Arenesulfonylation of DL-serine, L-proline, L-threonine, and DL-methionine in systems 1,4-dioxane—water and propan-2-ol—water

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Kinetics of interaction of DL-serine, L-proline, L-threonine, and DL-methionine with 3-nitrobenzenesulfonyl chloride in water (40%)—1,4-dioxane and water (40%)—isopropanol mixed solvents was studied spectrophotometrically at 298 K. The main reactive form of α-amino acids is shown to be anionic. Under conditions of arenesulfonylation, the basicity of α-amino acids is crucial in determining the reaction rate. Arenesulfonylation rate constants are 20—50 times lower than the constants of *N*-acylation of the same α-amino acids with benzoyl chloride and 10^4—10^5 times higher than the rate constants of their reactions with benzoic acid 4-nitrophenyl ester.

Key words: amino acids, kinetics, *N*-acylation, arenesulfonylation, benzoic acid, solvent, *ab initio* calculations.

Studying the sulfamide bond formation by α-amino acids is essential for both an understanding of the mechanisms of reactions occurring in biosystems and choosing optimal synthetic conditions for sulfamides, especially in view of the rather sparse available data on synthetically viable routes to produce acylamino acids.[1]

An interest in the principles of the N—S bond formation in biological objects is due to the important role of sulfonic acid derivatives in inhibition of a range of enzymes. Furthermore, the sulfonation of the amino group of amino acids is known to be used as a protection against formation of the α-carbon-centered radicals. Nitrogen- and sulfur-containing organic compounds are widely employed in QSAR (quantitative structure—activity relationship) studies that makes the knowledge of amino acid arenesulfonylation kinetics useful for optimization of the synthesis of biologically active sulfonylamides by conventional as well as combinatorial methods.

Previously,[2,3] the kinetic studies have been performed for the reactions of glycine, DL-α-alanine, and DL-valine with 3-nitrobenzenesulfonic acid chloroanhydride in isopropanol—water and 1,4-dioxane—water solvent systems.

Here we describe the results of the kinetic studies of reactions of DL-serine, L-proline, DL-threonine, and DL-methionine with 3-nitrobenzenesulfonyl chloride (3-NBSC) in the mixtures of 1,4-dioxane and isopropanol with water (40%) at 298 K. The water-organic mixed solvents were chosen with the aim to overcome the problems of insolubility of α-amino acids in organic solvents and strong hydrolysis of sulfonyl chloride in water (that suppresses acylation).

Experimental

α-Amino acids: DL-serine (chemically pure grade), L-proline (chemically pure grade), DL-methionine (analytical grade), and DL-threonine (pure grade) were dried at 150 °C and used without further purification. 3-Nitrobenzenesulfonyl chloride (pure grade) was recrystallized from hexane—isopropanol (9 : 1) with activated charcoal. 1,4-Dioxane (chemically pure grade) was dried over KOH and distilled on a column at atmospheric pressure in the presence of metal sodium. Isopropanol (chemically pure grade) was distilled on a column at atmospheric pressure. Sodium acetate (analytical grade) was recrystallized from water. Physicochemical constants of the purified reagents were in agreement with the literature data.[4] Acetic acid (chemically pure grade) was used as purchased. All aqueous solutions were prepared in doubly distilled water.

The course of the reaction was monitored spectrophotometerically by changes in 3-NBSC concentration at 242 nm using a SF-46 spectrophotometer equipped with a digital Shch-1312 voltmeter. Kinetic experiments were carried out as described in Ref. 2. The value of pH of the solution was maintained constant using the acetate buffer; pH of the working solutions was measured with an I-160M ionomer (with an ES-10603 pH glass electrode and ESr-10103 reference electrode). The H-function of a glass electrode was checked by calibration against perchloric acid solutions.

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Results and Discussion

In water and in water-organic solutions, α-amino acids can adopt four forms depending on pH, *viz.*, cationic, anionic, zwitterionic, and uncharged, with only two ones (molecular and anionic) reactive towards *N*-acylating reagents as containing nonprotonated amino groups.[5] 3-NBSC can react with the active forms of α-amino acids and water contained in a water-organic solvent *via* three parallel routes (R is amino acid radical):

$$NH_2CH(R)COOH + 3\text{-}O_2NC_6H_4SO_2Cl \xrightarrow{k_0} 3\text{-}O_2NC_6H_4SO_2NHCH(R)COOH + HCl, \quad (1)$$

$$NH_2CH(R)COO^- + 3\text{-}O_2NC_6H_4SO_2Cl \xrightarrow{k_-} 3\text{-}O_2NC_6H_4SO_2NHCH(R)COO^- + HCl, \quad (2)$$

$$H_2O + 3\text{-}O_2NC_6H_4SO_2Cl \xrightarrow{k_h} 3\text{-}O_2NC_6H_4SO_3H + HCl. \quad (3)$$

The rate of the solvolysis of sulfonyl chloride by the organic components of the solvents used in the experiments is negligibly small compared to those of reactions (1)—(3) (see Ref. 6) and thus can be ignored.

In accordance with reactions (1)—(3), when the amino acid concentration (C_{aa}) is 2—3 orders of magnitude higher than the sulfonyl chloride concentration (C_{sc}), the C_{sc} dynamics in the kinetic experiment will obey the relation

$$-(dC_{sc}/d\tau) = [k_h + (k_0\alpha_0 + k_-\alpha_-)C_{aa}]C_{sc}, \quad (4)$$

where α_0 and α_- are the mole fractions of uncharged and anionic α-amino acid forms, respectively; C_{aa} is the total concentration of all α-amino acid forms in solution; k_0 and k_- are the acylation rate constants for uncharged and anionic forms of α-amino acid, respectively; k_h is the rate constant of hydrolysis of 3-NBSC. The apparent first-order rate constant (k_{app}) is expressed as

$$k_{app} = k_h + (k_0\alpha_0 + k_-\alpha_-)C_{aa}. \quad (5)$$

The k_{app} values were derived from kinetic data by use of the Guggenheim equation:

$$-\ln\ln\frac{T_1}{T_2} = \ln\left|\ln\frac{T_\infty}{T_0}(1 - e^{-\Delta\cdot k_{app}})\right| - k_{app}\cdot\tau_1, \quad (6)$$

where T_1 and T_2 are the transmittance coefficients of the solution at time τ_1 and τ_2, respectively; $\tau_2 = \tau_1 + \Delta$ (Δ is a constant); T_0 and T_∞ are the transmittance coefficients of the solution before beginning and after completion of the reaction.

The left hand side of Eq. (6) is a linear function of τ_1 that allows estimation of the effective rate constants k_{app} by least squares without determining T_0 and T_∞.

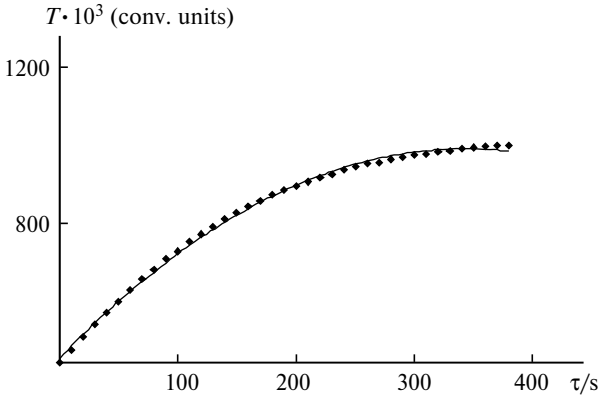

Fig. 1. Transmittance of solution (T) *vs.* time (τ) for reaction of L-proline with 3-NBSC in dioxane—water (40%) mixture at 298 K, C_{aa} = 0.0048 mol L^{-1}, $k_{app} = (8.60\pm0.06)\cdot10^{-3}$ s^{-1}. T values are given in conventional units (voltage readings of a digital voltmeter in mV) since for determining k_{app} by Guggenheim method the absolute T values need not be known.

Table 1. Effective rate constants (k_{app}) of reactions of α-amino acids with 3-NBSC at 298 K*

Dioxane—H_2O (40%)		Isopropanol—H_2O (40%)	
C_{aa}/mol L^{-1}	$k_{app}\cdot10^3$/s^{-1}	C_{aa}/mol L^{-1}	$k_{app}\cdot10^3$/s^{-1}
	DL-Met		
0.0010	10.25	0.0010	2.52
0.0030	10.39	0.0040	2.65
0.0040	10.43	0.0050	2.73
0.0050	10.48	0.0070	2.83
0.0060	10.52	0.0090	2.98
0.0080	10.70	—	—
0.0090	10.78	—	—
	DL-Ser		
0.0010	7.78	0.0010	3.32
0.0060	8.29	0.0020	3.36
0.0070	8.4	0.0030	3.38
0.0080	8.43	0.0040	3.40
0.0100	8.7	0.0050	3.43
—	—	0.0070	3.51
	L-Pro		
0.0032	6.19	0.0008	2.05
0.0048	8.60	0.0016	2.08
0.0056	8.67	0.0048	2.31
0.0064	9.02	0.0056	2.38
0.0080	11.2	0.0064	2.52
—	—	0.0072	2.64
	DL-Thr		
0.0010	9.32	0.0010	3.13
0.0020	9.39	0.0030	3.30
0.0040	9.51	0.0040	3.31
0.0060	9.72	0.0050	3.37
0.0070	9.81	0.0060	3.40
—	—	0.0070	3.46
—	—	0.0100	3.55

* C_{aa} is the starting concentration of amino acid.

The rate constant values were derived from 60—100 measurements of solution transmittance. Their accuracy was determined assessing statistical significance at 95% level. An example of thus obtained kinetic curve is given in Figure 1. The k_{app} values obtained from the experimental kinetic data are summarized in Table 1.

It was previously shown[5,7] for α-amino acid acylation with benzoyl chloride that the uncharged form does not contribute significantly to the effective reaction rate because of $k\_\alpha\_ >> k_0\alpha_0$. Under conditions of our experiment (pH 6.0—7.0), the mole fraction of the anionic α-amino acid form (α_) in the studied water-organic media is one or two orders of magnitude higher than that of the molecular form (α_0).[5,8] The reactivities of the anionic and molecular α-amino acid forms can be qualitatively compared with the aid of quantum chemical calculations.

The acylation reactions of amines and amino acids are known to proceed under orbital control,[5] which means the interaction between the HOMO of amine and LUMO of the acylating agent is the rate-limiting step. The energies of the interacting LUMO and HOMO orbitals of α-amino acid molecules and anions as well as of acylating agent molecules calculated for fully optimized geometries using the HyperChem 7.52 program[9] on the HF/6-31G* level of theory are collected in Table 2.

The energy difference between the HOMO and LUMO level (HOMO—LUMO gap) $\Delta E = E_{HOMO} - E_{LUMO}$ for the α-amino acid anions interacting with benzoyl chloride and 3-NBSC is substantially lower than for their uncharged forms (see Table 2), which accounts for the higher reactivity to *N*-acylation of the anionic form compared to molecular form. The above data imply that in the reactions considered, in common with reactions of α-amino acids with benzoyl chloride, $k\_\alpha\_ >> k_0\alpha_0$, so that Eq. (5) can be reduced to give

$$k_{app} = k_h + (k\_\alpha\_)C_{aa}. \quad (7)$$

Validity of this equation would require the apparent rate constant k_{app} to be the linear function of initial amino acid concentration C_{aa} with a slope equal to the effective rate constant $k_{eff} = k\_\alpha\_$. Eq (7) is valid for all reactions studied (see Table 1). Effective rate constants for the acylation of α-amino acids by 3-NBSC (k_{eff}) derived from this equation and its linear correlation coefficients (r) are given in Table 3.

In a number of works (*e.g.*, Ref. 5, 7) it was shown that the mole fraction of the anionic form (α_) can be represented as

$$\alpha\_ = K_{a_{II}}/(C_{H^+} + K_{a_{II}}), \quad (8)$$

where C_{H^+} is the concentration of H^+ ions in solution, and $K_{a_{II}}$ is the second thermodynamic dissociation constant of α-amino acid in a given solvent.

Table 2. HOMO energies (E_{HOMO}) of anionic and molecular forms of amino acids and LUMO energies (E_{LUMO}) of acylating agent molecules

Compound	Anion	Molecule
Amino acid	$-E_{HOMO}$/eV	
DL-Ser	5.56	10.92
L-Pro	5.02	10.22
L-Thr	5.39	10.54
DL-Met	5.38	9.10
Acylating agent	E_{LUMO}/eV	
Benzoyl chloride	—	1.90
3-NBSC	—	0.75

Under the conditions of kinetic experiment, C_{H^+} is of the order of 10^{-7}—10^{-8} mol L^{-1}, and $K_{a_{II}}$ for α-amino acids considered is 10^{-10}—10^{-11} mol L^{-1} (see Ref. 5), hence $K_{a_{II}}$ value in Eq. (8) can be neglected:

$$\alpha\_ = K_{a_{II}}/C_{H^+}, \quad (9)$$

to obtain

$$k_{eff} = k\_K_{a_{II}}/C_{H^+}, \quad (10)$$

which means that the acylation rate constants for α-amino acid anionic form ($k\_$) can be found as

$$k\_ = k_{eff}C_{H^+}/K_{a_{II}}. \quad (11)$$

The $k\_$ values for reactions of α-amino acids with 3-NBSC derived from Eq. (11), along with the experimental C_{H^+} values and $K_{a_{II}}$ of a protonated α-amino acid amino group in water—dioxane and water—isopropanol media (40% water)[5] are collected in Table 3.

From the data of Table 3 it follows that the reactivity of the studied α-amino acids in water—dioxane and water—isopropanol mixed solvents increases in a series

DL-Met < DL-Ser, DL-Thr << L-Pro.

Table 3. Kinetic characteristics of reactions of α-amino acids with 3-NBSC

α-Amino acid	$C_{H^+} \cdot 10^7$ /mol L^{-1}	$pK_{a_{II}}$	k_{eff}	$k\_$	r
			L mol^{-1} s^{-1}		
		Dioxane—H_2O (40%)			
DL-Met	2.11	10.16	0.064	196	0.991
DL-Ser	1.41	10.42	0.100	370	0.996
L-Pro	1.41	11.59	0.96	52880	0.971
DL-Thr	1.80	10.41	0.082	378	0.994
		Isopropanol—H_2O (40%)			
DL-Met	8.86	9.57	0.048	158	0.993
DL-Ser	7.45	10.02	0.029	228	0.992
L-Pro	21.41	11.17	0.0917	29040	0.971
DL-Thr	7.45	9.92	0.032	201	0.991

It should be noted that this series coincides with the basicity sequence for α-amino acids in both water-organic solvents (see Table 3). The rate of arenesulfonylation of L-proline is significantly higher compared to reactions of other α-amino acids with 3-NBSC, which is due to its higher basicity as well as to specific structural features. Higher reactivity of L-proline compared to other α-amino acids was found in a number of reactions, in particular, in the reactions of α-amino acids with benzoic acid chloroanhydride, and with its substituted phenyl esters as well.[5,10]

The logarithms of the rate constants of reaction (2) are proportional to $pK_{a_{II}}$ values in dioxane—water medium (40% water);[5] the corresponding line plotted using the $k\_$ rate constants of reactions of α-amino acids with 3-NBSC obtained previously under the similar conditions[2,3] is shown in Fig. 2. The similar linear relation holds for aqueous isopropanol.

There exists a linear relationship between the logarithms of the rate constants of reactions of α-amino acids with 3-NBSC in aqueous isopropanol ($\log k_{ips}$) and in aqueous dioxane ($\log k_{do}$) (determined herein as well as previously[2,3]):

$$\log k_{ips} = -(0.102\pm0.131) + (0.970\pm0.041) \cdot \log k_{do}\,. \quad (12)$$

An explanation of this proportionality is that the basicity of the amino group controls the rate of *N*-acylation of α-amino acids. The arenesulfonylation rate constants for α-amino acids ($k\_$) in aqueous dioxane are higher than in aqueous isopropanol, which is attributable to higher $pK_{a_{II}}$ values in aqueous dioxane (see Table 3). However, the reaction rate may also be affected by specific solvation of α-amino acid anions and the transition state by solvent components.[4]

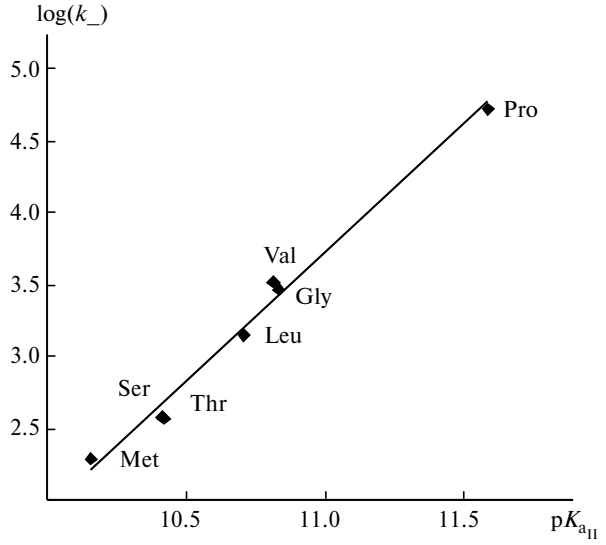

Fig. 2. Logarithms of acylation rate constants of α-amino acids ($\lg(k\_)$) in dioxane—water (40%) *vs.* $pK_{a_{II}}$ of the protonated amino group in aqueous dioxane.[5]

The rate constants of reaction (2) in aqueous dioxane are 20—50 times lower than the rate constants of *N*-acylation of the same α-amino acids with benzoyl chloride under similar conditions. At the same time, arenesulfonylation rate constants for the studied α-amino acids in aqueous isopropanol, $k\_$ are 4—5 orders of magnitude higher than the rate constants of their reactions with 4-nitrophenyl benzoate in the same solvent.[5] This is in agreement with the literature data on the relative reactivity of arenesulfonyl chlorides, chloroanhydrides, and aromatic carboxylic acid esters in *N*-acylation reactions.[5]

The logarithms of arenesulfonylation rate constants of α-amino acids in aqueous dioxane and in aqueous isopropanol ($\log k\_$) are related linearly to the logarithms of the corresponding rate constants of their acylation with benzoyl chloride in aqueous dioxane ($\log k_{bc}$) and with 4-nitrophenyl benzoate in aqueous isopropanol ($\log k_{es}$):

$$\log k\_ = (4.47\pm0.10) + (0.78\pm0.05) \cdot \log k_{es}, \quad (13)$$

$$\log k\_ = (0.14\pm0.21) + (0.74\pm0.05) \cdot \log k_{bc}. \quad (14)$$

These dependences are consistent with the concept of rate controlling basicity in *N*-acylation of amino acids and suggest that the key feature for the reactivity of α-amino acids in nucleophilic substitution reactions is the ability of amino nitrogen to the nucleophilic attack of electrophilic center, *i.e.*, the carbonyl carbon atom and sulfonyl sulfur atom.

In conclusion, the basicity of a protonated amino group appears to be a key factor that determines the rate of arenesulfonylation of α-amino acids along with the specific solvation of the amino acid anions by components of water-organic solvents.

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