ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 3, pp. 365–373. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © N.E. Borisova, V.A. Knizhnikov, T.G. Gulevich, M.Yu. Seliverstov, E.A. Borisov, M.D. Reshetova, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 3, pp. 377–385.

Pincer Ligands Based on α-Amino Acids: III.* New Ligands Based on 4-Substituted Phenols and Their Copper Complexes. Enantioselective Recognition of Tyrosine

N. E. Borisova[a], V. A. Knizhnikov[b], T. G. Gulevich[b], M. Yu. Seliverstov[a], E. A. Borisov[a], and M. D. Reshetova[a]

[a] *Faculty of Chemistry, Moscow State University, Vorob'evy gory 1, Moscow, 119992 Russia*
e-mail: Borisova.Nataliya@gmail.com

[b] *Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, ul. Surganova 13, Minsk, 220072 Belarus*

Received February 18, 2008

Abstract—Reactions of L-methionine, L-serine, and L-valine with 5-substituted-2-hydroxybenzene-1,3-dicarbaldehydes gave a series of chiral Schiff base pincer ligands which were reduced to the corresponding diamines. The new Schiff base ligands reacted with copper(II) chloride to form dinuclear copper complexes which were found to be capable of recognizing tyrosine enantiomers in aqueous solution. The structure of the complexes was determined on the basis of their spectral parameters.

DOI: 10.1134/S107042800903004X

Design of synthetic receptors for selective binding and separation of enantiomeric chiral substrates, as well as of enantioselective sensors for analytical determination of optical purity of chiral compounds, constitutes an important problem in modern chemistry. Synthetic receptors for biomolecules such as α-amino acids and peptides (that are the most important chiral substrates) attract specific interest. Studies on enantioselective recognition of these substrates have been initiated long ago; nevertheless, interest in this topic continuously increases, as follows from analysis of data published during the past decade. Up to now, various receptors and sensors based on chiral multidentate macromolecules have been proposed for recognition of chiral amino acids. Most studies were performed in nonpolar organic solvents, whereas receptors working in aqueous medium were studied to a lesser extent.

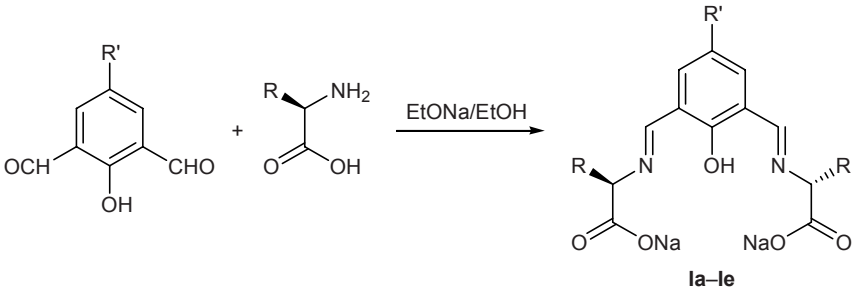
Among the examined classes of compounds, macrocycles on the basis of crown ethers and calixarenes should primarily be noted. Cross host–guest interaction between chiral crown ethers and α-amino acid methyl ester hydrochlorides was studied by spectrophotometric titration [2, 3] and mass spectrometry (FAB) [4]. Calix[4]arenes having side-chain chiral amino acid fragments were proposed as fluorescent sensors for α-amino acid tetrabutylammonium salts [5, 6]. Well developed anion recognition techniques (e.g., introduction of guanidinium fragments into receptor molecule) were applied to recognize neutral amino acids that exist as zwitterions. Effective combination of calixarene and crown ether scaffolds with guanidinium recognizing groups located in the vicinity of chiral centers made it possible to construct receptors capable of binding amino acids in aqueous medium [7, 8].

Among other types of receptors for enantioselective recognition of amino acids, chiral macrocycles derived from pyridine-2,6-dicarboxamide [9] and 2,6-diaminopyridine-based amides [10] and having chiral amino acid fragments in the macroring should be noted. Such systems were effective in recognizing stereoisomeric amino acid methyl esters and peptides. Liu et al. [11] described receptors for chiral recognition of amino acids in buffer solution (pH 7.2), which were synthesized on the basis of chiral β-cyclodextrins modified by substituted benzeneselenols.

The use of chiral metal complexes capable of coordinating molecules with donor groups seems to be a quite promising method for recognition of optical isomers. Belokon' and co-workers [12, 13] tried to

* For communication II, see [1].

Scheme 1.



Ia–Ie

R = $MeS(CH_2)_2$, R′ = *t*-Bu (**a**), Me (**b**); R = $HOCH_2$, R′ = *t*-Bu (**c**), Me (**d**); R = Me_2CH, R′ = *t*-Bu (e).

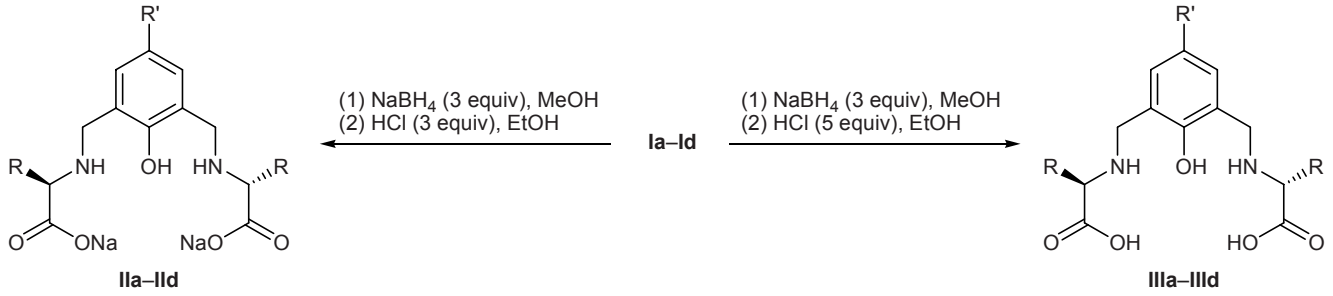
create enantiomeric receptors for chiral recognition of amino acids on the basis of mononuclear copper complexes with macrocyclic Schiff bases. However, the proposed systems showed no selectivity for enantiomeric amino acids [12]. Acyclic mononuclear systems based on optically active copper complexes with 2,6-bis(oxazol-2-yl)pyridines turned out to be capable of recognizing enantiomeric amino acids in 50% aqueous methanol at a submillimolar level; for example, the dissociation constants for the complexes with phenylalanine were K_d(L-Phe) = 1.95×10^{-4} and K_d(D-Phe) = 1.10×10^{-4}, but the enantioselectivity was poor [14].

We presumed that the use of dinuclear metal complexes could not only proportionally enhance binding of an amino acid substrate to metal ion but also increase the selectivity due to rigid fixation of amino acid molecule via coordination at two centers. It is known that tetranuclear copper complexes with Schiff bases derived from vanillin can be used as active components of ion-selective membrane electrodes [15].

The present work was aimed at synthesizing dinuclear copper complexes with chiral acyclic Schiff bases **Ia**–**Ie** and studying their interaction with optically active amino acids. Initial chiral Schiff bases were synthesized by reaction of 5-alkyl-2-hydroxybenzene-1,3-dicarbaldehydes with L-valine, L-serine, and L-methionine sodium salts in anhydrous ethanol and were isolated as the corresponding disodium salts **Ia**–**Ie** in 80–95% yield (Scheme 1). Illán-Cabeza et al. [16] previously reported on the reaction of L-histidine with 2-hydroxy-5-methylbenzene-1,3-dicarbaldehyde in boiling methanol at pH 6.5, which gave the corresponding Schiff base. However, this procedure cannot be extended to other amino acids, for histidine molecule possesses an additional basic center (imidazole nitrogen atom) which is protonated in the zwitterionic form of the amino acid; other amino acids in neutral medium exist as zwitterions with protonated nitrogen atom in the amino group [17]. Just that factor was responsible for the failure [16] to obtain analogous Schiff base from 2-hydroxy-5-methylbenzene-1,3-dicarbaldehyde and L-alanine. The use of the corresponding sodium salt instead of free amino acid eliminates limitations related to the substrate nature. Schiff base disodium salts **Ia**–**Ie** were yellow hygroscopic crystalline powders, which were poorly soluble in organic solvents and unstable on exposure to moisture. Their structure was determined by ^1H and ^{13}C NMR spectroscopy. The difference in the frequencies of symmetric and antisymmetric vibrations of the carboxylate ion indicated that the carboxy group acts as a unidentate ligand [18]. The NMR spectra were recorded from solutions in methanol, for both deuterated dimethyl sulfoxide and the more so D_2O [16] promoted hydrolysis of Schiff bases **Ia**–**Ie**. The presence of 2–4% of water in commercial methanol-d_4 did not induce hydrolysis of the ligands and did not interfere with signal resolution. The chemical shifts of the aromatic carbon atom linked to the phenolic hydroxy group were about δ_C 150 ppm; this value is typical of neutral phenols. In the spectrum of **Ia**, the corresponding signal was displaced downfield (δ_C 165.5 ppm), indicating deprotonation of the phenolic hydroxy group.

The reduction of Schiff bases **Ia**–**Id** with 3 equiv of sodium tetrahydridoborate in anhydrous methanol, followed by treatment of the reaction mixture with 3 equiv of ethanolic hydrogen chloride, gave sodium salts **IIa**–**IId**, which were isolated as individual substances (Scheme 2). By treatment of the reaction mixture with excess HCl (5 equiv) in ethanol we obtained free diacids **IIIa**–**IIId** in 75–85% yield. Pincer amino acid salts **IIa**–**IId** were yellow powders readly soluble in water and methanol and insoluble in other solvents. Unlike their sodium salts, free acids **IIIa**–**IIId** were isolated as white powders moderately soluble in alcohols and water.

Scheme 2.

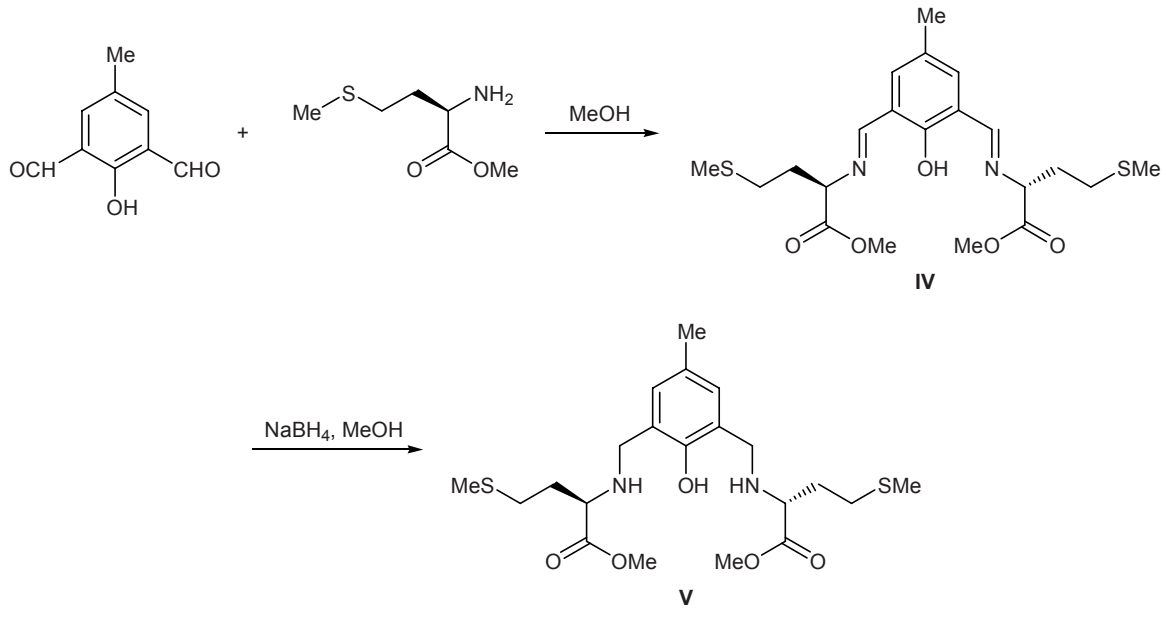


R = $MeS(CH_2)_2$, R′ = *t*-Bu (**a**), Me (**b**); R = $HOCH_2$, R′ = *t*-Bu (**c**), Me (**d**).

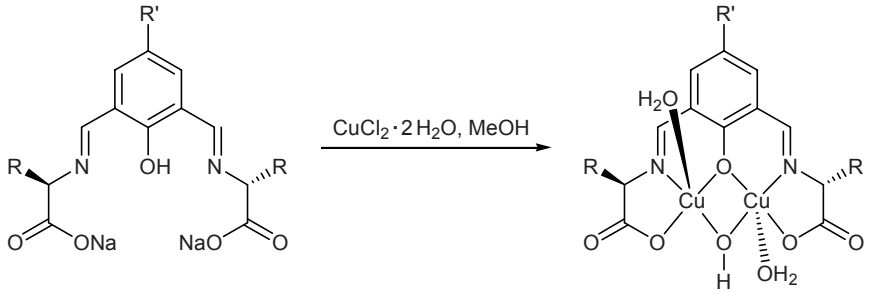
According to the IR data, the structure of salts **IIa**–**IId** is analogous to their precursors **Ia**–**Id**. The sodium ions are linked to the carboxy groups, as follows from the difference $\nu_{as} - \nu_s$ between the vibration frequencies of the carboxylate ion. The carboxy groups in free acids **IIIa**–**IIId** give rise to absorption at 1730–1750 cm^{-1}. Signals from the phenolic carbon atom (C–OH) in **IIa**–**IId** are located in the ^{13}C NMR spectra at about δ_C 155 ppm, i.e., in the region typical of undissociated hydroxy group in substituted phenols. Salts **IIa**–**IId** characteristically showed in the ^1H NMR spectra a large difference in the chemical shifts of diastereotopic protons in the NHC$\mathbf{H}_2$ group, and this difference did not depend on the temperature. This pattern originates from the specific steric structure of molecules **II** and **III**, where one hydrogen atom in the CH_2NH group appears in the vicinity of the carboxylato (**IIa**–**IId**) or carboxy group (**IIIa**–**IIId**). In the spectra of **IIIa**–**IIId**, the corresponding difference is much smaller or equal to zero. The C–OH signal in the ^{13}C NMR spectra shifts upfiled by 3–4 ppm in going from salts **IIa**–**IId** to acids **IIIa**–**IIId**, indicating weak coordination of sodium ion at the oxygen atom in the phenolic hydroxy group.

We also made an attempt to synthesize chiral Schiff bases from amino acid methyl esters. The products were expected to be better soluble in organic solvents than the corresponding derivatives of free amino acids. As model substrate we used L-methionine methyl ester. Its reaction with 2-hydroxy-5-methylbenzene-1,3-dicarbaldehyde gave methyl ester **IV** (Scheme 3) as a yellow oily substance readily soluble in most organic solvents, poorly soluble in saturated hydrocarbons, and readily hydrolyzable with water. Ester **IV** was characterized by spectral and analytical data. By reduction of **IV** with sodium tetrahydridoborate in anhydrous meth-

Scheme 3.



Scheme 4.



Ib, **Id**, **Ie** **VIb**, **VId**, **VIe**

R′ = Me, R = $MeS(CH_2)_2$ (**b**), $HOCH_2$ (**d**); R′ = *t*-Bu; R = Me_2CH (**e**).

anol we obtained pincer amino ester **V** in high yield. Compound **V** is readily soluble in polar organic solvents, insoluble in nonpolar hydrocarbons, and stable to hydrolysis.

Contrary to the expectation, both MALDI-TOF and ESI mass spectra of the synthesized Schiff bases and their reduction products turned out to be low informative. As a rule, no molecular ion peak was observed. Exception were negative ion mass spectra of Schiff base **Id** (*m*/*z* 339, I_{rel} 20%), acid **IIIa** (*m*/*z* 471, I_{rel} 10%), and diester **IV** (*m*/*z* 453, I_{rel} 100%). The spectra showed the presence of large amounts of oligomers (di- and even trimers), and their fragment ion peaks strongly complicated identification of the target products. The main fragmentation pathway of the Schiff bases derived from methionine and serine involves elimination of one amino acid fragment [$MeS(CH_2)_2CHCO_2H$ or $HOCH_2CHCO_2H$] as a result of cleavage of the C–H bond. The fragmentation of serine derivatives was also characterized by elimination of the entire amino acid residue and loss of CO_2 molecule.

Dimethyl ester **IV** reacted with copper salts to give a copper complex which we failed to isolate as individual substance. As a result of hydrolysis, copper complex with methionine methyl ester was isolated. Unlike diester **IV**, disodium salts **Ib**, **Id**, and **Ie** readily underwent transmetalation upon treatment with a concentrated solution of copper(II) chloride dihydrate in methanol, and the corresponding complexes **VIb**, **VId**, and **VIe** were isolated in high yields (Scheme 4).

Complexes **VIb**, **VId**, and **VIe** are green powders; they are soluble in methanol and water and poorly soluble in organic solvents. Their structure was proved by the IR spectra and elemental analyses. The complexes had similar structures, regardless of the amino acid nature. In the IR spectra of complexes **VIb**, **VId**, and **VIe** we observed an absorption band corresponding to the C=N bond involved in coordination to copper ion (~1610 cm^{-1}) and bands due to antisymmetric and symmetric stretching vibrations of the carboxylate ions at 1640 and 1360 cm^{-1}, respectively. Appreciably increased difference between the symmetric and antisymmetric vibration frequencies, as compared to the corresponding sodium salts, indicates a considerable covalent character of the bond between the copper ion and carboxylate oxygen atom [16, 18]. Simultaneously, the stretching vibration frequency of the phenolic C–O bond increases from 1220 cm^{-1} in the spectra of sodium salts **Ib**, **Id**, and **Ie** to 1320 cm^{-1} in the spectra of copper complexes **VIb**, **VId**, and **VIe**. The observed change is typical of coordination of metal ions to Schiff bases derived from salicylaldehyde [18]. These findings suggest that the copper coordination entity consists of the C=N nitrogen atom and three oxygen atoms. Among the latter, one oxygen atom belongs to the carboxylate group, and the two other, phenolic and hydroxy oxygen atoms, form bridges between two copper ions. The configuration of the copper ions is supplemented to tetragonal–pyramidal via apical coordination of a water molecule as extra ligand. In fact, an absorption band at 3400 cm^{-1} is present in the IR spectra due to OH stretching vibrations. The structure of the coordination polyhedron is determined mainly by the structure of the 2-hydroxy-5-methylbenzene-1,3-dicarbaldehyde moiety. It is known [19] that 2-hydroxy-5-methylbenzene-1,3-dicarbaldehyde is the key building block for the synthesis of dinuclear complexes with two bridging oxygen atoms.

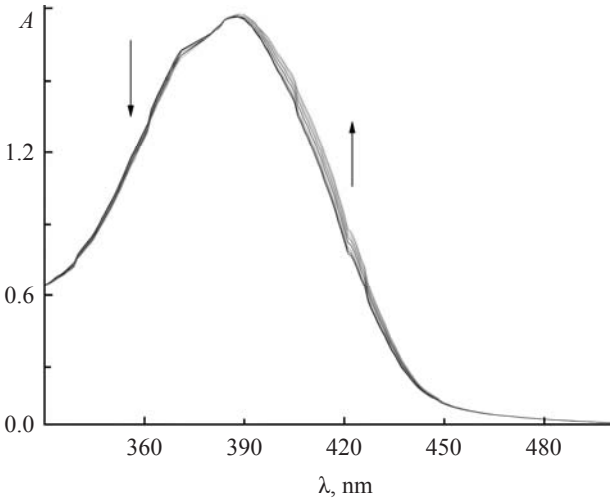
We examined cross interaction between dinuclear complex **VIe** and tyrosine enantiomers in aqueous solution using the equimolar series technique. It was found that complex **VIe** is capable of binding enantiomeric D- and L-tyrosine to form 1:2 and 1:1 adducts,

respectively. According to the spectrophotometric titration data, the main absorption maxima of the adducts almost coincided with those of the initial complex (see figure). In the course of titration, the long-wave part of the absorption band of complex **VIe** increased in intensity, while the intensity of the short-wave component slightly decreased. Thus we observe absorption of both initial complex **VIe** and its adduct with the amino acid at any wavelength during spectrophotometric titration. In addition, the isosbestic point is located near the absorption maximum of **VIe**. To calculate the binding constant it was necessary to find a point (wavelength) at which the difference in the absorbances of the initial complex and its adduct with the amino acid be maximal. Full shape analysis of the absorption band of the complex with D-tyrosine revealed two more long-wave bands with their maxima at λ 394.2 and 411.1 nm. The maximal difference in the absorbances was observed at λ 411 nm. Analogous procedure for the complex with L-tyrosine revealed one additional band with its maximum at λ 404 nm. The binding constants for the different tyrosine enantiomers were determined at λ 411 and 404 nm for the D- and L-isomers, respectively. The equilibrium constant for L-tyrosine was estimated at $\beta_1 = K_B(1:1) = 97(5)$ mol^{-1} ($r^2 = 0.980$), while only the constant $\beta_2 = K_B(1:1) \times K_B(1:2) = 4.4(4) \times 10^4$ mol^{-1} ($r^2 = 0.990$) was reliably determined for D-tyrosine.

To conclude, we have synthesized acyclic pincer Schiff base and amine ligands and examined their complex formation with copper ions. The complex with the Schiff base derived from L-valine showed analytical response toward tyrosine enantiomers. The proposed approach, which implies binding of amino acids by several metal ions with formation of rigid structure, seems to be promising from the viewpoint of design of enantioselective sensor systems.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^{1}H and ^{13}C NMR spectra were measured at 20°C on a Bruker Avance-400 spectrometer; the chemical shifts were determined relative to tetramethylsilane. Spectrophotometric titration was performed on a Helios & Thermo Scientific spectrophotometer in aqueous solutions with a zero ionic strength. The binding constants were determined in distilled water. Stoichiometric coefficients for extra ligand exchange were determined using the equimolar series method [20]. In the analysis



Variation of the electronic absorption spectrum of complex **VIe** upon addition of D-tyrosine.

of band shapes, absorption curves were approximated by Gauss functions. The parameters of the Gauss function for the initial complex (λ_{max} 382.6 nm) were determined by approximation of the absorption band of the pure complex at the same concentration. The purity in the determination of wavelength corresponding to maximum difference in the absorbances of the copper complex and its associate with tyrosine was ±3 nm for the D-stereoisomer and ±1 nm for the L-isomer. The mean-square deviation for the resultant function was 0.0028 ($r^2 = 0.993$) for D-tyrosine and 0.0021 ($r^2 = 0.995$) for L-tyrosine. The initial amino acid methyl esters were synthesized according to the procedures described in [21], and 2-hydroxy-5-alkylbenzene-1,3-dicarbaldehydes were prepared as reported in [22]. Methanol was distilled over calcium hydride under argon before use. The other reagents and solvents were used without additional purification.

Disodium salts Ia–Ie (*general procedure***).** L-Valine, L-serine, or L-methionine, 10 mmol, was added at room temperature to a solution of sodium ethoxide prepared from 0.23 g (10 mmol) of metallic sodium and 100 ml of anhydrous ethanol. The mixture was stirred for 1 h at room temperature, 5 mmol of the corresponding 5-alkyl-2-hydroxybenzene-1,3-dicarbaldehyde and 4 g of 3-Å molecular sieves were added, and the mixture was stirred for 10 h and filtered. The filtrate was concentrated under reduced pressure and cooled to –30°C, and the yellow precipitate (powder) was filtered off, washed with diethyl ether, and dried under reduced pressure.

Compound **Ia** was synthesized from 1.49 g of L-methionine and 2.06 g of 5-*tert*-butyl-2-hydroxyben-

zene-1,3-dicarbaldehyde. Yield 2.05 g (80%). IR spectrum, ν, cm^{-1}: 3426.2, 2956.3, 2916.5, 1648.6, 1629.7, 1584.8, 1510.3, 1393.3, 1359.4, 1336.7, 1224.9, 1041.0. ^1H NMR spectrum (methanol-d_4), δ, ppm: 1.33 s (9H, *t*-Bu), 2.09 s (6H, SCH_3), 2.15 m (2H, CHN), 2.25 m (2H, CHN), 2.55 m (4H, CH_2), 4.06 t (2H, CH, J = 4.7 Hz), 7.63 s (2H, CH), 8.42 s (2H, CH=N). ^{13}C NMR spectrum (methanol-d_4), δ_C, ppm: 13.8, 29.9, 30.2, 33.5, 33.7, 71.6, 117.3, 128.0, 137.4, 163.4, 165.5, 174.4.

Compound **Ib** was synthesized from 1.49 g of L-methionine and 1.64 g of 2-hydroxy-5-methylbenzene-1,3-dicarbaldehyde. Yield 2.00 g (85%). IR spectrum, ν, cm^{-1}: 3422.9, 2916.4, 1711.5, 1629.0, 1600.6, 1522.6, 1393.8, 1206.3, 1158.7, 552.8. ^1H NMR spectrum (methanol-d_4), δ, ppm: 2.02 m (4H, CH_2), 2.08 s (6H, SCH_3), 2.27 s (3H, CH_3), 2.59 t (4H, CH_2, J = 8.3 Hz), 4.03 d.d (2H, CH, J = 4.6, 3.7 Hz), 7.38 s (2H, CH), 8.36 s (2H, CH=N). ^{13}C NMR spectrum (methanol-d_4), δ_C, ppm: 13.7, 30.1, 31.5, 34.3, 72.2, 124.0, 137.5, 137.8, 155.7, 162.9, 179.8. Found, %: C 48.32; H 5.29; N 5.65. $C_{19}H_{24}N_2Na_2O_5S_2$. Calculated, %: C 48.50; H 5.14; N 5.95.

Compound **Ic** was synthesized from 1.05 g of L-serine and 2.06 g of 5-*tert*-butyl-2-hydroxybenzene-1,3-dicarbaldehyde. Yield 1.84 g (87%). IR spectrum, ν, cm^{-1}: 1633.2, 1520.2, 1391.9, 1359.8, 1224.3, 1041.6, 627.1. ^1H NMR spectrum (methanol-d_4), δ, ppm: 1.32 s (9H, *t*-Bu), 3.86 t (2H, CH, J = 11.3 Hz), 4.03 d (4H, C**H**$_2$OH, J = 11.3 Hz), 7.55 s (2H, CH), 8.33 s (2H, CH=N). ^{13}C NMR spectrum (methanol-d_4), δ_C, ppm: 30.2, 33.2, 63.8, 73.5, 117.9, 131.1, 151.7, 166.0, 178.8.

Compound **Id** was synthesized from 1.05 g of L-serine and 1.64 g of 2-hydroxy-5-methylbenzene-1,3-dicarbaldehyde. Yield 1.72 g (90%). IR spectrum, ν, cm^{-1}: 3405.7, 2922.9, 2854.6, 1628.5, 1527.8, 1394.7, 1218.3, 1033.3, 563.6. ^1H NMR spectrum (methanol-d_4), δ, ppm: 2.26 s (3H, CH_3), 3.89 t (2H, CH, J = 5.4 Hz), 4.00 d (4H, C**H**$_2$OH, J = 5.4 Hz), 7.35 s (2H, CH), 8.30 s (2H, CH=N). Mass spectrum, *m*/*z* (I_{rel}, %): MALDI-TOF, positive ions: 89 (100) $[HOCH_2CHCO_2H]^+$, 105 (28) $[Ser + H]^+$, 449 (30) $[M + Ser + 6H]^+$; MALDI-TOF, negative ions: 185 (100), 213 (60) $[M - HOCH_2CHCO_2H - CH_2OH]^-$, 265 (100) $[M - CH_2OH - CO_2]^-$, 339 (20) $[M]^-$; electrospray ionization: 333 (84) $[M - 5H]^+$, 275 (100) $[M - CO_2H - OH]^+$, 234 (50) $[M - Ser - H]^+$. Found, %: C 47.45; H 4.41; N 7.77. $C_{15}H_{16}N_2Na_2O_7$. Calculated, %: C 47.13; H 4.22; N 7.33.

Compound **Ie** was synthesized from 1.17 g of L-valine and 2.06 g of 5-*tert*-butyl-2-hydroxybenzene-1,3-dicarbaldehyde. Yield 2.13 g (95%). IR spectrum, ν, cm^{-1}: 1646.9, 1631.5, 1598.7, 1521.6, 1390.4, 1363.4, 1226.5. ^1H NMR spectrum (methanol-d_4), δ, ppm: 0.98 d (6H, CH_3, J = 6.61 Hz), 1.03 d (6H, CH_3, J = 6.36 Hz), 1.33 s (9H, *t*-Bu), 2.30 d.t (2H, CH, J = 6.61, 6.36 Hz), 3.65 br.s (2H, CH), 7.57 s (2H, CH), 8.30 s (2H, CH=N). ^{13}C NMR spectrum (methanol-d_4), δ_C, ppm: 17.3, 18.6, 30.1, 31.9, 33.1, 79.3, 121.5, 135.2, 136.4, 148.4, 163.1, 176.7.

Disodium salts IIa–IId (*general procedure***).** A solution of 5 mmol of Schiff base **Ia**–**Id** in 100 ml of anhydrous methanol was cooled to –30°C, 0.57 g (15 mmol) of sodium tetrahydridoborate was added, and the mixture was stirred for 1 h at –30°C and was allowed to warm up to room temperature. A 2 N solution of hydrogen chloride in ethanol, 7.5 ml, was slowly added dropwise, and the mixture was stirred for 1 h and evaporated under reduced pressure. The residue was extracted with anhydrous ethanol, the extract was filtered and evaporated, and the residue was treated with diethyl ether. The precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure.

Compound **IIa** was synthesized from 2.56 g of Schiff base disodium salt **Ia**. Yield 1.96 g (76%). IR spectrum, ν, cm^{-1}: 3425.9, 2960.2, 2918.6, 2863.9, 1602.8, 1485.8, 1395.1, 1362.8, 1274.5, 1218.3, 881.6. ^1H NMR spectrum (methanol-d_4), δ, ppm: 1.29 s (*t*-Bu), 2.10 s (6H, SCH_3), 2.15 m (4H, CH_2), 2.66 t (4H, CH_2, J = 7.09 Hz), 3.53 t (2H, CH, J = 5.1 Hz), 4.02 d and 4.18 d (2H each, CH_2N, J = –16.4 Hz), 7.23 s (2H, CH). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 14.0, 29.8, 30.9, 32.4, 33.2, 47.3, 62.6, 118.3, 123.9, 126.8, 156.1, 181.8. MALDI-TOF mass spectrum, *m*/*z* (I_{rel}, %): 635 (80) $[2M - C_{16}H_{24}NO_3S]^+$, 324 (100) $[M - Met]^+$, 105 (40) $[C_4H_8NO_2 + 3H]^+$, 72 (52) $[C_3H_7S - 3H]^+$.

Compound **IIb** was synthesized from 2.35 g of Schiff base disodium salt **Ib**. Yield 1.97 g (83%). IR spectrum, ν, cm^{-1}: 3423.8, 2960.8, 2916.9, 2853.9, 1608.6, 1483.3, 1402.8, 1342.7, 1241.8. ^1H NMR spectrum (D_2O), δ, ppm: 2.02 s (6H, SCH_3), 2.06 m (4H, CH_2), 2.17 s (3H, CH_3), 2.62 t (4H, CH_2, J = 7.6 Hz), 3.59 t (2H, CH, J = 6.1 Hz), 4.02 d and 4.15 d (2H each, CH_2N, J = –13.5 Hz), 7.07 s (2H, CH). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 14.0, 19.3, 29.1, 47.5, 53.9, 60.5, 119.7, 128.9, 132.5, 155.1, 174.5.

Compound **IIc** was synthesized from 2.12 g of Schiff base disodium salt **Ic**. Yield 1.67 g (78%). IR

spectrum, ν, cm^{-1}: 1601.8, 1488.9, 1451.4, 1409.5, 1364.2, 1203.1, 1132.5, 1086.3, 1048.7. ^1H NMR spectrum (D_2O), δ, ppm: 1.32 s (9H, *t*-Bu), 3.74 t (2H, CH, J = 3.7 Hz), 4.01 m and 4.06 d.d (4H, CH_2, J = 3.7, –12.47 Hz), 4.35 d and 4.38 d (2H each, CH_2N, J = 6.1 Hz), 7.47 s (2H, CH). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 30.6, 34.3, 47.2, 59.8, 62.6, 119.3, 128.7, 129.7, 154.7, 171.3.

Compound **IId** was synthesized from 1.91 g of Schiff base disodium salt **Id**. Yield 1.64 g (85%). IR spectrum, ν, cm^{-1}: 1603.8, 1579.3, 1434.7, 1397.5, 1349.3, 1237.2, 1200.4, 1072.3, 1043.4. ^1H NMR spectrum (D_2O), δ, ppm: 2.35 s (3H, CH_3), 3.87 t (2H, CH, J = 5.6 Hz), 4.02 d and 4.06 d (2H each, CHN, J = –2.2 Hz), 4.33 d (4H, CH_2, J = 5.6 Hz), 7.28 s (2H, CH).

Pincer amino acids IIIa–IIId (*general procedure***).** A solution of 5 mmol of Schiff base **Ia**–**Id** in 100 ml of anhydrous methanol was cooled to –30°C, 0.57 g (15 mmol) of sodium tetrahydridoborate was added, and the mixture was stirred for 1 h at –30°C and was allowed to warm up to room temperature. A 2 N solution of hydrogen chloride, 12.5 ml, was slowly added dropwise, and the mixture was stirred for 1 h and evaporated under reduced pressure. The residue was extracted with anhydrous ethanol, the extract was filtered and evaporated, and the residue was treated with diethyl ether. The precipitate was filtered off, washed with diethyl ether, and dried under reduced pressure.

***N*,*N*′-(5-*tert*-Butyl-2-hydroxybenzene-1,3-diyldimethylidene)bis[(2*S*)-2-amino-4-methylsulfanylbutanoic acid] (IIIa)** was synthesized from 2.56 g of Schiff base **Ia**. Yield 1.77 g (75%). IR spectrum, ν, cm^{-1}: 3419.5, 2964.2, 2921.3, 2868.0, 1742.9, 1492.4, 1437.6, 1218.3, 1031.9, 885.3. ^1H NMR spectrum (methanol-d_4), δ, ppm: 1.34 s (9H, *t*-Bu), 2.12 s (6H, SCH_3), 2.24 d.t (4H, CH_2, J = 6.6, 7.8 Hz), 2.68 t (4H, CH_2, J = 7.8 Hz), 3.96 t (2H, CH, J = 6.6 Hz), 4.31 d and 4.35 d (2H each, CH_2N, J = –13.2 Hz), 7.51 s (2H, CH). ^{13}C NMR spectrum (methanol-d_4), δ_C, ppm: 13.8, 29.2, 29.3, 30.4, 33.8, 46.3, 58.9, 119.3, 130.7, 144.0, 152.9, 170.7. Mass spectrum, m/z (I_{rel}, %): MALDI-TOF, positive ions: 368 (70) $[M + Na - MeS(CH_2)_2CHCO_2 + 5H]^+$, 346 (100); MALDI-TOF, negative ions: 471 (10) $[M - H]^-$, 148 (30) $[Met - H]^-$, 113 (100) $[MeS(CH_2)_2CHCO - 3H]^-$; electrospray ionization: 1210 (68) $[3M - Met - CO_2H - MeS(CH_2)_2]^+$, 904 (96) $[2M - CO_2 + 3H]^+$, 596 (100) $[2M - C_{18}H_{24}N_2O_3S]^+$, 340 (60) $[M - MeS(CH_2)_2CHCO_2H]^+$. Found, %: C 53.76; H 7.63; N 5.68. $C_{22}H_{36}N_2O_5S_2 \cdot H_2O$. Calculated, %: C 53.85; H 7.81; N 5.71.

***N*,*N*′-(2-Hydroxy-5-methylbenzene-1,3-diyldimethylidene)bis[(2*S*)-2-amino-4-methylsulfanylbutanoic acid] (IIIb)** was synthesized from 2.35 g of Schiff base **Ib**. Yield 1.68 g (78%). IR spectrum, ν, cm^{-1}: 1737.3, 1490.0, 1435.7, 1201.7, 1180.9, 1134.9, 720.6. ^1H NMR spectrum (methanol-d_4), δ, ppm: 2.12 s (6H, SCH_3), 2.20 m (4H, CH_2), 2.12 s (3H, CH_3), 2.68 t (4H, CH_2, J = 8.6 Hz), 3.68 t (2H, CH, J = 5.1 Hz), 4.16 d and 4.23 d (2H each, CH_2N, J = –12.9 Hz), 7.17 s (2H, CH). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 13.9, 19.2, 28.9, 29.0, 46.3, 60.2, 119.4, 131.7, 134.1, 151.0, 172.8. Found, %: C 49.32; H 6.20; N 5.79. $C_{19}H_{26}N_2O_5S_2 \cdot 2H_2O$. Calculated, %: C 49.33; H 6.54; N 6.06.

***N*,*N*′-(5-*tert*-Butyl-2-hydroxybenzene-1,3-diyldimethylidene)bis[(2*S*)-2-amino-3-hydroxypropanoic acid] (IIIc)** was synthesized from 2.12 g of Schiff base **Ic**. Yield 1.54 g (80%). IR spectrum, ν, cm^{-1}: 1739.4, 1494.6, 1215.8, 1078.4, 1044.1, 826.3. ^1H NMR spectrum (D_2O), δ, ppm: 1.28 s (9H, *t*-Bu), 4.08 m (6H, CH, CH_2), 4.43 br.s (4H, C**H**$_2$OH), 7.54 s (2H, CH). Found, %: C 51.62; H 7.63; N 6.47. $C_{18}H_{28}N_2O_7 \cdot 2H_2O$. Calculated, %: C 51.42; H 7.67; N 6.66.

***N*,*N*′-(2-Hydroxy-5-methylbenzene-1,3-diyldimethylidene)bis[(2*S*)-2-amino-3-hydroxypropanoic acid] (IIId).** A solution of 1.91 g (5 mmol) of Schiff base disodium salt **Id** in 100 ml of methanol was cooled to –30°C, 0.57 g (15 mmol) of sodium tetrahydridoborate was added, and the mixture was stirred for 1 h at –30°C and was allowed to warm up to room temperature. Trifluoroacetic acid, 25 mmol, was slowly added dropwise to the resulting solution, and the precipitate was filtered off, washed in succession with acetone and diethyl ether, and dried under reduced pressure. Yield 1.45 g (85%). IR spectrum, ν, cm^{-1}: 1736.8, 1492.6, 1203.3, 1199.5, 1072.2, 1045.2. ^1H NMR spectrum (D_2O), δ, ppm: 2.18 s (3H, CH_3), 3.72 d.d (2H, CH, J = 3.7, 5.6 Hz), 3.87 d.d (2H, CHN, J = 5.6, –12.5 Hz), 3.94 d.d (2H, CHN, J = 3.7, –12.5 Hz), 4.23 s (4H, CH_2), 7.17 s (2H, CH). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 19.2, 46.1, 59.3, 62.5, 119.4, 131.6, 133.9, 149.8, 171.1. Found, %: C 49.43; H 5.98; N 7.30. $C_{15}H_{18}N_2O_7 \cdot H_2O \cdot MeOH$. Calculated, %: C 49.48; H 6.23; N 7.21. Mass spectrum (ESI), m/z (I_{rel}, %): 715 (74) $[2M + MeO]^+$, 282 (100) $[M - CO_2 - O]^+$, 265 (96) $[282 - O]^+$.

Dimethyl *N*,*N*′-(2-hydroxy-5-methylbenzene-1,3-diyldimethylidene)bis[(2*S*)-2-amino-4-methylsulfanylbutanoate] (IV). 2-Hydroxy-5-methylbenzene-1,3-dicarbaldehyde, 1.23 g (10 mmol), was dissolved

in 100 ml of anhydrous methanol, 3.26 g (20 mmol) of freshly prepared L-methionine methyl ester, 2 g of magnesium sulfate, and 2 g of 3-Å molecular sieves were added, the mixture was stirred for 7 h and filtered, and the filtrate was evaporated under reduced pressure. The residue was extracted with diethyl ether, the extract was filtered and concentrated under reduced pressure, 100 ml of hexane was added, and the oily material was separated from the hexane solution, washed with hexane, and dried under reduced pressure at 40°C. Yield 3.41 g (75%). IR spectrum, ν, cm^{-1}: 1736.8, 1630.3, 1599.5, 1461.9, 1434.6, 1265.7, 1223.6, 1164.1, 1091.5, 980.1, 867.8, 570.9. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.04 s (6H, SCH_3), 2.1–2.7 m (8H, CH_2), 3.70 s (6H, OCH_3), 4.11 t (2H, CH, J = 6.4 Hz), 7.50 s (2H, CH), 8.06 s (2H, HC=N). MALDI-TOF mass spectrum, m/z (I_{rel}, %): positive ions: 908 (69) $[2M - H]^+$, 762 (100) $[2M - MeS(CH_2)_2CHCO_2Me]^+$; negative ions: 453 (100) $[M - H]^-$, 307 (43) $[M - MeS(CH_2)_2CHCO_2Me]^-$.

Dimethyl *N*,*N*′-(2-hydroxy-5-methylbenzene-1,3-diyldimethyl)bis[(2*S*)-2-amino-4-methylsulfanylbutanoate] (V). A solution of 2.27 g (5 mmol) of Schiff base **IV** in 75 ml of methanol was cooled to –30°C, 0.57 g (15 mmol) of sodium tetrahydridoborate was added, and the mixture was stirred for 1 h at –30°C and for 1 h at room temperature. A solution of 0.9 g (15 mmol) of acetic acid in 10 ml of methanol was then slowly added dropwise, the mixture was stirred for 1 h, and the solvent was removed on a rotary evaporator. The residue was extracted with diethyl ether, the extract was filtered and concentrated under reduced pressure, 100 ml of hexane was added, and the oily material was separated from the hexane solution, washed with hexane, and dried under reduced pressure at 45°C. Yield 1.61 g (70%), light yellow oily substance. IR spectrum: ν 1733 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.98 s (6H, SCH_3), 2.10–2.35 m (8H, CH_2), 2.33 s (3H, CH_3), 3.73 t (2H, CH, J = 6.6 Hz), 3.80 s (6H, OCH_3), 4.26 s (4H, CH_2N), 7.24 s (2H, CH). MALDI-TOF mass spectrum: m/z 1229 (I_{rel} = 100%) $[3M - MeS(CH_2)_2CHCO_2Me + 4H]^+$.

Copper complexes VIb, VId, and VIe (*general procedure*). A solution of 0.68 g (4 mmol) of copper(II) chloride dihydrate in 35 ml of methanol was added to a solution of 2 mmol of disodium salt **Ib**, **Id**, or **Ie** in 35 ml of anhydrous methanol. The mixture was stirred for about 1 h at room temperature, evaporated by half, and mixed with 15 ml of toluene. The green precipitate was filtered off, washed with ice water (3 × 1 ml), and dried first in air and then in a vacuum desiccator over phosphoric anhydride.

Complex **VIb** was obtained from 0.94 g of disodium salt **Ib**. Yield 0.55 g (45%). IR spectrum, ν, cm^{-1}: 3405.7, 3239.8, 2917.8, 2856.1, 1641.1, 1608.0, 1554.3, 1450.2, 1359.6, 1332.6, 1240, 1182.2, 1083.8. Found, %: C 37.82; H 4.70; N 4.61. $C_{19}H_{24}Cu_2N_2O_6S_2 \cdot 2H_2O$. Calculated, %: C 37.80; H 4.68; N 4.64.

Complex **VId** was obtained from 0.94 g of disodium salt **Id**. Yield 0.75 g (73%). IR spectrum, ν, cm^{-1}: 3399.9, 3299.6, 3243.7, 3156.9, 2967.9, 2935.1, 2888.8, 1639.2, 1606.4, 1561.5, 1452.1, 1398.1, 1353.8, 1315.2, 1101.2, 1052.9. Found, %: C 35.12; H 4.07; N 5.31. $C_{15}H_{16}Cu_2N_2O_8 \cdot 2H_2O$. Calculated, %: C 34.95; H 3.91; N 5.44.

Complex **VIe** was obtained from 0.90 g of disodium salt **Ie**. Yield 0.66 g (57%). IR spectrum, ν, cm^{-1}: 3432.7, 2962.1, 2931.3, 2873.4, 1648.8, 1613.7, 1554.3, 1468.6, 1454.1, 1392.4, 1365.4, 1322.9, 1278.6, 1232.3, 1072.2. Found, %: C 45.18; H 5.68; N 4.98. $C_{22}H_{30}Cu_2N_2O_6 \cdot 2H_2O$. Calculated, %: C 45.43; H 5.89; N 4.82.

This study was performed under financial support by the Byelorussian Foundation for Basic Research (project no. № Kh08R-051), by the Russian Foundation for Basic Research (project no. 08-03-90025), and partly by the President of the Russian Federation (project no. MK-3588.2008.3). The authors thank Prof. Yu.A. Ustynyuk for setting the task and helpful discussions.

REFERENCES

1. Cherevin, M.S., Gulevich, T.G., Borisova, N.E., Zubreichuk, Z.P., Kolesnikov, G.V., Reshetova, M.D., and Knizhnikov, V.A., *Russ. J. Org. Chem*., 2007, vol. 43, p. 1567.
2. Lee, Ch.-S., Teng, P.-F., Wong, W.-L., Kwong, H.-L., and Chan, A.S.C., *Tetrahedron*, 2005, vol. 61, p. 7924.
3. Turgut, Y., Demirel, N., and Hosgoren, H., *J. Inclusion Phenom. Macrocycl. Chem*., 2006, vol. 54, p. 29.
4. Sawada, M., Okumura, Y., Yamada, H., Takai, Y., Takahashi, Sh., Kaneda, T., Hirose, K., and Misumi, S., *Org. Mass Spectrom*., 1993, vol. 28, p. 1525.
5. Liu, Sh.-Y., He, Y.-B., Qing, G.-Y., Xu, K.-X., and Qin, H.-J., *Tetrahedron: Asymmetry*, 2005, vol. 16, p. 1527.
6. Qing, G.-Y., He, Y.-B., Zhao, Y., Hu, Ch.-G., Liu, Sh.-Y., and Yang, X., *Eur. J. Org. Chem*., 2006, p. 1574.
7. Lu, G., Liu, F., Song, W., He, W., Prados, P., and de Mendoza, J., *Mater. Sci. Eng. C*, 1999, vol. 10, p. 29.

8. Liu, F., Lu, G.-Y., He, W.-J., Liu, M.-H., and Zhu, L.-G., *Thin Solid Films*, 2004, vol. 468, p. 244.
9. Du, C.-P., You, J.-S., Yu, X.-Q., Liu, Ch.-L., Lana, J.-B., and Xie, R.-G., *Tetrahedron: Asymmetry*, 2003, vol. 14, p. 3651.
10. Dowden, J., Edwards, P.D., Flack, S.S., and Kilburn, J.D., *Chem. Eur. J*., 1999, vol. 5, p. 79.
11. Liu, Y., You, Ch.-Ch., Zhang, H.-Y., and Zhao, Y.-L., *Eur. J. Org. Chem*., 2003, p. 1415.
12. Belokon', Y.N., Pritula, L.K., Tatarov, V.I., Bakhmutov, V.I., Gusev, D.G., Saporovskaya, M.B., and Belikov, V.M., *J. Chem. Soc., Dalton Trans*., 1990, p. 1873.
13. Belokon', Yu.N., *Pure Appl. Chem*., 1992, vol. 64, p. 1917.
14. Kim, H.-J., Asif, R., Chung, D.S., and Hong, J.-I., *Tetrahedron Lett*., 2003, vol. 44, p. 4335.
15. Ye, G., Chai, Y.R., Zhou, L., Li, Y., and Zhang, L., *Anal. Sci*., 2007, vol. 23, p. 171.
16. Illán-Cabeza, N.A., Moreno-Carretero, M.N., and Costa Pessoa, J., *Inorg. Chim. Acta*, 2005, vol. 358, p. 2246.
17. Jakubke, H.-D. and Jeschkeit, H., *Amino Acids, Peptides, and Proteins: An Introduction*, New York: Wiley, 1977. Translated under the title *Aminokisloty. Peptidy. Belki*, Moscow: Mir, 1985, p. 33.
18. Nakamoto, K., Morimoto, Y., and Martell, A.E., *J. Am. Chem. Soc*., 1961, vol. 83, p. 4528.
19. Sorrell, T.N., Jameson, D.L., and O'Connor, Ch.J., *Inorg. Chem*., 1984, vol. 23, p. 190.
20. *Analytical Methods in Supramolecular Chemistry*, Schalley, Ch.A., Weinheim: Wiley, 2007, p. 484.
21. Gershkovich, A.A. and Kibirev, V.K., *Sintez peptidov. Reagenty i metody* (Synthesis of Peptides. Reagents and Methods), Kiev: Naukova Dumka, 1987, 264.
22. Lindoy, L.F., Meehan, G.V., and Svenstrup, N., *Synthesis*, 1998, p. 1029.