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Polynuclear Copper(II) Complexes with Polydentate Nanoligands on the Basis of Aminoderivatives of the Hyperbranched Polyesters

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Abstract—Coordinationally active polydentate nanoplatforms on the basis of amino-modified hyperbranched polyesters containing 7 terminal amino fragments are synthesized. Synthetic procedure is developed and polynuclear Cu(II) complexes with polyesteropolyamines are prepared. Their composition and stability of the complex forms in DMSO–water solutions are evaluated. It is found that all the compounds obtained exhibit biological activity with respect to the induced asparagine proteinase of *Candida albicans*.

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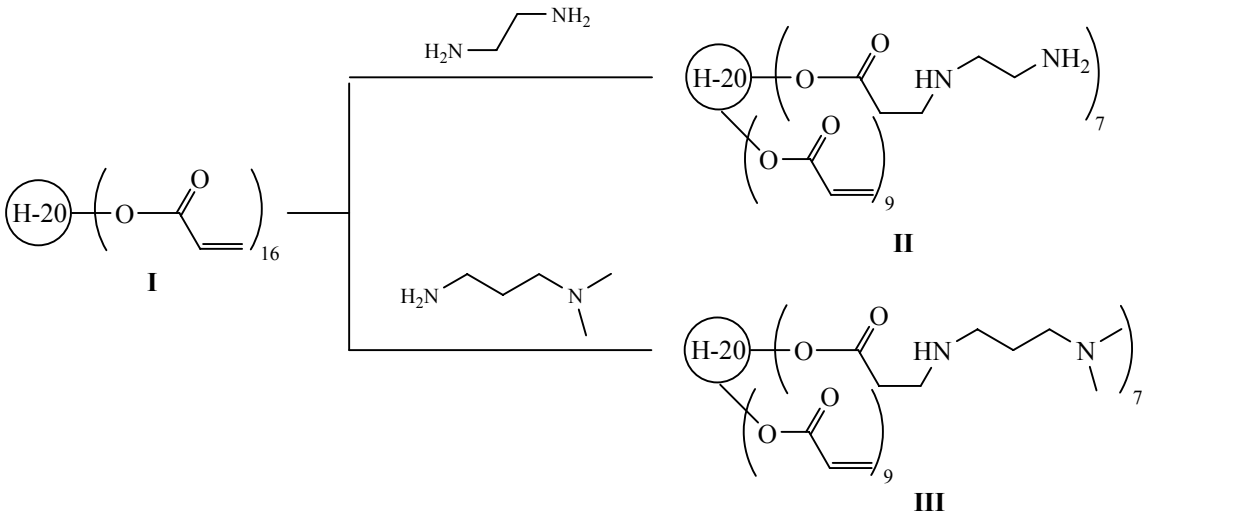
Nanodimensions and polyfunctionality of molecules of the hyperbranched polymers underlies their undoubted attractiveness for the purpose of directed synthesis of substances with the given coordinational properties [1–3]. This work continues the studies dealing with the synthesis of polydentate macroligands and polynuclear complexes on the basis of nontoxic hyperbranched polyesteropolyols exhibiting biological activity. In the previous works [4, 5] the carboxylated polydentate platforms on the basis of polyesteropolyol Boltorn H containing from 8 to 14 terminal carboxy groups were described and a procedure for prepartion of polynuclear Cu(II) complexes with the Boltorn H polyesterocarboxylates having the substitution degree 65 and 90% was developed. The modification of the surface of the esteropolyol with the amino groups capable of the effective formation of hydrogen bonds and creation of the surface charge is one of the approaches to obtaining of the drugs of new generation capable of highly specific recognition of the substrate. Among such systems the dendrimers like polyamidoamines PAMAM [6], the hyperbranched polyesteroamides HYBRANE [7], and the aminofunctionalyzed polylysine [8] became well known. Nevertheless, metal complex compounds of branched polyamines are only poorly described [9]. In this connection the development of procedures for preparing new nontoxic biochemically active branched polyaminoderivatives and their metal complexes is an actual problem.

Hyperbranched polyesteropolyols of second generation on the basis of 2,2-dimethylolpropionic acid were used as the precursors for preparing of nontoxic water-soluble hyperbranched polyesteropolyamines (HBPPA). Their synthesis includes two stages, that is, preparing of polyacrylate of polyesteropolyol **I** by complete esterification of all 16 terminal hydroxy groups of the starting polyol with the unsaturated carboxylic acids, and modification of polyacrylate obtained with diamines (ethylenediamine, *N,N*-dimethyl-1,3-diaminopropane) according to the scheme bellow.

Content of the amino groups in the compounds synthesized was evaluated by titration according to [10]. The evaluation of the amine number of polyesteropolyamines showed that the functionalyzation with diamines was as high as 50%. On the basis of polyamine derivatives of the hyperbranched polyesteropolyols Cu(II) complexes soluble in water, ethanol, and DMSO were prepared.

For the evaluation of stability and composition of complex compounds spectral studies were carried out. According to the electron absorption spectroscopy data compound HBP[OC(O)CH=CH_2]$_{16}$ **I** does not absorb either in visible or in the UV range in the DMSO–



water mixture (50% vol.). Polydentate platforms HBP[OC(O)CH=CH_2]$_9$[OC(O)(CH_2)$_2$NH(CH_2)$_2$$NH_2$]$_7$ **II** and HBP[OC(O)CH=CH_2]$_9$[OC(O)(CH_2)$_2$NH(CH_2)$_2$·$N(CH_3)_2$]$_7$ **III** have characteristic absorption bands at λ 395 and 350 nm respectively. Introduction of copper (II) nitrate in the solution of polymer **II** or **III** causes the disappearance of the absorption band of copper(II) salt at λ 840 nm and of the macroligands **II** and **III** and the appearance of new bands at 660 and 815 nm corresponding to complex compounds HBP[OC(O)·CH=CH_2]$_9$[OC(O)CH_2)$_2$NH(CH_2)$_2$$NH_2$Cu]$_7$ **IV** and HBP[OC(O)CH=CH_2]$_9$[OC(O)(CH_2)$_2$NH(CH_2)$_2$N·$(CH_2)_2$Cu]$_7$ **V**. For the calculation of stability constants and composition of complex compounds formed in the solution the isomolar series and molar ratio methods were used. It was found that the M:L composition is 7:1, and the stability of compound **IV** in DMSO solution –log β = 22.58. For compound **V** –log β = 20.82.

Aminoderivatives obtained and the coordination compounds on their basis exhibit biochemical activity in relation to the induced asparagine proteinase of *Candida albicans (SAP2C.alb.),* the main pathogenic factor of *Candida albicans* and the reason of circulating micoses [11, 12]. Hemoglobin was used as the substrate. The catalytic activity of the enzyme was evaluated by the decrease of concentration of substrate in a time unit in the presence of the enzyme. Water solutions of compounds **II, III, IV, V** in the concentration range 10^{-10}–10^{-3} M were used. It was found that the aminopolyesters **II** and **III** exhibit the inhibiting as well as the activating effect in relation to *SAP C.alb*. The inhibiting effect range for the compound **III** varies from 10^{-7} to 10^{-3} M while for compound **II** it is revealed in the concentration range 5×10^{-5}–10^{-3} M. Polynuclear copper(II) complexes **IV** and **V** also exhibit the modulating properties in relation to the enzyme. The catalytic activity of *SAP C.alb*. increases in the concentration range 5×10^{-5}–10^{-3} M for compound **IV** and 5×10^{-4}–10^{-3} M for compound **V**.

Inhibiting of the enzyme activity takes place in the concentration range 1×10^{-10}–1×10^{-6} and 1×10^{-10}–1×10^{-4} for the compounds **IV** and **V** respectively. Hence, aminoderivatives of the hyperbranched polyesteropolyols obtained by us and polynuclear complexes on their basis are the modulators of catalytic activity of the induced proteinase. This fact gives rise to the doubtless interest to these objects as probable components of the pharmaceutical antimicotic compositions and active substances.

EXPERIMENTAL

IR spectra were recorded on a Bruker Tensor 27 Fourier spectrometer (from film or KBr pellets). ^{1}H NMR spectra were taken on an Avance 600 (600 MHz) spectrometer in $CDCl_3$. Electron absorption spectra were obtained on a Lambda 35 (Perkin-Elmer, UK) spectrophotometer in the 190-900 nm range at 36±0.01°C using the temperature-controlled system including the temperature-controlled cell holder, the Julabo MB-5A flow thermostate and the Pelte thermostates PTP-1.

Synthesis of the hyperbranched polyacrylatopolyester (AN-20). A weighed portion of Boltorn (H-20), 6.8 g, was dissolved in dichloromethane, and 8.4 g of triethylamine and hydroquinone were added. After

that the reaction mixture was cooled to –5°C, and a solution of 7.6 g of acryloyl chloride in dichloromethane was added dropwise. The reaction mixture was kept at room temperature until the disappearance of a signal in the range 3400–3100 cm^{-1} in the IR spectrum. After that the reaction mixture was washed with 2M HCl and 2% solution of sodium hydrogen carbonate, dried over $MgSO_4$, and filtered. The solvent was removed in a vacuum to give 7.2 g (70%) of product **I**. IR spectrum, ν, cm^{-1}: 2982 v.s, 2967 v.s, 2886 s [$\nu_{as,s}(CH_3)$, $\nu_{as,s}(CH_2)$]; 1733 s [ν(C=O)]; 1635 m [ν(C=C)]; 1472 m [$\delta_{as}(CH_3)$]; 1374 m [$\delta_s(CH_3)$], 1133 s, 1045 s (O–C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 s, 1.23 s [24H, $OC(O)CCH_3$, internal fragments]; 1.25 s [12H, $OC(O)CCH_3$, outer fragments]; 3.40 t (16H, OCH_2CH_2O, $^3J_{HH}$ 6.3); 3.58 t (16H, OCH_2CH_2O, $^3J_{HH}$ 6.3); 4.26 d [48H, $CH_2OC(O)$]; 5.8 d.d (16H, $CH_AH_B{=}CH_A$, $^3J_{HH}$ 10.3, $^2J_{HH}$ 3.1); 6.1 q (16H, $CH_AH_B{=}CH_A$, $^3J_{HH}$ 10.3, $^3J_{HH}$ 17.1); 6.35 d (16H, $CH_AH_B{=}CH_A$, $^3J_{HH}$ 17.1, $^2J_{HH}$ 3.1). Found, %: C 55.86; H 5.95. $C_{115}H_{152}O_{58}$. Calculated, %: C 56.09; H 6.12.

Reaction of AH-20 with ethylenediamine. Ethylenediamine, 2.0 ml, was dissolved in 15 ml of ethanol, 2.3 g of AH-20 was added at room temperature under the dry argon flow, and the mixture obtained was stirred for 20 h. After that some part of the solvent was removed at a reduced pressure, and the reaction mixture formed was treated with benzene. The product **II** precipitated as the amorphous mass which was dried in a vacuum, yield 2.4 g (75%). IR spectrum, ν, cm^{-1}: 3352 s, 3293 s [ν(N–H)]; 2970 s, 2940 s, 2880 s [$\nu_{as,s}(CH_3)$, $\nu_{as,s}(CH_2)$]; 1732 v.s [ν(C=O)]; 1662, 1556 m [δ(N–H)]; 1464 m [$\delta_{as}(CH_3)$]; 1369 m [$\delta_s(CH_3)$]; 1125 s, 1054 s (O–C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 s, 1.19 s [$OC(O)CCH_3$, internal fragments]; 1.29 s [$OC(O)CCH_3$, outer fragments]; δ 2.37 t [$(O)CCH_2CH_2N$, $^3J_{HH}$ 6.2]; δ_1 2.67 t ([CH_2NH_2, $^3J_{HH}$ 5.8); δ_2 2.68 t (CH_2NH_2, $^3J_{HH}$ 5.8); δ_1 2.80 t (CH_2NH, $^3J_{HH}$ 5.1); δ_2 2.81 t (CH_2NH, $^3J_{HH}$ 5.1); δ_1 2.87 t (CH_2NH, $^3J_{HH}$ 5.8); δ_2 2.89 t (CH_2NH, $^3J_{HH}$ 5.8); 3.26 t (OCH_2CH_2O, $^3J_{HH}$ 5.8); 3.28 t (OCH_2CH_2O, $^3J_{HH}$ 5.8); 3.85 s (OCH_2C); 3.89 s (OCH_2C). Found, %: C 52.76; H 7.17; N 7.23. $C_{128}H_{208}N_{14}O^{58}$. Calculated, %: C 52.93; H 7.27; N 7.34.

Reaction of the hyperbranched polyesteropolyamine II with copper(II)nitrate. A weighed portion of polyesteropolyamine **II**, 1.2 g, was dissolved in an 1:2 ethanol–acetone mixture, and 1.6 g of copper(II)nitrate crystal hydrate was added in one portion. The mixture obtained was stirred at room temperature for 7 h. The reaction mixture became green, and a viscous mass was formed on the bottom of the flask. The product **IV** obtained, 1.9 g (68%) was dried in a vacuum and purified by reprecipitation. IR spectrum, ν, cm^{-1}: 3436 m, 3293 m [ν(N–H)]; 2974 m, 2891 m [$\nu_{as,s}(CH_3)$]; 1729 m [ν(C=O); 1664 m, 1578 m [δ(N–H)]; 1458 [$\delta_{as}(CH_3)$]; 1378 [$\delta_s(CH_3)$]; 1149 m-w, 1042 m (O–C). Found, %: C 36.73; H 5.17; N 9.27; Cu 10.2. $C_{132}H_{201}Cu_7N_{28}O_{10}$. Calculated, %: C 37.30; H 4.98; N 9.23; Cu 10.47.

Reaction of AH-20 with *N,N*-dimethyl-1,3-diaminopropane. To a solution of *N,N*-dimethyl-1,3-diaminopropane, 2.4 g, in 20 ml of carbon tetrachloride 4.1 g of AH-20 was added under the dry argon flow, and the reaction mixture was stirred at 50°C for 11 h. After that the product was separated from solvent on the separatory funnel and dried in a vacuum. The residue was product **III**, 5.1 g (78%). IR spectrum, ν, cm^{-1}: 3368 v.s [ν(N–H)]; 2949 v.s, 2875 s, 2823 s, 2781 s [$\nu_{as,s}(CH_3)$, $\nu_{as,s}(CH_2)$]; 1737 v.s [ν(O=C–O)]; 1653 m [ν(N–H)]; 1470 s [$\delta_{as}(CH_3)$]; 1374 m [$\delta_s(CH_3)$]; 1127 s, 1056 s (O–C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 s, 1.18 s [$OC(O)CCH_3$, internal fragments], 1.26 s [$OC(O)CCH_3$, outer fragments]; δ 1.65 m ($NCH_2CH_2CH_2N$, $^3J_{HH}$ 6.9. $^3J_{HH}$ 6.8); 2.23 br.s [$(CH_3)_2N$], 2.34 t (CH_2N, $^3J_{HH}$ 6.9); 2.43 t (CH_2N, $^3J_{HH}$ 6.9); 2.75, 2.98 d.t (CH_2NH, $^3J_{HH}$ 6.9); 2.92, 3.04 d.t (CH_2NH, $^3J_{HH}$ 6.2); 3.54 t (OCH_2CH_2O, $^3J_{HH}$ 7.2); 3.69 t (OCH_2CH_2O, $^3J_{HH}$ 7.2); 4.17 s (OCH_2O). Found, %: C 56.46; H 6.78; N 6.24. $C_{150}H_{250}N_{14}O_{60}$. Calculated, %: C 56.70; H 6.93; N 6.17.

Reaction of the hyperbranched polyesteropolyamine III with copper(II) nitrate. A weighed portion of polyesteropolyamine **III,** 3.1 g, was dissolved in the 1:2 ethanol–THF mixture, and 2.83 g of copper(II) nitrate crystal hydrate was added. The mixture obtained was stirred at room temperature for 7 h. The reaction mixture became green, and a viscous mass was formed on the bottom of a vessel. The product formed was dried in a vacuum and purified by reprecipitation. Yield 3.4 g (70%). IR spectrum, ν, cm^{-1}: 3356 m.s [ν(N–H)]; 2979 m, 2880 m. 2778 m [$\nu_{as,s}(CH_3)$, $\nu_{as,s}(CH_2)$]; 1735 s [ν(C=O)]; 1648 m, 1554 w [δ(N–H)]; 1470 [$\delta_{as}(CH_3)$]; 1378 [$\delta_s(CH_3)$]; 1134 m, 1042 m (O–C). Found, %: C 36.73; H 6.17; N 9.27; Cu 7.6. $C_{155}H_{306}Cu_7N_{30}O_{12}$. Calculated, %: C 37.45; H 6.20; N 8.65; Cu 8.06.

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