Quantum Mechanical Study of the Structure, NBO and HOMO–LUMO Analysis of Molecule Oxaliplatinium

Reza Ghiasi*, Nooshin Parseh

Department of Chemistry, Basic science faculty, East Tehran Branch, Islamic Azad University, Qiam Dasht, Tehran, IRAN

Received 22 Jun. 2014; Final version received 13 Aug. 2014

Abstract

Oxaliplatinium is an anticancer drug, used in chemotherapy. To investigate the oxaliplatinium structure based on frontier orbital analysis, thermodynamic analysis and natural bond orbital (NBO) theory is the main objective of the present research. The calculated HOMO and LUMO energies show that charge transfer occurs within molecule. The NBO charges, the values of electric dipole moment (μ) of the molecule were computed using DFT calculations. As a result, the optimized geometry shows a good agreement with the similar experimental results.

Keywords: *Oxaliplatin, DFT calculation, Molecular orbital analysis, NBO analysis, thermodynamic parameters.*

Introduction

Platinum-based coordination complexes had first been discovered as strong inhibitors of bacterial proliferation by Barnett Rosenberg in the 1960s [1]. Then, their cytostatic activity had been studied in tumor-bearing animals with the encouraging result of a complete inhibition of murine solid sarcoma-180 by cisplatin [2]. Today, cisplatin, *cis*-diamminedichloroplatinum(II), and carboplatin, cisdiammine(1,1-cyclobutanedicarboxylato)platinum(II), oxaliplatinium are routinely used in the clinic as anticancer compounds [3-6]. Oxaliplatin, developed by Kidani et al. [7], first attracted attention since its particularly high activity, even in cisplatin-resistant tumor models. As a result, it is at this time being investigated for its potential as a treatment choice after letdown of cisplatin or carboplatin therapy.

The present work reports a computational study on oxaliplatinium. The structural parameters,

*Corresponding author: Dr. Reza Ghiasi, Department of Chemistry, Basic science faculty, East Tehran Branch, Islamic Azad University, Qiam Dasht, Tehran, IRAN. E-mail: rghyasi@qd.ac.ir.

molecular orbital, natural bond orbital have been analyzed. Also, theromdynamic parameters have been calculated in different temperatures.

Computational method

All calculations were carried out with the Gaussian 2003 suite of program [8] using the standard 6-311G (d, p) basis set [9-12] for C, H, O, and N atoms. For Pt element standard LANL2DZ basis set [13-15] are used and Pt described by effective core potential (ECP) of Wadt and Hay pseudopotential [16] with a doublet-ξ valance using the LANL2DZ. Geometry optimization was performed utilizing one parameter hybrid functional with modified Perdew-Wang exchange and correlation (mpw1pw91) [17]. A vibrational analysis was performed at each stationary point found, that confirm its identity as an energy minimum. The population analysis has also been performed by the natural bond orbital method [18] using the natural bond orbital (NBO) program [19] under Gaussian 2003 program package.

Result and Discussion

Molecular geometry

Figure 1 indicates the structure of oxaliplatinium. The absolute energy and dipole moment of the optimized molecule have been gathered in Table 1. The optimized structural parameters of oxaliplatinium are listed in Table 2 and the atom numbering scheme also given in Figure 1. In the literature, we have found experimental data for (SP-4-3)-(4S-methyl-trans-1R,2R-cyclohexane-1,2-diamine)oxalatoplatinum(II) [6] and compared these values with our calculations. Most of the optimized bond lengths is slightly larger than the experimental values, otherwise Pt-O bonds. The cyclohexane ring adopts a chair conformation with the two amino groups in equatorial positions. The dihedral angles of this ring are shown in Figure 1. Although theoretical results are not exactly close to the experimental values for the title molecule, this may due to the fact that the theoretical calculations were aimed at the isolated molecule in gaseous phase and the experimental results were aimed at the molecule in the solid state, the calculated geometric parameters also represents good approximation and they can be used as foundation to calculate the other parameters for the compound.
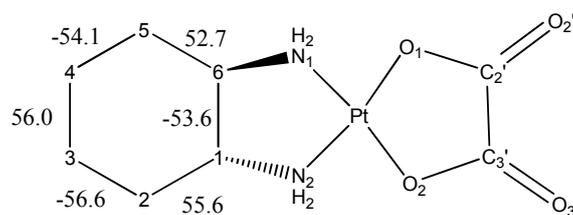
Figure 1. The structure and dihedral angles of oxaliplatinium.

Table 1. Absolute energy, Zero point vibration energy, energy, Molar capacity at constant volume, Entropy, Dipole moment of oxaliplatinium.

Parameters			
Absolute energy (Hartree)		-833.6452304	
Zero point vibration energy (Joules/Mol)		672981.1	
Rotational constants(GHZ)	1.24774	0.24999	0.22852
Rotational temperature (K)	0.05988	0.01200	0.01097
Energy (KCal/Mol)			
Translational		0.889	
Rotational		0.889	
Vibrational		167.891	
Total		169.668	
Molar capacity at constant volume (Cal/Mol-Kelvin)			
Translational		2.981	
Rotational		2.981	
Vibrational		47.283	
Total		53.244	
Entropy (Cal/Mol-Kelvin)			
Translational		43.828	
Rotational		32.778	
Vibrational		44.418	
Total		121.024	
Dipole moment (Debye)		14.0498	

Table 2. Structural parameters of oxaliplatinium.

Bond	R(Å)^{theo}	R(Å)^{exp,a}
Pt-O1	1.963	2.033
Pt-O2	1.963	2.022
C2'-O1	1.404	1.288
C3'-O2	1.404	1.291
C2'-O2'	1.241	1.234
C3'-O3'	1.241	1.226
Pt-N1	2.105	2.030
Pt-N2	2.106	2.026
C2'-C3'	1.594	1.548
N-C1	1.526	1.500
N-C6	1.526	1.509
C1-C2	1.553	1.524
C2-C3	1.548	1.548
C3-C4	1.548	1.533
C4-C5	1.548	1.531
C5-C6	1.548	1.520
C6-C1	1.557	1.517
Angle	(°)^{theo}	(°)^{exp}
N-Pt-N	83.36469	83.47
O-Pt-O	87.71270	82.27

^{a}(*SP*-4-3)-(4*S*-methyl-*trans*-1*R*,2*R*-cyclohexane-1,2-diamine)oxalatoplatinum(II)

Analysis of frontier molecular orbitals (FMOs)

Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very important parameters for quantum chemistry. The HOMO is the orbital that primarily acts as an electron donor and the LUMO is the orbital that largely acts as the electron acceptor [20]. The MOs are defined as eigen functions of the Fock operator, which exhibits the full symmetry of the nuclear point group, they necessarily form a basis for irreducible representations of full point-group symmetry. The energies of HOMO, LUMO, and their orbital energy gaps, have been gathered in Table3.

The pictorial illustration of the frontier molecular orbitals and their respective positive and negative regions are shown in Figure 2. Molecular orbitals, when viewed in a qualitative graphical representation, can provide insight into the nature of reactivity, and some of the structural and physical properties of molecules. The positive and negative phase is represented in red and green colour, respectively. The region of HOMO, HOMO-1 and HOMO-2 levels spread over the Pt and oxalate ligand. The region of LUMO, LUMO+1 and LUMO+2 levels spread approximately over the entire molecule and the calculated energy gap of HOMO–LUMO's explains the ultimate charge transfer interface within the molecule [21].

Global reactivity descriptors

Global reactivity descriptors [22-25] electronegativity (χ) chemical potential (μ), global hardness (η), global softness (S), and electrophilicity index (ω), determined on the basis of Koopman's theorem[26] are listed in Table 3.

$$\mu = \frac{E(H\quad) + E(Ll\quad)}{2}$$

$$\chi = \frac{E(H\quad) + E(Ll\quad)}{2}$$

$$\eta = \frac{E(Ll\quad) + E(H\quad)}{2}$$

where I and A which are called ionization potential and electron affinity, respectively and is I = -E(HOMO) and A = - E(LUMO). The chemical hardness and softness of a molecule is a good indicator of the chemical stability of a molecule. From the HOMO–LUMO energy gap, one can find whether the molecule is hard or soft. The molecules having large energy gap are known as hard and molecules having a small energy gap are known as soft molecules. The soft molecules are more polarizable than the hard ones because they need small energy to excitation.

Table 3. The frontier orbitals energies (Hartree), HOMO-LUMO gap (eV), Hardness (eV), softness (eV^{-1}), chemical potential and electrophilicity of oxaliplatinium.

E(HOMO)	E(LUMO)	E		S			
-0.11555	0.03487	0.294388	4.093169	0.48861	2.046584	-1.09772	0.294388

LUMO+2

LUMO+1

LUMO

HOMO

HOMO-1

HOMO-2
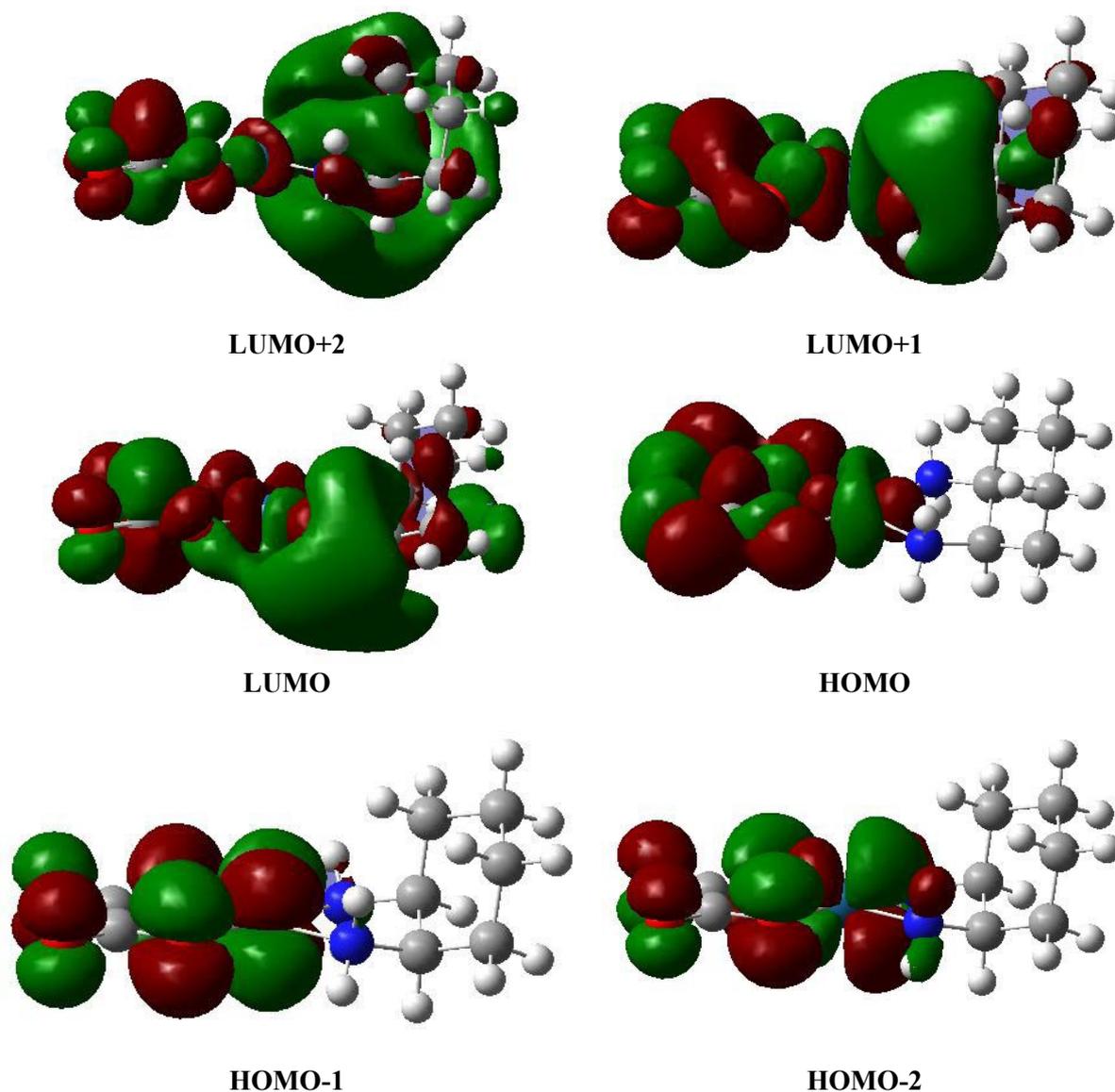
Figure 2. Frontier molecular orbitals (MOs) of the oxaliplatinium.

Temperature dependence of thermodynamic properties

The thermodynamic parameters have been tabulated in Tables 1 and 4. Also, the temperature dependence of the thermodynamic properties heat capacity at constant pressure (Cp), entropy (S) and enthalpy change for oxaliplatinium were also determined and listed in Table 4. Figure 3 depicts the correlation of heat capacity at constant pressure (Cp),

entropy (S) and enthalpy change with temperature along with the correlation equations. From Table 4, one can find that the entropies, heat capacities, and enthalpy changes are increasing with temperature ranging from 100 to 1000 K due to the fact that the molecular vibrational intensities increase with temperature. These observed relations of the thermodynamic functions vs. temperatures were fitted by quadratic formulas, and the corresponding fitting regression factors (R^2) are all not less than 0.988. The corresponding fitting equations for oxaliplatinium are:

$G = 1.07 \times 10^{-7} T^2 - 1.40 \times 10^{-4}T - 842.72;$ $R^2 = -0.9906086944$

$Cv = 1.02 \times 10^{-4} T^2 - 2.24 \times 10^{-1}T - 0.137;$ $R^2 = 0.9678808364$

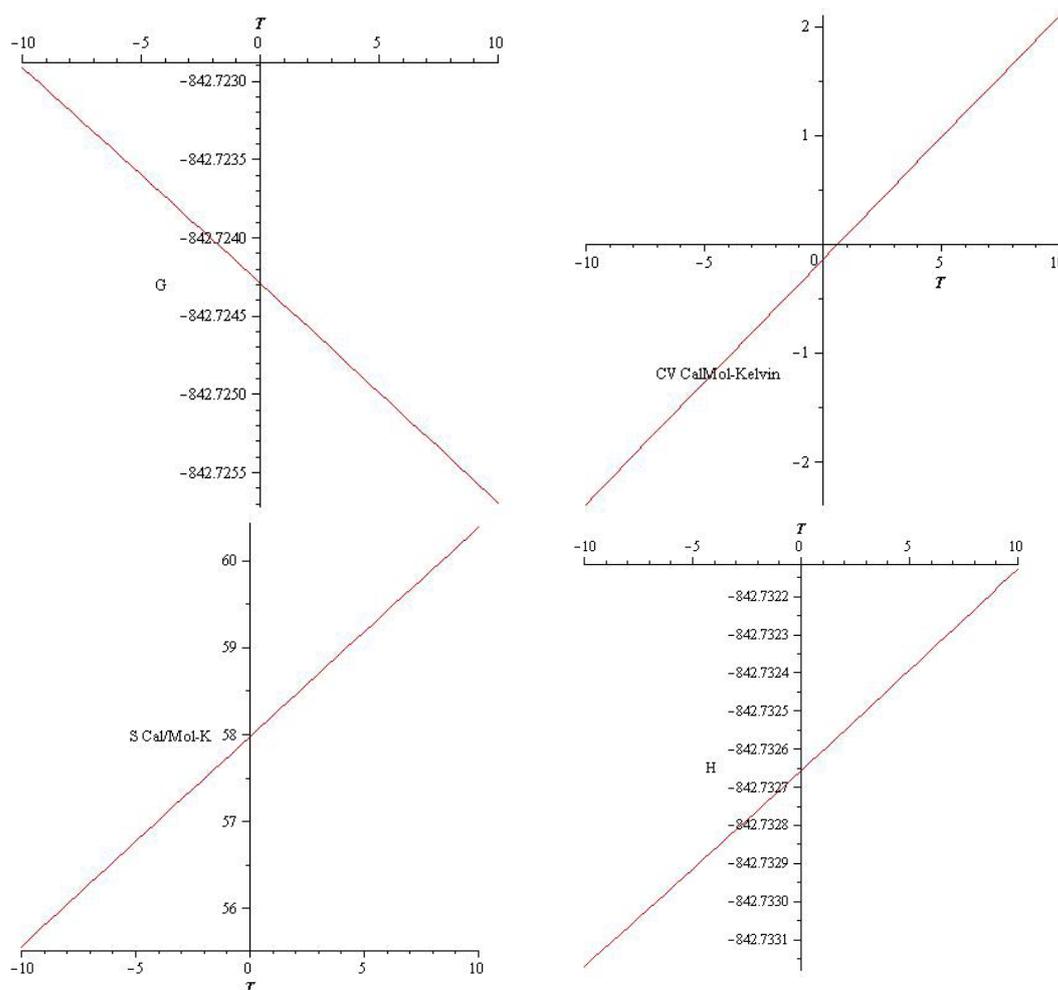$H = 7.77 \times 10^{-8} T^2 - 5.21 \times 10^{-5}T - 842.732;$ $R^2 = 0.9864464501$

$S = 6.89 \times 10^{-5} T^2 - 2.41 \times 10^{-1}T + 57.98;$ $R^2 = 0.9889797734$

Figure 3. The correlation of heat capacity at constant pressure (Cp), entropy (S) and enthalpy change with temperature.

Table 4. The temperature dependence of thermodynamic parameters of oxaliplatinium.

| T	G	H	S Cal/Mol-K	Cv Cal/Mol-Kelvin
100	-842.738816	-842.726026	80.256	21.584
200	-842.753357	-842.720950	101.680	38.131
300	-842.771124	-842.713219	121.119	54.951
400	-842.815620	-842.690074	157.562	84.828
500	-842.815620	-842.690074	157.562	84.828
600	-842.842086	-842.675306	174.427	96.154
700	-842.871159	-842.658905	190.274	105.404
800	-842.902677	-842.641163	205.129	113.054
900	-842.936489	-842.622304	219.060	119.469
1000	-842.972451	-842.602504	232.146	124.909

NBO analysis

The Natural Bond Orbital (NBO) analysis of oxaliplatinium has provided the detailed insight into the nature of electronic conjugation between the bonds in this molecule.

Figure 4 indicates bar diagram representing the charge distribution in oxaliplatinium. The largest negative charges (-0.84 e) are located on two nitrogens atoms, N1 and N2.
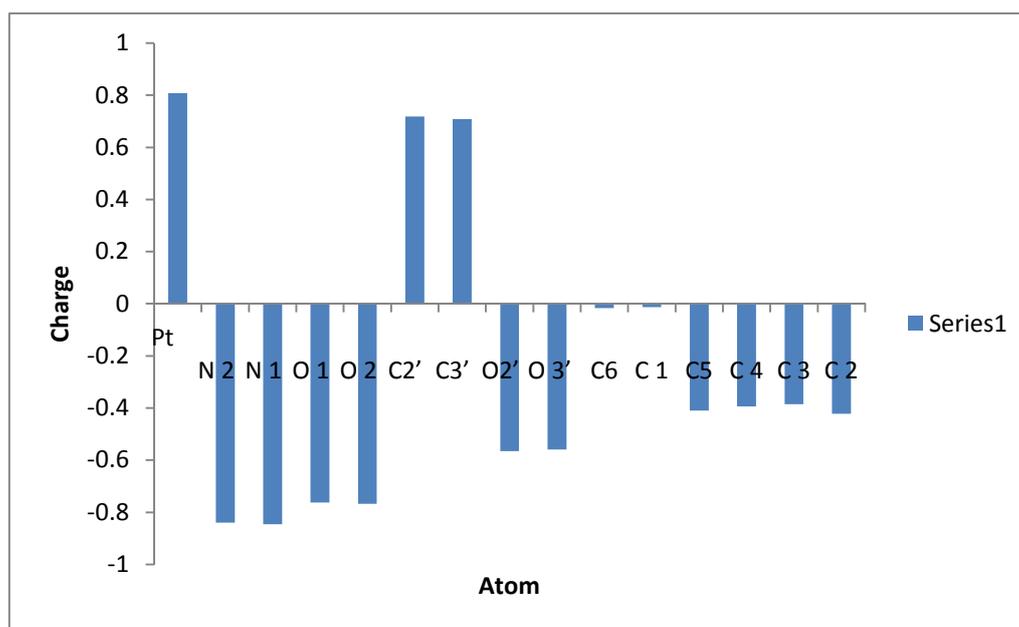
Figure 4. Bar diagram representing the charge distribution in oxaliplatinium.

According to the NBO results, the electron configuration of Pt is:

[core]6S(0.54)5d(8.61)6d(0.01)7p(0.02)
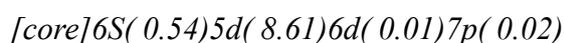
Thus, 68 core electrons, 9.15 valence electrons (on 5d and 6s atomic orbitals) and 0.03 Rydberg electrons (mainly on 6d and 7p orbitals) give the total of 77.18 electrons. This is consistent with the calculated natural charge on Pt atom in oxaliplatinium +0.82 e, which corresponds to the difference between 77.18e and the total number of electrons in the isolated Pt atom (78e).

According to calculations, the platinium atom forms a single bond (sigma bond) with two oxygen atoms O1 and O2 atoms, respectively. Occupancy of natural orbitals (NBOs) and hybrids of the σ(Pt-O) bonds are:

(1.94697) BD (1) Pt -O1: 0.4519 Pt s(44.39%) p 0.01 (0.38%) d 1.24 (55.23%)+0.8920 O1s (14.35%) p 5.97 (85.62%)d 0.00(0.04%).

(1.94744) BD (1)Pt -O 2: 0.4505 Pt s(44.35%) p 0.01(0.38%)d 1.25(55.28%)+0.8928 O 2 s(14.48%)p 5.90(85.48%)d 0.00(0.04%).

These values show that the σ(Pt-O) bonds are formed from an sd^n hybrid on platinium.

Also, the NBO analysis shows that the strongest interactions are the electron donations from a lone pair orbital on the phosphorous atoms, LP(1)N1 to the antibonding acceptor σ*(Pt-O2) orbitals and LP(1)N2 to the antibonding acceptor σ*(Pt-O1) orbitals.

Conclusion

Attempts have been made in the present study for investigation of structure, molecular orbitals, thermodynamic parameters, and NBO analysis of oxaliplatinium. The calculated structural parameters indicated good fit to experimental result in similar molecule. Molecular orbital analysis shows that region of HOMO, HOMO-1 and HOMO-2 levels spread over the Pt and oxalate ligand, but it spreads over entire molecule for The

LUMO, LUMO+1 and LUMO+2. After thermodynamic parameters calculation, these calculated in various temperatures. Then relations of the thermodynamic functions vs. temperatures were fitted by quadratic formulas. The Natural Bond Orbital (NBO) analysis provided the detailed insight into the type of hybridization and the nature of bonding in oxaliplatinium. The σ(Pt-O) bonds are formed from an sd^n hybrid on Pt atom.

References

[1] B. Rosenberg, L. V. Camp, T. Krigas, *Nature* 205, 698 (1995).

[2] B. Rosenberg, L. V. Camp, J. E. Trosko, V. H. Mansour, *Nature*, 222, 385 (1969).

[3] B, Rosenberg, *Interdiscip. Sci. Rev.*, 3, 134 (1978).

[4] P. J. O'Dwyer, J. P. Stevenson, S. W. Johnson, *Drugs*, 59, 19 (2000).

[5] M. A. Jakupec, M. Galanski, B. K. Keppler, *Rev. Physiol. Biochem.Pharmacol.*, 146, 1 (2003).

[6] M. Galanski, A.Yasemi, S. Slaby, M. A. Jakupec, V. B. Arion, M. Rausch, A. A. Nazarov, B. K. Keppler, *European Journal of Medicinal Chemistry*, 39, 707 (2004).

[7] Y. Kidani, M. Noji, T. Tashiro, Gann, 71, 637 (1980).

[8] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J.

Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Revision B.03 ed., Gaussian, Inc., Pittsburgh PA (2003).

[9] R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, J. Chem. Phys., 72, 650 (1980).

[10] A. J. H. Wachters, J. Chem. Phys., 52, 1033 (1970).

[11] P. J. Hay, *J. Chem. Phys*., 66, 4377 (1977).

[12] A. D. McLean, G. S. Chandler, *J. Chem. Phys*., 72, 5639 (1980).

[13]   P. J. Hay, W. R. Wadt, *J. Chem. Phys*, 82, 299 (1985).

[14]   P. J. Hay, W. R. Wadt, *J. Chem. Phys*, 82, 284 (1985).

[15] A. Schaefer, H. Horn, R. Ahlrichs, *J. Chem. Phys*., 97, 2571 (1992).

[16] P. J. Hay, W. R. Wadt, *J. Chem. Phys,* 82, 270 (1985).

[17] A. D. Becke, J. Chem. Phys, 98, 5648 (1993).

[18] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev*., 88, 899 (1988).

[19] E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold, 3.1. ed. (1988).

[20] J. M. Seminario, *Recent Developments and Applications of Modern Density Functional Theory*, Vol. 4, Elsevier.

[21] V. Arjunana, I. Saravananb, C. V. Mythilic, M. Kalaivania, S. Mohand, *Spectrochimica Acta Part A*, 92, 1 (2012).

[22] R. G. Pearson, *J. Org. Chem.* , 54, 1430 (1989).

[23] R. G. Parr, R. G. Pearson, *J. Am. Chem. Soc.* , 105, 7512 (1983).

[24] P. Geerlings, F. D. Proft, W. Langenaeker, *Chem. Rev*. , 103, 1793 (2003).

[25] R. G. Parr, L. Szentpۈly, S. Liu, *J. Am. Chem. Soc.* , 121, 1922 (1999).

[26] R. G. Parr, W. Yang, *Density functional Theory of Atoms and Molecules*, Oxford University Press, Oxford, New York (1989).