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SYNTHESIS AND CHARACTERISTICS OF FOUR NEW COPPER(II) CARBOXYLATE COMPLEXES WITH ADAMANTANE FRAGMENT

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Abstract. *The paper considers the results of synthesis, elemental analysis, and spectroscopic methods (IR, UV-vis) of four new copper(II) complexes with anions of 1-adamantanecarboxylic acid, 4-(1-adamantyl)benzoic acid and their L-valine derivatives as ligands. Based on the obtained spectral data, the authors assumed the biyaderic structure of these complexes with bidentate coordination of carboxylate ligands of the type* $[Cu^{2+}_2(RCOO^-)_4(H_2O)_2]$*, with* $RCOO^-$ *as carboxylate ligands. The synthesised compounds are of interest as low toxic potential therapeutic agents with anti-inflammatory and anti-cancer activity.*

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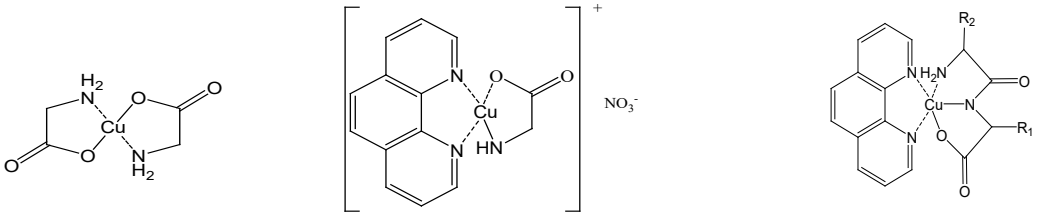
Introduction

Copper is one of the essential trace elements participating in many vital biological processes. Therefore, its homeostatic mechanisms in the body are strictly ordered [1]. Copper is crucial for the functioning of some enzymes and proteins involved in energy metabolism, respiration, DNA synthesis, etc. [2]. The main functions of complexes of copper ions with biomolecules include oxidation and reduction reactions, in which they directly react with molecular oxygen to form free radicals [2].

Copper(II) complexes with carboxylate ligands are the object of many researches in medicinal chemistry. Many of them represent potential therapeutic agents with antimicrobial [3], antibacterial [4], anti-inflammatory action [5, 6], etc., combined with reduced toxicity. Complexes of copper(II) with anions of amino acids and short peptides are of particular

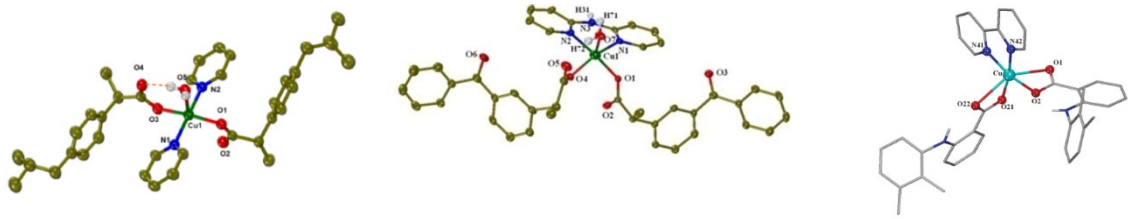
importance, as anticancer activity for many of them has been confirmed (Fig. 1). In particular, copper(II) glycinate has been shown to have cytotoxic activity against gastric cancer cells [7]. The three-component Cas-II-gly complex showed cytotoxic and antitumor activities with promising results *in vitro* and *in vivo* tests, and was approved for clinical trials [2, 8]. Copper(II) complexes based on dipeptides with hydrophobic side substituents, such as Gly-Val, Phe-Val, etc., and 4,7-diphenyl-1,10-phenanthroline (Phen) as an N,N-donor ligand show great promise as drug candidates, surpassing the cytotoxic activity of earlier analogs [9].



Copper glycinate (II), $[Cu(Gly)_2]$ | Pharmaceutical family Casiopeinas, Cas-II-gly | Copper (II) complexes based on dipeptides, [Cu(Gly-Val)(Phen)], [Cu(Phe-Val)(Phen)]

Fig. 1. Structures of some mixed-ligand O-carboxylate complexes of Cu(II)

We found that copper(II) complexes with anions of nonsteroidal anti-inflammatory drugs (NSAIDs) in the form of carboxylate ligand on a wide group of compounds (salicylates, ibuprofen, ketoprofen, indomethacin, diclofenac, etc.) were superior to free NSAIDs in terms of anti-inflammatory activity and showed reduced gastrotoxicity (Fig. 2) [10, 11, 12]. According to current studies, NSAIDs have some anticancer properties. Hence there is a relationship between their use and a reduction of various cancers risk [12].



$[Cu(ibu)_2(Py)_2(H_2O)]$ (ibu – ibuprofen) | $[Cu(ket)_2(Phen)(H_2O)]$ (ket – ketoprofen) | $[Cu(mef)_2(BiPy)]$ (mef - mefenamic acid)

Fig. 2. Spatial structures of copper (II) complexes with NSAID anions

For further search of new and effective copper(II) complexes possessing simultaneously the properties of anticancer agents and NSAIDs. It is important in terms of polypharmacology and the strategy of synthesizing drug molecules with multitarget activity. However, the choice of organic ligands plays a crucial role. Previously, we have shown high potential as NSAIDs of our synthesized sodium salts of amino acid derivatives of 4-(1-adamantyl)benzoic acid. Theyovercame*in vivo* tests on anti-inflammatory and analgesic activity of widely used pharmaceuticals and were low toxic. Indeed, the leader was a derivative of hydrophobic amino acid L-valine [13, 14]. In addition, amino acid derivatives of 1-adamantylacetic acid can effectively inhibit soluble epoxyhydrolase (sEH). It is one of the important targets to overcome inflammatory and pain conditions [15]. Thus, the strategy of introducing an adamantane

fragment into the ligand structure of coordination compounds is well established to increase cytotoxic activity by increasing their permeability through cell membranes [15].

Complexes of copper(II) with anions of some N-protected α-amino acids (N-acetyl, N-benzoyl) were previously synthesized and characterized [16, 17]. Meanwhile, data on carboxylate complexes of copper(II) with the adamantane fragment in the ligand structure are practically absent. Therefore, the purpose of the present study was to synthesize, characterize, and investigate the structure of carboxylate complexes of copper(II) with anions of 1-adamantanecarboxylic acid, 4-(1-adamantyl)benzoic acid and their L-valine derivatives.

Main body

We initially synthesized complex **1** by reaction of the initial 1-adamantanecarboxylic acid with $Cu(OAc)_2$-H_2O at a molar ratio of 2 to 1, respectively, in acetonitrile (Fig. 3, method **A**) [18]. However, unreacted starting acid is presented in the products. We further synthesized copper(II) complexes **1**-**4** by reaction of sodium salts of carboxylates, obtained by preliminary neutralization of the corresponding initial carboxylic acids, with $CuCl_2 \cdot 2H_2O$ at a molar ratio of 2 to 1, respectively, in a mixture of ethyl alcohol and water (4 to 1 by volume) (Fig. 3, method **B**). We isolated the final products by slowly concentrating the reaction mixture by evaporation at room temperature as blue or green-blue crystals in sufficiently high yields.

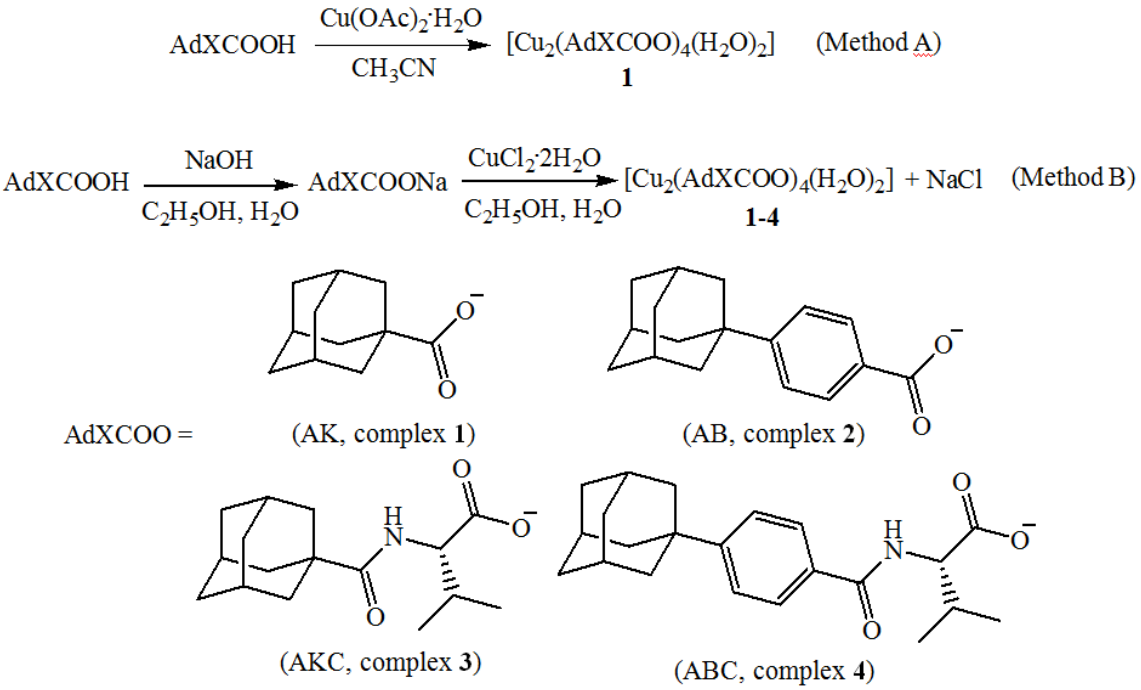


Fig. 3. Scheme of complex synthesis **1**-**4**

All the obtained complexes were characterized by elemental analysis, IR spectroscopy in the crystalline state, spectroscopy in the UV-visible range of solutions, and measurement of the solutions' molar electrical conductivity. All complexes were stable on air, soluble in dimethyl sulfoxide and N,N-dimethylformamide, complexes **3** and **4** were partially soluble, while **1** and **2** were sparingly soluble in ethyl alcohol, and all complexes were almost insoluble in water.

The infrared spectra of complexes **1**-**4** in the crystalline state were recorded in the region 4000–400 cm^{-1} and studied to confirm the ligand structure; the most probable mode of coordination of carboxylate ligands with copper(II) ions when compared with data for analogs (Table 1). Broad absorption bands were observed in the IR spectra of the obtained complexes in the region of 3450–3200 cm^{-1} of weak or medium intensity, related to the valence vibrations of the O-H bond of the water molecule. This confirms the presence of bound coordination water as a ligand [19]. Absorption bands of valence and strain vibrations of O-H and C=O bonds in carboxyl groups of initial acids (e.g., for NAC 1688, 1282, and 950 cm^{-1}) were absent in these spectra. This indicates deprotonation of carboxyl groups to carboxylate groups. Two characteristic bands present in the regions of 1612–1554 cm^{-1} and 1414–1400 cm^{-1}, corresponding to antisymmetric and symmetric valence vibrations in the carboxylate group, instead of the above bands in all cases. The value of $\Delta\nu = [\nu_{asym}(CO_2) - \nu_{sym}(CO_2)]$ can be used as a marker to determine the mode of ligand coordination in metal-carboxylate complexes. The most common are bidentate chelate ($\Delta\nu$ less than 120 cm^{-1}), bidentate *syn*,*syn*-bridging ($\Delta\nu$ around (170±10) cm^{-1}) and monodentate (usually $\Delta\nu$ more than 200 cm^{-1}) coordination with metal ions [6, 12, 19-21]. The values of $\nu_{asym}(CO_2)$ and $\nu_{sym}(CO_2)$ for the obtained complexes 1 and 2 were found to be shifted by 5–35 cm^{-1} to the higher wave number region and $\Delta\nu$ were 174 and 154 cm^{-1}, which were 30 and 12 cm^{-1} higher, respectively, compared to the sodium salts NaAK and NaAB. This seems to indicate *syn*,*syn*-η^1:η^1:μ_2-coordination of the carboxylate ligands in these complexes (Fig. 4), where the carboxylate is a bridging ligand between the two copper(II) ions. The I and II amide bands were practically not shifted during the formation of complexes **3** and **4**. However, the vibration bands of the carboxylate groups and $\Delta\nu$ were changed, as in the previous case (see Table 1, using NaABC and complex **4** as examples). In all cases, absorption bands were also observed in the 550-500 cm^{-1} region, described in the literature as characteristic of Cu-O bond vibrations [19, 20].

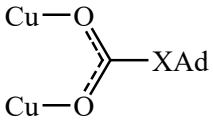


Fig. 4. Coordination of carboxylate ligands in complexes **1**-**4**

UV-visible spectra were obtained for solutions of complexes **1**-**4** in acetonitrile, and partially in DMSO. A weakly intense broad band was observed in all spectra with a maximum in the range 705–740 nm, which corresponds to the *d*-*d*-transition $^2E_g \rightarrow {}^2T_g$ (the so-called band I [22]). The position of this band indicates an octahedral or square-pyramidal local geometry for the ligand environment of copper ions. A band was also present in the spectra of the complexes in the interval 362–395 nm (the so-called band II [22]). Its presence is usually associated with electronic transitions between the orbitals of copper(II) ions within the biyaderic structure of the complexes. The band around 300-310 nm (the so-called band III [22]) is partially masked by the bands of $\pi \rightarrow \pi^*$ transitions of ligands and therefore appears as a shoulder, corresponded to the ligand-to-metal charge transfer (LMCT) in the complexes. Indeed, there is no significant shift of the indicated bands occurred in the spectra of the complexes when changing the solvent, as well as during dilution (e.g., for complex

3, band I in acetonitrile and DMSO at 709 and 713 nm, respectively), i.e., there was no solvatochromic effect in this case.

Table 1. Comparison of some spectral data for complexes **1**-**4** with analogs

Complex	IR			UV-visible, λ_{max}, nm (ε, l mol^{-1} cm^{-1})	Coordination mode	Geometry	Link
	$\nu_{asym}(CO_2)$, cm^{-1}	$\nu_{sym}(CO_2)$, cm^{-1}	$\Delta\nu^1$, cm^{-1}				
$[Cu_2(mef)_4(H_2O)_2]$	1,595 (very st.)	1,425 (very st.)	170	665[2] (60), 440[2] (150), 335[2] (7,800), 292[2] (14,200)	bidentate bridging	square-pyramidal	23
$[Cu_2(loxo\text{-}O,O')_4(H_2O)_2]$	1,582 (very st.)	1,407 (very st.)	175	715[2] (230), 295[2] (6,000)	the same	the same	12
$[Cu_2(ibu)_4]$	1,588 (very st.)	1,407 (med.)	181	670, 218-260	the same	the same	24
$[Cu_2(ket)_4(H_2O)_2]$	1,575 (very st.)	1,408 (med.)	167	720[2] (160), 309[2] (2,100), 290[2] (10,900)	the same	the same	5
$[Cu_2(OAc)_4(H_2O)_2]$	1,603 (very st.)	1,418 (st.)	185	700 (I), 370 (II), 250-330 (III)	the same	the same	22
$[Cu(AcVal)_2(H_2O)]_2$	1,610 (very st.)	1,410 (st.)	200	720 (I) 380 (II)	the same	the same	17
$[Cu_2(BzVal)_4(H_2O)_2]$	-	-	-	709 (I), 390 (II)	the same	the same	16
NaAK	1,547 (st.)	1,403 (st.)	144	-	-	-	this paper
NaAB	1,547 (st.)	1,405 (st.)	142	-	-	-	this paper
NaABC	1,592 (st.)	1,406 (st.)	186	-	-	-	this paper
$[Cu_2(AK)_4(H_2O)_2]$ (**1**)	1,582 (very st.)	1,408 (very st.)	174	705 (55, I), 362 (lever, II), 307 (7,000, III)	bidentate bridging	square-pyramidal	this paper
$[Cu_2(AБ)_4(H_2O)_2]$ (**2**)	1,554 (st.)	1,400 (very st.)	154	740 (50, I), 382 (lever, II), 320 (7,300, III)	the same	the same	this paper
$[Cu_2(AKB)_4(H_2O)_2]$ (**3**)	1,612	1,414	198	709 and 713[2] (90 and 95[2], I), 390 (lever, II), 313 (11,500, III)	the same	the same	this paper
$[Cu_2(AБB)_4(H_2O)_2]$ (**4**)	1,608	1,414	194	725 (105, I), 395 (lever, II), 308 (10,000, III)	the same	the same	this paper

[1]$\Delta\nu = \nu_{asym}(CO_2) - \nu_{sym}(CO_2)$; [2]data for solutions in DMSO; loxo - NSAID loxoprofen; very st. - very strong; st. - strong; AcVal - N-acetylvalinate; BzVal - N-benzoylvalinate.

The values of molar electrical conductivity measured for solutions of complexes **1**-**4** in DMSO were in the range of 3.0–9.0 cm cm^2 mol^{-1}. Thus, the obtained complexes are predominantly non-electrolytes [12]. Moreover, the combination of data obtained from electronic spectra of the complexes and molar electrical conductivity measurements may indicate that complexes **1**-**4** retain the integrity of their structure in solution.

Hence on the basis of comparison with similar copper(II) carboxylate complexes described in the literature [5, 12, 16, 17, 20-25], we can conclude complexes **1**-**4** have a structure similar to the "Chinese lantern" model. The optimized molecular structures of the clusters

of the synthesized complexes were obtained using the semiempirical PM7 method (Fig. 5, using complex **1** as an example) implemented in the MOPAC2016™ program. The coordination environment of each copper(II) ion (CuO_5) is formed by four oxygen atoms belonging to the four anions of the corresponding carboxylate ligands in a bidentate bridging mode in the biuclear complex, and an oxygen atom of a coordinated water molecule at the vertices of the distorted square pyramid. The values of interatomic distances Cu-Cu 2.859 Å, Cu-O(carboxylate) 1.935-1.950 Å and Cu-O(water) 2.005-2.010 Å obtained for complex **1** were quite close to the data of X-ray diffraction analysis for $[Cu_2(OAc)_4(H_2O)_2]$, equal to 2.616, 1.967 and 2.162 Å, respectively [22, 12]. A similar trend was obtained for other geometrical parameters, such as total bridge length (for **1** 6.40-6.42 Å, and for $[Cu_2(OAc)_4(H_2O)_2]$ 6.45-6.46 Å) and Cu-O(carboxylate)-C valence angles (for **1** 123.1-124.5°, and for $[Cu_2(OAc)_4(H_2O)_2]$ 122.5-123.0°).

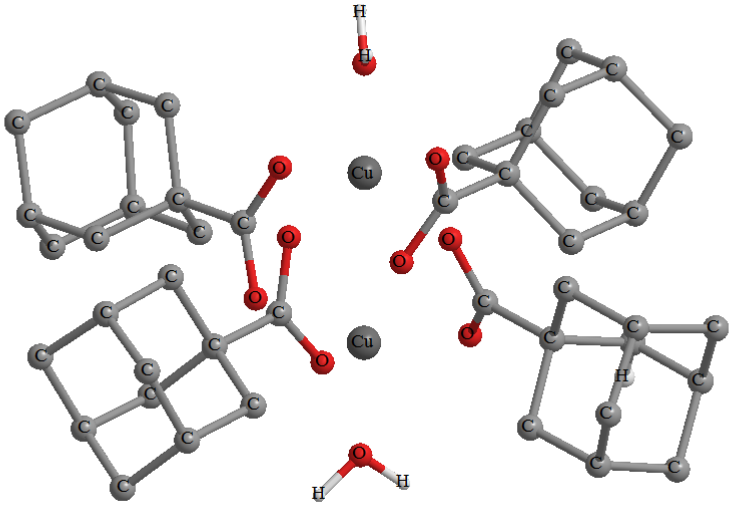


Fig. 5. Molecular structure of the complex $[Cu_2(AC)_4(H_2O)_2]$ (**1**) obtained by PM7 optimization. Cu atoms are shown in dark gray, C in gray, O in red, H atoms in the adamantyl fragment are omitted for convenience

Thus, the obtained results showed that copper(II) ions with anions of 1-adamantanecarboxylic acid, 4-(1-adamantyl)benzoic acid and their amino acid derivatives form sufficiently stable hydrated complexes, apparently, of a biuclear structure with bidentate coordination of ligands of the type $[Cu^{2+}_2(RCOO^-)_4(H_2O)_2]$, with $RCOO^-$ as carboxylate ligands. Obviously, in order to increase the probability of significant biological activity of these complexes it is necessary to introduce N-donor ligands, such as pyridine, picolines and phenanthroline, into their structure. It will be the subject of the following studies.

Experimental part

For this study we used commercially available reagents: copper(II) acetate monohydrate (analytical grade, 99.1%, Russia), copper(II) chloride dihydrate (high-purity grade, 98.7%, Russia), acetonitrile (reagent grade, Ecos-1), dimethyl sulfoxide (reagent grade, Ecos-1), ethyl alcohol (96%). The initial carboxylic acids with the adamantane fragment were synthesized according to the previously developed methods: 1-adamantankabonic acid from

1-bromadamantane [26], 4-(1-adamantyl)benzoic acid from 4-(1-adamantyl)toluene [13], and further their corresponding L-valine derivatives were obtained [13].

We performed elemental analysis using a FLASH EA 1112 C,H,N,S analyzer. We recorded the IR spectra on a Spectrum RX1 FTIR spectrometer (PerkinElmer) using the disturbed total internal reflection (TIR) method in the frequency range 4000–400 cm^{-1}. We obtained UV-visible spectra using an Ekros PE-5400UV spectrophotometer for solutions of the complexes in CH_3CN or DMSO (complex concentration 0.1–5.0 mmol/l). We measured the molar electrical conductivity for solutions of the complexes in DMSO (concentration 1.0 mmol/l) on an Expert-002-2-6-p conductometer.

*Synthesis $[Cu_2(AK)_4(H_2O)_2]$ (**1**) (method **A**).* We added 0.20 g (1 mmol) of $Cu(OAc)_2{\cdot}H_2O$ dissolved in 3 ml of acetonitrile to 0.36 g (2 mmol) of 1-adamantanecarboxylic acid in 10 ml of acetonitrile under stirring and heating. We stirred the obtained solution under heating for 2 h. After that we slowly evaporated the reaction mixture to 1/3 of the initial volume, filtered off the formed solid precipitate of blue color, which was dried in air. We obtained 0.20 g (45% based on the starting acid) of the product containing an impurity of the initial carboxylic acid according to IR spectroscopy.

*General procedure for the synthesis of copper(II) complexes with anions of 1-adamantanecarboxylic acid (**1**), 4-(1-adamantyl)benzoic acid (**2**) and their L-valine derivatives (**3, 4**) (method **B**).* We added 0.40 g (0.33 ml) of NaOH solution with a concentration of 20% to a solution of a 2 mmol suspension of the initial carboxylic acid in 10 ml of ethyl alcohol to neutralize it to a pH equal to 7. We slowly evaporated the resulting solution to form a solid residue of the sodium salt of carboxylic acid, which was further used without purification. For this purpose, we dissolved it in 10 ml of water and mixed it with 0.17 g (1 mmol) of $CuCl_2{\cdot}2H_2O$ dissolved in 2.5 ml of water, and then stirred the resulting reaction mixture at room temperature for 1 h. We filtered the resulting solid precipitate of blue color and dried it in air.

$[Cu_2(AK)_4(H_2O)_2]$ (**1**). Obtained 0.37 g (84%). Found, %: C 59.55; H 7.52. For $C_{44}H_{68}O_{10}Cu_2$ (M = 883.10) calculated, %: C 59.79; H 7.70. IR, ν_{max}, cm^{-1}: 3,362 med., ν_{linked}(O–H); 2,902 very st., $\nu_{asym}(CH_2)$; 2,850 st., $\nu_{sym}(CH_2)$; 1,582 very st., $\nu_{asym}(CO_2)$; 1,450 med., $\delta(CH_2)$; 1,408 st., $\nu_{sym}(CO_2)$; 504 med., ν(Cu–O). UV-visible (in CH_3CN), λ_{max}, nm (ε, l mol^{-1} cm^{-1}): 705 (55); 446 (250); 362 (lever); 307 (7,000). Λ_M, Cm cm^2 mol^{-1}: 3.0.

$[Cu_2(АБ)_4(H_2O)_2]$ (**2**). Obtained 0.52 g (88%). Found, %: C 68.39; H 7.22. For $C_{68}H_{84}O_{10}Cu_2$ (M = 1187.10) calculated, %: C 68.73; H 7.08. IR, ν_{max}, cm^{-1}: 3,370 med., ν_{linked}(O–H); 2,901 very st., $\nu_{asym}(CH_2)$; 2,848 st., $\nu_{sym}(CH_2)$; 1,599 st., ν(C=C); 1,554 med., $\nu_{asym}(CO_2)$; 1,448 med., $\delta(CH_2)$; 1,400 st., $\nu_{sym}(CO_2)$; 524 med., ν(Cu–O). UV-visible (in CH_3CN), λ_{max}, nm (ε, l mol^{-1} cm^{-1}): 740 (50); 474 (190); 382 (lever); 320 (7300). Λ_M, Cm cm^2 mol^{-1}: 4.0.

$[Cu_2(AQW)_4(H_2O)_2]$ (**3**) Obtained 0.47 g (73%). Found, %: C 60.30; H 8.35. For $C_{64}H_{104}N_4O_{14}Cu_2$ (M = 1279.10) calculated, %: C 60.04; H 8.13; N 4.38. IR, ν_{max}, cm^{-1}: 3,442 med., ν_{linked}(O–H); 3,418 med., ν(N–H); 2,903 very st., $\nu_{asym}(CH_2)$; 2,851 st., $\nu_{sym}(CH_2)$; 1,639 st., ν(C=O), I amide; 1,612 very st., $\nu_{asym}(CO_2)$; 1,513 st., δ(N–H), II amide; 1,448 med., $\delta(CH_2)$; 1,414 st., $\nu_{sym}(CO_2)$; 548 med., ν(Cu–O). UV-visible (in CH_3CN), λ_{max}, nm (ε, l mol^{-1} cm^{-1}): 709 (90); 464 (315); 390 (lever); 313 (11,500). Λ_M, Cm cm^2 mol^{-1}: 8.0.

$[Cu_2(АБВ)_4(H_2O)_2]$ (**4**). Obtained 0.55 g (70%). Found, %: C 66.45; H 7.31. For $C_{88}H_{120}N_4O_{14}Cu_2$ (M = 1,583.10) calculated, %: C 66.71; H 7.58; N 3.54. IR, ν_{max}, cm^{-1}: 3,424 med., ν(N–H); 3,340 med., ν_{linked}(O–H); 2,901 very st., $\nu_{asym}(CH_2)$; 2,848 st., $\nu_{sym}(CH_2)$; 1,646 st., ν(C=O), I amide; 1,608 very st., $\nu_{asym}(CO_2)$; 1,553 st., ν(C=C); 1,533 st., δ(N–H), II amide; 1,448 med., $\delta(CH_2)$; 1,414 st., $\nu_{sym}(CO_2)$; 544 med., ν(Cu–O). UV-visible (in CH_3CN), λ_{max}, nm (ε, l mol^{-1} cm^{-1}): 725 (105); 450 (280); 395 (lever); 308 (10,000). Λ_M, Cm cm^2 mol^{-1}: 9.0.

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