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AM1 STUDY ON ELECTRONIC STRUCTURE AND CONFORMATIONS OF LACTAM-LACTIM TAUTOMERISM IN METHICILLIN

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ABSTRACT

The electronic structure of lactam-lactim tautomerism in methicillin and its geometry and conformation have been optimized and calculated usually considering an isolated molecule surrounded by vacuum in the gas phase by semi-empirical molecular orbital AM1 method. The mechanism of protonation in lactim tautomer of methicillin has been studied by comparison of the different positions of net charges at 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 lactim tautomers and their stable conformations have also been performed.

Keywords: AM1, Lactam-lactim Tautomerism, Methicillin, Induction Effect, Frontier Molecular Orbital.

INTRODUCTION

Methicillin is one of the narrow-spectrum β–lactam antibiotic and active against both gram-positive bacteria and gram-negative cocci, such as meningococci and gonococci [1,2]. It is used to treat infections caused by susceptible gram-positive bacteria. Methicillin is not absorbed when administered orally and depending on the type of assay protein binding to serum albumin ranges 37% to 49% [3]. Immuno-fluorescent studies showed that dimethoxy-phenyl-penicilloyl and the hapten group of methicillin were firmly bound to kidney tissue together with immunoglobulin [4 to 6]. Methicillin was acted by inhibiting the synthesis of bacterial cell walls and the growth of both penicillin susceptible and penicillinase-producing staphylococci [7 to 11]. The presence of the ortho-dimethoxy-phenyl group directly attached to the side-chain carbonyl group of the penicillin nucleus was increased the β–lactamase resistance, since enzymes were relatively intolerant to the steric hindrance of the side-chain. The importance of tautomeric equilibria has recognized for the study of the processes of both organic chemistry and biochemistry [12,13]. The tautomerism of organic compounds was reported extensively theoretical and statistical-physical approaches [14]. Theoretical models of the salvation energies of tautomers [15]. The stability of tautomers [16,17] and equilibrium constants in electrostatic reaction field for heterocyclic compounds in aqueous solution [18] were studied. It is assumed that dipolar character of the drug could improve oral absorption [19].

Solutions to the Schrodinger's equation ($H\Psi=E\Psi$) in the field of quantum chemistry are used to predict the properties of molecules with a view to solve chemical problems. Austin Model-1 (AM1) is one of the semi-empirical quantum calculation methods based on the neglect of differential diatomic overlap integral approximation, which uses experimental parameters to optimize molecules for calculation of various properties [20-22]. In this way quantum chemistry simulates chemical structure and reactions numerically and allows studying chemical phenomena by running calculations on

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computer rather than by examining reactions experimentally. It is important to know the conformational changes in the molecule for the prediction of its reactivity. In view of these observations as part of ongoing, theoretical investigations [23,24], the lactam-lactim tautomerism in methicillin has fascinated much to carry out structural optimization of its anion and protonated forms with a view to investigate its stability and polarity.

The present study reveals on molecular conformation and electronic properties of methicillin (**1**) and its tautomerism in gas phase usually considering an isolated molecule surrounded by vacuum has been evaluated by AM1 method. Lactam-lactim tautomerism of methicillin involves the shifting of hydrogen atom from nitrogen atom in lactam (-HN-C=O) group to the oxygen atom of the same molecule to form lactim (-N=C-O-H) group as shown in Figure-2. It is observed that the lactam form predominates in the methicillin. From the obtained optimized electronic structure of lactam-lactim tautomerism of methicillin, the mechanism of protonation has been studied by comparison of the relative values of net charges at nitrogen atoms in different positions of the molecule. Taking lactim form of methicillin as a neutral molecule (**2**), the molecular geometry and conformations of mono-protonated (**3** & **4**) systems, di-protonated (**5**) system and anion (**6**) have been determined by full optimization calculations using semi-empirical molecular orbital AM1 method.

Computational methods

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 of MNDO, offering more accurate parameterizations for polar systems. 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. The initial molecular geometry was adopted as Pople's standard data [25,26] and subsequently fully optimized using an energy gradient method. The conformations were designated by Klyne-Prelog terms [27] 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 methicillin (1) and its lactim tautomer (2) mono-protonated (3 & 4), di-protonated (5) and anion (6)

The optimized electronic structure of methicillin (**1**) and its lactim tautomer (**2**) mono-protonated (**3** & **4**), di-protonated (**5**) and anion (**6**) are shown in Scheme-1. In this context, the numbering of lactim from of methicillin (**2)** is shown in Figure -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_{12}- atoms are -0.2348 and -0.2113 respectively in the case of lactim tautomer of methicillin (**2**). 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 lactim tautomer of methicillin (**2**) is increasing in the order of $N_{12} < N_7$. According to the negative charge distribution on nitrogen atoms, N_7- atom is predicted to be main protonation site of lactim tautomer of methicillin (**2**). The calculated values of frontier orbital energies (E_{HOMO} and E_{LUMO}) reveal that molecules **1, 2** and **6** have more electron-donor character whereas other molecules have electron-acceptor property. In the case of HOMO, the electron density is more at N_{12}- atoms for **1, 4** and **5** molecules. The results so obtained reveal 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 **1, 2, 3, 4**, and **5**, due to the presence of same sign and other molecule may undergo antara-facial path way is allowed due to the opposite sign [28]. The dipole moment of molecules depends 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 **4** < **1** < **2** < **5** < **3** < **6**. Anion (**6**) 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 [29] (μ_{ind}) of molecules can be estimated with respect to methicillin lactim form (**2**). It is found that the induction effect is increasing in the order of $\Delta\mu_{ind}$ (**4**) -2.520D < $\Delta\mu_{ind}$ (**2)** 0.260D < $\Delta\mu_{ind}$ (**5**) 0.638D < $\Delta\mu_{ind}$ (**3**) 7.191D < $\Delta\mu_{ind}$ (**6**) 18.181D. According to the heat of formation (ΔH_f^o) data, the stability of compounds have increased in the order of **5** < **4** < **3** < **2** < **1** < **6**. 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. The ionisation potential is increasing in the order of **6 < 2 < 1 < 4 < 3 < 5**. It is predicted that the protonation would take place preferably at N_7-atom than N_{12}-atom in the case of lactim form of methicillin (**2**). It is confirmed that the stability of mono-protonated lactim form of methicillin **3** (ΔH_f^o, -14.1982Kcal/mol) is more stable than **4** (ΔH_f^o, +6.7139Kcal/mol). The formation of lactim form of di-protonated methicillin **(5),** from mono-protonated lactim

form of methicillins (**3** & **4**) is possible with the heat of formation (ΔH_f^o) of +214.2717Kcal/mol.

The protonation site of lactim form of methicillin **(2)** at N_7- 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. The protonation at N_{12}-atom in the case of lactim form of methicillin (**2**) to mono-protonated form (**3**) is considered by decreasing net atomic charges at N_7-, N_{12}-, O_{15}-, O_{33}-, and O_{34}- atoms and increasing net atomic charges at O_{10}-, O_{19}-, and O_{21}- atoms. The protonation site of lactim form of methicillin (**2**) at N_7- atom to mono-protonated form (**4**) is considered by decreasing net atomic charges at N_7-, O_{15}-, O_{33}- and O_{34}-atoms and increasing at N_{12}-, O_{10}- and O_{19}-atoms. In the case of di-protonated form (**5**), the negative atomic charges are decreased at all hetero atoms except at N_{12}-, O_{10}-, O_{19}- and O_{21}-atoms. Anion of lactim form of methicillin (**6**) is formed by the removal of a proton on O_{10}-atom with increasing net charges at O_{10}-, O_{33}- and O_{34}- and decreasing at N_7-, N_{12}-, O_{15}-, O_{19}- and O_{21}-atoms.

The acid – base equilibrium of lactim form of methicillin and its protonated forms

Equilibrium is normally established in polar solvents, in order to investigate the basicity and it is found out the protonation sites of lactim form of methicillin (**2**) as per Scheme-1. N_7-atom is main basic centre in accordance with the negative charge distribution on N-atoms (Table-1). To determine the exact protonation centers of lactim form of methicillin (**2**), the proton affinities (PA) for the different nitrogen atoms of the molecule have been calculated by means of AM1 method. The stable conformation of the cations formed by the protonation of each nitrogen atom of the molecule is determined; the heats of formation are calculated with full geometry optimization. The cations formed by the protonation at N_7- or N_{12}- atoms of lactim form of methicillin (**2**) can exist in *anti*- or *syn*-conformations, according to the position of N-atoms as shown in Scheme-1. The conformation can be assigned by comparison of its geometry and electronic structure. The proton affinity (PA) [30] values for the different nitrogen atoms of lactim form of methicillin RH (**2**) were calculated by using the equation (1) and found to be 235.4926kcal/mol and 214.5805kcal/mol respectively in the case of mono-protonated methicillins (**3** and **4**). Di-protonated form (**5**) was formed from either of mono-protonated methicillins (**3** and **4**) respectively with PA 138.7301kcal/mol and 159.6422kcal/mol.

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

Where PA is the proton affinity, $\Delta H_f^o(B)$ is the heat of formation for lactim form of methicillin (**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 (367.2 kcal/mol). The proton affinity is in the order of N_{12} (235.4926 kcal/mol) > N_7 (214.5805 kcal/mol) and mono-protonated methicillin (**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. As per electron excitation energies (ΔE) (in eV), it is observed the reactivity is decreased in the order of **6** > **3** > **5** > **4** > **2** > **1**. It is confirmed that methicillin (**1**) is more stable than its lactim-form (**2**).

The conformations of lactam-lactim tautomerism in methicillin

Figure - 2 illustrates the formation of tautomeric form of methicillin (**1**). In the great majority of cases the molecules at chemical equilibrium under ordinary conditions, both forms of tautomers are possible. Instances are known when tautomeric forms are stable under ordinary conditions and capable of inter-conversion at higher temperatures, often with the aid of catalyst. Fully optimized AM1 calculations scrutinize only the main data of bond lengths (Table-II) and dihedral angles (Table-III) of molecules (**1** to **6**) for the sake of simplicity. From AM1 calculated heat of formation, the tautomeric equilibrium constant $\log K_T$ was calculated [31,32] according to the equation (2):

$$\log K_T = \frac{\Delta GT}{2.303\ R\ T} \approx \frac{\delta \Delta H}{2.303\ R\ T} \quad \ldots (2)$$

Where ΔGT is the free energy of the tautomeric equilibrium, δΔH 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 (2), $\log K_T$ value was calculated as 8.5372.

From the Table-II, Table-III, Figure-2 and Scheme-1, it is observed that methicillin (**1**) would undergo lactam-lactim tautomerism and form lactim of methicillin (**2**) with increasing bond length of O_{15}-C_{13} (1.3854Å) and decreasing bond length of C_{13}-N_{12} (1.2972Å). The change of conformation from ***+ap*** of $C_{14}C_{13}N_{12}C_{11}$, ***-sc*** of $C_{16}C_{14}C_{13}N_{12}$ and ***–sp*** of $O_{15}C_{13}N_{12}C_{11}$ are changed respectively to ***+sp, -ac*** and ***+sp*** conformations. Dihedral angle of $H_{46}O_{15}C_{13}N_{12}$ is formed ***+ap*** conformation in the lactim of methicillin (**2**).

The conformations of lactim form of methicillin (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 methicillin (**1**), and its lactim form of methicillin (**2**), mono-protonated forms (**3 & 4**), di-protonated form (**5**) and anion (**6**) 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. Fully optimized AM1 calculations scrutinize only the main data of bond lengths

(Table-II) and dihedral angles (Table-III) of molecules (**1** Table-III, it is observed that as per Scheme-1, mono-protonated lactim form of methicillin (**3**) is formed by the addition of proton at N_{12}-atom of lactim tautomer of methicillin (**2**), with increasing bond lengths at N_{12}-C_{11}, C_{13}-N_{12}, C_{11}-C_9 and H_{46}-O_{15} and decreasing bond lengths at O_{15}-C_{13} and C_{14}-C_{13}. . The change of dihedral angle of $O_{10}C_8C_4C_3$, $C_{14}C_{13}N_{12}C_{11}$, $O_{15}C_{13}N_{12}C_{11}$, $O_{33}C_8C_4C_3$ and $H_{31}O_{10}C_8C_4$, are converted from *-ap* to *-sc*, *+sp* to *+ap*, *+sp* to *-sp*, *+sp* to *+ac* and *+ap* to *-ap* conformations and all other conformations are moderately changed. It is observed that the protonation at N_{12}-atom is shown *+sc* conformation.

If the mono-protonated lactim form of methicillin (**4**) is formed by the addition of proton at N_7- atom of lactim tautomer of methicillin (**2**), with increasing bond lengths at C_{13}-N_{12} and C_9-N_7 and decreasing bond lengths at O_{34}-C_9, and O_{33}-C_8. The change of dihedral angle of $C_{14}C_{13}N_{12}C_{11}$ and $H_{35}O_{10}C_8C_4$ are converted from *+sp* to *–* to **6**) for the sake of simplicity. From the Table-II, and *ap* and *+ap* to *-ap* conformations 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 lactim form of methicillin (**5**), it is found that the change of conformation from *+sp* of $C_{14}C_{13}N_{12}C_{11}$, *+ap* of $H_{46}O_{15}C_{13}N_{12}$ and *+ap* of $H_{35}O_{10}C_8C_4$ are changed to *-ap* conformations respectively. It is also investigated that the protonation at N_7- atom and N_{12}-atom are shown respectively *-ap* and *+sc* conformations to form stable di-protonated lactim form of methicillin (**5**). It can be concluded that the anion (**6**) is formed with the removal of a proton on O_{10}- atom of lactim tautomer of methicillin (**2**), and the change of conformation from *-ap* of $O_{10}C_8C_4C_3$, *+sp* of $C_{14}C_{13}N_{12}C_{11}$ and *+sp* of $O_{15}C_{13}N_{12}C_{11}$ are changed to *+sp*, *+ap* and *–sp* conformations respectively to form stable anion (**6**) and rest of positions have moderate changes.

Table 1. 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_{12}, O_{10}, O_{15}, O_{19}, O_{21}, O_{33} and O_{34} of methicillin (1) and its lactim form(2), mono-protonated forms (3 & 4), di-protonated form (5), and anion (6) from AM1 calculation

Parameters	1	2	3	4	5	6
ΔH_f^o (kcal/mol)	-157.5533	-145.9056	-14.1982	+6.7139	+214.2717	-168.5109
Ionization potential (eV)	8.910	8.794	11.744	11.696	15.222	4.839
μ (Debye)	5.428	5.688	12.619	2.908	6.066	23.609
E_{HOMO} (eV)	-8.910	-8.794	-11.744	-11.696	-15.222	-4.839
E_{LUMO} (eV)	-0.203	-0.312	-4.814	-3.643	-7.844	+1.612
Electron excitation energies ($\Delta E = E_{LUMO} - E_{HOMO}$) (eV)	8.707	8.482	6.93	8.053	7.378	6.451
S_2 (atomic charge)	+0.0544	+0.1321	+0.1154	+0.1982	+0.2563	-0.1075
N_7 (atomic charge)	-0.2440	-0.2348	-0.2235	-0.1197	-0.1013	-0.1956
N_{12} (atomic charge)	-0.3571	-0.2113	-0.1883	-0.2817	-0.2673	-0.1772
O_{10} (atomic charge)	-0.2851	-0.2840	-0.3096	-0.3177	-0.3246	-0.5708
O_{15} (atomic charge)	-0.3335	-0.2934	-0.2105	-0.2905	-0.2269	-0.2906
O_{19} (atomic charge)	-0.2126	-0.2211	-0.2481	-0.2401	-0.2576	-0.2110
O_{21} (atomic charge)	-0.1920	-0.1881	-0.2425	-0.2031	-0.2625	-0.1835
O_{33} (atomic charge)	-0.3570	-0.3588	-0.3134	-0.2786	-0.2466	-0.5124
O_{34} (atomic charge)	-0.2410	-0.2503	-0.1864	-0.1070	-0.0503	-0.2576

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

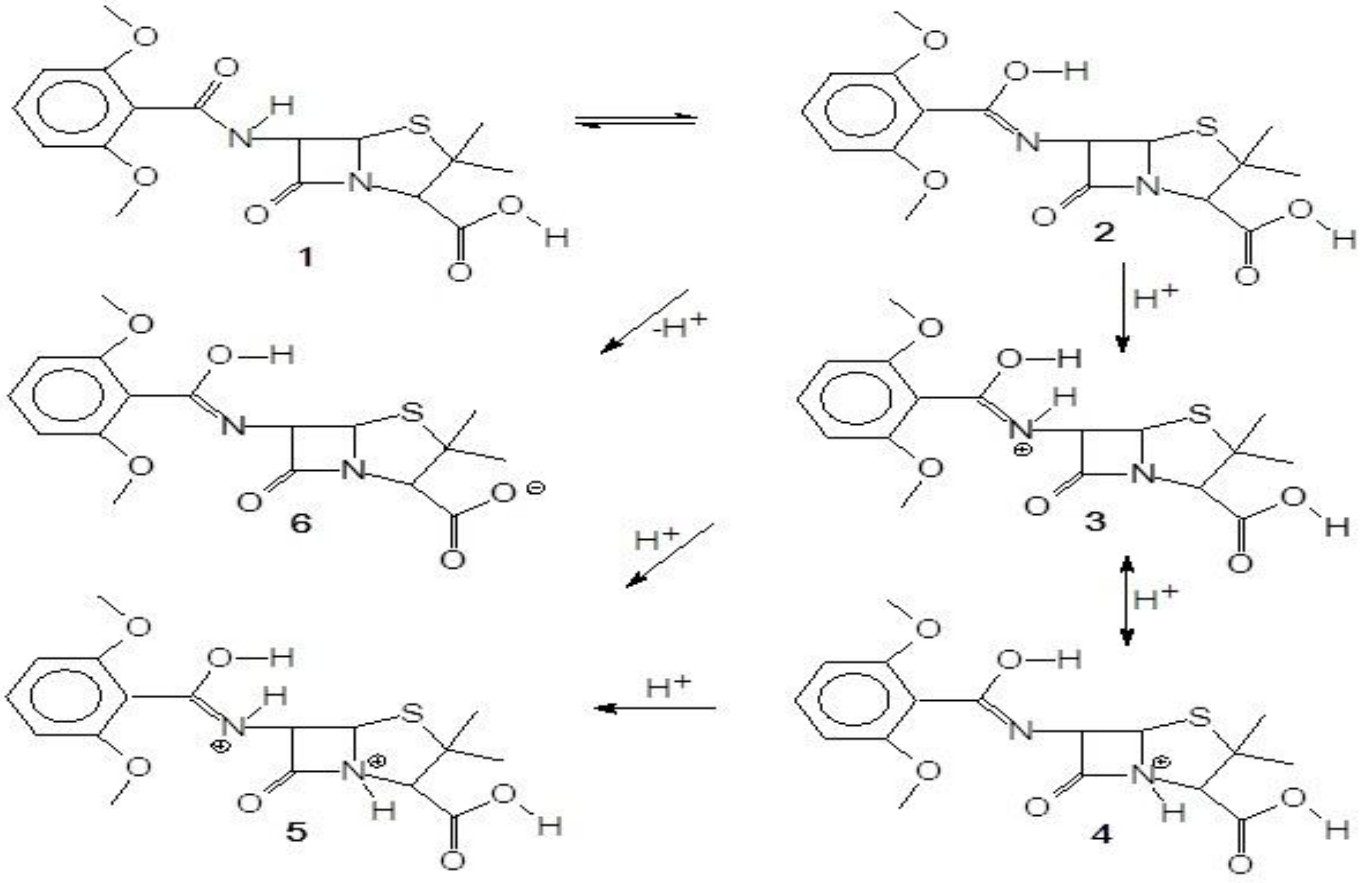
Bond lengths (Å)	1	2	3	4	5	6
C_9-N_7	1.4480	1.4469	1.4393	1.5713	1.5463	1.4319
N_{12}-C_{11}	1.4102	1.4251	1.4349	1.4184	1.4252	1.4246
C_{13}-N_{12}	1.3987	1.2972	1.3379	1.3103	1.3629	1.2914
C_{11}-C_9	1.5685	1.5643	1.5754	1.5549	1.5550	1.5786
O_{10}-C_8	1.3585	1.3586	1.3575	1.3584	1.3566	1.2619
O_{33}-C_8	1.2343	1.2341	1.2298	1.2264	1.2239	1.2523
O_{34}-C_9	1.2184	1.2187	1.2133	1.1984	1.1982	1.2188
O_{15}-C_{13}	1.2421	1.3854	1.3511	1.3735	1.3468	1.3912
C_{14}-C_{13}	1.4881	1.4785	1.4576	1.4699	1.4372	1.4819
H_{46}-O_{15}	- -	0.9681	0.9799	0.9724	0.9845	0.9672

H_{35}-O_{10}	0.9729	0.9725	0.9738	0.9760	0.9787	- -
H-N_7	- -	- -	- -	1.0203	1.0239	- -
H-N_{12}	0.9932	- -	1.0068	- -	1.0061	- -

Table 3. Dihedral angle (o) of methicillin (1) and its lactim form (2), mono-protonated forms (3 & 4), di-protonated form (5), and anion (6) from AM1 calculation

Dihedral angle (^{o})	**1**		**2**		**3**		**4**		**5**		**6**	
	Angle	(*)	Angle	(*)	Angle	(*)	Angle	(*)	Angle	(*)	Angle	(*)
$C_4C_3S_2C_1$	-19.69	*-sp*	-20.38	*-sp*	-19.19	*-sp*	-27.48	*-sp*	-28.72	*-sp*	-20.48	*-sp*
$C_8C_4C_3S_2$	+162.71	*+ap*	+162.51	*+ap*	+158.01	*+ap*	+163.58	*+ap*	+164.08	*+ap*	+165.56	*+ap*
$O_{10}C_8C_4C_3$	-167.36	*-ap*	-172.91	*-ap*	-86.52	*-sp*	-164.18	*-ap*	-159.06	*-ap*	+24.43	*+sp*
$C_{13}N_{12}C_{11}C_9$	-124.04	*-ac*	-108.54	*-ac*	-110.07	*-ac*	-103.33	*-ac*	-109.18	*-ac*	-101.75	*-ac*
$C_{14}C_{13}N_{12}C_{11}$	+178.79	*+ap*	+0.57	*+sp*	+177.28	*+ap*	-176.69	*-ap*	-176.99	*-ap*	+177.47	*+ap*
$C_{16}C_{14}C_{13}N_{12}$	-59.83	*-sc*	-123.76	*-ac*	-140.36	*-ac*	-128.45	*-ac*	-149.77	*-ac*	-107.65	*-ac*
$O_{15}C_{13}N_{12}C_{11}$	-2.71	*-sp*	+0.57	*+sp*	-1.19	*-sp*	+4.78	*+sp*	+4.92	*+sp*	-1.36	*-sp*
$H_{46}O_{15}C_{13}N_{12}$	- -	- -	+168.81	*+ap*	+178.08	*+ap*	+174.64	*+ap*	-175.37	*-ap*	+154.89	*+ap*
$O_{33}C_8C_4C_3$	+18.48	*+sp*	+12.87	*+sp*	+91.85	*+ac*	+20.76	*+sp*	+25.04	*+sp*	+24.43	*+sp*
$O_{34}C_9N_7C_4$	+58.22	*+sc*	+58.84	*+sc*	+65.84	*+sc*	+68.87	*+sc*	+71.04	*+sc*	+61.88	*+sc*
$H_{35}O_{10}C_8C_4$	+179.77	*+ap*	+179.60	*+ap*	-177.25	*-ap*	-177.57	*-ap*	-174.86	*-ap*	- -	- -
H-$N_{12}C_{11}C_9$	- -	- -	- -	- -	+71.38	*+sc*	- -	- -	+77.34	*+sc*	- -	- -
H-$N_7C_4C_3$	- -	- -	- -	- -	- -	- -	-153.92	*-ap*	-153.54	*-ap*	- -	- -

* Conformational analyses using prefixes *a* = anti, *s* = syn, *p* = peri-planar, *c* = clinal, and + & - signs[27].



Scheme - 1

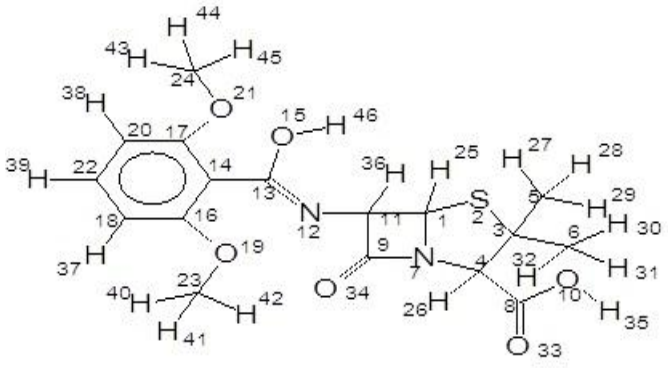


Figure - 1

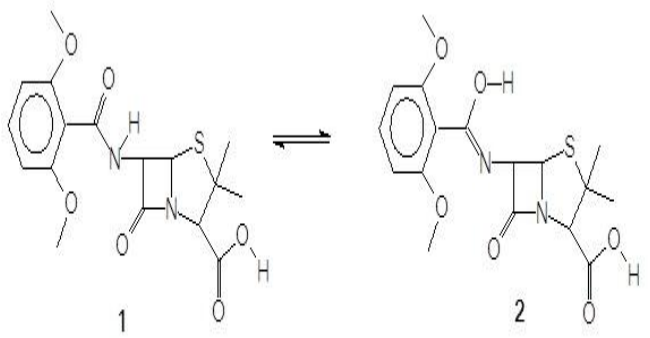


Figure - 2: Methicillin lactam-lactim rearrangement

CONCLUSION

AM1 calculations show that lactam-lactim tautomerism of methicillin and its protonated forms are nearly non-planar skeleton geometry, and the sequence of proton transfer at nitrogen atom is $N_{12} > N_7$. It is conformed that formation of mono-protonated lactim form of methicillin (**3**) is more stable than (**4**) as per heat of formation data. All protonated forms are solvated to form hydrogen bonds with the polar solvents which would affect the position of the equilibrium. The utility of theoretical predictions is important for evaluating the ability to cross cell wall barriers, biochemical mechanism to prevent cell wall synthesis in bacteria and binding to plasma protein. This study reveals about the stability of tautomers, conformations and molecular deformations.

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