

## HYDROLYSIS KINETICS AND MECHANISM OF N'-(3-N-METHYLCARBAMOYLOXYPHENYL)-N,N-DIMETHYL- FORMAMIDINE

Alexandr ČEGAN, Jaroslav ŠLOSAR and Miroslav VEČEŘA

*Department of Organic Chemistry*

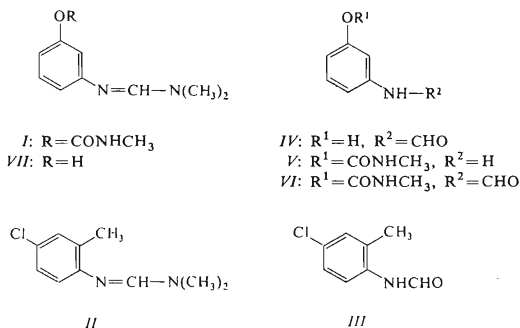
*Institute of Chemical Technology, 532 10 Pardubice*

Received March 21st, 1979

Hydrolysis of N'-(3-N-methylcarbamoyloxyphenyl)-N,N-dimethylformamide (*I*) has been studied in mixture water-dioxane (4 : 1) at pH 1 to 13. The hydrolysis rates of methylcarbamoyl and dimethylformamide groups are comparable within pH range 4 to 10, and they differ by as much as several orders of magnitude in pH ranges 1—3 and 11—13. The hydrolysis products of the whole pH range have been determined by paper chromatography, and reaction mechanism has been suggested on the basis of the measured hydrolysis rate constants. Effects of protonation and hydration of dimethylformamide group on the hydrolysis rate of the methylcarbamoyl group is discussed.

Formamide derivatives show biological activity, and some of them are used as specific insecticides in agriculture<sup>1,2</sup>. Out of them the most useful are N'-(3-N-methylcarbamoyloxyphenyl)-N,N-dimethylformamide (*I*) (Formetanat) and N'-(2-methyl-4-chlorophenyl)-N,N-dimethylformamide (*II*) (Chlordimeform), which represent the effective components of a commercial insecticide Fundal Forte<sup>3</sup>. Biological activity of these two compounds was studied in detail<sup>4</sup>, their metabolism is dealt with in ref.<sup>5</sup>, and another paper<sup>6</sup> described splitting of the formed substituted formamides by formamidase. Photochemical degradation of the compounds *I* and *II* in aqueous media of pH 7.1 and 3.1 is described in refs.<sup>7,8</sup>. The authors found that the splitting of *II* produces 95% 2-methyl-4-chloro-formanilide (*III*), whereas the compound *I* gives 60% 3-hydroxyformanilide (*IV*), 25% N-methyl-3-aminophenylcarbamate (*V*) and 10% N-methyl-3-formamidophenylcarbamate (*VI*) (Scheme 1). The compound *II* gives the same products both in hydrolysis and photolysis, whereas the hydrolysis and photolysis products of *I* are different. According to previous studies of hydrolysis of N-methylarylcarbamates<sup>9</sup> and N'-aryl-N,N-dimethylformamides<sup>10</sup> the hydrolysis of the compound *I* at pH 7.1 should not produce the compound *V*. At this pH hydrolysis rates of carbamoyl and formamide groups are of the same order of magnitude<sup>9,10</sup>, the subsequent hydrolysis of formanilide group to amine group being slower by several orders of magnitude. Therefrom it can be concluded that the

compound *V* represents the product of photolytic decomposition of the compound *I*, whereas the compounds *IV* and *VI* are hydrolysis products.



SCHEME 1

The aim of this paper is to support the presumption of different course of photolysis and hydrolysis of the compound *I* and to obtain further data about stability of this biologically active compound in aqueous media, and therefore hydrolysis of *I* has been studied in water-dioxane (4 : 1) mixture at pH 1 to 13.

## EXPERIMENTAL

### Reagents

*N'*-(3-*N*-Methylcarbamoyloxyphenyl)-*N,N*-dimethylformamidine (*I*). 16.4 g *N'*-3-Hydroxyphenyl-*N,N*-dimethylformamidine<sup>10</sup> was suspended in 100 ml tetrahydrofuran, and 6.3 g methyl isocyanate was added to the suspension. The mixture was stirred at room temperature 4 h, and then it was left to stand two days. Tetrahydrofuran was distilled off under reduced pressure and the residue was crystallized from ethyl acetate. M.p. 102.5–103°C (ref.<sup>11</sup> m.p. 102–103°C).

3-Hydroxyformanilide (*IV*) was prepared according to the procedure given in ref.<sup>10</sup>. M.p. 114–115°C (ref.<sup>12</sup> 116°C).

*N*-Methyl-3-aminophenylcarbamate (*V*). 1 g PtO<sub>2</sub> was suspended in solution of 3 g *N*-methyl-3-nitrophenylcarbamate in 100 ml ethyl acetate, and a slow stream of hydrogen was introduced therein for 80 min; the reduction course was followed chromatographically. After the reduction was finished ethyl acetate was distilled off under reduced pressure, and the product was crystallized from ethyl acetate. M.p. 92.5–93°C (ref.<sup>13</sup> 86–90°C).

*N*-Methyl-3-formamidophenylcarbamate (*VI*). Solution of 6 g 3-hydroxyformanilide in 10 ml tetrahydrofuran was treated with 4 g methyl isocyanate in 10 ml tetrahydrofuran. After 12 h

standing at 25°C the separated crystals were filtered off and recrystallized from chloroform-n-hexane (1 : 1) mixture. M.p. 149—151°C. For  $C_9H_{10}N_2O_3$  (194.2) calculated: 55.66% C, 5.19% H, 14.43% N; found: 55.42% C, 5.01% H, 14.66% N.

### Kinetic Measurements

The hydrolysis rate constants of the compound *I* were measured by discontinuous spectral method (pH 1 to 3), chromatographically (pH 4 to 10), or by spectrophotometric stopped flow method (pH 11 to 13). In the discontinuous method flasks containing 98 ml buffer were kept in thermostat 10 min, whereafter 2 ml  $3 \cdot 10^{-3} \text{ mol l}^{-1}$  solution of the compound *I* in dioxane was added. At suitable time intervals samples were withdrawn and cooled at 25°C, and their extinction was measured at 260 nm using a Zeiss PMQ II spectrophotometer. The second (chromatographical) method was used with respect to the fact that in the pH region 4 to 10 the reaction mixture contained four components with overlapping UV spectra. 100 ml buffer was tempered at a certain temperature, 0.0222 g compound *I* was added, the mixture was thoroughly mixed, and at definite time intervals samples were withdrawn and cooled in ice. From these samples 5  $\mu\text{l}$  was transferred on the chromatographic paper W 2 impregnated with 10% solution of formamide in acetone. Mixture chloroform-ethyl acetate (4 : 1) was used as eluent. The chromatogram was sprayed with 5% aqueous potassium hydroxide and (after 5 min) with 0.1% solution of 3,3'-dimethoxybiphenyl-4,4'-bisdiazonium tetrafluoroborate in 1% aqueous potassium hydroxide. Concentration of the reaction components was determined semiquantitatively by comparison of their spots with a calibration chromatogram. The products were identified chromatographically by comparison of their  $R_F$  values with those of pure standards. The hydrolysis products were differentiated chromatographically, too, by using various detection agents. The phenols were identified with a 1 : 1 mixture of 1.5% aqueous ferric chloride with 1% aqueous  $K_3(\text{Fe}(\text{CN})_6)$ , the amino compounds were identified with the Ehrlich reagent. In the course of the reaction concentration of the compound *I* ( $R_F$  0.46) decreases as it is decomposed into N-methyl-3-formamidophenylcarbamate ( $R_F$  0.64) and N'-3-hydroxyphenyl-N,N-dimethylformamidine ( $R_F$  0.08). These intermediates are further decomposed to 3-hydroxyformanilide which represents (at 60°C) the final hydrolysis product of the compound *I*. The measurement by the stopped flow method was carried out with a Durrum Gibson apparatus at 260 nm. For the measurements we used  $6 \cdot 10^{-5} \text{ mol l}^{-1}$  solution of *I* in 40% aqueous dioxane and  $2 \cdot 10^{-1}$  and  $2 \text{ mol l}^{-1}$  aqueous potassium hydroxide solutions. The solutions of *I* and KOH were mixed 1 : 1 in mixing chamber of the apparatus, and from the curve at its screen the reaction half-life was read.

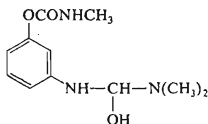
The rate constants were calculated from the kinetic data by known methods<sup>10</sup>. As the kinetic measurements had to be carried out at different temperatures (within 25 to 100°C), the obtained rate constants were extrapolated<sup>14</sup> graphically to 60°C using the relation  $\log k = \log A - E$  :  $(19.147 \cdot T)$ , where  $k$ ,  $E$  and  $T$  are the rate constant in  $\text{s}^{-1}$ , the activation energy in  $\text{kJ mol}^{-1}$  and absolute temperature in K, respectively.

### RESULTS AND DISCUSSION

Chromatography of the hydrolysis products of *I* showed that composition of the products depended on pH of the reaction medium. The hydrolysis carried out at 60°C within pH 1 to 3 and 9.5 to 13 produces N'-3-hydroxyphenyl-N,N-dimethylformamidine (*VII*). In the pH region 4 to 9 the products contained, besides *VII*, also N-methyl-

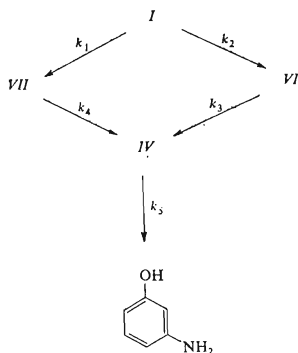
-3-formamidophenylcarbamate (VI) and 3-hydroxyformanilide (IV). The latter represents the final product of hydrolysis of the intermediates VI and VII (Scheme 2).

$$[I] = [I]_0 \cdot e^{-(k_1 + k_2)t} \quad (1)$$



VIII

At the reaction conditions chosen ( $T = 60^\circ\text{C}$ ) the subsequent hydrolysis of 3-hydroxyformanilide to 3-aminophenol is very slow, but its velocity increases with increasing temperature, too. The given reaction scheme describes the hydrolysis of *I* in the whole pH range at any temperature. In the pH range 4 to 9 it is  $k_1 \sim k_2 \sim k_3 \sim k_4 \gg k_5$  (i.e. consecutive competitive reactions), whereas in the pH range 9.5 to 13 and 1 to 3 it is  $k_1 \gg k_2 \sim k_4$  and  $k_1 \gg k_5$  (i.e. consecutive reaction). Concentration decrease of the substance *I* is given by equation (1) wherefrom it follows that the observed



SCHEME 2

rate constant is a sum of the rate constants  $k_1$  and  $k_2$ .

$$k_{\text{obs}} = k_1 + k_2 \quad (2)$$

The values  $\log k_{\text{obs}}$  are summarized in Table I. Dependence  $\log k_{\text{obs}}$  vs pH is represented by curve 1, Fig. 1; curve 2 gives the pH dependence of  $\log k$  of hydrolysis of N'-(3-nitrophenyl)-N,N-dimethylformamide which substitutes (with sufficient accuracy) for the dependence of logarithm of the rate constant of hydrolysis of dimethylformamide group of the compound *I* in which the effect of N-methylcarbamoyl group makes itself felt. This substitution is possible, because former measure-

TABLE I  
Values of  $\log k_{\text{obs}}$  of Hydrolysis of the Compound *I*

pH	$T, ^\circ\text{C}$	$\log k_{\text{obs}}$	pH	$T, ^\circ\text{C}$	$\log k_{\text{obs}}$
13	25	-1.210	6.55	68	-3.247
13	60	2.340 <sup>a</sup>	6.55	60	-3.903 <sup>a</sup>
12	25	-2.141	5.53	80	-3.530
12	60	1.070 <sup>a</sup>	5.53	60	-4.940 <sup>a</sup>
11.45	40	-1.567	4	100	-3.631
11.45	60	0.140 <sup>a</sup>	4	90	-4.088
10.50	40	-2.977	4	60	-5.900 <sup>a</sup>
10.50	50	-2.041	3	95	-4.091
10.50	60	-1.110 <sup>a</sup>	3	60	-6.150 <sup>a</sup>
9.28	60	-2.053	2	95	-4.143
7.90	60	-2.676	2	60	-6.200 <sup>a</sup>
7.25	60	-2.863	1	100	-4.073
6.55	80	-2.279	1	60	-6.100

<sup>a</sup> Extrapolated value of  $\log k_{\text{obs}}$ .

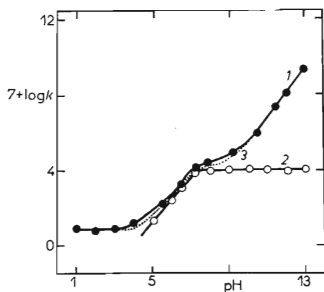
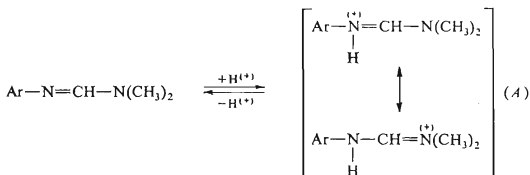


FIG. 1  
pH Dependence of  $\log k_{\text{obs}}$  of Hydrolysis of Compound *I* at  $60^\circ\text{C}$  at  $I = 0.5$  (curve 1), pH Dependence of  $\log k_{\text{obs}}$  of Hydrolysis of N'-(3-Nitrophenyl)-N,N-dimethylformamide<sup>10</sup> at  $60^\circ\text{C}$  (curve 2) and Calculated pH Dependence of  $\log k_1$  (curve 3)

ments<sup>10</sup> showed that hydrolysis rate of substituted *N'*-aryl-*N,N*-dimethylformamides was independent of the substituent in the pH region 4–8. In the pH region 9 to 13 the hydrolysis rate depends on substituent ( $\rho = -0.53$ ), but the  $\sigma$  values of the groups 3-OCONHCH<sub>3</sub> (+0.71) (ref.<sup>15</sup>) and 3-NO<sub>2</sub> (+0.70) (ref.<sup>16</sup>) are practically the same. The curve 3 represents pH dependence of  $\log k_1$ , and its values were calculated from Eq. (2). From Fig. 1 it is seen that the dependences  $\log k_{\text{obs}}$  vs pH are well linked together in the regions where chromatographic and spectral methods were used. However, course of this dependence is different from that of the published results describing hydrolysis of *N*-methylarylcabamates<sup>9</sup> and *N,N*-dimethylformamides<sup>10</sup>. The main difference consists in that the pH dependence of  $\log k$  of hydrolysis of the compound *I* is non-linear in the pH region 7 to 10. We ascribe this non-linearity to protonation of the dimethylformamide group present in *I* (Eq. (A)),



which results in change of polar effects of the substituent influencing the hydrolysis rate of *N*-methylcarbamoyl group. This presumption is also supported by the value of dissociation constant of the compound *I* ( $\text{p}K_{\text{A}} = 7.3$ ) derived from kinetic data, which, on the basis of the substituent effects of 3-OCONHCH<sub>3</sub> and 3-NO<sub>2</sub>, is almost identical with the  $\text{p}K_{\text{A}}$  value found for *N'*-3-nitrophenyl-*N,N*-dimethylformamide ( $\text{p}K_{\text{A}} = 7.15$ ) (ref.<sup>10</sup>). For further support of the presumed mechanism we used the Hammett equation for assessment of  $\sigma$  values of the protonated and non-protonated dimethylformamide group. For this assessment pH profiles of substituted *N*-methylarylcabamates<sup>9</sup> were used after extrapolation to 60°C according to the temperature dependence. In the medium of pH 4–7, where the protonated dimethylformamide group is presumed, the value  $\sigma = +0.60$  was obtained which agrees well with that given for 3-NH<sub>3</sub><sup>(+)</sup> group ( $\sigma = 0.634$ ) (ref.<sup>16</sup>). In alkaline region of pH 10 to 13 the found value of  $\sigma$  constant ( $-0.24$ ) approaches that given for 3-NH<sub>2</sub> group ( $\sigma = -0.15$ ) (ref.<sup>16</sup>).

The results obtained confirm that hydrolysis of *N*-methylcarbamoyl group of the compound *I* goes by E1cB mechanism, its rate being affected by the protonated or non-protonated *N,N*-dimethylformamide group. The results and calculations of  $\sigma$  constants agree with the previously suggested mechanism of hydrolysis of *N,N*-dimethylformamide group<sup>10</sup> involving rapid formation of the hydrated formamide (*VIII*) and its rapid splitting to *N*-methyl-3-formamidophenylcarbamate (*VI*) which

was proved in the reaction mixture within pH 5 to 9. Among the hydrolysis reaction products of the compound *I* it was impossible to find N-methyl-3-aminophenyl-carbamate (*V*), which is obviously produced by photolysis of *I*. Therefrom it follows that both hydrolysis and photolysis<sup>8</sup> of N-methylcarbamoyl group go by a mechanism giving the same products, whereas hydrolysis and photolysis of N,N-dimethyl-formamidine group<sup>7,8</sup> go by different mechanisms.

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Translated by J. Panchartek.