Asian Journal of Chemistry; Vol. 25, No. 10 (2013), 5337-5339

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.14177

Quantum Chemistry Study on Structure-Activity Relationship of Pyrimidinyl Thiourea Derivative

HUI-MIN BI*, PENG-TAO XIE, XING-QUAN CHAI, YAN LIU, FU-YING YOU, JUN-PING HU and JING ZHANG

Handan Key Laboratory of Organic Small Molecule Materials, Handan College, Handan 056002, Hebei Province, P.R. China

*Corresponding author: E-mail: binbi99@163.com

(*Received*: 7 June 2012; *Accepted*: 3 April 2013) AJC-13200

In order to investigate the relationship between the structure and the activity of pyrimidinyl thiourea derivative, the geometry optimization and single point energy of all compounds were calculated by HF methods at 6-31G* basis sets level, the information of electron density, energy levels, main composition and proportion of the frontier orbitals were obtained. It is found that the antifungicidal activities of these kinds of compounds have a relationship with the energy of frontier molecules orbital (HOMO and LUMO).

Key Words: Pyrimidinyl thiourea derivative, Activity, Quantum chemical study, Frontier orbitals.

INTRODUCTION

The biological activity of thiourea derivatives is excellent for the structure of (-NH-CS-NH-), such as insecticidal and acaricide, antifungicidal, antivirus, herbicide and regulation of plant growth *etc*., it is a hot issue about molecular design, synthesis and biological activity of thiourea derivatives[1-5]. Some heterocyclic active group inserted to the structure of thiourea derivatives recent years, it is enlarged the development space of these compound remarkably. The biological activity of pyrimidine derivatives is excellent in lots of research and reports[6,7], according to the principle of superposition of activated factor, 21 pyrimidinyl thiourea derivatives were synthesized by Sun *et al.*[8] and tested their biological activity.

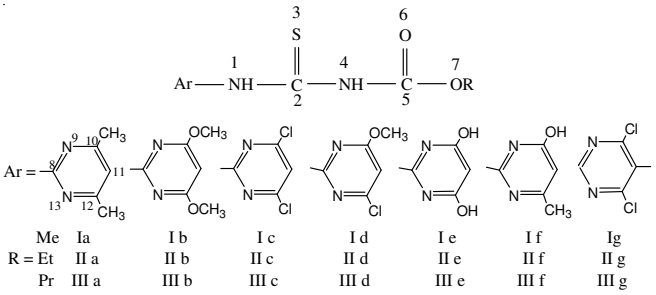
Quantum chemistry study on structure-activity relationship could analyze the active site of drug, it is due to the activity and mechanism of action of compounds is related with their structure and conformation. The geometry optimization and single point energy of all compounds were calculated, the information of electron density, energy levels, main composition and proportion of the frontier orbitals were obtained.

EXPERIMENTAL

The geometries of all compounds were optimized using the *ab initio* HF with the 6-31G* basis set. Harmonic vibrational frequencies calculated at the same level were used for characterization of stationary points as a minimum. All quantum calculations were performed with the Gaussian 03 program.

RESULTS AND DISCUSSION

Stability configurations and natural charge: The structure of compounds as follows:



The atom natural charge of compounds are given in Table-1. These data show that, the negative charge is mainly concentrated in the N(4), N(1) of thiourea group, O(6), O(7) of carboxyl and N(9), N(13) of pyrimidine ring, These atoms make the electronegative area, they could combine with positive area of receptor. the positive charge is mainly concentrated in the C(5) of carboxyl, C(8), C(12) of pyrimidine ring and C(2) of thiourea group, These atoms make the positive area, they could combine with negative area of receptor. The atom of S(3) is negative in series I and positive in series II and III.

Energy, main composition and proportion of the frontier molecules orbitals: According to the molecular orbital theory (MO), the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) have the greatest influence on the activity of compounds. The reaction between active molecule and receptor macromolecular operated on the frontier molecules orbitals. E_{HOMO} is the energy of HOMO, which relate to the ability of electron donor. E_{LUMO} is the energy of LUMO, which relate to the ability of acceptance of electronic. For pesticide molecules, too low-E_{LUMO} or too high-E_{HOMO} means that the molecule itself

TABLE-1
ATOM NATURAL CHARGE OF COMPOUNDS

Compound	N(1)	C(2)	S(3)	N(4)	C(5)	O(6)	O(7)	C(8)	N(9)	C(10)	C(11)	C(12)	N(13)
Ia	-0.704	0.400	-0.217	-0.768	1.140	-0.680	-0.654	0.757	-0.677	0.372	-0.405	0.375	-0.624
Ib	-0.703	0.398	-0.207	-0.767	1.140	-0.677	-0.658	0.785	-0.754	0.740	-0.493	0.740	-0.709
Ic	-0.702	0.386	-0.180	-0.764	1.140	-0.677	-0.651	0.763	-0.659	0.329	-0.423	0.332	-0.603
Id	-0.722	0.345	-0.076	-0.767	1.142	-0.687	-0.655	0.769	-0.605	0.315	-0.438	0.733	-0.692
Ie	-0.716	0.355	-0.097	-0.767	1.142	-0.687	-0.656	0.780	-0.681	0.733	-0.507	0.729	-0.724
If	-0.703	0.399	-0.210	-0.767	1.140	-0.680	-0.653	0.773	-0.701	0.370	-0.450	0.746	-0.696
Ig	-0.683	0.422	-0.252	-0.767	1.146	-0.731	-0.640	0.374	-0.555	0.321	0.009	0.284	-0.559
IIa	-0.718	0.100	0.309	-0.772	1.100	-0.742	-0.658	0.756	-0.680	0.373	-0.428	0.370	-0.642
IIb	-0.719	0.092	0.327	-0.776	1.100	-0.744	-0.667	0.747	-0.684	0.721	-0.488	0.706	-0.644
IIc	-0.723	0.157	0.211	-0.781	1.095	-0.730	-0.652	0.759	-0.651	0.178	-0.388	0.187	-0.626
IId	-0.720	0.136	0.274	-0.777	1.108	-0.740	-0.677	0.752	-0.661	0.250	-0.451	0.711	-0.641
IIe	-0.722	0.149	0.267	-0.778	1.110	-0.739	-0.689	0.747	-0.691	0.703	-0.487	0.709	-0.635
IIf	-0.719	0.153	0.253	-0.781	1.092	-0.742	-0.650	0.746	-0.666	0.369	-0.457	0.712	-0.639
IIg	-0.800	0.211	0.123	-0.832	1.089	-0.769	-0.633	0.371	-0.563	0.103	0.114	0.128	-0.566
IIIa	-0.714	0.086	0.325	-0.776	1.097	-0.741	-0.651	0.756	-0.680	0.374	-0.428	0.370	-0.643
IIIb	-0.719	0.092	0.326	-0.777	1.107	-0.745	-0.663	0.747	-0.684	0.721	-0.489	0.707	-0.644
IIIc	-0.720	0.113	0.260	-0.776	1.103	-0.733	-0.655	0.757	-0.653	0.178	-0.390	0.187	-0.627
IIId	-0.721	0.135	0.275	-0.776	1.092	-0.739	-0.647	0.752	-0.661	0.250	-0.452	0.711	-0.641
IIIe	-0.721	0.147	0.263	-0.776	1.081	-0.736	-0.639	0.747	-0.691	0.703	-0.487	0.709	-0.636
IIIf	-0.718	0.154	0.251	-0.782	1.094	-0.742	-0.648	0.746	-0.666	0.369	-0.457	0.711	-0.639
IIIg	-0.807	0.229	0.108	-0.835	1.118	-0.760	-0.657	0.357	-0.564	0.100	0.123	0.125	-0.567

activity is too strong, it is easy to be metabolized in organism, The effect of pesticide is difficult to control, so the E_{LUMO} or E_{HOMO} of the pesticide molecule should be suitable to estimate expected value[9-11].

Table-2 showed the E_{LUMO} of IIc and IIIc is low comparatively, it could accept electronic easily, On the other hand, the E_{HOMO} of IIc is low comparatively too, the ability is weak to provide electronic. The experimental results show that the biological activity of compound IIc and IIIc is higher. Therefore, the mechanism is that receptor provide electronic to pesticide molecule possibly. The E_{LUMO} of Ic is the lowest, the activity is too strong possibly and it is easy to be metabolized in organism. The analyses of theoretical results agree with the experimental data very well.

Table-3 showed the main composition and proportion of E_{HOMO} of compounds I in the N(1) and S(3) of thiourea group concentrated and the main composition and proportion of E_{LUMO} in the C of thiourea group and pyrimidine ring [C(2), C(8), C(10) and C(12)] concentrated; the main composition and proportion of E_{HOMO} of compounds II and III in the N(4) and N(1) of thiourea group and C(11) of pyrimidine ring concentrated and the main composition and proportion of E_{LUMO} in the C(2) and S(3) of thiourea group concentrated.

The main composition and proportion of E_{HOMO} of compound IIc is increased significantly in the S(3), the charge of S(3) is positive, The main composition and proportion of E_{HOMO} of other compounds in the N(4) and N(1), their charge is negative. The main composition and proportion of E_{HOMO} of compounds have significant difference, so the E_{HOMO} of compound IIc is relatively minimum, Its ability is weak to provide electronic. The main composition and proportion of E_{LUMO} of compound IIc in the positive area concentrated, so it has the ability to accept electronic. The pyrimidine ring of IIc connected with two -Cl, whose electron withdrawing ability is strong especially, so the positive of C(8) is highest comparatively, so the activity of IIc have great impact. The S(3) of Ic is negative and the proportion of E_{LUMO} of C(11) and N(9) is high in compound Ic, so the activity of Ic is lower than IIc and IIIc. The energy of E_{HOMO} of other compounds is high comparatively, their activity is low because of the low electron withdrawing ability.

TABLE-2
ENERGY OF THE FRONTIER MOLECULES ORBITALS

Compound	**Ia**	**Ib**	**Ic**	**Id**	**Ie**	**If**	**Ig**
E_{HOMO} (eV)	-8.531	-8.696	-8.974	-8.839	-8.840	-8.676	-9.168
E_{LUMO} (eV)	2.415	2.384	1.651	2.224	2.285	2.403	2.075
ΔE (eV)	10.946	11.080	10.625	11.063	11.125	11.079	11.243
	IIa	**IIb**	**IIc**	**IId**	**IIe**	**IIf**	**IIg**
E_{HOMO} (eV)	-8.530	-8.675	-8.946	-8.769	-8.833	-8.651	-9.138
E_{LUMO} (eV)	2.415	2.404	1.664	2.156	2.261	2.423	2.102
ΔE (eV)	10.945	11.079	10.610	10.925	11.094	11.074	11.240
	IIIa	**IIIb**	**IIIc**	**IIId**	**IIIe**	**IIIf**	**IIIg**
E_{HOMO} (eV)	-8.523	-8.667	-8.938	-8.761	-8.823	-8.642	-9.127
E_{LUMO} (eV)	2.421	2.414	1.671	2.162	2.270	2.430	2.112
ΔE (eV)	10.944	11.081	10.609	10.923	11.093	11.072	11.239

TABLE-3
MAIN COMPOSITION AND PROPORTION OF FRONTIER MOLECULES ORBITAL

Compd.	HOMO	LUMO
Ia	3S(61.3), 1N(15.6), 4N(5.52), 12N(5.38) 2C(4.55), 9N(2.76),	12C(25.3), 9N(16.3), 2C(11.9), 10C(7.87), 8C(6.14), 3S(5.76), 4N(1.74), 5C(1.33), 6O(1.11)
Ib	3S(56.2), 1N(15.4), 11C(9.18), 4N(4.84), 2C(4.14), 13N(3.18),	2C(32.1), 8C(16.4), 3S(15.5), 11C(8.41), 9N(4.79), 4N(4.37), 10C(4.10), 13N(3.08), 5C(2.99), 6O(2.57)
Ic	3S(76.8), 1N(8.53), 4N(5.88), 2C(4.03), 6O(2.64), 8C(1.05)	12C(33.6), 9N(19.3), 10C(13.2), 13N(6.94), 2C(6.45), 8C(5.52), Cl(4.25)3S(3.61), 11C(3.06)
Id	3S(72.0), 4N(6.44), 1N(6.98), 2C(4.05), 9N(3.80), 6O(2.11),11C(1.54)	2C(33.2), 3S(19.2), 8C(12.5), 11C(8.25), 10C(4.60), 13N(3.99), 4N(3.59), 5C(2.85), 6O(1.84), 9N(1.88)
Ie	3S(73.6), 1N(6.65), 4N(6.26), 2C(3.76), 9N(3.89), 6O(2.09), 11C(1.18)	2C(38.3), 3S(21.2), 8C(10.2), 11C(5.03), 4N(3.93), 5C(3.31), 9N(3.07), 13N(2.52), 6O(2.17), 1N(2.03)
If	3S(77.6), 1N(8.22), 4N(5.76), 2C(3.89), 6O(2.51)	2C(30.0), 8C(17.3), 3S(14.7), 11C(10.8), 10C(5.07), 13N(4.42), 4N(4.33), 9N(3.33), 5C(2.61), 6O(2.30)
Ig	3S(72.3), 1N(11.7), 4N(6.05), 2C(3.38), 10C(1.06), 11C(1.08)	8C(20.9), 11C(19.6), 2C(16.9), 12C(15.1), 3S(6.54), 9N(6.22), 10C(3.42), 5C(1.71), 1N(1.90), 13N(1.14)
IIa	1N(33.7), 4N(20.0), 11C(17.5), 13N(7.50), 9N(6.39), 8C(3.81), 3S(1.75)	2C(42.0), 3S(38.6), 5C(4.15), 6O(1.70), 8C(2.25)
IIb	1N(35.7), 4N(22.2),11C(14.7),13N(7.63), 9N(5.51), 8C(3.45), 5C(1.85), 3S(1.83),	2C(41.3), 3S(38.6), 5C(3.54), 6O(1.61), 8C(3.19)
IIc	3S(28.3), 11C(21.5), 1N(14.5), Cl(6.43), 4N(5.90), 13N(4.31), 8C(3.71),10C(3.10)	5C(3.50), 6O(1.32), 2C(40.9), 3S(36.0), 8C(6.30)
IId	1N(34.2), 4N(21.2), 11C(15.5), 13N(8.32), 3S(2.06), 8C(3.30), 0C(1.81),	2C(42.8), 3S(37.6), 8C(3.38), 5C(3.41), 6O(1.56)
IIe	1N(35.2), 4N(21.9), 11C(14.8), 13N(7.86), 9N(5.43), 8C(3.49), 3S(2.34)	2C(43.3), 3S(37.2), 8C(3.06), 5C(3.43), 6O(1.52)
IIf	1N(35.2), 4N(21.9), 11C(15.1), 13N(7.51),9N(5.70), 8C(3.66), 3S(2.06)	2C(42.7), 3S(36.8),5C(3.48), 8C(3.32), 6O(1.56)
IIg	3S(59.9), 4N(15.1), 1N(15.6), 6O(2.24)	2C(45.3), 3S(37.0),5C(2.38), 11C(1.86)
IIIa	1N(33.8), 4N(20.8),11C(17.0),13N(7.40), 9N(6.22), 8C(3.70), 10C(1.90), 3S(1.61)	2C(41.6), 3S(39.2), 5C(4.25), 6O(1.61), 8C(2.11)
IIIb	1N(35.9), 4N(22.6), 11C(14.3), 13N(7.53), 9N(5.40), 8C(3.36), 3S(1.75),	2C(41.4), 3S(38.7), 5C(3.53), 8C(3.20), 6O(1.63)
IIIc	3S(26.7), 11C(21.7), 1N(16.7), Cl(6.24), 4N(5.44), 13N(4.56), 8C(3.68), 0C(3.07)	5C(3.92), 6O(1.40), 2C(40.2), 3S(37.5), 8C(5.32)
IIId	1N(34.3), 4N(21.6), 11C(15.3), 13N(8.26), 9N(4.67), 8C(3.25), 3S(1.99),	2C(42.6), 3S(37.5), 8C(3.34), 5C(3.66), 6O(1.64)
IIIe	1N(35.5), 4N(22.4), 11C(14.5), 13N(7.79), 9N(5.35), 8C(3.42), 3S(2.18),	5C(4.07), 6O(1.77), 2C(42.6), 3S(36.9), 8C(3.01)
IIIf	1N(35.2), 4N(22.2), 11C(14.9), 13N(7.46), 9N(5.66), 8C(3.62), 3S(2.02)	5C(3.42), 6O(1.53), 2C(43.0), 3S(36.9), 8C(3.30)
IIIg	3S(58.3), 1N(17.5), 6O(2.05), 4N(12.2)	5C(2.11), 6O(1.16), 2C(43.8), 3S(35.9), 8C(1.43)

Conclusion

The characteristics of HOMO and LUMO are the main factors to influence antifungicidal activities of these kinds of compounds. The mechanism is that receptor provide electronic to pesticide molecule possibly. The results indicate that thiourea group and pyrimidine ring might be an important active site, of which the potency of electric charge translocation has a great influence on the antifungicidal activity of this kind of compounds. The group who has electron withdrawing ability connected with pyrimidine ring, it could improve the antifungicidal activity effectively.

ACKNOWLEDGEMENTS

This project was supported by the Science and Technology Projects of Hebei Province (Contract No. 10273939) and Handan Key Laboratory of Organic Small Molecule Materials, Handan College.

REFERENCES

1. A. Hakan, D. Nizam, O.S. Nefise and K. Nevzat, *Asian J. Chem.*, **18**, 1710 (2006).
2. Y.J. Li, Z.G. Zhang, K. Jin, Q.J. Peng, W.G. Ding and J. Liu, *Acta Chim. Sin.*, **65**, 834 (2007).
3. O. Zulbiye and C.D. Adeviye, *Asian J. Chem.*, **19**, 1455 (2007).
4. X.D. Yang, *Asian J. Chem.*, **20**, 2147 (2008).
5. S. Saeed, N. Rashid, M. Ali, R. Hussain and P.G. Jones, *Eur. J. Chem.*, **1**, 221 (2010).
6. Q. Wu, B.A. Song, L.H. Jin and D.Y. Hu, *Chin. J. Org. Chem.*, **29**, 365 (2009).
7. Y.M. Patel, K.M. Mehta and K.C. Patel, *Int. J. Chem. Technol. Res.*, **3**, 1734 (2011).
8. X.H. Sun, Y.F. Liu and H.F. Wang, *Chem. Eng.*, **34**, 54 (2006).
9. T.B. Wei, Y.L. Leng, Y.C. Wang, J.H. Zhang and Y.M. You, *Chin. J. Org. Chem.*, **29**, 216 (2009).
10. G.F. Yang, H.Y. Liu, Y.H. Zheng, Z.H. Yang and X.F. Yang, *Acta Chim. Sin.*, **56**, 729 (1998).
11. D.B. Zhang, Y.H. Ren, D.W. Fu, B. Yan, J.R. Song and X.Q. Lv, *Acta Chim. Sin.*, **66**, 2409 (2008).