ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 5, pp. 885–890. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © L.V. Kuritsyn, N.V. Kalinina, L.B. Kochetova, T.P. Kustova, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 5, pp. 782–787.

Kinetics of Acylation of Cyclohexylamine with Substituted Phenyl Benzoates

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

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

Received March 22, 2011

Abstract—Kinetics of acylation of cyclohexylamine with nitro-substituted phenyl benzoates is studied in water solutions of 2-propanol and dioxane. By means of RHF/6-31G* method quantum-chemical simulation of ester molecules and of cyclohexylamine solvatocomplexes was carried out. On the basis of correlation of rate constants and LUMO energies of esters and population of $2p_z$-orbitals of carbon atom of the acyl group a conclusion on the orbital control of the reactions was made.

DOI: 10.1134/S1070363212050143

An interest to the products of acylation of amines is caused by their wide use as polymers, dyes, surfactants, biologically active compounds, and drugs of wide spectrum of action. Optimization of conditions of the industrial synthesis of these substances requires performing kinetic studies and establishing quantitative dependences of rate constants of the above-mentioned processes on the structure of reagents and the effect of medium. In the series of studies kinetics is explored and the mechanisms are established of the reactions of aromatic and aliphatic amines with different acylating agents, among them with the carboxylic acid esters in the aprotic non-polar media. Kinetic data on the aminolysis of esters in water and some water-organic solvents are also mentioned [1–7].

In the course of years we study the acyl transfer reactions with the participation of different amines (aromatic, aliphatic including α-amino acids, and mixed). Aroyl and sulfonyl chlorides and also phenyl carboxylates were used as acylating agents. Specific feature of aminolysis of esters in water-containing media is the possibility of parallel proceeding of hydrolysis. The most important factor affecting the rate of aminolysis and hydrolysis is the pH of medium [8–11]. Note that adequate attention to the consideration of these factors rather scarce [6, 7]. We have developed procedures permitting strict accounting for the effect of pH and hydrolysis of acylating agents while calculation of acylation rate constants. Together with these studies quantum-chemical simulation of the reaction mechanisms and state of reagents in solution [12] was carried out. The aim of these studies is the investigation of structure of acylating agents like 2-,3-, and 4-nitrophenyl **I–III**; 2,4-, 2,5-, and 2,6-dinitrophenyl **IV–VI**, and 2,4,6-trinitrophenyl **VII** benzoates on the kinetics of their reaction with cyclohexyl amine. Binary mixtures of water (molar fraction 0.73) with 2-propanol (*i*-PrOH) and dioxane (Diox) were used as solvents.

Reaction of cyclohexylamine with esters under the conditions of kinetic experiments (pH 8.8) proceeds according to Eqs. (1)–(4) where R_1 is mono-, di- or trinitrosubstituted phenyl, k_{ac}, $k(H_2O)$, and k_{OH^-} are rate constants of the processes (1)–(3).

$$C_6H_5COOR_1 + C_6H_{11}NH_2 \xrightarrow{k_{ac}} C_6H_{11}NHCOC_6H_5 + R^1OH, \tag{1}$$

$$C_6H_5COOR_1 + H_2O \xrightarrow{k(H_2O)} C_6H_5COOH + R^1OH, \tag{2}$$

$$C_6H_5COOR^1 + OH^- \xrightarrow{k_{OH^-}} C_6H_5COO^- + R^1OH, \tag{3}$$

$$R^1OH + OH^- \xrightarrow{\text{fast}} R^1O^- + H_2O. \tag{4}$$

According to the Eqs. (1)–(4) the rate of change in the concentration of ester (c_{es}) in the kinetic experiment is described by Eqs. (5), (6).

$$-(dc_{ef})/(d\tau) = k_{ac}c_ac_{ef} + k(H_2O)c(H_2O)c_{ef} + k_{OH^-}c_{OH^-}c_{ef} = k_{obs}c_{ef}, \tag{5}$$

$$k_{obs} = k_{ac}c_a + k(H_2O)c(H_2O) + k_{OH^-}c_{OH^-}. \tag{6}$$

Here k_{obs} is the observed rate constant, c_{es}, c_a, $c(H_2O)$, c_{OH} are the concentrations of ester, amine, water, and hydroxide ions. For the evaluation of rate constant k_{ac} of the reaction (1) without the additional studies of kinetics of hydrolysis, a certain amount of hydrochloric acid was added in the amine solution. It caused the establishing of the following equilibrium:

$$C_6H_{11}NH_3^+ \overset{K_a}{\rightleftarrows} C_6H_{11}NH_2 + H^+. \quad (7)$$

Ratio of concentrations of the protonated amine (c_+) and its non-protonated form (c_a) determined pH of the medium and hence the rate of alkaline hydrolysis of ester. According to the data [9] phenyl benzoates do not hydrolyze in water. Due to that $k(H_2O)c(H_2O)$ value in the Eq. (6) is negligible.

$$k_{obs} = k_{ac}c_a + k_{OH^-}c_{OH^-}. \quad (8)$$

c_{OH^-} value can be found from following relationships:

$$K(H_2O) = c_{H^+}c_{OH^-}\gamma^2, \quad (9)$$

$$K_a = [(c_a c_{H^+})/c_+]\gamma^2 \quad (10)$$

Here $K(H_2O)$ is the ionization constant of water, γ is the activity coefficient. From that it follows:

$$c_{OH^-} = [K(H_2O)c_a]/(K_a c_+). \quad (11)$$

Using the Eqs. (8) and (11) we can obtain the equation of the observed rate constant of the first order reaction k_{obs} considering N-acylation of cyclohexylamine and hydrolysis of ester.

$$k_{obs} = k_{ac}c_a + k_{OH^-}[K(H_2O)c_a]/(K_a c_+). \quad (12)$$

From Eq. (12) it follows that the rate of hydrolysis of ester can be neglected under the conditions:

$$k_{OH^-}[K(H_2O)/(K_a c_+)] << k_{ac}. \quad (13)$$

Then the rate constant of acylation may be written as follows:

$$k_{ac} = k_{obs}/c_a. \quad (14)$$

Kinetic studies of acylation of aliphatic amines and α-amino acids with non-substituted phenyl benzoates in water-organic media carried out under different c_+/c_a ratio [8–11] persuaded us that hydrolysis may be completely suppressed only under the condition of $c_+/c_a \geq 4$. That is why in the kinetic experiments the above-mentioned ratio was maintained equal to 4. Results of kinetic measurements are listed in Table 1.

Values k_{ac} calculated according to the Eq. (14) within the limits of experimental error do not depend on the initial concentration of amine indicating the absence of significant contribution of hydrolysis of esters in the kinetics of reactions under study.

Considering the rate of the reaction between the esters under study and cyclohexylamine in water–2-propanol as well as in water–dioxane solutions permits to order the esters in the following series: **VII** > **IV** > **V** > **VI** > **III** > **I** >**II**. Analogous sequence is observed in the reactions of esters with α-amino acids [8–11]. Reactivity of mononitro derivatives is significantly lower than that of dinitro ones. The position of esters in the above-presented series is caused by the electron-acceptor effect of nitro group whose influence is strong in *para*- and *ortho*-positions while in *meta*-position it is significantly weaker. The strongest electronic effect of nitro group is observed in the case of ester **VII** which results from the cooperative action of three nitro groups located in *ortho*- and *para*-position of the phenyl ring.

Linear dependences exist between the logarithms of constants of cyclohexylamine acylation with esters [log (k_{ac})] and Hammet constants (σ^-) characterized by Eq. (15) in water-2-propanol and Eq. (16) in water-dioxane mixtures.

$$\log k_{ac} = -(3.73\pm0.13) + (1.61\pm0.08)\sigma^-, r\ 0.994, \quad (15)$$

$$\log k_{ac} = -(2.56\pm0.12) + (1.19\pm0.07)\sigma^-, r\ 0.991. \quad (16)$$

Rate constants of the reactions of cyclohexylamine with non-substituted phenyl benzoate in water–2-propanol and water–dioxane mixtures with the molar fraction of water 0.73 calculated according to Eqs. (15), (16) are 1.9×10^{-4} and 2.8×10^{-3} l mol^{-1} s^{-1} respectively. These values coincide with the constants of the reaction of glycine with ester **VIII** in water-2-propanol (2.1×10^{-4} l mol^{-1} s^{-1}) [10] and water-dioxane (1.3×10^{-3} l mol^{-1} s^{-1}) [12] mixtures. In the reactions with cyclohexylamine as well as in the reactions with glycine these values are significantly lower than the rate constants of aminolysis of nitro-substituted esters showing the determining effect of substituents in the phenoxide species on the reactivity of esters under investigation. The sensitivity of the reactions of cyclohexylamine to the effect of substituent in the leaving group of ester is higher in aqueous 2-propanol which can be connected with higher polarity of this solvent as compared to aqueous dioxane [1]. Yet the rate constants of the reactions under study are higher in aqueous dioxane than in water–2-propanol mixture.

Recently we suggested that the acylation of amino compounds is the orbital-controlled reaction, and the

Table 1. Rate constants k_H and k_{ac} of the reactions of cyclohexylamine with esters **I–VII**. C_a is the starting concentration of amine; $x(H_2O)=0.73$; 298 K

c_a, M	$(k_{ac}\pm Sk_{ac})\times10^3$, s^{-1}	$k_H\pm Sk_H$, l mol^{-1} s^{-1}	c_a, M	$(k_{ac}\pm Sk_{ac})\times10^3$, s^{-1}	$k_H\pm Sk_H$, l mol^{-1} s^{-1}
Water–2-propanol			Water–dioxane		
VII					
0.0220	84±6	3.8±0.3	0.00880	33±1	3.8±0.1
0.0110	40±4	3.7±0.4	0.00660	26±1	3.9±0.1
0.0055	21±1	3.8±0.1	0.00330	13.2±0.4	4.0±0.1
IV					
0.0667	20.8±0.5	0.312±0.007	0.0414	37.9±0.4	0.915±0.009
0.0262	7.62±0.03	0.291±0.001	0.0311	28.6±0.3	0.920±0.009
0.0147	4.57±0.03	0.311±0.002	0.0234	21.2±0.2	0.910±0.006
0.0110	3.26±0.08	0.296±0.007	0.0116	10.7±0.2	0.921±0.007
V					
0.0262	2.37±0.01	0.0906±0.0004	0.0466	12.9±0.2	0.277±0.004
0.0190	1.73±0.02	0.0910±0.0010	0.0226	6.32±0.01	0.279±0.002
0.0143	1.31±0.01	0.0914±0.0005	0.0116	3.23±0.02	0.278±0.002
0.0131	1.18±0.01	0.0907±0.0009	0.0087	2.46±0.02	0.283±0.002
VI					
0.0571	3.47±0.01	0.0607±0.0002	0.0909	18.2±0.04	0.200±0.004
0.0285	1.73±0.01	0.0600±0.0003	0.0455	8.89±0.03	0.195±0.001
0.0190	1.15±0.01	0.0605±0.0005	0.0301	6.20±0.05	0.206±0.002
0.0163	0.97±0.01	0.0596±0.0006	0.0201	3.98±0.07	0.198±0.003
III					
0.0799	1.66±0.01	0.0208±0.0002	0.0853	5.76±0.05	0.0675±0.0006
0.0622	1.30±0.05	0.0209±0.0004	0.0284	1.90±0.02	0.0669±0.0007
0.0311	0.640±0.003	0.0206±0.0001	0.0147	0.991±0.005	0.0674±0.0007
0.0147	0.319±0.002	0.0207±0.0002	0.00755	0.506±0.003	0.0670±0.0004
I					
0.189	0.618±0.003	0.00327±0.00002	0.176	3.54±0.02	0.0201±0.0001
0.0943	0.310±0.002	0.00329±0.00002	0.0853	1.72±0.02	0.0202±0.0003
0.0471	0.143±0.001	0.00320±0.00002	0.0426	0.878±0.002	0.0206±0.0001
0.0314	0.102±0.001	0.00326±0.00003	0.0213	0.435±0.001	0.0204±0.0001
II (water–2-propanol)					
0.189	0.413±0.005	0.00219±0.00003	0.0614	0.141±0.001	0.00230±0.00001
0.0943	0.195±0.001	0.00206±0.00001	0.0473	0.106±0.002	0.00225±0.00005

involved acylating agent being an electrophile allows its LUMO to the unshared electron pair of nitrogen atom. It was shown also that the rate constants of the reactions of a series of amino compounds with ester **III** in water-2-propanol mixture demonstrate linear dependence on the contribution of the nitrogen $2p_z$ atomic orbitals in HOMO, and also on the population of $2p_z$-AO of nitrogen [13].

To check the validity of this assumption for the reactions under study we carried out quantum-chemical calculations of solvate complexes of cyclohexylamine with the components of binary water-dioxane and water-2-propanol solvents with the composition 1:1 and 1:2, of the mixed complexes (1:1:1), and also of non-solvated amine molecule: $C_6H_{11}NH_2{\cdot}H_2O$ **Ia**; $C_6H_{11}NH_2{\cdot}(i\text{-PrOH})_n$, n = 1,2 **IIa**, **IIIa**; $C_6H_{11}NH_2{\cdot}H_2O{\cdot}(i\text{-PrOH})$ **IVa**; $C_6H_{11}NH_2{\cdot}(\text{Diox})_n$, n = 1,2, **Va, VIa**; $C_6H_{11}NH_2{\cdot}H_2O{\cdot}(\text{Diox})$ **VIIa**; **VIIIa**. Calculations were carried out with the help of HyperChem 7.52 software [14] using RHF/6-31G* method in supermolecular approximation with the complete optimization of geometry of the systems under study. The achievement of global minimum point on the surface of potential energy was evaluated by the absence of imaginary vibration frequencies in the vibrational spectrum.

The starting geometry of solvate complexes was taken so as the molecule of cyclohexylamine should be H-donor. Some quantum-chemical characteristics obtained as a result of optimization of structures are listed in Table 2. Values of energies of complex formation (ΔE_S) were found as differences of total energies of complexes and total energies of isolated molecules.

The simulation showed that one water molecule in the solvate complexes **Ia, IVa, VIIa** forming a hydrogen bond always is H-donor reacting with the unshared electron pair of nitrogen. Molecules of 2-propanol and dioxane in the complexes **IIa-VIIa** always exhibit the properties only of H-acceptors.

Solvate surrounding of the amine molecule does not practically influence bond lengths $r_{N–H}$ in the molecule of cyclohexylamine. In the structures **Ia–VIIa** these values vary in the range 1.002–1.004 Å. Hydrogen bond lengths in the solvate complexes are $r_{N\cdots H}$ 1.999-2.060 Å and $r_{O\cdots H}$ 2.215-2.446Å. Among them the complexes **IVa** and **VIIa** have the smallest $r_{N\cdots H}$ and $r_{O\cdots H}$ values. At the same time the orbital characteristics of solvate complexes strongly depend on their composition.

Among the compounds under study complexes **IVa** and **VIIa** are the most stable which is proved by the energies of their formation (see Table 2). ΔE_k of these species are equal, but the contributions of $2p_z$-AO of nitrogen atom in the HOMO [ΣCp_z(N)] and also the population of HOMO of solvate complexes (φp_z) for the complex **VIIa** is higher than that of **IVa**. Higher reactivity of cyclohexylamine in dioxane as compared to 2-propanol is connected evidently with this effect. Values of the above-mentioned orbital characteristics for the hydrated cyclohexylamine molecule **Ia** are lower than for the mixed complexes **IVa** and **VIIa**. Considering significantly less negative values of energies of complex formation of hydrate **Ia** it is possible to state that its contribution in the kinetics of the reaction (1) is significantly smaller as compared to the solvate complexes **IVa** and **VIIa**. Considering the orbital and energy characteristics of the solvate complexes **Ia**–**IIIa, Va, VIa** it is impossible to reject their participation also in the formation of the transition state and the reaction products. At the same time the results of calculations permit the assumption that the main contribution in the rate of the reaction (1) in the binary systems under study is brought by the solvate complexes **IVa** and **VIIa**. Hence, the results of simulation of the solvate complexes of cyclohexylamine agree with our assumption [15, 16] that the aminolysis of substituted phenyl benzoates in water-organic media proceed in parallel flows involving the amine solvate complexes having different reactivity.

Results of calculation of geometric, electronic, and energy parameters of the molecules of esters **I, II, III, V, VI** that we carried out by means of RHF/6-31G* method showed that the dependence between k_{ac} of cyclohexylamine and the charges on the carbon (q_C), and oxygen (q_{O^1}, q_{O^2}) atoms of the carboxy group of esters is absent (see Table 3). At the same time the acylation constants k_{ac} in the mixtures of water with dioxane and 2-propanol are bound by linear dependence with the orbital characteristics of acylating agents, namely, with the energies of their LUMO (E_{LUMO}) and polulation of $2p_z$-AO of the acyl group carbon atom (φp_z). These dependences are characterized by Eqs. (17), (18) in aqueous dioxane and Eqs. (19), (20) in aqueous 2-propanol.

$$k_{ac} = (0.379\pm0.033) - (0.208\pm0.022)E_{LUMO},\ r\ 0.98, \quad (17)$$

$$k_{ac} = (0.303\pm0.021) - (1.11\pm0.13)\varphi p_z,\ r\ 0.99, \quad (18)$$

$$k_{ac} = (0.123\pm0.009) - (0.070\pm0.007)E_{LUMO},\ r\ 0.98 \quad (19)$$

$$k_{ac} = (0.097\pm0.009) - (0.37\pm0.05)\varphi p_z,\ r\ 0.98 \quad (20)$$

Obtained results confirm the assumption on the dependence between the reactivity of the participants of acylation and the orbital characteristics of their molecules [12].

From the temperature dependences of rate constants k_{ac} the values of activation energy and entropy for the reaction of cyclohexylamine with the ester **III** in aqueous 2-propanol were evaluated. They were 48± 3 kJ mol^{-1} and –124±9 J mol^{-1} K^{-1} respectively. These values agree with the reported data on the activation energies and entropies of the reactions of aliphatic amines and α-amino acids with esters under the analogous conditions [9–12, 15] showing that these reactions proceed according to common mechanisms while performing them in water-organic media.

EXPERIMENTAL

Reaction rate was monitored spectrophotometrically by variation in the transmittance of light through the colored solution (λ 400 nm) by means of the KFK-2UKhL 4.2 photoelectrocolorimeter equipped with the digital V7-38 voltmeter. Temperature-controlled cell was used for the measurements, its temperature maintained with the accuracy ±0.1 K. The concentration of amine in the kinetic experiment exceeded the concentration of ester 100–1000 times. Observed rate constants were calculated according to the Guggenheim equation.

All physicochemical constants of reagents and solvents used in the experiments agree with the reported data [17].

Table 2. Quantum chemical characteristics of cyclohexylamine solvate complexes

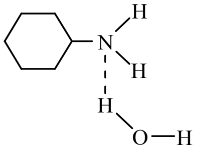
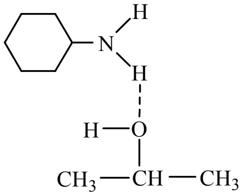
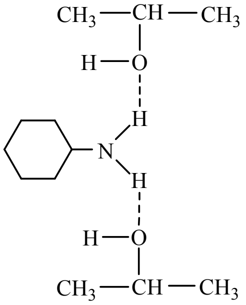
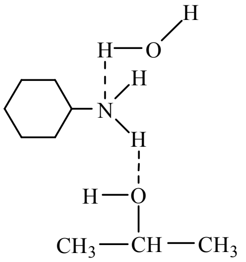
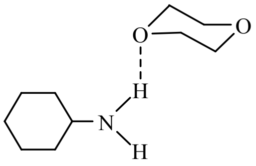
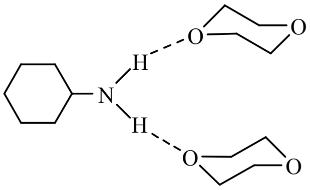
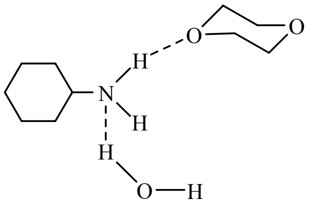
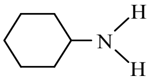
Comp. no.	Structure of complex	ΔE_k, kJ mol^{-1}	E_{HOMO}, eV	φp_z(N)	q(N), au	$r_{N–H}$, Å	$r_{N\cdots H}$, Å	$r_{O\cdots H}$, Å
Ia		–25.92	–10.71	1.579	–0.907	1.003	2.060	–
IIa		–9.20	–9.79	1.738	–0.903	1.002	–	2.382
IIIa		–14.21	–9.42	1.728	–0.932	1.002; 1.003	–	2.399; 2.443
IVa		–40.96	–10.33	1.650	–0.950	1.004	2.009	2.316
Va		–4.60	–9.81	1.596	–0.897	1.003	–	2.338
VIa		–8.78	–9.55	1.760	–0.930	1.002; 1.003	–	2.340; 2.446
VIIa		–40.96	–10.41	1.694	–0.957	1.004	1.999	2.215
VIIIa		–	–10.15	1.633	–0.866	1.003	–	–

Table 3. Some quantum-chemical characteristics of esters

Ester	E_{LUMO}, eV	φp_z	q_{C}	$q_{\mathrm{O^1}}$	$q_{\mathrm{O^2}}$
I	1.71	0.057	0.895	–0.561	–0.748
II	1.61	0.233	0.882	–0.571	–0.736
III	1.55	0.233	0.883	–0.571	–0.733
V	0.41	0.019	0.885	–0.566	–0.737
VI	1.00	0.097	0.904	–0.562	–0.737

ACKNOWLEDGMENTS

The work was carried out within the frames of RNP 2.2.1.1.2820 project of the Ministry of Education and Science of the Russian Federation.

REFERENCES

1. Litvinenko, L.M. and Oleinik, N.M., *Mekhanizmy deistviya organicheskikh katalizatorov. Osnovnoi i nukleofil'myi kataliz* (Mechanisms of Action of Organic Catalysts. Basic and Nucleophilic Catalysis), Kiev: Naukova Dumka. 1981.
2. Jenks, V., *Kataliz v khimii i enzimologii* (Catalysis in Chemistry and Enzimologi), Moscow: Mir, 1972.
3. Kustova, T.P. and Kuritsyn, L.V., *Zh. Obshch. Khim*., 1999, vol. 69, no. 2, p. 294.
4. Kuritsyn, L.V., Lebedukho, A.Yu., and Sadovnikov, A.I., *Zh. Obshch. Khim*., 2003, vol. 73, no. 4, p. 600.
5. Kuritsyn, L.V. and Kustova, T.P., *Zh. Obshch. Khim*., 2000. vol. 70, no. 3, p.491.
6. Um, I.H., Lee, J.Y., Fujio, M., and Tsuno, Y., *Org. Biomol. Chem*., 2006, no. 4, p. 2979.
7. Um, I.H., Chun, S.M., and Akhtar, K., *Bull. Korean Chem. Soc*., 2007, vol. 28, no. 2, p. 220.
8. Kuritsyn, L.V., Sadovnikov, A.I., Khripkova, L.N., Kalinina, N.V., and Shcherbakova, Yu.S., *Zh. Obshch. Khim*., 2006, vol. 76, no. 1, p. 49.
9. Khripkova, L.N., Kuritsyn, L.V., Kalinina, N.V., and Sadovnikov, A.I., *Zh. Obshch. Khim*., 2004, vol. 74, no. 10, p. 1665.
10. Kuritsyn, L.N., Kystov,a T.P., Sadovnikov, A.I., Kalinina, N.V., and Klyuev, M.V., *Kinetika reaktsii atsil'nogo perenosa* (Kinetics of the Acyl Transfer Reactions), Ivanovo: Ivanovo State University, 2006.
11. Kalinina, N.V., Kuritsyn, L.V., and Khripkova, L.N., *Vestnik Ivanov. Gos. Univ*., 2003, no3, p. 45.
12. Ishkulova, N.R., Oparina, L.E., Kochetova, L.B., Kustova, T.P., Kalinina, N.V., and Kuritsyn, L.V., *Zh. Obshch. Khim*., 2010, vol. 80, no. 5, p. 794.
13. Kustova, T.P., Kochetova, L.B., and Kalinina, N.V., *Zh. Obshch. Khim*., 2009, vol. 79, no. 5, p. 713.
14. *HyperChemO, Release 7.52 for Windows. Molecular Simulation System*, Gainesville:Hypercube Inc., 2005.
15. Oparina, L.E., Ishkulova, N.R., Kochetova, L.B., Kalinina, N.V., Kuristyn, L.V., Kustova, T.P., *Izv. Vysshikh Uchebnykh Zavedenii, Ser. Khim., Khim. Technol*., 2011, vol. 54, no. 2, p. 56.
16. Kuritsyn, L.V., Kalinina, N.V., Dorofeeva, Yu.S., *Izv. Vysshikh Uchebnykh Zavedenii, Ser. Khim., Khim. Technol*., 2010, vol. 53, no. 2, p. 45.
17. Potekhin, A.A., *Svoistva organicheskikh soedinenii* (Properties of Organic Compounds), Leningrad: Khimiya, 1984.