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THEORETICAL THERMOCHEMISTRY OF SIMPLIFIED METAL-CORTISOL ANTIBODY COMPLEX MODELS FOR BIOSENSORS CONTAINING METAL SUBSTRATES

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Abstract

There has been a growing interest in the measurement of cortisol as a precursor to clinically manifested events, such as post-traumatic stress disorder (PTSD) [1]. The metal-based nanomaterials using Sn, Au, Cu, Ag, Mo, etc. are surface-functionalized and integrated into the flexible electrode system with cortisol antibodies towards developing an affinity biosensor specific to the physiologically relevant range of cortisol [2-5]. For an ideal biosensor, metal-binding stability and specificity of the cortisol antibody need to be addressed. However, there has been a lack of understanding of the thermochemistry of the functionalized metal particle complexes with cortisol antibodies. Here, simplified 3-D molecular models were constructed for simple metal particle complexes produced between the terminal residue (Lys) of the cortisol antibody and metal particles functionalized with 1-mercapto-2-propanol to conduct theoretical PM7 approximations [6] in gas phases for the intrinsic thermochemical bond properties (i.e., stability and reactivity of the compounds generated). The newly obtained comparative thermochemical stability order in this study based on the obtained ΔH_f^0 for the metal-based particle complexes formed between functionalized metal particles and cortisol antibody's terminal residues was Sn-based particle complex (-2097.1567 kJ/mol) > Cu-based particle complex (-1935.0850kJ/mol) > Ag-based particle complex (-1733.1636 kJ/mol) > Au-based particle complex (-1686.2600 kJ/mol), which demonstrated an acceptable degree of stability. However, reaction enthalpies obtained showed that the reaction enthalpy to form an Ag-based particle complex with a cortisol antibody's terminal residue (ΔH_{rxn}^0 = -243.9659 kJ/mol) was the most favored than the ones of other metal-based particle complexes. This data indicates that the electrochemical cortisol immunosensor may well work most favorably with Ag-based nanocluster compound and follows the reactivity order found (Ag>Au>Sn>Cu) depending on metal particle sizes. These findings will also contribute toward new electrochemical biosensor fabrications and their applications to cortisol detections.

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Introduction

Secreted biomarkers such as cortisol, glucose, lactose, cytokine proteins, etc. enter the circulatory system and can be found in various bio-fluids such as interstitial fluid. Especially, there has been a growing interest in the measurement of cortisol as a precursor to medically and psychologically relevant events, among which the most recent distress is post-traumatic stress disorder (PTSD) [1]. Cortisol, a steroid hormone known to be implicated in acute and chronic stress, is secreted by the hypothalamic-pituitary-adrenal system [2]. It has been known as a good biomarker of psychological stress and is hence considered as the "stress hormone" [3]. If cortisol overexpression is prolonged and repeated, a disorder in the regulation of cortisol eventually occurs. Thus, a rapid point-of-care measurement to detect cortisol levels in the body can be an important diagnostic tool in everyday life, clinical settings, and during stress-intensive activities.

To detect relative variation in the body's natural fluctuations, a dynamic determination of cortisol levels is needed without the use of costly and cumbersome laboratory equipment. There is currently a small selection of portable or point-of-care diagnostic tools for the detection of cortisol. Cortisol electrochemical analysis is a non-invasive method that is potentially useful in enabling rapid measurement of cortisol levels [4]. For the detection techniques, electroanalytical techniques are preferred over other transduction methods due to increased accuracy and sensitivity with minimal instrumentation that utilizes low power sources [4]. The resulting electrochemical signal can be easily and reliably analyzed lending itself to wearable platforms that are relevant for the presented applications. For the electrochemical techniques, several nanomaterials containing metals such as Sn, Au, Cu, Ag, etc. are integrated into the electrode system as potential immobilizing matrices for immunosensor development [5,7]. These metal-based nanomaterials have been also used for the immobilization of proteins for electrochemical biosensing [7]. The metal-based nanomaterials are integrated into the flexible electrode system and surface-functionalized with cortisol antibodies towards developing an affinity biosensor specific to the physiologically relevant range of cortisol [4,5,8,9].

For an ideal biosensor, the metal-binding stability and specificity of the cortisol antibody need to be addressed. Although single-domain antibodies can retain binding specificity with improved stability, limitations should exist to sensor stability to sample acquisition in sensors and on functionalized metal surfaces [2,5,7]. Hence, it will be beneficial to obtain the functionalized metal-binding stability information of the cortisol's antibody binding site to fabricate the optimal real-time biosensor for cortisol detections.

In this study, simplified 3-D molecular models were made for metal particle complex compounds produced between terminal residues (Lys) of the cortisol antibody [10] and metal particles functionalized with 1-mercapto-2-propanol to conduct theoretical PM7 approximations [6] in gas phases for the intrinsic thermochemical bond properties (i.e., stability and reactivity of the metal complex compounds generated) to fabricate the optimal cortisol

biosensors containing metal nanomaterials. For this theoretical approach, quantum chemical 3-D molecular modeling techniques were explored for their theoretical thermochemical coordination bond properties via semi-empirical simulations to have an insight into the nano-level bonding properties [11-18].

The newly obtained comparative modeling results may well reveal the complete significant structural information and thermal biochemical reactivity of the coordinated cortisol antibody-nano-metal cluster complexes. This will not only allow for a better understanding of binding natures between functionalized metal-based particles and cortisol antibody residues but the development of optimal real-time cortisol biosensors helpful for post-traumatic stress disorder (PTSD) or fatigue management.

Experimental

The computer processor used was Intel® Core ™ i7-8650U CPU @ 1.9GHz 2.11 GHz, Installed (memory) Ram used 16.00GB, Microsoft Windows 10 Professional. The system type was a 64-bit operating system. Software programs used for semi-empirical calculations were ChemOffice® Professional version 18.0 (PerkinElmer, Inc. MA, U.S.A) for molecular modeling and theoretical calculations.

Molecular 3D models were created successfully with the right bond angles and lengths for all 1-mercapto-2-propanol-functionalized metal (Au, Ag, Cu, and Sn) particle complexes with the cortisol antibody's terminal residue (Lys) (Figure 1). Chem 3D software having Cartesian coordinates and z matrix functions was used to create the models. The molecular orbital package interface for PM7 (Parameterized Model number 7) was used for measuring the heat of formations of the targeted metal-based particle complexes having functionalized metal particles and the cortisol antibody's terminal residues (Lys) in the gas phase. The theories chosen for PM7 approximations in gas phases, were the EF (Eigenvector Following) optimizer, no solvent (gas), and default Hartree-Fock closed-shell (restricted) wave function, minimum RMS (0.1000), and shift virtual M.O. energy level of 80.

The average heat of formation values (ΔH_f^0) of all functionalized metal-based particle complex compounds were successfully obtained in the gas phase at STP with 4 measurements each. In addition, the reaction enthalpies (ΔH_{rxn}^0) of all 1-mercapto-2-propanol-functionalized metal-based particle complexes with the cortisol antibody's terminal residues were newly obtained from the heat of formations of 1-mercapto-2-propanol-functionalized metal particles, water, and the cortisol antibody terminal residue (Figure 2) with Hess's law. All molecular modeling data were treated with the chemometrics process.

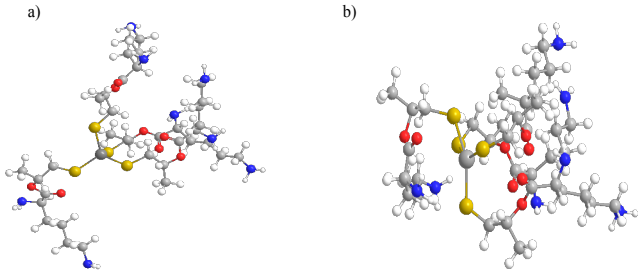

Figure 1. Representative 3-D molecular models constructed for 1-mercapto-2-propanol-functionalized Au- (a) and Ag-based (b) particle complexes with cortisol antibody terminal residues

Results and Discussion

For this study, the heat of formations (ΔH_f^0) of the cortisol antibody terminal residue (Lys) and all 1-mercapto-2-propanol-functionalized metal-based particles without cortisol antibody terminal residues were successfully obtained with the PM7 method, as shown in Table 1. Also, the heat of formations (ΔH_f^0) of all 1-mercapto-2-propanol-functionalized metal-based particle complexes with cortisol antibody terminal residues were successfully obtained, as shown in Table 2. Based on the obtained ΔH_f^0 for the functionalized metal-based particle complexes formed between functionalized metal-based particles and the cortisol antibody's terminal residue, a comparative thermochemical stability order in this study was found as follows: Sn-based particle complex

Table 1. Average heat of formations (ΔH_f^0)[a] of cortisol antibody's terminal residue (Lys) and all 1-mercapto-2-propanol-functionalized metal-based particles without cortisol antibody terminal residues.

Functionalized metal-based particles and Terminal residue (Lys)	Cortisol antibody's terminal residue (Lys)	Au-based particle	Ag-based particle	Cu-based particle	Sn-based particle
Heat of Formation (ΔH_f^0) kJ/mol	-430.7277 ± 0.0021	-715.4741 ± 0.0033	-733.6221 ± 0.0029	-1019.3103 ± 0.0035	-1151.0609 ± 0.0031

[a]Average values of four measurements

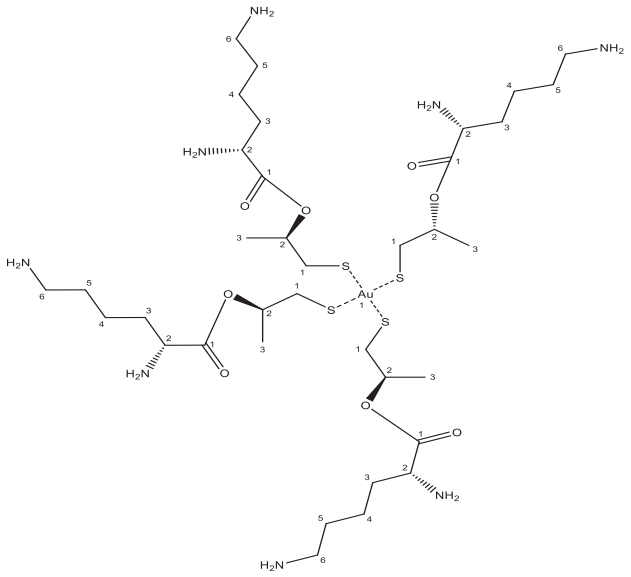

Figure 2. Representative optimized 2-D molecular model constructed for 1-mercapto-2-propanol- functionalized Au-based particle complex with cortisol antibody terminal residue for constructing a 3-D molecular model. A representative reaction equation used to form this Au-based particle complexes product: tetrakis (((R)-2 hydroxypropyl)thio)gold + 4 Lys --> tetrakis(((R)-2-((D lysyl)oxy)propyl)thio)gold + 4 H_2O

(-2097.1567 kJ/mol) > Cu-based particle complex (-1935.0850kJ/mol) > Ag-based particle complex (-1733.1636 kJ/mol) > Au-based particle complex (-1686.2600 kJ/mol), which demonstrated an acceptable degree of stability. However, reaction enthalpies calculated showed that the reaction enthalpy to form a functionalized Ag-based particle complex with the cortisol antibody terminal residue (ΔH_{rxn}^{0} = -243.9659 kJ/mol) was the most favored than the ones of other functionalized metal-based particle complexes. The obtained reaction enthalpies (ΔH_{rxn}^{0}) of other functionalized metal-based particle complexes of Au, Sn, and Cu were -215.2103 kJ/mol, -190.5202 kJ/mol, and -160.1991 kJ/mol, respectively (Figure 3). For these reaction enthalpy calculations, the heat of formation of water was approximated using the same PM7 method to obtain -241.834 ± 0.003 kJ/mol, which is in agreement with the reported values [19,20]. These data indicate that the electrochemical cortisol immunosensor works most favorably with Ag-based particle complex compound and follows the reactivity order found (Ag>Au>Sn>Cu), which will also contribute toward new electrochemical biosensor fabrications and their applications for cortisol detections.

In conclusion, all targeted 3D molecular models were successfully constructed for PM7 calculations in the gas phase. The newly obtained thermochemical stability order in this study based on the ΔH_f^0 for the metal-based particle complexes formed between functionalized metal-based particles and cortisol antibody's terminal residues is Sn-based particle complex > Cu-based particle complex > Ag-based particle complex > Au-based particle complex. However, reaction enthalpies calculated show that the electrochemical cortisol immunosensor works most favorably with Ag-based particle complex and follows the reactivity order found (Ag>Au>Sn>-Cu) (Figure 3). Simulated trends of bonding strengths of various functionalization metal atoms may well correlate with trends of bonding strengths with particles, clusters, or bulk samples of those metals. Bonding strengths may well be affected by particle or cluster size (# of atoms). These quantum chemical data will contribute toward a better understanding of functionalized metal-antibody binding properties, the development of new electrochemical biosensors, and their applications to cortisol detections helpful for post-traumatic stress disorder (PTSD) or stress management.

Table 2. Average heat of formations (ΔH_f^0)[a] of all 1-mercapto-2-propanol-functionalized metal-based particle complexes with cortisol antibody terminal residues.

Functionalized metal-based particle complex with cortisol antibody terminal residue	Au-based particle complex with terminal residue	Ag-based particle complex with terminal residue	Cu-based particle complex with terminal residue	Sn-based particle complex with terminal residue
Heat of Formation (ΔH_f^0) kJ/mol	-1686.2600 ± 0.0125	-1733.1636 ± 0.0133	-1935.0850 ± 0.0121	-2097.1567 ± 0.0143

[a]Average values of four measurements

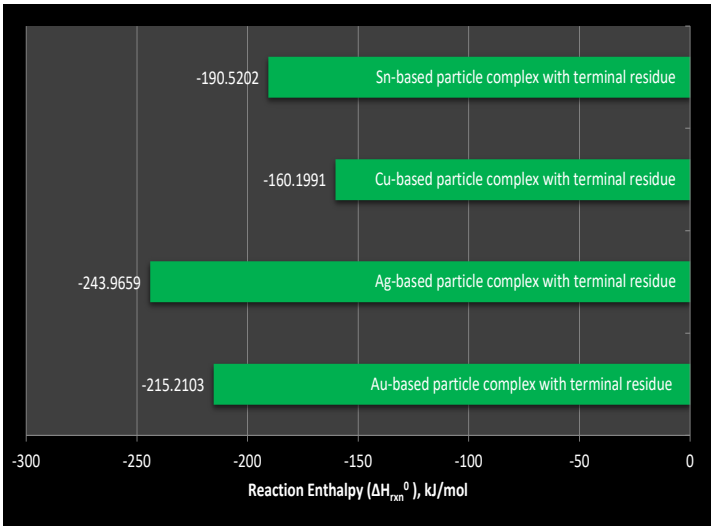

Figure 3. Reaction enthalpies (ΔH_{rxn}^{0}) obtained for functionalized metal-based particle complexes having cortisol antibody's terminal residues with reactivity order found (Ag>Au>Sn>Cu). The standard errors of ΔH_{rxn}^{0} obtained are within ± 0.0300.

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