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Coordination behavior of Coenzyme A towards gold ions: Spectroscopic, mass spectrometric and microbiological studies

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The interaction of Coenzyme A (CoA) with gold ions was investigated at various pH values by means of UV-*Vis*, FT-IR spectroscopy, as well as electrospray ionization-mass spectrometry. Furthermore, the protective role of CoA against gold induced toxicity in *Pichia pastoris* was studied. For the first time, we clearly showed that weak CoA-Au(I) complexes with 1:1 stoichiometry were formed at physiological pH. The complexation process was accompanied by gold reduction and it was strongly influenced by the reaction milieu. Moreover, a reaction byproduct, thiocoenzyme A, was identified by mass spectrometry.

Keywords: Coenzyme A; Au complexes; Spectroscopy; Mass spectrometry; *Pichia Pastoris*.

INTRODUCTION

Gold has been used since ancient times to treat smallpox, skin ulcers and measles and recently, the attention has been turned to possible therapeutic applications of gold-based materials [1,2]. A series of gold complexes capable of catalyzing chemical transformations in living organisms has been investigated in previous studies [3].The first gold complex was introduced by Robert Koch for the treatment of tuberculosis. Gold(III) chloride has been employed since 19th century in the treatment of syphilis. Moreover, gold(I) thiolate complexes were considered the drug of choice in the case of rheumatoid arthritis [4]. Auranofin, a Au(I) complex, and its analogs were found to exert a potent cytotoxic activity against certain types of cancer cells [5]. Furthermore, the proteasome is a target for Au(III) complexes [6]. It has been shown that Au(I) ions have a better affinity for thiolate S instead of O- or N-ligands. The aminoacid L-cysteine reduces Au(III) to Au(I) and forms a stable Au(I) complex in aqueous solutions [7]. This complex has recently been investigatedby UV-Vis and CD spectroscopy [8].A Au(I) complex with N-acetyl-L-cysteine ligand has also been reported [9]. Electrospray ionization-mass spectrometric analysis (negative ion mode)showed the presence of a glutathionato-S-Gold(III) during the reduction of auricyanide by L-glutathione [10]. Furthermore, methionine-gold interaction under acid conditions indicated that this amino acid plays the role of a bidentate ligand [11]. Thiol affinity for gold (I) was indirectly demonstrated since gold(I)-based catalysts were easily deactivated by these compounds [12]. Gold-protein complexes were intensively investigated, proteins containing cysteine residues being able to easily bind Au(I). Auoxo1, an Au(III) complex, has been shown to interact with cytochrome c, the resulting gold (I) being tightly attached to the protein [13]. In the bloodstream, gold is transported by albumin, in which Cys34 acts as a binding site [14]. Under acidic conditions, gold (III) has the ability to deprotonate the amide peptide group of GGH tripeptide [15]. Gold (III) complexes with Glycyl-Histidine and Alanyl-Histidine dipeptides have recently been reported [16]. Au(III) is tightly bound to xanthine derivatives, nucleosides or nucleotides [17,18]. In particular, the phosphate moiety could be involved in complexation [19]. Studies on microorganisms-gold interaction have been reported indicating that some microorganisms have the capacity to reduce Au(III) to Au(I) or gold nanoparticles [20 - 23].

In bacteria, many enzymes require Coenzyme A (CoA, Fig. 1) as a cofactor [24].

This biomolecule is involved in fatty acids oxidation pathway and/or in calmodulin-dependent protein kinase (CaMKII) activation [25]. The concentration of CoA in mitochondria is relatively high, in the range of 2.2–5 mM [26, 27]. CoA could be essential for proper cellular detoxification. In this respect, moderate CoA levels in *E. coli* impair the bacteria growth [28]. However, in certain bacterial species, CoA and its derivatives seem to play a significant role in maintaining the reducing environment of the cell, acting in a similar fashion as glutathione, which is missing in these microorganisms [29].

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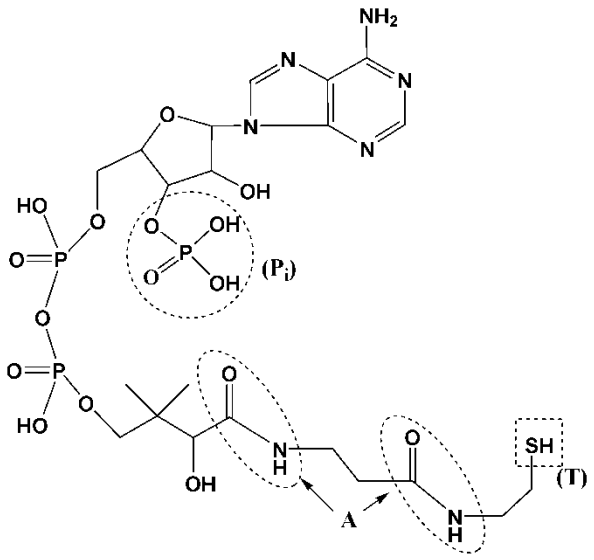

Fig. 1. Chemical structure of Coenzyme A (CoA). Phosphate (P_i), peptide bonds (A) and thiol (T) moieties were labeled.

An NMR study has drawn attention to the La-CoA complexes in aqueous solution [30]. CoA is a versatile ligand, forming stable complexes with both soft and borderline metal ions. Soft metal ions such as Hg^{2+} coordinate through the thiol sulfur and amide groups of CoA [31]. Based on this, a versatile sensor for biomolecules such as cysteine, Glutathion (GSH) or CoA was reported [32]. No preliminary study has reported the existence of Au-CoA complexes yet. Nevertheless, little is known about the relationship between CoA and gold ions in microorganisms. For this reason, in the present study Au-CoA complex was investigated by spectroscopic, mass spectrometric and/or toxicity methods (using *P. Pastoris* as a model microorganism). The complex was investigated at various pH values and in different buffer systems and the stoichiometry was also estimated.

EXPERIMENTAL

Materials

Sodium phosphate dibasic dihydrate was purchased from Sigma-Aldrich (Germany), disodium tetraborate decahydrate from Carl Roth (Karlsruhe, Germany), Glycine and Tris (base) from Carl Roth, ammonium acetate from Riedel-de Haen (Seelze, Germany), Gold (III) chloride from Titolchimica (Potecchio Polesine, Italy) and Coenzyme A (lithium salt) was a Walldorf (Germany) product. Potassium bromide was purchased from Fluka (Steinheim, Germany). All buffers were prepared using ultrapure water (Milli-Q, Millipore, 18.2 MΩ resistivity).

Methods

UV-Vis absorption spectra of free CoA and its complex were recorded on a Libra UV-Vis single beam spectrophotometer (Biochrom, Cambridge, UK) equipped with a Peltier thermostated to ensure a constant temperature (25 °C). The UV-*Vis* spectra were acquired in the wavelength range from 200 to 400 nm using a quartz cuvette (Helma/Müllheim) with a 1 cm path length.

The complex stoichiometry was estimated using the Yoe-Jones method [33]. The concentration of CoA was kept constant (0.25 mM) and the gold ion concentrations were varied (0.05-2.5 mM), depending on the buffer (borate, glycine, or Tris). The minimum of the curves corresponded to the maximum formation of the complex. The complex stoichiometry was estimated from the point where this curve changes its slope.

The IR spectra of CoA and its gold complex were acquired using a Jasco FT/IR660 Plus Fourier spectrometer in the range 4000 – 200 cm^{-1}. In order to prepare pellets, the reaction mixture was evaporated at room temperature or by heating the mixture at 70 ^{0}C and later mixed with 100 mg of dried KBr.

Electrospray ionization-mass spectrometric (ESI-MS) analyses were carried out on an Esquire 3000+ ion trap mass spectrometer (Bruker Daltonics, Bremen, Germany). Spectra were acquired in positive ion mode, in the 50 - 2500 m/z range. A mixture of CoA and metal salt at various molar ratios was prepared in 5 mM NH_4HCO_3, pH 7.4.

Similarly, *Pichia* (SMD1168H *P. Pastoris*, Invitrogen, USA) growth tests were performed in YEPD medium (10 g yeast extract, 20 g peptone and 20 g glucose in 1 L; pH 6.0). A 100 mL preculture was obtained in a 500 mL Erlenmeyer flask at 30 °C under continuous stirring (100 rpm). After one day of incubation, an optical density (580 nm) of 4.1 was reached. Both CoA (0.5 mM) and $AuCl_3$ (0.5; 1 or 1.5 mM) solutions were prepared in YEPD medium. A set of sterile 10 mL glass tubes containing 1 mL of YEPD medium and appropriate concentration of CoA and gold ions was used. After treatment, each sample was inoculated with 50 μL preculture and incubated at 30 ºC with stirring. The cells' densities were quantified by absorbance measurements of diluted samples at 580 nm after 8.0 h.

RESULTS AND DISCUSSION

Steady-state absoption study

CoA and its thioesters display two main characteristic absorption peaks at 200 and 260 nm. Initially, the formation of the complex, CoA-Au(III), was investigated at lower pH (Glycine buffer, pH 6.8) or mitochondrial pH (Tris buffer, pH 8.5). The characteristic band of the complex in the region 280-300 nm could not be observed at a CoA concentration of 10-20 μM. This result intrigued us, since the complex of CoA with mercury was easily assessed at pH 8 [31]. Considering that CoA contains a thiol group, with potential affinity for gold, we expected that the complexation would mainly be dictated by its ionization. The pKa value of the mercapto group of coenzyme A was estimated to be 10.4 [34]. This value is at least one unit higher than the pK values of common biological thiols (cysteine and glutathione). Moreover, the formation of CoA dimers, at pH higher than 8, should be taken into account. Therefore, these parameters should be considered for the complex formation and its stability.

After several trials, we found that the interaction of CoA with Au(III) ions could easily be assessed using an alkaline borate solution (pH 10). The contribution of free Au(III) ions (a peak with a maximum at 210 nm) was subtracted, since its absorbtion band superposed the one of the complex at higher concentration. Surprisingly, at a lower CoA concentration (57 μM, Fig. 2, solid line spectrum), the CoA-Au(III) complex was not observed. The shape of the spectra did not exhibit any major changes at 260 nm; however, the intensity decreased by 15% (Fig. 2, dotted-line spectrum). This behavior suggested an electrostatic interaction between the positively charged gold ions and their counterpart, CoA's phosphate moiety. However, a drastic decrease around 50% of the peak intensity at 200 nm was noticed. In addition, a bathochromic shift was observed and more individual peaks could be distinguished in this area. At a higher CoA concentration (171 μM), a low intensity band was observed around 300 nm, when a stoichiometric amount of Au(III) was used. The complex was quite difficult to assess, since at higher Au(III) concentration (higher than 750 μM $AuCl_3$) a very high intensity band was detected in the same region. However, at elevated CoA (250 μM) and Au(III) concentrations (2-3 equivalents), the intensity at 300 nm considerably increased (more than 50-60%). The spectral differences revealed two new absorption peaks at 280 and 300 nm, respectively. All the results presented above support the idea that higher ligand and CoA concentrations are a prerequisite for complex formation. The investigated complex is characterized by an apparent dissociation constant in millimolar range (around 2 mM) and a relatively higher molar extinction coefficient (2.58 ± 0.5 $mM^{-1}cm^{-1}$) than the corresponding value of uncomplexed Au(III) ions, 0.4 $mM^{-1}cm^{-1}$ at 300 nm. Thus, the complex is characterized by a moderate stability.

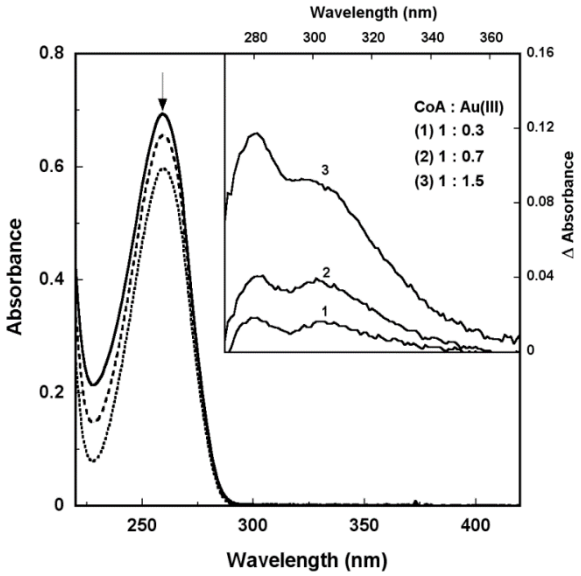

Fig. 2.UV-*Vis* spectra of CoA alone (57 μM) and in the presence of 1.8 or 4.6 equivalents of Au(III) recorded in borate buffer, pH 10. *Inset*: Difference spectra at various CoA:Au ratios (CoA concentration 220 μM).

The stoichiometry of the complex formed in 50 mM borate buffer at pH 10 was CoA: Au (I or III) = 0.9:1. Probably, the presence of borate ions in the complex outer shell could be attributed to this ratio. However, a similar stoichiometry for gold thiolate drugs with a molar excess of thiol over gold (I) has previously been reported [35].

Previous studies on CoA-Au(III) complexes under physiological conditions have been unsuccessful since gold ions could be sequestered by various buffer components. The most suitable buffers at pH 7 are for instance phosphate, HEPES, MES, Glycine, Tris. The drawback of phosphate buffer usage is that gold phosphate tends to precipitate in solution and cannot be used in spectral titration assays. HEPES and MES (Good's buffers) have the tendency to form blue nanoparticles [36]. At slightly acidic pH, glycine reduces Au(III) to Au(I) [37]. On the basis of these considerations, we decided to use Tris buffer instead of all systems mentioned above, although its optimal buffering capacity is situated up to one pH unit.

At an elevated CoA concentration (180 μM), the spectral differences at 300 nm were reasonable and the apparent dissociation constant was estimated to be 0.49±0.16 mM. Thus, we noticed that the

complex was more stable at pH 7 than at pH 10. At neutral pH, the complex was characterized by a lower dissociation constant (3-4 fold) than that of the well-studied CoA-Hg(II) system [31, 32]. Beside coenzyme A, another important thiol compound for organisms is glutathione, a tripeptide that displays a similar behavior towards metal ions (Fig. 3 inset). The spectral differences were more evident at 270 nm using a tripeptide concentration higher than 360 μM. In this particular case, the apparent dissociation constant was estimated to be 0.124±0.050 mM. For this reason, a competition between these two thiols, CoA and GSH, for gold ions is expected in the cells.

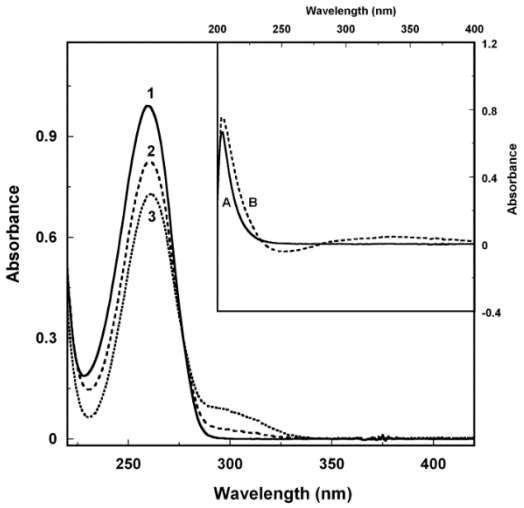

Fig. 3. Difference spectra at two different CoA:Au ratios (1:0.9 and 1:2, dotted) and their comparison with uncomplexed CoA (90 μM). *Inset*: Difference spectrum at GSH:Au molar ratios of 1:0.9 (dotted) in comparison with uncomplexed GSH (90 μM). Conditions: 50 mM Tris buffer, pH 7.

FT-IR studies

The FT-IR spectra of free CoA and its gold complex are shown in Fig. 4. Significant spectral changes were observed after adding gold ions. A couple of bands were detected in the region 400-500 cm^{-1} in the second derivate spectrum of complex. The most evident change in the parent spectrum of uncomplexed CoA was observed at 426 cm^{-1} (Fig. 4A, inset). This band could easily be attributed to a C-N out of plane bending. Furthermore, the signals at 476 and 485 cm^{-1} were assigned to the Au-N tetrahedral distortion. In this context it should be mentioned that the band at 515 cm^{-1}, which could be attributed to adenosine moiety, disappeared and a new band arose at 427 cm^{-1} after complexation. Other sensitive changes due to the CoA-gold complexation were noticed in the second derivative spectra. The complex possessed a small broad band centered at around 618 cm^{-1} that could be assigned to the C-S stretching vibration mode. The signals from 650-810 cm^{-1} region were characterized by lower intensity and most of them were slightly shifted (1-3 cm^{-1}) to higher wavenumbers. Only the signal from 680 cm^{-1} was shifted down (678 cm^{-1}). These are prominent features for a gold-nitrogen stretching vibration. Far FT-IR assignments attributed above are in agreement with data reported by Creutz's group [38]. Moreover, shifting from 790 to 798 cm^{-1} (Fig. 4A) can be assigned to adenine coordination through its N5 atom (Au-N stretching vibration).

Some stretching vibration bands corresponding to CoA's diphosphate moiety and its ether linkages were highlighted in the 900-1200 cm^{-1} region (Fig. 4B). The bands at 918, 989 and 1073 cm^{-1} were more pronounced in the complex and could be assigned to the P-O-P and P-O-H asymmetric stretching or to O-H deformation band (Fig. 4B. inset). Moreover, distinct bands were observed for the complex at 2142, 2151 and 2237 cm^{-1}. All those signals could be assigned to the symmetric stretching vibration of O-H groups of pyrophosphate moiety. Furthermore, the broad band observed in the second derivate spectra at 2464 cm^{-1} and two resolved bands noticed at 2641 and 2653 cm^{-1} corresponded to the asymmetric stretching vibration of O-H groups of pyrophosphate moiety. It should be taken into account that at pH 8, the phosphate groups are partly ionized. All the above data support the hypothesis that the diphosphate moiety undergoes significant conformational changes after gold coordination.

The bands observed in the spectrum of Coenzyme A, attributed to the S-H group, at 2560 and 2609 cm^{-1} were shifted to 2570 respectively 2612 cm^{-1} and were well defined in the complex [39].

Some spectral shifts were also determined in the 3100-3300 cm^{-1} region. Thus, a set of signals assigned to CoA were distinguished at 3120, 3130, 3139 and 3174 cm^{-1}. These peaks were slightly shifted to 3118, 3127, 3138 and 3173 cm^{-1} in the complex. More defined bands at 3224, 3232, 3266, 3277 and 3290 cm^{-1} were observed in the complex. These signals correspond to symmetric and antisymmetric N-H stretching vibration characteristic for associated amides. However, the amide I band (C=O stretching vibration) distinguished in free CoA declined slightly (1654 and 1669 cm^{-1}) in the complex. Simultaneously, a new band arose at 1225 cm^{-1} and signal intensity at 1252 cm^{-1} diminished (amide III band; N-H bending and C-N stretching along with deformation vibrations) [40]. All above data indicate that a number of small structural changes occur at the level of CoA's amide group(s) in the presence of gold ion.

Mass spectrometric analysis

In all mass spectra, CoA was denoted as H_3CoA for easy assignment of signals; the singly charged molecular ion at m/z 768.15 was assigned to Coenzyme A molecular ion ($[H_3CoA+H]^+$. Furthermore, in the mass spectra, peaks corresponding to singly charged lithium or potassium adducts of Coenzyme A ($[H_3CoA+Li]^+$ and $[H_3CoA+K]^+$ at m/z 774.14 and 806.05), respectively were also observed.

In order to determine the stoichiometry of the complex formed between the CoA and gold ions, a solution of CoA:$AuCl_3$ (molar ratio 1:1) in ammonium acetate buffer was analysed by mass spectrometry. Surprisingly, in addition to the signal corresponding to the gold containing complex, three different signals were detected that were attributed to singly charged protonated species of free thiocoenzyme A ($[H_3CoASSH+H]^+$, m/z 800.27) and its corresponding adducts with Na^+ and K^+ $[H_3CoASSH+Na]^+$, m/z = 822.25 and ($[H_3CoASSH+K]^+$, m/z = 838.16 (Fig. 5, Panel A). A similar result was earlier reported by Murray et al. [41]. In the recorded mass spectrum, characteristic peaks for both free CoA and CoA-gold complex with the stoichiometry 1:1 ($[H_3CoA+Au(I)]^+$ at m/z 964.09) were identified. Thus, singly charged gold-attached coenzyme A $[H_3CoA+Au(I)]^+$ ions were unambiguously detected by mass spectrometry. Furthermore, a weak signal at m/z 999.96 suggests that an intermediate compound $[H_2CoA+Au(I)+Cl+H]^+$ is formed. The reduction of Au(III) to Au(I) is not surprising. In a recent study, it has been shown that human angiotensin I peptide may form various complexes in the presence of Au (III), where gold ions are in a single or both oxidation states. However, in that report, singly, doubly and triply charged species were detected [42]. It is important to mention that this decapeptide has more peptidic moieties, a higher molecular weight and no cysteine residue to facilitate a complete gold reduction. The thiol group of CoA may confer an advantage in this process. Thus, we can not exclude the formation of a mixed gold (I) bisulfide (a brown colour was observed) during reaction. Furthermore, another weak signal at m/z 962.07 ($[HCoA+Au(III)]^+$ (Fig. 5, Panel B) was noticed. In this situation, two protons were expelled from the ligand (from thiol, respectively adenine) and most probably two new bonds (Au-S and Au-N) were formed. While Au(III) was found in tetra- or hexa-coordinated complexes, Au(I) complexes are linear or tetrahedral. In this respect, ionized phosphate and pyrophosphate groups and amides moieties of CoA could be essential to complete the gold coordination sphere.

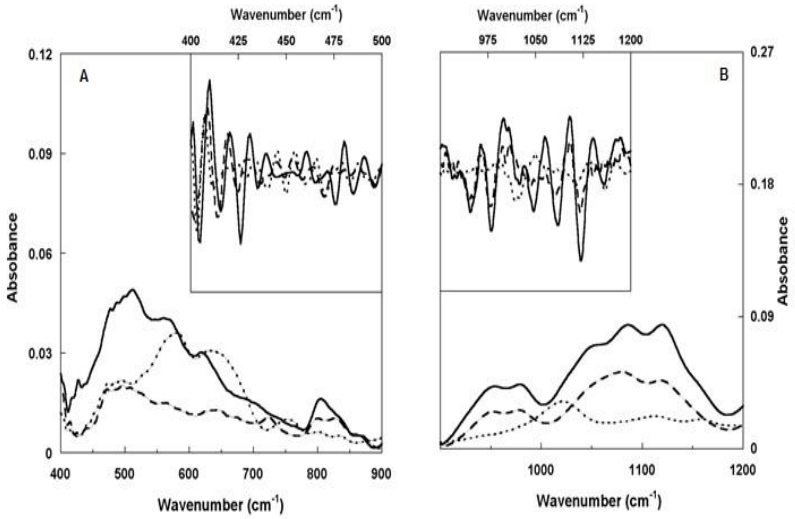

Fig.4. FT-IR spectra of free ligand (0.75µmol, dashed line), free Au(III)(10 equivalents, dotted line) and their complex (solid line). All reactions were performed in Tris 9 mM, pH 8. (A) 400-900 cm^{-1}; (B) 900-1200 cm^{-1}; Insets: second derivate spectra

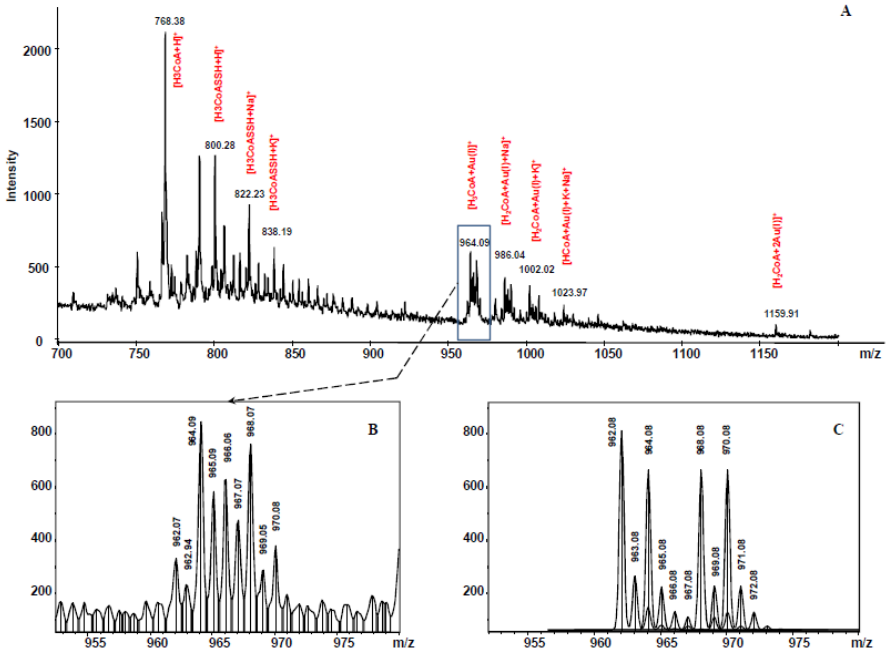

Fig.5.ESI-mass spectrum (positive ion mode) of CoA complexes with Au(III). (A) Full ESI-MS spectrum; (B) Au-CoA complex (m/z 964.09) experimental data; (C) Au-CoA complex (m/z 964.08) - simulated data.

In addition to this signal, two peaks corresponding to Na^+ and K^+ adducts of the gold (I) complex were observed (m/z 986.04 and 1002.02). Moreover, a singly charged gold-double-attached ion $[H_2CoA+2Au(I)]^+$ (m/z 1159.9) was detected by ESI-MS. On the basis of these data, we can conclude that Au(III) reduction accompanies the complexation process. The results reported here are in line with our assumptions, since Au(I) is a soft metal ion, possessing an electron configuration ($[Xe]4f^{14}5d^{10}$), and a remarkable thiophilicity.

Effect of CoA on Au(III) cytotoxicity

Yeast cells have the ability to immobilize Au(III) ions and reduce them to Au(0) in the peptidoglycan layer [43].The lethal doses of Au(III) on yeast cells are in millimolar range (0.2-1.5 mM) [44, 45].Our study on *Pichia pastoris* system demonstrated that even at 0.5 mM Au(III) concentration, the survival was moderate (about 20%) and slightly lowered at 1.5 and 2.5 mM. However, in the presence of CoA (stoichiometric amount), the toxicity was drastically impaired (Fig.6). An excess of Au(III) ions (3:1 or 5:1) increased the amount of the complex and decreased the free CoA concentration inside the *Pichia* cells. Since CoA is an important hybrid molecule for cell metabolism and division, its concentration can be well correlated by following microorganisms growing profile or their optical densities at various incubation times. These results are in agreement with our spectroscopic studies suggesting a moderate affinity of CoA for gold ions.

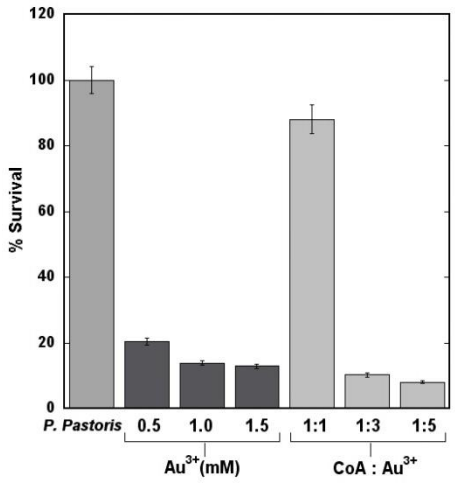

Fig.6. Effect of Au(III) on *P.Pastoris* cells (SMD1168H) in the absence (dark bars) and presence of CoA (lighter bars; the CoA (0.5 mM) and 1, 3 and 5 equivalents Au(III) were used).

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КООРДИНАЦИОННИ ОТНАСЯНИЯ НА КОЕНЗИМ А СПРЯМО ЗЛАТНИ ЙОНИ: СПЕКТРОСКОПСКИ, МАС-СПЕКТРОМЕТРИЧНИ И МИКРОБИОЛОГИЧНИ ИЗСЛЕДВАНИЯ

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(Резюме)

Взаимодействието на коензим А (CoA) със златни йони е изследвано при различни pH-стойности с помощта на UV-*Vis u* FT-IR-спектроскопии, както и с електро спрей-йонизационна мас-спектрометрия. Освен това е изследвана защитната роля на CoA срещу индуцираната токсичност на златните йони спрямо *Pichia pastoris.* За пръв път са показани слаботе комплекси CoA-Au(I) при стехиометрично отношение 1:1 при физиологични стойности на pH. Процесът на комплексообразуване е придружен от редукция на златото и силно зависи от реакционната среда. Тио-коензимът А е идентифициран чрез мас-спектрометрия като страничен продукт на реакцията.