

¹H chemical shifts in NMR, part 18¹. Ring currents and π -electron effects in hetero-aromatics.

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Abstract. The ¹H chemical shifts of a number of heteroaromatics and related compounds were obtained by the assignment of the NMR spectra in CDCl₃ 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 vinylmethylether, phenol, anisole, aniline, vinylmethylsulfide and thiophenol. The six membered heteroaromatics pyridine, pyrimidine, pyrazine, pyridazine, quinoline and iso-quinoline and a number of their methyl derivatives were also investigated.

The ¹H 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 $\delta = 1.9$ to 9.4ppm the rms error of observed vs. calculated shifts was 0.096ppm. 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 ¹H 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.

Keywords: NMR, ¹H chemical shifts, heteroaromatics, ring currents, π electron effects.

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Introduction

Heteroaromatic compounds comprise an important group of compounds in organic chemistry. They are of considerable commercial and practical importance, and are the subject of a voluminous literature². They are also of theoretical interest and the extent to which the properties of these compounds are determined by their aromatic character has interested chemists for many years.

With the original concept by Pople of the aromatic ring current of benzene³, it became possible in principle to determine the aromaticity of any molecule by measuring its ring current. In a pioneering study Abraham and Thomas⁴ compared the chemical shifts of selected 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. The chemical shifts of the H-2 proton and 2-methyl groups were used because of possible mesomeric effects (^-CH.CH=X^+ , X= O, S, N) on H-3 in the dihydro compounds. They stated that the ring currents in furan and thiophene “did not differ significantly” from the benzene ring current. Elvidge⁵ suggested that polyenes were better models than the dihydro compounds and he compared the methyl shift of an ‘in chain’ methyl group in a polyene with toluene, arguing that bond alternation is minimal in this system. He obtained values of the ring currents in furan, pyrrole and thiophene of 46, 59 and 75% that of benzene.

De Jongh and Wynberg⁶ used the same method as Abraham and Thomas but averaged the shifts of H-2 and H-3 in the dihydro compounds. They also compared benzene with cyclohexene for consistency with the furan to dihydrofuran shifts. They obtained values of the ring currents in furan and thiophene intermediate between those of ref. 4 and 5.

Apart from the investigations mentioned above no calculation of the ^1H shifts in these compounds has been given. In particular the calculation of the ^1H chemical shifts for heteroaromatics using the *ab initio* GIAO method has not been reported to date, the basis set dependence of such calculations being a severe problem. A recent investigation by Lampert et al⁷ 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 ^1H shifts in a number of condensed aromatic hydrocarbons was given in a previous part of this series⁸ 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 ^1H 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 sulphur compounds and aniline for the nitrogen heterocycles etc. The molecules considered here are shown with the atom numbering in figures 1 to 6 and are as follows.

figure 1. Oxygen heteroaromatics and related molecules; vinylmethylether (**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**).

figure 2. Sulphur heteroaromatics and related molecules; vinylmethylsulfide (**11**), thiopheneol (**12**), thiophene (**13**), 4, 5-dihydrothiophene (**14**), 2-methylthiophene (**15**), 2-methyl-4, 5-dihydrothiophene (**16**), 2,5-dimethylthiophene (**17**), 3-methylthiophene (**18**) and thionaphthene (**19**).

figure 3. Pyrroles and Indoles; 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**).

figure 4. Monocyclic amines; aniline (**31**), pyridine (**32**), 2,3, and 4-picoline (**33**, **34**, **35**).

figure 5. Bicyclic amines; quinoline (**36**) and 2-methyl (**37**), 2-Methyl-3, 4-dihydroquinoline (**38**), 3-methyl (**39**), 4-methyl (**40**) and 6-methylquinolines (**41**) and isoquinoline (**42**). 1-methylisoquinoline (**43**), 1-methyl-3, 4-dihydroisoquinoline (**44**) and 3-methylisoquinoline (**45**), pyrimidine (**46**), pyrazine (**47**) and pyridazine (**48**).

figure 6. Difunctional bases; imidazole (**49**), 2-methylimidazole (**50**), 2-methyl-4, 5-dihydroimidazole (**51**), thiazole (**52**), 2-methylthiazole (**53**), 2-methyl-4, 5-dihydrothiazole (**54**) and oxazole (**55**).

This large set of conformationally rigid molecules with fully assigned ^1H NMR spectra provides sufficient data for an analysis of the proton chemical shifts in heteroaromatics based on the CHARGE model^{1,8,9}. In this model it is necessary to identify and separate the various mechanisms responsible for the ^1H chemical shifts in these molecules. These are the ring current shifts, the π electron densities, the direct α , β and γ -effects of the heteroatoms 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 ^1H chemical shifts in the molecules investigated.

Figure 1. Oxygen hetero-aromatics and related molecules.

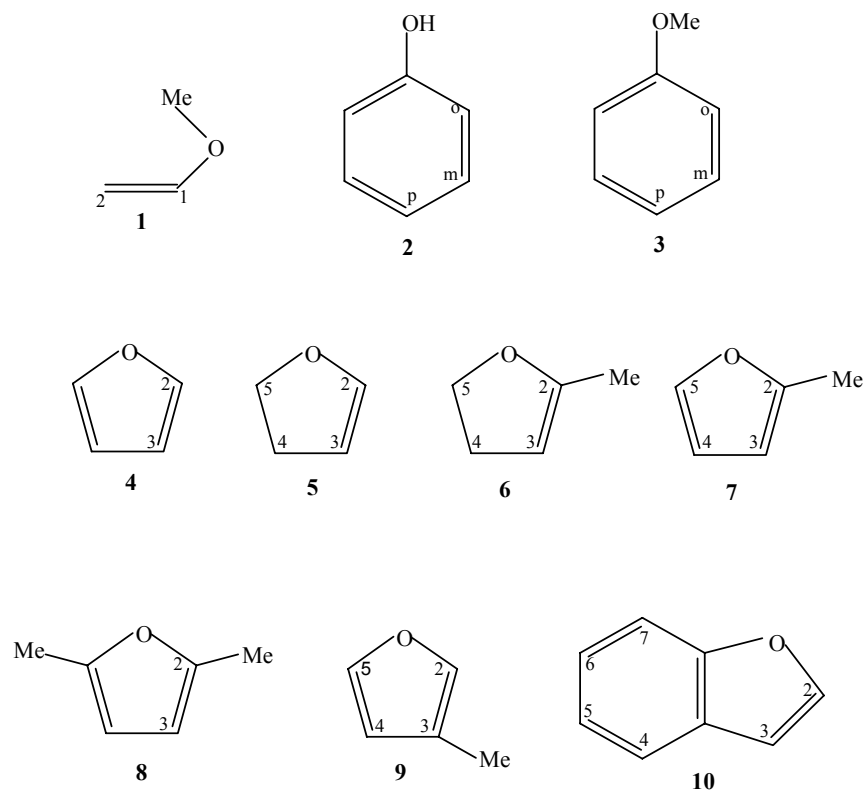


Figure 2. Sulphur hetero-aromatics and related molecules.

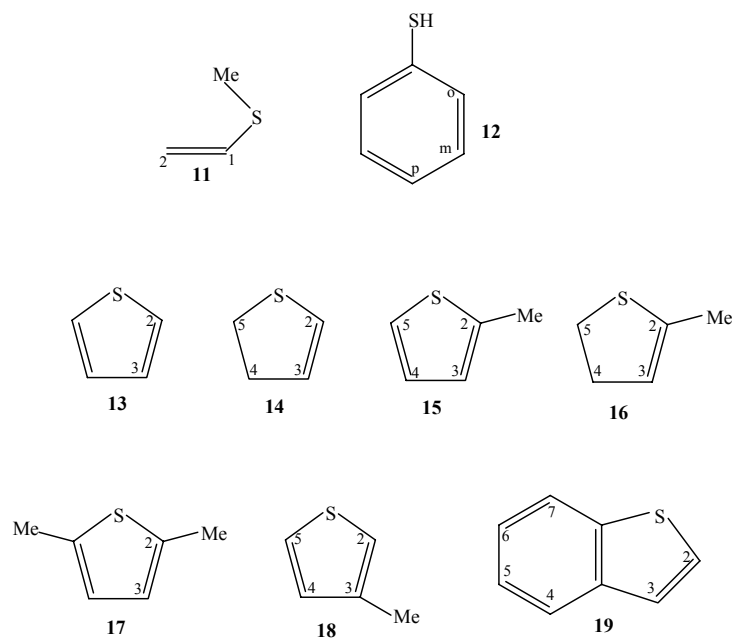


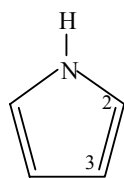
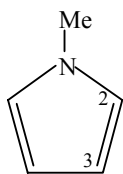
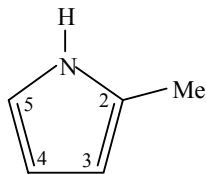
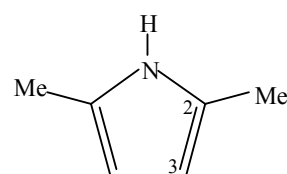
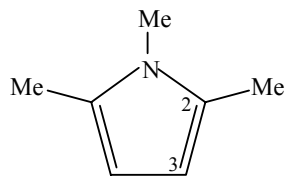
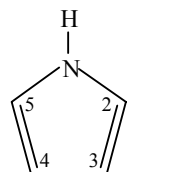
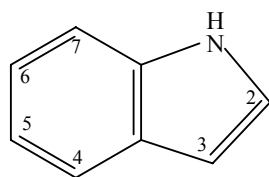
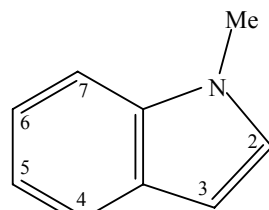
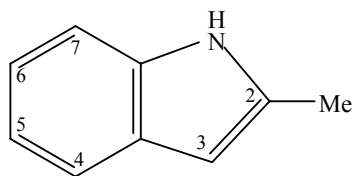
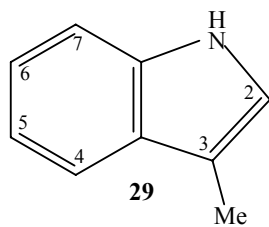
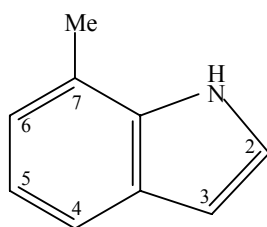
Figure 3. Pyrroles and Indoles.**20****21****22****23****24****25****26****27****28****29****30**

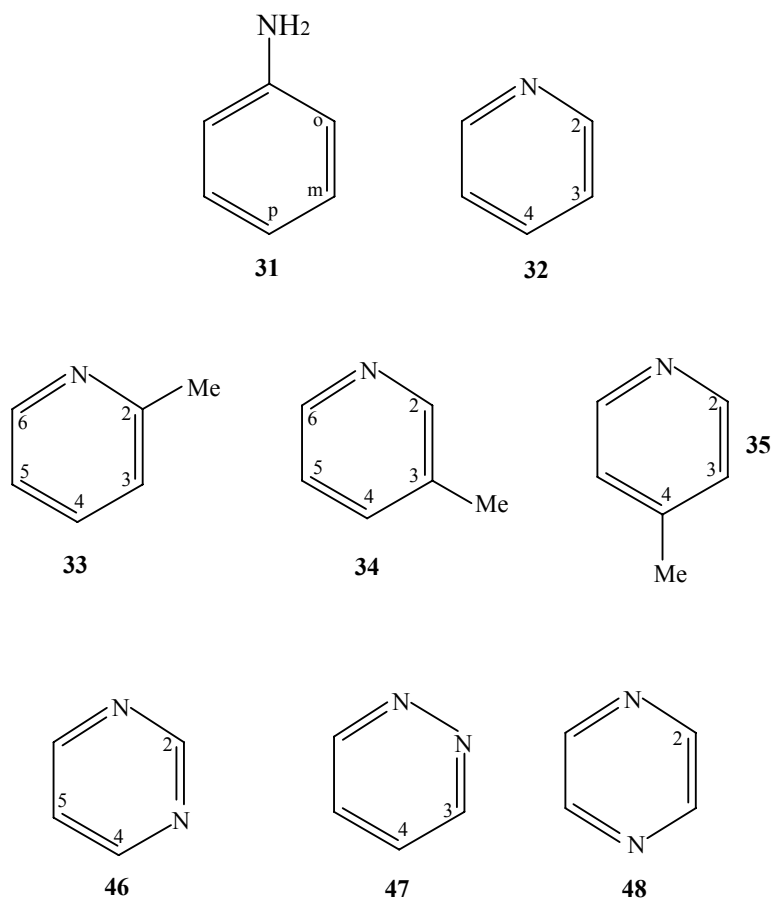
Figure 4. Monocyclic amines.

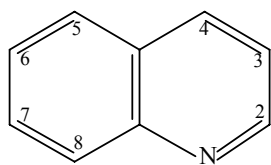
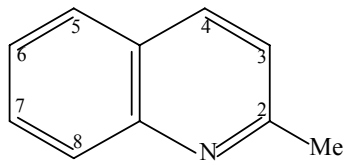
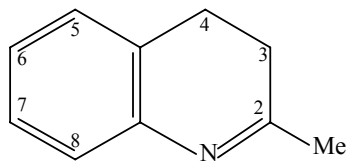
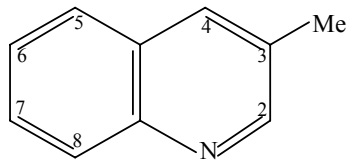
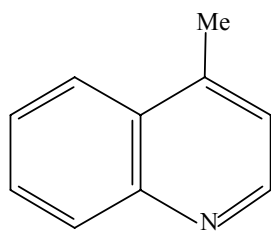
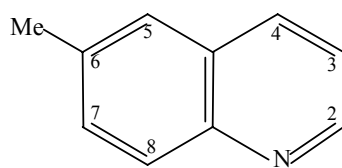
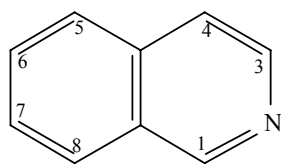
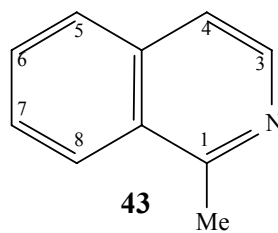
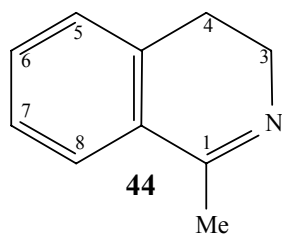
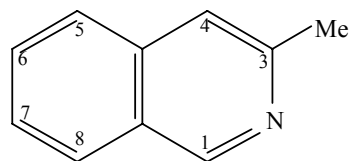
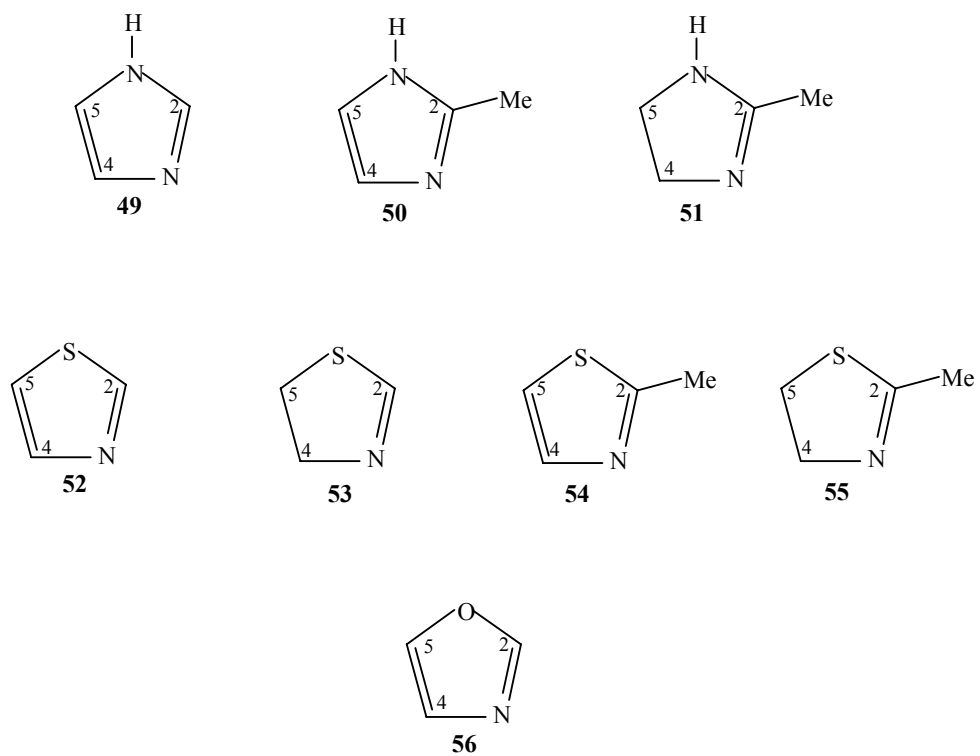
Figure 5. Bicyclic amines.**36****37****38****39****40****41****42****43****44****45**

Figure 6. Difunctional bases.

Theory

As the theory has been given previously^{1,8,9} only a brief summary of the latest version (CHARGE7) 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, S. However for the second row atoms (C,O,etc.) the γ effect (i.e. C.C.C.H) is parameterised separately and is given by eqn.1 where θ is the C.C.C.H dihedral angle and A and B empirical parameters.

$$\text{GSEF} = A + B \cos \theta \quad (1)$$

The coefficients A and B vary if the proton is in a CH, CH₂ or CH₃ fragment and there are also routines for the methyl γ effect and for the decrease in the γ effect of the electronegative oxygen and fluorine atoms for CX₂ and CX₃ groups. The total charge is given by summing these effects and the partial atomic charges (q) converted to shift values using eqn.2

$$\delta = 160.84q - 6.68 \quad (2)$$

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 (eqn.3).

$$\delta_{\text{steric}} = a_s / r^6 \quad (3)$$

Furthermore any X..H steric contribution on a methylene or methyl proton resulted in a push-pull effect (shielding) on the other proton(s) on the attached carbon.

The effects of the electric field of the C-X bonds (X= H,F,Cl,Br,I,O) were calculated from eqn.4 where A_Z was determined as 3.67×10^{-12} esu (63 ppm au) and E_Z is

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.

$$\delta_{el} = A_Z \cdot E_Z \quad (4)$$

The vector sum gives the total electric field at the proton concerned and the component of the electric field along the C-H bond considered is E_Z in eqn. 4. This procedure is both simpler and more accurate than the alternative calculation using bond dipoles.

The magnetic anisotropy of a bond with cylindrical symmetry (e.g. $C \equiv C$) was obtained using the McConnell eqn¹⁰. (eqn. 5), where R is the distance from the perturbing group to the nucleus of interest in Å, ϕ is the angle between the vector R and the symmetry axis and $\Delta\chi$ the anisotropy of the $C \equiv C$ bond. ($\Delta\chi = \chi_{parl} - \chi_{perp}$)

$$\delta_{an} = \Delta\chi (3\cos^2\phi - 1) / 3R^3 \quad (5)$$

where χ_{parl} and χ_{perp} are the susceptibilities parallel and perpendicular to the symmetry axis respectively.

For a non-symmetrical group such as the carbonyl group eqn 5 is replaced by the general McConnell eqn¹⁰. (eqn. 6) where $\Delta\chi_1 = \chi_x - \chi_y$, $\Delta\chi_2 = \chi_z - \chi_y$ and χ_x, χ_y

$$\delta_{an} = [\Delta\chi_1 (3\cos^2\theta_1 - 1) + \Delta\chi_2 (3\cos^2\theta_2 - 1)] / 3 R^3 \quad (6)$$

and χ_z are the magnetic susceptibilities along the x,y and z axes and θ_1 and θ_2 are the angles between the radius vector R and the x and z axes respectively.

Aromatic Compounds.

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. For the condensed aromatic hydrocarbons the aromatic ring current was calculated from the Pauling theory¹¹ and the equivalent dipole approximation (eqn. 7) used to calculate the ring current shifts⁸. In eqn. 7, R is the distance of the proton from the benzene ring centre, θ the angle of the

$$\delta_{rc} = fc \mu (3\cos^2\theta - 1) / R^3 \quad (7)$$

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 Huckel theory¹². The standard coulomb and resonance integrals for the Huckel routine are given by eqn.8, where α_0

$$\alpha_r = \alpha_0 + h_r \beta_0 \quad (8)$$

$$\beta_{rs} = k_{rs} \beta_0$$

and β_0 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 appropriate values of the coefficients h_r and k_{rs} in eqn.8 for the orbitals involving hetero atoms have to be found. These were obtained so that the π densities calculated from the Huckel 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.9. Δq_α and Δq_β are the excess π electron density at the α and β carbon atoms and the values of the coefficients a_1 and a_2 were found to be 10.0 and 2.0 ppm/electron⁸.

$$\delta_\pi = a_1 \Delta q_\alpha + a_2 \Delta q_\beta \quad (9)$$

The above contributions are added to the shifts of eqn.1 to give the calculated shift of eqn.10.

$$\delta_{\text{total}} = \delta_{\text{charge}} + \delta_{\text{steric}} + \delta_{\text{anisotropy}} + \delta_{\text{el}} + \delta_\pi + \delta_{\text{rc}} \quad (10)$$

Application to Heteroaromatics.

The major contributions to the proton 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. Initially 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.

The Pauling model¹¹ of ring current densities used for the condensed aromatic hydrocarbons is not applicable to heterocyclic systems. To determine the ring current density fc for the different hetero-aromatic ring systems under investigation two methods were used. Initially the method of ref 4 was used to determine the ring current.

In order to minimise possible extraneous effects (e.g. corrections for the missing double bond, the change in the hybridisation of the heteroatom, mesomeric effects etc.) only the C-2 methyl shifts were used. Thus this was restricted to those systems in which the 2-methyl substituent was present in both the aromatic and dihydro-aromatic analogue (i.e. furan, thiophene, imidazole, thiazole, quinoline and isoquinoline, figs. 1-6). For these systems the ring current was modified so that the calculated value of the difference in the chemical shift between the methyl protons in the aromatic and the dihydro compound matched the experimental value.

This method could not be used for the other systems considered as the appropriate dihydro compound was not available. In these cases 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. 11 and therefore the ratio of the ring current in a heterocyclic ring to that in

$$\mu = i A \quad (11)$$

$$i/i_B = \mu/\mu_B * A/A_B \quad (12)$$

benzene is given by eqn. 12. where μ_B and A_B are the benzene ring current and area 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 also found that the 3-21G basis set at the B3LYP level gave the best values of the dipole moments for the compounds investigated and as a result the π -electron densities from this basis set were used to parameterise the Huckel calculations.

The π systems in the range of hetero-aromatic compounds investigated are quite diverse. They range from the activated π systems of furan to the deactivated π systems of pyrimidine etc. and from aromatic systems to simple olefines. Because of this diversity it was necessary for the CHARGE model to differentiate the various π systems encountered. For example the non-aromatic π system of vinylmethylether differs from

that of furan and phenol. It was therefore necessary to treat these π systems separately. It was also necessary to differentiate the different types of nitrogen atoms present in these compounds. 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. This was achieved by determining the appropriate values of the atomic orbital coefficients h_r and k_{rs} (eqn 8) the Huckel integrals for Csp_2-X , where $X = O, S, N$ for the various π systems considered.

The accuracy of the π -electron densities calculated in the CHARGE scheme 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 general 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. Note that the π -electron densities for phenol, thiopheneol and aniline were calculated previously¹².

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.

Table 1. π charges (milli-electrons), and dipole moments μ (D) for methylvinylether, furan, thiophene, pyrrole, pyridine and indole^a.

Compound	Atom	Method				Observed ^c
		STO-3G	3-21G	6-31G	CHARGE	
Vinylmethyl 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} (Csp²-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
Vinylmethylether	1.05	0.59
Furan	1.69	0.59
Benzofuran	1.22	0.59
Thiopheneol	1.27	0.66
Vinylmethylsulfide	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

Experimental.

Phenol (**2**), anisole (**3**), benzofuran (**10**), thionaphthene (**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 ¹³C NMR were obtained on a Bruker Avance spectrometer operating at 400.13MHz for proton and 100.63MHz for carbon. HMQC, HMBC and NOE experiments were also performed. The spectra were recorded in 10mg cm⁻³ solutions (¹H) and ca.50mg cm⁻³ (¹³C) in CDCl₃ 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 3300Hz and 32k data points zero-filled to 128k. This gave an acquisition time of 5s and a digital resolution of 0.025Hz. The 2D experiments were conducted using the standard Bruker COSY-DQF and HMQC pulse sequences¹⁶.

The geometry of the compounds was first obtained using the molecular mechanics program PCMODEL Version 7.0¹⁷ and the geometry's then optimised using the Gaussian98 programme at the B3LYP/6-31G** levels¹⁸. 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.

Table 3. Observed¹⁹ and (calculated) bond lengths (Å) for hetero-aromatics

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) C₄-H 1.082 (1.086)

Spectral Analysis.

The ¹H chemical shifts for 2,5-dimethylfuran (**8**), thiopheneol (**12**), 2,5-dimethylthiophene (**17**), 3-methylthiophene (**18**), pyrrole (**20**) and the methylpyrroles (**21-24**), 4-picoline (**35**), isoquinoline (**42**) and 3-methylisoquinoline (**45**) and pyrimidine, pyrazine and pyridazine (**46-48**) were obtained directly from the Aldrich Spectra Catalogue²⁰; those for the furans and dihydrofurans (**4-7**), thiophenes and dihydrothiophenes (**13-16**), 2-methyl imidazole and imidazoline (**50,51**) and thiazole and dihydrothiazoles (**52-54**) from ref.4. and those for vinylmethylether (**1**), 3-methylfuran (**9**), vinylmethylsulphide (**11**), 2-methylpyrrole (**22**), 2-methyl 3,4-dihydroquinoline (**38**), imidazole (**49**) and oxazole (**55**) from refs.21-27 respectively. Pretsch et al²⁸ collected many of these chemical shifts in either CCl₄ or CDCl₃ solvent (see later). A number of the compounds were rerun and where necessary assigned using the techniques above to obtain the proton chemical shifts under standard conditions. These included phenol (**2**), anisole (**3**), aniline (**31**), pyridine (**32**), 2- and 3- Picoline (**33,34**), benzofuran (**10**), thionaphthene (**19**), indole (**26**), quinoline (**36**) and

isoquinoline (**42**). The assignments of the spectra of the methyl derivatives are given in more detail as follows. They were all first order spectra at 400 MHz except for (**41**).

N-methylindole (27). H-2 was immediately identified as a doublet occurring at ca.7.00 δ . The ^1H COSY plot assigns H-3 from its coupling to H-2. A NOE experiment irradiating H-3 allowed us to assign H-4 and the remaining protons were assigned from the ^1H COSY plot.

2-Methylindole (28). H-3 is immediately assigned as the multiplet occurring at ca.6.20 δ . This was confirmed from a ^1H COSY plot as H-3 couples with the methyl group. A 2D $^1\text{H}/^{13}\text{C}$ HMQC spectrum then assigned C-3 from its correlation with H-3. H-4 was then assigned by its correlation to C-3 in a 2D $^1\text{H}/^{13}\text{C}$ HMBC plot. The remaining protons were assigned from a ^1H COSY plot.

3-Methylindole (29). The assignment was made in a similar fashion to **28** via the coupling of H-2 with the methyl and a NOE of H-4 on irradiating the methyl group. The remaining resonances can then be assigned by examination of the ^1H COSY plot.

7-Methylindole (30). H-5 is immediately assigned as a double doublet pattern, coupling to H-6 and H-4 (ca.6Hz). H-6 is a complex doublet, coupling with H-4 and the methyl group. This was confirmed by an NOE experiment on the methyl group. H-4 is assigned from its coupling to H-5. H-3 is assigned by a NOE with H-4 and H-2 is then assigned from a ^1H COSY plot.

2-Methylquinoline (37). H-3 and 4 are identified as an AX pattern and from a ^1H COSY plot. By performing a 2D $^1\text{H}/^{13}\text{C}$ HMQC plot the ^{13}C assignment of C-3 and C-4 were made by correlations to the respective protons. H-5 was then assigned on the basis of a HMBC correlation to C-4. From the assignment of H-5, H-6, H-7 and H-8 were assigned from a ^1H COSY plot.

3-Methylquinoline (39). H-2 and 4 are immediately assigned as two doublets with a small coupling (ca.2.3Hz), with H-2 downfield due to the proximity of the nitrogen atom. The same procedure as used in the cases of quinoline and 2-methylquinoline was undertaken to assign H-5, H-6, H-7 and H-8.

4-Methylquinoline (40). H-2 and H-3 are immediately assigned as doublets, with H-2 shifted downfield due to the proximity of the nitrogen atom. H-5 was then assigned from an NOE experiment on the methyl group. Using a ^1H COSY plot, H-6, H-7 and H-8 were subsequently assigned from correlations starting from H-5.

6-Methylquinoline (41). Only four separate aromatic signals are observed in the ^1H spectrum. From the integrals, two resonances each of two protons occur at ca. 8.00 and 7.50 δ . H-5 is immediately assigned as a singlet at ca.7.50 δ and H-2 as a doublet of doublets at ca.8.80 δ due to the proximity of the nitrogen atom. A ^1H COSY plot then assigned H-3 and H-4. A 2D $^1\text{H}/^{13}\text{C}$ HMQC plot gave the ^{13}C assignment of C-5 by correlation to H-5. H-7 was then assigned on the basis of an HMBC correlation to C-5. With the assignment of H-7 made, H-8 was the only remaining resonance unaccounted for, the doublet overlapping with the resonance from H-4 at ca.8.00 δ .

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 0.1ppm 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 of Pretsch et al²⁸ gives for H₂-H₈ $\delta(\text{CDCl}_3)$ - $\delta(\text{CCl}_4)$ 0.12,0.12,0.14,0.12,0.10,0.10 and 0.07 res.,average 0.11ppm. Identical results hold for isoquinoline and indole. This constant low-field shift was previously observed in the aromatic hydrocarbons⁸ 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 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 eqn. 1, 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 CHAP8³⁰.

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 54 vs 55. For those systems in which the dihydro compounds were not available the ring current factor f_c 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

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 (olefine, furan) (phenol)	-0.554 0.032	-0.085 0.00	S.C=C.H (olefine) (thiophene) (thiopheneol)	0.092 -0.141 0.064	-0.434 -0.180 -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(sp³), Cb = C(sp²), N₁ = N in aniline, N₂ = N in pyrrole/indole, N₃ = N in pyridine/quinoline

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 X.C=CH fragment (X=O,S) differ for olefinic, heteroaromatic 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 N₁, N₂ and N₃ henceforth.

In the pyridines the β -effects of the N₃ atom on the ortho protons were given by the basic eqn. However for pyrazine the two bonded nitrogen atoms had an increased β -effect (1.35) and in pyrimidine the beta effect on H-2, which has two β N₃ 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 parameterised. 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 CHAP8³⁰. 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 7.6ppm with only four parameters (A and B values) to be determined. The iteration gave an rms. error (observed vs calculated shifts) of 0.073ppm. 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 7.7ppm with six unknown parameters to give an rms error of 0.107ppm. Similar results were obtained for the iterations for the other systems. The final parameterisation for all the systems considered therefore included π -electron densities, ring current and electronic effects operating on all protons in the molecules.

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

Compound	^1H Number	Observed	Calculated
Vinylmethylether (1)	1-gem	6.530	6.606
	2-cis	4.160	4.224
	2-trans	4.000	4.058
Phenol (2)	<u>o</u>	6.781	6.877
	<u>m</u>	7.321	7.212
	<u>p</u>	6.891	6.926
Anisole (3)	<u>o</u>	6.897	6.859
	<u>m</u>	7.277	7.232
	<u>p</u>	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 ^1H chemical shifts (δ) for sulphur compounds.

Compound	^1H Number	Observed	Calculated
Vinylmethylsulfide (11)	gem	6.460	6.549
	cis	5.200	5.189
	trans	4.970	4.833
Thiopheneol (12)	<u>o</u>	7.230	7.316
	<u>m</u>	7.190	7.276
	<u>p</u>	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 ^1H chemical shifts (δ) for compounds **20-25,31**.

Compound	^1H Number	Observed	Calculated
Aniline (31)	<u>o</u>	6.650	6.654
	<u>m</u>	7.136	7.132
	<u>p</u>	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 ^1H chemical shifts (δ) for compounds **26-30**.

Compound	^1H 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

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

^1H Number	32		33		34		35	
	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 ^1H 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**).

^1H Number	36		37		38		39		40		41	
	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 ^1H chemical shifts (δ) for isoquinoline (**42**) and 1-methyl (**43**), 1-methyl-3, 4-dihydro (**44**) and 3-methylisoquinoline (**45**).

^1H Number	42		43		44		45	
	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 ^a	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 ^1H chemical shifts (δ) for pyrimidine (**46**), pyrazine (**47**) and pyridazine (**48**).

^1H Number	46		47		48	
	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

Table 13 Observed vs. calculated ^1H 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**).

^1H No.	49		50		51		52		53		54		55	
	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.

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 0.096ppm over a range of 1.9 to 9.4ppm. and there are very few calculated chemical shifts with errors > 0.2ppm. H-2 in (**10**) is the only error 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 (0.25ppm) and this may be due to steric effects. In the indoles (table 8) the only significant error (ca 0.2ppm) is for H-4 which is calculated consistently lower than the observed shifts. The agreement for the quinolines (table 10) and isoquinolines (table 11) is particularly noteworthy with most of the calculated shifts accurate to <0.1ppm. 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.

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

The ring current shifts of the ring protons are ca 1.60ppm and that of the methyl protons ca 0.50 ppm. Similar effects are observed for the methyl group in 2-methylquinoline (0.51ppm), 1-methyl isoquinoline (0.65ppm), 2-methylthiazole (0.54ppm) and 2-methylimidazole (0.49ppm). 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 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

The difference in the experimental chemical shift of H-2 in furan and 4, 5-dihydrofuran is 1.11ppm. This is due to 1.60ppm 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, sulphur 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.1.0ppm for H-2 in thiazole (8.8ppm) 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 sulphur atom with a large β -effect.

Ring currents in heteroaromatics. 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 12 once the area of the current loops are known. The areas for benzene, furan and thiophene were taken from ref.4b. 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

Table 17. Ring currents and Equivalent Dipoles for Heteroaromatics.

Molecule	Ring current intensity (<i>f_c</i>)	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
Diazabenzene	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 eq dipoles for these compounds are the benzene/heterocyclic ring.

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 naphthalene from ref. 8 is given for comparison. There is a small decrease in the benzenoid ring current compared to naphthalene 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 heteroaromatic 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 heteroaromatic 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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