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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Optimization of the Synthesis Conditions of Products Formed in Arenesulfonylation of *N*-Alkylated Anilines

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Abstract—Fundamental kinetic aspects of the arenesulfonylation of *N*-alkylated anilines in aqueous-organic media, the nonaqueous component of which are alcohols, ethers, and acetonitrile were studied. It was shown that, with increasing fraction of water in the solvent, the reaction rate constant grows and the reactivity of *N*-alkyl anilines depends not only on the structure of the alkyl radical, but also on the content of water in the solvent. It was found that dimethyl sulfoxide has a catalytic effect on these processes. The strategy of choosing the medium in syntheses of biologically active sulfonyl derivatives of fatty-aromatic amines is discussed. A conclusion about the applicability of aqueous-organic media in the production technology of *N*-alkylated anilines is based on a calculation of the yield of their arenesulfonylation products.

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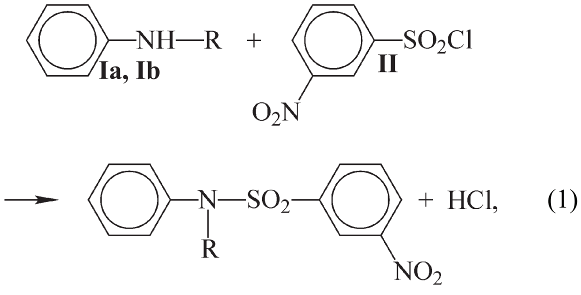
Studies of the fundamental kinetic aspects of how the sulfonamide bond (–NH–SO_2–) is formed in molecules of organic compounds are topical areas of modern organic chemistry and chemical technology because these substances possess quite a number of valuable properties: they exhibit thermal resistance and hydrolytic stability in alkaline media [1, 2] and can serve as medicinal preparations (antibacterial, diuretic, etc.) [3], enzyme inhibitors [4], etc.

Previously, the kinetics of reactions of aliphatic and aromatic amines, amino acids, and arene carbohydrazides with aromatic sulfonic acid chlorides in organic and aqueous-organic solvents has been studied [5–8]. The kinetics of reactions involving fatty-aromatic amines has been insufficiently studied [9]. At the same time, *N*-alkylated anilines are of indubitable interest due to the asymmetry of their structure (presence of an aromatic ring and alkyl moiety in the molecule) and, therefore, can be readily modified at each of the fragments. Use of water as a component of binary solvents seems to be promising because of its accelerating effect on a number of acylation processes of amino compounds. Thus, in view of the high practical importance of products formed in *N*-acylation of fatty-aromatic amines and necessity for finding ways to control their production process, studies of the fundamental kinetic aspects of these reactions seems to be topical.

The goal of our study was to optimize the synthesis conditions of sulfonyl derivatives of *N*-alkylanilines by analysis of the fundamental kinetic aspects of the arenesulfonylation of *N*-methyl- and *N*-ethylanilines with 3-nitrobenzenesulfonic acid chloride (**I**) in aqueous-alcoholic, aqueous-etheric solvents and in the water–acetonitrile system:



where R = Me (**Ia**), Et (**Ib**).

Together with the arenesulfonylation of amines (**Ia, Ib**) in aqueous-organic solvents, there occurs a concurrent process, hydrolysis of sulfonyl chloride(II). Therefore, provided that the initial concentration of the amine (c_a^0) is twice the initial concentration of the acid chloride (c^0), the variation rate of the concentration of the acylating agent is described by the equation

$$-\frac{dc}{d\tau}k_{ac}c_a c + k_h c = 2k_{ac}(c^0 - x)^2 + k_h(c^0 - x), \qquad (2)$$

where x is the change in the concentration of sulfonyl chloride by instant of time τ; c_a and c, running concentrations of the amine and acid chloride, respectively; k_{ac}, rate constant of the second-order reaction (M^{-1} s^{-1}); and k_h, rate constant of hydrolysis of the acid chloride (s^{-1}).

To study the kinetics of reaction (1), we used the conductometric method, with the electrical conductivity of the working solutions measured with an E7-14 immitance meter equipped with an OK-9023 ring platinum electrode at a frequency of 1 kHz. The value of c^0–x was calculated by the equation

$$c^0 - x = c^0\frac{\chi_\infty - \chi_\tau}{\chi_\infty - \chi_0}, \qquad (3)$$

where χ_0, χ_∞, and χ_τ are the electrical conductivities of the reaction mixture at the initial instant of time, instant of time τ, and upon the completion of the reaction, respectively.

The rate constant of the hydrolysis of sulfonyl chloride was determined in an independent kinetic experiment, k_h was calculated on the basis of 80–100 measurements of the electrical conductivity of the acylating agent solution by the Guggenheim method

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

where χ_i and χ_{i+1} are the electrical conductivities of the solution in the intervals of time τ_i and $\tau_{i-1} = \tau_i + \Delta$, and a and Δ are constants.

The errors in determining k_{ac} and k_h we calculated with a confidence probability of 0.95.

The rate constants k_{ac} obtained for the reactions of amines **Ia**, **Ib** with acid chloride(II) in the aqueous-organic solvents under study at various contents of water in the mixture are listed in Table 1.

The data in Table 1 demonstrate a monotonic rise in the acylation rate constant of amines **Ia**, **Ib** with increasing fraction of water in the binary solvent, with the value of k_{ac} possibly increasing by nearly an order of magnitude (see the data for aqueous 1,4-dioxane) on passing from a 10% aqueous solvent to that with 55% water. Among the solvents under study, the most technologically promising solvents are aqueous-alcoholic media because the highest rate constants, up to 0.1 M^{-1} s^{-1}, are observed just in these solvents.

It has been found previously [9] that the rate of arenesulfonylation of secondary fatty-aromatic amines is strongly affected by the steric factor: the larger and more branched the alkyl substituent in the amino group, the lower the acylation rate of the amine. This pattern was experimentally confirmed for a wide variety of secondary amines and solvents. In the reactions under study, k_{ac} depends in a complicated manner on the size of the alkyl radical; in low-polarity media (up to 20 wt % water) the steric factor noticeably affects the rate constant (for example, k_{ac} for the reaction involving *N*-methylaniline in aqueous dioxane is 1.5 times that for the reaction of *N*-ethylaniline). With increasing polarity of the medium, the effect of the steric factor on the rate of the processes under consideration becomes weaker, with the key role passing to the electronic effect of the electron-donor alkyl substituent in the aromatic ring of the amine.

The data in Table 1 suggest that k_{ac} only slightly varies between solvents of the same nature. For example, for 50 wt% water, the value of k_{ac} (**Ia**) in aqueous dioxane was 0.18 M^{-1} s^{-1}, whereas for aqueous THF, this value was 0.196 M^{-1} s^{-1}.

Comparison of the activation parameters of the reactions under study for the aqueous-organic solvent compositions under consideration demonstrates the general tendency toward a decrease in the activation barrier of the reaction with increasing fraction of water in the medium. In all probability, this is due to specific features of the solvation of the amine by molecules of solvent components. The values of $\Delta H^{\neq}_{298}$ vary within the range 20–30 kJ mol^{-1}. The activated complex of the reaction becomes more ordered (reaches a value $\Delta S^{\neq}_{298} = -200$ J mol^{-1} K^{-1}).

It should be noted that the rates of the processes under study in all the aqueous-organic system under study are rather low, and, therefore, it was of interest to find a catalyst. Based on the data of [10], the catalytic influence

Table 1. Rate constants of arenesulfonylation of *N*-alkylated anilines with 3-nitrobenzene sulfonyl chloride in aqueous-organic solvents at 298 K

$\omega(H_2O)$, wt %	$k_{ac} \times 10^2$, M^{-1} s^{-1}				
	$X(H_2O)$, ppm	**Ia**	**Ib**	$X(H_2O)$, ppm	**Ib**
	Water–ethanol as solvent			Water–2-propanol as solvent	
0	0	–	–	0	5.00 ± 0.01
5	0.12	16.4 ± 0.1	11.4 ± 0.6	0.15	–
10	0.22	20.0 ± 0.1	15.3 ± 0.2	0.27	10.60 ± 0.03
15	0.31	34.1 ± 0.2	21.2 ± 0.6	0.37	–
20	0.39	37.5 ± 0.2	28.1 ± 0.2	0.45	16.02 ± 0.01
30	0.52	41.5 ± 0.3	41.2 ± 0.8	0.59	21.50 ± 0.06
40	0.63	43.5 ± 0.4	55.7 ± 0.6	–	–
50	0.72	53.8 ± 0.6	–	–	–
60	0.79	85.5 ± 0.6	–	–	–
	Water–1,4-dioxane as solvent			Water–THF as solvent	
10	0.36	3.2 ± 0.1	–	–	–
15	0.46	4.9 ± 0.2	–	–	–
20	0.55	5.3 ± 0.2	3.6 ± 0.2	–	–
25	0.62	6.1 ± 0.3	6.9 ± 0.4	0.57	4.3 ± 0.2
30	0.68	8.4 ± 0.4	13.2 ± 0.7	0.63	5.9 ± 0.3
35	0.72	–	18.0 ± 0.9	0.68	6.3± 0.3
40	0.77	13.9 ± 0.7	50.0 ± 2.0	0.72	10.0 ± 0.5
45	0.80	14.9 ± 0.7	100.0 ± 5.0	0.76	12.5 ± 0.6
50	0.83	18.0 ± 0.9	–	0.80	19.6 ± 0.9
55	0.86	23.8 ± 1.0	–	–	–
	Water–acetonitrile as solvent				
5	0.11	2.26 ± 0.01			
10	0.20	2.89 ± 0.01			
30	0.49	3.45 ± 0.02			
40	0.60	4.70 ± 0.02			

on the acylation rate of amines is exerted by tertiary amines, hexamethylenephosphotriamide (HMPTA) and dimethyl sulfoxide (DMSO), with the latter regarded in pharmaceutical chemistry as a promising solvent for medicinal preparations. It is known that numerous reactions catalyzed by bases are substantially faster in DMSO, compared with protic solvents. In this context, we studied for the first time the effect of DMSO on the rate of the reaction of **Ia** with **II** in a water–1,4-dioxane binary solvent. It was impossible to use DMSO as a comonent of the binary aqueous-organic solvent because, according to [11], sulfonyl chlorides are unstable in DMSO because of the occurrence of side reactions in which the acid chloride is converted to the corresponding sulfonic acid. The values of k_{ac} for the reaction involving **Ia**, with DMSO as a catalytic acid, are listed in Table 2.

The data in Table 2 suggest that introduction of the DMSO catalytic additive leads to an increase in k_{ac}, with the acylation constant the higher, the lower the DMSO concentration. In all probability, the observed experimental fact can be accounted for by the occurrence of side reactions at equimolar ratios between DMSO and 3-nitrobenzene sulfonyl chloride.

In aqueous-organic media, a side process, hydrolysis of 3-nitrobenzene sulfonyl chloride, occurs together with main reaction of arenesulfonylation of *N*-alkylated anilines. Therefore, the system always contains, together with the target product, an admixture of arenesulfonic acid. Therefore, it was of interest to determine how the content of water in the binary solvent affects the yield α_{ac} of the target products 3-nitrobenzenesulfo(*N*-alkyl) anilides at various initial concentrations of the reagents. Using the kinetic data in Table 1 we calculated the yield α_{ac} of the arenesulfonylation product and the fraction α_h of the admixture of 3-nitrobenzene sulfonic acid by solving the system of differential equations (5) and (6) by the 4th order Runge–Kutta method:

$$\begin{cases} \dfrac{d\alpha_{ac}}{d\tau} = 2k_{ac}c^0(1-\alpha_{ac}-\alpha_h)^2, & (5) \\ \dfrac{d\alpha_h}{d\tau} = k_h(1-\alpha_{ac}-\alpha_h). & (6) \end{cases}$$

The calculated values of αac upon full completion of reaction (1) involving **Ia** in aqueous-etheric media are listed in Table 3.

In the case of aqueous-alcoholic solvents and the water–acetonitrile system, the yield of the target products at the initial reagent concentration of 0.5 M also exceeded 95%. This suggests that these media can be recommended for synthesis of arenesulfonylation products of *N*-alkylanilines.

Amines **Ia**, **Ib** (Aldrich) with 98–99% main substance were used without additional purification. The acid chloride(II) of pure grade was recrystallized from a 9 : 1 mixture of hexane and 2-propanol with addition of activated carbon. 1,4-Dioxane and THF, both of pure grade, were kept over KOH for seven days and distilled in a column over metallic sodium. Ethanol of pure grade, 2-propanol of chemically pure grade, and acetonitrile of pure grade were dried and distilled in a column under atmospheric pressure. Twice distilled water was used, with potassium permanganate added in the first distillation.

Table 2. Rate constants of acylation of (Ia) in a water–1,4-dioxane solvent in the presence of a catalytic DMSO additive, $\omega(H_2O)$ = 35 wt %, 298 K

c^0_{DMSO}, M	$k_{ac} \times 10^2$, M^{-1} s^{-1}	c^0_{DMSO}, M	$k_{ac} \times 10^2$, M^{-1} s^{-1}
0	11.40	0.009	62.10
0.002	170.00	0.01	50.00
0.006	96.30		

Table 3. Calculated yield α_{ac} of 3-nitrobenzenesulfo(*N*-methyl) anilide and fraction α_h of 3-NBSA admixture in aqueous-organic solvents at 298 K

$\omega(H_2O)$, wt %	c^0, M	α_{ac}	$\omega(H_2O)$, wt %	c^0, M	α_{ac}
		Water–1,4-dioxane			
10	0.1	0.968	40	0.1	0.916
	0.5	0.991		0.5	0.976
15	0.1	0.954	45	0.1	0.888
	0.5	0.988		0.5	0.967
20	0.1	0.929	50	0.1	0.899
	0.5	0.980		0.5	0.971
25	0.1	0.929	55	0.1	0.912
	0.5	0.980		0.5	0.975
30	0.1	0.933			
	0.5	0.982			
		Water–THF			
25	0.1	0.897	40	0.1	0.928
	0.5	0.970		0.5	0.980
30	0.1	0.915	45	0.1	0.932
	0.5	0.976		0.5	0.981
35	0.1	0.913	50	0.1	0.946
	0.5	0.975		0.5	0.986

CONCLUSIONS

(1) The acylation kinetics of *N*-methyl- and *N*-ethylaniline with 3-nitrobenzenesulfonic acid chloride in five aqueous-organic solvents whose nonaqueous components are ethanol, 2-propanol, acetonitrile, 1,4-dioxane and terahydrofuran, was studied. It was found that, with increasing content of water in the solvents, the rate constants of all the reactions under study grows, with its maximum value reached in aqueous-alcoholic systems.

(2) It was demonstrated the reactivity of *N*-alkylanilines is affected not only by the structure of the alkyl radical, but also by the solvent composition. In all the

aqueous-organic solvents studied, a higher reactivity in the arenesulfonylation reaction is demonstrated by *N*-methylaniline at low content of water (up to 20 wt %), and by *N*-ethylaniline at high content of water.

(3) It was found that dimethyl sulfoxide exerts a catalytic influence on the processes under consideration.

(4) The kinetic data obtained were used to calculate the yield of arenesulfonylation products of *N*-alkylated anilines. For all the solvents under study, the yield exceeded 95% at an initial reagent concentration of 0.1 M and more, which suggests that aqueous-organic systems can be used in the production technology of arenesulfo(*N*-alkyl)anilides.

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