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Method and Basis Set Investigations and Computational Spectral Studies for Oximato-Bridged trans-Platinum(II) Dimer Used as Anticancer Drug

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Abstract – Optimized molecular structure and vibrational spectra of oximato-bridged platinum(II) complex are investigated with different methods (HF, MP2, pure and hybrid DFT functions) and basis sets (CEP-4G, CEP-31G, CEP-121G, LANL2DZ, LANL2MB, SDD). Correlation coefficients of bond lengths and angles, CPU computational time and vibrational frequencies were used to determine the best method and basis set. The results show that HF/CEP-31G and MP2/CEP-31G are the best levels for optimized molecular structure and vibrational spectra, respectively. The UV-VIS and ^{1}H-NMR spectra of mentioned complex are calculated by using HF/CEP-31G level. The active sites of this complex are determined by using molecular electrostatic potential (MEP) map.

Keywords -
Oximato-Bridged Pt(II) complex,
Computational Study,
Spectral Analysis,
MEP maps

1. Introduction

Platinum complexes play an important role in chemotherapy [1-5]. Great effort have been undertaken to develop anticancer platinum-based drugs [6, 7]. Recent studies have been reported that Pt(II) complexes with ketoxime cause cell death via an apoptotic mechanism, posses a higher cytotoxicity, enhanced cellular accumulation and elevated DNA platination [8-11]. Di- and tri-nuclear platinum(II) complexes with bridging aliphatic [12-21] and aromatic [22] diamine ligands have been investigated.

trans-$[PtCl\{\mu\text{-}(Z)\text{-}CH_3(H)C{=}NO\}\{(E)\text{-}CH_3(H)C{=}NOH\}]_2$ oxime complex has been synthesized and anticancer properties of this complex have been investigated experimentally by Scaffidi-Domianello et al. in 2012 [23]. Different density functional theory methods (mPW1PW, BPV86, HCTH, PBEPBE, LSDA, PBE1PBE) have been used in calculations for platinum complexes [23-29]. But ab initio methods have not been tested for this type complexes. The aim of this work is to investigate the best level and to predict UV-VIS and ^{1}H-NMR spectra for the mentioned complex. For this purpose, correlation coefficient of bond lengths, bond angels, CPU computational time and average linear scale factors of vibrational frequencies are used to determine the best method and basis set for optimized complex structure. Additionally, UV-VIS and ^{1}H-NMR spectra are calculated by

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using best method and basis set. The active sites of this complex are determined by using MEP map.

2. Computational Methods

All calculations were performed using the Gaussian 09 package program [30, 31]. The structural parameters and vibrational spectrum of trans-platinum(II) complex were determined by the application of Hartree-Fock (HF), Moller-Plessent (MP2), hybrid Density functional theory (DFT) methods (B3LYP [32], B3PW91 [33], MPW1PW91 [34], BHandLYP [35]) and pure DFT methods (BP86 [36], BPW91 [37, 38], PW91PW91 [39, 40], SVWN5 [41]) with different basis sets including LANL2DZ [42], LANL2MB [43], SDD [43], CEP-4G [29], CEP-31G [29] and CEP-121G [29].

The LANL2DZ with effective core potential (ECP) basis set was used for all calculations [44]. This basis set replaces the 1s through 2p electron of the heavy atoms with a potential field for considerable computational savings. LANL2DZ specifies D95V on first row [45], Los Alamos ECP plus DZ on Na-La, Hf-Bi. SDD specifies D95V up to Ar [45] and Stuttgart/Dresden ECPs on the remainder of the periodic table [46, 47]. LANL2MB specifies the STO-3G on first row [48, 49], Los Alamos ECP plus MBS on Na-Bi [50]. CEP-4G, CEP-31G, CEP-121G specify Stevens/Basch/Krauss ECP minimal basis, split valance, triple-split valance, respectively [51-53].

Time dependent (TD) and GIAO methods were used for UV-VIS and NMR calculations, respectively. ^{1}H-NMR calculations were performed in methanol solvent. Solute-solvent interaction were taken into account with conductor-like polarizable continuum model (CPCM) [54]. In this model, interaction between solute and solvent is represented through a dielectric constant.

3. Results and Discussion

3.1. Geometry Optimization

The optimized molecular structure of platinum (II) complex at HF/CEP-31G level is represented in Fig. 1. Correlation coefficients are calculated for determination of the best structure. Correlation coefficients represent the agreement between theoretical and experimental geometrical parameters. Correlation coefficients at bond lengths and angles are given in Table 1 and 2, respectively.

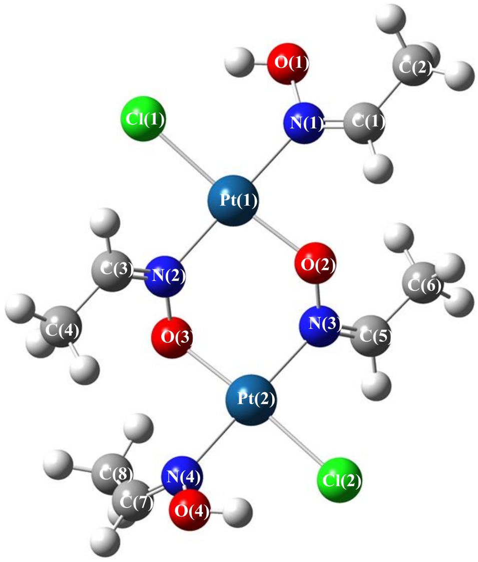

Fig. 1. Optimized structure of oximato-bridged trans-Pt(II) complex calculated with HF/CEP-31G level and atomic number scheme.

Table 1. Correlation coefficients of bond lengths calculated with different levels

Methods	Basis Sets					
	CEP-4G	CEP-31G	CEP-121G	LANL2DZ	LANL2MB	SDD
HF	0.9719	0.9867	0.9862	0.9823	0.9636	0.9839
MP2	0.9448	0.9862	0.9745	0.9742	0.9685	0.9732
B3LYP	0.9476	0.9814	0.9781	0.9745	0.9574	0.9814
B3P86	0.9497	0.9831	0.9800	0.9757	0.9589	0.9827
B3PW91	0.9497	0.9831	0.9805	0.9765	0.9599	0.9826
MPW1PW91	0.9578	0.9849	0.9835	0.9802	0.9567	0.9840
BHandLYP	0.9520	0.9841	0.9816	0.9772	0.9601	0.9833
BP86	0.9571	0.9782	0.9734	0.9692	0.9565	0.9720
BPW91	0.9369	0.9783	0.9794	0.9703	0.9770	0.9781
PW91PW91	0.9403	0.9784	0.9739	0.9697	0.9542	0.9784
SVWN5	0.9457	0.9800	0.9730	0.9706	0.9514	0.9825

Table 2. Correlation coefficients of bond angles calculated with different levels

Methods	Basis Sets					
	CEP-4G	CEP-31G	CEP-121G	LANL2DZ	LANL2MB	SDD
HF	0.9975	0.9966	0.9944	0.9942	0.9841	0.9939
MP2	0.9979	0.9944	0.9994	0.9994	0.9729	0.9995
B3LYP	0.9992	0.9904	0.9998	0.9995	0.9988	0.9887
B3P86	0.9992	0.9893	0.9999	0.9997	0.9991	0.9788
B3PW91	0.9993	0.9902	0.9998	0.9997	0.9994	0.9886
MPW1PW91	0.9990	0.9919	0.9990	0.9988	0.9986	0.9909
BHandLYP	0.9992	0.9902	0.9998	0.9997	0.9993	0.9884
BP86	0.9999	0.9893	0.9999	0.9998	0.9994	0.9998
BPW91	0.9993	0.9907	0.9899	0.9998	0.9693	0.9891
PW91PW91	0.9993	0.9891	0.9999	0.9998	0.9995	0.9880
SVWN5	0.9991	0.9845	0.9997	0.9998	0.9994	0.9828

Correlation coefficients of all levels in Table 1 are taken into account for the determination of the best basis set. The best results are obtained at HF/CEP-31G, MP2/CEP-31G,

B3LYP/CEP-31G, B3P86/CEP-31G, B3PW91/CEP-31G, MPW1PW91/CEP-31G, BHandLYP/CEP-31G, BP86/CEP-31G, BPW91/CEP-121G, PW91PW91/CEP-31G and SVWN5/SDD levels. As for the determination of the best method, the best results are obtained at HF/CEP-4G, HF/CEP-31G, HF/CEP-121G, HF/LANL2DZ, BPW91/LANL2MB and MPW1PW91/SDD levels. These two analyses results show that HF/CEP-31G level is mainly the best level for mentioned complex according to correlation coefficients value (0.9867). According to the Table 1, hybrid DFT functions give better results than pure DFT functions.

Five bond angles have been presented in Ref. 23. These experimental values and calculated results are used for determination of correlation coefficients. In Table 2, all correlation coefficients are mainly higher than 0.99. These values mean that the calculated structure of Pt(II) complex close the experimental structure. It is hard to determine the best method and basis set by using correlation coefficients of bond angles.

Job CPU time is an additional parameter which has been taken into account in the selection of the method adequate for prediction of the Pt(II) complex structure. Job CPU times are given in Table 3.

Table 3. Job CPU times of mentioned complex for different level calculations

Methods	Basis Sets					
	CEP-4G	CEP-31G	CEP-121G	LANL2DZ	LANL2MB	SDD
HF	5 h 5′	15 h 9′	1 d 19 h 35′	2 d 12 h 41′	2 h 47′	1 d 3 h 49′
MP2	1 d 15 h 19′	9 d 12 h 9′	34 d 5 h 2′	15 d 16 h 52′	22 h 22′	22 d 5 h 45′
B3LYP	23 h 10′	1 d 15 h 2′	3 d 7 h 47′	1 d 9 h 21′	7 h 27′	2 d 8 h 45′
B3P86	1 d 4 h 36′	1 d 16 h 57′	3 d 7 h 47′	1 d 12 h 29′	7 h 29′	2 d 15 h 11′
B3PW91	1 d 42′	1 d 11 h 36′	2 d 20 h 49′	1 d 4 h 42′	6 h 15′	2 d 13 h 53′
MPW1PW91	1 d 50′	1 d 13 h 39′	3 d 5 h 30′	1 d 4 h 16′	7 h 46′	2 d 14 h 34′
BHandLYP	11 h 15′	1 d 3 h 2′	6 d 14 h 32′	2 d 6 h 6′	7 h 22′	2 d 10 h 58′
BP86	4 h 32′	2 d 5 h 52′	4 d 11 h 13′	1 d 21 h 38′	20 h 25′	3 d 12 h 57′
BPW91	1 d 2 h 14′	2 d 57′	5 d 23 h 53′	6 d 10 h 13′	11 h 45′	4 d 5 h 48′
PW91PW91	1 d 14 h 44′	2 d 3 h 28′	3 d 6 h 6′	1 d 19 h 44′	16 h 50′	2 d 20 h 55′
SVWN5	1 d 1 h 47′	2 d 8 h 54′	4 d 16 h 8′	1 d 11 h 18′	6 h 30′	3 d 23 h 48′

According to job CPU times, two-step analyses are used for determination of the best method and basis set. The first step is to determine the best method. Performance rankings of methods were done for each basis set. According to job CPU times, HF method has mainly minimum job CPU time and maximum performance. These analyses show that HF method is the best method for our complex. Second step is to determine the best basis set. Basis set rankings are done for each method by using job CPU time. In HF method, the ranking of basis set should be:

LANL2MB < CEP-4G < CEP-31G < LANL2DZ < SDD < CEP-121G

According to this ranking, job CPU time of LANL2MB basis set is minimum and job CPU time of CEP-121G is maximum. But correlation coefficients of LANL2MB and CEP-4G at bond lengths are lower than CEP-31G.

Taken into account the correlation coefficients of bond lengths and job CPU times, HF/CEP-31G is the best level for our Pt(II) complex. The calculated structural parameters in HF/CEP-31G level are given in Table 4 with experimental data.

Table 4. Structural parameters of Pt(II) complex calculated with HF/CEP-31G level

Lengths (Å)	Calc.	Exp.[a]	Angles (deg.)	Calc.	Exp.[a]
Pt(1) – N(1)	2.097	2.032	N(1) – Pt(1) – N(2)	174.3	176.2
Pt(1) – N(2)	2.051	1.992	N(2) - Pt(1) - Cl(1)	89.6	91.6
Pt(1) – Cl(1)	2.403	2.282	N(1) - Pt(1) - Cl(1)	95.4	89.8
Pt(1) – O(2)	2.067	2.023	N(3) - Pt(2) - N(4)	174.3	177.5
Pt(2) – N(3)	2.051	1.974	N(3) - Pt(2) - Cl(2)	89.5	91.0
Pt(2) – N(4)	2.097	2.024	N(4) - Pt(2) - Cl(2)	95.4	90.4
Pt(2) – Cl(2)	2.403	2.291	-	-	-
Pt(2) – O(1)	2.067	2.036	-	-	-
N(1) – C(3)	1.415	1.264	-	-	-
N(2) – C(1)	1.280	1.260	-	-	-
N(3) – C(5)	1.280	1.278	-	-	-
N(4) – C(7)	1.413	1.268	-	-	-

[a]Experimental values were taken from *Ref. 23*.

3.2. Vibrational Spectra

Calculated and experimental vibrational frequencies and average linear scale factors ($\lambda_{Average}$) are listed in Table 5 by using HF, MP2 and DFT methods with CEP-31G basis set. Average linear scale factors are calculated by using Eq. (2).

$$\lambda_n = \frac{\nu_{exp.}}{\nu_{theo.}} \tag{1}$$

$$\lambda_{Average} = \frac{\sum \lambda_n}{n} \tag{2}$$

where n, $\nu_{exp.}$, $\nu_{theo.}$ are the number of linear scale factor in each method, experimental frequency and theoretical frequency, respectively.

Table 5. Calculated with CEP-31G basis set and experimental frequencies of mentioned complex and average linear scale factors (λ_{Av})

Methods	Assigment				λ_{Av}
	ν_{O-H}[a]	$\nu_{C=N}$[a]	$\nu_{C=N}$[a]	ν_{N-O}[a]	
HF	3834	1892	1860	1156	0.8553
MP2	3494	1642	1580	925	0.9994
B3LYP	3323	1680	1636	965	0.9862
B3P86	3313	1706	1663	1047	0.9598
B3PW91	3365	1701	1658	1041	0.9587
MPW1PW91	3400	1724	1681	1017	0.9551
BHandLYP	3528	1792	1747	1076	0.9152
BP86	3155	1614	1569	990	1.0139
BPW91	3251	1618	1574	907	1.0265
PW91PW91	3200	1621	1577	907	1.0295
SVWN5	2891	1640	1639	927	1.0384
Exp.	3143	1666	1620	969	-

[a] Frequencies were given in cm^{-1}

According to the Table 5, MP2/CEP-31G is the best level for determining the vibrational frequencies of mentioned complex. In addition, good correlation is also obtained by using B3LYP and BP86 methods. Average linear scale factor values of MP2, B3LYP and BP86 methods are 0.9994, 0.9862 and 1.0139, respectively. The calculated vibrational frequencies of oximato-bridged Pt(II) complex were obtained as $\nu_{O\text{-}H}$ (3494 cm^{-1}), $\nu_{C\text{-}H}$ (3218 – 3036 cm^{-1}), $\nu_{N=C}$ (1642, 1580 cm^{-1}), $\nu_{C\text{-}C}$ (991 cm^{-1}), $\nu_{N\text{-}O}$ (925 cm^{-1}), $\nu_{Pt\text{-}O}$ (776 cm^{-1}) and $\nu_{Pt\text{-}Cl}$ (365 cm^{-1}) in the best level. IR spectrum of Pt(II) oxime complex is shown in Fig. 2.

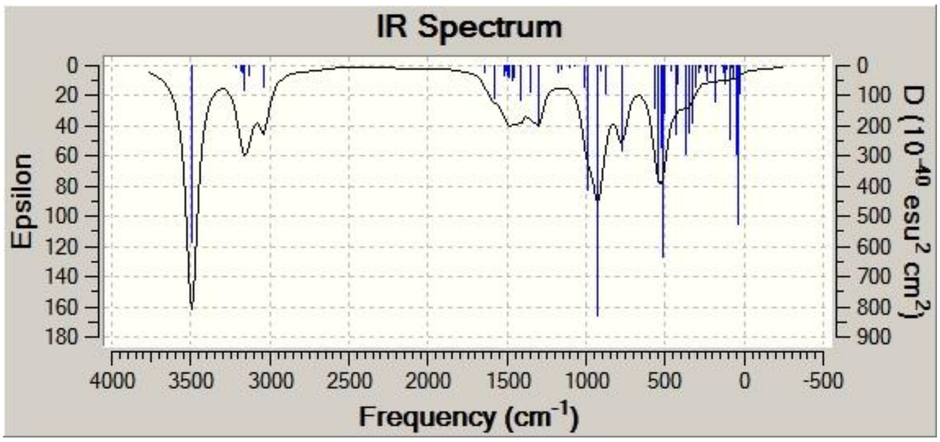

Fig. 2. IR Spectrum of oximato-bridged Pt(II) complex calculated with MP2/CEP-31G level.

3.3. UV-VIS Spectrum

One band is obtained from the UV-VIS spectrum of the title complex in UV region. This band forms different peaks. Wavelength of main peak with maximum oscillator strength is calculated at 164.8 nm by using TD-HF/CEP-31G level. UV-VIS spectrum of title complex is given in Fig. 3.

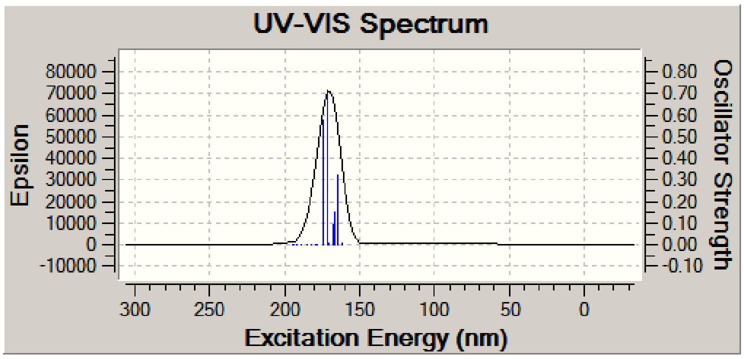

Fig. 3. UV-VIS spectrum of oximato-bridged Pt (II) complex calculated with TD-HF/CEP-31G level

This main peak can be analyzed with molecular orbital calculations. Therefore, atomic orbital coefficients are calculated at HF/CEP-31G level for mentioned complex. The character of the specific molecular orbital (OC%) are calculated by using atomic orbital coefficient with Eq. (3) [55, 56].

$$OC\% = \frac{n^2}{\Sigma n^2} x100 \qquad (3)$$

where n is the atomic orbital coefficient, Σn^2 is the sum of the squares of all atomic orbital coefficients in a specific molecular orbital. The main peak with 164.8 nm wavelength is formed from the transitions between different orbitals. The transition characters (*TC%*) were calculated by using Eq. (4) [57, 58].

$$TC\% = \frac{t^2}{\Sigma t^2} x100 \qquad (4)$$

where t is coefficient of the wavefunction for each excitation and Σt^2 is the sum of the squares of all coefficients of the wavefunction for each excitation in a specific peak. Ground state orbitals, exited state orbitals, OC%, TC% values are listed in Table 6 for the main peak with 164.8 nm wavelength.

As can be seen from Table 6, the TC% of HOMO-8→LUMO+1 transition for the main peak is calculated as 32.9%. This transition indicated that electron transfers ground state (HOMO-8) to excited state (LUMO+1). The orbital character of HOMO-8 is 52.3% ligand orbital and LUMO+1 is 88.0% Pt (II) ion orbital character. These results are basically indicates that the main peak occurs from the ligand-metal charge transfer (LMCT).

Table 6. Ground and exited states for the main peak with 164.8 nm wavelength and OC%, TC% values of ground and exited states

Ground State	OC%	Excited State	OC%	TC%
HOMO-10	54.9^a	LUMO+1	88.0^b	5.2
HOMO-8	52.3^a	LUMO+1	88.0^b	32.9
HOMO-8	52.3^a	LUMO+2	91.0^b	5.5
HOMO-7	63.5^b	LUMO	64.7^b	6.1
HOMO-6	67.2^b	LUMO+1	88.0^b	10.5
HOMO-2	57.1^b	LUMO+1	81.5^b	5.9
HOMO-1	36.2^a	LUMO+2	91.0^b	5.1
HOMO-1	36.2^a	LUMO+5	94.5^b	4.9
HOMO	55.3^a	LUMO	64.7^b	10.2
HOMO	55.3^a	LUMO+4	95.0^b	13.7

[a] OC% value of ligand, [b]OC% value of Pt (II) ion.

3.4. ^{1}H-NMR Spectra

NMR spectra is important analytical method to determining the molecular structure and this method has found a variety of applications in many different research fields. Chemical shifts are recognized as an important part of the information contained in NMR spectra. Experimental chemical shifts of hydrogen atoms in mentioned Pt(II) complex has been reported as 7.78, 7.38, 2.33 and 2.09 in Ref. 23. ^{1}H-NMR spectra of mentioned complex are calculated at GIAO/HF method with CEP-31G basis set in methanol. The calculated ^{1}H-NMR spectra is represented in Fig. 4.

Degeneracy tolerance is selected as 0.15 to interpreting the NMR spectrum. The chemical shifts values of hydrogen atoms are calculated: (N=C)*H* (8.06, 7.13 and 6.97), O*H* (6.50

and 6.14), CH_3 (2.62, 1.97, 1.72 and 1.39). The calculated ^{1}H-NMR shifts are compatible with experimental values.

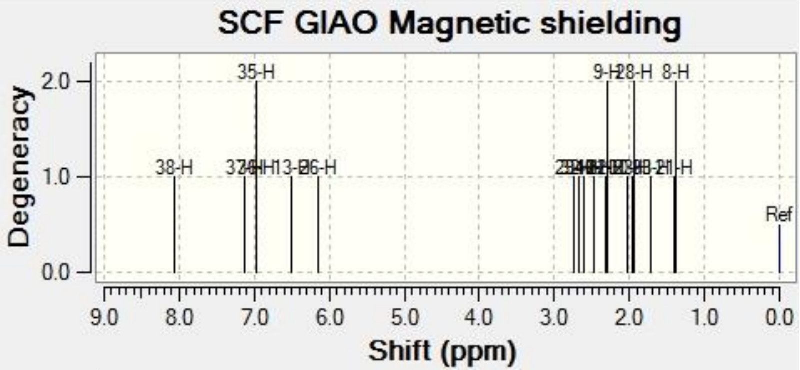

Fig. 4. ^{1}H-NMR spectrum of oximato-bridged Pt (II) complex calculated with GIAO-HF/CEP-31G level in methanol

3.5. Molecular electrostatic potential (MEP) maps

The determination of active sites of molecules is important to explain the reaction mechanism. Nucleophilic and electrophilic active regions can be determined by using MEP maps. In MEP maps, surface color changes depending on the electron density. There are different colors on MEP maps between red and blue. The red and blue regions imply the nucleophilic active region and electrophilic active region, respectively. The MEP map of mentioned complex is calculated and given in Fig. 5.

The electrons localized around Cl atoms and oxygen atoms. Therefore, red regions are appeared around the Cl atoms and yellow regions are localized around the oxygen atoms. Additionally, the blue regions are appeared around the hydrogen atoms.

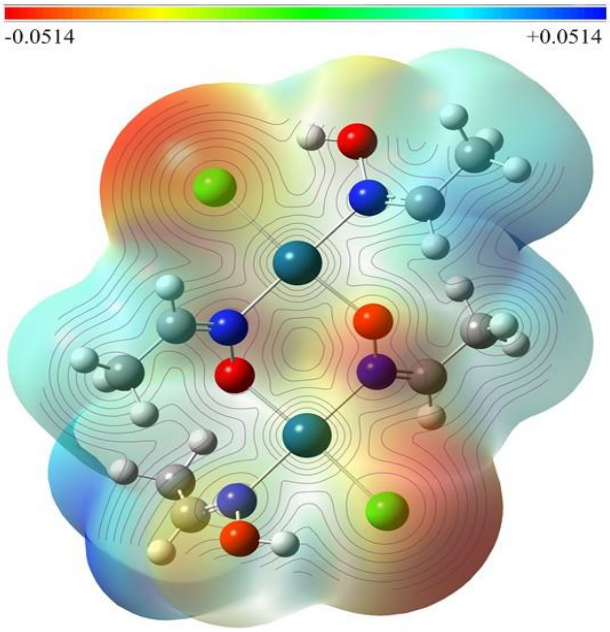

Fig. 5. MEP map of oximato-bridged Pt (II) complex calculated with HF/CEP-31G level in vacuum.

4. Conclusions

HF and MP2 methods, pure DFT functions (BP86, BPW91, PW91PW91, SVWN5) and hybrid DFT functions (B3LYP, B3P86, B3PW91, MPW1PW91, BHandLYP) with CEP-4G, CEP-31G, CEP-121G, LANL2DZ, LANL2MB and SDD basis sets were used to determine the best structure of oximato-bridged Pt(II) complex. Calculated geometrical parameters were subjected to correlation analyses with experimental results. CPU times of each level were obtained. HF/CEP-31G was found as the best level for mentioned Pt(II) complex. The vibrational frequency analyses were performed on Pt(II) complex by using each methods with CEP-31G basis set. Average linear scale factors were calculated for each method. For IR spectrum, the best level was found as MP2/CEP-31G by using linear scale factor. The UV-VIS spectrum of mentioned complex have not been studied and this spectra is calculated by using TD-HF/CEP-31G level in vacuum. Additionally, ^{1}H-NMR is calculated by using GIAO method in methanol solvent. There is an agreement between experimental and calculated chemical shifts values. The nucleophilic active regions are identified by using MEP map of Pt(II) complex.

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