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Theoretical and Experimental Study of Structural Aspects of 2-acetonyl-2-methyl Benzothiazoline

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ABSTRACT

Schiffs base 2-acetonyl-2-methyl benzothiazoline (AMBT) is prepared by the condensation of acetyl acetone with 2-aminothiophenol. The compound has been characterised by IR, ^{1}H NMR spectra. HyperChem 7.5 software is used to study the structural features of AMBT and theoretical data so obtained is compared with experimental spectral data. Quantum mechanical calculations were done by HyperChem 7.5 software. Ab Initio method is used for geometry optimization. Quantum calculation of molecular electronic structure and variables for Quantitative structure-activity relationships (QSAR) of AMBT were determined by applying Austin Model 1, or AM1 a semi-empirical method. Computation of HOMO and LUMO frontier orbital energies is also performed. The relationship between the structure and energy gap is studied. pH-metry studies confirm that in AMBT Molecule there exists only one proton which is dissociable.

Keywords: AMBT, Energy gap, Quantitative structure-activity relationships.

INTRODUCTION

As benzothiazolines contain two different hetero atoms linked by carbon in the ring many studies were made. It is reported that Benzothiazolines possess biological activities[1-4] and preparation of benzothiazolines is done by condensation of 2-aminothiophenol with aldehyde and ketones[5]. Derivatives of Benzothiazolines form an predominant group of ligands which can be bidentate as well as multidentate[6-8].

In natural medicines there is wide application of carbon-nitrogen bonds and in various natural bioactive products and pharmaceuticals. the structure of heterocycles is studied This is in view of their significant analgesics, antidiabetic, antiallergic, anticonvulsant, antidepressant, antimicrobials and antifungal properties. N-C-S group of benzothiazolines is known for pharmacological activity and is of appreciable chemotherapeutic interest. In order to understand the physiological activity of such compound a study is made on its capacity of chelation with traces of metal ions[9-11]. The acidity of 2-acetonyl-2-methyl benzothiazoline (AMBT), is estimated by determining its pKa value. In the present paper the structural properties of AMBT Fig.1 are described and a detailed discussion

of experimental data and theoretical data obtained by applying Hyperchem 7.5 Software[12] is done.

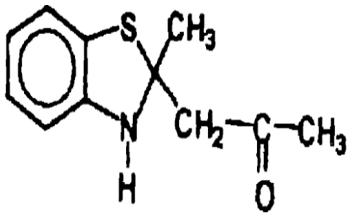


Fig. 1. Structure of 2-acetonyl-2-methyl benzothiazoline

EXPERIMENTAL

Synthesis of 2-acetonyl-2-methyl benzothiazoline

Synthesis of AMBT is done using the following procedure. Acetyl acetone 0.05 mole was melted in 15 mL methanol and cooled in an ice bath. The precooled 2-amino thio phenol (0.05 mole) dissolved in 10 mL methanol is added to the acetyl acetone solution. This solution is stirred briefly and was allowed to stand overnight. at -5°C to -10°C. The prismatic crystals so formed were collected by filtration and washed with chilled methanol and further recrystallised from warm methanol, m.p. 85°C -86°C (lit. 85°C -86°C).

Physical measurements

Employing Perkin elmer model no 435 infrared spectrometer, IR spectrum of 2-acetonyl-2-methyl benzothiazoline (AMBT) was documented in KBr phase. Using Bruker WH-270 MHz FT-NMR spectrometer 1H spectra of AMBT was analysed in $CDCl_3$ and DMSO-d6 using tetra methylsilane (TMS) as standard. Micro Mass spectrometer of V.G70-70H type administering at 70ev using direct inlet system is used for recording Mass spectra of AMBT.

Potentiometric method using pH-metric titration technique as adopted by Irving-Rossotti is employed to determine proton dissociation constant(pKa) of AMBT. Measurement of pH is done employing Digital pH meter. Digisun model: DI-707., by making use of combination or pH electrode. With the application of Hyperchem tools the molecule AMBT is constructed[12], and then by exercising Ab Initio optimized method of single point AM1. semi-empirical calculation the geometry optimization is executed.

RESULTS AND DISCUSSIONS

As per potentiometric titration data it is clear that in ligand 2-acetonyl-2-methyl benzothiazoline (AMBT) only one dissociable proton is present. Calculations indicated that the pKa value of AMBT is 8.79 for titration carried out in Methanol : Water (50:50)% (v/v) medium at temperature of 303 K and at ionic strength of 0.1 M KNO_3

The acidified ligand titration curve runs below the acid curve indicating non protonation of ligand. From the calculation of n^-_A values it is evident that there is one dissociable proton. (Table 1, Figure 2).

Table 1: Data for obtaining Proton-Ligand stability constants of AMBT in Methanol: Water (50:50)% (v/v) medium at temperature of 303 K and at ionic strength of 0.1 M KNO_3

Ligand/Medium	pH	n^-_A	log 1-n^-_A/ n^-_A
AMBT	8.4	0.74	-0.43
50%v/vmethanol-water medium	8.5	0.68	-0.32
	8.6	0.62	-0.21
	8.7	0.56	-0.1
	8.8	0.49	0.02
	8.9	0.44	0.13
	9	0.37	0.23
	9.1	0.3	0.34

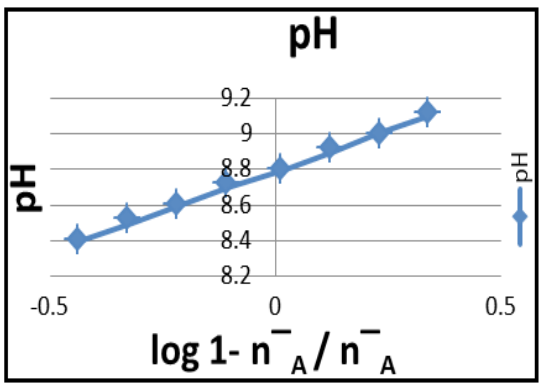


Fig. 2. Plots of log 1-n^-_A / n^-_A Vs pH of AMBT in Methanol: Water (50:50)% (v/v) medium at temperature of 303 K and at ionic strength of 0.1 M KNO_3

As the base is added enolisation of the ligand readily takes place and proton is dissociated from enol form in the pH region of 8 to 9. The dissociation constant value is comparable with the dissociation constant of acetyl acetone.

From the above titration data any ring cleavage or oxidative ring expansion are not evident. The proton from SH group in open ring Schiff base dissociates indicating release of one more proton, if ring cleavage occur to form tautomer of open ring type. There is no proof for such process for AMBT in solution under given experimental condition and hence the formation of open ring tautomer even at high pH is ruled out.

Formation of Binary metal chelates in solution

In the present study evidence for the interaction of various metal ions with AMBT has been obtained from the data of pH metric titrations of the AMBT ligand solution in presence and absence of metal ions.

The interaction of various bivalent metal ions Co(II) and Ni(II) ions with AMBT have been carried out by following Irving Rosotti pH titration technique in Methanol : Water (50:50)% (v/v) medium at temperature of 303 K and at ionic strength of 0.1 M KNO_3. The following observations indicate the complex formation (Figures 3 & 4, Tables 2 & 3).

1. On addition of metal ion solution to AMBT ligand solution, a decrease in pH is observed thereby suggesting the release of proton on coordination.
2. M(II)-AMBT titration curves lie below the AMBT ligand titration curve indicating complexation.
3. $\bar{n}$ values gradually increase and equilibrium is attained during titration.

The M(II)-AMBT stability constants indicate the extent of interaction between the metal ion and the compound AMBT.

Table 2: Data for obtaining formation curves of Co (II)-AMBT in Methanol:Water (50:50)% (v/v) medium at temperature of 303 K and at ionic strength of 0.1 M KNO_3

	Co (II)-AMBT	
$\bar{n}$	log 1-$\bar{n}$/$\bar{n}$	pL
0.78	-0.55	8.06
0.65	-0.27	8.3
0.59	-0.16	8.5
0.45	0.08	8.61
0.34	0.29	8.81
0.26	0.41	8.92

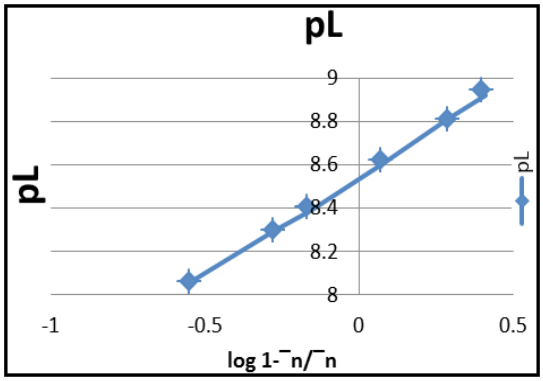


Fig. 3. Plots of pL Vs log 1-$\bar{n}$/$\bar{n}$ of Co (II)-AMBT in Methanol : Water (50:50)% (v/v) medium at temperature of 303 K and at ionic strength of 0.1 M KNO_3

Table 3: Data for obtaining formation curves of Ni(II)-AMBT in Methanol:Water (50:50)% (v/v) medium at temperature of 303 K and at ionic strength of 0.1 M KNO_3

	Ni (II)-AMBT	
$\bar{n}$	log 1-$\bar{n}$/$\bar{n}$	pL
0.72	-0.41	8.32
0.67	-0.31	8.38
0.54	-0.07	8.52
0.36	0.25	8.71
0.27	0.43	8.81
0.15	0.75	9.01

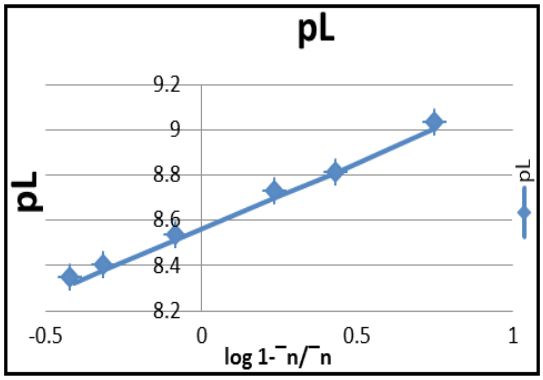


Fig. 4. Plots of pL Vs log 1-$\bar{n}$/$\bar{n}$ of Ni (II)-AMBT in Methanol : Water (50:50)% (v/v) medium at temperature of 303 K and at ionic strength of 0.1 M KNO_3

With the help of Hyperchem tools the molecule 2-acetonyl-2-methyl benzothiazoline was built and then by implementing Ab Initio method geometry optimization was done (Figs. 1 to 3). with the application of single point AM1 method approximation the spectral data is generated.

Certain input parameters like molecular geometry value, bond lengths values and values of columbic, resonance influence the calculations performed to some extent. Prospective view and active conformation of 2-acetonyl-2-methyl benzothiazoline (AMBT) as given by Hyperchem is shown in Figure 5 & 6.

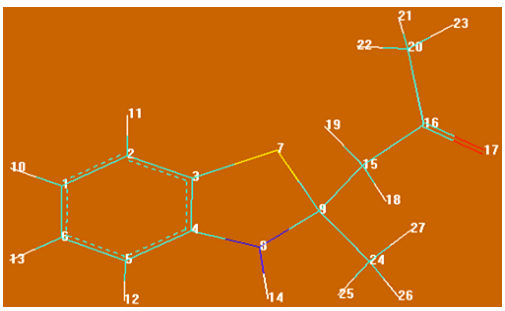
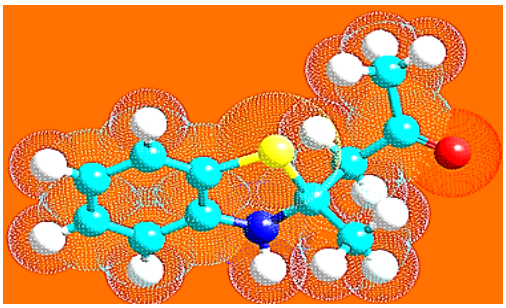
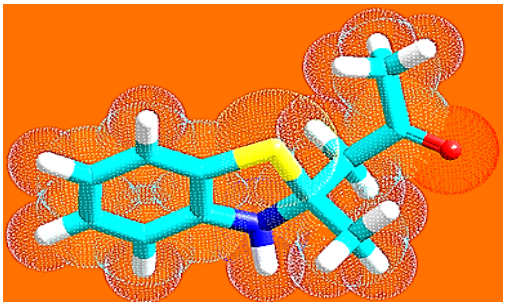


Fig. 5. Prospective view of 2-acetonyl-2-methyl benzothiazoline (AMBT)



(i) ball & cylinder display structure



(ii) tubes display structure

Fig. 6. Active conformations of 2-acetonyl-2-methyl benzothiazoline

Hyperchem data of 2-acetonyl-2-methyl benzothiazoline (AMBT) indicates that Single point energy as per Austin Model 1, or AM1 optimization is -2801.26 with Gradient of 1.618 and symmetry of C1.

IR spectrum of 2-acetonyl-2-methyl benzothiazoline

A comparative study is done for experimentally obtained IR spectral data of AMBT with the theoretical spectral IR data of AMBT as obtained by applying Ab Initio method of optimization of Austin Model 1, or AM1 a semi-empirical method.

IR spectrum of AMBT shows peaks at 3277 cm^{-1} which is assigned to –NH stretching vibration. In addition to these the aromatic C-H stretching frequencies and C-H (-CH_3) stretching frequencies are observed at 3148 cm^{-1} and 2936 cm^{-1} respectively. The band observed at 1797 cm^{-1} is assigned to C=0. Aromatic stretching vibrations are observed at 1569-1498 cm^{-1}.

IR spectrum of AMBT generated by semi empirical single point AM1 (Fig. 7) method 11-17 indicates that –NH stretching vibration is obtained at 3417.5 cm^{-1}. Aromatic C-H stretching frequencies are observed at 3206-3185 cm^{-1} and C-H(-CH_3) stretching frequencies at 3031 cm^{-1}.

A good acceptance of experimental IR spectral data with theoretical IR data is perceived (Table 4)

^{1}HNMR spectrum of 2-acetonyl-2-methyl benzothiazoline

Comparision of experimental ^{1}HNMR spectral data of AMBT with the theoretical NMR spectral data obtained by Austin Model 1, or AM1 a semi-empirical method is made.

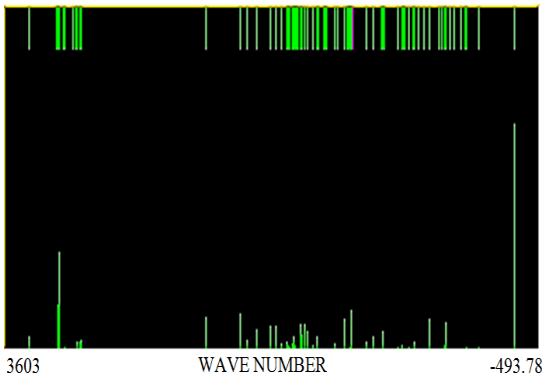


Fig. 7. IR spectrum of 2-acetonyl-2-methyl benzothiazoline-experimental

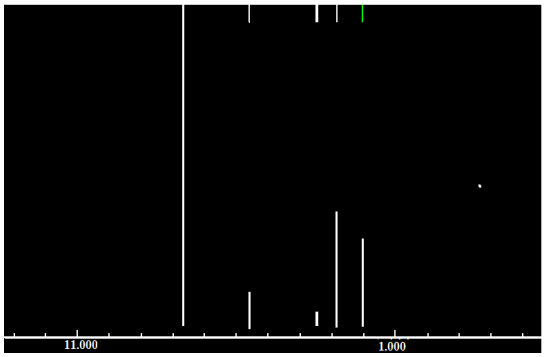


Fig. 8. ^{1}HNMR spectrum of 2-acetonyl-2-methyl benzothiazoline (AMBT) as given by Austin Model 1, or AM1 a semi-empirical method

Table 4: IR Spectral data of AMBT (Experimental)*/AMBT (semiempirical AM1)

Compound	$\upsilon\upsilon_{NH}$	υ_{CHaro}	$\upsilon\upsilon$C-H(-CH_3)$\upsilon\upsilon_{C=O}$(-CO-CH_3)		$\upsilon\upsilon$C=$_C$	$\upsilon\upsilon_{N-H}$ bending g	$\upsilon\upsilon_{S-H}$
AMBT* Experimental	3277 cm^{-1}	3148 cm^{-1}	2936 cm^{-1}	1943 cm^{-1}	1797 cm^{-1}	1606, 1590 cm^{-1}	1345, 1283 cm^{-1}
AMBT(semiempirical AM1)	3417.5 cm^{-1}	3206-3185 cm^{-1}	3031 cm^{-1}	2059 cm^{-1}	1794 cm^{-1}	1568, 1521 cm^{-1}	1336, 1279 cm^{-1}

Table 5: Shielding data of 2-acetonyl-2-methyl benzothiazoline (AMBT) as given by Austin Model 1, or AM1 a semi-empirical method

Index	1-10(H)	1-11(H)	1-12(H)	1-13(H)	1-14(H)	1-18(H)	1-19(H)	1-21(H)	1-22(H)	1-23(H)	1-25(H)	1-26(H)	1-27(H)
Shielding	16.271	16.271	16.271	16.271	18.368	20.476	20.476	21.118	21.118	21.118	21.898	21.898	21.898
Shift	7.68	7.68	7.68	7.68	5.583	3.475	3.475	2.833	2.833	2.833	2.053	2.053	2.053
Tau	2.32	2.32	2.32	2.32	4.417	6.525	6.525	7.167	7.167	7.167	7.947	7.947	7.947

Table 6: Coupling data of AMBT as given by Austin Model 1, or AM1 a semi-empirical method

Coupling	1-10(H)	1-11(H)	1-12(H)	1-13(H)	1-14(H)	1-18(H)	1-19(H)	1-21(H)	1-22(H)	1-23(H)	1-25(H)	1-26(H)	1-27(H)
1-10(H)	0	5.042	5.042	5.042	0.116	0.016	0.016	0	0	0	0.014	0.014	0.014
1-11(H)	5.042	0	5.042	5.042	0.116	0.016	0.016	0	0	0	0.014	0.014	0.014
1-12(H)	5.042	5.042	0	5.042	0.116	0.016	0.016	0	0	0	0.014	0.014	0.014
1-13(H)	5.042	5.042	5.042	0	0.116	0.016	0.016	0	0	0	0.014	0.014	0.014
1-14(H)	0.116	0.116	0.116	0.116	0	-0.397	-0.397	-0.042	-0.042	-0.042	-0.233	-0.233	-0.233
1-18(H)	0.016	0.016	0.016	0.016	-0.397	0	4.396	-0.602	-0.602	-0.602	-0.076	-0.076	-0.076
1-19(H)	0.016	0.016	0.016	0.016	-0.397	4.396	0	-0.602	-0.602	-0.602	-0.076	-0.076	-0.076
1-21(H)	0	0	0	0	-0.042	-0.602	-0.602	0	0.302	0.302	0.004	0.004	0.004
1-22(H)	0	0	0	0	-0.042	-0.602	-0.602	0.302	0	0.302	0.004	0.004	0.004
1-23(H)	0	0	0	0	-0.042	-0.602	-0.602	0.302	0.302	0	0.004	0.004	0.004
1-25(H)	0.014	0.014	0.014	0.014	-0.233	-0.076	-0.076	0.004	0.004	0.004	0	2.158	2.158
1-26(H)	0.014	0.014	0.014	0.014	-0.233	-0.076	-0.076	0.004	0.004	0.004	2.158	0	2.158
1-27(H)	0.014	0.014	0.014	0.014	-0.233	-0.076	-0.076	0.004	0.004	0.004	2.158	2.158	0

The experimental ^{1}HNMR spectral data of the AMBT in $CDCl_3$ recorded signal at 2.15 ppm (δ 3H, s, CH_3), 2.9 ppm (δ 3H, s, CH_3), 3.2 ppm (δ2H, q, CH_2) and a peak at 5.4 ppm is attributable to NH. The multiplet recorded at 6.55–7.18 ppm corresponds to aromatic protons. This experimental data is in good concurrence with the data of theoretical method as obtained by semiempirical AM1 method, as given the following table ^{1}HNMR spectral data of the AMBT as recorded by semiempirical AM1 method[11-17] (Fig. 8, Tables 5 & 6) shows a peak at 2.833 ppm which is attributed to three protons of -CH_3 i.e 1-21(H), 1-22(H), 1-23(H) and a peak at 2.053 ppm due to three protons of one more -CH_3 i.e $^{1\text{-}25}$(H), 1-26(H), 1-27(H). Apart from this peak observed at 5.58 ppm is due to NH and 7.68 ppm multiplet is due to protons aromatic ring.

From the above comparative study (Table 7) it is clear that for 2-acetonyl-2-methyl benzothiazoline (AMBT) there is good agreement between experimentally obtained ^{1}H NMR spectral data and spectral data obtained by semiempirical single point AM1 method.

Table 7: ^{1}H NMR Spectral data of AMBT (Experimental)*/AMBT (semiempirical AM1)

Compound	υδ4H,m, aromCH	δ–1H, s, NH	δ2H,q,CH_2	υδ3H, s, CH_3	υδ3H, s, CH_3
AMBT (Experimental)*	6.55–7.18 ppm	5.4 ppm	3.2 ppm	2.9 ppm	2.15 ppm
AMBT (semiempiricalAM1)	7.68 ppm				
	1-10(H)	5.58 ppm	3.475 ppm	2.833 ppm	2.053 ppm
	1-11(H)	1-14(H)	1-18(H)	1-21(H)	1-25(H)
	1-12(H)		1-19(H)	1-22(H)	1-26(H)
	1-13(H)			1-23(H)	1-27(H))

Interpretation of Quantitative structure activity relationship studies (QSAR studies) and Molecular properties of AMBT

Empolying single point AM1 method QSAR properties of AMBT were determined.These include properties like surface area, volume, hydration energy, log P, refractivity, polarisability, mass, total energy etc. (Table. 8). Molecular descriptors commonly used in quantitative structure activity relationship (QSAR) studies were computed[18-21] . This study amounts to analyse the relationship between structural descriptors of compounds and their physicochemical

properties and biological activities. Binding energy of AMBT is about -2801.26 kcal/mol as determined by AM1 calculation. AMBT has heat of formation of -5.186 kcal/mol and this shows it's exothermic nature. Dipole moment value is 2.145 D. A good acceptance between trends of the theoretical molecular properties with the experimental results is observed[25-27].

Table 8: QSAR and Molecular properties of 2-acetonyl-2-methyl benzothiazoline (AMBT)

QSAR and Molecular properties of AMBT	
Overall Net charge	0.00 e
approx Surface area	347.31°A^2
Grid Surface area	394.87°A^2
Volume	629.72°A^3
Energy of Hydration	-3.15 kcal/mol
Log P value	2.76
value of Refractivity	61.28°A^3
value of Polarisability	23.27°A^3
Molar Mass	207.29 amu
Total energy	-53244.06 kcal/mol
Energy of Binding	-2801.26 kcal/mol
value of Heat of formation	-5.186 kcal/mol
value of Electronic energy	-308034.78 kcal/mol
value of Nuclear energy	254790.72 kcal/mol
Dipole moment value	2.145 D
X Dipole	-2.043 D
Y Dipole	-0.5018 D
Z Dipole	-0.4209 D
RMS gradient	1.618 kcal/°A mol
X Gradient	0.3382 kcal/°A mol
Y Gradient	1.0999 kcal/°A mol
Z Gradient	1.1378 kcal/°A mol

Quantum Chemical Studies of 2-acetonyl-2-methyl benzothiazoline (AMBT)

Quantum chemical calculations were employed for studying donor and acceptor properties of AMBT molecule. Fig. 9 &10 indicate the values of E_{HOMO} (energy of the highest occupied molecular orbitals), E_{LUMO} (energy of the lowest unoccupied molecular orbitals) and $E_{LUMO-HOMO}$ (the energy gap between them)for AMBT molecule.

Energies of Frontier molecular orbital E_{HOMO} and E_{LUMO}[22-24] is one of the most important factor for assessing the extent to which a chemical species is reactive. Value of E_{HOMO} is measure for ability of a molecule to donate electrons while the E_{LUMO} value indicates tendency of molecule for accepting electrons.

Hence high value of E_{HOMO} is an indication of inclination of AMBT molecule for donation of electron(s) to a suitable molecule which can accept electrons and which is provided with empty molecular orbital possessing low energy.

The values of E_{HOMO} is -8.179 eV, E_{LUMO} is 0.1067 eV and $E_{LUMO-HOMO}$ of 2-acetonyl-2-methyl benzothiazoline (AMBT) is recorded to be -8.0723 eV. The correlation of static first hyperpolarizability and energy gap is considered. AMBT has a reduced $E_{LUMO-HOMO}$ energy gap indicating its significant donor character and this enables the compound for nonlinear optical applications.

The highest occupied molecular orbitals (HOMO) in AMBT, are localized on the, N-H bonds of the molecule (Fig. 9). while the lowest unoccupied molecular orbitals (LUMO) are present on the C=O of acetonyl group , N-H, and aromatic C=C bonds of AMBT (Figure 10).

Ligand AMBT is considered as a potential donor molecule as well as acceptor molecule as HOMO and LUMO frontier orbitals are concentrated on all groups.

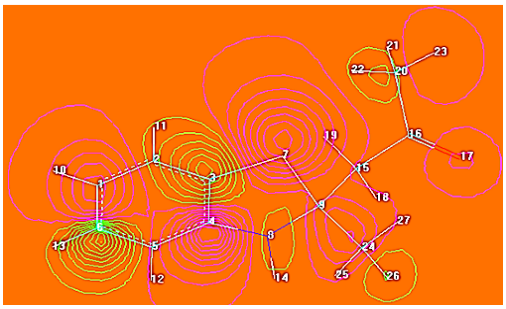


Fig. 9. HOMO (Highest occupied molecular orbital) of 2-acetonyl-2-methyl benzothiazoline (AMBT) E_{HOMO} = -8.179 eV

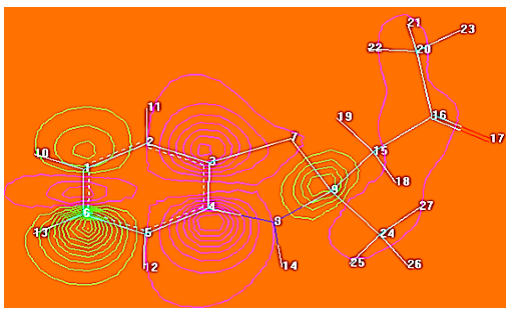


Fig. 10. LUMO (Lowest unoccupied molecular orbital) of 2-acetonyl-2-methyl benzothiazoline (AMBT) E_{LUMO} = 0.1067 eV

$E_{LUMO-HOMO}$ gap (Frontier molecular orbital energy gap) namely (Eg) is indication of chemical activity of the molecule. In the present study $E_{LUMO-HOMO}$ gap of 2-acetonyl-2-methyl benzothiazoline (AMBT) molecule as determined by Hyperchem is

8.2857 eV. As the value of $E_{LUMO-HOMO}$ gap (Eg) of AMBT is higher[25-26] it indicates that there is smaller delocalization of electrons.

Total charge density of AMBT- Molecular graph

Charge density is defined as the electric charge measured per unit surface area, or per unit volume of a object or field. The charge density value indicates the amount of stored charge for a definite field. It is estimated in forms of volume, area, or length.

Semi-empirical methods of HyperChem include only the valence charge density but not inner-shell electrons. An illustration of areas around the molecule with equal electron probability density is obtained by electron density surface. Molecular graph[28] of AMBT showing total charge density is given in Fig. 11. This indicates the size of AMBT molecule and its tendency for electrophilic attack.

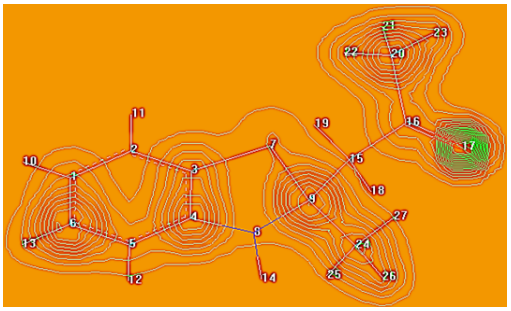


Fig. 11. Molecular graph of AMBT showing total charge density

Total spin density of AMBT-Molecular graph

Electron density is called as Spin density with respect to free radicals. Total spin density is difference of total electron density of electrons of two different spins. Empolying Hyperchem software it is possible to estimate Spin density and can be displayed. This is possible for chemical systems with unpaired electrons. Molecular graph[27] of AMBT showing total spin density is given in Figure 12.

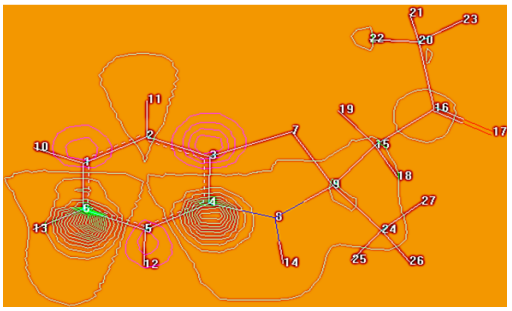


Fig. 12. Molecular graph of AMBT showing total spin density

Electrostatic potential of AMBT

The amount of work done for moving a unit charge from a reference point to a specific point without any acceleration inside the field is Electrostatic potential.Electrostatic potential is also known as electric field potential, electric potential, or potential drop.

Applying the routine MNDO and Polak–Ribiere conjugated gradient algorithm semi-empirical calculations were carried and the program MNDO is employed to perform semi-empirical computations. In AMBT molecule nucleophilic site is indicated by the areas close to the carbon atom and these are shown as green regions.

With the help of molecular electrostatic potential (MEP) it can be established that the reactive sites are present towards reactants which are positively or negatively charged. From this the possibility of presence of H-bonding and structure–activity relationships[28] in AMBT molecule are also established.

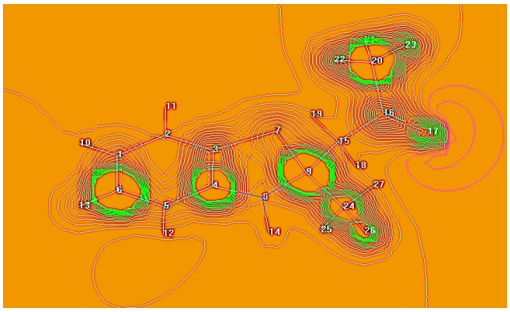


Fig. 13. Molecular graph of AMBT showing electrostatic potential

A strong coorelation of electrostatic potential, electronegativity, partial charges, and dipole moment in AMBT is confirmed from Quantum chemical calculations. The relative polarity of a molecule is strongly recognized by molecular electrostatic potential plot of AMBT (Figure 13).

CONCLUSION

In this study structural data, ab initio and electronic and vibrational contribution to polarizabilities of 2-acetonyl-2-methyl benzothiazoline (AMBT) were investigated. A valid knowledge of geometrical structure of AMBT is established from these numerical simulations.Theoretical study of Compound AMBT is performed applying Hyperchem 7.5 software and the results so obtained

were compared with Experimental data. A good agreement of experimental IR and NMR spectral data with theoretical spectral data obtained by using hyperchem is observed. Presence of only one dissociable proton in AMBT is indicated from the results obtained by Potentiometric titrations. Application of Hyperchem 7.5 software in determining QSAR properties and obtaining molecular graphs is well demonstrated in this Paper.

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Conflict of interest

The author declare that we have no conflict of interest.

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