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Kinetics of Glycine Arenesulfonylation in the Water–Propan-2-ol System

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Abstract—The kinetics of the glycine N-acylation with 3-nitrobenzenesulfonyl chloride in the water–propan-2-ol mixture containing 40–80 wt % water was studied at 298 K. In going from the mixture containing 40% water to that containing 80% water, the arenesulfonylation rate constant increases by a factor of 40. Glycine is considerably more reactive in the arenesulfonylation than aminobenzoic acids.

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Numerous functional derivatives of arenesulfonic acids form an important class of biologically active compounds [1, 2]. More than 50 substances containing $-NH-SO_2-$ group (according to the Merck Index lists [3]) are widely used in the clinical practice for the medical treatment and prophylaxis of bacterial infections. Furthermore, this class of compounds exhibits the diuretic, hypoglycemic, antihypertensive, and some other properties [4].

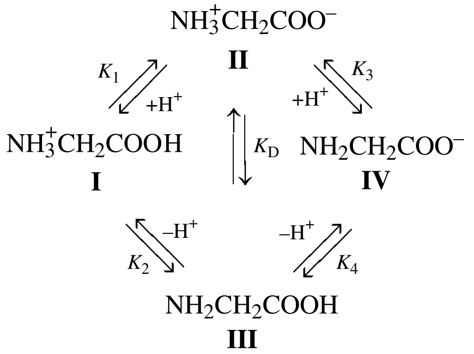
Some of arenesulfonic acid derivatives are enzyme inhibitors [5]. In view of the proteinic nature of enzymes, it is of particular interest to study the reactivity of their structural units, α-amino acids, in the arenesulfonylation. No precision kinetic data on this subject have been reported, due to problems considered below.

Here we report on a kinetic study of the glycine arenesulfonylation with 3-nitrobenzenesulfonyl chloride in the water–propan-2-ol system. A wide range of compositions of the binary solvent was examined. We have studied previously [6] the reactivity of aminobenzoic acids in the arenesulfonylation with 3- and 4-nitrobenzenesulfonyl chlorides in water–propan-2-ol mixtures. The kinetics of the reaction of α-amino acids with arenesulfonyl chlorides was not studied up to now. The factors complicating such studies are as follows: lack of reliable data on the thermodynamics of dissociation of α-amino acids in water–propan-2-ol mixtures, necessary for evaluating the contributions of the active forms of the amino acids in arenesulfonylation; need in exact control of pH in the solutions under investigation, as pH affects not only the ratio of the ionic species of the amino acids, but also the rate of hydrolysis of sulfonyl chloride; and some other factors.

Our kinetic study of the glycine arenelsulfonylation with 3-nitrobenzenesulfonyl chloride was performed at 298 K in water–propan-2-ol mixtures with the water content varying from 40 to 80% wt %.

As known, glycine and all the other α-amino acids exist in water–organic solvent mixtures as a set of nonionized and ionized species (Scheme 1) depending on pH.

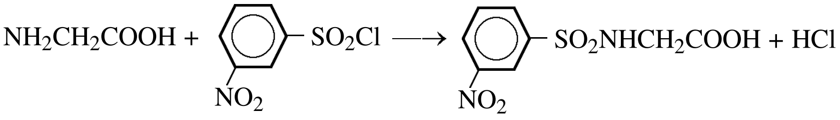
Scheme 1.



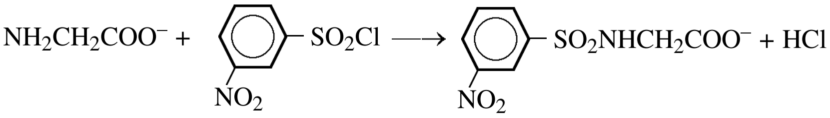
Here K_1 and K_2 are the acid dissociation constants of the cationic form of glycine, K_3 is that of the zwitterionic form, and K_4, that of the uncharged form; K_D characterizes the equilibrium $\mathbf{II} \rightleftarrows \mathbf{III}$. It was found previously [7] that in water and aqueous-organic mixtures with the organic component content of up to 90 wt % the relative content of the α-amino acid zwitterions exceeds that of the uncharged molecules by a factor of 10^4–10^5. Therefore, the acid dissociation of α-amino acids follows the pathway $\mathbf{I}\rightleftarrows\mathbf{II}\rightleftarrows\mathbf{IV}$. Hence, the experimentally evaluated thermodynamic constants of the acid dissociation of glycine in acidic and basic solutions, K_{aI} and K_{aII}, can be referred to the equilibria $\mathbf{I}\rightleftarrows\mathbf{II}$ and $\mathbf{II}\rightleftarrows\mathbf{IV}$, respectively.

3-Nitrobenzenesulfonyl chloride can react only with the neutral (**III**) and anionic (**IV**) forms of glycine containing the nonprotonated amino group; therefore, the arenesulfonation can occur along two pathways (Schemes 2, 3).

Scheme 2.

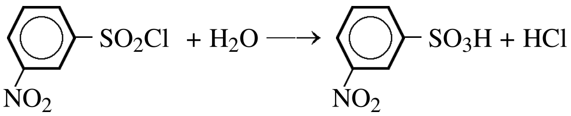


Scheme 3.



The acylation of glycine in a water–propan-2-ol mixture is accompanied by hydrolysis (Scheme 4) and alcoholysis of the sulfonyl chloride.

Scheme 4.



According to Schemes 2 and 3, the rate of a decrease in the concentration of sulfonyl chloride at the glycine–acid chloride ratio C_g/C_s 10^2–10^3 is determined by the following equation:

$$-dC_s/d\tau = [k_h + (k_0\alpha_0 + k_{-}\alpha_{-})C_g]C_s = k_{ob}C_s, \tag{1}$$

where $k_{ob} = k_h + (k_0\alpha_0 + k_{-}\alpha_{-})C_g$ is the observed first-order rate constant evaluated in the kinetic experiment; k_h is the rate constant of the acid chloride hydrolysis; k_0 and k_{-} are the second-order rate constants of the nonionized and anionic forms of glycine; α_0 and α_{-} are the fractions of these forms in solution. The alcoholysis of 3-nitrobenzenesulfonyl chloride was neglected because it was shown previously that the contribution of methanolysis competing with acylation does not exceed 2–3%, and in the case of other alcohols it is still lower.

The thermodynamic dissociation constants of a series of α-amino acids in water–propan-2-ol mixtures (K_{aI} and K_{aII}) were evaluated in [8, 9]. These quantities were used for calculating the relative content of ionic species of α-amino acids in solution at different pH values. The data obtained show that, under the conditions of our experiment (pH 5–6), the fraction of the anionic form of glycine in water–propan-2-ol mixtures with the water content exceeding 40 wt % exceeds the fraction of the molecular form by a factor of 10–100. As we showed in [10, 11], in the reaction of glycine with benzoyl chloride the neutral form does not significantly contribute to the observed reaction rate. Based on these data, it can be assumed that in the reaction under study $k_0\alpha_0 << k_{-}\alpha_{-}$, and Eq. (1) can be transformed into (2).

$$-dC_s/d\tau = [k_h + (k_{-}\alpha_{-})C_g]C_s. \tag{2}$$

Here $k_{ob} = k_h + (k_{-}\alpha_{-})C_g$.

The fraction of the anionic form α_{-} is determined by Eq. (3).

$$\alpha_{-} = \frac{K_{aII}}{C_{H^+} + K_{aII}}. \tag{3}$$

For glycine, K_{aII} is $\sim 10^{-10}$ [2], and under the conditions of the kinetic experiment $C_{H^+} \approx 10^{-6}$ M. Therefore, the term K_{aII} in the denominator of Eq. (3) can be neglected. Then,

$$\alpha_{-} = \frac{K_{aII}}{C_{H^+}}, \tag{4}$$

$$k_o = k_h + \frac{k_{-}K_{aII}C_g}{C_{H^+}}. \tag{5}$$

Kinetic characteristics of the reaction of glycine with 3-nitrobenzenesulfonyl chloride in water–propan-2-ol mixtures, 298 K

ω_{H_2O}, wt%	$10^6 \times C_{H^+}$, M	pK_{aII} [a]	$10^4 \times k_h$, s^{-1}	$10 \times k_{app}C^{-1}_{H^+}$, s^{-1}	$10^{-3} \times k_{-}$, $l\,mol^{-1}\,s^{-1}$
39.80	2.29	10.01	5.62 ± 0.55	0.34 ± 0.08	0.80 ± 0.19
50.10	2.47	9.98	6.47 ± 1.27	1.18 ± 0.22	2.78 ± 0.52
60.17	3.22	9.91	7.50 ± 1.16	1.86 ± 0.19	4.87 ± 0.50
70.12	4.79	9.92	12.90 ± 1.40	3.10 ± 0.22	12.37 ± 0.88
80.15	6.31	9.91	20.00 ± 2.10	6.31 ± 0.34	32.37 ± 1.74

[a] Data from [7].

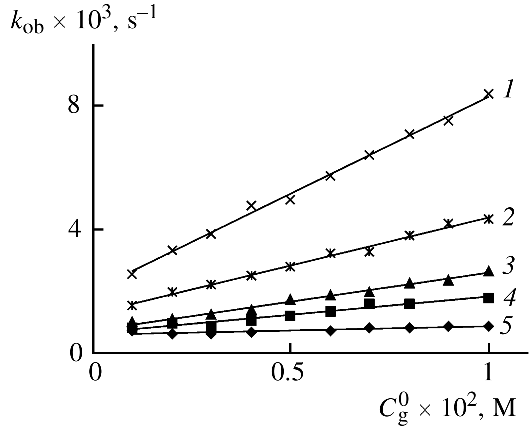
It follows from Eq. (5) that, when C_{H^+} is constant, the dependence of k_{ob} on C_g is linear with a slope of $k_{-}K_{aII}(C_{H^+})^{-1}$. Similar dependences with the correlation coefficients of 0.960–0.998 were obtained for all the water–propan-2-ol mixtures under study (see figure).

The quantity $k_{-}K_{aII}$ can be regarded as apparent rate constant of glycine N-acylation.

$$k_{app} = k_{-}K_{aII}. \qquad (6)$$

The rate constants of the acid chloride hydrolysis k_h, apparent rate constants k_{app}, and rate constants of arenesulfonylation of the anionic form of glycine k_{-} are listed in the table.

The data presented show that glycine is more active in arenesulfonylation than the previously studied aminobenzoic acids [6]. For all the compositions of water–propan-2-ol mixtures, the rate constants differ by a factor of 10^4–10^5. Similar ratios of the rate constants of the reactions of benzoyl chloride with glycine and aminobenzoic acids in the water–dioxane system (10^3–10^4) were found in [10]. In going from 40 to 70% water–propan-2-ol solution, k_{-} for the reaction under consideration increases by a factor of 15, whereas for aminobenzoic acids the increase is somewhat less pronounced (by a factor of 3–7). This means that the solvation effects are stronger in the arenesulfonylation of glycine.



Observed rate constant of the reaction of glycine with 3-nitrobenzenesulfonyl chloride at 298 K as a function of the initial glycine concentration. Solvent water–propan-2-ol; (*1*) 80.15, (*2*) 70.12, (*3*) 60.17, (*4*) 50.10, and (*5*) 39.80 wt% water.

EXPERIMENTAL

Glycine (pure grade) was dried at 150°C and used without additional purification. 3-Nitrobenzenesulfonyl chloride (pure grade) was recrystallized from hexane. Propan-2-ol (chemically pure grade) was dried with anhydrous copper(II) sulfate and distilled on a column at atmospheric pressure. Sodium acetate (analytically pure grade) was recrystallized from water. Acetic acid (analytically pure grade) was used without additional purification. All the water-containing solutions were prepared with double-distilled water. The physicochemical constants (mp, bp) of the reagents after the purification were in agreement with the reference data [12].

The glycine N-acylation rate was monitored by measuring the sulfonyl chloride concentration with an SF-46 spectrophotometer at λ 242 nm using an Shch 1312 digital voltmeter. The working glycine solution in the water–propan-2-ol mixture containing acetate buffer (0.05 M CH_3COOH and 0.008 M CH_3COONa) was prepared just before the kinetic experiment. The working solution was placed in a cell (l = 1 cm) located in the temperature-controlled block of the spectrophotometer. After reaching the required temperature, a solution of 3-nitrobenzenesulfonyl chloride in propan-2-ol was added into the cell in an amount providing the 3-nitrobenzenesulfonyl chloride concentration in the reaction mixture of 5×10^{-3} M. The pH measurements of the working solutions were carried out with an I-160M pH meter equipped with an ES-10603 glass electrode and an ESr-10103 reference electrode. The H function of the glass electrode, $-\log C_{H^+} = a + b\,\mathrm{pH}$, was determined for each solution composition by calibration with perchloric acid. The a and b values for the water–propan-2-ol mixtures studied are presented below: ω_{H_2O} = 39.80 wt %, a = –0.30 ± 0.10, b = 0.995 ± 0.029, r = 0.999; ω_{H_2O} = 50.10 wt %, a = –0.26 ± 0.41, b = 0.999 ± 0.118, r = 0.995; ω_{H_2O} = 60.17 wt %, a = –0.24 ± 0.18, b = 0.997 ± 0.051, r = 0.999; ω_{H_2O} = 70.12 wt %, a = –0.14 ± 0.05, b = 0.978 ± 0.015, r = 0.999; ω_{H_2O} = 80.15 wt %, a = –0.08 ± 0.07, b = 0.978 ± 0.022, r = 0.999.

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REFERENCES

1. Kalir, A. and Kalir, H.H., Biological Activity of Sulfonic Acid Derivatives, *The Chemistry of Sulfonic Acids, Esters, and Their Derivatives,* Patai, S. and Rappoport, Z., Eds., Wiley, 1991, p. 767.
2. Prilezhaeva, E.N., *Usp. Khim.,* 2000, vol. 69, no. 5, p. 403.
3. *Merck Index,* Budavari, S., Ed., Rahway: Merck, 1989, 11th ed., p. 1416.
4. *The Pharmacological Basis of Theraupeutics,* Goodman, L.S., Rall, T.W., Murad, F., and Macmillan, F., Eds., New York, 1985, 7th ed.
5. Scozzafava, A. and Supuran, C.T., *Bioorg. Med. Chem.,* 2000, vol. 8, no. 3, p. 637.
6. Kustova, T.P., Kuritsyn, L.V., and Khripkova, L.N., *Zh. Obshch. Khim.,* 2001, vol. 71, no. 4, p. 668.
7. Kuritsyn, L.V., Kustova, T.P., Sadovnikov, A.I., Kalinina, N.V., and Klyuev, M.V., *Kinetika reaktsii atsil'nogo perenosa* (Kinetics of Acyl Transfer Reactions), Kuritsyn, L.V., Ed., Ivanovo: Ivanov. Gos. Univ., 2006.
8. Kuritsyn, L.V., Kalinina, N.V., and Khripkova, L.N., *Zh. Fiz. Khim.,* 2000, vol. 74, no. 9, p. 1721.
9. Kuritsyn, L.V., Kalinina, N.V., and Khripkova, L.N., *Zh. Fiz. Khim.,* 1998, vol. 72, no. 12, p. 2264.
10. Kuritsyn, L.V., Kalinina, N.V., and Kampal, A.K., *Zh. Org. Khim.,* 1988, vol. 24, no. 12, p. 2562.
11. Kalinina, N.V. and Kuritsyn, L.V., *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.,* 1988, vol. 31, no. 10, p. 39.
12. *Svoistva organicheskikh soedinenii* (Properties of Organic Compounds), Potekhin, A.A., Ed., Leningrad: Khimiya, 1984.