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Geometric and Electronic Structure of Isoxazole and Isothiazole Derivatives by PM3 and Density Functional Theory

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The geometric and electronic structure of isoxazole and isothiazole and the effect of methyl group substitution in isoxazole and isothiazole derivatives have been studied by PM3 method and density functional theory. In the present work, the calculated values, namely net charges, bond length, dipole moments, ionization potentials, electron-affinities and heats of formation are reported and discussed in terms of the reactivity of isoxazole and isothiazole derivatives.

Key Words: PM3, DFT, HOMO, LUMO, Isoxazole, Isothiazole.

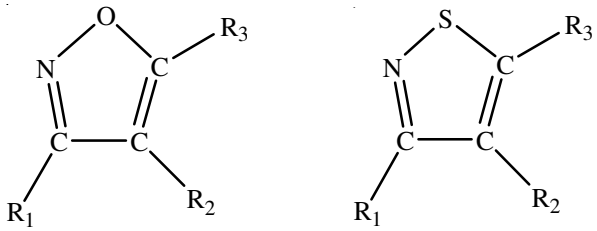
INTRODUCTION

Over the past decades, the frequency of resistance in antimicrobial agents has increased dramatically[1]. Therefore this places new emphasis on the search for alternative substances which are effective against organisms resistant to currently available drugs.

Isoxazole and isothiazole derivatives have been investigated intensively for the last several years because of their various biological activities. There are various experimental methods developed for the synthesis of isoxazole and isothiazole derivatives[2]; but it is a few theoretical works on isoxazoles and isothiazoles[3,4]. Recently, antiinflammatory[5] and antibacterial[6] properties have been ascribed to molecules possessing such heterocyclic functionalities.

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties, some of which researchers are not able to obtain otherwise[7]. To obtain highly accurate geometries and physical properties for molecules that are built from electronegative elements, expensive *ab initio* electron correlation methods are required[6]. Density functional theory methods offer an alternative use of inexpensive computational methods which could handle relatively large molecules[7].

In present case, we have studied the effect of methyl substitution on isoxazole systems (Fig. 1a) by using the PM3 method[8] which includes valence electrons and DFT method[7]. For a complete and comparative study, we have also taken isothiazole systems as well (Fig. 1b).



(1a) (1b)

Fig. 1. Scheme of isoxazoles (1a) and isothiazoles (1b)

1. $R_1 = R_2 = R_3 = H$
2. $R_1 = CH_3$, $R_2 = R_3 = H$
3. $R_1 = R_3 = H$, $R_2 = CH_3$
4. $R_1 = R_2 = H$, $R_3 = CH_3$
5. $R_1 = R_2 = CH_3$, $R_3 = H$
6. $R_1 = R_3 = CH_3$, $R_2 = H$
7. $R_1 = H$, $R_2 = R_3 = CH_3$
8. $R_1 = R_2 = R_3 = CH_3$

EXPERIMENTAL

All calculations were performed by using HyperChem 8.1 software[9]. The geometries of isoxazole and isothiazole and their methyl derivatives were first fully optimized by molecular mechanics (MM+), a force-field method (rms = 0.001 Kcal/Å). We also used the molecular dynamics for the conformational research, with following options: 1000 K, *in vacuo*, step size: 0.001 ps, relaxation time: 0.1 ps.

Further, geometries were fully re-optimized by PM3 method. A parallel study has been made using DFT/B3LYP exchange-correlation potential[10] with 6-31G** basis and *ab initio*/HF (6-31G**). The calculated results have been reported in the present work.

RESULTS AND DISCUSSION

The efficiency of PM3 method may be scrutinized by comparison with the results obtained by more elaborate calculation such as *ab inito* (HF/6-31G**) and DFT(B3LYP/6-31G**).

Present results concerning bond length values for isoxazole and isothiazole (Table-1) and charge densities (Table-2). We can note a good correlation between the PM3 and other quantum methods for all the bond length except for the S-N bond for with a discrepancy exists 1.73 Å (PM3), 1.66 Å (*ab initio*).

Charge densities calculated by the PM3 method provided a surprising result for electronic charge of carbon 3 in the isothiazole. The calculated values of methyl substituted isoxazole and isothiazole systems are given in Tables 3-6. In Table-3, heat of formation, dipole moment, HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) and their difference (ΔE) are reported for isoxazole, isothiazole and its methyl derivatives. It can be seen from the heat of formation data that approximately 9 kcal/mol is decreased at each addition of methyl group in the base compound isoxazole irrespective of the number of substitutions. The ionization potential values in compounds **1-8** show a decreasing trend which depicts increasing trend in the easy flow of charges in higher energy states of these compounds.

Oxygen and nitrogen contribute eight and seven electron density of isoxazoles, respectively. The net atomic charges on oxygen in the compounds **1-8** is weakened considerably (Tables-4), but on nitrogen is enhanced (Tables-4) except for compounds **3** and **7**.

In the mono-substituted methyl group category, the 5-methyl isoxazole (compound **4**) showing maximum charges on 4th position carbon (-0.0733) which leads to electrophilic substitution (Tables-4).

This is further supported by the least HOMO-LUMO energy gap (0.09645) (Tables-3) which depicts the chemical reactivity of the compound; higher is the HOMO-LUMO energy gap, lesser is the flow of electrons to the higher energy state, making the molecular hard and less reactive. On the other hand in lesser HOMO-LUMO gap, there is easy flow of electrons to the higher energy state making it softer and higher reactive

TABLE-1
CALCULATED BOND LENGTHS (Å) OF ISOXAZOLE AND ISOTHIAZOLE

Isoxazole	PM3	*ab initio*/HF (6-31G**)	DFT(B3LYP)/ (6-31G**)	Isothiazole	PM3	*ab initio*/HF (6-31G**)	DFT(B3LYP)/ (6-31G**)
O-N	1.425	1.380	1.474	S-N	1.727	1.655	1.762
N-C3	1.324	1.281	1.323	N-C3	1.320	1.286	1.324
C3-C4	1.445	1.427	1.431	C3-C4	1.441	1.434	1.433
C4-C5	1.371	1.340	1.361	C4-C5	1.366	1.347	1.365
C5-O	1.364	1.321	1.371	C5-S	1.719	1.711	1.764

TABLE-2
NET CHARGE DISTRIBUTION OF ISOXAZOLE AND ISOTHIAZOLE

Isoxazole	PM3	*ab initio*/HF (6-31G**)	DFT(B3LYP)/ (6-31G**)	Isothiazole	PM3	*ab initio*/HF (6-31G**)	DFT(B3LYP)/ (6-31G**)
O	-0.072	-0.440	-0.347	S	0.290	0.453	0.371
N	-0.042	-0.142	-0.172	N	-0.186	-0.567	-0.483
C3	0.003	0.107	0.116	C3	-0.292	0.103	0.083
C4	-0.256	-0.331	-0.184	C4	-0.059	-0.173	-0.048
C5	0.257	0.252	0.209	C5	-0.179	-0.344	-0.295

TABLE-3
ENERGIES OF ISOXAZOLE AND ITS DERIVATIVES

Compound	System	Heat of formation (Kcal/mol)	-HOMO (eV)	-LUMO (eV)	ΔE (eV)	μ (D)
1	Isoxazole	34.98	3.113	3.423	0.310	2.75
2	3-Methyl isoxazole	25.69	3.311	3.842	0.531	2.77
3	4-Methyl isoxazole	25.49	3.309	3.839	0.530	2.94
4	5-Methyl isoxazole	25.98	3.363	3.459	0.096	2.93
5	3,4-Dimethyl isoxazole	16.22	3.549	3.936	0.387	3.02
6	3,5-Dimethyl isoxazole	16.71	3.433	3.773	0.340	2.93
7	4,5-Dimethyl isoxazole	16.59	3.485	3.765	0.280	3.11
8	3,4,5-Trimethyl isoxazole	7.31	3.796	3.874	0.078	3.14

TABLE-4
NET ATOMIC CHARGES ON RING ATOMS FOR ISOXAZOLE COMPOUNDS **1-8**

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Oxygen	-0.0721	-0.0662	-0.0683	-0.0670	-0.0669	-0.0634	-0.0647	-0.0639
Nitrogen	-0.0416	-0.0467	-0.0402	-0.0419	-0.0425	-0.0469	-0.0410	-0.0423
C-3	0.0029	-0.0023	-0.0068	0.0143	-0.0060	0.0129	0.0082	0.0095
C-4	-0.0711	-0.0549	-0.0692	-0.0733	-0.0521	-0.0529	-0.0681	-0.0516
C-5	0.2573	0.2493	0.2289	0.2548	0.2256	0.2506	0.2588	0.2249
C-methyl 3	–	-0.0437	–	–	-0.0531	-0.0439	–	-0.0512
C-methyl 4	–	–	-0.0234	–	-0.0304	–	-0.0216	-0.0287
C-methyl 5	–	–	–	-0.0508	–	-0.0505	-0.0496	-0.0488

TABLE-5
ENERGIES OF ISOTHIAZOLE AND ITS DERIVATIES

Compound	System	Heat of formation (Kcal/mol)	-HOMO (eV)	-LUMO (eV)	ΔE (eV)	μ (D)
1	Isothiazole	28.38	2.495	3.329	0.834	2.43
2	3-Methyl isothiazole	19.26	3.371	3.562	0.191	2.51
3	4-Methyl isothiazole	18.73	3.276	3.465	0.189	2.68
4	5-Methyl isothiazole	20.39	3.292	3.468	0.176	2.70
5	3,4-Dimethyl isothiazole	11.58	3.437	3.793	0.356	2.79
6	3,5-Dimethyl isothiazole	11.25	3.489	3.737	0.248	2.72
7	4,5-Dimethyl isothiazole	11.40	3.324	3.778	0.454	2.91
8	3,4,5-Trimethyl isothiazole	2.45	3.769	3.863	0.094	2.95

TABLE-6
NET ATOMIC CHARGES ON RING ATOMS FOR ISOTHIAZOLE COMPOUNDS **1-8**

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Sulphur	0.2885	0.2835	0.2898	0.2731	0.2896	0.2746	0.2654	0.2799
Nitrogen	-0.1855	-0.1829	-0.1842	-0.1847	-0.1907	-0.1921	-0.1799	-0.1949
C-3	-0.2921	-0.2901	-0.3047	-0.2468	-0.0315	-0.2483	-0.2488	-0.0232
C-4	-0.0592	-0.0364	-0.0542	-0.0518	-0.1425	-0.0295	-0.0529	-0.1533
C-5	-0.1785	-0.1770	-0.1498	-0.1924	-0.3041	-0.1848	-0.1611	-0.2592
C-methyl 3	–	-0.0512	–	–	-0.0542	-0.0524	–	-0.0572
C-methyl 4	–	–	-0.0411	–	-0.0423	–	-0.0401	-0.0438
C-methyl 5	–	–	–	-0.0419	–	-0.0415	-0.0403	-0.0384

(HSAB principle). Compound **4** also shows an important dipole moment value. These results are in close agreement with the experiment[7].

In the case of dimethyl substituted isoxazole the C-5 position (compound **7**) shows maximum charge (0.2588), least HOMO-LUMO energy gap (0.280) and high dipole moment value (Table-4) which leads to preferential site of nucleophilic attack. This conclusion finds support from experimental evidence. In search of basicity, N atom is predicted to be the main basic centre of the isoxazole systems (**1-8**) in accordance with the electron densities (Table-4).

The C-H hyper-conjugation is the principal mode of electron release by the methyl group (pseudo-hetero atom) and stabilizes excited states more than ground state[8]. The order of increasing number of conjugated methyl groups decreases ionization potentials (IP) in the case of compounds **1-8** as expected[9] from those listed in Table-4. In trimethyl isoxazole, the O-atom has maximum charge (-0.0639) and predicted to be the most preferred site of electrophilic attack in comparison to N-atom.

In the present work, we have studied methyl substituted isothiazoles along the same line of isoxazoles is for a comparative study. It is interesting to note that the heat of formation approximately 9 Kcal/mol is decreased, for each addition of methyl group irrespective of oxygen or sulfur in the ring but the ionization potential values do not show decreasing trend as isoxazole systems due to diamagnetic nature of sulfur atom. There is net positive charge on sulfur and net negative charge on nitrogen in all isothiazole systems (compounds **1-8**).

In mono-substituted methyl derivatives, 5-methyl isothiazole is predicted to be more chemically reactive than 3-methyl isothiazole and 4-methyl isothiazole on the basis of least HOMO-LUMO energy gap (Table-5). The carbon C-3 in 5-methyl isothiazole shows maximum negative charge (-0.2468) leading to favoured site for electrophilic attack and nucleophilic attack on sulfur atom (+0.2731) (Table-6).

In disubstituted isothiazole systems, 3,5-dimethyl isothiazole (compound **6**) seems to be more reactive than the other two compounds **5** and **7**, due to least HOMO-LUMO energy gap (Table-3). The compound (**8**) is predicted to be the most reactive with least HOMO-LUMO energy gap of all the isothiazole systems and N-2 is the most preferential site for electrophilic attack (Table-4).

The 2-D and 3-D electrostatic potential and charge density maps are reported in support of present theoretical studies for the selected compounds

Conclusion

The present work on the isoxazoles and isothiazoles reveals that the substitution of methyl group does not affect the heat of formation but the electronic parameters due to charge disturbance in the ring. The 5-methyl and 4,5-dimethyl-substituted isoxazole compounds are found to be more reactive and in isothiazoles it is compound **4** and compound **6**. The PM3 molecular orbital and density functional methods can be used quite satisfactorily in predicting the chemical reactivity of the molecules and the effect of substitution of either electron donating or electron withdrawing groups.

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