaction path was suggested (Scheme 2) having the activated complex A protonated at nitrogen[7]. For this case the dependence of k_{exp} on the acidity of medium was defined by Eq. (*3*), where k_{N} an k_{O} are the rate constants of hydrolyses going simultaneously through the activated complexes protonated

at nitrogen and oxygen, respectively (Schemes 1 and 2)

$$k_{\exp} = k_N(1 - \alpha)\left[H^+\right] a_{H_2O} + k_0 \alpha a_{H_2O}. \tag{3}$$

Almost all the interpretations inclusive of the suggested reaction mechanisms of amide hydrolyses were based on the found dependences $k_{\exp}$ *vs* acidity of medium, and, therefore, they depend on the presumptions made with respect to the ratio of the activity coefficients of the reacting species. Often it is possible to obtain more information of better reliability for determination of reaction mechanism from studies of substituents influence on the rate constants. Therefore, in the present paper we have followed the hydrolysis kinetics of *m*- and *p*-substituted formanilides in diluted sulphuric acid. In contrast to acetanilides, formanilides react relatively fast even at the room temperature.

EXPERIMENTAL

Substituted formanilides. 4-Methyl- (*I*), unsubstituted (*II*), 3-methoxy- (*III*), 4-bromo- (*IV*), 3-chloro (*V*), 3-nitro- (*VI*), 4-acetyl- (*VII*), 4-cyano- (*VIII*) and 4-nitro (*IX*) derivatives were described in the previous report[9].

For measurement of rate and protonation constants were prepared $2 . 10^{-2}$ M and $5 . 10^{-2}$ M solutions of the formanilides in 50% (by vol.) aqueous ethanol containing Na_2HPO_4 and KH_2PO_4 of $5 . 10^{-3}$ M concentration. Determination of pK_{BH^+}: 35 µl $5 . 10^{-2}$ M formanilide solution was injected into 10 ml diluted sulphuric acid at 25°C with stirring. A part of the solution was placed in a 1 cm quartz cell located in the thermostatted cell compartment of a VSU-2P spectrophotometer (Zeiss, Jena), and the absorbances were measured at 280 nm (compound *I* and *II*), 275 nm (compd. *V*) and 240 nm (compd. *VI*). As the hydrolysis takes place during the measurements, the absorbances were measured at short time intervals, and extrapolation of the values measured to zero time gave the absorbance at the moment of mixing.

Kinetic measurements. 25 µl $2 . 10^{-2}$ M formanilide solution was injected with stirring into 10 ml diluted sulphuric acid; further the procedure was analogous to that of pK_{BH^+} determination. The absorbance change was followed within 3 to 4 half-lives, and the value A_∞ was determined after 7 to 8 half-lives. The absorbances were measured at 250, 290, 270 and 322 nm (for compounds *I*– *VI*, *VII*, *VIII* and *IX*, respectively), and the rate constants were calculated from the relation $k.t = -2 \cdot 303 \log (A_t - A_\infty) + \text{const.}$

RESULTS AND DISCUSSION

The concentration ratio *I* of the protonated and non-protonated amide *I*, *II*, *V* and *VI* was calculated from Eq. (*4*),

$$I = \left[BH^+\right]/\left[B\right] = (A - A_B)/(A_{BH^+} - A), \tag{4}$$

where A, A_B and A_{BH^+} stand for absorbance of the measured solution, non-protonated and protonated formanilide, respectively. The obtained I values are subject to considerable error. The difference of absorbances of the protonated and non-

Values of Protonisation Constants K_{BH^+} and Rate Constants (in s^{-1}) of Hydrolysis of Formanilides $I-IX$ in Diluted Sulphuric Acid Solutions at 25°C

Compound	$-pK_{BH^+}$	$k_{exp} \cdot 10^{4,a}$	$k_2{}^a$	$k_2 \cdot 10^{4,b}$
I	$2 \cdot 63 \pm 0 \cdot 02$	$2 \cdot 08$	$0 \cdot 085$	$0 \cdot 316$
II	$2 \cdot 71 \pm 0 \cdot 02$	$2 \cdot 95$	$0 \cdot 150$	$0 \cdot 742$
III	$(2 \cdot 76)^c$	$4 \cdot 08$	$0 \cdot 235$	$1 \cdot 48$
IV	$(2 \cdot 82)^c$	$4 \cdot 68$	$0 \cdot 309$	$1 \cdot 95$
V	$2 \cdot 87 \pm 0 \cdot 03$	$5 \cdot 38$	$0 \cdot 400$	$2 \cdot 95$
VI	$3 \cdot 03 \pm 0 \cdot 06$	$6 \cdot 46$	$0 \cdot 692$	$14 \cdot 5$
VII	$(2 \cdot 96)^c$	$13 \cdot 2$	$1 \cdot 20$	$83 \cdot 0$
$VIII$	$(3 \cdot 03)^c$	$13 \cdot 5$	$1 \cdot 45$	$43 \cdot 7$
IX	$(3 \cdot 08)^c$	$16 \cdot 6$	$2 \cdot 00$	$110 \cdot 0$

[a] For H_A 0; [b] for $H_A -3 \cdot 2$; [c] calculated from the Hammett equation.

-protonated forms was maximum 20%. The value A_{BH^+} increased with increasing concentration of sulphuric acid (influence of medium), and hydrolysis took place during the measurements, so that the absorbance values measured had to be extrapolated to zero time. The latter reason made it impossible to measure the I values of the amides $VII-IX$, as they were hydrolyzed very quickly during the measurement. The pK_{BH^+} values (Table I) were determined graphically by plotting $\log I$ against the acidity function[10] H_A. The dependences were linear with the slopes within $0 \cdot 92-0 \cdot 95$. Correlation of $-pK_{BH^+}$ vs the Hammett σ constants gave the reaction constant ϱ $0 \cdot 48 \pm 0 \cdot 10$. Magnitude of this constant indicates that the protona-
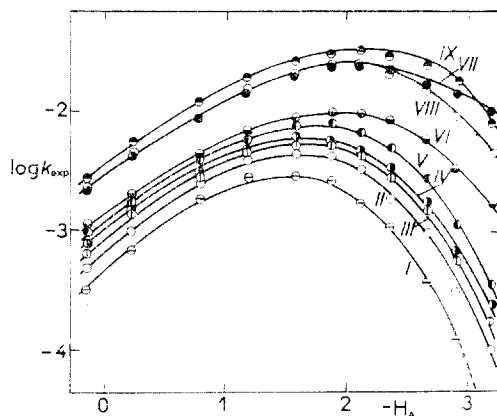

FIG. 1

Dependence of Logarithms of Rate Constants k_{exp} (s^{-1}) of Hydrolysis of Formanilides $I-IX$ in Sulphuric Acid Solution at 25°C on H_A Function
⊖ I; ○ II, $VIII$; ◎ III; ◑ IV; ◐ V; ◓ VI; ● VII; ◔ IX,

tion takes place at oxygen and not at nitrogen, as in the latter case the ϱ constant should have been greater than unity. (Dissociation of formanilides involving the N—H bond splitting[9] has ϱ 1·53). From the Hammett equation the pK_{BH^+} values of the remaining amides (*III*, *IV*, *VII*−*IX*) were computed, too (Table I). When calculating pK_{BH^+} of the derivatives *VII*−*IX* we used also σ and not σ^- values. (The use of σ values is justified as it follows from this finding: the $-H_A$ values at maximum k_{exp} given in Fig. 1 correlate with σ constants for all the derivatives, and the ϱ value is again about 0·5 − the maximum k_{exp} values depend on the degree of protonation.) The pK_{BH^+} value thus calculated for the nitro derivative *IX* (where the type of the substituent constant used has the greatest influence) is by 0·08 smaller than that calculated from the dependence of k_{exp} on the concentration of sulphuric acid[11] at 25°C.

The dependences k_{exp} *vs* H_A (Fig. 1) have the form characteristical for hydrolysis of amides in acid medium. At the lowest sulphuric acid concentrations the predominant part of the amide is present in the non-protonated form, and the experimental rate constant is defined by Eq. (5), where h_A is negative antilogarithm of H_A.

$$k_{exp} = k_2 h_A / K_{BH^+} . \tag{5}$$

At the highest sulphuric acid concentrations the greatest part of the substrate is protonated and the experimental rate constant value approaches the k_2 value. At H_A −3·2 the k_2 values were computed from k_{exp} and pK_{BH^+} (the maximum difference was encountered with the derivative *IX*, where k_2 is 1·75 times greater than k_{exp}). The logarithms of k_2 correlate with σ^- constants [12] according to Eq. (6) (Fig. 2, the straight line *1*).

$$\log k_2 = (1·75 \pm 0·04) \sigma^- + (4·13 \pm 0·02) . \tag{6}$$

This correlation does not involve the acetyl derivative *VII* the anomalous behaviour of which is explained below.

In the region of low sulphuric acid concentrations (Fig. 1) the studied formanilides *I*−*IX* split into two groups. The derivatives *VII*−*IX* containing substituents of −M type at the *para* position react faster than the derivatives *I*−*VI*. This difference is due to that the protonation of amides is controlled predominantly by the inductive effect of a substituent (correlation with σ constants), whereas in the subsequent step both the mesomeric and inductive effects are significant (correlation with σ^- constants), which results in acceleration of the hydrolysis[13]. Thus cortherelation of k_{exp} *vs* σ constants can be used only with the derivatives *I*−*VI*. At H_A equal zero is $h_A = 1$, and Eq. (7) is obtained for $\log k_{exp}$ of the derivatives *I*−*VI*. The dependence

$$\log k_{exp} = \log k_2 - \log K_{BH^+} = -\varrho_{K_{BH^+}}\sigma + \varrho_{k_2}\sigma + \text{const.} =$$
$$= (-\varrho_{K_{BH^+}} + \varrho_{k_2}) \sigma + \text{const.} = \varrho_{exp}\sigma + \text{const} . \tag{7}$$

$\log k_{\text{exp}}$ *vs* σ (Fig. 2, curve *3*) is non-linear. The slope is about unity with the least reactive formanilides (*I* and *II*) and about 0·25 with the most reactive ones. Such a non-linear concave dependence is typical for reactions exhibiting a change in the rate-limiting step[14]. If we add a value 0·48 (ϱ constant for $pK_{\text{BH}+}$) to the slopes of dependences given in Fig. 2 (curve *3*), we obtain a slope corresponding to the dependence $\log k_2$ *vs* σ constants (Eq. (7)) with the values about 1·5 and 0·75 (Fig. 2, curve *2*).

The Fig. 2, curve *2* gives also the dependence of $\log k_2$ (calculated from Eq. (5) for amides *VII—IX* at H_A equal zero) *vs* σ^- constants. These k_0 values lie along the straight line with the slope 0·8 (scattering of the value is somewhat greater in this case than with the previous correlations due to errors in determination resp. calculation of $pK_{\text{BH}+}$ values).

The value 1·5 of angular coefficient of the dependence on σ (resp. σ^-) constants of amides *I* and *II* at H_A 0 (Fig. 2, curve *2*) is practically the same as the ϱ value of correlation $\log k_2$ *vs* σ^- in the more concentrated sulphuric acid media (Fig. 2, straight line *1*). Therefrom it can be deduced that the rate-limiting step of hydrolysis of the formanilides *I* and *II* in diluted acids (H_A 0) is the same as that of all the formanilides *I—IX* in more concentrated acid solutions. The reaction mechanism given in Scheme 3 can be suggested for the reaction of the protonated formanilides with water.

In diluted acid solutions the decomposition of carbinolamine (*B*) into products is probably rate-limiting in the case of the amides *I* and *II*, whereas the attack of water on the protonated amide is rate-limiting for derivatives with greater positive value of σ constant. Increasing concentration of acid results in decrease of water activity, whereby the decomposition of carbinolamine becomes slower[15], and becomes gradually rate-limiting for the other formanilides, too. Such a change in the rate-limiting step brought about by increasing acidity of medium was found with acid-catalyzed hydrolysis of benzylideneanilines[16] which has a similar reaction mechanism as the hydrolysis of anilides.
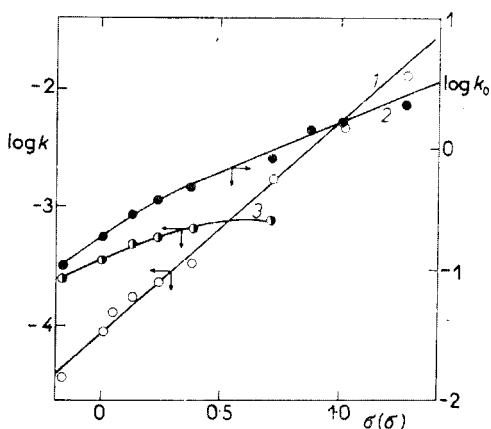

FIG. 2

Dependence of Rate Constants (s^{-1}) of Hydrolysis of Formanilides *I—IX* in Diluted Sulphuric Acid at 25°C on σ resp. σ^- Constants

*1* $\log k_2$ at H_A -3.2; *2* $\log k_2$ at H_A 0; *3* $\log k_{\text{exp}}$ at H_A 0.

No oxygen isotopic exchange between carbonyl group of amide and water was found with hydrolysis of benzamide in 0·1M-HCl (ref.[17]) and 0·5M-HCl (ref.[18]), which indicated that the attack of water on the protonated amine was rate-limiting. This mechanism was generalized to the acid-catalyzed hydrolyses of all types of amides inclusive of anilides. All the same the hydrolysis of acetanilide and N-acetylsulphanilic acid in diluted sulphuric acid medium was found[19] to have relatively high values (0·60 and 0·70, respectively) of the Bunnett parameter Φ indicating that water acts here as a proton-transfer-agent and not nucleophile. Even the less reliable values of the Bunnett parameter ω (3·95 and 2·85, respectively) stand near the border of the mechanisms discussed (a value about 3).
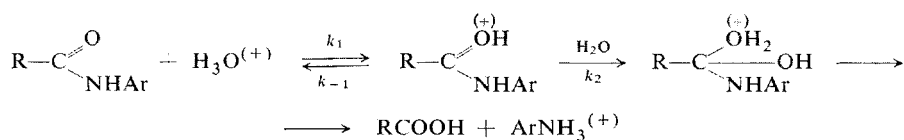
SCHEME 1
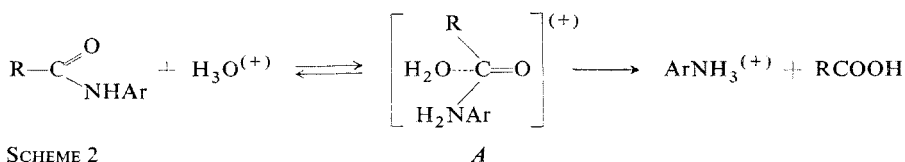
SCHEME 2   *A*
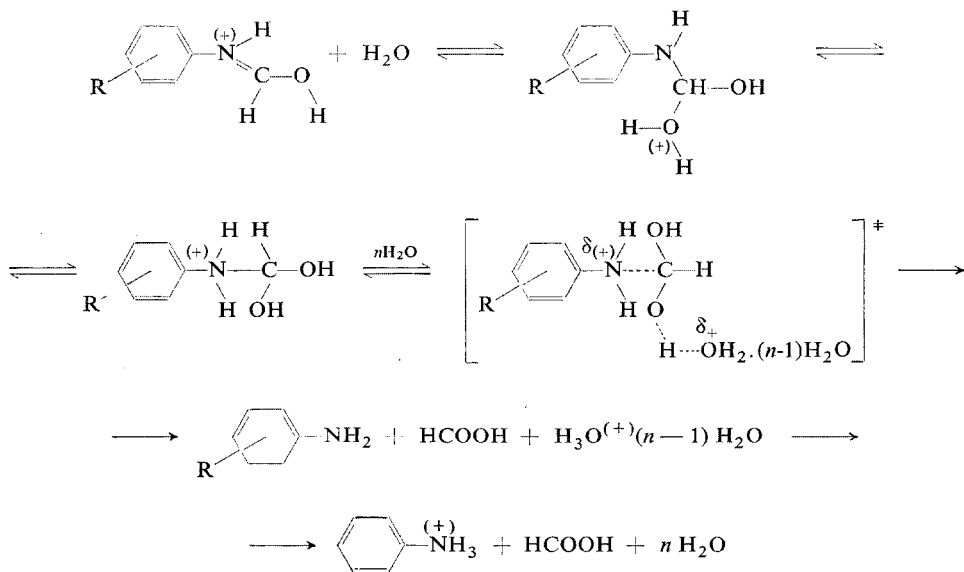
SCHEME 3

In all the correlations 3-methoxy derivative *III* was found to react faster than it should react according to σ constant. The same acceleration was observed with kinetic experiments carried out simultaneously in diluted solutions of hydrochloric and perchloric acids. The σ value of methoxy group (as that of hydroxy group) depends on medium[20]. In diluted mineral acids hydrogen bonding is increasingly formed to methoxy group, its electron-attracting effect being thereby increased, which in turn accelerates the hydrolysis.

p-Acetyl derivative *VII* shows a slower decrease of the rate constant with increasing sulphuric acid concentration than the other formanilides do (Fig. 1). The activated complex of the rate-limiting step of this reaction involves splitting off of *p*-amino-acetophenone (Scheme 3).

Protonation at nitrogen cannot take place in the activated complex. However, a protonation (at least partial) can take place at carbonyl oxygen of acetyl group the basicity of which increases due to formation of free amino group. Relative amount of the protonated acetyl group in the activated complex increases with increasing sulphuric acid concentration. As the protonated acetyl group must have a far greater value of σ_p^-, this proton-catalyzed hydrolysis is faster, and the overall decrease of k_{exp} is milder.

Basicity of acetyl group of 4-aminoacetophenone can be roughly estimated from the following data. The pK_{BH^+} value of acetophenone is -6.72, and $\log K_{BH^+}$ of acetophenones correlate with σ^+ values, the ϱ value being 2.17 (ref.[21]); σ^+ value of *p*-amino group is -1.73 (ref.[22]). The calculated pK_{BH^+} of the 4-aminoacetophenone protonated at the acetyl group is -3.9 (the given pK_{BH^+} values hold for the acidity function H_0) resp. -2.8 (relative to the acidity function H_A). The anomalous hydrolysis rate of the acetyl derivative *VII* (Fig. 1) becomes marked at the acid concentration corresponding to the mentioned H_A value.

REFERENCES

1. O'Connor C.: Quart. Rev. *24*, 553 (1970).
2. Bunnett J. F.: J. Am. Chem. Soc. *84*, 4956 (1961).
3. Bunnett J. F.: J. Am. Chem. Soc. *84*, 4968 (1961).
4. Bunnett J. F.: J. Am. Chem. Soc. *84*, 4973 (1961).
5. Bunnett J. F.: J. Am. Chem. Soc. *84*, 4978 (1961).
6. Bunnett J. F., Olsen F. P.: Can. J. Chem. *44*, 1917 (1966).
7. Bunton C. A., O'Connor J. C., Turney T. A.: Chem. Ind. (London) *1967*, 1835.
8. Armstrong V. C., Farlow D. W., Modie R. B.: J. Chem. Soc. (B) *1968*, 1099.
9. Kaválek J., Štěrba V.: This Journal *40*, 1176 (1975).
10. Yates K., Stevens I. B., Katritzky A. R.: Can. J. Chem. *42*, 1957 (1964).
11. Medvedskaja I. M., Vinnik M. I.: Ž. Phys. Chim. *43*, 2067 (1969).
12. Jaffé H. H.: Chem. Rev. *1953*, 191.
13. Hoffmann J., Klicnar J., Štěrba V.: This Journal *36*, 4057 (1971).
14. Jencks W. P. in the book: *Progress in Physical Organic Chemistry* (I. H. Cohen, A. Streit-wieser, W. Taft, Eds). Vol. 2, p. 63. Wiley, New York 1964.
15. Cordes E. H., Jencks W. P.: J. Am. Chem. Soc. *84*, 832 (1962).
16. Hoffmann J., Štěrba V.: This Journal *38*, 2091 (1973).

17. Bender R. M., Ginger R. D.: J. Am. Chem. Soc. 77, 348 (1955).
18. Bunton C. A., Lewis T. A., Llewellyn D. R.: Chem. Ind. (London) *1954*, 1154.
19. Barnett J. W., O'Connor C.: J. Chem. Soc., Perkin 2, 2378 (1972); *1973*, 220.
20. Leffler J. E.,Grunwald E.: *Rates and Equilibria of Organic Reactions*, p. 174. Wiley, New York 1963.
21. Stewart R., Yates K.: J. Am. Chem. Soc. *80*, 6355 (1958).
22. Exner O. in the book: *Advances in Linear Free Energy Relationships* (N. B. Chapman, J. Shorter, Eds), p. 32. Plenum Press, New York 1972.