Docking Interaction of Chromium(III) Picolinate and Chromate Ion Compounds with Protein Tyrosine Phosphatase as Insulin Receptors

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Abstract: The Chromium(III) compounds have been shown to reduce glucose levels in type 2 diabetics, however, the role of chromium(III) in glucose metabolism cannot be clearly explained. Based on in vitro studies, there are two opinions regarding the mechanism of the role of chromium(III), the first opinion states that the chromium(III) that enters the body directly interacts with protein tyrosine phosphatase (PTP). Second opinion, chromium(III) which enters the body undergoes oxidation to become chromium(VI), and chromium(VI) interacts with PTP. To determine the mechanism that occurs, modeling using chromium(III) picolinate as a chromium(III) complex and chromate ion as chromium(VI) interacts with PTP. The structure optimization compounds was carried out using the Hartree-Fock computation method based on the 6-31G(d). The interaction study was studied using the Autodock Vina and ONIOM methods. The interaction results of chromium(III) picolinate docking interact with Leu(13), Ile(16), Ser(47), Trp(49), Asn(50), and Tyr(131) with interaction energy of -7.00 kcal.mol^{-1}. Chromate ion interacts with amino acids Leu(13), Gly(14), Ile(16), Cys(17) and Arg(18) with an interaction energy of -4.10 kcal.mol^{-1}. The result of interaction energy of chromium(III) picolinate is lower than that of chromate ion, which indicates that the interaction of chromium(III) picolinate with PTP is better than chromate ion.

Keywords: chromium(III) picolinate, chromate ion, docking, protein tyrosine phosphatase.

1. INTRODUCTION

The research on Chromium(III) complex compounds as antidiabetic has been carried out by several researchers. Several Cr(III) complexes, namely Cr(III) picolinate, Cr(III) nicotinate, Cr(III) propionate, Cr(III) histidine, and Cr(III) phenylalanine, have been tested for their potential as antidiabetic in vitro/ in vivo [1]. Since 1980 chromium(III) picolinate [$Cr(pic)_3$] has been mass produced as an antidiabetic supplement. Supplement $Cr(pic)_3$ can increase the body's insulin sensitivity so that it helps digest sugar or carbohydrates better, which is needed for diabetics. The $Cr(pic)_3$ compounds can improve insulin performance, so that it can maintain the balance of blood sugar levels and increase the efficiency of insulin work. The Cr(III) compounds have been widely used as antidiabetic supplements, but until now the mechanism of Cr(III) in the human body is not certain. Several studies have expressed hypotheses regarding this interaction. The first hypothesis is that there is a biologically active form of Cr (III) known as LMWCr (low molecular-weight chromium), or chromodullin, which is a low molecular weight oligopeptide that binds Cr(III) [2]. The second hypothesis is that the Cr(III) complex can improve the performance of insulin receptors through the extracellular oxidation process, which then the oxidation product $[CrO_4]^{2-}$ inhibits the performance of PTP [3].

The results of an in vitro study by Vincent demonstrated the ability of the Cr(III) complex to activate PTP and PTK on insulin receptors. The proposed chromodulin mechanism occurs in the cell wall, starting from apoLMWCr (chromodulin has not yet bind to Cr(III) ion) which has not yet bound to insulin receptors in an inactive form. Insulin then binds to the insulin receptor so that it changes the insulin receptor in its active form, followed by binding of Cr(III) ions to apoLMWCr to form

chromodulin. The chromodulin that is formed then activates the insulin receptor. These activated insulin receptors can then regulate glucose levels in the blood by regulating glucose transporters [2].

The mechanism of the oxidation reaction of chromium (III) compounds in the body begins with the entry of Cr (III) ions in the form of $[CrCl_2(H_2O)_4]^+$ which undergo hydrolysis to produce $[Cr(OH)_2(H_2O)_4]^+$, in the presence of amino acids causes Cr(III) compounds to form chelate complexes with amino acids. The results of this study state a postulate that the anti-diabetic supplement in the form of Cr(III) will be oxidized to Cr(V) and or Cr(VI) before interacting with the target protein. The chelate that is formed reacts with an oxidizing agent (XO) to form a complex $Cr(L)_2(OH)(XO)$ with L being the amino acid bidentate ligand. Then the Cr(III) oxidation to Cr(V) but the presence of a biological reducing agent in the body (RH = NADPH, NADH) causes Cr(V) to be reduced to Cr(IV). In the presence of glycoproteins in the body the Cr (III) complex is oxidized to Cr(VI) to form complex $[CrO_4]^{2-}$. This complex is thought to inhibit protein tyrosine phosphatase (protein tyrosine phosphatase PTP) [4]. The results of Levina and Lay's research indicated that the Cr(VI) compound which was oxidized by the biological system was chromate ion $[CrO_4]^{2-}$. The mechanism of $[CrO_4]^{2-}$ in glucose metabolism is thought to resemble the performance of vanadate ion, $[VO_4]^{3-}$, which is capable of inhibiting protein tyrosine phosphatase (PTP). PTP inhibition can affect glucose metabolism by stimulating phosphorylation of insulin receptor tyrosine residues [4].

In this study, a modeling of the interaction between chromium (III) picolinate and chromate ion with tyrosine phosphate protein as insulin receptor was carried out.

2. Materials and Methods

Optimization of the complex structure of chromium(III) picolinate and chromate ion was calculated using quantum mechanical methods. Docking stage with protein tyrosine phosphatase using Autodck Vina with molecular dynamics method. The combination of complex compounds with protein tyrosine phosphates uses the ONIOM method, which is a combination of quantum mechanics and molecular dynamics. The software used is Gaussian, Autodock Vina, Gauss View 5.0, Yasara, Jmol, and Avogadro. Gaussian 09 software is used for geometry optimization and energy calculation of the complex compound Cr(III) picolinate and chromate ion. Autodock Vina was used for docking calculations and Gauss View 5.0 is used to create ONIOM input files. The Yasara, Jmol and Avogadro software was used to visualize the molecular structure of Cr(III) picolinate compounds and chromate ions as a result of geometry optimization and visualization of docking results and ONIOM.

3. Results and Discussion

The structure of the Cr(III) picolinate complexes

Picolinate acid is an organic molecule containing carboxylic and pyridine groups, this molecule has the potential as a bidentate ligand with two donor atoms, namely an N atom in the pyridine and an O atom in the carboxylate group. When bound with Cr(III) ion, it can form a five loop with three picolinate ligands. The structural model $[Cr(pic)_3]$ was created based on experimental data obtained in previous studies [5]. The Cr(III) complex with picolinate ligands can be seen in Figure 1**.**

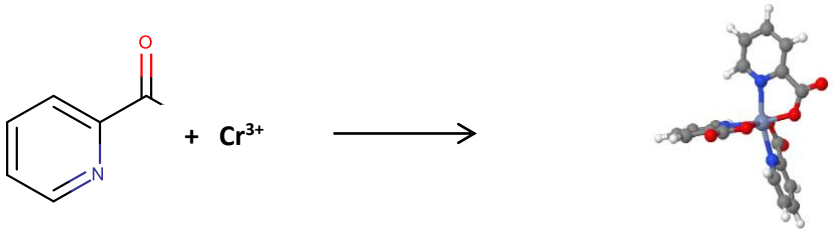


Figure 1. Optimized Cr(III) picolinate structure

The calculation result of ΔE value for complex $[Cr(pic)_3]$ -2788.649 kcal.mol^{-1}, this value indicates that the complex $[Cr(pic)_3]$ has a thermodynamically stable structure. The value of ΔE is obtained from the

difference in energy of the complex [Cr(pic)$_3$] with the total energy of 3 picolinic ligands and 1 Cr(III) ion. The structural stability of the complex [Cr(pic)$_3$] is indicated by the value of the bond length between the Cr(III) ion and the nicotinic ligand, namely the length of the Cr-N and Cr-O bonds.

Based on the optimized [Cr(pic)$_3$] structure, the average bond lengths for Cr-O and Cr-N are 1.967 Å and 2.063 Å, respectively. These results indicate that the length of the Cr-O bond is shorter than that of Cr-N, which can be explained by the electronegativity value of the O atom which is greater than that of the N atom. The bond lengths of Cr-O and Cr-N in the complex [Cr(pic)$_3$] computational results approximate single crystal data [Cr(pic)$_3$] [5]. The computational data on the bond length of Cr-O and Cr-N and single crystals are presented in Table 1.

Table 1. The lengths of the Cr-O and Cr-N bonds in the structure [Cr(pic)$_3$] computation results and single crystals

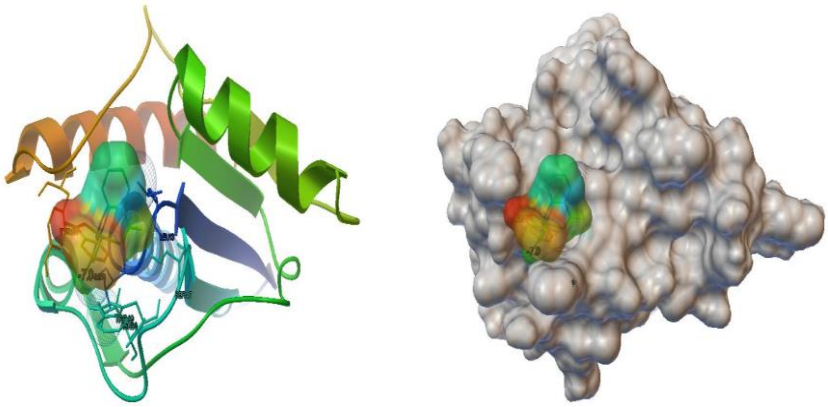
No	Bond length	Computed bond length (Å)	Single crystal data bond length (Å)	The difference
1	Cr-O1	1.971	1.957	0.014
2	Cr-O2	2.012	1.949	0.063
3	Cr-O3	1.917	1.950	0.033
4	Cr-N1	2.056	2.047	0.009
5	Cr-N2	2.054	2.053	0.001
6	Cr-N3	2.050	2.058	0.008

Based on the data in Table 1, the Cr-O3 bond length (1.917Å) is shorter than the Cr-O1 (1.971Å) and Cr-O2 (2.012Å) bond lengths. This can be seen from the Mulliken charge, which shows the electron population in each donor atom that binds to the Cr(III) ion. The Mulliken charge on the O3 atom (-0.616) is more negative than the O1 (-0.603) and O2 (-0.583) atoms. Mulliken O3 charge is more negative than O1 and O2 atoms, these data show that around O3 atoms have more electron populations, so that the interaction of O3 with Cr(III) ions becomes stronger. Mulliken charge data were obtained from the computational calculation of the structure optimization [Cr(pic)$_3$]. The results of this calculation are strengthened by the electronegativity data of O and N atoms, in theory the electronegativity values of O and N atoms are 3.44 and 3.04, respectively. Based on the electronegativity value, the O atom is more negative than the N atom [6].

Docking and ONIOM of Cr(III) Picolinate Complex and PTP

The results of docking calculations [Cr(pic)$_3$] with PTP show that the interacting amino acids are Leu(13), Ile(16), Ser(47), Trp(49), Asn(50) and Tyr(131). A small proportion of the interacting amino acids are on the active side of PTP, namely Leu(13) and Ile(16) and some others are outside the active center, namely Ser(47), Trp(49), Asn(50) and Tyr(131). This happens because complex [Cr(pic)$_3$] has a large structure as a PTP substrate, so that all [Cr(pic)$_3$] complexes cannot enter the active site. As can be seen in Figure 2, complex [Cr(pic)$_3$] is partially outside covering the active site of PTP, only one picolinate ligand is inside the active site. Amino acids that interact more occur on the outside of the active side of PTP.

The result of interaction docking calculation between [Cr(pic)$_3$] and PTP can be seen in the following figure.



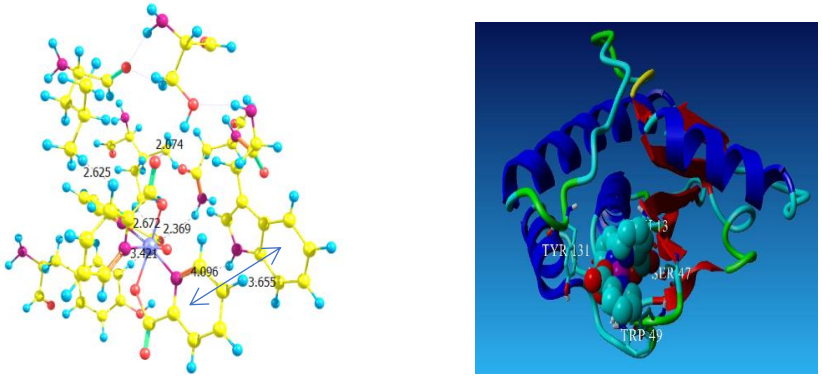
(a) (b)

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

In Figure 2. (a) PTP is depicted with a band model, amino acid interactions resulting from docking are represented by a green and blue sticks model, Cr(III) picolinate is represented by an orange, yellow and green surface model. (b) PTP is depicted with a white surface model and the orange, yellow and green Cr(III) picolinate complex is made using the PMV program.

The interaction energy [Cr(pic)$_3$] with PTP is -7.000 kcal.mol^{-1}, this value indicates that there is a good interaction with PTP. The smaller the interaction energy value, the better the interaction between protein and the substrate. The interaction energy of the [Cr(pic)$_3$] complex is lower than that of the Cr(III) nicotinate complex, which is a picolinate isomer with a monodentate ligand. The results of docking calculations show that the interaction between the amino acids PTP and [Cr(pic)$_3$] does not occur directly at the central Cr(III) atom, but occurs between the ligands and amino acids. This study shows that the [Cr(pic)$_3$] complex does not break the bond between the ligand and the Cr(III) ion, so that all interactions occur in the picolinate ligand with the amino acid PTP.

The ONIOM results for complex [Cr(pic)$_3$] show the presence of hydrogen bonding interactions between the O and N donor picolinic ligands atoms with the H atoms of the amino acid PTP. These amino acids are Leu(13), Ile(16), Ser(47), Trp(49), Asn(50) and Tyr(131). In addition, a dipole-dipole interaction was also observed between the benzene ring of the picolinate ligand and the benzene ring (amino acid Trp(49)). The ONIOM results also show the distance between the complex [Cr(pic)$_3$] and the amino acid PTP, that is, the hydrogen bonding interaction is 2.0-3.4Å and the dipole-dipole interaction is 3.6Å. The following is the calculation result of ONIOM to determine the interaction between [Cr(pic)$_3$] and the amino acid PTP.



(a) (b)

Figure 3. Identify the interaction of Cr (III) picolinate with PTP

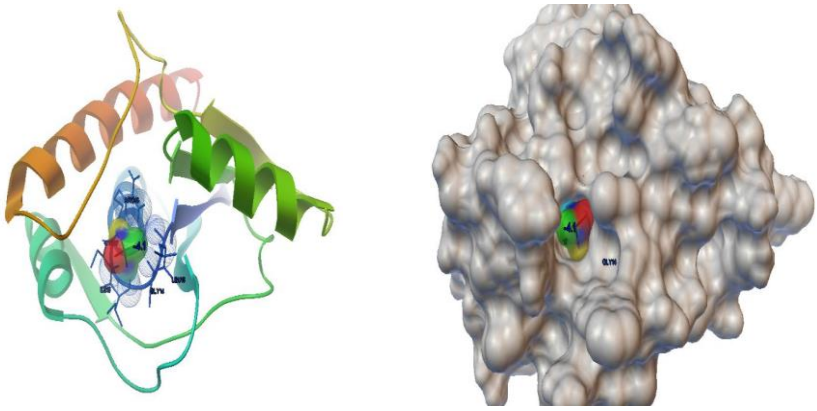
The central Cr (III) atom is represented by gray balls and sticks. The interaction of the hydrogen bond with the amino acid PTP is represented by a dashed line, the symbol ⟷ is a dipole-dipole interaction

made using the Chemcraft program. (b) PTP is represented in a band model, the interacting amino acids are shown in white, the Cr (III) picolinate complex is represented by balls. Figure (b) was created using the YASARA program.

Figure 3(a) The most interactions come from hydrogen bonds, whereas the observed dipole-dipole interactions are only one interaction, the whole interaction is the interaction between amino acids and picolinic ligands. In Figure (b) it can be seen that only one picolinate ligand enters the active site of PTP, while the other 2 picolinic ligands are outside the active site. This result is linear with the docking calculations obtained previously. This is due to the complex structure $[Cr(pic)_3]$ which is large enough, so that it cannot enter the active side of the PTP.

Interaction of Chromate Ion Complexes with PTP

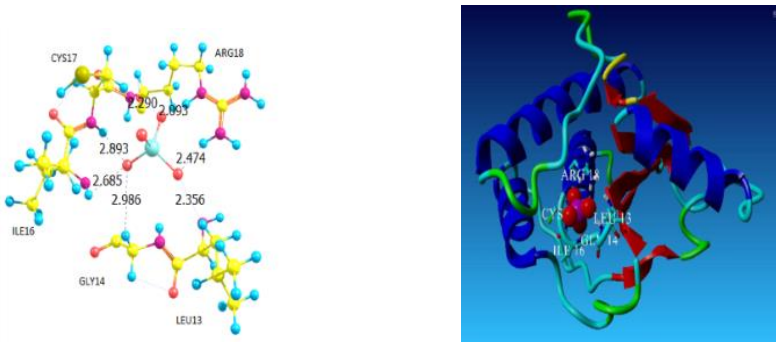
In this study the complex interaction with a smaller species, namely chromate ion $[CrO_4]^{2-}$ with PTP was also calculated. The calculations using docking show that the interaction of the ion $[CrO_4]^{2-}$ as a form of chromium (VI) is just inside the active side of PTP.



(a) (b)

Figure 4. The interaction of chromate (III) ions with PTP

The results of docking calculations show that ion $[CrO_4]^{2-}$ interacts with amino acids Leu(13), Gly(14), Ile(16), Cys(17) and Arg(18) in Figure 4. All the amino acids that interact are in the active side of the PTP bag, this data shows that there is a very good interaction in the bag. The interaction energy of the ion $[CrO_4]^{2-}$ chromate to PTP is -4,100 kcal.mol^{-1}, this value shows a good interaction between chromate ion and PTP, and the RMSD value is 0.492Å.



(a) (b)

Figure 5. Identify the interaction of the chromate ion with PTP

The results of ONIOM calculations (Figure 5) in the image above show that the interaction between the chromate ion and the amino acid PTP is a hydrogen bonding interaction. All hydrogen bonds are formed from the O atom chromate ion with the H atom from the amino acids Leu(13), Gly(14), Ile(16), Cys(17) and Arg(18). The length of the bonds formed is between 1.9Å to 2.1Å, this interaction distance is the shortest compared to the interaction distance between Cr(III) and PTP that has been discussed previously.

A short distance indicates that the interaction is very strong or so stable that it is difficult to break up. The chromate ion as a small species can interact appropriately in the active side pocket of PTP, this data is consistent with previous studies, that the vanadate ion interacts in the same place and can act as a PTP inhibitor [7]. With the same position as the active site, it can be said that the chromate ion can be an inhibitor of PTP such as vanadate. This data is strengthened by the results of the calculation of interaction energy using ONIOM. The total energy value of the interaction between chromate ion and PTP is -95.668 kcal.mol^{-1}, indicating that the chromate ion can inhibit PTP well. Based on the description above, chromate ions can interact right in the active side pocket of PTP, indicating that the chromate ion has the potential to act as a PTP inhibitor. In this research, the results of computational studies can explain the molecular interactions between PTP and the Cr(III) complex and chromate ions. The experimental results also observed that ion $[CrO_4]^{2-}$ was able to inhibit PTP performance [3]. The results of chromium(III) picolinate docking were similar to those of chromium(III) nicotinate [8] and Chromium(III) Phenylalanine [9].

4. Conclusions

The yield energy of formation (ΔE) is −2788.649 kcal.mol^{-1}, the interaction of chromium (III) picolinate docking interacts with Leu(13), Ile(16), Ser(47), Trp(49), Asn(50), and Tyr131) with an interaction energy of -7.00 kcal.mol^{-1}. The results of PTP docking with ion $[CrO_4]^{2-}$ showed that there were 4 amino acids on the active side of PTP that interacted with the ion $[CrO_4]^{2-}$ namely Leu(13), Gly(14), Ile(16), Cys(17), Arg(18). Meanwhile, the interaction energy obtained is -4,100 kcal.mol^{-1}, which is smaller than the chromium(III) monodentate and bidentate complexes. The ONIOM results showed that 6 hydrogen bonds were formed with the interaction of chromate ion with the amino acid PTP with a distance of 1.9-2.1Å, which is shorter than the chromium (III) monodentate and bidentate complexes.

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