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Reactivity of α-Amino Acids at Their Arenesulfonation in the Water–1,4-Dioxane and Water–2-Propanol Systems

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Abstract—The kinetics of arenesulfonation of D,L-threonine, D,L-leucine and L-isoleucine with 3-nitrobenzenesulfonyl chloride in the water–1,4-dioxane and water–2-propanol solvents in the temperature range 298–313 K was studied. Calculations of effective values of activation parameters of reactions were carried out. Kinetic parameters of the studied processes were compared with the results of previous studies of the reaction of acyl transfer involving α-amino acids.

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An important aspect in the study of the reactivity of α-amino acids in acyl transfer reactions, in particular, in arenesulfonation, is revealing the influence of water and organic solvents on the rate of these processes. The water–organic systems we have chosen for the study belong to the well-studied binary mixtures, which by some physicochemical properties (polarity, dielectric constant, etc.) are closer to biological fluids than water and therefore the processes of formation of sulfonylamide structure in aqueous 1,4-dioxane and aqueous 2-propanol can be regarded as models of biological objects.

At present, the interest in sulfonyl-substituted nitrogen-containing systems markedly increased, and tens of thousands of sulfonyl derivatives of amines and amino acids were synthesized. Biological screening of some of the synthesized compounds demonstrated their high effectiveness as enzyme inhibitors [1]. In this connection the studies of kinetic regularities of the arenesulfonation of α-amino acids are obviously topical. The knowledge of such regularities would allow the performance of the respective reactions under optimal conditions (temperature, solvent) even at the step of creation of combinatorial libraries of sulfonylamides and thereby to reduce significantly financial and time expenditure.

Earlier [2–4] we studied the reactivity of glycine (Gly), D,L-α-alanine (D,L-α-Ala), and D,L-valine (D,L-Val) in the arenesulfonation with 3-nitrobenzenesulfonyl chloride in water–1,4-dioxane and water–2-propanol systems, and calculated activation parameters of these reactions. In order to replenish the bank of the kinetic data on the reaction of α-amino acids with aromatic sulfonic acid chlorides and in continuation of the earlier studies, we examined kinetics of the reactions of D,L-threonine (D,L-Thr), D, L-leucine (D,L-Leu), and L-isoleucine (L-Ile) with 3-nitrobenzenesulfonyl chloride in two aqueous-organic systems: water–1,4-dioxane and water–2-propanol in polythermal conditions.

In water and aqueous-organic solvents the amino acids are in nonionized or variously ionized forms (cationic, anionic and zwitterionic) depending on the medium pH [5]. As stated earlier [4,5], in our experimental conditions at pH 6–8 in the course of arenesulfonation predominates interaction of anionic forms of amino acids with the acylating agent. At lower pH the proportion of active forms of amino acid in the reaction system is too low and at pH > 8 a prominent role plays the side process of 3-nitrobenzenesulfonyl chloride hydrolysis.

The results of the performed kinetic studies are summarized in Tables 1 and 2. The data in Tables 1 and 2 show that the rate constants of the reactions of α-amino acids with 3-nitrobenzenesulfonyl chloride in aqueous dioxane are higher than in aqueous 2-propanol (1.5–15 times) throughout the temperature range. There is a general trend of growth in the absolute value of the activation entropy in the reactions involving amino acid with the branched structure (Val, Leu, Ile

Table 1. Kinetic parameters of the reactions of α-amino acids with 3-nitrobenzenesulfonyl chloride in aqueous dioxane [ω(H_2O) = 40 wt %]

T, K	pK_{II} [a]	$k_{-}\times10^{-3}$, l mol^{-1} s^{-1} [b]	$C_{H^+}\times10^8$, mol l^{-1} [c]	$\Delta H^{\neq}_{298}$, kJ mol^{-1}	$-\Delta S^{\neq}_{298}$, J mol^{-1} K^{-1}
			Glycine [3]		
298	10.81	3.35	35	21±4	107±16
			D,L-α-Alanine [4		
298	11.13	1.16	23.9	38±3	54±11
			D,L-Valine [4]		
298	10.83	2.98	14.6	20±3	112±11
			D,L-Leucine		
298	10.71	1.43	1.41	16±2	131±8
303	10.61	1.60	1.34		
308	10.51	1.71	1.31		
313	10.41	2.05	1.31		
			L-Isoleucine		
298	10.80	1.89	1.42	6±1	162±4
303	10.70	2.00	1.40		
308	10.60	2.11	1.31		
313	10.50	2.22	1.33		
			D,L-Threonine		
298	10.41	0.38	1.41	6±1	174±4
303	10.31	0.40	1.34		
308	10.21	0.41	1.31		
313	10.11	0.45	1.31		

[a] The thermodynamic dissociation constants of α-amino acids determined by potentiometric titration with alkali in circuits without transfer [6]. [b] The value of k was found from the slope of the linear plot (which included 10–15 experimental points) of the observed reaction rate constant vs. the current concentration of amino acids [2], the error in determining k on the average is less than 5%. [c] In the course of kinetic experiments the pH value of working solutions was strictly controlled, for each of the solvent verification of the H-function of the ion meter glass electrode was carried out by graduation with perchloric acid.

and Thr) which obviously creates a steric hindrance at the reaction center of the molecule (NH_2 group) to attack of the electrophile 3-nitrobenzenesulfonyl chloride on the nucleophilic center.

Activation energy of all the studied reactions in the case of aqueous 2-propanol is significantly higher than in aqueous dioxane. The absolute value of $\Delta S^{\neq}_{298}$ decreased almost twofold in going from the water–1,4-dioxane to water–2-propanol system (with the exception of D,L-leucine, for which these values are comparable within the errors of their determination). This observation gives grounds to assume that the mutual orientation of the reactants before the formation of the activated complex plays a lesser role in aqueous 2-propanol compared with aqueous dioxane. This, in turn, is due to the different nature of the specific solvation of amino acids and sulfonyl chloride. A similar situation was observed earlier [4] for the reactions of D,L-α-alanine and D,L-valine with 3-nitrobenzenesulfonyl chloride in the same binary systems.

For all the studied processes a compensation effect is observed, that is, a decrease in the activation entropy at the increase in the activation enthalpy of the reactions. Isokinetic temperature for the reaction series, including glycine, D,L-α-alanine, D,L-valine, D,L-threonine, D,L-leucine and L-isoleucine in aqueous dioxane is in the range (273±16) K, in aqueous 2-propanol (274±11) K. It can be assumed that the reaction of 3-nitrobenzenesulfonyl chloride with these α-amino acids in the selected aqueous-organic systems proceeds through a common mechanism.

To study the effect of the solvent water–2-propanol composition on the rate of arenesulfonation we investigated the reaction kinetics of D,L-leucine with 3-nitrobenzenesulfonyl chloride in aqueous 2-propanol at different content of water (Table 3).

Table 2. Kinetic parameters of reactions of α-amino acids with 3-nitrobenzenesulfonyl chloride in aqueous 2-propanol [ω(H_2O) = 40 wt %]

T, K	pK_{II}[a]	$k_-\times10^{-3}$, l mol^{-1} s^{-1}	$C_{H^+}\times10^7$, mol l^{-1}	$\Delta H^{\neq}_{298}$, kJ mol^{-1}	$-\Delta S^{\neq}_{298}$, J mol^{-1} K^{-1}
			Glycine [2]		
298	10.01	0.800	22.9	–	–
			D,L-α-Ala [4]		
298	11.00	1.010	2.08	45±3	27±11
			D,L-Val [4]		
298	9.99	1.660	1.99	34±3	64±11
			D,L-Leu		
298	10.03	0.081	1.05	28±3	114±11
303	9.93	0.101	1.61		
308	9.83	0.126	1.86		
313	9.73	0.145	0.87		
			L-Ile		
298	10.00	0.163	1.05	48±5	40±20
303	9.90	0.234	1.70		
308	9.80	0.335	2.09		
313	9.70	0.446	0.89		
			D,L-Thr		
298	9.92	0.107	0.91	45±4	54±16
303	9.82	0.137	1.61		
308	9.72	0.196	1.70		
313	9.62	0.291	2.10		

[a] The thermodynamic dissociation constants of α-amino acids determined by potentiometric titration with alkali in circuits without transfer [7].

From the data of Table 3 follows that at the increase of the fraction of water in the system, the rate constant increases more than 40 times in going from 40 to 70% content of water in the solution.

The explanation of the medium effect on the rate of arenesulfonation of α-amino acids can be given by the consideration of specific solvation of the reactants and the activated complex with the solvent molecules. Earlier [5] it was shown that solvation of the amine decisively influences the rate of reaction of nucleophilic substitution at the sulfonyl center with amines, whereas the solvation of sulfonyl chloride plays a minor role. The kinetic regularities we obtained can be explained by the ability of amino acids to form solvatocomplexes with the molecules of water, cyclic ether and alcohol, as well as to form mixed complexes.

Table 3. Kinetic parameters of reaction of D,L-leucine with 3-nitrobenzenesulfonyl chloride in water–2-propanol solvent, 298 K

ω(H_2O), wt %	$C_{H^+}\times10^7$, mol l^{-1}	pK_{II}	$k_-\times10^{-3}$, l mol^{-1} s^{-1}
40.01	1.05	10.03	0.08
49.95	14.00	10.25	0.69
60.05	13.20	9.93	2.37
70.00	19.97	9.85	3.62

We carried out [8, 9] computer simulations of these complexes which showed that the more reactive are those where the amino group acts as H-donor resulting in the weakening of N–H bond in the transition state and facilitating its cleavage in the course of the reaction. The solvated complexes formed by donor-acceptor interaction between the electron lone pair at the nitrogen atom of the amino group and hydrogen atoms of the components of the solvent (NH_2 group acts as H-acceptor), are less reactive at the arene-sulfonation because the participation of the lone electron pair of nitrogen atom in the complex substantially reduces its nucleophilic properties.

Thus, the study of the reaction kinetics of α-amino acids with 3-nitrobenzenesulfonyl chloride showed that the highest reactivity in the studied water-organic solvents demonstrate Gly and D,L-Val, which in this

series are the most basic amino acids. Previously, similar trends were observed for N-acylation of α-amino acid esters [5] in aqueous-organic media that was explained by the features of solvation of reactants and activated complex in the respective reactions.

EXPERIMENTAL

The amino acids of "pure" grade were dried at 180°C for 1 h and then used without further purification. 3-Nitrobenzenesulfonyl chloride of "pure" grade was recrystallized from a hexane–2-propanol (9:1) mixture with adding activated carbon. 1,4-Dioxane ("chemically pure" grade) was dried over KOH, then distilled on a column over metallic sodium at atmospheric pressure. 2-Propanol ("chemically pure" grade) was distilled on a column at atmospheric pressure.

The rates of the studied reactions were measured using spectrophotometric method (λ = 242 nm) by the change in the concentration of 3-nitrobenzenesulfonyl chloride. The concentration of amino acids in the system was 10^2 to 10^3 times higher than the concentration of acylating agent and virtually remained unchanged in the course of the experiment. The experimental procedures and the equation for calculating the rate constants of arenesulfonation of amino acids are given in [2].

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