ISSN 2249 – 0345

Original Article

AM1 study on the conformations and electronic properties of Phenoxymethylpenicillin

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Received 15 July 2012; accepted 30 July 2012

Abstract

The geometry, conformation and electronic structure of phenoxymethylpenicillin have been optimized and calculated in the gas phase by semi-empirical molecular orbital AM1 method usually considering an isolated molecule surrounded by vacuum. Further, the mechanism of protonation in phenoxymethylpenicillin 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 ($\Delta H_f$), dipole moment ($\mu$), 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 and their stable conformations have also been performed.

Key words: AM1, phenoxymethylpenicillin, induction effect, frontier molecular orbital.

Introduction

Penicillin derivatives have been studied extensively because of their broad anti-microbial spectra, more favourable absorption patterns and reduced undesirable side effects¹. Significance of β-Lactam ring of penicillin has been known to block the activity irreversible by bonding covalently with the functional end of the enzyme². Penicillins are two categories; (a) biosynthetic penicillins are harvested from the mould itself through fermentation naturally and (b) semi-synthetic penicillins with the basic penicillin structure are modified chemically by substituting the acyl-side chain to produce specific properties, such as resistance to stomach acids, a degree of resistance to penicillase and activity against some gram-negative bacteria³. Enzymatic splitting of natural penicillin’s (G & V) and isolation of the important intermediate, 6-aminopenicillanic acid was led the preparation of several semi-synthetic penicillins⁴. Quantitative structure–activity relationship (QSAR) studies indicate that hydrophobic groups in the side chain appear to be largely responsible for 50 to 60% to plasma protein binding⁵. In practice, penicillins had expected to influence selective penetration through the porin channels of the cell membrane⁶. It is reasonable to assume that dipolar character of the drug could improve oral absorption⁷. A therapeutic advantage is due to a selective inhibition of bacterial cell wall synthesis. Austin Model-1 (AM1) is one of the semi-empirical quantum calculations based on the neglect of differential diatomic overlap integral approximation, which includes experimental parameters and extensive simplification of the Schrodinger’s equation (HΨ=EΨ) to optimize molecules for calculation of various properties to solve chemical problems⁸. It is important to know the conformational changes in the molecule for the prediction of its reactivity and pharmacological action. 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. In this connection, theoretical investigations of HMO study on the effect of methyl group perturbations⁹ and AM1 study on conformational analyses¹⁰, [1,3]sigmatropic hydrogen migration¹¹, electronic structure¹², correlation studies¹³ and computational studies¹⁴ were carried out. In view of these observations, the present study on molecular conformation and electronic properties of phenoxymethylpenicillin (Penicillin-V) (I) in gas phase usually considering an isolated molecule surrounded by...
vacuum has been evaluated by AM1 method. From the obtained optimized electronic structure of phenoxymethylpenicillin, the mechanism of protonation has been studied by comparison of the relative values of net charges for nitrogen atoms in different positions of the molecule. Taking phenoxymethylpenicillin 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**

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 and transition states. Geometry calculations in the ground state (keywords: PRECISE, equivalent to Gnorm=1.0, 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 Poplc’s standard data, and subsequently fully optimized using an energy gradient method. The conformations were designated by Klyne-Prelog terms using $s = syn$, $a = anti$, $p = peri-planar (0^\circ-30^\circ$ & $180^\circ-30^\circ)$ and all other angles $c = clinal.

**Results & Discussion**

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

The optimized electronic structure of phenoxymethylpenicillin (1) and its mono-protonated (2 & 3), di-protonated (4) and anion (5) are shown in Scheme-1. In this context, the numbering of phenoxymethylpenicillin is shown in Figure 1. The calculated heats of formation ($\Delta H^0$), ionization potential (IP), dipole moment ($\mu$), 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-1. It is observed that the net charges on N$_{11}$- and N$_{12}$- atoms are -0.2497 and -0.3778 respectively in the case of phenoxymethylpenicillin (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 phenoxymethylpenicillin (1) is increasing in the order of N$_{1}$ < N$_{12}$. Thus, N$_{12}$- atom is predicted to be main protonation site of phenoxymethylpenicillin (1), according to the negative charge distribution on nitrogen atoms. 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 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 to 4, due to the presence of same sign$^7$. 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 2 < 4 < 1 < 3 < 5. Anion (5) shows higher dipole moment. The electron-negative heteroatoms cause displacement of electrons that induces an additional dipole moment in the molecule. The magnitude of the induction effect $^{18}$ ($\Delta \mu_{ind}$) of molecules can be estimated with respect to phenoxymethylpenicillin (1). It is found that the induction effect is increasing in the case of $\Delta \mu_{ind}$ (3) 5.6318D and $\Delta \mu_{ind}$ (5) 10.0298D and decreasing in the case of $\Delta \mu_{ind}$ (2) 1.347D and $\Delta \mu_{ind}$ (4) 0.589D. According to the heat of formation ($\Delta H^0$) data, the stability of compounds have decreased in the order of 5 > 3 > 2 > 4. 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$_{1}$-atom in the case of phenoxymethylpenicillin (1), this is due to the increased bond length of C$_{13}$-N$_{1}$ (1.4402 Å) than C$_{13}$N$_{12}$ (1.3929 Å). It is confirmed that the stability of mono-protonated phenoxymethylpenicillin, 3 ($\Delta H^0$, +49.9048 Kcal/mol) is more stable than 2 ($\Delta H^0$, +59.6821 Kcal/mol).

![Figure 1](image)

**Figure - 1**

The formation of di-protonated phenoxymethylpenicillin (4), from mono-protonated phenoxymethylpenicillin, (2 & 3) is possible with the heat of formation ($\Delta H^0$) of +305.3188 Kcal/mol. The protonation site of phenoxymethylpenicillin (1) at N$_{1}$- 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$_{1}$-atom in the case of neutral phenoxymethylpenicillin (1) to mono-protonated form (3) is considered by increasing net atomic charges at N$_{12}$-atom and decreasing at N$_{1}$-, O$_{11}$-, O$_{12}$-, O$_{33}$-, O$_{35}$- and O$_{35}$- atoms. The protonation site of phenoxymethylpenicillin (1) at N$_{12}$- atom to mono-protonated form (2) is considered by decreasing net atomic charges at N$_{1}$, N$_{12}$-, O$_{11}$-, O$_{12}$-, O$_{25}$- and O$_{35}$- atoms. In the case of di-protonated form (4), the negative atomic charges are decreased at all hetero
atoms except O₁₅⁻ atom. Anion of phenoxymethylpenicillin (5) is formed by the removal of a proton on O₁₁⁻ atom with increasing net charges at O₁₁⁻, O₁₅⁻, O₂₄⁻, O₂₅⁻, and O₃₅⁻, and decreasing at N₁₀⁻ and N₁₁⁻ atoms.

The acid – base equilibrium of phenoxymethylpenicillin (1 to 5)
Equilibrium is normally established in polar solvents, in order to investigate the basicity and it is found out the protonation sites of phenoxymethylpenicillin (1) as per Scheme-1. N₁₀⁻ and N₁₁⁻ atoms are main basic centre in accordance with the negative charge distribution on N-atoms (Table-I). To determine the exact protonation centres of phenoxymethylpenicillin (1), 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 N₁₀⁻ or N₁₁⁻ atoms of phenoxymethylpenicillin (1) can exist in anti- or syn-conformations, according to the position of N-atoms as shown in Scheme-1. Its conformation can be assigned by comparison of its geometry and electronic structure. The proton affinity (PA) values for the different nitrogen atoms of phenoxymethylpenicillin, RH (1) were calculated by using the equation (1) and found to be 187.7314 kcal/mol and 197.5087 kcal/mol respectively in the case of mono-protonated phenoxymethylpenicillin (2 and 3). Di-protonated phenoxymethylpenicillin (4) was formed from either of mono-protonated phenoxymethylpenicillins (2 and 3) respectively with PA 121.5633 kcal/mol and 111.786 kcal/mol.

\[ \text{PA} = \Delta H^\circ (\text{H}^+ \rightarrow \text{B}^+) - \Delta H^\circ (\text{BH}^+ \rightarrow \text{BH}^+) \ldots (1). \]

Where PA is the proton affinity, \( \Delta H^\circ (\text{B}) \) is the heat of formation for phenoxymethylpenicillin, \( \Delta H^\circ (\text{BH}^+) \) is the heat of formation for the cation, and \( \Delta H^\circ (\text{H}^+) \) is heat of formation for the proton (367.2 kcal/mol). The proton affinity is in the order of N₁₀⁻ (197.5087 kcal/mol) > N₁₁⁻ (187.7314 kcal/mol) and mono-protonated phenoxymethylpenicillin (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](image)

The conformations of phenoxymethylpenicillin (1) and its mono-protonated (2and3), di-protonated (4)and anion R (5). The change in energy content of the protonation may depend on the changes in the parameters of dihedral angles. The spatial arrangement of atoms in phenoxymethylpenicillin (1), and its mono-protonated forms (2 & 3), di-protonated form (4) and anion (5) are considered to study the conformations. These can exist in anti- or syn- conformation, according to the position of atoms. In this context, Figure-1 illustrates the atomic numbering of phenoxymethylpenicillin (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 phenoxymethylpenicillin (2) is formed by the addition of proton at N₁₁⁻ atom of phenoxymethylpenicillin (1), with

<table>
<thead>
<tr>
<th>Parameters</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta H^\circ ) (kcal/mol)</td>
<td>-119.7865</td>
<td>+59.6821</td>
<td>+49.9048</td>
<td>+305.3188</td>
<td>-152.0708</td>
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<tr>
<td>Ionization potential (eV)</td>
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<td>12.0244</td>
<td>11.3584</td>
<td>14.4811</td>
<td>5.1027</td>
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<tr>
<td>( \mu ) (Debye)</td>
<td>5.3910</td>
<td>4.0440</td>
<td>11.0228</td>
<td>4.8020</td>
<td>15.4208</td>
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<tr>
<td>E(_{\text{HOMO}}) (eV)</td>
<td>-9.068</td>
<td>-12.024</td>
<td>-11.358</td>
<td>-14.481</td>
<td>-5.103</td>
</tr>
<tr>
<td>E(_{\text{LUMO}}) (eV)</td>
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<td>-4.719</td>
<td>-4.847</td>
<td>-8.761</td>
<td>+2.301</td>
</tr>
<tr>
<td>( S_i ) (atomic charge)</td>
<td>+0.0696</td>
<td>+0.1346</td>
<td>+0.2229</td>
<td>+0.3235</td>
<td>-0.0438</td>
</tr>
<tr>
<td>( N_i ) (atomic charge)</td>
<td>-0.2497</td>
<td>-0.2165</td>
<td>-0.1215</td>
<td>-0.0985</td>
<td>-0.1838</td>
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<tr>
<td>( O_1 ) (atomic charge)</td>
<td>-0.3778</td>
<td>-0.1033</td>
<td>-0.3940</td>
<td>-0.1295</td>
<td>-0.3603</td>
</tr>
<tr>
<td>( O_2 ) (atomic charge)</td>
<td>-0.3168</td>
<td>-0.3003</td>
<td>-0.2703</td>
<td>-0.2558</td>
<td>-0.5514</td>
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<tr>
<td>( O_3 ) (atomic charge)</td>
<td>-0.1847</td>
<td>-0.1663</td>
<td>-0.1741</td>
<td>-0.2321</td>
<td>-0.1952</td>
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<tr>
<td>( O_4 ) (atomic charge)</td>
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<td>-0.0326</td>
<td>-0.3185</td>
</tr>
<tr>
<td>( O_5 ) (atomic charge)</td>
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<td>-0.3160</td>
<td>-0.3230</td>
<td>-0.3093</td>
<td>-0.5327</td>
</tr>
</tbody>
</table>

Table-1: Heat of formation (\( \Delta H^\circ \)) in kcal/mol, ionization potential (eV), dipole moment (\( \mu \) in Debye), energies of frontier molecular orbitals (eV) and the atomic charges on \( S_i \), \( N_i \), \( O_1 \), \( O_2 \), \( O_3 \), \( O_4 \), \( O_5 \) of phenoxymethylpenicillin (1) and its mono-protonated forms (2 & 3), di-protonated form (4), and anion (5) from AM1 calculation.
increasing bond lengths at C11-N12 and decreasing bond lengths at C5-N3, O35-C13, O23-C5 and C12p-C13. The change of conformation is observed -ap conformation at the protonation of N12- atom and all other conformations are unaltered. If the mono-protonated phenoxymethylpenicillin (3) is formed by the addition of proton at N1- atom of phenoxymethylpenicillin (1), with increasing bond lengths at C5-N3 and C11-N12 and decreasing bond lengths at O35-C13, O23-C5 and C12p-C13. The change of dihedral angle of Cα-N1-Cαs is converted -sp to +sp conformation. Dihedral angle of O1-Cα-Cα-N1, C35-N12-C13, O35-C13-N12, C12p-O35-C13, O23-Cαs-N12 and O23-Cαs-N12 are changed -ac to -ap, +ac to +ap, -sp to +sp and +ap to +sp conformations and all other conformations are unaltered. It is also observed that the protonation at N1- atom is shown -ac conformation. In the case of formation of di-protonated phenoxymethylpenicillin (4), it is found that the dihedral angle of Cα-N1-Cαs, O1-Cα-Cαs, O12p-Cαs-N12, C13p-O35-C13, O35-C13-N12, C12p-N12-C13 and H34-N12-C13 are changed conformations, -sp to +sp, -ap to +ap, -ac to +ap, +sc to +ac, -ap to +sp, +sp to +sp, -ac to +sp and -ac to -sp conformations respectively. It is also investigated that the protonation at N1- atom and N12-atom are shown respectively -ac and -ap conformations to form stable diprotonated phenoxymethylpenicillin (4). It is investigated that the stable anion R (5) was formed from phenoxymethylpenicillin (1) with the removal of a proton on O1- atom and it is also observed moderate changes in the conformations

**Conclusion**

Austin Model-1 (AM1) is one of the semi-empirical quantum calculations, which includes experimental parameters and extensive simplification of the Schrodinger’s equation (HΨ=EΨ) to optimize phenoxymethylpenicillin for prediction of various conformational changes and its reactivity & pharmacological action. 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. The protonation of phenoxymethylpenicillin is predicted to be the main basic centre along with the negative charge distribution on nitrogen atoms (N3 > N12). Further, the utility of theoretical predictions is important for evaluating the ability to cross cell wall barriers and binding to serum proteins. This study reveals about the stability of conformations, which are highly dependent relative upon the polarity of the medium.

**Acknowledgement**

This research work has been carried out by one of the authors (Smt. Ravadi Premalatha) with cooperation of the Principal and grateful to Dr. E. Suresh, Reader & Head, Department of Chemistry, Pingle Govt College for Women, Waddepally, Warangal for constructive discussions and to the Head, Department of Chemistry, Kakatiya University.
Warangal for encouragement.

References

18. 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; 171.

Source of support: Nil; Conflict of interest: None declared