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Theoretical Investigations on Thermo-Dynamic Properties and Molecular Structure of the Phosphorus-Containing Derivative of Chromone

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Özet. 3-(1-Amino-etilidin)-2metoksi-2-okzo-2,3-dihidro-2λ^5-benzo[e][1,2]okzafosfonin-4-on olası tautomerik formları Hartree-Fock (HF) ve Yoğunluk Fonksiyonel teorisi (DFT) metodları kullanılarak araştırıldı. Hesaplanan bağ uzunlukları ve bağ açıları deneysel verilerle kıyaslandı. Tautomerlerin yapıları, enerjileri ve relatif kararlıkları karşılaştırıldı ve analiz edildi. Amin-keto ve imin-enol tautomerizmi, iki form arasındaki reaktivite farkını oranlamak için dikkate alındı. Keto formunun enol formundan daha kararlı olduğu gözlendi. Asitlik sabiti ve fizikokimyasal parametreler yarı-deneysel metodlarla hesaplandı.

Anahtar Kelimeler. Kumarin türevleri, asitlik sabiti, QSAR, x-ışını, kuantum kimyasal hesaplama.

Abstract. The possible tautomeric forms of 3-(1-amino-ethylidene)-2methoxy-2-oxo-2,3-dihydro-2λ^5-benzo[e][1,2]oxaphosphinin-4-one molecule were searched by utilizing Hartree-Fock (HF) and Density Functional Theory (DFT) methods. The computed bond lengths and bond angles were compared with the experimental data. The structure, energies and relative stability of tautomers were compared and analyzed. The amine-keto and imino-enol tautomerism was taken into account to rationalize the difference in reactivity between the two forms. The keto form was found to be more stable than the enol form. The acidity constant and physicochemical parameters were computed by semi-empirical methods.

Keywords. Coumarin derivatives, acidity constant, QSAR, x-ray, quantum chemical calculation.

1. Introduction

The acidity constant, pK_{a}, of a compound is an important property and is fundamental in understanding of many chemical and biochemical processes [1, 2, 3]. The

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pK_a value of a molecule indicate the amount of protonated and unprotonated forms at a certain pH and shows the equilibrium state of the chemical system [4]. In many biological systems, proton-transfer reactions take place to provide communication between the exo and intra cellular media and the rate of the proton transfer reaction depend, among many other factors, on the pK_a value of the species involved [5]. Moreover, to elucidate the reaction mechanisms and reactivity correctly, tautomeric equilibrium constant is important to have some information about the tautomeric structures of heterocyclic compounds as well.

Phosphorus containing chromone and coumarin derivatives are novel classes of biologically interesting compounds [6, 7, 8]. Some metal complexes of coumarin ligand act as anti-coagulant and anti-tumor reagents [9, 10, 11]. In particular, complexes with cerium(III), zirconium(IV), copper(II), zinc(II), bismuth(III) and cadmium(II) exhibit a pronounced cytotoxic activity [12, 13]. Recent reports on synthesis and biological activities of some chromone derivatives exist in the literature [14, 15, 16, 17]. We, however, did not come across any systematic theoretical work on these derivatives. In order to fill this gap we have computed some physical and thermodynamic parameters for title molecule to elucidate and confirm the previously reported crystal structure and protolytic properties [18].

Existence of amine-keto form **A** and imino-enol form **B** makes the 3-(1-amino-ethylidene)-2methoxy-2-oxo-2,3-dihydro-2λ^5-benzo[e][1,2]oxaphosphinin-4-one molecule interesting from structure activity relationship (QSAR) and quantitative structure-property relationship (QSPR) point of view. The crystal structure studies, therefore, were undertaken in order to enlighten in which form the crystal lattice exists in solid phase and what kind of structural changes occur in aqueous solution.

With the recent advances in computer hardware and software, the theoretical chemistry has become much more established than ever before. Several important chemical and physical properties of the molecular system can be predicted using various computational techniques. Following our work on crystal structures of 1,2-bis(diphenylphosphinoyl)ethane and phenol, triphenylphosphine oxide and hydroquinone molecules by quantum chemical methods [19, 20], we have now reported on the molecular structure, tautomerization and some physical parameters of 3-(1-amino-ethylidene)-2-methoxy-2-oxo- 2,3-dihydro-2λ^5-benzo[e][1,2]oxaphosphinin-4-one molecule by using DFT and HF methods with different basis sets and some semi empirical methods.

2. Computational Method

All calculations were carried out using the CAChe Work System Pro. V.6.1.12 [21] and Gaussian03W program [22]. The DFT and HF methods were applied. Bond lengths, bond angles along with physical and thermodynamic parameters were calculated. Using these obtained parameters some dynamic equilibrium such as tautomeric equilibrium constants, K_{T}, for keto-amine and enol-imino forms of the title molecule was determined. The geometries were optimized by DFT and HF methods. All calculations were performed using the HF, B3PW91, BLYP, B3LYP methods which were implemented in the Gaussian03W package software together with the 3-21G(d) and 6-31G(d,p) basis sets [23]. The equilibrium constants, K_{T} and acidity constants, pK_{a} were calculated in the aqueous-phase by semi-empirical methods (AM1, PM3 and PM5), while the other parameters were calculated in the gas phase by *ab initio* HF and DFT (B3PW91, BLYP and B3LYP) methods.

As seen in Figure 1, the structure of the title compound consists of a benzene ring fused with an oxaphosphinane ring. The possible tautomerisation and protonation patterns for title molecule **A** are depicted in Figure 2.

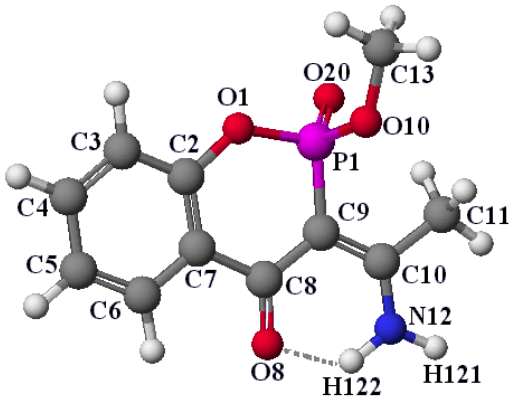

FIGURE 1. A perspective view of the molecule forming intramolecular hydrogen bond and the numbering system of 3-(1-aminoethylidene)-2-methoxy-2-oxo-2,3-dihydro-2λ^5-benzo[e][1,2]oxaphosphinin-4-one molecule.

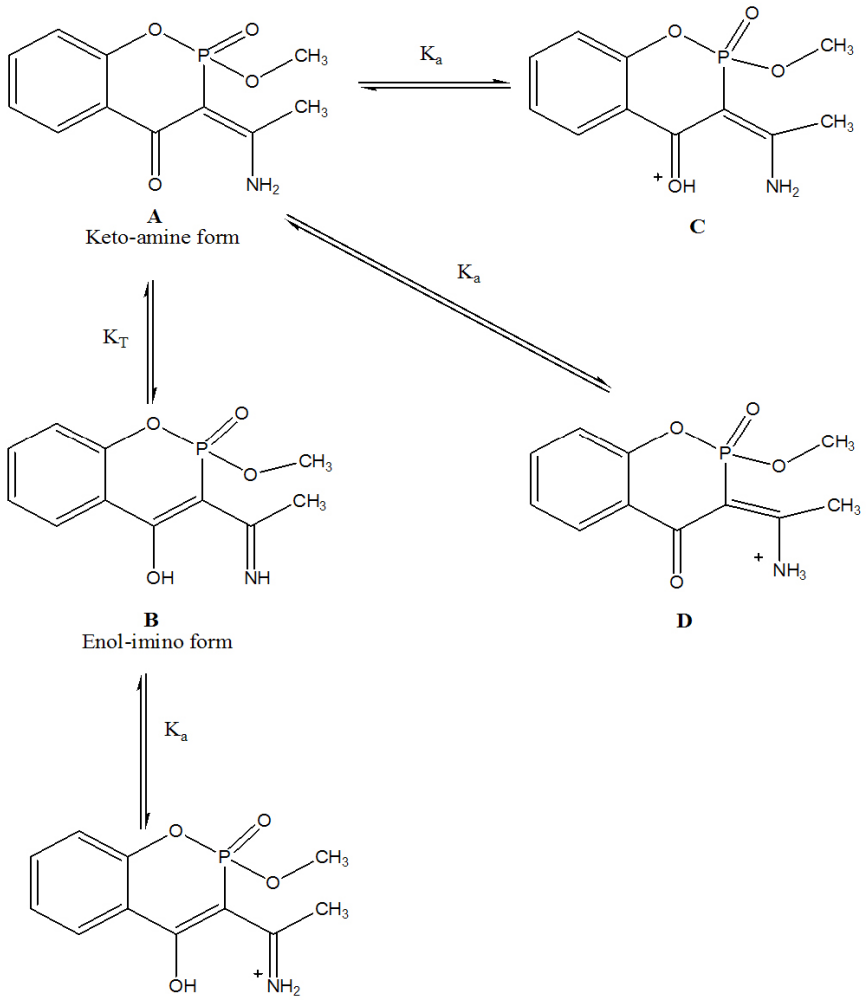

FIGURE 2. The possible tautomerisation and protonation patterns for 3-(1-aminoethylidene)-2-methoxy-2-oxo-2,3-dihydro-2λ^5-benzo[e][1,2]oxaphosphinin-4-one molecule **A**.

3. Results and Discussion

The computed thermodynamic and calculated physical parameters along with the tautomeric forms **A** (i.e. keto-amine) and **B** (i.e. enol-imino) of 3-(1-amino-ethylidene)-2-methoxy-2-oxo-2,3-dihydro-2λ^5-benzo[e][1,2]oxaphosphinin-4-one molecule are shown in Tables 1-9. The obtained data was evaluated as follows:

a) Molecular structure. The standard bond lengths and angles were selected as starting point to conduct geometric optimization calculations. The aim was to calculate the properties of the molecule accurately. The converged calculations then

provided the optimal geometric bond lengths and bond angles for **A** form of title molecule.

The computed bond lengths for molecule **A** were depicted in Table 1. It seems that the best fit to experimental results was achieved by BLYP/3-21G(d) calculation with a regression of 0.990. However, we must admit that the other methods closely follow this trend (Table 1). In fact, in heteroatom-containing P(1)-O(20), N(12)-C(10) and O(8)-C(8) bonds, calculations done with HF/3-21G(d) and BLYP/6-31G(d,p) basis sets seem to perform better.

The computed bond angles were depicted in Table 2. The regression values of Table 2 indicate the best fit comes from BLYP/6-31G(d,p) with a R^2 value of 0.917. From the theoretical values, it can be deduced that most of the optimized bond lengths are slightly higher than the experimental values. The largest deviation of bond lengths and bond angles from the experimental values are 0.144 Å and 10.4° respectively. This deviation can be attributed to the fact that the theoretical calculations were carried out as the isolated molecules in the gaseous phase and the experimental results were obtained in solid state.

The bond lengths for C8-C9, C10-N12 are 1.447 and 1.331 Å, respectively and they are clearly shorter than normal single bonds, while the distance C8-O8 (1.271 Å), C9-C10 (1.404 Å) are longer than normal double bonds calculated with BLYP/3-21G(d) method. The N12 atom seems to involved both in intra and inter molecular hydrogen bonding. The intra-molecular hydrogen bond N12-H122...O8 is effective in newly formed six member ring N12-H122...O8-C8-C9-C10. This newly formed six member ring is almost planar with the main molecule. Possibility of intermolecular hydrogen bonding was reflected in N12-H121...O20 bond. The possible intra-molecular hydrogen bond distances can be seen in Table 3 for keto-amine and enol-imino forms of title molecule. The calculated N12-H122 bond length (1.040 Å) was found to be longer than N12-H121 bond length (1.013 Å) calculated with BLYP/3-21G(d) level of theory. This explained by the intra-molecular H-bonding between O8-H122 as reported in the literature [18]. Such variations in N12-H122 (1.000 Å) and N12-H121 (0.870 Å) bond lengths were observed in some complexes which are changed by the substitution in the coumarin ring as well as by intra-molecular H-bonding [24].

The values of some thermodynamically parameters (such as zero point energy, E_{HOMO}, E_{LUMO}, Gibbs free energy, etc.) of keto-amine and enol-imino forms of title molecule are listed in Table 4. Zero point energy, entropy, enthalpy, Gibbs free

TABLE 1. Calculated and experimental bond lengths (Å) for keto-amine form of molecule **A**

Bond	**HF**		**B3PW91**		**BLYP**		**B3LYP**		**Exp**[a]
	3-21G(d)	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	
P(1) - O(20)	1.463	1.456	1.487	1.482	1.487	1.482	1.489	1.486	1.464
P(1) - O(10)	1.583	1.588	1.611	1.620	1.612	1.622	1.615	1.619	1.574
P(1) - O(1)	1.598	1.606	1.631	1.642	1.630	1.642	1.632	1.633	1.598
P(1) - C(9)	1.749	1.765	1.753	1.769	1.757	1.774	1.758	1.780	1.750
O(8) - C(8)	1.240	1.217	1.274	1.248	1.271	1.247	1.272	1.251	1.246
O(10) - C(13)	1.462	1.421	1.480	1.434	1.484	1.440	1.486	1.443	1.448
O(1) - C(2)	1.378	1.360	1.388	1.372	1.393	1.378	1.394	1.373	1.397
N(12) - C(10)	1.319	1.322	1.328	1.329	1.331	1.333	1.335	1.336	1.315
N(12) - H(121)	0.996	0.994	1.014	1.007	1.013	1.006	1.004	1.012	0.870
N(12) - H(122)	1.008	1.000	1.049	1.029	1.040	1.023	1.029	1.026	1.000
C(10) - C(9)	1.393	1.394	1.409	1.405	1.407	1.405	1.406	1.410	1.413
C(10) - C(11)	1.515	1.510	1.508	1.502	1.515	1.508	1.517	1.511	1.498
C(8) - C(9)	1.447	1.459	1.444	1.454	1.447	1.459	1.448	1.462	1.444
C(8) - C(7)	1.487	1.497	1.482	1.488	1.487	1.493	1.486	1.494	1.489
C(5) - C(6)	1.376	1.379	1.387	1.386	1.387	1.388	1.389	1.391	1.379
C(5) - C(4)	1.389	1.393	1.401	1.398	1.401	1.399	1.403	1.404	1.384
C(7) - C(2)	1.380	1.388	1.398	1.402	1.398	1.403	1.398	1.405	1.396
C(7) - C(6)	1.390	1.397	1.402	1.402	1.402	1.404	1.403	1.409	1.402
C(4) - C(3)	1.378	1.381	1.389	1.389	1.390	1.390	1.392	1.394	1.388
C(2) - C(3)	1.381	1.387	1.394	1.394	1.394	1.395	1.395	1.398	1.377
Correlation Coefficient	0.981	0.974	0.988	0.983	0.990	0.985	0.980	0.974	

[a]Taken from [18].

TABLE 2. Calculated and experimental bond angle (°) values for keto-amine form of molecule **A**

Bond angle	**HF**		**B3PW91**		**BLYP**		**B3LYP**		**Exp**[a]
	3-21G(d)	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	
O(20)-P(1)-O(10)	111.7	113.4	112.9	114.4	112.6	114.3	112.6	113.1	113.8
O(20)-P(1)-O(1)	112.3	110.9	111.7	109.9	111.2	110.2	112.1	110.7	107.7
O(10)-P(1)-O(1)	103.3	103.4	103.2	103.5	103.1	103.4	103.3	102.0	104.9
O(20)-P(1)-C(9)	118.9	119.3	119.7	120.1	119.5	119.8	119.5	121.7	119.4
O(10)-(P1)-C(9)	105.2	105.0	103.4	103.4	103.4	103.6	103.3	103.8	105.0
O(1)-P(1)-C(9)	103.7	103.4	104.3	103.8	104.4	103.9	104.4	103.3	104.9
C(13)-O(10)-P(1)	122.4	121.3	118.7	118.3	119.1	118.8	118.9	120.2	119.2
C(2)-O(1)-P(1)	129.6	122.9	127.2	122.1	127.4	122.4	127.2	123.2	119.2
C(10)-N(12)-H(121)	121.2	120.5	121.4	120.6	121.3	120.5	121.2	120.6	120.0
C(10)-N(12)-H(122)	117.4	119.5	114.0	115.8	114.8	116.6	115.1	116.8	117.2
H(121)-N(12)-H(122)	121.3	120.0	124.7	123.6	123.9	122.9	123.7	122.7	122.2
N(12)-C(10)-C(9)	123.1	122.4	120.9	120.3	121.5	120.8	121.7	120.6	121.4
N(12)-C(10)-C(11)	116.6	114.9	118.9	116.5	118.3	116.0	118.3	116.5	116.0
C(9)-C(10)-C(11)	120.1	122.6	120.2	123.2	120.2	123.2	120.0	122.9	122.6
O(8)-C(8)-C(9)	122.8	122.9	122.6	122.6	122.7	122.5	122.6	120.4	122.8
O(8)-C(8)-C(7)	117.6	118.1	117.9	118.1	117.8	118.0	117.9	118.1	118.2
C(9)-C(8)-C(7)	119.6	119.0	119.5	119.3	119.5	119.4	119.5	121.5	119.0
C(10)-C(9)-C(8)	119.4	120.9	119.2	120.5	119.4	120.6	119.6	121.7	121.4
C(10)-C(9)-P(1)	118.4	120.7	117.9	120.2	117.9	120.2	117.7	118.5	120.9
C(8)-C(9)-P(1)	122.2	118.4	122.9	119.2	122.7	119.1	122.7	119.7	117.7
C(6)-C(5)-C(4)	119.4	119.4	119.4	119.5	119.5	119.6	119.4	119.6	120.1
C(2)-C(7)-C(6)	118.7	118.3	118.8	118.2	118.7	118.1	118.8	117.9	117.1
C(2)-C(7)-C(8)	123.3	122.9	123.5	123.3	123.5	123.3	123.6	124.0	123.3
C(6)-C(7)-C(8)	118.0	118.8	117.7	118.5	117.8	118.6	117.6	118.1	119.6
C(5)-C(6)-C(7)	120.9	121.1	121.1	121.3	121.1	121.2	121.0	121.3	120.0
C(5)-C(4)-C(3)	120.4	120.5	120.3	120.4	120.3	120.3	120.3	120.3	120.5
C(3)-C(2)-C(7)	121.1	121.3	120.6	121.0	120.7	121.2	120.7	121.4	122.7
C(3)-C(2)-O(1)	117.3	117.0	116.9	116.5	116.8	116.5	116.8	116.0	117.4
C(7)-C(2)-O(1)	121.5	121.7	122.6	122.4	122.4	122.3	122.5	122.6	119.9
C(2)-C(3)-C(4)	119.5	119.3	119.9	119.6	119.8	119.6	119.8	119.5	118.6
Correlation Coefficient	0.799	0.937	0.818	0.917	0.834	0.956	0.826	0.917	

[a]Taken from [18].

TABLE 3. Possible hydrogen bond lengths (Å) for molecule **A** and **B**

O(8) - H(122)	**HF**		**B3PW91**		**BLYP**		**B3LYP**	
	3-21G(d)	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**
Molecule A	1.979	1.864	1.638	1.715	1.686	1.756	1.790	1.851
Molecule B	5.190	4.532	4.630	4.796	4.649	3.377	4.834	4.583

TABLE 4. The computed physical parameters for molecules **A** and **B**

Molecule A	**HF**		**B3PW91**		**BLYP**		**B3LYP**	
	3-21G(d)	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**
Zero Point Energy (kcal/mol)	151.857	149.975	141.190	139.307	141.817	139.935	141.817	139.307
Dipole Moment (Debye)	3.076	2.614	2.991	2.574	2.971	2.564	2.973	2.567
Entropy (kcal/mol K)	160.804	159.510	150.975	149.748	151.457	150.125	151.360	149.452
Enthalpy (cal/mol K)	121.520	123.786	124.732	128.155	124.205	127.800	124.857	127.652
Gibbs Free Energy (kcal/mol K)	124.591	122.622	113.805	111.558	114.444	112.041	114.153	111.412
HOMO (eV)	−9.007	−9.061	−7.782	−8.000	−7.701	−8.055	−6.177	−6.694
LUMO (eV)	2.231	1.782	−1.632	−1.714	−1.279	−1.279	−1.524	−2.014
Molecule B								
Zero Point Energy (kcal/mol)	151.230	149.350	139.935	142.444	140.562	138.68	139.935	138.680
Dipole Moment (Debye)	4.708	1.920	4.690	4.654	4.634	4.634	2.186	1.992
Entropy (kcal/mol K)	160.658	158.691	150.132	148.244	150.510	148.767	149.673	148.849
Enthalpy (cal/mol K)	123.471	125.732	126.953	128.425	126.072	127.024	128.342	130.967
Gibbs Free Energy (kcal/mol K)	123.864	121.223	112.300	109.973	112.941	110.914	111.427	109.821
HOMO (eV)	−8.762	−8.871	−7.864	−7.946	−7.891	−8.109	−4.572	−8.844
LUMO (eV)	1.769	1.252	−1.796	−1.687	−1.360	−1.442	−2.313	−2.096

energy values of molecule **A** and **B** are almost equal to each other for all methods. E_{HOMO}, E_{LUMO} values are close to each other except for those of calculated at B3LYP. There is a large deviation in dipole moment values since molecule **B** is tautomer form of molecule **A**.

b) Acid dissociation constants and tautomerism. As we mentioned earlier, the information about acidity constant of a substance is useful in many aspects. Acidity constants, pK_a, by defining the pH range in which a substance is least ionized, indicate the conditions under which it can be isolated in maximal yield and this information has many values in preparative chemistry. Acidity constants can also help to discover the structure of a newly isolated substance as it was done in the present work. When tautomerism is possible, the structure with the more weakly acidic proton is favored because it must have the mobile hydrogen more firmly bonded. Many pairs of geometrical isomers have had their members correctly assigned by comparison of acidity constants [25].

The protonation reaction equilibrium for an organic base can be defined as in (1):

$$B + AH \rightleftharpoons BH^+ + A^- \tag{1}$$

in which **B** is the neutral base, **AH** is the acidic proton containing molecule, $\mathbf{BH}^+$ is the protonated base molecule (i.e. conjugate acid) and $\mathbf{A}^-$ is the anion of the acid. For the above ionization equilibrium we can derive (2) to calculate the equilibrium constant

$$K_a = [BH^+][A^-]/[B][AH]. \tag{2}$$

We can use (3) to calculate other physical and thermodynamic parameters.

$$\Delta G = -R\,T \ln K_a = \Delta H - T\Delta S. \tag{3}$$

Then it will be possible to calculate K_a values also by using (4) and (5)

$$\delta\Delta G = [\Delta G_B + \Delta G_{AH}] - [\Delta G_{BH^+} + \Delta G_{A^-}], \tag{4}$$

$$pK_a = \delta\Delta G/(2.303RT). \tag{5}$$

Equation (6) can be used for the tautomeric equilibrium:

$$\underset{\text{keto-amine}}{\mathbf{A}} \quad \rightleftharpoons \quad \underset{\text{imino-enol}}{\mathbf{B}} \tag{6}$$

then (7) can be written for this equilibrium:

$$K_{\mathrm{T}} = \frac{[\mathrm{A}]}{[\mathrm{B}]}. \tag{7}$$

The rearrangement of (7) will give us (8) to calculate the pK_{T} values with acidity constants.

$$\mathrm{p}K_{\mathrm{T}} = \mathrm{p}K_{\mathrm{a(A)}} - \mathrm{p}K_{\mathrm{a(B)}}. \tag{8}$$

As its depicted in Figure 2, there are two protonation centers for molecule **A** and there exist a competition between amino (NH_2) and carbonyl (C=O) group. To clarify this point we have calculated the ionization constants (i.e. acidity constants; pK_{a} values) for both amine and keto protonations and related data were depicted in Tables 5-7. Among the other data the PM5 calculated pK_{a} value of 3.821 (Table 7) found to be the closest to the experimental one (i.e. 3.70) [18]. So we can conclude that the 3-(1-aminoethylidene)-2-methoxy-2-oxo-2,3-dihydro-2λ^5-benzo[e][1,2]oxaphosphinin-4-one molecule exist in tautomeric form **B** in acidic media and molecule protonates at imino group by **B** $\rightleftharpoons$ **E** pattern.

The relative stability of tautomeric forms is of fundamental importance for the prediction of the probability of spontaneous mutations in biomechanism. The relative stability values (RS) were found as -0.03, -0.25 by using HF/3-21G(d), HF/6-31G(d,p) methods. These negative values are indicating the stability of keto-amine form **A** in aqueous media. The other methods produced positive RS values (i.e. 0.060, 0.036 and 0.058, 0.012 and 0.04, 0.04 with B3PW91/3-21G(d), B3PW91/6-31G(d,p), BLYP/3-21G(d), BLYP/6-31G(d,p) and B3LYP/3-21G(d), B3LYP/6-31G(d,p) methods respectively, which are indicative of predominance of keto-amine form **A** over the enol-imino form **B** (Table 8), correctly.

The calculated K_{T} values are indicating the predominance of keto-amine form **A** over the enol-imino form **B** within a range of 10^{-2} - 10^{-5} using different methods (Table 8). Mole fractions calculated with four methods and eight basis sets indicate the predominance of keto-amine form **A** (Table 9).

c) Nucleophicility criteria. As seen from Table 9, molecule **A** was found to be more powerful nucleophile by HF/6-31G(d,p) and B3LYP/6-31G(d,p) methods whereas molecule **B** was found to be more powerful nucleophile by other six methods. So we can conclude that in the metal complexes **A** form would exist in the crystal structure predominantly.

TABLE 5. Semi-empirical method aqueous-phase AM1, PM3 and PM5 calculated physical parameters for the title molecules.

Compound					
	ΔH_f (kcal/mol)	**ΔS (cal/mol K)**	**[a]ΔG_f (kcal/mol)**	**ΔH (cal/mol)**	**[b]ΔG (kcal/mol)**
			AM1		
H_2O	−59.248	45.097	−72.687	2369.356	−11.070
H_3O^+	50.579	48.331	36.176	2375.013	−12.028
A	−205.973	126.827	−243.767	10058.581	−27.736
B	−190.252	129.523	−228.850	10501.117	−28.097
C	−96.748	125.102	−134.028	10005.402	−27.274
D	−88.734	127.466	−126.718	10038.113	−27.946
E	−97.385	125.751	−134.859	9923.143	−27.551
			PM3		
H_2O	−58.031	45.001	−71.441	2369.930	−11.040
H_3O^+	67.348	46.005	53.638	2374.6386	−11.334
A	−180.045	128.854	−218.443	10659.691	−27.739
B	−172.014	136.451	−212.676	11479.540	−29.182
C	−78.573	130.378	−117.426	10824.096	−28.028
D	−79.323	124.254	−116.351	10091.030	−26.937
E	−77.441	123.081	−114.149	10114.552	−26.563
			PM5		
H_2O	−59.475	44.987	−72.881	2371.632	−11.034
H_3O^+	46.392	45.880	32.720	2381.021	−11.291
A	−224.766	125.889	−262.281	10452.156	−27.062
B	−210.863	122.624	−247.405	10249.965	−26.292
C	−112.307	127.324	−150.250	10718.396	−27.224
D	−114.438	126.270	−152.066	10539.840	−27.089
E	−110.898	121.279	−147.039	10119.849	−26.021

[a]ΔG_f(kcal/mol) = ΔH$_f$(kcal/mol) − TΔS(kcal/mol/K),[b] ΔG(kcal/mol) = ΔH(kcal/mol) − TΔS(kcal/mol K)

TABLE 6. Aqueous phase semi-empirical AM1, PM3 and PM5 calculated tautomeric equilibrium constants K_{T} of investigated molecules **A** and **B** ($\boldsymbol{K_{\mathrm{T}}} = [\mathbf{A}]/[\mathbf{B}]$)

Tautomerisation Equilibrium	[a]$\delta\Delta\mathbf{G}_f$**(kcal/mol)**	[b]$\boldsymbol{K}_{\mathbf{T}f}$	[c]$\mathbf{p}\boldsymbol{K}_{\mathbf{T}f}$	[d]$\delta\Delta\mathbf{G}$**(kcal/mol)**	[e]$\boldsymbol{K}_{\mathbf{T}}$	[f]$\mathbf{p}\boldsymbol{K}_{\mathbf{T}}$
AM1						
A $\rightleftharpoons$ B	−14.917	8.773×10^{10}	−10.943	0.361	0.543	0.265
PM3						
A $\rightleftharpoons$ B	−6.017	2.595×10^{4}	−4.14	1.443	0.087	1.060
PM5						
A $\rightleftharpoons$ B	−14.876	8.187×10^{10}	−10.913	−0.77	3.672	−0.565

[a]$\delta\Delta\mathrm{G}_f = \Delta\mathrm{G}_{f(\mathrm{k})} - \Delta\mathrm{G}_{f(\mathrm{e})}$, [b]$K_{\mathrm{T}f} = \mathrm{e}^{(-\delta\Delta\mathrm{G}_f/(\mathrm{RT}))}$, R = 1.987×10^{-3}kcal/mol K, T = 298K
[c]$\mathrm{p}K_{\mathrm{T}f} = -\log K_{\mathrm{T}f}$, [d]$\delta\Delta\mathrm{G} = \Delta\mathrm{G}_{(\mathrm{k})} - \Delta\mathrm{G}_{(\mathrm{e})}$, [e]$K_{\mathrm{T}} = \mathrm{e}^{(-\delta\Delta\mathrm{G}/(\mathrm{RT}))}$, [f]$\mathrm{p}K_{\mathrm{T}} = -\log K_{\mathrm{T}}$.
The negative sign of $\mathrm{p}K_{\mathrm{T}}$ indicates the stability of keto-amine form **A**.

TABLE 7. Aqueous phase semi-empirical AM1, PM3 and PM5 calculated acidity constants, $\mathrm{p}K_{\mathrm{a}}$, values for protonation of investigated molecules **A** and **B**

Protonation	[a]$\delta\Delta\mathbf{G}_{f(\mathbf{BH}^+)}$	[b]$\mathbf{p}\boldsymbol{K}_{\mathbf{a}f(\mathbf{BH}^+)}$	[c]$\delta\Delta\mathbf{G}_{(\mathbf{BH}^+)}$	[d]$\mathbf{p}\boldsymbol{K}_{\mathbf{a}(\mathbf{BH}^+)}$
AM1				
A $\rightleftharpoons$ C	−0.876	−0.643	−1.420	−1.042
A $\rightleftharpoons$ D	−8.876	−6.512	−0.748	−0.549
B $\rightleftharpoons$ E	14.872	10.910	22.552	16.544
PM3				
A $\rightleftharpoons$ C	24.062	17.652	-5×10^{-3}	-3.668×10^{-3}
A $\rightleftharpoons$ D	22.987	16.863	−1.096	−0.804
B $\rightleftharpoons$ E	26.552	19.381	−2.913	−2.126
PM5				
A $\rightleftharpoons$ C	−6.430	−4.717	−0.095	−0.069
A $\rightleftharpoons$ D	−4.614	−3.385	−0.230	−0.169
B $\rightleftharpoons$ E	5.235	3.821	−0.528	−0.385

[a]$\delta\Delta\mathrm{G}_{f(\mathrm{BH}^+)} = [\Delta\mathrm{G}_{f(\mathrm{B})} + \Delta\mathrm{G}_{f(\mathrm{H3O}^+)}] - [\Delta\mathrm{G}_{f(\mathrm{BH}^+)} + \Delta\mathrm{G}_{f(\mathrm{H2O})}]$, [b]$\mathrm{p}K_{\mathrm{a}f(\mathrm{BH}^+)} = \delta\Delta\mathrm{G}_{f(\mathrm{BH}^+)}/(2.303\mathrm{RT})$
[c]$\delta\Delta\mathrm{G}_{(\mathrm{BH}^+)} = [\Delta\mathrm{G}_{(\mathrm{B})} + \Delta\mathrm{G}_{(\mathrm{H3O}^+)}] - [\Delta\mathrm{G}_{(\mathrm{BH}^+)} + \Delta\mathrm{G}_{(\mathrm{H2O})}]$,
[d]$\mathrm{p}K_{\mathrm{a}(\mathrm{BH}^+)} = \delta\Delta\mathrm{G}_{(\mathrm{BH}^+)}/(2.303\mathrm{RT}), \mathrm{R} = 1.987 \times 10^{-3}$ kcal/mol K, T = 298K.

TABLE 8. Calculated relative stability (kcal/mol), K_{T} values investigated molecule

Relative Stability ([a]RS)	**HF**		**B3PW91**		**BLYP**		**B3LYP**	
	3-21G(d)	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**
A ⇌ B	−0.03	−0.25	0.060	0.036	0.058	0.012	0.04	0.04
Tautomeric equilibria [b]K_{T}	**HF**		**B3PW91**		**BLYP**		**B3LYP**	
	3-21G(d)	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**	**3-21G(d)**	**6-31G(d,p)**
A ⇌ B	0.059	0.0043	0.0028	0.0021	0.0028	0.0125	0.00002	0.00205

[a]RS $= \Delta \mathrm{H}_{f(\mathrm{imin})} - \Delta \mathrm{H}_{f(\mathrm{amin})}$ the positive sign indicates the stability of keto-amine form **A**.
$\delta\Delta \mathrm{G} = \Delta \mathrm{G}_{(\mathrm{imino})} - \Delta \mathrm{G}_{(\mathrm{amine})}$, [b] $K_{\mathrm{T}} = 10^{-(\delta \Delta \mathrm{G}/\mathrm{RT})}$.

TABLE 9. Calculated nucleophilicity values and mole fractions values of tautomer molecules, **A** and **B**

Methods	**HF**		**B3PW91**		**BLYP**		**B3LYP**	
Basis sets	**3-21G***	**6-31G****	**3-21G***	**6-31G****	**3-21G***	**6-31G****	**3-21G***	**6-31G****
				[a]**Mole fraction**				
N_{a}	0.944	0.996	0.997	0.998	0.997	0.988	1.000	0.998
N_{b}	0.056	0.004	0.003	0.002	0.003	0.012	0.000	0.002
				[b]***n***				
A molecule	−0.413	−0.367	−0.224	−0.231	−0.240	−0.249	−0.171	−0.172
B molecule	−0.387	−0.372	−0.223	−0.230	−0.240	−0.245	−0.083	−0.248

[a]$N_{\mathrm{a}} = 1/(1 + K_{\mathrm{T}})$, $N_{\mathrm{b}} = K_{\mathrm{T}}/(1 + K_{\mathrm{T}})$.
[b]Nucleophilicity ($n = \mathrm{E}_{\mathrm{HOMO}} - \mathrm{E}_{\mathrm{LUMO}}$).

4. Conclusions

The investigation of 3-(1-aminoethylidene)-2-metoxy-2-oxo-2,3-dihydro-2l5-benzo[e][1,2]oxaphosphinin-4-one **A** in crystal form (i.e. solid phase) by HF and DFT methods revealed that the title compound exist in a keto-amine tautomeric form, which is probably stabilized by a strong NH...O=C hydrogen bonding and by the conjugated double bond system. The computed bond distances and angles in the molecule are in a good agreement with experimental values and suggest that it is possible to use the computational methods in predictive manner safely.

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