KINETICS OF HYDROLYSIS AND METHANOLYSIS OF SUBSTITUTED N-METHYLFORMANILIDES

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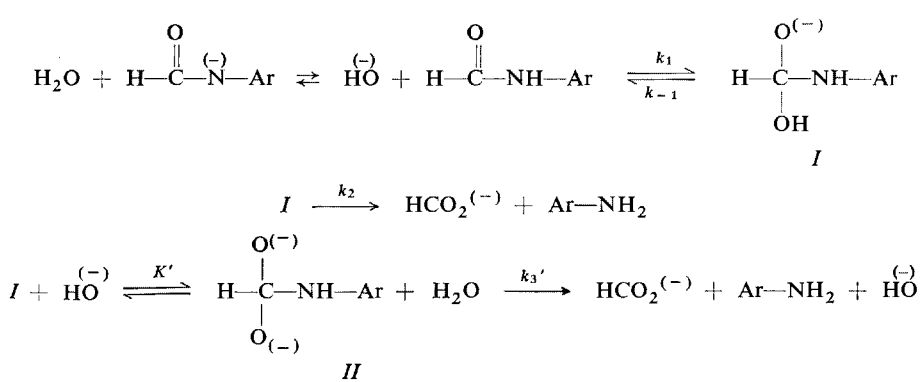
A series of *m*- and *p*-substituted N-methylformanilides have been prepared, and rate constants of their base-catalyzed hydrolysis and methanolysis have been measured. The dependence of log *k* on σ constants is non-linear in the both cases, and its slope increases with increasing σ value. Increasing basicity of medium and decreasing activity of water resp. methanol cause the differences in log *k* to increase. This has been explained by gradual change of structure of the activated complex. Dissociation constants have been measured for six *m*- and *p*-substituted formanilides in methanol.

Alkaline hydrolysis of formanilides[1] is described by Scheme 1 and follows the kinetic equation (*1*)

$$v = k_{obs}[\text{amide}]_{tot} = \frac{k_1[OH^-]}{1 + K_{HA}[OH^-]/K_w} \cdot \frac{k_2 + k_3[OH^-]}{k_{-1} + k_2 + k_3[OH^-]}[\text{amide}]_{tot} =$$
$$= k_{corr}[\text{amide}]_{tot}/(1 + K_{HA}[OH^-]/K_w)\,, \qquad (1)$$

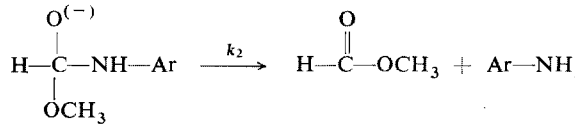
where K_{HA} is the dissociation constant of the formanilides, and $k_3 = K'k'_3$. At higher hydroxyl ion concentrations (pH > 13) the transformation of the dianion *II* into products is rate determining for all the formanilides (except 4-nitro derivative), and k_{corr} is expressed by Eq. (*2*).

$$k_{corr} = (k_1 k_3/k_{-1})\,[OH^-]^2\,. \qquad (2)$$



SCHEME 1

The rate-limiting step of alkaline methanolysis consists in transformation of the monoanion *III* into products (Eq. (*A*)), and k_{corr} is defined by Eq. (*3*).



(*A*)

$$k_{corr} = (k_1 k_3 / k_{-1})\,[CH_3O^{(-)}]\,. \qquad (3)$$

Dependence of log $(k_1 k_3/k_{-1})$ on σ constants is non-linear in the series of the substituted formanilides[1], its slope being increased from a value 0·5 for the parent substance to about 6 for its 4-nitro derivative. Non-linear dependence log k *vs* σ in the case of hydrolysis of substituted N-methyltrifluoroacetanilides was explained[2,3] by a change of the rate-limiting step. For substituents with negative σ value protonation of nitrogen atom in the dianion *II* (usually by a solvent molecule) is rate limiting, whereas for those with positive σ value splitting of C—N bond of the protonated intermediate is rate limiting. Another possible explanation consists in gradual change of the activated complex[1]. In the case of substituents with negative σ value the proton transfer to the dianion *II* is practically finished in the activated complex, whereas the C—N bond splitting is but slight. Increasing σ value results in increasing extent of the C—N bond splitting in the activated complex, and at the same time the extent of the proton transfer from acid resp. water to nitrogen atom of the dianion is decreased.

The purpose of the present paper was the determination of the rate constants of basic hydrolysis and methanolysis of substituted N-methylformanilides and estimation of influence of strong basicity increase of medium on their values. N-Methylformanilides do not have any dissociable proton, so that $k_{corr} = k_{obs}$, and evaluation and discussion of the rate constants is not complicated by influence of changes of medium on the antecedent equilibrium.

EXPERIMENTAL

The substituted N-*methylanilines* were prepared by the described methods (the parent substance, 4-methyl and 4-chloro derivatives)[4]; (3- and 4-nitro)[5]; (4-bromo)[6] and (4-acetyl)[7]. N-Formyl derivatives of the mentioned methylanilines were prepared by azeotropic formylation (benzene and 99% formic acid)[1] and purified by vacuum distillation: N-methylformanilide *IVb* (n_D^{20} 1·5579); 4-methyl-N-methylformanilide *IVa* (n_D^{20} 1·5504); 3-chloro-N-methylformanilide *IVd* (n_D^{20} 1·5791), or by crystallization: 4-bromo-N-methylformanilide *IVc* (m.p. 59—60° C); 3-nitro-N-methylformanilide *IVe* (m.p. 64—65°C); 4-nitro-N-methylformanilide *IVg* (m.p. 116·5—117·5°C) and 4-acetyl-N-methylformanilide *IVf* (m.p. 53·5—55°C). Their structure was verified by NMR spectra.

Preparation of the substituted formanilides was described elsewhere[1]. The other reagents used were commercial chemicals of *p.a.* purity grade. Dimethyl sulphoxide was dried by boiling with calcium oxide and distilled *in vacuo*. Methanolic solutions of sodium methoxide were prepared under nitrogen, and their concentration was determined by titration with 1M hydrochloric acid.

For kinetic measurements methanolic 10^{-2}M solutions of the N-methylformanilides were prepared and stabilized by addition of sodium acetate (10^{-3}M). Preliminary kinetic experiments were carried out with a spectrophotometer Unicam SP 800 in the wavelength ranges 250 to 400 and 300 to 460 nm for the methylformanilides (*IVa–d* and *IVf*) and (*IVe* and *IVg*), respectively. All these kinetic runs gave spectra with well developed isosbestic points, and spectra of the reaction solutions did not change after finished hydrolysis resp. methanolysis.

Kinetic measurements were carried out with a spectrophotometer VSU-2P (Zeiss, Jena) in 1 cm quartz cells at 25°C. 20 to 100 µl solution of the substituted N-methylformanilide was injected into 2·4 ml temperated aqueous solutions of sodium hydroxide resp. methanolic solution of methoxide resp. solution of sodium hydroxide in a mixture water–dimethyl sulphoxide. Absorbance of the formed N-methylaniline was then measured at suitable time intervals. The rate constant was calculated from the relation $k_{obs}t = -2{\cdot}303 \log (A_\infty - A_t) + \text{const.}$

Dissociation constants of the substituted formanilides in methanol were measured in the same way as those in water[1]. As methanolysis was negligibly slow under the conditions of measurements, it was not necessary to extrapolate the absorbance values to zero time. The pK_a values were calculated from Eq. (*4*) where H_M stands for the acidity function for methanolic solutions with methanol as the standard state[8].

$$pK_a = H_M + \log ([HA]/[A^-]) \,. \tag{4}$$

RESULTS AND DISCUSSION

Hydrolysis of the N-methylformanilides *IVa–e* in aqueous sodium hydroxide solutions was followed up to the concentration 1M-NaOH. In the case of the compounds *IVa–d* the k_{obs} values were proportional to the square of hydroxyl ion concentration in the whole range measured, *i.e.* the calculated ratio k_1k_3/k_{-1} was constant in this concentration range. In the case of 3-nitro derivative *IVe* this value increased at $[OH^-] > 0{\cdot}6$M and was by 30% greater at $[OH^-] = 1{\cdot}0$M. The compounds *IVf* and *IVg*, which reacted faster, were measured in the $[OH^-]$ ranges 0·3 to 0·5M and $7 \,.\, 10^{-3}$ to $6 \,.\, 10^{-2}$M, respectively. In the case of the 4-acetyl derivative *IVf* the k_{obs} value was again found proportional to the square of hydroxyl ion concentration. For all these compounds the rate-limiting step consists in the transformation of the N-methyl derivative of dianion *II* into products. The reaction order > 2, which was found for 3-nitro derivative *IVe* in 1M-NaOH, is due to the influence of medium on the structure (and hence also activity) of the activated complex. In the case of the compound *IVg* the reaction order was less than 2 and approached unity with increasing OH^- concentration, because addition of OH^- to the carbonyl group of the formanilide *IVa* was becoming the rate-limiting step. The rate constants k_1k_3/k_{-1} and k_1 were determined graphically[1] from Eq. (*5*). Again the dependence $\log (k_1k_3/k_{-1})$ *vs* σ constants is non-linear, its character being the same as in the case of hydrolysis of formanilides[1]. (Dependence of $\log (k_1k_3/k_{-1})$ of substituted N-methyl-

$$[OH^-]/k_{obs} = k_{-1}/k_1k_3[OH^-] + 1/k_1 \tag{5}$$

formanilides on the corresponding value of formanilides is practically linear with the slope 0·9.) The hydrolysis rate constants of N-methylformanilides *IVa–f* (Table I) are about 3 times lower than those of formanilides. The rate constant $k_1 = 0{\cdot}8\ \mathrm{l}\,.\,\mathrm{mol}^{-1}$ of the 4-nitro derivative *IVg* is lower than the rate constant k_1 of 4-nitroformanilide, but the value k_1k_3/k_{-1} is about 6 times greater.

Table II gives the k_{obs} values for various concentrations of dimethyl sulphoxide in 0·5M aqueous NaOH. With increasing dimethyl sulphoxide concentration the basicity of medium and, hence, also the concentration of the dianion type *II* increase, which should result in higher k_{obs} value. On the other hand, the water activity is decreasing, and thus the tendency to protonation of nitrogen in the activated complex is decreasing, too. This latter fact should lead to a decrease in k_{obs}, and the effect should be the greater the greater is the extent of the proton transfer in the activated complex. In the case of the compounds *IVa* and *IVb* k_{obs} is lower in 25% dimethyl sulphoxide than in water, which means that the second factor is predominating with these two derivatives. With the 4-bromo derivative *IVc* the rates are the same in the both cases, whereas with *IVd* and even more with *IVe* acceleration is encountered. This observation suggests that with increasing value of σ constant the kinetic significance of the proton transfer is gradually decreasing, which stands in accordance with the abovegiven interpretation of non-linear dependence log (k_1k_3/k_{-1}) *vs* σ constants (change of the structure of the activated complex).

In 50% dimethyl sulphoxide the value k_{obs} of all the derivatives *IVa–e* increases, and the acceleration increases with increasing σ constant (Table II). In this medium

TABLE I

Rate Constants of Hydrolysis k_1k_3/k_{-1} and Methanolysis k_1k_2/k_{-1} (in 1 $\mathrm{mol}^{-1}\ \mathrm{s}^{-1}$) of Substituted N-Methylformanilides *IVa–g* at 25°C

Compound	λ, nm	$10^3k_1k_3/k_{-1}$	$10^5k_1k_2/k_{-1}$
IVa	294	0·61 ± 0·02	—
IVb	285, 310[a]	1·08 ± 0·05	1·78
IVc	295, 310[a]	1·82 ± 0·15	4·13
IVd	295, 310[a]	2·19 ± 0·12	5·13
IVe	380, 410[a]	10·4 ± 0·4	29·2
IVf	336	39·2 ± 3·0	3 400
IVg	410	103 000	11 000 ± 800

[a] For methanolysis.

the reactivity differences between individual derivatives *IVa–e* are far greater than those in aqueous sodium hydroxide. Whereas the ϱ value increases from 0·5 (for *IVb*) to about 2 (for *IVe*) in aqueous medium, in 50% dimethyl sulphoxide its value increases from 2·0 to about 4·5.

Dimethyl sulphoxide lowered slightly the hydrolysis rates of 4-methoxy and unsubstituted N-methylacetanilides and increased considerably that of the 4-nitro derivative[9]. This was explained by the different effect of the change of medium on the rate-determining decomposition of dianion in the case of 4-methoxy and unsubstituted N-methylacetanilide and on the rate-determining addition of OH^- to the 4-nitro derivative.

The hydrolysis rates of the nitro derivative *IVe* were also measured in 0·3 and 0·4M-NaOH. Whereas in 25% dimethyl sulphoxide the dependence k_{obs} *vs* $[OH^-]$ is practically quadratic, in 50% dimethyl sulphoxide k_{obs} increases far more steeply. This is due to the basicity of medium increasing faster than OH^- ion concentration.

For alkaline methanolysis the dependence k_{obs} *vs* $[CH_3O^-]$ is linear in the whole measured range of 4-nitro derivative *IVg* (0·01 to 0·1M) and up to 0·5M-$NaOCH_3$ in the case of 3-nitro and 4-acetyl derivatives *IVe–f*. At higher concentrations k_{obs} increase faster than $[CH_3O^-]$; *e.g.* for *IVf* the calculated value k_1k_2/k_{-1} in 1M-$NaOCH_3$ is higher than that in 0·5M-$NaOCH_3$ by 40%. Table I gives the k_1k_2/k_{-1} values calculated from the k_{obs} measured in 1·0M-$NaOCH_3$ (except for the 4-nitro derivative *IVg*; the derivatives *IVb–d* reacted much too slow, and therefore they were not measured at concentrations lower than 1M-$NaOCH_3$). Again the dependence of $\log(k_1k_2/k_{-1})$ on the σ constants is non-linear, but, in this case, the 4-acetyl derivative *IVf* reacts almost as fast as the 3-nitro derivative *IVe*, and the 4-nitro derivative *IVg* reacts faster than 3-nitro derivative *IVe* by only two orders of magnitude.

TABLE II

Hydrolysis Rate Constants of Substituted N-Methylformanilides *IVa–e* in 0·5M-NaOH in Mixtures Water–Dimethyl Sulphoxide at 25°C

% DMSO by Vol.	10^3k_{obs}, s^{-1}				
	IVa[a]	*IVb*	*IVc*	*IVd*	*IVe*
0	0·58	0·34	0·40	0·50	2·50 (1·66[b], 0·886[c])
25	0·47	0·18	0·41	0·63	5·55 (2·90[b], 1·68[c])
50	0·53	0·24	0·85	1·80	45·4 (23·1[b], 9·25[c])

[a] Measured in 1M-NaOH; [b] 0·4M-NaOH; [c] 0·3M-NaOH.

Table III gives the values of methanolysis rate constants at methoxide concentrations 1 to 4M. Again the differences between log k of individual derivatives increase with increasing basicity of medium (and simultaneously decreasing activity of methanol).

In spite of that formanilides are hydrolyzed about 3 times faster than N-methylformanilides, their methanolysis was so slow even in 1M to 2M-$NaOCH_3$ (except for 4-nitroformanilide) that it was impossible to obtain even approximative values of rate constants. (Higher methoxide concentrations do not accelerate the reaction, because dissociation of formanilide takes place simultaneously, so that the methanolysis rate does not increase.) The found value of the rate constant k_1k_2/k_{-1} of 4-nitroformanilide is $2{\cdot}5 \,.\, 10^{-3}$ l mol^{-1} s^{-1} which is 45× lower value than that of 4-nitro-N-methylformanilide *IVg*. In contrast to dissociation of formanilides in aqueous sodium hydroxide the dissociation in methanol proceeds at substantially higher methoxide ion concentrations, and the dependence of log ([HA]/[A$^-$]) on log . . [CH_3O^-] is not linear (except for 4-nitro- and partially for 3-nitroformanilides). Two acidity functions H_M have been tabulated for measurements of N—H bond acidity in methanol; one of them for substituted indols[10] and the other, much steeper, for substituted anilines and diphenylamines[11]. Neither of the two fits the substituted formanilides. Therefore, the dependence of log ([HA]/[A$^-$]) on methoxide ion concentration was used with Eq. (*4*) for construction of a H_M function for formanilides. Its values lie roughly in the middle between the both abovementioned functions H_M: [CH_3O^-] (H_M); 0·2M (16·22); 0·6M (16·73); 1·0M (17·08); 1·5M (17·46); 2M (17·80); 2·5M (18·16); 3M (18·5).

Application of Eq. (*4*) and this acidity function gave the following pK_a values of substituted formanilides: 17·60 ± 0·02 (4-CH_3); 17·44 + 0·03 (unsubst.); 16·92 ±

TABLE III

Methanolysis Rate Constants of Substituted N-Methylformanilides *IVb*–*f* at 25°C at CH_3O^- Concentration 1 to 4 mol . l^{-1}

Compound	10^4k_{obs}, s^{-1}			
	1·0M	2·0M	3·0M	4·0M
IVb	0·18	0·34	0·57	1·2
IVc	0·41	0·72	2·1	5·1
IVd	0·51	1·3	3·6	9·4
IVe	2·9	12·2	53·0	220·0
IVf	3·4	19·5	—	—

$\pm$ 0·03 (4-Br); 16·77 $\pm$ 0·05 (3-Cl); 16·21 $\pm$ 0·03 (3-NO_2); 15·90 $\pm$ 0·02 (4-NO_2). The dependence of pK_a on σ constants is linear except for 4-nitroformanilide; the value of ϱ constant is $-1·70 \pm 0·04$.

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