ISSN 1070-3632, Russian Journal of General Chemistry, 2011, Vol. 81, No. 10, pp. 2114–2120. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © L.B. Kochetova, N.V. Kalinina, L.V. Kuritsyn, T.P. Kustova, 2011, published in Zhurnal Obshchei Khimii, 2011, Vol. 81, No. 10, pp. 1661–1667.

# Ammonia Reactivity in the Acylation with 4-Nitrophenyl Benzoate in a Water–2-Propanol System

**L. B. Kochetova, N. V. Kalinina, L. V. Kuritsyn, and T. P. Kustova**

*Ivanovo State University, ul. Ermaka 39, Ivanovo, 153025 Russia*
*e-mail: kochetova_lb@mail.ru*

Received September 9, 2010

**Abstract**—The kinetics of acylation of ammonia with 4-nitrophenylbenzoates in water–2-propanol mixtures was studied. Increase in the reaction rate with increasing proportion of water in the system is attributed to the formation of ammonia solvato complexes with the components of the solvent. By the RHF/6-31G* method were calculated structural and energetic properties of the solvato complexes. The potential energy surfaces of the acylation reaction of ammonia and its solvato complexes were calculated. It was shown that solvation of the transition state decreases the reaction activation energy compared to the gas-phase process. All the reactions proceed by $S_N2$ mechanism without formation of intermediates, with only one transition state.

**DOI:** 10.1134/S1070363211100136

Previously, we investigated the kinetics of the reactions of α-amino acids and aliphatic amines at their reactions with the carboxylic acid ester in an aqueous–organic media. It was established that changes in the composition of the solvent has a significant effect on the acylation rate [1–3]. Effect of the aqueous–organic solvents on the reactivity of ammonia, the ancestor of the class of aliphatic amines, in its reaction with the phenyl benzoates has not been studied yet. These data are of interest for the understanding the general principles of the reactions of acyl transfer, and therefore the purpose of this study was the kinetic study of the reaction of ammonia with 4-nitrophenyl ester benzoate (**I**) in the water–2-propanol mixtures, as well as quantum-chemical interpretation of the results obtained.

The studied reaction proceeds according to Eq. (1). In parallel with reaction (1) in aqueous–organic medium can proceed hydrolysis of the ester [Eq. (2)]:

$$C_6H_5COOC_6H_4NO_2 + NH_3 \xrightarrow{k_{\text{acylation}}} C_6H_5CONH_2 + HOC_6H_4NO_2, \quad (1)$$

$$C_6H_5COOC_6H_4NO_2 + H_2O \xrightarrow{k_{\text{hydrolysis}}} C_6H_5COOH + HOC_6H_4NO_2. \quad (2)$$

The reaction course was monitored spectrophotometrically by the indicator method (λ = 400 nm). The reaction was carried out in the first order conditions with $10^2$–$10^3$ excess ammonia concentration $c_0$ compared with the concentration of ester. The observed rate constant ($k_{\text{obs}}$) taking into account the possible hydrolysis is determined by the equation:

$$k_{\text{obs}} = k_{\text{hydrolysis}} + k_{\text{acylation}}c_0, \quad (3)$$

As the starting reagent was used ammonium chloride. To the solution was added a certain amount of NaOH solution to provide a certain concentration ratio of free ammonia ($c_0$) and the nonreactive ammonium ion ($c_+$), for holding the conditions: $k_{\text{hydrolysis}} << k_{\text{acylation}}c_0$, that is, hydrolysis rate is negligible compared with the rate of acylation, and its contribution to the overall reaction rate can be ignored. The ratio $c_+/c_0$ varied in the range 4–7. The value of $k_{\text{acylation}}$ in the absence of hydrolysis should be determined by the expression:

$$k_{\text{acylation}} = k_{\text{obs}}/c_0. \quad (4)$$

The results of kinetic studies are shown in Table 1. The values of $k_{\text{acylation}}$ calculated with Eq. (4) at different $c_0$ at the same composition of the solvent differ only slightly indicating that contribution from the hydrolysis of esters in the overall reaction rate is not essential. In this regard, at the analysis of the data obtained were used arithmetic average values of the acylation constants.

Activation energy and entropy of the reaction (1) in aqueous isopropanol calculated from the temperature

**Table 1.** Kinetic data on the acylation of ammonia with ester **I** in water–2-propanol solvent (298 K; $X$ is water mole fraction)

| $X$ | $c_0$, M | $k_{obs}\times10^3$, $s^{-1}$ | $k_{acylation}\times10^3$, $l\ mol^{-1}\ s^{-1}$ | $T$, K | $c_0$, M | $k_{obs}\times10^3$, $s^{-1}$ | $k_{acylation}\times10^3$, $l\ mol^{-1}\ s^{-1}$ |
|---|---|---|---|---|---|---|---|
| 298 K | | | | $X$ 0.690 | | | |
| 0.769 | 0.212 | 0.575±0.09 | 2.71±0.04 | 298 | 0.222 | 0.466±0.002 | 2.01±0.01 |
| | 0.106 | 0.285±0.002 | 2.69±0.02 | | 0.111 | 0.212±0.001 | 1.91±0.01 |
| | 0.0595 | 0.159±0.002 | 2.67±0.03 | | 0.0554 | 0.117±0.001 | 2.12±0.02 |
| 0.833 | 0.209 | 0.681±0.01 | 3.26±0.05 | 303 | 0.222 | 0.779±0.009 | 3.51±0.05 |
| | 0.139 | 0.463±0.006 | 3.33±0.04 | | 0.111 | 0.398±0.006 | 3.59±0.05 |
| | 0.0696 | 0.228±0.004 | 3.28±0.06 | | 0.0554 | 0.193±0.003 | 3.48±0.06 |
| 0.886 | 0.212 | 0.820±0.07 | 3.87±0.03 | 308 | 0.222 | 1.16±0.01 | 5.23±0.05 |
| | 0.105 | 0.422±0.006 | 4.02±0.06 | | 0.111 | 0.586±0.009 | 5.28±0.08 |
| | 0.0503 | 0.188±0.002 | 3.73±0.04 | | 0.0554 | 0.284±0.001 | 5.12±0.02 |
| 0.930 | 0.216 | 0.957±0.08 | 4.43±0.04 | 313 | 0.133 | 1.03±0.01 | 7.74±0.05 |
| | 0.108 | 0.484±0.03 | 4.48±0.03 | | 0.0890 | 0.697±0.003 | 7.83±0.04 |
| | 0.0540 | 0.236±0.02 | 4.37±0.04 | | 0.0554 | 0.423±0.003 | 7.63±0.07 |

dependence of $k_{acylation}$ (Table 1) at the water 0.69 mole fraction were found equal to (69 ± 3) kJ $mol^{-1}$ and –(81 ± 9) J $mol^{-1}$ $K^{-1}$ . These parameters are somewhat higher than the activation energy and entropy of the reactions of α-amino acids and aliphatic amines **I** under the same conditions [3], which is associated with a weakening of the nucleophilic properties of the nitrogen atom in ammonia due to the lack of the electron-donating substituents near to it. From Table 1 follows that with increasing water content in the solvent from 40 to 80 wt % the $k_{acylation}$ value increases more than twice. Dependence of ln ($k_{acylation}$) on the Kirkwood function is not linear (Fig. 1), which indicates the important role of specific solvation of ammonia and the reaction transition state in aqueous isopropanol. Solvation of acylating agents in reactions of acyl transfer, according to available data [3, 4], plays a minor role.

Effect of composition of the binary aqueous–organic solvent on the rate constant for reaction (1) can be explained on the basis of the approach outlined in several publications [3–5]. Ammonia exists in water–isopropyl alcohol solution as the molecular complexes with the solvent of different structure, which are in a dynamic equilibrium. In this regard, the reaction of the ester with ammonia can proceed in parallel streams, with the participation of different solvated composition, and the rate constant of acylation $k_{acylation}$ can be considered as a sum of the constants of acylation $k_i$ of different solvato complexes with accounting for their concentrations in the solution:

$$k_{acylation} = \Sigma k_i \alpha_i, \tag{5}$$

where $\alpha_i = c_i/c_0$ is a fraction of the concentration of the solvato complex of $i$th composition $c_i$ of the total concentration of ammonia in the solution $c_0$.

In this case, between the reaction rate constant $k_{acylation}$ and the composition of the water–organic solvent there may be a relationship [5]:

$$k_{acylation} = k_1X_1 + k_2X_2 + k_3X_1X_2, \tag{6}$$

where $k_1$ and $k_2$ are the rate constant for the reaction in isopropyl alcohol and water, respectively; $k_3$ is a constant value accounting for the deviation from additivity, $X_1$ and $X_2$ are the mole fraction of isopropyl alcohol and water in the reaction mixture.

Based on the published data on the acylation of amines [3, 4], we can assume that $k_1$ is very small compared with the other terms and can be neglected, then Eq. (6) becomes:

$$k_{acylation}/X_2 = k_2 + k_3X_1. \tag{7}$$

Treatment of kinetic data (Table 1) using Eq. (7) showed that this dependence is correct with a correlation coefficient 0.999. The deviations of the values calculated with Eq. (7) from the experimental values of $k_{acylation}$ do not exceed 2%. The reaction (1) rate constant in water $k_2$ is (5.27 ± 0.05)×$10^{-3}$ l $mol^{-1}$ $s^{-1}$.

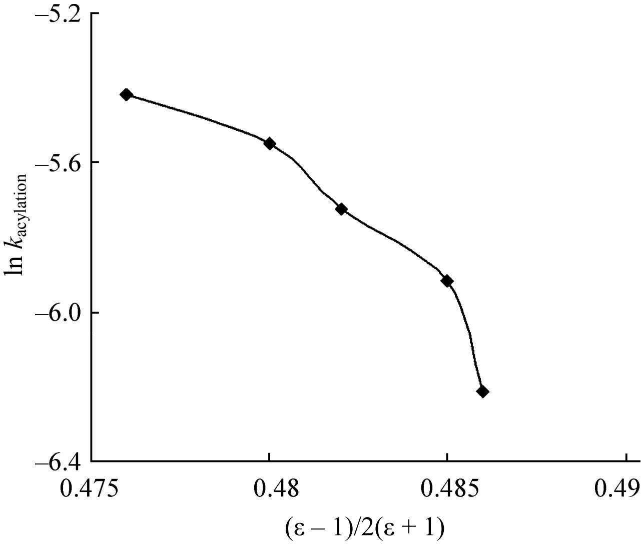


**Fig. 1.** Logarithm of the reaction (1) rate vs. the Kirkwood function.

The constant $k_3$ in Eq. (7), which takes into account a non-additive effect of a mixture of components on the rate constant is quite large: –(7.7 ± 0.2)$\times10^{-3}$ l $mol^{-1}$ $s^{-1}$, which confirms the significant contribution of specific solvation in the kinetics of the reaction under study. The negative $k_3$ value suggests that the interaction with components of water–organic solvent leads to blocking the electron lone pair on the nitrogen atom and reduces the ammonia reactivity in the acylation.

To estimate the influence of solvation on the reactivity of ammonia, we carried out quantum-chemical modeling of its solvato complexes with water and isopropanol molecules of the composition $NH_3{\cdot}(H_2O)_n$, $n$ = 1–2 (**IIa, IIb**), $NH_3{\cdot}H_2O{\cdot}i$-PrOH (**IIc**), and $NH_3{\cdot}$($i$-PrOH)$_n$, $n$ = 1–2 (**IId, IIe**). For the calculations we used the HyperChem® 7.52 software package [6].

The structural and energetic properties of the complexes were calculated by RHF/6-31G* method in the supermolecular approximation with full geometry optimization of the system. During the calculations was carried out monitoring of the stationary points on the potential energy surface. Reaching the global minimum on the PES was determined by the absence of imaginary frequencies in the vibration spectrum.

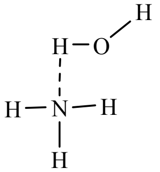
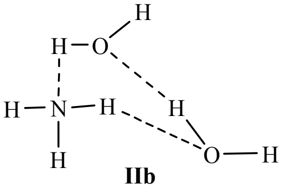
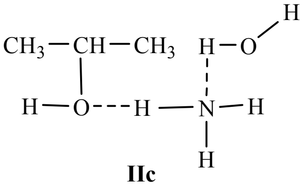
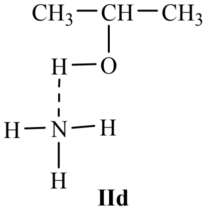
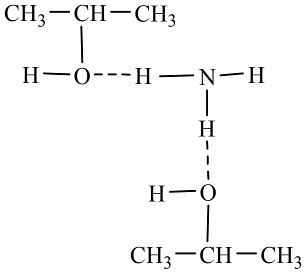
In the starting structures of the solvato complexes the ammonia molecule always acts as an H-donor, but in some cases at the geometry optimization it undergoes significant changes. Schematic patterns of the optimized solvato complexes as well as some of their quantum-chemical characteristics are given in Table 2. Energy of complex formation ($\Delta E_{complex}$) was found as a difference between the total energy of the complex and the total energies of isolated molecules.

The simulation shows that one of the water molecules in the solvato complexes **IIa–IIc** acts as H-donor, forming a hydrogen bond with the lone electron pair of the nitrogen atom. Similarly behaves the 2-propanol molecule in the complex **IId**. Thus, the calculated data agree with the conclusion drawn from the results of calculations with Eq. (7).

The charges on the nitrogen atom are almost independent from the composition of the solvato complexes **IIa–IIe**: the range of their variation is 1.03–1.08 au. Changing the solvato complex structure affects much stronger its orbital characteristics (Table 2). In particular, due to blocking the lone electron pair the formation of H-complex **IIa** with water reduces significantly the $2p_z$-AO [$\varphi p_z$(N)] population and the contribution of $2p_z$-AO [$Cp_z$(N)] of the nitrogen atom in the HOMO compared to the unsolvated molecule of ammonia **II**. Solvation of ammonia with two molecules of water leads to an increase in the specified orbital parameters of the complex **IIb**, and this should result in an increase of the nucleophilicity of nitrogen atom and, consequently, the reactivity of **IIb** compared to **IIa**. The maximum $\varphi p_z$(N) and $Cp_z$(N) values has complex **IIe**, in which ammonia is H-donor only. However, this complex is less stable, as evidences the value of its complexation energy $\Delta E_{complex}$. The most stable among the studied structures are **IIb** and **IIc**. Comparing the orbital characteristics of solvato complexes and the data on their stability with the results of kinetic studies suggests that in the studied range of the water–isopropyl alcohol solvent compositions the ammonia solvato coplexes **IIb** and **IIc** are in maximal concentrations. These particles are the major contributors to the kinetics of reaction (1).

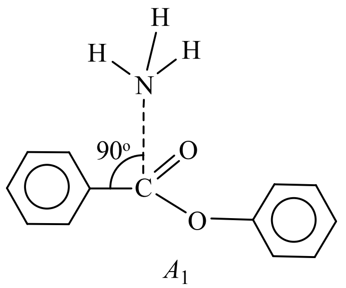
In accordance with the transition state theory, not only the interaction of reactant molecules with the molecules of the medium contributes to the reaction rate constant, but also the interaction of the medium with the activated complex. To reveal the role of the components of binary solvent in the reaction (1) mechanism, we calculated the potential energy surface (PES) of a model reaction of phenyl benzoate with ammonia in the gas phase (**III**) and in solvent: in the presence of one (**IIIa**) and two (**IIIb**) water molecules, as well as one water and one 2-propanol molecule (**IIIc**).

**Table 2.** Geometric, electronic and energy characteristics of the ammonia solvato complexes with the water–2-propanol solvent components

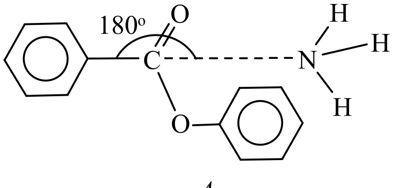
| Structure of solvato complex | $\Delta E_{complex}$, kJ mol$^{-1}$ | C$p_z$(N) | φ$p_z$(N) | $q$(N), au | $r_{N–H}$, Å | $r_{N\cdots H}$, Å | $r_{O\cdots H}$, Å |
|---|---|---|---|---|---|---|---|
|  **IIa** | –27.30 | 0.189 | 0.633 | –1.03 | 1.003 | 2.083 | 1.974 |
|  **IIb** | –68.38 | 0.335 | 0.655 | –1.07 | 1.006 | 2.014 | – |
|  **IIc** | –46.65 | 0.354 | 0.655 | –1.08 | 1.005 | 2.030 | 2.229 |
|  **IId** | –27.7 | 0.005 | 0.675 | –1.03 | 1.003 | 2.073 | – |
|  **IIe** | –22.4 | 0.469 | 0.68 | –1.06 | 1.004 | – | 2.419;<br>2.370 |
| $NH_3$ (**II**) | – | 0.954 | 0.909 | –1.07 | 1.003 | – | – |

We considered in a supermolecular approximation the two possible paths of the attack of nucleophile on the reaction center: frontal and axial attack of the ammonia molecule on the ester group.

At the frontal attack ($A_1$) the nucleophile attacks perpendicular to the plane of the aromatic rings at the angle 90° to the ester $C_{Ar}$–C bond. At the axial attack ($A_2$), the nitrogen atom of the ammonia molecule lies on the axis of the $C_{Ar}$–C bond ($\angle C_{Ar}CN = 180°$). Rear attack of the nucleophile was not considered, since while constructing the starting configuration of the reacting system the ester molecule was taken as a planar *Z*-conformation, and the frontal attack of the nucleophile was similar to the rear. Therefore, it was built a fragment of the PES corresponding to the frontal–axial direction of the attack. Noteworthy that in the process of geometry optimization the ester



$A_1$



$A_2$

transformed from the flat *Z*-conformation into the *E*-conformation upon the convergence with the nucleophile molecule [7].

As the reaction coordinate, we considered the length of the appearing bond *r*(C–N) and the angle of attack $\angle C_{Ar}CN$. Computations were carried out by the method described in [8].

We obtained of the PES fragments of the similar type: with a single maximum and only slightly differing by the localization of the saddle point. Figure 2 shows as an example a contour map of a fragment of the PES in the reaction of ammonia solvated by two water molecules with the ester.

All the built PPS show only one possible reaction route and one saddle point corresponding to the reaction transition state (Fig. 3). The reactions take place in one stage: no minima corresponding to the formation of intermediates was noted in the contour maps. A complicated route is revealed: the attack by the nucleophile begins in the direction close to the frontal (the angle of attack is 100°), then, during the mutual approach of the reacting molecules, the angle of attack increases, and at the moment of formation of the activated complex it reaches 140°–150° (Table 3). Formation of products occurs at *r*(C–N) = 1.2 Å and is accompanied by an increase in the $\angle C_{Ar}CN$ angle to 150°–160°. At this moment occurs cleavage of C–O and N–H bonds. A small difference in the $\angle C_{Ar}CN$ angles in the benzamide for different PES seems indicating that its conformation can slightly vary under the influence of the solvate environment.

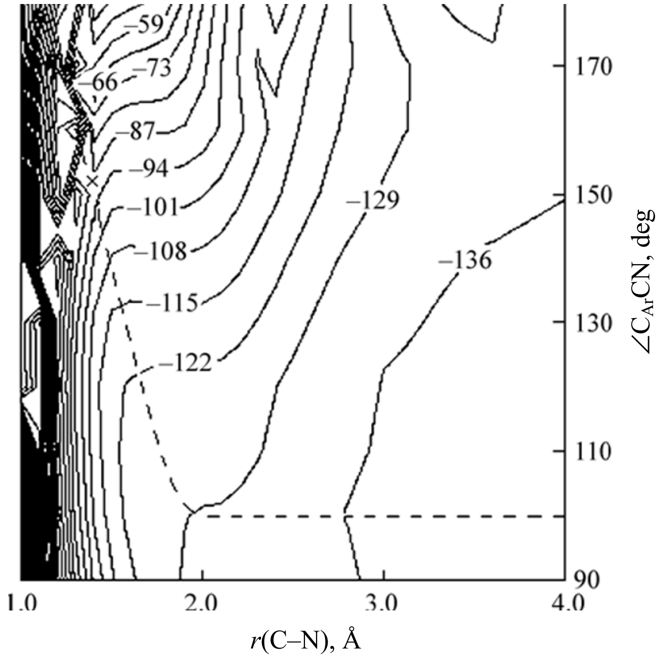
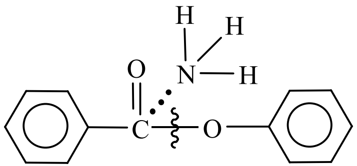


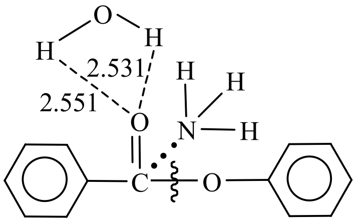
**Fig. 2.** Potential energy surface contour map of the ammonia solvated by two water molecules acylation with phenyl benzoate (covers the direction of attack by the nucleophile from the front to the axial).

Using the *Transition State* procedure, we calculated structural parameters of the activated complexes. Reaching the saddle point on the potential energy surface that corresponds to the formation of activated complex was confirmed by the presence of one imaginary vibration frequency in the vibration spectrum. The schematic patterns of the activated complexes are shown below. The geometric and energy parameters of activated complexes are given in Table 3.

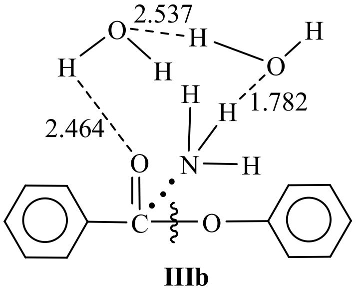
The configuration of the reaction center in all the transition states is a somewhat distorted tetrahedron. The length of the resulting (C–N) and cleaving (C–O) bonds in the activated complexes are similar (Table 3). Together with the presence of a single saddle point on the PES, this indicates that the aminolysis of the ester both in the gas phase and in solvent proceeds in accordance with the $S_N2$ mechanism. The sum of the bond orders exceeds unity in all the calculated activated complex (approximately 1.6) that corresponds to the “compressed” transition state in which the cleavage of the old bond occurs behind the formation of a new one.



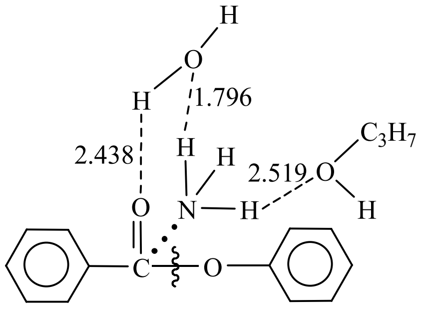
**III**



**IIIa**



**IIIb**



**IIIc**

From the differences in the formation energies of the transition states and initial reactants we calculated the activation energy of the reactions under study (Table 3), which are found increasing in the sequence: **IIIb** < **IIIa** < **IIIc** < **III**. The high activation barrier of the reaction in the gas phase decreases with increasing number of water molecules involved in the transition state, due to the formation of rings in **IIIa** and **IIIb**. In the transition state **IIIc** the isopropanol molecule can not participate in the ring formation, which increases significantly the activation energy and reduces the acylation rate. These facts are consistent with the found experimentally growth of the rate constants with increasing fraction of water in the water–2-propanol solvent (Table 1).

The results of simulation of ammonia solvato complex and analysis of the possible reaction mechanisms in view of the kinetic data leads to several conclusions.

The determined experimentally acylation rate constants $k_{\text{acylation}}$ of ammonia are effective values, which include the acylation constant of the ammonia solvato complexes of different structure.

Along with differences in the reactivity of the solvato complexes, an important role in the kinetics of acylation plays their concentration in solution. Increased water content in isopropanol shifts the equilibrium towards a more reactive solvato complex, which causes an increase in the acylation rate constant.

Significant contribution to the rate of ammonia acylation makes the solvation of the activated complex by the components of the solvent. Increased number of water molecules involved in the transition state decreases the activation barrier, while isopropanol increases it, which is consistent with the data of kinetic experiments.

The reaction studied proceeds through the $S_N2$ mechanism both in the gas phase and in solvent,

**Table 3.** Structural and energetic properties of the activated complexes

| Complex | C–N Bond length, Å | C–N Bond order | C–O, Bond length, Å | C–O Bond order | N–H, Bond length, Å | N–H Bond order | $\angle C_{Ar}CN$, deg | $E_a$, kJ mol$^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| **III** | 1.409 | 0.91 | 1.576 | 0.68 | 1.017 | 0.95 | 150 | 226 |
| **IIIa** | 1.363 | 0.93 | 1.538 | 0.73 | 1.018 | 0.95 | 140 | 190 |
| **IIIb** | 1.409 | 0.91 | 1.568 | 0.70 | 1.016 | 0.95 | 150 | 186 |
| **IIIc** | 1.408 | 0.91 | 1.602 | 0.65 | 1.020 | 0.94 | 150 | 197 |

therewith the bond orders sum exceeds unity, which corresponds to the “compressed” transition state, which is typical of most bimolecular substitution reactions.

## ACKNOWLEDGMENTS

This work was carried out in the framework of the project RNP.2.2.1.1.2820 of the Ministry of Education and Science of Russian Federation.

## REFERENCES

1. Kuritsyn, L.V., Kalinina, N.V., and Kampal, A.K., *Zh. Org. Khim*., 1988, vol. 24, no. 12, p. 2562.
2. Khripkova, L.N., Kuritsyn, L.V., and Kalinina, N.V., *Zh. Obshch. Khim*., 2004, vol. 74, no. 10, p. 1665.
3. Kuritsyn, L.V., Kustova, T.P., Sadovnikov, A.I., Kalinina, N.V., and Klyuev, M.V., *Kinetika reaktsii atsil’nogo perenosa* (Kinetics of the Reaction of Acyl Transfer), Ivanovo: Ivanov. State Univ., 2006.
4. Bobko, L.A. and Kuritsyn, L.V., *Izv. Vuzov, Ser. Khimiya i Khim. Tekhnol*., 1985, vol. 28, no. 10, p. 21.
5. Kuritsyn, L.V. and Kustova, T.P., *Izv. Vuzov, Ser. Khimiya i Khim. Tekhnol*., 1991, vol. 34, no. 5, p. 33.
6. *HyperChem$^{TM}$ Release 7.52 for Windows. Molecular Modeling System. Seriennr. 12–750–1503700446*, Gainesville: Hypercube Inc., 2005.
7. Traven’, V.F., *Elektronnaya struktura i svoistva organicheskikh molekul* (Electronic Structure and Properties of Organic Molecules), Moscow: Khimiya, 1989.
8. Kochetova, L.B. and Kustova, T.P., *Izv. Vuzov, Ser. Khimiya i Khim. Tekhnol*., 2009, vol. 52, no. 5, p. 12.