Egyptian Journal of Chemistry

Chemical reactivity study of anew suggested Chemotherapy agent using DFT

Lekaa Husina Khdaim[a] and Abbas Abd Ali Drea[b]

[a] Al-Kufa University , College of Education forWomen, Al-Najafe,54001, [b] University of Babylon , College of Science , Babil-Al Hashimiyah,51012, [a,b] Department of Chemistry

Abstract

Cisplatin is ([PtCl$_2$(NH$_3$)$_2$] (CDDP) or its antitumor properties, including the treatment of various solid tumor's). Clinical use of CDDP confirmed for different kind of cancer have been treated, including usage of complexes   as Sb (antiprotozoal), Bi (antiulcer), Au (antiarthritic), Fe (antimalarial), Ag (antimicrobial) and Pt (anticancer) in the treatment of different drugs.
Materials and methods: This study was involve Our new suggested chemotherapy agent is diaminobis((methylthio)oxy)platinum(VI)chloride (DMOP) complex. The agent has been described to be as effective anticancer therapy, the investigation is carried by a method of DFT based on B3LYP and LANL2DZ basis set. Suggested transition states formation of DMOP (II) complex(square planer) with purine bases(guanine and adenine) are studied by DFT/B3LYP method.
 Results: The energy gap 0.02632 kCal.Mol^{-1} is small value of indicate of high chemical reactivity for DMOP complex. Gibbs free energy of DMOP (IV) conversion into DMOP (II) is -14.92823 kCal.Mol^{-1}. The reaction is most probable of the complex with guanine bases than adenine bases by total energy value equal to -792.613k Cal mol^{-1}. The compounds formation of guanine bases with a platinum complex is the most probably than other suggested states by ZPE value equal to113.326 kCal mol^{-1}.
Keywords: Chemotherapy, Cis-platinum, Geometry optimization, transition state, DFT.

_____

Introduction

Cisplatin ([PtCl$_2$(NH$_3$)$_2$] or CDDP) is strong chemotherapy drugs widely with observance to its antitumor properties, including the treatment of various solid tumor's) "[1], Clinical use of CDDP confirmed for different kind of cancer have been treated, including use of compounds as Sb, Bi , Au, Fe , Ag and Pt in the treatment of different drugs. The wide range of compounds for activity of antitumor[2]. Cisplatin is square planar d8 PtII complexes that death of cancer cell by binding to nuclear DNA, distorting its structure1. The PtII complexes readily react with N7 of guanine in DNA strand. The process is well known by conversion of Pt(IV) complex to Pt(II) is Metabolic proceed. The global reactivity descriptors of molecule such an (IP), (EA), (A), (μ) and (ω) is very important for the appreciation of anticarcinogenic activities. "A lot of theoretical methods have emerged to estimate these global reactivity factors"[3]. Molecular modelling of the drug can be discovery and synthesis new useful optimizing structures candidate

[4]. Computational chemistry plays an important rule in drug discovery and modification of discovered drugs for that are used in chemotherapy."As Pt(II) and Pt(IV) complexes are widely used complexes with cytotoxic activity", although Pt(IV)"complexes are more inert than Pt(II) complexes". Because their containing axial ligands that are reduced in the lived tissues and converted into Pt(II) species, and therefore are more resistant to unwanted side-reactions [5,6]. This interaction displays the stability of the Pt(II) complex has been used The "DFT for calculating the electronic properties, HOMO and LUMO energies, Mulliken charge of atoms"[7], "The one of the quantum mechanics which is used to investigate the electronic structure of atoms, molecules is DFT "and it can also be applied to large molecules [8,9].

The aim of the paper is to suggest of DMOP (IV) complex and the combination of DMOP (II) complex with nucleobase in DNA and molecular geometry, optimized parameters and vibrational frequencies of DMOP (IV) complex and complex with nucleobase

_____

_____

by DFT/B3LYP with LANL2DZ using the Gaussian 09 package of programs[10-12].

Methods

The DMOP complex is theoretically prepared in vacuum by one molecule of $PtCl_4$ with ex NH_3, ex H_2O_2 and add of axial ligand ($HOSCH_3$) as follows[18]:

$$PtCl_4^{-2} + exNH_3 \longrightarrow Pt(NH_3)Cl_2 + exH_2O_2 \longrightarrow Pt(NH_3)Cl_2(OH)_2 \ ^{18}$$

Tetrachloro platinum (II)   Cisplatin (II)   Cis-dichloro-diamine dihydro Platinum (IV)
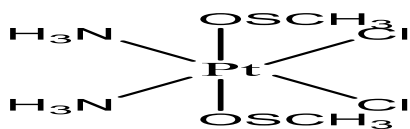
Ex HOSCH₃

$$H_2O \ + Pt(NH_3)Cl_2(OSCH_3)_2 \ ^{18}$$
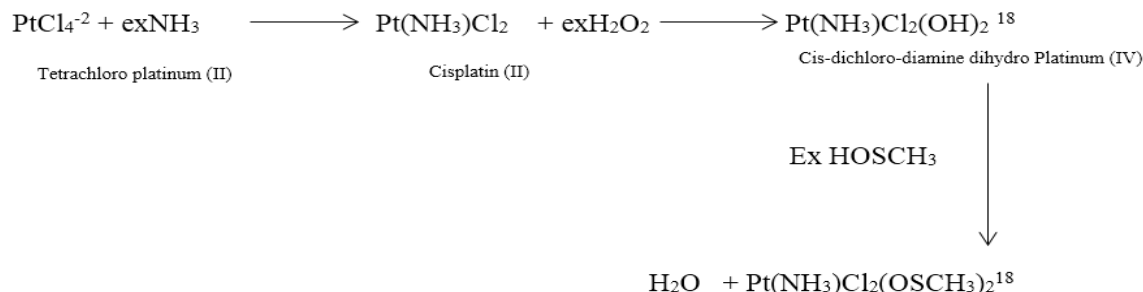
Scheme 1. The chemical reaction of complex formation.

Computational details

In the present work, All geometry optimization of a ground state was calculated and performed using Gaussian 09 program package[13] by using DFT/B3LYP method. The calculations were based on LANL2DZ (5d,7f) basis set. The imaginary frequencies indicate that the energy minima are best optimized geometries . The HOMO, LUMO, and energy gap are indicated for the reactivity of DMOP complex towered reactions. The different reactivity and selectivity descriptors such as chemical hardness, chemical potential, nucleophilicity, and electrophilicity were calculated as well as total density, dipole moment, electrostatic and Mulliken charge. The electronic transitions and vibrational transitions and NMR (C13, H1) spectra of DMOP (IV)complex . The chemical structures of the suggest DMOP (IV)complex is represented in Fig. 1 by using ChemDraw professional 15.0."

Results and discussions

Geometrical parameters

The geometry optimized structure of DMOP complex is represented in Fig. 2. "The geometry optimization process stops when the force resultant on atoms equal to zero". The local symmetry around the metal centre. Table 1. Shows the structural properties of DMOP complex, some of the bond lengths, bond angle (θ) and dihedral angle (φ)parameters are selected. They found agreement between the experimental values of X-ray diffraction measurments[14] and different computational values for bond lengths of DMOP (IV) complex such as Pt1-Cl2, Pt1-O6, Pt1-N5 are equal to 2.290, 1.940, 1.976 Å respectively. Bond angles such as N5-Pt1-N3, Pt1-N3-O6, and Pt1-Cl2-N3 are equal to 82.2°,90.0°,180° respectively. The dihedral angle in the molecule (S7-O6-Pt1-Cl2), (C8-S7-O6-Pt1) and (S10-O9-Pt1-Cl2) are (180°,-180°,180°) respectively. The bond length between Pt atom and O, N, Cl atoms in DMOP complex are very important in a load of charge transfer between donor and acceptor. From the dipole moment value of DMOP complex less than 15 value, therefore, is indicate quite a polar complex[15].
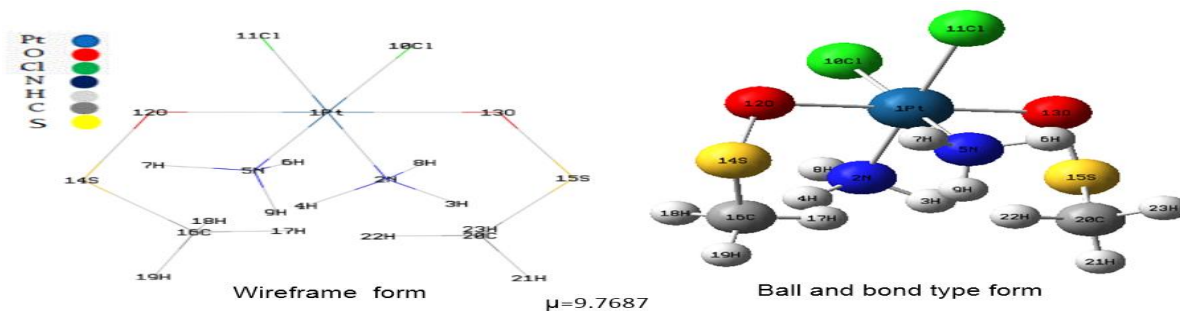

Diaminobis((methylthio)oxy)platinum(VI) chloride(DMOP).

Fig.1. Name and chemical structure of Pt(IV)complex.

_____

Fig.2. Geometry optimized Structure of DMOP comple

Atomic charges and electron density

Milliken analysis of DMOP complex, Atomic charges are calculated, since the charge distribution is shown in Fig. 3. It may be noted that the oxygen atom has a negative charge and the carbon atom has the highest positive charge. The Chlorine atoms have slightly negative more than other atoms. "All nitrogen atoms in DMOP (IV) complex have a negative charge and the nitrogen N5 atom has more negative than nitrogen N2, also the hydrogen atoms for the amino group have large net positive charge (H3, H6, H7, H8, H9) atoms. "The presence of a large number of negative charges on carbons (C16, C20) atoms and the positive charge on hydrogen in methyl group (H17, H18, H19, H21, H22, H23) atoms easy formation of quite a large number of intra and intermolecular hydrogen bonding in the complex[16]. "

The electron density is typically shown a comparison of the identified electron density with that predictable by spherical models of the atoms and that is called distortion electron density. The electron density was calculated of ESP with SCF density matrix. Figures. 3, and 4 represented Mulliken charge, electron density respectively
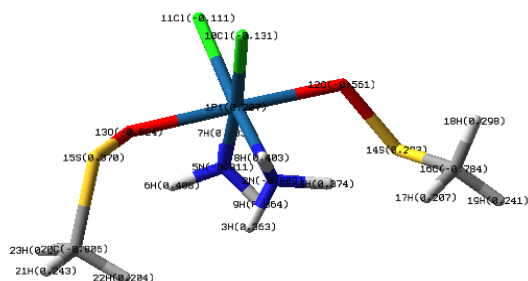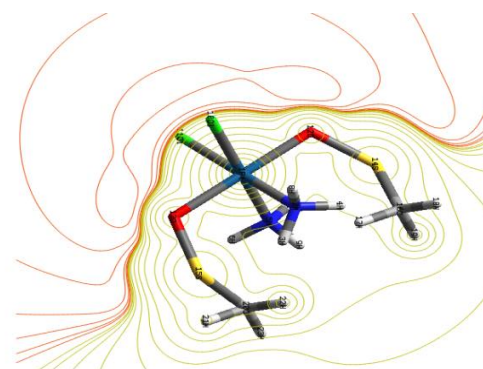

Fig.4. The total density of Pt(IV)complex.

The energy of Molecular Orbitals

HOMO and LUMO are the important orbitals to describe the chemical reactivity[17,18], "optical properties[19] and biological activity[20]. The energy gap value of 0.02632 kCal.Mol-1 between HOMO and LUMO is the small bandgap of DMOP complex lead to the easy electrons transfer. Decreasing of the energy gap leads to the increase of the intramolecular charge transfer and is indicated of more reactivity for a reaction of DMOP complex characters[21], Fig. 5. Shows different view of molecular orbitals of DMOP.

Fig.3. Mulliken charge of Pt(IV)complex.
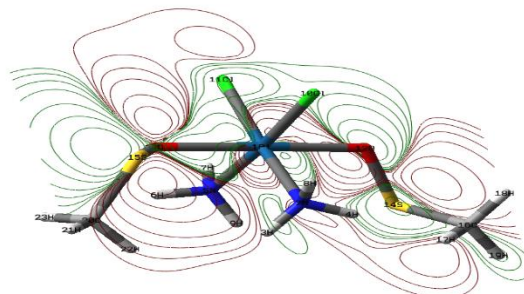
A- two-dimensional view of Wireframe molecular orbitals.

_____

$E_{HOMO} = -0.01949$ $\Delta E_{gap} = 0.02632$ $E_{LUMO} = 0.00683$
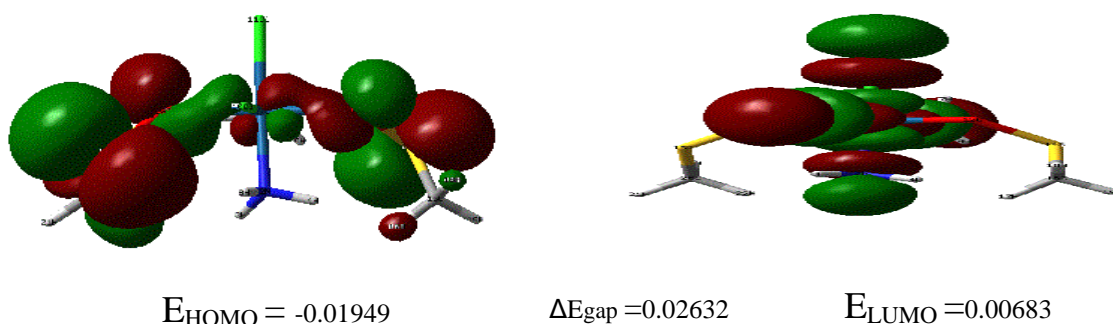
B- three-dimensional view of molecular orbital's.

Fig. 5. Frontier molecular orbitals of 3D for DMOP complex.

Energetic parameters and global reactivity

Thermodynamic parameters are calculated at DFT/B3LYP level using a LANL2DZ basis set as shown in Table 2, the stability of DMOP complex is determined by the total energy, according to its low value is most stable complex. Zero-point energy has the lowest power possible in a quantum mechanical system from the low value of the zero-point energy can be known as a stable complex, calculated standard enthalpy and entropy for DMOP complex is given in Table 2. Also, the global reactivity of complex is the values of chemical hardness softness shows that the decrease in the hardness and softness leads to an increase in the complex activity [22]. The high value

of electrophilic which have the highest capability to the good donor of electrons[23].

3.5.   Reactivity toward Purine Bases

Cisplatin ([PtCl2(NH3)2] or CDDP) is a square planar d8 contain two cis chloride ligands and two ammine ligands. The Pt-N bonds are kinetically inert and thermodynamically stable, but Pt-Cl bonds are unstable and Pt-OH2 are more reactive. The chloride ligands can be slowly exchanged with water (aquatint) or by other nucleophiles. The non-ammine ligands are replaced by two N7 atoms of two adjacent guanines and adenine on the same DNA strand as shown in Scheme 2.
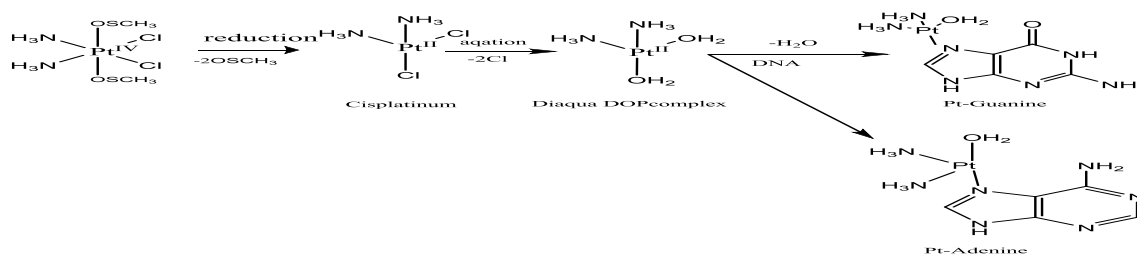
Scheme 2. The competitive reaction of DMOP complex with Purine Bases at DNA strand

Gibbs free energy of prodrug DMOP (IV) conversion into drug DMOP (II) is -14.92823 kCal.Mol-1, the reaction is forward into drug formation. The combination reaction with Guanine is exothermic, the value of -792.613 a.u. is more probable than a combination with Adenine value of -773.479 a.u. . Also is indicate a spontaneous reaction towards guanine than adenine. Different transition states are proposed for DMOP complex with Guanine and Adnene, Table 2. shows energetic values of different transition states that are conversion interaction within the Cis-Platinum complex. According to the total

energy value of geometry optimization, we found TS4-Guanine is the most optimized state with a value of -792.613 kCal mol-1 than all other proposed transition states. At the same time, ZPE value of TS4 is equal to 113.326k Cal Mol-1 while the ZPE of TS4-Adenine is equal to 121.68Cal Mol-1, that's mean another proofing is present about TS4-Guanine is the most probable by a factor of 7.354 kCal.Mol-1, it's more stable and has a long lifetime. So Platinum complex is binding to N7 in Guanine base of DNA strand.

_____

Table 2. Configuration interaction energetic values of Cis-Pt complexes at different suggested probabilities of transition states formations.

Energies	Configuration interaction of Guanine				Configuration interaction of Adenine			
	TS1	TS2	TS3	TS4	TS1	TS2	TS3	TS4
Total energy (a. u.)	-644.288	-792.29	-792.58	-792.613	-774.106	-773.42	-773.42	-773.479
G(kCal.Mol^{-1}	91.177	78.313	69.591	68.606	94.565	94.440	85.090	82.925
S(kCal.Mol^{-1}	119.96	123.75	121.861	124.932	124.175	124.94	121.02	127.86
H(kCal.Mol^{-1}	126.945	115.21	105.924	104.662	131.588	131.652	121.172	121.047
ZPE(kCal.Mol^{-1}	94.91	96.23	105.63	113.63	110.64	111.61	121.66	121.68

The molecular modelling of adenine and guanine contains four main negative regions corresponding to the four N lone electron pairs on the nitrogen atoms(N1, N3, N7, and N9). the results are showed that the best site for platinum complex binding from less total energy by a.u in the N7 position of guanine than adenine, in Table 5, Fig.7 & 8. The results are showed guanine are contained the oxo group at the C6 position allows for the formation of a hydrogen bond with ammine or water in [Pt(NH3)2(H2O)2]2[27], also the amino group at the C6 position in adenine. Whereas the oxo and amino groups at the C6 position of the guanine and adenine respectively, are hydrogen-bond acceptors. The oxo group in guanine is better hydrogen-bond acceptor than the amino group in adenine, therefore, the guanine the best stable than adenine as well as the energy values are the lowest in the quinine compared with the adenine[28-29]

Conclusion

The bond length between Pt atom and O, N, Cl atoms in DMOP complex are very important in a load of charge transfer between donor and acceptor. The small value of the energy gap implies low electronic stability and high reactivity of complexes toward binding with nitrogen bases. The dissociation value is exothermic (-14.92823 kCal.Mol-1) of prodrug IV converted into drug II. The DOP complex is more reactive with guanine than adenine.

References

1. Jorgensen,W.L. Science,2004,1818, 303, 1813.
2. Vivo, D.e.; Bridging, M. Front. Biosci., Landmark Ed.,2011,16, 1619−1633.
3. Eweas, A. F.; Maghrabi, I. A; Namarneh, A. I. Der Pharma Chemica,2014 ,6(6),211-228.
4. Zhang, J. Z.; Bonnitcha, P.; Wexselblatt, E; Klein, A. V.; Najajreh, Y.; Gibson, D.; Hambley, T.W. Chem. Eur. J.,2013,19, 1672–1676.
5. Reedij k. J.; Pure Appl. Chem.,2011, 83, 1709, 2011.
6. Paola, A.; Oliveira, S.; Lucas, M. S.; Nicolás, A. R.;, Hélio, F. D. ; Marcone, A. L. ; Luiz A. S. , J. Braz. Chem. Soc.,2013, 24, 1732-1738.
7. Dolezel,P. ; Kuban,V.,Chem., 2002, 56(4),236—240 .
8. Desolze,B.,ANTICANCER RESEARCH, 2004, 24: 1529-1544.
9. Humberto L. M.-H, J. Mex. Chem. Soc., 2014, 58(4), 416-423.
10. Dheivamalar, S. ; Sugi, L. ; Ambigai, K. Computational Chemistry ,2016,4,17-31.
11. Hannon, F. H. International Journal of New Technology and Research (IJNTR), 2017, 2, 54-60.
12. Oprea, C. I. ; Panait, P. ; Cimpoesu, F.; Ferbinteanu M.; Gîrţu, M. A. Materials,2013,6, 2372-2392.
13. Shargh, N.; Roohi, D.; Deyhimi, F.; Naeem-Abyaneh, R. Journal of Molecular Structure: THEOCHEM,2006, 763, 21-28.
14. Frisch, M.J.; Trucks, G.W., et al. GAUSSIAN 98 (Revision A. 3) Gaussian Incumbent. Pittsburgh, PA, USA. ,1998.
15. He, H.Q.; Liu, J.Y.; Li, Z.S.; Sun, C.C. THEOCHEM, 2006,763, 59- 66.
16. Khalil .S. M., Naturforsch .Z, 2008, 63, 42.
17. Frisch, M. J.; Trucks, G.W.; Schlegel, H. B. Gaussian 03;Revision D.01. Gaussian, Inc.: Wallingford, 2004.
18. Varbonov, H.P. ; Jakupec, M.A. ; Roller, A. ; Jensen, F. ;. Galanski, M. , Keppler, B.K .J.Med . chem.,2013,293, 330-344.
19. Faggian, R.; Howard-lock, HE.; CJI, Lippert, B.; Rosenberg, B. J.chem, 1982,60,529.

20. Karagoz, Z.; Tekin, S.; Sandal, S.; Genc, M. Res. Chem. Inter-med. 2015.

21. Fleming, J. Wiley, London, 1976, 111–155.

22. Vaz,W.F.;Custodio,M.F.;Rodrigues,N.M.N;Santin ,L.G.;Oliveria,S.S.J.Mol.Model,2017,23,315.

23. Sajan, D.; Lakshmi,K. U.; Erdogdu, Y.;.Joe,I.H,Spectrochim.Acta,2011, 78A, 113–121.

24. Eren, B.; Unal, A. Spectrochim. Acta Part A,2013, 103, 222–231.

25. Bourass, M. ; Touimi, A. B.; Benzakour, M. ; Mcharfi, M. ; Hamidi, M.; Bouzzine, S.M. ; Serein-Spirau, F., Jarrosson, T.; Lère-Porte, J. P.; Sotiropoulos, J. M.; Bouachrine, M J. Mater. Environ. Sci.,2015, 6 (6), 1542-1553.

26. Mahmoud, S. S. ; Zaheda, A. N Pak. J. Anal. Environ. Chem. ,2012, 13, 40-47.

27. Suzuki, A.; Oku, T., The Irago Conference, 2015,1709, 020013-1–020013-8.

28. Irena, K., Recent Patents on Anti-Cancer Drug Discovery, 2006, 1, 1-22.

29. Mu-Hyun, B.;Richard, A. F. ;

30. Stephen, J. L. J. AM. CHEM. SOC., 2003..