Research Journal of Chemical Sciences ISSN 2231-606X
Vol. **4(11),** 56-61, November **(2014)** *Res. J. Chem. Sci.*

A Density Functional Theory (DFT) Perspective on Organotin(IV)-Drug Interaction: Dimethyltin(IV) Derivative of Chlordiazepoxide

Pokharia Sandeep
Chemistry Section, Mahila Mahavidyalaya, Banaras Hindu University, Varanasi-221005, U.P., INDIA

Available online at: www.isca.in, www.isca.me
Received 10th November 2014, revised 15th November 2014, accepted 18th November 2014

Abstract

The density functional theory (DFT) based quantum-mechanical calculations have been performed on dimethyltin(IV) derivative of chlordiazepoxide using the Gaussian09 software package. The ground state optimization of the possible tetrahedral structure was achieved using B3LYP functional with 6-31G(d,p) basis set for all the atoms, except the tin(IV) atom which was described by LANL2DZ basis set along with the effective core potential. The harmonic vibrational frequencies were computed at the same level of theory to find the true potential energy surface (PES) minima. The charge distribution within the ligand and its dimethyltin(IV) derivative was calculated using Mulliken population analysis, Hirshfeld population analysis and natural population analysis. The conceptual-DFT based global reactivity descriptors such as, electronic chemical potential, electronegativity, chemical hardness, global softness and electrophilicity index for the complex have been obtained using the frontier molecular orbital analysis. The nature of O–Sn, C–Sn and N–O bond is discussed in terms of the natural bond orbital (NBO) analysis. The structural analysis in terms of the selected bond lengths and bond angles, and vibrational analysis of characteristic infrared vibrational frequencies of chlordiazepoxide and its studied dimethyltin(IV) derivative is carried out to obtain a theoretical explanation for its possible formation.

Keywords: Chlordiazepoxide, conceptual reactivity descriptors, DFT, dimethyltin(IV), organotin(IV).

Introduction

The importance of metal ions lies in the fact that they are essential components for various physico-chemical processes occurring in the living systems as well as they have potential use as metallopharmaceuticals especially anti-tumour drugs. The initial success of platinum chemotherapeutic metallopharmaceuticals has prompted the researchers to non-platinum chemotherapeutics starting from the basic *cis*-platin framework with the aim to optimize the efficiency of such drugs[1]. Further, in the past two decades, the chemistry of metal complexes of active drugs has emerged as a promising approach towards design of novel therapeutic and diagnostic agents with broader pharmacological profile and wide range of biological activity[2].

Among the non-platinum chemotherapeutics, organotin(IV) derivatives of ligands containing hetero donor sites have emerged as potential biologically active metallopharmaceuticals owing to their unique structural features and also due to their wide range of potential biological applications most prominently anti-tumour activity[1-4]. The biological profile of organotin(IV) moieties has been expanded owing to the potential use of their derivatives formed with active drugs as anticancer and antiviral[5,6], antiinflammatory[7], and antituberculosis[8] agents.

The drug chlordiazepoxide (figure-1) is a benzodiazepine derivative with hypnotic action. Recently, the diorganotin(IV) and triorganotin(IV) derivatives of chlordiazepoxide have been synthesized and reported to exhibit marked antibacterial activity against a number of indicator strains particularly *Pseudomonas aeruginosa* and *Vibrio cholerae*[9]. These promising results have motivation in understanding the electronic properties of such complexes so as to design the new organotin(IV) derivatives with much broader biological activity. In the contemporary research, the density functional theory (DFT) based quantum-chemical methods holds special significance in order to understand the detailed electronic structure of the molecules and to calculate the properties, so as to form the theoretical basis for the experimental observations. The DFT has been successfully utilized to account for the experimental observations for several organotin (IV) derivatives with hetero donor atoms[10-13]. However, to the best knowledge of the author, electronic structure calculations using DFT on organotin (IV)-drug system has not been carried out so far. In order to expand the scope of such studies to organotin(IV)-drug system, the present study reports the DFT based quantum-mechanical calculations on the dimethyltin(IV) derivative of chlordiazepoxide.

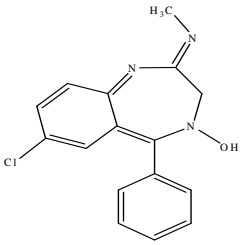


Figure-1
Structure of Chlordiazepoxide

Methodology

All the quantum mechanical calculations have been performed using the Gaussian09 software package[14]. The molecular structure of chlordiazepoxide and its dimethyltin(IV) derivative was optimized at the density functional theory (DFT) level using the B3LYP functional (combination of Becke's three parameter (B3) gradient corrected hybrid exchange functional[15], with the dynamical correlation functional of Lee, Yang and Parr (LYP)[16]). All the calculations were carried out without any symmetry constraint. The tin(IV) atom was described with LANL2DZ pseudo-potential basis set[17], whereas other atoms were described with standard 6-31G(d,p) basis set[18]. The absence of imaginary frequencies in a harmonic frequency calculation carried out at the same level of theory indicates that the calculated geometry is a true minimum on the potential energy surface. The optimized geometrical parameters, frontier molecular orbitals, fundamental vibrational frequencies and the atomic charges were calculated theoretically using Gaussian09 package. The conceptual-DFT based global reactivity descriptors *viz.* electronic chemical potential (μ), electronegativity (χ), chemical hardness (η), global softness (S) and electrophilicity index (ω) have been calculated using Koopman's approximation[19,20]. In order to gain an insight into the nature of possible coordination in the studied derivative Natural Bond Orbital (NBO) analysis was carried out using the Gaussian NBO version 3.1[21].

Results and Discussion

Geometry Optimization and Electronic Properties: The ground state optimization and harmonic frequency calculations (in the gas phase) of the chlordiazepoxide and its Me_2Sn(IV) derivative was achieved using DFT at B3LYP/6-31G(d,p)/ LANL2DZ(Sn) basis set. The optimized structure and atom notation of the studied derivative is presented in figure-2. The calculated electronic properties are summarized in table-1. The band gap ($\Delta E = E_{LUMO} - E_{HOMO}$) and various conceptual-DFT based global reactivity descriptors (on the basis of frontier molecular orbital analysis) for the studied Me_2Sn(IV) derivative are also calculated and summarized in table-1. The Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) plots of the Me_2Sn(IV) derivative of chlordiazepoxide are presented in figure-3.

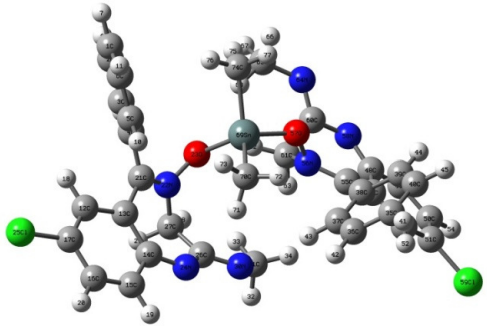


Figure-2
The ground state optimized geometry of the Me_2Sn(IV) derivative of chlordiazepoxide calculated at B3LYP/6-31G(d,p)/LANL2DZ(Sn) level of theory

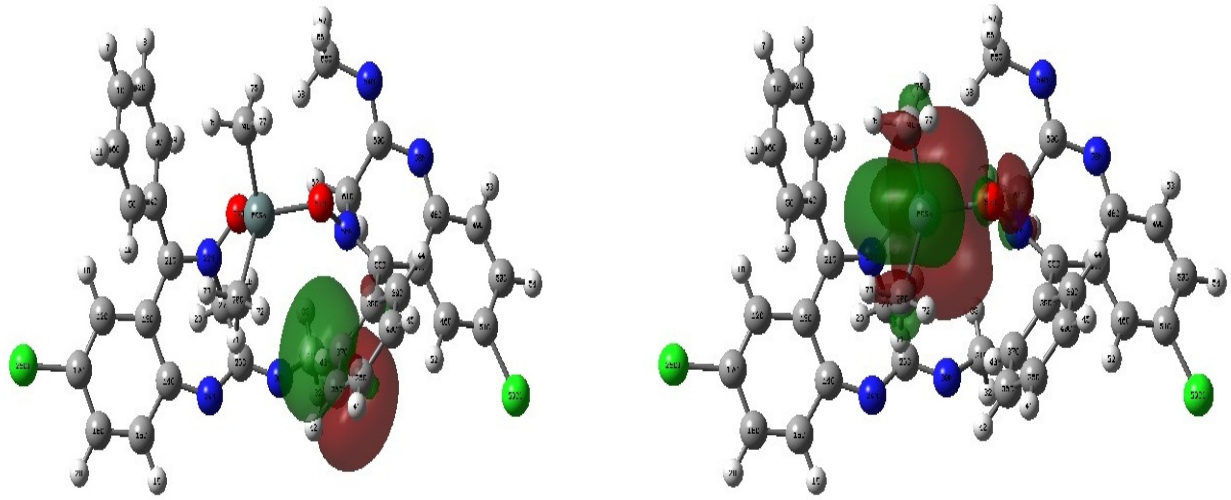
The band gap measures the stability and reactivity of the system[20]. The observed band gap (ΔE) value indicates that the complex is stable. Further, as evident from the figure-3, the LUMO of the complex is concentrated around the tin(IV) center. Furthermore, the chemical hardness (η) of a system implies resistance to charge transfer, whereas global softness (S) is proportional to the polarizability of the system[20]. The observed values of η and S (table-1) for the studied derivative suggests that the complex resist the charge transfer and hence possess low polarizability.

Table-1
Calculated thermodynamic properties and conceptual-DFT based global reactivity descriptors of the Me_2Sn(IV) derivative of chlordiazepoxide

Property	B3LYP/6-31G(d,p)/LANL2DZ(Sn)
SCF energy (a.u.)[a]	–2717.45357108
Enthalpy$_{(thermal)}$ (a.u.)[b]	–2716.814748
Free energy$_{(thermal)}$ (a.u.)[c]	–2716.937900
Zero-point vibrational energy (kcal/Mol)	373.18698
Dipole moment (Debye)	8.9676
E_{HOMO} (eV)	–6.89
E_{LUMO} (eV)	–0.49
ΔE ($E_{LUMO} - E_{HOMO}$)(eV)	6.40
Electronic chemical potential ($\mu = \frac{E_{LUMO} + E_{HOMO}}{2}$)	–3.69
Electronegativity ($\chi = -\mu$)	3.69
Chemical hardness ($\eta = E_{LUMO} - E_{HOMO}$)	6.40
Global softness ($S = \frac{1}{\eta}$)	0.1563
Electrophilicity index ($\omega = \frac{\mu^2}{2\eta}$)	1.064

[a]Total electronic energy without zero-point correction. [b]Sum of electronic and thermal enthalpy at 1 atm and 298.15 K. [c]Sum of electronic and thermal free energy at 1 atm and 298.15 K.

Atomic Charges and NBO Analysis: The atomic charge distribution of the chlordiazepoxide and its $Me_2Sn(IV)$ derivative was determined by Mulliken population analysis (MPA), Hirshfeld population analysis (HPA) and Natural population analysis (NPA) at B3LYP/6-31G(d,p) /LANL2DZ(Sn) level of theory. The results for the selected atoms are presented in table-2. Population analysis allows the attribution of net atomic charges in the molecular system[22]. Further, the distribution of positive and negative charges is significant from the perspective of increase or decrease in the bond length between atoms. The results (table-2) indicate that the most negative atomic charges are attributed to oxygen and nitrogen atoms in the ligand, and to oxygen, nitrogen and organotin(IV) carbon atoms in its $Me_2Sn(IV)$ derivative. In the NBO analysis of the $Me_2Sn(IV)$ derivative, the most negative charges are at the organic carbon atoms. Further, in the tetrahedral arrangement of ligands around the $Me_2Sn(IV)$ moiety, the nitrogen (N(22) and N(56)) has high positive charge than the oxygen (O(23) and O(57)) atom, and also upon complexation the charge become more negative on the oxygen atom and more positive on the nitrogen atom relative to the ligand because of the involvement of oxygen atom in coordination to the tin(IV) atom. Furthermore, the charge on the selected atoms in the ligand is smaller than the neutral complex, probably due to the high positive charge of tin(IV) atom, as reported for other organotin(IV)-oxygen system[10].



(a) **(b)**

Figure-3
(a) HOMO and (b) LUMO plots of the $Me_2Sn(IV)$ derivative of chlordiazepoxide calculated at B3LYP/6-31G(d,p)/LANL2DZ(Sn) level of theory

Table-2
Atomic charges (a.u.) in terms of MPA, HPA and NPA of the selected atoms of chlordiazepoxide (HL) and its $Me_2Sn(IV)$ derivative at B3LYP/6-31G(d,p)/LANL2DZ(Sn) level of theory

Element	MPA		HPA		NPA	
	HL	Me_2SnL_2	HL	Me_2SnL_2	HL	Me_2SnL_2
Sn	–	1.529	–	0.809	–	2.312
C(70)	–	–0.737	–	–0.092	–	–1.284
C(74)	–	–0.704	–	–0.090	–	–1.286
O(23)	–0.394	–0.650	0.030	–0.253	–0.570	–0.773
O(57)	–	–0.643	–	–0.259	–	–0.751
N(22)	–0.259	–0.073	0.020	0.046	–0.098	–0.024
N(56)	–	–0.114	–	0.035	–	–0.051
C(21)	0.242	0.177	0.073	0.067	0.259	0.245
C(27)	–0.115	–0.118	0.090	0.10	–0.341	–0.334
C(55)	–	0.190	–	0.075	–	0.268
C(61)	–	–0.137	–	0.076	–	–0.338

Structural Analysis: The selected calculated geometric parameters *viz.* bond lengths and bond angles of the chlordiazepoxide and its $Me_2Sn(IV)$ derivative are summarized in Table 3. The standard 6-31G (d,p) basis set, which contains d, p polarization function, is a sufficient basis set for an accurate prediction of geometric parameters for organic part of the compounds. Also, the LANL2DZ pseudo-potential is sufficient to account for the relativistic effects on the tin(IV) atom. The experimental XRD data for the studied derivative is not available, but the calculated Sn–C, Sn–O and N–C bond lengths are comparable to the reported bond lengths for various diorganotin(IV) systems which possess coordination of organotin(IV) moiety with the hetero donor atoms[1,3,10-13,23,24]. Further, the calculated bond angles suggest that the ligand molecules and two methyl groups are arranged around the tin(IV) atom in such a way that it leads to a distorted tetrahedral arrangement, as reported for other diorganotin(IV) derivatives of chlordiazepoxide[9].

Vibrational Analysis: The $Me_2Sn(IV)$ derivative of chlordiazepoxide consists of 77 atoms, hence it has 225 normal modes of vibration. The harmonic vibration frequencies were calculated for the neutral molecule in the gas phase at B3LYP/6-31G(d,p)/LANL2DZ(Sn) level of theory. The theoretical infrared spectrum of the $Me_2Sn(IV)$ derivative of chlordiazepoxide is presented in figure-4. The strong absorption bands at 572 and 574 cm^{-1} were observed in the studied $Me_2Sn(IV)$ derivative, which were otherwise absent in the free ligand, this confirms the coordination of hydroxyl oxygen to the tin(IV) atom. These bands are assigned to the Sn–O stretching vibration, as previously reported for the number of diorganotin(IV) –oxygen derivatives[1,3,10-12,23,24]. Further, the ν_{asym}(Sn–C) and ν_{sym}(Sn–C) bands in the studied $Me_2Sn(IV)$ derivative of chlordiazepoxide were observed at 543 and 523 cm^{-1}, respectively, which suggests the existence of a bent C–Sn–C moiety[1,3,23,24]. The characteristic N–O stretching vibration was observed in the region 1130–1140 cm^{-1}, relative to 1117 cm^{-1} in the free ligand. The result indicates that there is a shift of electron density within the molecule towards the oxygen atom upon its coordination to the tin(IV) atom, which lowers its bond length with consequent increase in the bond strength.

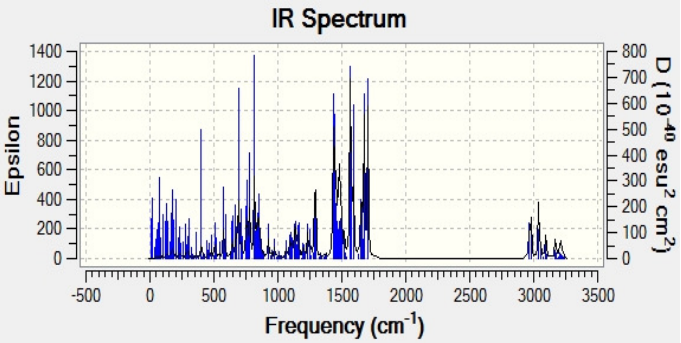


Figure-4
Theoretical infrared spectrum of $Me_2Sn(IV)$ derivative of chlordiazepoxide calculated at B3LYP/6-31G(d,p)/LANL2DZ(Sn) level of theory

Conclusion

The present study has satisfactorily achieved the electronic structure calculation of dimethyltin(IV)-chlordiazepoxide system at B3LYP/6-31G(d,p)/LANL2DZ(Sn) level of theory. The atomic charge calculations and the NBO analysis suggest that upon coordination of chlordiazepoxide molecule to dimethyltin(IV) moiety, the electron density is concentrated around coordinating oxygen atom. The frontier molecular orbital analysis and its use in the calculation of conceptual-DFT based global reactivity descriptors can rationalize the possible interaction of diorganotin(IV)-chlordiazepoxide derivative with macromolecular receptors, so as to account for its probable biological activity. Most significantly, the present work emphasizes the growing importance of DFT based quantum-chemical methods for the electronic structure calculations of organotin(IV)-drug system, so as to design and synthesize novel metallopharmaceuticals.

Acknowledgements

The author is thankful to Banaras Hindu University, Varanasi for providing necessary infrastructural facilities.

Table-3
Selected bond lengths (Å) and bond angles (°) of $Me_2Sn(IV)$ derivative of chlordiazepoxide calculated at B3LYP/6-31G(d,p)/LANL2DZ(Sn) level of theory

Bond Lengths										
	Sn–C (70)	Sn–C (74)	Sn–O (23)	Sn–O (57)	O(23)–N (22)	O(57)–N (56)	N(22)–C (21)	N(22)–C (27)	N(56)–C (55)	N(56)–C (61)
C[a]	2.121	2.117	2.026	1.974	1.384	1.398	1.343	1.453	1.354	1.453
L[b]	–	–	–	–	1.418	–	1.364	1.452	–	–
Bond angles										
	C(70)–Sn–C(74)		O(23)–Sn–O(57)		O(23)–Sn–C(70)		O(23)–Sn–C(74)	O(57)–Sn–C(70)	O(57)–Sn–C(74)	
C[a]	118.9		103.2		110.1		108.5	117.0	97.6	

[a]Dimethyltin(IV) derivative of chlordiazepoxide. [b]Neutral chlordiazepoxide molecule.

References

1. Nath M., Pokharia S., Eng G., Song X. and Kumar A.,

New triorganotin(IV) derivatives of dipeptides as anti-inflammatory-antimicrobial agents, *Eur. J. Med. Chem.*, **40**, 289-298 (**2005**)

2. Ronconi L. and Sadler P.J., Using coordination chemistry to design new medicines, *Coord. Chem. Rev.*, **251**, 1633-1648 (**2007**)

3. Nath M., Pokharia S., Song X., Eng G., Gielen M., Kemmer M., Biesemans M., Willem R. and deVos D., New organotin(IV) derivatives of dipeptides as models for metal-protein interaction: in vitro anti-tumour activity, *Appl. Organometal. Chem.*, **17**, 305-314 (**2003**)

4. Alama A., Tasso B., Novelli F. and Sparatore F., Organometallic compounds in oncology: implications of novel organotin as antitumor agents, *Drug Discov. Today*, **14**, 500-508 (**2009**)

5. Carraher C., Sabir T., Roner M., Shahi K., Bleicher R., Roehr J. and Bassett K., Synthesis of organotin polyamine ethers containing acyclovir and their preliminary anticancer and antiviral activity, *J. Inorg. Organomet. Polym. Mater.*, **16**, 249-257 (**2006**)

6. Dokorou V., Primikiri A. and Kovala-Demertzi D., The triphenyltin(IV) complexes of NSAIDs and derivatives. Synthesis, crystal structure and antiproliferative activity. Potent anticancer agents, *J. Inorg. Biochem.*, **105**, 195-201 (**2011**)

7. El-Gamel N.E.A., The interactions of metal ions with nonsteroidal anti-inflammatory drugs (oxicams), *J. Coord. Chem.*, **62**, 2239-2260 (**2009**)

8. Kovala-Demertzi D., Dokorou V., Primikiri A., Vargas R., Silvestru C., Russo U. and Demertzis M.A., Organotin meclofenamic complexes: synthesis, crystal structures and antiproliferative activity of the first complexes of meclofenamic acid-novel anti-tuberculosis agents, *J. Inorg. Biochem.*, **103**, 738-744 (**2009**)

9. Dhir K., Kaur H., Puri J.K. and Mittu B., Synthesis, characterization and biological activity of diorgano and triorganotin(IV) complexes of Chlordiazepoxide, Choline theophyllinate and Phenobarbitone sodium, *J. Organomet. Chem.*, **755**, 101-109 (**2014**)

10. Naseh M., Sedaghat T., Tarassoli A. and Shakerzadeh E., DFT studies of ONO Schiff bases, their anions and diorganotin(IV) complexes: Tautomerism, NBO and AIM analysis, *Comput. Theor. Chem.*, **1005**, 53-57 (**2013**)

11. Latrous L., Tortajada J., Haldys V., Léon E., Correia C. and Salpin J.-Y., Gas-phase interactions of organotin compounds with glycine, *J. Mass Spectrom.*, **48**, 795-806 (**2013**)

12. Şirikci G., Ancın N., Öztaş S.G., Yenişehirli G. and Öztaş N.A., Synthesis, spectral, theoretical studies and in vitro antimicrobial activities of novel diphenyltin(IV) complexes of Schiff bases derived from phenacylamine, *Appl. Organometal. Chem.*, **28**, 537-544 (**2014**)

13. Matczak P., Theoretical investigation of the N→Sn coordination in $(Me_3SnCN)_2$, *Struct. Chem.* (**2014**) (doi: 10.1007/s11224-014-0485-4)

14. Frisch M.J., Trucks G.W., Schlegel H.B., Scuseria G.E., Robb M.A., Cheeseman J.R., Scalmani G., Barone V., Mennucci B., Petersson G.A., Nakatsuji H., Caricato M., Li X., Hratchian H.P., Izmaylov A.F., Bloino J., Zheng G., Sonnenberg J.L., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Vreven T., Montgomery, J.A.Jr., Peralta J.E., Ogliaro F., Bearpark M., Heyd J.J., Brothers E., Kudin K.N., Staroverov V.N., Keith T., Kobayashi R., Normand J., Raghavachari K., Rendell A., Burant J.C., Iyengar S.S., Tomasi J., Cossi M., Rega N., Millam J.M., Klene M., Knox J.E., Cross J.B., Bakken V., Adamo C., Jaramillo J., Gomperts R., Stratmann R.E., Yazyev O., Austin A.J., Cammi R., Pomelli C., Ochterski J.W., Martin R.L., Morokuma K., Zakrzewski V.G., Voth G.A., Salvador P., Dannenberg J.J., Dapprich S., Daniels A.D., Farkas O., Foresman J.B., Ortiz J.V., Cioslowski J. and Fox D.J., Gaussian09, Revision B.01, Gaussian, Inc., Wallingford CT (**2010**)

15. Becke A.D., Density functional thermochemistry.III. The role of exact exchange, *J. Chem. Phys.*, **98**, 5648-5652 (**1993**)

16. Lee C., Yang W. and Parr R.G., Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev. B*, **37**, 785-789 (**1988**)

17. Hay P.J. and Wadt W.R., Ab initio effective core potentials for molecular calculations-potentials for K to Au including the outermost core orbitals, *J. Chem. Phys.*, **82**, 299-310 (**1985**)

18. Petersson G.A. and Al-Laham M.A., A complete basis set model chemistry. II. Open-shell systems and the total energies of the first-row atoms, *J. Chem. Phys.*, **94**, 6081-6090 (**1991**)

19. Geerlings P., De Proft F. and Langenaeker W., Conceptual Density Functional Theory, *Chem. Rev.*, **103**, 1793-1873 (**2003**)

20. Roy R.K. and Saha S., Studies of regioselectivity of large molecular systems using DFT based reactivity descriptors, *Annu. Rep. Prog. Chem., Sect. C*, **106**, 118-162 (**2010**)

21. Glendening E.D., Reed A.E., Carpenter J.E. and Weinhold F., NBO Version 3.1.

22. Berger G., Using conceptual density functional theory to rationalize regioselectivity: A case study on the nucleophilic ring-opening of activated aziridines,

Comput. Theor. Chem., **1010**, 11-18 (**2013**)

23. Nath M., Singh H., Eng G. and Song X., New di- and triorganotin(IV) derivatives of tyrosinylphenylalanine as models for metal-protein interactions: Synthesis and structural characterization. Crystal structure of Me_2Sn(Tyr-Phe).MeOH, *J. Organomet. Chem.*, **693**, 2541-2550 (**2008**)

24. Nath M., Singh H., Kumar P., Kumar A., Song X. and Eng G., Organotin(IV) tryptophanylglycinates: potential non-steroidal anti-inflammatory agents; crystal structure of dibutyltin(IV)tryptophanylglycinate, *Appl. Organometal. Chem.*, **23**, 347-358 (**2009**)