KINETICS OF METHANOLYSIS OF 1-(2-HALOGENO AND 2,6-DIHALOGENOBENZOYL)-3-(4-CHLOROPHENYL)UREAS

Jaromír KAVÁLEK, Lubomír KACETL and Marcela KAVÁLKOVÁ*

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

Dedicated to Prof. Pavol Kristián on the occasion of his 60th birthday.

The methanolysis kinetics has been measured of 1-(2,6-difluorobenzoyl)-3-(4-chlorophenyl)urea (a larvicidal insecticide Dimilin) and of four other mono- and dihalogenobenzoyl derivatives. Polar and steric effects of halogen on the rate and dissociation constants is discussed.

Dimilin (Duphar BV, Amsterdam), 1-(2,6-difluorobenzoyl)-3-(4-chlorophenyl)urea (*V*) is a selective insecticide of the so-called larvicidal character which causes, after eating or contact, changes in formation of pupae of caterpillars. The compound *V* attacks active centres of chitin-forming chain, and the caterpillars lose their ability to pupate and die in the larval phase. This insecticide has practically no effects on mammals, fish, and birds. The compound does not penetrate into plant leaves, and no effect on photosynthesis has been observed[1,2]. When degraded in soil (in nature), compound *V* undergoes (to 80%) hydrolytic splitting into 2,6-difluorobenzoic acid and 4-chlorophenylurea[1]. The aim of the present work is to measure the solvolysis rate of compound *V* and other halogeno derivatives of benzoylphenylurea which were tested for insecticidal activity[3,4].
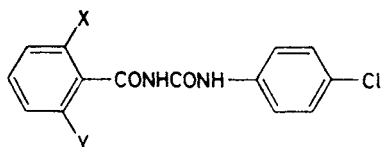
I, X = H ; Y = F	*IV*, X = Cl ; Y = Cl
II, X = H ; Y = Cl	*V*, X = F ; Y = F
III, X = H ; Y = Br	*VI*, X = H ; Y = H

EXPERIMENTAL

Reagents

2,6-*Difluorobenzoic acid* was prepared by carboxylation of 2,6-difluorophenyllithium in tetra-hydrofurane medium[5]. Difluorophenyllithium was prepared ba reaction of 1,3-difluorobenzene with butyllithium at −50°C (ref.[6]). The yield of the acid was 50%, m.p. 157—159°C. 2-*Fluoro-benzoic* and 2,6-*dichlorobenzoic acids* were prepared from the respective halogenotoluenes by oxidation with potassium permanganate. 2-*Chloro-* and 2-*bromobenzoic acids* were prepared by the Sandmayer reaction from anthranilic acid. Chlorides and amides of the above-mentioned acids were prepared by known procedures. 4-*Chlorophenyl isocyanate* was prepared by phosgenation of 4-chloroaniline in chlorobenzene medium and was isolated by vacuum distillation (b.p. 115—117°C at 6 kPa). 4-*Chlorophenylurea* was prepared by reaction of 4-chloroaniline with potassium cyanate. The melting points of all the substances prepared agreed with the tabulated values.

1-(2-*Fluorobenzoyl*)-3-(4-*chlorophenyl*)urea (I). A solution of 7 g (0·05 mol) 2-fluorobenzamide in 100 ml dried toluene was treated with 7·6 g (0·05 mol) 4-chlorophenyl isocyanate, and the mixture was heated to boiling for 5 h. After cooling, the separated solid was filtered off, washed with ether, and recrystallized from acetone. Yield 11·7 g (80%), m.p. 235—237°C. For $C_{14}H_{10}$·.ClFN$_2$O$_2$ (292·5) calculated: 57·44% C, 3·42% H; found: 57·70% C, 3·40% H. Similar procedure was also applied to preparation of 1-(2-*chlorobenzoyl*)-3-(4-*chlorophenyl*)urea (II), m.p. 198 to 200°C, for $C_{14}H_{10}Cl_2N_2O_2$ (308·1) calculated: 54·54% C, 3·25% H, 9·09% N; found: 54·31% C, 3·40% H, 9·31% N; 1-(2-*bromobenzoyl*)-3-(4-*chlorophenyl*)urea (III), m.p. 201—203°C, for $C_{14}H_{10}BrClN_2O_2$ (353·6) calculated: 47·52% C, 2·83% H; found: 47·73% C, 3·01% H; 1-(2,6--*dichlorobenzoyl*)-3-(4-*chlorophenyl*)urea (IV), m.p. 231—233°C in accordance with ref.[3].

1-(2,6-*Difluorobenzoyl*)-3-(4-*chlorophenyl*)urea (V) was prepared by the above-described procedure, m.p. 230—32°C in accordance with ref.[3], or without application of isocyanates — by acylation of 4-chlorophenylurea: A solution of 17 g (0·1 mol) 4-chlorophenylurea in 150 ml toluene was treated with 17·6 g (0·1 mol) 2,6-difluorobenzoyl chloride, and the mixture was refluxed 7 h. After cooling, the precipitated solid was collected and washed with ether. Fraction crystallization from ethanol gave 20·8 g (67%) compound V and 5 g N-(2,6-difluorobenzoyl)-4-chloroaniline, m.p. 148·5—150°C.

Measurement of Dissociation Constants of Compounds I—V

The procedure used for compound I: 1 cm quartz cells with lids were charged with 0 to 2·5 ml (by 0·2 ml steps) 0·01 mol l^{-1} or 0·5 to 2·5 ml (by 0·5 ml steps) 0·1 mol l^{-1} sodium methoxide and the volume was adjusted at 2·5 ml by addition of methanol. The methoxide solutions thus prepared (10^{-3} to 8 . 10^{-2} mol l^{-1}) were thermostated at 25°C, whereupon 0·5 ml 2 . 10^{-4} mol . . l^{-1} methanolic solution of the fluoro derivative I was added at the time $t = 0$. The cell content was mixed and its absorbance was measured at the wavelength of 300 nm. The absorbances extrapolated to $t = 0$ were used for the calculation.

The procedure used for compounds II—V whose methanolysis rates are so low that they do not interfere with the measurement of dissociation constants: sodium methoxide solutions (0 to 1 mol l^{-1}) were prepared in 10 ml calibrated flasks, and 0·5 or 0·7 ml methanolic solutions of compounds II—V (10^{-3} mol l^{-1}) were added, whereupon spectra of the solutions were measured within the interval from 230 to 360 nm.

The values of dissociation constants were calculated from the equation $pK_a = pK_s + \log$ [CH$_3$O$^-$] − log R, where K_a is the dissociation constant measured, $pK_s = 16·92$ (ref.[7]), and R

means the concentration ratio of the conjugated base S^- and the acid SH of the substance measured which was calculated from the absorbances found: $R = [S^-]/[SH] = (A - A_{SH})/(A_{S^-} - A)$, where A_{SH}, A_{S^-}, and A are the absorbances of the substrate, its conjugated base, and the solution measured, respectively.

Kinetic Measurements of Methanolysis

The procedures were different depending on the compound type and temperature.

Compound I *at* 25°C: a quartz cell with a lid was charged with 1 ml methoxide solution (for concentrations see Table I), and 1 ml methanolic solution of compound *I* (10^{-4} mol l^{-1}) was added, whereupon the absorbance decrease with time was followed at 310 nm. The rate constants k_{obs} were calculated from the equation $k_{obs}t = -2.3 \log (A_t - A_\infty) + \text{const.}$, where A_∞ and A_t are the absorbances measured after six half-lives and at the time t, respectively.

Compounds II *and* V *at* 25°C: 0.5 ml 3 . 10^{-3} mol l^{-1} methanolic solution of compound *II* or *V* was added to 1.95 ml sodium methoxide in a thermostated cell, and the spectra were measured at suitable time intervals within the wavelength range from 230 to 360 nm. The rate constants were calculated in a similar way as those for compound *I*.

Compounds III, IV, *and* V *at higher temperatures*: 30 ml sodium methoxide solution of a known concentration and 1.5 ml methanolic solution of 10^{-3} mol l^{-1} compound *III, IV* or *V* were mixed in a flask. The mixture (2 ml) was placed in glass ampoules which were sealed and placed in a thermostat (40, 50, 55, 67, 82 or 100°C, see Table I). At definite time intervals, the individual ampoules were taken out from the thermostat bath, cooled in ice water, their content was transferred into 1 cm quartz cell and its spectrum was measured in the wavelength range from 230 to 360 nm. The k_{obs} values were obtained graphically from the absorbance decreases as in the case of compound *I*.

RESULTS AND DISCUSSION

The methanolysis of benzoyl derivatives $I - V$ was of the first order with respect to the benzoyl derivative in all the cases, and its course is represented in Scheme 1.

The observed rate coefficient (k_{obs}) is defined by Eq. *(1)* at methoxide concentrations below 0.1 mol l^{-1}.

$$k_{obs} = \frac{k[CH_3O^-]}{1 + K[CH_3O^-]} = \frac{k[CH_3O^-]}{1 + [CH_3O^-]K_a/K_S} . \tag{1}$$

In this equation $k = k_1 k_2/(k_{-1} + k_2)$, $K_S = 10^{-16.92}$ is the autoprotolytic constant of methanol[7], and the expression $[CH_3O^-]/(1 + [CH_3O^-]K_a/K_S)$ corresponds to the mol fraction of the non-dissociated benzoylurea $I - V$ in its mixture with its conjugated base.

At low methoxide concentrations $\log k_{obs}$ increases practically linearly with increasing $\log [CH_3O^-]$ (Fig. 1). If most of the benzoyl derivative is $-$ due to dissociation $-$ transformed into the anion (which does not undergo the methanolysis), then the solvolysis rate becomes independent of the methoxide concentration. At the methoxide concentrations above 0.1 mol l^{-1} the rate coefficients measured are

TABLE I

The observed rate coefficients (k_{obs}, s^{-1}) of methanolysis of compounds $I-V$ at various methoxide concentrations c (mol l^{-1}) at 25°C

I		II		III		IV		V	
c	$k_{obs} \cdot 10^4$	c	$k_{obs} \cdot 10^4$	c	$k_{obs} \cdot 10^4$	c	$k_{obs} \cdot 10^4$	c	$k_{obs} \cdot 10^4$
0·00145	1·82	0·0097	0·88	0·048	6·83	0·048	0·42[d]	0·05	0·13
0·00080	0·93	0·048	1·00	0·097	7·17	0·060	0·45[d]	0·039	2·00[b]
0·0025	2·76	0·097	1·07	0·048	2·65[a]	0·032	1·67[e]	0·070	1·67[b]
0·050	4·85			0·063	2·75[a]	0·048	1·55[e]	0·080	1·83[b]
0·087	6·30			0·097	2·62[a]	0·048	11·7[f]	0·048	9·83[d]
0·0091	6·50			0·0048	4·10[c]	0·096	10·2[f]	0·070	10·5[d]
0·022	8·33			0·0097	5·97[c]			0·016	23·3[e]
0·050	10·1			0·029	9·33[c]			0·040	21·7[e]
0·091	8·63			0·070	8·33[c]			0·048	21·7[e]
0·25	7·07			0·097	8·67[c]				
0·50	4·40			0·011	20·0[d]				
				0·029	21·8[d]				

[a] 40°C; [b] 50°C, [c] 55°C; [d] 67°C; [e] 82°C; [f] 100°C.
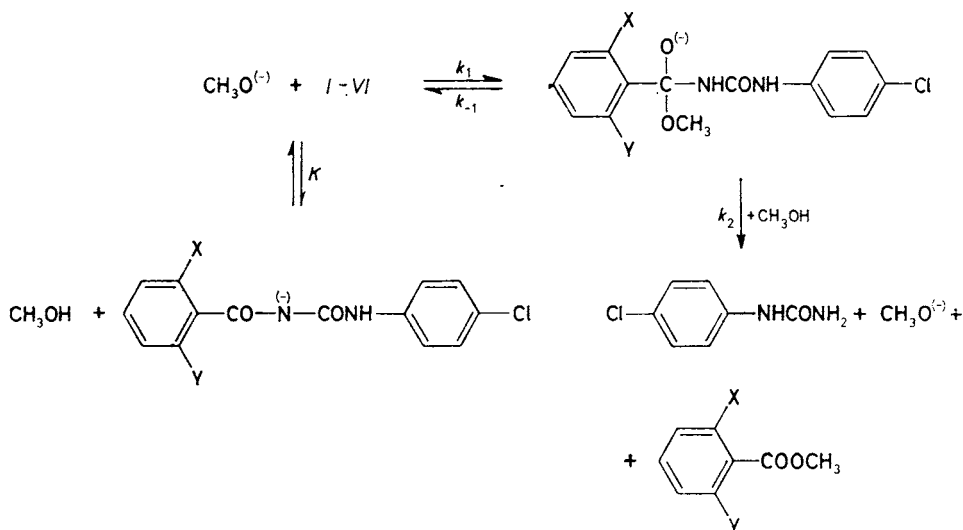
SCHEME 1

lower than those calculated from Eq. (1) (the solid line in Fig. 1). In our opinion, these differences are due to the fact that in the comparatively concentrated methoxide solutions used the activity coefficients of reacting components are considerably and unequally affected: the activity coefficient of the anion of substrate increases more slowly than that of the transition state of the rate-limiting step of solvolysis. Therefore, increasing methoxide concentration supports the formation of unreactive conjugated base of substrate more than the solvolysis itself[8-10].
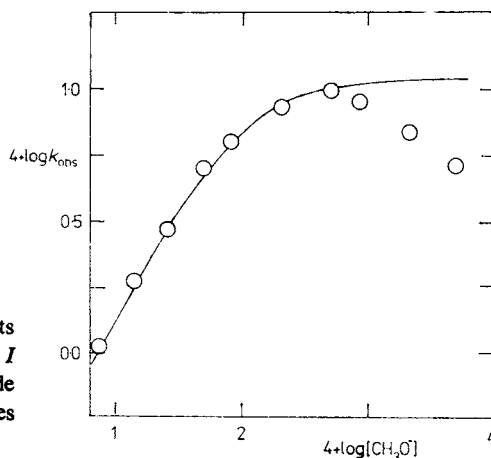

FIG. 1

Dependence of observed rate coefficients (k_{obs}, s^{-1}) of methanolysis of compound I on concentration of sodium methoxide (mol l^{-1}) at 25°C. The solid line expresses the k_{obs} values calculated from Eq. (1)

The rate constants k were calculated from Eq. (1) and the k_{obs} values measured at the methoxide concentrations below $0.1 \, \text{mol} \, l^{-1}$. As the K values were obtained at 25°C, the rate constants had to be determined at the same temperature. With compounds $III - V$ the kinetic measurements were also carried out at higher temperatures, because their solvolyses at 25°C are very slow. The rate coefficients k_{obs} for 25°C were determined from the linear dependence of $\log k_{obs}$ on $1/T$ and from the long-term experiments carried out at 25°C. The values of coefficients obtained in these two ways differed by as much as 40%, because the error of extrapolation is considerable. With the dichloro derivative IV, however, only the extrapolated k_{obs} value was obtained, because the reaction half-life is several thousands of minutes at 25°C.

The halogen at 2-position of the benzoyl group affects the solvolysis rate by both its polar and steric effects, the two effects acting in opposite directions. The polar effect accelerates the solvolysis, and compounds $I - III$ should be solvolyzed roughly 3 to 10 times faster (the substituent constant σ is $0.3 - 0.6$ for *ortho* halogen[11] and the ϱ constant of methanolysis of 2-subst.benzoyl-3-phenylureas[10] has the value of 1.7) than the non-substituted 1-benzoyl-3-(4-chlorophenyl)urea[8] VI (Table II). A small acceleration was observed only with the fluoro derivative I $\left(k^I : k^{VI} \approx 2\right)$ in which the sterical effect of fluorine does not predominate over its activating effect. The k values of the chloro and bromo derivatives II and III are 4 and 7 times smaller, respectively, than the rate constant of compound VI (Table II). The sterical effect of the 2,6-dihalogeno derivatives IV and V was particularly significant with the bulkier dichloro derivative IV which reacts almost $40 \times$ more slowly than the mono-chloro derivative II. In the case of the fluoro derivatives I and V the retardation is only eightfold.

TABLE II

Equilibrium constants $K = K_a/K_S$ in methanol and rate constants k ($l \, \text{mol}^{-1} \, s^{-1}$) of methanolysis of substituted benzoylureas $I - VI$

Compound	$k \cdot 10^2$	K	pK_a
I	13·7	112	14·87 $\pm$ 0·07
II	1·33	130	14·81 $\pm$ 0·10
III	0·82	115	14·86 $\pm$ 0·10
IV	0·035	1 048	13·90 $\pm$ 0·08
V	1·7	1 000	13·92 $\pm$ 0·05
VI	5·6^a	87	14·98

^{a} Ref.[8].

The dissociation constants of the monohalogeno derivatives $I-III$ (Table II) differ only within experimental error, which agrees with the data about the dissociation constants of o-halogenobenzoic acids in water[12] $(1\cdot2$ to $1\cdot4)$. 10^{-3}.

REFERENCES

1. Maas W., Hes R., Grosscurt A. C., Deul D. H.: *Chemie der Pflanzenschutz und Schädling-bekämpfungsmittel* (R. Wegler, Ed.), p. 424. Springer, Berlin 1981.
2. Hajjar N. P. in: *Insecticides (Progress in Pesticide Biochemistry and Toxicology)* (D. H. Hutson and T. R. Roberts, Eds), Vol. 5. p. 275. Wiley, New York 1985.
3. Nakagawa Y., Kitahara K., Nishioka T., Iwamura H., Fujita T.: Pestic. Biochem. Physiol. *21*, 309 (1984).
4. Nakagawa Y., Iwamura H., Fujita T.: Pestic. Biochem. Physiol. *23*, 7 (1985).
5. Gilman H., Soddy T. S.: J. Org. Chem. *22*, 1715 (1957).
6. Roe A. M., Burton R. A., Reavill D. R.: J. Chem. Soc., Chem. Commun. *1965*, 582.
7. Rochester C. H., Rossal B.: J. Chem. Soc., B *1967*, 437.
8. Kaválek J., Said El Bahaie, Štěrba V.: Collect. Czech. Chem. Commun. *49*, 2103 (1984).
9. Kaválek J., Jirman J., Štěrba V.: Collect. Czech. Chem. Commun. *52*, 120 (1987).
10. Kaválek J., Jirman J., Macháček V., Štěrba V.: Collect. Czech. Chem. Commun. *53*, 593 (1988).
11. Charton M.: Prog. Phys. Org. Chem. *8*, 235 (1971).
12. Kortüm G., Vogel W., Andrussow K.: *Dissociation Constants of Organic Acids in Aqueous Solution*. Butterworths, London 1961.

Translated by J. Panchartek.