^{1}H chemical shifts in NMR. Part 18.[1] Ring currents and π-electron effects in hetero-aromatics

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The ^{1}H chemical shifts of a number of hetero-aromatics and related compounds were obtained by the assignment of the NMR spectra in $CDCl_3$ solution or from the literature. These included furan, pyrrole, thiophene, oxazole, imidazole and thiazole, various methyl and 4,5-dihydro derivatives, the benzo derivatives benzofuran, indole and benzothiophene plus the related compounds vinyl methyl ether, phenol, anisole, aniline, vinyl methyl sulfide and thiophenol. The six membered hetero-aromatics pyridine, pyrimidine, pyrazine, pyridazine, quinoline and isoquinoline and a number of their methyl derivatives were also investigated. The ^{1}H chemical shifts in these molecules were analysed in terms of the ring currents and π-electron effects together with a model (CHARGE7h) for the calculation of the two-bond and three-bond electronic effects. This model gives the first comprehensive calculation of the proton chemical shifts in these compounds. For the data set considered (215 proton chemical shifts) ranging from δ = 1.9 to 9.4 ppm the rms error of observed *vs.* calculated shifts was 0.096 ppm. The model also allows the interpretation of the chemical shifts in terms of the separate interactions calculated in the programme. This showed the large effects of the ring currents and π-electron densities on the ^{1}H chemical shifts. Methyl substitution has a large effect on the chemical shifts which is due to increased π-electron densities in the methyl compounds. The ring currents in furan, pyrrole and thiophene were found to be equal to the benzene ring current, but the introduction of an aza nitrogen decreased the ring current by *ca.* 10% in both the five and six-membered heterocyclics. The effect was cumulative in the diazabenzenes.

Introduction

Hetero-aromatic compounds comprise an important group of compounds in organic chemistry. They are of considerable commercial importance and the extent to which the properties of these compounds are determined by their aromatic character has interested chemists for many years.[2]

The discovery of the aromatic ring current of benzene[3] allowed in principle the determination of the aromaticity of any molecule by measuring its ring current. In a pioneering study Abraham and Thomas[4] compared the chemical shifts of the H-2 and 2-methyl protons in furan, thiophene, thiazole, imidazole and benzene and their methyl derivatives with those of similarly constituted protons in the 4,5-dihydro compounds where there is no ring current. They proposed that the observed differences in the proton chemical shifts were a measure of the ring currents in these compounds and found that the ring currents in furan and thiophene "did not differ significantly" from the benzene ring current. Elvidge[5] using polyenes as models obtained values of the ring currents in furan, pyrrole and thiophene of 46, 59 and 75% that of benzene.

De Jongh and Wynberg[6] used the same method as ref. 4 but averaged the shifts of H-2 and H-3 in the dihydro compounds. They obtained values of the ring currents in furan and thiophene between those of ref. 4 and 5.

Since this early work no calculation of the ^{1}H shifts in these compounds has been given. In particular the calculation of these chemical shifts using the *ab initio* GIAO method has not been reported to date. Lampert *et al.*[7] compared the observed *vs.* calculated NMR chemical shifts for phenol and benzaldehyde and for 13 substituted derivatives, using a variety of basis sets and computational procedures within the GAUSSIAN94 program. The calculated shielding of the aromatic protons with respect to methane varied by *ca.* 0.5–1.0 ppm. depending on the procedure and basis set used and this may well represent the limit of accuracy of such calculations.

A calculation of the ^{1}H shifts in condensed aromatic hydrocarbons was given in a previous part of this series[8] based on ring current and π-electron effects. For the data set of 55 protons spanning 3 ppm the rms error of the observed *vs.* calculated shifts was 0.1 ppm, which is a useful predictive accuracy for synthetic chemists. We now wish to apply the same procedure to hetero-aromatics. We give here a complete analysis of the ^{1}H chemical shifts of a number of hetero-aromatic and related compounds in $CDCl_3$ solution. It was convenient for the purposes of parametrisation to include some related compounds; *e.g.* vinyl methyl ether and thio ether were useful additions to the oxygen and sulfur compounds and aniline for the nitrogen heterocycles *etc.* The molecules considered here are shown with the atom numbering in Figs. 1 to 6 and are as follows.

Fig. 1 vinyl methyl ether (**1**), phenol (**2**), anisole (**3**), furan (**4**), 4,5-dihydrofuran (**5**), 2-methylfuran (**6**), 2-methyl-4,5-dihydrofuran (**7**), 2,5-dimethylfuran (**8**), 3-methylfuran (**9**) and benzofuran (**10**).

Fig. 2 vinyl methyl sulfide (**11**), thiophenol (**12**), thiophene (**13**), 4,5-dihydrothiophene (**14**), 2-methylthiophene (**15**), 2-methyl-4,5-dihydrothiophene (**16**), 2,5-dimethylthiophene (**17**), 3-methylthiophene (**18**) and benzothiophene (**19**).

Fig. 3 pyrrole (**20**), *N*-methylpyrrole (**21**), 2-methylpyrrole (**22**), 2,5-dimethylpyrrole (**23**), 1,2,5-trimethylpyrrole (**24**), 3-methylpyrrole (**25**), indole (**26**) and *N*-methyl- (**27**), 2-methyl- (**28**), 3-methyl- (**29**) and 7-methylindoles (**30**).

Fig. 4 aniline (**31**), pyridine (**32**), 2-, 3-, and 4-picoline (**33**, **34**, **35**), pyrimidine (**46**), pyrazine (**47**) and pyridazine (**48**).

Fig. 5 quinoline (**36**), 2-methyl- (**37**) and 2-methyl-3,4-dihydroquinoline (**38**), 3-methyl- (**39**), 4-methyl- (**40**) and 6-methylquinolines (**41**) and isoquinoline (**42**), 1-methyl-

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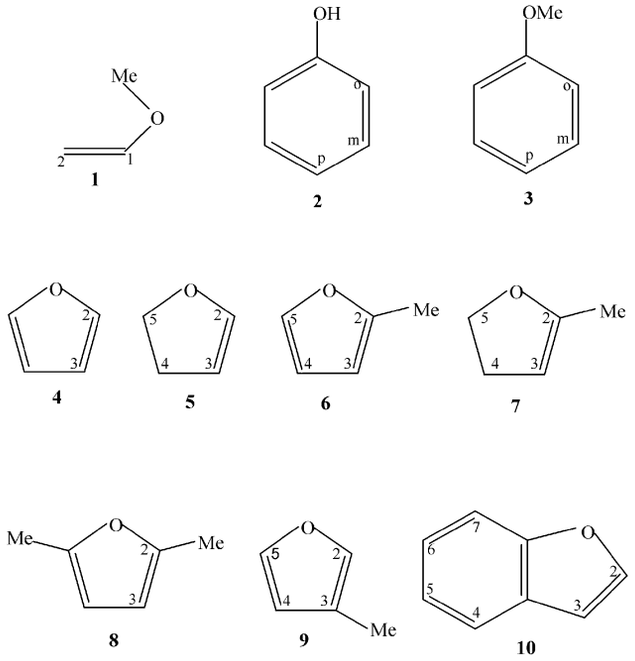


Fig. 1 Oxygen hetero-aromatics and related molecules.

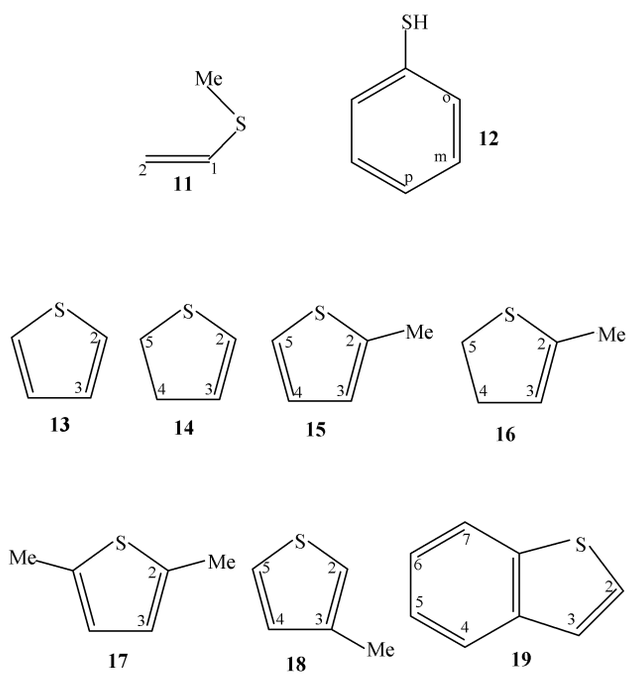
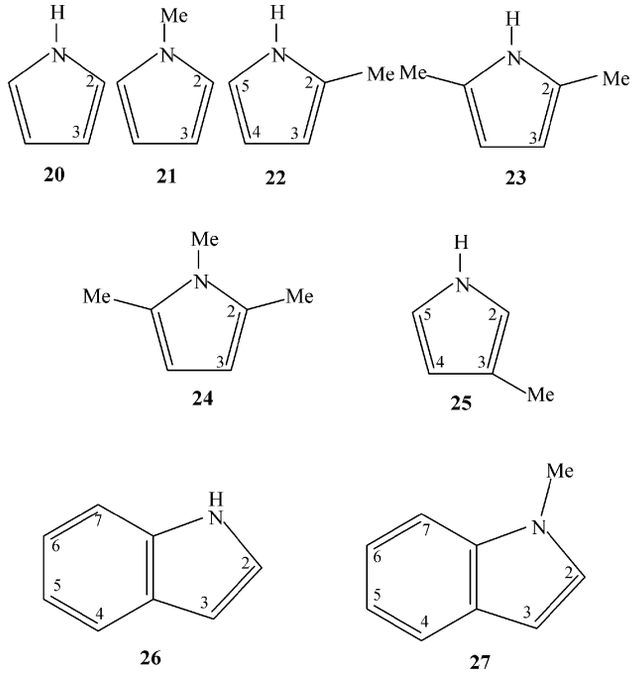


Fig. 2 Sulfur hetero-aromatics and related molecules.

isoquinoline (**43**), 1-methyl-3,4-dihydroisoquinoline (**44**) and 3-methylisoquinoline (**45**).

Fig. 6 imidazole (**49**), 2-methylimidazole (**50**), 2-methyl-4,5-dihydroimidazole (**51**), 1,3-thiazole (**52**), 2-methyl-1,3-thiazole (**53**), 2-methyl-4,5-dihydro-1,3-thiazole (**54**), oxazole (**55**).

This large set of rigid molecules with fully assigned ^{1}H NMR spectra provides sufficient data for an analysis of the proton chemical shifts in hetero-aromatics based on the CHARGE model.[1,8,9] In this model it is necessary to identify and separate the various mechanisms responsible for the ^{1}H chemical shifts in these molecules. These are the ring current shifts, the π-electron densities, the direct α, β and γ-effects of the hetero-atoms and the long range steric, electrostatic and anisotropic effects at the protons. We shall show that it is possible to identify and quantify these effects and that the resulting model gives a very good account of the ^{1}H chemical shifts in the molecules investigated.



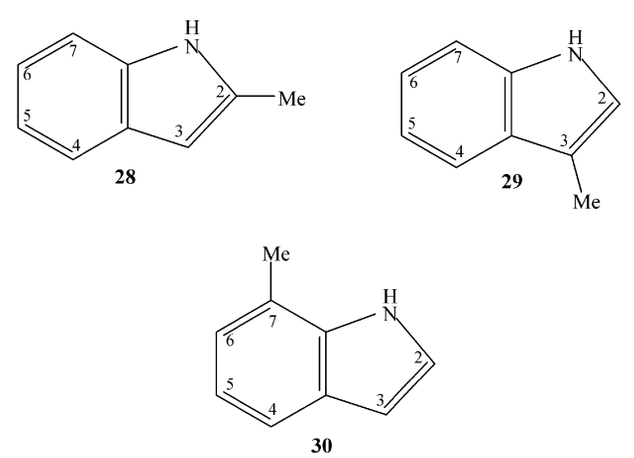


Fig. 3 Pyrroles and indoles.

Theory

As the theory has been given previously[1,8,9] only a brief summary of the latest version (CHARGE7h)[10] will be given here. The theory distinguishes between substituent effects over one, two and three bonds, which are attributed to the electronic effects of the substituents and longer-range effects due to the electric fields, steric effects and anisotropy of the substituents.

The CHARGE scheme calculates the effects of atoms on the partial atomic charge of the atom under consideration, based upon classical concepts of inductive and resonance contributions. If we consider an atom I in a four atom fragment I–J–K–L the partial atomic charge on I is due to three effects. There is a α-effect from atom J given by the difference in the electronegativity of atoms I and J. A β-effect from atom K proportional to both the electronegativity of atom K and the polarisability of atom I. There is also a γ-effect from atom L given by the product of the atomic polarisabilities of atoms I and L for I = H and L = F, Cl, Br, I. However for chain atoms (C, N, O, S *etc.*) the γ-effect (*i.e.* C–C–C–H) is parametrised separately and is given by $A + B\cos\theta$ where θ is the C–C–C–H dihedral angle and A and B are empirical parameters.

The total charge is given by summing these effects and the partial atomic charges (q) converted to shift values using eqn. (1).

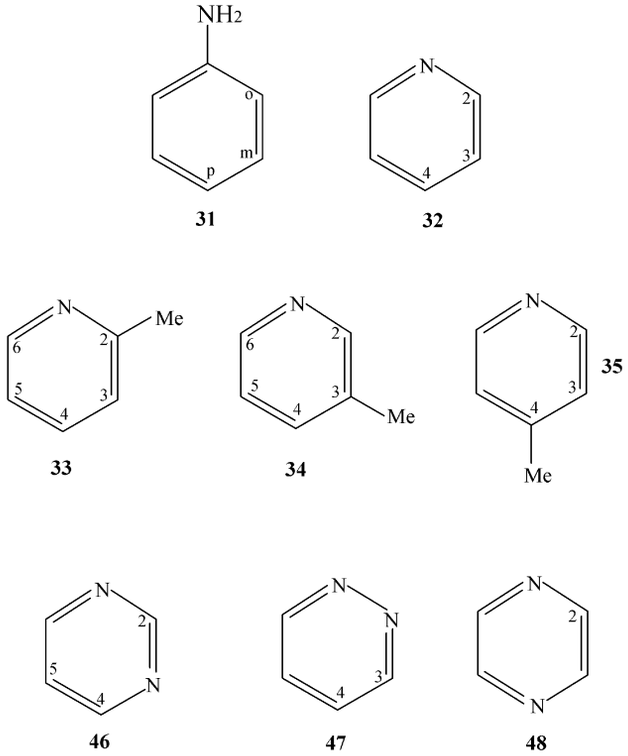


Fig. 4 Monocyclic amines.

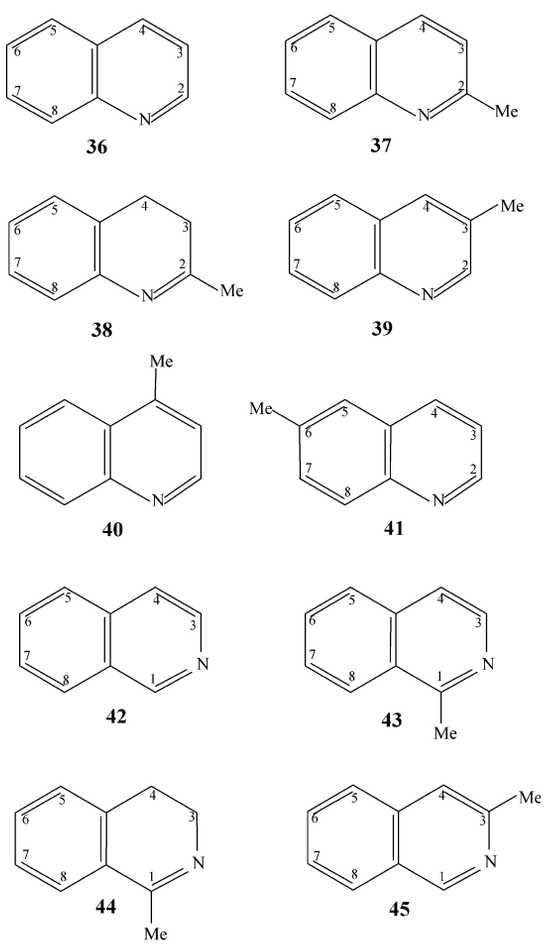


Fig. 5 Bicyclic amines.

$$\delta = 160.84q - 6.68 \quad (1)$$

The effects of more distant atoms on the proton chemical shifts are due to steric, anisotropic and electric field contributions. H · · · H steric interactions were found to be shielding in alkanes and deshielding in aromatics and X · · · H (X = C, O, Cl, Br, I) interactions deshielding, according to a simple r^{-6} dependence.[9]

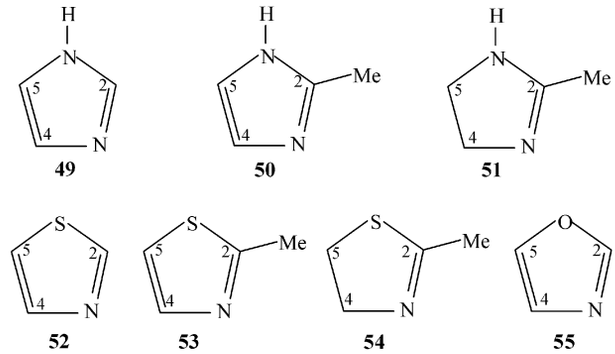


Fig. 6 Difunctional bases.

The effects of the electric field of the C–X bonds (X = H, F, Cl, Br, I, O) on the C–H protons are obtained from the component of the electric field along the C–H bond. The electric field for a univalent atom (*e.g.* fluorine) is calculated as due to the charge on the fluorine atom and an equal and opposite charge on the attached carbon atom.[9]

The bond magnetic anisotropy for cylindrically symmetric groups (*e.g.* C≡C) and for non-symmetric groups (*e.g.* C=O) is given by the two McConnell equations.[11]

For aromatic compounds it is necessary to include the shifts due to the aromatic ring current and the π-electron densities in the aromatic ring.[8] The equivalent dipole approximation [eqn. (2)] was used to calculate the ring current shifts. In eqn. (2),

$$\delta_{rc} = fc\mu\,(3\cos^2\theta - 1)/R^3 \quad (2)$$

R is the distance of the proton from the benzene ring centre, θ the angle of the R vector with the ring symmetry axis, μ the equivalent dipole of the aromatic ring and fc the π-electron current density for the ring, being 1.0 for benzene.

The π-electron densities are calculated from Hückel theory.[12] The standard coulomb and resonance integrals for the Hückel routine are given by eqn. (3), $\beta_{rs} = k_{rs}\beta_0$ where α_0 and β_{rs}

$$\alpha_r = \alpha_0 + h_r\beta_0 \quad (3)$$

are the coulomb and resonance integrals for a carbon $2p_z$ atomic orbital and h_r and k_{rs} the factors modifying these integrals for orbitals other than sp^2 carbon. For substituted aromatics the values of the coefficients h_r and k_{rs} in eqn. (3) for the orbitals involving hetero atoms have to be found. These were obtained so that the π densities calculated from the Hückel routine reproduce the π densities from *ab initio* calculations.

The effect of the excess π-electron density at a given carbon atom on the proton chemical shifts of the neighbouring protons is given by eqn. (4) where Δq_α and Δq_β are the excess π-electron density at the α and β carbon atoms.[8]

$$\delta_\pi = 10.0\Delta q_\alpha + 2.0\Delta q_\beta \quad (4)$$

The above contributions are added to eqn. (1) to give the calculated shift of eqn. (5).

$$\delta_{total} = \delta_{charge} + \delta_{steric} + \delta_{anisotropy} + \delta_{el} + \delta_\pi + \delta_{rc} \quad (5)$$

Application to hetero-aromatics

The major contributions to the ^{1}H chemical shifts in hetero-aromatic compounds are ring current and π-electron effects,

with smaller contributions due to the α, β and γ-effects of the hetero atom and the long-range contributions. Subroutines were added to the CHARGE programme in order to identify the hetero-aromatic systems. It was then necessary to determine the π-electron densities at each atom and the ring currents in the compounds investigated.

Ring currents. To determine the ring current density *fc* for the different hetero-aromatic ring systems under investigation two methods were used. For those systems in which a 2-methyl substituent was present in both the aromatic and dihydroaromatic compound the method of ref. 4 was used to determine the ring current using the C-2 methyl shifts. If the appropriate dihydro compound was not available the ring current density *fc* was obtained by including this factor in the parametrisation, using all the proton chemical shifts in the ring systems.

The equivalent dipole μ of a current loop of radius A and current i is given by eqn. (6) and therefore the ratio of the ring current in a heterocyclic ring to that in benzene is given by eqn. 7, where μ_B and A_B are the benzene ring current and area

$$\mu = iA \tag{6}$$

$$i/i_B = \mu/\mu_B \times A/A_B \tag{7}$$

respectively. Using this equation the ratio of the ring currents in the hetero-aromatic molecules to that in benzene will be determined (see later).

π-electron densities. The π-electron densities were reproduced from those calculated from *ab initio* calculations. As has been noted previously[8,12] the results from *ab initio* calculations are very dependent on the basis set used. It was found that the 3-21G basis set at the B3LYP level gave the best values of the dipole moments for the compounds investigated and therefore the π-electron densities from this basis set were used to parametrise the Hückel calculations.

The π systems in the hetero-aromatic compounds investigated are quite diverse. For example the π systems of vinyl methyl ether, furan and phenol are very different. It was therefore necessary to treat these π systems separately in CHARGE. Similarly the nitrogen atom in aniline is non-planar and therefore in a different hybridisation to that of the planar nitrogen atom in pyrrole and pyridine. These were differentiated by determining the appropriate values of the atomic orbital coefficients h_r and k_{rs} [eqn. (3)] and the Hückel integrals for Csp^2–X, where X = O, S, N for the various π systems.

The accuracy of the π-electron densities calculated in CHARGE may be examined by comparing the calculated π-electron densities and dipole moments of some hetero-aromatics with those obtained by *ab initio* theory using various basis sets (Table 1).

The good agreement of the calculated *vs.* observed dipoles in Table 1 is strong support for the calculations. The values of k_{rs} and h_r used for the various Csp^2–X bonds in these molecules are given in Table 2. The π-electron densities for phenol, thiophenol and aniline were calculated previously.[12]

These modifications were the only ones needed to apply the CHARGE routine to these hetero-aromatic compounds. However it is still necessary to calculate the charge densities at the various protons in the molecules and thus to quantify the appropriate α, β, and γ-effects. Also the long range effects must be included. These are the steric, electric field and anisotropic effects of the atoms in the molecules. These have all been calculated previously and no further parametrisation is required.

Experimental

Phenol (**2**), anisole (**3**), benzofuran (**10**), benzothiophene (**19**), indole (**26**) and *N*-methyl- (**27**), 2-methyl- (**28**), 3-methyl- (**29**) and 7-methylindoles (**30**), aniline (**31**), pyridine (**32**), 2-picoline (**33**), 3-picoline (**34**), quinoline (**36**), 2-methyl- (**37**), 3-methyl- (**39**), 4-methyl- (**40**) and 6-methylquinolines (**41**) and isoquinoline (**42**) were obtained commercially.[14,15]

^1H and ^{13}C NMR were obtained on a Bruker Avance spectrometer operating at 400.13 MHz for proton and 100.63 MHz for carbon. HMQC, HMBC and NOE experiments were also performed. The spectra were recorded in 10 mg cm^{-3} solutions (^1H) and *ca.* 50 mg cm^{-3} (^{13}C) in $CDCl_3$ with a probe temperature of *ca.* 25 °C and referenced to TMS unless indicated otherwise. Typical running conditions (^1H spectra) were 128 transients, spectral width 3300 Hz and 32k data points zero-filled to 128k. This gave an acquisition time of 5 s and a digital resolution of 0.025 Hz. The 2D experiments were conducted using the standard Bruker COSY-DQF and HMQC pulse sequences.[16]

The geometry of the compounds was first obtained using the molecular mechanics program PCMODEL Version 7.0[17] and the geometry is then optimised using the GAUSSIAN98 programme at the B3LYP/6-31G** levels.[18] All the calculations were carried out using a PC. The optimised geometries for the hetero-aromatics were in excellent agreement with the experimental geometries. For example, the observed *vs.* calculated bond lengths for furan, thiophene, pyrrole and pyridine are given in Table 3 and there is complete agreement of the two data sets.

Spectral analysis

The ^1H chemical shifts for compounds **8**, **12**, **17**, **18**, **20**, **21**–**24**, **35**, **42**, **45** and **46**–**48** were obtained from the Aldrich Spectra Catalogue;[20] those for the furans (**4**–**7**), thiophenes (**13**–**16**), imidazoles (**50**,**51**) and thiazoles (**52**–**54**) from ref. 4 and those for **1**, **9**, **11**, **22**, **38**, **49** and **55** from refs. 21–27 respectively. Pretsch *et al.*[28] collected many of these chemical shifts in either CCl_4 or $CDCl_3$ solvent (see later). A number of the compounds were re-run and where necessary assigned using the techniques above to obtain the proton chemical shifts under standard conditions. These included compounds **2**, **3**, **10**, **19**, **26**, **31**–**34**, **36** and **42**. The complete assignments of the spectra of the methyl derivatives **27**–**30**, **37** and **39**–**41** were performed using where necessary ^1H COSY, NOE, $^1H/^{13}C$ HMQC and HMBC experiments. They were all first order spectra at 400 MHz except for **41**. Further details of all the assignments plus spectra are given in ref. 29. The ^1H chemical shifts of all the compounds investigated are given in Tables 5–13 with the calculated chemical shifts from the CHARGE model.

Results

The chemical shifts measured here compare well with those of previous investigations. There is however an almost constant difference of *ca.* 0.1 ppm in the shifts given here in $CDCl_3$ with those measured previously in CCl_4 solution; *e.g.* comparison of the data for quinoline (**36**) with that found by Pretsch *et al.*[28] gives for H-2–H-8 $\delta(CDCl_3) - \delta(CCl_4)$ 0.12, 0.12, 0.14, 0.12, 0.10, 0.10 and 0.07 respectively, average 0.11 ppm. Identical results hold for isoquinoline and indole. This constant low-field shift was previously observed in the aromatic hydrocarbons[8] and it appears to be a general effect for both non-polar and polar solutes.

The chemical shifts can now be used to test the application of the CHARGE model and also to investigate the shielding mechanisms in these molecules; in particular the effects of ring currents and π-electron densities on the proton chemical shifts. The only other unknowns in the CHARGE model are the

Table 1 π charges (milli-electrons), and dipole moments μ (D) for methyl vinyl ether, furan, thiophene, pyrrole, pyridine and indole[a]

Compound	Atom	Method				
		STO-3G	3-21G	6-31G	CHARGE	Observed[c]
Vinyl methyl ether	C-1	−58	−18	−11	−9	
	C-2	−132	−156	−137	−70	
	O	216	236	193	74	
	μ	*1.46*	*1.09*	*1.319*	*0.96*	*1.11*
Furan	C-2	−89[b]	−107	−94	−48	
	C-3	−71	−75	−68	−33	
	O	320	364	323	162	
	μ	*0.40*	*0.71*	*0.97*	*0.88*	*0.72*
Thiophene	C-2	−113	−130	−133	−61	
	C-3	−58	−35	−32	−18	
	S	342	330	331	157	
	μ	*0.57*	*0.72*	*0.82*	*0.70*	*0.53*
Pyrrole	C-2	−100[b]	−125	−92	−75	
	C-3	−91	−93	−87	−57	
	N	383	436	394	264	
	μ	*1.90*	*2.03*	*1.93*	*1.59*	*1.74*
Pyridine	C-2	11[b]	22	36	47	
	C-3	−2	−3	−2	3	
	C-4	33	39	41	30	
	N	−51	−78	−110	−119	
	μ	*2.07*	2.25	*2.49*	*2.02*	*2.15*
Indole	C-2	−83	−76	−66	−48	
	C-3	−97	−106	−102	−70	
	C-4	−13	−11	−13	−9	
	C-5	−29	−37	−36	−21	
	C-6	−18	−22	−21	−13	
	C-7	−52	−57	−55	−21	
	N	392	394	347	234	
	μ	*2.15*	*2.26*	*2.16*	*1.78*	*2.09*

[a] μ, phenol 1.56 calc. (1.50 obs.), quinoline 2.20 calc. (1.94 obs.). [b] Ref. 12. [c] Ref. 13.

Table 2 k_{rs} (Csp^2–X) and h_r (X) for (X = O, S, N) in hetero-aromatic and related compounds

Compound	k_{rs}	h_r
Phenol	1.45	0.90
Vinyl methyl ether	1.05	0.59
Furan	1.69	0.59
Benzofuran	1.22	0.59
Thiophenol	1.27	0.66
Vinyl methyl sulfide	0.97	0.40
Thiophene	1.27	0.47
Benzothiophene	0.79	0.47
Pyrrole	1.60	1.28
Indole	1.50	1.28
Pyridine	0.30	1.00
Imidazole (C-2–N-3)	0.16	1.00
Imidazole (N-1–C-2)	1.60	1.28

α, β and γ electronic effects of the atoms. The α and β-effects are calculated directly from the atom electronegativity and polarisability, but the γ-effects are given by $A + B\cos\theta$, where the parameters A and B are obtained from the observed shifts. The values of all the unknown parameters were obtained by iteration using a non-linear least mean squares programme CHAP8.[30]

For those systems in which the 2-methyl shifts could be determined for both the aromatic and dihydro compounds the ring currents were determined directly from the difference in these shifts; *i.e.* for furan compound **7** *vs.* **6**, thiophene **15** *vs.* **16**, quinoline **37** *vs.* **38**, isoquinoline **43** *vs.* **44**, imidazole **50** *vs.* **51** and thiazole **53** *vs.* **54**. For those systems in which the dihydro compounds were not available the ring current factor *fc* was included in the iteration procedure. These factors are given in Table 17.

The coefficients A and B of the γ-effects obtained are shown in Table 4. The γ-effect of any substituent on a methyl hydrogen atom is treated separately in CHARGE from that of the same substituent on methine and methylene protons partly because the orientation dependance averages to zero for a methyl group, thus the coefficient $B = 0.0$. Only γ-effects on the methyl protons were determined for the alkyl protons. Note also that the coefficients A and B for the XC=CH fragment (X = O, S) differ for olefinic, hetero-aromatic and benzenoid systems. In the latter there is only one dihedral angle of 0° thus only one parameter can be obtained. For the nitrogen atoms a different procedure is used. The nitrogen atoms in aniline, pyrroles/indoles and pyridines/quinolines are treated differently reflecting the different hybridisation of the N atoms in these molecules. These are termed N_1, N_2 and N_3 henceforth.

In the pyridines the β-effects of the N_3 atom on the *ortho* protons were given by the basic equation. However for pyrazine the two bonded nitrogen atoms had an increased β-effect (1.35) and in pyrimidine the β-effect on H-2, which has two β N_3 atoms required a reduced value of the coefficient of 0.83.

Also in imidazole, thiazole and oxazole the β-effects of the hetero atoms on H-2 need to be obtained. Both adjacent heteroatoms influence the chemical shift, hence three separate effects need to be parametrised. The coefficients for the β-effects on H-2 in imidazole, thiazole and oxazole were 0.60, 1.12 and 0.34 respectively.

All the coefficients were obtained by iterations on the observed shifts using CHAP8.[30] It is important to note that these iterations were always very over-determined; *e.g.* in the furan case a total of 26 chemical shifts (Table 5) were included in the iteration spanning a range of *ca.* 1.8 to 7.6 ppm with only four parameters (A and B values) to be determined. The iteration gave an rms error (observed *vs.* calculated shifts) of 0.073 ppm. For the pyrrole/indole case the ring current factor *fc* was included in the iteration and this gave a total of 49 chemical shifts (Tables 9, 10) from 2.0 to 7.7 ppm with six unknown parameters to give an rms error of 0.107 ppm. Similar results were obtained for the iterations for the other systems. The final

Table 3 Observed[19] and (calculated) bond lengths (Å) for hetero-aromatics

Bond	Bond length/Å			
	Furan	Pyrrole	Thiophene	Pyridine[a]
X-1–C-2	1.362 (1.364)	1.370 (1.375)	1.714 (1.736)	1.338 (1.339)
C-2–C-3	1.361 (1.361)	1.382 (1.378)	1.370 (1.367)	1.394 (1.396)
C-3–C-4	1.431 (1.436)	1.417 (1.425)	1.423 (1.430)	1.392 (1.394)
C-2–H	1.075 (1.079)	1.076 (1.080)	1.078 (1.081)	1.087 (1.089)
C-3–H	1.077 (1.080)	1.077 (1.081)	1.081 (1.084)	1.088 (1.086)

[a] C_4–H 1.082 (1.086).

Table 4 *A* and *B* values [eqn. (1)] for γ-effects

H···C[a] fragment	*A*	*B*	H···C[a] fragment	*A*	*B*
O–C=C–H			S–C=C–H		
(Olefin, furan)	−0.554	−0.085	(Olefin)	0.092	−0.434
(Phenol)	0.032	0.00	(Thiophene)	−0.141	−0.180
			(Thiophenol)	0.064	−0.249
O–Cb–CH_3	0.20	0.0	S–Cb–CH_3	0.36	0.00
Cb–O–Cb–H	0.428	0.0	Cb–S–Cb–H	−0.159	0.00
Ca–O– Cb–H	0.563	0.0	Ca–S– Cb–H	−0.157	0.00
N_1–C=C–H	0.050	0.0	N_3–C=C–H	0.093	−0.326
N_2–C=C–H	0.300	−0.293	N_3–Cb–CH_3	0.50	0.00
N_2–Cb–CH_3	0.19	0.0	Cb–N_3–Cb–H	−0.107	0.143
Ca–N_2–Cb–H	−0.070	0.0			
Cb–N_2–Cb–H	0.188	0.0			

[a] Ca = C(sp^3), Cb = C(sp^2), N_1 = N in aniline, N_2 = N in pyrrole/indole, N_3 = N in pyridine/quinoline.

Table 5 Observed *vs.* calculated ^{1}H chemical shifts (δ) for oxygen compounds

Compound	^{1}H Number	Observed	Calculated
Vinyl methyl ether (**1**)	1-*gem*	6.530	6.606
	2-*cis*	4.160	4.224
	2-*trans*	4.000	4.058
Phenol (**2**)	*o*	6.824	6.877
	m	7.239	7.212
	p	6.927	6.926
Anisole (**3**)	*o*	6.897	6.859
	m	7.277	7.232
	p	6.934	6.926
	Me	3.789	3.738
Furan (**4**)	2	7.420	7.415
	3	6.380	6.360
4,5-Dihydrofuran (**5**)	2	6.310	6.153
	3	4.950	4.939
	4	2.580	2.384
	5	4.310	4.224
2-Methylfuran (**6**)	3	5.940	6.058
	4	6.230	6.289
	5	7.270	7.189
	Me	2.280	2.278
2-Methyl-4,5-dihydrofuran (**7**)	3	4.570	4.496
	4	2.580	2.432
	5	4.310	4.273
	Me	1.790	1.867
2,5-Dimethylfuran (**8**)	3	5.810	5.983
	Me	2.220	2.295
3-Methylfuran (**9**)	2	7.160	7.052
	4	6.220	6.327
	5	7.290	7.450
	Me	2.030	2.172
Benzofuran (**10**)	2	7.607	7.807
	3	6.758	6.671
	4	7.593	7.514
	5	7.225	7.239
	6	7.285	7.312
	7	7.502	7.400

Table 6 Observed *vs.* calculated ^{1}H chemical shifts (δ) for sulfur compounds

Compound	^{1}H Number	Observed	Calculated
Vinyl methyl sulfide (**11**)	*gem*	6.460	6.549
	cis	5.200	5.189
	trans	4.970	4.833
Thiophenol (**12**)	*o*	7.230	7.316
	m	7.190	7.276
	p	7.110	7.081
Thiophene (**13**)	2	7.310	7.263
	3	7.090	7.044
4,5-Dihydrothiophene (**14**)	2	6.170	6.076
	3	5.630	5.717
	4	2.740	2.592
	5	3.220	3.169
2-Methylthiophene (**15**)	3	6.720	6.733
	4	6.870	6.970
	5	7.040	7.017
	Me	2.480	2.470
2-Methyl-4,5-dihydrothiophene (**16**)	3	5.250	5.248
	4	2.790	2.657
	5	3.260	3.195
	Me	1.940	2.009
2,5-Dimethylthiophene (**17**)	3	6.560	6.655
	Me	2.400	2.481
3-Methylthiophene (**18**)	2	6.870	6.898
	4	6.870	7.020
	5	7.190	7.305.
	Me	2.280	2.214
Benzothiophene (**19**)	2	7.422	7.523
	3	7.325	7.347
	4	7.780	7.642
	5	7.330	7.302
	6	7.310	7.340
	7	7.860	7.996

Table 7 Observed *vs.* calculated ^{1}H chemical shifts (δ) for compounds **20**–**25**,**31**

Compound	^{1}H Number	Observed	Calculated
Aniline (**31**)	*o*	6.650	6.654
	m	7.136	7.132
	p	6.740	6.676
Pyrrole (**20**)	2	6.710	6.708
	3	6.230	6.187
N-Methylpyrrole (**21**)	2	6.670	6.590
	3	6.110	6.155
	N–Me	3.600	3.513
2-Methylpyrrole (**22**)	3	5.890	5.919
	4	6.110	6.112
	5	6.640	6.507
	Me	2.270	2.285
2,5-Dimethylpyrrole (**23**)	3	5.720	5.839
	Me	2.200	2.300
1,2,5-Trimethylpyrrole (**24**)	3	5.750	5.813
	2,5-Me	2.190	2.246
	N–Me	3.330	3.586
3-Methylpyrrole (**25**)	2	6.530	6.400
	4	6.020	6.122
	5	6.650	6.722
	Me	2.090	2.153

Table 8 Observed *vs.* calculated ^{1}H chemical shifts (δ) for compounds **26**–**30**

Compound	^{1}H Number	Observed	Calculated
Indole (**26**)	2	7.207	7.321
	3	6.558	6.643
	4	7.647	7.489
	5	7.115	7.212
	6	7.185	7.263
	7	7.396	7.358
N-Methylindole (**27**)	2	7.001	7.204
	3	6.466	6.611
	4	7.615	7.488
	5	7.092	7.211
	6	7.204	7.258
	7	7.292	7.330
	N–Me	3.742	3.813
2-Methylindole (**28**)	3	6.216	6.325
	4	7.508	7.443
	5	7.059	7.186
	6	7.104	7.202
	7	7.282	7.347
	Me	2.445	2.469
3-Methylindole (**29**)	2	6.964	6.969
	4	7.584	7.496
	5	7.121	7.212
	6	7.189	7.264
	7	7.301	7.370
	Me	2.335	2.427
7-Methylindole (**30**)	2	7.207	7.326
	3	6.563	6.654
	4	7.498	7.276
	5	7.031	7.143
	6	6.994	7.029
	Me	2.502	2.620

parametrisation for all the systems considered therefore included π-electron densities, ring current and electronic effects operating on all protons in the molecules.

Discussion

There is generally very good agreement of the observed *vs.* calculated chemical shifts. For the 215 data points in Tables 5–13 the rms error (obs. *vs.* calc. shifts) is 0.096 ppm over a range of 1.9 to 9.4 ppm. and there are very few calculated chemical shifts with errors >0.2 ppm. H-2 in **10** is the only one with an error of 0.2 ppm in Table 5. All the thiophene shifts (Table 6) are calculated to better than this accuracy. The *N*-methyl in **24** is the only such error in Table 7 (0.25 ppm) and this may be due to steric effects. In the indoles (Table 8) the only significant error (*ca.* 0.2 ppm) is for H-4 which is calculated consistently lower than the observed shifts. The agreement for the quinolines (Table 10) and

Table 9 Observed *vs.* calculated ^{1}H chemical shifts (δ) for pyridine (**32**), 2-picoline (**33**), 3-picoline (**34**) and 4-picoline (**35**)

	32		**33**		**34**		**35**	
^{1}H Number	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
2	8.609	8.577	2.547[a]	2.518	8.440	8.459	8.440	8.584
3	7.266	7.279	7.014	7.162	2.320[a]	2.319	7.080	7.162
4	7.657	7.574	7.571	7.574	7.465	7.454	2.320[a]	2.310
5	7.266	7.279	7.195	7.213	7.159	7.268	7.080	7.162
6	8.609	8.577	8.599	8.597	8.407	8.499	8.440	8.583

[a] Methyl.

Table 10 Observed *vs.* calculated ^{1}H chemical shifts (δ) for quinoline (**36**) and 2-methyl- (**37**), 2-methyl-3,4-dihydro (**38**), 3-methyl (**39**), 4-methyl (**40**) and 6-methylquinoline (**41**)

	36		**37**		**38**		**39**		**40**		**41**	
^{1}H Number	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
2	8.915	8.865	2.757[a]	2.626	2.10[a]	2.155	8.760	8.790	8.770	8.865	8.825	8.836
3	7.377	7.429	7.295	7.351	2.35	2.59	2.482[a]	2.416	7.212	7.283	7.303	7.419
4	8.139	8.122	8.055	8.141	2.70	2.90	7.876	7.957	2.692[a]	2.531	8.005	8.109
5	7.803	7.841	7.778	7.844	[b]	7.28	7.714	7.827	7.985	7.822	7.522	7.681
6	7.533	7.509	7.485	7.482	[b]	7.35	7.489	7.500	7.552	7.499	2.501[a]	2.416
7	7.709	7.571	7.627	7.561	[b]	7.29	7.627	7.542	7.697	7.569	7.512	7.502
8	8.114	8.060	8.024	8.050	[b]	7.78	8.066	8.062	8.104	8.067	7.995	8.071

[a] Methyl. [b] 6.70–7.50.

Table 11 Observed *vs.* calculated ^{1}H chemical shifts (δ) for isoquinoline (**42**) and 1-methyl- (**43**), 1-methyl-3,4-dihydro (**44**) and 3-methylisoquinoline (**45**)

	42		**43**		**44**		**45**	
^{1}H Number	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
1	9.251	9.177	2.910[a]	2.759	2.400[a]	2.334	9.150	9.207
3	8.522	8.539	8.370	8.556	3.670	3.831	2.690[a]	2.617
4	7.635	7.621	7.440	7.538	2.710	2.812	7.410	7.464
5	7.808	7.800	7.730	7.817	7.180	7.345	7.680	7.793
6	7.680	7.596	7.600	7.595	7.360	7.477	7.590	7.588
7	7.594	7.533	7.510	7.526	7.300	7.350	7.480	7.507
8	7.955	7.915	8.040	7.897	7.480	7.417	7.880	7.918

[a] Methyl.

Table 12 Observed *vs.* calculated ^{1}H chemical shifts (δ) for pyrimidine (**46**), pyrazine (**47**) and pyridazine (**48**)

	46		**47**		**48**	
^{1}H Number	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
2	9.250	9.248	—	—	8.600	8.476
3	—	—	9.220	9.316	8.600	8.476
4	8.770	8.856	7.560	7.646	—	—
5	7.270	7.245	7.560	7.646	8.600	8.476
6	8.770	8.856	9.220	9.316	8.600	8.476

isoquinolines (Table 11) is particularly noteworthy with most of the calculated shifts accurate to <0.1 ppm. There are larger differences in the calculated *vs.* observed shifts in Table 13; *e.g.* H-4 in oxazole **55** and 2-methylthiazole **53**. This latter value is intriguing as H-4 in thiazole (**52**) is calculated accurately.

The calculations also provide an insight into the interpretation of these proton chemical shifts as the different interactions responsible for the calculated values are separately identified and quantified in the CHARGE model. It is of interest to examine the individual contributions to the chemical shifts and Tables 14–16 give the observed *versus* calculated chemical shifts for selected molecules, together with the electric field, ring current and π-shift contributions. The results in Tables 14–16 clearly demonstrate the significant ring current and π-contributions to the proton chemical shifts in these molecules.

The ring current shifts of the ring protons are *ca.* 1.60 ppm and that of the methyl protons *ca.* 0.50 ppm. Similar effects are observed for the methyl group in 2-methylquinoline (0.51 ppm), 1-methylisoquinoline (0.65 ppm), 2-methylthiazole (0.54 ppm) and 2-methylimidazole (0.49 ppm). The introduction of a methyl group has a large effect on the π-electron density in the heterocyclic rings and thus on the chemical shifts. All the protons in the 2-methyl and 3-methyl derivatives of furan and pyrrole are shifted upfield with respect to the parent compound, especially protons that are γ to the methyl group. This is clearly due to the increased π-electron density in the heterocyclic ring of the methyl compounds. A similar but smaller effect is observed in thiophene. Large π-shifts are also observed in the benzo derivatives but the differences in the chemical shifts of the ring protons in the benzo derivatives compared to the parent heterocycles are due mainly to the increased ring current shift.

The ring current calculations again provide evidence for the accuracy of the simple equivalent dipole model of the benzene ring current. The calculations show that the ring current is not the only factor in the difference between the H-2 and H-3 protons in aromatic heterocycles (furan, thiophene, *etc.*) and their non-aromatic derivatives.

Table 13 Observed *vs.* calculated ^{1}H chemical shifts (δ) for imidazole (**49**), 2-methyl (**50**) and 2-methyl-3,4-dihydroimidazole (**51**), thiazole (**52**), 2-methyl (**53**) and 2-methyl-3,4-dihydrothiazole (**54**) and oxazole (**55**)

	49		**50**		**51**		**52**		**53**		**54**		**55**	
^{1}H Number	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
2	7.74	7.78	2.44[a]	2.40	1.95[a]	1.95	8.88	8.84	2.74[a]	2.81	2.20[a]	2.27	7.90	7.82
4	7.13	6.99	6.97	6.90	3.60	3.42	7.98	8.08	7.64	8.10	4.22	3.99	7.15	7.49
5	7.13	6.99	6.97	6.90	3.60	3.42	7.41	7.40	7.17	7.17	3.32	3.17	7.68	7.60

[a] Methyl.

Table 14 Calc. *vs.* obs. chemical shifts (δ) with C–H electric field, ring current and π-shift contributions for furan (**4**), 2-methyl- (**6**) 3-methylfuran (**9**) and benzofuran (**10**)

Compound	^{1}H Number	Observed	Calculated	C–H Electric field	Ring current	π-shift
4	2	7.420	7.415	−0.110	1.600	−0.549
	3	6.380	6.360	−0.057	1.507	−0.487
6	3	5.940	5.923	−0.126	1.514	−0.733
	4	6.230	6.289	−0.024	1.503	−0.585
	5	7.270	7.189	−0.077	1.595	−0.799
	Me	2.280	2.278	−0.054	0.500	0.000
9	2	7.160	6.917	−0.180	1.596	−0.855
	4	6.220	6.193	−0.121	1.513	−0.464
	5	7.290	7.450	−0.082	1.607	−0.534
	Me	2.030	2.172	−0.077	0.466	0.000
10	2	7.607	7.807	−0.030	1.905	−0.536
	3	6.758	6.671	−0.079	1.958	−0.664
	4	7.593	7.514	−0.151	1.967	−0.175
	5	7.225	7.239	−0.060	1.771	−0.250
	6	7.285	7.312	−0.046	1.762	−0.184
	7	7.502	7.400	−0.121	1.985	−0.246

Table 15 Calc. *vs.* obs. chemical shift (δ) with calculated contributions for thiophene (**13**), 2-methyl- (**15**), 3-methylthiophene (**18**) and benzothiophene (**19**)

Compound	^{1}H Number	Observed	Calculated	C–H Electric field	Ring current	π-shift
13	2	7.310	7.263	−0.095	1.679	−0.641
	3	7.090	7.044	−0.052	1.764	−0.333
15	3	6.720	6.598	−0.130	1.775	−0.588
	4	6.870	6.970	−0.023	1.761	−0.430
	5	7.040	7.017	−0.068	1.667	−0.898
	Me	2.480	2.470	−0.045	0.542	0.000
18	2	6.870	6.886	−0.171	1.692	−0.620
	4	6.870	6.866	−0.122	1.773	−0.303
	5	7.190	7.305.	−0.065	1.676	−0.620
	Me	2.280	2.214	−0.072	0.564	0.000
19	2	7.422	7.523	−0.026	1.934	−0.702
	3	7.325	7.347	−0.089	2.235	−0.545
	4	7.780	7.642	−0.162	2.095	−0.122
	5	7.330	7.302	−0.061	1.786	−0.172
	6	7.310	7.340	−0.046	1.778	−0.140
	7	7.860	7.996	−0.115	2.058	−0.175

Table 16 Calc. *vs.* obs. chemical shifts (δ) with calculated contributions for pyrrole (**20**), 2-methyl- (**22**) 3-methylpyrrole (**25**) and indole (**26**)

Compound	^{1}H Number	Observed	Calculated	C–H Electric field	Ring current	π-shift
20	2	6.710	6.708	−0.105	1.645	−0.865
	3	6.230	6.187	−0.054	1.633	−0.830
22	3	5.890	5.784	−0.125	1.641	−1.043
	4	6.110	6.112	−0.023	1.628	−0.928
	5	6.640	6.508	−0.075	1.640	−1.088
	Me	2.270	2.285	−0.051	0.510	0.000
25	2	6.530	6.264	−0.176	1.652	−1.117
	4	6.020	5.988	−0.120	1.639	−0.839
	5	6.650	6.722	−0.077	1.641	−0.872
	Me	2.090	2.153	−0.073	0.503	0.000
26	2	7.207	7.321	−0.029	1.938	−0.618
	3	6.558	6.643	−0.081	2.083	−0.866
	4	7.647	7.489	−0.153	2.016	−0.196
	5	7.115	7.212	−0.060	1.775	−0.254
	6	7.185	7.263	−0.046	1.767	−0.212
	7	7.396	7.358	−0.118	2.002	−0.272

Table 17 Ring currents and equivalent dipoles for hetero-aromatics

Molecule	Ring current intensity (*fc*)	Eq. dipole (μ)	Ring current ratio i/i_B
Benzene	1.00	26.23	1.00
Furan	0.67	17.6	1.04
Thiophene	0.83	21.8	1.08
Pyrrole	0.72	19.0	1.03
Oxazole	0.67	16.6	0.94
Thiazole	0.76	20.0	0.95
Imidazole	0.61	16.0	0.89
Pyridine	0.85	22.22	0.85
Diazabenzenes	0.72	18.83	0.74
Napthalene	0.93	24.39	0.93
Benzofuran[a]	0.90	23.6/17.6	—
Benzothiophene[a]	0.90	23.6/21.8	—
Indole[a]	0.90	23.6/19.0	—
Quinolines/isoquinolines	0.75	19.7	0.75

[a] The equivalent dipoles for these compounds are for the benzene/heterocyclic ring.

The difference in the experimental chemical shift of H-2 in furan and 4,5-dihydrofuran is 1.11 ppm. This is due to 1.60 ppm from the ring current but the π-electrons compensate to some extent as the π shift is −0.55 ppm compared to −0.47 ppm in dihydrofuran. The remainder is due to σ electronic effects from the olefinic carbon atoms.

Examination of Tables 14, 15 and 16 shows the significant changes in the chemical shift of the ring protons H-2 and H-3 as the heteroatom varies from oxygen, sulfur and nitrogen. The ring current contributions to the shifts of H-2 and H-3 remain fairly constant throughout but there are very different π-contributions, due to the different π-electron density in these molecules. There are also different γ-effects in furan, thiophene and pyrrole due to the different hetero atoms in these systems.

In benzofuran, benzothiophene and indole there is a similar pattern to furan, thiophene and pyrrole with a constant but increased ring current contribution to the chemical shifts. This is also the case for quinoline compared to those in pyridine.

The chemical shifts of the difunctional bases imidazole, thiazole and oxazole (Table 13) are of some interest. There is a large downfield shift of *ca.* 1.0 ppm for H-2 in thiazole (8.8 ppm) compared to that in imidazole and oxazole. The ring current effect on H-2 is similar in these molecules and there is a small π-contribution to the shift of H-2 in thiazole and oxazole. The main contribution to the large downfield shift of H-2 in thiazole is due to electronic effects of the sulfur atom with a large β-effect.

Ring currents in hetero-aromatics

The ring current intensities *fc* and equivalent dipoles (μ) for the systems considered are given in Table 17. The ratio of the ring current in these molecules to that in benzene i/i_B can be obtained from the equivalent dipoles using eqn. (7) once the areas of the current loops are known. The areas for benzene, furan and thiophene were taken from ref. 4*b* and the program PC Model was used to calculate the areas of the remaining compounds. The results of these calculations are given in Table 17. It should be noted though that the area of the current loop may not be exactly the same as the area of the molecule. With this caveat it is clear from the results in the table that the ring currents in furan, thiophene and pyrrole are essentially identical to that in benzene. In contrast the insertion of an aza nitrogen atom in the aromatic ring as in pyridine does decrease the ring current by *ca.* 15% and the effect is seen to be cumulative in the diazabenzenes. An analogous effect is observed in the five membered rings of oxazole, thiazole and imidazole with a decrease in the ring current with respect to the parent heterocycle of *ca.* 10%. In the bicyclic compounds the data for napthalene from ref. 8 are given for comparison. There is a small decrease in the benzenoid ring current compared to napthalene in benzofuran, thiophene and indole but again a larger decrease in the quinoline and isoquinoline systems.

Conclusions

The agreement of the observed *vs.* calculated proton chemical shifts is very good and shows very clearly that the CHARGE model can be applied to hetero-aromatic compounds. The ring current calculations provide further evidence for the accuracy of the simple equivalent dipole model of the benzene ring current and also demonstrate that the ring current effect is not the only factor responsible for the difference between the chemical shifts in the aromatic and non-aromatic heterocyclic compounds.

The use of suitable dihydro compounds as reference compounds is a useful method for determining the ring currents in these systems.

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