SETSCI Conference Indexing System,
Volume 3 (2018), 1586-1591

ISAS 2018-Winter
2nd International Symposium on Innovative Approaches in Scientific Studies
November 30 – December 2, 2018, Samsun, Turkey

The structural, spectroscopic and molecular docking analysis on phosphorusenitrogen compounds

Sultan ERKAN[1]*,Burak TÜZÜN[2]

[1]*Chemistry and Chemical Processing Technologies, Sivas Cumhuriyet University
[2]Science Department, Sivas Cumhuriyet University

**Corresponding author:* sultanerkan58@gmail.com
+*Speaker:* sultanerkan58@gmail.com
Presentation/Paper Type: Oral / Full Paper

Abstract

The (9) and (12) compounds are optimized at B3LYP/6-31G(d,p) level in gas phase. The calculated bond length and bond angles are compared with experimental values. Also, the calculated vibrational frequencies are assignment for mentioned compounds according to bond stretching mode. NMR chemical shift values are calculated for ^{31}P. Some quantum chemical parameters are associated with the experimental biological activity. In this way, structural activity relationships are examined. Finally, crystal structure of phosphomannose isomerase from Candida albicans complexed with 5-phospho-d-arabinonhydrazide are selected from protein data bank (PDB ID= 1PMİ). Molecular docking studies performed for the mentioned compounds with target protein. The binding energy and binding mode examined between ligands with target protein. Molecular electrostatic potential (MEP) maps are prepared to identify electronic regions in molecules.

Key words: *Phosphoruse nitrogen compounds, DFT, Molecular docking*

1. Introduction

The combination of phosphorus and nitrogen atoms produces a variety of exceptionally rich inorganic heterocyclic ring systems. In addition, aminocyclotripphosphazine derivatives have attracted great attention, particularly as anti-cancer agents [1]. Due to the anticancer and antimicrobial effects of cyclotriphosphazene derivatives, they have been studied extensively [2-6]. The chemical and physical properties of cycloposphazenes vary with the nature of the substituted side groups. Furthermore, especially the aminocyclotyposphazene derivatives have attracted a greater interest as anti-cancer agents [7,8]. The same mono and poly amino-substituted cyclotripphosphazenes have been found to be very active in several tumor cell lines such as aziridine, spermine and spermidine [9,10]. The mono(4-fluorobenzyl) spirocyclotriphosphazenes (9) and tetra-1,4-dioxa-8-azaspiro [4,5]decaphosphazenes (12) were synthesized by Akbaş, et al. in 2013. In this study, we researched to (9) and (12) compounds with computational chemistry method.

2. Calculation procedure

The structures of phosphoruse nitrogen compounds were drawn by Gaussian package programs GausView 5.0.8 and the calculations were performed in Gaussian IA32W-G09RevA.02 and Gaussian AS64L-G09RevD.01 [11-13]. The mentioned compounds were optimized by using B3LYP/6-31G(d,p) level in gas phase. IR spectra of (9) and (12) compounds were examined in detail. NMR spectra of studied compounds were detail by using gauge-independent atomic orbital (GIAO) method.

The structural-activity relationships of phosphoruse nitrogen compounds were examined by some quantum chemical parameters and these quantum chemical parameters were compared each other. These quantum chemical descriptors are energy of the highest occupied molecular orbital (E_{HOMO}), energy of the lowest unoccupied molecular orbital (E_{LUMO}), the energy gap (EGAP), absolute hardness (η), absolute softness (σ), absolute electronegativity (χ), chemical potential (CP), electrophilicity index (ω), nucleophilicity index (ε) and additional electronic charges (ΔNMax). The quantum chemical parameters were calculated according to Eq. (1)–(8). Additionally, molecular electrostatic potential (MEP) maps were created for to determine the electrophilic and nucleophilic regions within the molecule. Molecular docking calculations were done between mentioned compounds and protein which PDB ID is 1PMI.

$$E_{GAP} = E_{LUMO} - E_{HOMO} \tag{1}$$

$$\eta = \frac{I - A}{2} = \frac{E_{LUMO} - E_{HOMO}}{2} \tag{2}$$

$$\sigma = \frac{1}{\eta} \tag{3}$$

$$\chi = \frac{|I + A|}{2} = \frac{|-E_{HOMO} - E_{LUMO}|}{2} \tag{4}$$

$$CP = -\chi \tag{5}$$

$$\varepsilon = \mu * \eta \tag{6}$$

$$\omega = \frac{CP^2}{2\eta} \tag{7}$$

$$\Delta N_{max} = -\frac{CP}{\eta} \tag{8}$$

3. Results and discussion

3.1. The optimization structures

The investigated compounds are optimized at B3LYP/6-31G(d,p) level. The optimized structures are reconstruct with Spartan style in Chemcraft license program and are shown in Figure 1.

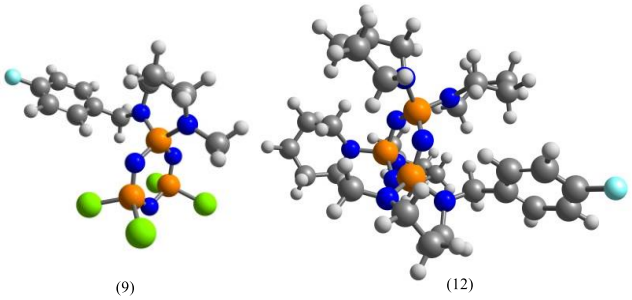

Figure 1. The optimized structures of (9) and (12) compounds.

In figure 1, the phosphoruse nitrogen compounds structures are very different from each other. For phosphorusenitrogen compounds that are so different, the calculation details made may also be different. In fact, the aim here is to present these differences with numerical data.

3.2. Structural parameters of phosphoruse nitrogen compounds

Experimental parameters are available for (9) and (12) compounds. The correlation between the structural parameters and the experimental parameters calculated at the B3LYP/6-31G(d,p) level was compared and the other all results from the obtained calculation for (9) and (12) compounds were proposed in accordance with this agreement.

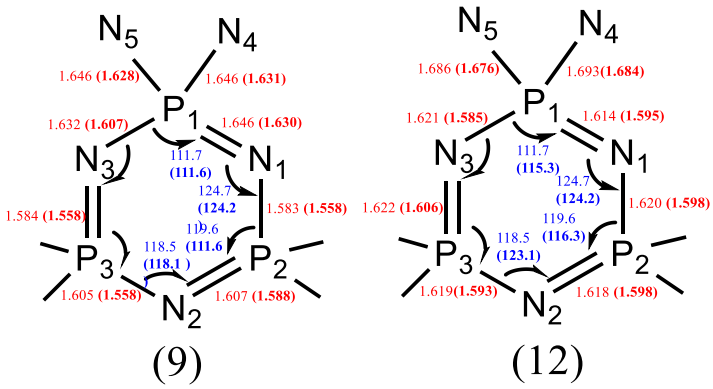

Figure 2. Structural parameters of (9) and (12) compound

In beside the calculated bond lengths and bond angles, experimental values are given in bold in brackets. According to Figure 2, the experimental and calculated bond lengths and bond angles are quite compatible.

3.3. IR spectra

IR spectra is very important in building structure skeletons in chemistry. The methods of computational chemistry offer a bond stretching in detail. The numbered IR spectra for the mentioned compounds are given in Figure 3 and the bond stretching modes corresponding to the numbered IR spectra were labeled in Table 1. The calculated frequencies are harmonic frequencies. In beside the calculated bond stretching, experimental values are given in bold in brackets. The calculated and experimental bond stretching are compatible with each other. The binding stretching which non-experimentally values are proposed in Table 3 for compounds.

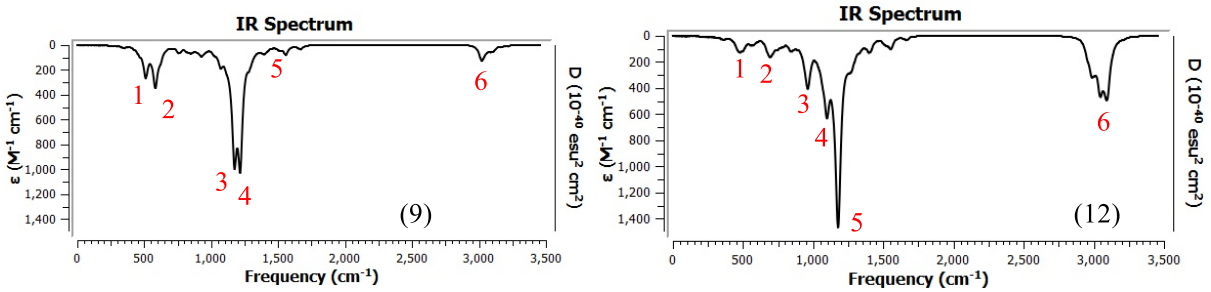

Figure 3. IR spectra of the mentioned compounds.

Table 1. The labeled bond stretching (cm^{-1}) corresponding to the numbered IR spectra for (9) and (12) compounds

	(9)			(12)	
1	511.34 **(511)**	νP-Cl	1	501.48	WaggingP-N
2	581.47 **(582)**	WaggingP-N	2	690.41	νP-N
3	1173.87**(1169)**	Rocking P-N	3	960.35	νP-N
4	1216.86**(1227)**	νP=N	4	1067.05**(1184)**	νP=N
5	1282.22**(1045)**	νC-F	5	1554.98**(1043)**	νC-F
6	3018.65**(3045)**	νC_{ali}-H	6	3098.51**(3061)**	νC_{ali}-H

3.4. ^{31}P-NMR spectra

The NMR spectrum is one of the most preferred techniques for determination by researchers in spectroscopic studies. There are no experimental ^{31}P-NMR chemical shift values.

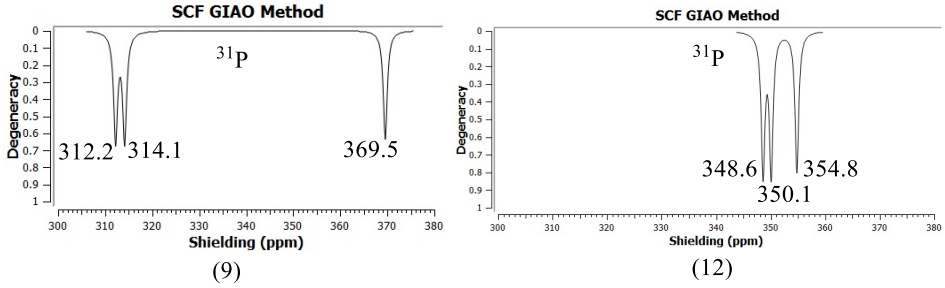

Figure 4. ^{31}P-NMR chemical shift of the investigation compounds

For the (9) and (12), three piece ^{31}P-NMR chemical shift values are given in Figure 4. These are 312.2, 314.1 and 369.5 ppm for (9) compound and 348.6, 350.1 and 354.8 for (12) compound, respectively. In (12) compound, these values are very close to each other. However, as can be seen from the NMR spectra, there is a shift in the ^{31}P-NMR value for (9) compound. This can be explained by the fact that the phosphorus atoms in the (9) compound are bound to electronegative chlorine atoms. The calculated results are consistent with theoretical expectations.

3.5. Quantum chemical descriptors

Biological activity may correlate with the increase and/or decrease of calculated parameters. For example, the biological activity of a chemical species increases with the increase of HOMO, softness and electronegativity. Biological activity decreases with decreasing LUMO energy, energy gap, hardness and chemical potential. Also, biological activity decreasing of electrophilicity index and increases with increasing of nucleophilicity index. Additionally, ΔN_{max} is corelated with charges of compounds and the biological activity of compound increases with increasing of ΔNmax values. The calculated the quantum chemical descriptors of the compounds in Table 2 are given. In view of this information, according to the parameters in Table 2, the (9) compound is biologically more active than the (12) compound.

Table 2. The calculated quantum chemical descriptors of the mentioned compounds

	(9)	**(12)**
$\mathbf{E_{HOMO}}$*	-6.502	-5.237
$\mathbf{E_{LUMO}}$*	-1.740	-0.152
ΔE*	4.762	5.085
η*	2.381	2.542
σ**	0.420	0.393
χ*	4.121	2.695
CP*	-4.121	-2.695
ω	3.567	1.428
ε	-9.812	-6.851
$\mathbf{\Delta N_{max}}$	1.731	1.060
*** is in (eV) unit ** is in (eV^{-1}) unit**		

3.6. Molecular electrostatic potential (MEP) and molecular docking

Molecular electrostatic potential (MEP) maps were calculated to determine the electron distribution on the molecular surface. The active regions on the molecule are red and these map are represented in Figure 5. Additionally, the basis for molecular docking is: the target of anticancer drugs is intracellular, and their activity depends on the binding capacity. This feature is the main goal in the development of new and more effective drugs. In this context, the structure representing the crystal structure of Candida albicans phosphomannose isomerase (PDB ID:1PMI) was chosen as the target protein and the studied compounds are docked with target protein in DockingServer. According to docking results, binding mode of the between phosphoruse nitrogen compounds with target protein are presented in Figure 5. Also, the binding energy of (9) compound and (12) compounds are 23.74 kcal/mol and 585.91 kcal/mol, respectively. These results show that there is stronger interaction between the investigated compounds and the target protein than electrostatic interactions. As a result, the mentioned compounds alter their genetic structure of the protein can are bond formation rather than by interaction with the target protein. The (9) compound has a hydrogen bonds and also polar, hydrophobic, pi-pi, cation-pi interactions and halogen-bond. The (12) compound has eleven hydrogen bonds and also polar, hydrophobic, cation-pi interactions and halogen-bond.

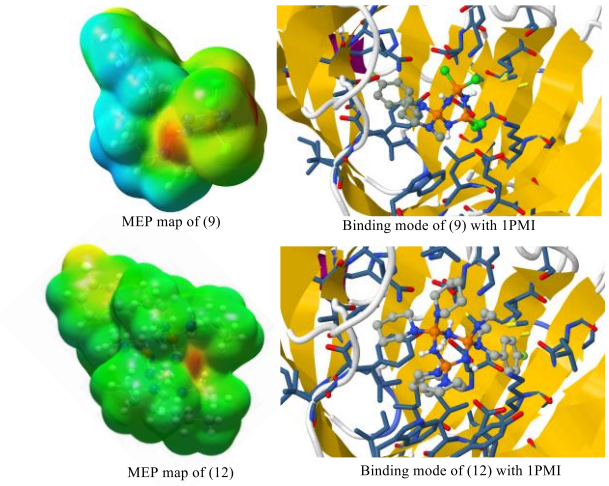

Figure 5. MEP maps and binding modes of (9) and (12)

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