

## KINETICS OF BASE-CATALYZED HYDROLYSIS OF SUBSTITUTED FORMANILIDES

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Dissociation and alkaline hydrolysis rate constants of eight *m*- and *p*-substituted formanilides have been measured and correlated with  $\sigma$  constants. A very good linear dependence with the slope  $\rho = 1.53$  has been obtained from correlation of the dissociation constants with  $\sigma^0 + 0.4 \cdot (\sigma^- - \sigma^0)$ . The dependence of  $\log k$  vs  $\sigma^0$  and  $\sigma^-$  constants is non-linear, its angular coefficient gradually increasing from the value 0.5 (unsubstituted formanilide) to about 6 (*p*-nitro derivative).

A number of recent papers dealt with alkaline hydrolysis of substituted acylanilines, *e.g.* reports of Pollack and Schowen<sup>1,2</sup> who also gave a survey of previous works. The course of the reaction can be expressed by Scheme 1 and Eq. (1), where  $K_{\text{AH}}$  is the dissociation constant of amide, and  $k_3 = K'k'_s$ .

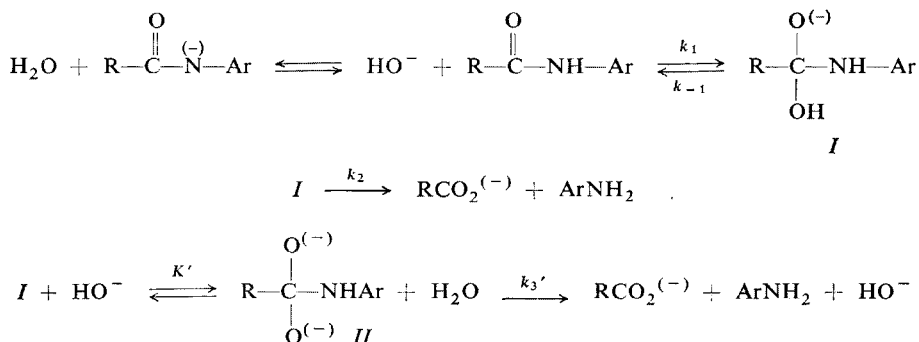
$$v = k_{\text{exp}}[\text{Amide}]_{\text{tot}} = \frac{k_1[\text{OH}^-]}{1 + K_{\text{AH}}[\text{OH}^-]/K_w} \frac{k_2 + k_3[\text{OH}^-]}{k_{-1} + k_2 + k_3[\text{OH}^-]} [\text{Amide}]_{\text{tot}}$$

$$= k_{\text{corr}}[\text{Amide}]_{\text{tot}} / (1 + K_{\text{AH}}[\text{OH}^-]/K_w) \quad (1)$$

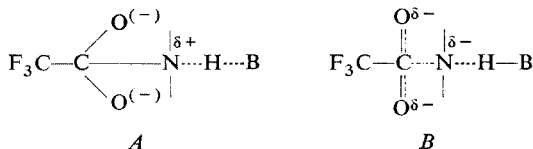
At lower  $\text{OH}^-$  concentrations the decomposition of the intermediate *I* into products is rate-limiting (rate constant  $k_2$ ), and the velocity is proportional to sodium hydroxide concentration. Increasing hydroxide concentration results in that the conversion of dianion *II* into products becomes gradually more and more the rate-limiting step. The reaction velocity related to the undissociated amide becomes proportional to the square of  $\text{OH}^-$  concentration. Further increase in pH makes the decomposition of the intermediate *I* into products faster than the reverse reaction, and the reaction of the undissociated amide with  $\text{OH}^-$  ion becomes rate-limiting. The ratio  $k_3/k_2$  increases with increasing electron-acceptor properties of both the acyl and substituted phenyl groups<sup>3</sup>. Whereas in the case of acetanilides<sup>4</sup> the decomposition of the intermediate *II* becomes significant at pH 13, the respective changes take place already at pH 11 and 10 in the cases of *p*-nitroacetanilide<sup>3,5</sup> and trifluoroacetanilide<sup>6</sup>, respectively. Both the decomposition of the intermediate *I* into products and that of the intermediate *II* (at least in some cases) are reactions showing general acid catalysis<sup>2</sup>.

Bender<sup>4</sup> studied the hydrolysis kinetics of five substituted acetanilides (4-methoxy to 3-nitro) under the conditions of the decomposition of the intermediate *I* being rate-limiting, and he found the rate constants to be practically independent of substituents. He explained his findings by the electron-acceptor substituents increasing  $k_1$  ( $\rho = +1$ ) and lowering the ratio  $k_2/k_{-1}$  ( $\rho = -1$ ). Schowen<sup>7</sup> studied the hydrolysis kinetics of ten substituted N-methyltrifluoroacetanilides (4-me-

thoxy to 3-nitro) under the conditions of the reaction being both 1. and 2. order in  $\text{OH}^-$ . In the both cases he found that both the dependences  $\log(k_1 k_2/k_{-1})$  and  $\log(k_1 k_3/k_{-1})$  on  $\sigma$  were non-linear, but they could be divided into two linear sections (4-methoxy derivative to the unsubstituted acetanilide, and 3-methoxy to 3-nitro derivative) having the respective slopes 0.1 and 1.1 for the reaction of the 1. order in  $\text{OH}^-$  and 0.3 and 2.4 for that of the 2. order in  $\text{OH}^-$ . The increase in constant was explained<sup>2,7</sup> by that the proton addition (from water or the acidic buffer component) to the nitrogen atom of the intermediate *I* or *II* was rate-limiting in the case of substituents having negative  $\sigma$  values (inclusive of H). (In the case of the intermediate *I* the diffusion of the N-protonated intermediate from the basic buffer component is considered to be the rate-limiting step<sup>2</sup>.) In the case of substituents with positive  $\sigma$  values the rate-limiting step consists in splitting of the C—N bond at the nitrogen atom of the protonated intermediate. The hydrolysis rate constants of 4-nitroacetanilide<sup>5</sup> and 4-nitrotrifluoroacetanilide<sup>1,8</sup> are far higher than those calculated with the use of the estimated  $\rho$  constants.



SCHEME 1



Although there was much attention paid to the influence of substituents on the hydrolysis rate of anilides, this influence on the dissociation constants was studied only in the series of eight substituted trifluoroacetanilides (4-methoxy to 3-chloro)<sup>9</sup>, the  $\rho$  value found from the (rather poor) correlation  $\log K$  vs  $\sigma$  being 0.7. Substituted formanilides seem to be very advantageous for a study of hydrolysis kinetics and dissociation constants. So far only one paper<sup>3</sup> has dealt with alkaline hydrolysis of these compounds. Twelve substituted formanilides were measured in media of 0.05 to 0.5M-NaOH, and the rate constant values found were correlated with  $\sigma$  constants. The authors state that, except for 4-cyano and 4-nitro derivatives, the hydrolysis velocities are practically independent of substituents, and they explain this finding in accord with Bender<sup>4</sup> by antagonistic influence of substituents on formation rate of the intermediate and its decomposition rate into products. The authors did not take into account that the individual formanilides were dissociated to various degrees under the reaction conditions and that increasing  $\sigma$  value caused the decomposition of the intermediate *II* to be gradually more and more significant as the rate-limiting step.

The aim of the present paper was a quantitative determination and interpretation of the influence of substituents on both the dissociation constants and the hydrolysis kinetics of substituted formanilides under the conditions of the decomposition of the intermediate *II* into products being rate-limiting.

### EXPERIMENTAL

*Reagents.* All the formanilides studied were prepared by heating the respective substituted anilines with 98% formic acid and purified by crystallization (after eventual vacuum distillation). Formanilide (*III*) was distilled and crystallized from a mixture ether–light petroleum, m.p. 43.5–46°C (ref.<sup>10</sup> m.p. 46–47°C). 4-Bromoformanilide (*IV*, from aqueous ethanol) m.p. 116 to 117°C (ref.<sup>3</sup> m.p. 117°C). 3-Chloroformanilide (*V*) was distilled and crystallized from a mixture cyclohexane–tetrachloromethane, m.p. 51–53°C (ref.<sup>3</sup> m.p. 56–57°C). 3-Methoxyformanilide (*VI*) was purified as *V* and melted at 56–58°C (ref.<sup>3</sup> m.p. 55–57°C). 3-Nitroformanilide (*VII*, from aqueous ethanol) m.p. 134–136°C (ref.<sup>3</sup> m.p. 134°C). 4-Nitroformanilide (*VIII*, from water) m.p. 202–203°C (ref.<sup>3</sup> 192–194°C). 4-Cyanoformanilide (*IX*, from aqueous ethanol) m.p. 188 to 190°C (ref.<sup>3</sup> m.p. 189°C) 4-Acetylformanilide (*X*, from benzene) m.p. 102–103°C (ref.<sup>11</sup> m.p. 113–114°C); its purity was checked by NMR spectrum showing only the proton signals of 4-acetylformanilide.

Solutions for kinetic and dissociation constants measurements of the formanilides were prepared from the redistilled water which was kept safe from atmospheric carbon dioxide. Sodium hydroxide *p.a.* was used for preparation of 2*M*-NaOH which was further diluted. The same holds for the 5*M*-NaOH solution used for determination of the extinction coefficient of the dissociated form of formanilide and its 4-bromo and 3-methoxy derivatives. Stock solutions containing  $5 \cdot 10^{-4}$  mol/l formanilides and also  $5 \cdot 10^{-4}$  mol/l primary and secondary phosphates (to suppress autocatalytic acid hydrolysis of formanilides) were used for the measurements. In order to find the optimum wavelength for the rate and dissociation constants measurements, the electronic spectra of the formanilides prepared (concentration  $10^{-4}$ *M*) were measured in water and

TABLE I

Values of Dissociation Constants and Rate Constants ( $l^2 \text{ mol}^{-2} \text{ s}^{-1}$ ) of Alkaline Hydrolysis of Substituted Formanilides *III*–*X* at 20°C

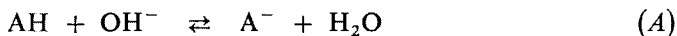
Compound	$pK_{HA}$	$\lambda_{\text{anal}}$ , nm	$(k_1 k_3 / k_{-1}) \cdot 10^2$
<i>III</i>	13.89	270	0.31
<i>VI</i>	13.68	265	0.34
<i>IV</i>	13.39	280	0.53
<i>V</i>	13.24	275	0.65
<i>VII</i>	12.79	270	2.1
<i>X</i>	12.83	320	8.3
<i>IX</i>	12.66	294	9.7
<i>VIII</i>	12.31	400	1 700

hydroxide solutions of various concentration by means of a Unicam SP 800 spectrophotometer and 1 cm quartz cells. From these spectra it was possible to estimate the approximate values of dissociation constants of the formanilides. At the same time, the spectra were measured at appropriate time intervals with such hydroxide concentrations that the hydrolysis proceeded already at sufficient rate. These spectral records showed well developed isosbestic points.

The measurements of rate and dissociation constants were carried out with the use of a VSU 2P spectrophotometer (Zeiss, Jena) at  $25 \pm 0.1^\circ\text{C}$  as it follows: 2 ml  $5 \cdot 10^{-4}\text{M}$  solution of a substituted formanilide was quickly added into 8 ml tempered solution of sodium hydroxide of appropriate concentration. A part of the solution was placed in a 1 cm quartz cell located in a thermostatted cell compartment of the spectrophotometer, and its absorbance was measured at the chosen time intervals and wavelengths (Table I). The absorbance value decreased in the course of the experiments due to hydrolysis of the formanilides (except for the 4-nitro derivative VIII in which case it increased). At lower hydroxide concentrations (slow hydrolysis) the measured absorbances were extrapolated to the zero time to determine the value at the moment of initial mixing of reagents. In other experiments the absorbance was measured as far as two or three half-lives, and its value at zero time was determined graphically from the dependence  $\log(A_\infty - A_t)$  vs time  $t$ . At the same time the hydrolysis rate constants were measured.

## RESULTS AND DISCUSSION

The formanilides III–X react reversibly with hydroxide ion in alkaline solutions (Eq. (A)).



In sufficiently diluted solutions the ratio of activity coefficients of hydroxyl and anilide ions is close to unity and the concentration ratio is given by Eq. (2), where  $K_{\text{AH}}$  and  $K_w$  are the dissociation constant of formanilide and the ionic product of water,

$$[\text{A}^-]/[\text{AH}] = K_{\text{AH}}[\text{OH}^-]/K_w \quad (2)$$

respectively. The study<sup>12</sup> of the structurally similar thioacetamides showed that this equation holds as far as 1M-NaOH concentration. For higher hydroxide concentration it is necessary to use  $1/\text{H}_-$  ( $\text{H}_-$  is acidity function) instead of  $[\text{OH}^-]/K_w$  in Eq. (2).

We used Eq. (2) for the studied series of formanilides, too. The ratio  $[\text{A}^-]/[\text{AH}]$  was determined in usual way from Eq. (3),

$$[\text{A}^-]/[\text{AH}] = (A_0^{\text{AH}} - A_0)/(A_0 - A_0^{\text{A}^-}), \quad (3)$$

$$\log K_{\text{AH}} = (1.53 \pm 0.04)(\sigma^0 + 0.4(\sigma^- - \sigma^0)) - (13.04 \pm 0.02), \quad (4)$$

where  $A_0^{\text{AH}}$ ,  $A_0^{\text{A}^-}$  and  $A_0$  are the absorbances of formanilide, its anion and the measured solution extrapolated to zero time, respectively. The dependence of  $\log([\text{A}^-]/[\text{AH}])$  on  $\log[\text{OH}^-]$  found for formanilides was linear (as it was

the case with thioacetamides), the slope being unity up to  $[\text{OH}^-] = 1$ . The values  $\log K_{\text{AH}}$  found (Table I) were correlated with  $\sigma^0$  (ref.<sup>13</sup>) and  $\sigma^-$  constants<sup>14</sup> according to Eq. (4). The value  $\rho = 1.53$  (correlation coefficient 0.998) is lower than that of dissociation of anilinium ions<sup>15</sup> (2.89). The main reason of the low  $\rho$  value of formanilides is that the formyl group attracts considerably the free electron pair at nitrogen atom of formanilide ion, and thus the effect of ring substituents is less manifested than in the case of substituted anilines. This levelling effect<sup>16</sup> can be seen especially in the cases when  $\pi$  electrons of conjugated systems are stabilized by action of substituent with a strong mesomeric effect.

Hydrolysis kinetics of the substituted formanilides (except for the nitro derivative VIII) were measured in 0.5–1.6M-NaOH. From the hydrolysis kinetic data of acetanilides<sup>4,5</sup>, trifluoroacetanilides<sup>6</sup> and formanilides<sup>3</sup> it follows that the decomposition of the intermediate II should be rate-limiting in this hydroxide concentration range. This presumption proved correct. In all the cases the dependence of  $\log k_{\text{corr}}$  (calculated from  $k_{\text{exp}}$  according to Eq. (1)) on  $\log [\text{OH}^-]$  (or  $\text{H}_- - K_w$  for  $[\text{OH}^-] > 1\text{M}$ ) (ref.<sup>12</sup>) was linear with the slope 2. Table I gives the values  $k_{\text{corr}}$  read from the given dependence at the point of 1M-NaOH concentration when  $k_{\text{corr}} = k_1 k_3 / k_{-1}$ . Hydrolysis of the nitro derivative VIII was followed in the range 0.02 to 0.4M-NaOH. The dependence of  $\log k_{\text{corr}}$  vs  $\log [\text{OH}^-]$  is non-linear. The slope is less than 2 and gradually decreases with increasing hydroxide concentration. It means that there occurs a gradual change in the rate-limiting step, viz. from the decomposition of the intermediate II to the addition of the hydroxide ion to the formanilide VIII. The rate constants  $k_1 k_3 / k_{-1}$  ( $17 \text{ l}^2 \text{ mol}^{-2} \text{ s}^{-1}$ ) and  $k_1$  ( $2.01 \text{ mol}^{-1} \text{ s}^{-1}$ ) were calculated graphically from the Eq. (5).

$$[\text{OH}^-]/k_{\text{corr}} = k_{-1}/k_1 k_3 [\text{OH}^-] + 1/k_1 \quad (5)$$

De Wolfe<sup>3</sup> found the respective values  $30.4 \text{ l}^2 \text{ mol}^{-2} \text{ s}^{-1}$  and  $2.01 \text{ mol}^{-1} \text{ s}^{-1}$  at 30°C at ionic strength 1. The dependence of  $\log(k_1 k_3 / k_{-1})$  on  $\sigma^0$  resp.  $\sigma_p^-$  constants\* is non-linear in the whole range, its slope being minimum (0.5) for formanilide (III), about 1.5–2 for the derivative VII, and maximum (about 6) for the nitro derivative VIII. A similar course was observed by Schowen<sup>7</sup> in the case of N-methyltrifluoroacetanilides (ring substituents: 4-methoxy to 3-nitro). The authors give two mechanisms for decomposition of the intermediate II: in the case of 4-methoxy up to the unsubstituted anilide the rate-limiting step consists in the proton-transfer from the acid BH (acidic buffer component or water) to nitrogen (structure A), and then the C—N bond splitting takes

\* The use of  $\sigma_p^-$  constants for the substituents having —M effect is justified first from the chemical point of view, next directly from the kinetic results; e.g. 4-acetyl derivative X is about  $4 \times$  more reactive than the 3-nitro derivative VII although  $\sigma_p$  of  $\text{CH}_3\text{CO}$  group is substantially smaller than  $\sigma_m$  of  $\text{NO}_2$  group.

place; in the case of 3-methoxy up to 3-nitro anilide the C—N bond rupture of the intermediate is rate-limiting, (B). The acid BH acts as a so called solvatizing catalyst, and the protontransfer is completed in the subsequent step.

This explanation does not fit the 4-nitro derivative VIII which, in our case, reacts much faster than it would correspond to the  $\rho$  constant of the second mentioned mechanism (going through an activated complex analogous to the complex B). An extraordinary increase in hydrolysis rate was observed also with 4-nitroacetanilide<sup>5</sup> and 4-nitrotrifluoroacetanilide<sup>1</sup>. In addition to it no acid catalysis was found with decomposition of the intermediate II in the case of 4-nitrotrifluoroacetanilide even in the presence of relatively strongly acidic buffer components (their pK were about 7)<sup>1,8</sup>.

The gradually increasing effect of substituents on the rate of splitting and the absence of general acid catalysis in the case of 4-nitro derivatives could be explained by gradual change of the activated complex structure, so that it would not be necessary to consider two different ways of decomposition of the intermediate II and, on the top of that, another different mechanism for the 4-nitro derivative<sup>1</sup>. In the cases in which the hydrolysis produces a relatively strong base (e.g. aniline), the rate-limiting step consists in a simple proton-transfer from water resp. acidic buffer component to nitrogen atom of the intermediate II (structure A). The value of  $\rho$  constant is here small, because the influences of substituents on the addition of OH<sup>-</sup> ion and subsequent proton splitting from OH group with formation of the intermediate II are comparable in magnitude but reverse in direction as compared with the influence of substituents on the addition of the proton to nitrogen of this intermediate II (leading to formation of the activated complex type A). With decreasing basicity of the aniline the C—N bond of the activated complex tends increasingly to split. At the same time the extent of the proton-transfer from acid (resp. water) to nitrogen atom decreases. Both these changes in the activated complex structure bring about an increase in  $\rho$  constant. A similar case of a gradually increasing extent of C—O bond splitting and decreasing extent of protonation was published in the case of the generally acid-catalyzed hydrolysis of acetals<sup>17</sup>. With the 4-nitro derivative only C—N bond is being split in the activated complex and thus the value of  $\rho$  constant reaches its maximum, and no general acid catalysis was experimentally detected.

The  $\rho$  value about 6 for the nitro derivative is quite acceptable. The  $\rho$  constant for  $k_1$  is about 1–1.2 (ref.<sup>4,7</sup>), so that the  $\rho$  value of the equilibrium constant of formation of the intermediate I can be 1.5 to 2. For splitting of O—H bond (giving the intermediate II) we can estimate the  $\rho$  value to be about 0.5. The influence of an aniline ring substituent on the C—N bond splitting is far greater than that on the N—H bond splitting<sup>18</sup>, and, therefore, we can consider the  $\rho$  value of this reaction step to be in the range 3–4. The  $\rho$  value about 6 estimated from the correlation represents a sum of the abovementioned  $\rho$  constants corresponding to individual reaction steps.

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