Substituent Effect on the Aromaticity of 1,3-Azole Systems

Selçuk Gümüş[a,*] and Lemi Türker[b]

[a] Yuzuncu Yil University, Faculty of Sciences, Department of Chemistry, 65080, Kampüs, Van, Turkey

[b] Middle East Technical University, Faculty of Arts and Sciences, Department of Chemistry, 06531, Ankara, Turkey

Correspondin Author

e-mail: gumuss@gmail.com

Tel: 90 432 2251024 / 2248

Fax: 90 432 2251188

Postal Adress: Yuzuncu Yil University,

Faculty of Arts and Sciences,

Department of Chemistry, 65080,

Kampüs, Van, Turkey

Abstract: The effects of substituent type and position on the aromaticity of certain derivatives of three 1,3- azoles (oxazole, imidazole and thiazole) have been investigated theoretically by using density functional theory at the level of B3LYP/6-31G(d,p) method. The second heteroatom substitution decreased the aromaticities of furan, pyrrole and thiophene. The decreased aromaticity has been found to be gained back to some extent by the substitution of strong electron withdrawing groups or atoms (**NO_2** and **F**). NICS data have been considered in order to judge the aromaticities of the systems. The most effective substitution to enhance the aromaticity has been calculated to be at position- 4. The variation of the bond lengths of the main skeleton supported the findings through NICS calculations. The frontier molecular orbital energies have also been reported to draw a general correlation between these energies and the aromaticity of the system.

Keywords: Oxazole, imidazole, thiazole, aromaticity, NICS

1. Introduction

Aromaticity continues to be an actively investigated area of chemistry of cyclic structures. It has been shown to be a useful quantity in the rationalization of structure, stability and reactivity of many molecules. The simplest criterion for aromatic compounds is that they possess cyclic conjugated π-systems containing the proper number of π-electrons. While this criterion is robust enough to predict the aromaticity of a host of neutral and charged ring systems, it is not always a clear indicator of aromaticity for more complex systems [1,2].

Aromaticity is expressed by a set of combination of properties in cyclic delocalized systems. In general, aromaticity is discussed in terms of energetic, structural and magnetic criteria [3-8]. In 1996, Schleyer has introduced a simple and efficient probe for aromaticity: Nucleus-independent chemical shift (NICS) [9], which is the computed value of the negative magnetic shielding at some selected points in space, generally, in a ring or a cage center. Negative NICS values denote aromaticity (-11.5 for benzene, -11.4 for naphthalene) and positive NICS values denote antiaromaticity (28.8 for cyclobutadiene) while small NICS values indicate non-aromaticity (-3.1 for 1,3-cyclopentadiene). NICS may be a useful indicator of aromaticity that usually correlates well with the other energetic, structural and magnetic criteria for aromaticity [10-13]. Resonance energies and magnetic susceptibilities are measures of the overall aromaticity of a polycycle, but do not provide information about the individual rings. However, NICS is an effective probe for local aromaticity of individual rings of polycyclic systems.

Furan, pyrrole and thiophene are the most common five membered aromatic heterocycles. They show aromatic delocalization involving the unshared electrons located on respective heteroatom of the ring system. The nitrogen atom of pyrrole is of ideal size to permit extension of the conjugation around the entire ring leading the maximum aromatic character among the three [14]. Through the same argument of size alterations, furan and thiophene become less aromatic than pyrrole.

Introduction of a second heteroatom, nitrogen in the present case, creates azoles. By means of centric perturbation at position-3, oxazole, imidazole and thiazole (1,3-azoles) are structurally obtained from furan, pyrrole and thiophene, respectively. It is expected that the introduction of a second heteroatom (nitrogen) will reduce the

aromaticity of the parent heterocyclic structures due to less effective ring current because of some electron localization arising from electronegativity of aza nitrogen at the perturbed cite. The present article aims to investigate the substituent effect on the aromaticity of 1,3-azoles. The effects of type and the position of certain substituents on these systems have been studied theoretically by means of DFT calculations focusing a special interest on NICS values.

2. Method of Calculation

The geometry optimizations of all the structures were achieved within the framework of density functional theory (DFT, B3LYP) [15,16]. The exchange term of B3LYP consists of hybrid Hartree-Fock and local spin density (LSD) exchange functions with Becke's gradient correlation to LSD exchange [17]. The correlation term of B3LYP consists of the Vosko, Wilk, Nusair (VWN3) local correlation functional [18] and Lee, Yang, Parr (LYP) correlation correction functional [19]. The BLYP method gives a better improvement over the SCF-HF results. Its predictions are in qualitative agreement with experiment [20-22].

The normal mode analysis for each structure yielded no imaginary frequencies for the $3N-6$ vibrational degrees of freedom, where N is the number of atoms in the system. This indicates that the structure of each molecule corresponds to at least a local minimum on the potential energy surface.

Absolute NMR shielding values [23] were calculated using the Gauge-Independent Atomic Orbital method [24] with the restricted closed shell formalism

employing 6-31G(d,p) basis set over B3LYP/6-31G(d,p) optimized geometries. NICS values were obtained by calculating absolute NMR shielding at the ring centers, NICS(0).

The geometry optimizations and NICS calculations of the present systems have been performed by the use of Gaussian 03 package program [25].

3. Results and Discussion

The effect of centric perturbation of an heteroatom to the central ring, and/or substitution of an heteroatom or heterogroup with the hydrogens of well-known aromatic compounds have always found application in both theoretical and experimental studies. In the present article, 1,3-azoles (oxazole, imidazole and thiazole) and their susbtituted (**NO_2**, **F**, **NH_2**) counterparts have been investigated theoretically by the performing DFT calculations at the level of B3LYP/6-31G(d,p) in order to judge their stabilities and aromaticities.

The structures and numbering of the compounds are given in Figure 1.

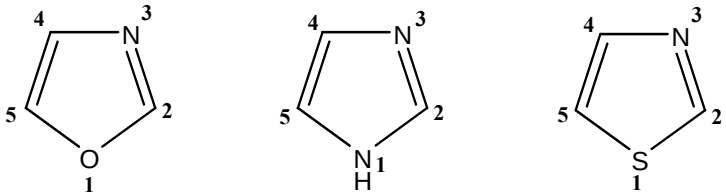

Figure 1. 1,3-azoles under consideration.

Energetics:

The zero point corrected total electronic energies of the present systems have been obtained by the aforementioned method and the results are given in Table 1. At the first glance, one may think that either inductively and/or mesomerically electron attracting groups decrease the aromatic stability of the parent as well as its aza substituted derivatives, 1,3-azoles, by pulling some of the electron density out of the ring current. This might be valid for five-membered one heteroatom containing systems. On the other hand, if the heteroatom has already caused some electron population localization on itself, thus affecting proper ring current destructively, then electron withdrawing substituent may counter balance this localization effect to restore the ring current. Hence, positional effects of substituents arise. Similar type of arguments could be asserted for electron donating substituents which may restore the already disturbed ring current present in the parent ring system. The most stable isomer for each series depends on the type of the substituent and there is no general trend for $\mathbf{NO_2}$ and **F** derivatives. However, substitution on position-2 creates the most stable derivatives in the case of $\mathbf{NH_2}$ substituted heterosystems which can be attributed to the electron donating ability of $\mathbf{NH_2}$ into the expectedly most electron deficient point of the structures. For $\mathbf{NH_2}$ substituted systems, the stability order is 2>4>5 in terms of position of the substitution.

Table 1. Zero point energy corrected total electronic energies of the present structures.

System	Substituent	Energy (au)		
		2	4	5
Oxazole		-450.5568215	-450.5651230	-450.5623468
Imidazole	**NO_2**	-430.7186220	-430.7203484	-430.7214935
Thiazole		-773.5398071	-773.5437326	-773.5408173
Oxazole		-345.3034534	-345.3011643	-345.2983534
Imidazole	**F**	-325.4524601	-325.4520865	-325.4450461
Thiazole		-668.2791475	-668.2811163	-668.2689070
Oxazole		-301.4391176	-301.4335140	-301.4303801
Imidazole	**NH_2**	-281.5839305	-281.5805658	-281.5770517
Thiazole		-624.4140277	-624.4118814	-624.4040885

NICS:

The delocalization of certain number of π-electrons freely in a ring accounts for the aromaticity in that ring which results in better stability. NICS is a measure of aromaticity related to the magnetic properties of the ring under consideration.

The most well-known aromatic compound is benzene where there exists a perfect delocalization of six π-electrons. Therefore, in an aromatic ring substitution of an heteroatom decreases the aromaticity of the system to some extent due to the electronegativity difference between carbon and other atoms. The aromaticity of that ring even decreases more with the substitution of a second heteroatom as in the present case. However, this diminished aromaticity can be restored back up to a certain extent by the substitution of one of the hydrogens of the system by certain atoms or groups, thus

improving cyclic delocalization of the ring electrons, as explained above in the section of energetics. In our case, the effects of substitution of electronegative **NO_2** group and **F** atom, and electron donating **NH_2** group have been investigated by obtaining the NICS data at the ring centers (NICS(0)) and the results are tabulated in Table 2. The NICS values for the unsubstituted parent (1,3-azoles) and grand parent heterocycles (pyrrole, furan and thiophen) have also been calculated at the same level in order to observe the change on the aromaticity, via both centric susbtitution of C with N to form azoles and substitution of H with **NO_2**, **F** and **NH_2**.

Table 2. Calculated NICS data for the present systems together with unsubstituted parent systems.

System	Substituent	NICS		
		2	4	5
Furan		-13.58		
Pyrrole	**Unsubstituted**	-16.06		
Thiophene		-14.34		
Oxazole		-12.56		
Imidazole	**Unsubstituted**	-14.94		
Thiazole		-13.84		
Oxazole		-12.00	-12.83	-11.47
Imidazole	**NO_2**	-14.54	-15.22	-13.08
Thiazole		-13.00	-13.96	-12.54
Oxazole		-11.49	-13.59	-11.70
Imidazole	**F**	-14.54	-15.80	-14.91
Thiazole		-12.85	-13.91	-12.46
Oxazole		-10.42	-12.37	-11.83
Imidazole	**NH_2**	-13.43	-14.36	-14.22
Thiazole		-11.54	-12.69	-11.75

Pyrrole possess better aromaticity than furan and thiophene as already reported before in the literature [14]. The very high electronegativity of oxygen disturbs the perfect delocalization of π-electrons over the periphery of furan ring forming the least aromatic structure among the three one-heteroatom-containing five-membered molecules. The NICS data represent successfully the expected decrease of the aromatic character after second heteroatom substitution into the ring.

Going through the NICS data for different positions of the substituents, the results reveal that substitution to position-4 becomes more effective to enhance the aromaticity for **NO_2** and **F** substituted cases. The strongly electron withdarwing **NO_2** group and electronegative **F** atom pulls the electrons located on the aza nitrogen at position-3 into the ring resulting greater (absolutely) NICS values than the parent azole. However, the decrease of the aromaticity when substitution exists on position-5, can be attributed to withdrawal of the electrons on the double bond. The two unpaired electrons on the first heteroatom (O, NH and S) which completes the aromatic sextet can be targeted by the electron poor substituents, too.

Figure 2 gives the 3D electrostatic potential maps of some of the derivatives considered herein together with the parent imidazole. Red, green and blue represent strongly negative, slightly positive and strongly positive. Location of the negative charge is clearly observed on position-3 of parent imidazole. The carbon between the two nitrogens of the main skeleton is more positive than the other two. Substitution of the **NO_2** group on position 2 results in a much more positively charged point-2 carbon, thus, a much worse electron distribution for the enhancement of the aromaticity. When this group is attached to position-5, it is so far to the aza nitrogen that the electrons localized

on the aza nitrogen can not be pulled into the ring. In other words, the aromaticity of the imidazole skeleton is maximized when NO_2 group is located on position-4. The inductive effect of NH_2 substituted on position-4 makes carbons on position 4 more positive, hence the electron poor main ring gets even more electron deficient and less aromatic.

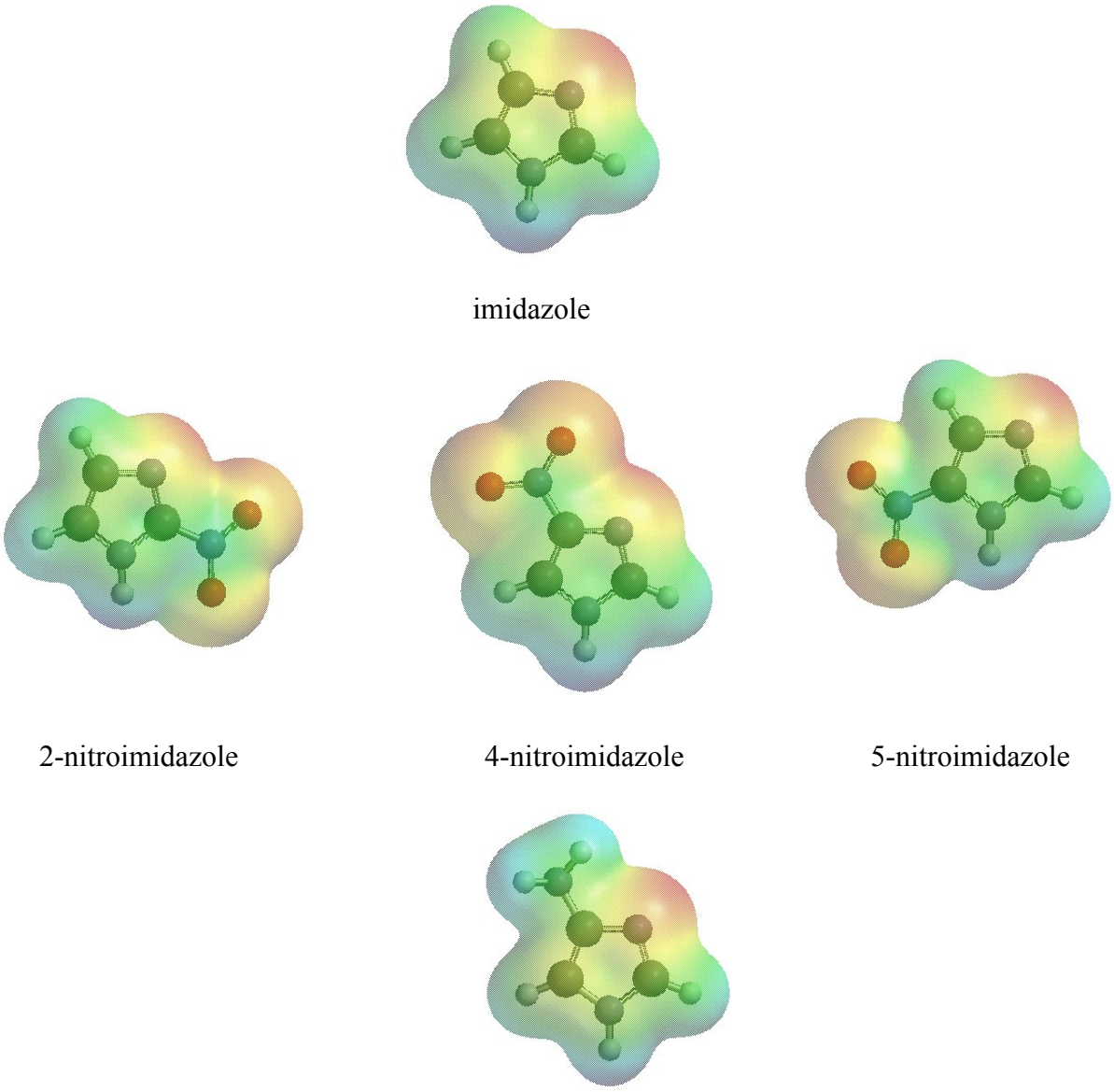

Figure 2. 3D electrostatic potential maps of some selected 1,3-azole derivatives.

Bond Lengths:

Table 3 gives the bond lengths of the main skeleton obtained after the geometry optimizations. The position of the substituent has been found to be highly effective on the bond lengths in the systems. The shortening of the 3,4 bond for **NO_2** and **F** derivatives proves the pulling of electrons from the nitrogen at point-3. On the other hand, the same bond length remains the same or sligthly shortened in the case on **NH_2** derivatives. The effect of substitution on the other centers has a very small effect on the shortening of this bond.

When the substitution takes place at position 5, the 5,1-bond becomes shorter, too, which may be an implication of the shift of unshared π-electrons towards the substituent on this position. In the case of **NH_2** substituted derivatives, 5,1 bond is lengthened, therefore, the system ends up with a less aromatic character.

Table 3. The effect of substitution on the bond lengths (Å).

Substituent	Bond	Oxazole			Imidazole			Thiazole		
		2	4	5	2	4	5	2	4	5
Unsubstituted	1,2	1.358			1.367			1.750		
	2,3	1.294			1.315			1.300		
	3,4	1.392			1.378			1.378		
	4,5	1.356			1.372			1.365		
	5,1	1.371			1.380			1.733		
NO_2	1,2	1.347	1.367	1.353	1.362	1.375	1.356	1.741	1.757	1.741
	2,3	1.293	1.292	1.301	1.312	1.312	1.326	1.294	1.298	1.308
	3,4	1.383	1.375	1.380	1.367	1.363	1.364	1.369	1.363	1.367
	4,5	1.363	1.360	1.362	1.384	1.376	1.379	1.373	1.367	1.370
	5,1	1.365	1.358	1.360	1.367	1.368	1.374	1.728	1.721	1.735
F	1,2	1.341	1.352	1.372	1.359	1.362	1.375	1.752	1.745	1.760
	2,3	1.285	1.298	1.291	1.296	1.321	1.312	1.283	1.303	1.297
	3,4	1.398	1.369	1.395	1.388	1.354	1.383	1.384	1.360	1.378
	4,5	1.353	1.357	1.353	1.368	1.371	1.365	1.361	1.364	1.360
	5,1	1.386	1.376	1.353	1.391	1.386	1.372	1.746	1.733	1.745
NH_2	1,2	1.356	1.345	1.380	1.368	1.358	1.367	1.775	1.740	1.764
	2,3	1.303	1.297	1.287	1.315	1.319	1.315	1.304	1.301	1.294
	3,4	1.395	1.390	1.395	1.385	1.376	1.379	1.380	1.381	1.377
	4,5	1.350	1.364	1.367	1.367	1.379	1.376	1.358	1.374	1.372
	5,1	1.393	1.385	1.364	1.391	1.390	1.383	1.755	1.738	1.753

The HOMO-LUMO gap

Haddon and Fukunaga showed that a direct relationship exists between the resonance energies and the HOMO-LUMO energy gaps in [4n+2] annulenes [26]. The HOMO-LUMO energy gap is an approximation to the global hardness of the system measuring stability [1]. Thus, the hardness and aromaticity show some relationship. A small HOMO-LUMO energy gap has been associated with antiaromaticity [27-29]. However, Fowler pointed out that the HOMO-LUMO separation cannot be considered as

a general criterion for the aromaticity or kinetic stability of polycyclic aromatic hydrocarbons, since this energy gap generally tends to be smaller for the larger hydrocarbons whether they are kinetically stable [30]. However, in the present study it can be used to visualize the positional effects of substituents on the aromaticity of the ring as long as the ring system is the same.

Table 4 gives the calculated HOMO and LUMO energies together with the interfrontier molecular orbital energy gaps. The nitro derivatives which are generally more aromatic structures possess lower HOMO and LUMO values. Their HOMO-LUMO energy gaps are narrower than the systems having other substituents, **F** and **NH_2**, with a few exceptions. Thus, a direct correlation can be drawn between these energies and the aromaticities of the systems such that, the more aromatic the system is the lower HOMO and LUMO energies or the more aromatic the system the narrower the HOMO-LUMO gap.

Table 4. Frontier molecular orbital energies of the systems (eV).

System	Position	2			4			5		
	Substituent	HOMO	LUMO	Δε	HOMO	LUMO	Δε	HOMO	LUMO	Δε
Oxazole		-7.95	-2.94	5.01	-7.99	-2.57	5.42	-8.08	-2.93	5.15
Imidazole	**NO_2**	-7.29	-2.58	4.71	-7.30	-2.02	5.28	-7.45	-2.59	4.86
Thiazole		-7.78	-3.03	4.75	-7.88	-2.56	5.33	-7.94	-3.01	4.93
Oxazole		-6.93	-0.02	6.92	-6.88	-0.38	6.50	-6.83	-0.13	6.69
Imidazole	**F**	-6.22	0.88	7.10	-6.16	0.51	6.68	-6.17	0.77	6.94
Thiazole		-6.87	-0.73	6.14	-6.83	-1.07	5.76	-6.85	-0.87	5.98
Oxazole		-5.46	0.95	6.41	-5.60	0.24	5.84	-5.25	0.75	6.00
Imidazole	**NH_2**	-5.35	1.23	6.58	-5.02	1.03	6.05	-5.66	1.04	6.71
Thiazole		-5.49	0.17	5.66	-5.55	-0.49	5.06	-5.72	-0.32	5.40

On the other hand, position-wise inspection of substituent effects on the interfrontier molecular orbital energy gaps reveals that in the cases of **NO_2** and **F** substitutions, Δε values follow the order of 4>5>2 and 4<5<2 , respectively. Whereas, the amino substitution exhibits the order of 4<5<2 for oxazole and thiazole but 4<2<5 for imidazole.

4. Conclusion

The effect of substitution on the aromaticity of double heteroatom containing 1,3-azole heterocycles has been investigated theoretically via NICS calculations at B3LYP/6-31G(d,p) level of theory. The decreased aromaticity by the introduction of the aza nitrogen heteroatom into the ring has been proved to be gained back by the substitution of the strongly electron withdrawing groups or atoms. Aromaticity is enhanced mostly when the substitution takes place at position-4 where the substituent is closest to the pyridine like nitrogen. The variarion of the bond lengths of the main skeleton by the positioning of the substitutent provides support for the NICS data and the aromaticities of the present systems. Generally, the frontier molecular orbital energies (HOMO and LUMO) are smaller for the structures with greater aromatic character.

References

[1] Proft FD, Geerlings P. Conceptual and Computational DFT in the Study of Aromaticity. *Chem. Rev.* 2001, 101:1451-1464.

[2] Garrat PJ. *Aromaticity.* New York:Wiley, 1986.

[3] Minkin VI. Glukhovtsev MN. Simkin BY. *Aromaticity and antiaromaticity: electronic and structural aspects.* New York:Wiley, 1994.

[4] Schleyer PR. Jiao H. *What is aromaticity*? Pure Appl. Chem. 1996, 68:209-218.

[5] Glukhovtsev MN. Aromaticity today: energetic and structural criteria. *J. Chem. Educ.* 1997, 74:132-136.

[6] Krygowski TM. Cyranski MK. Czarnocki Z. Hafelinger G. Katritzky AR. Aromaticity: a theoretical concept of immense practical importance. *Tetrahedron* 2000, 56:1783-1796.

[7] Schleyer PR. Introduction: aromaticity. *Chem. Rev.* 2001, 101:1115-1118.

[8] Cyranski MK. Krygowski TM. Katritzky AR. Schleyer PR. To what extent can aromaticity be defined uniquely? *J. Org. Chem.* 2002, 67:1333-1338.

[9] Schleyer PR. Maerker C. Dransfeld A. Jiao H. Hommes NJRE. Nucleus independent chemical shifts: a simple and efficient aromaticity probe. *J. Am. Chem. Soc.* 1996, 118:6317-6318.

[10] Jiao H. Schleyer PR. Aromaticity of pericyclic reaction transition structures: magnetic evidence. *J. Phys. Org. Chem.* 1998, 111:655-662.

[11] Schleyer PR. Kiran B. Simion DV. Sorensen TS. Does $Cr(CO)_3$ complexation reduce the aromaticity of benzene? *J. Am. Chem. Soc.* 2000, 122:510-513.

[12] Quinonero D. Garau C. Frontera A. Ballester P. Costa A. Deya PM. Quantification of aromaticity in oxocarbons: the problem of the fictitious "nonaromatic" reference system. *Chem. Eur. J.* 2002, 8:433-438.

[13] Patchkovskii S. Thiel W. Nucleus–independent chemical shifts from semiempirical calculations. *J. Mol. Model.* 2002, 6:67-75.

[14] Cordell FR. Boggs JE. Structure and degree of aromatic character in furan, pyrrole, and thiophene. *J. Mol. Struct. (THEOCHEM)* 1981, 85:163-178.

[15] Kohn W. Sham LJ. Self-consistent equations including exchange and correlation effects. *Phys. Rev.* 1965, 140:A1133-A1138.

[16] Parr RG. Yang W. *Density functional theory of atoms and molecules*. London:Oxford University Press, 1989.

[17] Becke AD. Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A* 1988, 38:3098-3100.

[18] Vosko SH. Vilk L. Nusair M. Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.* 1980, 58:1200-1211.

[19] Lee C. Yang W. Parr RG. Development of the colle–salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* 1988, 37:785-789.

[20] Scuseria GE. Comparison of coupled-cluster results with a hybrid of Hartree–Fock and density functional theory. *J. Chem. Phys.* 1992, 97:7528-7530.

[21] Sosa C. Lee C. Density functional description of transition structures using nonlocal corrections. Silylene insertion reactions into the hydrogen molecule. *J. Chem. Phys.* 1993, 98:8004-8011.

[22] Wilson PJ. Amos RD. Handy NC. Density functional predictions for metal and ligand nuclear shielding constants in diamagnetic closed-shell first-row transition-metal complexes. *Phys. Chem. Chem. Phys.* 2000, 2:187-194.

[23] Pulay P. Hinton JF. Wolinski K. *Nuclear magnetic shieldings and molecular structure.* Tossel, J.A. Ed.; NATO ASI Series C vol. 386, Kluwer: Netherlands, 1993, pp. 243.

[24] Hehre WJ. Radom L. Schleyer PR. Pople JA. *ab initio molecular orbital theory.* New York:Wiley, 1986.

[25] MJ Frisch et al., Gaussian 03, Revision D01, Gaussian Inc., Wallingford, CT, 2004.

[26] Haddon RC. Fukunaga T. Unified theory of the thermodynamic and kinetic criteria of aromatic character in the [4n+2]annulenes. *Tetrahedron Lett.* 1980, 21:1191-1192.

[27] Cava MP. Mitchell MJ. *Cyclobutadiene and related compounds.* New York:Academic Press, 1967.

[28] Dewar MJS. Aromatizitat und pericyclische reaktionen. *Angew. Chem.* 1971, 83:859-875.

[29] Willner I. Rabinowitz M. Cycloocta[def]fluorene: a planar cyclooctatetraene derivative. Paratropicity of hydrocarbon and anion. *J. Org. Chem.* 1980, 45:1628-1633.

[30] Fowler P. Aromaticity revisited. *Nature* 1991, 350:20-21.