Arylsulfonylation of *N*-isobutylaniline and its derivatives: experimental study and quantum-chemical calculations

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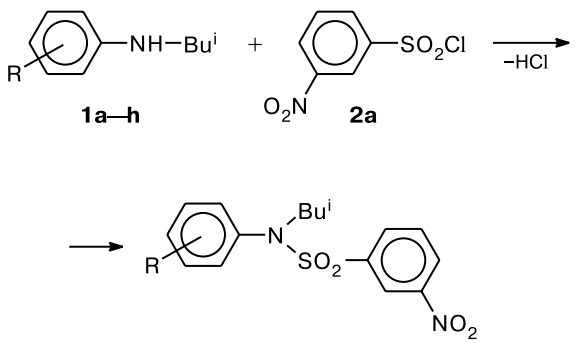
The kinetics of the reactions of benzene-substituted *N*-isobutylanilines **1a**—**h** with 3-nitrobenzenesulfonyl chloride in propan-2-ol was studied at 298 K. To analyze the reactivities of compounds **1a**—**h** in the arylsulfonylation reactions and substantiate the possible mechanism of these reactions, the geometric, electronic, and energy characteristics of the reagents and a series of model compounds were calculated by the semiempirical quantum-chemical AM1 and PM3 methods. The rate of arylsulfonylation of *N*-isobutylaniline and its derivatives increases directly proportional to the contributions of the s and p_z orbitals of the N atoms to HOMO of amine and of the S atoms to LUMO of sulfonyl chloride. The coefficients of these AOs can be considered as the reactivity indices of the reagents used for arylsulfonylation of substituted *N*-isobutylanilines with aromatic sulfonyl chlorides. It was proposed that the reaction under study is orbital-controlled.

Key word: arylsulfonylation, alkylarylamines, kinetics, quantum-chemical calculations, reactivity, arenesulfonyl chlorides.

Sulfonylamides, which are prepared by the reactions of *N*-alkyl-substituted aromatic amines with benzenesulfonyl chlorides, have widespread application as drugs and dyes and are used for the preparation of biologically active compounds. With the aim of studying the reactivities of secondary fatty aromatic amines in the arylsulfonylation reactions, we examined the kinetics of the reactions of benzene-substituted *N*-isobutylanilines (**1a**—**h**) with 3-nitrobenzenesulfonyl chloride (**2a**) (Scheme 1) and calculated the geometric, electronic, and energy characteristics by the semiempirical quantum-chemical AM1 and PM3 methods.

Scheme 1



1: R = H (**a**), 4-Me (**b**), 3-Me (**c**), 4-Et (**d**), 3-Et (**e**), 4-COOMe (**f**), 3-COOMe (**g**), 4-COOEt (**h**)

Experimental

The kinetics of the reactions (see Scheme 1) was studied by the spectrophotometric indicator method on a KFK-2 photoelectric colorimeter equipped with a V7-38 digital voltmeter and a temperature-controlled cell.[1] The working wavelength of the instrument was 400 nm. Lithium 2,6-dinitrophenoxide was used as the indicator.

The reaction rate is described by the second-order kinetic equation

$$-dC_{sc}/d\tau = kC_{am}C_{sc}, \quad (1)$$

where k is the rate constant of the reaction (see Scheme 1) and C_{am} and C_{sc} are the current concentrations of amine and sulfonyl chloride, respectively.

In all kinetic experiments, the initial concentration of alkylarylamine was 10^2—10^3 times higher than that of arylsulfonyl chloride, which allowed us to calculate the pseudofirst-order rate constants k_1 by the Guggenheim method. The second-order rate constants were calculated by the equation

$$k = k_1/C^0_{am}, \quad (2)$$

where C^0_{am} is the initial concentration of fatty aromatic amine.

The error of the estimation of k was calculated with the confidence coefficient of 0.95; the random error of the constant k was no high than 2—3%.

Aniline (**3**) and its 3-methyl-, 3-ethyl-, and 4-ethyl-substituted derivatives (pure grade), which were used for the preparation of the corresponding *N*-isobutylanilines according to a procedure described previously,[2] were dried with KOH and purified

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by simple distillation. 4-Methylaniline (pure grade) was recrystallized from water. Methyl 4-aminobenzoate, ethyl 4-aminobenzoate, and methyl 3-aminobenzoate (high-purity grade) were used without additional purification. Compound **2a** (pure grade) was recrystallized from heptane. Propan-2-ol (reagent grade) was distilled on a column under atmospheric pressure immediately after drying with $CuSO_4$. Lithium 2,6-dinitrophenoxide, which was used as the indicator in the spectrophotometric study of the kinetics of arylsulfonylation of alkylarylamines, was prepared by the reaction of the corresponding phenol with LiOH.

The physicochemical constants (m.p. and b.p.) of the reagents were consistent with the published data.[3]

Calculation procedure

The geometric, electronic, and energy characteristics of the molecules were calculated by the quantum-chemical AM1 and PM3 methods. The semiempirical calculations were carried out by the restricted Hartree—Fock method without considering the electron correlation. The geometry was optimized without restrictions imposed on the molecular symmetry. After completion of the geometry optimization, vibrational spectra were calculated to check the type of the stationary points.

Results and Discussion

The kinetics of arylsulfonylation of alkylarylamines **1a—h** with sulfonyl chloride **2a** in propan-2-ol was studied at 298 K. The rate constants of the reactions (see Scheme 1) are given below.

Compound	$k \cdot 10^2$ /L mol^{-1} s^{-1}	Compound	$k \cdot 10^2$ /L mol^{-1} s^{-1}
1a	0.81±0.02	**1e**	1.54±0.05
1b	3.48±0.07	**1f**	0.22±0.01
1c	1.69±0.03	**1g**	0.43±0.01
1d	3.38±0.06	**1h**	0.16±0.00

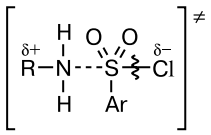
The effect of the substituents in the benzene ring of the arylsulfonylated aniline is well described by the Hammet equation:

$$\log k = (-1.85\pm0.05) - (1.43\pm0.14)\sigma,\ r = 0.97,\ n = 8, \quad (3)$$

where σ is the Hammet constant of the substituent.[4]

It was found that the introduction of the isobutyl substituent into the amino group of aniline leads to a decrease in the rate constant of the reaction with compound **2a** by a factor of ~10 compared to the rate constant of arylsulfonylation of aniline.[5] This fact is indicative of the strong influence of the steric factor on the reaction kinetics (see Scheme 1).

A comparative analysis of the reactivities of arylamines and secondary alkylarylamines in the arylsulfonylation reactions has not been carried out previously. Besides, there is no consensus of opinion as to the mechanism of the reactions under study. Both the S_N2 and S_AN mechanisms are considered as probable pathways. The latter mechanism assumes the formation of a bond between the S atom and attacking nucleophile accompanied by the cleavage of the S—Cl bond. It should be noted that most scientists[6,7] are inclined to believe that the formation of the N—S bond accompanied by a weakening of the S—Cl bond in the transition state (**4**) is the rate-determining step of arylsulfonylation of amines, *i.e.*, the S_N2 mechanism is favored by most of researchers. With the aim of analyzing the reactivities of *N*-isobutylaniline and its derivatives in the arylsulfonylation and substantiating the possible mechanism of this reaction, we calculated the geometric, electronic, and energy characteristics of the reacting molecules and a series of other model compounds by quantum-chemical methods.



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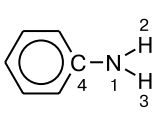
In the initial stage of the study, we had to choose the method for calculations of the molecular parameters. In particular, it is known[8,9] that the structural and electronic characteristics of organic molecules can be successfully calculated by the AM1 and PM3 methods. Hence, we employed these methods to calculate the bond lengths (Table 1) and charges on the nucleophilic centers in the molecules of aniline (**3**) and alkylamines RCH_2NH_2 (**5**), whose structural parameters have been experimentally determined.[10,11]

Table 1. Geometric and electronic characteristics of aniline **3** and alkylamines **5a—e**

Compound	Bond length/Å		*q*(N(1)) /au	Method*
	N(1)—C(4)	N(1)—H(2)		
3	1.400	0.996	–0.327	AM1
	1.400	0.988	0.051	PM3
	1.402(2)	—	—	MW
5a	1.432	1.000	–0.352	AM1
	1.469	0.999	–0.030	PM3
	1.472(3)	—	—	GE, MW
5b	1.444	1.000	–0.350	AM1
	1.480	0.998	–0.038	PM3
	1.470(10)	—	—	GE, MW
5c	1.444	1.000	–0.349	AM1
	1.480	0.999	–0.036	PM3
5d	1.444	1.000	–0.349	AM1
	1.480	0.998	–0.036	PM3
5e	1.465	1.001	–0.329	AM1
	1.497	0.999	–0.040	PM3
	1.493(6)	—	—	GE, MW

* GE is gas electron diffraction analysis and MW is microwave spectroscopy.[10,11]



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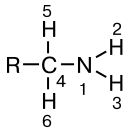
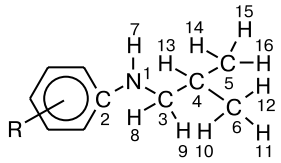


5a—e

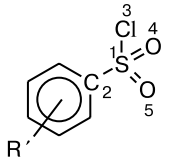
5: R = H (**a**), Me (**b**), Et (**c**), Pr (**d**), Bu^t (**e**)

As can be seen from Table 1, the PM3 method gives a better agreement between the calculated geometric characteristics and the experimental data (see also Ref. 7) as compared to the AM1 method, which slightly underestimates the interatomic distances. In addition, it is known[9] that of semiempirical methods employing the NDDO approximation, the PM3 method provides the highest accuracy of the calculated structural parameters of sulfonyl compounds. However, the charges on the N atoms calculated by the PM3 method are very small, whereas the N atom in aniline (**3**) bears the positive charge (q(N) = 0.051 au), which is doubtful because the amino group serves as the nucleophilic center. Taking all the aforesaid into account, the further analysis of the reactivities of secondary fatty aromatic amines in the arylsulfonylation was carried out with the use of the geometric parameters of the molecules, which were calculated by the PM3 method, and the electronic and energy characteristics, which were calculated by the AM1 method.

The calculations of the geometric and electronic characteristics of secondary fatty aromatic amines **1a—h** and arenesulfonyl chlorides **2a—d** by the above-mentioned quantum-chemical methods demonstrated that the N(1)—H(7), S(1)—Cl(3), and S(1)—O(4) bond lengths, effective charges on the N, H, S, Cl, and O atoms, and bond angles in the compounds under study are virtually independent of the substituents in the benzene rings of the reagents. Hence, these characteristics cannot be used to explain the reactivities of alkylarylamines in the arylsulfonylation with benzenesulfonyl chlorides.



1a—h



2a—d

2: R′ = 3-NO_2 (**a**), H (**b**), 4-Me (**c**), 4-NO_2 (**d**)

The method of reactivity indices (RI) is widely used[12] on consideration of the characteristic features of the reaction pathways. For example, analysis of the character of HOMOs and LUMOs of the reacting molecules can provide information on the manner in which their reactivities vary in chemical transformations, *i.e.*, the energy gaps between the frontier MOs of the reagents $\Delta E_1 = E_{HOMO}$(**1a—h**) $- E_{LUMO}$(**2a—d**) and $\Delta E_2 = E_{HOMO}$(**2a—d**) $- E_{LUMO}$(**1a—h**) can be used to calculate the reactivity indices. Hence, we determined the energy characteristics of molecules **1a—h** and **2a—d** and used them to calculate E_1 and ΔE_2 (Table 2).

Table 2. Energy gaps ΔE_1 and ΔE_2 (in parentheses) between the frontier MOs of alkylarylamines **1a—h** and arenesulfonyl chlorides **2a—d** (AM1)

Compound	ΔE/au			
	2a	**2b**	**2c**	**2d**
1a	5.80 (10.84)	6.34 (10.01)	6.41 (9.97)	5.67 (10.70)
1b	5.66 (10.87)	6.19 (10.04)	6.26 (10.01)	5.53 (10.73)
1c	5.77 (10.88)	6.30 (10.05)	6.28 (10.02)	5.64 (10.74)
1d	5.68 (10.87)	6.21 (10.04)	6.28 (10.00)	5.55 (10.73)
1e	5.76 (10.88)	6.29 (10.05)	6.37 (10.01)	5.63 (10.73)
1f	6.10 (11.40)	6.63 (10.57)	6.71 (10.53)	5.97 (11.26)
1g	6.09 (11.29)	6.62 (10.46)	6.69 (10.42)	5.96 (11.15)
1h	6.09 (11.43)	6.62 (10.60)	6.69 (10.56)	5.96 (11.29)

As can be seen from Table 2, $\Delta E_1 < \Delta E_2$ in the case under consideration, *i.e.*, it is most probable that arylsulfonylation proceeds involving HOMOs of amines **1a—h** and LUMOs of arenesulfonyl chlorides **2a—d**. This is the case when the reaction proceeds through the S_N2 mechanism to give adduct **4**. When analyzing the frontier MOs of the reagents, it was of importance to examine the contribution of the N atom to HOMOs of amine **1a—h** and the contribution of the S atom to LUMOs of sulfonyl chlorides **2a—d**. The contribution of the N atom to HOMO and the contribution of the S atom to LUMO involve four components, *viz.*, the s, p_x, p_y, and p_z orbitals. According to the results of our calculations, the s and p_z orbitals of these atoms make the highest contributions (Table 3).

A comparison of the rates of arylsulfonylation of amines **1a—h** by sulfonyl chloride **2a** with the contributions of the s (x) and p_z (y) orbitals of the N atom to HOMOs of the amines gave the following nearly linear dependence:

$$\log k = (20.99\pm0.02)x - (17.55\pm0.02)y + (4.20\pm0.02), \quad (4)$$

$$r = 0.97, \; n = 8.$$

A comparison of the rates of arylsulfonylation of amine **1b** by benzenesulfonyl chloride **2b** and its derivatives (**2a**,**c**,**d**) with the contributions of the s and p_z orbitals of the S atom to LUMO of sulfonyl chloride gave an analo-

Table 3. Contributions of AOs of the N atom to HOMOs of amines **1a**—**h** and of the S atom to LUMOs of sulfonyl chlorides **2a**—**d** (AM1)

Compound	Contribution of the atomic orbital (%)			
	s	p_x	p_y	p_z
1a	2.13	0.01	0.02	28.09
1b	1.96	0.01	0.07	24.80
1c	2.10	0.03	0.00	27.25
1d	1.99	1.49	0.61	23.23
1e	2.13	0.12	0.01	27.14
1f	1.42	0.02	0.04	28.94
1g	2.25	0.02	0.00	30.03
1h	1.44	0.03	0.04	28.84
2a	31.14	0.45	0.49	10.89
2b	32.83	0.85	0.00	11.49
2c	32.26	1.02	0.00	11.29
2d	23.43	0.67	0.00	9.86

gous dependence. This dependence is also nearly linear and is described by the equation

$$\log k = (26.12\pm0.04)x' - (121.90\pm0.04)y' + (24.13\pm0.04), \quad (5)$$

$$r = 0.95,\ n = 4,$$

where x' and y' are the coefficients of the s and p_z orbitals, respectively, of the S atom involved in LUMOs of compounds **2a**—**d**. Hence, the coefficients of the s and p_z orbitals of the N atoms in compounds **1a**—**h** and of the S atoms in compounds **2a**—**d** can be considered as the reactivity indices of reagents in the arylsulfonylation reactions of *N*-isobutylanilines with aromatic sulfonyl chlorides.

Based on the results of our quantum-chemical calculations, it can be suggested that the reactions of alkylarylamines with benzenesulfonyl chlorides are orbital-controlled because the N atom makes a large contribution to HOMOs of amines **1a**—**h**, whereas the S atom makes a large contribution to LUMOs of arenesulfonyl chlorides **2a**—**d**. This is evidence in favor of the S_N2 mechanism of the reaction (see Scheme 1).

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