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Docking Interaction of Protein Tyrosine Phosphatase and Complex Chromium(III) Nicotinate Compounds

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Abstract

Docking simulation is important in the process of drug design, mainly used for the prediction of interactions receptor(protein)–substrate. This study aims to understand the interaction between Chromium(III) nicotinate $[Cr(O\text{-}nic)_2(OH^-)(H_2O)_3]$ and $[Cr(N\text{-}nic)_2(OH^-)(H_2O)_3]$ with the position of *trans* and *cis* as a substrate with receptors Protein Tyrosine Phosphatase (PTP). The chromium(III) nicotinic complexes an antidiabetic supplement that have been demonstrated *in vitro*, to determine the role of chromium(III) nicotinic as a supplement antidiabetic learned through the docking mechanism. The optimization of the complex structure of chromium(III) nicotinic using Gaussian 09, the docking process is performed using Autodock Vina. The docking results showed that *trans*$[Cr(O\text{-}nic)_2(OH^-)(H_2O)_3]$ position interact with Leu13, Gly14, Cys17, Arg18, Trp49 and Asn50 with the interaction energy is -6.5 kcal/mol. As for the structure model *cis*$[Cr(O\text{-}nic)_2(OH^-)(H_2O)_3]$ have -6.1 kcal/mol interaction energy and the amino acid Ile16, Trp49, Asn50, Arg53, Asp56 and Tyr131. The similar things at model of N-coordinated to Cr with *trans*$[Cr(N\text{-}nic)_2(OH^-)(H_2O)_3]$ position interact with amino acids Leu13, Ser47, Trp49, Asn50 and Tyr131 the interaction energy is -6.5 kcal/mol. The ONIOM calculation showed the bond between the complexes of chromium(III) nicotinic with PTP is hydrogen bonding. The best interactions with the receptor is the structure model *trans*$[Cr(O\text{-}nic)_2(OH^-)(H_2O)_3]$ with the lowest interaction energy interaction.

Keywords: *Chromium(III) nicotinate, docking, gaussian, ONIOM, PTP.*

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1. INTRODUCTION

Diabetes is one disease that can lead to death, known as the “silent killer”. The number of people with diabetes increased from year to year, based on data estimated the prevalence of Diabetes Mellitus number of diabetics in the world reached 285 million in 2010 and expected to rise to 439 million by 2030. People with diabetes in Indonesia reached 7 million in 2010 and is predicted to rising to 20 million in 2030 (Shaw et al., 2010).

Along with cases of diabetes are increasing rapidly, many researchers are working to find new supplements as an alternative for diabetics, especially for diabetes type 2. As had been widely developed additional food supplements containing chromium compounds, especially Cr(III), which is believed to be a substance of to treat type 2 diabetes (Cefalu and Hu, 2004).

The chromium(III) nicotinate is known as the antidiabetic supplement based on studies Schwarz and Mertz (1959), the isolation of yeasts and obtain compounds containing chromium(III), nicotinic acid, glutamic acid, glycine and cysteine are known as Glucose Tolerance Factor (GTF). The GTF can stimulate insulin so that it can lower glucose

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levels in the blood. Subsequent studies reported the isolation of GTF from brewer's yeast and reports that contain GTF chromium (III), nicotinic acid, glutamic acid, glycine and cysteine (Toepfer et al, 1977). Yeast isolation results conducted by Barrett, report the form of chromium(III) nicotinate is octahedral with two nicotinic ligands that are connected through the N atoms of pyridine with *trans* position, four other ligands are chloride. The same results reported by Mertz, states that the structure of the chromium(III) nicotinate is octahedral have two nicotinic acids with the N atom of pyridine bound to Cr, the other two bidentate ligands is the donor of the amino acid glycine and cysteine. Chromium(III) nicotinate is predicted to interact with a Protein Tyrosine Phosphatase (PTP) which is the insulin receptor to activate the insulin, similary with vanadat (Thompson et al, 2009). After active insulin sendS a signal to transport glucose to enter glucose from outside the cell to inside the cell, so that the levels of glucose in the blood falls. Although chromium(III) nicotinic has been widely marketed as an antidiabetic supplement, but its single crystal structure has so far not been obtained. Chromium (III) nicotinate used as a supplement in the form of a polymer.

Until now no one has experimentally succeeded in isolating the active center PTP interacting with chromium(III) nicotinate of complex compounds. Therefore, in this research, molecular modeling the interaction between of chromium(III) nicotinate of complex compounds with the active site PTP using docking methods and ONIOM. Calculations using a docking method to determine the active site of PTP interacting with chromium complex. Furthermore, the calculation is continued using the hybrid method ONIOM that include various levels of theory in its calculations but applied to atoms of different subunits in the molecule. The advantages of this method is in addition to calculating the interaction the active site of PTP with chromium(III) nicotinate complex compounds, and can know the atomic type of amino acid interacted with Cr(III) nicotinate.

The purpose of this research is studying the interaction of complex compounds of Cr(III) nicotinate with a protein tyrosine phosphatase (PTP) computationally. The results of this study were used to understand the molecular mechanisms of

complex compounds of Cr(III) nicotinate as an antidiabetic. (GTF). The GTF can stimulate insulin so that it can lower glucose levels in the blood. Subsequent studies reported the isolation of GTF from brewer's yeast and reports that contain GTF chromium (III), nicotinic acid, glutamic acid, glycine and cysteine (Toepfer et al, 1977). Yeast isolation results conducted by Barrett, report the form of chromium(III) nicotinate is octahedral with two nicotinic ligands that are connected through the N atoms of pyridine with *trans* position, four other ligands are chloride. The same results reported by Mertz, states that the structure of the chromium(III) nicotinate is octahedral have two nicotinic acids with the N atom of pyridine bound to Cr, the other two bidentate ligands is the donor of the amino acid glycine and cysteine. Chromium(III) nicotinate is predicted to interact with a Protein Tyrosine Phosphatase (PTP) which is the insulin receptor to activate the insulin, similary with vanadat (Thompson et al, 2009). After active insulin sendS a signal to transport glucose to enter glucose from outside the cell to inside the cell, so that the levels of glucose in the blood falls. Although chromium(III) nicotinic has been widely marketed as an antidiabetic supplement, but its single crystal structure has so far not been obtained. Chromium (III) nicotinate used as a supplement in the form of a polymer.

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tyrosine phosphatase (PTP) computationally. The results of this study were used to understand the molecular mechanisms of complex compounds of Cr(III) nicotinate as an antidiabetic.

2. MATERIALS AND METHODS

This research is consists of three stages: 1) The determining thermodynamic stability, which conducted a study of computing the structures of complex compounds of Cr(III) nicotinate with various models of structures. This phase is carried out to obtain the four structures of complex compounds are the most thermodynamically stable. 2) Stage docking, which conducted a study of the interaction of complex compounds of Cr(III) nicotinate with PTP with docking method. The results of this study aim to identify the types of amino acids in the PTP interacting with complex compounds Cr(III) nicotinate, 3) Phase ONIOM calculation, namely to study the interaction of complex compounds of Cr(III) nicotinate with PTP with ONIOM method. This stage aims to determine the types of atoms of amino acids that interact with the Cr(III) nicotinate complex.

The theory used was density functional theory (DFT) with B3LYP theory level at basis set 6-31G(d). The entire computational calculations performed in this study use the Gaussian 09 software version December 2012 and computer HPC ITB with 20 nodes and each nodes consisting of 24 Intel processor cores 16 GB with Rock Cluster system. The results of computational calculations were visualized by software Chemcraft, Jmol, and Avogadro. All calculation in this study does not involve solvents, all simulations performed in a gaseous stated.

The stability thermodynamic of Cr(III)-nic complexes was determined by Energy and Enthalpy values. The formation energy total of complexes (ΔE) was determined by calculating the difference between the energy of the complex to the center atomic energy with ligands in a separate state (Cramer, 2004). The negative values of energy and formation enthalpy indicate that the compounds are thermodynamically stable, the two energy parameters are defined in equations (1) and (2).

$$\Delta \boldsymbol{E} = \boldsymbol{E}_{complex} - [\boldsymbol{E}_{Cr} + \boldsymbol{E}_{nic} + \boldsymbol{E}_{OH^-} + \boldsymbol{E}H_2O] \quad (1)$$

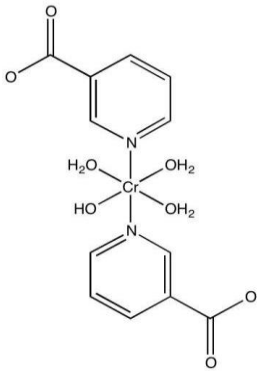
$$\Delta \boldsymbol{H} = \boldsymbol{H}_{complex} - [\boldsymbol{H}_{Cr} + \boldsymbol{H}_{nic} + \boldsymbol{H}_{OH^-} + \boldsymbol{H}H_2O] \quad (2)$$

3. RESULTS AND DISCUSSION

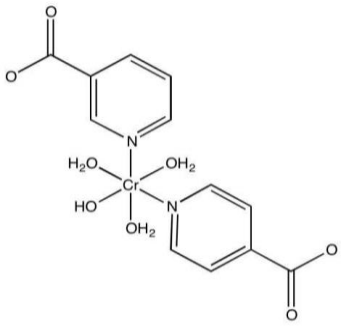
The chromium(III) nicotinate used as a model in this study has the molecular formula of $[Cr(nic)_2(OH^-)(H_2O)_3]$ according to previous research reports (Toepfer et al, 1977). Model structure of Cr(III) nicotinate made by i) variation of donor atoms N and O, ii) variations in the position of *trans* and *cis*, thus will be discussed four models of the structure of the Cr(III) nicotinate which interacts with PTP. Here are the four model of the structure of the chromium (III) nicotinic.

Figure 1 parts A and B is a complex of $Cr(N\text{-}nic)_2(OH^-)(H_2O)_3$ with the position of trans and cis, while the C and D is a complex of $Cr(O\text{-}nic)_2(OH^-)(H_2O)_3$ for the same position.

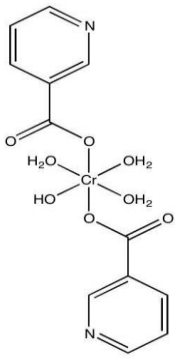
The value of formation energy for structure model A. *trans*$Cr(N\text{-}nic)_2(OH^-)(H_2O)_3$ is -1731.280 kcal/mol, while for the model B. *cis*$Cr(N\text{-}nic)_2(OH^-)\ (H_2O)_3$ is -1747.595 kcal/mol. Both are models of structures with the N atom attached to the position of Cr, while for the position of O atoms bonded to Cr, the value formation energy models C. *trans* $Cr(O\text{-}nic)_2(OH^-)(H_2O)_3$ is -1885.019 kcal/mol. Model D. *cis* $Cr(N\text{-}nic)_2(OH^-)\ (H_2O)_3$ is -1844.858 kcal/mol for formation energy values. The formation energy calculations showing the position of O atoms bonded to Cr is more stable than N atoms. The four structural models above have low energy, all of which are over -1700 kcal/mol, so the four models will be very likely to be formed experimentally. After four models optimized then continued with docking calculations and ONIOM. The docking calculations made between Cr(III) nicotinate as the substrate with the protein tyrosine phosphatase (PTP), all docking calculations aimed at the active site of PTP, which is the amino acid to 12 to 18. The type of PTP used is 1Z12, which is taken from Protein Data Bank (PDB, 2012). PTP 1Z12 was determined based on previous studies (Zhang et al, 1998), which reported an interaction between vanadate and PTP as antidiabetic.



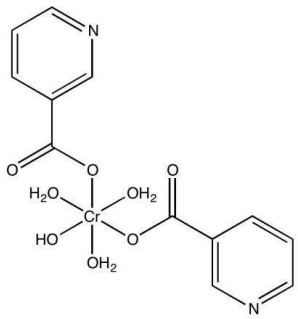
A. *trans*Cr(N-nic)$_2$(OH$^-$)(H$_2$O)$_3$



B. *cis*Cr(N-nic)$_2$(OH$^-$)(H$_2$O)$_3$



C. *trans*Cr(O-nic)$_2$(OH$^-$)(H$_2$O)$_3$



D. *cis*Cr(O-nic)$_2$(OH$^-$)(H$_2$O)$_3$

Figure 1. Variations the structure of chromium(III) nicotinate

Interactions Chromium(III) Nicotinate with PTP

The docking methods used to predict drug (substrate) the right to bind to the enzyme (protein) (Smith *et al.*, 2007). The results docking calculations show that four models of structures interacting with amino acids different. Here is a form of interaction PTP with four models of the structure. The forms of interaction docking calculation results shown in Figure 2 below.

Figure 2. (a) and (b) is a complex of chromium(III) nicotinic, with N atoms coordinated to Cr the position of *trans* and *cis*. In the structure of *trans*Cr(N-nic)$_2$ interaction with the amino acids Leu13, Ser47, Trp49, Asn50 and Tyr131, while the structure interaction *cis*Cr(N-nic)$_2$ the amino acid Ser47, Trp49, Asn50 and Tyr131. Interactions they both are outside the active site, which differs by only one amino acid in the structure *trans*Cr(N-nic)$_2$, namely Leu13 which is located on the active side. The calculation result most of the interaction occurs outside the active site of PTP, it can be predicted to model the structure of Cr(N-nic)$_2$ both *trans* and *cis* not be the inhibition of PTP, but has other properties that until now unknown.

Figure 2. (c) shows that most of the interaction at the active site of PTP, whereas (d) shows the interaction outside the active site. Both of these figures are the complex Cr(III) nicotinic with O coordinated to Cr. Figure (c) is a structure in the *trans* position that interacts with the amino acids Leu13, Gly14, Cys17, Arg18, Trp49 and Asn50. While the figure (d) in position *cis* interacts with the amino acid Ile16, Trp49, Asn50, Arg53 and Tyr131, turned out to be a structure with two ligands nicotinic the same have different interactions with amino acids of PTP. It can be concluded that the position *trans*Cr(O-nic)$_2$ have better interaction than *cis*Cr(O-nic)$_2$ position, this is similar to the model of interaction energy value that *trans* lower than *cis*.

The energy interaction value on the complex Cr(III) nicotinate is -6.5 kcal/mol for

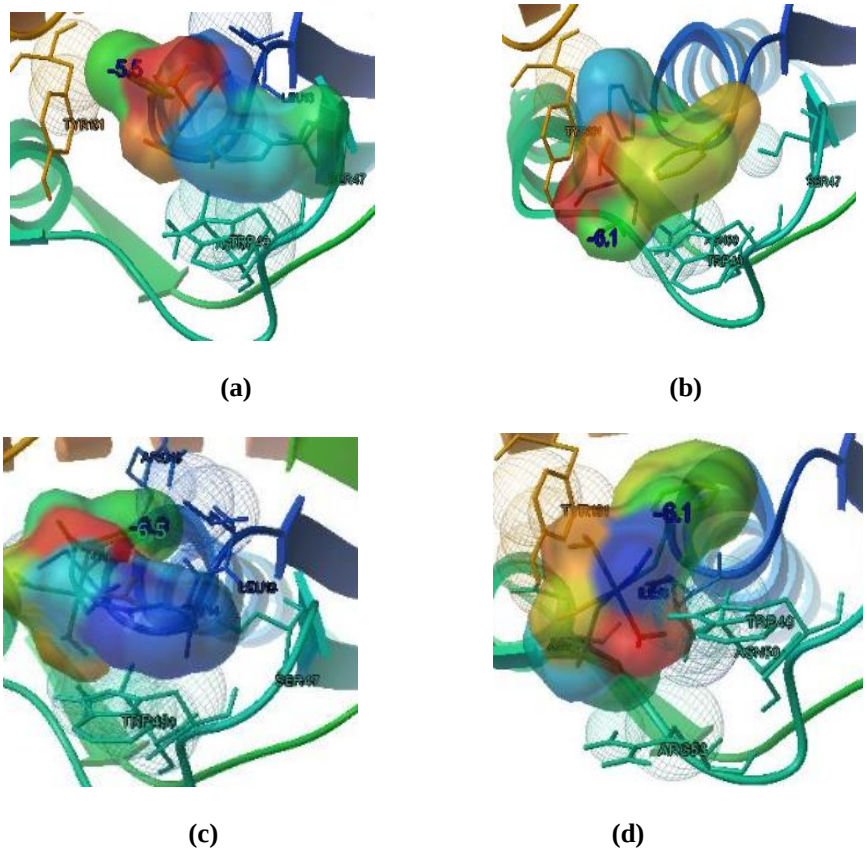
*trans*Cr(O-nic)$_2$ structure, and -6.1 kcal/mol for *cis*Cr(N-nic)$_2$. As for the structure *trans*Cr(N-nic)$_2$ is -5.5 kcal/mol and -6.1 kcal/mol for the structure of the *cis*Cr(N-nic)$_2$. Based on these data which has the lowest energy structure is *trans*Cr(O-nic)$_2$ with a value of -6.5 kcal/mol, this shows that the model of *trans*Cr(O-nic)$_2$ most stable between amino acids of PTP with complex chromium (III) with two nicotinic ligands, either N or O atom coordinated Cr.

The Identification of interaction Chromium(III) nicotinate with PTP

After being known amino acids of PTP interacting with Cr(III) nicotinate, performed ONIOM calculations to determine the bond formed in the interaction (Vreven and Morokuma, 2006). The following is the ONIOM calculation result of interaction Cr(III) nicotinic with PTP.

Table 2. Data docking calculation interaction PTP with Cr(III) nicotinate

Models	Formula Structure	Amino Acid PTP	Interaction Energy (kcal/mol)
A	*trans*Cr(N-nic)$_2$ (OH$^-$) (H_2O)$_3$	Leu13, Ser47, Trp49, Asn50, Tyr131	-5.5
B	*cis*Cr(N-nic)$_2$ (OH$^-$) (H_2O)$_3$	Ser47, Trp49, Asn50, Tyr131	-6.1
C	*trans*Cr(O-nic)$_2$ (OH$^-$) (H_2O)$_3$	Leu13, Gly14, Cys17, Arg18, Trp49, Asn50	-6.5
D	*cis*Cr(O-nic)$_2$ (OH$^-$) (H_2O)$_3$	Ile16, Trp49, Asn50, Arg53, Tyr131	-6.1



(a) **(b)**

(c) **(d)**

Figure 2. (a) structure interaction *trans*Cr(N-nic)$_2$ with PTP, (b) *cis*Cr(N-nic)$_2$, (c) *trans*Cr(O-nic)$_2$, (d) *cis*Cr(O-nic)$_2$.

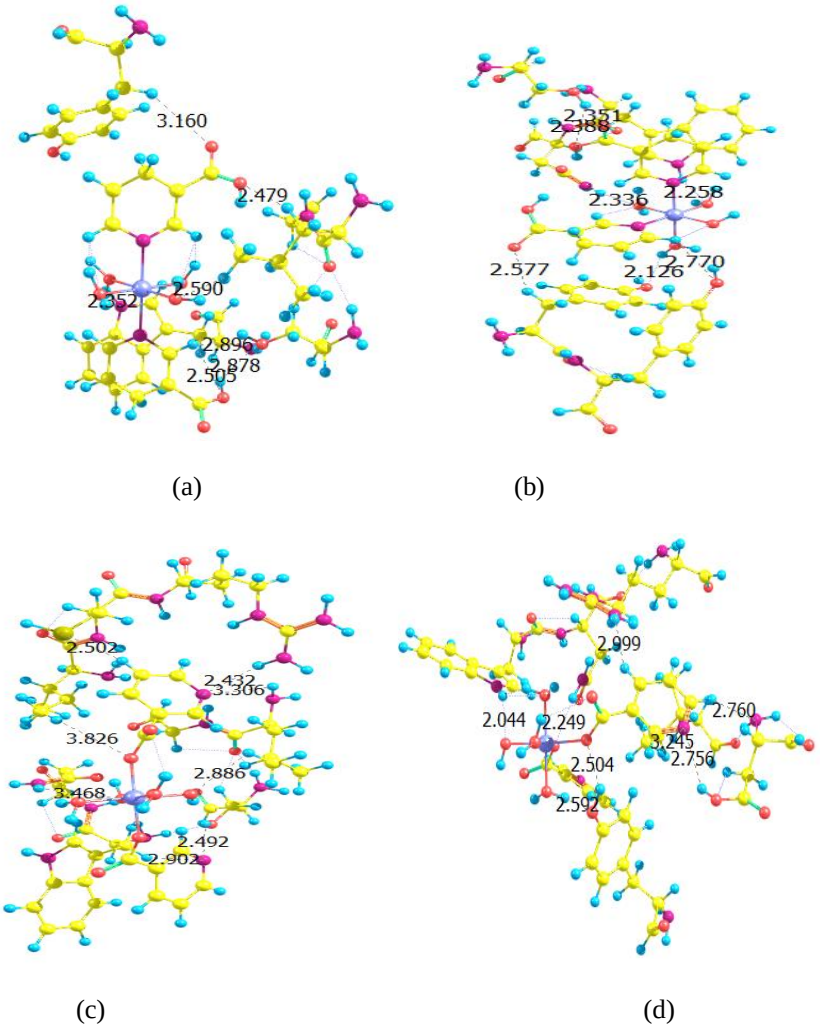


Figure 3. (a) interaction *trans* Cr(N-nic)$_2$ with amino acids, (b) *cis* Cr(N-nic)$_2$, (c) *trans* Cr(O-nic)$_2$, (d) *cis* Cr(O-nic)$_2$

The structure of *trans*Cr(N-nic)$_2$ and *cis*Cr(N-nic)$_2$ in Figure 3 (a) and (b) shows the interaction similar, all interacting with four amino acids outside of the active site, the difference in structure *trans*Cr(N-nic)$_2$ interact with Leu(13). The interaction at position *trans*Cr(N-nic)$_2$ form of six hydrogen bonds with the bond distance 2,4-3,2Å, while the position of the *cis* form of seven hydrogen bonds with a distance 2,1-2,6Å. The number of hydrogen bonds formed at the *cis* position with a shorter bond distance of *trans* position causes the interaction energy *cis*Cr(N-nic)$_2$ lower than *trans*Cr(N-nic)$_2$.

The result of the interaction of amino acids with chromium two nicotinic that is exactly the position of the active site of PTP is the structure *trans*Cr(O-nic)$_2$ in figure 3.(c) above. The bond that formed is the hydrogen bonding of atoms O and N atoms in *trans*Cr(O-nic)$_2$ with H atom of the amino acid, other than that there is a bond formed from the sulfide S atom of Cys17 with H atoms of *trans*Cr(O-nic)$_2$ at a distance of 2.5 Å bond. The types of these bonds streng then the stability of the complex interaction of chromium with PTP, so the interaction energy becomes the lowest compared with other model is -6.5 kcal/mol. This sulfide bond which became one of the characteristics of its inhibition occurred at PTP (Zhang et al, 1998). There are four amino acids in the active site that bind to the complex *trans*Cr(O-nic)$_2$ and 2 amino acids outside the active site.

While *cis*Cr(O-nic)$_2$ structure figure 3. (d) there is only one amino acid is the active site that interacts Ile(16) and five others are outside the active site of PTP. The model structure *cis*Cr(O-nic)$_2$ interaction is quite stable with six the amino acids, that the bond formed is the eight hydrogen bonding at a distance 2.0-3.2Å, the many hydrogen bonds formed causes the interaction energy becomes low at -6.1 kcal/mol, but the interaction at outside the active site of PTP.

4. CONCLUSION

The results of computational calculations indicate that the best interaction wit PTP is *trans*Cr(O-nic)$_2$ structure model with the lowest interaction energy is -6.5 kcal/mol. The bond is formed consisting of seven hydrogen bond and a sulfide bond with 2.5 Å distance.

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