

Hydrogen Bonding And Charge Transfer Interaction On 4-Methoxy Triamterene Cardiovascular Drug Using DFT Method

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Abstract: Quantum chemical calculations of energies, geometrical structure and vibrational wavenumbers of 4-methoxy triamterene(4MT) have been investigated with the help of B3LYP /6-311G(d,p) basis set. Vibrational analysis were predicted theoretically from the calculated intensities. The calculated molecular geometry has been compared with the experimental data. Natural bond orbital (NBO) analysis confirms the presence of intramolecular charge transfer and the hydrogen bonding interaction. The HOMO-LUMO analysis reveals the charge transfer of the compound.

Index Terms: DFT, MEP, NMR, TD-DFT

1. INTROUDTCION

4-methoxy triamterene (4MT) is a potassium-sparing diuretic used in combination with thiazide diuretics for the treatment of hypertension and edema [1]. The present work reports a study on 4MT using spectroscopic techniques and also encompasses the possibility of hydrogen bonding and charge transfer interactions. The natural bond orbital (NBO) analysis has been carried out to interpret hyperconjugative interaction and intramolecular charge transfer (ICT). The calculated value of HOMO-LUMO energy gap and Molecular electrostatic potential is used to interpret the cardiovascular activity of the molecule. Intramolecular hydrogen bonding interactions have received much attention from theoretical perspectives as they can determine the structures and cardiovascular activities of the compound.

2 COMPUTATIONAL DETAILS

The DFT computations for the 4MT was carried out in the Gaussian 09 program package using "ultrafine" integration grids. The calculations were performed at the BLYP level with the standard 6-311G(d,p) basis set in order to derive the optimized geometry, vibrational wavenumbers and natural bond orbital analysis of 4-methoxy triamterene [2].

3.RESULT AND DISCUSSION

3.1Optimized geometry

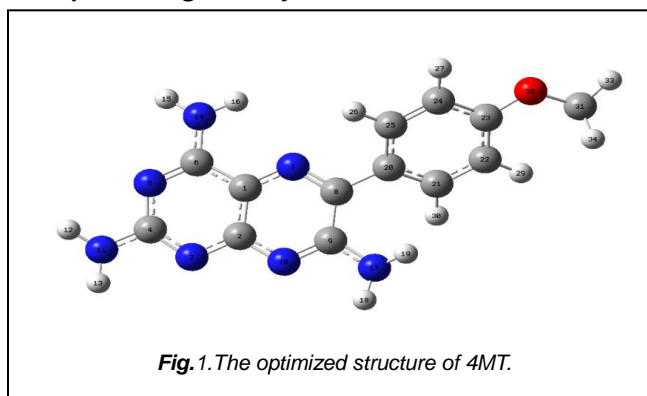


Fig. 1. The optimized structure of 4MT.

The calculated data of 4MT are in close agreement with the experimental values [4][Table1]. In the title compound, the C₁-C₆ bond length is increased due to the presence of amino group[3]. The decrease in length is appeared in bond C₄-N₁₁ due to the presence of N₁₁-H₁₃...N₃ hydrogen bonding. The bond length C₂₂-C₂₃ is slightly shortented this is due to the presence of the methoxy groups which get connected to the ring. In benzene ring, the bond length C₂₂-H₂₉ when compared to other C-H bonds. This is due to the influence of steric effect between H₂₉ and H₃₄. The bond angles (HCH) at the methyl group are almost equal 109°. The computed structural parameters confirm the fact that the substitution of methoxy group in benzene ring slightly out of the regular hexagonal structure. These distortions are explained in terms of the change in hybridization affected by the substituent at the carbon site to which it is appended [4]. The torsional angle C₉-C₈-C₂₀-C₂₅ (-140.2°) shows non planar nature.

Table 1

Optimized geometry of 4MT at B3LYP/ 6-311G(D,P) level.

Parameters	Experimental datas	Calculated datas
C ₂ -C ₃	1.359Å	1.347Å
C ₁ -C ₆	1.436 Å	1.436Å
C ₄ -N ₁₁	1.355 Å	1.362Å
H ₃₂ -C ₃₁ -H ₃₃	109.3°	109.2°
H ₃₂ -C ₃₁ -H ₃₄	109.5°	109.3°

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H ₃₃ -C ₃₁ -H ₃₄	109.4°	109.2°
C ₉ -C ₈ -N ₂₀ -C ₂₅	147.5°	-140.2°

3.2 Charge analysis

The calculated atomic charge values from the natural population analysis (NPA) procedures can be done using the B3LYP 6-311G(d,p) method. The presence of O₂₈ atom in methoxy groups, because of more electro negativity, makes the carbons atom C₂₃ more positive. All the H atoms in benzene ring as well as in methyl group are positive as they lose their electrons to the nearby carbon atoms. The oxygen atom O₂₈ are more negative, due to the involvement of C₃₁-H₃₄...O₂₈, C₃₁-H₃₃...O₂₈ and C₃₁-H₃₂...O₂₈ intramolecular hyperconjugation interaction.

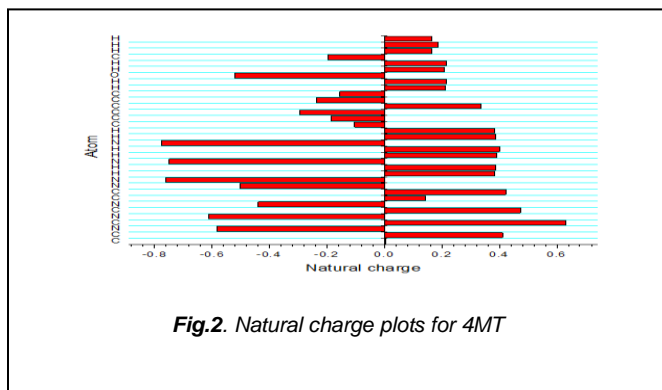


Fig.2. Natural charge plots for 4MT

3.3 Vibrational analysis

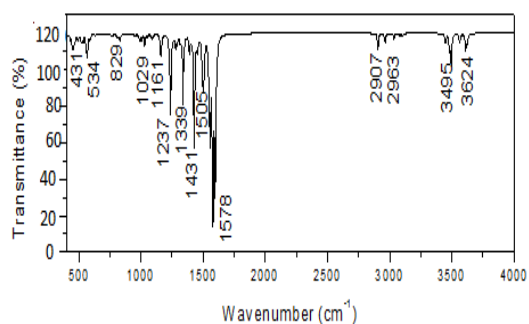


Fig.3. FTIR spectrum of 4MT

NH₂ stretching

For primary amines, the asymmetric NH₂ stretching will give rise to a band in the range 3500–3420 cm⁻¹, while symmetric stretching will appear between 3420 and 3280 cm⁻¹ [5]. The calculation shows the asymmetric NH₂ stretching wavenumber in at 3624. Symmetric NH₂ stretching appears at 3565cm⁻¹. The increase in wavenumber shows strong NH...N hydrogen bonding [5][Fig.3].

C-H stretching

The C-H stretching vibrations normally lies between 3100 and 3000cm⁻¹. In this region the bands are not affected appreciably by the nature of substituents. The C-H symmetric and asymmetric stretching is observed at 3097 and 3083 cm⁻¹[7].

Methoxy group vibration

The expected value of methoxy group in the range 3050-2980 cm⁻¹ is due to asymmetric stretching vibration, the symmetric stretching band generally occurs in the region 3000-2870 cm⁻¹. In the present study, the theoretical asymmetric vibrations of

CH₃ group is observed at 3034 cm⁻¹ and symmetric stretching vibrations of CH₃ group is observed at 2906cm⁻¹. The decrease in wavenumber exhibits the possibility of C₃₁-H₃₄...O₂₈, C₃₁-H₃₃...O₂₈ and C₃₁-H₃₂...O₂₈ intramolecular hyperconjugation interaction as supported by NBO analysis. The CH₃ wagging is observed at 1137 cm⁻¹, CH₃ twisting lies at 1434 cm⁻¹ and the methyl rocking appears at 1136 cm⁻¹ [8].

3.4 NBO analysis

In NBO analysis, the intramolecular hyperconjugative interactions are formed through orbital overlap between π (C–C) and π* (C–C) bond orbitals, which results in an intramolecular charge transfer (ICT) by stabilizing the system. In 4-methoxy triamterene the stabilization energy contributions from the σ(C₅-C₆) → σ*(C₄-N₁₁) and σ(C₂₃-O₂₈) → σ*(C₂₄-C₂₅) interactions are 12.2 and 5.8 kJmol⁻¹ [Table.2]. The intramolecular hyperconjugative interaction (C₃₁-H₃₂...O₂₈) are formed by the orbital overlap between LP(1) O₂₈ → σ* (C₃₁-H₃₂), σ* (C₃₁-H₃₃) and σ* (C₃₁-H₃₄) bond orbitals which results in ICT causing stabilization of the system, resulting stabilization energies are 2.9,12.6 and 3.0 kJmol⁻¹, respectively. The strong intramolecular N-H...N hydrogen bonding interaction of (N₁₄-H₁₆) from N₇ of n(N₇) → σ* (N₁₄-H₁₆) leading to stabilization of 2.5 kJmol⁻¹.

Table 2: NBO analysis for 4MT

Donor NBO (i)	ED (i) (e)	Acceptor NBO (j)	ED (j) (e)	E ⁽²⁾ (kJ/mol)
σ (C ₅ -C ₆)	1.982	σ*(C ₄ -N ₁₁)	0.479	12.2
σ (C ₂₃ -O ₂₈)	1.990	σ*(C ₂₄ -C ₂₅)	0.599	5.8
LP ₍₂₎ N(7)	1.916	σ*(N ₁₄ -H ₁₆)	0.429	2.5
LP ₍₂₎ O(28)	1.962	σ*(C ₃₁ -H ₃₂)	0.372	2.9
		σ*(C ₃₁ -H ₃₃)	0.393	12.6
		σ*(C ₃₁ -H ₃₄)	0.371	3.0

3.5 Molecular electrostatic potential (MESP)

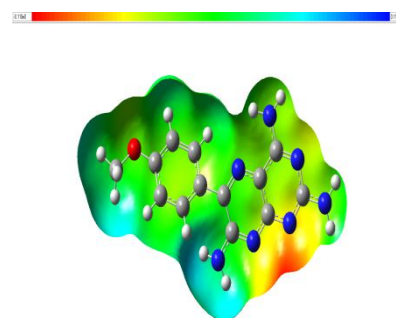


Fig.4 MEP plots for 4MT

In 4MT, the red colour shows negative potential region at N₃ and N₁₀ atoms in the cardiovascular active region pteridine ring. The blue colour shows positive potential region around methoxy group and amino group. The yellowish colour shows charge transfer interaction of the compound. In 4MT, the potential varies from -0.110e0 to 0.110e0. The low value potential of 4MT shows cardiovascular activity of the compound [9].

3.6 HOMO-LUMO analysis

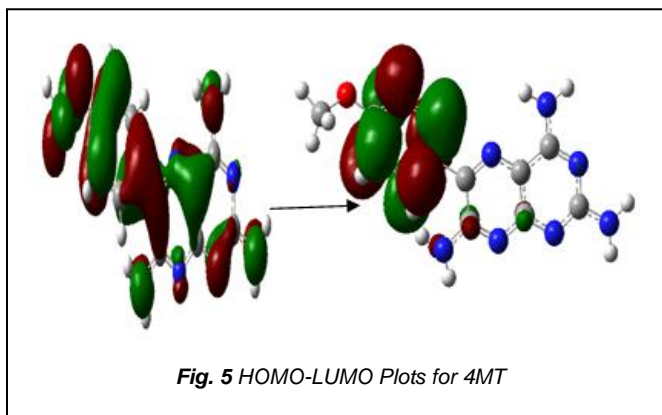


Fig. 5 HOMO-LUMO Plots for 4MT

Spatial distribution of molecular orbitals especially those of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are excellent indicators of electron transport in molecular system[10][Fig.5]. The energy gap of HOMO-LUMO is -0.099 eV. The charge transfer from pteridine ring to phenyl ring.

IV CONCLUSION

The equilibrium geometries of 4MT were determined and analyzed at the DFT level. The calculated values of the vibrational wavenumbers were analyzed. NH stretching shows strong NH...N hydrogen bonding. NBO analysis reveals that the intramolecular hyperconjugative interactions between $n(1) O_{28} \rightarrow \sigma^*(C_{31}-H_{32})$ bond orbitals. The intramolecular hydrogen bonding interactions between $n(N_7) \rightarrow \sigma^*(N_{14}-H_{16})$, this can be verified by N-H stretching wavenumber. The lowering of HOMO-LUMO energy gap shows the charge transfer interactions taking place within the molecule. Strong hydrogen bonding, low HOMO-LUMO energy gap and MESP clearly reveals the cardiovascular activity of the compound.

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