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Investigating the Prospect of Copper-Histidine Complex Modified Gold Electrode for Histidine and Human Serum Albumin Recognition

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Abstract

Histidine monolayer was adsorbed on the surface of the gold electrode and further tailored with Cu^{2+} cation with the aim to investigate adsorption of histidine (His) and human serum albumin (HSA). Formation of the layer on the surface of the gold electrode was confirmed with quartz crystal microbalance. Binding of the His and HSA onto the modified electrode was successfully done for a wide range of tested concentrations. Electrode response was linearly proportional to the concentration of His and HSA with the correlation coefficients R^2 = 0.9895 and R^2 = 0.9952 respectively.

Keywords: gold electrode, copper, histidine, human serum albumin, quartz crystal microbalance

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Introduction

Histidine (His) is an essential amino acid for humans[1] and has a significant role in metabolism and wide range of physiological processes[2], and measuring His concentration is of outmost importance. Analytical methods have been developed for the determination of histidine, such as chemiluminiscence[3], high pressure liquid chromatography[4], capillary electrophoresis[5], potentiometric[6], and recently, amperometric[7] method. However, expensive instrumentation, large sample volumes and use of eco-unfriendly solvents present disadvantages of these techniques.

Human serum albumin (HSA) is the most abundant serum protein[8]. Spectrum of its functions in human physiology ranges from the preservation of the colloid osmotic pressure and binding and transportation of a large number of ligands[9]. Ligands that bind to HSA are of endogenous and exogenous origin such as bilirubin, long chain fatty acids, numerous pharmaceuticals and inorganic ions[10]. One study revealed the catalytic function and pleiotropic properties of HSA[11]. HSA is used as a therapeutic agent and its primary function is in restoration and maintenance of blood volume in situations that cause blood loss and plasma exchange[12]. Furthermore, it is used as a stabilizing agent in vaccine formulations[13]. Recent studies have demonstrated that HSA binds to variety of organic pollutants and toxins such as triclosan[14], atrazine[15], ochratoxins[16], methyl parathion[17] and poncean S[18], having a significant impact on human health. Methods for determination of HSA concentration have been developed. Routine analysis includes binding to anionic dyes, bromocresol green[19] and bromocresol green purple[20], electrophoresis[21] and spectrophotometric COBAS method[22]. Drawbacks of these methods include eco-unfriendly dyes and expensive instrumentation. Without doubt, investigating binding mechanism of His and HSA to various ligands, as well as improving the measurement techniques, stands out as an important research field in terms of human health.

Adsorption of histidine to the gold surface has been thoroughly investigated. Liedberg et al.[23] concluded that histidine coordinates to gold over one oxygen of the carboxyl group while Marti et al.[24] suggested that the both oxygen atoms of the carboxyl group coordinate to gold. Whatever the case, other parts of histidine, i.e. amino group and imidazole nitrogen atom, are available for further metal cation complexation. Research of copper(II)-histidine complexes has been done in detail[25-27] and the structure was well established. Histidine and Cu^{2+} cation can form multidentate complexes[28-31]. Coordination number for copper(II)-histidine complex can be 1 or 2. Higher stability was determined for 2:1 histidine to copper ratio[32]. This capability of Cu-His (1:1) complex to produce a stable complex in coordination with another histidine and human serum albumin was tested in this study.

Quartz crystal microbalance (QCM) is a sensitive weight measuring device based on the piezoelectric effect. Sauerbrey first recognized the possibilities in application of QCM technology[33] and from then on QCM was used for numerous objectives.

In the present work we investigated the formation of His layer further modified with Cu^{2+} cation on the surface of the gold electrode (AuQCM/His/Cu^{2+}). Considering that histidine and histidine rich native proteins have a strong affinity to transition metal ions, the binding His and HSA was investigated with QCM on the prepared surface.

Materials and Methods

Chemicals and solutions

All the reagents used were of analytical grade. L-histidine (His) and human serum albumin (HSA) were obtained from Sigma-Aldrich (St. Louis, USA). 0.1 M acetate buffer containing 0.1 M sodium perchlorate pH = 4.6 (AB) was used. Acetic acid, sodium acetate, copper(II) nitrate and sodium perchlorate were from Kemika (Zagreb, Croatia). All the solutions were prepared with deaerated double deionized water from Millipore-MilliQ system (USA).

Preparation of AuQCM/His electrode

5 mHz AT-cut quartz crystal gold electrode (AuQCM) was purchased from Stanford Research Systems, USA. The electrode was cleaned in ethanol for 5 minutes, rinsed with ultrapure water and then immersed in Piranha solution ($V(H_2O_2$, 30%.):$V(H_2SO_4$, conc.) = 1:3) for 3 minutes.

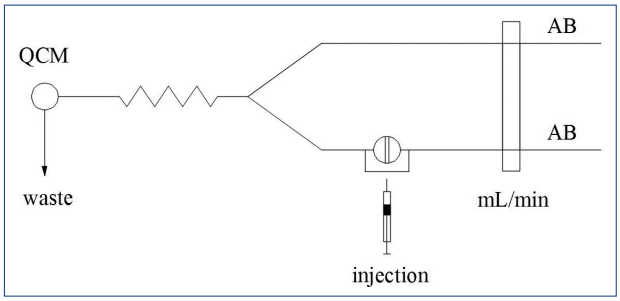

Figure 1.

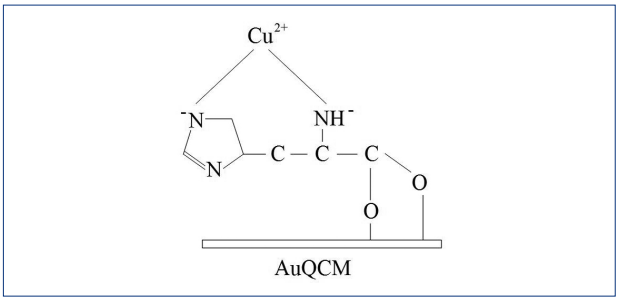

Figure 3.

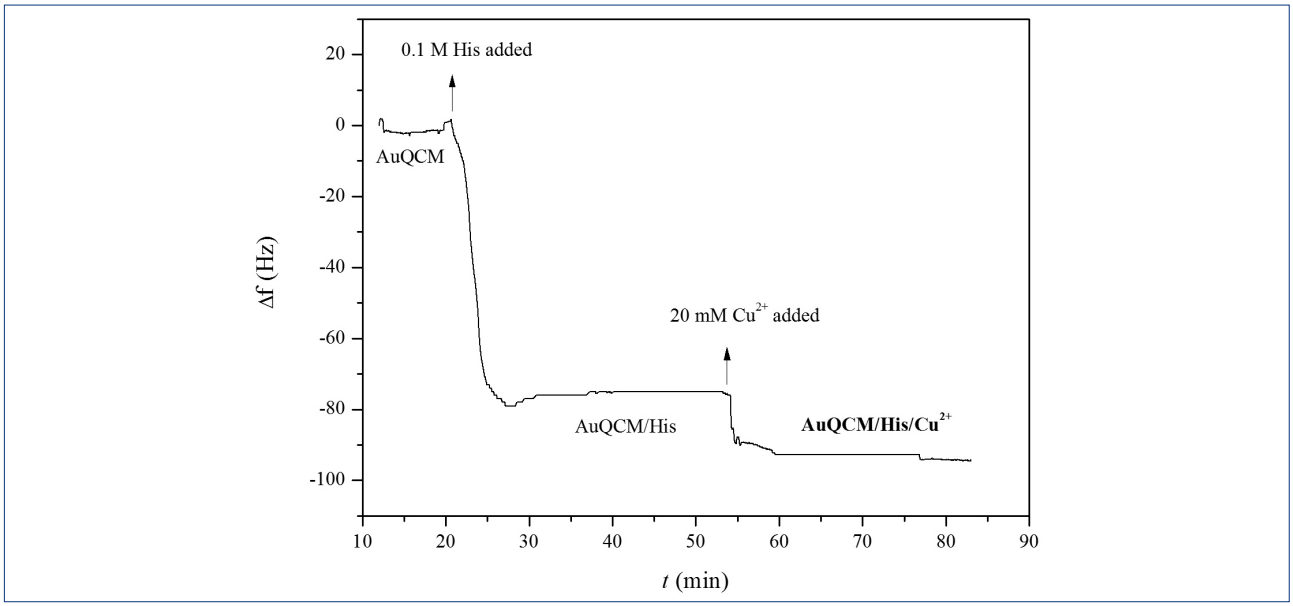

Figure 2.

Modification of the gold electrode was performed in 100 mM His water solution for approximately 2 hours at room temperature. After removal from His solution the electrode was rinsed with ultrapure water to eliminate physically adsorbed species.

Instrumentation

Quartz crystal microbalance measurement was performed on Quartz Crystal Digital Controller, QCM200 (Stanford Research Systems, USA) connected to a computer by LabVIEW. QCM measurements were performed in the flow-through system (FIA). Transportation of the carrier solution in FIA mode was made by a double tubing peristaltic pump. Sample injection into carrier stream was done by a syringe using injector valve Rheodyne Model 7125 and the sample loop of 10 µL (Figure 1).

Results and Discussion

QCM measurements were performed to describe the formation of His layer on the AuQCM electrode. The measurement (Figure 2) was performed on AuQCM gold electrode in AB (base frequency 0). Upon injection of 0.1 M His solution the change in frequency (~ 80 Hz) is evident. After 10 minutes solution of His in the measuring cell was replaced with AB. Thus that final change in the frequency (slightly less than 80 Hz) can be attributed to the His adsorbed on the AuQCM electrode. Subsequently 20 mM Cu^{2+} solution was added and additional ~ 20 Hz change in frequency is obvious (Figure 2). Figure 3 illustrates a possible attachment mode of His to AuQCM surface and complexation with Cu^{2+} result of which is the formation of AuQCM/His/Cu^{2+} surface modification.

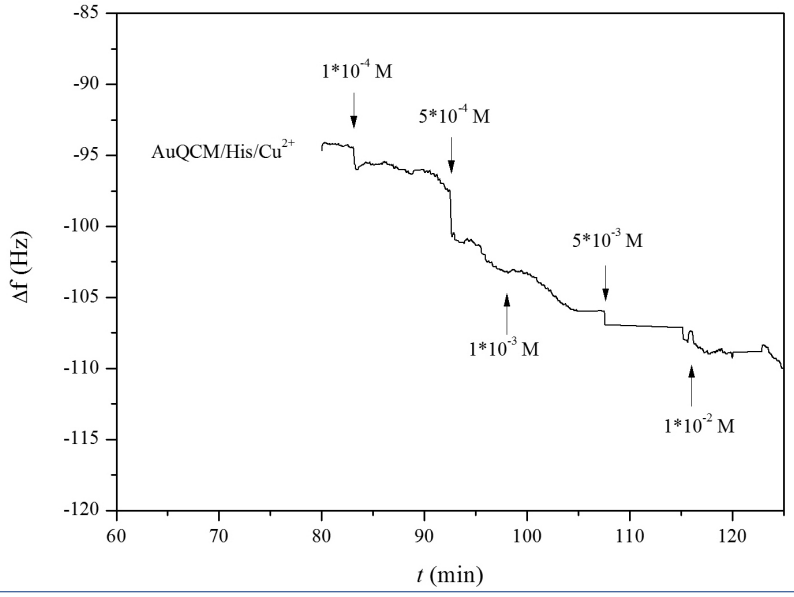

Figure 4.

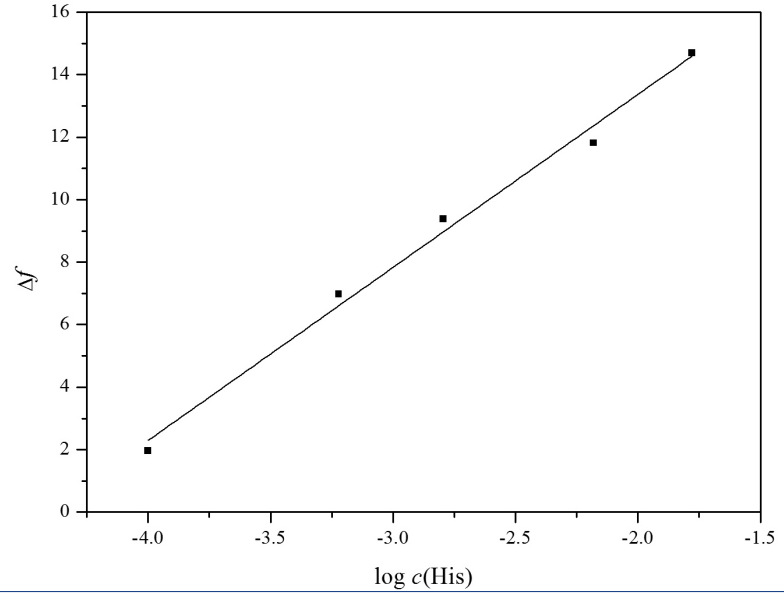

Figure 6.

It has not been established with certainty in which way His adsorbs to gold. If we assume that His binds to gold over both oxygen atoms of the carboxyl group, then Cu^{2+} can be coordinated with amino group and imidazole nitrogen.

Capability of prepared AuQCM/His/Cu^{2+} electrode for complexation of His was tested in the concentration range from 10^{-4} to 10^{-2} M. QCM measurements were performed in the flow-through system in a AB at a flow rate of 0.36 mL/min. Figure 4 illustrates time dependence of frequency change for AuQCM/His/Cu^{2+} electrode after adsorption of His. The time required to rinse the cell, i.e. to stabilize the frequency response for each individual concentration, was approximately 10 minutes. His was adsorbed onto the modified electrode cumulative from minimum to maximum concentration. FIA measurements demonstrated a small change in frequency, about 5 Hz for every His concentration. Histidine has a small molecular weight (155.2 g/mol) and for this reason only a slight change in frequency is evident. From

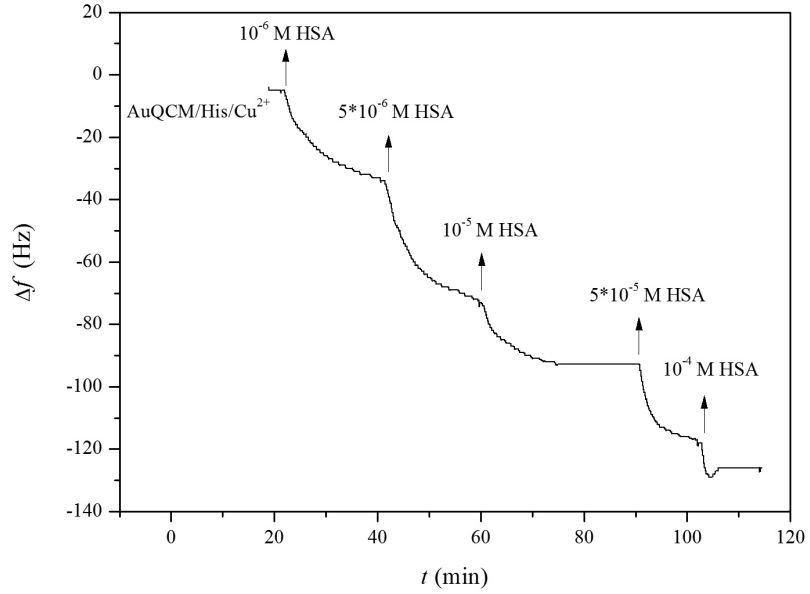

Figure 4.

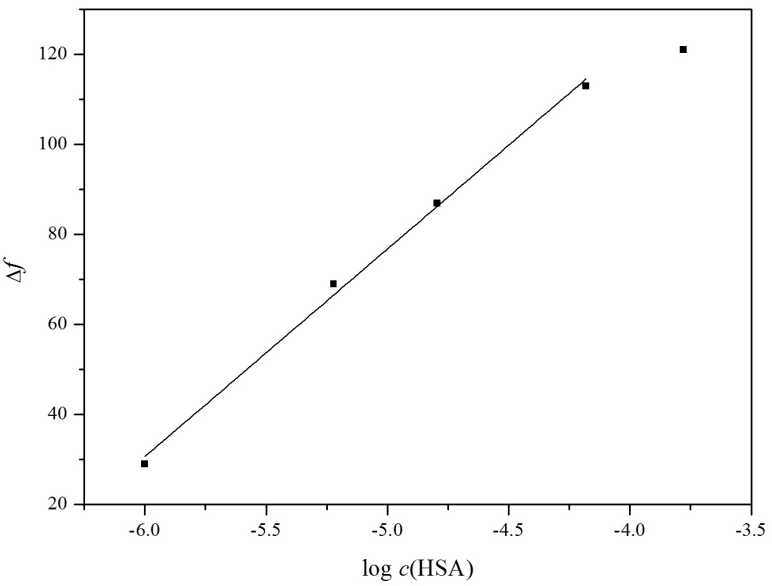

Figure 7.

FIA measurement calibration curve Df vs. log c(His) was constructed (Figure 5). The relation between Δf (Δf – difference between the base AuQCM/His/Cu^{2+} frequency in AB and every individual His addition) and log *c* (His) exhibits linear relationship and can be described by regression equation and correlation coefficient: $\triangle f = (24.44 \pm 0.82) + (5.54 \pm 0.28) \cdot \log c$ (His), $R^2 = 0.9895$. Stability constant for Cu-His complex is $pK_a = 10.1$[32] and for His-Cu-His is $pK_a = 17.5$[32] which means that the second complex is more stable hence the response (Figure 4) is due to adsorption of His onto the AuQCM/His/Cu^{2+} modified electrode. Furthermore, the ability of prepared AuQCM/His/Cu^{2+} electrode for HSA complexation was tested in the concentration range from 10^{-6} to 10^{-4} M. The measurement setup was the same as for His adsorption. Figure 6 displays time dependence of frequency change for AuQCM/His/Cu^{2+} electrode after adsorption of HSA. The time required to rinse the cell i.e. to stabilize the frequency response for each individual concentration was approximately 30 min. HSA was adsorbed onto

the modified electrode cumulative from minimum to maximum concentration. FIA measurements demonstrated a significant change in frequency, about 30 Hz for every individual HSA concentration. Human serum albumin is a molecule with large molecular weight (67 kDa) hence substantial change in frequency is obvious. Slow binding kinetics is manifested which as well can be explained with bulky protein structure and large molecular weight. From FIA measurement calibration curve Df vs. log *c* (His) was constructed (Figure 7). Relation between Δ*f* (Δ*f* – difference between the base AuQCM/His/Cu^{2+} frequency in AB and every individual HSA addition) and log *c* (HSA) exhibits linear relationship and can be described by regression equation and correlation coefficient: $\Delta f = (307.35 \pm 9.39) + (46.11 \pm 1.84) \cdot \log c$ (HSA), $R^2 = 0.9952$. Because His-Cu-HSA complex is considerably stable than Cu-HSA (p*K* (His-Cu-HSA) = 21,74, p*K* (Cu-HSA) = 15,54[34]) it can be concluded that the response (Figure 6) was the result of HSA adsorption onto the AuQCM/His/Cu^{2+} modified electrode.

Conclusion

In this research quartz crystal microbalance was used to describe interaction between gold electrode, histidine and Cu^{2+}. QCM was also employed to test the capability of the prepared modified electrode for His and HSA complexation. Complexes of transition metals with amino acids in proteins and peptides are utilized in numerous biological processes. This principle has been a model for the development of sensor for histidine and human serum albumin. Complex matrices which could be examined, like human blood or saliva, contain numerous interferents might need preparation of the sample (dilution, precipitation, filtration or centrifugation) to achieve necessary selectivity and sensitivity. The study in real samples is yet to be carried out but the proof-of-principle has been demonstrated.

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ZLATNA ELEKTRODA MODIFICIRANA KOMPLEKSOM BAKAR-HISTIDIN KAO MOGUĆA SENZORSKA POVRŠINA ZA PREPOZNAVANJE HISTIDINA I HUMANOG ALBUMINA

Sažetak

Histidinski monosloj adsorbiran je na zlatnu elektrodu i dalje modificiran kationom Cu^{2+}. Cilj je bio istražiti vezanje histidina (His) i humanog albumina (HSA) na tako pripremljenu površinu. Formiranje sloja na površini zlatne elektrode potvrđeno je kvarcnom mikrovagom. Vezanje histidina i humanog albumina na modificiranu elektrodu uspješno je izvršeno za širok raspon ispitivanih koncentracija. Dobiven je odziv linearno proporcionalan koncentraciji histidina i humanog albumina s koeficijentom korelacije $R^2 = 0,9895$ odnosno $R^2 = 0,9952$.

Ključne riječi: zlatna elektroda, bakar, histidin, humani albumin, kvarcna kristalna mikrovaga