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AM1 study on the conformations and electronic properties of phenethicillin

Banda Upender Reddy, Bojja Rajeshwar Rao[1] and Battu Satyanarayana*

Department of Chemistry, University College of Science, Osmania University, Hyderabad-500 007, Telangana State, India and [1]Chemical Division, Kakatiya Thermal Power Project (O&M), Chelpur- 506 170, Telangana state, India

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ABSTRACT

The geometry, conformation and electronic structure of phenethicillin have been optimized and calculated in the gas phase, usually considering an isolated molecule surrounded in a vacuum by using semi-empirical molecular orbital AM1 method. Further, the mechanism of protonation in phenethicillin has been studied by comparison of the different positions of net charges on nitrogen atoms in the molecule. In this connection, 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 and discussed. The conformational analyses of mono- and di-protonated species have also been performed for stable conformations.

Key words: AM1, Phenethicillin, Induction effect, Frontier molecular orbital.

INTRODUCTION

Phenethicillin is one of the penicillin derivatives and studied extensively due to their favourable absorption patterns and reduced undesirable side effects [1, 2, 3, 4]. Phenethicillin is less active invitro against streptococci and pneumococci, but invivo this is partly offset by the higher blood levels in chemotherapy of bacterial infections [5, 6]. Enzymatic splitting of natural penicillins and isolation of the important intermediate, 6-aminopenicillanic acid was led the preparation of several semi-synthetic penicillins [7, 8]. Phenethicillin is also tested in the treatment of gonorrhoea and compared with other semi-synthetic penicillin derivatives [9, 10]. In practice, penicillins were expected to assume the dipolar character of the drugs, which were improved oral absorption [11, 12]. Austin Model-1 (AM1) is one of the semi-empirical methods with using 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 [13, 14, 15]. It is important to know the exact position of protonation centres' by the different positions of net charges on hetero atoms in the molecule. In this way quantum chemistry simulates chemical structure and reactions numerically and allows studying chemical phenomena by running calculations on computer rather than by examining reactions experimentally. Hence, it has been attracted that phenethicillin exists as anion and protonated forms and is considerably altered polarity, which are an advantage for inhibiting the synthesis of bacterial cell walls. In view of these observations, the present study on molecular conformation and electronic properties of phenethicillin (**1**) in gas phase usually considering an isolated molecule surrounded by vacuum has been evaluated by AM1 method. From the obtained optimized electronic structure of phenethicillin, the mechanism of protonation has been studied by comparison of the relative values of net charges for nitrogen atoms at different positions of the molecule. Considering phenethicillin as a neutral molecule (**1)**, the molecular geometry and conformations of mono-protonated (**2** & **3**) systems, di-protonated (**4**) system and anion (**5**) have been determined by full optimization calculations using semi-empirical molecular orbital AM1 method.

Computational methods [13, 14]: Austin Model 1 (AM1) Semi-empirical molecular orbital calculations were performed on the molecules shown in Scheme-1 using the MOPAC93 in WinMOPAC ver. 5.13 program by means of Intel Dualcore D102GGC2 DDR2 1GB SDRAM PC. The AM1 semi-empirical method is a modification

***Corresponding Author Address:** Battu Satyanarayana, Department of Chemistry, University College of Science, Osmania University, Hyderabad-500 007, Telangana State, India, E-mail: satyambchem@yahoo.co.in*

of MNDO, offering more accurate parameterizations for polar systems and transition states. Geometry calculations 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) were completely optimized until the lowest energy conformation was found. The position of the atom in the molecule is mentioned as subscript (Figure-1). The initial molecular geometry was adopted as Pople's standard data [16], and subsequently fully optimized using an energy gradient method. The conformations were designated by Klyne-Prelog terms [17, 18] using *s* = syn, *a* = anti, *p* = peri-planar (0 ± 30^0 & 180 ± 30^0) and all other angles *c* = clinal.

RESULTS & DISCUSSION

Electronic structure of phenethicillin (1) and its mono-protonated (2&3), di-protonated (4) and anion (5):

The optimized electronic structure of phenethicillin (**1**) and its mono-protonated (**2** & **3**), di-protonated (**4**) and anion (**5**) are shown in Scheme-1. In this context, the numbering of phenethicillin is shown in Figure -1. The calculated heats of formation (ΔH_f^0), 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 **5**) are presented in Table-I. It is observed that the net charges on N_7- and N_{12}- atoms are -0.2402 and -0.3507 respectively in the case of phenethicillin (**1**). Usually, the nitrogen atom with larger negative value of net charge accepts proton more easily. It is also investigated that the sequence of protonation for nitrogen atoms of phenethicillin (**1**) is increasing in the order of $N_7 < N_{12}$. Thus, the negative charge distribution on nitrogen atoms N_{12}-atom is predicted to be main protonation site of phenethicillin (**1**).

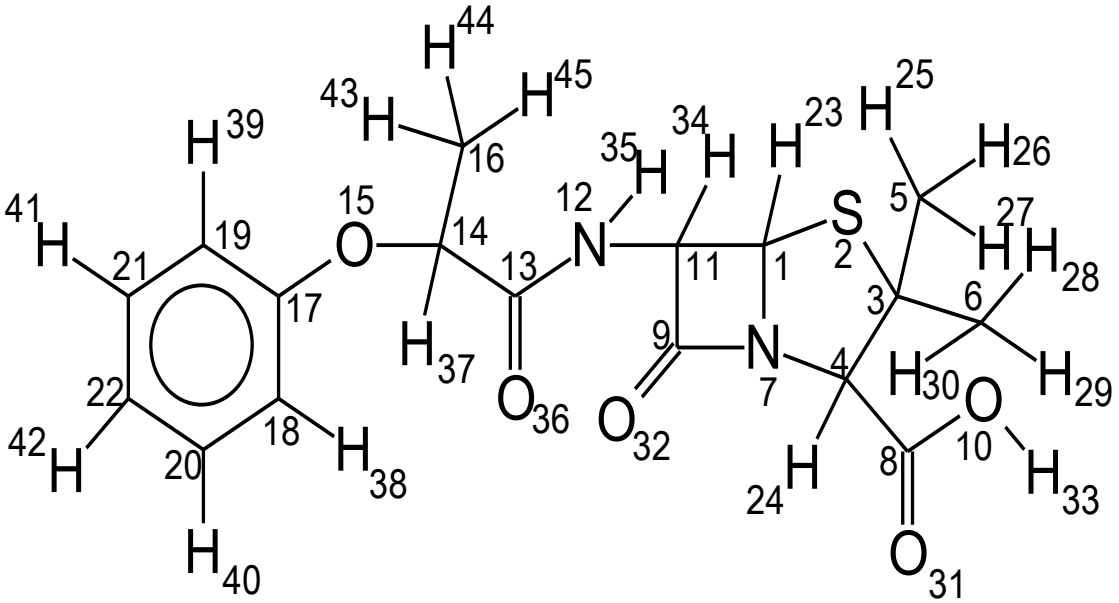


Figure - 1

It is also observed that ionization potential values are increased in the order of molecules **5** < **1** < **3** < **2** < **4**. The di-protonated system (**4**) has more ionization potential. The calculated values of frontier orbital energies (E_{HOMO} and E_{LUMO}) reveal that molecules **1** and **5** have more electron-donor character whereas other molecules have electron-acceptor property. In the case of HOMO, the electron density is highest at N_{12}- atoms for molecules **1, 3, 4** and **5**. The results revealed that the electronic properties and reactivity of molecule depend on its conformational structure. The promotion of an electron from HOMO to LUMO, in a photochemical reaction, the supra-facial path way is allowed in the case of molecules **2** to **4**, due to the presence of same sign and antara-facial path

way is allowed in the case of **1** and **5,** due to the presence of opposite sign [19, 20]. The dipole moments of molecules depend on the nature of the atoms and bonds comprising the molecules and on their arrangement.

The dipole moment is increasing in the order of molecules **1** < **4** < **2** < **3** < **5**. Anion (**5**) shows higher dipole moment. The electronegative hetero-atoms cause displacement of electrons that induces an additional dipole moment in the molecule. The magnitude of the induction effect [21] (μ_{ind}) of molecules can be estimated with respect to phenethicillin (**1**). It is found that the induction effect is increasing in the case of $\Delta\mu_{ind}$ (**4**) 0.352D < $\Delta\mu_{ind}$ (**2**) 2.977D < $\Delta\mu_{ind}$ (**3**) 3.042D < $\Delta\mu_{ind}$ (**5**) 16.595D. According to the heat of formation (ΔH_f^o) data, the stability of compounds have decreased in the order of **4** > **2** > **3** > **1** > **5**. It is investigated that the anion of phenethicillin (**5**) is more stable. But geometry calculations in the ground state were completely optimized until the lowest energy conformation was found in the individual ions or molecules.

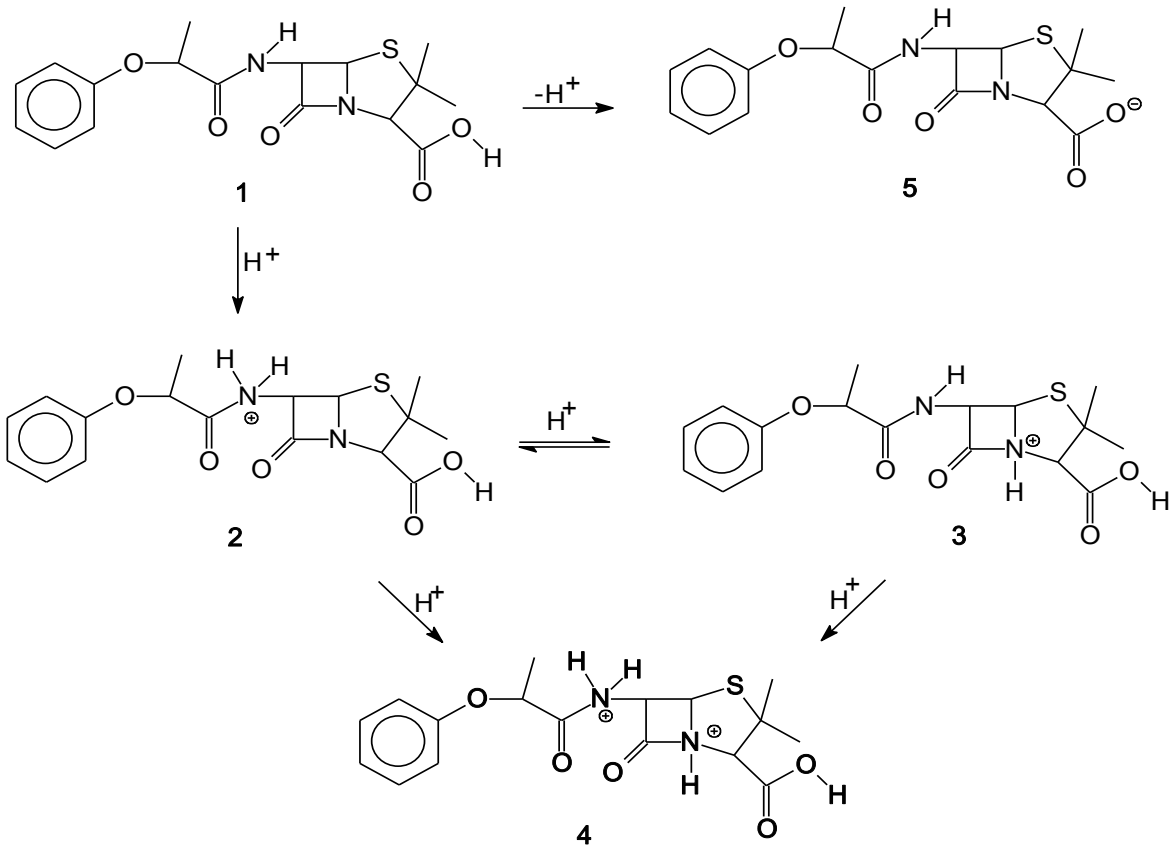
It can be assumed that the electronic properties and reactivity of the molecule depend on its conformational structure. It is predicted that the protonation would take place preferably at N_{12}-atom than N_7-atom in the case of phenethicillin (**1**), this is due to the increased bond lengths of N_{12}-C_{11} (1.4752 Å), C_{13}-N_{12} (1.5248 Å) and C_{11}-C_9 (1.5793 Å). It is found that the stability of mono-protonated phenethicillin **3** (ΔH_f^o, +39.0467 kcal/mol) is more stable than **2** (ΔH_f^o, +57.3982 kcal/mol). The formation of di-protonated phenethicillin **(4),** from mono-protonated phenethicillins (**2** & **3**) is possible with the heat of formation (ΔH_f^o, +294.7399 kcal/mol). The protonation site of phenethicillin **(1)** at N_{12}- atom is predicted to be the main basic centre of molecule. However, negative atomic charges are also present on the other atoms of the molecule. In the case of neutral phenethicillin (**1**), the protonation at N_7-atom to form mono-protonated cation (**3**) is considered by increasing net atomic charges at N_{12}-, O_{10}- and O_{36}- atoms and decreasing at N_7-, O_{15}-, O_{31}- and O_{32}- atoms. The protonation site of phenethicillin (**1**) at N_{12}- atom to form mono-protonated cation (**2**) is considered by decreasing net atomic charges at N_7-, N_{12}-, O_{15}-, O_{31}-, O_{32}- and O_{36}-atoms and increasing at O_{10}-atom only. In the case of di-protonated cation (**4**), the negative atomic charges are decreased at N_7-, N_{12}-, O_{31}-, O_{32}- and O_{36}- atoms and increased at O_{10}-, and O_{15}- atoms. Anion of phenethicillin (**5**) is formed by the removal of a proton from O_{10}-atom of phenethicillin (**1**) with increasing net charges at N_{12}-, O_{10}-, O_{31}- and O_{32}- atoms and decreasing at N_7-, O_{15}- and O_{36}- atoms.

The acid – base equilibrium of phenethicillin (1 to 5):

Equilibrium of the protonation of phenethicillin (**1**) is usually found in polar solvents, and it is established as per Scheme-1. N_{12}-atom is main basic centre in accordance with the negative charge distribution on N-atoms (Table-1). To determine the exact protonation centres of phenethicillin (**1**), the proton affinities (PA) for the different nitrogen atoms of the molecule have been calculated by means of AM1 method. The stable conformations of the cations are determined by the protonation of each nitrogen atom of the molecule and calculated the heat of formation (ΔH_f^o) with full geometry optimization. Thus, formed cations with the protonation at N_7- or N_{12}- atoms of phenethicillin (**1**) can exist in *anti*- or *syn*-conformations, as shown in Scheme-1. Its conformation can be assigned by comparison of its geometry and electronic structure. The proton affinity (PA) [22] values for the different nitrogen atoms of phenethicillin RH (**1**) were calculated by using the equation (1) and found to be 182.8360 kcal/mol and 202.1875 kcal/mol respectively in the case of mono-protonated phenethicillins (**2** and **3**). Di-protonated phenethicillin (**4**) was formed from either of mono-protonated phenethicillins (**2** and **3**) respectively with PA 129.8583 kcal/mol and 111.5068 kcal/mol.

$$PA=\Delta H_f^o(H^+) + \Delta H_f^o(B) - \Delta H_f^o(BH^+). \ldots (1).$$

Where PA is the proton affinity, $\Delta H_f^o(B)$ is the heat of formation for phenethicillin, $\Delta H_f^o(BH^+)$ is the heat of formation for the cation, and $\Delta H_f^o(H^+)$ is heat of formation for the proton (367.2 kcal/mol). The proton affinity is in the order of N_7 (202.1875 kcal/mol) > N_{12} (182.8360 kcal/mol) and mono-protonated phenethicillin (**3**) appears to be more stable. All cations are solvated to form hydrogen bonds with the polar solvents which would affect the position of the equilibrium.



Scheme - 1

The conformations of phenethicillin (1) and its mono-protonated (2 and 3), di-protonated (4) and anion R^- (5):

The spatial arrangement of atoms in a molecule is considered to study the conformations of phenethicillin (**1**), and its mono-protonated cations (**2 & 3**), di-protonated cation (**4**) and anion (**5**) with a view to investigate molecular deformations. These can exist in *anti*- or *syn*- conformation, according to the position of atoms. In this context, the change in energy content of the protonation may depend on the changes in the parameters of dihedral angles. Figure-1 illustrates the atomic numbering of phenethicillin (**1**). Fully optimized AM1 calculations scrutinize only the main data of bond lengths (Table-II) and dihedral angles (Table-III) of molecules (**1** to **5**) for the sake of simplicity. From the Table-II, Table-III and Scheme-1, mono-protonated phenethicillin (**2**) is formed by the addition of proton at N_{12}-atom of phenethicillin (**1**), with increasing bond lengths at N_{12}-C_{11}, C_{13}-N_{12} and C_{11}-C_9 and decreasing bond lengths at C_9-N_7 and O_{36}-C_{13}. The change of conformation from *–ap* of $O_{10}C_8C_4C_3$, *-sc* of $O_{15}C_{14}C_{13}N_{12}$ and *-sc* of $C_{16}C_{14}C_{13}N_{12}$ are changed to *-ac*, *+ac* and *+sp* conformations respectively. The dihedral angle of *-ac* of $C_{13}N_{12}C_{11}C_9$, *+ap* of $H_{33}O_{10}C_8C_4$ and *+ap* of $C_{14}C_{13}N_{12}C_{11}$ are changed to *–ap* conformation. The conformations of *+ac* of $C_{17}O_{15}C_{14}C_{13}$ and *+sp* of $O_{31}C_8C_4C_3$ are changed to *+sc* conformation. It is also observed that the protonation at N_{12}- atom is shown *–sc* conformation. If the mono-protonated phenethicillin (**3**) is formed by the addition of proton at N_7- atom of phenethicillin (**1**), with increasing bond lengths at C_{13}-N_{12} and C_9-N_7 and decreasing bond lengths at O_{31}-C_8, O_{32}-C_9 and N_{12}-C_{11}. The change of conformation from *–ac* of $C_{13}N_{12}C_{11}C_9$ and *-sc* of $C_{16}C_{14}C_{13}N_{12}$ are changed to *+sc* conformation. The dihedral angle of *+ap* of $C_{14}C_{13}N_{12}C_{11}$ and $H_{33}O_{10}C_8C_4$ are changed to *–ap* conformation. The conformations of *-sc* of $O_{15}C_{14}C_{13}N_{12}$ and *+sc* of $H_{35}N_{12}C_{11}C_9$ are changed to *-ac* conformation and all other conformations are unaltered. It is observed that the protonation at N_7-atom is shown *-ap* conformation. In the case of formation of di-protonated phenethicillin (**4**), it is found that the dihedral angles of $O_{10}C_8C_4C_3$, $C_{13}N_{12}C_{11}C_9$, $C_{14}C_{13}N_{12}C_{11}$, $O_{15}C_{14}C_{13}N_{12}$, $C_{16}C_{14}C_{13}N_{12}$, $O_{31}C_8C_4C_3$, $H_{33}O_{10}C_8C_4$ and $H_{35}N_{12}C_{11}C_9$ are changed conformations from *-ap* to *-ac*, *-ac* to *+ac*, *+ap* to *-ap*, *-sc* to *+sp*, *-sc* to *-ac*, *+sp* to *+sc*, *+ap* to *-ap* and *+sc* to *+sp* conformations respectively. It is also investigated that the protonation at N_7- atom and N_{12}-atom are shown respectively *-ac* and *+ac* conformations to form stable di-protonated phenethicillin (**4**). It can

be concluded that the anion (**5**) is formed with the removal of a proton from O_{10}- atom of phenethicillin (**1**), and the dihedral angle of $O_{10}C_8C_4C_3$, $O_{15}C_{14}C_{13}N_{12}$, $C_{16}C_{14}C_{13}N_{12}$, $C_{17}O_{15}C_{14}C_{13}$, $O_{31}C_8C_4C_3$ and $O_{36}C_{13}N_{12}C_{11}$ are changed the conformations from *-ap* to *+sp*, *-sc* to *+ap*, *-sc* to *+sc*, *+ac* to *+sc*, *+sp* to *-ap* and *+sp* to *-sp* respectively to form stable anion R^- (**5**) and observed the rest of positions have moderate changes.

CONCLUSION

AM1 calculations show that protonated phenethicillins are nearly non-planar skeleton geometry, and the protonation at nitrogen atom is in the sequence of $N_{12} > N_7$. But, it is investigated that N_7- protonated is more stable than N_{12}-protonated phenethicillin. The positions of the equilibrium of phenethicillin cations are solvated to form hydrogen bonds with the polar solvents. It is also predicted the stability of molecule in acid medium due to acid resistant. Further, the utility of theoretical predictions is important for evaluating the stability of conformations and molecular deformations, which is useful for favourable absorption patterns and reduced undesirable side effects.

ACKNOWLEDGEMENT

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Table –I : Heat of formation (ΔH_f^o in kcal/mol), ionization potential (eV), dipole moment (μ in Debye), energies of frontier molecular orbitals (in eV) and the atomic charges on S_2, N_7, N_{12}, O_{10}, O_{15}, O_{31}, O_{32} and O_{36} of phenethicillin (**1**) and its mono-protonated forms (**2** & **3**), di-protonated form (**4**), and anion (**5**) from AM1 calculations.

Parameters	**1**	**2**	**3**	**4**	**5**
ΔH_f^o (kcal/mol)	-125.9658	+57.3982	+39.0467	+294.7399	-151.1979
Ionization potential (eV)	9.1224	12.0307	11.4159	14.5981	5.1143
μ (Debye)	3.109	6.086	6.151	3.461	19.704
E_{HOMO} (eV)	-9.1224	-12.0307	-11.4159	-14.5981	-5.1143
E_{LUMO} (eV)	+0.099	-4.594	-4.381	-8.474	+1.994
Electron excitation energies (E_{HOMO}-E_{LUMO})	9.221	7.437	7.035	6.124	7.108
S_2 (atomic charge)	+0.0526	+0.1404	+0.1941	+0.3183	-0.0834
N_7 (atomic charge)	-0.2402	-0.2196	-0.0981	-0.0941	-0.1953
N_{12} (atomic charge)	-0.3507	-0.0902	-0.3757	-0.1230	-0.3532
O_{10} (atomic charge)	-0.2865	-0.3030	-0.3129	-0.3443	-0.5628
O_{15} (atomic charge)	-0.2261	-0.1813	-0.1925	-0.2585	-0.1956
O_{31} (atomic charge)	-0.3519	-0.3117	-0.2769	-0.2226	-0.5126
O_{32} (atomic charge)	-0.2363	-0.1799	-0.0941	-0.0271	-0.2513
O_{36} (atomic charge)	-0.3522	-0.1334	-0.3740	-0.1353	-0.3422

Table –II : Bond lengths of phenethicillin (**1**) and its mono-protonated forms (**2** & **3**), di-protonated form (**4**), and anion (**5**) from AM1 calculations.

Bond lengths (Å)	**1**	**2**	**3**	**4**	**5**
C_3-S_2	1.8142	1.8232	1.8202	1.8097	1.8510
C_9-N_7	1.4491	1.4183	1.5552	1.5329	1.4329
N_{12}-C_{11}	1.4125	1.4752	1.4077	1.4680	1.4204
C_{13}-N_{12}	1.3831	1.5248	1.3995	1.5580	1.3786
C_{11}-C_9	1.5696	1.5793	1.5672	1.5410	1.5768
O_{10}-C_8	1.3583	1.3560	1.3565	1.3563	1.2603
O_{31}-C_8	1.2334	1.2307	1.2262	1.2224	1.2522
O_{32}-C_9	1.2176	1.2131	1.1990	1.1989	1.2192
O_{36}-C_{13}	1.2443	1.2159	1.2449	1.2101	1.2437
H_{33}-O_{10}	0.9731	0.9749	0.9765	0.9794	-
H_{35}-N_{12}	0.9946	1.0298	0.9964	1.0323	0.9922
H-N_7	-	-	1.0282	1.0247	-
H-N_{12}	-	1.0311	-	1.0331	-

Table – III Dihedral angle (°) of phenethicillin (**1**) and its mono-protonated forms (**2** & **3**), di-protonated form (**4**), and anion (**5**) from AM1 calculations.

Dihedral angle (°)	**1**		**2**		**3**		**4**		**5**	
	Angle	(*)	Angle	(*)	Angle	(*)	Angle	(*)	Angle	(*)
$C_4C_3S_2C_1$	-21.06	*-sp*	-18.34	*-sp*	-27.49	*-sp*	-28.67	*-sp*	-20.34	*-sp*
$C_8C_4C_3S_2$	+163.25	*+ap*	+160.06	*+ap*	+165.89	*+ap*	+158.71	*+ap*	+165.81	*+ap*
$O_{10}C_8C_4C_3$	-173.78	*-ap*	-110.24	*-ac*	-161.79	*-ap*	-95.35	*-ac*	+21.86	*+sp*
$C_{13}N_{12}C_{11}C_9$	-126.91	*-ac*	-156.42	*-ap*	+52.99	*+sc*	-148.31	*+ac*	-132.98	*-ac*
$C_{14}C_{13}N_{12}C_{11}$	+179.33	*+ap*	-178.43	*-ap*	-179.85	*-ap*	-175.86	*-ap*	+177.48	*+ap*
$O_{15}C_{14}C_{13}N_{12}$	+50.06	*+sc*	+144.58	*+ac*	+148.04	*+ac*	+26.88	*+sp*	+172.25	*+ap*
$C_{16}C_{14}C_{13}N_{12}$	-67.73	*-sc*	+27.49	*+sp*	+30.78	*+sc*	-91.74	*-ac*	+55.82	*+sc*
$C_{17}O_{15}C_{14}C_{13}$	+99.15	*+ac*	+83.92	*+sc*	+98.46	*+ac*	+119.68	*+ac*	+89.23	*+sc*
$O_{31}C_8C_4C_3$	+11.66	*+sp*	+69.66	*+sc*	+22.72	*+sp*	+83.63	*+sc*	-163.28	*-ap*
$O_{32}C_9N_7C_4$	+59.33	*+sc*	+65.42	*+sc*	+64.06	*+sc*	+78.28	*+sc*	+62.01	*+sc*
$H_{33}O_{10}C_8C_4$	+179.98	*+ap*	-177.95	*-ap*	-177.17	*-ap*	-179.89	*-ap*	- -	- -
$O_{36}C_{13}N_{12}C_{11}$	+0.85	*+sp*	+2.00	*+sp*	+2.02	*+sp*	+5.93	*+sp*	-1.24	*-sp*
$H_{35}N_{12}C_{11}C_9$	+57.52	*+sc*	+81.05	*+sc*	-121.88	*-ac*	-27.82	*+sp*	+45.88	*+sc*
$HN_{12}C_{11}C_9$	- -	- -	-35.08	*-sc*	- -	- -	+90.10	*+ac*	- -	- -
$HN_7C_4C_3$	- -	- -	- -	- -	-158.53	*-ap*	-145.13	*-ac*	- -	- -

* Conformational analyses using prefixes a = anti, s = syn, p = peri-planar, c = clinal, and + & - signs [17].

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