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Reactivity of α-Amino Acids in the N-Acylation with Benzoic Acid Esters in Aqueous Dioxane

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Abstract—The effect of the nitro group as a substituent in the phenoxide part of phenyl benzoate on the rate of N-acylation of glycine, L-proline,and L-valine in the water (40 wt %)–dioxane solvent was studied. The activation parameters of glycine reactions with the esters were measured. The existence of compensation effect and the linear relation of the logarithms of the acylation constants to the Hammett constants were revealed. The energy of the LUMO of esters can serve as the descriptors of the easters reactivity.

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Study of kinetic relations in the reactions of acylation of α-amino acids leading to the formation of amide (peptide) bonds is important for understanding the mechanism of peptide formation. The acyl derivatives of amino acids having physiological and surface activity and low toxicity are widely used in pharmaceuticals, perfumes, cosmetics, as biodegradable surfactants, corrosion inhibitors, flotation reagents, etc.

Along with anhydrides and acid halides, as the acylating agents in the synthesis of the amino acids acyl derivatives activated esters of carboxylic acids are used, and as the medium water and organic solvents are used. Development of industrial methods for producing acylamino acids requires development of continuous processes, which require the data on the reactivity of amino acids in the reactions of acyl transfer. There is only a limited number of publications concerning this problem [1].

In some works the kinetics of aminolysis of esters in nonaqueous media was studied, the influence of the structure of acyl radical R in the acyl part of RCOX on the reaction of the carboxylic acids phenyl esters with various amines in dioxane [2–5]. Investigations were carried out on the kinetics of N-acylation of α-amino acids with benzoyl chloride in water–dioxane solvent [6, 7]. Reactions of α-amino acids with the carboxylic acids esters were studied in the solvents water–2-propanol, water–2-methyl-2-propanol, and water–acetonitrile [8–10]. A strong influence of solvent and structure of the ester on the reaction rate was shown.

This paper presents the results of kinetic studies of reactions of glycine (Gly), L-valine (L-Val), and L-proline (L-Pro) with 4-nitrophenyl (**I**), 2,4 -, 2,5 -, and 2,6-dinitrophenyl (**II–IV**) and 2,4,6-trinitrophenyl (**V**) benzoates in the water (40 wt %)–1,4-dioxane solvent.

It was previously found that at the acylation in aqueous-organic medium, the main reaction form of α-amino acids is the anion [6–10]. The reaction of the α-amino acid anions with the acylation agents is shown by the example of glycine.

$$NH_2CH_2COO^- + \mathbf{I–V} \xrightarrow{OH^-} C_6H_5CONHCH_2COO^- + RO^-. \quad (1)$$

Here R are the substituents in compounds **I–V**.

It is known from [8–10] that when the ratio of concentrations of anionic (C_a) and zwitter-ionic (C_{zw}) forms of α-amino acid is in the range from 1:4 to 1:10 the rate of hydrolysis of esters **I–V** can be neglected. The necessary concentration of the amino acid anions ($\sim 10^{-2}$ mol l^{-1}) was created by adding a solution of a certain amount of alkali. The reaction was performed under first order conditions with a 100-fold excess in concentration of amino acid compared to the ester. The

Table 1. The values of k_a for the reactions of amino acids with benzoic acid esters in water (40 wt %)–1,4-dioxane, C_a: C_{zw} = 1:4

Comp. no.	k_a, l mol^{-1} s^{-1}				
	Gly			L-Val	L-Pro
	298 K	308 K	303 K	298 K	298 K
I	0.095±0.001	0.140±0.001	0.188±0.003	0.011±0.001	1.11±0.01
II	2.12±0.04	2.66±0.03	3.32±0.06	0.54±0.01	11.1±0.1
III	0.420±0.003	0.559±0.001	0.739±0.003	0.090±0.001	7.9±0.1
IV	0.296±0.002	0.379±0.004	0.522±0.003	0.057±0.007	2.97±0.07
V	11.2±0.2	13.3±0.3	14.9±0.5	5.2±0.1	36.5±0.5
VI[a]	1.4×10^{-3}	–	–	9.6×10^{-5}	5.6×10^{-2}
VII[a]	0.015			0.0018	0.320

[a] k_a was calculated by Eqs. (3)–(5).

second order rate constants k_a was calculated by Eq. (2).

$$k_a = k_{obs}/C_a. \quad (2)$$

Here k_{obs} is the observed first order rate constant.

Table 1 shows the values of the rate constant k_a for the reactions of amino acids with the esters **I–V** in the water–dioxane solvent. It is seen from these data that reactivity of α-amino acids increases in the sequence: L-valine, glycine, L-proline. A similar trend, that is due to structural features and differences of in the basicity of α-amino acids, is observed in other reaction series, in particular, in the reactions of α-amino acids with benzoyl chloride [7], arenesulfonyl chlorides [11], and with esters in aqueous isopropanol [10].

For all studied amino acids the values of k_a in the reactions with esters increase in the order: **I > IV > III > II > V**. This sequence is defined by the electron-acceptor influence of the nitro group, which is more pronounced in the positions *2* and *4* of phenoxide ring and weaker in the position *3*. At the use of the most reactive ester **V** instead of the less reactive **I** the acylation rate of L-proline in aqueous dioxane increases 33 times, of glycine, 118 times, and of L-valine, 720 times.

Between the logarithms of the acylation constants and the constants σ^- of substituents in the phenoxide radical [12] a linear relationship exists represented by Eqs. (3)–(5).

$$\log (k_a^{gly}) = -(2.9 \pm 0.2) + (1.5 \pm 0.1)\sigma^-, r = 0.994, \quad (3)$$

$$\log (k_a^{pro}) = -(1.3 \pm 0.2) + (1.07 \pm 0.08)\sigma^-, r = 0.995, \quad (4)$$

$$\log (k_a^{val}) = -(4.3 \pm 0.2) + (1.9 \pm 0.1)\sigma^-, r = 0.997. \quad (5)$$

These relationships are not found for ester **III**: its reactivity is higher than predicted by the Eqs. (3)–(5). A similar phenomenon was observed for the reaction with amino acid of esters in aqueous isopropanol [10]. Perhaps the increase in the rate constants of reactions of amino acids with ester **III** is associated with features of its solvation in aqueous-organic medium.

The rate constant of acylation of glycine, L-proline and L-valine by unsubstituted phenyl benzoate **VI** in aqueous dioxane determined from Eqs. (3)–(5) are given in Table. 1. These values are significantly less than the rate constants of reactions of the same amino acids with the nitro-substituted esters **I–V**. Equations (3)–(5) were used to predict the values of k_a in the reactions of glycine, L-proline and L-valine with 3-nitrophenyl benzoate **VII** (Table 1). Kinetics of the reactions of amino acids with **VII** in aqueous dioxane has not been experimentally studied owing to low solubility of the products.

From the temperature dependence of k_a of glycine were calculated the values of the activation energy, enthalpy, entropy and of pre-exponential factor *B* in the Arrhenius equation, listed in Table 2. These data show that the introduction to a molecule of ester of an electron-acceptor substituent reduces activation energy and enthalpy of acylation. The observed decrease in the activation entropy is due to the fact that the structure of the activated complex becomes more ordered.

In the reactions of glycine with esters in aqueous dioxane an isokinetic relationship was observed [Eq. (6)].

$$\Delta H^{\neq} = (97540\pm1930)-(489\pm15)\Delta S^{\neq}, r\ 0.999. \quad (6)$$

Table 2. Activation parameters of reactions of esters **I–V** with glycine in the solvent water (40 wt %)–dioxane, and LUMO energies of esters

Comp. no.	E, kJ mol^{-1}	$\Delta H^{\neq}$, kJ mol^{-1}	$-\Delta S^{\neq}$, J mol^{-1} K^{-1}	log B	E_{LUMO}, eV
I	52.1±3.2	49.6±3.2	98±9	8.1±0.6	1.555
II	33.7±0.5	31.2±0.5	134±2	6.3±0.1	0.843
III	43.1±0.4	40.6±0.4	116±2	7.2±0.1	0.406
IV	43.3±3.7	40.8±3.7	118±9	7.0±0.7	0.998
V	21.8±2.2	19.5±2.2	160±7	4.9±0.4	0.311

The isokinetic temperature of the reaction series is 489 K, which is considerably higher than the solvent boiling point. Experimental study of the reaction kinetics at that temperature is not possible.

The existence of dependences (3)–(6), as well as similarity in the values of activation energy and entropy in the reactions of glycine with various esters indicate that the introduction of one or more nitro groups as substituents in the phenoxide radical of the ester affects the rate of acylation, without changing the reaction mechanism.

In order to identify descriptors of reactivity of esters **I–V,** we carried out quantum-chemical calculations of their geometric, electronic and energy characteristics. The calculations were made using program package HyperChem® 7.52 by RHF/6-31G* method with full geometry optimization of the tested molecules and monitoring the type of stationary points on the potential energy surface (PES). Reaching the global minimum on the PES was confirmed by the absence in the vibrational spectrum of the bands with imaginary frequency. Calculated LUMO energies of molecules of esters **I–V** (E_{LUMO}) are presented in Table 2.

Previously we have suggested [13] that the reaction of α-amino acids with the esters are orbital-controlled, and in the interaction are involved the HOMO of the amino acids and the LUMO of the esters. The comparison of the results of quantum-chemical calculations with the reactivity of the esters **I-V** showed that at a decrease in their E_{LUMO} the acylation constant k_a increases, and the activation energy decreases, therewith between these parameters there are linear relations.

$$E = (1.49\pm0.36)\times10^4 + (2.47\pm0.35)\times10^4 E_{LUMO}, \quad r = 0.98, \quad (7)$$

$$\log (k_a^{gly}) = (1.77\pm0.36) - (2.20\pm0.31)E_{LUMO}, \quad r = 0.97. \quad (8)$$

These results are consistent with the hypothesis about the relationship of reactivity of the participants of acylation with orbital characteristics of their molecules. Thus, the E_{LUMO} value of the benzoic acid esters can serve as descriptors of the reactivity in the studied reaction series.

EXPERIMENTAL

The kinetics of the reactions of Gly, L-Val, L-Pro (all analytical grade) with the esters **I–V** was studied by spectrophotometric measuring the change in the concentrations of nitrophenol ions liberated in the reaction at an operating wavelength 400 nm. For the optical density measurement was used a photo-electrocolorimeter KFK-2UKhL 4.2 with tempera-ture-controlled cell holder and digital voltmeter Shch-300.

1,4-Dioxane of analytical grade was dried for 2 weeks over KOH and distilled with a column from the metallic sodium. To prepare the reaction mixtures a saturated solution of NaOH was used (reagent grade) and distilled water. Esters **I-V** were synthesized by acylation of respective nitrophenols with benzoyl chloride, and were identified by measuring their melting points [14]. The observed constants of the reaction rate k_{obs} were calculated using the Guggenheim equation [15]. Errors in the k_{obs} were determined with a confidence level 0.95, the random error does not exceed 2%. All physicochemical constants of the reactants and solvents used in the study were consistent with the published data [12, 14].

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