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INCORPORATION OF ZIRCONOCENE INTO N-PHTHALOYL AMINO ACIDS AND KETOXIMES: OPTIMIZED STRUCTURE OF $C_{26}H_{28}N_2O_5Zr$ AND OPTIMIZED ENERGY BASED ON COMPUTATIONAL ANALYSIS

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ABSTRACT
Incorporation of zirconocene into N-phthaloyl amino acids and ketooximes was accomplished by the reaction of zirconocene dichloride with these two ligands in the presence of triethylamine in 1:1:1:2 molar ratios in refluxing dry THF. This interaction afforded solid products of the type Cp_2ZrLA. A pentacoordinated geometry may be assigned to these complexes with the assistance of mass and spectroscopic studies. In these complexes, the coordination behavior of N-phthaloyl amino acids and ketoximes is bidentate and monodentate, respectively. The optimized structure, energy, geometry, energy gap and stability of one representative zirconocene complex were studied by using DFT(B3LYP) to corroborate the structures of these products.

Keywords: DFT, zirconocene complexes, N-phthaloyl amino acids, ketoximes, optimized geometry.

INTRODUCTION
Oximes constitute an important class of versatile ligands which are used for protection and structural elucidation of huge carbonyl compounds. A large number of oxime derivatives have been synthesized[1] and studied for their pharmacological importance. Oximes have been reported to demonstrate anticancer, anti-inflammatory[2] and antioxidant[3] activities. The reaction of carbonyl compound with hydroxylamine or a hydroxyl ammonium salt results in the incorporation of oxime group into organic molecules. The conversion of carbonyl functionality into oxime group is a convenient approach for the synthesis of these biological agents which are important in medicinal research[4]–[6]. The high polarity of oxime groups may result into different ways of interaction with receptor binding sites[2]. Amino acids and their derivatives play a significant role in biology, pharmacy and industry[7]–[9]. The importance of amino acids in biological system may be correlated with their solubility properties and peculiar mechanism of transport. Amino acids are precursors for generating a large number of structural derivatives having different functionalities[10], [11] as well as their metal complexes.
In recent years, metal complexes of amino acid derivatives[8], [10]–[13] and ketoxime[13] / oxime derivatives[14], [15] have attracted the attention of researchers because the biological activity of these complexes was enhanced as compared to the parent ligands. A plenteous interest has been developed in the chemistry of zirconocene complexes containing different ligands as these complexes have a vast range of

applications in catalysis[16]–[18]. Zirconocene complexes also demonstrated potential anticancer[19] and antimicrobial activity[20], [21].

In the present communication, we report the incorporation of zirconocene into N-phthaloyl amino acids and ketoximes which afforded pentacoordinated zirconocene complexes. DFT(B3LYP) was employed to investigate the optimized structure, energy, geometry, energy gap and stability of one representative zirconocene complex $(C_5H_5)_2ZrA_{(1)}L_{(1)}$ (complex 1).

II. EXPERIMENTAL

Zirconocene dichloride and ketoxime($L_{(1)}H$ and $L_{(2)}H$) are commercially available. N-protection of amino acids was carried out by reported method of 'Sheehan'[22] for synthesizing N-phthaloyl amino acid($A_{(1)}H$ and $A_{(2)}H$). Standard methods were used for drying of solvents. The experimental work was carried out under strictly anhydrous conditions. The preparation of $(C_5H_5)_2ZrA_{(2)}L_{(2)}$ (Complex 3) is described in detail and analytical data of other analogous complexes are summarized in Table 1.

2.1 Preparation of $(C_5H_5)_2ZrA_{(2)}L_{(2)}$ (Complex 3)

N-phthaloyl-β-alanine ($A_{(2)}H$=1,3-dihydro-1,3-dioxo-2H-isoindole-2-propanoic acid) (0..45 gm, 2.07 mmol) and acetophenoneoxime $L_{(2)}H$=N-(1-phenylethylidene) hydroxylamine) (0.28 gm, 2.07 mmol) were dissolved in dry THF and then, this solution of the two organic ligands was added to a dry THF solution of zirconocene dichloride, Cp_2ZrCl_2 (0.60 gm, 2.07 mmol). After this, triethylamine (0.42 gm, 4.15 mmol) was added to this mixture immediately. Continuous refluxing with stirring of the above mentioned reaction mixture was done for approximately 8 hours. After completion of the reaction, filtration of solid triethylamine hydrochloride, was carried out. The excess solvent was removed in vacuo. A coloured solid product was isolated which was recrystallized from benzene pet-ether mixture.

TABLE 1. Analytical data of Zirconocene complexes

Complex formula (Empirical formula)	Reagents in g (mmol)				Et_3N.HCl Found (Calc.)	% Yield	% Zr Found (Calc.)
	Et_3N	AH	LH	Cp_2ZrCl_2			
$Cp_2ZrA_{(1)}L_{(1)}$ ($C_{26}H_{28}N_2O_5Zr$) Complex 1	0.35 (3.45)	0.42 (1.72)	0.12 (1.72)	0.50 (1.72)	0.46 (0.47)	58	16.87 (16.89)
$Cp_2ZrA_{(1)}L_{(2)}$ ($C_{31}H_{30}N_2O_5Zr$) Complex 2	0.46 (4.54)	0.56 (2.27)	0.30(2.27)	0.66 (2.27)	0.60 (0.62)	65	15.14 (15.15)
$Cp_2ZrA_{(2)}L_{(2)}$ ($C_{29}H_{26}N_2O_5Zr$) Complex3	0.42 (4.15)	0.45 (2.07)	0.28 (2.07)	0.60 (2.07)	0.55 (0.56)	60	15.88 (15.89)

III. RESULTS & DISCUSSION

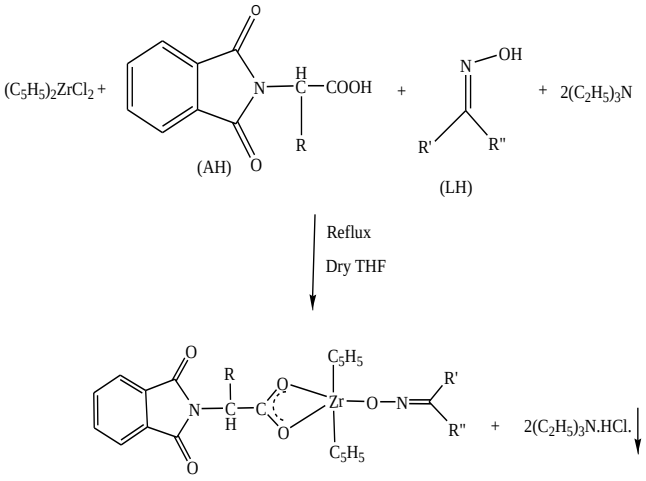
Incorporation of zirconocene into N-phthaloyl amino acids and ketoximes was carried out by the reaction of zirconocene dichloride with these two different ligands in the presence of triethylamine in 1:1:1:2 molar ratio in boiling dry THF as depicted in scheme 1.

Zirconocene complexes having the general formula Cp_2ZrAL [where AH = $(\overline{C(O)C_6H_4C(O)N}CH(R)COOH)$ and LH= R'R"CNOH where R= $-CH(CH_3)_2$ ($A_{(1)}H$), CHR= $-CH_2CH_2-$ ($A_{(2)}H$), R'=R"= $-CH_3$ ($L_{(1)}H$), R'=CH_3, R"=C_6H_5 ($L_{(2)}H$)] were obtained. The byproduct, $(C_2H_5)_3N.HCl$ formed in these reactions, was filtered out. Tentative structures of these products were

characterized by mass, spectral and DFT studies. These zirconocene complexes were characterized with the help of mass and spectroscopic (IR and ^{1}H NMR) studies.

3.1 FT-IR spectra

The FT-IR spectra of these zirconocene complexes of N-phthaloyl amino acids and ketoximes were recorded as KBr pellets in the region 4000-400 cm^{-1}. In the IR spectra of zirconocene complexes, two medium intensity bands were appeared in the regions 559.07-542.65cm^{-1} and 651.03 - 632.76 cm^{-1} which may be attributed to Zr-O bonds . The $\upsilon(COO)_{sym}$ and the imido $\upsilon(CO)_{asym}$ vibrations of N-phthaloyl amino acids ($A_{(1)}H$ and $A_{(2)}H$) appeared in the regions 1390-1380 cm^{-1} and 1770-1760 cm^{-1}, respectively[23]. In the IR spectra of zirconocene complexes, $\upsilon(COO)_{sym}$ was observed in the region 1397.72-1362.20 cm^{-1} and $\upsilon(CO)_{asym}$ appeared in the region 1783.78 -1780.27 cm^{-1}. The $\upsilon(CO)_{sym}$ and $\upsilon(COO)_{asym}$ bands of the ligands ($A_{(1)}H$ and $A_{(2)}H$) have merged together and were observed as a broad band at 1740-1690 cm^{-1}[23]. This band splits into two bands in zirconocene complexes. The $\upsilon(COO)_{asym}$ vibration appeared in the region 1630.85-1614.63 cm^{-1} whereas $\upsilon(CO)_{sym}$ vibration was observed in the region 1733.95-1704.67 cm^{-1}. The calculated values of $\Delta\upsilon$ [$\upsilon(COO)_{asym}$- $\upsilon(COO)_{sym}$] for these zirconocene complexes are in the range 252.43-233.13 cm^{-1}. These values suggest the chelating bidentate nature of N-phthaloyl amino acids in zirconocene complexes. The IR spectra of the free ketoximes, exhibit weak intensity band at 1570 cm^{-1} which may be due to >C=N- stretching. This band shifts towards lower wave number in zirconocene complexes and appeared in the region 1541.29 -1533.04 cm^{-1}. In the IR spectra of free ketoximes, a band for N-O absorption appeared in the region 930-920 cm^{-1}. This band shifts to lower wave numbers in the IR spectra of the corresponding complexes and was observed in the region 896.52 -892.80 cm^{-1}.



Where

$R= -CH(CH_3)_2$; $R'= -CH_3$; $R''= -CH_3$ $(C_5H_5)_2ZrA_{(1)}L_{(1)}$ complex 1

$R= -CH(CH_3)_2$; $R'= -CH_3$; $R''= -C_6H_5$ $(C_5H_5)_2ZrA_{(1)}L_{(2)}$ complex 2

$CHR= -CH_2CH_2-$; $R'= -CH_3$; $R'' = -C_6H_5$ $(C_5H_5)_2ZrA_{(2)}L_{(2)}$ complex 3

Scheme 1 Synthesis of zirconocene complexes

3.2 ^{1}H NMR spectra

The ^{1}H NMR spectra of zirconocene complexes were recorded in $CDCl_3$ and TMS was used as an internal standard. The data of ^{1}H NMR spectra are depicted in table 2.

TABLE 2 ^{1}H-NMR data of zirconocene complexes of N-phthaloyl amino acids and ketoximes in (δ)ppm

Ligand/Complex	$(\overline{C(O)C_6H_4C(O)}NCH(R)COOH)$ (AH)					R'R"CNOH(LH)			
	COOH	C_6H_4	CH_2	CH	CH_3	NOH	C_6H_5	CH_3	C_5H_5
$A_{(1)}H$[a]	8.90 (bs)	7.28-7.89 (m)		4.63 (d) , 2.76 (m)	1.17 (d), 0.90 (d)				
$A_{(2)}H$	7.99 (s)	7.77-7.84 (m)	3.90,3.88, 3.86(t), 2.65,2.63, 2.61 (t)						
$L_{(1)}H$[b]						9.87 (bs)		1.90(s) 1.91(s)	
$L_{(2)}H$[b]						9.53 (bs)	7.37-7.64 (m)	2.31(s)	
$Cp_2ZrA_{(1)}L_{(1)}$ Complex 1	-	7.17-7.90 (m)		4.76(d), 2.25-2.71(m) (ur)	1.04(d), 0.92(d)	-		1.88(s) 2.04(s)	6.43 (s)
$Cp_2ZrA_{(1)}L_{(2)}$ Complex 2	-	7.15-7.85 (m)		4.33(d), 2.41-2.50(m) (ur)	1.24(d), 1.01(d)	-	*	**	6.46 (s)
$Cp_2ZrA_{(2)}L_{(2)}$ Complex 3	-	7.14-7.85 (m)	3.83 (t) 2.72 (t)			-	*	2.43(s)	6.50 (s)

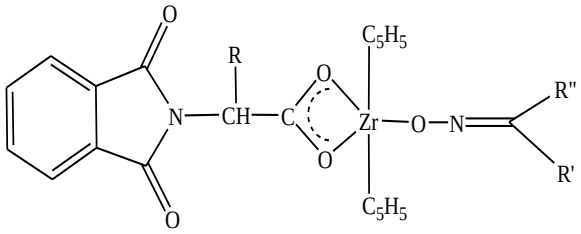
*overlapping with amino acid phenyl region;**overlapping with amino acid aliphatic protons; ur= unresolved; s = singlet; a=ref [24]; b=ref [23]

Table 3 Selected structural parameters (bond lengths and bond angles) of $(C_5H_5)_2$ $ZrA_{(1)}L_{(1)}$ (complex 1)

Atom label	Bond length(Å)	Atom label	Bond length(Å)	Atom label	Bond angle (°)	Atom label	Bond angel(°)
Zr1-Cp1	2.286	C1-O4	1.264	Cp1-Zr-Cp2	129.12	Zr1-O4-C1	90.84
Zr1-Cp2	2.280	C1=O1	1.272	Cp1-Zr-O5	97.90	Zr1-O1=C1	94.68
Zr1-O5	2.055	N2-O5	1.390	Cp1-Zr-O4	97.03	O4-C1=O1	119.06
Zr1-O1	2.305			Cp1-Zr-O1	115.79	Zr1-O5-N2	127.34
Zr1-O4	2.392			O4-Zr1-O1	55.43		

In the ^{1}H NMR spectra of N-phthaloyl amino acids and ketoximes, the singlet/broad singlet of the carboxylic and >C=N-OH groups were observed in the regions δ 7.99– 8.90 and δ 9.53-9.87, respectively. These singlet/broad singlets were not present in the ^{1}H NMR spectra of zirconocene complexes. The disappearance of these signal/broad signals indicates deprotonation of these two ligands and the formation of Zr-O bond in zirconocene complexes. Aromatic protons of N-phthaloyl amino acids and acetophenone oxime($L_{(2)}H$) were observed as a complex pattern in the region δ 7.14 - 7.90. The signal for

cyclopentadienyl ring protons in zirconocene complexes 1,2 and 3 appeared as singlets at δ 6.43, δ 6.46 and δ 6.50, respectively.



Where

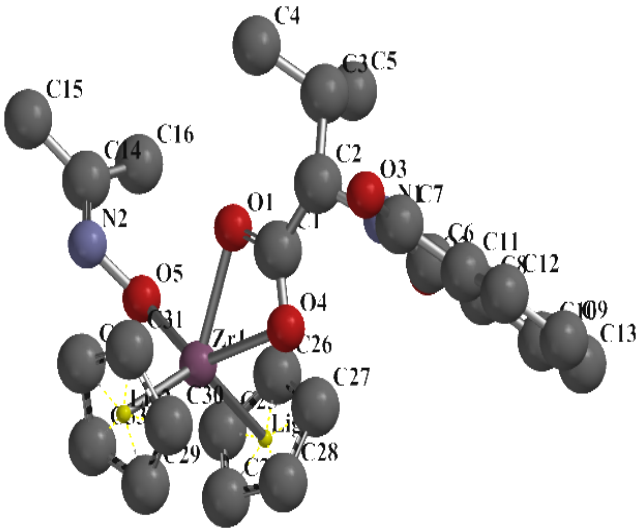
R= -CH(CH_3)$_2$; R'= -CH_3; R"= -CH_3 (C_5H_5)$_2$Zr$A_{(1)}$L $_{(1)}$ complex 1
R= -CH(CH_3)$_2$; R'= -CH_3; R"= -C_6H_5 (C_5H_5)$_2$Zr$A_{(1)}$L $_{(2)}$ complex 2
CHR= -CH_2CH_2-; R'= -CH_3; R" = -C_6H_5 (C_5H_5)$_2$Zr$A_{(2)}$L $_{(2)}$ complex 3

Figure 1 Structure of zirconocene complexes

3.3 Mass spectrum

Mass spectrum of (C_5H_5)$_2$Zr$A_{(1)}$L$_{(2)}$ (complex 2) was recorded. This spectrum demonstrated a number of peaks associated with various fragments which were formed due to loss of the ligands and side chain.
On the basis of mass and spectroscopic (IR and ^{1}H NMR) studies, a pentacoordinated geometry (figure 1) may be suggested for these zirconocene complexes.

3.4 Computational study



Where Lig1=Cp1; Lig2=Cp2

Figure 2 Optimized molecular structure of complex 1 (hydrogens are omitted)

DFT(B3LYP) was used to calculate optimized structure, optimized structural parameters (bond lengths and bond angles) of the complex (C_5H_5)$_2$Zr$A_{(1)}$L $_{(1)}$ (complex 1).The geometry of zirconocene complex has been optimized and important structural parameters (selected bond lengths and bond angles) are listed in table 3. The energy and dipole moment of the studied complex are -1540.00067 au and 3.37 debye, respectively. The frontier molecular orbital analysis has been done to understand the reactivity of the complex1 [25], [26]. In

this complex, E_{HOMO} and E_{LUMO} are -5.8 eV and -2.3 eV, respectively. The ΔEgap is equal to 3.5 eV which in turn demonstrates high chemical reactivity and less stability of this complex.

IV. CONCLUSION

Incorporation of zirconocene into N-phthaloyl amino acids and ketoximes was carried out by the reaction of Cp_2ZrCl_2 with these two ligands in the presence of Et_3N in 1:1:1:2 molar ratio in boiling tetrahydrofuran. These monomeric coloured products were recrystallized from benzene-pet.ether mixture. These newly generated zirconocene complexes were characterized with the help of mass and spectroscopic (IR and ^1H NMR) evidences. Density Functional Theory(B3LYP) was employed to investigate the optimized structure, energy, geometry and stability of one representative zirconocene complex to support the structures of these complexes. A penta coordinated topology may be suggested for these zirconocene complexes on the basis of mass, spectroscopic and DFT studies.

REFERENCES

1. L. Saikia, J. M. Baruah, and A. J. Thakur, "A rapid, convenient, solventless green approach for the synthesis of oximes using grindstone chemistry," *Org. Med. Chem. Lett.*, 1, 12, 2011.
2. I. A. Schepetkin, M. B. Plotnikov, A. I. Khlebnikov, T. M. Plotnikova, and M. T. Quinn, "Oximes: Novel Therapeutics with Anticancer and Anti-Inflammatory Potential," *Biomolecules*, 11, 777, 2021.
3. M. Özyürek, D. Akpınar, M. Bener, B. Türkkan, K. Güçlü, and R. Apak, "Novel oxime based flavanone, naringin-oxime: Synthesis, characterization and screening for antioxidant activity," *Chem. Biol. Interact.*, 212, 40–46, 2014.
4. T. Sahyoun, A. Arrault, and R. Schneider, "Amidoximes and Oximes: Synthesis, Structure, and Their Key Role as NO Donors," *Molecules*, 24, 2470, 2019.
5. E. Abele and E. Lukevics, "Furan and Thiophene Oximes: Synthesis, Reactions, and Biological Activity. (Review)," *Chem. Heterocycl. Compd.*, 37, 141–169, 2001.
6. E. Abele, R. Abele, and E. Lukevics, "Pyrrole Oximes: Synthesis, Reactions, and Biological Activity. (Review)," *Chem. Heterocycl. Compd.*, 40, 1–15, 2004.
7. M. Luisa Di Gioia, A. Leggio, F. Malagrinò, E. Romio, C. Siciliano, and A. Liguori, "N-Methylated α-Amino Acids And Peptides: Synthesis And Biological Activity," *Mini Rev. Med. Chem.*, 16, 683–690, 2016.
8. [8] Z. H. Chohan, M. Arif, M. A. Akhtar, and C. T. Supuran, "Metal-Based Antibacterial and Antifungal Agents: Synthesis, Characterization, and In Vitro Biological Evaluation of Co(II), Cu(II), Ni(II), and Zn(II) Complexes with Amino Acid-Derived Compounds," *Bioinorg. Chem. Appl.*, 2006, e83131, 2006.
9. C. Camacho-Camacho, I. Rojas-Oviedo, A. Garza-Ortiz, R. A. Toscano, L. Sánchez-Sánchez, and J. Cardenas, "Tributyltin(IV) Schiff base complexes with amino acid derivatives: synthesis, characterization and biological activity," *Appl. Organomet. Chem.*, 30, 199–207, 2016.
10. M. Nath and R. Yadav, "Spectral Studies and In Vitro Antimicrobial Activity of New Organotin(IV) Complexes of Schiff Bases Derived from Amino Acids," *Bull. Chem. Soc. Jpn.*, 70, 1331–1337, 1997.
11. V. Fernández-Moreira, M. L. Ortego, C. F. Williams, M. P. Coogan, M. D. Villacampa, and M. C. Gimeno, "Bioconjugated Rhenium(I) Complexes with Amino Acid Derivatives: Synthesis, Photophysical Properties, and Cell Imaging Studies," *Organometallics*, 31, 5950–5957, 2012.
12. K. Maheshwari, M. K. Srivastava, S. Saxena, and A. Jain, "Investigation of pharmacophore and antipharmacophore features of certain dimethyltin (IV) complexes of flexible N-protected amino acids and fluorinated β-diketone/β-diketones," *Appl. Organomet. Chem.*, 31, e3570, 2017.

13. A. Sharma, A. Jain, and S. Saxena, "Diorganotin (IV) complexes of flexible N-protected amino acids and ketoximes: preparation and structure–antimicrobial activity relationship," *Can. J. Chem.*, 94, 155–162, 2016.
14. F. Samy and M. Shebl, "Synthesis, spectroscopic, biological, and theoretical studies of new complexes from (E)-3-(2-(5, 6- diphenyl-1,2,4 - triazin-3- yl)hydrazono)butan-2- one oxime," *Appl. Organomet. Chem.*, 34, e5502, 2020.
15. M. Alinaghi, K. Karami, A. Shahpiri, A. Kazeminsab, A.A.Momtazi-Borojeni, E.Abdollahi and J. Lipkowski, "A Pd(II) complex derived from pyridine-2-carbaldehyde oxime ligand: Synthesis, characterization, DNA and BSA interaction studies and in vitro anticancer activity," *J. Mol. Struct.*, 1219, 128479, 2020.
16. S. Anga, K. Naktode, H. Adimulam, and T. K. Panda, "Titanium and zirconium complexes of the N, N ′-bis(2,6-diisopropylphenyl)-1,4-diaza-butadiene ligand: syntheses, structures and uses in catalytic hydrosilylation reactions," *Dalton Trans.*, 43, 14876–14888, 2014.
17. H. G. Alt and R. Ernst, "Dinuclear ansa zirconocene complexes as dual-site catalysts for the polymerization of ethylene," *J. Mol. Catal. Chem.*, 195, 11–27, 2003.
18. G. G. Hlatky, H. W. Turner, and R. R. Eckman, "Ionic, base-free zirconocene catalysts for ethylene polymerization," *J. Am. Chem. Soc.*, 111, 2728–2729, 1989.
19. O. R. Allen, R. J. Knox, and P. C. McGowan, "Functionalised cyclopentadienyl zirconium compounds as potential anticancer drugs," *Dalton Trans.*, 39, 5293–5295, 2008.
20. S. Sharma, A. Jain, and S. Saxena, "Synthesis, Characterization and Antimicrobial Activity of Zirconium (IV) Complexes," *J. Korean Chem. Soc.*, 56, 440–447, 2012.
21. S. K. Sengupta, O. P. Pandey, B. K. Srivastava, and V. K. Sharma, "Synthesis, structural and biochemical aspects of titanocene and zirconocene chelates of acetylferrocenyl thiosemicarbazones," *Transit. Met. Chem.*, 23, 349–353, 1998.
22. J. C. Sheehan, D. W. Chapman, and R. W. Roth, "The Synthesis of Stereochemically Pure Peptide Derivatives by the Phthaloyl Method," *J. Am. Chem. Soc.*, 74, 3822-3825, 1959.
23. S. Sharma, A. Jain, and S. Saxena, "N-Protected Amino Acids and Ketooximes-Modified Dibutyltindichloride: Synthetic Strategy and Structural Aspects Based Upon Spectral [IR, NMR (1H, 13C & 119Sn)] Studies," *Main Group Met. Chem.*, 30, 63–74, 2007.
24. K. Maheshwari, M. K. Srivastava, S. Saxena, and A. Jain, "Effect of fluorinated/non-fluorinated β-diketones and side-chain branching of N-protected amino acids on the antibacterial potential of new heptacoordinated monobutyltin (IV) complexes," *Appl. Organomet. Chem.*, 31, e3628, 2017.
25. S. Budania, S. Saxena, and A. Jain, "Assessment of DFT based optimized molecular structure-antioxidant efficacy relationship of trimethylgermanium(IV) complexes," *J. Indian Chem. Soc.*, 99, 100419, 2022.
26. K. Soni, S. Saxena, and A. Jain, "Recent advances in DFT assisted optimized energy, stability and distortions of optimized topologies of certain biopotent dimethyltin(IV) complexes," *J. Indian Chem. Soc.*, 99, 100332, 2022.