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RESEARCH PAPER

CHEMICAL REACTIVITY, DIPOLE MOMENT AND FIRST HYPERPOLARIZABILITY OF ARISTOLOCHIC ACID I

Bhawani Datt Joshi[1,2]
[1]*Department of Physics, Siddhanath Sc. Campus, Tribhuvan University, Mahendranagar, Nepal*
[2]*Departamento de Física, Universidade Federal do Ceará, Fortaleza, CE, Brazil*
Corresponding email: pbdjoshi@gmail.com

ABSTRACT

Aristolochic acids (AAs) have been used in the treatment of oedema in Chinese herb medicine since long ago. In this paper, molecular electrostatic potential, chemical reactivity and non linear optical properties of aristolochic acid I (AA I) have been analyzed using density functional theory employing 6-311++G(d,p) basis set. The chemical reactivity of the molecule has been explained with the help of chemical reactivity descriptors, molar refractivity and the molecular electrostatic potential surface (ESP). The calculated dipole moment and first order hyperpolarizability show that the molecule possesses non-linear optical property.

Keywords: AA I, DFT, Chemical reactivity, MEP, Hyperpolarizability

INTRODUCTION

Plant based natural products cover a major sector of the medicinal field. As such, focus on plant research has increased all over the world. Herbs containing aristolochic acids (AAs), a family of nitrophenanthrene carboxylic acids (Aristolochiaceae), have an increasing global medical attention (Cronin *et al.* 2002). Mixture of aristolochic acid I (AA I) and aristolochic acid II (AA II) is a principal chemical constituent of *Aristolochia* species (Pailer *et al*. 1995). Herbal drugs derived from *Aristolochia* spp. have been known before middle age in the treatment of snake bites (Rosenmund & Reichstein 1943). Their roots have different biological functions such as; treatment of stomach-ache, hypertension relief, leukocyte enhancement, rheumatism relief, edema therapy, toothache, gout, eczema etc (Kupchan & Doscoth 1962; Mizuno *et al.* 1991; Tang and Eisenbrand 1992; Bensky *et al.* 1993). Thirugnanasampandan *et al*. 2008 reported the antioxidant properties of different *Aristolochia* spp. However, AAs are found to have nephrotoxic and carcinogenic properties, and may cause renal failure in human (Zheng *et al*. 2000; Li *et al*. 2001; Balachandran *et al*. 2005; Cosyns 2003; Attaluri *et al*. 2010; Das 2016).

Alkaloids have very complex structure and occupy unique place in the field of natural products. Their structural elucidation, synthesis and the determination of constituents is a big challenging problem. Vibrational spectroscopy is a valuable method for studying electronic structures and dynamical behavior of the alkaloids (Mishra *et al*. 2014). Raman and IR spectroscopic methods are the traditional methods of vibrational analysis, and particularly useful for non-destructive characterization of substances (Chamers 2002). In the recent years, there has been increasing interest in the application of *ab initio* calculations to alkaloids as the calculations provide additional interpretation of the vibrational spectroscopic data as demonstrated in our earlier studies (Joshi *et al*. 2014; Mishra *et al*. 2014). In this communication, the chemical reactivity and non linear optical properties have been calculated as an aid to our previous publication (Joshi *et al.* 2013). The calculations have been made by the density functional theory (DFT) (Hohenberg & Kohn 1964) using Gaussian 09 program (Frisch *et al.* 2009) employing 6-311++G (d,p) basis set. The chemical structure of AA I is shown in the Fig. 1.

MATERIALS AND METHODS

Computational method

Using the standard parameters, geometry optimization has been made as the first task by DFT (Hohenberg & Kohn 1964) method, without any constraints of molecular symmetry. The optimized parameters have been used for all the other calculations. The calculations were carried in the personal system using Gaussian 09 program (Frisch *et al.* 2009) in the frame work of closed-shell Becke's three parameters (Lee-Yang-Parr hybrid exchange correlation) functional (B3LYP) (Becke 1993, Lee *et al*. 1988, Perdew & Wang 1992) employing 6-311++G(d,p) basis set. The optimized ground state structure was confirmed to be a minimum energy and shown in the Fig. 2. The chemical reactivity descriptors, which are helpful to explain the stability and reactivity of the molecule has been calculated on the basis of Koopmans's theorem (Parr & Yang 1998) using B3LYP/6-311++G(d,p). Visualization and confirmation of the calculated data were done by using the program CHEMCRAFT (Zhurko & Zhurko 2005).

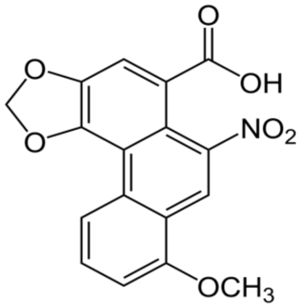

Fig.1. Chemical structure of AA I.

RESULTS AND DISCUSSION

Chemical reactivity

The chemical reactivity of a molecule can be explained in three ways: (i) by MEP (molecular electrostatic potential surface) mapping (ii) global and local reactivity descriptors, and (iii) the molar refractivity (MR).

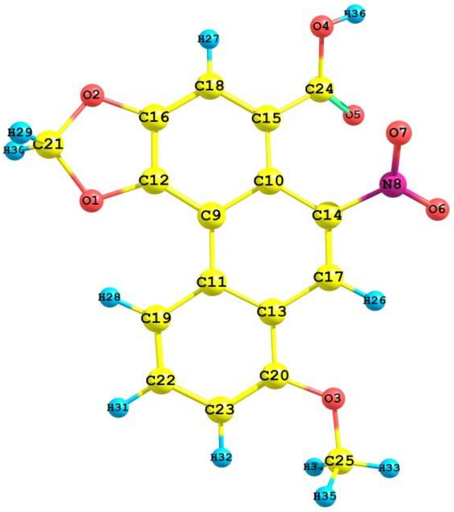

Fig.2. Optimized structure of AA I.

Molecular electrostatic potential surface (MEP): The MEP is a visualization method to understand the relative polarity, reactivity, size and the structure-activity of a molecule including biomolecules and drugs (Chidangil *et al*. 1998). In such surfaces, the negative electrostatic potential corresponds to attraction of the protons by the concentrated electron density in the molecule (from lone pair, pi-bonds etc.). Similarly, positive electrostatic potential corresponds to the repulsion of the proton by the atomic nuclei in the region where low electron density exists and the nuclear charge is incompletely shielded. The MEP mapping together with electron density (ED) and electrostatic potential surface (ESP) of AA I were given in our previous publication (Joshi *et al*. 2013). In a surface, the potential increases in the color order red < orange < yellow < green < blue. Fig. 3 shows the distribution of Mulliken charges and natural charges in the molecule whereas a comparison of Mulliken charges and natural charges obtained by different basis sets is listed in the Table 1.

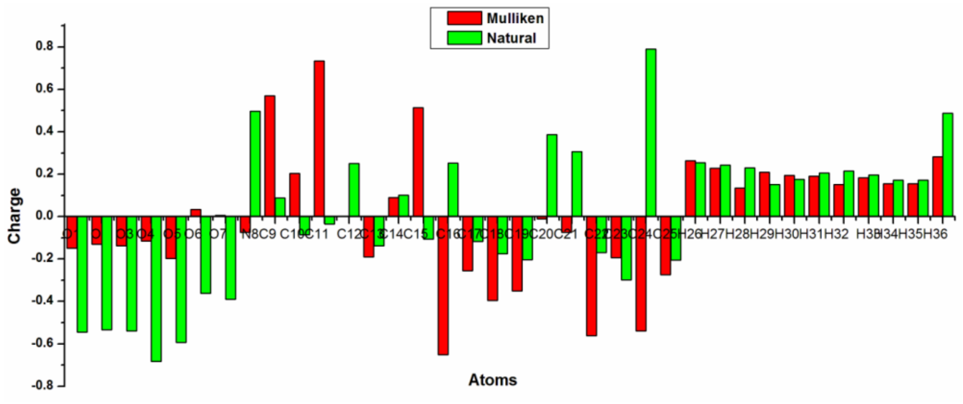

Fig. 3. Plot of Mulliken charges and Natural charges obtained by B3LYP/6-311++G(d,p).

Table 1. Comparison between Mulliken charges and Natural charges obtained by B3LYP.

Atoms	Mulliken charges (e.s.u.)			Natural charges (e.s.u.)		
	6-31G	6-311G(d,p)	6-311++G(d,p)	6-31G	6-311G(d,p)	6-311++G(d,p)
O1	-0.553889	-0.364277	-0.148084	-0.52820	-0.54145	-0.54378
O2	-0.538214	-0.340688	-0.131092	-0.51548	-0.52447	-0.53301
O3	-0.519301	-0.353728	-0.137756	-0.51470	-0.52630	-0.53966
O4	-0.488296	-0.322872	-0.115072	-0.69602	-0.68833	-0.68305
O5	-0.475640	-0.334223	-0.197542	-0.56936	-0.59525	-0.59412
O6	-0.373744	-0.247574	0.033987	-0.35045	-0.36809	-0.36154
O7	-0.398553	-0.276055	0.005448	-0.37538	-0.38906	-0.39037
N8	0.369272	0.159421	-0.074267	0.48666	0.52178	0.49671
C9	0.014524	-0.058968	0.570488	-0.05574	-0.06229	0.08893
C10	0.103679	0.111570	0.203150	-0.02709	-0.02893	-0.08512
C11	0.093333	0.020729	0.733601	-0.01421	-0.00888	-0.03411
C12	0.237359	0.077054	-0.000386	0.27848	0.29838	0.25043
C13	0.012557	-0.150005	-0.190015	-0.08802	-0.09364	-0.13762
C14	0.167990	0.070922	0.090220	0.09265	0.10279	0.10065
C15	0.017303	-0.075092	0.513649	-0.12112	-0.12469	-0.10558
C16	0.330580	0.189616	-0.651163	0.24361	0.26639	0.25292
C17	-0.096866	0.093222	-0.254518	-0.17170	-0.14288	-0.11780
C18	-0.133807	-0.002244	-0.395913	-0.22496	-0.20032	-0.17532
C19	-0.130233	-0.029274	-0.350947	-0.24397	-0.21510	-0.20279
C20	0.318066	0.199718	-0.010963	0.34423	0.36943	0.38610
C21	0.289326	0.174379	-0.074135	0.17547	0.31780	0.30682
C22	-0.103199	-0.092125	-0.561252	-0.20649	-0.15646	-0.16978
C23	-0.132462	-0.101236	-0.193857	-0.32317	-0.29494	-0.29866
C24	0.528521	0.331738	-0.539927	0.77191	0.82079	0.79036
C25	-0.083123	-0.132033	-0.274446	-0.35254	-0.19504	-0.20427
H26	0.151888	0.133533	0.264118	0.29317	0.25067	0.25420
H27	0.134594	0.121709	0.227601	0.28475	0.24062	0.24232

H28	0.116816	0.111899	0.134226	0.27025	0.22801	0.23000
H29	0.123653	0.122977	0.210389	0.21366	0.14663	0.15173
H30	0.131733	0.131284	0.195307	0.23969	0.16912	0.17525
H31	0.093661	0.096751	0.191062	0.24900	0.20347	0.20669
H32	0.092427	0.106959	0.152074	0.24956	0.21207	0.21460
H33	0.135005	0.137823	0.184332	0.24893	0.19052	0.19686
H34	0.118847	0.116404	0.154732	0.21768	0.16797	0.17305
H35	0.118125	0.115942	0.155489	0.21681	0.16740	0.17251
H36	0.328067	0.256744	0.281461	0.50206	0.48228	0.48706

Global reactivity descriptors: The global reactivity descriptors; chemical potential (μ), hardness (η), softness (s), electronegativity (χ) and electrophilicity index (ω) to explore reactivity, has been calculated using DFT efficiently (Geerling *et al*. 2003, Chattaraj & Giri 2007). The chemical potential, measure of the tendency of electron donation from the equilibrium position is given by:

$$\mu = \frac{1}{2}(E_{LUMO} + E_{HOMO}) = -\chi \qquad (1)$$

The global hardness (η), that indicates the resistance to transfer the charge and the softness (s), that measures the charge transfer properties are defined by:

$$\eta = \frac{1}{2}(E_{LUMO} - E_{HOMO}) \qquad (2)$$

$$s = 1/2\eta \qquad (3)$$

E_{HOMO} and E_{HOMO} in equations (1) and (2) are the energies of frontier molecular orbitals; the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), respectively.

Similarly, the electrophilicity index (ω) which represents the property of molecule to accept the electron from the surroundings can be calculated as:

$$\omega = \frac{1}{2}\left(\frac{\mu^2}{\eta}\right) \qquad (4)$$

Further, a new reactivity index (ΔN), which indicates the stabilization in energy when the system acquires additional charge from the environment up to the saturation, was calculated as:

$$\Delta N = -\frac{\mu}{2\eta} \qquad (5)$$

The calculated values of these indices are listed in the Table 2. The calculated high value of electrophilicity index (ω) shows that the molecule behaves as a strong electrophile.

Table 2. Calculated E_{HOMO}, E_{LUMO}, energy band gap (ΔE), electronegativity (χ), chemical potential (μ), global hardness (η), global softness (S), global electrophilicity index (ω) and additional electronic charge (ΔN_{max}) (in eV) for AA I, using B3LYP/6-311++G(d,p).

E_{HOMO}	E_{LUMO}	ΔE	μ	η	S	ω	ΔN_{max}
-6.216580	-2.690827	-3.525754	- 4.453703	1.762877	0.283627	5.625880	2.526383

Local reactivity descriptors: The global chemical reactivity descriptors forecast the reactivity of the molecular system but can't elucidate the site. Therefore, the local reactivity descriptors, which reveal the reactivity sites, have been calculated. Applying Hirshfeld population method, Fukui functions (f_k^+, f_k^-, f_k^o) (Parr *et al.* 1999, Geerlings *et al.* 2003) were calculated using B3LYP/6-311++G(d,p) level of theory. The sites with higher values of Fukui function are more reactive centers in chemical species. The Fukui function is a local reactivity descriptor that indicates the propensity of the electronic density to deform a given atomic site upon accepting or donating electrons (Mendoza-Huizar & Rios-Reyes 2011; Komorowski *et al.* 2011). Further, with the help of these functions, local softness (s_k^+, s_k^-, s_k^o) and local electrophilicity indices (ω_k^+, ω_k^-, ω_k^o) have been calculated using the equations (6 - 10) and listed in the Table 3.

f_k^+ = q_k(N+1) –q_k(N) for nucleophilic attack. (6)

f_k^- = q_k(N) – q_k(N-1) for electrophilic attack (7)

f_k^o = q_k(N+1) – q_k(N-1) for radical attack (8)

where q is the gross charge of atom k.

$s_k^+ = \mathrm{S}f_k^+$, $s_k^- = \mathrm{S}f_k^-$ and $s_k^o = \mathrm{S}f_k^o$ (9)

$\omega_k^+ = \omega f_k^+$, $\omega_k^- = \omega f_k^-$ and $\omega_k^0 = \omega f_k^o$ (10)

Table 3. Hirshfeld atomic charges (in e.s.u.), Fukui functions (f_k^+, f_k^-, f_k^o); Local softness (s_k^+, s_k^-, s_k^o); and local electrophilicity indices ($\omega_k^+, \omega_k^-, \omega_k^o$); in eV for atomic sites of AA I, using Hirshfeld population analysis at B3LYP/6-311++G(d,p) level.

Atom no.	Hirshfeld atomic charges			Fukui functions			Local softness			Local electrophilicity indices	
	q_N	q_{N+1}	q_{N-1}	f_k^+	f_k^-	f_k^o	s_k^+	s_k^-	s_k^o	ω_k^+	ω_k^-
O1	-0.1192	-0.0838	-0.1462	0.0354	0.0270	0.0624	0.0101	0.0076	0.0177	0.1993	0.1517
O2	-0.1409	-0.0830	-0.1722	0.0579	0.0313	0.0892	0.0164	0.0089	0.0253	0.3257	0.1760
O3	-0.1175	-0.0823	-0.1358	0.0352	0.0183	0.0535	0.0100	0.0052	0.0152	0.1982	0.1029
O4	0.0131	0.0502	-0.0242	0.0371	0.0373	0.0744	0.0105	0.0106	0.0211	0.2086	0.2100
O5	-0.2850	-0.2550	-0.3131	0.0300	0.0281	0.0581	0.0085	0.0080	0.0165	0.1687	0.1583
O6	-0.1989	-0.1580	-0.2810	0.0409	0.0821	0.1230	0.0116	0.0233	0.0349	0.2302	0.4620
O7	-0.2130	-0.1809	-0.2920	0.0322	0.0790	0.1111	0.0091	0.0224	0.0315	0.1810	0.4443
N8	0.2617	0.2675	0.2225	0.0059	0.0391	0.0450	0.0017	0.0111	0.0128	0.0331	0.2200
C9	-0.0015	0.0088	-0.0135	0.0103	0.0119	0.0223	0.0029	0.0034	0.0063	0.0581	0.0672
C10	0.0006	0.0253	-0.0016	0.0246	0.0023	0.0269	0.0070	0.0006	0.0076	0.1386	0.0127
C11	0.0070	0.0180	-0.0299	0.0110	0.0369	0.0479	0.0031	0.0105	0.0136	0.0617	0.2077
C12	0.0654	0.0967	0.0341	0.0313	0.0313	0.0626	0.0089	0.0089	0.0178	0.1759	0.1762
C13	-0.0124	0.0139	-0.0345	0.0263	0.0221	0.0484	0.0075	0.0063	0.0137	0.1480	0.1242
C14	0.0246	0.0647	-0.0152	0.0401	0.0398	0.0799	0.0114	0.0113	0.0227	0.2258	0.2239
C15	-0.0183	0.0286	-0.0485	0.0469	0.0301	0.0771	0.0133	0.0085	0.0219	0.2641	0.1695
C16	0.0558	0.1078	0.0269	0.0521	0.0288	0.0809	0.0148	0.0082	0.0229	0.2928	0.1622

C17	0.0208	0.0842	-0.0710	0.0633	0.0919	0.1552	0.0180	0.0261	0.0440	0.3564	0.5168
C18	0.0206	0.0718	-0.0466	0.0512	0.0672	0.1184	0.0145	0.0191	0.0336	0.2881	0.3780
C19	-0.0253	0.0281	-0.0579	0.0534	0.0326	0.0860	0.0152	0.0092	0.0244	0.3007	0.1832
C20	0.0860	0.1231	0.0621	0.0370	0.0239	0.0610	0.0105	0.0068	0.0173	0.2083	0.1347
C21	0.2332	0.3091	0.1915	0.0759	0.0417	0.1176	0.0215	0.0118	0.0333	0.4269	0.2345
C22	0.0145	0.0925	-0.0768	0.0780	0.0912	0.1692	0.0221	0.0259	0.0480	0.4390	0.5132
C23	-0.0245	0.0290	-0.0828	0.0535	0.0582	0.1118	0.0152	0.0165	0.0317	0.3011	0.3276
C24	0.2070	0.2168	0.2009	0.0098	0.0060	0.0158	0.0028	0.0017	0.0045	0.0551	0.0340
C25	0.1466	0.2071	0.1044	0.0605	0.0422	0.1027	0.0172	0.0120	0.0291	0.3402	0.2375

From the Table, the oxygen atoms O2 (at five member ring), O4 (at carboxyl group) and the carbon atoms C17, C21, C22 (in rings) and C25 (at methoxy group) have suitable high potential for nucleophilic attack and where s_k^+ and ω_k^+ values are maximum. Similarly, oxygen atoms O6 and O7 of nitro group and, carbon atom C17 in the ring are prone to the electrophilic attack where s_k^- and ω_k^- values are maximum. Therefore, it can be noticed that the nitro groups are more reactive in comparison to the methoxy and carboxyl group.

Molar refractivity: MR is important property used in quantitative structure property relationship. It reflects arrangements of the electron shells of ions in molecules and yields information about their electronic polarization. It relates the refractive index, molecular weight and the density, and is accomplished by a change in properties of ions under the influence of electric fields of the neighbouring ions. The molar refractivity (R; cm^3mol^{-1}) is given by Lorentz-Lorentz (Padrón *et al*. 2002, Verma *et al*. 2005) expression:

$$R = \pi \left[\frac{n^2-1}{n^2+2}\right]\left[\frac{M}{\rho}\right] = \frac{4}{3}\pi N_A \alpha \qquad (11)$$

where n is refractive index, M is the molar mass, ρ is the density, α electronic polarizability and N_A the Avogadro's constant.

Thus the molar refractivity measures the polarizability of the ions i.e., the displacement of the electronic shell/s with respect to its nucleus. The above equation holds for both the liquid and solid state of the system. The value of R depends upon the wavelength of the light used to measure the refractive index. For radiation of infinite wavelength it represents the real volume of the molecular system. The molar refractivity, which is responsible for the binding property of the title molecule with different amino acids, was calculated to be 49.8163 units.

NON LINEAR OPTICAL (NLO) PROPERTIES

NLO deals with the interaction of materials in the presence of applied electromagnetic field, which changes the wave number, phase and the other physical properties (Shen 1984). In presence of an applied electric field, the energy of a system is a function of the field. In recent years, the NLO phenomena have attracted much attention because of their potential applications in optical communication, optical sensing, data storage, computing etc (Zhang *et al*. 2002; Zhang *et al*. 2007; Kolev *et al*. 2008). The first hyperpolarizability (β_o) of the molecular system, and the related properties polarizability ($|\alpha_o|$) and anisotropy of polarizability ($\Delta\alpha$) have been calculated using 6-311++G(d,p) basis set. First order hyperpolarizability is a third rank tensor that can be described by 3x3x3 matrix. The 27 components of 3d-matrix can be reduced to 10 components by Kleinman symmetry (Kleinman 1962). The hyperpolarizability (β) can be defined as the coefficients of Taylor series expansion of the energy expansion in the external electric field.

During the weak and homogeneous electric field the expression becomes:

$$E = E_o - \sum_i \mu_i F^i - \frac{1}{2}\sum_{ij} \alpha_{ij} F^i F^j - 16ijk\beta ijkFiFjFk\ldots\ldots \quad (12)$$

where, E_o is the energy of unperturbed molecule, F^i is the field at the origin μ_i, α_{ij} and β_{ijk} are the components of dipole moment, polarizability and first hyperpolarizability, respectively. The components of hyperpolarizability tensor are listed in the Table 4.

The total static dipole moment (μ_o), mean polarizability ($\Delta\alpha$), anisotropy of polarizability ($|\alpha_o|$) and first hyperpolarizability (β_o) can be expressed as [Karna *et al*. 1991]:

$$\mu_o = \left(\mu_x^2 + \mu_y^2 + \mu_z^2\right)^{1/2} \quad (13)$$

$$|\alpha_o| = \frac{1}{3}\left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right) \quad (14)$$

$$\Delta\alpha = \frac{1}{2}\left[\left(\alpha_{xx} - \alpha_{yy}\right)^2 + \left(\alpha_{yy} - \alpha_{zz}\right)^2 + \alpha zz{-}\alpha xx2{+}6\mu xx212 \quad (15)$$

$$\beta_o = \left[\left(\beta_{xxx} + \beta_{xyy} + \beta_{xzz}\right)^2 + \left(\beta_{yyy} + \beta_{xxy} + \beta_{yzz}\right)^2 + \left(\beta_{zzz} + \beta_{xxz} + \beta_{yyz}\right)^2\right]^{1/2} \quad (16)$$

Table 4. Dipolemoment (μ; Debye), polarizability (α x10^{-24} esu) and first hyperpolarizability (β_0 x10^{-31} e.s.u.) calculated by using 6-311++ G(d,p) method.

Dipole moment			Polarizability			Hyperpolarizability		
	DFT	HF		DFT	HF		DFT	HF
μ_x	-3.1124	-3.0788	α_{xx}	-107.6370	-106.5696	β_{xxx}	-104.1119	-96.8022
μ_y	6.5909	6.4846	α_{yy}	-143.6665	-144.8090	β_{yyy}	121.0077	118.4245
μ_z	0.0154	0.0949	α_{zz}	-148.4044	-149.9088	β_{zzz}	3.8081	4.2826
μ_0	7.28884	7.17900	α_{xy}	4.0978	3.0428	β_{xyy}	28.6413	25.6489
			α_{xz}	-1.2982	-1.1461	β_{xxy}	-45.5336	-48.1363
			α_{yz}	2.7365	2.5102	β_{xxz}	-19.9328	-19.5949
			$\lvert\alpha_0\rvert$	19.7589	19.8236	β_{xzz}	6.0327	6.1301
			$\Delta\alpha$	21.2375	19.8152	β_{yzz}	4.1590	4.3517
						β_{yyz}	4.8116	6.6062
						β_{xyz}	13.2848	13.3827
						β_0	10.7805	8.6044

As x, y, z components of $|\alpha_o|$ and β_o obtained from Gaussian 09 output are in atomic unit (a.u.), the values were converted into electrostatic units (e.s.u.) using conversion factors (for $|\alpha_o|$: 1 a.u. = 0.1482 x10^{-24} esu; for β_o: 1 a.u. = 0.0086393 x10^{-30} e.s.u.) and listed in the Table 4. Urea is one of the molecules which have the good non linear optical property and it is used as a critical parameter for comparative studies (μ = 1.3732 Debye and β = 3.7289x10^{-31} cm^5/e.s.u.). For the title compound the first order hyperpolarizability by B3LYP/6-31++G(d,p) method is 10.7805 x10^{-31} cm^5/e.s.u. which is about three times more than that of urea, while by HF/6-31++G(d,p) the first order hyperpolarizability is 8.6044x10^{-31} cm^5/e.s.u., which is about two times more than that of urea. Hence, the compound under study has a good non linear property.

CONCLUSION

The chemical reactivity, molecular electrostatic potential surface (MEP) and the non linear optical properties of molecule AA I have been calculated using DFT employing 6-311++G(d,p) basis set. The calculated local electrophilicity indices show that the oxygen atoms O2, O4 and the carbon atoms C21, C22 and C25 are prone to the nucleophilic attack. But the oxygen atoms O6 and O7 at the nitro group and the carbon atom C17 suitable for the electrophilic attack. The carboxyl group is more reactive than the methoxy group and less reactive than the nitro group. The value of dipole moment is 7.5888 D and the first order hyperbolarizability obtained by DFT/HF about 3/2 times higher than of urea show the strong non linear optical property of the molecule.

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