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AM1 STUDY ON THE CONFORMATIONS OF ZWITTERIONS OF BENZYLPENICILLIN LACTIM TAUTOMER

Dasari Chandrasekhar Rao and Bojja Rajeshwar Rao*

Department of Chemistry, Kakatiya University, Warangal-506 009, India.

*Chemical Division, Kakatiya Thermal Power Project (O&M), Chelpur- 506 170, India.

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***Corresponding Author**
Bojja Rajeshwar Rao
Chemical Division, Kakatiya Thermal Power Project (O&M), Chelpur- 506 170, India.

ABSTRACT

The conformation and electronic structure of zwitterions of benzylpenicillin lactim 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 lactim 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 lactim tautomer, AM1, zwitterions, induction effect, frontier molecular orbital.

INTRODUCTION

The significance of benzylpenicillin has been recognized as a broad spectrum anti-biotic in chemotherapy for the treatment of infections.[1] It is used against infections of the upper and lower respiratory tract, skin and related soft tissue, urinary tract, bones and joints, septicaemias, endocarditic, intra-abdominal and bile tract infections caused by gram(+) organisms.[2] Quantitative structure–activity relationship (QSAR) studies indicate that hydrophobic groups in the side chain appear to be moderately responsible for 45 to 50% protein binding in plasma and cleared rapidly by the kidneys.[3] In practice, most penicillins are undergoing tautomerism and unstable in aqueous solutions. The dipolar character of the

molecule has 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 and to solve 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 attracted much attention that benzylpenicillin lactim tautomer exists as zwitterions over a broad pH range and is considerably increased polarity; the present investigation focuses on the evaluation of the significance of the molecular conformation and electronic properties of benzylpenicillin lactim tautomer (**1**) and its zwitterions $RH^{\pm}$ (**2** & **3**). The mechanism of proton transfer in benzylpenicillin lactim 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 lactim tautomer, as a neutral molecule (RH) (**1**), the conformation and electronic structures of zwitterions $RH^{\pm}$ (**2** & **3**) system, in which are included $RH^{\pm}$ ($N_{12}H^{\pm}$) (**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[12] using *s* = syn, *a* = anti, *p* = peri-planar (0 ± 30^0 & 180 ± 30^0) and all other angles *c* = clinal.

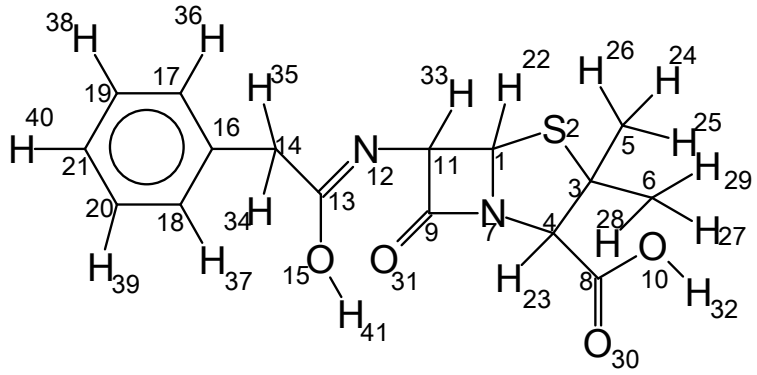


Figure - 1

RESULTS AND DISCUSSION

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

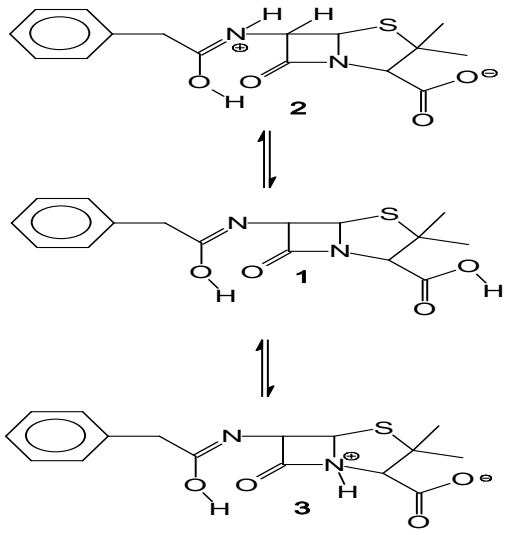
The optimized electronic structure of benzylpenicillin lactim tautomer (**1**) and its zwitterions $RH^{\pm}$ (**2** and **3**) along with the numbering of the system in this context are shown in Figure -1. The calculated heats of formation (ΔH_f^o), dipole moment (μ), the energies of frontier molecular 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_{12}- atoms are -0.2572 and -0.2701 respectively in the case of benzylpenicillin lactim 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 $N_7 < N_{12}$. 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 supra-facial path way is allowed in the case of zwitterions RH+ (2 and 3) due to the presence of same 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 lactim tautomer (**1**) by using the equation (1).

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

Then the inductive effect is increasing in the order of $\Delta\mu_{ind}$ (**3**) 21.4284D < $\Delta\mu_{ind}$ (**2**) 9.0807D. 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 lactim 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 +60.32 kcal/mol and +47.5825 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 lactim tautomer (**1**) to zwitterion (**3**) is lower energy process than the conversion of (**1**) to (**2**). The protonation site of benzylpenicillin lactim tautomer (**1**), containing 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. The proton shifting from O_{10}- atom to N_{12}- atom in the case of benzylpenicillin lactim tautomer (**1**) to zwitterion (**2**) is considered by increasing net atomic charges at S_2-, O_{10}-, O_{30}- and O_{31}- and decreasing at N_7-, N_{12}- and O_{15}- 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 N_7-, N_{12}-, O_{15}- and O_{30}- and increasing at S_2-, O_{10}- and O_{31}- atoms.

The equilibrium of zwitterions (1 to 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_{12}- atoms of benzylpenicillin lactim 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 lactim 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 lactim 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_{12} (-60.32 kcal/mol) > N_7 (-47.5825 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 lactim 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 lactim 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 (**1**). Fully optimized AM1 calculations scrutinize only the main data of dihedral angles (Table-II) of molecules (**1** to **3**) for the sake of simplicity.

From the Table-II and Scheme-1, it can be concluded that the zwitterion $RH^{\pm}$ ($N_{12}H^{\pm}$) (**2**) is formed by the proton transfer between O_{10}-atom to N_{12}-atom of RH (**1**) with the change of conformation from -*ap* of $C_{14}C_{13}N_{12}C_{11}$ and +*sp* of $O_{15}C_{13}N_{12}C_{11}$ are changed to +*ap* and -*sp*

conformations respectively to form more stable zwitterion and all other positions are not as much of altered. Dihedral angle of $HN_{12}C_{11}C_9$ 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 angle of +*ac* of $O_{10}C_8C_4C_3$ and –*sc* of $O_{30}C_8C_4C_3$ are changed to –*ac* and +*sc* conformations respectively to form stable zwitterion and all other positions are altered insignificant. It is found the +*ac* 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 lactim tautomer (1) and its zwitterions (2 and 3) from AM1 calculations.

Parameters	**1**	**2**	**3**
ΔH_f^o (kcal/mol)	-82.8829	-22.5629	-35.3004
Ionization potential (eV)	8.9467	7.6427	9.1895
μ (Debye)	1.8352	23.2636	10.9159
E_{HOMO} (eV)	-8.947	-7.643	-9.189
E_{LUMO} (eV)	+0.086	-2.514	-1.449
Electron excitation energies ($\Delta E = E_{LUMO} - E_{HOMO}$) (eV)	9.033	5.029	7.740
S_2 (atomic charge)	+0.0935	-0.0909	-0.1255
N_7 (atomic charge)	-0.2572	-0.1353	-0.0710
N_{12} (atomic charge)	-0.2701	-0.1943	-0.2660
O_{10} (atomic charge)	-0.3178	-0.5100	-0.5250
O_{15} (atomic charge)	-0.2892	-0.2125	-0.2784
O_{30} (atomic charge)	-0.3342	-0.4991	-0.1646
O_{31} (atomic charge)	-0.2740	-0.2958	-0.4448

Table – II	**Dihedral angle (^{o}) of benzylpenicillin lactim tautomer (1) and its zwitterions (2 and 3) from AM1 calculations.**					
Dihedral angle (^{o})	**1**		**2**		**3**	
	Angle	(*)	Angle	(*)	Angle	(*)
$O_{10}C_8C_4C_3$	+98.43	+*ac*	+94.01	+*ac*	-110.49	-*ac*
$N_{12}C_{11}C_9N_7$	-123.04	-*ac*	-120.29	-*ac*	-120.37	-*ac*
$C_{13}N_{12}C_{11}C_9$	-52.15	-*sc*	-60.64	-*sc*	-51.34	-*sc*
$C_{14}C_{13}N_{12}C_{11}$	-176.35	-*ap*	+179.36	+*ap*	-177.79	-*ap*
$O_{15}C_{13}N_{12}C_{11}$	+1.40	+*sp*	-3.46	-*sp*	+1.96	+*sp*
$H_{23}C_4C_3S_2$	-113.95	-*ac*	-115.84	-*ac*	-93.61	-*ac*
$O_{30}C_8C_4C_3$	-81.92	-*sc*	-85.09	-*sc*	+70.33	+*sc*
$O_{31}C_9N_7C_4$	-51.94	-*sc*	-55.86	-*sc*	-65.98	-*sc*
$H_{32}O_{10}C_8C_4$	+179.04	+*ap*	- -	- -	- -	- -
$H_{41}O_{15}C_{13}N_{12}$	+8.21	+*sp*	+12.90	+*sp*	+5.33	+*sp*
$HN_7C_4C_3$	- -	- -	- -	- -	+111.17	+*ac*
$HN_{12}C_{11}C_9$	- -	- -	+110.71	+*ac*	- -	- -

* Conformational analyses using prefixes *a* = anti, *s* = syn, *p* = peri-planar (0 ± 30^0 & 180 ± 30^0), *c* = clinal, and + & - signs[15].

CONCLUSION

AM1 calculations show that zwitterions of benzylpenicillin lactim tautomer are nearly non-planar skeleton geometry and the sequence of proton transfer at nitrogen atom is $N_{12} > N_7$. Zwitterions are solvated to form hydrogen bonds with the polar solvents which would affect the position of the equilibrium. Further, the utility of theoretical predictions is important for evaluating the stability of conformations, which is dependent upon the polarity of the medium.

REFERENCES

1. Wolfe S, Demain AL, Jensen SE, Westlake DWS, Enzymatic approach to synthesis of unnatural beta-lactams, *Science*, 1984; 226: 1386-92.
2. Morin R B & Gorman M, Eds, *Chemistry and Biology of Beta-lactam Antibiotics*, Volumes 1-3, (Academic press, New york), 1982.
3. Perlman D, Eds, *Structure Activity Relationships among the semi-synthetic Antibiotics*, (Academic press, New York), 1977.
4. John H Block & John M Beak Jr, *Wilson and Gisvold's Text Book of Organic Medicinal and Pharmaceutical Chemistry*, 11th edn, (Lippincott Williams & Wilkins, New York) 2004.
5. Dewar MJS, Zeobisch EG, Healy EF, Stewart JJP, AM1: a new general purpose quantum mechanical molecular model, *J am chem soc*, 1985; 107: 3902-9.
6. Stewart JJP, *MOPAC, A general molecular orbital package, QCPE 455*, 5th edn, 1988.
7. Pople JA, Beveridge DL, *Approximate molecular orbital theory*, (McGraw-Hill, New York) 1970.
8. Rajeshwar Rao B, Oxazoles: Perturbations by methyl groups, *Indian J. Chem*, 2000; 39B: 154-155.
9. Rajeshwar Rao Bojja, HMO study on the effect of methyl group perturbations in isoxazoles, *Indian J. Chem*, 2002; 41B(8): 1694 -1696.
10. Rajeshwar Rao Bojja, AM1 study on the conformations of 6-aminopecillanic acid, *Indian J. Chem.* 2002; 41B(8): 1697-1701.
11. Mandla Venugopal, Raveendra Reddy P, Rajeshwar Rao B, AM1 study on the conformations of zwitterions of benzylpenicillin, *World J. Pharm Res*, 2017; 6(7): 1149-1157. www.wjpr.net.
12. Rajeshwar Rao Bojja, Lingamurthy S, AM1 study on the conformations of zwitterions of 6-aminopenicillanic acid (6-APA), *Indian J. Chem*, 2006; 45B(5): 1250-1253.

13. Rajeshwar Rao Bojja, Study of [1,3]Sigmatropic hydrogen migration in cytosine and cytidine by AM1 method, *Indian J. Chem*, 2003; 42B(12): 3081-3088.
14. Rajeshwar Rao Bojja, Study of [1,3]Sigmatropic hydrogen migration in uracil, uridine and uridylic acid by AM1 method, *Indian J. Chem*, 2006; 45B(9): 2083-2090.
15. Rajeshwar Rao Bojja, Study of [1,3]sigmatropic hydrogen migration in thymine, thymidine and thymidylic acid by AM1 method, *Indian J. Chem*, 2009; 48B(10): 1411- 1415.
16. Mandla Venugopal, Raveendra Reddy Papammagari, Rajeshwar Rao Bojja, AM1 study on the conformational analyses of tautomers in benzylpenicillin, *Inter J Pharm and Chem Sci*, 2013; 2(3): Jul-Sep, 1150-1156. www.ijpcsonline.com.
17. Rajeshwar Rao Bojja, Chandra Sekhar Rao D, Sanjeeva Reddy Ch, AM1 study of the Electronic structure of 7- aminodeacetoxycephalosporanic acid (7-ADCA). *Indian J. Chem*, 2012; 51B(1): 307-312.
18. Ranga Reddy S, Rajeshwar Rao B, Manikyamba P, Correlation analysis in the reactions of benzyl bromide with N-substituted anilines, *Indian J. Chem*, 2007; 46(A): 436-439.
19. Ranga Reddy S, Kalyani P, Rajeswara Rao B, Manikyamba P, Computaional studies and reactivity of nucleophiles in benzylation reactions, *Indian J. Chem*, 2008; 47A(2): 236-239.
20. Woodward RB, Hoffmann R, *The conservation of orbital symmetry*, (Academic press, Inc, New York) 1970.
21. Paperno TYA, Pozdnyakov VP, Smirnova AA, Elagin LM, *Physico-Chemical Laboratory Techniques in Organic and Biological Chemistry (Translated from Russian by Oleg Glebov)*, (MIR Publishers, Moscow), 1979.
22. Saltek N, Abbasogulu R, Ikizler A, A quantum-chemical study on 3,3'-bi(1H-1,2,4-triazole). *Acta chim hung, Models in chemistry*, 1996; 133: 43-51.