ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Electronic Structure and Effect of Methyl Substitution in Oxazole and Thiazole by Quantum Chemical Calculations.

Salah Belaidi*, Radhia Mazri, Malika Mellaoui, Aicha Kerassa and Houmam Belaidi.

Group of Computational and pharmaceutical Chemistry, LMCE Laboratory, Department of chemistry, Faculty of sciences, University of Biskra, 07000, Biskra, Algeria.

ABSTRACT

Geometric and electronic structure of oxazole and thiazole and the effect of methyl group substitution in thiazole and oxazole have been studied by PM3, ab initio 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 oxazole and thiazole systems.

Keywords: PM3, DFT, HOMO, LUMO, oxazole and thiazole.

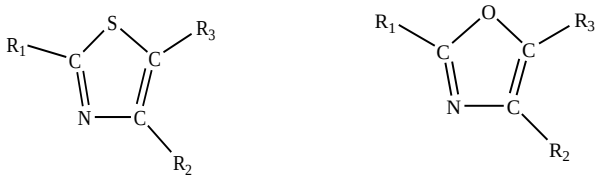
Corresponding author

ISSN: 0975-8585

INTRODUCTION

Aromatic heterocyclic compounds containing nitrogen and sulphur have an important role in biological activity of many compounds and industrial uses. These compounds are widely used for manufacturing biocides, fungicides, pharmaceuticals, and dyes. The thiazole moiety represents an important part of vitamin B1 and epothilone, a potent anti-cancer drug. In general, thiazoles and oxazoles are well represented in biomolecules [1, 2].

In this work, we have studied the molecular structures of oxazole and thiazole. The effect of methyl substitution on oxazole systems (Fig.1a) by using the PM3 method [3] which includes valence electrons and quantum methods [4]. For a complete and comparative study, we have taken thiazole systems also (Fig. 1b).



(1a) (1b)

Fig 1: Scheme of thiazoles (1a) and oxazoles (1b).

1. R1=R2=R3=H
2. R1=CH3.R2=R3=H
3. R1=R3=H.R2=CH3
4. R1=R2=H.R3=CH3
5. R1=R2=CH3.R3=H
6. R1=R3=CH3.R2=H
7. R1=H.R2=R3=CH3
8. R1=R2=R3=CH3

EXPERIMENTAL

All calculations were performed by using HyperChem 8.1 software [5] and Gaussian 09 program package [6]. The geometries of thiazole, oxazole and their methyl derivatives were first fully optimized by molecular mechanics (MM+), a force-field method (rms = 0.001 Kcal /Å). Geometries were fully re-optimized by PM3 method. A parallel study has been made using DFT/B3LYP exchange-correlation potential [7] 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**).A very good agreement between predicted geometries (bond lengths, bond angles) (Table 1) and corresponding experimental data [8]. Charge densities calculated by the ab initio/HF are similar than DFT/ B3LYP method (Table 2). The geometry of the thiazole and

ISSN: 0975-8585

oxazole is planar; dihedral angles are almost equal to zero (Figure 2). Thiazoles are characterized by a larger delocalization of the p-electrons than the corresponding oxazoles and therefore possess larger aromatic character.

Table 1: Calculated bond lengths (angstrom) of oxazole and thiazole

Oxazole	PM3	Ab initio/HF (6-31G**)	DFT/(B3LYP) (6-31G**)	Thiazole	PM3	Ab initio/HF (6-31G**)	DFT/(B3LYP) (6-31G**)
O–C2	1,372	1.329	1.391	S1-C2	1.724	1.727	1.749
C2–N	1,326	1.268	1.301	C2-N3	1.304	1.275	1.300
N–C4	1.416	1.388	1.417	N3-C4	1.372	1.378	1.377
C4–C5	1.368	1.33	1.353	C4-C5	1.367	1.342	1.365
C5–O	1.379	1.355	1.404	C5-S1	1.713	1.726	1.733

Table 2: Net charge distribution of oxazole and thiazole

Oxazole	Ab initio/HF (6-31G**)	DFT(B3LYP) (6-31G**)	Thiazole	Ab initio/HF (6-31G**)	DFT/(B3LYP) (6-31G**)
O	−0.527	−0.439	S1	0.270	0.245
N	−0.387	−0.317	C2	-0.064	-0.075
C2	0.519	0.429	N3	-0.454	-0.362
C4	−0.022	−0.017	C4	0.098	0.101
C5	0.107	0.124	C5	-0.390	-0.301

(a) (b)

Fig 2: 3D conformation of thiazole (a) and oxazole (b) (Gauss View 5.0.8)

The calculated values of methyl substituted oxazole and thiazole systems are given in Tables 3-6. In Tables 3, heat of formation, dipole moment, HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) and their difference (ΔE) are reported for oxazole, thiazole and its methyl derivatives.

It can be seen from the heat of formation data that approximately 9 kcal/mol is increased at each addition of methyl group, in the base compound oxazole 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 oxazoles, respectively.

The negative atomic charge on oxygen is increased considerably for methyl derivatives, but on nitrogen is enhanced except for compounds 4(Table 4).

In the monosubstituted methyl group category, the 5-methyl oxazole (compound 4) shows maximum charge on 2th position carbon (0.390)which leads to nucleophilic substitution (Table 4). This is further supported by the least HOMO-LUMO energy gap (13.76) (Table 3) which depicts the chemical reactivity of the compound; the higher is the HOMO-LUMO energy gap, the 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 more reactive (HSAB principle: hard and soft acids and bases). Hard bases have highest occupied molecular orbitals (HOMO) of low energy, and hard acids have lowest unoccupied molecular orbitals (LUMO) of high energy [9]. Compound 4 also shows maximum dipole moment value. These results are in close agreement with the experiment [10].

In the case of dimethyl-substituted, oxazole the C-2-position (compound 6) shows maximum charge (0.564), least HOMO-LUMO energy gap (13.58), and high dipole moment value (Table 3) 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 oxazole systems in accordance with the electron densities (Table 4).

The C–H hyperconjugation is the principal mode of electron release by the methyl group (pseudohetero atom) and stabilizes excited states more than ground state [11].

In the order of increasing number of conjugated methyl groups, ionization potentials (IPs) decreases in the case of compounds1–8 as expected from those listed in (Table 3).

The 2, 4, 5-trimethyl oxazole (compound8) is predicted to be the most reactive with least HOMO-LUMO energy gap of all the oxazole systems and, respectively, C2, C4, and C5 are the most preferential sites for nucleophilic attack (Table 4).

These results are in close agreement with the experiment, [10] and we found in our literature that the majority of trisubstituted oxazoles have biological activity [10,12,13,14].

We note also that the methyl substituent (donor effect) has the effect of increasing the energy of the HOMO, with little change of the LUMO (Table 3).

ISSN: 0975-8585

Table 3: Energies of oxazole and its derivatives

System		Heat of formation Kcal/mol	-HOMO (eV)	LUMO (eV)	ΔE (eV)	μ(D)
1	Oxazole	-1.58	9.534	4.491	14.024	1.58
2	2-methyl oxazole	-10.57	9.180	4.629	13.811	1.38
3	4-methyl oxazole	-11.22	9.222	4.678	13.900	1.35
4	5-methyl oxazole	-10.40	9.064	4.691	13.755	2.16
5	2,4-dimethyl oxazole	-20.19	8.908	4.804	13.709	1.06
6	2,5-dimethyl oxazole	-19.32	8.747	4.801	13.578	1.88
7	4,5-dimethyl oxazole	-19.95	8.780	4.854	13.634	1.89
8	2,4,5-trimethyl oxazole	-28.86	8.497	4.956	13.454	1.57

Table 4: Net atomic charges on ring atoms for oxazole compounds 1-8

Compound	1	2	3	4	5	6	7	8
Oxygen	-0.5273	-0.5584	-0.5338	-0.5558	-0.5626	-0.5839	-0.5619	-0.5910
C-2	0.3869	0.5754	0.3 910	0.3902	0.5701	0.5642	0.3948	0.5685
Nitrogen	-0.5190	-0.5495	-0.5300	-0.5105	-0.5653	-0.5455	-0.5289	-0.5663
C-4	-0.0217	-0.0188	0.1385	-0.0422	0.1426	-0.0288	0.1185	0.1230
C-5	0.1069	0.1024	0.0890	0.2914	0.0841	0.2899	0.2743	0.2709
C-methyl 2	—	-0.3949	—	—	-0.3768	-0.3769	—	-0.3759
C-methyl 4	—	—	-0.3437	—	-0.3436	—	-0.3413	-0.3410
C-methyl 5	—	—	—	-0.3733	—	-0.3734	-0.3676	-0.3675

In the present work, we have studied methyl substituted thiazoles (Fig. 1) along the same line of oxazoles is for a comparative study. It is interesting to note that the heat of formation data that approximately 28 kcal/mol is increased at each addition of methyl group in the base compound thiazole irrespective of the number of substitutions.

The ionization potential values in compounds 1–8 show a decreasing trend, which means increasing trend in the easy flow of charges in higher energy states of these compounds. Sulfur and nitrogen contribute 16 and 7 electron density of thiazoles, respectively.

In the mono-substituted methyl group category, the 4-methyl thiazole (compound 3) showing maximum charge on 5th position carbon (-0.433) which leads to electrophilic substitution (Table-6). This is further supported by the least HOMO-LUMO energy gap (12.63) (Table-5) 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 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 more reactive (HSAB principle: hard and soft acids and bases). Hard bases have highest occupied molecular orbitals (HOMO) of low energy and hard acids have lowest-unoccupied molecular orbitals (LUMO) of high energy [15,16].

Compound 3 also shows a high dipole moment value. These results are in close agreement with the experiment [17].

In the case of dimethyl substituted thiazole the C4 position (compound 7) shows a maximum positive charge (0.234),least HOMO-LUMO energy gap (12.46) and high dipole moment value (Table 5) 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 thiazole systems in accordance with the electron densities (Table-6). 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 [11].

In the order of increasing number of conjugated methyl groups, ionization potentials (IPs) decrease in the case of compounds 1-8 as expected from those listed in (Table-5).

The 2,4,5-trimethylthiazole (compound 8) is predicted to be the most reactive with least HOMO-LUMO energy gap of all the thiazole systems and, respectively C2,C4,are the most preferential sites for nucleophilic attack and C5 for electrophilic attack (Table-4).

These results are in close agreement with the experiment[11] and we found in literature that the majority of tri-substituted thiazoles have an important biological activity [11,18,19].

It is also noted that the methyl substituent (donor effect) has the effect of increasing the energy of the HOMO, with little change of the LUMO (Table-4).

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

Table 5: Energies of thiazole and its derivatives

System		Heat of formation Kcal/mol	-HOMO (eV)	LUMO (eV)	ΔE (eV)	μ(D)
1	Thiazole	259.667	9.468	3.348	12.816	1.552
2	2-Methyl thiazole	287.121	9.135	3.512	12.647	1.036
3	4-Methyl thiazole	285.574	9.117	3.508	12.625	1.124
4	5-Methyl thiazole	359.742	9.174	3.462	12.636	1.843
5	2,4-Methyl thiazole	313.079	8.821	3.668	12.489	0.616
6	2,5-Methyl thiazole	314.204	8.862	3.620	12.482	1.310
7	4,5-Methyl thiazole	313.413	8.862	3.602	12.464	1.526
8	2,4,5-Methyl thiazole	340.939	8.592	3.758	12.350	0.950

ISSN: 0975-8585

Table 6: Net atomic charges on ring atoms for thiazole compounds 1-8

Compound	1	2	3	4	5	6	7	8
Sulphur 1	0.2701	0.2669	0.2693	0.2660	0.2503	0.2480	0.2498	0.2399
C 2	-0.0641	0.0962	-0.0694	-0.0753	0.0840	0.0810	-0.0744	0.0861
N3	-0.4544	-0.4993	-0.4778	-0.4561	-0.5025	-0.4841	-0.4655	-0.5024
C4	0.0984	0.0994	0.2645	0.0723	0.2579	0.0787	0.2342	0.2436
C5	-0.3901	-0.4131	-0.4337	-0.2446	-0.4284	-0.2509	-0.2777	-0.2796
C-Methyl 2	–	-0.4038	–	–	-0.3875	-0.3868	–	-0.3871
C-Methyl 4	–	–	-0.3742	–	-0.3563	–	-0.3565	-0.3568
C-Methyl 5	–	–	–	-0.3751	–	-0.3585	-0.3541	-0.3539

CONCLUSION

The present work on the oxazole 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 2,5-dimethyl substituted oxazole compounds are found to be more reactive and in thiazoles it is 4-Methyl thiazole and 4,5-Methyl thiazole. 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 with drawing groups.

REFERENCES

[1] Hegelund F, Wugt Larsen b R, Palmer M H. J Mol Spectroscopy 2007; 244: 63–78.
[2] Garbarczyk J, Kamyszeka G, Boese R. J Mol Str 1999; 479: 21–30.
[3] Stewart JJP. J Comp Chem 1989; 221: 20.
[4] Hehre W J. Practical Strategies for Electronic Structure Calculations Wave function Inc Irvine California 1995.
[5] Hypercube, Inc. Hyper Chem Molecular Modeling System USA 2007.
[6] Frisch M J, Trucks G W, Schlegel H B, Scuseria G E, Robb M A, Cheeseman J R, Scalmani G, Barone V, Mennucci B, Petersson G A, Nakatsuji H, Caricato M, Li X, Hratchian H P, Izmaylov A F, Bloino J, Zheng G, Sonnenberg J L, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery J A, Peralta J E, Ogliaro F, Bearpark M, Heyd J J, Brothers E, Kudin K N, Staroverov V N, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant J C, Iyengar S S, Tomasi J, Cossi M, Rega N, Millam J M, Klene M, Knox J E, Cross J B, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann R E, Yazyev O, Austin A J, Cammi R, Pomelli C, Ochterski J W, Martin R L, Morokuma K, Zakrzewski V G, Voth G A, Salvador P, Dannenberg J J, Dapprich S, Daniels A D, Farkas Foresman J B, Ortiz J V, Cioslowski J, Fox D J. Wallingford CT 2009.
[7] Becke A D. J Chem Phys 1993; 5648: 98.

[8] Nygaafu L, Asmussen E, Hog J H, Maheshwari R C, Nielsen C H, Petersen I B, Rastrup-Andersen J, Sorensen G . J Mol Str 1971; 8: 225-233
[9] Miessler G L, Tarr D A. Inorganic Chemistry, Upper Saddle River NJ USA 2nd edition 1999.
[10] Weissberger A. The Chemistry of Heterocyclic Compounds John Wiley & Sons, New York NY USA 1993.
[11] Kier LB. Molecular Orbital Theory in Drug Research Academic Press New York NY USA 1971.
[12] Agirbas H, Guner S, Budak F et al. Bioorg Med Chem 2007; 15: 2322–2333.
[13] Shablykin O V, Brovarets V S, Drach B S. Russian J Gen Chem 2007; 77: 1308–1309.
[14] Martin YC. Quantitative Drug Design, Marcel Dekker, New York, USA 1978.
[15] Nygaard L, Asmussen E, Hog J H, Maheshwari R C, Nielsen C H, Petersen L B, Rastrup-Andersen J, Sorensen G O. J Mol Str 1971; 8: 225.
[16] Miessler G L, Tarr D A. Inorg Chem 1999; 2: 181.
[17] Weissberger A. The Chemistry of Heterocyclic Compounds, John Wiley & Sons New York 1993.
[18] Olszewski T K, Boduszek B. Tetrahedron 2010; 66: 8661.
[19] Geronikaki A, Vicini P, Dabarakis N, Lagunin A, Poroikov V, Dearden J, Modarresi H, Hewitt M, Theophilidis G. Eur J Med Chem 2009; 44: 473.