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Effect of the Composition of the Aqueous Organic Solvent on the Kinetics of N-Acylation of α-Amino Acids with 4-Nitrophenyl 4-Nitrobenzoate

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Abstract—Equations relating the *N*-acylation rate constants of glycine, L-α-alanine, DL-threonine, and L-proline with 4-nitrophenyl 4-nitrobenzoate in water–acetonitrile, water–2-propanol, and water–2-methyl-2-propanol solvents to the composition of the medium were obtained, and reaction rate constants in water were calculated.

It is known that the composition of the binary solvent strongly affects both thermodynamic and kinetic parameters of reactions in solutions. The effect of the composition of the aqueous organic solvent on the reactivity [1–4] and dissociation [5–9] of α-amino acids has been studied. The use of aqueous organic solvents allows N-acylation of α-amino acids to occur in homogeneous conditions and makes possible a kinetic study of this reaction. Kinetics of N-acylation of α-amino acids are difficult to study in organic solvents because of the poor solubility of these compounds.

The present work deals with the kinetics of N-acylation of glycine (Gly), L-α-alanine (Ala), L-serine (Ser), DL-threonine (Thr), and L-proline (Pro) with 4-nitrophenyl 4-nitrobenzoate (**I**) in aqueous organic solvents, such as water–acetonitrile (**A**), water–2-propanol (**B**), and water–2-methyl-2-propanol (**C**), in medium composition ranges.

It is known that capable of N-acylation are the anionic and neutral forms of α-amino acids [6] (the rate of N-acylation of the neutral form is low, and this reaction pathway can be neglected). The N-acylation of α-amino acids occurs by scheme (1).

$$\mathrm{NH_2CHRCOO^-} + \mathbf{I} \xrightarrow{\mathrm{HO^-}} \mathrm{ArCONHCHCOO^-} + \mathrm{AtO^-}. \quad (1)$$

Here $NH_2CHRCOO^-$ is the anionic form of an α-amino acid; R, radical at the α-carbon atom; and Ar = $4\text{-}NO_2C_6H_4$.

The kinetics of a first-order reaction (1) were followed by spectrophotometry. The rate constants (*k*) calculated as described in [4] are listed in Table 1. The error in the rate constants was no higher than 1–2% (confidence level 0.95).

As seen from Table 1, the reactivity of the α-amino acids decreases in the order Pro >> Gly > Ala >> Ser > Thr. The N-acylation rate constant of Pro is much higher than of the other α-amino acids. The highest reactivity of Pro owes to the fact that it is the strongest base among the α-amino acids studied [7].

The rate constants increase with increasing water

Table 1. Rate constants $k \times 10^2$ ($\mathrm{l\,mol^{-1}\,s^{-1}}$) of N-acylation of α-amino acids in systems **A**–**C** at 298 K

Amino acid	Water content, wt%				
	40	50	60	70	80
			A		
Gly	18.9	21.6	26.5	34.0	41.6
Ala	5.12	6.11	8.02	12.8	16.0
Ser	0.401	0.897	1.36	2.26	3.84
Pro	112	124	147	203	438
			B		
Gly	60.2	62.9	69.5	77.3	94.2
Ala	14.5	16.1	18.2	19.8	26.9
Ser	3.38	3.50	3.75	4.09	4.58
Thr	1.89	2.02	2.44	3.54	–
Pro	473	505	521	600	694
			C		
Gly	57.5	61.0	63.3	67.4	79.5
Ala	13.2	13.5	14.2	18.1	23.5
Ser	2.47	2.67	3.05	3.53	5.12
Thr	1.55	1.71	1.79	2.03	–
Pro	467	494	569	608	658

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Table 2. Equations of the rate constants of N-acylation of α-amino acids with ester **I** in systems **A**–**C** (*r* is the correlation coefficient)

Amino acid	Equation	*r*
	A	
Gly	$k = (0.763\pm0.032)X_2 + (1.51\pm0.29)X_1X_2 + (-4.35\pm0.56)X_1X_2^2$	0.985
Ala	$k = (0.297\pm0.051)X_2 + (0.441\pm0.051)X_1X_2 + (-1.48\pm0.09)X_1X_2^2$	0.998
Ser	$k = (6.69\pm0.41)\times10^{-2}X_2 + (0.084\pm0.009)X_1X_2 + (-0.384\pm0.072)X_1X_2^2$	0.989
Pro	$k = (8.06\pm0.81)X_2 + (27.7\pm7.5)X_1X_2 + (-70.8\pm11.5)X_1X_2^2$	0.989
	B	
Gly	$k = (10.14\pm0.31)X_2 + (4.75\pm0.63)X_1X_2 + (-8.40\pm1.00)X_1X_2^2$	0.983
Ala	$k = (0.352\pm0.021)X_2 + (1.39\pm0.42)X_1X_2 + (-2.65\pm0.67)X_1X_2^2$	0.971
Ser	$k = (5.53\pm0.06)\times10^{-2}X_2 + (0.182\pm0.010)X_1X_2 + (-0.293\pm0.017)X_1X_2^2$	0.999
Thr	$k = (3.57\pm0.08)\times10^{-2}X_2 + (0.21\pm0.08)X_1X_2 + -?0.42\pm0.11)X_1X_2^2$	0.997
Pro	$k = (8.75\pm0.28)X_2 + (33.4\pm5.5)X_1X_2 + (-56.5\pm7.9)X_1X_2^2$	0.992
	C	
Gly	$k = (0.991\pm0.09)X_2 + (4.79\pm0.71)X_1X_2 + (-7.94\pm0.99)X_1X_2^2$	0.988
Ala	$k = (0.309\pm0.009)X_2 + (2.45\pm0.29)X_1X_2 + (-3.97\pm0.42)X_1X_2^2$	0.994
Ser	$k = (6.69\pm0.27)\times10^{-2}X_2 + (0.507\pm0.085)X_1X_2 + (-0.85\pm0.12)X_1X_2^2$	0.992
Thr	$k = (2.92\pm0.16)\times10^{-2}X_2 + (0.188\pm0.051)X_1X_2 + (-0.289\pm0.071)X_1X_2^2$	0.981
Pro	$k = (7.81\pm0.16)X_2 + (30.8\pm2.7)X_1X_2 + (-49.1\pm3.9)X_1X_2^2$	0.999

content of the organic solvent. At the same water content, the rate constants in systems **B** and **C** are higher than in system **A**. The same effect of the composition of the aqueous organic solvent has been observed earlier [10] in acylation of 4-nitroaniline with benzoyl chloride.

Varied composition of the binary solvent varies the polarity of the medium, thus affecting the rate of reactions in this medium.

Figure 1 shows the plots of N-acylation rate constants vs. Kirkwood function for Gly and Ala. Similar dependences are observed for the other α-amino acids studied. The fact that log *k* is nonlinear in (ε – 1)/(2ε + 1) (ε is the dielectric constant of the solvent) points to a strong effect specific solvation of the reagents and transitions state exerts on the reaction rate constant. However, we failed to analyze the effect of other solvent properties, such as polarizability and donor and acceptor power (Koppel'–Pal'm equation parameters), since quantitative characteristics of these properties are known only for one-component solvents [12].

The components of the binary solvents interact both with each other and with both reagents, which results in an intricate dependence of the reaction rate constant on the mole fraction of water in the system (Fig. 2).

The effect of the composition of the aqueous organic solvent on the acylation rate constants of α-amino acids can be described by Eq. (2) [13], which

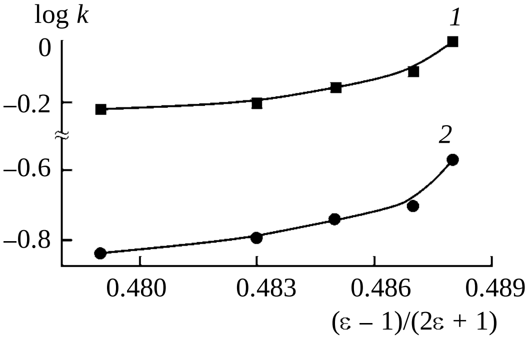

Fig. 1. Plot of log *k* vs. Kirkwood function for acylation of Gly and Ala in system **B** at 298 K. (*1*) Gly and (*2*) Ala.

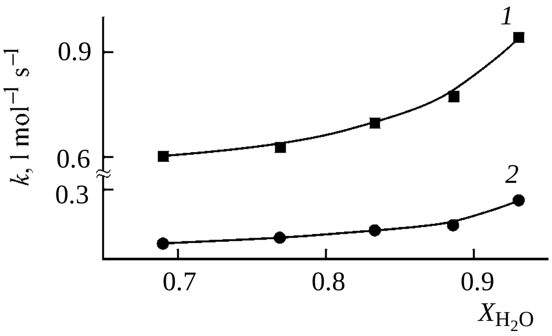

Fig. 2. Plot of *k* vs. mole fraction of water for acylation of Gly and Ala in system **B** at 298 K. (*1*) Gly and (*2*) Ala.

takes account of specific solvation of the reagents by the components of the medium.

$$k = k_1X_1 + k_2X_2 + k_{12}X_1X_2 + k'_{12}X_2^2. \qquad (2)$$

Here k_1 and k_2 are the reaction rate constants in a pure organic solvent and in water; k_{12} and k'_{12}, constants relating to specific interaction between the components of the solvent and the reagents [13] and accounting for deviations from additivity; and X_1 and X_2, mole fractions of the organic components and water, respectively.

In our case, like in [14], the reaction rates in pure solvents are very low and can be neglected. The k_2, k_{12}, and k'_{12} values in Eq. (2) were calculated by the multiple regression technique [15] at a confidence level of 0.95. Table 2 shows the rate-constant equations for the systems studied.

These equations make possible estimation of the reaction rate constant in water k_2 (coefficient of X_2) which is quite difficult to determine experimentally. The estimates for k_2 for the same α-amino acids in the three binary solvents studied are close to each other, providing evidence for the validity of these estimates. The mean k_2 values ($\mathrm{l\,mol^{-1}\,s^{-1}}$) for Gly, Ala, Ser, Pro, and Thr are 0.97 ± 0.14, 0.32 ± 0.03, $(6.31 \pm 0.3) \times 10^{-2}$, 8.2 ± 0.4, and $(3.3 \pm 0.1) \times 10^{-2}$, respectively.

EXPERIMENTAL

The rates of N-acylation of Gly, Ala, Ser, Thr, and Pro (analytical grade all) were measured by following the concentration of the 4-nitrophenolate ion by spectrophotometry (λ 400 mn) using a KFK-2UKhL 4.2 photoelectrocolorimeter with a temperature-controlled cell holder and an Shch-300 digital voltmeter. Acetonitrile (analytical grade) was distilled over phosphorus pentoxide. 2-Propanol (chemical grade) was distilled on a column. 2-Methyl-2-propanol (chemical grade) was purified by the procedure in [16]. Reaction mixtures were prepared using a concentrated solution of NaOH (analytical grade), the concentrations of α-amino acids were 0.05–0.08 M at 1 : 5 and 1 : 10 ratios of the anionic and zwitter ionic forms, depending on the composition of the binary solvent [4].

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