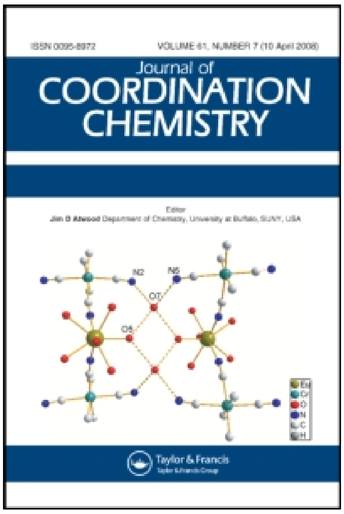

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INVESTIGATION OF THE SOLUTION STRUCTURE OF Cu(II) MIXED-LIGAND COMPLEXES OF ADENOSINE 5′-MONOPHOSPHATE AND CYTIDINE 5′-MONOPHOSPHATE AND POLYAMINES

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The coordination mode of complexes formed in the systems Cu(II)/NMP/PA; (NMP =adenosine 5′-monophosphate, cytidine 5′-monophosphate; PA = 1,4-diaminopropane (putrescine, Put), 1,7-diamino-4-azaheptane (3,3-tri) and 1,11-diamino-4,8-diazaundekane (3,3,3-tet)) was determined on the basis of the equilibrium and spectroscopic studies. The presence of the following mixed complexes was established: Cu(CMP)H(Put), Cu(AMP)H_2(3,3-tri) and Cu(CMP)H_2(3,3-tri), Cu(CMP)H_4(3,3-tri) and coordination compounds of MLL′ type – Cu(CMP)(3,3,3-tet), Cu(AMP)(3,3,3-tet). A significant influence of the polyamine length on the solution structure of the complexes was observed. In mixed-ligand complexes Cu(NMP)(3,3,3-tet) a {N4,O} chromophore is formed, and metallation involves all nitrogen atoms from 3,3,3-tet. In the analogous system with 3,3-tri, protonated complexes occur. Non-covalent intramolecular interaction between the protonated amine groups and donor atoms from the purine ring from the nucleotide results in an increase of complex stability.

Keywords: Copper(II); Polyamines; Adenosine 5′-monophosphate; Cytidine 5′-monophosphate; Complexes; Solution structure

INTRODUCTION

A group of aliphatic polyamines putrescine (Put), spermidine (Spd) and spermine (Spm) plays a significant role in many reactions which take place in living organisms, in particular in the process of genetic information transfer. Inhibition of biosynthesis of the biogenic amines prevents correct

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*Corresponding author.

development of cells [1–4]. The above bioligands have been found to form molecular complexes with nucleosides and nucleotides, and the tendency towards formation of adducts in general increases with increasing length of methylene chains [5–8]. The centres of non-covalent interactions are potential sites of coordination and therefore metal ions should be treated as interfering in the reactions of the bioligands. Interestingly, the tendency towards formation of coordination compounds decreases with increasing length of the polyamine chain contrary to adduct formation [5, 7, 8]. Moreover, characteristic differences were observed in the solution structure of the mixed complexes of metal ions with polyamines containing nucleosides or nucleotides as the second ligand [7, 9]. This paper reports further results on the mode of coordination of copper(II) ternary complexes with adenosine and cytidine monophosphates including 1,4-diaminobutane (putrescine, Put), 1,7-diamino-4-azaheptane (3,3-tri) and 1,11-diamino-4,8-diazaundekane (3,3,3-tet), which has been discussed recently [10].

EXPERIMENTAL

Potentiometric measurements of the systems Cu(II) with adenosine-5′-monophosphate (AMP) and cytidine-5′-monophosphate (CMP) as well as the polyamines putrescine (Put), 1,7-diamino-4-azaheptane (3,3-tri) and 1,11-diamino-4,8-diazaundecane (3,3,3-tet) were performed on a Multi-Titrator DTS 800 Radiometer with a GK-2401c electrode. The electrode was calibrated according to the procedure previously given [11]. The stability constants and composition of the complexes were determined using the program SUPERQUAD [12]. The criteria for the correct choice of model have been described earlier [13]. ^{13}C NMR spectra were measured (at $M:L$ of 1 : 100) on a Gemini 300 VT Varian instrument with dioxane as internal standard. The positions of NMR signals are given on the TMS scale. ^{31}P NMR measurements were carried out on a Varian Unity 300 spectrometer (standard – H_3PO_4). IR spectra were measured on a Bruker IFS-113v spectrophotometer, electronic spectra on a Shimadzu UV 160, and EPR on an SE/X 2547 Radiopan instrument. Detailed information on experimental conditions and analysis of potentiometric data are given in the literature [10].

RESULTS AND DISCUSSION

In the systems Cu/CMP/Put, Cu/CMP/3,3-tri, Cu/AMP/3,3-tri, Cu/CMP/3,3,3-tet and Cu/AMP/3,3,3-tet, the presence of the following complexes was detected: Cu(CMP)H(Put), Cu(AMP)H_2(3,3-tri), Cu(CMP)H_2(3,3-tri), Cu(CMP)H_4(3,3-tri), Cu(CMP)(3,3,3-tet) and Cu(AMP)(3,3,3-tet). In the protonated complexes only one nitrogen atom from the polyamine is involved in coordination (taking into account the degree of protonation of the nucleotide and the polyamine) [10]. Equilibrium defined by Eqs. (1)–(3), are 5.48, 6.72 and 5.47, $\left(\log K_e = \log \beta_{\mathrm{Cu(NMP)H\times(PA)}} - \log \beta_{\mathrm{H\times(PA)}}\right)$, for given conditions [10].

$$\mathrm{Cu(CMP)} + \mathrm{H(Put)} \leftrightharpoons \mathrm{Cu(CMP)H(Put)} \tag{1}$$

$$\mathrm{Cu(AMP)} + \mathrm{H_2(3,3\text{-}tri)} \leftrightharpoons \mathrm{Cu(AMP)H_2(3,3\text{-}tri)} \tag{2}$$

$$\mathrm{Cu(CMP)} + \mathrm{H_2(3,3\text{-}tri)} \leftrightharpoons \mathrm{Cu(CMP)H_2(3,3\text{-}tri)} \tag{3}$$

The equilibrium constant, $\log K_e$ of binary complex formation

$$\mathrm{Cu} + \mathrm{H(Put)} \leftrightharpoons \mathrm{CuHPut} \tag{4}$$

is 5.00. The higher values of $\log K_e$ for reactions (1), (2) and (3) indicate additional stabilization of the mixed complexes.

Analysis of the changes in the positions of ^{13}C and ^{31}P NMR signals shows that the formation of Cu(CMP)H(Put) involves the N(3) atom and oxygen atoms from the phosphate group of the nucleotide. The controversial question of NMR studies of paramagnetic systems has been discussed earlier and has led to the conclusion that a critical analysis of results (including good correlation between results of independent methods) makes it possible to draw reliable inferences about the coordination mode from changes in signal positions [5,7,8,14,15]. For instance at pH 6, at which the dominant species is Cu(CMP)H(Put), the shifts of signals assigned to C(2) and C(4), adjacent to N(3), are 0.295 and 0.349 ppm, respectively (Tab. I), whereas the shifts of signals from C(5′) (next to the phosphate group) and from the phosphorus atom are 0.302 and 0.139 ppm, respectively. At the same pH, the shifts of the atoms C(5) and C(6), which are not next to the donor atoms, are only 0.002 and 0.023 ppm, respectively. No change in the IR stretch assigned to the C=O group of CMP excludes the involvement of the oxygen atoms in metallation (Fig. 1a, Tab. I).

Shifts in the positions of the signals assigned to C(1) and C(2) of putrescine at pH = 6 are 0.094 and 0.123 ppm, which testifies to the involvement of the two nitrogen atoms from the polyamine in complex formation (Fig. 1b). Analysis of the electronic and EPR spectra suggests the presence of the {N1,O} chromophore with one nitrogen atom from the polyamine and oxygen atoms from the phosphate group which take part in the metallation [16–18] (characteristic parameters are given in Tab. I).

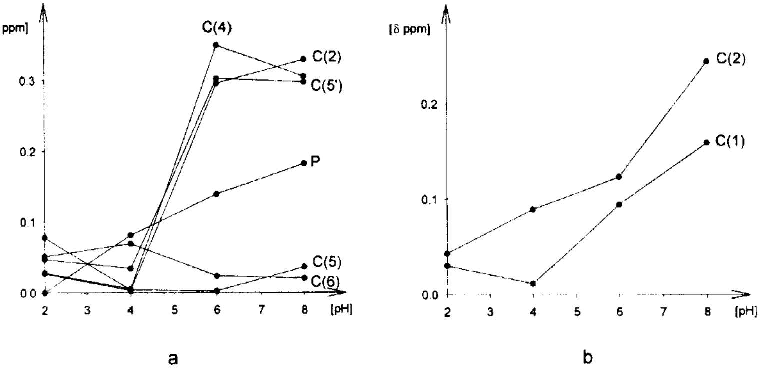


FIGURE 1 Changes in ^{13}C and ^{31}P NMR signal positions as a function of pH for the Cu/CMP/Put system (in relation to free ligands); CMP – a; Put – b; $C_{CMP} = C_{Put} = 0.05$ M; $C_{Cu} = 0.0005$ M.

Therefore, as follows from the equilibrium and spectroscopic studies, the second (protonated) nitrogen atom from putrescine is involved in non-covalent interactions with the donor centres in the pyrimidine ring of the nucleotide.

Similarly, for Cu(AMP)H_2(3,3-tri) and Cu(CMP)H_2(3,3-tri), analysis of ^{13}C and ^{31}P NMR data shows that complex formation involves the nitrogen atom and the phosphate group of the nucleotide and all nitrogen atoms from 3,3-tri. At pH = 6, for Cu(AMP)H_2(3,3-tri), the shifts of the signals from the carbon atoms neighboring N(1) and N(7), that is C(2), C(6), C(5) and C(8), are 0.187, 0.285, 0.170 and 0.388 ppm, respectively (Tab. I). The signal assigned to C(5′) is changed by 0.228 ppm and that assigned to the phosphorus atom by 0.219 ppm (Fig. 2a).

Signals assigned to the carbon atoms C(1), C(2) and C(3) of 3,3-tri are shifted by 2.037, 2.287 and 1.502 ppm (Fig. 2b), while the positions of the signals from the carbon atoms of AMP which are far from the coordination sites are practically unchanged (*e.g.*, for C(4) at pH = 6 the shift is 0.016 ppm, Fig. 2a). Similar to the complex with putrescine, electronic and EPR data suggest the presence of a {N1,O} chromophore (Tab. I). The other nitrogen atoms of the polyamine take part in non-covalent interactions with the donor atoms of the AMP purine ring. The value of $\log K_e$ for Cu(AMP)H_2(3,3-tri) is higher than that for the formation of Cu(CMP)H(Put). As follows from the data, additional stabilization of the complex with AMP is a result of non-covalent interactions of two protonated nitrogen atoms from the polyamine with N(1) and N(7) in the purine ring. In Cu(CMP)H(Put) it is a consequence of the interaction of the

TABLE I Spectroscopic data and overall stability constants (log β) for Cu(II)/NMP/polyamine systems

	$Cu(CMP)H(Put)$ $pH=6$	$Cu(AMP)H_2(3,3\text{-}tri)$ $pH=6$	$Cu(CMP)H_4(3,3\text{-}tri)$ $pH=4$	$Cu(AMP)(3,3,3\text{-}tet)$ $pH=6$
log β	19.02(8)	29.96(15)	39.71(5)	20.15(4)
Changes in ^{13}C NMR signal positions (ppm)	C(2) 0.295 C(4) 0.349 C(5) 0.002 C(6) 0.023	C(8) 0.388 C(5) 0.170 C(6) 0.285 C(2) 0.187	C(2) 1.070 C(4) 2.282 C(5) 0.116 C(6) 0.307	C(8) 0.011 C(5) 0.016 C(6) 0.025 C(2) 0.019
Changes in ^{31}P NMR signal positions (ppm)	P(phosphate) 0.139	P(phosphate) 0.219	P(phosphate) 0.987	P(phosphate) 0.098
Electronic spectra λ_{max} (nm)	736	725	798	578
EPR parameters	$g_{\parallel}=2.2473$ $A_{\parallel}=186$	$g_{\parallel}=2.2446$ $A_{\parallel}=163$	$g_{\parallel}=2.3382$ $A_{\parallel}=161$	$g_{\parallel}=2.2332$ $A_{\parallel}=175$

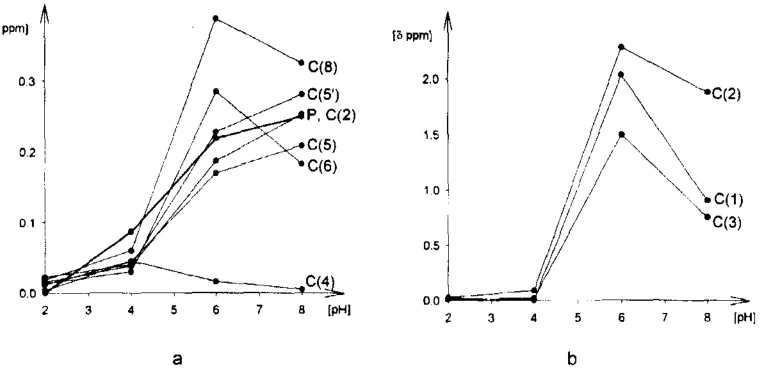
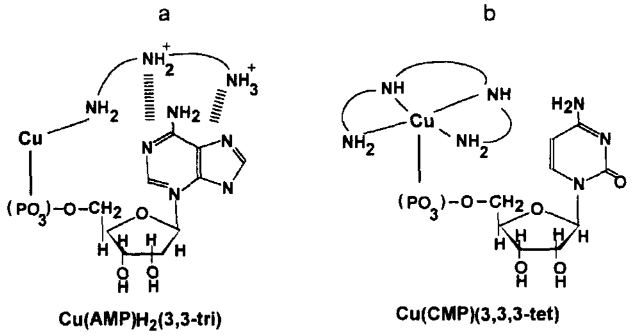


FIGURE 2 Changes in ^{13}C and ^{31}P NMR signal positions as a function of pH for the Cu/AMP/3,3-tri system (in relation to free ligands); AMP – a; 3,3-tri – b; $C_{AMP}=C_{3,3\text{-tri}}=$ 0.05M; $C_{Cu}=0.0005M$.



3,3-tri = $NH_2(CH_2)_3NH(CH_2)_3NH_2$
3,3,3-tet = $NH_2(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$

SCHEME 1

protonated nitrogen atom from putrescine with the donor nitrogen atom of the pyrimidine ring. The same type of interaction has been found in the $Cu(CMP)H_2$(3,3-tri) complex. Scheme 1a presents a tentative model of interactions in the mixed protonated complexes. The above results, indicating the mode of coordination, do not allow a determination of the degree of the molecule deformation.

In the system Cu/CMP/3,3-tri, a molecular complex $Cu(CMP)H_4$(3,3-tri) is formed and at pH = 4.5 it is the only species in the system. As follows from NMR analysis, the nitrogen atom N(3), oxygen atoms from the phosphate moiety of CMP (Tab. I) as well as all nitrogen atoms from the polyamine are involved in coordination (Fig. 3a, b).

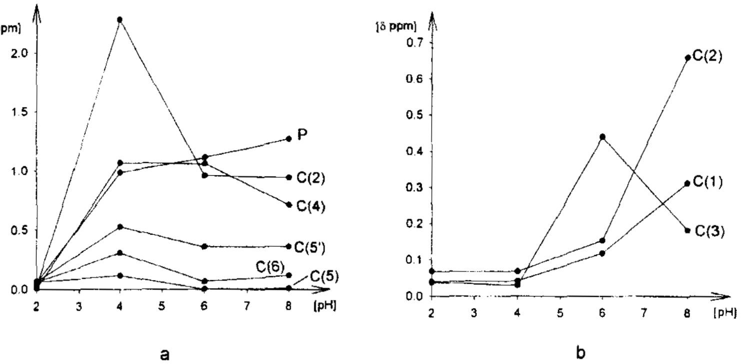


FIGURE 3 Changes in ^{13}C and ^{31}P NMR signal positions as a function of pH for the Cu/CMP/3,3-tri system (in relation to free ligands); CMP – a; 3,3-tri – b; $C_{CMP} = C_{3,3\text{-tri}} = 0.05\,M$; $C_{Cu} = 0.0005\,M$.

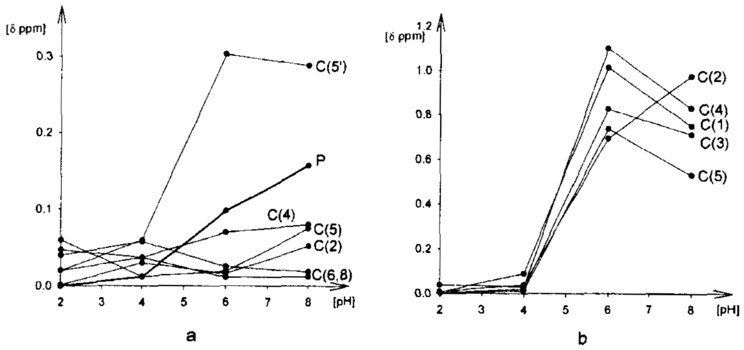


FIGURE 4 Changes in ^{13}C and ^{31}P NMR signal positions as a function of pH for the Cu/AMP/3,3,3-tet system (in relation to free ligands); AMP – a; 3,3,3-tet – b; $C_{AMP} = C_{3,3,3\text{-tet}} = 0.05\,M$; $C_{Cu} = 0.0005\,M$.

For example, at pH = 4, the shifts of the ^{13}C NMR signals assigned to C(1), C(2) and C(3) from the polyamine are 0.012, 0.038 and 0.030 ppm, respectively. The results of electronic and EPR studies (Tab. I) suggest a Cu—O chromophore, so coordination of copper ion occurs only by the oxygen atoms of the phosphate group, while the protonated polyamine is outside the inner coordination sphere. Interactions of a similar type have been earlier observed in the system Cu/AMP/Spm [7, 9].

A different type of coordination has been observed in the MLL′ complex with 3,3,3-tet. According to the NMR, all nitrogen atoms from the polyamine and oxygen atoms from the phosphate group of the nucleotide are involved in coordination (Fig. 4a, b)

The formation of a {N4,O} chromophore is supported by the results of the electronic and EPR study (Tab. I). For the complex with CMP, $\lambda_{max} = 587\,nm$, $g_{\|} = 2.2115$ and $A_{\|} = 190.0$. The mode of coordination in these complexes (substantially different from that in an analogous system with spermine [7,9]) is presented in Scheme 1b. The above evidence shows clearly the significant effect of a small difference in the length of the methylene chain (Spm and 3,3,3-tet) on the solution structure of the complexes.

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