



COMPUTATIONAL DFT STUDY OF 3-FLURO-4-MORPHOLINOANILINE: STRUCTURAL PARAMETERS, NLO PROPERTIES, THERMODYNAMIC FUNCTIONS, NBO ANALYSIS AND FUKUI FUNCTIONS

B. S. Yadav¹, Ajeet Singh¹, Jayant Teotia^{1*}, Ritu Saran¹, Deepa Teotia², Vinita³, Ravish Kumar Uppadhayay¹, Vikas Kumar¹

Abstract

The present work deals with the theoretical study of 3-fluro-4-morpholinoaniline (FMA). The molecule FMA is analyzed for drug likeliness with Swiss ADME program. The theoretical calculations are computed with Gaussian 09 program which employs Density Functional Theory (DFT). The method used in DFT calculations is B3LYP with 6-311++G(d,p) and cc-pVDZ basis sets. The optimized structure of the molecule is obtained and the bond length and bond angle of the FMA molecule are calculated by DFT. The thermodynamic functions (Specific heat, Entropy and Enthalpy) are calculated for temperatures ranging from 100 to 1000 Kelvin. The Natural Bond Orbital (NBO) analysis is done to check the hybridization and covalent effects. The first and second-order hyperpolarizability which are non-linear optical (NLO) properties of the molecule are calculated by DFT at both basis sets. The chemical reactivity and site selectivity of the molecule is studied by Fukui analysis.

Keywords: NBO, NLO, DFT, Thermodynamic Functions, Fukui Function.

^{1*}Molecular Spectroscopy and Biophysics Laboratory, Department of Physics, Deva Nagri College, C.C.S. University, Meerut, U.P., India, 250002

²Department of Botany, Kisan P.G. College, Simbhaoli, Hapur, U.P., India, 245207

³Department of Chemistry, D.N. College, Gulaothi, Bulandshahr, U.P., India, 203408

*Corresponding author: jayant.phy@gmail.com

***Corresponding Author:** - Jayant Teotia

*Molecular Spectroscopy and Biophysics Laboratory, Department of Physics, Deva Nagri College, C.C.S. University, Meerut, U.P., India, 250002

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1. Introduction

Morpholine derivatives have been subject to various applications and studied by researchers and academicians. Amanda K. Leonardi et al. studied N-Substituted Morpholine as an antifouling coating agent [1]. C. Cheng et al. studied morpholine surfactant for the production of potash fertilizer at low temperatures [2]. R. R. Sagam et al. synthesized and studied morpholine-benzimidazole-pyrazole hybrids as an anticancer agent [3]. M. D. Pascale et al. investigated morpholine isosteres as metabolically stable mTOR kinase inhibitors [4]. A. R. Jeon et al. convert ester to morpholine amides which are used to synthesize ketones and aldehydes [5]. F. Arshad et al. [6] reviewed morpholine derivatives as anticancer agents. M. A. Salem et al. [7] synthesize and evaluate the molecules containing morpholine moiety as an antimicrobial agent. R.H. Mennen et al. studied morpholines as gene regulators in the cardiac embryonic stem cell test [8]. K. Dhahagani et al. [9] synthesize and characterize schiff base complexes containing 4-(4-aminophenyl)morpholine derivatives for antimicrobial and anticancer studies. The vibrational spectral investigation and molecular docking analysis are carried out by B. Edwin et al. to study 4-(2-Aminoethyl) morpholine as an anti-neuronal drug [10].

Due to applications of morpholine derivatives in various fields, these molecules are subjected to computational study by density functional theory (DFT) to calculate various parameters. B. S. Yadav et al. studied Benzyl(3-Fluoro-4-Morpholinophenyl)Carbamate by DFT to calculate structural parameters, non-linear optical properties, thermodynamic functions, NBO analysis, and Fukui functions [11]. V.S. Jeba Reeda et al. analyzes morpholine derivative by vibrational, fukui, ELF, LOL, and molecular docking studies [12]. B. M. Philip et al. synthesized and did the spectroscopic investigation, NBO analysis, and molecular docking studies of (6-Fluoro-2-oxo-2H-chromen-4-yl) methyl morpholine-4-carbodithioate [13]. Z. Fakhri et al. [14] did an experimental and molecular dynamics simulation study of the binary mixtures of morpholine glycol to calculate thermodynamic properties.

The present study deals with the density functional theory (DFT) study of 3-fluoro-4-morpholinoaniline (FMA). The molecule FMA is studied by N. A. More et al. and molecular docking studies assessed

the FMA molecule as an anti-cancer agent in breast cancer cells [15]. In this study, DFT computations for the molecule FMA are used to analyze structural parameters, thermodynamic functions, Non-linear optical (NLO) properties, Natural Bond Orbital (NBO) analysis, and Fukui function analysis.

2. Computational Analysis

The theoretical calculations of the molecule FMA are performed by Density functional theory (DFT) using the Gaussian 09 program package [16]. The method used for the DFT calculations is B3LYP which employs Becke's three-parameter exchange functional B3 and Lee-Yang-Parr correlation functional LYP) [17]. The basis sets used are 6-311++G(d,p) and cc-pVDZ. The Gauss View program [18] is used to analyse the calculated results view the molecular structure. The bond length and bond angle of the optimized structure of FMA are calculated at 6-311++G(d,p) and cc-pVDZ basis sets. The thermodynamic functions Entropy, Specific heat and Enthalpy are computed for a temperature range of 100 K to 1000 K at 6-311++G(d,p) basis set. The orbital with maximum electron density is calculated by Natural Bond Orbital (NBO) analysis at B3LYP/6-311++G(d,p) basis set. The Non-linear optical (NLO) properties such as first and second-order hyperpolarizability are calculated at 6-311++G(d,p) and cc-pVDZ basis sets. Fukui functions are computed by DFT to calculate the chemical reactivity and selectivity of the molecule which is related to frontier molecular orbital. The biological activity of the FMA molecule is calculated by the SwissADME program which gives the drug likeliness of the molecule.

3. Drug Likeliness

Drug-likeliness is of great importance that helps in understanding various physiochemical and pharmacokinetic properties of the molecule. The compound must obey Lipinski's rule of five [19] for greater chances of drug-likeness. The drug-likeness of the FMA molecule was studied using the Swiss ADME program [20]. The FMA molecule shows zero violation of Lipinski's rule of five and exhibits a good bioavailability score of 0.55 as shown in Table 1. Based on the above observations it can be stated that the FMA molecule has the potential to be used in the pharmaceutical industry.

Table 1: Drug likeliness of the FMA molecule.

Descriptor value	Value
Hydrogen Bond Donor (HBD)	1
Hydrogen Bond Acceptor (HBA)	2
AlogP ¹	1.79
Topological polar surface area (TPSA) [Å ²]	38.49
Number of atoms	27
Number of rotatable bonds	1
Molecular weight	196.22
Bioavailability score	0.55

4. Nonlinear optical (NLO) properties

NLO properties are important for the development of electronic device applications. The NLO properties arise due to the changes in the amplitude, phase, and frequency in the presence of an electromagnetic field [21]. The mean polarizability $\langle\alpha\rangle$, anisotropy of the polarizability $\Delta\alpha$, total first-order hyperpolarizability β_{total} , and second-order hyperpolarizability are studied by J. Teotia et al. and other researchers [22-25] and can be calculated by the following equations.

$$\langle\alpha\rangle = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) / 3$$

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

$$\beta_{\text{total}} = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2} \text{ where}$$

$$\beta_x = (\beta_{xxx} + \beta_{xyy} + \beta_{yzz}), \beta_y = (\beta_{yyy} + \beta_{xxy} + \beta_{yzz}), \beta_z = (\beta_{zzz} + \beta_{xxz} + \beta_{yyz})$$

$$\langle\gamma\rangle = (\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2\gamma_{xxyy} + 2\gamma_{xxzz} + 2\gamma_{yyzz}) / 5$$

$$\mu = (\mu_x + \mu_y + \mu_z)^{1/2}$$

In the present work the dipole moment, polarizabilities α and hyperpolarizabilities β in atomic mass units (a.u.) for the FMA molecule

have been obtained at B3LYP/6-311++G(d,p) and B3LYP/cc-pVDZ basis sets as shown in Table 2. The maximum negative value of polarizability corresponds to α_{zz} of -86.6465 a.u. and the most positive value of polarizability corresponds to α_{yz} component which is equal to 2.2320 a.u. The maximum value of first-order hyperpolarizability is 121.1806 a.u. corresponding to β_{xxx} component and the value of total first-order hyperpolarizability is 114.1575 a.u. and 114.1677 a.u. respectively in 6-311++G(d,p) and cc-pVDZ basis sets. The total dipole moment is 3.1040 debye and 2.9387 debye in the 6-311++G(d,p) and cc-pVDZ basis set respectively. The second-order hyperpolarizability γ_{xxxx} has the most negative value of -3304.4821 a.u. and γ_{xxyy} component has the maximum positive value of 6.0927 a.u. The total value of second-order hyperpolarizability is -1402.892 a.u. The above calculations exhibit large values of polarizability and hyperpolarizability and hence the FMA molecule can be used in non-linear optical applications.

Table 2: Non-linear Optical Parameters (Polarizability, First order Hyperpolarizability and Second order Hyperpolarizability) of the FMA molecule calculated at B3LYP/6-311++G(d,p) and B3LYP/cc-pVDZ basis sets.

Parameters	B3LYP/6-311++G (d, p)	B3LYP/ cc-pVDZ
Dipole Moment (Debye)		
μ_x	2.6617	2.5659
μ_y	-1.3939	-1.1510
μ_z	-0.7793	-0.8531
Total	3.1040	2.9387
Molecular Polarizability (a.u.)		
α_{xx}	-77.2253	-73.7285
α_{yy}	-2.2156	-1.9844
α_{zz}	-78.1622	-77.1225
α_{xy}	-3.0258	-3.5413
α_{yz}	2.2320	1.8524
α_{zz}	-86.6465	-84.7205
Mean polarizability $\langle\alpha\rangle$	-80.678	-78.5238
Anisotropic polarizability $\Delta\alpha$	11.7451	12.4405
Hyperpolarizability (a.u.)		
β_{xxx}	121.1806	118.7994
β_{xyy}	5.2800	2.8179
β_{yyy}	0.8825	0.6917
β_{xxy}	-0.1164	4.1066
β_{yyz}	-39.0033	-35.6746
β_{yyz}	-10.9150	-8.8888
β_{yzz}	2.1251	1.1221
β_{xzz}	-16.6506	-13.2161
β_{yzz}	6.4780	6.5532
β_{zzz}	-5.3666	-4.9222
β_x	105.4125	106.275
β_y	11.6416	13.4777
β_z	-42.2448	-39.4747
β_{Total}	114.1575	114.1677
γ_{xxxx}	-3304.4821	-3148.8977
γ_{yyyy}	-695.2187	-680.6221
γ_{zzzz}	-218.5275	-202.8588
γ_{xxyy}	-53.4333	-49.4253
γ_{xxyy}	-103.8969	-111.9647
γ_{yyzz}	0.4796	2.4740
γ_{yyzz}	-3.8340	-5.7056
γ_{zzxx}	-11.3293	-11.3541
γ_{zzxx}	-3.1251	-5.0625
γ_{xxyy}	-591.2210	-590.6437
γ_{xxyy}	-651.1494	-625.6393
γ_{yyzz}	-155.7456	-150.0622
γ_{yyzz}	6.0927	6.3481
γ_{zzxx}	1.2487	-0.3255
γ_{zzxx}	3.1008	3.4906
Average second order hyperpolarizability $\langle\gamma\rangle$	-1402.892	-1353.0138

5. Structural Parameters

DFT calculations are performed to obtain the optimized structure of the FMA molecule. This optimized molecule obtained by DFT is used to calculate the structural parameters bond lengths and bond angles. The molecular structure of FMA with the numbering of atoms is shown in Figure 1. The optimized bond lengths and bond angles for the molecule are calculated at B3LYP/6-311++G (d,p) and B3LYP/cc-pVDZ basis sets as shown in Table 3. The bond length between C3-F7 is 1.36 Å and 1.35 Å at 6-311++G (d,p) and cc-pVDZ basis sets respectively. The bond lengths between C-C atoms range from 1.3807–1.5279 Å for both basis sets. The bond length is minimum for C2-C3 and maximum for C12-C14. The bond length for C-H atoms ranges from 1.084-1.1132 Å which is minimum for C2-H24 and maximum for C12-H17. The bond length between O8-C13 is 1.4245 Å and 1.4218 Å at 6-311++G (d,p) and cc-pVDZ basis sets respectively and that for O8-C14 is 1.422 Å and 1.4195 Å at 6-311++G (d,p) and cc-pVDZ basis sets respectively. The bond length between N-C atoms ranges from 1.4-1.4721 Å for both basis

sets which is minimum for C1-N10 and maximum for N9-C11. The bond lengths calculated at cc-pVDZ basis sets are slightly greater than that calculated at the 6-311++G(d,p) basis set except for bond length between N-C atoms which are greater for the 6-311++G(d,p) basis set. The bond angles between the atoms in the ring range from 109.5660° to 123.2518°. The bond angles between the atoms C-C-C range from 115.3763° for C3-C4-C5 to 123.8755° for C2-C3-C4. The bond angles between the atoms C-C-N range from 120.1573° for C3-C4-N9 to 124.4202° for C5-C4-N9. The bond angle between C2-C3-F7 is 117.2763° and 117.6199° at 6-311++G (d,p) and cc-pVDZ basis sets respectively and for C4-C3-F7 is 118.8456° and 118.7757° at 6-311++G (d,p) and cc-pVDZ basis sets respectively. The bond angles between the atoms C-C-H range from 18.6241° for C14-C12-H17 to 121.5162° for C1-C2-H24. The least bond angle among all the bond angles is for O8-C13-H19 and is equal to 106.4061° and 106.5106° at 6-311++G (d,p) and cc-pVDZ basis sets respectively.

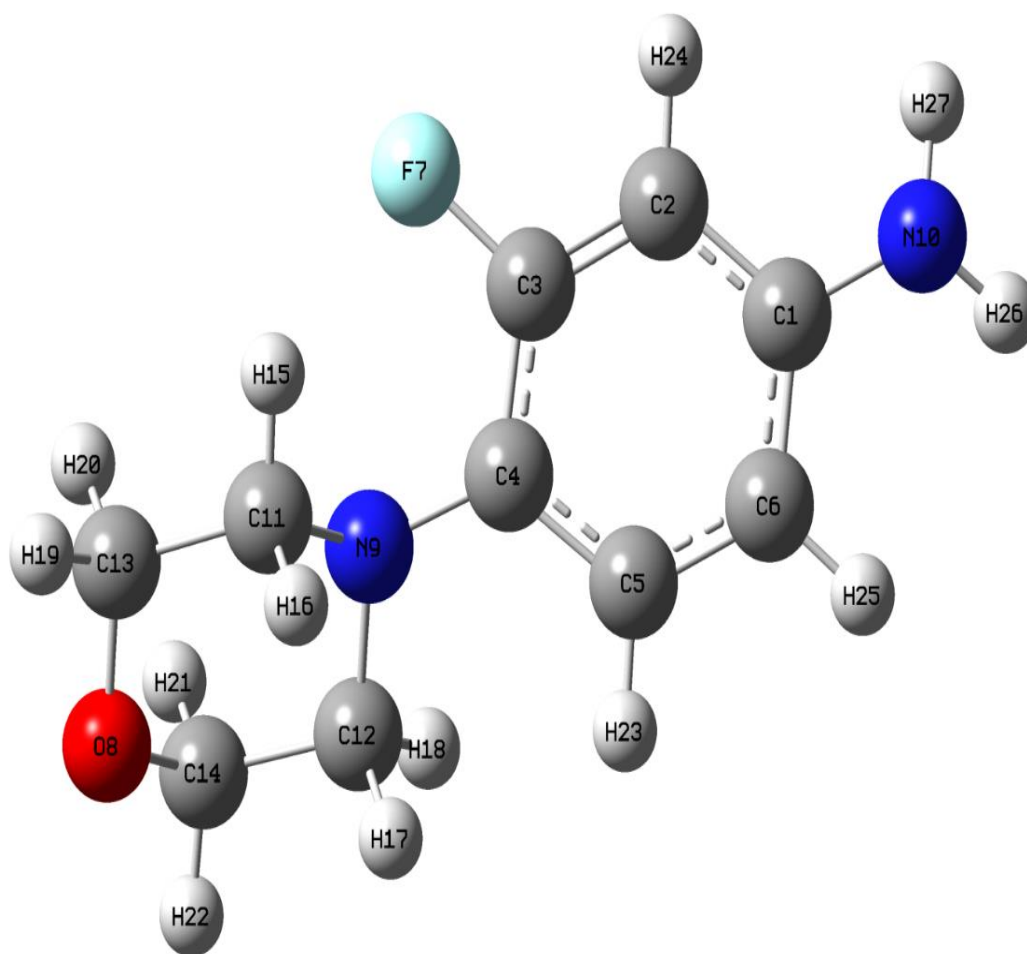


Figure 1: The optimized structure of FMA with atom numbering.

Table 3: Optimized structural parameters (Bond Length and Bond Angle) calculated at B3LYP/cc-pVDZ and B3LYP/6-311++G (d,p) basis sets.

Bond Length (Å)	B3LYP/ 6-311G++ (d, p)	B3LYP/ CCPVDZ	Bond Angle (°)	B3LYP/ 6-311G++ (d, p)	B3LYP/ CPVDZ
C1-C2	1.4017	1.4074	C2-C1-C6	117.952	117.7824
C1-C6	1.3985	1.4036	C2-C1-N10	120.5747	120.6122
C1-N10	1.4	1.4006	C6-C1-N10	121.4124	121.5298
C2-C3	1.3807	1.3853	C1-C2-C3	119.8137	120.0196
C2-H24	1.084	1.0919	C1-C2-H24	121.5162	121.5508
C3-C4	1.4026	1.4078	C3-C2-H24	118.6642	118.4218
C3-F7	1.36	1.358	C2-C3-C4	123.8755	123.6043
C4-C5	1.4018	1.4053	C2-C3-F7	117.2763	117.6199
C4-N9	1.4153	1.4174	C4-C3-F7	118.8456	118.7757
C5-C6	1.3929	1.3973	C3-C4-C5	115.1573	115.3763
C5-H23	1.0823	1.0902	C3-C4-N9	120.5327	120.1573
C6-H25	1.0849	1.093	C5-C4-N9	124.2654	124.4202
O8-C13	1.4245	1.4218	C4-C5-C6	122.3004	122.2197
O8-C14	1.422	1.4195	C4-C5-H23	119.2924	119.3562
N9-C11	1.4721	1.4708	C6-C5-H23	118.4068	118.4238
N9-C12	1.4604	1.4592	C1-C6-C5	120.8839	120.9745
N10-H26	1.0095	1.0162	C1-C6-H25	119.7491	119.6521
N10-H27	1.0097	1.0164	C5-C6-H25	119.36	119.367
C11-C13	1.5236	1.5248	C13-O8-C14	110.919	110.4687
C11-H15	1.0895	1.0974	C4-N9-C11	116.0628	116.0356
C11-H16	1.1033	1.112	C4-N9-C12	117.031	117.011
C12-C14	1.5265	1.5279	C11-N9-C12	111.016	110.9102
C12-H17	1.1045	1.1132	C1-N10-H26	115.1397	113.862
C12-H18	1.0932	1.1015	C1-N10-H27	115.4321	114.1092
C13-H19	1.0914	1.1003	H26-N10-H27	111.7261	111.8237
C13-H20	1.0995	1.1093	N9-C11-C13	109.7101	109.5294
C14-H21	1.0997	1.1094	N9-C11-H15	109.5262	109.4542
C14-H22	1.0917	1.1004	N9-C11-H16	110.4716	110.4715
			C13-C11-H15	109.345	109.4877
			C13-C11-H16	109.4263	109.3098
			H15-C11-H16	108.3359	108.2889
			N9-C12-C14	109.4776	109.3806
			N9-C12-H17	112.0442	112.1708
			N9-C12-H18	109.1648	109.1956
			C14-C12-H17	108.6961	108.6241
			C14-C12-H18	109.2418	109.4732
			H17-C12-H18	108.1709	107.9563
			O8-C13-C11	111.5081	111.5886
			O8-C13-H19	106.4061	106.5106
			O8-C13-H20	109.7626	110.1117
			C11-C13-H19	110.5304	110.5111
			C11-C13-H20	109.6248	109.2671
			H19-C13-H20	108.9344	108.7894
			O8-C14-C12	111.5641	111.6253
			O8-C14-H21	109.865	110.2145
			O8-C14-H22	106.4689	106.5762
			C12-C14-H21	109.5622	109.2504
			C12-C14-H22	110.4085	110.3684
			H21-C14-H22	108.9003	108.7431

6. Thermodynamic Functions

Various thermodynamic parameters such as zero-point vibrational energy, thermal energy, specific heat, entropy of the FMA molecule have been studied and obtained at 298.15 K using DFT calculations at B3LYP/6311++G(d,p) and B3LYP/cc-pVDZ basis sets and are tabulated in Table 4. The variation in specific heat, enthalpy and

entropy with temperature ranging from 100 K to 1000 K is shown in Table 5 and the corresponding plot is shown in figure 2. Table 4 clearly shows that with the increase in temperature, all three thermodynamic parameters also increase as reported by many researchers [26-28].

Table 4: Thermodynamic parameters of the FMA molecule computed at B3LYP/6311++G(d,p) and B3LYP/cc-pVDZ basis sets.

Parameter	B3LYP/6311++G(d,p)	B3LYP/cc-pVDZ
Zero-Point		
Vibrational Energy(kJ/mol)	585.9519	585.6567
Rotational Constants (GHz)	1.75925	1.75752
	0.37454	0.37392
	0.32445	0.32351
Thermal energy(kcal/Mol)		
Total	147.675	147.570
Translational	0.889	0.889
Rotational	0.889	0.889
Vibrational	145.897	145.793
Specific heat (Cal/mol ⁻¹ K ⁻¹)		
Total	48.648	48.500
Translational	2.981	2.981
Rotational	2.981	2.981
Vibrational	42.686	42.538
Entropy (Cal/mol ⁻¹ K ⁻¹)		
Total	107.865	107.629
Translational	41.726	41.726
Rotational	31.686	31.692
Vibrational	34.453	34.212

Table 5: Variation of Entropy (S), Specific Heat (C_p) and Enthalpy ddH content with temperature using B3LYP/6-311++G(d,p) basis set of BFMC molecule.

T (K)	S (J/mol.K)	C_p (J/mol.K)	ddH (kJ/mol)
100	303.75	81.742	5.367
150	342.931	113.721	10.253
200	380.049	145.961	16.743
250	416.149	178.966	24.862
298.15	450.429	211.238	34.256
300	451.74	212.475	34.648
350	486.984	245.456	46.101
400	521.831	276.845	59.167
450	556.144	305.957	73.747
500	589.777	332.516	89.72
550	622.616	356.544	106.957
600	654.585	378.219	125.335
650	685.644	397.784	144.743
700	715.782	415.489	165.082
750	745.005	431.565	186.265
800	773.332	446.212	208.215
850	800.791	459.601	230.865
900	827.414	471.873	254.157
950	853.233	483.152	278.036
1000	878.283	493.538	302.457

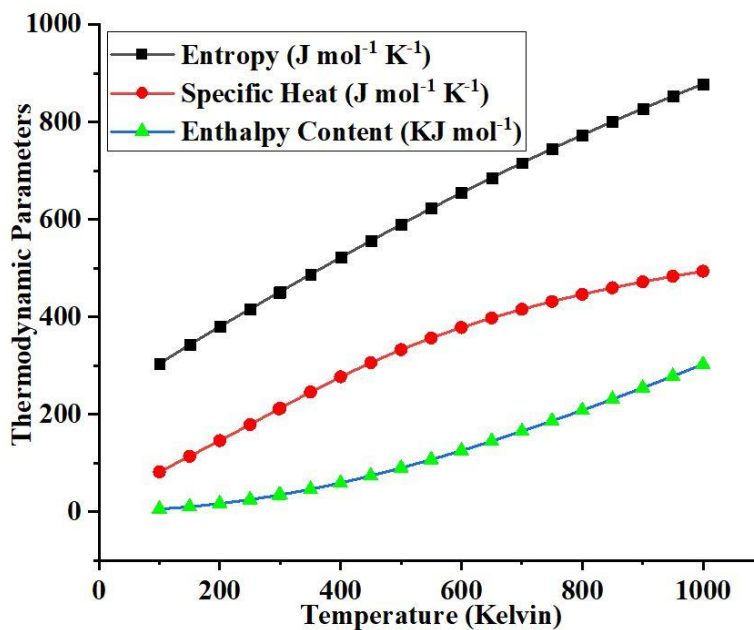


Figure 2: Variation of the thermodynamic parameters with temperature of the FMA compound.

7. Natural bond orbital (NBO)

The Natural Bond Orbital (NBO) helps in studying the hybridization and covalent effects in polyatomic wave functions based on local eigenvectors of one particle density matrix. In NBO analysis, the second-order perturbation theory is used to study the interaction of acceptor non-Lewis NBOs and donor Lewis NBOs for which electron densities are used [13, 26, 28]. Table 6 shows the stabilization energy, energy difference of donor (i) and acceptor (j) NBO orbitals, Fock matrix element between orbitals of i and j NBO and the occupancy of donor and acceptor NBOs of the FMA molecule.

The interaction between donor NBO and acceptor NBO is the maximum for which the stabilization energy is large. For the lone pair interaction, the maximum calculated stabilization energy is 25.21 kcal/mol for LP(1) N10 corresponding to the $\sigma^*(2)$ C1-C6 interaction. The second maximum stabilization energy of 23.22 kcal/mol corresponds to the interaction between $\sigma(2)$ C1-C6 and $\sigma^*(2)$ C4-C5. It can be seen from the table that the values of the stabilization energy between π - π^* is more as compared to σ - σ^* for most of the donor-acceptor NBO interactions.

Table 6: Second order perturbation theory of Fock matrix in NBO basis related to intra-molecular bonds of the FMA molecule computed at B3LYP/6-311++G (d,p) basis set [E(2) is stabilization energy; E(j)-E(i) is energy difference of donor(i) and acceptor (j) NBO orbitals; F(i,j) is Fock matrix element between orbitals of i and j NBO, ED/e is occupancy].

Donor NBO(i)	ED/e	Energy E(i)	Acceptor NBO(j)	Energy E(j)	E (2) ^a kcal/mol	E(j)-E(i) ^b (a.u.)	F(i,j) ^c (a.u.)
σ(1) C1 – C2	1.96836	-0.70236	σ*(1) C1- C6	0.56764	3.70	1.27	0.061
			σ*(1) C2 – C3	0.56764	2.64	1.27	0.052
			σ*(1) C3 - F7	0.25764	3.70	0.96	0.053
σ(1) C1–C6	1.97289	-0.70156	σ*(1) C6 – H25	0.42764	2.41	1.13	0.047
			σ*(1) C1 – C2	0.55844	3.67	1.26	0.061
			σ*(1) C2 – H24	0.41844	2.52	1.12	0.048
σ(2) C1– C6	1.65413	-0.25467	σ*(1) C5 - C6	0.58844	2.96	1.29	0.055
			σ*(2) C2 – C3	0.01533	17.19	0.27	0.062
			σ*(2) C4 – C5	0.02533	23.22	0.28	0.073
σ(1)C1– N10	1.99173	-0.80585	σ*(1) C1 – C2	0.56415	1.41	1.37	0.039
			σ*(1) C1 - C6	0.56415	1.60	1.37	0.042
			σ*(1) C5 – C6	0.58415	1.42	1.39	0.040
σ(1) C2 – C3	1.97814	-0.72294	σ*(1) C1 - C2	0.55706	3.00	1.28	0.055
			σ*(1) C1 – N10	0.42706	3.75	1.15	0.059
			σ*(1) C3 - C4	0.54706	4.47	1.27	0.068
σ(2) C2 – C3	1.72813	-0.27165	σ*(2) C1 – C6	0.02835	20.21	0.30	0.072
			σ*(2) C4 – C5	0.02835	15.52	0.30	0.063
			σ*(1) C1 – C6	0.57146	3.82	1.10	0.058
σ(1)C2 – H24	1.97558	-0.52854	σ*(1) C3 – C4	0.55146	4.27	1.08	0.061
			σ*(1) C2 – C3	0.56923	4.11	1.28	0.065
			σ*(1) C4 – C5	0.55923	3.24	1.27	0.057
σ(1) C3 – C4	1.97378	-0.71077	σ*(1) C5 – H23	0.44923	2.56	1.16	0.049
			σ*(1) C1 – C2	0.56363	1.22	1.57	0.039
			σ*(1) C4 – C5	0.56363	1.51	1.57	0.044
σ(1) C4 – C5	1.96894	-0.70037	σ*(1) C3 – C4	0.54963	3.31	1.25	0.058
			σ*(1) C3 – F7	0.25963	4.16	0.96	0.056
			σ*(1) C5 – C6	0.57963	3.16	1.28	0.057
σ(2) C4 – C5	1.68178	-0.25734	σ*(2) C1 - C6	0.02266	17.00	0.28	0.064
			σ*(2) C2 – C3	0.02266	22.89	0.28	0.072
			σ*(1) C2 – C3	0.56843	1.42	1.33	0.039
σ(1) C4 – N9	1.98199	-0.76157	σ*(1) C4 – C5	0.56843	1.97	1.33	0.046
			σ*(1) C5 – C6	0.58843	1.25	1.35	0.037
			σ*(1) C4 – N9	0.42995	3.91	1.13	0.059
σ(1) C5 - C6	1.97455	-0.70005	σ*(1) C1 – N10	0.42995	4.07	1.13	0.061
			σ*(1) C1 – C6	0.56916	3.67	1.09	0.056
			σ*(1) C3 – C4	0.54916	3.71	1.07	0.056
σ(1)C5 – H23	1.97601	-0.52084	σ*(1) C1 – C2	0.56035	4.14	1.08	0.060
			σ*(1) C4 – C5	0.56035	4.02	1.08	0.059
			σ*(1) C11– H15	0.42309	0.85	1.22	0.029
σ(1)O8 -C13	1.99047	-0.79691	σ*(1) C14– H22	0.40309	0.97	1.20	0.030
			σ*(1) C12– H18	0.40008	0.88	1.20	0.029
			σ*(1) C13– H19	0.6905	0.94	1.20	0.030
σ(1)C11-H15	1.97731	-0.50950	σ*(1) C4 – C5	0.56463	1.79	1.26	0.042
			σ*(2) C4 – C5	0.02463	1.64	0.72	0.034
			σ*(1) C3 – C4	0.54898	2.32	1.26	0.048
σ(1)N9 - C11	1.97623	-0.69537	σ*(1) C4 – N9	0.42898	1.16	1.14	0.032
			σ*(1) C1- C2	0.55975	3.96	1.21	0.062
			σ*(1) C1- C6	0.56956	3.93	1.22	0.062
σ(1)N9 – C12	1.98325	-0.71102	σ*(1) C11– H16	0.23673	3.21	0.86	0.047
			σ*(1) O8 – C13	0.18673	3.88	0.81	0.050
			σ*(1) C13– H20	0.38911	2.48	0.89	0.042
σ(1)C11 - H16	1.98368	-0.50089	σ*(1) C4 – N9	0.4248	2.82	1.05	0.049
			σ*(1) C14– H21	0.38268	2.55	0.89	0.043
			σ*(1) O8 – C14	0.30718	3.82	0.82	0.050
σ(1)C12 – C14	1.98617	-0.62520	σ*(1) N9 – C11	0.33718	3.33	0.85	0.048
			σ*(1) O8 – C14	0.30071	3.04	0.81	0.044
			σ*(1) N9- C11	0.34071	3.15	0.85	0.046
σ(1) C12 - H17	1.98370	-0.50732	σ*(1) C11- H16	0.38432	2.79	0.89	0.045
			σ*(1) C12– H17	0.38247	2.70	0.89	0.044
			σ*(1) O8- C13	0.29898	3.03	0.81	0.044
σ(1) C12 - H18	1.97729	-0.51282	σ*(1) N9 – C12	0.34898	3.12	0.86	0.046
			σ*(1) C2 – C3	0.5716	0.95	1.61	0.035
			σ*(1) C3 – C4	0.5516	1.05	1.59	0.037
LP (1) F7	1.98978	-1.03840	σ*(1) C2 – C3	0.57235	5.50	0.99	0.066
			σ*(1) C3 – C4	0.55235	5.79	0.97	0.067
			σ*(1) C2 – C3	0.02301	17.53	0.44	0.085
LP (2) F7	1.97232	-0.41765	σ*(1) C13– H19	0.40655	2.41	0.97	0.043
			σ*(1)C14 – H22	0.40655	2.44	0.97	0.044
			σ*(1)C13 – H20	0.38834	6.27	0.68	0.059
LP (3) F7	1.93006	-0.41699	σ*(1)C14 – H22	0.40655	2.44	0.97	0.044
			σ*(1)C13 – H20	0.38834	6.27	0.68	0.059
			σ*(1)C14 – H21	0.37834	6.35	0.67	0.059
LP (1) O8	1.96476	-0.56345	σ*(1)C13 – H20	0.38834	6.27	0.68	0.059
			σ*(1)C14 – H21	0.37834	6.35	0.67	0.059
			σ*(1)C14 – H21	0.37834	6.35	0.67	0.059
LP (2) O8	1.92060	-0.29166	σ*(1)C13 – H20	0.38834	6.27	0.68	0.059
			σ*(1)C14 – H21	0.37834	6.35	0.67	0.059
			σ*(1)C14 – H21	0.37834	6.35	0.67	0.059

LP (1) N9	1.83103	-0.26601	$\sigma^*(2)$ C4 – C5	0.02399	15.48	0.29	0.064
			$\sigma^*(1)$ C11 – H16	0.38399	7.81	0.65	0.066
			$\sigma^*(1)$ C12 – H17	0.37399	8.71	0.64	0.069
LP (1) N10	1.85834	-0.30360	$\sigma^*(2)$ C1 – C6	0.0264	25.21	0.33	0.088

8. Fukui Function

Fukui function is electron density descriptor used to understand the change of absolute electron number with a fixed geometry. Fukui function is used as a local density functional descriptor to model chemical reactivity and site selectivity [29]. In this present work, Fukui functions for electrophilic and nucleophilic attacks have been computed for the anions and cations for the title molecule along with neutral molecule using DFT at B3LYP/6-311++ G (d, p) level of theory. It is possible to define the condensed or aromatic Fukui functions on the j^{th} atom site as

$$f_j^+ = q_j(N + 1) - q_j(N)$$

for nucleophilic attack

$$f_j^- = q_j(N) - q_j(N - 1) \quad \text{for}$$

electrophilic attack

$$f_j^0 = \frac{1}{2} [q_j(N + 1) - q_j(N - 1)]$$

for radical attack

In the above equations, the electrons in neutral, anionic, and cationic state of j^{th} site of atom are denoted by N, N+1, N-1 chemical species. Chattaraj et al. [30] introduced the thought of generalized philicity. It contains most of the information concerning well-known completely

global, local reactivity and selectivity descriptors and the data concerning electrophilic/nucleophilic power at a given atomic site of a molecule. Morell et al. [31] conceptualized a dual descriptor $\Delta F(r)$, which is defined as the difference between the nucleophilic and electrophilic Fukui function and is given by the equation,

$$\Delta F(r) = q_j^+ - q_j^-$$

The site is favored for a nucleophilic attack if $\Delta F(r) > 0$ and the site is favored for an electrophilic attack if $\Delta F(r) < 0$ values as reported in Table 7 which clearly indicates that in the titled compound, the reactivity order for the nucleophiles is $H_{26} > H_{27} > H_{25} > H_{22} > H_{18} > H_{24}$ and that for electrophiles is $N_9 > N_{10} > C_1 > C_6 > C_4 > C_5$. According to the condition for dual descriptor, nucleophilic sites in the 3-fluoro-4-morpholinoaniline molecule are $H_{18}, H_{21}, H_{22}, H_{23}, H_{24}, H_{25}, H_{26}, H_{27}$ as these have positive values i.e $\Delta F(r) > 0$. Similarly, the electrophilic sites are $C_1, C_2, C_3, C_4, C_5, C_6, F_7, O_8, N_9, N_{10}, C_{11}, C_{12}, C_{13}, C_{14}, H_{15}, H_{16}, H_{17}, H_{19}, H_{20}$ that have negative values i.e $\Delta F(r) < 0$. The behaviour of a molecule as an electrophile or a nucleophile in a reaction depends on the local behaviour of the molecule. Fukui function should always have a positive value as it represents the electron density of the HOMO for f_j^- and of the LUMO in the case of f_j^+ [29].

Table 7: Computed values of the Fukui function using Hirshfeld charges for the FMA molecule.

Atoms	Hirshfeld charges			Fukui functions			
	q(N)	q(N+1)	q(N-1)	f^-	f^+	f^0	CDD
C ₁	0.0402	0.0308	0.0977	0.0575	0.0094	0.0334	-0.0481
C ₂	-0.0790	-0.0961	-0.0358	0.0432	0.0171	0.0302	-0.0261
C ₃	0.0787	0.0648	0.1199	0.0412	0.0140	0.0276	-0.0272
C ₄	0.0136	0.0015	0.0607	0.0471	0.0121	0.0296	-0.0350
C ₅	-0.0546	-0.0700	-0.0108	0.0438	0.0154	0.0296	-0.0284
C ₆	-0.0725	-0.0927	-0.0154	0.0571	0.0202	0.0386	-0.0369
F ₇	-0.1124	-0.1265	-0.0740	0.0384	0.0141	0.0262	-0.0244
O ₈	-0.1900	-0.1987	-0.1658	0.00243	0.0087	0.0165	-0.0156
N ₉	-0.0883	-0.0917	0.0275	0.1158	0.0034	0.0596	-0.1123
N ₁₀	-0.1756	-0.2013	-0.0767	0.0989	0.0257	0.0623	-0.0732
C ₁₁	-0.0143	-0.0192	0.0061	0.0204	0.0049	0.0126	-0.0156
C ₁₂	-0.0115	-0.0224	0.0058	0.0172	0.0109	0.0141	-0.0063
C ₁₃	0.0247	0.0180	0.0374	0.0127	0.0067	0.0097	-0.0061
C ₁₄	0.0245	0.0111	0.0395	0.0150	0.0134	0.0142	-0.0016
H ₁₅	0.0363	0.0279	0.0534	0.0171	0.0084	0.0128	-0.0086
H ₁₆	0.0188	0.0051	0.0578	0.0390	0.0137	0.0263	-0.0253
H ₁₇	0.0196	-0.0125	0.0563	0.0367	0.0322	0.0344	-0.0045
H ₁₈	0.0394	-0.0096	0.0580	0.0186	0.0490	0.0338	0.0305
H ₁₉	0.0448	0.0291	0.0687	0.0238	0.0158	0.0198	-0.0081
H ₂₀	0.0290	0.0200	0.0447	0.0157	0.0090	0.0124	-0.0067
H ₂₁	0.0276	0.0083	0.0440	0.0164	0.0193	0.0178	0.0029
H ₂₂	0.0437	-0.0178	0.0688	0.0251	0.0615	0.0433	0.0363
H ₂₃	0.0409	-0.0016	0.0681	0.0271	0.0426	0.0349	0.0154
H ₂₄	0.0479	-0.0027	0.0787	0.0308	0.0505	0.0407	0.0197
H ₂₅	0.0387	-0.0501	0.025	0.0339	0.0888	0.0613	0.0550
H ₂₆	0.1151	-0.0647	0.1560	0.0409	0.1798	0.1103	0.1389
H ₂₇	0.1154	-0.0556	0.1574	0.0420	0.1710	0.1065	0.1290

9. Conclusion

This work deals with the computational study of biologically active organic molecule 3-fluro-4-morpholinoaniline which is reported as an anti-cancer agent. The theoretical study of the molecule is carried out by density functional theory at B3LYP level with 6-311++G (d,p) and cc-pVDZ basis sets. The DFT calculations are used to calculate the optimized bond angles and bond lengths. The specific heat, entropy and enthalpy of the molecule are calculated for the temperature range of 100 to 1000 Kelvin. The inter and

intramolecular interactions of the FMA molecule are verified by Natural Bond Orbital (NBO) analysis. The large first-order and second-order hyperpolarizability of the molecule shows that the molecule can be applicable to non-linear optical activities. The Fukui function study is used to calculate the local density functional descriptor along with chemical reactivity and site selectivity inside the molecule. These results will be helpful for the study of this molecule in various applications.

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