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Docking Interaction of Chromium(III) Phenylalanine with Protein Tyrosine Phosphatase

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Abstract. Chromium(III) complexes have been known to increase insulin absorption and decrease glucose levels in the blood, so Cr(III) complexes can be used as an antidiabetic supplement especially for people with diabetes type 2. The experimentally Cr(III) complexes proven to decrease glucose level, but the role mechanism of Cr(III) complexes in the body until now there is no explain in detail. In this research, the interaction of Cr(III) phenylalanine [Cr(phe)₃] with protein tyrosine phosphatase (PTP) was studied by molecular docking. The aims this study was to identify the active site of PTP that binding with those Cr(III) phenylalanine. This research performed by computational calculations Hartree-Fock with basis set 6-31G, the interaction with PTP used the Autodock Vina software. The results showed that [Cr(phe)₃] interact with 5 amino acids of PTP, i.e Leu(13), Arg(18), Ser(94), Asp(129) and Tyr(131) with the interaction energy of -6,6 Kcal/mol. The results showed that the interaction Cr(III) phenylalanine with PTP indicate hydrogen bonding with bond length from 1,8 Å to 2,9 Å.

1.Introduction

Diabetes mellitus is a metabolic disorder that is characterized by high glucose levels in the blood. The number of diabetics is increasing, so many researchers are trying to find new drugs/supplements as antidiabetic, especially for type 2 diabetes. At present, antidiabetic-based transition metal complex compounds have been widely studied, such as vanadium(IV and V), chromium(III), and zinc(II) complexes [1]. Vanadium(IV) complexes, *trans*-bis-(ethylmalato)-oxovanadium(IV), has now reached phase II a clinical trials [2].

Diabetes is associated with insulin produced from the pancreas. There are two types of diabetes, type 1 diabetes which is caused by the pancreas not functioning properly so that it cannot produce insulin, also called IDDM (Insulin Dependent Diabetes Mellitus). Type 2 diabetes is caused by insufficient insulin produced by the pancreas but the insulin receptor cannot respond properly or is called insulin receptor defect which is also called NIDDM (Non Insulin Dependent Diabetes Mellitus) [3].

Research carried out in 1955 showed that mice that were given nutritional intake containing chromium chloride [CrCl₃], had lower blood sugar levels. The results showed that Cr(III) chloride compounds can act as glucose tolerance factors (GTF). GTF is a molecule that makes insulin work better to reduce glucose levels [4].



Research on the chromium complex (Cr (III)) as antidiabetic has been carried out by several researchers. Some Cr(III) complexes, namely Cr(III) pikolinat, Cr(III) nicotinic, Cr(III) propionate, Cr(III) histidine, and Cr(III) phenylalanine, have been tested for their potential as antidiabetic in vitro/in vivo [5]. Although it has been produced as an antidiabetic supplement, until now the mechanism of action of the chromium(III) complex has not been clearly known in reducing glucose levels.

In the GTF structure, chromium is the active component so that without central or core Cr, GTF cannot work to affect insulin [6]. The mechanism of GTF in the glucose and amino acid transport system is to increase insulin action with its specific receptors on the target organ. When insulin binds to its specific receptor, glucose and amino acids can enter the cell easily, in this case the function of GTF is to increase the effectiveness of insulin potential. The main problem in diabetics is the lack of sensitivity of insulin receptors, so that insulin does not work properly.

The presence of chromium can activate insulin receptors so that insulin in the body is more efficient and a balance of blood sugar levels is maintained. Chromium also helps digest the protein and fat [7]. Cr(III) compounds commonly used as antidiabetic supplements include chromium pikolinat $[\text{Cr}(\text{pic})_3]$, pic=pyridine-2-carboxylic, and chromium propionate $[\text{Cr}_3\text{O}(\text{OCOEt})_6(\text{OH}_2)]^{3+}$ [8].

At this time Cr(III) complex was developed with ligand amino acids as antidiabetes. The amino acids that have been researched are phenylalanine, Cr(III) phenylalanine complex shows a better reaction than Cr(III) pikolinat complex in reducing glucose levels experimentally [9].

In this research, computational studies have been carried out on the interaction of Cr(III) phenylalanine with PTP using docking method. The docking method is used to identify the type and number of amino acids PTP that interact with the Cr(III) phenylalanine complexes. The docking method is used to identify the type and number of PTP amino acids that interact with the Cr(III) phenylalanine complex. The advantage of this method is that it can determine the type of active side PTP interaction with the Cr(III) phenylalanine complex and the overall energy of the amino acids contained in PTP.

Protein tyrosine phosphatase (PTP) is a group of enzymes that function to catalyze dephosphorylation of phosphotyrosine residues through intermediate formation of transient cysteine-phosphate. The level of tyrosine phosphorylation reflects the balance of performance between PTP and PTK (protein tyrosine kinase) [10]. Based on the sequence homology and substrate type, PTP can be divided into several types, namely high molecular weight PTP, low molecular weight PTP, and PTP with varying molecular weights. High and low molecular weight PTPs have similarities in active centers, namely the CXXXXXR sequence, with C being a cysteine residue (12), arginine residual R (18), and X other residues. According to Zhang the active center of PTP are Cys(12), Leu(13), Gly(14), Asn(15), Ile(16), Cys(17) and Arg(18). The tyrosine phosphatase protein used in this study is 1Z12 type PTP taken from Bank Data Protein. This PTP has an active side of cysteine(12), glycine(14), isoleucine(16), cysteine(17) and arginine(18) [10].

2. Materials and Methods

This study consists of three stages: i) the stage of determining thermodynamic stability, which is to do computational studies of the structure of complex compounds $[\text{Cr}(\text{phe})_3]$. This stage is carried out to obtain the structure of the four complex compounds which are the most thermodynamically stable. ii) The docking phase, which is to study the interaction of $[\text{Cr}(\text{phe})_3]$ complex compounds with PTP using docking method. The results of this study aim to identify the types of amino acids in PTP that interact with $[\text{Cr}(\text{phe})_3]$ complex compounds, iii) ONIOM calculation phase, which is to study the interaction of $[\text{Cr}(\text{phe})_3]$ complex compounds with PTP using the ONIOM method. This stage aims to determine the type of interaction between $\text{Cr}(\text{phe})_3$ and PTP.

The software used in this study is the December 2012 version of Gaussian 09, Autodock Vina, Gauss View 5.0, Chemcraft, Yasara, Jmol, and Avogadro. The Gaussian 09 software is used for geometry optimization and calculation of the structural energy of Cr (III) complex compounds, chromate ions, and vanadate ions. Autodock Vina is used for docking calculations and Gauss View 5.0

is used to create ONIOM input files. The software of Chemcraft, Yasara, Jmol and Avogadro are used to visualize the molecular structure of Cr(III) compounds, chromate ions, and vanadate ions from geometry optimization and visualization of docking and ONIOM results.

The hardware used in this study is HPC ITB computer with 20 nodes and each node consists of 24 Intel 16 GB processor cores with the Rocks Cluster operating system.

3. Results and Discussion

3.1. The structure of the Cr (III) phenylalanine complexes

Phenylalanine is an aromatic amino acid that has a benzene ring as a side chain. Like previous histidine amino acids, phenylalanine has 2 donor atoms namely N from amines and O from carboxylates. These two donor atoms are used to bind to the Cr(III) ion to form an octahedral structure as in the following figure.

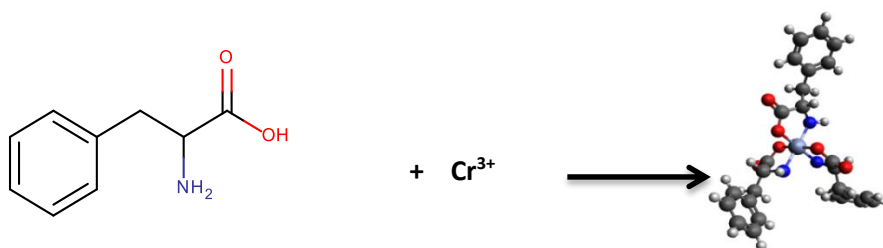


Figure 1. Optimized Cr(III) phenylalanine structure

The results of computational studies show the total energy formation value (ΔE) of complex $[\text{Cr}(\text{phe})_3]$ is $\Delta E = -2799,084 \text{ kcal.mol}^{-1}$. The value (ΔE) of menunjukkan shows the stability of the formation of complex $[\text{Cr}(\text{phe})_3]$.

Based on the geometry obtained, the complex $[\text{Cr}(\text{phe})_3]$ has an average bond length of Cr-O and Cr-N of 1.907 Å and 2.044 Å, respectively. The Cr-N bond length is greater than the Cr-O bond length, because the electronegativity of O is greater than N, the same thing as the previous Cr(III) bidentate complex, the bond length data can be seen in the following table.

Table 1. The bond lengths of Cr-O and Cr-N on the structure $[\text{Cr}(\text{phe})_3]$

No	Type of Bond	Computational bond Length (Å)
1	Cr-O1	1,881
2	Cr-O2	1,915
3	Cr-O3	1,924
4	Cr-N1	2,052
5	Cr-N2	2,058
6	Cr-N3	2,023

The calculation results on the complex $[\text{Cr}(\text{phe})_3]$ can be seen in the three values of the Cr-O bond length, which is almost the same, namely 1.9 Å, while the Cr-N bond length is slightly different. The length of the Cr-N3 bond is slightly smaller than the others, which is 2.023 Å, however the difference in the length of the 0.055 bond is still considered computationally the same. The bond length in the complex $[\text{Cr}(\text{phe})_3]$ is slightly affected by the presence of benzene groups as side chains.

The benzene group is an electron-attracting group which can affect the basic properties of amines which bind to Cr(III) ions, the presence of benzene groups causes the basic properties of amines in the complex $[\text{Cr}(\text{phe})_3]$ to be smaller. With the reduced nature of the amine in the complex $[\text{Cr}(\text{phe})_3]$ causes the bond formed with Cr(III) ion to have a greater bond length.

3.2. Docking of Cr(III) Phenylalanine Complex and PTP

Protein Tyrosine Phosphatase (PTP) is a target biomolecule used in studying the potential of a complex compound as antidiabetic. In this study docking analysis was conducted between Cr(III) phenylalanine and PTP complexes. The structure of PTP used contains amino acids as the active side, namely cys(12), gly(14), ile(16), cys(17) and arg(18) (cys = cysteine, gly = glycine, ile = isoleucine, arg = arginine). PTP is type 1Z12, which is obtained from Bank Data Protein (GDP) [10]. The following is a picture of the interaction between $[\text{Cr}(\text{phe})_3]$ and PTP.

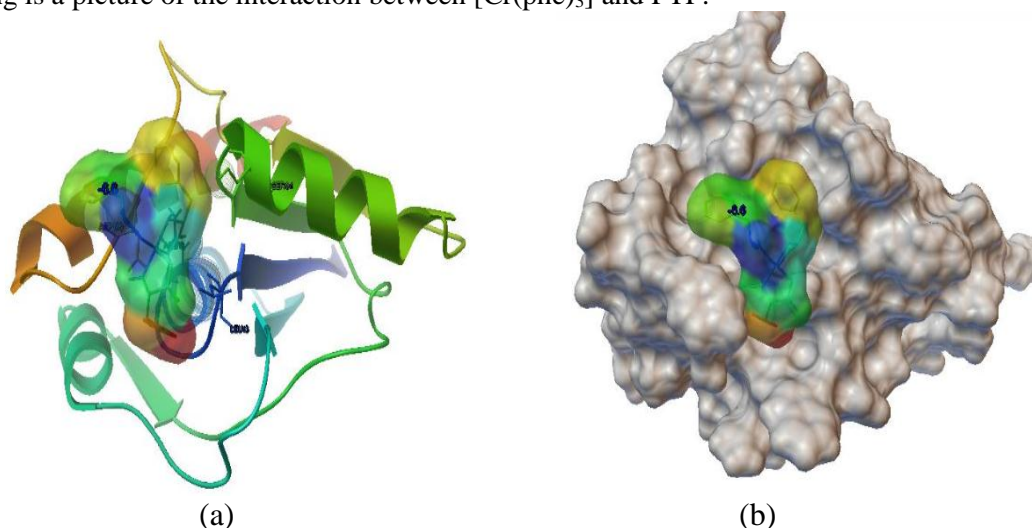


Figure 2. Interaction of Cr(III) phenylalanine with PTP

The results of interaction docking calculations occur in the amino acids Leu(13), Arg(18), Ser(94), Asp(129) and Tyr(131). Figure 2. (b) shows that most of the interactions are outside the active side of PTP, there are only 2 amino acids from the active side that interact, namely Leu(13) and Arg(18).

Based on the docking results of the $[\text{Cr}(\text{phe})_3]$ complex with PTP, shows a low interaction energy value of $-6.6 \text{ kcal.mol}^{-1}$. So it can be said that the complex can bind or interact well with amino acids from PTP. In the docking image, the interaction with the amino acids is good and the surface shape can be seen that the $[\text{Cr}(\text{phe})_3]$ complex is on the active side surface, so it can be predicted that this complex can inhibit PTP. These results are consistent with several studies which show that this complex can play a role in glucose metabolism to reduce glucose levels in the blood [8, 9]. Thus it can be predicted that what happens in the Cr (phe) 3 complex does not directly interact with PTP but changes before interacting. And interactions that occur not in Cr central atoms, but between PTP amino acids and phenylalanine ligands.

3.3. ONIOM of Cr(III) Phenylalanine and PTP

The ONIOM calculations have been carried out on the complex $[\text{Cr}(\text{phe})_3]$, in order to determine the type of interaction between the Cr(III) complex and the PTP amino acids. In ONIOM calculations the interaction of Cr(III) phenylalanine with PTP changes the shape of the complex structure $[\text{Cr}(\text{phe})_3]$ from its initial form. It is predicted that this will happen because the complex $[\text{Cr}(\text{phe})_3]$ attempts to adjust to the active side of PTP, following the picture after ONIOM calculation.

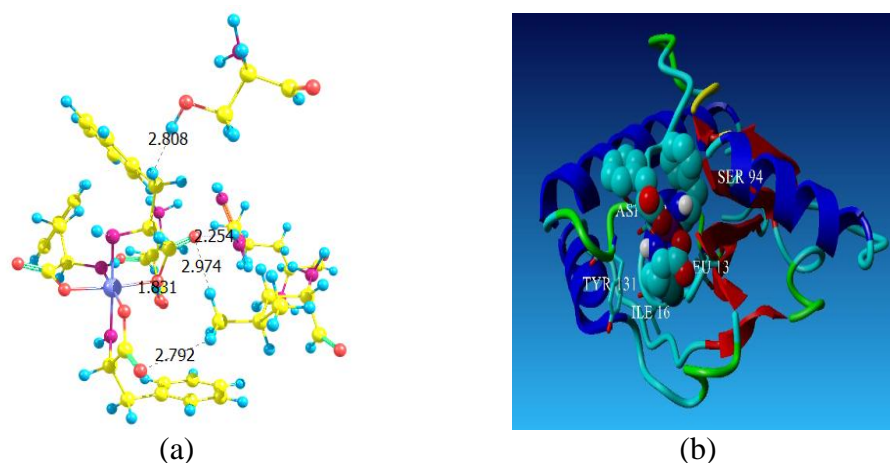


Figure 3. Identification of the interaction of Cr(III) phenylalanine with PTP

Figure 3 (a) shows the complex structure of $[\text{Cr}(\text{phe})_3]$ there is a change in shape on the benzene circumference that is more bent than the initial position of optimization. Form changes occur because the ONIOM calculation involves the effects of flexibility and flexibility of complex polarity $[\text{Cr}(\text{phe})_3]$ and PTP, the effect of this flexibility which causes a complex form to change $[\text{Cr}(\text{phe})_3]$ from complex initial forms which are optimization results.

The bond formed is the hydrogen bond between the O atom of the complex $[\text{Cr}(\text{phe})_3]$ and the H atom of PTP, there are 5 amino acids involved in this interaction and all of them contribute hydrogen bonds with a bond length of 1.8 Å to 2.9 Å. There are 2 amino acids on the active side involved and 3 amino acids are outside the active side, so that the $[\text{Cr}(\text{phe})_3]$ complex is non-inhibitor PTP.

The results of the calculation of the interaction energy $[\text{Cr}(\text{phe})_3]$ of -6.6 kcal.mol is lower than the interaction energy of chromium(III) nicotinic $[\text{Cr}(\text{nic})_3]$ of -6.4 kcal.mol [12]. This data shows that the interaction of PTP with chromium(III) complex uses amino acid ligands is better than the interaction of chromium(III) complex using synthesis ligands.

4. Conclusions

This study is modeling complex $[\text{Cr}(\text{phe})_3]$, with formation energy for complex $[\text{Cr}(\text{phe})_3]$ $\Delta E = -2799,084 \text{ kcal.mol}^{-1}$, is a very stable complex. The docking results with PTP for the complex $[\text{Cr}(\text{phe})_3]$ interact with the amino acids Leu(13), Arg(18), Ser(94), Asp(129) and Tyr(131) with an interaction energy of $-6.6 \text{ kcal.mol}^{-1}$. The bond that occurs is a hydrogen bond with bond distance of 1.8 Å to 2.9Å.

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