

# Kinetics and Mechanism of Reaction of Methoxide Ion with *O*-(*N*-Arylcarbamoyl)benzophenone Oximes

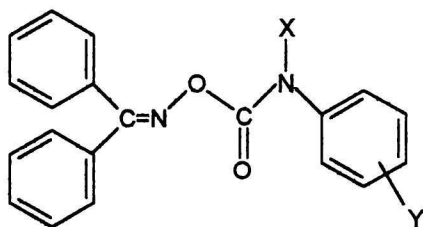
V KOŽENÝ, J. MINDL, and V ŠTĚRBA

Department of Organic Chemistry, Faculty of Chemical Technology, University Pardubice, CZ-532 10 Pardubice

Received 25 April 1996

A series of nine *O*-(*N*-arylcarbamoyl)benzophenone oximes and their two *N*-methyl derivatives has been prepared and characterized. For estimation of mechanism E1cB of the above-mentioned compounds a new simple competition test using butylamine and kinetic studies were used. Hammett reaction constants for the given reaction  $\rho_{\text{obs}} = 0.68$  and  $\rho_{k_2} = -1.32$  were calculated.

The reaction of substituted *O*-(*N*-phenylcarbamoyl)benzophenone oximes with dibutylamine in toluene was studied by Levine and Fecz [1]. The present communication represents a continuation of our previous study of hydrolysis of *O*-(*N*-4-nitrophenylcarbamoyl)benzaldehyde oximes [2, 3]. The aim of our work was to complete the knowledge about the substitution influence from the ring joined to a nitrogen atom. We have also tried to verify a simple way for the evaluation of the reaction mechanism. The change of *O*-(*N*-arylcarbamoyl)benzaldehyde oximes for *O*-(*N*-arylcarbamoyl)benzophenone oximes (*Ia*—*IIf*, Formula 1) was chosen taking into account the decreased number of isomeric and subsequent products that could be formed. Methanol was chosen to ensure the homogeneity of the reaction mixture and to eliminate the decarboxylation.



I, II

<i>I</i>	X	Y	<i>I</i>	X	Y
<i>a</i>	H	H	<i>h</i>	H	3-NO <sub>2</sub>
<i>b</i>	H	4-Me	<i>i</i>	H	4-NO <sub>2</sub>
<i>c</i>	H	3-Me			
<i>d</i>	H	4-OMe	II		
<i>e</i>	H	3-Cl			
<i>f</i>	H	4-Cl	<i>a</i>	Me	H
<i>g</i>	H	3-CF <sub>3</sub>	<i>b</i>	Me	4-NO <sub>2</sub>

Formula 1

## EXPERIMENTAL

Benzophenone oxime was prepared by oximation of benzophenone [4]. *N*-Methyl-*N*-phenylcarbamoyl chloride and *N*-methyl-*N*-(4-nitrophenyl)carbamoyl chloride were prepared by a standard procedure from corresponding anilines by reaction with phosgene according to our previous paper [2]. Methyl *N*-(3-nitrophenyl)carbamate (Ref. [5] gives m.p. = 148—150°C) was prepared by heating 3-nitrophenylisocyanate in methanol solutions for 10 min. Methyl *N*-methyl-*N*-(4-nitrophenyl)carbamate, m.p. = 132—134°C, was prepared from *N*-methyl-*N*-(4-nitrophenyl)carbamoyl chloride by a similar way [6]. *N*-Butyl-*N'*-(3-nitrophenyl)urea (m.p. = 127—128°C) was prepared by the reaction of 3-nitrophenylisocyanate with butylamine in ether [7].

*O*-(*N*-Arylcarbamoyl)benzophenone oximes (*Ia*—*IIf*). Solution of 0.01 mol of benzophenone oxime in 10 cm<sup>3</sup> of toluene was mixed with a solution of 0.01 mol of arylisocyanate in 5 cm<sup>3</sup> of toluene. The mixture was heated at 100°C in a sealed ampoule for 3 h. The product crystallized after cooling and was recrystallized from propan-1-ol and then kept in dark. The yields, melting points, and results of elemental analyses are given in Table 1.

*O*-(*N*-Methyl-*N*-arylcarbamoyl)benzophenone oximes (*IIa*, *IIb*). 0.6 g of sodium was dissolved in 25 cm<sup>3</sup> of methanol, and a solution of 0.025 mol of benzophenone oxime in 25 cm<sup>3</sup> of methanol was added thereto. Methanol was distilled off in vacuum and the residue was washed three times with benzene. Then a solution of 0.025 mol of the corresponding carbamoyl chloride in 50 cm<sup>3</sup> of benzene was added. The mixture was heated under reflux for 2 h. After cooling the precipitated sodium chloride was filtered off, the benzene solution was washed with 100 cm<sup>3</sup> of water, dried with sodium sulfate and concentrated for crystallization. The raw products were crystallized from

Table 1. Characterization of the Prepared *O*-[*N*-(*X*-Aryl)carbamoyl]benzophenone Oxime

Compound	Formula	$M_r$	$w_i$ (calc.)/%			Yield	M.p.
			$w_i$ (found)/%				
			C	H	N	%	°C
<i>Ib</i>	$C_{21}H_{18}N_2O_2$	330.43	76.33	5.49	8.48	71	135.0—137.0
			76.02	5.40	8.22		
<i>Ic</i>	$C_{21}H_{18}N_2O_2$	330.43	76.33	5.49	8.48	64	118.0—119.5
			76.07	5.17	8.59		
<i>Ie</i>	$C_{20}H_{15}ClN_2O_2$	350.84	68.56	4.32	8.00	75	117.5—119.0
			68.29	4.15	7.75		
<i>Ig</i>	$C_{21}H_{15}F_3N_2O_2$	384.41	65.61	3.94	7.29	48	125.5—127.0
			65.30	4.13	7.15		
<i>Ih</i>	$C_{20}H_{15}N_3O_4$	361.46	66.41	4.15	11.63	78	161.0—163.0
			66.45	4.35	11.39		
<i>Ila</i>	$C_{21}H_{18}N_2O_2$	330.43	76.27	5.45	8.47	57	124.5—126.0
			76.51	5.79	8.33		
<i>Ilb</i>	$C_{21}H_{17}N_3O_4$	375.45	67.58	4.57	11.20	62	173.0—175.5
			67.99	4.63	11.00		

*Ia*: M.p. = 177.0—179.0°C, Ref. [1] gives m.p. = 178.0—180.0°C; *Id*: m.p. = 125.5—127.0°C, Ref. [1] gives m.p. = 126.0—127.0°C; *If*: m.p. = 150.0—152.5°C, Ref. [1] gives m.p. = 151.5—153.0°C; *Ii*: m.p. = 162.0—164.0°C, Ref. [1] gives m.p. = 162.0—164.0°C.

ethanol, dried and kept in dark. The yields, melting points, and elemental analyses are given in Table 1.

### Identification of Reaction Products of *Ih* and *Ilb*

The solution of 0.1 g of *Ih* or *Ilb* in 1 cm<sup>3</sup> of dioxane and 10 cm<sup>3</sup> of 5 % sodium methoxide in methanol was heated at 100°C for 30 min and then gaseous dry hydrogen chloride was passed into the solution to achieve pH 5. Sodium chloride was filtered off and methanol from organic filtrate was evaporated. The residue was submitted to TLC on Silufol UV 254, using methanol—chloroform as eluent ( $\varphi_r = 1/8$ ). Positions of individual fractions were detected by the UV<sub>254 nm</sub> lamp and the retention times of the expected reaction products decreased in the order:  $R_F$  (methyl *N*-(3-nitrophenyl)carbamate),  $R_F$  (methyl *N*-methyl-*N*-(4-nitrophenyl)carbamate),  $R_F$  (benzophenone oxime),  $R_F$  (*N*-butyl-*N'*-(3-nitrophenyl)urea).

The reaction of *Ih* and sodium methoxide ( $c = 0.7$  mol dm<sup>-3</sup>) in methanol was carried out in the presence of butylamine ( $c = 0.7$  mol dm<sup>-3</sup>) and the products were analyzed at the same conditions.

Solutions of *Ih* or *Ilb* in methanol were heated to 100°C for 12 h in sealed ampoules and then analyzed in a similar way.

### Kinetic Measurements

The measurements were carried out in a  $1 \times 10^{-2}$ — $2.5$  mol dm<sup>-3</sup> sodium methoxide solution in methanol under nitrogen. For the measurement about 10 mm<sup>3</sup> of dioxane or methanolic solutions of the compounds *Ia*—*Ilb* were injected into 3 cm<sup>3</sup> of methoxide solution in a cuvette. The measurements were carried out from 25°C to 45°C. Concentrations of *Ia*—

*Ilb* in the reaction mixtures were  $(1$  to  $2) \times 10^{-5}$  mol dm<sup>-3</sup>. The progress of the reaction was monitored by recording the UV spectra in the region from 220 nm to 450 nm at various time intervals. The decrease of concentrations of *Ia*—*Ilb* was followed by a measurement of absorption on a Packard HP 8452A-diode array spectrophotometer. Rate constants were determined from the relation  $\ln(A_\infty - A_t) = k_{\text{obs}} t$ , where  $A_\infty$  and  $A_t$  represent the final absorption and the absorption at time  $t$ , respectively. In case of slowly proceeding reactions at 25°C the reaction constants were calculated using the similar ones measured at higher temperatures at the Eyring equation  $\ln k_{\text{obs}} = \ln(kT/h) - \Delta H^\ddagger/RT + \Delta S^\ddagger/R$ . For this case we have also calculated the activation parameters ( $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ ).

The concentration of sodium methoxide was determined by alkaline titration (phenolphthalein) at 25°C.

## RESULTS AND DISCUSSION

Compounds *I* or *II* form white crystals soluble in alcohols. After a daylight exposition for many days 0.5 to 2 % of decomposition products were observed. Methanolysis in pure methanol did not take place even if the solution of *I* or *II* was heated at 100°C for 12 h. Studying the structurally similar *O*-(4-nitrophenylcarbamoyl)benzaldehyde oximes we observed a spontaneous hydrolysis [3].

In the presence of sodium methoxide in methanol formation of sodium salts of benzophenone oximes and corresponding methyl *N*-phenylcarbamates was observed. The rates of reactions of methoxide ion with *I* or *II* followed the pseudo-first-order kinetics in all the cases. The concentration dependences ( $\log\{c_{\text{NaOMe}}\}$ ) of  $\log\{k_{\text{obs}}\}$  are given in Fig. 1.

The evaluation of the rate constant  $k_{\text{OMe}} =$

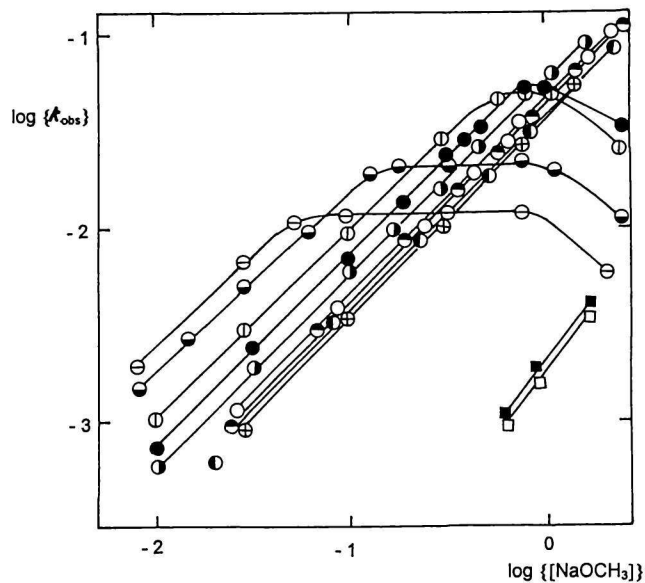


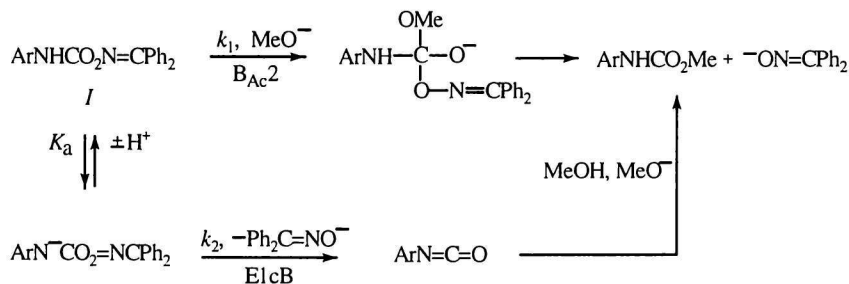
Fig. 1. Dependence of  $\log\{k_{\text{obs}}\}$  of methanolysis of *O*-(*N*-phenylcarbamoyl)benzophenone oximes and their *N*-methyl derivatives on  $\log\{c_{\text{NaOMe}}\}$  at 25 °C. Compound *Ia* is indicated by the point (O), *Ib* (●), *Ic* (⊙), *Id* (⊗), *Ie* (⊠), *If* (⊡), *Ig* (⊙), *Ih* (⊠), *Ii* (⊡), *IIa* (□), *IIb* (■).

$k_{\text{obs}}/c_{\text{NaOMe}}$  was carried out in the concentration range where the rate is proportional to the concentration of the  $\text{OMe}^-$  ion. The values of  $k_{\text{OMe}}$  are given

in Table 2. Two mechanisms can be considered for the reaction of sodium methoxide with *I* in methanolic media (Scheme 1).

The reaction of *I* with methoxide *via*  $\text{B}_{\text{Ac}2}$  involves direct attack of carbonyl group of the neutral substrate by methoxide ion with simultaneous splitting off of the benzophenone oximate ion. The  $\text{E1cB}$  mechanism involves decomposition of the conjugated base of *I* into oximate ion and aryl isocyanate in the rate-limiting step. In the subsequent rapid step the isocyanate reacts with methanol to give methyl *N*-arylcabamate. With the *N*-methyl derivative only the  $\text{B}_{\text{Ac}2}$  mechanism is possible. The literature gives various criteria for the determination of the mechanism of the hydrolysis of carbamates [8]. Among those that can be used for methanolyses belongs the comparison of the reaction rates and activation entropies of the corresponding *N*-methyl derivatives. The very reliable one is the evaluation of the substitution influences from the aromatic ring [8]. The reaction rate of *I* with methoxide ion at its low concentration is faster by 1–2 orders of magnitude than that of the corresponding *N*-methyl derivatives *II*. This fact could suggest different mechanism [9] in the two series, but the difference could be interpreted as steric or inductive effect of the methyl group. From Scheme 1 eqns (1) and (2) can be derived for the two reaction paths

$$k_{\text{obs}} = k_1 K_{\text{MeOH}} / (K_{\text{a}} + a_{\text{H}}) \quad (1)$$



Scheme 1

Table 2. Rate Constants  $k_{\text{OMe}}/(\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1})$  and  $k_2/\text{s}^{-1}$  at 25 °C of the Reaction of Methoxide Ion with *O*-(*N*-Arylcabamoyl)benzophenone Oximes

Compound	$10^4 \{k_{\text{OMe}}\}$	$10^4 \{k_2\}$	Compound	$10^4 \{k_{\text{OMe}}\}$	$10^4 \{k_2\}$
<i>Ia</i>	467 ( $r = 0.99$ ; $s = 23$ )		<i>Ig</i>	883 ( $r = 0.98$ ; $s = 116$ )	299
<i>Ib</i>	396 ( $r = 0.99$ ; $s = 21$ ) <sup>a</sup>		<i>Ih</i>	1240 ( $r = 0.99$ ; $s = 80$ )	242
<i>Ic</i>	430 ( $r = 0.99$ ; $s = 32$ )		<i>Ii</i>	1370 ( $r = 0.99$ ; $s = 95$ )	203
<i>Id</i>	321 ( $r = 0.98$ ; $s = 53$ )		<i>IIa</i>	3.34 ( $r = 0.99$ ; $s = 0.04$ ) <sup>a</sup>	
<i>Ie</i>	741 ( $r = 0.99$ ; $s = 45$ ) <sup>a</sup>	311	<i>IIb</i>	3.02 ( $r = 0.99$ ; $s = 0.07$ )	
<i>If</i>	580 ( $r = 0.99$ ; $s = 31$ ) <sup>a</sup>				

<sup>a</sup>) Values of rate constants at 25 °C were calculated from the similar rate constants at higher temperatures. Activation parameters  $\Delta H^\ddagger$  (kJ mol<sup>-1</sup>),  $\Delta S^\ddagger$  (J K<sup>-1</sup> mol<sup>-1</sup>) for *Ib*: 83.0, -3.3; *Ie*: 76.2, -16.9; *If*: 74.1, 10.2; *IIa*: 51.3, -119.7.

$$k_{\text{obs}} = k_2 \frac{K_a}{(K_a + a_{\text{H}})} \quad (2)$$

These two equations are kinetically equivalent at all concentrations of sodium methoxide and cannot be used to distinguish the two pathways. When  $a_{\text{H}} \gg K_a$ , then in the first case  $k_{\text{obs}} = k_1 c_{\text{NaOMe}}$  and in the second one  $k_{\text{obs}} = k_2 \frac{K_a}{K_a + c_{\text{NaOMe}}/K_{\text{MeOH}}}$  (Fig. 1). When  $a_{\text{H}} \ll K_a$ , then in the first case  $k_{\text{obs}} = k_1 \frac{K_{\text{MeOH}}}{K_a}$ , whereas in the second one  $k_{\text{obs}} = k_2$ . The formation of the tetrahedral intermediate in the reaction proceeding by the B<sub>Ac</sub>2 mechanism is characterized by a high negative value of the activation entropy [8]. Table 2 gives the comparison of this value for the compounds *Ib*, *Ie*, *If*, and *Iia*. The activation entropy of *N*-methyl derivative (*Iia*) is negative and by about 100 e.u. higher than those for the compounds *I*.

To evaluate the influence of the substituent on the ring joined to a nitrogen atom on  $k_{\text{OMe}}$ , we selected eight substituents in the series of carbamates *Ia*–*Ih*, with Hammett parameters  $\sigma$ . From the dependence of  $\log k_{\text{OMe}}$  vs.  $\sigma$  we obtain  $\log k_{\text{OMe}} = 0.68\sigma - 2.74$  ( $r = 0.97$ ,  $s = 0.04$ ). Similar value of the reaction constant for phenyl *N*-arylcarbamates  $\rho_{\text{obs}} = 0.64$  was observed by *Hegarty* and *Frost* [10]. From eqns (1) and (2) we can derive the relation  $\log k_{\text{OMe}} = \log k_2 + \log K_a + \text{p}K_{\text{MeOH}}$  for the E1cB mechanism and consequently the reaction constant  $\rho_{\text{OMe}} = \rho_{K_a} + \rho_{k_2}$ . The break of the increasing dependence of  $\log \{k_{\text{obs}}\}$  on  $\log \{[\text{NaOMe}]\}$  for compounds *Ia*–*Ih* in Fig. 1 is represented by kinetic values  $K_a$ . Those ones increase with the increasing  $\sigma$  values of the substituents adjacent to *N*-aryl group. On the other hand,  $k_2$  values which were derived from eqn (2) as the "plateau"  $k_{\text{obs}}$  have a reversed relationship to  $\sigma$  values. The constants  $k_2$  are given in Table 2.

The Hammett dependence  $\log k_2 = -1.32\sigma - 0.61$ . Using both reaction constants  $\rho_{\text{OMe}}$  and  $\rho_{k_2}$  the value  $\rho_{K_a} = 2.0$  can be calculated for the ionization of *I*. The decrease of  $k_{\text{obs}}$  of 3-Cl, 3-CF<sub>3</sub>, 3-NO<sub>2</sub>, and 4-NO<sub>2</sub> derivatives at high concentrations of methoxide ions is due to the influence of medium on the activity coefficients of transition states of conjugate bases. Spectral characteristics of the starting reagents *Ie*, *Ig*–*Ii* and their products are practically the same within the concentration range  $\log \{c_{\text{MeONa}}\} = 0.0$  to 0.3 as those in the "plateau" area. The similar dependence was observed in the reaction of 1,3-diacylthioureas with methoxide ion [11], or in the reactions of benzoyl derivatives of the substituted phenylthioureas with methoxide ion [12]. In both cases that decrease was observed even at the concentrations  $\log \{c_{\text{MeONa}}\} \geq -0.7$ . The observed rate constants of *Iia* and *Iib* increase linearly with increasing methoxide ion con-

centration (Fig. 1). The slope of the linear dependence of  $\log k_{\text{obs}}$  on  $\sigma$  constant is ca. 0 in accordance with the B<sub>Ac</sub>2 mechanism. We observed similar dependence in the hydrolysis of (*E*)-*O*-(*N*-methyl-*N*-4-nitrophenylcarbamoyl)benzaldehyde oximes [2].

We have used butylamine to determine the mechanism of the reaction in another simple way. Butylamine in dioxane solution reacted with compound *Ih* to give *N*-butyl-*N'*-(3-nitrophenyl)urea. The mixture of 0.7 mol dm<sup>-3</sup> sodium methoxide and 0.7 mol dm<sup>-3</sup> butylamine in pure methanol with *Ih* gave an almost equivalent mixture of methyl *N*-(3-nitrophenyl)carbamate and *N*-butyl-*N'*-(3-nitrophenyl)urea. The same amount of butylamine in pure methanol reacted with *Ih* to yield a mixture with almost the same ratio of products as in the previous experiment. The concentration of methoxide ions in 0.7 mol dm<sup>-3</sup> butylamine in methanol is ca.  $2 \times 10^{-3}$  mol dm<sup>-3</sup> (according to Ref. [13]  $\text{p}K_a$  of protonated butylamine in methanol is 11.7). This experiment supports the mechanism E1cB.

If the methanolysis proceeded by B<sub>Ac</sub>2 the amount of methyl *N*-(3-nitrophenyl)carbamate should be more than two orders of magnitude smaller in this experiment.

*This research work was sponsored by the Grant Agency of the Czech Republic, Grant No. 203/97/0545.*

## REFERENCES

1. Levine, A. W. and Fech, J., Jr., *J. Org. Chem.* 37, 2455 (1972).
2. Hladká, J., Mindl, J., and Večeřa, M., *Collect. Czech. Chem. Commun.* 42, 3316 (1977).
3. Mindl, J., Radonský, F., Klicnar, J., and Večeřa, M., *Collect. Czech. Chem. Commun.* 44, 2401 (1979).
4. Lachman, A., *Org. Synth. Coll. Vol. II*, 70 (1943).
5. Hoeke, F., *Rec. Trav. Chim. Pays-Bas* 54, 505 (1935).
6. Rohr, W., Shirmer, U., and Wuerzer, B. (BASF A.G.), *Ger. Offen.* 2846625 (1980); *Chem. Abstr.* 93, 167983a (1980).
7. Micich, T. J., *J. Am. Oil Chem. Soc.* 59, 448 (1982).
8. Williamson, A. and Douglas, K. T., *Chem. Rev.* 75, 627 (1975).
9. Christenson, I., *Acta Chem. Scand.* 18, 904 (1964).
10. Hegarty, A. F. and Frost, L. N., *J. Chem. Soc., Perkin Trans. 2* 1973, 1719.
11. Kaválek, J., Jirman, J., and Štěřba, V., *Collect. Czech. Chem. Commun.* 52, 120 (1987).
12. Kaválek, J., Said El Bahaie, and Štěřba, V., *Collect. Czech. Chem. Commun.* 49, 2103 (1984).
13. Goodhue, L. D. and Hixon, R. H., *J. Am. Chem. Soc.* 56, 1329 (1934).

Translated by J. Mindl