

Solvent Effects in the Arenesulfonylation of *N*-Alkylanilines

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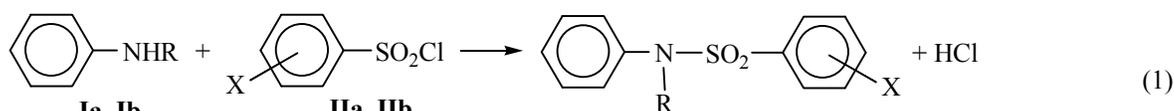
Abstract—The kinetics of arenesulfonylation of *N*-methyl- and *N*-ethylaniline with 3-nitro- and 4-methylbenzenesulfonyl chlorides in aqueous 1,4-dioxane have been studied. Comparison of the solvent effects on the reaction of *N*-alkylanilines with arenesulfonyl chlorides has revealed higher yields of the arenesulfonylation products (more than 90%) in water–1,4-dioxane mixtures over a wide range of solvent composition as compared to water–alcohol mixtures studied previously.

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The reactivity of secondary fatty–aromatic amines in the arenesulfonylation with arenesulfonyl chlorides in aqueous organic systems has been studied insufficiently, which is related to some difficulties in the synthesis and isolation of such amines, as well as to low reaction rates and complications due to concurrent processes. Meanwhile, reactions of fatty–aromatic amines with arenesulfonyl chlorides are very important from the practical point of view since the products, the corresponding sulfonamides are widely used for the preparation of medicines and other

biologically active substances, dyes, disinfectants, decontaminating agents, and plasticizers. We previously studied [1–4] the effect of a number of organic solvents and water–alcohol mixtures on the rate of the title reaction.

In the present article we report on the kinetics of arenesulfonylation of *N*-methyl- and *N*-ethylaniline with 3-nitro- and 4-methylbenzenesulfonyl chlorides in aqueous 1,4-dioxane and discuss solvent effects on this reaction [Scheme (1)].



R = Me (**Ia**), Et (**Ib**); X = 3-NO₂ (**IIa**), 4-Me (**IIb**).

The acylation of amines with sulfonyl chlorides in aqueous–organic solvents is accompanied by hydrolysis of the electrophile. Therefore, provided that the initial amine concentration (c_a^0) is twice as high as the initial concentration of sulfonyl chloride (c^0), the concentration of the latter changes according to Eq. (2).

$$-\partial c/\partial \tau = k_{ac}c_a c + k_h c = 2k_{ac}(c^0 - x)^2 + k_h(c^0 - x). \quad (2)$$

Here, x is the change of the concentration of sulfonyl chloride by a moment of time τ ; c_a and c are, respectively, the current concentrations of amine and sulfonyl chloride; k_{ac} is the second-order rate constant (L mol⁻¹ s⁻¹); and k_h is the rate constant of hydrolysis of sulfonyl chloride (s⁻¹).

The kinetics of reaction (1) were studied by conductometry, so that variation of the sulfonyl chloride concentration may be described by Eq. (2)

$$(c^0 - x) = c^0[(\chi_\infty - \chi_\tau)/(\chi_\infty - \chi_0)], \quad (3)$$

where χ_0 , χ_∞ , and χ_τ are the conductivities of the reaction mixtures at the initial moment, moment τ , and by the end of the process.

The rate constant for the hydrolysis of sulfonyl chloride was determined by special kinetic experiment. The k_h value was calculated according to Guggenheim equation (4) from 80–100 measurements of the conductivity of a sulfonyl chloride solution.

$$\ln(\chi_{i+1} - \chi_i) = a + k_h \tau_i \quad (4)$$

Here, χ_i and χ_{i+1} are the conductivities of the solution at time τ_i and $\tau_{i+1} = \tau_i + \Delta$, and a and Δ are constant parameters. The error in the determination of k_{ac} and k_h was calculated with a confidence probability of 0.95.

The rate constants k_{ac} and k_h for the reactions of amines **Ia** and **Ib** with 3-nitrobenzoyl chloride (**IIa**) in water–1,4-dioxane mixtures with different water concentrations are given in Table 1.

The data in Table 1 show that the rate constant k_{ac} increases as the concentration of water in the binary solvent rises. In going from 10 to 30% aqueous dioxane the rate constant for the reaction with *N*-methylaniline increases almost threefold. According to published data [2], the rate constant of the reaction of aniline with 4-nitrobenzenesulfonyl chloride in 40% aqueous dioxane was higher than that in pure dioxane by a factor of more than 5000. These data suggest a strong accelerating effect of water–dioxane mixture on the acylation process. The observed monotonic dependence of the rate constant on the solvent composition is very consistent with the data [5] of thermochemical study of the water–1,4-dioxane binary system. In the examined range of dioxane concentrations ($X_2 = 0.23$ – 0.64), the dependence of the heat of mixing of the components on the solvent composition is also monotonic.

The dynamics of variation of the rate constants of arenesulfonylation of *N*-methyl- and *N*-ethylanilines indicated their comparable reactivities in this reaction. On the basis of our experimental data obtained in the present work for aqueous 1,4-dioxane and those published previously [4] for water–alcohol mixtures, we cannot state with certainty which characteristic of the *N*-alkyl substituent is determining for the reaction kinetics, whether it is its electron-donating power or steric size. In more polar media (with a concentration of water of 0.6 mole fraction and higher), the inductive effect of the alkyl substituent in the secondary amine is operative (nucleophilicity of the amino nitrogen atom increases), and the rate of the reaction with amine **Ib** is higher than with **Ia**. If the binary mixture is enriched with nonpolar component, steric hindrances to attack by electrophile (arenesulfonyl chloride) on the nucleophilic center (amino group) become appreciable, so that the reaction slows down in going from *N*-methyl- to *N*-ethyl- and *N*-butylaniline [2].

The temperature dependence of the rate constants for the reactions of amines **Ia** and **Ib** with sulfonyl

Table 1. Rate constants for the arenesulfonylation of amines **Ia** and **Ib** with sulfonyl chloride **IIa** and hydrolysis of the latter in water–1,4-dioxane mixtures at 298 K

ω_{water} , wt % (X_2 , mole fraction) ^a	$k_h \times 10^4$, s ⁻¹	$k_c \times 10^2$, L mol ⁻¹ s ⁻¹	
		Ia	Ib
10 (0.64)	0.43±0.02	3.20±0.16	–
15 (0.54)	0.99±0.05	4.90±0.20	–
20 (0.45)	1.86±0.09	5.30±0.25	3.63±0.18
25 (0.38)	2.12±0.11	6.10±0.30	6.91±0.35
30 (0.32)	2.74±0.13	8.40±0.40	13.2±0.66

^a Dioxane mole fraction.

chloride **IIa** in aqueous 1,4-dioxane conformed to the Arrhenius equation, and it was used to estimate the activation parameters (Table 2). Comparison of the activation parameters for the reaction of amine **Ib** with 4-nitrobenzenesulfonyl chloride (**IIa**) in water–dioxane mixtures with three different compositions revealed a general tendency for the activation barrier to decrease with rise in the concentration of water. This may be due to specific features of solvation of amine by the solvent components, in particular due to increased fraction of amine–water and amine–dioxane solvate complexes. Loosening of the N–H bond in the activated complex facilitates its cleavage in the arenesulfonylation process.

The energies of activation and changes of the entropies of activation for the reaction of amine **Ia** with arenesulfonyl chloride **IIa** in aqueous 1,4-dioxane and aqueous ethanol with the same water content ($X_2 = 0.38$) turned out to be fairly similar (Table 2; $E_a = 42 \pm 2$ kJ/mol, $-\Delta S^\ddagger = 170 \pm 7$ J mol⁻¹ K⁻¹ for water–ethanol mixtures [4]). Therefore, we can presume similarity in the effects of specific solvation of the reactants and transition state on the reaction rate in water–alcohol and water–dioxane mixtures and a common reaction mechanism in these media.

The kinetic parameters of the arenesulfonylation of *N*-ethylaniline (**Ib**) with 4-methylbenzenesulfonyl chloride (**IIb**) are presented in Table 3. As follows from the data in Tables 1 and 3, sulfonyl chlorides **IIa** and **IIb** are characterized by considerably different reactivities toward **Ib**: the rate constant k_{ac} for **IIa** in water–1,4-dioxane mixtures containing 20 and 30 wt % of water is appreciably higher than the rate constant for **IIb**. This is fully consistent with the classical concepts on the mechanism of arenesulfonylation. Electron-donating methyl group in the *para* position of

Table 2. Kinetic parameters of the arenesulfonylation of amines **Ia** and **Ib** with sulfonyl chloride **IIa** in water–1,4-dioxane mixtures

ω_{water} , wt %	T , K	$k_{\text{ac}} \times 10^2$, L mol ⁻¹ s ⁻¹	ΔH^\ddagger_{298} , kJ/mol	$-\Delta S^\ddagger_{298}$, J mol ⁻¹ K ⁻¹
Ia				
25	298	6.10±0.30	39±2	136±7
	303	10.85±0.54		
	308	19.6±0.98		
	313	20.0±1.00		
Ib				
20	298	3.63±0.18	40±3	107±9
	303	5.13±0.26		
	308	6.76±0.34		
	313	8.71±0.44		
25	298	6.91±0.35	38±3	100±8
	303	9.77±0.49		
	308	12.59±0.63		
	313	15.85±0.79		
30	298	13.20±0.66	32±2	117±9
	303	17.40±0.87		
	308	21.90±1.09		
	313	26.30±1.32		

Table 3. Kinetic parameters of the arenesulfonylation of amine **Ib** with sulfonyl chloride **IIb** in water–1,4-dioxane mixtures

ω_{water} , wt %	T , K	$k_{\text{ac}} \times 10^2$, L mol ⁻¹ s ⁻¹	ΔH^\ddagger_{298} , kJ/mol	$-\Delta S^\ddagger_{298}$, J mol ⁻¹ K ⁻¹
20	298	1.26±0.06	34±2	130±8
	303	1.74±0.09		
	308	2.14±0.11		
	313	2.63±0.13		
30	298	1.58±0.08	39±3	110±9
	303	2.29±0.11		
	308	2.88±0.14		
	313	3.72±0.19		
35	298	3.46±0.17	41±3	96±8
	303	5.01±0.25		
	308	6.46±0.32		
	313	8.51±0.43		
40	298	5.37±0.27	31±2	126±8
	303	7.24±0.36		
	308	8.71±0.44		
	313	10.72±0.54		
45	298	7.08±0.35	19±2	163±10
	303	8.71±0.44		
	308	9.77±0.49		
	313	11.20±0.56		
50	298	7.58±0.38	22±2	153±9
	303	9.33±0.47		
	308	10.72±0.54		
	313	12.50±0.63		

arenesulfonyl chloride **IIb** reduces electrophilicity of the sulfonyl sulfur atom, whereas electron-withdrawing nitro group in **IIa** enhances the electrophilicity, which favors nucleophilic attack by the amino group of **Ib**. Analysis of the activation parameters suggests fairly ordered transition state in the examined reactions (high negative values of ΔS^\ddagger_{298}).

Arenesulfonylation of *N*-alkylanilines in aqueous–organic solvents is always accompanied by hydrolysis of arenesulfonyl chloride, leading to the corresponding arenesulfonic acid as by-product. Taking this into account, we examined the effect of the concentration of water in the binary solvent on the yield of *N*-alkyl-*N*-phenylarenesulfonamides at different initial reactant concentrations. The yields of the acylation product (α_{ac}) and arenesulfonic acid impurity (α_{h}) were

estimated on the basis of the kinetic data (Table 1, 3) by solving differential equation system (5), (6) by the fourth-order Runge–Kutta method.

$$\partial \alpha_{\text{ac}} / \partial \tau = 2k_{\text{ac}}c^0(1 - \alpha_{\text{ac}} - \alpha_{\text{h}})^2; \quad (5)$$

$$\partial \alpha_{\text{h}} / \partial \tau = k_{\text{h}}(1 - \alpha_{\text{ac}} - \alpha_{\text{h}}). \quad (6)$$

The calculated yields of the acylation products α_{ac} are collected in Table 4. It is seen that at an initial reactant concentration higher than 0.1 M, the yield of the sulfonylation product exceeds 90%, regardless of the solvent composition. Therefore, the water–1,4-dioxane system may be recommended as a medium for arenesulfonylation of *N*-alkylanilines.

EXPERIMENTAL

Amines **Ia** and **Ib** (from Aldrich) with a purity of 98–99% were used without additional purification.

Table 4. Calculated yields of the arenesulfonylation products [α_{ac} , reaction (1)] in aqueous–1,4-dioxane at 298 K

ω_{waters} , wt %	c^0 , M	α_{ac} , %		
		Ia + IIa	Ib + IIa	Ib + IIb
10	0.1	96.6	–	91.2
	0.5	99.1	–	97.5
15	0.1	95.3	–	93.6
	0.5	98.7	–	98.2
20	0.1	79.0	91.2	95.3
	0.5	93.3	97.5	98.7
25	0.1	92.9	93.6	91.3
	0.5	98.0	98.2	97.5
30	0.1	93.3	95.3	92.1
	0.5	98.1	98.7	97.8
35	0.1	–	–	95.1
	0.5	–	–	98.7
40	0.1	–	–	96.5
	0.5	–	–	99.1
45	0.1	–	–	96.8
	0.5	–	–	99.2
50	0.1	–	–	96.9
	0.5	–	–	99.2

Sulfonyl chlorides **IIa** and **IIb** of pure grade were recrystallized from hexane–propan-2-ol (9 : 1) with addition of activated charcoal. 1,4-Dioxane (pure grade) was kept for several days over potassium hydroxide and was distilled over metallic sodium

through a column. Distilled water was additionally distilled twice with addition of potassium permanganate in the first distillation.

The kinetics of reaction (1) were studied by the conductometric method with the aid of an E7-14 LCR meter equipped with an OK-9023 platinum ring electrode.

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