Molecular Orbital Calculations for the Reactions of 2,5-dimethyl Pyrrole with Phenylsulfonyl Chloride

Mi-Kyung Seo, Jin-Beom Kim, Seeyearl Seong,†,* and Young-key Shim*

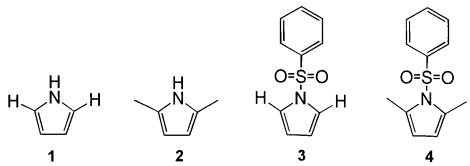
Korea Research Institute of Chemical Technology, Bio-Organic Science Division, Yusong-Gu, P.O. Box 107, Taejon 305-600, Korea
†Computer Aided Molecular Design Center, Soongsil University, Dongjak-Gu, Sangdo-5 Dong, Seoul 156-743, Korea
Received April 22, 1999

Electrophilic substitutions on β-position of 2,5-dimethyl pyrrole have been investigated theoretically. The electron donating methyl groups enrich electron densities on C-3, C-4 positions and π* interactions with methyl groups substituted on C-2 and C-5 positions pushed up the HOMO level of the pyrroles consequently induce rapid substitutions on C-3, C-4 sites. Substitution of phenylsulfonyl group on nitrogen stabilized LUMO levels through weak π bonding interactions. Unexpected deoxidation reaction underwent on the sulfonyl group substituted at C-3 position. The structures were solved by X-ray crystallography. Meanwhile, gas phase HF/6-31G* and density functional method (B3LYP/6-31G*) calculations gave favorable energies for 1-phenylsulfinyl pyrrole (**6**) over 3-phenylsulfinyl pyrrole (**5**) by 3.6-4.7 kcal/mol which is contrary to the experimental result. However the methods involve the effects of molecular polarizability and solvent, molecular dynamics (MD) and ab-initio self consistent reaction field (SCRF) calculations showed same trend as experiments. According to MD calculations, compound **5** is more stable than compound **6** by 4.15 kcal/mol and the SCRF, HF/6-31G* calculations gave more stable energy value for structure **5** than **6** by 0.03 kcal/mol.

Introduction

Pyrroles are component of many natural products which show interesting biological activities. In the reaction of pyrrole ring systems, the nucleophiles substitute preferentially at the 1- or 2- position and direct introduction of the substituent at C-3 position is mostly difficult as it contains π-excessive heteroatom.[1-3] Some photoinduced aroylation of five membered ring systems has been described by Oda *et al.* [4] Therefore, new synthetic methods leading to 3-substituted pyrroles have been required and the investigation of efficient methods for preparing C-3 substituted pyrroles is one of the important goals in pyrrole chemistry because of their frequent uses for obtaining various biological active compounds such as porphyrins. For the substitution on C-3 position, Friedel-Crafts acylation or alkylation on pyrrole bearing electron-withdrawing substituent at C-2[5-9] or N-1[10,11] has been widely investigated.

Friedel-Crafts acylations on N-phenylsulfonylpyrrole, masked acyl group[12] at C-3 position in order to obtain 2,4-diacylpyrroles also have been studied extensively, but arylsulfonylation on 2,5-disubstituted pyrrole has not been reported yet. We have been investigated to prepare new pyrroles having symmetric and asymmetric substituents on 3,4-position by manipulating 2,5-dimethylpyrrole with phenylsulfonyl chloride, but 1,3-diphenylsulfonyl-pyrrole was obtained unexpectedly.[13] The electronic structures of some pyrrole derivatives (Scheme 1) and the reasons behind formation of 1,3-diphenylsulfonyl-2,5-dimethyl pyrrole as well as rare deoxidation reaction of 1,3-bis (phenylsulfonyl)-2,5-(dimethyl)pyrrole are studied theoretically.

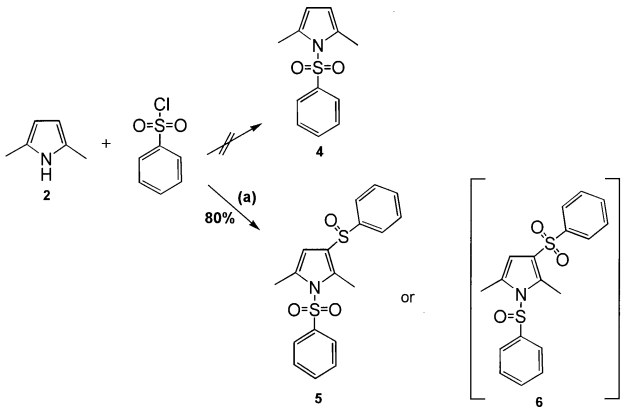


Scheme 1

Methods of Calculations

Calculations were performed using Gaussian 94[14] and Cerius2[15] programs on both Cray-C90 and O2 Silicon Graphics computer systems. These programs search for the optimum geometries using the criteria of minimum energy. All the structures were studied by molecular mechanics (MM, MD),[16] PM3[17] and HF/6-31G*[14,18] level calculations. The input data consists of a set of bond distances, bond angles and dihedral angles arranged in Z-matrix. The effects of electron correlation on the relative energies of the molecules were taken into account by performing Becke's gradient corrected exchange functional[19] combined with Lee, Yang and Parr's gradient corrected correlation functional.[20] The RHF/6-31G* polarization basis set is used to fully geometry optimization of the molecules.

Formation of 1-sulfonyl-3-sulfinyl pyrrole. Direct Friedel-Crafts acylation on 2,5-dimethylpyrrole also gives 3,4-symmetric acyl compounds, but normally the yield is very low (<5%) when no electron withdrawing groups are on the substituted pyrroles.[13] Therefore we introduced phenylsulfonyl group on N1-position using phenylsulfonyl chloride as usual. Expecting 1-phenylsulfonyl-2,5-dimethylpyrrole, 2,5-dimethylpyrrole **2** reacted with phenylsulfonyl chloride, tetrabutylammonium hydrogensulfate as a phase



Scheme 2. (a) n-Bu_4NHSO_4 50% NaOH, CH_2Cl_2, 0 °C to 40 °C, 20h.

transfer catalyst, and 50% sodium hydroxide solution in dichloromethane as described in the literature.[11] However, 1,3-disubstituted product **5** was obtained unexpectedly instead of N1-phenylsulfonyl pyrrole **3** (Scheme 2). The product, however was confirmed to lack one oxygen by Mass spectrum, that can not tell which sulfur loses one oxygen. Another possible compound **6** could be obtained, but the structure was confirmed as 1-phenylsulfonyl-3-phenylsulfinyl-2,5-dimethylpyrrole,[21] **5** by X-ray crystallography (Figure 1). The structures optimized by ab-initio RHF/6-31G* calculations compared with experimentals in Table 1 and 2.

In order to confirm disubstituted pyrrole, the compound **5** was further oxidized with OXONE and tetrabutylammonium hydrogensulfate in dichloromethane at room temperature for overnight to give 1,3-diphenylsulfonyl-2,5-dimethylpyrrole, **7** quantitatively[22] (Scheme 3), which showed very stable in standing at normal condition. The crystal structure of this product also can be determined by X-ray crystallography (Figure 1b). These sulfo-compounds can be used as important intermediates for preparation of symmetric and asymmetric pyrroles as well as for the synthesis of substituted peripheral porphyrins.

Electronic Structure of 2,5-Dimethyl Pyrrole Derivatives. The electronic structure and reactivity of pyrrole

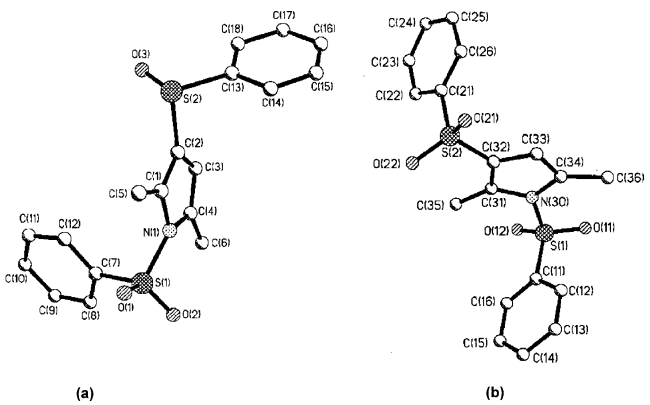


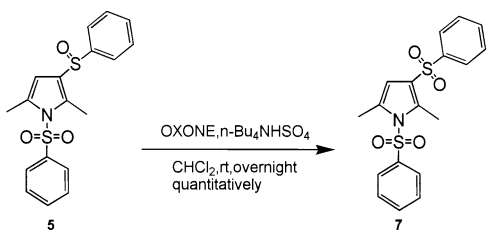
Figure 1. (a) X-ray structure of 1-phenylsulfonyl-3-phenylsulfinyl-2,5-dimethylpyrrole (**5**) and (b) X-ray structure of 1,3-diphenylsulfonyl-2,5-dimethylpyrrole (**7**).

Table 1. Comparison of structural parameters obtained by X-ray crystallography and calculations (RHF/6-31G*) for 1-phenylsulfonyl-3-phenylsulfinyl-2,5-dimethyl pyrrole (**5**)

Parameters	1-phenylsulfonyl-3-phenylsulfinyl -2,5-dimethyl pyrrole(**5**)	
	Experiment	Calculation
Bond length (Å)		
S(1)-O(1)	1.42	1.42
S(1)-N(1)	1.68	1.67
S(1)-C(7)	1.75	1.77
S(2)-C(2)	1.76	1.77
S(2)-C(13)	1.80	1.80
N(1)-C(4)	1.43	1.41
C(4)-C(6)	1.49	1.50
C(7)-C(12)	1.37	1.38
C(13)-C(14)	1.37	1.38
Bond angle (deg)		
O(1)-S(1)-O(2)	119.6	120.3
C(1)-N(1)-C(4)	108.7	109.1
C(4)-N(1)-S(1)	121.7	123.9
S(2)-C(2)-C(3)	126.4	125.3
O(3)-S(2)-C(2)	107.3	107.5
C(2)-S(2)-C(13)	97.9	99.1
S(1)-C(7)-C(8)	119.2	119.9

Table 2. Comparison of structural parameters obtained by X-ray crystallography and calculations (RHF/6-31G*) for 1,3-diphenylsulfonyl-2,5-dimethyl pyrrole (**7**)

Parameters	1,3-diphenylsulfonyl-2,5-dimethyl pyrrole (**7**)	
	Experiment	Calculation
Bond length (Å)		
S(1)-O(12)	1.43	1.42
S(1)-N(30)	1.69	1.68
S(1)-C(11)	1.75	1.77
S(2)-C(32)	1.75	1.76
S(2)-C(21)	1.44	1.44
N(30)-C(31)	1.41	1.40
C(31)-C(35)	1.49	1.50
C(11)-C(16)	1.36	1.39
C(21)-C(26)	1.38	1.39
Bond angle (deg)		
O(12)-S(1)-O(11)	119.5	120.4
C(34)-N(30)-C(31)	109.7	109.6
C(31)-N(30)-S(1)	123.3	126.8
C(31)-C(32)-S(2)	127.1	128.9
O(21)-S(2)-C(32)	106.2	105.8
C(32)-S(2)-C(21)	105.3	105.6
C(12)-C(11)-S(1)	119.2	118.8



Scheme 3

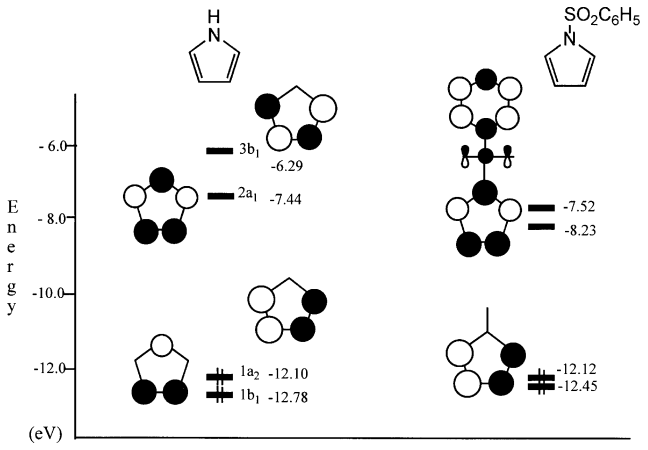


Figure 2. Electronic structures of pyrrole (**1**) and N-phenylsulfonyl pyrrole (**3**).

derivatives has been calculated using *ab-initio*, RHF/6-31G* calculations. The site preference of pyrrole ring was analyzed by comparison of physical constants, such as atomic charges, polarities, HOMO-LUMO energies and orbital interactions. The electronic structures of four different pyrrole derivatives are shown in Figure 2 and Figure 3. The structures were optimized by RHF/6-31G* and then the orbital interaction analyzed with simple EHT method for the convenience of analysis. The HOMO-LUMO gap is decreased with substitution of phenylsulfonyl group at nitrogen atom. The LUMO level is stabilized by bonding interaction between sulfur and nitrogen atom.

On the other hand, the HOMO level of 2,5-dimethyl pyrrole was destabilized by 0.33 eV owing to π^* interaction between methyl p and $1a_2$ orbital (Figure 3). Again, HOMO-LUMO gap decreases down to 3.59 eV. The charges on C-2 and C-5 of pyrrole increased along with the substitution of methyl group and negative charge on nitrogen increases to –0.91 by introduction of sulfonyl group (Figure 4). According to the calculations, 2,5-dimethyl pyrrol is expected to have lower ionization potential (I.P) than pyrrole. The electron density decreased in the order of **3** < **1** < **4** < **2**.

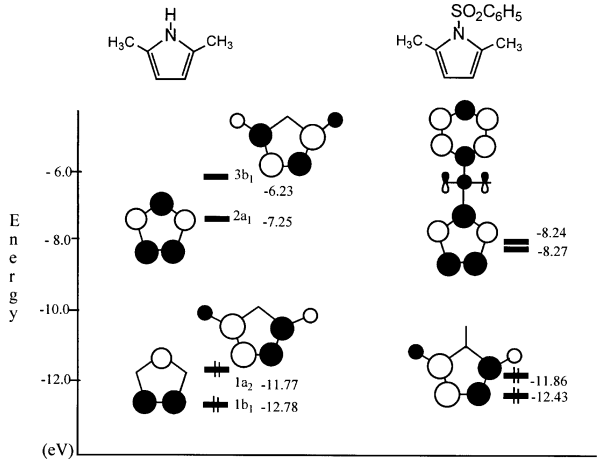


Figure 3. Electronic structures of 2,5-dimethyl pyrrole (**2**) and N-phenylsulfonyl-2,5-dimeth pyrrole (**4**).

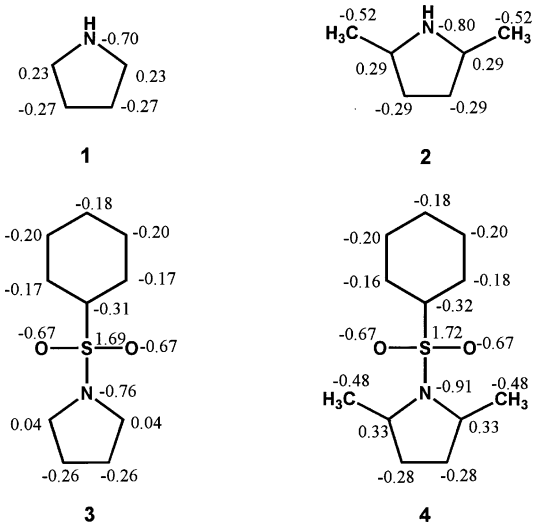


Figure 4. Charges on carbon atoms in pyrrole derivatives.

Structure of 1-phenylsulfonyl-3-phenylsulfinyl-2,5-dimethyl pyrrole. As mentioned previously, base catalytic reaction converts N-phenylsulfonyl-2,5-dimethyl pyrrole to 1,3-diphenylsulfonyl-2,5-dimethyl pyrrole followed by rapid deoxidation giving 1-phenylsulfonyl-3-phenylsulfinyl-2,5-dimethyl pyrrole. Resonance effect between pyrrole and phenyl rings is not likely occur since the geometry around sulfur atom is tetrahedral. The increases of negative charge on nitrogen atom thus resulted from electron transfer from a symmetry matching bonding orbital of phenylsulfonyl group toward an antibonding orbital of pyrrole moiety.

The stabilities of two different deoxydation products (**5**, **6**) examined with ab-initio RHF/6-31G* and density functional calculations (B3LYP/6-31G*). Both semiempirical (PM3) and ab-initio quantum mechanical calculations show that **6** is more stable by 3.6-4.7 kcal/mol than **5** which is contrast to experimental observations. Nonetheless, molecular dynamic (MD) calculations performed for 700 ps, showed **5** is more favorable over **6** by 4.15 kcal/mol which is same as experimental result. Calculated total (potential + kinetic) energies for isomer **5** and **6** were 60.21 (23.58 + 36.63) kcal/mol and 64.36 (36.78 + 27.58) kcal/mol respectively. Meantime, solvent effects have been considered by ab-initio, self consistent reaction field (SCRF) method. The calculated solvent effects on the conformational equilibrium of some organic molecules were studied by Wiberg *et al.* and were found to agree well with experiment. The simple self SCRF method, which consider a spherical cavity and single center multipole expansion of the solute charge density[23] has been proved to be useful in predicting the effect of solvation on number of properties such as tautomeric equilibria[24,25] and barriers for rotation.[26] The calculations in water as a solvent showed that the structure **5** is more stable than **6** by 0.03 kcal/mol.

Discussions

1,3-disulfonylation of 2,5-dimethylpyrrole. The α-position of pyrrole has positive charge according to the MO

calculations thus, electrophillic substitutions would occur at β-position under presence of acidic catalyst such as $AlCl_3$.[10,11] The β-positions of pyrrole ring are known as not active for the sulfonylation in basic conditions. However, the electron densities on C-3 and C-4 positions increased along with substitution of two methyl groups on C-2, C-5 positions (see Figure 4). The values of negative charges increased with methylation from –0.27 to –0.29 on C-3, C-4 of pyrroles and from –0.26 to –0.28 on N-sulfonylated pyrroles, respectively. At the same time, the HOMO levels of 2,5-dimethyl substituted pyrroles are substancially higher than the non-substituted pyrroles: the HOMO level of 2,5-dimethyl pyrrole pushed up 0.33 eV whereas that of N-sulfonyl-2,5-dimethyl pyrrole pushed up 0.26 eV (Figure 2, 3) from the HOMO levels of corresponding pyrroles. The elevation of HOMO level means the activation of C-3, C-4 sites for electrophillic substitution and thus, the 2,5-dimethyl pyrrole undergoes di-sulfonylation on these positions. Tri-sulfonylated product, 1,3,4-trisulfonylpyrrole was not formed due to severe steric hinderence around the substitutional site.

Deoxidation Products. Two types of deoxidation products, 3-phenylsulfinyl pyrrole (**5**) and 1-phenylsulfinyl pyrrole (**6**) were compared. Gas phase RHF/6-31G* and density functional method (B3LYP/6-31G*) calculations yielded favorable energies for **6** over **5** by 3.6-4.7 kcal/mol however empirically parameterized molecular dynamics (MD) calculations[16] showed opposite trend which is same as experiment. It is attributed to the facts that the molecular dynamic program involves the calculations for the polarizability of the molecule. The results of ab-initio calculations, self consistent reaction field (SCRF) method support this result since it includes the polarizability of the molecule and dipole moment of solvent during the calculations. The SCRF, HF/6-31G* calculations showed that the structure **5** is 0.03 kcal/mol more stable than **6** in water. Although, such a small energy difference does not give a realistic information, it may implicate that the existence of high energy barrier for the deoxidation process on phenylsulfonyl group substituted at nitrogen. More sophisticated studies including transition state structure are necessary to find out the mechanisms of deoxidations.

Conclusions

Experimentally, formation of disubstituted pyrrole, from the reaction between 2,5-dimethyl pyrrole and phenylsulfonyl chloride can not be avoided in any reaction conditions. Calculations show that the electron donating methyl groups enrich electron densities on C-3, C-4 positions. The elevation of HOMO levels activated the C-3 and C-4 sites for the electrophyllic substitutions. These two factors are considered to be the main reasons for 1,3-disulfonylation on 2,5-dimethylpyrrole. Further investigation is on going to find out the reasons behind deoxidation of sulfonyl group at C-3 position.

Because the mono-sulfonated compound **3**, 1-phenylsulfonyl-2,5-dimethylpyrrole, can not be obtained in this reaction condition, it is not clear whether the phenylsulfonyl group on C1-position migrates to C3-position or the second molecule of phenylsulfonyl chloride attacks the C3-position directly. However, the result of MO calculations was helpful for understanding the reaction of 2,5-dimethyl pyrrole with sulfonyl chloride qualitatively by comparing the change of charges and HOMO, LUMO levels, orbital coefficients as well as energetics of optimized structures.

Acknowledgment. This work was supported in part by Cooperative Research Program Among Government Supported Research Institutes by Ministry of Science and Technology, and Nuclear Energy Research Fund (KN-9710, KN-9718). S. Seong thanks for the support from Center for Molecular Science at Korea Advanced Institute of Science and Technology. Also, thanks for helpful discussions to professor K.T. No, at Computer Aided Molecular Design Center in Soongsil University.

Supporting Information Available. Tables of crystallographic details, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters (7 pages). The supporting materials will be given upon your request to the correspondence author.

References

1. Jones, R. A. *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J. Eds.; Academic Press: New York, London, 1970; Vol. 11, p 383.
2. Marino, G. *ibid*, 1971; Vol. 13, p 235.
3. Bird, C. W.; Cheesman, G. W. H. *Comprehensive Heterocyclic Chemistry*; Katritzky, A.; Ress, C. W. Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 39.
4. Oda, K.; Machida, M. *Chem. Pharm. Bull*. **1993**, *41*, 1299.
5. Cooper, G. *J. Org. Chem*. **1971**, *36*, 2897.
6. Olah, G. A.; *Friedel-Crafts and Related Reactions*; Interscience Publishers: New York, 1964; Vol. I-IV.
7. Jones, R. A. *Comprehensive Heterocyclic Chemistry*; Katritzky, A.; Ress, C. W. Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 217.
8. Tani, M.; Ariyasu, T.; Nishiyama, C.; Hagiwara, H.; Watanabe, T.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull*. **1996**, *44*, 48.
9. Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353.
10. Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem*. **1983**, *48*, 3214.
11. Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem*. **1985**, *63*, 896.
12. Cadamuro, S.; Degani, I.; Dughera, S.; Fochi, R.; Gatti, A.; Piscopo, L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 273.
13. Kim, J. B.; Jin, G.; Seong, S.; Yu, C. M.; Shim, Y. K. *Bull. Korean Chem. Soc.* **1999**, *20*, 271.
14. Gaussian 94, Frisch, M. T.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petterson, G. A.; Montgomery, J. A.; Raghavanchari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.;

Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fax, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A., Gaussian, Inc., Pittsburgh, PA. 1995.
15. Molecular Simulation Inc., Cerius 2, Ver. 3.6.
16. (a) Allinger, N. L.; Chen, K.; Rahman, M.; Pathiaseril, A.; *J. Am. Chem. Soc.* **1991**, *113*, 2810. (b) Gunsteren, W. F.; Berendsen, H. J. C. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 992.
17. (a) Stewart, J. J. P. *J. Comp. Chem*. **1989**, *10*, 209. (b) Stewart, J. J. P. *J. Comp. Chem*. **1989**, *10*, 221.
18. (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys*. **1971**, *54*, 724. (b) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.
19. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
20. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
21. Melting points are uncorrected and were measured on a Fisher/Johns microscopic hot stage apparatus. Mass spectra were obtained on a Shimadzu GC MS-QD 5050A mass spectrometer using a direct insertion probe (EI). All the X-ray data were collected on a Siemens P4 X-ray Diffractometer equipped with a Mo X-ray tube and a graphite crystal monochromator. 1H-NMR spectra were obtained using a Varian EM360 spectrometer, and chemical shifts are reported relative to TMS at 0.00. IR spectra were obtained using a Bio-Rad Win IR spectrometer. Compound **4** (Yield; 60%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71-7.39 (10H, m, aromatic), 5.78 (1H, s, -CH), 2.68 (3H, s, -CH3), 2.27 (3H, s, -CH3); Mass, m/e (rel intensity) 342 (100), 359 (4); IR (KBr, cm^{-1}), 1369.9 (s), 1186.0 (s) , 1043.69 (s); mp 129-130 ^{o}C.
22. Compound **3** (Yield; qunatitatively): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88-7.48 (10H, m, aromatic), 6.29 (1H,s, -CH), 2.65 (3H, s, -CH3), 2.38 (3H, s, -CH3). Mass, m/e (rel intensity) 234 (100), 375 (70); IR (KBr, cm^{-1}), 1373.0 (s), 1309.8 (s), 1190.2 (s), 1157.0 (s); mp 107-108.4 ^{o}C.
23. Tapia, O.; Goschinski, O. *Mol. Phys.* **1975**, *29*, 1563.
24. Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc*. **1992**, *114*, 1645.
25. Parchment, O. G.; Hiller, I. H.; Green, D. V. S. *J. Chem. Soc., Perkin. Trans. 2* **1991**, 799.
26. Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc*. **1991**, *113*, 4776.