1st International Conference
on Chemo and BioInformatics
ICCBIKG 2021

ICCBIKG

1st International Conference on
Chemo and BioInformatics

BOOK OF PROCEEDINGS

October 26-27th, 2021,
Kragujevac, Serbia

www.iccbikg.kg.ac.rs

Ministry of Education, Science and Technological Development of the Republic of Serbia

SHIMADZU
Excellence in Science

KEFO
SINCE 1949

Alfamed

UNI-CHEM

SUPERLAB
Your Lab - Our Passion

ART WINE

doi:10.46793/ICCBI21.391K

SUBSTITUTION REACTIONS OF THE MONOFUNCTIONAL GOLD(III) COMPLEX AND SULPHUR-DONOR BIOLOGICALLY IMPORTANT LIGANDS

Ana S. Kesić[1], Snežana R. Radisavljević[2], Biljana V. Petrović[2]

[1] Institute for Information Technologies
University of Kragujevac, Jovana Cvijica bb, 34000 Kragujevac, Serbia
e-mail: akesic@uni.ac.kg.rs
[2] Faculty of Science,
University of Kragujevac, R. Domanovica 12, 34000 Kragujevac, Serbia
e-mail: snezana.radisavljevic@pmf.kg.ac.rs , biljana.petrovic@pmf.kg.ac.rs

Abstract:

Gold(III) complexes have found application in catalysis, materials science and medical inorganic chemistry. Considering that the right choice of inert ligands in the structure of Au(III) complexes is crucial for their properties and reactivity toward biomolecules, we have studied the substitution reactions between monofunctional Au(III) complex, [Au(Cl-Ph-tpy)Cl]Cl_2 (Cl-Ph-tpy = 4′-(4-chlorophenyl)-2,2′:6′, 2″-terpyridine) and sulfur-donor biomolecules, glutathione (GSH) and L-methionine (L-Met), in 25 mM Hepes buffer (pH = 7.2) and 40 mM NaCl. The reactions were followed under the *pseudo*-first-order conditions as a function of ligand concentration and temperature, using the stopped-flow technique. Calculations were made by Microsoft Excel 2019 and Origin2019b 64Bit. Observed kinetics traces follow a single exponential function, suggesting that the process of the substitution undergoes as one reversible step. Also, L-Met was more reactive than GSH. This order is related to the positive inductive effect of the methyl group, which increases the nucleophilicity of the thioether. According to the values of the activation parameters, the reactions follow an associative model. These results demonstrate the strong connection between the reactivity of Au(III) complexes and the structural and electronic characteristics of the biologically important ligands.

Keywords: gold(III), complex, kinetics, substitution, S-donor ligands

1. Introduction

The introduction of metal ions or metal ion binding components into a biological system for the treatment of diseases is one of the main subdivisions in the field of bioinorganic chemistry. Metal-based drugs have been broadly applied in the treatment of diseases, such as rheumatoid arthritis, diabetes, cancer, and antimicrobial agents [1,2,3]. In addition, organometallic Au(III) complexes have found wide application in catalysis, materials science, and medical inorganic chemistry [4,5,6]. Some non-platinum compounds, including gold complexes, have shown encouraging results in cancer treatment, and some of them are in various stages of clinical trials. Gold is another metal among platinum group metals that is being explored in the research of better metal-based cancer drugs. Published results also confirmed that the right choice of ligands in the structure of Au(III) complexes is crucial for adjusting their properties and reactivity. Numerous mechanistic studies strongly suggest that the interactions of Au(I)/(II)/(III) compounds with DNA molecules are not as strong as those reported for the Pt(II) and Pd(II) complexes, suggesting possible different biological pathways for cytotoxicity of gold complexes [7 - 11].

2. Material and Methods

2.1 Chemicals

Nucleophiles, glutathione (GSH) and methionine (Met) were obtained from Acros Organics. Ligand 4′-(4-chlorophenyl)-2,2′:6′,2″-terpyridine and Hepes buffer (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) were obtained from Acros Organics. The initial potassium-tetrachloridoaurate(III) complex, $K[AuCl_4]$, was purchased from ABCR GmbH & Co. KG, 98%. All chemicals were commercially available and were used without further purification. Ultrapure water was used in all experiments. The solutions of complexes and ligands for kinetic measurements were prepared in 25 mM Hepes buffer and 40mM NaCl (pH = 7.2).

2.2. Kinetic measurements

Spectral changes caused after mixing complex and ligand solutions were recorded in the range between 220–300 nm to determine the suitable wavelength at which kinetic measurements can be performed. The kinetics were monitored by the stopped-flow technique, as a change in the absorbance with time at the working wavelength under the *pseudo*-first-order conditions. The concentration of nucleophiles was always at least 10 times higher than the concentration of complex. All kinetic sequences are equipped with individual exponents for substitution reactions of the monofunctional complex [Au(Cl-Ph-tpi)Cl]Cl2. The observed *pseudo*-first-order rate constants, k_{obs}, were calculated as average from five to eight independent kinetic cycles. The temperature dependence of k_{obs} was studied at three different temperatures (288, 298, and 310K). All calculations were performed using Microsoft Excel 2019 and Origin2019b 64Bit. The data are summarized in Figure 2 and Table 1.

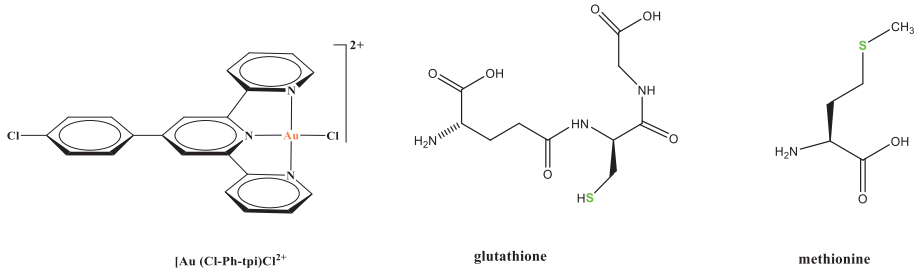


Fig. 1. Structures of the investigated Au(III) complex and studied sulfur-donor nucleophiles

3. Results and discussion

Observed kinetics traces follow a single exponential function, suggesting that the process of the substitution undergoes as one reversible step (Scheme 1). In all tested concentration ratios and at all tested temperatures, the Au(III) complex and sulfur-donor ligands react in a 1:1 ratio.

$$[\text{Au(Cl-Ph-tpy)}\mathbf{Cl}]^{2+} + \mathbf{Nu} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{Au(Cl-Ph-tpy)}\mathbf{Nu}]^{3+} + \mathbf{Cl}^-$$

Nu = GSH, L-Met

Scheme 1. Schematic representation of the substitution mechanism of the investigated complex

The observed rate constant, k_{obs}, as a function of the total concentration of the nucleophile is described by Eqn. 1[12].

$$k_{obs} = k_{-1} + k_1[Nu] \quad (1)$$

Using Eqn. 1, the rate constant for the direct substitution reaction, k_1, and the rate constant of the reverse reaction, k_{-1}, are calculated. In most cases, the values for k_{-1} was almost zero (Figure 2), which illustrates that the solvent cannot effectively replace coordinated nucleophiles. The temperature dependences of these velocity constants enabled the calculation of the enthalpy and entropy of activation using the Eyring equation. Rate constants and activation parameters derived from these experiments are shown in Table 1.

	λ(nm)	T(K)	$k_1/M^{-1}s^{-1}$	$\Delta H_2^{\neq}$/kJmol^{-1}	$\Delta S_2^{\neq}$/JK^{-1}mol^{-1}	k_{-1}/s^{-1}
[Au(Cl-Ph-tpy)Cl]$^{2+}$						
		288	$(1.06 \pm 0.03)\cdot 10^4$			$(2.2 \pm 0.5)\cdot 10^{-1}$
L-Met	280	**298**	$\mathbf{(1.19 \pm 0.04)\cdot 10^4}$	7,8 ± 0.8	-157± 3	$(5.3 \pm 0.6)\cdot 10^{-1}$
		310	$(1,43 \pm 0,04)\cdot 10^4$			$(8,4 \pm 0.7)\cdot 10^{-1}$
		288	$(9,30 \pm 0.07)\cdot 10^3$			$(5,3 \pm 0.2)\cdot 10^{-2}$
GSH	240	**298**	$\mathbf{(1,12 \pm 0.04)\cdot 10^4}$	9,8 ± 0.8	-150± 3	$(3,1 \pm 0.6)\cdot 10^{-1}$
		310	$(1,34 \pm 0,03)\cdot 10^4$			$(6,7 \pm 0.4)\cdot 10^{-1}$

Table 1. Rate constants and activation parameters for the substitution reactions of [Au(Cl-Ph-tpy)Cl]Cl_2 complex in 25 mM Hepes buffer and 40mM NaCl (pH = 7.2).

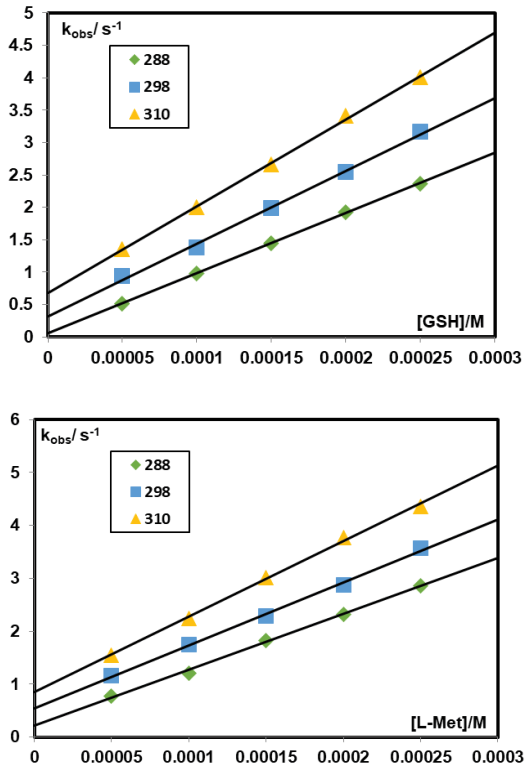


Fig. 2. *Pseudo*-first order rate constants, k_{obs}, as a function of ligand concentration and temperature for the substitution reactions between complex [Au(Cl-Ph-tpy)Cl]Cl_2 and nucleophiles in 25 mM Hepes buffer, 40mM NaCl (pH = 7.2)

4. Conclusions

Kinetic traces analyzed for individual exponentials shows that only a 1:1 complex is formed in both reaction systems. Regarding the reactivity of the examined nucleophiles, the results have shown that L-Met was more reactive than GSH. This order refers to the positive inductive effect of the methyl group, which increases the nucleophilicity of the thioether [13]. This order of reactivity is in the case of similar gold(III) complexes under physiological conditions was already published. Another main reason for this order of reactivity is the greater voluminosity of GSH compared to the L-Met ligand. According to the values of the activation parameters, all studied reactions follow the mechanism of associative substitution. The substitution rate constants for the feedback reaction, k_{-1}, are about 10^5 times slower than the constant for the direct substitution reaction, k_1. These results demonstrate the strong connection between the reactivity of Au(III) complexes and the structural and electronic characteristics of the biologically important ligands.

Acknowledgment: The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Agreement No. 451-03-9/2021-14/200378 and Agreement No. 451-03-68/2021-14/200122) for financial support.

References

[1] K. D. Mjos, C. Orvig., *Metallodrugs in Medicinal Inorganic Chemistry*, Chemical Reviews, 8 (2014) 4540−4563.
[2] S. Gukathasan, S. Parkin, S. G. Awuah., *Cyclometalated Gold(III) Complexes Bearing DACH Ligands,* Inorganic Chemistry, 58 (2019) 9326−9340.
[3] R. O. Omondia, S. O. Ojwacha, D. Jaganyi., *Review of comparative studies of cytotoxic activities of Pt(II), Pd(II), Ru(II)/(III) and Au(III) complexes, their kinetics of ligand substitution reactions and DNA/BSA interactions,* Inorganica Chimica Acta, 512 (2020) 119883- 119898.
[4] K. B. Huang, F. Y. Wang, X. M. Tang, Z. F. Che, Y. C. Liu, Y. N. Liu, H. Liang., *Organometallic Gold(III) Complexes Similar to Tetrahydroisoquinoline Induce ER-Stress Mediated Apoptosis and Pro-Death Autophagy in A549 Cancer*Cells, Journal of Medicinal Chemistry, 61 8 (2018) 3478−3490.
[5] R. Casado, M. Contel, M. Laguna, P. Romero, S. Sanz., *Organometallic Gold(III) Compounds as Catalysts for the Addition of Water and Methanol to Terminal Alkynes*, Journal of the American Chemical Society, 25 39 (2003)11925−11935.
[6] M. S. Messina, J. M. Stauber, M. A. Waddington, A. L Rheingold, H. D. Maynard, A. M. Spokoyny., *Organometallic Gold(III) Reagents for Cysteine Arylation*, Journal of the American Chemical Society, 140 23 (2018) 7065−7069.
[7] Casini, L. Messori., *Molecular Mechanisms and Proposed Targets for Selected Anticancer Gold CompoundsCurr,* Current Topics in Medicinal Chemistry, 11 (2011) 2647–2660.
[8] E. M. Nagy, L. Ronconi, C. Nardon, D. Fregona., *Noble metal-dithiocarbamates precious allies in the fight against cancer,* Mini-Reviews in Medicinal Chemistry, 12 (2012) 1216–1229.
[9] Ott., *On the medicinal chemistry of gold complexes as anticancer drugs,* Coordination Chemistry Reviews, 253 (2009) 1670–1681.
[10] T. Zou, C. T. Lum, C. N. Lok, J. J. Zhang, C. M. Che., *Chemical biology of anticancer gold(iii) and gold(i) complexes*, Chemical Society Reviews, 44 (2015) 8786–8801.
[11] Nardon, G. Boscutti, D. Fregona., *Beyond Platinums: Gold Complexes as Anticancer Agents,* Anticancer Research, 34 (2014) 487–492.
[12] M. L. Tobe, J. Burgess., *Inorganic Reaction Mechanisms*, Addison Wesley Longman Inc, Essex, (999) 70-112.
[13] M. D. Đurović, Ž. D. Bugarčić, F. W. Heinemannb, R. van Eldik., *Substitution versus redox reactions of gold(III) complexes with L-cysteine, L-methionine and glutathione,* Dalton Transactions, 43 (2014) 3911-3921.

1st International Conference on Chemo and BioInformatics

ICCBIKG International Conference on Chemo and BioInformatics

October 26-27, 2021, Kragujevac, Serbia

SUBSTITUTION REACTIONS OF THE MONOFUNCTIONAL GOLD(III) COMPLEX AND SULPHUR-DONOR BIOLOGICALLY IMPORTANT LIGANDS

Ana S. Kesić[1], Snežana R. Radisavljević[2], Biljana V. Petrović[2]

[1] University of Kragujevac, Institute for Information Technologies, J. Cvijica bb, 34000 Kragujevac, Serbia
[2] University of Kragujevac, Faculty of Science, R. Domanovica 12, 34000 Kragujevac, Serbia

Gold(III) complexes have found application in catalysis, materials science and medical inorganic chemistry. Considering that the right choice of inert ligands in the structure of Au(III) complexes is crucial for their properties and reactivity toward biomolecules, we have studied the substitution reactions between monofunctional Au(III) complex, $[Au(Cl\text{-}Ph\text{-}tpy)Cl]Cl_2$ (Cl-Ph-tpy = 4′-(4-chlorophenyl)-2,2′:6′, 2″-terpyridine) and sulfur-donor biomolecules, glutathione (GSH) and L-methionine (L-Met), in 25 mM Hepes buffer (pH = 7.2) and 40 mM NaCl. The reactions were followed under the *pseudo*-first-order conditions as a function of ligand concentration and temperature, using the stopped-flow technique. Calculations were made by Microsoft Excel 2019 and Origin2019b 64Bit.

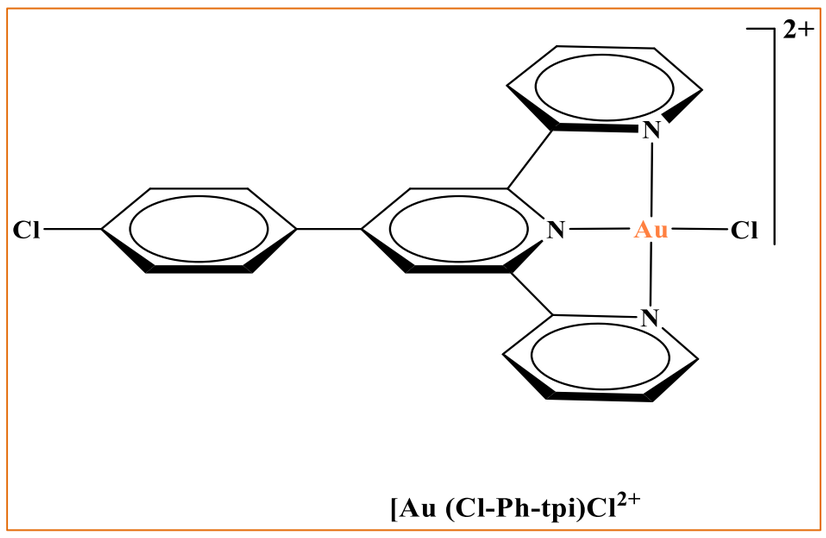
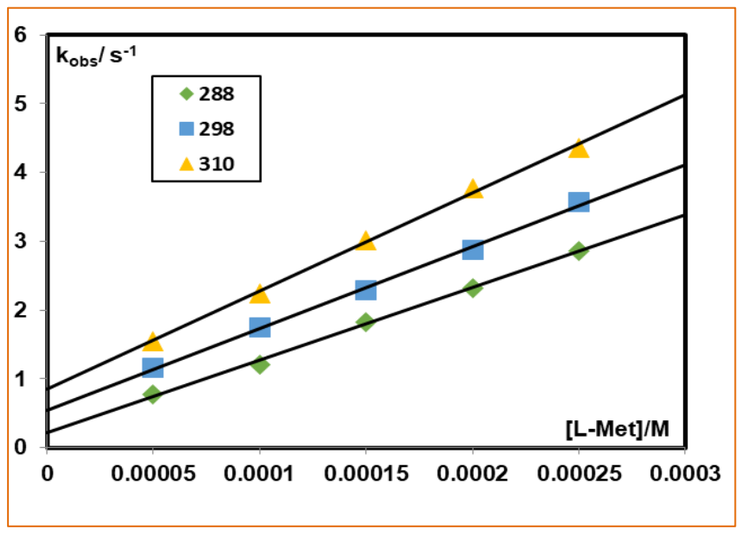


***Fig. 1**. Structures of the investigated Au(III) complex*



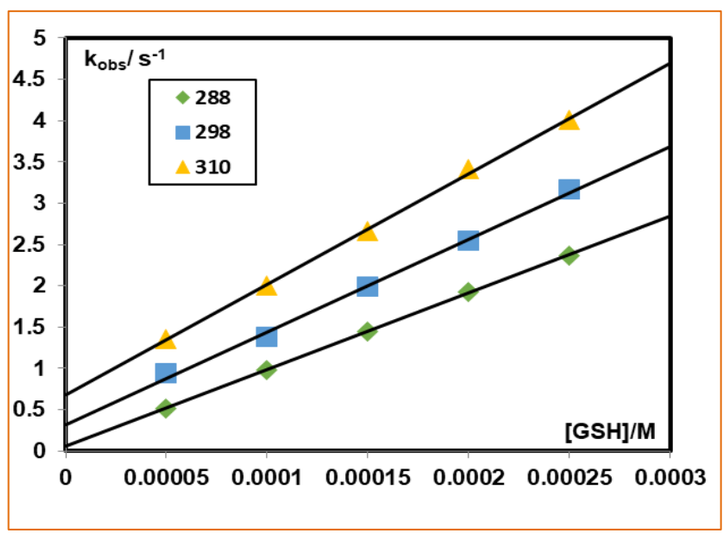


***Fig. 3**. Pseudo-first order rate constants, k_{obs}, as a function of ligand concentration and temperature for the substitution reactions between complex $[Au(Cl\text{-}Ph\text{-}tpy)Cl]Cl_2$ and nucleophiles in 25 mM Hepes buffer, 40mM NaCl (pH = 7.2)*

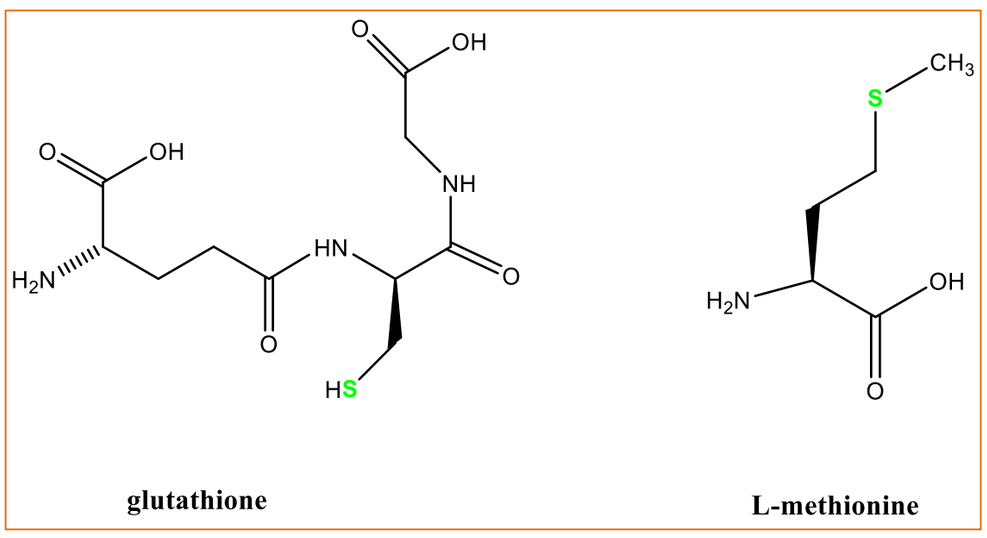


***Fig. 2**. Structures of the studied sulfur-donor nucleophiles*

Using Eqn, $\mathbf{k_{obs} = k_{-1} + k_1[Nu]}$ the rate constant for the direct substitution reaction, k_1, and the rate constant of the reverse reaction, k_{-1}, are calculated. The temperature dependences of these constants enabled the calculation of the enthalpy and entropy of activation using the **Eyring equation**

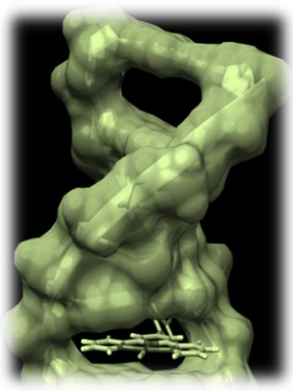
$$[Au(Cl\text{-}Ph\text{-}tpy)\mathbf{Cl}]^{2+} + \mathbf{Nu} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Au(Cl\text{-}Ph\text{-}tpy)\mathbf{Nu}]^{3+} + \mathbf{Cl^-}$$

Nu = GSH, L-Met

***Scheme.** Schematic representation of the substitution mechanism of the investigated complex*

***Table .** Rate constants and activation parameters for the substitution reactions of $[Au(Cl\text{-}Ph\text{-}tpy)Cl]Cl_2$ complex in 25 mM Hepes buffer and 40mM NaCl (pH = 7.2).*

	λ(nm)	T(K)	$k_1/M^{-1}s^{-1}$	$\Delta H^{\neq}/kJmol^{-1}$	$\Delta S^{\neq}/JK^{-1}mol^{-1}$	k_{-1}/s^{-1}
$[Au(Cl\text{-}Ph\text{-}tpy)Cl]^{2+}$						
L-Met	280	288 **298** 310	$(1.06 \pm 0.03)\cdot10^4$ $\mathbf{(1.19 \pm 0.04)\cdot10^4}$ $(1.43 \pm 0.04)\cdot10^4$	7.8 ± 0.8	-157± 3	$(2.2 \pm 0.5)\cdot10^{-1}$ $(5.3 \pm 0.6)\cdot10^{-1}$ $(8.4 \pm 0.7)\cdot10^{-1}$
GSH	240	288 **298** 310	$(9.30 \pm 0.07)\cdot10^3$ $\mathbf{(1.12 \pm 0.04)\cdot10^4}$ $(1.34 \pm 0.03)\cdot10^4$	9.8 ± 0.8	-150± 3	$(5.3 \pm 0.2)\cdot10^{-2}$ $(3.1 \pm 0.6)\cdot10^{-1}$ $(6.7 \pm 0.4)\cdot10^{-1}$



DNA connection

Protein connection

Conclusions:

- Observed kinetics traces follow a single exponential function, suggesting that the process of the substitution undergoes as one reversible step.
- L-Met was more reactive than GSH. This order is related to the positive inductive effect of the methyl group, which increases the nucleophilicity of the thioether.
- According to the values of the activation parameters, the reactions follow an associative model.
- These results demonstrate the strong connection between the reactivity of Au(III) complexes and the structural and electronic characteristics of the biologically important ligands.

Acknowledgment: The authors are grateful to the Ministry of Education, Science and Technological Development of the Republic of Serbia (Agreement No. 451-03-9/2021-14/200378 and Agreement No. 451-03-68/2021-14/200122) for financial support.