

Comparison of Carboxamides Reactivity with Respect to Benzoyl Chloride and Diphenyl Chlorophosphate in Acetonitrile

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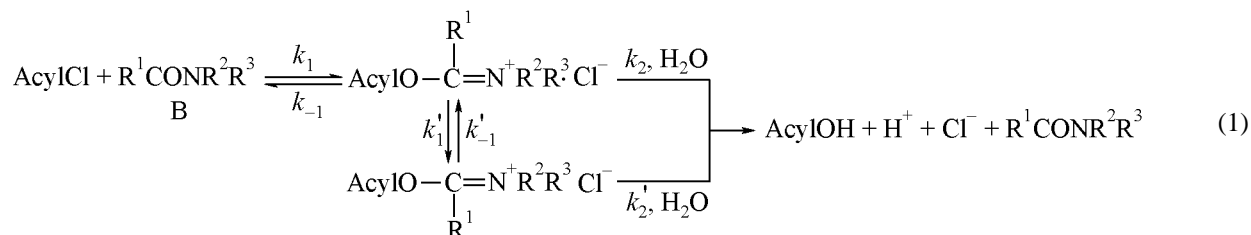
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Abstract—For amides belonging to series RCONH₂ (**I**), RCONHMe (**II**), RCONHPh (**III**), and RCONMe₂ (**IV**) rate constants k_1 (l mol⁻¹ s⁻¹) were determined (in acetonitrile at 25°C) specifying the nucleophilic reactivity of the oxygen atom in amides toward benzoyl chloride and diphenyl chlorophosphate. The lack of substrate selectivity in the reactions in question was established. For equal values of inductive constants σ^* of the R substituents the reactivity sequence of amides with respect to both substrates is the same (**I** >> **IV** > **II**, and **III** > **II**), and it does not follow the corresponding sequence of basicities. A conclusion was drawn that both groups of reactions proceed through cyclic transition states resembling reagents: six-membered with amides **I** and **III**, and five-membered with amides **II** and **IV**.

The quantitative aspect of the nucleophilic reactivity of carboxylic acids amides in aprotic solvents unlike their catalytic activity is poorly investigated. Before our studies [1, 2] virtually nothing related to this problem.

Basing on our kinetic measurements [1, 2] we suggested a nucleophilic mechanism of the catalytic action of carboxamides (B) in the hydrolysis reactions of diphenyl chlorophosphate and benzoyl chloride in acetonitrile.



AcyI = C₆H₅CO, (C₆H₅O)₂PO; R¹, R², R³ = H, Alk, Ar.

Carrying out reaction (1) at special concentrations gave a possibility to determine rate constants k_1 (l mol⁻¹ s⁻¹) specifying the nucleophilic reactivity of the oxygen atom in amides toward the mentioned substrates. From the results of a correlation analysis we presumed that the reaction of amides with the benzoyl chloride proceeded through cyclic transition states: six-membered for NH₂- and NHPH-amides and five-membered for NHMe- and NMe₂-amides [2]. In this connection it is interesting to perform similar studies on reactivity of amides toward electrophilic substrate where in the process of

the nucleophilic substitution the geometry of the transition state is not tetrahedral. As such substrate we chose diphenyl chlorophosphate whose reaction with a number of amides had been previously studied under the same conditions [1] as with benzoyl chloride [2]. Since the amount of kinetic data [1, 2] was insufficient for the proper comparison of amides reactions with benzoyl chloride and diphenyl chlorophosphate we undertook additional investigation of reactivity of some amides with respect to the above substrates. The experiments were performed as before [1, 2] in acetonitrile at 25° at molar concentrations of

Table 1. Second order rate constants k_1 of reaction between carboxamides and benzoyl chloride or diphenyl chlorophosphate [acetonitrile, 25°C, $c(\text{H}_2\text{O})$ 0.4 mol l⁻¹]

Compd. no.	Amide	k_1 , ^a l mol ⁻¹ s ⁻¹	
		C ₆ H ₅ COCl [2]	(C ₆ H ₅ O) ₂ POCl [1]
Ia	2-Methylpropanamide	8.62	7.44 ± 0.35 ^b
Ib	Acetamide	8.12	7.16
Ic	Formamide	0.144	0.0565 ± 0.0032 ^b
Id	Benzamide	2.88	2.52
If	Chloroacetamide	1.85	1.69
Ig	3-Nitrobenzamide	1.16 ± 0.11 ^b	1.14 ± 0.10 ^b
Ih	4-Nitrobenzamide	0.253 ± 0.028 ^b	0.248 ± 0.13 ^b
Ii	3,5-Dinitrobenzamide	0.474	0.593 ± 0.044 ^b
Ij	Trichloroacetamide	0.470	0.391 ± 0.018 ^b
IIa	<i>N</i> -Methyl-2-methylpropanamide	0.210	0.154 ± 0.004 ^b
IIb	<i>N</i> -Methylbenzamide	0.125	0.0756 ± 0.0041 ^b
IIc	<i>N</i> -Methyl-4-chlorobenzamide	0.102	0.0764 ± 0.0044 ^b
IIj	<i>N</i> -Methyltrichloroacetamide	0.0395	0.0291 ± 0.0023 ^b
IIIa	2-Methylpropananilide	1.00	0.910 ± 0.047 ^b
IIIb	Acetanilide	0.604	0.505
IIIc	Benzanilide	0.354	0.275
IIIj	Trichloroacetanilide	0.0518	0.0390 ± 0.0030 ^b
IVa	<i>N,N</i> -Dimethyl-2-methylpropanamide	1.19	0.610
IVb	<i>N,N</i> -Dimethylacetamide	0.881	0.623
IVc	<i>N,N</i> -Dimethylformamide	0.551	0.403
IVd	<i>N,N</i> -Dimethylbenzamide	0.516	0.386
IVh	<i>N,N</i> -Dimethyl-4-nitrobenzamide	0.156 ± 0.016 ^b	0.129
IVi	<i>N,N</i> -Dimethyl-3,5-dinitrobenzamide	0.157 ± 0.011 ^b	0.136 ± 0.016 ^b
IVj	<i>N,N</i> -Dimethyltrichloroacetamide	0.131	0.121 ± 0.013 ^b
V	Acet-3-methylanilide	0.609 ± 0.040 ^b	0.462
VI	γ-Caprolactam	0.130 ± 0.011 ^b	0.0767
VII	<i>N</i> -Methyl-2-pyridone	0.0341 ± 0.0030 ^b	0.00766
VIII	<i>N</i> -Methyl-γ-butyrolactam	0.0975 ± 0.0027 ^b	0.0957

^a Constants k_1 were calculated with accounting for the rate constant of uncatalyzed hydrolysis k_h equal to 3.00×10^{-4} s⁻¹ [3] and 2.16×10^{-5} s⁻¹ [4] for benzoyl chloride and diphenyl chlorophosphate respectively [$c(\text{H}_2\text{O})$ 0.4 mol l⁻¹].

^b Values of k_1 are obtained in this study.

Table 2. Parameters of correlations following Taft equation for reactions of carboxamides with benzoyl chloride and diphenyl chlorophosphate [acetonitrile, 25°C, $c(\text{H}_2\text{O})$ 0.4 mol l⁻¹]^a

Series no.	C ₆ H ₅ COCl					(C ₆ H ₅ O) ₂ POCl				
	log k_1^0	-ρ*	-r	s_0	n	log k_1^0	-ρ	-r	s_0	n
I^b	0.83 ± 0.05	0.52 ± 0.04	0.988	0.086	7	0.77 ± 0.03	0.50 ± 0.02	0.994	0.058	7
II	-0.73 ± 0.01	0.27 ± 0.01	0.999	0.008	4	-0.89 ± 0.03	0.27 ± 0.03	0.991	0.048	4
III	-0.15 ± 0.04	0.46 ± 0.03	0.995	0.066	4	-0.22 ± 0.05	0.48 ± 0.04	0.993	0.085	4
IV^b	-0.045 ± 0.024	0.35 ± 0.02	0.995	0.043	6	-0.24 ± 0.02	0.28 ± 0.02	0.995	0.034	6

^a Constants σ^* for R substituents (for substituted phenyls constants σ^0) are taken from tables [5]. Values σ^* for phenyl substituents are calculated by the formula $\sigma_{\text{XC}_6\text{H}_4}^* = \sigma_{\text{C}_6\text{H}_4}^* + \sigma_{\text{XC}_6\text{H}_4}^0$ [6, p.174].

^b Table values are refined with respect to those previously published [1, 2].

the reagents $c(\text{AcylCl}) \ll c(\text{B}) \ll c(\text{H}_2\text{O})$; $c(\text{AcylCl}) \sim 10^{-6} - 10^{-5} \text{ mol l}^{-1}$, $c(\text{H}_2\text{O}) 0.4 \text{ mol l}^{-1}$. The reaction progress was monitored by conductometric method measuring the accumulation of ionic species in the solution.

The apparent pseudofirst order constants k (c^{-1}) either remain constants or slightly decrease in the course of the process (usually at low amide concentrations). The latter is due to inhibition of reaction (1) with chlorine ions that is observed when the rate of reaction between the intermediate products with water is commensurable with the rate of reverse processes. For each amide concentration were calculated averaged rate constants or extrapolated to the zero time $k_{t=0}$ (c^{-1}), and then by equation (2) the rate constant k_1 was estimated:

$$k_{t=0} = k_h + k_1 [\text{B}], \quad (2)$$

where k_h (c^{-1}) is the rate constant of uncatalyzed hydrolysis of the substrate (see in more detail [1, 2]). The k_1 values measured in this and previous [1, 2] studies are presented in Table 1.

The amides under study (Table 1) belong to the reaction series **I-IV** save some examples.

R-CONH₂ R-CONHMe R-CONHPh R-CONMe₂

Ia-d, f-j **IIa, d, e, j** **IIIa, b, d, j** **IVa-d, h-j**

R (in the order of increasing σ -constants): *i*-Pr (**a**), Me (**b**), H (**c**), Ph (**d**), 4-ClC₆H₄ (**e**), CH₂Cl (**f**), 3-NO₂C₆H₄ (**g**), 4-NO₂C₆H₄ (**h**), 3,5-(NO₂)₂C₆H₃ (**i**), CCl₃ (**j**).

We also studied reactions of 3-methylacetanilide (**V**) and cyclic amides: ϵ -caprolactam (**VI**), *N*-methyl-2-pyridone (**VII**), and *N*-methyl- γ -butyrolactam (**VIII**).

The effect of R substituent on the rate of reactions of amides **I-IV** with benzoyl chloride and diphenyl chlorophosphate fits well to the Taft equation (Table 2).

$$\log k_1 = \log k_1^0 + \rho^* \sigma^* \quad (3)$$

In the series of amides **I** the value $\log k_1$ for formamide (**Ic**) suffers a significant negative deviation from the linear relation (3): $\Delta \log k_1$ is -1.8 and -1.4 in reactions with diphenyl chlorophosphate and benzoyl chloride respectively [the k_1 values for formamide are not included into the correlation according to equation (3)]. Interestingly, in the reaction series containing *N,N*-dimethylamides the points

for amide **Ivc** fit well to the general correlation. The deviation of the formamide point may be caused [2] by hampered conjugation of the lone electron pair of the nitrogen with the π -bond of the carbonyl group due to the nonplanar structure of the CONH₂ bond in this amide.

A notable but not so large deviation from the correlation (3) is observed for amides of series **I** and **IV** with R = 4-NO₂C₆H₄. In reaction with benzoyl chloride $\Delta \log k_1 = -0.67$ for 4-nitrobenzamide (**Ih**) and -0.25 for *N,N*-dimethyl-4-nitrobenzamide (**IVh**); in reaction with diphenyl chlorophosphate these values for the above amides are -0.65 and -0.24 respectively. Therefore these points were not included in correlations (3). Since the values $\log k_1$ for substituents 3-NO₂C₆H₄ and 3,5-(NO₂)₂C₆H₃ fit well to the general correlation with the other substituents it is presumable that the reduced reactivity of 4-nitrobenzamides **Ih** and **IVh** originates from the direct polar conjugation between the amide moiety and the 4-nitro group.

The analysis of parameters of the correlations obtained (Table 2) leads to the following conclusions. Firstly, virtually total coincidence of ρ values is observed for amide reactions with benzoyl chloride and diphenyl chlorophosphate for each of the amide series under study. Secondly, in each amide series the reactivity toward both substrates is similar (no substrate selectivity exists), although with other nucleophiles benzoyl chloride and diphenyl chlorophosphate react with different rates. For instance, the rate ratio of the neutral hydrolysis of these substrates in acetonitrile at $c(\text{H}_2\text{O}) 0.4 \text{ mol l}^{-1}$ is equal to ~ 14 [3, 4]. With pyridine and pyridine *N*-oxide in acetonitrile the benzoyl chloride [3] reacts respectively 11 and 170 times faster than diphenyl chlorophosphate [7]. Thirdly, at equal values of inductive constants σ^* of R substituents (in the range of σ^* values from -1 to 3) the same reactivity series are observed both in reactions with diphenyl chlorophosphate and benzoyl chloride [2]: **I** \gg **IV** $>$ **II** and **III** $>$ **II**.

A logical consequence of the found rules is the linear dependence between the values $\log k_1$ for amides reactions with benzoyl chloride ($\log k_1^{\text{BCl}}$) and diphenyl chlorophosphate ($\log k_1^{\text{DPCIP}}$):

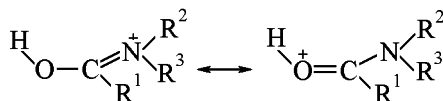
$$\log k_1^{\text{BCl}} = (0.06 \pm 0.03) + (0.89 \pm 0.03) \log k_1^{\text{DPCIP}} \quad (4)$$

$$r 0.982, s_0 0.12, n 28$$

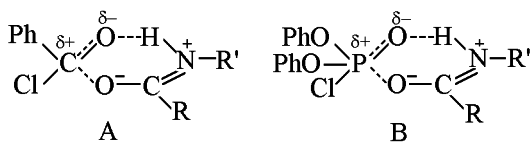
It is interesting that correlation (4) includes also those amides which failed to fit Taft equations

(amides **Ic**, **Ih**, **IVh**), and also amides **V–VIII** not belonging to series **I–IV**.

The slope of the straight line (4) is close to unity that may be considered as indication of similar effect of amide structure in the reactions with benzoyl chloride and diphenyl chlorophosphate, and thus the structure of the transition states in these processes should be alike. The lack of substrate selectivity allows an assumption of similarity of these transition states to the reagents, and small absolute values of ρ^* indicate the low polar (cyclic) character of the transition states. It is also significant that the above stated reactivity series do not coincide with the corresponding basicity series in water: **I** \leq **II** $<$ **IV** and **III** $<$ **II** (data from [8]). The latter fact apparently originates from additional interactions between the nucleophile and electrophile in the transition states of the reactions in question (see below structures A, C, D, E) as compared to the protonated amide form.

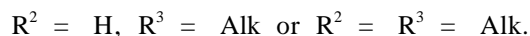
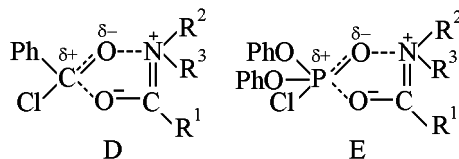


The close values of ρ^* for the reaction series with amides **I** and **III**, and amides **II** and **IV** involving both substrates (Table 2) allow an assumption that these reactions proceed through transition states of one type structure for the above amide pairs. In the case of *N*-unsubstituted amides **I** and anilides **III** these are presumably six-membered cyclic transition states A (for reaction with benzoyl chloride) and C (for reaction with diphenyl chlorophosphate); the cycle is closed by a fragment including a hydrogen bond (see also [2]).



With *N*-methanilides **II** which cannot form cycles of the above type [1, 2], and with *N,N*-dimethylamides **IV** where such cycles are impossible the corresponding transition states D and E are apparently five-membered cycles. The cycle closure is accomplished here by charge interaction between

partially charged atoms of nitrogen in amino group and oxygen in the acyl.



The reagent-like structure in the above shown transition states consists in the fact that the bond with the leaving group (C–Cl or P–Cl bond) is practically unaffected in the transition state. Otherwise due to the different geometry of the transition state at substitution by the electrophilic C=O center (tetrahedral transition state structure) and by P=O center (bipyramidal structure) the complete analogy of the amide structure effects on their reactivity toward the substrates studied hardly could be expected.

EXPERIMENTAL

The method of conductometric measurements and procedures for purification of acetonitrile, diphenyl chlorophosphate, benzoyl chloride, and all amides but two, also the isolation of hydrolysis products were previously described [1, 2]. 4-Nitrobenzamide and *N,N*-dimethyl-3,5-dinitrobenzamide were recrystallized from ethanol.

REFERENCES

1. Popov, A.F., Sadovskii, Yu.S., Solomoichenko, T.N., Savelova, V.A., Lobanova, O.V., and Piskunova, Zh.P., *Zh. Org. Khim.*, 2000, vol. 36, no. 5, pp. 742–751.
2. Popov, A.F., Savelova, V.A., Sadovskii, Yu.S., Solomoichenko, T.N., Piskunova, Zh.P., and Lobanova, O.V., *Zh. Org. Khim.*, 2001, vol. 37, no. 8, pp. 1176–1182.
3. Savelova, V.A., Popov, A.F., Solomoichenko, T.N., Sadovskii, Yu.S., Piskunova, Zh.P., and Lobanova, O.V., *Zh. Org. Khim.*, 2000, vol. 36, no. 10, pp. 1502–1510.
4. Solomoichenko, T.N., Savelova, V.A., Ved' T.V., and Yakovets, A.A., *Reakts. Sposobn. Org. Soed.*, 1988, vol. 25, no. 2(90), pp. 224–234.
5. *Tablitsy konstant skorosti i ravnovesiya geteroliticheskikh organicheskikh reaktsii* (Tables of Rate Constants and Equilibria of Heterolytic Organic Reactions)

- stants and Equilibrium Constants of Weak Organic Bases), Pal'm, V.A., Moscow: VINITI, 1979, vol. 5, 283 p.
6. Pal'm, V.A., *Osnovy kolichestvennoi teorii organicheskikh reaktsii* (Principles of Quantitative Theory of Organic Reactions), Leningrad: Khimiya, 1977.
 7. Savelova, V.A., Solomoichenko, T.N., Ved', T.V., Sadovskii, Yu.S. and Simanenko, Yu.S., *Zh. Org. Khim.*, 1993, vol. 29, no. 4, pp. 666–677.
 8. *Comprehensive Organic Chemistry*, Barton, D., and Ollis, U., Ed., Moscow: Khimiya, 1983, vol. 4, pp. 388–536; Ostrovskii, V.A. and Koldobskii, G.I., *Slabye organicheskie osnovaniya* (Weak Organic Bases), Leningrad: Izd. Leningrad. Univ., 1990.