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

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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, antiviral, herbicide and regulation of plant growth *etc.*, it is a hot issue about molecular design, synthesis and biological activity of thiourea derivatives¹⁻⁵. 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-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)
IIIf	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.

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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).