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Arenesulfonylation of *N*-alkylanilines: reaction kinetics and mechanism

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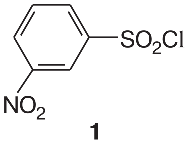
Kinetic regularities of arenesulfonylation of *N*-alkylanilines in binary water-organic solvents of variable composition have been studied. The rate constants for these reactions increase with increasing the water content in a system. The steric factor has the decisive influence on reactivity of *N*-alkylamines. The character of the influence of the composition and nature of a solvent on the rate constants for arenesulfonylation was discussed with the assistance of results of quantum chemical simulation of molecular complexes of the nucleophiles studied with the components of the binary systems. Calculation of potential energy surface for the reaction of *N*-methylaniline with benzenesulfonyl chloride showed that in the gas phase the process occurs by the S_N2 mechanism.

Key words: sulfonylation, *N*-alkylanilines, arenesulfonyl chlorides, aqueous organic solvents, quantum chemical simulation, reactions mechanisms.

Elucidation of the correlation between kinetic characteristics of reactions and molecular parameters of the reactants allows one to predict the reactivity of compounds in various processes, to quantificate it, and also presents a tool for the indirect establishment of the reaction mechanisms enabling the targeted management of the reaction course.

Nowadays, kinetics and mechanisms of the acyl transfer are intensively studied.[1—7] We have shown,[1—4] that reactivity of substituted arylamines, aminobenzoic acids and diamino acids in *N*-acylation was determined by both electronic and orbital characteristics of nucleophilic agents. Quantum chemical modeling of the reaction path for D,L-α-alanine and 3-nitrobenzenesulfonyl chloride (**1**) under conditions whereby mono-, di-, and trihydrates of alanine are formed has shown that the reaction energy profile depends significantly on the specific solvation of alanine by water molecules.[1] Rate constants and activation parameters for reactions of morpholine and piperidine with 4-toluenesulfonyl chloride and benzenesulfonyl chloride in water (40 wt.%)—1,4-dioxane mixture were determined.[2] Using the method for construction of the potential energy surface (PES), the reaction between piperidine and benzenesulfonyl chloride was established to proceed according to the S_N2-mechanism. Under the same conditions, kinetics of arenesulfonylation of α- and β-alanine, dipeptides derived therefrom, glycylglycine, L-proline, and L-asparagine was studied. Correlations between the rate constants for arenesulfonylation of amino acids and dipeptides, and the rate constants for interaction of the latter compounds with acyl donors (benzoyl chlorides and picryl benzoate) were established, suggesting the basicity of the amino groups of amino acids and dipeptides to be a key factor in their nucleophilic reactivity.[3] It should be noted that the data on quantitative studies of acetylation and benzoylation of amines in various media is covered in literature much more widely compared to the quantitative characteristics of sulfonylation of these compounds.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Studies of the processes of sulfamide formation is of current concern, since the products of such reactions have valuable properties (such as *e.g.*, thermostability and hydrolytic stability in alkaline media[8]) making these compounds useful in synthesis of thermostable and chemically stable polymers. Being bioactive, these compounds are widely used in pharmacology and medicine as anaesthetics, in treatment of bacterial infections, display diuretic and antihypertensive action, inhibit enzymes,[9—12] *etc.*

N-Alkylated anilines extend the capabilities of organic and pharmaceutical synthesis due to a presence of aromatic ring and alkyl group in their molecules, allowing functionalization of each of these moieties. Literature data on reactivity of mixed amines in reactions affording compounds containing the sulfamide bond are rather scarce.[13,14] In the present study, kinetic data for the reactions of *N*-methyl, *N*-ethyl, and *N*-butylanilines (**2a—c**) with compound **1** in mixtures of water with EtOH, propan-

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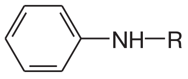
2-ol, 1,4-dioxane, THF and acetonitrile of variable composition were analyzed within the framework of the QSPR-approach (Quantitative Structure — Property Relationship).



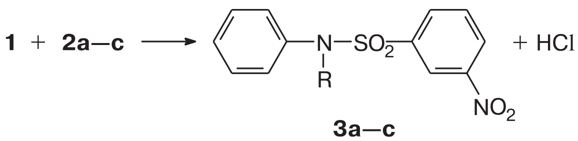
2a—c

R = Me (**a**), Et (**b**), Bu (**c**)

Experimental

N-Alkylanilines **2a—c** react with compound **1** according to Scheme 1.

Scheme 1



3a—c

R = Me (**a**), Et (**b**), Bu (**c**)

The reaction kinetics (see Scheme 1) was studied using conductometric method. Electrical conductivities of the work solutions were measured on a E7-14 LCR meter equipped with OK-9023 platinum ring electrode at a frequency of 1 kHz.

Arenesulfonylation of amines in water— organic solvents is accompanied by hydrolysis of sulfonyl chloride, therefore the rate of the change in the sulfonylation agent concentration provided that concentration of an amine ($c_a{}^0$) is twofold higher than the initial concentration of an acid chloride (c^0), follows the equation

$$-dc/d\tau = k_{ac}c_ac + k_hc = 2k_{ac}(c^0 - x)^2 + k_h(c^0 - x). \quad (1)$$

Herein x is the change in the concentration of sulfonyl chloride by the time τ; c_a and c are current concentrations of an amine and an acid chloride, respectively; k_{ac} is the rate constant for the second order reaction (L mol^{-1} s^{-1}); k_h is the rate constant for the acid chloride hydrolysis (s^{-1}). The value of ($c^0 - x$) was calculated according the equation

$$(c_0 - x) = c_0(\chi_\infty - \chi_\tau)/(\chi_\infty - \chi_0), \quad (2)$$

wherein χ_0, χ_τ, and χ_∞ are electrical conductivities of the reaction mixture at the start time, at the time τ, and after completion of the reaction, respectively.

The rate constant for hydrolysis of sulfonyl chloride **1** was determined in the independent kinetic experiment, k_h value was calculated from 80—100 measurements of the electrical conductivity of the solution of the given agent by the Guggenheim method:[14]

$$\ln(\chi_{i+1} - \chi_i) = \mathrm{A} + k_h\tau_i. \quad (3)$$

Herein χ_i and χ_{i+1} are the electrical conductivities of a solution at the time τ_i and $\tau_{i+1} = \tau_i + \Delta$, A and Δ are constants. Measurement errors for k_{ac} and k_h were calculated with a confidence level of 0.95.

Secondary amines **2a—c** (Aldrich, 98—99%) were used as purchased. Compound **1** («pure grade») was recrystallized from a (9 : 1) hexane—propan-2-ol mixture with addition of activated carbon; 1,4-dioxane («pure grade») and THF («pure grade») were stored over KOH for seven days, and distilled over sodium metal. Ethanol («pure grade»), propan-2-ol («pure grade»), and acetonitrile («pure grade») were dried and distilled with Vigreux column at atmospheric pressure. Water—organic solvents were prepared using bidistillate obtained on a DW-1 demineralized water generator.

Results and Discussion

Results of the previous kinetic study of reactions between a series of secondary alkylamines and arenesulfonyl chlorides in individual organic solvents[15] suggest that on a number of parameters these processes are similar to arenesulfonylation of anilines. At the same time, substituents at the amino group of the unsymmetric amines have a noticeable effect on their reactivity. For example, rate constants for the reaction of substituted *N*-isobutylanilines ($\mathrm{ArNHBu^i}$) and sulfonyl chloride **1** are significantly lower (Table 1) compared to the corresponding less basic anilines $\mathrm{ArNH_2}$ (*cf* pK_a = 5.43 for the protonated $\mathrm{PhNHBu^i}$ and 4.60 for $\mathrm{PhNH_2}$).[16] On the one hand, introduction of an alkyl substitutent into the amino group of an arylamine increases the nucleophilicity of the N atom, rising its reactivity. On the other hand, the alkyl radical creates steric hindrances during formation of an activated complex, what should diminish the acylation rate. As can be seen from Table 2, the steric factor dominates in reaction of sulfonyl chloride **1** with *N*-alkylanilines, the more branched is an alkyl substituent and the higher volume it has, the lower is the reaction rate.[15]

Rate constants for the reaction of compound **2a** and benzenesulfonyl chloride (T = 298 K) in various organic solvents ($k \cdot 10^2$/L mol^{-1} s^{-1}) were determined[15] being 1.82±0.02 for propan-2-ol, 13.22±0.06 for DMF, 1.35±0.02 for acetonitrile, 0.062±0.002 for ethyl methyl

Table 1. Rate constants for the reactions of anilines and *N*-*iso*-butylanilines with compound **1** in propan-2-ol (298 K)[15]

Ar	$k \cdot 10^2$/L mol^{-1} s^{-1}	
	$\mathrm{ArNHBu^i}$	$\mathrm{ArNH_2}$
4-$\mathrm{MeC_6H_4}$	3.48±0.07	93.7±2.1
3-$\mathrm{MeC_6H_4}$	1.69±0.03	45.3±2.1
4-$\mathrm{EtC_6H_4}$	3.38±0.06	76.2±4.6
3-$\mathrm{EtC_6H_4}$	1.54±0.05	47.6±2.2
Ph	0.81±0.02	29.2±1.0
3-$\mathrm{MeO_2CC_6H_4}$	0.43±0.01	3.83±0.10
4-$\mathrm{MeO_2CC_6H_4}$	0.22±0.01	0.51 ±0.05
4-$\mathrm{EtO_2CC_6H_4}$	0.16±0.01	0.40±0.04

Table 2. Rate constants for the reaction of amines PhNHAlk with compound **1** in propan-2-ol (298 K)[15]

Alk	$k \cdot 10^2$/L mol^{-1} s^{-1}
Me	7.03±0.02
Et	5.02±0.01
Pr^i	0.25±0.01
Bu	3.21±0.02
Bu^i	0.81±0.02
$Me_2CH(CH_2)_2$	1.98±0.03
$PrCH(Me)CH_2$	0.86±0.01
Et_2CHCH_2	0.98±0.01
n-C_7H_{15}	1.15±0.01
n-C_8H_{17}	1.46 ±0.02

ketone, and 0.34±0.01 for acetone. Linear relationships between log*k* and parameters of basicity (*B*) and electrophilicity (*E*) of a solvent were established:

$$\lg k = -(14.57\pm0.73) + (0.05\pm0.01)B,$$
$$r = 0.99,\ s = 0.06,\ n = 3, \qquad (4)$$

$$\lg k = -(10.36\pm2.55) + (0.18\pm0.06)E,$$
$$r = 0.91,\ s = 0.34,\ n = 4. \qquad (5)$$

Relationships (4) and (5) suggest a significantly higher contribution of specific interactions in solution compared to non-specific ones in kinetics of the reaction between amine **2a** and $PhSO_2Cl$. Similar effect is also typical of reactions between areneamines and sulfonyl chlorides in organic media.[17]

Addition of water into the system increases markedly the rates of acylation reactions for many amino compounds[15,18] including anilines. For example, *k* value for the reaction of aniline with $4\text{-}O_2NC_6H_4SO_2Cl$ increases sevenfold upon changing the water content in 1,4-dioxane from 30 up to 60 wt.%.[14] Results on studying the effect of composition of water—alcohol mixtures on kinetics of reactions between *N*-alkylanilines **2a—c** and sulfonyl chlorides **1** are presented in Table 3.

Reference to Table 3 shows that given the same proportion of water in the system, the rate constants for the amine **2b** sulfonylation are higher by a factor of 1.5—2 over the aqueous ethanol, thus correlating with polarity and solvating capacity of these solvents. Reactivity of amines rises in the row **2c** < **2b** < **2a**, suggesting that steric factors play a decisive role in kinetics of arenesulfonylation in water—alcohol media as well as in the individual solvents. As the molar fraction of water increases up to 0.63, a reversion of reactivity of **2b** and **2a** is observed, allowing anticipating more profound influence of steric effects of a substituent in low-polarity media.

Rates of all the reactions rise on increasing the molar proportion of water (X_1) in the system, however, changing the solvent has a little effect on the rate constant, and moving from organic solvents to water—alcohol mixtures increases it by no more than five times.

Results of kinetic study of reactions of *N*-methyl- (**2a**) and *N*-ethylanilines (**2b**) with sulfonyl chloride **1** in aqueous solutions of 1,4-dioxane, THF, and acetonitrile are given in Table 4.

Significant decrease in the *k* value of arenesulfonylation of the unsymmetric amines compared to that for aniline[15] suggests that sterical hindrances due to the introduction of an alkyl substituent into the amino group has stronger influence on the reaction rate compared to its electronic effect increasing the nucleophilicity of the N atom.

Activation parameters for the reaction **2b** + **1** in aqueous 1,4-dioxane are presented in Table 5. The activation barrier tends to decrease a little as the water percentage in the system increases, which may be connected with peculiarities of the solvation of an amine and the transition state by the components of a binary solvent.

Table 3. Rate constants[15] for the reactions between *N*-alkylanilines **2a—c** and compound **1** in water-alcohol media (T = 298 K)

X_1*	$k \cdot 10^2$/L mol^{-1} s^{-1}	
	2a	**2b**
Water—ethanol		
0	—	—
0.12 (5)	16.4±0.1	11.4±0.6
0.22 (10)	20.0±0.1	15.3±0.2
0.31 (15)	34.1±0.2	21.2±0.6
0.39 (20)	37.5± 0.2	28.1±0.2
0.52 (30)	41.5±0.3	41.2±0.8
0.63 (40)	43.5±0.4	55.7±0.6
0.72 (50)	53.8±0.6	—
0.79 (60)	85.5±0.6	—

X_1*	$k \cdot 10^2$/L mol^{-1} s^{-1}	
	2b	**2c**
Water—propan-2-ol		
0	5.00±0.01	3.21±0.02
0.15	—	5.21±0.04
0.27	10.60±0.03	7.45±0.04
0.37	—	9.45±0.04
0.45	16.02±0.01	11.20±0.08
0.59	21.50±0.06	13.10±0.25

* Molar fraction of water in a solvent (given in parentheses is weight percentage).

Table 4. Rate constants for the reactions between *N*-alkylanilines **2a**,**b** and compound **1** (T = 298 K)

X_1*	$k \cdot 10^2$/L mol^{-1} s^{-1}		X_1*	$k \cdot 10^2$/L mol^{-1} s^{-1}
	2a	**2b**		**2a**
Water —1,4-Dioxane			Water—THF	
0.36	3.2±0.1	—	0.57	4.3±0.2
0.46	4.9±0.2	—	0.68	6.3±0.3
0.55	5.3±0.2	3.6±0.2	0.72	10.0±0.5
0.62	6.1±0.3	6.9±0.4	0.76	12.5±0.6
0.68	8.4±0.4	13.2±0.7	Water—acetonitrile	
0.77	13.9±0.7	50±2	0.11	2.26±0.01
0.80	14.9±0.7	100±5	0.20	2.89±0.01
0.83	18.0±0.9	—	0.49	3.45±0.02
0.86	24±1	—	0.60	4.70±0.02

* Molar fraction of water in a solvent.

Table 5. Kinetic characteristics and activation parameters for the reaction between *N*-ethylaniline **2b** and compound **1** in aqueous 1,4-dioxane

ω* (wt.%)	T/K	$k \cdot 10^2$ /L mol^{-1} s^{-1}	$\Delta H^{\neq}_{298}$ /kJ mol^{-1}	$-\Delta S^{\neq}_{298}$ / kJ mol^{-1} K^{-1}
20	303	5.1±0.3	43±2	82±7
	308	6.8±0.3	43±2	82±7
	313	8.7±0.4	43±2	82±7
25	303	9.8±0.5	40±2	132±7
	308	12.6±0.6	40±2	132±7
	313	15.9±0.8	40±2	132±7
30	303	17.4±0.9	33±2	150±7
	308	21.9±1.1	33±2	150±7
	313	26.3±1.3	33±2	150±7

* Weight percent of H_2O in the solvent.

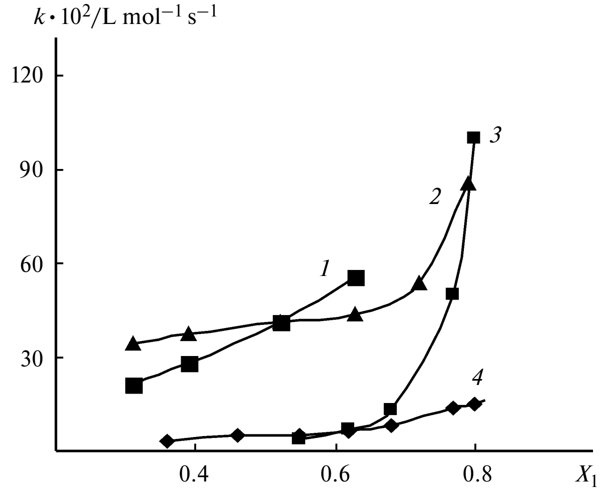


Fig. 1. Relationships between k values for sulfonylation of *N*-alkylanilines **2a**,**b** with reagent **1** and composition of water-organic solvents: **2b** (*1*), water—ethanol; **2a** (*2*), water—ethanol; **2b** (*3*), water—1,4-dioxane; **2a** (*4*), water—1,4-dioxane (X_1 is a molar proportion of water).

Sulfonylation rate constants rise with an increase in the water content in all the binary solvents tested. The most intensive rise of the k value (by nearly 30-fold) takes place in the reaction **2b** + **1** in the system water—1,4-dioxane, and the most high values of k are observed in water-alcohol media (see Tables 3, 4 and Fig. 1). Monotonic character of the relationship between k and the solvent composition is in good agreement with the data on thermochemical study of the water-alcohol and water-dioxane mixtures:[19] heats of mixing of components of these mixtures in the tested range of compositions also demonstrate monotonic changes.

Of special attention is the character of relationship between the rate constants for sulfonylation of **2a** and **2b** and the composition of water-alcohol and water-ether solvents (see Fig. 1). In low-polarity media (up to 20 wt.% of water) the rate constant for the reaction **2a** + **1** is nearly 1.5 times higher than that for **2b** + **1** reaction, what is apparently connected with the predominant influence of the steric factor on the reaction rate. It may be assumed that the steric hindrance effect falls off with increase in the medium polarity, and the electron-donating effect of an alkyl substituent in the amino group begins to play a decisive role, therefore the ratio of the rate constants changes in favor of **2b** in both binary systems. At the same time, along with the change in solvent polarity and electronic effects of substituents, the reaction rate may be influenced by the changes in the reagent solvation, occurring upon changing the medium composition.

The data[7,15—17] testify to the fact that specific solvation of an amine has a predominant influence on the reaction rate in arenesulfonylation as well as in the other acyl transfer reactions involving amines, the solvation of a sulfonating agent playing a small part. This conclusion is consistent with the data on the reported thermochemical studies.[20]

It should be noted that the existence of 1 : 1 H-complexes of aniline in the solvents of various nature including 1,4-dioxane,[21] methanol, and water[22—24] was confirmed experimentally. In THF[25,26] 1 : 1 and 1 : 2 complexes were detected. Formation of H-complexes of aniline and a series of organic solvents is also confirmed by the quantum chemistry methods.[22,25,26]

It is believed that similar to arylamines, *N*-alkylarylamines exist in solution as amine—solvent molecular complexes of various structure. In solution, a dynamic equilibrium between solvatocomplexes takes place, which can be shifted upon changes in a binary system composition. Reactivity of solvatocomplexes is to depend on their structure and stability. Since, as noted above, solvation of sulfonyl chloride has no meaningful effect on the rate of sulfonylation of amines, so the rate constants of the reactions

Table 6. Quantum chemical parameters of solvatocomplexes of *N*-alkylanilines **2a,b** (calculated using the RHF/6-31G(d) method)

Complex	$-\Delta E_k$/kJ mol^{-1}	E_{HOMO}/eV	$C_{2pz}(N)^2$	$\varphi_{2pz}(N)$	$q(N)/e$	$r(N-H)$/Å
2a·$2H_2O$	29	−7.95	0.163	1.418	−0.832	0.999
2a·H_2O·EtOH	31	−7.89	0.231	1.538	−0.835	0.999
2a·H_2O·1,4-dioxane	37	−7.86	0.178	1.443	−0.861	0.997
2b·$2H_2O$	36	−7.97	0.306	1.703	−0.846	1.001
2b·H_2O·EtOH	50	−7.73	0.279	1.623	−0.859	1.000
2b·H_2O·1,4-dioxane	45	−7.81	0.237	1.562	−0.878	1.001

Note. $-\Delta E_k$ is the energy of complex formation calculated as a difference between total energies of complexes and separate molecules forming the complexes, E_{HOMO} is energy of the highest occupied molecular orbital of an amine, $C_{2pz}(N)$ and $\varphi_{2pz}(N)$ are contribution of the $2p_z$-orbital of the N atom of the amino group to the HOMO of amine and its occupation, $q(N)$ is an amount of charge on the N atom, $r(N-H)$ is a N—H bond length in an amine.

under consideration can be associated with the structure and properties of solvatocomplexes of the mixed amines with components of water-organic solvents.

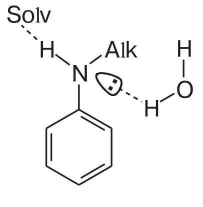
To elucidate the role of the specific solvation of *N*-alkylanilines in kinetics of their arenesulfonylation within the framework of the QSPR-approach, we carried out quantum-chemical modeling of solvatocomplexes **2a** and **2b** with water, 1,4-dioxane, and EtOH having the following compositions: **2a**·$2H_2O$, **2a**·H_2O·EtOH, **2a**·H_2O·1,4-dioxane, **2b**·$2H_2O$, **2b**·H_2O·EtOH, and **2b**·H_2O·1,4-dioxane. Calculations were performed using Firefly 7.1G software.[27] Selected data of calculations are given in Table 6.

As can be seen from Table 6, energies of complex formation (ΔE_K) for all solvatocomplexes have high negative values, suggesting stability of these particles and high probability of their existence in solution.

Comparison of geometrical and charge characteristics of reaction centers, *i.e.* imino groups of the solvated amines with the rate constants for the reactions **2a** + **1** or **2b** + **1** showed no correlation. Earlier we have found that acylation of aliphatic amines and α-amino acids presents orbital-controlled reactions, wherein the values of occupation density ($\varphi_{2pz}(N)$) and squared contributions of $2p_z$-AO of the nitrogen atom in HOMO ($C_{2pz}(N)^2$) can serve as descriptors of reactivity of amino compounds and their molecular compexes with the solvent components.[3,17,18] Therefore, kinetic data on reactions between *N*-alkylanilines **2a—c** with sulfonyl chloride **1** and characteristics of the nitrogen $2p_z$-AO in solvatocomplexes of nitrogen **2a** and **2b** were compared. It was found that the experimentally observed increase in the *k* value for arenesulfonylation in aqueous alcohols by contrast to aqueous 1,4-dioxane (see Fig. 1, Tables 3, 4) correlates with higher values of occupancies and squared contributions of the nitrogen $2p_z$-AO to HOMO in complexes of amines with H_2O and EtOH as compared to complexes of amines with H_2O and 1,4-dioxane (see Table 6).

Change in the reactivity ratio for **2a** and **2b** with an increase in proportion of water in the binary solvent (see Fig. 1) can also be explained within the framework of the QSPR-approach. It should be noted that in all complexes, a molecule of water (or one of the water molecules) is an H-donor forming hydrogen bond with lone-pair electrons of the N atom, while the molecule of the second component of a solvent or the second molecule of water presents an H-acceptor forming a bond with the H atom of the amino group.

One can assume that at small concentrations of water in the binary systems, amines **2a,b** exist mostly as mixed complexes of **2b**·H_2O·Solv and **2a**·H_2O·Solv composition (Solv is a molecule of ethanol or 1,4-dioxane). Judging from higher values of $\varphi_{2pz}(N)$ and $C_{2pz}(N)^2$, particles of **2b**·H_2O·Solv should be more reactive compared to those of **2a**·H_2O·Solv. However the formation of a transition state requires some energy to break the H-bond with the water molecule which is an H-donor. Energy requirements will be higher for more stable **2b**·H_2O·Solv complexes having higher absolute values of energies of complex formation ΔE_K (see Table 6). Because of this, reactivity of **2b**·H_2O·Solv in media with a high proportion of an organic component will be lower than that of **2a**·H_2O·Solv.



Solv is the molecule of ethanol or 1,4-dioxane.

As the content of water rises, equilibrium in solution can shift towards **2b**·$2H_2O$ and **2a**·$2H_2O$ complexes. Dihydr ates **2b** should be more reactive than dihydrates **2a** having lower values of $C_{2pz}(N)^2$ and $\varphi_{2pz}(N)$. As a result, with increasing the proportion of water in both binary systems, the rate constant for the reaction **2b** + **1** rises compared to the *k* value of **2a** arenesulfonylation. Since the complexes **2b**·2H_2O are the most reactive among all modeled structures (see Table 6), at X_1 = 0.8 the rate constant for the reaction **2b** + **1** in aqueous 1,4-dioxane becomes higher than that in aqueous ethanol.

Thus, an inversion of the ratio of the rates of reactions between sulfonyl chloride **1** and **2b** or **2a**, taking place on change in the composition of binary solvents, is associated with an effect of several factors. In the media enriched with an organic component (1,4-dioxane or alcohol), reactivity of amines is influenced mainly by steric hindrances caused by ethyl group of amine **2b**, as well as by high energy consumption for desolvation of the molecule of this amine before the transition state formation, lowering the reactivity of the above amine compared to that of **2a**. With increase in the water content in the system, reactive dihydrates **2b** are formed whereby the sulfonylation rate for **2b** exceeds that for **2a**.

Since the rates of reactions between *N*-alkylanilines and arenesulfonyl chlorides in the tested solvents are moderate, the search for a catalyst is necessary. Addition of DMSO to a solution was found to increase the rate of the reaction **2a** + **1**, the less is the DMSO concentration (c_{DMSO}), the higher is the reaction rate (Table 7). The observed experimental fact can apparently be attributed to the side reactions proceeding with equimolar amounts of DMSO and sulfonyl chloride **1**.

Catalytic effect of DMSO can be accounted for its ability to activate *N*-methylaniline (**2a**) due to the transfer of the amine proton to the O atom of the S=O moiety. This proposal is confirmed by the data on the quantum chemical modeling of interaction between molecules of **2a** and DMSO (Table 8). Results of calculations demonstrated that formation of a hydrogen bond between the amino group hydrogen atoms and the DMSO oxygen atom increases the reactivity of the system **2a** — DMSO both due to an increase in the negative charge on the N atom, and an increase in the values of the HOMO energy, occupancies (φ_{2pz}(N)), and squared contributions of the nitrogen 2p_z-AO to the HOMO ($C_{2pz}(N)^2$).

To elucidate the reaction mechanism for arenesulfonylation of *N*-alkylanilines we performed the quantum chemical calculation of PES for the reaction between amine **2a** and $PhSO_2Cl$ in the gaseous phase. The calculations were performed in the supermolecular approximation using DFT//B3LYP/6-311G(d,p) method. Three-dimensional PES was calculated in coordinates of *r*(S—N) distance ranging from 1.5 to 4.5 Å, and an attack angle of a nucleophile (amine) on the (C_{Ar}—S—N) sulfonyl group ranging from 90° (frontal attack) to 180° (axial attack) with a step of 10°.

Table 7. Rate constants for the reaction between *N*-methylaniline **2a** and compound **1** in water—1,4-dioxane mixture (proportion of H_2O is 35 wt.%) with addition of DMSO

c_{DMSO} /mol L^{-1}	$k \cdot 10^2$ /L mol^{-1} s^{-1}
0	11.4±0.3
0.002	170±5
0.006	96±3
0.009	62±2
0.01	50±2

Table 8. Results of the quantum chemical modeling of the interaction between molecules of *N*-methylaniline **2a** and DMSO (RHF/6-31G(d) method)

Parameter	**2a**	**2a**·DMSO
q(N)/*e*	−0.767	−0.821
r(N—H)/Å	0.997	0.998
E_{HOMO}/eV	−7.76	−7.07
φ_{2pz}(N)	1.758	1.769
$C_{2pz}(N)^2$	0.372	0.425

The above parameters were recorded in each point of PES, and geometry of the reacting system of molecules was optimized. Basing on the results of analysis of the PES obtained, the position of the saddle point corresponding to the reaction transition state (TS) was determined. Consistency between the structure found and activated reaction complex was confirmed by the presence of one imaginary frequency in the vibrational spectrum. The PES obtained is shown in Fig. 2.

There is a single saddle point on the contour map, answering to the reaction TS and lying on the path of minimal energy which corresponds to the frontal attack of nucleophile on the sulfonyl reaction center at an angle of ~100°. Throughout the interaction this angle varies only slightly reaching 96° in the TS and increasing up to 110° in the sulfamide reaction product. Reaction products are formed at *r*(S—N) ≈ 1.8 Å. At the same time an abstraction of HCl takes place, this being testified by the lengths of the breaking N—H and S—Cl bonds which are equal to 1.027 and 2.828 Å in the TS and constitute 1.931 and 4.272 Å in the product, respectively, as well as by the length of the H—Cl bond being formed: the latter is 2.062 Å in the TS, and 1.321 Å in the product. In this case the N—H and S—Cl bonds become coplanar, as evidenced by the value of the torsion angle Cl—S—N—H which is equal to 7.03° in the TS, and to 0.61° in the product.

Thus, the reaction proceeds without formation of intermediates, with a single TS at *r*(S—N) = 2.6 Å according the bimolecular nucleophilic substitution (S_N2) mechanism, what is in an agreement with the results of modeling of other acyl transfer reactions.[28]

Resuts of calculation of the activated complex (AC) of the reaction are given in Table 9 and in Fig. 3.

As can be seen from Fig. 3 and Table 9, AC of the above reaction has a structure similar to a tetragonal pyramid.

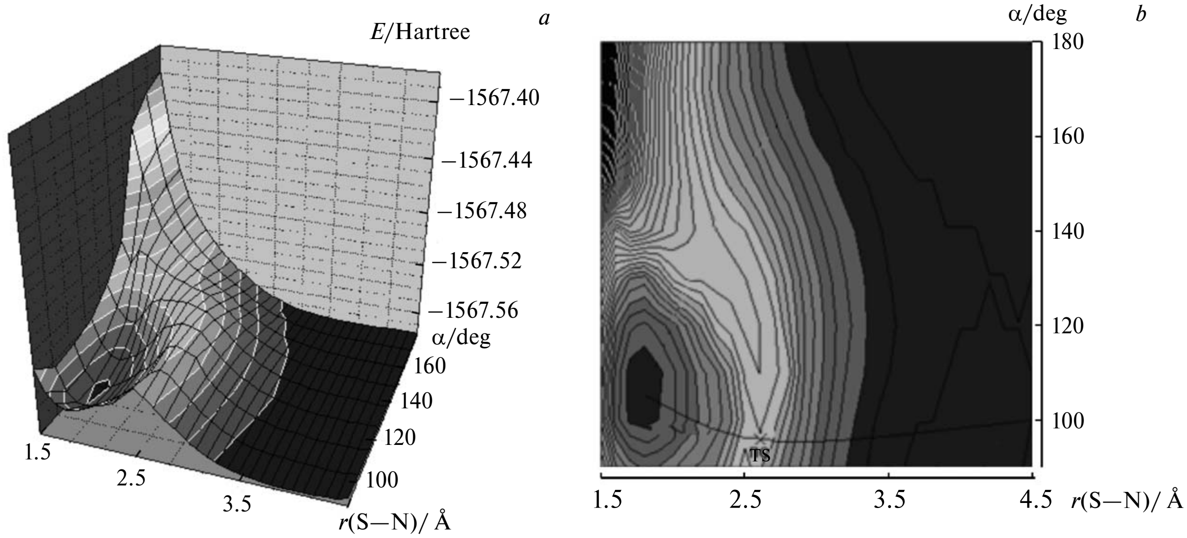


Fig. 2. Three-dimensional view (*a*) and contour map (*b*) of PES for the reaction between *N*-methylaniline **2a** and $PhSO_2Cl$ (direction of attack of molecule **2a** changes from the frontal to the axial one); α is an angle of attack (C_{Ar}—S—N), × is a transition state (TS) for the reaction.

This is consistent with the literature data[29] from which it follows that in the case of frontal attack of a nucleophile the TS is formed having the structure of tetrahedral pyramid with the S atom in its base.

The value of the activation energy of the reaction under investigation calculated as a difference in the energies of formation of the AC and reactants proved to be 112.8 kJ mol^{-1}; this high value can be explained by the fact that the process was modeled for the gaseous phase. According to the literature data,[28,30] modeling the acyl transfer reactions in view of the influence of solvation of amino compounds decreases significantly the reaction energy barriers.

In conclusion, we have studied kinetics of arenesulfonylation of *N*-alkylanilines PhNHAlk (**2a—c**) in binary mixtures of water and ethanol, propan-2-ol, 1,4-dioxane, THF, and acetonitrile, having a variable composition. Reactivity of amines rises along the row of **2c** < **2b** < **2a** (Bu < Et < Me) suggesting the predominant role of steric factors in kinetics of arenesulfonylation. The growth of the rate constants for arenesulfonylation of amines **2a—c**, observed on increasing the content of water in all tested binary systems was established. Effect of nature and composition of the binary solvents on reactivity is explained using quantum chemical modeling data on the basis of specific solvation of the mixed amines in solution. According to the calculations, sulfonylation of amino compounds in the gaseous phase proceeds by the bimolecular concerted mechanism.

Table 9. Geometrical and energy characteristics of the activated complex of amine **2a** with $PhSO_2Cl$

Parameter	Value
r(S—N)/Å	2.600
r(S—Cl)/Å	2.828
P(S—N)	0.19
P(S—Cl)	0.31
C_{Ar}—S—N/deg	96
Cl—S—N—H/deg	−0.61
E_{act}/kJ mol^{-1}	−112.8

Note. P is a bond order.

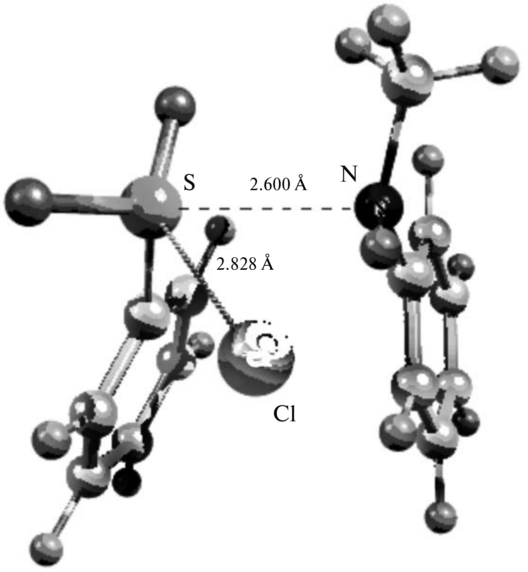


Fig. 3. Structure of activated complex of the reaction between *N*-methylaniline (**2a**) and $PhSO_2Cl$.

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