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A Theoretical Study on Charge Transfer and Hyperpolarizability of (S)-2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic Acid

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Abstract. The DFT approach was used to investigate the antihypertensive molecule (S)-2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic acid at the B3LYP/6-311++G(d,p) level of theory. The electron-hole analysis of three excited states has been performed, in which the maximum charge transfer length (2.727Å) has been calculated for the first excited state and the minimum for the third excited state (1.626 Å). On the other hand, the electron-hole overlap is found to be almost negligible for the first excited state and it is found to be maximum for the second excited state. The variation of thermodynamic properties with temperature is studied. The correlation graphs are obtained between the thermodynamic quantities (heat capacity, enthalpy, entropy) and temperature with a very high value of R^2 (>0.99). The values of dipole moment, mean polarizability, anisotropy of polarizability, first hyperpolarizability and second hyperpolarizability are found to be 3.5250 Debye, $12.6980\times$10-24$esu, 19.8162\times10^{-24}$esu, 0.9017×10^{-30}esu and -0.0412×10^{-35}esu, respectively. These values are higher than the value of urea.

Keywords: Charge transfer, Nonlinear optical (NLO) properties, Thermodynamic properties

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1. INTRODUCTION

Methyldopa, also known as (S)-2-amino-3-(3,4-dihydrox yphenyl)-2-methyl-propanoic acid, is a centrally acting antihypertensive medication [1]. Methyldopa consists of an amino acid skeleton with a pyrocatechol group and a methyl group. It contains amine, carboxylic acid and hydroxyl functional groups. It lowers blood pressure by acting through a central mechanism involving the biotransformation of methyl norepinephrine [2]. Methyldopa is the most preferred medicine for the treatment of preeclampsia and gestational hypertension [3]. However, it has some side effects like impairment of renal function, depression, sedation and bad dreams [3, 4]. Since methyldopa has fewer side effects on infants, it is considered a safer medicine to use by a breast feeding mother [5]. The literature review reveals combined density functional theory (DFT) studies on structures in different solvents, molecular electrostatic surface potential (MEP), natural bond orbital (NBO) analysis and vibrational studies on the title molecule [2, 6, 7] Methyldopa exhibits an electropositive region over oxygen atoms and a negative region over hydrogen atoms of hydroxyl groups [6]. The study on frontier molecular orbitals and energy gaps indicates intramolecular charge transfer in the molecule [7]. The energy gap of methyldopa is generally found to be lower than the energy gap of its derivatives [6, 8]. The majority of the previous work on the title molecule was done with small basis sets. On the other hand, higher basis sets with polarized and diffused functions are required for more accurate and reliable results [9]. Hence, the present work has been conducted using B3LYP/6-311++G(d,p). The electron-hole distribution has been analysed, which provides additional verification of the intramolecular charge transfer. The variation of thermodynamic properties with varying temperatures has been

studied and essential thermodynamic relations have been deduced. Furthermore, methyldopa, being an organic molecule, should possess significant nonlinear optical (NLO) properties [10]. Thus, the quantities like dipole moment, mean polarizability, anisotropy of polarizabilty, first hyperpolarizability and second hyperpolarizability has been determined. The optimized structure of the methyldopa at B3LYP/6-311++G(d,p) has been shown in Fig. 1.

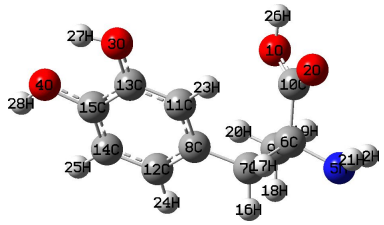

FIGURE 1: Optimized structure of methyldopa at B3LYP/6-311++G(d,p).

2. MATERIALS AND METHODS

2.1 Computational Aspects

The computational study of methyldopa monomer has been performed using density functional theory (DFT) [11] employing the Gaussian 09 program [12]. The molecule's geometry was optimized using the B3LYP/6-311++(d,p) level of theory [13, 14]. Gaussview 05 software [15] was used to visualize and interpret the output data of Gaussian-09. The electron-hole distribution in the molecule has been analysed using Multiwfn 3.8 [16]. The non-linear optical properties and thermal properties have been computed at the B3LYP/6-311++(d,p) level of theory.

For the characterization of a charge transfer (CT) due to excitation in a molecule, the electron-hole overlapping and charge transfer lengths are calculated using the given relations [17].

The electron hole overlapping

$$S_r = \int \sqrt{\rho^{hole}(r)\rho^{ele}(r)} \tag{1}$$

Charge Transfer length

$$D = \sqrt{D_X^2 + D_y^2 + D_z^2} \tag{2}$$

where, $D_x = X_{ele} - X_{hole}$, $D_y = Y_{ele} - Y_{hole}$ and $D_Z = Z_{ele} - Z_{hole}$.

Here, X_{ele}, Y_{ele} and Z_{ele} represents X, Y and Z coordinates of centroid of electron and X_{hole}, Y_{hole} and Z_{hole} represents X, Y and Z coordinates of centroid of hole.

The quantity describing NLO properties like first hyperpolarizabilty (β_0) and second hyperpolarizability (γ_0) alongwith dipole moment (μ_0), mean polarizability ($|\alpha_0|$) and anisotropy of polarizability ($\Delta\alpha$), can be calculated using
the equations [18, 19]:

$$\mu_0 = (\mu_X^2 + \mu_y^2 + \mu_z^2)^{1/2} \tag{3}$$

$$|\alpha_0| = \frac{1}{3}(\mu_{xx} + \mu_{yy} + \mu zz) \tag{4}$$

$$\Delta\alpha = 2^{-1/2}[(\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6\alpha_{xx}^2]^{1/2} \tag{5}$$

$$\beta_0 = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{xxy} + \beta_{yzz})^2 + (\beta_{zzz} + \beta_{xxy} + \beta_{yyz})^2]^{1/2} \tag{6}$$

$$\gamma_0 = \frac{1}{5}[\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2(\gamma_{xxyy} + \gamma_{yyzz} + \gamma_{zzxx})] \tag{7}$$

The thermodynamic properties of a system are determined by the Boltzmann distribution and the partition function q(V, T) [20].The contributions to entropy, enthalpy, and heat capacity result from translational, rotational, electronic and vibrational motion. The partition functions used for different motions can be stated as below [21]. Translational partition function,

$$q_t = \left(\frac{2\pi m k_B T}{h^2}\right)^{3/2} V \tag{8}$$

Rotational partition function,

$$q_r = \frac{1}{\sigma_r}\left(\frac{T}{\theta_r}\right) \tag{9}$$

Electronic partition function

$$q_e = \omega_0^{-\varepsilon_0/k_B T} + \omega_1^{-\varepsilon_1/k_B T} + \omega_2^{-\varepsilon_2/k_B T} + \ldots \tag{10}$$

Vibrational partition function

$$q_k = \Pi_k \frac{1}{1 - e^{\Theta_{v,k/T}}} \tag{11}$$

where, k_B represents Boltzmann constant, ω represents degeneracy of the energy level, ε_n is the energy of the n-th level and $\Theta = h^2/8^2 I k_B$.

3. RESULT AND DISCUSSIONS

3.1 Electron-Hole Distribution

The charge transfer (CT) due to excitation in the molecule, is scrutinized by analyzing the CT due to excitation using Multiwfn. In the only case, in which the excitation is directly represented by the HOMO-LUMO transition, the hole and electron are equivalent to HOMO and LUMO, respectively [17]. The plots of electron-hole (green-blue) distribution for different excited states and their respective electron-hole overlap (S) have been shown in Fig. 2. The values for electron-hole overlap integral (S), charge transfer length (D) and Δr for all three excitation modes are presented in Table 1. The charge transfer-length (D) represents the distance between the centroid of electrons and the centroid of holes, and Δr represents the quantitative electron excitation mode [22].The overlap integral for the first, second and third excited states is found to be 0.2706, 0.5825, 0.4500 and their charge transfer length is found to be 2.727 Å, 1.831 Å and 1.626 Å, respectively. The electron-hole analysis showed that, first and third excited states have large value of Δr index (>2Å) hence, the CT is probable in these two states. However, the overlap integral (S) of electron-hole is higher for the third excited state than the first excited state, the charge transfer is less probable in the third excited state. Besides this, the charge transfer length (D) is also high in the first excited state, which means the charge transfer is more probable in the first excited state. Therefore, on the basis of overlap integral and charge transfer length, it is concluded that the first excited state corresponds to strong intra molecular charge transfer due to excitation.

TABLE I: Overlap integral of electron-hole, charge transfer length (D), Δr and excitation energy of first, second and third excited states of methyldopa.

Excitation states	Overlap integral (S)	Charge transfer length (D)(Å)	Δ r (Å)	Excitation energy(E)eV
First	0.2706	2.727	2.7642	4.612
Second	0.5825	1.831	1.8493	4.705
Third	0.4500	1.626	2.9874	4.995

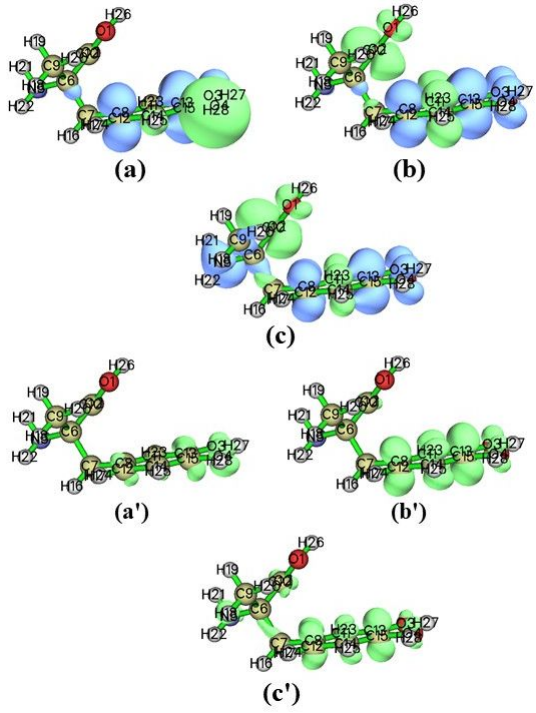

FIGURE 2: Electron-hole excitation of (a) first, (b) second (c) third excited states and overlap for (a') first, (b') second, (c') third excited states.

3.2 NLO Properties

The molecules that have π- conjugated interaction between donor-acceptor group can exhibit significant nonlinear optical (NLO) properties [23, 24]. NLO properties are applicable for optical signal processing, telecommunication, optical computing, etc [24]. The estimated value of the quantity The dipole moment (μ_0), mean polarizability ($|\alpha_0|$), anisotropy of polarizability ($\Delta\alpha$),first hyperpolarizability (β_0) and second hyperpoarizabilty(γ_0) describing the NLO phenomena of methyldopa has been delineated in Table 2. The estimated value of first hyperpolarizability 0.9017×10^{-30} esu is slightly greater than the value of reference molecule urea 0.3728×10^{-30} esu). But, the value of first hyperpolarizability calculated by Prabakaran and Muthu using the 6-31G(d,p) basis set was 3.782×10^{-30} esu [7]. This difference in the value may be due to use of different basis sets for the calculation. The value of μ_0, $|\alpha_0|$, $\Delta\alpha$, β_0 and γ_0 is found to have the negative value, -0.0412×10^{-35} esu. The negative value of γ_0 is one of the important factors that can be utilized in constructing NLO devices with controllable NLO properties [24, 25]. Hence, the molecule could be a potential candidate for studying NLO properties in the future.

3.3 Thermodynamic Properties

Thermodynamic properties are used to assess the drug molecule's stability and chemical reactivity [26, 27]. Boltzmann distribution and partition function are used to evaluate the thermodynamic parameters. In the literature, the variation of thermodynamic quantities of methyldopa have been studied at each interval of 100K [7]. How-

TABLE II: The estimated dipole momentμ_o, mean polarizability $|\alpha_o|$, anisotropy of polarizability $\Delta\alpha_o$, first hyperpolarizability β_o and second hyperpolarizability γ_o of methyldopa.

Dipole moment Debye	Polarizability ($\times10^{-24}$esu)	First hyperpolarizability ($\times10^{-30}$esu)	Second hyperpolarizabilty ($\times10^{-35}$esu)
μ_x= 1.6148	α_{xx} = -76.8156	β_{xxx} = 54.7143	γ_{xxxx}= -2741.6992
μ_y= -1.8569	α_{xy} = -6.6647	β_{xxy} = -12.4652	γ_{yyyy}= -911.8254
μ_z= 2.5238	α_{yy} = -89.8383	β_{xyy} = 24.8604	γ_{zzzz}= -432.5846
μ_o= 3.5250	α_{xz} = 0.1714	β_{yyy} = 4.2333	γ_{xxyy}= -676.5233
μ_o(Urea)= 1.3732	α_{yz} = 1.3593	β_{xxz} = 37.0746	γ_{xxzz}= -605.0103
	α_{zz} = -90.3878	β_{xyz} = -6.741	γ_{yyzz}= -611.3782
	$\|\alpha_o\|$ = 12.6980	β_{yyz} = 12.7285	γ_o= -211.7205
	$\Delta\alpha_o$ = 19.8162	β_{xzz} = 12.0654	
	$\Delta\alpha_o$(Urea) = 9.7710	β_{yzz} = 6.9303	
		β_{yzz} = 10.2229	
		β_o = 0.4440	

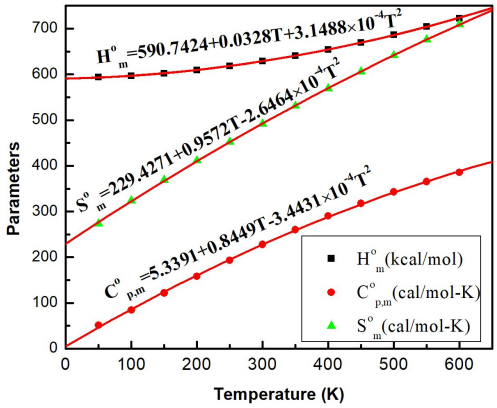

FIGURE 3: Correlation of enthalpy, heat capacity, entropy and temperature for methyldopa.

ever, to study the behavior of thermodynamic quantities more precisely, we have studied these properties even at a smaller interval of 50K.The variation of thermodynamic properties has been observed in the range of 50 K to 600 K. The estimated values of thermodynamic parameters are tabulated in Table 3. The graph representing variation of heat capacity, enthalpy and entropy with respect to temperature has been depicted in Fig. 3. As stated by an earlier study, these three quantities are positively correlated with temperature. The values of R^2 were found to be 1, 0.9995 and 0.9999 for enthalpy, heat capacity and entropy. The positive value of R^2 states that all the thermodynamic properties increase with the increasing temperature due to the reason that vibrational energy of the molecules increases with the temperature [28]. The given equations represent the correlation of enthalpy (H_m^o), heat capacity $(C_{p,m}^o)$, entropy (S_m^o) and temperature.

$$H_m^o = 590.7424 + 0.0328T + 3.1488 \times 10^{-4}T^2 \quad (12)$$

$$C_{p,m}^o = 1.2755 + 0.2019T - 8.2253 \times 10^{-4}T^2 \quad (13)$$

$$S_m^o = 229.4271 + 0.9572T - 2.6464 \times 10^{-4}T^2 \quad (14)$$

Further, utilizing the above equations, the Gibbs free energy can be determined, which further helps to judge the spontaneity of the reactions. In addition, these thermodynamic relations are helpful for studying the thermodynamic energies and estimating the direction of the reaction according to the second law of thermodynamics[18].

4. CONCLUSION

The intramolecular charge transfer, thermal properties and non-linear optical properties of methyldopa have been determined using DFT method at the B3LYP/6-311++G(d,p) level of approximation. In the electron-hole analysis of three excited states, the first excited state, was found to have the highest charge transfer length (2.727Å) and a negligible electron-hole overlap (S=0.2706). Hence, the intramolecular charge transfer due to excitation corresponds to the first excited states. The thermodynamic relations of heat capacity, enthalpy, and entropy have been obtained, which is useful in determining the spontaneity and direction of the reaction. A very high positive correlation is found be-

TABLE III: Thermodynamic parameters of methyldopa at various temperature.

Temperature (K)	Enthalpy (Kcal/Mol)	Heat capacity Cal/Mol-Kelvin)	Entropy (Cal/Mol-Kelvin)	Zero-point energy (Joules/Mol)	Total energy (eV)
50	141.863	12.223	65.349	591651.1	-20260.7940
100	142.661	20.173	77.474	591651.1	-20260.7940
150	143.894	29.130	88.159	591651.1	-20260.7940
200	145.569	37.794	98.304	591651.1	-20260.7940
250	147.670	46.210	108.089	591651.1	-20260.7940
300	150.186	54.369	117.603	591651.1	-20260.7940
350	153.100	62.136	126.879	591651.1	-20260.7940
400	156.390	69.369	135.920	591651.1	-20260.7940
450	160.027	75.984	144.713	591651.1	-20260.7940
500	163.978	81.964	153.243	591651.1	-20260.7940
550	168.213	87.339	161.501	591651.1	-20260.7940
600	172.703	92.167	169.484	591651.1	-20260.7940

tween the thermodynamic properties and the temperature. This indicates that the thermodynamic properties increase with the increase in temperature due to the increase of molecular vibrations. The title molecule has a higher dipole moment (3.5250 Debye), mean polarizabilty (12.6980×10^{-24}esu), and the first hyperpolarizability (0.9017×10^{-30}esu) than urea. In addition, it has a negative value of second hyperpolarizability (-0.0412×10^{-35}esu), which makes it more suitable for constructing NLO devices. Hence, methyldopa exhibits significant NLO properties and could be a good candidate for NLO devices.

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