

Theoretical Investigation of Structural, Thermodynamical and HOMO, LUMO Analysis of 6-Aminopenicillanic Acid

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Abstract: Quantum chemical calculations using density functional theory and 6-311G (d) basis set have been applied to analyze the interactions of β -lactam compounds and the electronic structural properties including thermochemical parameters have been investigated. The present investigation is extended to calculate the HOMO–LUMO energy gap. The calculated HOMO–LUMO energy gap shows that the charge transfer occurs within the molecule. The frontier orbital and molecular electrostatic potential surface studies have been employed to understand the active structure. The results presented in this article will be helpful to improve existing model and will open up a whole new arena of study to understand the antimicrobial characteristic from natural products against the photosensitizing DNA damage induce by 6-aminopenicillanic acid extracts and enable amuch clearer understanding of how antimicrobial drugs mediate their effects on the specific spot.

Keywords: HOMO, LUMO, DFT, 6-Aminopenicillanic acid

Introduction

The β -lactam four-membered ring (2-azetidinone system) is a unit of antibiotics of penicillin and cephalosporin types the most widely employed family of antimicrobial agents to date accounting for 50% of the world's total antibiotic market^{1,2}. In the mid 1970s, a new class of β -lactam antibiotics characterized by a single monocyclic structure, called monobactams, were discovered³ and some of them, of natural origin, have already been isolated and identified⁴. The reactive β -lactam ring is the important structural moiety for their antibacterial activity, which requires: a ring of sufficient strain; possibilities for electron delocalization outside the lactam ring and some conformational features⁵. Therefore, deep knowledge of the β -lactam nucleus is essential for designing a new series of these antibiotics or establishing a structure–activity relationship. The importance of 6-Aminopenicillanic acid (6-APA) as a starting point for the preparation of semisynthetic penicillins provided a strong stimulus for research into the production of this compound. Although 6-APA was first obtained as a naturally occurring

fermentation product, the yields were always considerably lower than those of penicillin G or penicillin V obtained in fermentations in which the appropriate precursor was used. Moreover, the isolation of 6-APA from the fermentation broth was not easy. It seemed possible that an alternative route to 6-APA might be the enzymatic removal of the side-chain of the penicillin molecule. Examination of various microorganisms in our laboratories revealed that at least two types of penicillin deacylase occurred in nature⁶. One type was found to be widely distributed among the actinomycetes and filamentous fungi. This type of enzyme hydrolysed penicillin V readily but penicillin G was hydrolysed only slowly. The other type of deacylase was detected among bacteria; it hydrolysed penicillin G very readily but penicillin V was split only at about 20% of the rate. A process for the manufacture of 6-APA by deacylation of penicillin was first developed in our laboratories using a deacylase obtained from *Streptomyces lavendulae* with penicillin V as substrate; a patent for this process was filed in March 1959. Subsequently the deacylase of bacterial origin was discovered independently in a number of laboratories⁶⁻⁹ and a process for 6-APA production was then developed using this type of enzyme with penicillin G as substrate. With the availability of 6-APA and the opportunity to prepare semisynthetic penicillins, a number of objectives presented themselves. We have studied the theoretical investigation on the 6-APA and zwitterion of 6-APA (Figure 1). Quantum chemical analyses of 6-APA and zwitterion of 6-APA have been successful in contributing to our understanding of the frontier orbital (HOMO and LUMO) and thermochemistry of penicillin antibiotics with their target molecules.

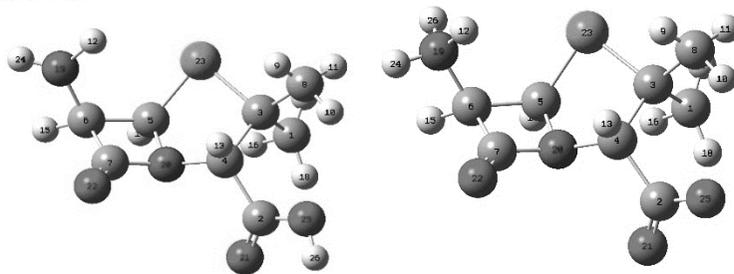


Figure 1. Molecular structure with atoms numbering of 6-APA and zwitterion of 6-APA

Experimental

All DFT calculations were performed using the Gaussian 03W program package at B3LYP method with 6-31G(d) basis set level¹⁰ with the default convergence criteria, without any constraint on the geometry¹¹.

Results and Discussion

Frontier molecular orbital analysis

The frontier orbital (HOMO and LUMO) of the chemical species are very important in defining its reactivity^{12,13}. Energies of HOMO and LUMO are popular quantum mechanical descriptors. It has been shown¹⁴ that these orbital's play a major role in governing many chemical reactions and are also responsible for charge transfer complexes¹⁵. The energy of the HOMO is directly related to the ionization potential and characterizes the susceptibility of the molecule towards attack of electrophiles. The energy of LUMO is directly related to the electron affinity and characterizes the susceptibility of the molecule towards attack of nucleophiles. The concept of hard and soft nucleophiles and electrophiles have been also directly related to the relative energies of the HOMO and LUMO orbital's. Hard nucleophiles

have a low energy HOMO, soft nucleophiles have a high energy HOMO, hard electrophiles have a high energy LUMO and soft electrophiles have a low energy LUMO¹⁶. HOMO–LUMO gap is an important stability index¹⁷(Figure 2). Molecular orbital energies are molecular properties whereas orbital densities are atomic properties, and provide useful information about donor acceptor interaction¹⁸. According to frontier electron reactivity theory, the chemical reaction takes place at a position where overlap of the HOMO and LUMO are the maximum¹⁹. In the case of donor molecule the HOMO density and in case of acceptor molecule the LUMO density is important for any reaction. Frontier orbital densities can strictly be used to describe the reactivity of different atoms in the same molecule¹⁵⁻¹⁹. The electronegativity and hardness are of course used extensively to make predictions about chemical behavior.

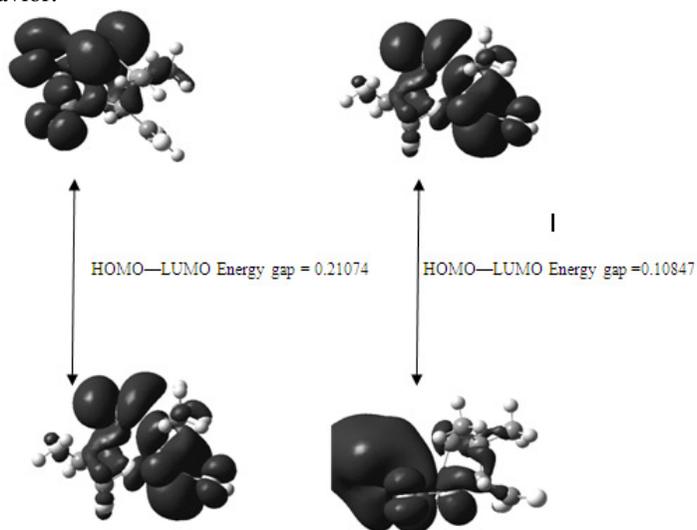


Figure 2. HOMO LUMO of Energy gap for 6-APA and witterions of 6-APA

According to, the Koopmans' theorem, Ionization potential (IE), Electron affinity (EA), Global electronegativity (χ), Chemical hardness (η), Global softness (S) and Global Electrophilicity index (ω) can be expressed as follows.

$$IE = -E_{\text{HOMO}}, EA = -E_{\text{LUMO}}, \chi = \frac{(IE + EA)}{2}, \eta = \frac{(IE + EA)}{2}, S = \frac{1}{\eta}, \omega = \frac{\mu^2}{2\eta}$$

The highest occupied molecular orbital (HOMO) energies, the lowest unoccupied molecular orbital (LUMO) energies, hardness (η), ionization energy (IE), electronegativity (χ), total energy and dipole moment have been calculated and are given in Table 1. The total energy of 6-APA in comparison with witterions of 6-APA is that it is more stable units; it is well-known that molecules with large HOMO–LUMO gaps are generally stable and unreactive; while those with small gaps are generally reactive²⁰. According to our results in this table, we note that witterions of 6-APA molecule have the smallest and reactive in orbital energy difference. The ionization energy (IE) can be expressed through HOMO orbital energies as IE and electron affinity (EA) can be expressed through LUMO orbital energies²¹ as EA.

Table 1. The values of parameters of 6-APA and zwitterion of 6-APA obtained by DFT B3LYP/6-31G(d) method

Parameters	6-APA	Zwitterion of 6-APA
ϵ_{HOMO} (eV)	-0.24643	-0.19584
ϵ_{LUMO} (eV)	-0.03569	-0.08737
Orbital energy difference (ΔE) eV	0.21074	0.10847
Total energy (Arbitr. Units)	-1045.4247	-1045.3504
Ionization potential (IE) eV	0.24643	0.19584
Electron affinity (EA) eV	0.03569	0.08737
Chemical potential (μ) eV	-0.14106	-0.14160
Global electronegativity (χ) eV	0.14106	0.141605
Chemical hardness (η) eV	0.10537	0.054235
Global electrophilicity index (ω)	0.09442	0.18486
Chemical softness (S)	9.4904	18.4383
Dipole moment (Debye)	2.1057	16.2604

The hardness (η) corresponds to the gap between the HOMO and LUMO orbital energies. The larger the HOMO–LUMO orbital energy gap, the harder the molecule. In the present study the HOMO LUMO gap of the molecule is 0.21074 eV as shown in Table 1. It clearly indicates that 6-APA molecule is very stable. The ionization potential values obtained by the theoretical method also support the stability of the 6-APA molecule. The calculated dipole moment value shows that zwitterion of 6-APA is highly polar in nature.

Frequency calculations

The vibrational frequencies of 6-APA and Zwitterion of 6-APA were calculated at the DFT (B3LYP) levels of theory using the 6-31G(d) basis set²². The entropies and heat capacities were calculated using statistical mechanics based on the vibrational frequencies²³. The nature of all stationary point structures were determined by analytical frequency analysis, which also provided zero-point vibrational energies (ZPEs)²⁴. Electronic energies, enthalpies, Gibbs free energies and zero point vibrational energies for both the compounds using frequency calculation at 298.15 K temperatures are presented in Table 2. Thermochemistry analysis follows the frequency and normal mode data.

Table 2. Thermochemistry values for 6-APA and zwitterion of 6-APA at 298.15 K 1.00 atmosphere pressure obtained by DFT B3LYP/6-31G(d) method

	E_{ZPE}	E_{tot}	H_{corr}	G_{corr}	$\epsilon_0 + E_{\text{ZPE}}$	$\epsilon_0 + E_{\text{tot}}$	$\epsilon_0 + H_{\text{corr}}$	$\epsilon_0 + G_{\text{corr}}$
6-APA	129.888	138.630	139.223	104.422	-1045.217	-1045.203	-1045.202	-1045.258
Zwitterion of 6-APA	129.832	138.340	138.933	104.862	-1045.143	-1045.129	-1045.128	-1045.183
	E_{tot} (Thermal)	$(C_v)_{\text{tot}}$	S_{tot}	$Q_{\text{tot BOT}}$	$Q_{\text{tot V=0}}$	$\text{LN}(Q)_{\text{tot BOT}}$	$\text{LN}(Q)_{\text{tot V=0}}$	
6-APA	138.631	52.573	116.724	0.287D-76	0.464D+19	-176.244	42.983	
Zwitterion of 6-APA	138.340	51.690	114.273	0.136D-76	0.200D+19	-176.987	42.144	

$$E_{\text{tot}} = E_t + E_r + E_v + E_e, H_{\text{corr}} = E_{\text{tot}} + K_B T, G_{\text{corr}} = H_{\text{corr}} - T S_{\text{tot}}, S_{\text{tot}} = S_t + S_r + S_v + S_e$$

Sum of electronic and zero-point energies = $\Delta E_0 + E_{ZPE}$

Sum of electronic and thermal energies = $\Delta E_0 + E_{tot}$

Sum of electronic and thermal enthalpies = $\Delta E_0 + H_{corr}$

Sum of electronic and thermal free energies = $\Delta E_0 + G_{corr}$

Where ΔE_0 is the total electronic energy at $T = 0$ K, G_{corr} and H_{corr} represent the thermal correction to Gibbs free energy and enthalpy, respectively. The internal thermal energy E_{tot} is contributed from translational (E_t), rotational (E_r), vibrational (E_v) and electronic (E_e) energies, and S_{tot} , S_t , S_r , S_v , S_e are the corresponding entropies²⁵. The next section is the individual contribution to the internal thermal energy (E_{tot}), constant volume molar heat capacity (C_v)_{tot}, entropy (S_{tot}) and partition function (Q)²⁶. The partition functions are also computed, with both the bottom of the vibrational well and the lowest (zero-point) vibrational state as reference. The comparison of thermochemistry values were calculated for two structures, which show that with increasing total energy, these values increase in both structures and also these values for 6-APA at thermochemistry are more than witterions of 6-APA which shows the greater dipole moment of 6-APA. The comparison of thermochemistry parameters of two structures show that with increasing stability the thermal correction free energy and enthalpy (H_{corr}), the internal thermal energy (E_{tot}), constant volume molar heat capacity (C_v)_{tot}, entropy (S_{tot}) and the individual contributions to the internal thermal energy (E_{tot}) increase in both structures.

Conclusion

In the present study, we used a combination of theoretical tools to compare 6-APA and witterions of 6-APA structures. The following conclusions are obtained from the current study, thermochemistry is the best tool to investigate the energy properties and andreaction mechanisms into the human organism or physiological conditions. The calculated dipole moment value shows that witterions of 6-APA is highly polar in nature but 6-APA more stable of witterions of 6-APA and 6-APA at greater internal thermal energy of witterions of 6-APA. A correlation between The larger the HOMO and LUMO orbital energy gap the stable and unreactive. Finally, the HOMO and LUMO orbital energy gap values of witterions of 6-APA is smaller than that of 6-APA. In contrast, with the increase of stability values of 6-APA. So, our results reveal that the calculated HOMO and LUMO parameters of witterions of 6-APA is higher chemical softness and dipole moment.

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