Hydrogenation *N*-alkylation of α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate on organometallic catalysts

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New nickel- and palladium-containing catalysts for reductive *N*-alkylation of α-alanyl-α-proline dipeptide with ethyl 2-oxo-4-phenylbutanoate have been investigated. Based on the empirical data obtained, the optimal scheme for the catalytic synthesis of enalapril was proposed.

Key words: hydroalkylation, α-alanyl-α-proline, ethyl 2-oxo-4-phenylbutanoate, organometallic catalysts.

The synthesis and studies of enalapril (vasotec, 1-[*N*-((*S*)-1-carboxy-3-phenylpropyl)-α-alanyl]-α-proline-1′-ethyl ester) are described in the literature.[1,2] The drug belongs to antihypertensive agents, and the search for more cost-efficient methods for its obtaining is currently underway. One of the possible options for improving the process is the development of new catalysts, since catalytic methods for the synthesis of pharmaceuticals occupy an important place in the modern organic synthesis of medicinal substances.[3,4] Traditional heterogeneous systems are usually used, for example, catalysts for the multistage synthesis of enalapril or its derivatives.[5,6] The multistage process results in a decrease in the target product yield and an increase in the cost of its production. It was of interest to develop a one-step process for the synthesis of enalapril and compare the catalytic properties of metal-containing polymer catalysts and their heterogeneous analogs in the reaction of hydrogenation or reductive *N*-alkylation of α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate (or hydrogenation or reductive amination of ethyl 2-oxo-4-phenylbutanoate with α-alanyl-α-proline). This type of catalysts are efficient in the synthesis of various medicinal.[7—10]

The purpose of the present work is to study the catalytic synthesis of enalapril (1-[*N*-((*S*)-1-carboxy-3-phenylpropyl)-α-alanyl]-α-proline-1′-ethyl ester) by the reaction of hydrogenation *N*-alkylation of α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate on nickel- or palladium-containing organometallic and heterogeneous catalysts.

Experimental

Dipeptide α-alanyl-α-proline purified by recrystallization from ethanol and ethyl 2-oxo-4-phenylbutanoate (reagent grade) were used in the work. Other reagents (pure and reagent grade) were additionally purified by recrystallization according to standard methods. Hydrogen was obtained electrolytically, stored in a gas meter under a layer of distilled water, and used without additional purification.

Preparation of palladium- or nickel-containing anion exchangers includes several stages. *1. Conversion of the anion exchanger into the OH-form.* Anionite AV-17-8 (10 g) was placed into a 100-mL conical flask, followed by the addition of 1 *M* hydrochloric acid (20 mL) and storage for 3 h. Then, the anion exchanger was filtered and washed with distilled water until the filtrate was acid-free. The washed anion exchanger was transferred into a 100-mL flask, followed by the addition of 1 *M* sodium hydroxide (60 mL) and storage for 3 h with occasional stirring. Then, the anion exchanger was filtered, sequentially washed with water until of neutral reaction, acetone (50 mL), diethyl ether or ethanol (50 mL), and dried in air. Other anionites were converted into the OH-form following this procedure. If an anionite with granules of a certain size was needed, the material was ground in a mortar and sieved through sieves to select a required fraction. The cation exchangers were not subjected to additional processing.

2. Preparation of palladium-containing anion exchanger. Potassium tetrachloropalladate (0.1208 g) was dissolved in water (10 mL). The resulting solution was placed into a 50-mL flask containing already anion exchanger AB-17-8 in the OH form (1 g) and water (1 mL). The content of the flask was magnetically stirred for 1—2 h at 25 °C. Then the catalyst was filtered, washed with water (100 mL) and acetone (50 mL), and dried in air. The palladium content in the catalyst was 4.00±0.01 wt.%. Other palladium-containing catalysts and samples with different metal contents were synthesized similarly. To obtain nickel-containing anion and cation exchangers, they were treated with nickel sulfate in appropriate proportions. The synthesis of heterogeneous catalysts Pd/C, Ni/C, $Pd/CaCO_3$, and $Ni//CaCO_3$ (with the addition of lead acetate, the Lindlar catalyst) was described in detail earlier.[11]

3. Catalyst activation. A weighed sample of the catalyst (10 g) was loaded into a glass thermostated reactor equipped with a stirrer. Ethanol (50 mL) and sodium borohydride (0.5 g) were

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Table 1. Yield (Y) and effective reaction rate constant (k_{eff}/mol L^{-1} s^{-1} (kg cat.)$^{-1}$) in the synthesis of Enalapril in the presence of palladium-containing catalysts and various solvent*

Catalyst	Yield and effective rate constant in various solvents							
	Ethanol		Butanol		Hexane		Toluene	
	Y (%)	$k_{eff} \cdot 10^3$	Y (%)	$k_{eff} \cdot 10^3$	Y (%)	$k_{eff} \cdot 10^3$	Y (%)	$k_{eff} \cdot 10^3$
AV-17-8-Pd	70	17.0	69	15.0	67	5.40	67	4.00
AN-1-Pd	65	10.4	63	13.3	61	4.40	60	3.40
KF-1-Pd	43	7.00	42	4.50	40	2.00	41	2.20
$Pd/CaCO_3$	38	6.80	37	4.30	36	1.80	35	2.00
Pd/C	35	5.00	34	4.00	33	1.50	34	1.80

* Conditions: solvent volume 50 mL, H_2 pressure 1 atm, temperature 45 °C, catalyst weight 0.4 g, metal content (palladium or nickel) 4 wt.%, particle diameter d = 0.075—0.102 mm, molar ratio of substrates α-alanyl-α-proline and ethyl 2-oxo-4-phenylbutanoate 1 : 1. The error in determining the yield of the target product is ±3—5%.

added at a temperature of 45 °C. After purging the reactor with hydrogen, the catalyst was activated by passing hydrogen for 60 min with vigorous stirring. Then, the catalyst was filtered and washed with water and acetone (50 mL). The ready-to-use catalyst was stored under a layer of acetone.

Research methods. *Determination of the metal content in the catalyst*. The palladium content in the catalyst was determined from the decrease in the concentration of the $[PdCl_4]^{2-}$ ions in solution as they were immobilized on the support. For this, the concentration of $[PdCl_4]^{2-}$ in the mother liquor was measured using a Specord-UV instrument and quartz cells with a 1 cm pathlength, λ = 280 nm. The decrease in the concentration of nickel ions was determined similarly.

Thin layer chromatography. Qualitative analysis of reaction mixtures was carried out by TLC on Silufol plates, acetone—toluene—ammonia (1 : 1 : 1). The plates were visualized under UV light.

Procedure for hydrogenation N-alkylation of α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate. A weighed sample of the catalyst (100—500 mg) was loaded under a layer of solvent (50 mL) in a glass reactor equipped with a jacket for thermostating and a magnetic stirrer for stirring in a flow of hydrogen. The catalyst was activated with hydrogen for 20—30 min. Then, α-alanyl-α-proline (4 g, 0.022 mol) and ethyl 2-oxo-4-phenylbutanoate (10 g, 0.043 mol) were introduced into the reactor in a flow of hydrogen. The reaction mixtures were stirred at a constant rate of 900—1100 rpm at a hydrogen pressure of 98—103 kPa. After the reaction completion, the mixture was filtered and concentrated by evaporation to give a pale yellow oily residue (6.0 g). Then, the oily residue was dispersed in a solution of sodium chloride (20 g) in water (100 mL), the pH of which was adjusted to 8.5 with K_2HPO_4, and extracted with ethyl acetate (2×100 mL). The aqueous solution was acidified with 1 M H_3PO_4 to pH 4.2 and again extracted with ethyl acetate (4×100 mL). The extract was dried with anhydrous sodium sulfate and concentrated to obtain an oily substance (3.30 g). Then, the residue of the oily substance was dissolved in warm water (100 mL, 60 °C) and filtered. Upon cooling the filtrate, a white amorphous substance of enalapril is formed (the highest yield on the AV-17-8-Pd catalyst was 2.63 g, 70 wt.%). The mass yields for all the studied catalysts are given in Tables 1 and 2 and ranging from 30 to 70 wt.%. The purity of the obtained enalapril, as determined by TLC, was no less than 98.0%.

Effective reaction rate was measured volumetrically by the volume of absorbed hydrogen per unit time, as well as by analyzing samples of reaction mixtures by TLC or GLC at each time point. Anion and cation exchangers, in contrast to heterogeneous analogs, have swelling propensity the extent of which depends on the nature of polymer and solvent. This tendency was taken into account when selecting the process conditions. All the anion and cation exchangers have a three-dimensional cross-linking structure of macromolecules. The specific surface area of the porous ion exchangers (depending on the structure) is 20—130 m^2 g^{-1}, while for the gel ion exchangers it usually does

Table 2. Yield (Y) and effective reaction rate constant (k_{eff}/mol L^{-1} s^{-1} (kg cat.)$^{-1}$) in the synthesis of Enalapril in the presence of nickel-containing catalyst and various solvent*

Catalyst	Yield and effective rate constant in various solvents							
	Ethanol		Butanol		Hexane		Toluene	
	Y (%)	$k_{eff} \cdot 10^3$	Y (%)	$k_{eff} \cdot 10^3$	Y (%)	$k_{eff} \cdot 10^3$	Y (%)	$k_{eff} \cdot 10^3$
AV-17-8-Ni	62	5.00	57	3.00	50	1.50	48	1.70
AN-1-Ni	60	4.60	56	2.40	50	0.84	49	0.90
KF-1-Ni	45	3.10	40	1.00	38	0.60	40	0.68
$Ni//CaCO_3$	35	2.70	33	0.70	32	0.58	33	0.67
Ni/C	32	2.40	30	0.60	31	0.52	30	0.64

* Conditions see Table 1.

not exceed 5 $m^2 g^{-1}$. The pore diameters of the porous ion exchangers reaches 20—100 nm; the pore diameters of the gel ion exchangers is no more than 5 nm.

The procedure for carrying out liquid-phase catalytic hydrogenation *N*-alkylation in batch reactors under normal conditions, analysis of reaction mixtures, isolation, purification, and identification of reaction products, preparation of heterogeneous and organometallic catalysts have also been described in detail earlier.[12—14]

Results and Discussion

To carry out the catalytic synthesis of enalapril, we obtained modified palladium- or nickel-containing catalysts based on low-basic, high-basic, weakly cross-linked and strongly cross-linked ion exchange resins, cation exchangers or anion exchangers AV-17-8-Pd, AN-1-Pd, KF-1-Pd or AV-17-8-Ni, AN-1-Ni, KF-1-Ni. Their catalytic characteristics are comparable with characteristics obtained for conventional heterogeneous analogs such as Pd/C, Ni/C, $Pd/CaCO_3$, and $Ni//CaCO_3$.

To find out the region where the catalytic reaction proceeds, the diffusion inhibition factor can be calculated, which is expressed by the Thiele modulus (Φ_s). According to the Weiss—Prater criterion, diffusion is a limiting step of the process if the following conditions are met: 1) $\Phi_s > 0.3$ for second-order reactions, 2) $\Phi_s > 1$ for first-order reactions, and 3) $\Phi_s > 6$ for zero-order reactions. In the present work, it is shown that the Thiele modulus values in the studied catalytic reactions do not exceed 0.5, which for the first-order reactions indicates the kinetic region of the process. Since the reactions are kinetically controlled, we studied the dependences of the effective rate constant on hydrogen pressure (Fig. 1), catalyst weighed sample (Fig. 2), and substrate concentration (Fig. 3) in order to select the optimal conditions.

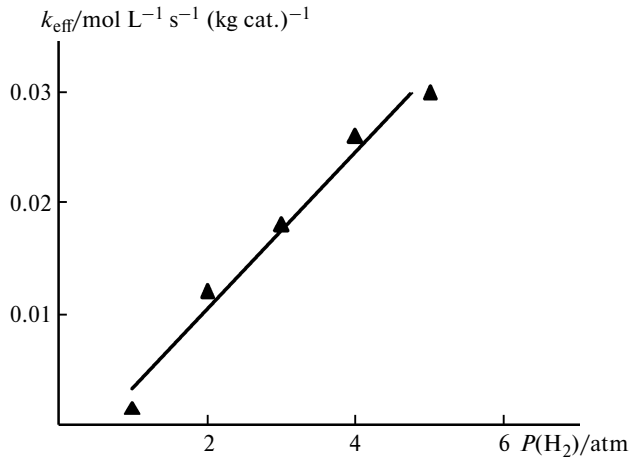


Fig. 1. The effective rate constant of the reductive *N*-alkylation of α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate *versus* the initial hydrogen pressure on AV-17-8-Pd.

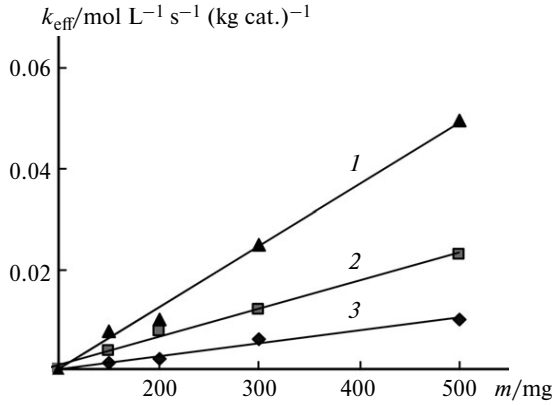


Fig. 2. The effective rate constant of the reductive *N*-alkylation of α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate *versus* catalyst weight: AV-17-8-Pd (*1*), AN-1-Pd (*2*), Pd/C (*3*).

It was found that the reaction of reductive *N*-alkylation of α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate has the first order in hydrogen and catalyst, as well as zero order with respect to the substrate. Some dependencies typical of all the catalysts studied in the work are shown in Figs 1—3. The data in the Figures show that the total rate of the process is directly proportional to the hydrogen pressure and the number of active sites of the catalyst. However, carrying out the reaction at an elevated hydrogen pressure requires a more sophisticated equipment. Taking into account all the factors, we have chosen the atmospheric pressure of hydrogen and the minimum amount of the catalyst as the most optimal regime for carrying out the reductive alkylation process. The optimum parameters such as the temperature of the reaction mixture, hydrogen pressure, type of solvent, and substrate concen-

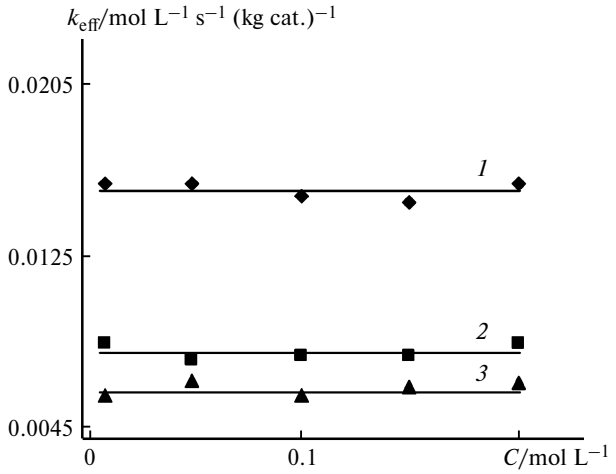


Fig. 3. The effective rate constant of the reductive *N*-alkylation of α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate *versus* the initial concentration of α-alanyl-α-proline: AV-17-8-Pd (*1*), AN-1-Pd (*2*), Pd/C (*3*). The alkylating agent, ethyl 2-oxo-4-phenylbutanoate, was taken in excess.

tration (see Table 1) were used in the main synthesis of enalapril.

The obtained experimental results on the yields of the target product 1-[*N*-((*S*)-1-carboxy-3-phenylpropyl)-α-alanyl]-α-proline-1′-ethyl ester and the effective rate constant values in various organic solvents are given in Tables 1 and 2.

The data on the synthesis of enalapril carried out by the reaction of hydrogenation *N*-alkylation of dipeptide α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate on nickel- or palladium-containing catalysts in organic solvents at atmospheric pressure of hydrogen and a temperature of 25—45 °C are summarized in Tables 1 and 2. These data indicate that the nature of the catalyst and solvent has the most significant effect on the yield of the target product and the reaction rate. Thus, when heterogeneous contacts are replaced by metal polymers (MPs), the effective rate constant increases more than three-fold, and on going from non-polar (aromatic hydrocarbons) to polar solvents (alcohols), a more than four-fold increase in the constant is observed. The increased activity of catalysts based on MPs is most likely associated with the macroporous three-dimensional structure of the polymers, which facilitates the access of substrate molecules to the active sites of the catalyst. The effect of the solvent on the course of the reaction can be explained by swelling propensity of the MPs in organic solvents, with alcohols promoting swelling to a greater extent than hydrocarbons. As a result, the three-dimensional polymer chain of macromolecules acquires additional flexibility, which, in turn, increases the availability of active sites of palladium or nickel catalysts for substrate molecules.

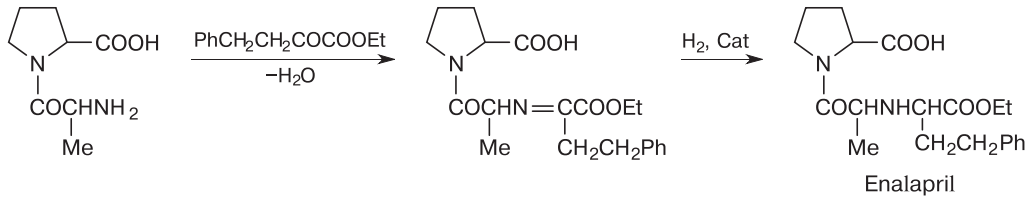
The inner cell diameter of the polymer support, according to the literature data[15—17] varies within wide limits with an average values of 16—17 Å. Consequently, not all components of the reaction mixture can penetrate into the polymer matrix, and by controlling the swelling effect of the solvent on the polymer cell size, it is possible to achieve absolute selectivity of the process with respect to one of the substrates in the presence of their mixture. According to some data,[4,5—17] it is possible to control the size of the three-dimensional polymer cell over a wide range by choosing degree of the support cross-linking and solvents, thereby achieving practically molecular or even atomic precision and selectivity of the synthesis. With the maximum swelling, almost all active sites of the MP become as accessible as in homogeneous catalysts; therefore, the concept of a surface for MPs in the cases under consideration is practically absent, although the MP itself forms a gel-like mass easily separable from the liquid phase.

Thus, MPs combine the advantages of both homogeneous and heterogeneous catalysts. However, despite a decrease in the rate of the process for both metallopolymers and heterogeneous analogs (see Tables 1 and 2), the selectivity practically does not change, although it is known that the selectivity of the process, as a rule, increases with a decrease in the reaction rate. The reaction proceeds in one step by combining the reaction of condensation of the amine and the carbonyl compound with hydrogenation of the azomethine bond (Scheme 1).

From the data in Tables 1 and 2, it is also seen that, in general, the catalysts based on palladium-containing highly basic anion exchangers showed the highest efficiency. Nickel-containing catalysts of all types proved to be low-efficient, most likely due to the nature of the metal, since it is known that nickel catalysts are significantly inferior to palladium-containing analogs, at least, to heterogeneous systems. At the same time, MPs turned out to be more efficient than their heterogeneous analogues. This is due to the catalytic acceleration of the step of condensation of the carbonyl compound (ethyl 2-oxo-4-phenylbutanoate) and the amine (dipeptide α-alanyl-α-proline) with the formation of an intermediate product, namely, azomethine or Schiff base (the first step in Scheme 1). It is the acceleration at this step that is responsible for the greatest catalytic effect of the newly obtained catalysts.

A similar effect was observed earlier[16] in the hydrogenation amination of aliphatic or heterocyclic aldehydes with aromatic amines or their precursors, nitro compounds. It is known that the process of condensation of amines with carbonyl compounds is catalytically accelerated by acids or bases. However, a comparison of the data in Tables 1 and 2 shows that anion exchangers are most efficient regardless of the nature of the metal (nickel or palladium). Therefore, it can be assumed that the nature of the basic or acidic functional groups of the polymer support has a significant effect on the overall efficiency of the process, namely, at the step of the amine and carbonyl

Scheme 1



Cat is the nickel- or palladium-containing catalyst.

compound condensation with the formation of azomethine (*i.e.*, accelerates the attainment of equilibrium). At the same time, the hydrogenation of the azomethine bond of the formed Schiff base proceeds on active metal nanoparticles. Hydrogenation of the azomethine bond with the conversion of the compound into the target product, in turn, also contributes to the formation of the intermediate condensation product, azomethine, especially since the hydrogenation step, in contrast to the condensation, is a non-equilibrium process. Thus, the high yield of the target product is achieved due to both the acceleration of the process of condensation of amine with carbonyl compound and the non-equilibrium step of hydrogenation of the azomethine bond in the intermediate product. Concerning selectivity and activity in the one-step synthesis of enalapril by reductive *N*-alkylation of dipeptide α-alanyl-α-proline with ethyl 2-oxo-4-phenylbutanoate, palladium-containing catalysts are superior to nickel-containing metal-polymer and heterogeneous analogs.

In conclusion, nickel- or palladium-containing polymers turned out to be efficient in the catalytic synthesis of the drug 1-[*N*-((*S*)-1-carboxy-3-phenylpropyl)-α-alanyl]-α-proline-1′-ethyl ether, or enalapril, under mild conditions of the process. The highest selectivity is displayed by palladium catalysts based on industrial anion exchangers; therefore, these contacts can become the basis for the development of efficient methods for obtaining medicinal organic substances.

References

1. A. A. Patchet, *Nature*, 1980, **288**, 280—283.
2. A. A. Patchet, *Br. J. Clin. Pharmac.*, 1984, **18**, 201—207.
3. I. P. Beletskaya, L. M. Kustov, *Russ. Chem. Rev.*, 2010, **79**, 493—515.
4. V. P. Ananikov, *Russ. Chem. Rev.*, 2014, **83**, 885—887.
5. A. T. Soldatenkov, N. M. Kolyadina, I. V. Shendrik, *Osnovy organicheskoy khimii lekarstvennykh veshchestv* [*Fundamentals of Organic Chemistry of Medicinal Substances*], Mir, Moscow, 2003, p. 97—98 (in Russian).
6. M. A. Huffman, P. J. Reider, *Tetrahedron Lett.*, 1999, **40**, 831—834.
7. M. V. Klyuev, M. G. Abdullaev, Z. Sh. Abdullaeva, *Pharm. Chem. J.*, 2010, **44**, No. 8, 446—451.
8. K. N. Gusak, Zh. V. Ignatovich, E. V. Koroleva, *Russ. Chem. Rev.*, 2015, **84**, 288—309.
9. M. G. Abdullaev, *Vestn. DGU, Ser. 1, Estestvennye nauki* [*Dag. State Univ. Lett., Ser. 1, Nat. Sci.*], 2016, **31**, No. 2, 67—73 (in Russian).
10. M. G. Abdullaev, *Pharm. Chem. J.*, 2018, **52**, 865—867.
11. H. M. Colquhoun, J. Holton, D. J. Thompson, M. V. Twigg, *New Pathways for Organic Synthesis,* Plenum Press, New York—London, 1984, 400 pp.
12. V. Slavinska, Dz. Sile, G. I. Chipens, Yu. Balodis, G. Rozenthal, K. Venteris, E. Lukevics, *Chem. Heterocycl. Compnd.*, 2003, **39**, 1579—1583.
13. M. J. Wyvratt, E. W. Tristram, T. J. Ikeler, N. S. Lohr, H. Joshua, J. P. Springer, B. H. Arison, A. A. Patchett, *J. Org. Chem.*, 1984, **49**, 2816—2819.
14. M. G. Abdullaev, Z. Sh. Abdullaeva, M. V. Klyuev, Z. G. Gebekova, *Pharm. Chem. J.*, 2014, **48**, No. 5, 343—346.
15. M. V. Klyuev, E. F. Vainshtein, *Metallsoderzhashchie polimery — osobyy tip katalizatorov* [*Metal-Containing Polymers — a Special Type of Catalysts*], IKhR RAN, Ivanovo, 2014, p. 58—65 (in Russian).
16. M. V. Klyuev, M. G. Abdullaev, *Kataliticheskiy sintez aminov* [*Catalytic Synthesis of Amines*], Izd-vo IvGU, Ivanovo, 2014, p. 130—138 (in Russian).
17. K. M. Saldadze, V. D. Kopylova-Valova, *Kompleksoobrazuyushchie ionity*, [*Complexing Ion Exchangers*], Khimiya, Moscow, 1980, p. 330—340 (in Russian).

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