J.Serb.Chem.Soc. *69*(3)187–193(2004) UDC 546.562+546.17:615.281
JSCS – 3144 *Original scientific paper*

The preparation and characterization of Cu(II) complexes with *N,N',N",N'"*-tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane and 2,6-diacetylpyridine bis(semi/thiosemicarbazones)

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(Received 24 April, revised 13 October 2003)

Abstract: Two new Cu(II) mixed-ligand complexes with octadentate *N,N',N",N'"*-tetrakis(2-pyridylmethyl))-1,4,8,11-tetraazacyclotetradecane (tpmc) and potentially pentadentate ligands 2,6-diacetylpyridine bis(semicarbazone) ($DAPsc_2$) or 2,6-diacetylpyridine bis(thiosemicarbazone) ($DAPtsc_2$) were prepared. The general formulas: $[Cu_4\,DAPsc_2(tpmc)_2]ClO_4)_8 \cdot 5CH_3COCH_3 \cdot H_2O$ and $[Cu_2\,DAPtsc_2(tpmc)](ClO_4)_4 \cdot 7\,C_2H_5OH$ were proposed on the basis of elemental analyses and conductometric measurements. The complexes were characterized by magnetic measurement, electronic absorption and IR spectroscopy. For the dinuclear complex, an *exo* coordination of Cu(II) with four nitrogens from tpmc and μ-bonded $DAPtsc_2$ through sulfurs and possibly terminal hydrazinic (azomethine) nitrogens is assumed. For the tetranuclear complex, it is supposed that one $DAPsc_2$ bridges two $[Cu_2\,tpmc]^{4+}$ units using oxygens and terminal hydrazinic nitrogens as ligators. Finally, some antibacterial activity of the complexes was found.

Keywords: Cu(II) complexes, *N,N',N",N'"*-tetrakis(2-pyridylmethyl))-1,4,8,11-tetraazacyclotetradecane (tpmc), 2,6-diacetylpyridine bis(semicarbazone), 2,6-diacetylpyridine bis(thiosemicarbazone), antibacterial activity.

INTRODUCTION

N,N',N",N'"-tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane (tpmc) (Scheme 1) as a macrocyclic ligand with pendant 2-pyridylmethyl groups is flexible and adaptable towards ligands of different size, thus it is capable of forming stable mixed-ligand complexes. Complexes of Cu(II) with tpmc are numerous exhibiting a variety of properties (structural, redox, spectral, magnetic).[1] On the other hands, many derivatives of semi- and thiosemicarbazones and their metal complexes are efficient drugs against influenza, TBC and some kinds of tumors.[2,3] Among them,

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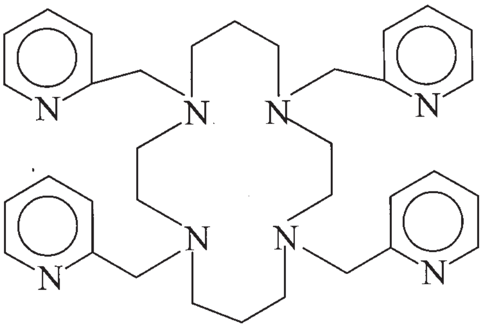
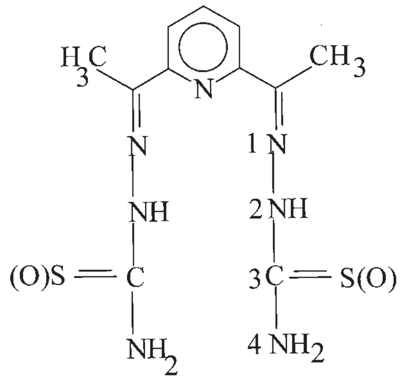


Scheme 1.



Scheme 2.

2,6-diacetylpyridine bis(semicarbazone) ($DAPsc_2$) and 2,6-diacetylpyridine bis(thiosemicarbazone) ($DAPtsc_2$) have been specially investigated.

The aim of this work was to optimise the conditions for the preparation of mixed-ligand Cu(II) complexes with tpmc and $DAPsc_2$ or $DAPtsc_2$ and compare their spectral properties with earlier described binuclear tpmc complexes of Cu(II) containing familiar but simpler ligands: urea (u), thiourea (tu), semicarbazide (sc) and thiosemicarbazide (tsc).[4] Thermogravimetrical analyses, mass spectroscopy, as well as UV-VIS and IR spectroscopy showed that sc and tsc are bidentates bonded to Cu(II) through O (or S) and the terminal hydrazinic (azomethine) N, whereas u and tu are μ–O,N (or S,N) bonded. Some of these complexes showed antibacterial activity.[4] In addition we wanted to suggest the geometry of Cu(II) in the new complexes. Finally, antimicrobial tests of the complexes were also performed.

These types of complexes are of interest as first examples of Cu(II) complexes containing, besides tpmc, bulky, potentially pentadentate ligands. The competition between $DAPsc_2$ ($DAPtsc_2$) and tpmc for the coordination sites means that different kind of isomers and geometries around the Cu(II) are possible. In all binuclear and tetranuclear Cu(II) tpmc complexes isolated up to now, the tpmc was tetradentate engaging 4 nitrogen atoms (2 from pyridine and 2 from the cyclam ring) and adopted either a *chair* or a *boat* conformation. Earlier, with ligands having multidonor atoms (malonato, bicyclic dicarboxylato, isophthalato dianions) besides tpmc, Cu(II) formed several rare tetranuclear complexes due to the steric hindrance and inductive effects of the additional ligand groups.[1b–c] On the other hand, $DAPsc_2$ ($DAPtsc_2$) have the tendency to keep the planarity of its molecule during coordination. By using models, it is obvious that some structures are less of more favourable depending on the ligators included.

EXPERIMENTAL

Safety note! *Perchlorate metal salts with organic ligands are potentially explosive and should be handled with extreme care (never shake them vigorously, do not heat more than a few crystals of the complexes in the solid state and always prepare small quantities).*

Preparation

All used chemicals were p.a. grade purity. The starting complex $[Cu_2\ tpmc](ClO_4)_4$ and $DAPtsc_2$ were prepared according to described procedure.[5,6] $DAPsc_2$ was prepared according to a slightly modified literature procedure.[7] All the experimental conditions were as in reference 7 except that the preparation was achieved at room temperature. The purity of ligands was checked by: elemental analyses, melting points, and IR and ^{1}H-NMR spectroscopy.

$[Cu_4\ DAPsc_2(tpmc)_2]ClO_4)_8 \cdot 5CH_3COCH_3 \cdot H_2O$ **(*1*)**: To a solution of $[Cu_2\ tpmc](ClO_4)_4$ (113 mg; 0.1 mmol) in acetone (10 cm^3) was added a solution of $DAPsc_2$ (31 mg; 0.06 mmol) in acetone (10 cm^3) containing the minimal amount of water. The reactants were stirred for 2 h at room temperature. After standing overnight in a refrigerator, light blue crystals appeared, which were separated by vacuum filtration and dried in a desiccator over $CaCl_2$. The compound was well soluble in acetone, methanol and acetonitrile. Anal: Calcd. for $C_{94}H_{135}N_{23}O_{38}Cl_8\ Cu_4$ (%): C, 41.28; H, 4.97; N, 11.78; Cu, 9.29. Found: C, 40.81; H, 5.02; N, 11.72; Cu, 9.16. Yield 39 %.

$[Cu_2\ DAPtsc_2(tpmc)](ClO_4)_4 \cdot 7\ C_2H_5OH$ **(2)**: A solution of $[Cu_2\ tpmc](ClO_4)_4$ (116 mg; 0.1 mmol) in acetonitrile (10 cm^3) and $DAPtsc_2$ (33 mg; 0.06 mmol) in 10 cm^3 of acetonitrile/water (5:1 v/v) were mixed and refluxed for 2 h at 80 ºC. Subsequently, a small amount of ethanol was added. Upon cooling the reaction mixture in a refrigerator overnight, a crude olive-green precipitate, containing a small amount of dark-brown impurity, appeared. This was recrystallizated from acetonitrile containing a small amount of ethanol. The further procedure was as for complex **1**. The pure olive-green microcrystals were well soluble in methanol and acetone, but insoluble in water. Anal: Calcd. for $C_{59}H_{101}N_{15}\ O_{23}S_2Cl_4\ Cu_2$ (%): C, 41.14; H, 5.87; N, 12.20; Cu, 7.38. Found: C, 41.47; H, 5.42; N, 12.01; Cu, 7.45. Yield 21 %.

Measurements and applied methods

Elemental analyses (C,H,N) were carried out by standard micromethods in the Center for Instrumental Analysis, Faculty of Chemistry, Belgrade. The Cu analyses were made using a Perkin-Elmer AAS-5100/PC atomic absorption spectrophotometer. The electronic spectra in acetonitrile ($c = 10^{-3}$ mol/cm^3) were recorded on a GBC UV/VIS 911 A spectrophotometer. The IR spectra (KBr disc technique) were recorded using a Perkin-Elmer 31725X FTIR spectrophotometer. The electrical conductivity was measured in acetonitrile using Janway 4010 conductometer at room temperature (20±2 ºC). The magnetic susceptibilities were determined at room temperature 20±2 ºC) using a MBS-MKI balance. The data were corrected for diamagnetic susceptibilities using Pascal's constants.[8] Antimicrobial activity was tested against: *Escherichia coli* (ATCC 35218), *Bacillus subtilis* (ATCC 10707), *Staphylococcus aureus* (ATCC 12228), *Sarcina lutea* (ATCC 9341) and *Candida albicans* (ATCC 24433) by monitoring the suppression of the growth, using the disc diffusion technique. Agar Tripton "Torlak" was used. Aliquots of 50 µl per disc (10^{-3} mol/dm^3 solutions of the complexes in acetonitrile) were applied. The ^{1}H-NMR spectra of the ligands were recorded using a Bruker AM 600 spectrospin spectrophotometer.

RESULTS AND DISCUSSION

Optimization of the conditions for the preparation of complexes

Mixed-ligand Cu(II) complexes with tpmc (Scheme 1) and $DAPsc_2$ ($DAPtsc_2$) (Scheme 2) were prepared by the reaction of $[Cu_2\ tpmc](ClO_4)_4$ with $DAPsc_2$ or $DAPtsc_2$ in the mole ratio 2:1, or 1:1. Different products were obtained depending on the experimental conditions (temperature, solvents).

Complex with $DAPsc_2$

a) Synthesis from acetonitrile, by an analogous procedure as that used for the previously prepared Cu(II) complexes with tpmc and either urea (u), thiourea (tu), semicarbazide (sc), or thiosemicarbazide (tsc),[4] failed. Namely, on heating the reaction mixture at 80 ºC, the colour turned from violet to greenish but the reaction mixture always returned to violet on cooling and [Cu_2 tpmc]$(ClO_4)_4$ and non-coordinated ligand $DAPsc_2$ crystallized.

b) When *N*,*N*-dimethylformamide was used as the solvent and the reaction mixture was heated at 150 ºC, an oily black-green product was obtained, the recrystallization and purification of which were difficult.

The elemental analysis of %C 41.49; %H 4.68; %N 12.85 was not consistent with any of the theoretically possible formulas. There was a strong peak at 258 nm in the UV/VIS spectrum of this product in acetonitrile, most probably arising from CT. The IR spectrum of this compound showed several strong, broad bands, the interpretation of which was difficult. It seems likely that the products decomposed under these conditions (high temperature and applied solvent).

c) Using methanol-ethanol (10:1, v/v) as the solvent and by heating the reaction mixture at 80 ºC, the colour changed to blue-green. From this solution, by fractional crystallization, first a light-blue compound (yield 26 %), and then a green product (yield 7 %) separated. Elemental analysis of the blue product corresponded to the formula [Cu_4 $DAPsc_2(tpmc)_2$]$(ClO_4)_8 \cdot 9\ C_2H_5OH$, whereas two formulas are possible for the green product: [Cu_4 $DAPsc_2(tpmc)_2$]$(ClO_4)_8 \cdot 9\ CH_3OH$ and [Cu_3 $DAPsc_2$(tpmc)]$(ClO_4)_6 \cdot 8\ C_2H_5OH$.

d) When acetone was used as the solvent and the reaction mixture was stirred at room temperature, only one, the most stable blue product [Cu_4 $DAPsc_2(tpmc)_2$]$(ClO_4)_8 \cdot 5\ CH_3COCH_3 \cdot H_2O$, was obtained in a relatively good yield (39 %).

Complex with $DAPtsc_2$

a) At lower temperatures (till 60 ºC), several products of different colours (yellow, green-yellow, brown-green and blue-green) were obtained in yields from 1.0 to 5.5 % when a mixture of methanol-ethanol (10:1, v/v) was used as the solvent.

b) When the same mixture was used as the solvent at 80 ºC, two products, one dark-brown (yield 10 %) and the other green (yield 20 %), appeared. They were separated by fractional crystallization.

c) When the preparation was performed in acetonitrile (80 ºC) there were two fractions: a dark-brown one (yield 8 %) and a green one (yield 21 %). The products from the methanol-ethanol mixture and acetonitrile were the same, as was confirmed by elemental analyses and the similar UV/VIS and IR spectral data. The formula of the green product is [Cu_2 $DAPtsc_2$(tpmc)]$(ClO_4)_4 \cdot 7\ C_2H_5OH$ while the brown product in both cases was a Cu(II) complex with $DAPtsc_2$.

$DAPsc_2$ ($DAPtsc_2$) usually coordinates through the terminal hydrazinic nitrogen (azomethine) (Scheme 2, atom N1) and oxygen (sulfur) thus forming a stable five-membered metalocycle.

Besides, complexes of Cu(II), Ni(II), Zn(II), Co(II) with S-alkylisothiosemicarbazides (tsc-SR) are known but they are not so numerous. In these complexes the S is blocked and thus not included in the coordination. This is understandable because the nitrogen atom, N (4) as the second ligator is not such a good electron donor as the sulfur atom in non-alkylated analogues.[3]

Cu(II) is a moderate soft (hard) acid according to Pearson. $DAPtsc_2$ is a soft base when sulfur is the ligator whereas $DAPsc_2$ is a hard base if the oxygen is included in the coordination.

As can be seen from the experimental, the (C,H,N,Cu) analyses were in agreement with the tetranuclear and binuclear structures with the formulas $[Cu_4\ DAPsc_2(tpmc)_2](ClO_4)_8 \cdot 5\ CH_3COCH_3 \cdot H_2O$ (**1**) and $[Cu_2\ DAPtsc_2(tpmc)](ClO_4)_4 \cdot 7\ C_2H_5OH$ (**2**), respectively. The conductivities of complexes **1** and **2** in acetonitrile were 780 and 460 S $cm^2\ mol^{-1}$, respectively which can be ascribed to 1:8 and 1:4 electrolyte types, respectively. In the VIS region of the electronic spectrum of complex **1** in acetonitrile there is a λ_{max} at 664 nm (ε = 1127 $dm^3\ mol^{-1}\ cm^{-1}$) and for complex **2** at 670 nm (ε = 444 $dm^3\ mol^{-1}\ cm^{-1}$). The origin of these maxima are d–d transitions.[9] On comparing these results, it can be seen that there is a hypsochromic shift when $DAPtsc_2$ is replaced by $DAPsc_2$ if the coordination is achieved through S of O.[2] This is in accordance with the fact that the former ligand has a stronger ligand field.

When the spectra of the newly prepared complexes are compared with those of complexes with similar but simpler ligands u, tu, sc, tsc (see Table I), a hypsochromic shift of the absorption maxima of complex **1** compared with those of the u or sc analogues, as well as of those of complex **2** compared with those of the tu or tsc analogous complexes is observed. Nevertheless, the position of the absorption maxima and their shape suggest the same or similar chromophore. The ε value is highest for complex **1**, which is probably due to it having the most asymmetric (tetranuclear) structure.

TABLE I. Position of λ_{max} (nm) and molar absorption coefficients ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$) in acetonitrile

Complex	λ_{max}/cm^{-1} ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$)
$[Cu_4\ DAPsc_2(tpmc)_2]^{8+}$	664 (1127)
$[Cu_2\ (u)\ tpmc]^{4+}$*	678 (376)
$[Cu_2\ (sc)\ tpmc]^{4+}$*	682 (464)
$[Cu_2\ (DAPtsc_2)\ tpmc]^{4+}$	670 (444)
$[Cu_2\ (tu)\ tpmc]^{4+}$*	679 (331)
$[Cu_2\ (tsc)\ tpmc]^{4+}$*	675 (444)

*data from literature[4]

The most relevant bands in the IR spectra of both complexes are $\nu(ClO_4^-)$ at 1093 cm^{-1} (strong, broad), δ (ClO_4^-) at 625 cm^{-1} (medium, sharp), skeletal pyridine bands at about 1612 cm^{-1} (strong, sharp). The ν (C=O) at 1695 cm^{-1} in the spectrum of complex **1** is shifted by 12 cm^{-1} towards lower wave numbers when compared to the same band in the spectrum of the free $DAPsc_2$ ligand. This indicated the participation of oxygen in the bond formation. The ν(C=S) band of complex **2** at 763 cm^{-1} is shifted by 54 cm^{-1} towards lower wave numbers in comparison to the same band of the free $DAPtsc_2$ ligand, which confirmed S-coordination.[10] From IR analysis, it was not possible to give a more precise description of $DAPtsc_2$ ($DAPsc_2$) bonding, *i.e.*, the eventual participation of carbamide or azomethine N-atoms in coordination, because of the overlapping of the bands belonging to the ν(OH^-) and ν(ClO_4^-).

The observed magnetic moments at room temperature μ_{eff}/Cu, 1.85 BM for complex **1** and 1.81 BM for complex **2**, lie in the range of values (1.73 – 2.20 BM/Cu) experimentally observed when there is no appreciable interaction between the copper ions.

On the bases of all the mentioned results, it can be assumed that in the teranuclear Cu(II) complex **1** two tpmc units are bridged with one $DAPsc_2$. Besides the participation of O atoms, it can be assumed that the azomethine Ns are also included in the coordination. Analogously with the previously described numerous transition metal complexes with sc derivatives, it is less likely that instead of the azomethine nitrogen atom (N 1, Scheme 2), the second hydrazinic atoms (N2) or carbamide nitrogens (N4) participate in the coordination. In the binuclear complex **2**, two Cu(II) atoms are bridged by $DAPtsc_2$ through S, and maybe the azomethine N, while the tpmc adopts the "boat" conformation.

Further efforts to grow single crystals of complexes **1** and **2** suitable for X-ray analyses are in progress.

Antimicrobial activity

The biological activities of the complexes were tested by the diffusion method through agar plates (nutrition power agar was Tripton "Torlak") towards the following strains of microorganisms: *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Sarcina lutea* and *Candida albicans*. Both complexes showed antibacterial activity for *B. subtilis* with an inhibition zone of 23 cm in diameter, while complex **2** exhibited activity towards *E. coli* with an inhibition zone of 14 cm. Under the same conditions, the free ligands (tpmc, $DAPsc_2$, $DAPtsc_2$), the starting complex $[Cu_2\ tpmc](ClO_4)_4$ and acetonitrile were inactive.

Acknowledgement: The authors are grateful to the Ministry of Science and Technology of the Republic of Serbia for financial support (Project 1318). Our thanks are also due to Mr. Ilija Brčeski, Ph. D., for antimicrobial test screening.

ИЗВОД

ДОБИЈАЊЕ И КАРАКТЕРИЗАЦИЈА Cu(II) КОМПЛЕКСА СА *N,N',N'',N'''*-ТЕТРАКИС(2-ПИРИДИЛМЕТИЛ)-1,4,8,11-ТЕТРААЗАЦИКЛОТЕТРАДЕКАНОМ И БИС(СЕМИ/ТИОСЕМИКАРБАЗОНОМ) 2,6-ДИАЦЕТИЛПИРИДИНА

СЛАЂАНА Б. ТАНАСКОВИЋ[а] и ГОРДАНА ВУЧКОВИЋ[б]

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Изолована су два нова Cu(II) мешовито-лигандна комплекса са октадентатним *N,N',N'',N'''*-тетракис(2-пиридилметил)-1,4,8,11-тетраазациклотетрадеканом (tpmc) и потенцијално пентадентатним лигандима бис(семикарбазоном) 2,6-диацетилпиридина ($DAPsc_2$) или бис(тиосемикарбазоном) 2,6-диацетилпиридина ($DAPtsc_2$). Опште формуле комплекса: $[Cu_4\ DAPsc_2(tpmc)_2]ClO_4)_8 \cdot 5CH_3COCH_3 \cdot H_2O$ и $[Cu_2\ DAPtsc_2(tpmc)](ClO_4)_4 \cdot 7\ C_2H_5OH$ претпостављене су на основу елементалне анализе и кондуктометријских мерења. Комплекси су окарактерисани магнетним мерењима, електронском апсорпционом и ИЦ спектроскопијом. За динуклеарни комплекс претпостављена је *exo* координација Cu(II) за 4 азотова атома tpmc-а и μ-везивање $DAPtsc_2$ преко сумпора и евентуално азометинских (терминалних хидразинских) атома азота. За тетрануклеарни комплекс претпостављено је да један $DAPsc_2$ премошћује две $[Cu_2tpmc]^{4+}$ јединице користећи кисеоникове и азометинске атоме азота за везивање. Најзад, утврђена је извесна антибактеријска активност добијених комплекса.

(Примљено 24. априла, а ревидирано 13. октобра 2003)

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