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Computed NMR shielding increments over benzo-analogs of unsaturated five-membered ring heterocyclic compounds as a measure of aromaticity

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ABSTRACT

The GIAO-HF method in Gaussian 03 was used to calculate the isotropic shielding value of the proximal hydrogen of a diatomic hydrogen probe moved in a square grid 2.5 Å above the plane of 15 benzo-fused analogs of conjugated five-membered ring heterocyclic compounds: pyrrole, furan, thiophene, and phosphole and their 2- and 3-nitrogen analogs. Subtraction of the calculated isotropic shielding value of diatomic hydrogen from each of these isotropic shielding values gave the shielding increment ($\Delta\sigma$) for each probe position. Plotting this value against Cartesian coordinates of the probe position allowed determination of the computed through-space shielding increment surfaces for these compounds. Substantial shielding was observed above the center of each ring, as expected for aromatic compounds. The magnitude of the shielding increment 2.5 Å above the heterocyclic ring center correlated reasonably well with the only other published method of assessing aromaticity of these systems ASE (aromatic stabilization energy) and with our calculated NICS (nucleus-independent chemical shift) values, another magnetic criterion. The magnitude of the shielding increment measured over the benzene ring midpoint did not correlate well with other measures of aromaticity, however.

1. Introduction

Despite the development of numerous methods for the measurement of the extent of aromaticity since Kekulé first introduced the concept 144 years ago [1], no single method has gained universal acceptance. This is in part because aromaticity is a multidimensional property, composed of geometrical, energetic and magnetic components, whereas most measures focus on only one aspect [2]. As an example, the harmonic oscillator model of aromaticity, HOMA [3–6] relies on bond length similarity. Others rely on energetics, such as aromatic stabilization energy, ASE [7–11]. A third category depends on magnetic properties, including exaltation of magnetic susceptibility, Λ [12–14], anisotropy of the magnetic susceptibility [15], nuclear magnetic resonance shifts [16–18], and nucleus-independent chemical shifts, NICS [19,20]. The latter is a measure of the diatropic (for aromatic compounds) or paratropic (for antiaromatic compounds) ring current. NICS or one of its variations, such as aromatic ring current shieldings (ARCS) computed from NICS measurements perpendicular to the plane of aromatic rings [21], Kleinpeter and Klod's [22,23] graphical maps of an array of NICS, named isochemical shielding surfaces (ICSS), or Stanger's partitioned NICS [24] are newer methods to measure or predict aromaticity. Cyrański et al. [25,26] showed that loose correlations exist among the four most widely used measures of aromaticity: ASE, Λ, HOMA and NICS for a series of 75 five-membered ring π-electron systems and 30 ring-substituted compounds (including aromatic, nonaromatic and antiaromatic systems. Although NICS measurements in some form have become the most widely used measure of aromaticity, they have limitations in terms of predicting aromaticity *vs.* antiaromaticity. For instance, the NICS value of the antiaromatic cyclopropenyl anion is negative, indicative of an aromatic structure. The correct assignments of aromaticity and antiaromaticity are obtained if a probe molecule, such as diatomic hydrogen, is used to determine the through-space shielding effect [27]. The use of a molecular probe includes not only magnetic effects, but also polarization effects, which are important in predicting through-space chemical shift effects [28,29]. In contrast, the NICS method involves computing only the magnetic shielding at a point in space.

We have reported the results of GIAO-HF calculations to calculate through-space NMR shielding effects on a probe molecule and to map the resulting through-space NMR shielding increments in aromatic ring π-stacked complexes [30]. The computed shielding effects and the relationship between the computed shielding effects and the extent of aromaticity of linear polycyclic aromatic hydrocarbons (PAHs) [31] have been reported. Reasonable correlations between computed shielding increments using a diatomic hydrogen probe and several common measures of aromaticity have recently been demonstrated for conjugated five-

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membered ring heterocyclic compounds [32]. However, little has been published thus far on measures of aromaticity of benzo-analogs of conjugated five-membered ring heterocyclic compounds.

2. Computational methods

Structures of the benzo-derivatives of conjugated five-membered ring heterocyclic compounds in this study are shown in Fig. 1. They consist of indole (**1**), furan (**2**), benzo[b]phosphole (**3**) and benzo[b]thiophene (**4**) and their α-aza (**1a, 2a, 3a,** and **4a)** and β-aza derivatives (**1b, 2b, 3b,** and **4b**), plus isoindole (**5**), isobenzofuran (**6**), benzo[c]thiophene (**7**). A model of each of these was built in Titan [33], and equilibrium geometries were obtained at the Hartree-Fock level of theory using the 6-31G(d,p) basis set [34]. These structures are all planar, which allowed the Cartesian coordinate molecule description to be oriented with the atoms in the *XY* plane having the center of the bond between the rings at the origin of Cartesian space and the heterocyclic portion in the positive *X* direction. A diatomic hydrogen (H_2) probe [28], previously geometry optimized at HF/6-31G(d,p), was placed along the *Z* axis with the proximal hydrogen at a distance of 2.5 Å from the plane of each molecule (Fig. 2a). A series of single point GIAO calculations[1] was performed in Gaussian 03 [36] on these supramolecules using the same method and basis set, moving the H_2 in 0.5 Å increments in both the *X* and *Y* directions in separate calculations. Calculations were also performed with the diatomic hydrogen probe above the geometric midpoint of each ring. These calculations covered a square grid that extended beyond the positions of the carbon atoms in the *X* and *Y* directions (Fig. 2b). The symmetry of some of the structures allowed only one-half of the grid to be calculated and the data to be replicated by a reflection across the *Y* axis. The shielding increment ($\Delta\sigma$, in ppm) at a given point in Cartesian space was determined by taking the difference between the calculated isotropic shielding value of one of the hydrogens in an isolated H_2 (26.77 ppm) and that of the proximal hydrogen of the H_2 probe at that point (in Cartesian coordinates *XYZ*) relative to the heterocyclic structures. Thus, $\Delta\sigma = \sigma H_{XYZ} - 26.77$ (in ppm). Computed isotropic shift values greater than that of isolated H_2 result in positive $\Delta\sigma$ values (shielding); those with smaller values yield negative $\Delta\sigma$ values (deshielding). The shielding increments ($\Delta\sigma$) are therefore equal in magnitude but opposite in sign to differences in ^{1}H NMR chemical shifts ($\Delta\delta$). Three-dimensional NMR shielding increment isosurface contour plots ($\Delta\sigma$ vs. *X* and *Y* at a fixed value of *Z*) were prepared using SigmaPlot [37] to represent graphically the shielding surface 2.5 Å over the molecules in the study.

Linear correlations were determined for shielding increments computed 2.5 Å over the heterocyclic ring centers ($\Delta\sigma_{2.5}$) against the only other published measure of aromaticity for these compounds (ASE) collected by Bird [38] and against NICS, NICS(1) and NICS(2.5) computed using the same theory and basis set used in the shielding increment calculations.

3. Results and discussion

In previous work [32] where calculations were performed at 2.5 Å, 3.0 Å and 4.0 Å above the plane of each aromatic compound it was demonstrated that by far the greatest shielding (and deshielding) was found using probe distances close to plane of the aromatic compound being studied. For that reason, only shielding increment surfaces at 2.5 Å were determined. Shielding increment surfaces at 2.5 Å above the plane of indole **1** and its α-aza and β-aza derivatives (indazole **1a** and benzimidazole **1b**) are shown in Fig. 3. Each of the shielding increment surfaces shows a dominant mound of shielding near the center of the benzene ring, with slightly less shielding over the heterocyclic ring and a region of slight deshielding beyond the vicinity of the α,β π bond and the second heteroatom. The maximum shielding values ($\Delta\sigma_{2.5}$, computed over the center of the benzene ring and the heterocyclic ring) for each structure in the study are gathered in Table 1, along with the only other published measure of the extent of aromaticity of these structures, ASE, taken from Bird [38] and our calculated values of NICS, NICS(1), and NICS(2.5). Published data were not available (na) for most of the structures in this study. Addition of a second heteroatom (nitrogen) increases the maximum shielding observed over the heterocyclic ring by about 0.3 ppm. This trend was observed throughout the compounds in this study.

The maximum shielding observed over the heterocyclic portion of the oxygen-containing heterocyclic structures benzofuran **2**, 1,2-benzisoxazole **2a** and 1,3-benzoxazole **2b** (Fig. 4) is somewhat less than that observed over indole and its aza analogs. Shielding is greater in the aza analogs, as was observed with indole. The maximum shielding over the benzene ring is essentially the same as was observed over indole and its aza analogs. The benzene portion has enhanced shielding relative to benzene itself (3.0 ppm) [27]. This was observed with most of the compounds in this study. As observed with indole and its analogs, slight deshielding is observed in the region beyond the oxygen and nitrogen heteroatoms.

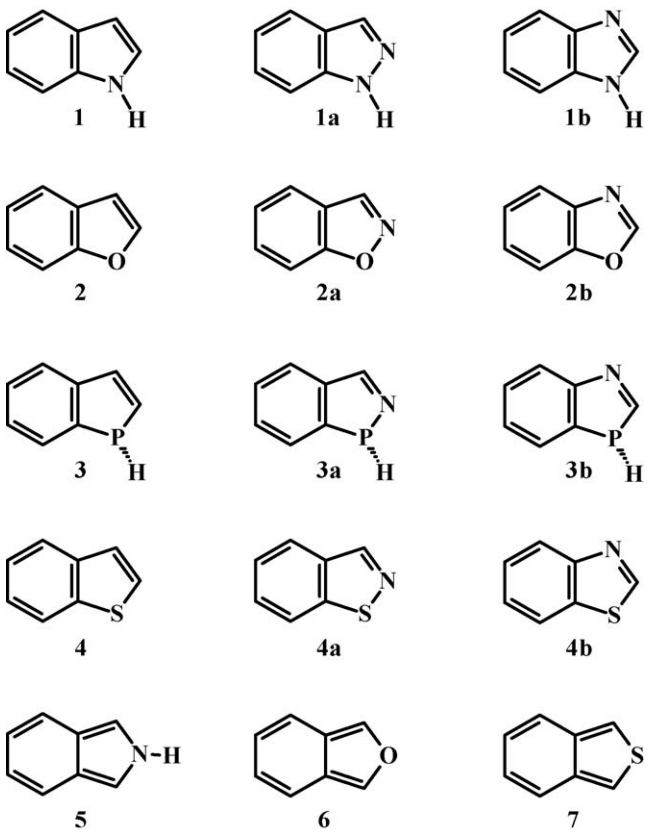

Fig. 1. Structures of the benzo-fused five-membered ring heterocyclic compunds in the study.

[1] Previous calculations [30] have shown that basis set superposition error, as measured by the counterpoise method of Boys and Bernardi [35], introduces a negligible effect on shielding values. BSSE is typically no greater than 0.05 ppm. Also, the difference between the shielding values obtained using single point calculations and constrained geometry-optimized calculations is also negligible [28].

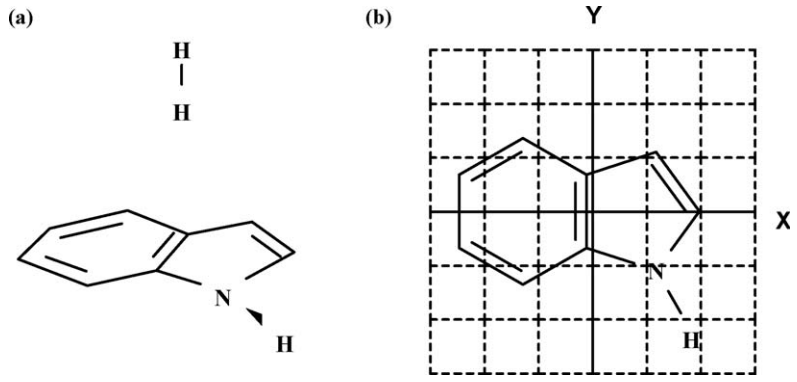

Fig. 2. (a) Orientation of the diatomic hydrogen probe at one location over indole, and (b) Grid used to move the probe molecule over the surface of indole.

Benzo[b]phosphole **3** and its aza analogs 1,2-benzisophosphazole **3a** and 1,3-benzophosphazole **3b** (Fig. 5) show very different shielding increment surfaces from indole, benzofuran and their aza analogs. The explanation is based on structure differences. Benzo[b]phosphole and its nitrogen analogs have a pyramidal phosphorus with a lone pair of electrons projecting from the plane on one side of the ring and a P–H bond projecting from the plane on the other side. In a study of five-membered ring heterocycles, separate GIAO calculations were performed on phosphole and its analogs with the diatomic hydrogen probe on both sides of the ring [32]. Interestingly, the qualitative results are very similar; the major differences are quantitative. Regardless of which side the probe was placed, the maximum shielding increment over the ring center is much less than is observed over pyrrole, furan, and their aza analogs. In the benzo-analogs, a region of substantial deshielding (−1.4 to −1.6 ppm) was observed beyond the phosphorus. This is reminiscent of phosphole and its aza analogs, but the effect was greater in the five-membered ring compounds. The maximum shielding increment in the five-membered ring series was about 0.3 ppm more over the ring center on the lone pair side. In this study of benzo-analogs, calculations were only performed on the lone pair side. As observed previously in the indole and benzofuran series, slightly less shielding occurs beyond the nitrogen heteroatom in the aza analogs.

Benzo[b]thiophene **4** and its aza analogs 1,2-benzisothiazole **4a** and 1,3-benzothiazole **4b** display substantial shielding over their ring centers and moderate deshielding beyond the sulfur (and slight deshielding beyond the nitrogen heteroatom in the aza analogs; Fig. 6). The maximum shielding increment over benzothiophene and its aza analogs is greater than that observed over benzofuran or benzophosphole and their aza analog (Table 1), and about the same as that observed over indole and its analogs. The greatest deshielding (−0.7 to −0.9 ppm) is much less deshielding than that observed in the phosphole series.

The substantial deshielding seen near sulfur and phosphorus (Figs. 5 and 6) is expected because of their larger van der Waals radii (1.82 Å and 1.85 Å, respectively) as compared to nitrogen and

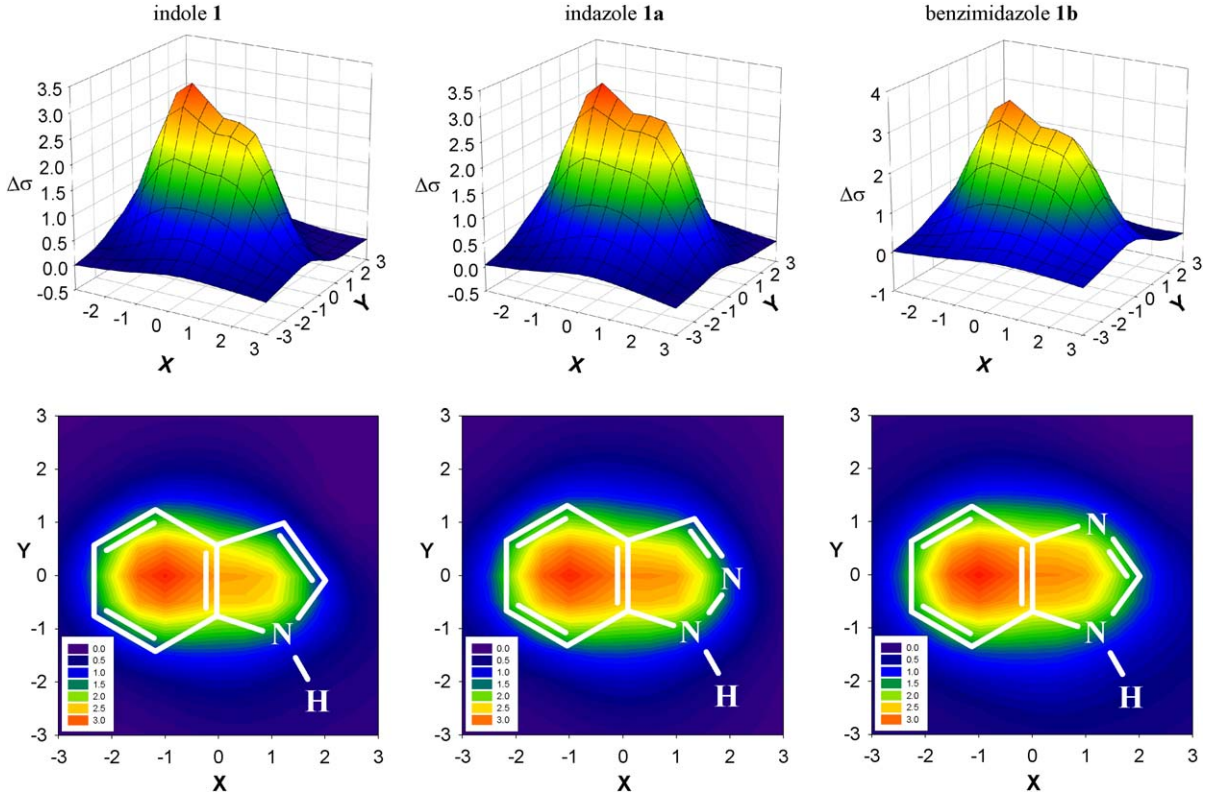

Fig. 3. Calculated shielding increment surfaces (in ppm) of indole, indazole, and benzimidazole at 2.5 Å.

Table 1
Maximum shielding increments calculated 2.5 Å above the center of the benzene ring ($\Delta\sigma_{bz}$) and the heterocyclic ring ($\Delta\sigma_{het}$) in ppm, along with aromatic stabilization energies (ASE, in kcal/mol) tabulated by Bird [38] and nucleus-independent chemical shift values (NICS, NICS(1), and NICS(2.5)), in ppm, computed over the heterocyclic ring center.

Compound	$\Delta\sigma_{bz}$	$\Delta\sigma_{het}$	ASE	NICS	NICS(1)	NICS(2.5)
Indole **1**	3.2	2.4	73.8	−15.4	−11.8	−2.8
Indazole **1a**	3.3	2.7	75.7	−15.9	−13.0	−3.0
Benzimidazole **1b**	3.3	2.7	78.9	−13.2	−11.0	−2.8
Benzofuran **2**	3.3	2.0	77.6	−11.8	−9.5	−2.3
1,2-Benzisoxazole **2a**	3.4	2.3	55.4	−12.0	−10.3	−2.5
1,3-Benzoxazole **2b**	3.4	2.4	na	−10.1	−9.1	−2.4
Benzo[b]phosphole **3**	3.1	1.5	na	−3.1	−3.8	−1.7
1,2-Benzisophosphazole **3a**	3.3	1.7	na	−3.5	−4.1	−1.8
1,3-Benzophosphazole **3b**	3.2	1.9	na	−1.6	−4.1	−1.9
Benzo[b]thiophene **4**	3.3	2.4	na	−11.7	−9.0	−2.6
1,2-Benzisothiazole **4a**	3.4	2.7	na	−12.1	−9.5	−2.7
1,3-Benzothiazole **4b**	3.4	2.7	na	−10.7	−9.3	−2.7
Isoindole **5**	2.4	3.0	na	−20.7	−15.1	−3.3
Isobenzofuran **6**	1.8	2.6	na	−18.0	−13.0	−2.8
Benzo[c]thiophene **7**	2.2	3.1	na	−21.1	−14.1	−3.3

oxygen (1.53 Å and 1.50 Å, respectively) [39]. The greater deshielding in benzo[b]phosphole and its aza analogs (compared to benzo[b]thiophene and its aza analogs) is because thiophene is more aromatic than phosphole. One of the lone pairs of electrons of the thiophene portion of benzo[b]thiophene is much more involved in delocalization with the other π electrons, leading to a greater ring current and therefore greater shielding over the ring center, as observed previously ($\Delta\sigma_{2.5}$ = 2.4 ppm over thiophene *vs.* 1.4 ppm over phosphole) [32]. The other lone pair of electrons on sulfur can be thought to occupy an sp^2 hybrid orbital in the plane of the molecule. In contrast, the lone pair of electrons in phosphole is more localized on the pyramidal phosphorus, resulting in less aromaticity, decreased ring current, and therefore less shielding over the ring center. Furthermore, localized lone pair electrons on the phosphorus give rise to greater van der Waals deshielding. The P–H bond projecting from the molecular plane on the opposite face also causes substantial van der Waals deshielding.

The shielding increment surfaces of isoindole **5**, isobenzofuran **6** and benzo[c]thiophene **7** are shown in Fig. 7. All three of these shielding surfaces differ from the others in this study in that the maximum shielding is observed over the heterocyclic ring in each of these rather than over the benzene ring, and the benzene portion has less shielding than benzene itself (3.0 ppm) [27]. The maximum shielding in each of these is also less than the maximum

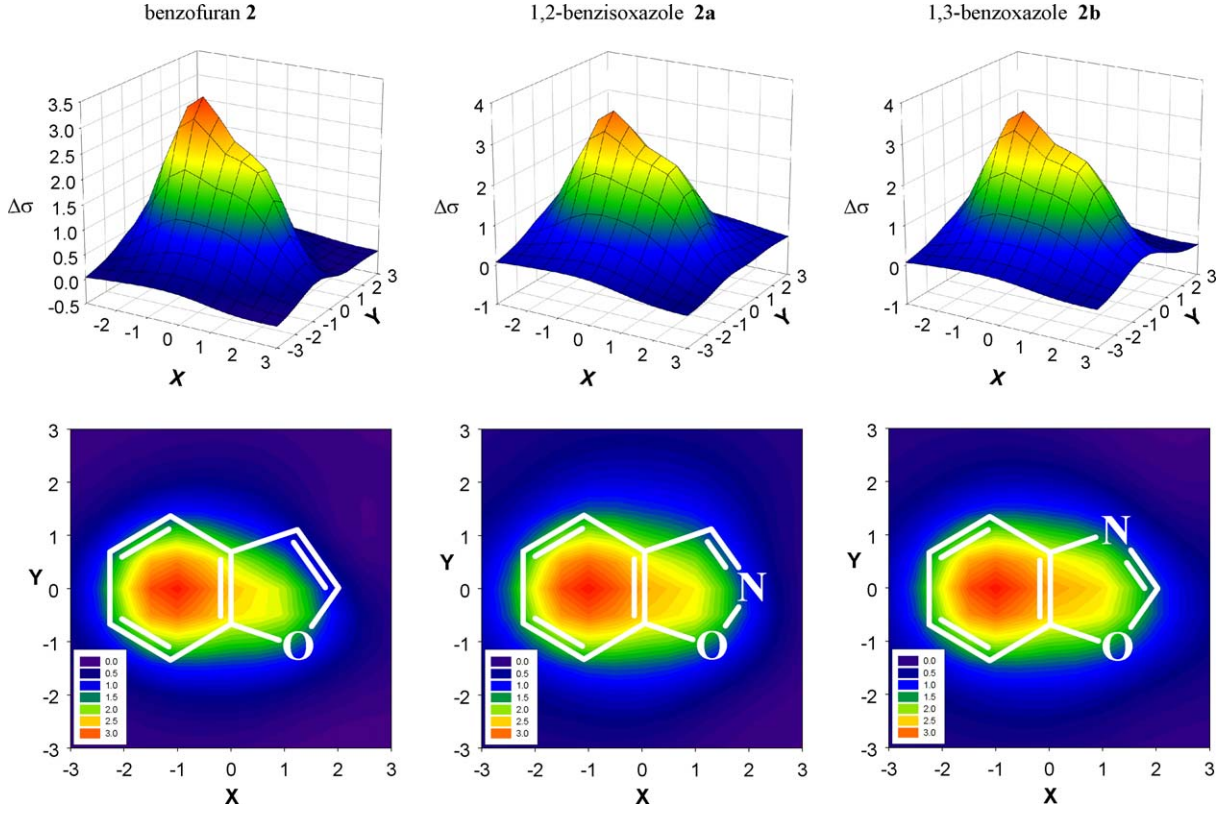

Fig. 4. Calculated shielding increment surfaces (in ppm) of benzofuran, 1,2-benzisoxazole, and 1,3-benzoxazole at 2.5 Å.

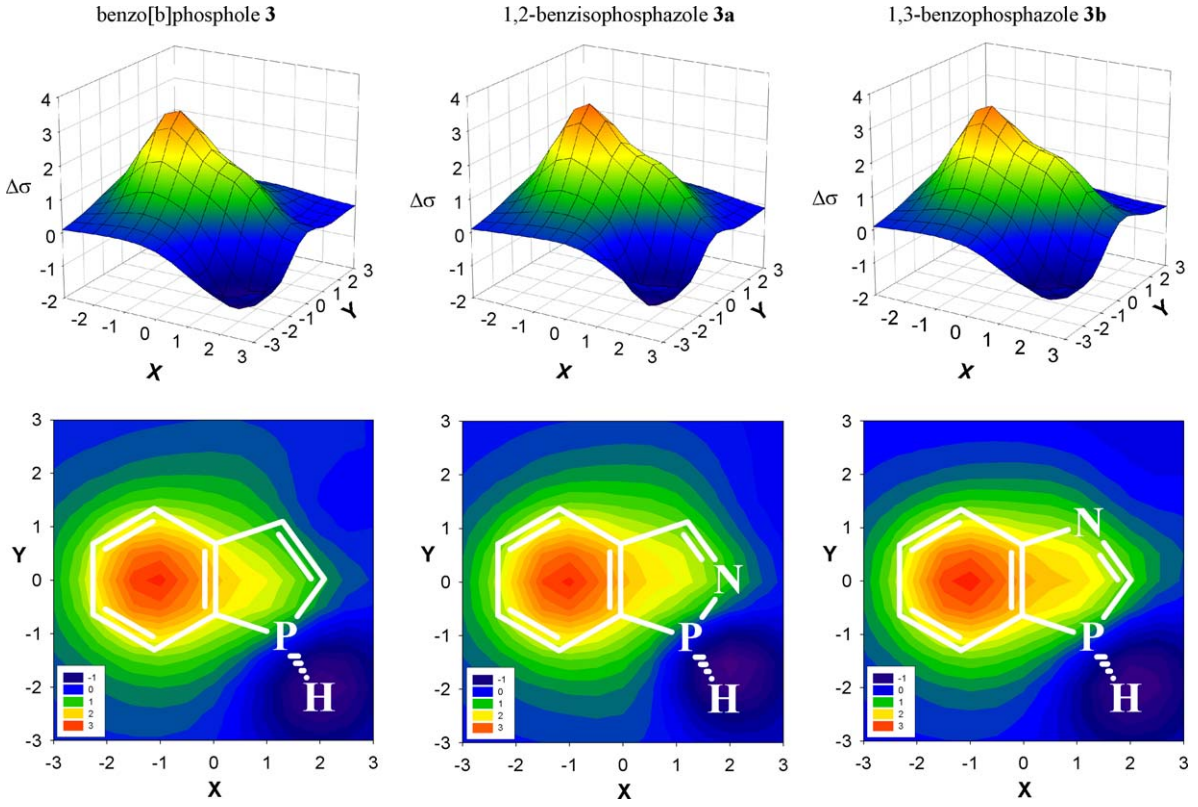

Fig. 5. Calculated shielding increment surfaces (in ppm) of benzo[b]phosphole (lp side), 1,2-benzisophosphazole (lp side), and 1,3-benzphosphazole (lp side) at 2.5 Å.

shielding in their parent structures (Table 1). It should be noted that enhanced shielding over a ring is not necessarily indicative of greater aromaticity, although NICS calculations of these compounds give the largest negative values, suggestive of aromaticity. For aromaticity, the heteroatom must share a lone pair of electrons, giving a formal positive charge to the heteroatom. The positive charge contributes to the computed shielding effect by polarizing the H_2 probe [28].

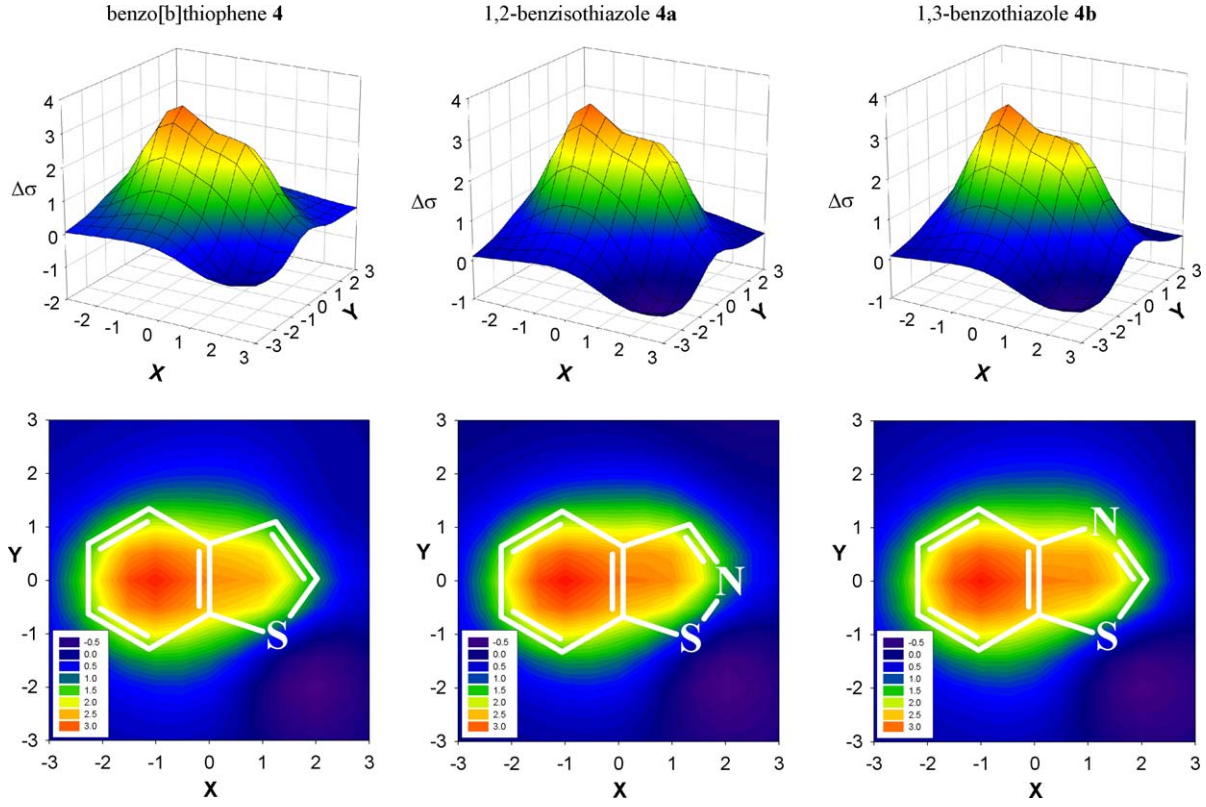

Fig. 6. Calculated shielding increment surfaces (in ppm) of benzo[b]thiophene, 1,2-benzisothiazole, and 1,3-benzothiazole at 2.5 Å.

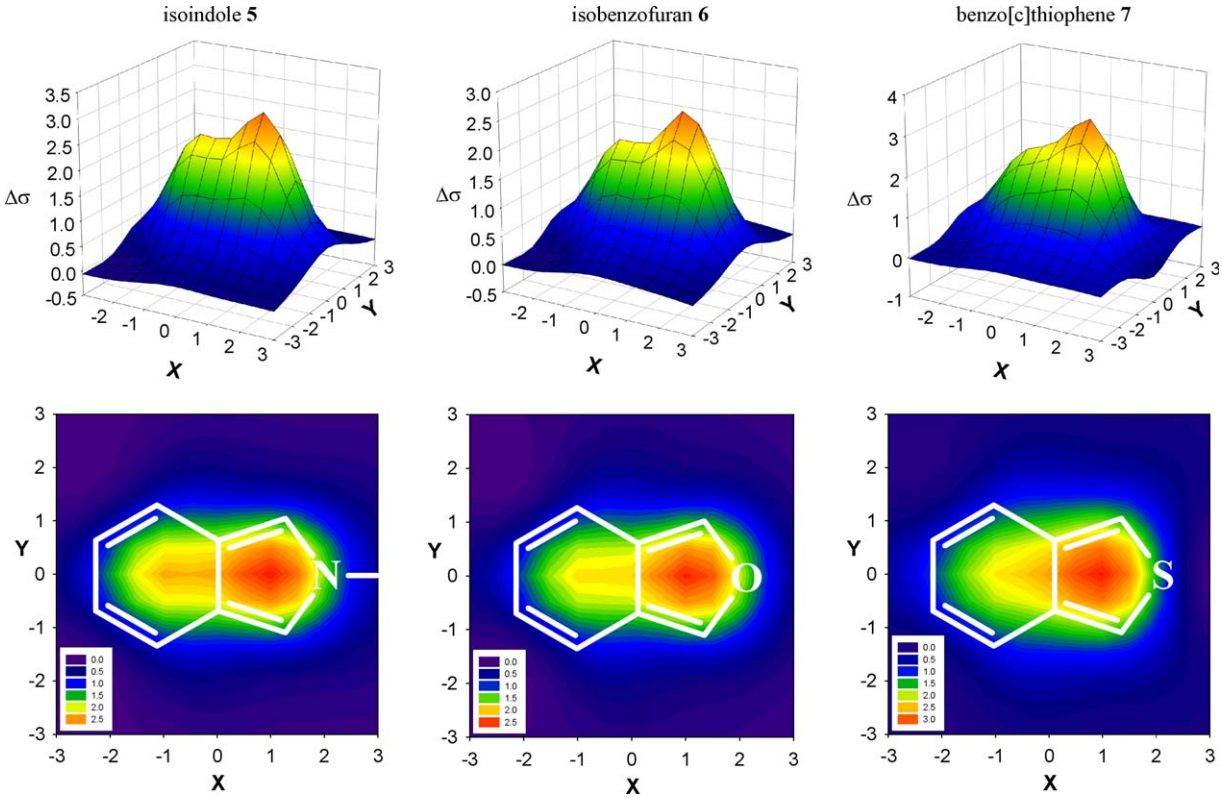

Fig. 7. Calculated shielding increment surfaces (in ppm) of isoindole, isobenzofuran, and benzo[c]thiophene at 2.5 Å.

Linear correlations were determined between the $\Delta\sigma_{2.5}$ values computed in this study and an energetic measure of aromaticity (ASE) collected by Bird [38] as well as NICS, NICS(1) and NICS(2.5). The NICS(1) values for benzophosphole and its aza analogs are computed on the P–H side. The coefficients of determination (r^2 values) for each correlation are shown in Table 2. From the data it is clear that no single measure of aromaticity correlates highly with any other measure. This has been well documented, and supports the multidimensional nature of aromaticity [40]. However, it is also evident from the data in Table 2 that $\Delta\sigma_{2.5}$ values correlate with the other measures the same as ASE, slightly better than HOMA, but not quite as well as NICS(1) values do. The advantage of shielding increment values (and the 3D shielding increment isosurface maps) over NICS values is that shielding increments have been shown to be reliable predictors of chemical shifts of protons as a function of position over the molecule in question, whereas NICS do not reliably predict chemical shift effects [28]. This is due in part to the fact that $\Delta\sigma$ values, unlike NICS measurements, include orbital interactions and bond polarization effects, both important aspects of the net magnetic shielding experienced by protons near π electron systems [28,29].

Table 2
Coefficients of determination (r^2) for linear correlation of $\Delta\sigma_{2.5}$ values (in ppm) over the heterocyclic ring midpoints *vs.* Bird's ASE values (in kcal/mol) [38], NICS, NICS(1) and NICS(2.5) computed over the heterocyclic ring (in ppm). For benzo[b]phosphole and its aza analogs, $\Delta\sigma_{2.5}$ and all NICS values were calculated on the side with the lone pair of electrons.

	$\Delta\sigma_{het}$	ASE	NICS	NICS(1)	NICS(2.5)
$\Delta\sigma_{het}$	–	0.67	0.71	0.80	0.95
ASE	–	–	0.49	0.53	0.71
NICS	–	–	–	0.94	0.86
NICS(1)	–	–	–	–	0.93
NICS(2.5)	–	–	–	–	–

4. Conclusions

NMR shielding calculations have been performed with the proximal hydrogen of a diatomic hydrogen probe juxtaposed at various positions over a series of 15 benzo-fused conjugated five-membered ring heterocyclic compounds. Subtraction of the shielding value of diatomic hydrogen by itself gives the shielding increment ($\Delta\sigma$). Plots of the shielding increment *vs.* Cartesian coordinates using SigmaPlot provide shielding increment isosurfaces for each of the heterocycles. Mounds of shielding are evident near the center of each ring, with slight deshielding in the region beyond the heteroatom(s). With the benzo-derivatives of phosphole, thiophene and their aza analogs, substantial deshielding was observed beyond their sulfur or phosphorus heteroatom, attributed to van der Waals deshielding. Benzo-analogs of thiophene display greater shielding than benzo-analogs of phosphole, consistent with the greater aromaticity of thiophene than phosphole. In contrast, benzo-derivatives of phosphole show greater deshielding beyond the heteroatom than do corresponding benzo derivatives of thiophene. This is consistent with greater delocalization of the lone pair electrons of thiophene than those on phosphole. Linear correlations between the maximum computed shielding 2.5 Å above each ring ($\Delta\sigma_{2.5}$) and various published measures of aromaticity, including those related to energy (ASE), geometry (HOMA) and magnetic properties (NICS) show that $\Delta\sigma_{2.5}$ correlates with the other measures slightly better than HOMA, the same as ASE, and almost as well as NICS(1).

Acknowledgments

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