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STUDY OF THE ELECTRONIC STRUCTURE AND CONFORMATIONAL ANALYSES ON ZWITTERIONS OF BENZYLPENICILLIN ENOL TAUTOMER BY AM1 METHOD

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ABSTRACT

The electronic structure and conformations on zwitterions of benzylpenicillin enol tautomer have been optimized and calculated in the gas phase by semi-empirical molecular orbital AM1 method usually considering an isolated molecule surrounded by vacuum. The formation of zwitterions of benzylpenicillin enol tautomer 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), full atomic charges and energies of frontier molecular orbitals (E_{HOMO} and E_{LUMO}) have been performed and discussed. The effect of conformational changes and their stabilities have been determined.

KEYWORDS: Benzylpenicillin enol tautomer, AM1, zwitterions, induction effect, frontier molecular orbital.

INTRODUCTION

Antibiotics have always been a magic bullet, killing the microbes without poisoning the infected individual. Antibiotics can be organized into different classes according to their effect and mode of action. Their effect is either bactericidal or bacteriostatic, where the former kills the bacteria and the latter inhibits the growth of the bacteria. The immune system is allowed to deal with the infection. The significance of benzylpenicillin has been recognized as a broad spectrum anti-biotic in chemotherapy for the treatment of infections[1,2]. Antibiotics that contain the *β*-lactam ring structure constitute the dominant class of agents

currently employed for the chemotherapy of bacterial infections. *β*-lactam antibiotics are broad class of antibiotics, consisting of all antibiotic agents that contain a *β*-lactam nucleus in its molecular structure having a lactam group with a heteroatom structure consisting of a four membered cyclic-amide with three carbon atoms and one nitrogen atom. *β*-lactam antibiotics inhibit the growth of many gram-positive and gram-negative bacteria, exert their lethal action by interfering with the bacterial cell wall biosynthesis[3]. In practice, most penicillins are undergoing tautomerism and the dipolar character of the molecule have been expected to influence selective penetration through the porin channels of the cell membrane[4].

Quantum chemistry is the field in which solutions to the Schrodingers' equation ($H\Psi = E\Psi$) are used to predict the properties of molecules for solving chemical problems. Austin Model-1 (AM1) is one of the semi-empirical methods which uses experimental parameters and extensive simplification of Schrodingers' equation to optimize molecules for calculation of various properties[5,6,7]. In this context, HMO method on methyl perturbations of oxazoles[8] and isoxazoles[9] and AM1 study on conformational analyses[10,11,12], [1,3]sigmatropic hydrogen migration[13,14,15], electronic structure[16,17], correlation studies[18] and computational studies[19] were reported.

Hence, it has fascinated to carry out zwitterions of benzylpenicillin enol tautomer which is having considerably increased polarity. The present investigation focuses on the evaluation of the significance of the molecular conformation and electronic properties of benzylpenicillin enol tautomer (**1**) and its zwitterions $RH^{\pm}$ (**2** & **3**). The mechanism of proton transfer in benzylpenicillin enol tautomer has been studied by the different positions of net charges on nitrogen atoms in the molecule. It would be important to know the exact position of protonation centers[5]. Taking benzylpenicillin enol tautomer, as a neutral molecule (RH) (**1**), the conformation and electronic structures of zwitterions $RH^{\pm}$ (**2** & **3**) system, in which are included $RH^{\pm}$ ($N_{13}H^{\pm}$) (**2**) and $RH^{\pm}$ ($N_7H^{\pm}$) (**3**) have been determined by full optimization calculations, using semi-empirical molecular orbital AM1 method.

Computational methods[6]

Semi-empirical molecular orbital calculations were performed using the AM1 (Austin Model 1) method included in the MOPAC93 in WinMOPAC ver 5.13 program by means of Intel P4 PC. Geometry calculations in the ground state (keywords: PRECISE, equivalent to GNORM=5, 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[7], and subsequently fully optimized using an energy gradient method. The conformations were designated by Klyne-Prelog terms[10] using *s* = syn, *a* = anti, *p* = peri-planar (0 ± 30^0 & 180 ± 30^0) and all other angles *c* = clinal.

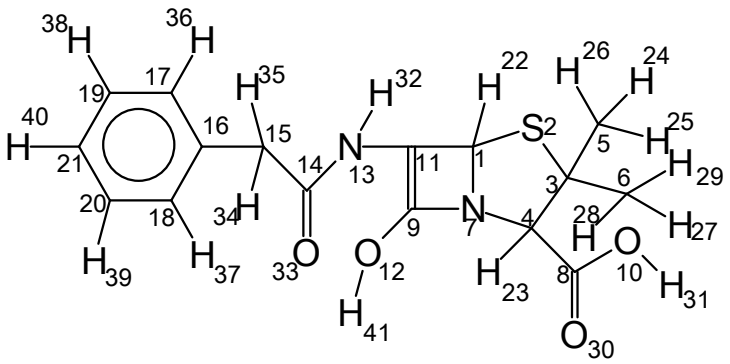


Figure - 1

RESULTS AND DISCUSSION

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

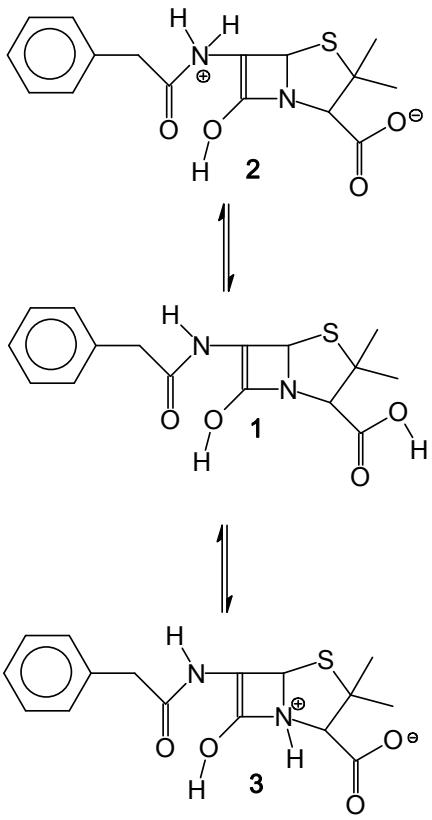
The optimized electronic structure of benzylpenicillin enol tautomer (**1**) and its zwitterions $RH^{\pm}$ (**2** and **3**) along with the numbering of the system in this context are shown in Figure -1. The calculated heats of formation (ΔH_f^o), dipole moment (μ), the energies of frontier molecular orbitals (E_{HOMO} and E_{LUMO}) and net charges on hetero atoms of the molecules are presented in Table-I. The net charges on N_7- and N_{13}- atoms are -0.1588 and -0.2917 respectively in the case of benzylpenicillin enol tautomer (1). Usually, the nitrogen atom with larger negative value of net charge accepts proton more easily. Thus, the sequence of protonation for nitrogen atoms is increasing in the order of $N_7 < N_{13}$. The calculated values of frontier orbital energies (E_{HOMO} and E_{LUMO}) reveal that promotion of an electron from HOMO to LUMO, in a photochemical reaction, the antara-facial path way is allowed in the case of zwitterions RH+ (2 and 3) due to the presence of opposite sign[20].

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 **1** < **3** < **2**. Zwitterion $RH^{\pm}$ ($N_{12}H^{\pm}$) (**2**) shows higher dipole moment. The electronegative heteroatoms cause displacement of electrons that induces an additional dipole

moment in the molecule. The magnitude of the induction effect[21] (μ_{ind}) of zwitterions can be estimated with respect to benzylpenicillin enol tautomer (**1**) by using the equation (1).

$\Delta\mu_{ind}(\text{zwitterion}) = \mu(RH^{\pm}) - \mu(RH)$ . . . (1)

Then the inductive effect is decreasing in the order of $\Delta\mu_{ind}$ (**2**) 19.6295D > $\Delta\mu_{ind}$ (**3**) 9.0449D > $\Delta\mu$ind (**1**) 2.4264D. The results so obtained reveal that the electronic properties and reactivity of the molecule depend on its conformational structure. From the reactivity point of view, the search of protonation sites of benzylpenicillin enol tautomer molecule having different positions of oxygen and nitrogen atoms is important. According to the heat of formation (ΔH_f^o) data, the stability of the compounds have increased in the order of **2** < **3** < **1**. But geometry calculations in the ground state were completely optimized until the lowest energy conformation was found in the individual zwitterions.



Scheme - 1

Zwitterions are formed with the difference in the heat of formation (ΔH_f^o) of +66.0527 kcal/mol and +35.7584 kcal/ mol respectively in the conversion of (**1**) to (**2**) and (**1**) to (**3**). It can be predicted that the conversion of neutral molecule benzylpenicillin enol tautomer (**1**) to zwitterion (**3**) is lower energy process than the conversion of (**1**) to (**2**). The protonation site

of benzylpenicillin enol tautomer (**1**), containing N_{13}- 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 proton shifting from O_{10}- atom to N_{13}- atom in the case of benzylpenicillin enol tautomer (**1**) to zwitterion (**2**) is considered by increasing net atomic charges at S_2-, O_{10}-, O_{30}- and decreasing at all other hetero-atoms. When, the proton transfer from O_{10}- atom to N_7- atom in the case of (**1**) to (**3**) is considered by decreasing net atomic charges at S_2-, N_7-, N_{13}- and increasing at all other hetero-atoms.

The equilibrium of zwitterions (1, 2 & 3)

Equilibrium is normally established in polar solvents by rapid inter- or intra-molecular proton transfer from O_{10}-atom to N_7- and N_{13}- atoms of benzylpenicillin enol tautomer as shown in Scheme-1. When one zwitterion is formed predominantly in a polar solution, its conformation can be assigned by comparison of its geometry and electronic structure. The position of proton transfer equilibrium can be affected by the nature of the solvent and concentration of the solution. The proton affinity (PA)[22] values for the different nitrogen atoms of benzylpenicillin enol tautomer RH (**1**) were calculated by using the equation (2).

$$PA = \Delta H_f^o(H^+) + \Delta H_f^o(B) - \Delta H_f^o(BH^+) \quad \ldots (2).$$

Where PA is the proton affinity, $\Delta H_f^o(B)$ is the heat of formation for the molecule, $\Delta H_f^o(BH^+)$ 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). It can be assumed that $\Delta H_f^o(H^+)$ is to be neglected in polar medium, due to the inter- or intra-molecular proton transfer in the equilibrium as per the equation (3).

$$RH \xrightarrow{\text{Polar medium}} RH^{\pm} \quad \ldots (3)$$

Thus, the equilibrium (2) becomes

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

Where $\Delta H_f^o(RH)$ is the heat of formation of benzylpenicillin enol tautomer (**1**) and $\Delta H_f^o(RH^{\pm})$ is the heat of formation of zwitterions (**2** or **3**). The proton affinity is in the order of N_{13} (-66.0527 kcal/mol) > N_7 (-35.7584 kcal/mol). However, zwitterion (**3**) appears to be more stable. Zwitterions are solvated to form hydrogen bonds with the polar solvents which would affect the position of the equilibrium.

The conformations of benzylpenicillin enol tautomer RH (1) and its zwitterions $RH^{\pm}$(2 & 3)

The spatial arrangement of atoms in a molecule is considered to study the conformations of benzylpenicillin enol tautomer (**1**) and its zwitterions (**2** & **3**) with a view to undergoing molecular deformations. Zwitterions can exist in *anti*- or *syn*- conformation, according to the position of atoms. In this context, the change in energy content of the zwitterion may depend on the changes in the parameters of dihedral angles. The conformational analyses of zwitterions reveal about molecular deformations. Figure-1 illustrates the atomic numbering of benzylpenicillin enol tautomer (**1**). Fully optimized AM1 calculations scrutinize only the main data of dihedral angles (Table-II) of molecules (**1, 2 & 3**) for the sake of simplicity.

From the Table-II and Scheme-1, it can be concluded that the zwitterion $RH^{\pm}$ ($N_{13}H^{\pm}$) (**2**) is formed by the proton transfer between O_{10}-atom to N_{13}-atom of RH (**1**) with the change of conformation from -*ap* of $N_{13}C_{11}C_9N_7$, +*sc* of $C_{14}N_{13}C_{11}C_9$, -*sc* of $H_{23}C_4C_3S_2$ and -*sp* of $O_{33}C_{14}N_{13}C_{11}$ are changed to +*ap*, -*sp*, -*ac* and +*sp* conformations respectively to form more stable zwitterion and all other positions are not as much of altered. Dihedral angle of $HN_{13}C_{11}C_9$ is formed with +*ac* conformation.

If the transfer of proton between O_{10}-atom to N_7-atom of RH (**1**) forms the zwitterion $RH^{\pm}$ ($N_7H^{\pm}$) (**3**) with the change of dihedral angles of +*sc* of $C_{14}N_{13}C_{11}C_9$, -*ac* of $H_{32}N_{13}C_{11}C_9$, -*sp* of $O_{33}C_{14}N_{13}C_{11}$ and +*sp* of $H_{41}O_{12}C_9N_7$ are changed to +*ac*, -*sc*, +*sp* and -*sc* conformations respectively to form stable zwitterion and all other positions are altered insignificant. It is found the -*ap* conformation in the case of dihedral angle of $HN_7C_4C_3$ and rest of positions have moderate changes.

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), electron excitation energies (ΔE) (in eV) and the atomic charges on hetero-atoms of benzylpenicillin enol tautomer (1) and its zwitterions (2 and 3) from AM1 calculations.

Parameters	**1**	**2**($N_{13}H^{\pm}$)	**3**($N_7H^{\pm}$)
ΔH_f^o (kcal/mol)	-70.6933	-4.6406	-34.9349
Ionization potential (eV)	8.7991	8.3072	9.4117
μ (Debye)	2.4264	19.6295	9.0449
E_{HOMO} (eV)	-8.799	-8.307	-9.412
E_{LUMO} (eV)	+0.063	-1.443	-0.864
Electron excitation energies ($\Delta E = E_{LUMO} - E_{HOMO}$) (eV)	8.862	7.864	8.548
S_2 (atomic charge)	+0.0685	-0.0361	+0.1121
N_7 (atomic charge)	-0.1588	-0.1531	+0.0041
N_{13} (atomic charge)	-0.2917	+0.0699	-0.2903
O_{10} (atomic charge)	-0.3200	-0.5933	-0.5533
O_{12} (atomic charge)	-0.2025	-0.2016	-0.2093
O_{30} (atomic charge)	-0.3540	-0.4712	-0.4474
O_{33} (atomic charge)	-0.3412	-0.1296	-0.3492

Table – II: Dihedral angle (^{o}) of benzylpenicillin enol tautomer (1) and its zwitterions (2 and 3) from AM1 calculations.

Dihedral angle (^{o})	**1**		**2 ($N_{13}H^{\pm}$)**		**3 ($N_7H^{\pm}$)**	
	Angle	**(*)**	**Angle**	**(*)**	**Angle**	**(*)**
$O_{10}C_8C_4C_3$	-136.12	*-ac*	-98.81	*-ac*	-134.39	*-ac*
$N_{13}C_{11}C_9N_7$	-173.86	*-ap*	+178.99	*+ap*	-174.73	*-ap*
$C_{14}N_{13}C_{11}C_9$	+59.03	*+sc*	-14.99	*-sp*	+131.62	*+ac*
$C_{15}C_{14}N_{13}C_{11}$	-178.79	*-ap*	-173.26	*-ap*	-177.75	*-ap*
$O_{12}C_9N_7C_4$	+67.28	*+sc*	+72.17	*+sc*	+72.06	*+sc*
$H_{23}C_4C_3S_2$	-84.36	*-sc*	-101.00	*-sc*	-81.12	*-sc*
$O_{30}C_8C_4C_3$	+47.29	*+sc*	+80.36	*+sc*	+48.69	*+sc*
$H_{31}O_{10}C_8C_4$	-178.41	*-ap*	- -	- -	- -	- -
$H_{32}N_{13}C_{11}C_9$	-126.67	*-ac*	-137.07	*-sc*	-46.36	*-sc*
$O_{33}C_{14}N_{13}C_{11}$	-1.27	*-sp*	+5.43	*+sp*	+1.65	*+sp*
$H_{41}O_{12}C_9N_7$	+26.05	*+sp*	-27.53	*-sp*	-42.49	*-sc*
$HN_7C_4C_3$	- -	- -	- -	- -	-153.59	*-ap*
$HN_{13}C_{11}C_9$	- -	- -	+107.37	*+ac*	- -	- -
* Conformational analyses using prefixes *a* = anti, *s* = syn, *p* = peri-planar (0 ± 30^0 & 180 ± 30^0), *c* = clinal, and + & - signs.						

CONCLUSION

AM1 calculations show that zwitterions of benzylpenicillin enol tautomer are nearly non-planar skeleton geometry, and the sequence of proton transfer at nitrogen atom is $N_{13} > N_7$. As per dipole moment data, zwitterions are solvated to form hydrogen bonds with the polar

solvents which would affect the position of the equilibrium in the formation of keto-enol tautomerism. Further, the utility of theoretical predictions is important for evaluating the stability of conformations in the polarity of the medium.

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