ISSN 1070-3632, Russian Journal of General Chemistry, 2009, Vol. 79, No. 4, pp. 794–796. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © N.G. Shcheglova, T.P. Kustova, L.B. Kochetova, N.V. Kalinina, 2009, published in Zhurnal Obshchei Khimii, 2009, Vol. 79, No. 4, pp. 631–633.

Kinetics of Arenesulfonylation of Glycine, *D,L*-α-Alanine, and *D,L*-Valine in Water-Organic Media

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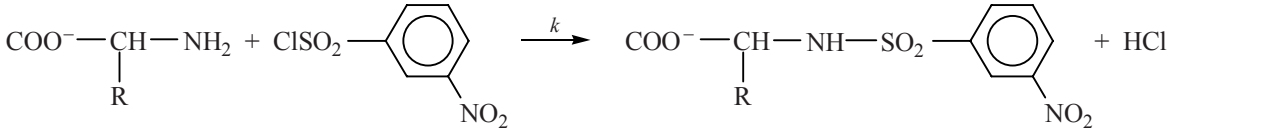
Received July 15, 2008

Abstract—Kinetics of arenesulfonylation of glycine, *D,L*-α-alanine, and *D,L*-valine with 3-nitrobenzenesulfonyl chloride were studied in solvent systems water–1,4-dioxane and water–2-propanol at water content 40 wt % and at different temperatures (298–313 K). The effective values of activation parameters of the reaction were calculated. The kinetic characteristics of the studied reactions were compared with the corresponding data for glycine, alanine, and valine in reaction with benzoyl chloride in aqueous dioxane.

DOI: 10.1134/S1070363209040197

The mechanism of N–S bonds formation in biologic systems has been the object of a rapt attention throughout the last decade since the derivatives of sulfonic acids has been proved to play an important role in inhibition of a number of enzymes, for instance, the enzymes responsible for the proliferation of leukemia cells *L1210* and *P388* [1], collagenases from *Clostridium histolyticum* [2], anhydrases [3, 4], etc. Besides the sulfonylation of amino acids at the NH_2-group is applied for the protection from the radicals formation at the α-carbon atom [5]. These facts show the urgency of the investigations of the reactivity of amino acid, monomers of the natural proteins, in the arenesulfonylation within the framework of one among the priority fields of development of the modern chemistry, the chemistry of living matter.

We formerly [6, 7] studied the glycine reactivity in the arenesulfonylation with 3-nitrobenzenesulfonyl chloride in the solvent systems water–1,4-dioxane and water–2-propanol. A different effect of solvent on the reaction rate constant (k) was established: in the aqueous 2-propanol the rate constant grew with the growing water fraction , and in the aqueous dioxane it on the contrary decreased. In extension of this research the target of the present investigation was the arenesulfonylation kinetics of two aliphatic amino acids, *D,L*-α-alanine (*D,L*-α-*Ala*) and *D,L*-valine (*D,L*-*Val*), with 3-nitrobenzenesulfonyl chloride (3-NBSC) in the systems water–1,4-dioxane and water–2-propanol at different temperatures, and the comparison of the findings obtained with the kinetic characteristics of glycine arenesulfonylation.



As shown before [8], the acylation of α-amino acid proceeds by two parallel routes involving anionic and neutral forms of the amino acid. The published [8] values of the thermodynamic dissociation constants of a series of α-amino acids in the solvents water–1,4-dioxane and water–2-propanol suggest that under the conditions of our experiments (pH = 6–6.5) the fraction of the anionic form is 10–100 times greater than that of the molecular form, and besides the neutral amino acid is significantly less reactive in this process

Table 1. Kinetic characteristics of arenesulfonylation of α-amino acids with 3-NBSC in binary organic solvents; $\omega(H_2O)$ = 40.0 wt %

T, K	$C_H^+ \times 10^7$, [a] M	$k \times 10^{-3}$, [b] l mol^{-1} s^{-1}	E_a, kJ mol^{-1}	$\Delta H^{\neq}$, kJ mol^{-1}	$-\Delta S^{\neq}$, J mol^{-1} K^{-1}
D,L-α-alanine; solvent: water–1,4-dioxane					
298	2.39	1.16	40±3	38±3	54± 11
303	1.90	3.86			
308	1.90	6.72			
313	1.81	7.37			
D,L-α-alanine; solvent: water– 2-propanol					
298	2.08	1.01	47±3	45±3	27±11
303	2.08	1.05			
308	2.04	1.56			
313	2.08	1.89			
D,L-valine; solvent: water–1,4-dioxane					
298	1.46	2.98	23±3	20±3	112±11
303	1.75	3.78			
308	1.75	4.88			
313	1.79	5.01			
D,L-valine; solvent: water–2-propanol					
298	1.99	1.66	37±3	34±3	64±11
303	1.99	2.36			
313	1.90	3.45			

[a] In the course of kinetic experiments the pH of the reaction solutions was precisely monitored; for each solvent composition the *H*-function of the glass electrode of the ionometer was checked by graduation using perchloric acid. [b] The value of *k* was estimated from the slope of the linear relationship (including 10–15 experimental points) of the apparent reaction rate constant to the running concentration of the amino acid [6]; the average error in the estimation of *k* did not exceed 5%.

than the anionic form; consequently, the second reaction route may be neglected. The reaction of the anionic forms of amino acids with 3-NBSC is shown on Scheme 1, where *R* is an alkyl radical in *D,L*-α-*Ala* and *D,L*-*Val, H* in glycine.

The rate constants of the arenesulfonylation of *D,L*-α- *Ala* and *D,L*-*Val* with 3-NBSC in the studied water-organic solvents, and also the values of the activation parameters of reactions under study calculated by Eyring equation are compiled in Table 1.

The data in Table 1 show that the reaction rate constants of alanine and valine with 3-NBSC in the studied temperature range in the aqueous dioxane more that 1.5-fold exceed the rate constants in the aqueous 2-propanol. The energies of activation of these reactions in aqueous 2-propanol are considerably higher than in aqueous dioxane. The absolute value $\Delta S_{298}^{\neq}$ in going from the system water–1,4-dioxane to the system water–2-propanol decreased nearly twofold suggesting that the mutual orientation of the reagents before the formation of the activated complex plays less important role at replacing cyclic ether in the system for alcohol. The latter in its turn originates from the unlike character of the specific solvation of the amino acid and the sulfonyl chloride.

The comparison of the activation parameters of reactions of *D,L*-α-alanine and *D,L*-valine with 3-NBSC in aqueous dioxane showed that with the growing bulk of the substituent at the α-carbon of the amino acid the absolute value of $\Delta S_{298}^{\neq}$ increased evidently due to the steric hindrances to the attack of the nucleophile on the electrophilic site (sulfonyl chloride group). To compare, the activation parameters of glycine reaction with 3-NBSC in 40% aqueous dioxane were E_a = 23 kJ mol^{-1}, $\Delta H_{298}^{\neq}$ = 21 kJ mol^{-1}, $-S_{298}^{\neq}$ = 107 J mol^{-1} K^{-1} [7]. As seen, the effective energy of activation and enthalpy of activation for these reactions have close values. In the processes under study a compensation effect was found, i.e., the increase in the enthalpy of activation was compensated by the decrease in the entropy of activation. It is presumable that the reactions of glycine, *D,L*-valine,

Table 2. Comparison of reactivity of amino acids in acylation with 3-NBSC and BC in a solvent water (40 wt%)–1,4-dioxane; 298.15 K

Parameter	Amino acid					
	Gly		*D,L-Val*		*D,L*-α-*Ala*	
	3-NBSC	BC [a]	3-NBSC	BC [a]	3-NBSC	BC [a]
$k\times10^{-3}$, l mol^{-1} s^{-1}	3.35	39.8	2.98	24.6	1.16	21.4
E_a, kJ mol^{-1}	23	26	23	4	40	36
$-\Delta S^{\neq}_{298}$, J mol^{-1} K^{-1}	107	75	112	75	54	53

[a] Data of [8].

and *D,L*-α-alanine with 3-NBSC in aqueous dioxane and aqueous 2-propanol proceed by the same mechanism.

It seemed also interesting to compare the data of the reactivity of amino acids in the arenesulfonylation with 3-NBSC in aqueous 1,4-dioxane with the results previously obtained in [8] for the reactions of α-amino acids with benzoyl chloride (BC). The kinetic characteristics of the compared reactions are given in Table 2.

As follows from the data of Table 2, the amino acids form a unique series with respect to their growing reactivity in acylation with acid chlorides of aromatic carboxylic and sulfonic acids: alanine < valine < glycine. As showed the results of our earlier studies [8] on the rates of aromatic amines ($PhNH_2$) acylation with the chlorides of benzoic (BC) and benzenesulfonic (BSC) acids, the ratio of the rate constants $k_{BC}/k_{BSC} = 10^2$–10^4 depending on the character and composition of the solvent. The acylation agent we used, 3-NBSC (see scheme), contained in the *m*-position of the aromatic ring an electron-withdrawing substituent (NO_2) strengthening the electrophilic property of the sulfonyl sulfur. Therefore the ratio of the rate constants $k_{BC}/k_{3\text{-NBSC}} = 10$–$20$ (Table 2).

On the whole, same as in the acylation of the α-amino acids with the benzoyl chloride, the important factors affecting the reaction rate are the bascity of the amino acid and the size of the alkyl substituent at the α-carbon atom.

EXPERIMENTAL

The reaction rates were measured by the consumption of the acylating agent (3-NBSC) by means of spectrophotometry (λ = 242 nm). The experimental procedure and the equations for the calculation of the rate constants of the arenesulfonylation of the amino acids (by an example of glycine) were published in [6].

D,L-α-Alanine ("pure" grade) and *D,L*-valine ("pure" grade) were dried at 180°C and were used further without additional purification. 1,4-Dioxane ("chemically pure" grade) was dried with KOH and then was distilled over metallic sodium at atmospheric pressure.

ACKNOWLEDGMENTS

The study was carried out in the framework of the project no. RN.2.2.1.1.7181 of the Ministry of Education and Science of the Russian Federation.

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