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COMPUTATIONAL STUDY ON THE ELECTRONIC STRUCTURE OF PHENETHICILLIN ZWITTERIONS BY AUSTIN MODEL-1 (AM1) METHOD

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ABSTRACT

The geometry, conformation and electronic structure of phenethicillin zwitterions have been optimized and calculated by using semi-empirical molecular orbital method (AM1), which includes experimental parameters and extensive simplification of the Schrodinger's equation ($H\Psi=E\Psi$) for calculation of various properties in the gas phase. The mechanism of formation of zwitterions has been studied by comparison of the different 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 changes and electronic properties have also been discussed for stable conformations.

KEYWORDS: Phenethicillin, zwitterions, HOMO, LUMO, frontier molecular orbitals.

INTRODUCTION

Isolation of the important intermediate, 6-aminopenicillanic acid was led the preparation of several semi-synthetic penicillins.[1] Phenethicillin is one of the penicillin derivatives and studied extensively due to their favourable absorption patterns and reduced undesirable side effects[2] particularly in the treatment of gonorrhoea.[3] Austin Model-1 (AM1)[4] 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. In this way quantum chemistry simulates chemical

structure and reactions numerically and allows studying chemical phenomena by running calculations on computer rather than examining reactions experimentally.[5]

In view of these observations and continuation of our investigation[6], the mechanism of formation of zwitterions $\mathbf{RH^{\pm}}$ (**2** and **3**) in gas phase has been evaluated by AM1 method from the optimized electronic structure of Phenethicillin **RH** (**1**).

Computational methods[4]

Semi-empirical molecular orbital calculations were performed using Austin Model-1 (AM1). Geometry calculations in the ground state (key words: GNORM=5, MMOK, GEO-OK, CHARGE, and PRECISE) were completely optimized until get the lowest energy conformation. The initial molecular geometry was adopted as Pople's standard data[7], and subsequently using fully optimized energy gradient method. 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.

RESULTS AND DISCUSSION

Electronic structure of phenethicillin (RH, 1) and its zwitterions ($\mathbf{RH^{\pm}}$, 2&3)

The optimized electronic structure of Phenethicillin **RH** (**1**) and its zwitterions $\mathbf{RH^{\pm}}$(**2**&**3**) are shown in Scheme-1. In this context, the numbering of phenethicillin 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 **3**) 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 sequence of protonation for nitrogen atoms of phenethicillin (**1**) is observed in the order of N_7 < N_{12}. It is also observed that ionization potential values are increased in the order of **2** < **3** < **1** and zwitterions (**2** and **3**) are found less ionization potential.

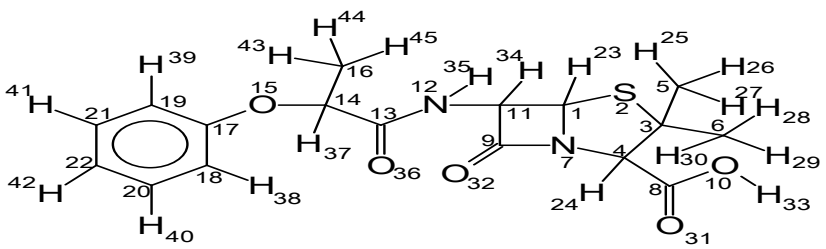


Figure - 1

The calculated values of frontier orbital energies (E_{HOMO} and E_{LUMO}) reveal the promotion of an electron from HOMO to LUMO, in a photochemical reaction, the supra-facial path way is allowed in the case of zwitterions **2** and **3**, due to the presence of same sign and antara-facial path way is allowed in the case of phenethicillin (**1**)**,** due to the presence of opposite sign.[9] The electron density is highest at N_{12}- atoms for **1** and **3**. The results revealed that the electronic properties and reactivity of molecule depend on its conformational structure. 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 **2** > **3** > **1** and zwitterion (**2**) showed 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[10] (μ_{ind}) of molecules can be estimated with respect to phenethicillin (**1**) by using the equation (1).

Induction effect (μ_{ind}) = $\mu(\mathbf{RH^{\pm}}) - \mu(\mathbf{RH})$ ---------- (1)

It is found that the induction effect is increasing in the case of $\Delta\mu_{ind}$ (**3**) 10.661D < $\Delta\mu_{ind}$(**2**) 19.874D. According to the heat of formation (ΔH_f^o) data, the stability of compounds have been increased in the order of **2** < **3** < **1**. It is investigated that the phenethicillin (**1**) is more stable than zwitterions (**2** and **3**). 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**). But, it is found that the stability of zwitterion $\mathbf{N_7H^{\pm}}$ (**3**) (ΔH_f^o, -72.1992 kcal/mol) is more stable than $\mathbf{N_{12}H^{\pm}}$ (**2**) (ΔH_f^o, -31.5528 kcal/mol).

In the case of formation of zwitterions (**2** and **3**) is considered by the removal of a proton from O_{10}-atom of phenethicillin (**1**) and the protonation at N_{12}- atom in the case of $\mathbf{N_{12}H^{\pm}}$ (**2**) is considered by decreasing net atomic charges at N_7-, N_{12}-, O_{15}-, O_{32}- and O_{36}-atoms and increasing at O_{10}- and O_{31}- atoms. The protonation site of phenethicillin (**1**) at N_7-atom is considered in the case of $\mathbf{N_7H^{\pm}}$ (**3**) by increasing net atomic charges at N_{12}-,O_{10}- and O_{31}-atoms and decreasing at N_7-, O_{15}-, O_{32}- and O_{36}- atoms.

Equilibrium of phenethicillin (RH, 1) and its zwitterions ($\mathbf{RH^{\pm}}$, 2&3): Equilibrium is typically found in polar solvents by rapid inter- or intra-molecular proton transfer from O_{10}-atom to N_7- or N_{12}- atoms of phenethicillin (**1**) 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 proton-migration in phenethicillin (**1**), the proton affinities (PA) have been calculated from the heat of formation (ΔH_f^o) with full geometry optimization of AM1 method to attain the stable conformations of the zwitterions $\mathbf{RH^{\pm}}$ (**2**&**3**).

Thus, formed zwitterions $\mathbf{RH^{\pm}}$ (**2** and **3**) with the protonation at N_7- or N_{12}- atoms of phenethicillin (**1**) can exist in *anti*- or *syn*-conformations. Its conformation can be assigned by comparison of its geometry and electronic structure. The proton affinity (PA)[11] values for the different nitrogen atoms of phenethicillin RH (**1**) 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 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 (367.2kcal/mol). It can be assumed that $\Delta H_f^o(H^+)$ is to be neglected in the inter- or intra-molecular proton transfer in the equilibrium as per equation (3).

$$RH \xrightarrow[\text{proton transfer}]{\text{Inter- or Intra-molecular}} RH^{\pm} \quad \text{- - - - - --- - - - - (3)}$$

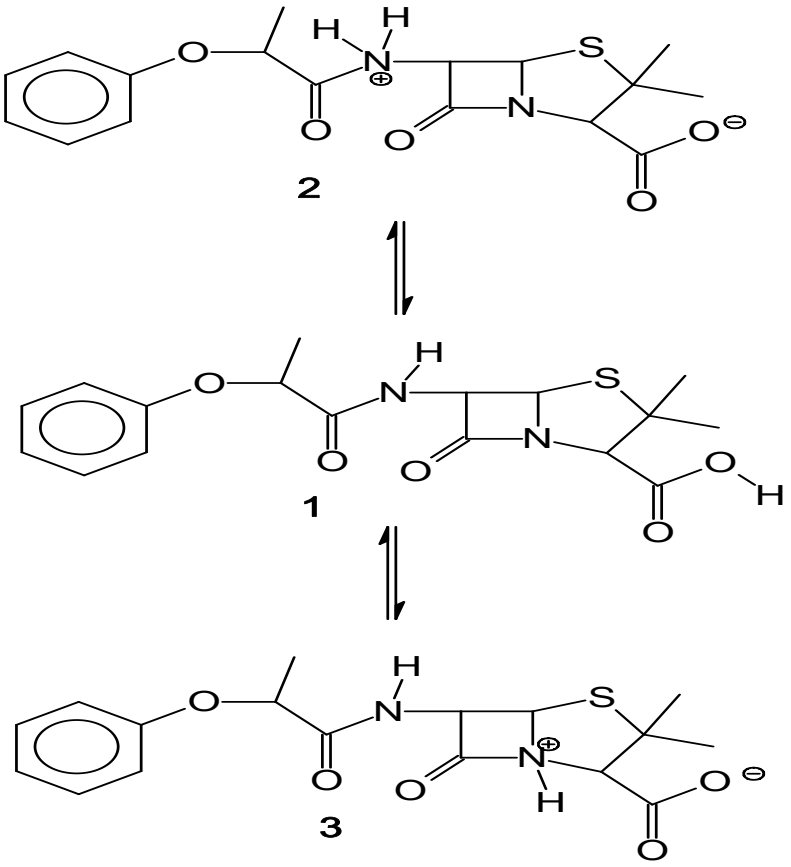
Thus, the proton affinity (PA) becomes

$$PA = \Delta H_f^o(\mathbf{RH}) - \Delta H_f^o(\mathbf{RH^{\pm}}) \quad \text{. . . (4).}$$

Where ΔH_f^o (**RH**) is the heat of formation of phenethicillin RH (**1**) and $\Delta H_f^o(\mathbf{RH^{\pm}})$ is the heat of formation of zwitterions $\mathbf{RH^{\pm}}$ (**2** and **3**). The proton affinity is found to be 94.4130 kcal/mol and 53.7666 kcal/mol respectively in the case of zwitterions $\mathbf{N_{12}H^{\pm}}$ (**2**) and $\mathbf{N_7H^{\pm}}$ (**3**).

The conformations of phenethicillin (RH, 1) and its zwitterions ($\mathbf{RH^{\pm}}$, 2&3)

The spatial arrangement of atoms in a molecule is considered to study the conformations of phenethicillin (**1**), and its zwitterions (**2 & 3**) with a view to investigate *anti*- or *syn*-conformation, according to the position of atoms. In this context, the change in energy content may depend upon the changes in the dihedral angles. The atomic numbering of phenethicillin (**1**) is revealed as per Figure-1 and incorporated the main data of dihedral angles (Table - II) of molecules (**1** to **3**) for the sake of discussion.



Scheme - 1

From the Table-II and Scheme-1, the zwitterion $\mathbf{N_{12}H^{\pm}}$ (**2**) is formed by the transfer of a proton from O_{10}-atom to N_{12}- atom of phenethicillin (**1**). It is investigated that conformation ***–ap*** of $O_{10}C_8C_4C_3$, ***-ac*** of $C_{13}N_{12}C_{11}C_9$, ***+ap*** of $C_{14}C_{13}N_{12}C_{11}$ and ***+sc*** of $O_{15}C_{14}C_{13}N_{12}$ are changed to ***-ac, -ap, -ap*** and ***+ap*** conformations respectively. The dihedral angle of ***-sc*** of $C_{16}C_{14}C_{13}N_{12}$, ***+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 ***–ac*** conformation in the case of $HN_{12}C_{11}C_9$. If the phenethicillin zwitterion $\mathbf{N_7H^{\pm}}$ (**3**) is formed by the transfer of a proton from O_{10}-atom to N_7- atom of phenethicillin (**1**), with the conformation ***-ac*** of $C_{13}N_{12}C_{11}C_9$, ***-sc*** of $C_{16}C_{14}C_{13}N_{12}$ and ***+sp*** of $O_{31}C_8C_4C_3$ are changed to ***+sc*** conformation. The dihedral angle of ***–ap*** of $O_{10}C_8C_4C_3$ and ***+sc*** of $H_{35}N_{12}C_{11}C_9$ are changed to ***–ac*** conformation. The conformations of ***+ap*** of $C_{14}C_{13}N_{12}C_{11}$ and ***+sc*** of $O_{15}C_{14}C_{13}N_{12}$ are changed to ***-ap*** conformation and observed the rest of positions have moderate changes. It is found that the protonation at N_7-atom is shown ***-ap*** conformation in the case of $HN_7C_4C_3$.

Table I: Heat of formation (ΔH_f^oin kcal/mol), ionization potential (eV), dipole moment (μ in Debye), energies of frontier molecular orbitals (in eV) and the atomic charges on hetero-atoms of phenethicillin (1) and its zwitterions (2&3) from AM1 calculations.

Parameters	1	2 ($N_{12}H^{\pm}$)	3 ($N_7H^{\pm}$)
ΔH_f^o(kcal/mol)	-125.9658	-31.5528	-72.1992
Ionization potential (eV)	9.1224	7.8569	8.9588
μ (Debye)	3.109	22.983	13.770
E_{HOMO} (eV)	-9.122	-7.857	-8.959
E_{LUMO} (eV)	+0.099	-2.222	-0.815
Electron excitation energies (E_{HOMO}-E_{LUMO})	9.221	5.635	8.144
S_2 (atomic charge)	+0.0526	+0.0120	+0.0617
N_7 (atomic charge)	-0.2402	-0.1548	-0.0364
N_{12} (atomic charge)	-0.3507	-0.0716	-0.3784
O_{10} (atomic charge)	-0.2865	-0.5115	-0.4920
O_{15}(atomic charge)	-0.2261	-0.1813	-0.1834
O_{31}(atomic charge)	-0.3519	-0.5084	-0.4709
O_{32}(atomic charge)	-0.2363	-0.2061	-0.0816
O_{36}(atomic charge)	-0.3522	-0.1295	-0.3423

Table II: Dihedral angle (^{o}) of phenethicillin (1) and its zwitterions (2&3) from AM1 calculations.

Dihedral angle (^{o})	1		2 ($N_{12}H^{\pm}$)		3 ($N_7H^{\pm}$)	
	Angle	(*)	Angle	(*)	Angle	(*)
$C_4C_3S_2C_1$	-21.06	***-sp***	-21.69	***-sp***	-26.67	***-sp***
$C_8C_4C_3S_2$	+163.25	***+ap***	+158.09	***+ap***	+161.59	***+ap***
$O_{10}C_8C_4C_3$	-173.78	***-ap***	-119.29	***-ac***	-139.71	***-ac***
$C_{13}N_{12}C_{11}C_9$	-126.91	***-ac***	-160.44	***-ap***	+56.24	***+sc***
$C_{14}C_{13}N_{12}C_{11}$	+179.33	***+ap***	-176.86	***-ap***	-179.36	***-ap***
$O_{15}C_{14}C_{13}N_{12}$	+50.06	***-sc***	+172.51	***+ap***	-176.89	***-ap***
$C_{16}C_{14}C_{13}N_{12}$	-67.73	***+sc***	+56.43	***+sc***	+66.98	***+sc***
$C_{17}O_{15}C_{14}C_{13}$	+99.15	***+ac***	+81.93	***+sp***	+90.62	***+ac***
$O_{31}C_8C_4C_3$	+11.66	***+sp***	+61.54	***+sc***	+42.70	***+sc***
$O_{32}C_9N_7C_4$	+59.33	***+sc***	+79.06	***+sc***	+72.83	***+sc***
$H_{33}O_{10}C_8C_4$	+179.98	***+ap***	- -	- -	- -	- -
$O_{36}C_{13}N_{12}C_{11}$	+0.85	***+sp***	+4.89	***+sp***	+0.78	***+sp***
$H_{35}N_{12}C_{11}C_9$	+57.52	***+sc***	+75.54	***+sc***	-120.29	***-ac***
$HN_{12}C_{11}C_9$	- -	- -	-40.45	***-ac***	- -	- -
$HN_7C_4C_3$	- -	- -	- -	- -	-153.31	***-ap***
*Conformational analyses using prefixes a = anti, s = syn, p = peri-planar, c = clinal, and + & - signs[7].						

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