EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

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COMPUTATIONAL REACTION MECHANISM STUDY OF THE SCHIFF BASE FORMATION BETWEEN PARA-SUBSTITUTED ANILINE AND PYRROLE-2-CARBALDEHYDE

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ABSTRACT

Computational reaction mechanism study based on the Restricted Hartree- Fock calculations (RHF/3-21G) of the formation of Schiff base of para-methoxyaniline, para-methylaniline and anline with Pyrrole-2-carbaldehyde was conducted. The reaction mechanism was found to involve two steps, namely: (1) formation of a carbinolamine and (2) dehydration of the carbinolamine to give the final schiff base, through six-membered ring transition states. The carbinolamine is intermediate and dehydration is rate determining step of the reaction. The formation of Schiff base between the para-substituented aniline and pyrrole adehyde requires the contribution of one auxiliary water molecule as a true reactive in order to facilitate proton transfer, and allows the nucleophilic attack of the incoming amine to carbonyl group. The para-methoxy substituent has less energy barrier than the other two substituents, according to more electron withdrawing effect.

KEYWORDS: Schiff base, Six-membered ring transition state, Restricted Hartree-Fock.

INTRODUCTION

A Schiff base is a neutral molecule with an electron pair and contains a carbon-nitrogen double bond. This class of compound was discovered in 1864 by Hugo Schiff, when he reacted an aldehyde and amine, leading to a Schiff base.[1]

The Schiff bases are also called as imines[2], anilis and azomithines. The kinetic studies of Schiff base formation as well as other carbonyl addition reaction have been interesting to chemists for some time. Schiff bases derived from anilines and its derivative with aromatic aldehyde have a wide variety of applications in biological[3,4] and analytical chemistry.[5] Schiff bases are known to be neoplasm inhibitors[6,7], antiviral[8], anticonvulsants[9], antimicrobial[10], anticancer[11], plant growth regulator[12] and antituburecular agents.[13]

Schiff bases formation involves a two step reaction between the carbonyl compound and the amino compound. First, addition takes place to form a carbinolamine which then undergoes dehydration.[14] Both step are reversible and subject to general acid – base catalyst.[15]

The study of substituent effects on molecules containing the fundamental functional groups of organic chemistry by the use of quantum chemical calculations has been the subject of intense interest in recent years.[16] The effect of substituents on chemical reactions is accepted by workers as steric and electronic factors. Other factors are also important in individual cases.[17] The steric effect is determined by the size of the substituent. The presence of electron releasing or withdrawing substituents is known as the electronic effect.[18] The resonance (delocalization of π -electrons) effect is a stabilizing effect. It leads to electron withdrawal from a negatively charged center or releases electrons to a positively charged center. Because the overall electronic effect is a combination of inductive, field and resonance effects, groups like NH_2 and OCH_3 are electron releasing (by resonance) in some cases, depending on the structure even though they are electron withdrawing when only field and inductive effects are considered.

In our previous work[19,20], Theoretical study based on the Restricted Hartree- Fock calculations (RHF/3-21G) of the formation of Schiff base of para-substituted aniline with furaldehyde and thiophene-2-carbaldehyde were conducted. The reaction mechanism was found to involve two steps, namely: (1) formation of a carbinolamine and (2) dehydration of the carbinolamine to give the final Schiff base, through six-membered ring transition states.

In this work, the substituent effect on the reactivity of pyrrole-2-carbaldehyde with para-substituted aniline as regards to Schiff base formation will be discussed by means of the description of the energy, the geometry, and the topology of the intermediate and the stability of transition state structures involved in such reaction. This information provides a detailed energy profile for Schiff base formation that matches conclusions which have been obtained experimentally.

METHOD OF CALCULATIONS

A molecular complex consisting of pyrrole-2-carbaldehyde, aniline, para-methoxy, para-methyl aniline and one water molecule was chosen as model compound to study the Schiff base formation. The purpose of including one water molecule in the model molecular complex was not the simulation of water solvation environment but its consideration as reactive species for the processing of the reaction. In the present study Restricted Hartree-Fock (RHF) calculations were performed with the Gaussian09 [21] software packages, running in an Intel Pentum (R) 1.86 GB personal computer. All structures were fully optimized at the Restricted Hartree Fock (RHF) level, using the 3-21G basis set in gas phase. Also, the geometries of the reactants, products, intermediates, and transition states involved in the reactions were all fully optimized by using RHF/3-21G. The structures thus obtained were subjected to vibrational analysis calculations toward their characterization as local minima (all positive force constants) or transition states (one imaginary force constant only). For the later structures, IRC[22] calculations were performed along the transition vector defined by the vibration mode of this imaginary frequency in order to asses that the saddle point structure connected downhill the corresponding forward and backward minima. This methodology allowed the identification of the reaction intermediates and transition state structures along the reaction path. The standard state is 1 atm, which is the default in Gaussian calculations.

RESULTS AND DISCUSSION

The mechanism of the Schiff base formation reactions of para-substituted-aniline with pyrrole-2-carbaldehyde involves two steps, namely: (1) formation of carbinolamine (1-3 in scheme 1) and (2) dehydration of the carbinolamine to give the imine (3-5 in scheme 1), scheme 1 shows the atoms directly involved in the reaction and the overall process. Figure 1 shows the energy profiles for the process in the gas phase with RHF/3-21G. Tables 1 and 3 show the relative energies, ΔH°, ΔG° and ΔS° data for the structures involved, and table 2

show the bond length for each substituent of the structures of the reaction path from reactants to products in Angstrom.
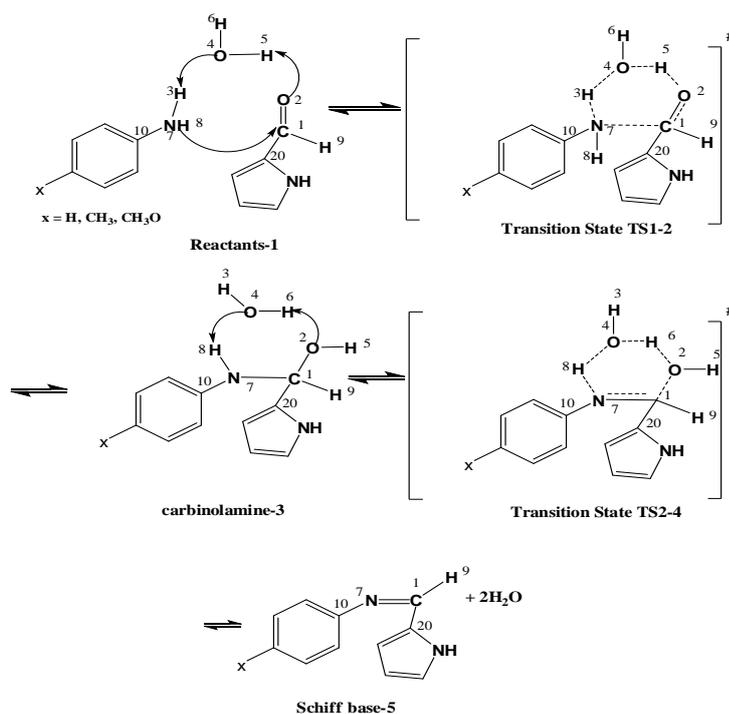
Scheme 1: **Mechanism of Schiff base formation between para-substituted aniline and Pyrrole-2-carbaldehyde**
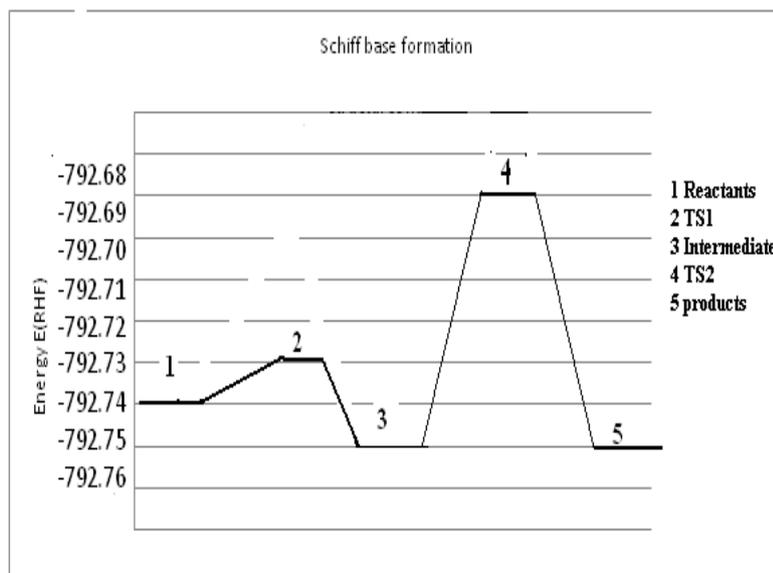

Figure 1: Energy profile for the reaction, for Schiff base formation between para-methoxyaniline and Pyrrole-2-carbaldehyde, Energy is in a.u.

Table 1: Energies (RHF) for each of the structures of the reaction path from the standard thermochemistry output of a frequency calculation [a]

Structure	E(RHF)		
	X=CH$_3$O	X=CH$_3$	X=H
1[b]	-792.7487	-718.3443	-679.5249
2[c]	-792.7314	-718.2998	-679.4786
3[d]	-792.7574	-718.3329	-679.5122
4[e]	-792.6967	-718.2652	-679.4445
5[f]	-792.7542	-718.3178	-679.4971

[a]All structures were fully optimized. Cartesian coordinates of all structures are available as supplementary material. Energy in a.u.

[b,c,d,e,f]   reactants, cyclic transition state-TS1, intermediate, cyclic transition state-TS2 and product respectively (refer to Scheme 1).

Carbinolamine Formation: The starting point for this concerted step process is structure 1(scheme 1) where the incoming amino group (N7) of the para-substituted aniline is the site of the nucleophilic attack on the carbonyl carbon in pyrrole-2-carbaldehyde (C1). The distance N7-C1 is 2.242, 5.423 and 5.420 Å at the start for methoxy, methyl and hydrogen substituents respectively (table 2, scheme 1). The existence of auxiliary water molecule in this reaction facilitates the transfer of the amine proton to the water molecule H3…O4 which distance is 1.927, 1.952 and 1.945 Å for methoxy, methyl and hydrogen substituents respectively (table 2, scheme 1). The simultaneous transfer of water proton to aldeyhde oxygen H5…O2 which distance is 1.650, 1.724 and 1.7230 Å for methoxy, methyl and hydrogen substituents respectively (scheme 1 and figure 1). This mechanism occurs via six-membered ring transition state TS1-2 clearly involving the formation of an N7-C1 bond (1.672 Å), H3-O4 bond (1.927 Å) and O2-H5 bond (1.650 Å). Then partial breaking of N7…H3 (1.006 Å), O4…H5 bond (0.992 Å) and C1…O2 bond (1.239 Å) occurs in the case of methoxy substituent. The energy barriers for the reaction of para-methoxy-aniline with pyrrole-2-carbaldehyde to form six-membered ring transition state (TS1) is 10.855, 27.913 and 29.053 kcal mol^{-1} for methoxy, methyl and hydrogen substituents respectively (table 3), downhill from these transition state structure, the system evolves to the carbinolamine form 3 (scheme1) via the formation of an N7-C1 covalent bond and complete transfer of the water proton (H5) to carbonyl oxygen (O2), and complete transfer of amine proton (H3) to water oxygen (O4), scheme 1 and figure 2.This results explained that the formation of six – membered ring transition state in the case of methoxy substituent is of less energy (10.855

kcal mol^{-1}) than methyl (27.913 kcal mol^{-1}) and hydrogen (29.053 kcal mol^{-1}) according to electron withdrawing power of methoxy substituent.

Water has been shown to take part in similar reactions in other simple systems where the energy barrier for carbinolamine formation by proton transfer was found to be reduced if explicit water molecules were used to facilitate proton transfer [23]. On the basis of experimental work on other molecular systems, these protonation reactions are pH-dependent in acid-base equilibria.[24,25]

Table 2: Bond length for each substituent of the structures of the reaction path from reactants to products in Angstrom

Bond length in Å	Reactants-1	Transition state TS1-2	Carbinol-amine-3	Transition state TS2-4	Schiff base-5
N7-C1, x=CH$_3$O	2.2424	1.6723	1.5478	1.3206	1.2805
x=CH$_3$	5.4225	1.6757	1.5058	1.3220	1.2727
x =H	5.4200	1.6800	1.5065	1.3234	1.2728
H3(8)…O4,x=CH$_3$O	1.9274	1.6304	1.0118	1.3580	1.0120
x=CH$_3$	1.9515	1.6223	0.9885	1.3419	0.9888
x =H	1.9455	1.6147	0.9880	1.3311	0.9883
H5(6)…O2,x=CH$_3$O	1.6508	1.2109	0.9757	1.1142	0.9934
x=CH$_3$	1.7237	1.2062	0.9727	1.1152	0.9857
x =H	1.7230	1.2031	0.9727	1.1143	0.9856
N7…H3(8),x=CH$_3$O	1.0068	1.0589	1.5981	1.1442	1.5320
x=CH$_3$	1.0028	1.0606	1.8426	1.1544	1.8079
x =H	1.0032	1.0621	1.8487	1.1618	1.8121
O4…H5(6),x=CH$_3$O	0.9922	1.2080	1.6186	1.3115	1.5088
x=CH$_3$	0.9648	1.2127	1.9479	1.3095	1.6983
x =H	0.9856	1.2159	1.9468	1.3105	1.6987
C1…O2, x=CH$_3$O	1.2397	1.3529	1.4127	1.9864	1.1040
x=CH$_3$	1.2306	1.3527	1.4240	1.9729	3.0997
x =H	1.2307	1.3520	1.4238	1.9628	3.0959
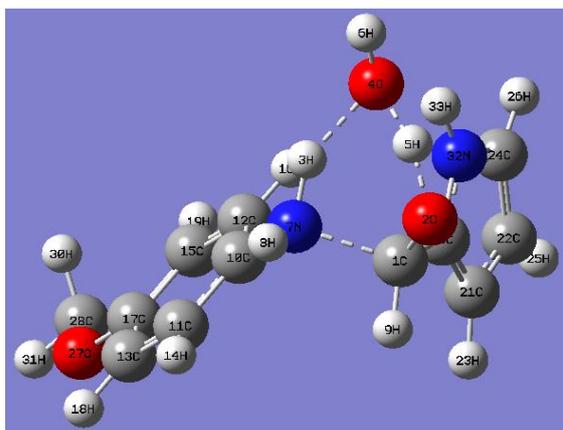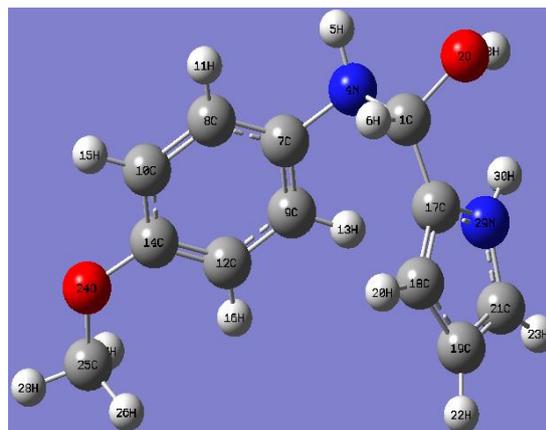
Transition state -TS1   **Intermediate carbinolamine -3**
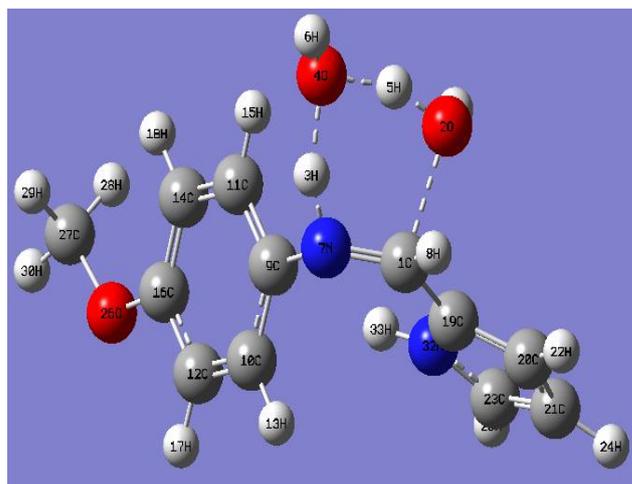
Transition state -TS2

Figure 2: Optimized structures of six-membered ring transitions states TS1, TS2 and carbinolamine intermediate 3 of the above reaction in the case of methoxy substituent calculated by RHF/3-21G.

Table 3: Calculated energies of reactants, six-membered ring transition states, carbinolamine and products using RHF/3-21G in kcal mol^{-1} [a,b] of methoxy, methyl and Hydrogen substituent's,

Compound	ΔE kcal mol^{-1}	ΔG kcal mol^{-1}	ΔH kcal mol^{-1}	ΔS Cal mol^{-1}K^{-1}
CH$_3$O 1[c]	0	0	0	0
TS1-2[d]	10.855	23.763	2.297	-133.874
3[e]	-16.315	-14.544	-1.114	45.044
TS2-4[f]	38.089	33.093	20.768	-41.34
5[g]	-36.081	-25.772	-2.215	79.013
CH$_3$ 1[c]	0	0	0	0
TS1-2[d]	27.913	25.024	12.976	-86.874
3[e]	-20.770	-14.950	-2.623	39.334
TS2-4[f]	42.481	32.766	22.147	-35.616
5[g]	-33.006	-26.353	-2.636	79.551
H 1[c]	0	0	0	0
TS1-2[d]	29.053	25.674	0.037	-85.992
3[e]	-21.084	-16.093	-2.739	44.791
TS2-4[f]	42.481	34.172	21.952	-40.988
5[g]	-33.006	-26.707	-2.718	80.462

[a] All structures were fully optimized. Cartesian coordinates of all structures are available as supplementary material.

[b] Energies reported relative to the sum of energies of separated reactants.

[c,d,e,f,g] Reactants, cyclic transition state-TS1, intermediate, cyclic transition state-TS2 and product respectively (refer to Scheme 1).

Schiff base formation: In this step the carbinolamine is dehydrated to give the corresponding Schiff base through the six-membered ring transition state TS2 (Scheme 1, figure 2) in the presence of the auxiliary water molecule to facilitate the reaction, in which the second amine proton (H8) transfer to water oxygen(O4), simultaneously the water proton (H6) is transferred to hydroxyl oxygen (O2) of carbinolamine , and C1-O2 start to break to release water molecule, this step causes the formation of an imine double bond between C1 and N7. In fact the distance between these two atoms decreases from 1.547 Å in structure 3 to 1.320 Å in structure 4 (table 2, Scheme 1) in the case of methoxy substituent. The energy barriers for the reaction of carbinolamine with water to form six-membered ring transition state (TS2) is 54.404, 63.251 and 63.565 kcal mol^{-1} for methoxy, methyl and hydrogen substituents respectively (table 3).

If we consider the energy values (table 3) calculations (RHF/3-21G) show that the initial attack of Pyrrole aldehyde has energy barrier of is 10.855, 27.913 and 29.053 kcal mol^{-1} for methoxy, methyl and hydrogen substituents respectively, whereas the potential energy barrier for dehydration of the carbinolamine is 54.404, 63.251 and 63.565 kcal mol^{-1}. This suggests that the carbinolamine deyhdration is the rate-determining step of the process. Similar conclusions for this type of reaction have been drawn from the theoretical and experimental results for other simpler systems.[26,27, 28]

If Gibbs energy is considered, RHF calculations show barriers of 23.763, 25.024 and 225.674 kcal mol^{-1}for initial attack for methoxy, methyl and hydrogen substituents respectively, and 47.637, 47.716 and 50.265 kcal mol^{-1} for the dehydration of carbinolamine to form the Schiff base. If we compare the effect of these substituents in the case of dehydration of carbinolamine to form the Schiff base, we find that methoxy is also more favorable than the other two substituents.

According to calculations, the energy of formation of our Schiff base from these substituents are in the following order: methoxy(-792.7487a.u)>methyl(-718.344 a.u) > H (-679.5249 a.u) table1.

CONCLUSIONS

On the bases of our Schiff base formation model, water plays a prominent role in all protons transfers, by which the two amine protons were exchanged through two six-membered ring transition states to form carbinolamine intermediate and Schiff base respectively. Dehydration of carbinolamine to form Schiff base is rate-determining step.

The para-methoxy substituent is more powerfull electron withdrawing effect than the other two substituents to form six – membered ring transition state and dehydration of carbinolamine to form the Schiff base.

SUPPLEMENTARY INFORMATIONS

Supplementary information (output results of RHF calculations) are available free of charge on request.

REFERENCES

1. Schiff H., Ann. Suppl., 1864; 3: 343-345.
2. Jerry March; Advanced Organic Chemistry, Mechanism and Methods of Determining Them, 4th ed. Wiley India Pvt, Ltd. 1992.
3. Jadhav SM, Shelke VA, Munde AS, Shankarwar SG, Chondhekar TK, J. Coord. Chem., 2010; 63: 4153.
4. Shelke VA, Jadhav SM, Shankarwar SG, Munde AS, Chondhekar TK, J. Korean Chem. Soc., 2011; 55: 436.
5. Patel PR and Zele S. Ind. Chem., 1999; 38A: 563.
6. Chatterjee SP, Sur B and Chaudhary SR, Oncology., 1990; 47(5): 433.
7. Jolly VS, Orient J. Chem. 1994; 10(3): 297.
8. Wag PH, Keck JG and Michael L, J. Med. Chem., 1990; 33(2): 608.
9. Cates AL and Rasheed. Pharm. Res., 1984; 6: 271.
10. Shelke VA, Jadhav SM, Shankarwar SG, Munde AS, Chondhekar TK,. Bull. Chem. Soc. Ethiop., 2011; 25(3): 1.
11. Sharma KP, Jolly VS and Phatak. Ultra Sci.Phys.Sci., 1998; 10(2): 263.
12. Gaodeng Xuexiao Huaxe Xuebao and D Yin. 1996; 7(1): 91.
13. Polasa H. Indian .J. Pharm.Sci., 1985; 47: 202.
14. A Lapworth A, J. Chem. Sco., 1903 P Bartlett. J. Am. Chem. Sco., 1932, 54, 2881.
15. Kyu Sun Bai and Leussing DL, J. Am. Chem. Soc., 1967; 89: 24.
16. McAllister M. A. and Tidwell T. T., J. Org. Chem., 1994; 59: 4506.

17. Morrison R. T and Boyd R. N., Organic Chemistry, 3rd ed., Allyn and Bacon, Inc., Boston: 1986, p. 36.

18. Carey F. A. and Sundburg R. J., Advanced Organic Chemistry, Part A: Structure and Mechanism 3rd ed., Plenum Press, New York, USA: 1990, p. 196 – 208.

19. Musa E. Mohamed; Christina Y. Ishak ; Hajir I.Wahbi, Der Chemica Sinica, 2011; 2(4):133-139.

20. 20. Musa E. Mohamed; Christina Y. Ishak ; Hajir I.Wahbi, International Journal of Pharmaceutical and Phytopharmacological Research, 2012; 2(3): 185-189.

21. M. J. Frisch, G. W. T., H. B. Schlegel, G. E. Scuseria, ; M. A. Robb, J. R. C., J. A. Montgomery, Jr., T. Vreven, ; K. N. Kudin, J. C. B., J. M. Millam, S. S. Iyengar, J. Tomasi, ; V. Barone, B. M., M. Cossi, G. Scalmani, N. Rega, ; G. A. Petersson, H. N., M. Hada, M. Ehara, K. Toyota, ; R. Fukuda, J. H., M. Ishida, T. Nakajima, Y. Honda, O. Kitao, ; H. Nakai, M. K., X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, ; C. Adamo, J. J., R. Gomperts, R. E. Stratmann, O. Yazyev, ; A. J. Austin, R. C., C. Pomelli, J. W. Ochterski, P. Y. Ayala, ; K. Morokuma, G. A. V., P. Salvador, J. J. Dannenberg, ; V. G. Zakrzewski, S. D., A. D. Daniels, M. C. Strain, ; O. Farkas, D. K. M., A. D. Rabuck, K. Raghavachari, ; J. B. Foresman, J. V. O., Q. Cui, A. G. Baboul, S. Clifford, ; J. Cioslowski, B. B. S., G. Liu, A. Liashenko, P. Piskorz, ; I. Komaromi, R. L. M., D. J. Fox, T. Keith, M. A. Al-Laham, ; C. Y. Peng, A. N., M. Challacombe, P. M. W. Gill, ; B. Johnson, W. C., M. W. Wong, C. Gonzalez, and J. A. Pople, ; ; Revision B.03 ed.; Gaussian, Inc. : Pittsburgh PA, 2003.

22. Fukui, K., "The path of chemical-reactions - The IRC approach," Acc. Chem. Res., 1981; 14: 363-68.

23. Hall, N. E.; Smith, B. J. J. Phys. Chem. A 1998; 102: 4930–4938.

24. Baymak, M. S.; Zuman, P. Tetrahedron, 2007; 63: 5450–5454.

25. Muangsiri, W.; Kearney, W. R.; Teesch, L. M.; Kirsch, L. E. Int.J. Pharm., 2005; 289: 133–150.

26. Antoni Salva`, Josefa Donoso,* Juan Frau, and Francisco Mun˜oz* J. Phys. Chem. A, 2003; 107: 9409-9414.

27. Ortega-Castro, Adrover, J. M. ; Frau, J.; Salva, A.; Donoso, J. and Mun˜oz, F. J. Phys. Chem. A, 2010, 114, 4634–4640.

28. Liao, R.-Z.; Ding, W.-J.; Yu, J.-G.; Fang, W.-H.; Liu, R.-Z.J. Comput. Chem., 2008; 29: 1919–1929.