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Study of Interaction between Complexes of Copper (II) and Melanin Pigment by Molecular Modeling

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Abstract

Tyrosinase is a metalloenzyme belonging to the group of oxidoreductase enzymes. Like many redox enzymes, copper (Cu) ion is present in its active site. We designed an *in silico* study of 8 previously reported complexes of copper, which catalyze the oxidation reaction of catechol ortho-quinone with different re-activities by calculating steric energies using EMO and Gaussian09 program. The catalytic activity of these complexes depends on several factors such as size of the side chain hydroxyl group. These interesting results could lead to new developments in synthetic biochemistry such as generating more stable conformers.

**Keywords:** Tyrosinase; Molecular modeling; Copper (II) complexes; Enzyme action

Introduction

Understanding the mechanisms of enzyme action is crucial in medical research to give appropriate therapies and help to identify individuals at greatest risk of drug interactions and adverse events [1]. Computational molecular modeling has been employed as a powerful tool to predict the events involved in molecular interactions such as molecular recognition, complexations and enzyme catalysis. Recently, Kamal and his colleagues at King Abdulaziz University started computational study of acetylcholinesterase interaction with two anti-cancer drugs, cyclophosphamide and methotrexate [2-4], while now collaborating with Ghalem and his team at University of Tlemcen on interaction between complexes of copper (II) and melanin pigment [5-9].
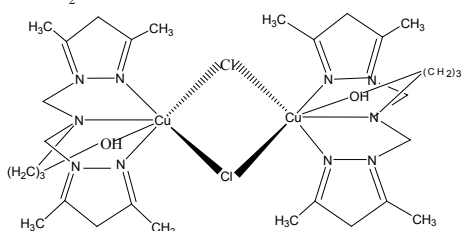
Materials and Methods

Following 8 previously reported complexes of copper have been selected for the current study:
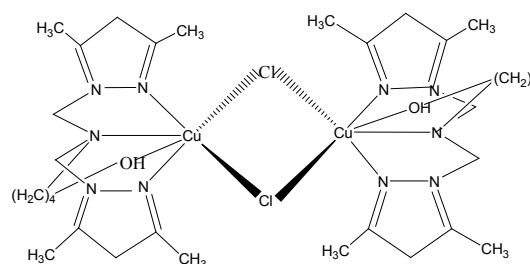
1. 2-{bis[(3,5-diméthyl-1H-pyrazol-1-yl)amino} ethanoldichlorure de cuivre (II) monohydraté: [Cu(bp1mae) Cl]$_2$,2[Cl.H$_2$O] [10-12].
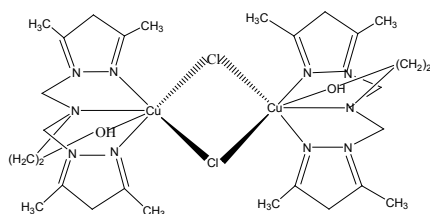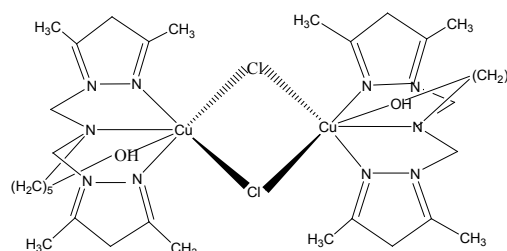

2. 2-{bis[(3,5-diméthyl-1H-pyrazol-1-yl)méthyl]amino} propanoldichlorure de cuivre (II) monohydraté: [Cu(bp1mapr) Cl]$_2$, 2[Cl.H$_2$O] [10-12].

3. 2-{bis[(3,5-diméthyl-1H-pyrazol-1-yl)méthyl]amino} butanoldichlorure de cuivre (II) monohydraté: [Cu(bp1mab) Cl]$_2$, 2[Cl.H$_2$O] [10-12].

4. 2-{bis[(3,5-diméthyl-1H-pyrazol-1-yl)méthyl]amino} pentanoldichlorurede cuivre (II) monohydraté: [Cu(bp1map) Cl]$_2$, 2[Cl.H$_2$O] [10-12].
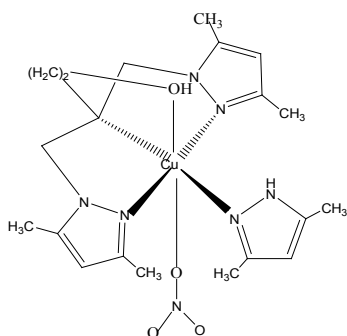

5. [N,N-bis(3,5-diméthyl-1H-pyrazol-1-ylméthyl-KN^2)-2-hydroxyéthyl-amine-KN] nitratocuivre(II)nitrate: [Cu(bp1mae)L$_0$(NO$_3$)](NO$_3$) [13-15].

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6. [N,N-bis(3,5-diméthyl-1*H*-pyrazol-1-ylméthyl-KN²)-2-hydroxypropyl-amine-KN] nitratocuivre(II)nitrate: [Cu(bp1mapr)L$_0$(NO$_3$)](NO$_3$) [13-15].
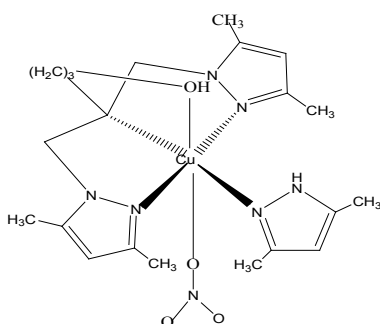
7. [N,N-bis(3,5-diméthyl-1*H*-pyrazol-1-ylméthyl-KN²)-2-hydroxybutyl-amine-KN] nitratocuivre(II)nitrate: [Cu(bp1mab)L$_0$(NO$_3$)](NO$_3$) [13,14,15].
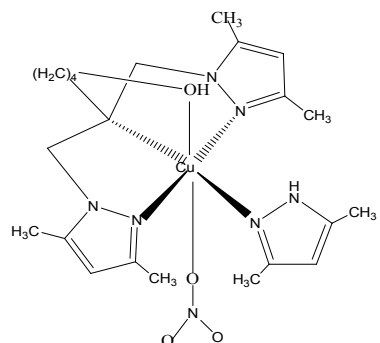
8. [N,N-bis(3,5-diméthyl-1*H*-pyrazol-1-ylméthyl-KN²)-2-hydroxypentyl-amine-KN] nitratocuivre(II)nitrate: [Cu(bp1map)L$_0$(NO$_3$)](NO$_3$) [13,14,15].

The theoretical binding energies of the above complexes were calculated using EMO (Energy of molecule) program; Version 2010 [16,17] based on the principle of force field MM2. In this relaxation method of molecular mechanical calculations, EMO uses a truncated parabolic potential, equal to -16.7 KJ per bond at the optimal distance of 1.85Aº, and to zero at 1.25 or 2.45 Aº. The program protocol includes an entry of the molecule in which atoms are codified according to its hybridization, geometric handling 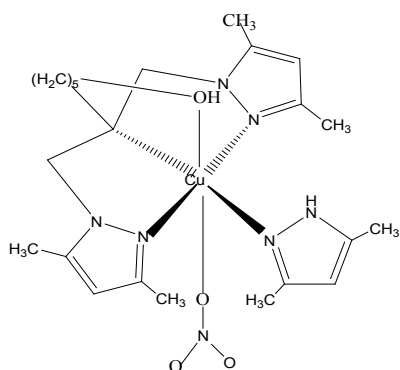of the submitted molecule and followed by energy minimization by molecular mechanics. The most stable conformation is obtained from various geometries, after optimization. In order to avoid the local minima corresponding to unstable conformers, we carried out it with the option "SCAN" which makes it possible to sweep the surface of potential energy (PES). This enabled us to eliminate the geometries having little chance to generate the most stable conformation.

Gaussian09 program [18], also used to calculate theoretical binding energies of copper complexes containing pyrazole II and to explain the influence of the length of the side chain on their stability. The data generated from EMO and Gaussian09 program has been analyzed and compared with the experimental data obtained from Mohamed Laboratory.

Results and Discussion

Influence of the lateral chain on the stability of the complexes

Chloride complexes: These complexes activate the oxidation reaction of catechol to o-quinone with different re-activities as shown by the results reported in the following table 1.

Experimental results: Rate varying from a high 2.67 µmole substrate per mg catalyst per min for n=5 complex, the catalytic activities depend strongly on the length of the lateral chains [19].

Theoretical results: In the case of anion Cl⁻ for which the complex ligands having a rather long lateral chain (4 or 5 carbon) have the lowest energy but for the chains of n=2 or 3 in this case the Cl⁻ forms the strong bonds with the cation and the oxygen of the side chain and forms a cycle of 5 or 6-chelating atoms stable [20], and find difficulties in the coordination of the substrate which explains the low catalytic activity of this type of complex. With a longer chain of 4 or 5 carbons, the cycle of chelation of 7 or 8 atoms is much less stable [20] allow the substrate to coordinate to the metal without difficulty which leads to a significant catalytic activity (Table 2).

Nitrate complex

Experimental results: Rate varying from a high concentration of

Complexes	Carbon number (n)	Catalytic activity (u) (μ mol / mg / min)
[Cu(bp1mae)Cl]$_2$,2[Cl.H$_2$O]	2	0.16
[Cu(bp1mab)Cl]$_2$,2[Cl.H$_2$O]	4	1.77
[Cu(bp1map)Cl]$_2$,2[Cl.H$_2$O]	5	2.67

Table 1: Kinetic data of Chloride complexes [19].

Complexes	Carbon number (n)	Energy (kJ / mol) EMO	Energy (KJ/mol) Gaussian
[Cu(bp1mae)Cl]$_2$,2[Cl.H$_2$O]	2	1739.83	1501.24
[Cu(bp1mapr)Cl]$_2$,2[Cl.H$_2$O]	3	2020.97	1955.47
[Cu(bp1mab)Cl]$_2$,2[Cl.H$_2$O]	4	2304.38	2090.57
[Cu(bp1map)Cl]$_2$,2[Cl.H$_2$O]	5	2709.66	2486.74

Table 2: Energies (kJ/mol) obtained using the program Gaussian09 and EMO.

0.08 μmol substrate per mg catalyst per min for the n=4 complex the catalytic activities depend strongly on both the length of the lateral chains [19] (Table 3).

Theoretical results: In light of the results for both types of complexes it was noticed that the steric energy, the energy of van der walls, the torsional energy, the strain energy and the energy of elongation increases with the number carbon of the side chain. This can be explained by the steric hindrance of this latter. Higher the carbon numbers, the more the congestion is important. According to the literature, a series of chelation of four or five-member cycle is more stable than six-member chelating itself and more stable than a seven-member chelate cycle [20]. The complex which acts as a good catalyst is the less stable and dissociate easily (Table 4).

Comparison between the Complexes of Chloride and nitrate Complexes

Experimental results (Table 5)

Theoretical results (Table 6)

Based on the results presented in the current study in the tables and figures, we observed that the nature of the anion plays a very important role. By comparing the results, we found that our two kinds of complexes have similar results as obtained by Boyd et al. [21]. We note that chloride complexes are much less stable than the nitrate complex, so the chloride complexes react better as catalysts, which explains the catalytic activity of these complexes. This factor may contribute in the explanation of the dependence of the catalytic activity of the oxidation of catechol to quinone of the anion nature (Figure 1).

Conclusion

Based on steric energies of different complexes studied, the current study demonstrated the difference in catalytic activities of 8 different complexes, which depends on the size of the side chain carrying the hydroxyl group. The complexes of ligands having a side chain rather long (4 or 5 carbons) provide a catalytic activity greater than the complex ligands of having only two carbons on the side chain. Since

Complexes	Carbon number (n)	Catalytic activity (υ) (μ mol/mg/min)
[Cu(bp1mae)L_0(NO_3)](NO_3)	2	0.01
[Cu(bp1mab)L_0(NO_3)](NO_3)	4	0.08
[Cu(bp1map)L_0(NO_3)](NO_3)	5	0.03

Table 3: Kinetic data of Nitrate complex [19].

Complexes	Carbon number (n)	Energy (KJ/mol) EMO	Energy (KJ/mol) Gaussian09
[Cu(bp1mae)Cl]$_2$,2[Cl.H_2O]	2	566,84	471,05
[Cu(bp1mapr)Cl]$_2$,2[Cl.H_2O]	3	606,25	507,28
[Cu(bp1mab)Cl]$_2$,2[Cl.H_2O]	4	676,42	631,75
[Cu(bp1map)Cl]$_2$,2[Cl.H_2O]	5	795,72	691,24

Table 4: Energies (kJ/mol) obtained using the program EMO and Gaussian 09.

Carbon number (n)	Catalytic activity (υ) of Chlorure complexe (μ mol / mg / min)	Catalytic activity (υ) of Nitrate complexe (μ mol / mg / min)
2	0.16	0.01
4	0.77	0.08
5	2.67	0.03

Table 5: Kinetic data Comparison between the complexes of Chloride and Nitrate complexes [19].

Carbon number (n)	2	3	4	5
Energy (KJ /mol) of Chlorure complexe	1501,24	1955,47	2090,57	2486,74
Energy (KJ /mol) of Nitrate complexe	471,05	507,28	631,75	691,24

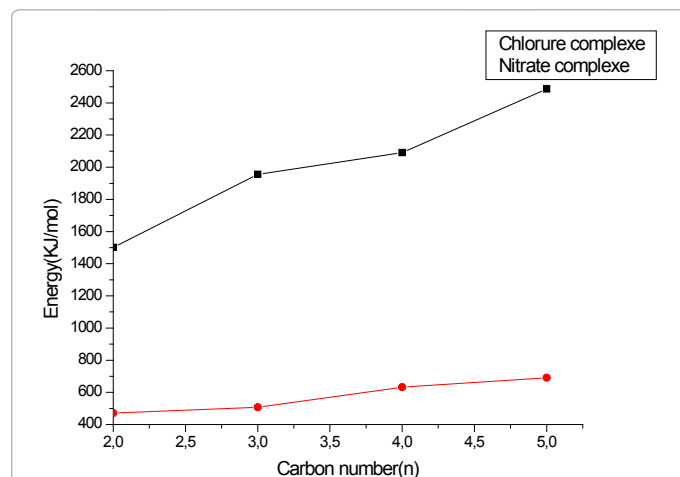**Table 6:** Energies (kJ/mol) obtained using the program Gaussian 09.

Figure 1: Steric energy as a function of carbon number of the side chain of the two complexes.

the ions NO_3^- and Cl^- form bonds with strong enough with the cation and oxygen of the side chain and forms a ring having 5 atoms chelating stable will allow the substrate to coordinate to the metal without difficulty, which leads to important catalytic activity. These results shows the difference in stability of each copper ion-ligand complex as present in the enzyme tyrosinase and which might influence enzyme activity and synthesis of melanin and other pigments. Even though this work has some limitations as not been assisted with potentiometric analysis, this interesting results could lead to new developments in synthetic biochemistry such as generating more stable conformers.

References

1. Bibi Z (2008) Role of cytochrome P450 in drug interactions. Nutrition & Metabolism 5: 27.

2. Shakil S, Kamal MA, Tabrez S, Abuzenadah AM, Chaudhary AGA, et al. (2012) Molecular interaction of the antineoplastic drug, methotrexate with human brain acetylcholinesterase: a docking study. CNS Neurol Disord Drug Targets 11: 142-147.

3. Shakil S, Khan R, Tabrez S, Alam Q, Jabir NR, et al. (2011) Interaction of human brain acetylcholinesterase with cyclophosphamide: a molecular modeling and docking study. CNS Neurol Disord Drug Targets 10: 845-848.

4. Al-Jafari AA, Shakil S, Reale M, Kamal MA (2011) Human platelet acetylcholinesterase inhibition by cyclophosphamide: a combined experimental and computational approach. CNS Neurol Disord Drug Targets 10: 928-935.

5. Jung S, Kim DH, Son JH, Nam K, Ahn DU, et al. (2012) The functional property of egg yolk phosvitin as a melanogenesis inhibitor. Food chem 135: 993-998.

6. Ha YM, Park YJ, Kim J-A, Park D, Park JY, et al. (2012) Design and synthesis of 5-(substituted benzylidene)thiazolidine-2,4-dione derivatives as novel tyrosinase inhibitors. Eu J Med Chem 49: 245-252.

7. Lou S-N, Yu M-W, Ho CT (2012) Tyrosinase inhibitory components of immature calamondin peel. Food chem 135: 1091-1096.

8. Si Y-X, Wang Z-J, Park D, Chung HY, Wang S-F, et al. (2012) Effect of hesperetin on tyrosinase: inhibition kinetics integrated computational simulation study. Int j biol macromol 50: 257-262.

9. Toubi Y, Touzani R, Radi S, El Kadiri S (2012) Synthesis, characterization and catecholase activity of copper (II) complexes with bispyrazole tri-podal Ligands. J Mater Environ Sci 3: 328-341.

10. Pennings YCM, Driessen WL, Reedijk J (1988) Copper(I) coordination compounds with two bidentate chelating pyrazole ligands. X-ray crystal structures of Dl-μ-chloro-bis[[N,N-bis(1- pyrazolylmethyl)aminoethane] copper(I)] and [bis(N,N-bis(1-pyrazolylmethyl)aminoethane]copper(I) triflate. Polyhedron 7: 2583-2589.

11. Leaver SA, Kilner CA, Halcrow MA (2003) Di-μ-hydroxo-bis([bis[2-(2-pyridyl) ethyl]amine-κ 3 N]copper(II)) dichloride hexahydrate. Acta Crystallographica Section C Crystal Structure Communications 60: m1-m3.

12. Chang WK, Lee GH, Wang Y, Ho TI, Su YO, et al. (1994) Synthesis, properties and molecular structure of copper(II) and cobalt(II) 1,2-bis(pyrazol-1-ylmethyl) benzene complexes. Inorganica Chimica Acta 223: 139-144.

13. Driessen WL, Wiesmeijer WGR, Schipper-Zablotskaja M, De Graaff RAG, Reedijk J (1989) Transition metal coordination compounds of two pyrazole-substituted ammonia ligands. X-ray structure of [Biss(1-pyrazolylmethyl) aminecobalt(II)] bis(nitrate). Inorganica Chimica Acta 162: 233-238.

14. Barszcz B, Głowiak T, Jezierska J, Kurdziel K (2002) Comparison of 1-hydroxymethyl-3,5-dimethylpyrazole and 1-benzyl-2-hydroxymethylimidazole coordination properties towards copper(II). Inorg Chem Commun 5: 1056-1058.

15. Driessen WL (1982) Synthesis of some new pyrazole-containing chelating agents. Recueil des Travaux Chimiques des Pays-Bas 101: 441-443.

16. Blaive B, Legsaï G, Laï R (1995) Utilization of d^0, d^1, d^2 electron configurations to obtain parameters for transition metals in the molecular mechanics of dioxo- or diimido-tetrahedral complexes (Cr, Mo, Re, Os). J Mol Str 354: 245-250.

17. Zinelabidine A, Bouraoui A, Mhenni F, Blaive B, Gallo R (1993) Molecular mechanics modelling of siderophores. J Mol Str: THEOCHEM 286: 267-274.

18. Frisch MJ, Trucks GW, Schlegel HB, et al. (2009) Gaussian 09 Revision A.02. Gaussian, Inc,. USA.: Wallingford, Conn.

19. Med. El Kodadi (2005) Thèse de doctorat,. Oujda: Université de Mohamed Premier

20. Lehn JM, Sauvage JP (1975) Cryptates. XVI. [2]-Cryptates. Stability and selectivity of alkali and alkaline-earth macrobicyclic complexes. J Am Chem Soc 97: 6700-6707.

21. Boyd PDW, Burrell AK, Rickard CEF (1997) [N , N -Bis(3,5-dimethylpyrazol-1-ylmethyl)-1-hydroxy-2-aminoethane](3,5-dimethylpyrazole)copper(II) Diperchlorate. Acta Crystallographica Section C Crystal Structure Communications 53: 1549-1551.