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COMPUTATIONAL STUDY ON THE PROTONATION OF PHENOXYMETHYLPENICILLIN-LACTIM-ENOL BY AM1 METHOD

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ABSTRACT

The geometry, conformation and electronic structure of phenoxymethylpenicillin-lactim-enol tautomer has been optimized and calculated in the gas phase, usually considering an isolated molecule surrounded by vacuum, using semi-empirical molecular orbital AM1 method. In this connection, the mechanism of lactam-lactim and keto-enol tautomerism and protonation on phenoxymethylpenicillin-lactim-enol has been studied with the different positions of net charges at nitrogen atoms in the molecule. It is observed that the net charges on N_7- and N_{13}- atoms are respectively -0.1340 and -0.1609 in the case of phenoxymethylpenicillin-lactim-enol and also investigated that the stability of mono-protonated phenoxymethylpenicillin-lactim-enols are discussed. Further, the heats of formation (ΔH_f^o), dipole moment (μ), ionization potential (IP), full atomic charges and energies of frontier molecular orbitals (E_{HOMO} and E_{LUMO}) have been performed. The conformational analyses of mono- and di-protonated phenoxymethylpenicillin-lactim-enol and their stable conformations have also been evaluated.

KEYWORDS: AM1, Lactam-lactim, keto-enol tautomerism, phenoxymethylpenicillin, induction effect, frontier molecular orbitals.

INTRODUCTION

Isolation of the important intermediate, 6-aminopenicillanic acid from enzymatic splitting of natural penicillin's (G & V) was led the preparation of several semi-synthetic penicillins[1] with chemical modification by substituting the acyl-side chain to produce specific properties, such as resistance to stomach acids, a degree of resistance to penicillinase activity against some gram-negative bacteria.[2] Consequent importance of β-Lactam ring of penicillin has been identified to block the activity irreversible and their derivatives studied extensively as broad anti-microbial spectra for reducing undesirable side effects.[3] In actual fact, penicillins had selective penetration through the porin channels of the cell membrane and the dipolar character of the drug enhances oral absorption.[4]

Austin Model-1 (AM1) is one of the semi-empirical quantum calculations, which includes experimental parameters and extensive simplification of the Schrodinger's equation ($H\Psi=E\Psi$) to optimize molecules for calculation of various properties to solve chemical problems[5]. In view of these observations, it is prompted us, to carry out the research work on phenoxymethylpenicillin (Penicillin-V)[5], the present study deals on the protonation of phenoxymethylpenicillin-lactim-enol (**2**) and thus obtained mono-protonated (**3** & **4**), di-protonated (**5**) and anion (**6**) in gas phase has been evaluated by AM1 method, usually allowing an isolated molecule surrounded by vacuum.

Computational methods[6]

AM1 Semi-empirical molecular orbital calculations were performed on the molecules shown in Scheme-1 by means of Intel Dual core D102GGC2 DDR2 1GB SDRAM PC. The initial molecular geometry was adopted as Pople's standard data[7], and subsequently fully optimized using an energy gradient method in the ground state (keywords: PRECISE, equivalent to GNORM=5.0, CHARGE, GEO-OK, and MMOK to correct the increase in the barrier to rotation of the amide linkage) until the lowest energy conformation was found. The conformations were designated by Klyne-Prelog terms[8] using *s* = syn, *a* = anti, *p* = peri-planar (0 ± 30^0 & 180 ± 30^0) and all other angles *c* = clinal. In this context, the numbering of phenoxymethylpenicillin-lactim-enol (**2**) is shown in Figure -1. The values of optimized AM1 calculations were included the main data of physical properties (Table-I), bond lengths (Table-II) and dihedral angles (Table-III) of molecules (**1** to **6**) for the sake of discussion.

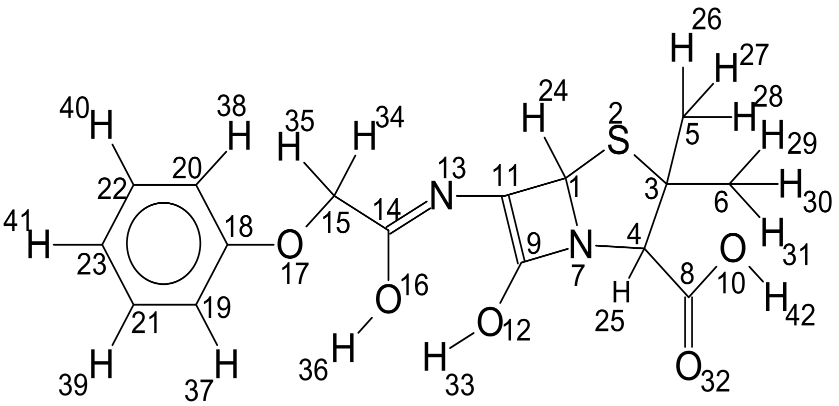


Figure- 1 :Structure of Phenoxymethyl-lactim-enol

RESULTS AND DISCUSSION

Electronic structure of phenoxymethylpenicillin (1) and its lactim-enol-form (2), mono-protonated (3 & 4) di-protonated (5) and anion (6)

The optimized electronic structure of phenoxymethylpenicillin (**1**) and its lactim-enol-form (**2**), mono-protonated (**3** & **4**), and di-protonated (**5**) anion (**6)** are shown in Scheme-1. The calculated heats of formation (ΔH_f^o), ionization potential (IP), dipole moment (μ), the energies of frontier molecular orbitals (E_{HOMO} and E_{LUMO}) and net charges on hetero atoms of the molecules (**1** to **6**) are presented in **Table-I**. It is observed that the net charges on N_7- and N_{13}- atoms are respectively -0.1340 and -0.1609 in the case of phenoxymethylpenicillin-lactim-enol (**2**). Usually, it is also investigated that the sequence of protonation for nitrogen atoms of phenoxymethylpenicillin-lactim-enol (2) in the order of $N_7 < N_{13}$.

Heat of formation (ΔH_f^o in kcal/mol), ionization potential (eV), dipole moment (μ in Debye), energies of frontier molecular orbitals (in eV), electron excitation energies (ΔE) (in eV) and the atomic charges on S_2, N_7, N_{13}, O_{10}, O_{12}, O_{16}, O_{17} and O_{32} of phenoxymethylpenicillin(**1**) and its lactim-enol-form(**2**), mono-protonated forms (**3** & **4**), di-protonated form (**5**) and anion(**6**) from AM1 calculation.

Table-I

Parameters	1	2	3	4	5	6
ΔH_f^o (kcal/mol)	-118.4089	-90.6115	+59.9332	+56.9942	+247.3275	-134.9740
Ionization potential (eV)	9.1342	8.3326	11.8603	11.8449	14.4843	5.1917
μ (Debye)	2.8946	2.8554	6.4526	5.9085	5.5667	14.1898
E_{HOMO} (eV)	-9.134	-8.333	-11.860	-11.845	-14.484	-5.192
E_{LUMO} (eV)	+0.045	-0.158	-4.966	-5.470	-8.643	+2.409
Electron excitation energies ($\Delta E = E_{LUMO} - E_{HOMO}$) (eV)	9.179	8.175	6.864	6.375	5.841	7.601
S_2 (atomic charge)	+0.0664	+0.0803	+0.1323	+0.3309	+0.6310	-0.0766
N_7 (atomic charge)	-0.2361	-0.1340	-0.1249	-0.2040	-0.2164	-0.1726
N_{13} (atomic charge)	-0.3698	-0.1609	-0.0239	-0.2857	-0.1454	-0.0916
O_{10} (atomic charge)	-0.2857	-0.3111	-0.2860	-0.2849	-0.2753	-0.5802
O_{12} (atomic charge)	-0.2361	-0.1893	-0.1337	-0.1963	-0.2020	-0.2206
O_{16} (atomic charge)	-0.3255	-0.2853	-0.1991	-0.2432	-0.2105	-0.3261
O_{17} (atomic charge)	-0.1944	-0.2277	-0.2014	-0.2242	-0.1806	-0.2039
O_{32} (atomic charge)	-0.3527	-0.3369	-0.3463	-0.3118	-0.2932	-0.5287

The calculated values of frontier orbital energies (E_{HOMO} and E_{LUMO}) reveal the electron excitation energies are observed decreasing in the order of **1 > 2 > 6 > 3 > 4 > 5**. The results so obtained reveal that the electronic properties and reactivity of molecule depend on its conformational structure. In the photochemical reaction, the promotion of an electron from HOMO to LUMO is allowed antara-facial pathway in the case of **1** and **6**, due to presence of different sign whereas molecules 2 to 5 allowed supra-facial path way, due to the presence of same sign.[9] The ionization potential values are examined in the order of **5** > **3** > **4** > **1** > **2** > **6** and it is confirmed that di-protonated phenoxymethylpenicillin-lactim-enol (**5)** is more IP than all others.

The dipole moment of molecules depends on their arrangement of the atoms in comprising the molecules and it is found increasing in the order of **2 < 1** < **5** < **4** < **3** < **6**. Anion (**6**) shows higher dipole moment. It is observed, that electronegative heteroatom's cause displacement of electrons, which induces an additional dipole moment in the molecule. The magnitude of the induction effect[10] (μ_{ind}) of molecules can be estimated with respect to phenoxymethylpenicillin-lactim-enol (**2**). It is found that the induction effect is increasing in the case of $\Delta\mu_{ind}$ (**1**) 0.0392 D, $\Delta\mu_{ind}$ (**5**) 2.7113 D, $\Delta\mu_{ind}$ (**4**) 3.0531 D, $\Delta\mu_{ind}$ (**3**) 3.5972 D and $\Delta\mu_{ind}$ (**6**) 11.3344 D. According to the heat of formation (ΔH_f^o) data, the stability of compounds have decreased in the order of **6** > **1 > 2 > 4 > 3 > 5**. But, it is predicted that the protonation would take place preferably at N_{13}-atom than N_7-atom in the case of phenoxymethylpenicillin-lactim-enol (**2**), this is due to the stability of mono-protonated

phenoxymethylpenicillin-lactim-enol, **4** (ΔH_f^o, +56.9942 Kcal/mol) is more stable than **3** (ΔH_f^o, +59.9332 Kcal/mol). The formation of di-protonated phenoxymethylpenicillin-lactim-enol **(5)** is possible (with the heat of formation ΔH_f^o of +247.3275 Kcal/mol**)** from mono-protonated phenoxymethylpenicillin-lactim-enol, (**3** & **4**). The change of atomic charges on the other atoms of the molecule is also observed at the time of protonation site of N_7-, and N_{13}- atom of phenoxymethylpenicillin-lactim-enol **(2)**. However,. The protonation at N_{13}-atom in the case of phenoxymethylpenicillin-lactim-enol (**2**) to mono-protonated form (**3**) is considered by decreasing net atomic charges at N_7-, N_{13}-, O_{12}-, O_{16}-, O_{17}- and increasing at O_{32}- atom. The protonation site of phenoxymethylpenicillin-lactim-enol (**2**) at N_7- atom to mono-protonated form (**4**) is considered by decreasing net atomic charges at O_{10}-, O_{16}- O_{17}-, O_{32}- and increasing at N_7-, N_{13}-, O_{12}- atoms. In the case of di-protonated form (**5**), the negative atomic charges are decreasing at N_{13}-, O_{10}-, O_{16}-, O_{17}-, O_{32}- atoms and increasing at N_7-, O_{12}-atoms. Anion of phenoxymethylpenicillin- lactim-enol (**6**) is formed by the removal of a proton from O_{10}-atom with decreasing net charges at N_{13}-, O_{17}- atoms and increasing at N_7-, O_{10}-, O_{12}-, O_{16}- and O_{32}- atoms.

Bond lengths of phenoxymethylpenicillin (**1**) and its lactim-enol-form(**2**), mono-protonated forms (**3** & **4**), di-protonated form (**5**) and anion(**6**) from AM1 calculation.

Table-II

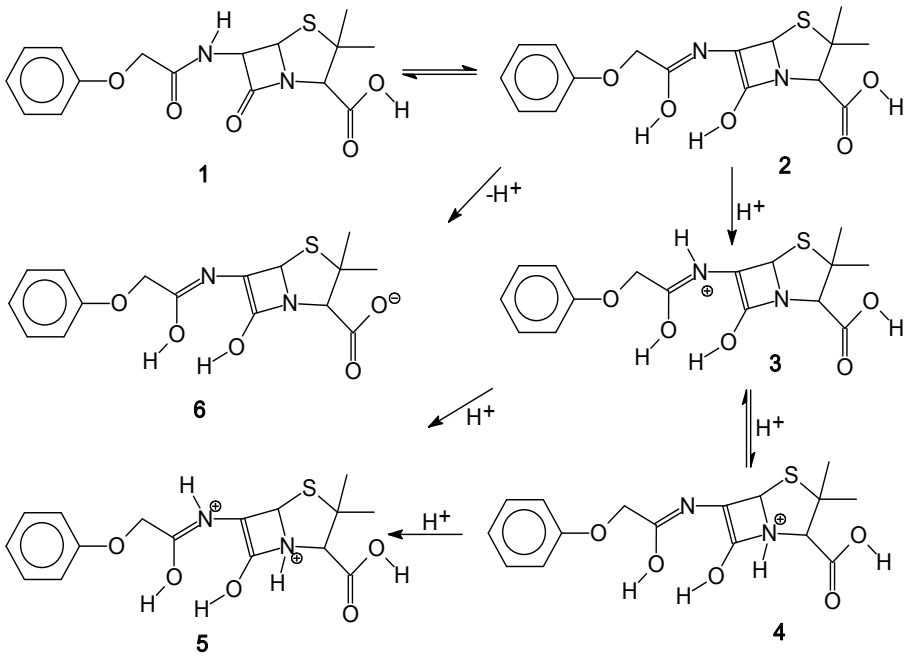
Bond lengths (Å)	1	2	3	4	5	6
O_{10}-C_8	1.3583	1.3629	1.2328	1.3524	1.3463	1.2633
C_{11}-C_9	1.5654	1.3826	1.3934	1.4957	1.4546	1.3993
O_{12}-C_9	1.2182	1.3488	1.3344	1.3447	1.3609	1.3289
N_{13}-C_{11}	1.4133	1.3660	1.3776	1.3813	1.4232	1.3611
C_{14}-N_{13}	1.3903	1.2997	1.3278	1.3168	1.3387	1.2970
O_{16}-C_{14}	1.2413	1.3803	1.3568	1.3565	1.3393	1.3932
O_{32}-C_8	1.2337	1.2312	1.3539	1.2295	1.2295	1.2568
H_{33}-O_{12}	- -	0.9739	0.9749	0.9810	0.9773	0.9989
H_{36}-O_{16}	- -	0.9710	0.9775	0.9795	0.9920	0.9733
H_{42}-O_{10}	0.9731	0.9718	0.9748	0.9766	0.9799	- -
H-N_7	- -	- -	- -	1.0105	1.0321	- -
H-N_{13}	- -	- -	1.0124	- -	1.0066	- -

Lactam-lactim and Keto-enol tautomerism of phenoxymethylpenicillin (1)

In the great majority of cases molecules under ordinary conditions, tautomerism is possible for inter-conversion at higher temperatures, often with the aid of catalyst. The AM1 calculated heat of formation, and the tautomeric equilibrium constants $\log K_T$ was calculated[11] according to the equation (1):

$$\log K_T = \frac{\Delta G_T}{2.303\ R\ T} = \frac{\delta \Delta H}{2.303\ R\ T} \quad \text{----------} \quad (1)$$

Where ΔG_T is the free energy of the tautomeric equilibrium, $\delta\Delta H$ is the difference in the calculated heats of formation of the tautomeric species participating in this equilibrium. R is the gas constant and T is the absolute temperature. From this equation (1), $\log K_T$ value was calculated as 1.4086. The formation of two tautomeric forms of phenoxymethylpenicillin (**1**) and phenoxymethylpenicillin-lactim-enol (**2**) are expected with increasing bond lengths of O_{12}-C_9 (1.2182 to 1.3488 Å), O_{16}-C_{14} (1.2413 to 1.3804 Å) and decreasing bond length of C_{11}-C_9 (1.5654 to 1.3826 Å), C_{14}-N_{13} (1.3903 to 1.2997 Å) with the formation of H_{33}-O_{12} (0.9739 Å), H_{36}-O_{16} (0.9710 Å) as per Scheme-1 Table-II. From the Table-III and Scheme-1, it is observed that the change of conformation from *–ac* of $N_{13}C_{11}C_9N_7$ and $C_{14}N_{13}C_{11}C_9$ are changed to respectively ***+ac*** and ***+ap***. The conformation of ***-ap*** of $O_{10}C_8C_4C_3$ and $H_{42}O_{10}C_8C_4$ are changed to ***+ac*** and ***+a***p respectively. The dihedral angle ***+sp*** of $O_{16}C_{14}N_{13}C_{11}$ and ***+sc*** of $C_{18}O_{17}C_{15}C_{14}$ are changed to ***-sp*** and ***-ap*** conformations along with the formation of $H_{33}O_{12}C_9N_7$ and of $H_{36}O_{16}C_{14}N_{13}$ with ***-ap*** conformation.



Scheme - 1

The protonation of phenoxymethylpenicillin-lactim-enol (2)

The proton affinity (PA)[12] values for different nitrogen atoms of phenoxymethylpenicillin-lactim-enol (**2**) were calculated by using the equation (2):

$$PA = \Delta H_f^{o}(H^{+}) + \Delta H_f^{o}(B) - \Delta H_f^{o}(BH^{+}) \quad \text{---------- (2)}$$

Where PA is the proton affinity, $\Delta H_f^{o}(B)$ is the heat of formation of phenoxymethylpenicillin-lactim-enol (**2**), $\Delta H_f^{o}(BH^{+})$ is the heat of formation for the cation, and $\Delta H_f^{o}(H^{+})$ is heat of formation for the proton (367.2kcal/mol). The proton affinity is in the order of N_{13} (216.6553 kcal/mol) < N_7 (219.5943 kcal/mol) in the formation of mono-protonated phenoxymethylpenicillin-lactim-enol respectively **3** and **4**. Di-protonated form (**5**) was formed from either of mono-protonated phenoxymethylpenicillin-lactim-enol (**3** and **4**) respectively with PA 179.8057 kcal/mol and 176.8667 kcal/mol.

The conformations of phenoxymethylpenicillin-lactim-enol (2) and its mono-protonated (3 & 4), di-protonated (5) and anion (6)

The spatial arrangement of atoms in a molecule is considered to study the conformations of phenoxymethylpenicillin (**1**), and its lactim-enol-form (**2**), mono-protonated forms (**3 & 4**), di-protonated form (**5**) and anion (**6**) with a view to investigate molecular *anti*- or *syn*-conformations. The change in energy content of the protonation may depend on the changes in the parameters of dihedral angles. From the Table-II, Table-III and as per Scheme-1, mono-protonated phenoxymethylpenicillin-lactim-enol (**3**) is formed by the addition of proton at N_{13}-atom of phenoxymethylpenicillin-lactim-enol (**2**), with increasing bond lengths at C_{11}-C_9, N_{13}-C_{11}, C_{14}-N_{13}, O_{32}-C_8, H_{33}-O_{12}, H_{36}-O_{16}, H_{42}-O_{10} and decreasing bond lengths at O_{10}-C_8, O_{12}-C_9, and O_{16}-C_{14} with the formation of bond H-N_{13}. The change of dihedral angle of $C_8C_4C_3S_2$, $N_{13}C_{11}C_9N_7$, $C_{18}O_{17}C_{15}C_{14}$, $O_{32}C_8C_4C_3$ and $H_{36}O_{16}C_{14}N_{13}$ are converted from ***+ap*** to ***+ac, +ap*** to ***-ap, -ap*** to ***+ac, +sc*** to ***-sc,*** and ***-ap*** to ***+ap*** conformations respectively and all other conformations are moderately changed. It is also observed that the protonation at N_{13}-atom is shown ***-sc*** conformation.

If the mono-protonated phenoxymethylpenicillin-lactim--enol (**4**) is formed by the addition of proton at N_7- atom of phenoxymethylpenicillin-lactim-enol (**2**), with increasing bond lengths at C_{11}-C_9, N_{13}-C_{11}, C_{14}-N_{13}, H_{33}-O_{12}, H_{36}-O_{16}, H_{42}-O_{10} and decreasing bond lengths at O_{10}-C_8, O_{12}-C_9, O_{32}-C_8, and O_{16}-C_{14} with the formation of bond H-N_7. The change of dihedral angle of ***+ap*** of $N_{13}C_{11}C_9N_7$, ***+ap*** of $C_{15}C_{14}N_{13}C_{11}$, ***-sp*** of $O_{16}C_{14}N_{13}C_{11}$, ***-ap*** of $C_{18}O_{17}C_{15}C_{14}$, ***+sc*** of $O_{32}C_8C_4C_3$ and ***+ap*** of $H_{42}O_{10}C_8C_4$ are converted to ***+ac , -ap, +sp, +ac, -ac*** and ***-ap*** conformations respectively and all other conformations are changed moderately. It is also observed that the protonation at N_7-atom is made known ***+ac*** conformation.

In the case of di-protonated phenoxymethylpenicillin-lactim-enol (**5**), it is formed by the addition of protons at N_7- and N_{13}-atoms of phenoxymethylpenicillin-lactim-enol (**2**), with increasing bond lengths at C_{11}-C_9, O_{12}-C_9, N_{13}-C_{11}, C_{14}-N_{13}, H_{33}-O_{12}, H_{36}-O_{16}, H_{42}-O_{10} and decreasing bond lengths at O_{32}-C_8, O_{10}-C_8, and O_{16}-C_{14} with the formation of bonds at H-N_7 and H-N_{13}. The change of dihedral angle of ***+ac*** of $O_{10}C_8C_4C_3$, ***+ap*** of $N_{13}C_{11}C_9N_7$, ***-ap*** of $C_{18}O_{17}C_{15}C_{14}$ and ***+sc*** of $O_{32}C_8C_4C_3$ are converted to ***+sc, -ac, +ac*** and ***–ac*** conformations respectively and all other conformations are changed moderately. It is also investigated that the protonation at N_7- atom and N_{13}-atom are shown respectively ***+ac*** and ***-sc*** conformations to form stable di-protonated phenoxymethylpenicillin-lactim-enol (**5**). It can be concluded that the anion (**6**) is formed with the removal of a proton from O_{10}- atom of phenoxymethylpenicillin-lactim-enol (**2**) with increasing bond lengths of C_{11}-C_9, O_{16}-C_{14}, O_{32}-C_8, H_{33}-O_{12}, H_{36}-O_{16} and decreasing bond lengths at O_{10}-C_8, O_{12}-C_9, N_{13}-C_{11} and C_{14}-N_{13}. It is also examined that the dihedral angles ***+ac*** of $O_{10}C_8C_4C_3$, ***+ap*** of $N_{13}C_{11}C_9N_7$, ***+ap*** of $C_{15}C_{14}N_{13}C_{11}$, ***-sp*** of $O_{16}C_{14}N_{13}C_{11}$, ***-ap*** of $C_{18}O_{17}C_{15}C_{14}$, ***-ap*** of $H_{33}O_{12}C_9N_7$ and ***-ap*** of $H_{36}O_{16}C_{14}N_{13}$ are converted respectively to ***–ac, -ap, -ap, +sc, +sc, -sc*** and ***+sc*** conformations in the formation of stable anion (**6**) and rest of positions have moderate changes.

Table III: Dihedral angles (^{0}) of phenoxymethylpenicillin (1) and its lactim-enol-form (2), mono-protonated forms (3 & 4), di-protonated form (5) and anion (6) from AM1 calculation.

Dihedral angle (^{0})	1		2		3		4		5		6	
	Angle	**(*)**	**Angle**	**(*)**	**Angle**	**(*)**	**Angle**	**(*)**	**Angle**	**(*)**	**Angle**	**(*)**
$C_4C_3S_2C_1$	-20.59	***-sp***	**-17.53**	***-sp***	-16.11	***-sp***	**-17.27**	***-sp***	**-2.95**	***-sp***	-16.43	***-sp***
$C_8C_4C_3S_2$	+163.04	***+ap***	**+151.49**	***+ap***	**+146.75**	***+ac***	**-165.45**	***+ap***	**+172.94**	***+ap***	+157.69	***+ap***
$O_{10}C_8C_4C_3$	**-169.46**	***-ap***	**+104.90**	***+ac***	**+92.14**	***+ac***	**+90.39**	***+ac***	**+74.89**	***+sc***	**-109.46**	***-ac***
$N_{13}C_{11}C_9N_7$	**-114.93**	***-ac***	**-174.87**	***+ap***	**-171.95**	***-ap***	**+124.46**	***+ac***	**-143.15**	***-ac***	***-168.53***	***-ap***
$C_{14}N_{13}C_{11}C_9$	**-129.94**	***-ac***	**+159.59**	***+ap***	+146.79	***+ac***	**+171.22**	***+ap***	+143.61	***+ac***	-165.01	***-ap***
$C_{15}C_{14}N_{13}C_{11}$	+179.80	*+ap*	**+178.12**	***+ap***	+175.29	*+ap*	**-172.32**	***-ap***	+178.48	***+ap***	**+179.68**	***-ap***
$O_{16}C_{14}N_{13}C_{11}$	**+1.39**	***+sp***	**-2.36**	***-sp***	-2.69	*-sp*	**+6.89**	***+sp***	-2.26	***-sp***	**+58.46**	***+sc***
$C_{18}O_{17}C_{15}C_{14}$	**+86.13**	***+sc***	**-177.99**	***-ap***	**+95.07**	***+ac***	**+98.85**	***+ac***	**+94.73**	***+ac***	**+68.51**	***+sc***
$O_{32}C_8C_4C_3$	+16.23	***+sp***	**-74.10**	***+sc***	**-87.23**	***-sc***	**-91.79**	***-ac***	**-107.36**	***-ac***	+70.46	***+sc***
$H_{42}O_{10}C_8C_4$	**-179.96**	***-ap***	**+179.21**	***+ap***	+179.75	***+ap***	**-178.86**	***-ap***	+178.08	*+ap*	- -	- -
$H_{33}O_{12}C_9N_7$	- -	- -	**-170.96**	***-ap***	-178.22	*-ap*	-175.56	*-ap*	-159.53	*-ap*	**-19.46**	***-sc***
$H_{36}O_{16}C_{14}N_{13}$	- -	- -	**-178.03**	***-ap***	**+175.58**	***+ap***	-177.85	*-ap*	-172.89	***-ap***	**+19.78**	***+sc***
H-$N_7C_4C_3$	- -	- -	- -	- -	- -	- -	**+137.75**	***+ac***	**+112.98**	***+ac***	- -	- -
H-$N_{13}C_{11}C_9$	- -	- -	- -	- -	**-35.48**	***-sc***	- -	- -	**-37.61**	***-sc***	- -	- -

* The conformations were designated by Klyne-Prelog terms[8] using *s* = syn, *a* = anti, *p* = peri-planar (0 ± 30^0 & 180 ± 30^0) and all other angles *c* = clinal, and + & - signs.

CONCLUSION

Austin Model-1 (AM1) is one of the semi-empirical quantum calculations, which includes experimental parameters and extensive simplification of the Schrodinger's equation (HΨ=EΨ) to optimize phenoxymethylpenicillin-lactim-enol and its protonated forms for prediction of various conformational changes and its reactivity & pharmacological action. The protonation of phenoxymethylpenicillin-lactim-enol is predicted with the negative charge distribution on nitrogen atoms ($N_{13} > N_7$). It is established that mono-protonated at N_7 is more stable than N_{13}. Further, the utility of theoretical predictions is important for evaluating the ability to cross cell wall barriers, biochemical mechanism to prevent cell wall synthesis and binding to serum proteins. This study reveals about the stability of protonated forms.

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