Benzene fused five-membered heterocycles.
A theoretical approach

Ana Martínez,* Marco-Vinicio Vázquez, José Luis Carreón-Macedo, Luis E. Sansores
and Roberto Salcedo

Instituto de Investigaciones en Materiales, UNAM. Circuito Exterior s/n, Ciudad Universitaria,04510, Coyoacán, México, DF, Mexico

Abstract—The Nuclear Independent Chemical Shift of each ring, as a criterion of aromaticity, is used to explain the stability order of benzopyrrole, benzofuran and benzothiophene, and their isomers. The results indicate that the benzene ring is aromatic in all the systems. The five-membered rings of benzopyrrole, benzofuran and benzothiophene are also aromatic, whereas those of isobenzopyrrole, isobenzofuran and isobenzothiophene are non-aromatic. This could be an explanation of the stability of the former molecules. The molecular orbitals and the condensed Fukui functions derived from the electronic structure calculations are also reported. These reactivity indices explain the expected electrophilic substitution of these compounds. The theoretical structure, ionization energies, order of aromaticity, stability and reactivity are in good agreement with the experimental results. The usefulness of this approach to determine the reactivity is discussed since their stability and reactivity may be understood. The reactivity indices are useful to explain and confirm the experimental information, and for molecules with unknown reactive behavior, this approach could help to predict some of the reactions.

1. Introduction

Benzene fused, five-membered heterocycles compounds have been the subject of sustained interest[1–3] because they are useful reactants for organic synthesis.[4] There are many experimental results for benzopyrrole, benzofuran, benzo-thiophene, and their corresponding isomers[5–9] (Fig. 1). Benzopyrrole and isobenzopyrrole have similar chemical properties and stability. However, benzofuran and iso-benzofuran present different stabilities. The existence of isobenzofuran has been clearly demonstrated,[5,8] but this compound is unstable in solution and it reacts rapidly with dienophiles to give the corresponding Diels–Alder products.[9] This reactivity has been used in many synthetic applications. Some authors have referred to this compound as 'the most reactive isolated diene for cycloaddition purposes'.[1,10] In contrast, benzofuran is very stable and can be obtained with several synthetic methods.[7] For the two benzothiophenes, it was reported that isobenzothio-phene is more reactive than benzothiophene.[11]

From a theoretical point of view, there are many semi empirical and low level ab initio studies of the reactivity of these compounds.[12,13] In a qualitative prediction for the reactivity of isobenzofuran, it was reported that positions 1
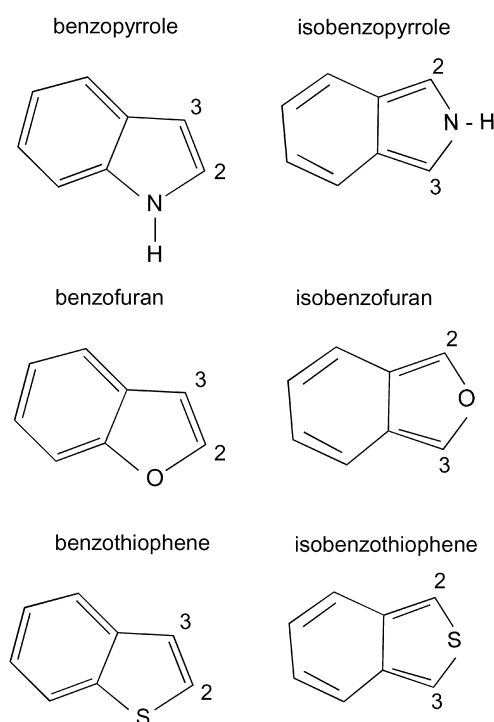
Figure 1. Compounds under study: benzopyrrole, isobenzopyrrole, benzofuran, isobenzofuran, benzothiophene, and isobenzothiophene.

and 3 (Fig. 1) are the most reactive to attack by radical and electrophilic reagents. Jursic and Zdravkovski[14] reported a theoretical study of the suitability of pyrrole as diene for Diels–Alder reactions, and the AM1 results of dienophile addition to indole and isoindole.[15]

Jursic and co-workers[16–21] have demonstrated that the B3LYP density functional theory is a reliable method for the calculation of the geometries and energies of these compounds. The B3LYP structures and the magnetic properties of thiophene, pyrrole, furan and their benzo derivatives were calculated in order to determine their reactivity as dienes for Diels–Alder reactions.[20] Based on the structural uniformity and magnetic susceptibility anisotropies, the relative aromaticity of these systems was predicted. From the theoretical results, the experimental stability was accurately described. The differences in stability were explained in terms of aromaticity. For the stable compounds, a high π molecular orbital delocalization exists between the two aromatic rings, which may not be present in the less stable isomers. The computed magnetic susceptibility anisotropies for the fused rings follow the same order as the aromatic, five-membered heterocycles.[20]

The aromaticity is related to the thermodynamic stability of the systems. There is also a relationship between hardness and stability. In 1987, Pearson concluded that 'there seems to be a rule of nature that molecules arrange themselves to be as hard as possible'[22,23] Parr and co-workers also reported this statement, called the principle of maximum hardness.[22–24] In addition, density functional theory (DFT) has the advantage of providing definitions of important universal concepts of molecular structure and reactivity. Work based on DFT[23] has developed an operational approximation for absolute hardness:

$$\eta = \tfrac{1}{2}(I - A)$$

where I is the vertical ionization energy and A is the vertical electron affinity. Upon application of the Koopmans theorem, the hardness corresponds to the energy gap between the HOMO and the LUMO orbitals. Hence, the principle of maximum hardness confirms previous results that claim that the stability of aromatic hydrocarbons depends on the HOMO−LUMO energy gap. The larger the gap, the harder the molecule.

The hard and soft acids and bases (HSAB) principle has been very useful to predict and analyze the reactivity of chemical systems. Recently,[24] the HSAB principle has been used in a local sense in terms of density functional concepts such as the Fukui function [$f(r)$]. In this context, the response of a chemical system to different types of reagents is related with the idea that larger values of the Fukui function imply greater reactivity. This seems to be a very useful approach to explain the chemical reactivity of a large variety of molecules.[25–30] The procedure to obtain information on $f(r)$ was reported by Gázquez et al.[30] This procedure condenses the values around each atomic site into a single value that characterizes the atom in the molecule. With this approximation, the condensed Fukui function becomes

$$f_{AK}^+ = q_{AK}(N_A + 1) - q_{AK}(N_A) \text{ for nucleophilic attack} \quad (1)$$

$$f_{AK}^- = q_{AK}(N_A) - q_{AK}(N_A - 1) \text{ for electrophilic attack} \quad (2)$$

$$f_{AK}^0 = \tfrac{1}{2}[q_{AK}(N_A + 1) - q_{AK}(N_A - 1)]$$

$$\text{for radical attack} \quad (3)$$

where q_{AK} is the charge of the kth atom in the molecule A. Systems with $N+1$ (anions), N (neutral) and $N-1$ (cations) electrons are calculated with the ground state geometries of the N electron system. The simplest procedure to determine the charge is to use the Mulliken population analysis. In this work, a reactivity analysis for the electrophilic attack of benzopyrrole, benzofuran, benzothiophene, and the related isomers will be presented.

The problem of aromaticity and reactivity of benzene fused five-membered heterocycles raises several questions. The matter is of interest for those chemists involved in heterocyclic and aromatic chemistry. Jursic[20] reported the correlation between the 'global' aromaticity of these compounds and their relative stability. The aim of the present study is to further examine these compounds from a theoretical point of view. Our goal is to analyze these molecules using the aromaticity of each ring rather than the global aromaticity that Jursic[20] employed to explain the relative stability. For this purpose, DFT calculations on these molecules were performed. Using Nuclear Independent Chemical Shifts (NICS) as a criterion of aromaticity, we compare the aromaticity of the two rings (benzene and five-membered heterocyclic ring). In terms of the aromatic behavior in each ring, it is possible to explain the stability of these compounds. Optimized structures, ionization energies, atomic charges, HOMO−LUMO gaps, Fukui functions, and frontier molecular orbitals of these molecules are reported and used to explain the experimental behavior of these systems.

Since these molecules play a fundamental role in many organic reactions, it is important to make use of DFT to calculate reactivity parameters that could help to understand their chemical behavior. Experimentally, the chemical reactivity of these molecules is well known. The reactivity indices that are presented here explain and confirm the experimental information. For those molecules with unknown reactivity, these parameters could help to understand and predict their reactivity behavior.

2. Methodology

Full geometry optimization was carried out without symmetry constraints using the Gaussian 98-code.[31] Two different functionals, Perdew–Wang91 (PW91)[32] and B3LYP,[33] and the standard Gaussian 6-311+G(2d,p) basis set were used.[34] B3LYP was used to calculate the magnetic properties (NICS), using the continuous set of gauge transformation method.[35] The initial geometries and visualization of the results were performed with the Cerius package[36] and the MOLEKEL.[37]

Schleyer et al.[38] using the same or similar levels of theory,
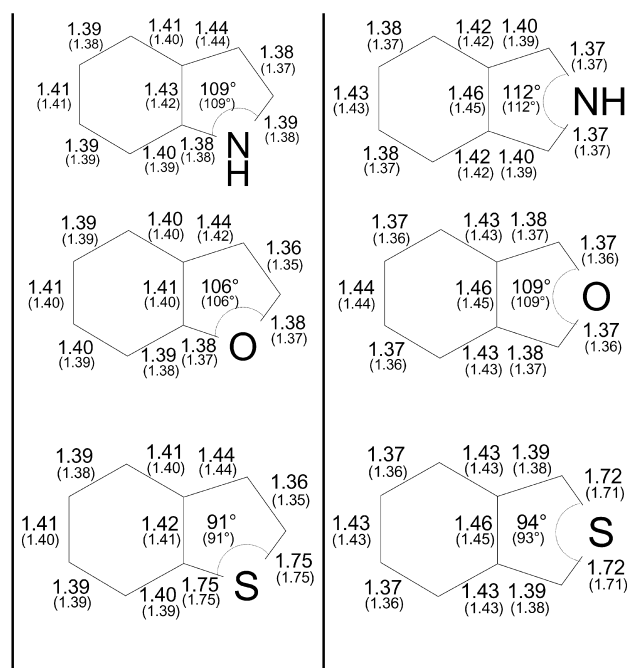
Figure 2. Optimized structures with B3LYP and PW91 functionals. Bond lengths in Å. B3LYP in parenthesis.

reported the NICS values of several systems as a simple and efficient probe of aromaticity. In this work, this criterion was also used to carry out the respective aromaticity comparisons. Furthermore, the NICS value of benzene as −9.7 from reference 38 has been taken as a reference for our aromaticity measurements, and the same criterion, that an absolute value of NICS lower than −9.7 should correspond to a non-aromatic character for the ring, has been adopted. In order to be able to perform a straight forward comparison with previous results, we used B3LYP for the NICS calculations. The geometry was optimized and the magnetic properties obtained with B3LYP. Since B3LYP and PW91 results are similar (Fig. 2), we only present the results using PW91 for the optimized structures, atomic charges,

ionization energies, HOMO−LUMO gap, Fukui functions and frontier orbitals. B3LYP was used only for the calculation of the magnetic properties (NICS).

The NICS values had been the subject of several analysis,[39] detecting some problems with its application, mainly in the comparison of the intrinsic value of this index.[40] However, other authors demonstrated that this index can be used for the study of local aromaticity in polycyclic compounds.[41] Therefore we applied this NICS criterion considering the relative trends within the studied set of molecules.

3. Results and discussion

This section is organized into three subsections. Section 3.1 discusses the results of the geometry optimization and the relationship between thermodynamic stability and other properties of these systems. In Section 3.2, the molecular orbitals are analyzed. Section 3.3 presents some reactivity parameters for benzene fused, five-membered heterocycles.
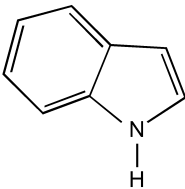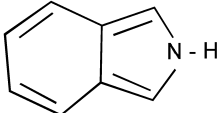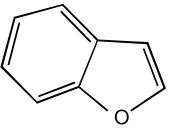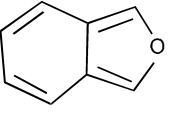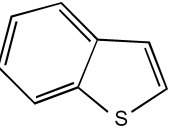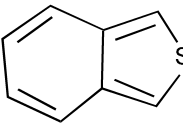
3.1. Geometry optimization and the analysis of properties

The optimized geometries are shown in Figure 2. The harmonic vibrational frequencies are positive, implying that the structures are minima on the potential energy surface. Table 1 shows the total energy difference (in kcal/mol) between two possible isomers of the benzene fused, five-membered heterocycles. In all cases in Table 1, the benzo derivatives are more stable than the isobenzo compounds. The largest energy difference is between isobenzofuran and benzofuran. This agrees with experimental results that established a high reactivity for isobenzofuran, and a greater stability for benzofuran. The smallest energy difference is between benzopyrrole and isobenzopyrrole, the former being around 8.1 kcal/mol more stable than the later (the theoretical error for this type of calculations is 5 kcal/mol). The benzothiophenes lie between the benzopyrroles and

Table 1. Total energy difference (in kcal/mol) between two possible isomers of the benzene fused five-membered heterocycles. Benzopyrrole, benzofuran and benzothiophene are the more stable of the two isomers

	PW91/6-311+G(2d,p)
	$\Delta E=8.1$
	$\Delta E=13.2$
	$\Delta E=9.3$

Table 2. HOMO–LUMO gap (Δ_{H-L}) and HOMO−[HOMO-1] energy difference ($\Delta_{H-H'}$) in eV, for the benzene fused five-membered heterocycles. All calculations with Perdew−Wang 1991.[31] Theoretical ionization energies with available experimental results (in italics)[40]

Δ_{H-L}=3.8	Δ_{H-L}=3.0	Δ_{H-L}= 4.0	Δ_{H-L}= 2.7	Δ_{H-L}= 3.8	Δ_{H-L}= 2.7
$\Delta_{H-H'}$=0.5	$\Delta_{H-H'}$=1.3	$\Delta_{H-H'}$=0.4	$\Delta_{H-H'}$=1.6	$\Delta_{H-H'}$=0.5	$\Delta_{H-H'}$=1.1
Ionization energies					
7.47		**8.03**		**7.83**	**7.40**
(7.76)		*(8.36)*		*(8.13)*	*(7.75)*

benzofurans. Isobenzothiophene is less stable than benzothiophene by 9.3 kcal/mol. These results are in agreement with the experimental information concerning the reactivity of these systems, namely, benzo isomers are more stable than the corresponding isobenzo derivatives.

In Table 2, theoretical ionization energies (in eV) and some experimental values available in the literature[42] are shown. The HOMO−LUMO gap (in eV) for the benzene fused five-membered heterocycles is also reported. Theoretical ionization energies are in good agreement with the experimental values. For all the molecules, the HOMO−LUMO gap is larger for the most stable isomers. This confirms previous results that claim that the stability of aromatic hydrocarbons depends on the HOMO−LUMO gap. The principle of maximum hardness establishes that the system would be more stable if the global hardness, related to the HOMO−LUMO gap, is a maximum. As shown in Table 2, the HOMO−LUMO gap correlate well with the expected stability of these molecules. Therefore, it is possible to use hardness as a criterion of stability.
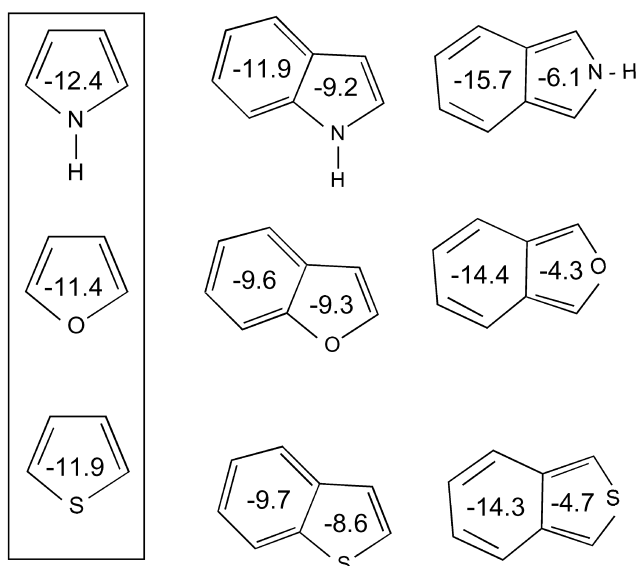
Figure 3. NICS values for the two rings of benzene fused five-membered heterocycles compounds. These results were obtained at B3LYP level. For comparison, NICS values reported before with the same methodology[43] for pyrrole, furan and thiophene are reported.

The NICS values for the two rings of benzene fused, five-membered heterocycles compounds, are reported in Figure 3. These results were obtained at the B3LYP level, which is a good option for this analysis. Moreover, under these conditions the comparison with Schleyer's results is direct. For benzopyrrole, the NICS values are −11.9 and −9.2 for benzene and pyrrole, respectively. For isobenzopyrrole the values are −15.7 and −6.1 for the benzene and pyrrole rings, respectively. Both rings of benzopyrrole are aromatic, whereas for isobenzopyrrole, the benzene ring is aromatic but the pyrrole one is almost non-aromatic. This could explain the stability ordering i.e. benzopyrrole is more stable than isobenzopyrrole because in the former both rings are aromatic. In Figure 3, the sum of the NICS values for the two rings is about the same in the benzo and in the isobenzo isomers. This is just a coincidence and it is not an indication of their reactive behavior.

For benzofuran and isobenzofuran, the results are similar. For benzofuran, the NICS are −9.6 and −9.3, for benzene and furan rings, respectively, while for isobenzofuran the values are −14.4 and −4.3 in that order. Hence, benzofuran is more stable than isobenzofuran because for the former, both rings are aromatic. Analyzing the results of the benzothiophenes, the NICS for benzothiophene are −9.7 and −8.6 for the benzene and thiophene portions, respectively, and for isobenzothiophene, the values are −14.3 and −4.7 in that order. Again, benzothiophene could be the most stable isomer because both rings are aromatic, whereas for isobenzothiophene the benzene ring is aromatic but the thiophene is non-aromatic. In summary, in going from benzo derivatives to isobenzo compounds, one ring gains aromaticity whereas the other loses it. For the isobenzo compounds, only its benzene portion is found to be aromatic, while for the benzo derivatives, both rings are aromatic.

It is possible to compare these NICS results with those reported before for the isolated rings. For benzene[38] it is −9.7. For pyrrole, furan, and thiophene, they are −12.4, −11.4 and −11.9, respectively[43] (Fig. 3). Thus, for pyrrole, thiophene and furan, the aromaticity of the isolated molecules is bigger than the aromaticity of the benzene derivatives. Hence, the aromaticity of benzene increases when it is bonded to a five-membered heterocyclic ring, while the aromaticity of the five-membered rings decreases when they are bound to benzene.

3.2. Molecular orbitals

In Figures 4–6, the frontier molecular orbital pictures of the six molecules under study are shown. We present only the HOMO, LUMO and HOMO-1. The energy difference between the HOMO and HOMO-1 for benzopyrrole, benzofuran and benzothiophene (Table 2) is smaller than for isobenzopyrrole, isobenzofuran, and isobenzothiophene.

For benzopyrrole, a π molecular orbital delocalization exists between the two aromatic rings. For isobenzopyrrole, the HOMO-1 of the five-membered ring is localized on N, C1 and C3, and there is no π molecular orbital delocalization on the pyrrole ring. In the pictorial context of molecular orbitals these results are in agreement with the NICS values. For isobenzopyrrole, the pyrrole is non-aromatic, while for benzopyrrole, both rings are aromatic.

The same situation was found for the other molecules (Figs. 5 and 6), namely, the HOMO-1 for the isocycles is localized on the heteroatom, C1 and C3, and there is no π molecular orbital delocalization. On the other hand, for benzothiophene and benzofuran there is a π molecular orbital delocalization between the two aromatic rings.
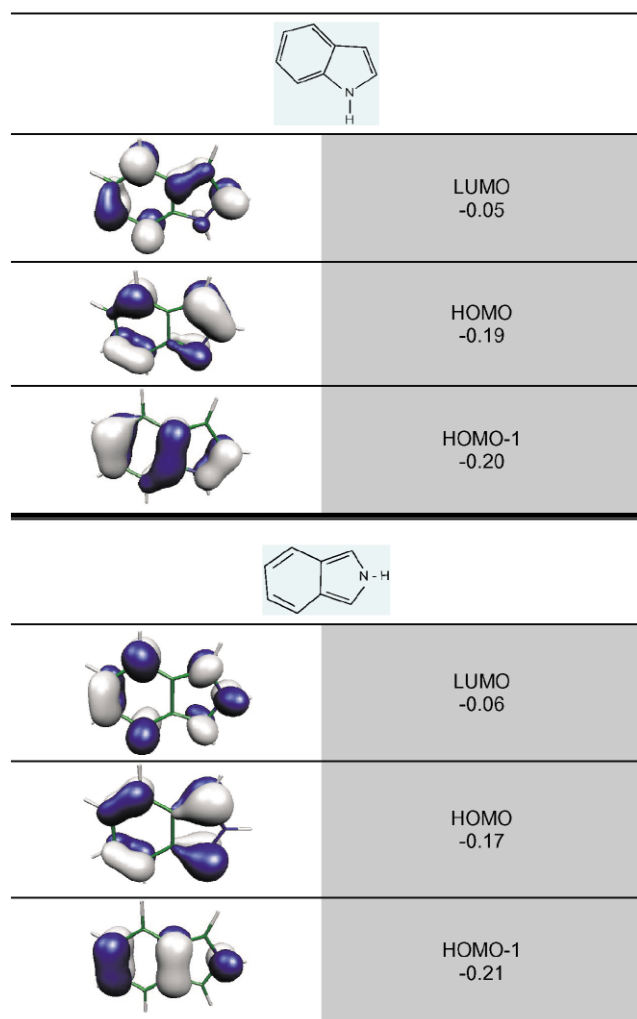

Figure 4. HOMO, LUMO, and HOMO-1 orbitals of benzopyrrole and isobenzopyrrole. PW91 results are shown.
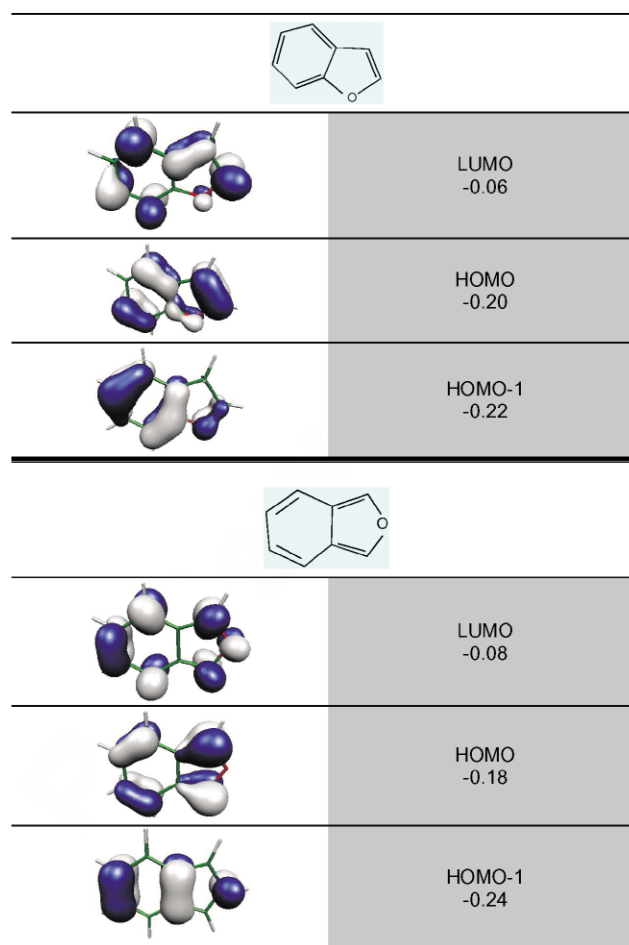

Figure 5. HOMO, LUMO, and HOMO-1 orbitals of benzofuran and isobenzofuran. PW91 results are shown.

Again, these results are in agreement with the NICS values that we found for both rings of these molecules.

With this molecular orbitals analysis, the stability and aromaticity of these compounds are explained. The π molecular delocalization agrees with the aromatic behavior of the two rings in these systems. It is possible to see the delocalization with two frontier molecular orbitals. However, caution is required for other systems where perhaps more occupied molecular orbitals are required.

3.3. Reactivity parameters for benzene fused five-membered heterocycles

Reactivity indexes derived from the DFT calculations have been successfully applied in describing and understanding chemical reactivity.[29,30,43] As outlined in the Introduction, it is possible to define atomic reactivity indices, such as the condensed Fukui function, for a given atom in a molecule. For instance, it is expected that electrophilic aromatic substitution reactions occur with the benzene fused, five-membered heterocycles. For this reaction, the condensed Fukui function is obtained according to Eq. (2).

A Mulliken population analysis was used to estimate the condensed reactivity indexes. In Table 3, the absolute values for the condensed Fukui function for electrophilic attack are
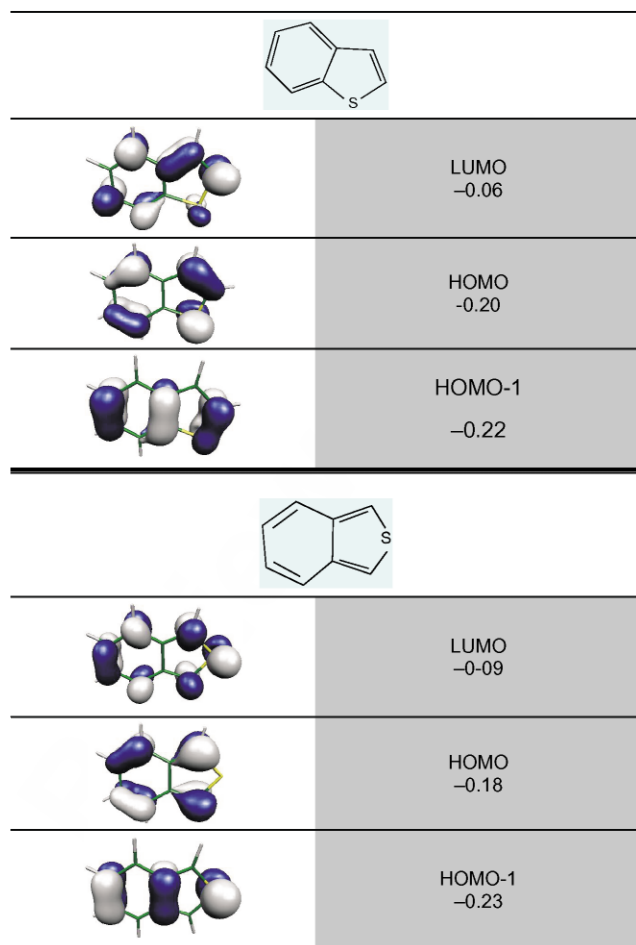
Figure 6. HOMO, LUMO, and HOMO-1 orbitals of benzothiophene and isobenzothiophene. PW91 results are shown.

Table 3. Calculated Fukui functions (absolute values), f_q^-, for electrophilic attack at the qth atom, from the Mulliken population analysis for the most stable isomers. (PW91/ 6-311+G(2d,p))

	Fukui functions for electrophilic attack	
	N	0.08
	C2	0.05
	C3	0.18
	O	0.09
	C2	0.09
	C3	0.12
	S	0.20
	C2	0.07
	C3	0.13

Table 4. Calculated Fukui functions (absolute values), f_q^-, for electrophilic attack at the qth atom, from the Mulliken population analysis for the iso benzo derivatives. (PW91/ 6-311+G(2d,p))

	Fukui functions for electrophilic attack	
	N	0.03
	C2	0.13
	C3	0.13
	O	0.07
	C2	0.10
	C3	0.10
	S	0.12
	C2	0.15
	C3	0.15

shown for the relevant atoms in the heterocyclic compounds. For benzopyrrole, the largest of f_{AK}^- belongs to C3 in the five-membered heterocyclic compounds. This means that C3 should be the most reactive site towards an electrophilic attack for this molecule. For benzofuran, C2 and C3 of the five-membered heterocyclic compounds yield similar values of f_{AK}^-, indicating that both C2 and C3 should be the most reactive site for an electrophilic attack. For benzothiophene, S and C3 are the most reactive sites. Note the large condensed Fukui function on the S atom of benzothiophene. According to these indexes, the S atom should be the most reactive site for an electrophilic attack. Experimental information indicates that it is possible to observe an electrophilic attack on the S atom, but the products of the reaction are not very stable. Theoretical results from the reactivity indexes are in complete agreement with the observed reactivity,[44] and with Gimarc's Topological Charge Stabilization Principle.[45]

In Table 4, the absolute values of the condensed Fukui function for electrophilic attack are shown for the relevant atoms of the isobenzo derivatives. The largest (absolute) value of f_{AK}^- belongs to C2 and C3 in the five-membered heterocyclic compounds. Hence, C2 and C3 should be the most reactive site towards an electrophilic attack for these molecules.

4. Conclusions

Optimized structures of benzene fused five-membered heterocycles and the stability of their isomers were reported. The ionization energies are in good agreement with the experimental results. The results concur with the

experimental information concerning the reactivity and stability of these systems. The principle of maximum hardness establishes that the system would be more stable if the global hardness, related to the HOMO−LUMO gap, was a maximum. The HOMO−LUMO gap correlates well with the expected stability of these molecules. This is an indication of the possibility to use hardness as a criterion of stability.

The stability order of these molecules can be explained using the NICS values of each ring. The NICS indicate that the benzene ring is aromatic in all of the systems. However, for the isobenzo derivatives, only the benzene ring is consider aromatic, whereas for the benzo compounds both rings are consider aromatic. This confirms that the first three molecules are the most stable isomers. We can say that one ring gains aromaticity, whereas the other loses it, when we proceed from benzo derivatives to isobenzo compounds. The aromaticity of benzene increases when it is bonded to a five-membered heterocyclic ring, but decreases when they are connected to benzene.

For benzopyrrole, benzofuran and benzothiophene, there is a π molecular orbital delocalization between the two aromatic rings. For isobenzopyrrole, isobenzofuran and isobenzothiophene, the orbitals of the five-membered rings are localized on the heteroatom, C1 and C3, and there is no π molecular orbital delocalization on the heterocyclic five-membered rings. These results are in agreement with the theoretical aromaticity of these molecules. Theoretical results from the reactivity indexes are in complete agreement with the observed reactivity of these compounds.

Acknowledgements

References

1. Rickborn, B. *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich, CT, 1989; Vol. 1.

2. Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093–2138.

3. Wege, D. *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich, CT, 1989; Vol. 4, pp 1–52.

4. Boger, D. L.; Weinreb, S. N. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: New York, 1987.

5. Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135.

6. Sunderberg, R. J. *Pyrroles and Their Benzo Derivatives: Synthesis and Applications in Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ress, C. W., Eds.; Pergoman: New York, 1984; Vol. 4, p 313 Part 3.

7. Bender, D. R.; Hears, J. E.; Rappoport, H. *J. Org. Chem.* **1979**, *44*, 2176–2179.

8. Fieser, L. F.; Haddadin, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 2081–2082.

9. McCulloch, R.; Rye, A. R. *Tetrahedron Lett.* **1969**, 5231–5234.

10. Thibault, M. E.; Pacarynuk, L. A.; Closson, T. L. L.; Dibble, P. W. *Tetrahedron Lett.* **2001**, *42*, 789–791.

11. (a) Jursic, B. S. *J. Heterocycl. Chem.* **1995**, *32*, 1499–1508. (b) Jursic, B. S. *J. Heterocycl. Chem.* **1995**, *32*, 1445–1456.

12. Klasinc, L.; Pop, E.; Trinajstic, N.; Knop, J. V. *Tetrahedron* **1972**, *28*, 3465–3474.

13. Jursic, B. S. *J. Mol. Struct. (Theochem)* **1998**, *427*, 165–170.

14. Jursic, B. S.; Zdravskovski, Z. *J. Heterocycl. Chem.* **1994**, *31*, 1429–1432.

15. Jursic, B. S. *Can. J. Chem.* **1996**, *74*, 114.

16. Jursic, B. S.; Zdravskovski, Z. *Int. J. Quantum Chem.* **1994**, *54*, 161–166.

17. Jursic, B. S. *Chem. Phys. Lett.* **1995**, *236*, 206–210.

18. Jursic, B. S.; Zdravkovski, Z. *J. Chem. Soc. Perkin Trans. 2* **1995**, 1223–1226.

19. Jursic, B. S. *J. Org. Chem.* **1995**, *60*, 4721–4724.

20. Jursic, B. S. *J. Heterocycl. Chem.* **1996**, *33*, 1079–1081.

21. Jursic, B. S. *J. Chem. Soc. Perkin Trans. 2* **1995**, 1217.

22. (a) Pearson, R. G. *J. Chem. Ed.* **1987**, *64*, 561–562. (b) Parr, R. G.; Chattaraj, P. K. *J. Am. Chem. Soc.* **1991**, *113*, 1854–1855.

23. (a) Pearson, R. G. *J. Chem. Ed.* **1985**, *107*, 6801–6806. (b) Parr, R. G.; Pearson, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 7512–7516.

24. Parr, R. G.; Yang, W. *Functional Theory of Atoms and Molecules*; 1989; Oxford, New York.

25. Yang, W.; Mortier, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 5708.

26. Lee, C.; Yang, W.; Parr, R. G. *J. Mol. Struct. (Theochem)* **1988**, *163*, 305.

27. Langenaeker, W.; De Decker, M.; Geerlings, P. *J. Mol. Struct. (Theochem)* **1990**, *207*, 115.

28. Langenaeker, W.; Demel, K.; Geerlings, P. *J. Mol. Struct. (Theochem)* **1991**, *234*, 329.

29. Méndez, F.; Galván, M.; Garritz, A.; Vela, A.; Gázquez, J. L. *J. Mol. Struct. (Theochem)* **1992**, *277*, 81.

30. Gázquez, J. L.; Méndez, F. *J. Phys. Chem.* **1994**, *98*, 4591–4593.

31. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, 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.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker J.; Stewart, J. P.; Head-Gordon, M.; González, C.; Pople, J. A. *Gaussian 98, Revision A.9*; Gaussian Inc.: Pittsburg, PA, 1995.

32. (a) Becke, A. D. *Phys. Rev. A.* **1988**, *38*, 3098. (b) Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1992**, *45*, 13244.

33. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

34. For gaussian basis sets:Foresman, J. B.; Frisch, Æ *Exploring Chemistry with Electronic Structure Methods: A Guide to Using Gaussian*; Gaussian: Pittsburg, PA, 1993.

35. (a) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1993**, *210*, 223–231. (b) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1992**, *194*, 1–8.

36. *Cerius2*™ Forcefield-Based Simulations, April 1997; Molecular Simulations, Inc.: San Diego, 1997.

37. MOLEKEL 4.2, Flükiger, P.; Lüthi, H. P.; Portmann, S.;

Weber, J. Swiss Centre for Scientific Computing: Manno (Switzerland), 2000–2002.

38. (a) Schleyer, P. v. R.; Maerker, C.; Dransfled, A.; Jiao, H.; Hommes, N. J. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317–6318. (b) Jiao, H.; Schleyer, P. v. R.; Mo, Y.; McAllister, M. A.; Tidwell, T. T. J. *J. Am. Chem. Soc.* **1997**, *119*, 7075–7083, and references therein.

39. (a) DeProft, F.; Geerlings, P. *Chem. Rev.* **2001**, *101*, 1451–1464. (b) Gomes, J. A. N. F.; Mallion, R. B. *Chem. Rev.* **2001**, *101*, 1349–1383. (c) Aihara, J. *Chem. Phys. Lett.* **2002**, *365*, 34–39. (d) Jemmis, E. D.; Kiran, B. *Inorg. Chem.* **1998**, *37*, 2110–2116. (e) Lazzeretti, P. *Prog. Nucl. Mag. Res.* **2000**, *36*, 1–88.

40. (a) Havenith, R. W. A.; van Lenthe, J. H.; Dijkstra, F.; Jenneskens, L. W. *J. Phys. Chem. A* **2001**, *105*, 3838–3845. (b) Cyransky, M. K.; Krygowski, T. M. *Tetrahedron* **1999**, *55*, 6205–6210. (c) Krygowski, T. M.; Cyransky, M. K.; Czarnocki, Z.; Häfelinger, G.; Katritzky, A. R. *Tetrahedron* **2000**, *56*, 1783–1796.

41. (a) Juselius, J.; Sundholm, D. *J. Org. Chem.* **2000**, *65*, 5233–5237. (b) Katritzky, A. R.; Jug, K.; Oniciu, D. C. *Chem. Rev.* **2001**, *101*, 1421–1449. (c) Jiao, H.; van Eikema-Hommes, N. J. R.; von Rague Schleyer, P. *Org. Lett.* **2002**, *4*, 2393–2396. (d) Salcedo, R.; Zaragoza, I. P.; Martínez-Magadán, J. M.; García Cruz, I. *J. Mol. Struct. (Theochem)* **2003**, *626*, 195–201.

42. (a) For benzopyrrole: Hager, J. W.; Wallace, S. C. *Anal. Chem.* **1988**, *60*, 5. (b) For benzothiophene and benzofuran: Gusten, H.; Klasinc, L. R. *Z. Naturforsch. A* **1976**, *31*, 1051–1056. (c) For isobenzothiophene: Clark, P. A.; Gleiter, R.; Heilbronner, E. *Tetrahedron* **1973**, *29*, 3085–3090.

43. Salcedo, R.; Martínez, A.; Sansores, L. E. *Tetrahedron* **2001**, *57*, 8759–8765.

44. Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwel Science: Oxford, 2000.

45. Gimarc, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 1979–1984.