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Ab-initio Molecular Orbital and DFT Studies on the Effect of Methyl Group Perturbations in Isoxazoles and Thiazoles

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The effect of methyl group substitution in isoxazoles and thiazoles have been studied by *ab-initio* and density functional methods. In the present work, the calculated values, namely, net charges, dipole moment, ionization potential, electron-affinity and heat of formation are reported and discussed in terms of the reactivity of isoxazole systems.

Key Words: ***ab-initio*, DFT studies, Isoxazoles, Thiazoles.**

INTRODUCTION

The quantum chemistry has provided very powerful tools known as molecular orbital methods to encode the electronic structure of molecules. Hickel molecular orbital method which deals with electrons in valence states of the molecules, has been extensively used in chemistry[1], biochemistry[2] and drug research[3]. Hence, it is of paramount importance to develop a quantitative treatment of molecular properties, accurate, reliable and cheap enough, to be of practical value in chemistry, particularly in those areas where experimental data are lacking or procedures fail. The correlation between electron density and reactivity of isoxazoles was examined and found to be valid[4].

Recently, Rao[5] reported his results on the use of HMO method to study the effect of methyl perturbation on isoxazole systems. In this, electrons had been taken into account and the reactivity was discussed. In our case, we have studied the effect of methyl substitution on isoxazole systems (Fig. 1) by using *ab-initio* and density functional theoretical methods, which include all electrons (core and valence). Our reported results are slighty different from the electrons-only systems, but closer to the experimental results. For a complete and comparative study, we have taken thiazole system also (Fig. 2).

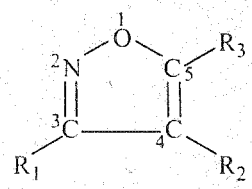

Fig. 1

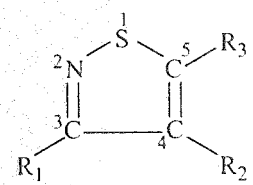

Fig. 2

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

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EXPERIMENTAL

All calculations were performed by using Hyperchem 7.5 software[6]. The geometries of isoxazole and thiazole and their methyl derivatives were first fully optimized by molecular mechanics (MM+), a force-field method (rms = 0.001 kcal/Å), by varying bond-dipole parameter for energy minimization. Further, it was fully reoptimized by using *ab-initio* molecular orbital method at 3–21 G level. The Polak-Reiberre potential gradient has been used for energy minimization.

The parallel study has been made at 3–21 G basis set level by using density functional theory, with B3LYP exchange-correlation potential. The calculated results have been reported in the present work.

RESULTS AND DISCUSSION

The calculated values of methyl substituted isoxazole and thiazole systems are given in Tables 1–4. In Table-1, the heats of formation, dipole moment, HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) and their difference (E) are reported for isoxazole and its methyl derivatives. It can be seen from the heats of formation data that approximately 38.5 a.u. is increased 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.

TABLE-1
ENERGETICS OF ISOXAZOLE AND ITS DERIVATIVES[a]

System	Heat of formation (a.u.)	HOMO (ev)	LUMO (ev)	E (ev)	μ (debye)
Isoxazole	–241.5	–8.5839	6.7170	15.3009	2.6442 (2.7331)
3-Methyl	–280.1	–8.3717	6.8646	15.2363	2.6709 (2.7503)
4-Methyl	–280.1	–8.2461	6.8649	15.1110	2.9410 (2.9537)
5-Methyl	–280.1	–8.1258	6.8834	15.0092	2.8451 (2.8401)
3,4-Dimethyl	–318.7	–8.1157	7.0366	15.1523	2.9628 (2.9675)
3,5-Dimethyl	–318.3	–8.1914	3.4729	11.6643	3.9608 (3.9215)
4,5-Dimethyl	–318.7	–7.7919	6.9617	14.7536	3.0619 (3.0421)
3,4,5-Trimethyl	–357.3	–7.4857	8.0821	15.5678	3.0046 (3.0175)

a. See Fig. 1.
The values in parentheses are from DFT study.

Oxygen and nitrogen contribute eight and seven electrons to the total electron density of isoxazoles. The net atomic charges (negative) on oxygen and nitrogen in the compounds **1–8** is enhanced considerably (Table-2) axcept for compounds[6].

TABLE-2
NET ATOMIC CHARGES ON RING ATOMS FOR COMPOUNDS **1–8**

	Compounds							
Position	1	2	3	4	5	6	7	8
Oxygen	–0.1323	–0.1361	–0.1350	–0.1326	–0.1395	–0.1014	–0.1439	–0.1658
Nitrogen	–0.1094	–0.1269	–0.1107	–0.1167	–0.1269	–0.0200	–0.1183	–0.0980
Carbon	0.0087	0.0847	0.0011	0.0080	0.0784	–0.0165	0.0010	0.0655
Carbon	–0.1129	–0.1197	–0.0324	–0.1259	0.0500	–0.0640	0.1272	0.1122
Methyl	—	0.0540	—	—	0.0341	0.0311	—	0.0260
Methyl	—	—	0.0401	—	0.0492	—	0.0580	0.0400
Methyl	—	—	—	0.0510	—	0.0322	0.0320	0.0460

*Using ab-initio method.

In the mono-substituted methyl group category, it is the 5-methyl isoxazole (compound **4**) showing maximum charges on oxygen (0.1426) and 4th position carbon (–0.1259) which leads to electrophilic substitution at 4-position, *i.e.*, formation of 4-sulphonated, 4-halogenated and 4-nitrated derivatives (Table-2). This is further supported by the least HOMO-LUMO energy gap (Table-1) which depicts the chemical reactivity of the compound, *i.e.*, higher is the HOMO-LUMO energy gap, lesser is the flow of electrons to the higher energy state, making the molecule 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 highly reactive (HSAB principle). Compound **4** also shows maximum dipole moment value. These results are in close agreement with the experiment[7].

In the case of dimethyl substituted isoxazole the C-4 position (Compound **6**) shows maximum negative charge (–0.064), least HOMO-LUMO energy gap and high dipole moment value (Table-2) which leads to preferential site of electrophilic 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 system (**1–8**) in accordance with the electron densities (Table-2).

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-2. In trimethhyl isoxazole, the O-atom has maximum charge (–0.1658) 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 thiazoles (Fig. 2) along the same line of isoxazoles for a comparative study. It is interesting to note that the heat of formation is approximately 39.0 a.u. for each addition of methyl group irrespective of oxygen or sulphur in the ring but the ionization potential

values do not show decreasing trend as isoxazole systems due to diamagnetic nature of sulphur atom (Table-3). There is net positive charge on sulphur and net negative charge on nitrogen in all thiazole systems (Compounds **1–8**).

In mono-substituted methyl derivatives, 4-methyl thiazole is predicted to be more chemically reactive than 3-methyl thiazoles on the basis of least HOMO-LUMO energy gap (Table-3). The carbon at 5th position (C-5) in 4-methyl thiazole shows maximum negative charge (0.1869) leading to favoured site for electrophilic attack and nucleophilic attack on sulphur-atom (Table-4).

TABLE-3
ENERGETICS OF THIAZOLE AND ITS DERIVATIVES[a]

System	Heat of formation (a.u.)	HOMO (ev)	LUMO (ev)	E (ev)	μ (debye)
Thiazole	–560.8	–7.7096	6.6948	14.4044	2.0759 (2.0800)
3-methyl	–599.4	–7.4837	6.8805	14.3642	1.9608 (1.9612)
4-methyl	–599.4	–7.4030	6.7772	14.1802	2.2323 (2.2431)
5-methyl	–599.4	–7.6023	6.7726	14.3749	2.4204 (2.4041)
3,4-dimethyl	–638.0	–7.2169	6.9760	14.1929	2.1412 (2.1437)
3,5-dimethyl	–678.0	–7.3734	6.9323	14.3057	2.2846 (2.3046)
4,5-dimethyl	–638.0	–7.2940	6.8323	14.1263	2.5048 (2.5248)
3,4,5-trimethyl	–676.6	–7.1267	6.9876	14.1143	2.3686 (2.3186)

[a]See Fig. 2.
The values in parentheses are from DFT study.

TABLE-4
NET ATOMIC CHARGES ON RING ATOMS FOR COMPOUNDS (1–8) OF THIAZOLE SYSTEM

Position	1	2	3	4	5	6	7	8
Sulphur	0.332	0.326	0.329	0.316	0.319	0.307	0.313	0.305
Nitrogen	–0.309	–0.325	–0.311	–0.313	–0.324	–0.326	–0.314	–0.328
Carbon	0.014	0.090	0.010	0.015	0.086	0.091	0.010	0.086
Carbon	–0.098	–0.102	–0.019	–0.110	–0.024	–0.115	–0.031	–0.036
Carbon	–0.175	–0.177	–0.187	–0.092	–0.187	–0.093	–0.103	–0.103
Methyl	—	0.035	—	—	0.030	0.032	—	0.027
Methyl	—	—	0.035	—	0.019	—	0.018	0.014
Methyl	—	—	—	0.038	—	0.036	0.031	0.036

*Using *ab-initio* method.

In di-substituted thiazole systems, 4,5-dimethyl thiazole (Compound **6**) seems to be more reactive than the other two compounds **4** and **5**, 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 thiazole systems and N-2 positive is the most preferential site for electrophilic attack (Table-4). The 2-D electrostatic potential and charge density maps are reported in support of our theoretical studies for the selected compounds.

Conclusions

The present study on the isoxazole and thiazole systems 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 3,5-dimethyl-substituted isoxazole compounds are found to be more reactive and in thiazoles it is 4-methyl and 4,5-dimethyl-substituted compounds. The *ab-initio* 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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