DOI: 10.1002/ejoc.200500564

A Haigh–Mallion-Based Approach for the Evaluation of the Intensity Factors of Aromatic Rings

Cristiano Zonta*[a] and Ottorino De Lucchi[a]

Keywords: Ab initio calculations / Aromaticity / Magnetic properties / NMR spectroscopy

A novel method for the determination of intensity factors of benzenoid systems based on the Haigh–Mallion (HM) theory has been developed. In this paper, the magnetic anisotropy generated by the ring-current effect in polycondensed arenes has been quantitatively calculated as nuclear independent chemical shieldings (NICSs) in a three-dimensional grid of points using the B3LYP/6-31G(d) method implemented in the Gaussian 98 program. The fitting of the calculated values to the HM model gives intensity factors for each ring. A comparison of the obtained values with Schleyer's $NICS_0$ is given. The obtained intensity factors may find application in software using ^1H NMR chemical shifts for structure determination.

Introduction

The concept of aromaticity is still a topic of intense study.[1] Although the thermodynamic and geometric properties of benzene are well defined, they become difficult to generalize for benzenoid rings. In recent years one method for the evaluation of aromaticity has been the measure of the characteristic anisotropy generated by the π-system.[2–4] This effect arises from the π-electrons circulating around the ring in response to an applied magnetic field. This "ring current" generates a local magnetic field, which opposes the applied magnetic field. This phenomenon produces the characteristic low-field shifts of aromatic protons and the high-field shifts of protons positioned in close proximity to the centre of the aromatic systems.

In order to measure the intensity of the ring current, Schleyer has used Nucleus Independent Chemical Shifts (NICSs) calculated in the centre of the ring system ($NICS_0$).[5] This approach has emerged as a good indicator of aromaticity and has been widely adopted. This is due to the simplicity of the involved calculations, the reliability of the values and their ease of interpretation. However, some objections have been directed towards Schleyer's method.[6] In particular, the magnetic anisotropy of neighbouring groups, which can be of great importance for systems presenting a certain degree of distortion from planarity, is neglected,[7] and this may often gives spurious results.

In the present study, a method which takes into account the contributions of neighbouring rings has been developed. It adopts the common strategies for the evaluation of magnetic anisotropy of functional groups.[8] The outcome can be inserted into the software for structure determination that uses ^1H NMR information. This technique relies on the variation of chemical shifts experienced by protons close to functional groups possessing magnetic anisotropy. Common software usually approximates the anisotropy of fused aromatic rings to the sum of the anisotropy of isolated benzene rings (e.g. naphthalene as a sum of two benzene rings). The aim of this paper is a detailed quantification of intensity factors that can be used for the calculation of the anisotropy effect of polycyclic aromatic hydrocarbons (PAHs).

Results and Discussion

Recently, we have been involved in the development of software for structure determination using ^1H NMR chemical shifts.[9] NMR structure determination is becoming an important source of information for supramolecular and biomolecular structures. It is based on the estimation of the effects of different functional groups on chemical shifts. Three theories are commonly used to describe the effect arising from aromatic rings: the quantum-mechanical method of Haigh and Mallion (HM), the semi-classical method of Johnson and Bovey and the classical point-dipole model of Pople.[10] These theories describe the effect on the chemical shift of a proton in proximity to an aromatic ring (δ_{rc}) by the general formula:

$\delta_{rc} = I{\cdot}B{\cdot}G(r)$

where I is the intensity factor that varies with the characteristics of the aromatic ring, B is a constant and G(r) is the spatial function that describes the coordinates of the proton. As shown recently by Scott, the accuracy of these methods is similar.[11] Recently, Gomes and Mallion have proposed a comparison between NICS and ring currents

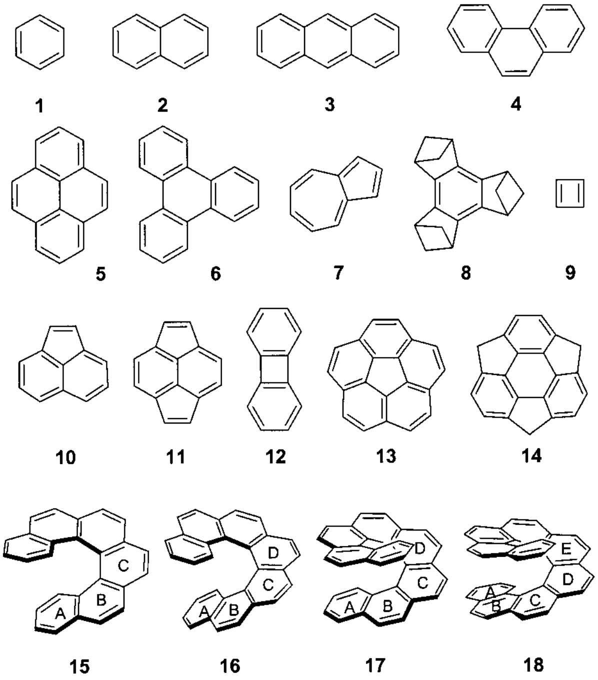
---

[a] Dipartimento di Chimica, Università Ca' Foscari di Venezia,
Dorsoduro 2137, 30123 Venezia, Italy
E-mail: zontac@unive.it

calculated semi-empirically for a series of molecules.[4] This study represents a further investigation in the subject.

NICS values were calculated for shielding points in proximity to the aromatic ring and then fitted to the HM model allowing for variation of the intensity factor *I*.[12] In multiple-ring systems, the simultaneous fitting of the different intensity factors takes into account the contribution of every single ring to the shielding values. In this way the approach reproduces the ring anisotropy without neglecting the contribution of nearby rings, thereby taking into consideration all rings for each point.

Several classes of aromatic compounds were considered for the calculations, such as the aromatic conjugated systems **1**–**7**, the strained aromatic ring **8**, the non-aromatic rings **9**–**12** and the non-planar aromatic rings **13**–**18** (Scheme 1). All these molecules were geometry-optimised at the B3LYP/6-31G(d) DFT level using Gaussian 98.[13]



Scheme 1. Molecules used for the calculation of the aromatic ring current.

Shielding points were positioned in a cube utilizing a Fortran-based routine, with the considered ring occupying its centre. Shielding points were rejected within 2.4 Å from a proton or 3.0 Å from a carbon (given a van der Waals radius of 1.2 Å for a proton, this is the closest distance for a proton without significant repulsion effects). Similarly, to produce a homogeneous distribution, shielding points were rejected if positioned at a distance shorter than 1.6 Å from each other. In the case of multiple-ring systems, the same procedure was repeated for each ring. For example, 178 points were associated with the three rings of anthracene **3** (Figure 1). NICS values were then calculated at the B3LYP/6-31G(d) DFT level implemented in Gaussian 98 and fitted to the HM model allowing for the variation of the intensity factors *I*. In the case of multiple rings for every single point the contribution of each ring was calculated and the intensity factors optimised to reproduce the NICS values.[14] The level of accuracy is represented by R^2, which is the correlation between NICS and HM calculated values. The calculation results are summarised in Table 1.

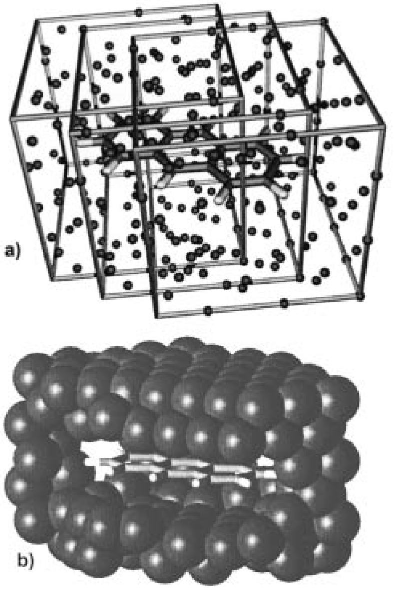


Figure 1. Distribution of shielding points for **3**. a) Three cubes containing 178 shielding points are generated in correspondence of the six-membered rings of anthracene (**3**). b) Section showing the shielding points outside the van der Waals surface of the molecule.

A good correlation factor (R^2) was observed between NICS and HM calculated anisotropies in the case of polybenzenoid systems, thus confirming the ability of the HM model to reproduce the aromatic anisotropy. It is also worth mentioning that a lower correlation was obtained for compounds containing non-aromatic units (**9**, **11**, **12**). These results reveal the poorer ability of the HM model to reproduce paratropic systems. Moreover, the modest correlation displayed by the trisannelated compound **8** can be ascribed to the anisotropy of the bicyclic structure.

The HM intensity factors give an indication of the rings' aromatic character. These values were normalised to the value of benzene (I_n). A comparison of the intensity factors (I_n) with the Schleyer $NICS_0$ values showed a linear correlation (Figure 2).[15] Among the 39 rings investigated in the current work, a linear correspondence between the two methods was found. Small deviations were observed in the aromatic region. However, the only point presenting a notable error was that associated with biphenylene **12**. This low correlation can be ascribed to the poor ability of HM to reproduce cyclobutadiene-type systems.

It is also worth noting that the aromatic character of systems **13**–**15** is not affected by the non-planar arrangement. For example, sumanene (**14**) displays intensity factors (and $NICS_0$ values) similar to triphenylene **6**. A good correlation has been similarly observed for the helicene series.

Furthermore, it should be noted that the practice of approximating the anisotropy of polybenzenoid systems as a

Table 1. Intensity factor for the set of compounds in Scheme 1 compared with Schleyer's $NICS_0$ values.

Compounds		I	I_n[a]	$NICS_0$[b]	Points[c]	R_2[d]
Benzene (**1**)		1.12	1.00	–11.5	109	0.99
Naphthalene (**2**)		1.10	0.98	–11.4	144	0.99
Anthracene (**3**)	outer	1.09	0.97	–9.6	178	0.99
	central	1.20	1.07	–14.3		
Phenanthrene (**4**)	outer	1.14	1.02	–11.7	164	0.99
	central	0.86	0.77	–7.4		
Pyrene (**5**)	outer	1.35	1.20	–12.8	161	0.99
	central	0.79	0.70	–5.0		
Triphenylene (**6**)	central	0.73	0.65	–3.0	183	0.98
	outer	1.14	1.02	–10.8		
Azulene (**7**)	7-ring	0.90	0.81	–8.3	141	0.99
	5-ring	1.60	1.43	–21.5		
Trisbicyclo[2.1.1](**8**)[e]		0.81	0.73	–7.5	64	0.90
Cyclobutadiene (**9**)		–1.20	–1.07	28.8	125	0.87
Acenaphthylene (**10**)	6-ring	1.02	0.91	–9.8	156	0.99
	5-ring	0.34	0.30	2.1		
Pyracyclene(**11**)	6-ring	0.33	0.29	0.1	168	0.47
	5-ring	–0.45	–0.40	16.8		
Biphenylene (**12**)	6-ring	0.34	0.30	–6.5	154	0.84
	4-ring	–0.46	–0.41	18.2		
Corannulene (**13**)[e]		1.03	1.02	–6.7	194	0.99
Sumanene (**14**)[e]	central	0.70	0.62	–2.9	182	0.99
	outer	1.04	0.93	–9.8		
6-Helicene (**15**)[f]	A	1.13	1.01	–10.2	227	0.99
	B	0.95	0.85	–6.8		
	C	0.98	0.87	–7.1		
7-Helicene (**16**)[f]	A	1.10	0.98	–10.8	232	0.99
	B	0.97	0.86	–7.5		
	C	0.94	0.84	–6.3		
	D	0.88	0.79	–6.6		
8-Helicene (**17**)[f]	A	1.14	1.02	–10.9	234	0.99
	B	0.97	0.87	–9.0		
	C	0.96	0.86	–7.2		
	D	0.87	0.78	–5.8		
9-Helicene (**18**)[f]	A	1.12	1.00	–11.1	240	0.99
	B	0.96	0.86	–8.2		
	C	0.94	0.84	–7.8		
	D	0.89	0.79	–6.6		
	E	0.82	0.73	–5.0		

[a] Intensity factors normalised to benzene. [b] See ref.[5a] [c] Number of sampling points associated with each structure. [d] Correlation factor between the calculated NICS value and the values computed with the HM model. [e] $NICS_0$ value calculated at the B3LYP/6-31G(d) DFT level at the centre of the ring. [f] NICS values calculated in ref.[7b]

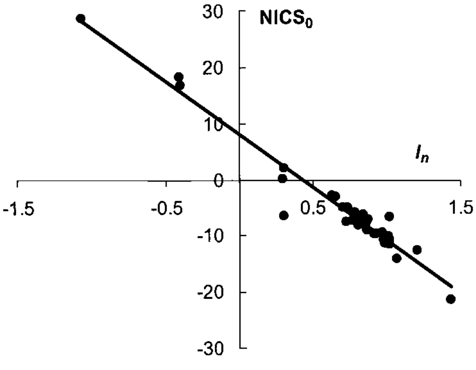


Figure 2. Plot of the aromatic factor calculated using Schleyer $NICS_0$ values vs. the normalised intensity factors, I_n, calculated using the HM model. The correlation factor for the equation $y = –18.9x + 8.0$ is 0.95.

sum of benzene rings could lead to poor estimates of the generated anisotropy. As a demonstration of the higher accuracy obtained with this method, the case of phenanthrene (**4**) is exemplary (Figure 3). We used the ring factors reported in Table 1 for the reproduction of the three-dimensional anisotropy as shown in Figure 3a. All the NICS calculated points were well reproduced by the HM method. However, when the calculation for the same system was executed approximating the anisotropy as the sum of the ring factors of benzene, a poor correlation was observed. The discrepancy increases for more-deshielded points, as shown in Figure 3b.

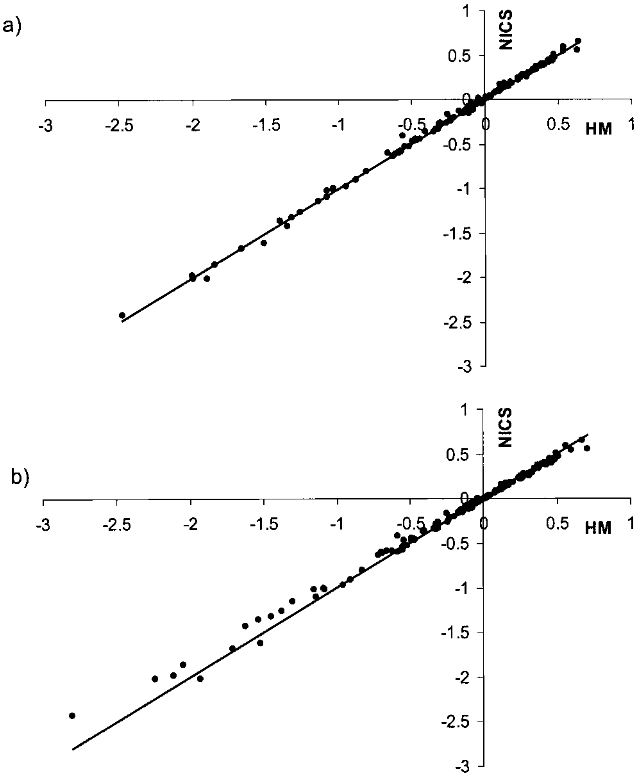


Figure 3. Plot of the NICS calculated values vs. the HM calculated values for the phenanthrene system using: a) ring factors reported in Table 1 and b) ring factors of 1.12 (I of benzene) for each ring. The black lines represent the linear correlation.

Conclusions

In conclusion, a method for the calculation of intensity factors has been developed. The HM method correlates well with Schleyer's $NICS_0$. The calculated intensity factors could complement current software for NMR structure determination and NMR drug discovery.[16]

Experimental Section

Computational Methods

All molecular structures in Scheme 1 were optimised at the B3LYP hybrid density functional method (DFT) level in the 6-31G(d) basis set with the Gaussian 98 program.[13] The gauge-including atomic orbital (GIAO) method was used to perform B3LYP/6-31G(d) calculations of NICSs using the Gaussian 98 software. Schleyer's $NICS_0$ values were computed at the ring centres.[5]

The molecule was placed in the centre of a grid of points ranging from –4.0 Å to +4.0 Å.[17] Shielding points were rejected if within van der Waals radius from the molecule (2.4 Å from a proton, 3.0 Å from a carbon) or if positioned at a distance shorter than 1.6 Å one from another.[18] NICS values were then calculated at the B3LYP/6-31G(d) level and fitted to the Haigh–Mallion model allowing for the variation of intensity factors. Ghost atoms have been used efficiently by others for the prediction of through-space shielding effects on chemical shifts.[17] They have shown good correlation with ^{1}H shieldings outside the van der Waals surface of aromatic rings.[19] R^2 represents the correlation between NICS and HM calculated anisotropies. The size of the cubic box (±4.0 Å, ±6.0 Å, ±8.0 Å) and the shielding points minimum allowed distance (1.4–1.8 Å) were found to have no influence on the size of the ring-current effect in a determination of the intensity factor of benzene.

Acknowledgments

This work was co-funded by MURST within the national project “Stereoselezione in Sintesi Organica: Metodologie e Applicazioni”.

---

[1] a) P. von Ragué Schleyer, *Chem. Rev.* **2001**, *101*, 1115–1117; b) T. M. Krigowski, M. K. Cyrański, *Chem. Rev.* **2001**, *101*, 1385–1419.

[2] R. H. Mitchell, *Chem. Rev.* **2001**, *101*, 1301–1315.

[3] P. Lazzeretti, *Prog. Nucl. Magn. Reson. Spectrosc.* **2000**, *36*, 1–88.

[4] J. A. N. F. Gomes, R. B. Mallion, *Chem. Rev.* **2001**, *101*, 1349–1384.

[5] a) P. von Ragué Schleyer, C. Maerker, A. Dransfeld, H. Jiao, N. J. R. van Eikema Hommes, *J. Am. Chem. Soc.* **1996**, *118*, 6317–6318; b) P. von Ragué Schleyer, M. Manoharan, Z.-X. Wang, B. Kiran, H. Jiao, R. Puchta, N. J. R. van Eikema Hommes, *Org. Lett.* **2001**, *3*, 2465; c) C. S. Wannere, C. Corminboeuf, W. D. Allen, H. F. Schaefer III, P. von Ragué Schleyer, *Org. Lett.* **2005**, *7*, 1457–1460.

[6] a) M. K. Cyrański, T. M. Krygowski, *Tetrahedron* **1998**, *54*, 14919–14924; b) J. Aihara, *Chem. Phys. Lett.* **2002**, *365*, 34–39.

[7] a) J. Poater, M. Solà, R. G. Viglione, R. Zanasi, *J. Org. Chem.* **2004**, *69*, 7537–7542; b) G. Portella, J. Poater, J. M. Bofill, P. Alemany, M. Solà, *J. Org. Chem.* **2005**, *70*, 2509–2521.

[8] a) L. Szilágyi, *Prog. Nucl. Magn. Reson. Spectrosc.* **1995**, *27*, 325–420; b) C. Hunter, M. J. Packer, C. Zonta, *Prog. Nucl. Magn. Reson. Spectrosc*. **2005**, *47*, 27–39.

[9] a) C. A. Hunter, M. J. Packer, *Chem. Eur. J.* **1999**, *5*, 1891–1897; C. A. Hunter, C. M. R. Low, M. J. Packer, S. E. Spey, J. G. Vinter, M. O. Vysotsky, C. Zonta, *Angew. Chem. Int. Ed.* **2001**, *40*, 2678–2682; b) M. J. Packer, C. Zonta, C. A. Hunter, *J. Magn. Reson.* **2003**, *162*, 102–112.

[10] a) C. W. Haigh, R. B. Mallion, *Mol. Phys.* **1971**, *22*, 955–970; b) C. E. Johnson, F. A. Bovey, *J. Chem. Phys.* **1958**, *29*, 1012–1014; c) J. A. Pople, *J. Chem. Phys.* **1956**, *24*, 1111; d) S. Perkins, *J. Biol. Magn. Reson.* **1982**, *4*, 193–336. For an alternative ring-current analysis see ref.[3] orR. C. Haddon, *Tetrahedron* **1972**, *28*, 3613–3633; e) R. C. Haddon, *Tetrahedron* **1972**, *28*, 3635–3655.

[11] G. Moyna, R. J. Zauhar, H. W. Williams, R. J. Nachman, A. I. Scott, *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 702–709.

[12] For the HM calculation routine developed in the original software by Williamson, see: M. P. Williamson, T. J. Asakura, *J. Magn. Reson. Ser. B* **1993**, *101*, 63–71.

[13] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *Gaussian 98, Revision A.9*, Gaussian, Inc., Pittsburgh, PA, **1998**.

[14] A Simplex routine written in Fortran was used for this purpose. Simplex starting points were varied in order to find the global minima, see J. C. Nash, *Compact Numerical Methods for Computers: Linear Algebra and Function Minimisation*, Adam Hilger Ltd., Bristol, **1980**.

[15] For a comparison of different aromatic indexes with NICS values, see: M. K. Cyrañski, T. M. Krygowski, A. R. Katrizky, P. von Ragué Schleyer, *J. Org. Chem.* **2002**, *67*, 1333–1338.

[16] a) M. Pellecchia, D. S. Sem, K. Wüthrich, *Nature Rev. Drug Discov.* **2002**, *1*, 211–219; b) M. A. McCoy, D. F. Wyss, *J. Am. Chem. Soc.* **2002**, *124*, 11758–11763.

[17] A similar approach has been used to visualize the effect of anisotropy for various functional groups: S. Klod, E. Kleinpeter, *J. Chem. Soc., Perkin Trans. 2* **2001**, 1893–1898.

[18] G. Chessari, C. A. Hunter, C. M. R. Low, M. J. Packer, J. G. Vinter, C. Zonta, *Chem. Eur. J.* **2002**, *8*, 2860–2867.

[19] N. H. Martin, D. M. Loveless, D. C. Wade, *J. Mol. Graphics Modell.* **2004**, *23*, 285–290.

Received: July 26, 2005