

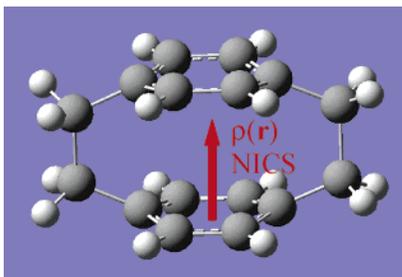
Role of Electron Density and Magnetic Couplings on the Nucleus-Independent Chemical Shift (NICS) Profiles of [2.2]Paracyclophane and Related Species

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The nucleus-independent chemical shifts (NICS) and electron density profiles along the inner and outer regions defined by the two stacked aromatic rings of [2.2]paracyclophane have been analyzed and compared to those of free benzene and *p*-xylene and benzene dimers taken as reference models. It is found that stacked aromatic rings show a reduction of the NICS indicator of aromaticity as compared to the same free aromatic systems. This decrease of the NICS values upon stacking is not due to an increase of the electron density in the inner region between the rings (as claimed in a previous work) but is related to the magnetic couplings between superimposed rings that affect this measure of local aromaticity. The increase of local aromaticity in superimposed aromatic rings indicated by NICS is not real but the result of the coupling between the magnetic fields generated by the two stacked rings. This result warns about the use of NICS as a descriptor of aromaticity for species having superimposed aromatic rings.

Cyclophanes are organic compounds having phenylene groups connected by $-\text{[CH}_2\text{]}_n-$ bridges.^{1,2} The relevance of cyclophanes relies on their applications in different chemical fields such as

asymmetric synthesis, selective catalysis, or supramolecular chemistry, as well as in biology.³ [2.2]Cyclophanes (i.e., [2.2]-paracyclophane, [2.2]metacyclophane, and [2.2]metaparacyclophane) are particularly interesting because the two benzene rings are held at short distances. Also remarkable in these systems are the boat-type deformation of the aromatic rings caused by the large strain induced by the short aliphatic bridge connecting the two phenylene groups. For these reasons, [2.2]cyclophanes have been used as probes to discuss the relation between aromaticity and strain, the $\pi-\pi$ interactions, and the substituent effects.^{2,3} However, despite the chemical relevance of these species, few theoretical studies have been devoted to the analysis of the molecular structure and aromaticity of [2.2]cyclophanes. Noticeably, very recently, Caramori, Galembeck, and Laali (CGL) have published the first high-level theoretical study³ in which geometries, conformations, strain, and relative aromaticity have been concisely examined for a series of isomeric [2.2]-cyclophanes, together with benzene and xylene dimers as reference models. By means of the harmonic oscillator model of aromaticity (HOMA)^{4,5} and the nucleus-independent chemical shift (NICS)^{6,7} measures, CGL have found that phenyl rings in [2.2]cyclophanes are aromatic, even though these rings are not completely planar and present alternant C–C bond lengths. The authors have also reported that when aromatic rings are stacked, as in [2.2]paracyclophane or in the benzene and xylene dimers, the NICS of the aromatic rings decreases, thus indicating an increase in their aromatic character. The observed NICS reduction has been attributed to an increase in the electronic density in the inner region of the stacked aromatic rings. However, our previous experience points out that the decrease of NICS upon stacking is caused by the coupling between, i.e., the sum of, the magnetic fields created by the electron current densities of the two rings one placed above the other and is not due to an increase of the electron density in the inner region of the rings. Our hypothesis emerges from a recent study⁸ in which we have analyzed the aromaticity of a series of $[n]$ helicenes. In this work, we have observed a particular behavior of NICS that has been attributed to the magnetic couplings between superimposed rings, which completely modify the trends in local aromaticities as compared to other aromaticity criteria.

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(1) Jones, C. J. *Chem. Soc. Rev.* **1998**, 27, 289.

(2) Diederich, F. N. *Cyclophanes*; Stoddart, J. F., Ed.; Royal Society of Chemistry Monographs in Supramolecular Chemistry; Royal Society of Chemistry: Cambridge, 1991. (b) Bickelhaupt, F. *Pure Appl. Chem.* **1990**, 62, 373.

(3) Caramori, G. F.; Galembeck, S. E.; Laali, K. K. *J. Org. Chem.* **2005**, 70, 3242.

(4) Kruszewski, J.; Krygowski, T. M. *Tetrahedron Lett.* **1972**, 3839.

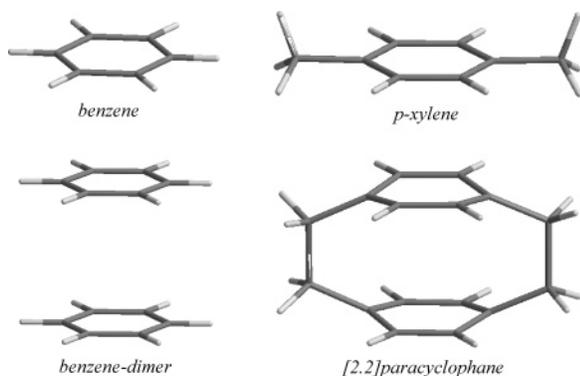
(5) Krygowski, T. M. *J. Chem. Inf. Comput. Sci.* **1993**, 33, 70.

(6) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; van Eikema Hommes, N. J. R. *J. Am. Chem. Soc.* **1996**, 118, 6317.

(7) Schleyer, P. v. R. *Chem. Rev.* **2005**, 105, 3433.

(8) Portella, G.; Poater, J.; Bofill, J. M.; Alemany, P.; Solà, M. *J. Org. Chem.* **2005**, 70, 2509; Erratum **2005**, 70, 4560.

SCHEME 1



To clarify the origin of the NICS reduction in stacked rings, we have chosen benzene, *p*-xylene, the benzene dimer, and [2.2]-paracyclophane (see Scheme 1) optimized at the MP2/6-31+G(d,p) level. For these systems, we have calculated the NICS values at different points along the *z*-axis of these compounds at the B3LYP/6-31+G(d,p) level of theory with the GIAO method.⁹ The perpendicular component to the ring plane of NICS (NICS_{zz}) has also been reported, as it has recently been considered to better represent the effect of the induced magnetic field.¹⁰ Moreover, at the same points where NICS have been measured, values of the electron density, at the MP2/6-31+G(d,p) level, have been calculated. Geometry optimizations and NICS calculations have been carried out by means of Gaussian03,¹¹ and electron density values have been obtained with the AIMPAC package.^{12,13}

Figure 1 shows the evolution of NICS when moving along the *z*-axis of the four systems under study. *R* = 0 corresponds to the center of the ring and will be referred as NICS(0), whereas positive values of *R* correspond to the inner region between aromatic rings (NICS(in)) and negative *R* correspond to the outer region (NICS(out)). It is seen how dimerization of benzene causes a decrease of NICS along the whole *z*-axis, more pronounced in the inner region between the two phenyl rings (positive *R* values). This decrease is expected from the empirical model of shielding for benzene determined by Johnson and Bovey using a current loop model.¹⁴ Stacking of the two rings

(9) Wolinski, K.; Hilton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.

(10) Corminboeuf, C.; Heine, T.; Seifert, G.; Schleyer, P. v. R.; Weber, J. *Phys. Chem. Chem. Phys.* **2004**, *6*, 273.

(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C.01 ed.; Gaussian, Inc.: Pittsburgh, PA, 2003.

(12) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Clarendon: Oxford, U.K., 1990.

(13) Biegler-König, F. W.; Bader, R. F. W.; Tang, T.-H. *J. Comput. Chem.* **1982**, *3*, 317.

(14) Johnson, C. E.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012.

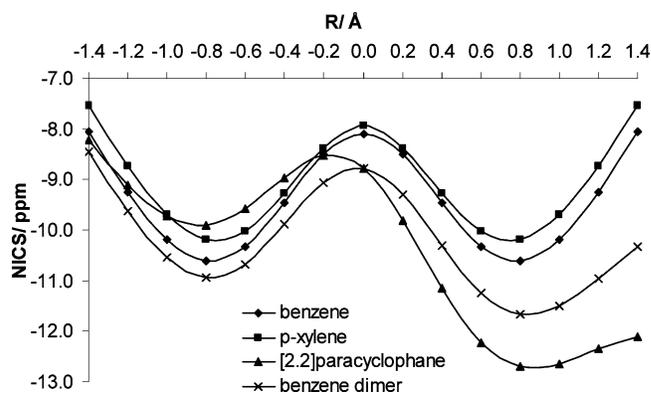


FIGURE 1. Evolution of NICS along the *z*-axis of benzene, *p*-xylene and benzene dimer, and [2.2]paracyclophane. *R* represents the distance from the center of the ring; positive *R* values correspond to NICS(in) and negative *R* values correspond to NICS(out).

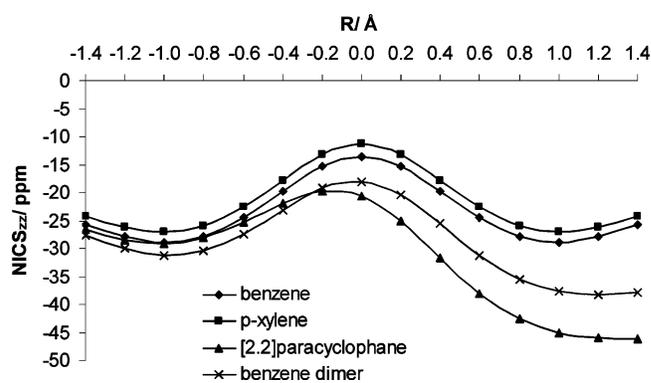


FIGURE 2. Evolution of NICS_{zz} along the *z*-axis of benzene, *p*-xylene and benzene dimer, and [2.2]paracyclophane. *R* represents the distance from the center of the ring; positive *R* values correspond to NICS(in) and negative *R* values correspond to NICS(out).

to give [2.2]paracyclophane causes an additional decrease of NICS in the inner region; however, in the outer region NICS unexpectedly increases. This increase of NICS in the outer region of [2.2]paracyclophane is likely due to the not completely parallel disposition of the two benzene units in this compound (vide supra). Figure 2 represents the corresponding values of NICS_{zz}, which should better describe the ring current due to the π -electrons as being the out of plane component of NICS.^{10,15} In this case, it is seen how NICS values follow basically the same trend as NICS_{zz}. It should be pointed out that the particular behavior of NICS and NICS_{zz} in [2.2]paracyclophane could be caused by the benzene rings not being completely planar. This might bias the in- and out-plane components of NICS, thus reducing the meaning of NICS_{zz}.¹⁵ In this sense, it is worth mentioning that electron current densities contain more information than the simple NICS measure that can be obtained from the electron current densities by integration. For this reason, they are more useful to discuss aromaticity than the NICS value itself.¹⁵

NICS values have been widely commented on in the paper by CGL,³ and thus no further comment will be done in the present work. Nevertheless, it is worth mentioning that for benzene dimer we have used the fully optimized geometry (distance between rings \approx 3.8 Å), whereas CGL constrained

(15) Lazzarotti, P. *Phys. Chem. Chem. Phys.* **2004**, *6*, 217.

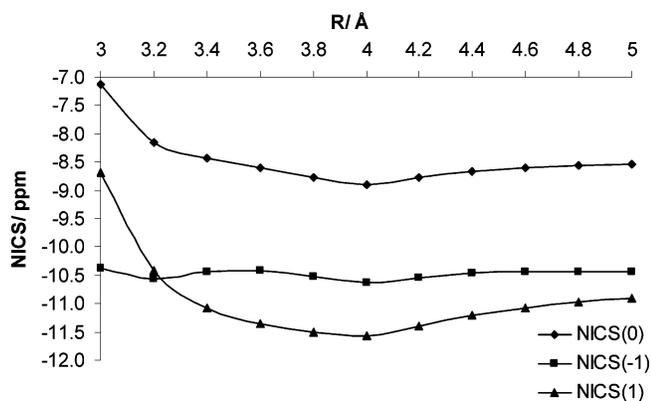


FIGURE 3. Evolution of NICS(0), NICS(1) (inner region), and NICS(-1) (outer region) for the benzene dimer when increasing the separation between the two phenyl rings from $R = 3$ to 5 \AA .

the phenyl rings at the same distance as for [2.2]paracyclophane ($\approx 3.1 \text{ \AA}$). The result of this difference is that for our benzene dimer geometry the NICS(1) (NICS calculated at 1 \AA above the center of one benzene ring toward the inner region between the two benzene rings) is lower than NICS(-1) (NICS calculated at 1 \AA below the center of one benzene ring toward the outer region of the dimer), the opposite to what CGL have obtained. This can be better seen by means of Figure 3 in which NICS(0), NICS(1), and NICS(-1) are calculated for the benzene dimer at different distances between the phenyl rings (from 3 to 5 \AA). This figure clearly shows that the NICS of a certain ring is largely affected by the presence of another ring above and that this effect depends on the distance at which it is located.⁸ It is clearly seen also that at $R \approx 3.2 \text{ \AA}$ there is a crossing in the values between NICS(1) and NICS(-1) that explains the differences in the benzene dimer NICS values reported by CGL and us. The large reduction of NICS(0) and NICS(1) for distances between the benzene rings smaller than 3.2 \AA may be likely due to the influence of the overlap between the π orbitals of the two benzene units.

The next step of the study is to prove that the above decrease in NICS(in) and also in NICS_{zz}(in) observed for the dimers cannot be attributed to an increase of the electron density in this inner region.³ To check this hypothesis, we have computed the electron density along the z -axis, and the corresponding values can be visualized in Figure 4. As it can be seen from the graph, the electron density for the dimers in both inner and outer regions is almost identical for the same $\pm R$ distance and also equivalent to that of the benzene and *p*-xylene rings alone. Therefore, no increase of the electron density is observed in the inner region of the dimers, thus confirming our hypothesis that the decrease of NICS and NICS_{zz} in the inner region has to be associated only to magnetic couplings with neighboring rings placed above⁸ and not to significant electron density changes in the aromatic rings. Thus, the apparent increase in local aromaticity in superimposed aromatic rings indicated by NICS is not real but rather the result of the magnetic field generated in one ring by the electron current density of the other ring placed above it. This result is reinforced by other aromaticity descriptors such as HOMA that shows, for instance, a small reduction of aromaticity when going from benzene to [2.2]-paracyclophane.³

Finally, the present results reveal a limitation of the NICS indicator of aromaticity^{6,7} and suggest that NICS values should be used carefully to discuss local aromaticity in systems having

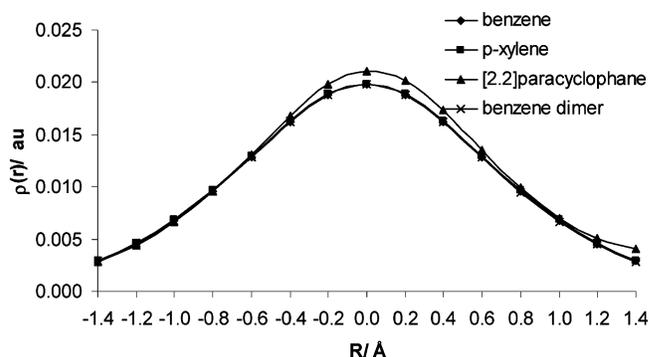


FIGURE 4. Evolution of the electron density along the z -axis of benzene, *p*-xylene and benzene dimers, and [2.2]paracyclophane. R represents the distance from the center of the ring; positive R corresponds to the inner region between the rings and negative R corresponds to the outer region.

superimposed aromatic rings.^{8,15} Thus, it is not only that the NICS indicator of aromaticity can potentially incorporate some spurious information arising from the electron flow perpendicular to the molecular plane^{15,16} and/or that ring currents of neighboring rings in polycyclic compounds can produce a large effect on the NICS values of a given ring,¹⁷ but also that the NICS values of the studied ring can be largely affected by paratropic (or diatropic) ring currents of rings located above or below. In our opinion, this proves that, for some systems, the assessment of local aromaticities based on NICS values only must be made with great care. Indeed, it has been recently shown that ring current analyses are more reliable than integrated properties such as NICS, magnetizability measures, or ^1H magnetic shieldings for planar conjugated hydrocarbons, as these last properties are biased by other parallel π -ring currents.^{18,19} Nevertheless, it must be also stressed that NICS works properly for many other systems and is easier to compute and to deal with than other magnetic criteria.

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Supporting Information Available: Cartesian coordinates and total energies of the four systems. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) Lazzarretti, P. In *Progress in Nuclear Magnetic Resonance Spectroscopy*; Emsley, J. W., Feeney, J., Sutcliffe, L. H., Eds.; Elsevier: Amsterdam, 2000; Vol. 36, p 1.

(17) Poater, J.; Solà, M.; Viglione, R. G.; Zanasi, R. *J. Org. Chem.* **2004**, *69*, 7537.

(18) Wannere, C. S.; Corminboeuf, C.; Allen, W. D.; Schaeffer, H. F., III; Schleyer, P. v. R. *Org. Lett.* **2005**, *7*, 1457.

(19) Faglioni, F.; Ligabue, A.; Pelloni, S.; Soncini, A.; Viglione, R. G.; Ferraro, M. B.; Zanasi, R.; Lazzarretti, P. *Org. Lett.* **2005**, *7*, 3457.