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^{1}H chemical shifts in NMR. Part 20† — Anisotropic and steric effects in halogen substituent chemical shifts (SCS), a modelling and *ab initio* investigation

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The ^{1}H NMR spectra of 1-halonaphthalenes were recorded and assigned. These data together with the known ^{1}H chemical shifts of the halobenzenes and of H-5 in 4-halophenanthrenes were used to investigate different models of halogen SCS using the CHARGE program. Good agreement was obtained with the observed shifts for the fluoro compounds, but a new model which included the anisotropy of the C—X bond (X=Cl, Br, I) and steric and electric field effects was required to give an accurate description of the observed chemical shifts for the other halogens. A previous observation of an anomalous ^{1}H SCS on the *meta* protons in halobenzenes was further investigated using the 1-halonaphthalenes plus the observed ^{1}H shifts of a number of 2-substituted bromobenzenes. The *meta* SCS of the bromo substituent in the bromobenzenes was only observed on H-5. When a substituent was attached to C-2, H-3 showed no appreciable effect. This remarkable effect was investigated by CHARGE and GIAO calculations and shown to be due to the π-electron system. It was reproduced in CHARGE as a γ effect from the C—X carbon atom. The observed ^{1}H chemical shifts in the above compounds were compared with those calculated by CHARGE, the GIAO technique and by the ACD database program. The recommended *ab initio* basis set for the iodo compounds (Lan12DZ) gave very poor calculated shifts, which suggests that ^{1}H chemical shifts of fourth-row atoms when calculated with the GIAO technique should be viewed with caution. In contrast, the recommended 6–31G basis set with the B3LYP technique in the Gaussian98 program gave calculated values in reasonable agreement with the observed data, as did the ACD package. These different prediction methods were compared by pie charts, scatter plots and r.m.s. errors and the CHARGE program was shown to be more accurate for the compounds considered here than the other two methods. The different philosophies of these programs are discussed together with the results obtained. Copyright © 2004 John Wiley & Sons, Ltd.**

KEYWORDS: NMR; ^{1}H NMR; halogens; SCS; anisotropy; steric; NMR prediction; GIAO; ACD

INTRODUCTION

The halogens are an important class of chemicals for chemists and their effects on the chemical shifts of both ^{13}C and ^{1}H nuclei have been studied since the early days of NMR.[2–6] In their studies of the effects induced by halogens on the chemical shifts of protons and carbons, Spiesecke and Schneider concluded that a correlation of the observed chemical shifts could only be related to the electronegativity of the halogens, if magnetic anisotropy contributions were allowed.[2] In a subsequent study of halobenzenes, again they found the anisotropy effect to be crucial for the explanation of the observed results. They also found that the effect on the ^{13}C shift due to the change in π-density on the carbon atoms brought on by the substituent was proportional to the change in the proton shifts. They did, however, find an anomalous effect on the *meta*-protons which could not be correlated with chemical shift changes in the attached carbon.[3] Although these studies provided good evidence for the existence of the mentioned effects, no attempt was made to determine any values. Subsequently, Hruska *et al.*[4] correlated the observed SCSs of the *ortho* protons to the polarizability (P) of the C—X bond using the quantity Q, according to $Q = P/Ir^3$, where I is the first ionization potential of X and r is the C—X bond length. They showed that a good correlation to the polarizability could be found for the *ortho* protons whereas the relation could not be used to predict the shift of *meta* and *para* protons.[4] Later, Zurcher[6] used additive effects consisting of the electric field of the C—X bond dipole, the van der Waals effect of the substituent, the magnetic anisotropy and solvent effects to explain the chlorine SCS in a set of aliphatic chloro compounds. The anisotropy term in his equation was shown to improve his data only slightly. The C—Cl anisotropy was calculated empirically and found to be

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small [(0–5) × 10^{-30} cm^3/molecule] and positive. Homer and Callagham,[7] in contrast, used only the magnetic anisotropy of the C—F and C—Cl bonds to calculate the ^{1}H chemical shifts in a range of haloalkanes. Later, Davis *et al.*[8] analysed chloro and bromo SCS in halo steroids and obtained poor results when only the electric field was used. When a magnetic anisotropy term was introduced, their calculations compared well with the experimental values. The best agreement was obtained when the magnetic dipole was placed at the halogen atom. Smith and Proulx[9] combined a modified version of the *Q* value with the reactivity parameters of Swain and Lupton. Their data consisted of carbon, proton and fluorine chemical shifts in a wide varietey of organic compounds containing a range of funtionalities. Although good correlations could found in most cases, the validity of the use of reactivity factors is in some doubt. This concern was raised very early by Spiesecke and Schneider,[3] when looking at the original Hammet constants, where they express that 'there remains some doubt as to exactly what is being compared if one attempts to correlate the nuclear resonance shifts with reactivity parameters'. Their concerns were due to the many factors involved in determining these primary kinetically derived constants. The rate constants reflect energy differences between the anion or the transition state and the ground state of the molecule, which are not directly related to the ^{1}H chemical shifts.

More recently, Schneider *et al.*[10] investigated a number of haloandrostanes. They used only the C—X electric field in their calculations and obtained satisfactory results. Including the magnetic anisotropy made the results worse. Subsequently, they extended their data to include halo derivatives of *trans*-decalin. The data still fitted well with the experimental values but the correlation worsened on going from chlorine to bromine and iodine. Umarani,[11] in a study of 2-phenylthiazolidines, again correlated the SCS of several different substituents to the Hammett coefficients and the Swain–Lupton reactivity models. Including the halogens gave much poorer correlation coefficients for this system. Again, there is some doubt as to exactly what the correlation to the chemical shift is.

Later, Abraham *et al.*[12,13] found that both the C—X electric field and a steric contribution were needed to calculate halogen SCSs for a range of Cl, Br and I alkanes. However, fluorine SCSs were explained using only the C—F electric field. They obtained good agreement with the observed shifts for a range of haloalkanes. Later, Abraham *et al.*[14] calculated ^{1}H shifts in aromatic systems by including ring current and π effects. They obtained good results for the *ortho* and *para* protons of the halobenzenes, but observed anomalous effects on the *meta* protons, which were particularly noticeable for the larger halogens (cf. Ref. 3). Similar but smaller effects were observed for the 3,5eq protons of 1eq-chlorocyclohexane[12,13] and it was suggested that these shifts may be due to a through-bond W effect.

Although the halogen ^{1}H SCS has been investigated and discussed for many years, there is still no agreement as to the detailed mechanism of these shifts, and there is still no practical and reliable tool for proton NMR prediction of these compounds.

The CHARGE model in its current form provides good predictions for halogens in aliphatic systems but there are still some shortcomings when applied to halo aromatics. We have already discussed the unaccounted effect on the *meta* protons and, in an investigation of hydrogen bonding in phenols,[15] it was noted that the halogen steric term given previously[12,13] was always much too large for the OH proton of 2-halophenols.

We shall show here that the effect on the *meta* protons is due to electronic effects in aromatic systems and can be incorporated into the CHARGE model. It is also necessary to determine the steric term for aromatic halogen compounds, or to modify the model used for the halogens to reproduce satisfactorily the observed SCSs for both aliphatic and aromatic systems. For this purpose, aromatic compounds with a proton in spatial proximity to the halogen substituent and more than three bonds removed are needed. The 1-halonaphthalenes and 4-halophenanthrenes fulfil these criteria and are used here as model compounds. The chemical shifts of H-5 in 4-halophenanthrenes have been given.[16] Here we present the assignments of the ^{1}H spectra of all the 1-halonaphthalenes and show that the calculation of these ^{1}H chemical shifts can be well reproduced by the CHARGE model.

An alternative method of calculating NMR chemical shifts is by the *ab initio* gauge-invariant atomic orbital (GIAO) method in which the nuclear shielding tensor is calculated. This method has been used successfully in the calculation of heavy atom chemical shifts.[17] Pulay *et al.*,[17] in a discussion of the GIAO method, note that since the chemical shift range of ^{1}H is the smallest of all atoms, it will be very sensitive to variations in the methodology such as the geometry or basis set. Also, since the protons are located on the periphery of the molecule, their chemical shifts will be more sensitive to intermolecular interactions (solvent effects, etc.), which have so far not been included in these calculations. However, recently this method has been used to calculate ^{1}H chemical shifts in organic compounds. Lampert *et al.*[18] calculated the ^{1}H shifts of a range of aromatic aldehydes and phenols and Colombo *et al.*[19] used these calculations to determine the configuration of the 3-hydroxy metabolites of the synthetic steroid tibolone. The major problem with these calculations is the basis set dependence. Colombo *et al.*[19] used a variety of basis sets and methodology (6–31G* and 6–31G** with HF, B3LYP, B3PW91) in their calculations. These six different calculations give variations in the calculated ^{1}H shifts of 0.5–1.5 ppm, depending on the particular proton considered. Hence this method cannot be used to calculate the ^{1}H shifts of an unknown compound as an uncertainty of 1.5 ppm is too large to be of much use. We use a different approach in that only one GIAO method and basis set (except for iodo compounds, see later) will be used to calculate the ^{1}H shifts of halo compounds and the reference compound. This is the recommended B3LYP/6–31G** method in the Gaussian98[20] program.

Another method of predicting ^{1}H chemical shifts is the database approach, probably the most widely used approach in industry. Here we use the Advanced Chemistry Development (ACD) predictor[21] as an example. There are few publications[22] on ^{1}H NMR predictions by ACD. Brühl *et al.*[23] found that for ^{13}C predictions of pyridines ACD gave good answers. Masunov,[24] in a review of ACD/I-Lab 4.5 (an Internet service), noted that the average error of the data based methods is usually smaller when applied to common compounds. For less common compounds the predictions can be very poor. This is because if the atom site being analysed is in the database good comparisons will be obtained, but if the atom site being predicted is not found in the database poorer results would be expected. Other points of uncertainty present when analysing proton chemical shifts are solvent and concentration effects, which can have a significant impact on the chemical shift. If the data in the database are not obtained in the same solvent or concentration, less good predictions may be produced. Masunov[24] also noted that better results are obtained if the user interacts with the database and expands the data with their own range of compounds.

It is of general interest to compare the existing models for proton predictions. Here we compare the chemical shifts predicted by CHARGE with those calculated by the GIAO technique and from the ^{1}HNMR predictor of ACD.

THEORY

As the theory has been given previously,[1,25] only a brief summary of the latest version (CHARGE7) will be given here. The theory distinguishes between short-range substituent effects over one, two and three bonds, which are attributed to the electronic effects of the substituents and long-range effects due to the electric fields, steric effects and anisotropy of the substituents.

Short-range effects

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 an α effect from atom J proportional to 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 polarizability 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 parameterized 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

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

Long-range effects

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:[13]

$$\delta_{\text{steric}} = (a_S/r)^6 \quad (2)$$

where a_S is the steric coefficient for any given atom.

The effects of the electric field of the C—X bonds (X=H, F, Cl, Br, I, O) were calculated from the equation

$$\delta_{\text{elec}} = A_Z E_Z \quad (3)$$

where A_Z, the linear electric field coefficient, was equal to 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 single-bonded atom (e.g. Cl) is calculated as being due to the charge on the chlorine atom and an equal and opposite charge on the attached carbon atom. The vector sum gives the total electric field at the proton and the component of this field along the CH bond is E_Z in Eqn (3).

The magnetic anisotropy of a bond with cylindrical symmetry (e.g. C≡C) is obtained from the appropriate McConnell equation:

$$\delta_{\text{anis}} = \Delta\chi(3\cos^2\varphi - 1)/3R^3 \quad (4)$$

where R is the distance of the perturbing group to the nucleus of interest in Å, φ is the angle between the vector R and the symmetry axis, $\Delta\chi(\chi_{\text{parl}} - \chi_{\text{perp}})$ is the molar anisotropy of the C≡C bond and χ_{parl} and χ_{perp} are the susceptibilities parallel and perpendicular to the symmetry axis, respectively. For a non-symmetric group such as the carbonyl group, Eqn (4) is replaced by the full McConnell equation involving the parallel and perpendicular anisotropy for the bond considered.[1]

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.[26–28] The equivalent dipole approximation [Eqn (5)] was used to calculate the ring current shifts:

$$\delta_{\text{rc}} = f_c\mu(3\cos^2\theta - 1)/R^3 \quad (5)$$

where 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 f_c the π-electron current density for the ring, being 1.0 for substituted benzenes.

The π-electron densities are calculated from Hückel theory.[27,28] The standard coulomb and resonance integrals for the Hückel routine are given by

$$\alpha_r = \alpha_0 + h_r\beta_0 \quad (6)$$

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

where α_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 values of the coefficients h_r and k_{rs} in Eqn (6) for the orbitals involving heteroatoms 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

$$\delta_{\pi} = 10.0\Delta q_{\alpha} + 2.0\Delta q_{\beta} \qquad (7)$$

where Δq_{α} and Δq_{β} are the excess π-electron density at the α- and β-carbon atoms.

The above contributions are added to Eqn (1) to give the calculated shift:

$$\delta_{\text{total}} = \delta_{\text{charge}} + \delta_{\text{steric}} + \delta_{\text{anis}} + \delta_{\text{el}} + \delta_{\pi} + \delta_{\text{rc}} \qquad (8)$$

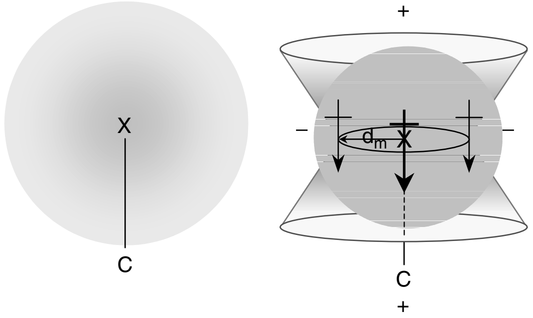
APPLICATION TO HALOAROMATICS

In the CHARGE scheme, the halogen SCS over more than three bonds is given by the steric term [Eqn (2)] and the electric field term [Eqn (3)]. Two alternative models were suggested (Fig. 1). In model A the steric coefficient for an aromatic halogen differs from that for the corresponding aliphatic halogen. This may be rationalized on the basis that the C—X bond length differs considerably between aliphatic and aromatic systems. In the second model, an anisotropy term [Eqn (4)] was added for the halogens. In order to take account of the large spread of the halogen electron cloud the anisotropy of the C—X bond was considered to be due to four magnetic dipoles parallel to but placed perpendicular to the C—X bond at a given distance (d_m) This model is consistent with the observed negative SCSs of the *para* and *meta* protons[14] of halobenzenes.

EXPERIMENTAL

All the compounds and solvents were obtained commercially. $CDCl_3$ solvent was stored over molecular sieves and used without further purification.

^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance spectrometer operating at 400.13 MHz for proton and 100.63 MHz for carbon. COSY, HMQC and HMBC experiments were also performed. The ^{1}H and COSY spectra of all the naphthalenes were also obtained at 700 MHz at GSK Stevenage. The spectra were recorded in 10 mg cm^{-3} solutions (^{1}H) and ca 30 mg cm^{-3} (^{13}C) in $CDCl_3$ with a probe temperature of ca 300 K and referenced to TMS (as an internal standard) unless indicated otherwise. Typical running conditions (^{1}H spectra) were 128 transients, spectral width 3300 Hz and 32 K data points zero-filled to 128 K. This gave an acquisition time of 5 s and a digital resolution of 0.025 Hz.



(a) (b)

Figure 1. Models of C — X shielding. (a) Only steric term; (b) steric plus an anisotropy term. from X (model B). The result is a shielding cone as shown in (b) (model B).

COMPUTATIONAL

All the structures were minimized using the Gaussian 98W program[20] at the B3LYP level of theory with the 6–31G** basis set, except the substituted bromobenzenes, which were minimized much faster using the MMFF94 forcefield in PCModel.[29] For the iodo compounds the 6–31G** basis set could not be used and the recommended basis set (Lanl2DZ)[30] produced bond lengths which were in poor agreement with experiment. The C—C bond lengths of the benzene ring are hardly affected by the halogen substituent (cf. calculated, benzene 1.395 Å, chlorobenzene 1.395 Å, bromobenzene 1.395 Å), thus the basic geometry of the benzene ring was used and the C—I bond length for iodobenzene taken as the experimental value of 2.05 Å.[31] For iodonaphthalene and phenanthrene no experimental geometries are available. In the calculated structures of the chloro- and bromonaphthalenes and phenanthrenes the C—X bond length is elongated slightly compared with the halobenzenes, probably owing to steric interactions, and the same effect would be expected for the iodo compounds. Therefore, slightly longer C—I bond lengths were used for iodonaphthalene (2.07 Å) and phenanthrene (2.09 Å). For the aliphatic systems the same procedure was adopted and the experimental C—I bond length of 2.14 Å was used.

The GIAO calculations were all performed using the B3LYP theory and 6–31G** basis set. The chemical shifts were referenced to methane (minimized and calculated in the same manner) and converted to TMS using the methane experimental chemical shift ($\delta = 0.23$ ppm). The SCS values were referenced to cyclohexane, benzene and naphthalene, which were treated in the same way. For the iodo compounds the Lanl2DZ basis set was used for the GIAO calculations. All calculations were performed on a PC.

All ACD[21] predictions were performed at GSK in Stevenage using the ACD HNMR Predictor version 5.

SPECTRAL ASSIGNMENTS

The assignments were made by COSY, HMQC and HMBC plots together with the ^{1}H and ^{13}C spectra. The spectra of the halonaphthalenes were previously assigned by Cerfontain *et al.*[16] but some of these assignments were found to be incorrect. For the fluorine compound C2 was assigned from the characteristic ^2J(C,F) coupling, and the HMQC plot gave the assignment of H-2. The remaining protons could then be assigned from the COSY plot. A fluorine-decoupled proton spectrum was obtained to give more accurate ^{1}H chemical shifts. For the other naphthalenes the COSY plot was sufficient to assign the spectra as H-8 and H-3 were readily assigned.

The 1-halocyclohexanes were previously assigned from spectra at −85 °C using a 50 : 50 mixture of $CDCl_3$ and $CFCl_3$.[12,13] A re-examination of these spectra suggested that the assignments of the 4ax proton of 1ax- and 1eq-chlorocyclohexane should be reversed. The ^1H chemical shifts of the halobenzenes were taken from the previously reported data measured in $CDCl_3$.[32] The ^1H chemical shifts of 2-substituted bromobenzenes in $CDCl_3$ solution were taken from the Aldrich spectral library[33] and easily assigned and are given in Table 4.

The H-5 protons of 4-halophenanthrenes were assigned in CCl_4,[16] thus the SCSs reported here are referenced to phenanthrene in CCl_4.[14] These chemical shifts are given in Table 2, those of the halobenzenes in Table 5 and those of the 1-halonaphthalenes in Table 7.

RESULTS

The (CHARGE) calculated chemical shift for the H-8 proton in 1-fluoronaphthalene was in good agreement with the observed shift. This was as expected as the fluorine SCS has no steric contribution and is due solely to the electric field effect. For Cl, Br and I the calculated SCS were too large, owing to the large steric effect. In model A the shifts of the H-8 proton in the 1-halonaphthalenes were used to determine the steric coefficient for aromatic halogens. In model B the steric and anisotropy terms are required to fit both aliphatic and aromatic systems. Two aliphatic (ax- and eq-halocyclohexane) and two aromatic systems (halobenzene/-naphthalene) were used and the results are given in Table 1. In model A the halogen steric coefficients for the naphthalenes are smaller than those for the alkanes. In model B including the magnetic anisotropy term further reduces the steric coefficient but the Cl, Br, I relationship is preserved for both. The magnetic dipole displacement term (d_m) also increases with the atomic radius of the halogen.

Both models gave improved results compared with the original steric term. The r.m.s. error (observed—calculated shifts) was <0.1 ppm for both Cl and Br with model B slightly better in all cases.

The chemical shift data for H-5 in the 4-halophenanthrenes provides a more definitive test of the two models and these results are given in Table 2. It is clear that model B gives much better agreement with the observed data and it will be used in CHARGE henceforth.

The '*meta*' effect

The failure of the classical steric, π-electron and electric field effects to explain the SCS on the *meta* protons in halobenzenes was noted by Abraham *et al*,[14] who suggested that this may be due to a through-bond W effect, since the 3,5eq proton chemical shifts of the 1eq-halocyclohexanes were also not calculated very well by CHARGE. However, the current model of CHARGE accurately predicts the 1eq-halocyclohexane chemical shifts. In the 1-halonaphthalenes (see Table 6), the magnitude of the SCS on the *meta* protons is larger than that in the corresponding halobenzenes, which suggests that this effect may be due to the aromaticity of the system. This is confirmed by the data in Table 3, in which the observed SCS of the 3,5eq protons in 1eq-halocyclohexanes and of the *meta* protons in halobenzenes and -naphthalenes is compared with that calculated by CHARGE and by the GIAO routine. For the 3,5eq protons of the 1eq-halocyclohexanes both the observed and calculated SCS are positive and well represented by CHARGE but not so well represented by the GIAO calculations. For the *meta* protons of the haloaromatics, the observed SCS is negative, which agrees with the GIAO SCS but not with the CHARGE SCS, which are positive. This suggests that the negative *meta* SCS is due to the aromaticity of the compound and not to a through-space effect. The GIAO calculation on the iodo compound is very overestimated (most likely since a different basis set had to be used) but it follows the general trend.

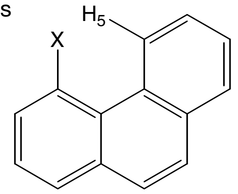
Table 1. Comparison of model A and model B

	Model A		Model B		
Halogen	a_s(alkanes)[a]	a_s(aromatic)[a]	a_s[a]	$\Delta\chi^{C—X}$[b]	d_m[a]
Cl	2.305	2.205	2.117	12	0.5
Br	2.518	2.236	2.136	17	1
I	2.720	2.265	2.221	22	1.2

[a] Å.

[b] $\times 10^{-30}$ cm^3/molecule.

Table 2. Observed[a] vs Calculated SCS of H-5 in 4-halophenanthrenes



Halogen	SCS obs.	Calc. model A	Calc. model B
Cl	0.98	0.65	0.77
Br	1.21	0.59	1.14
I	1.28	0.53	1.39

[a] Ref. 16.

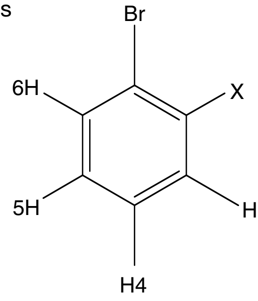
Table 3. Observed vs calculated SCSs of 3,5eq-H in 1eq-halocyclohexanes and *meta* protons of halobenzenes and halonaphthalenes

Halogen	Obs.	CHARGE	GIAO
3,5eq protons of 1eq-halocyclohexanes			
Cl	0.148	0.119	0.342
Br	0.110	0.081	0.342
I	−0.022	0.045	−0.767
Meta protons of halobenzenes			
Cl	−0.045	0.029	−0.075
Br	−0.104	0.025	−0.086
I	−0.271	−0.008	−0.741
Meta proton of halonaphthalenes			
Cl	−0.134	−0.001	−0.116
Br	−0.243	0.002	−0.135
I	−0.313	−0.024	−0.804

The C-3 carbon in the halobenzenes is calculated both in CHARGE (using the Hückel routine) and at the B3LYP/6–31G(d,p) level, to have a (positive) π-excess. This would lead to a positive π-shift, according to Eqn (7), and would therefore not explain the observed large negative SCS on the *meta* protons.

In order to obtain more detailed data on this effect, a set of *ortho*-substituted bromo benzenes were selected and the bromo SCS determined. Bromobenzenes were used since the SCS of the halogen on the *meta* proton is fairly large and also the geometry of the bromobenzenes is more reliable than that of the iodo compounds when modelled. The observed data (Table 4) clearly show a remarkable effect. The *meta* effect is present in all cases for H-5 but not for H-3. The effect practically disappears for H-3 if there is any atom other than hydrogen at the *ortho* position. Using additive tables,[34] the SCS of the H-3 proton of *o*-methylbromobenzene is −0.28 (observed, −0.16) whereas that for the H-5 proton is −0.30 (observed, −0.33). The large discrepancy at the H-3 proton disappears if the *meta* SCS of the halogen (−0.08) is removed. Similar observations that the additive SCS tables poorly represent the observed data for *ortho*-substituted benzenes have been made previously but no attempt has been made to resolve this problem.[35,36] The remarkable *meta* effect was reproduced in CHARGE by simply introducing a γ effect from C-1 to the *meta* proton provided that no α-substituent was present. The three-bond effect of C-1 in naphthalene to H-8 remains at zero. This was required since H-8 is affected by steric, anisotropic and electric field effects, hence this contribution cannot be isolated and determined. Support for this treatment comes from the ^3J(C,H) coupling. A ^{13}C experiment with gated ^{1}H decoupling allowed this coupling to be determined. In bromobenzene the ^3J(C,H) coupling (C-1–H-3) was 10.6 Hz, whereas in 9-bromoanthracene the ^3J(C,H) (C-9–H-1) coupling was only 6.3 Hz. This large reduction is most likely due to the W orientation of C-1 and H-3 and suggests that the *meta* and *peri* interactions differ and should be handled separately. This model gives the calculated chemical shifts in Table 4, which are in excellent agreement with the experimental data. Hence the CHARGE model now accurately predicts the ^{1}H chemical shifts for any aromatic halogen compound.

Table 4. Observed[33] vs CHARGE-calculated ^{1}H chemical shifts for *ortho*-substituted bromobenzenes



X		H-3	H-4	H-5	H-6
H	Observed	7.24	7.30	7.24	7.50
	Calculated	7.24	7.30	7.24	7.49
CH_3	Observed	7.18	7.18	7.01	7.50
	Calculated	7.16	7.23	7.05	7.44
OH	Observed	7.02	7.22	6.80	7.46
	Calculated	6.91	7.19	6.82	7.37
CN	Observed	7.65	7.45	7.45	7.65
	Calculated	7.72	7.50	7.46	7.72
Cl	Observed	7.40	7.20	7.10	7.60
	Calculated	7.35	7.21	7.14	7.51
Br	Observed	7.55	7.15	7.15	7.55
	Calculated	7.52	7.16	7.16	7.52
I	Observed	7.85	6.95	7.15	7.60
	Calculated	7.75	7.00	7.17	7.49

Quantum chemical NMR calculations

An alternative method for ^{1}H NMR prediction is the quantum mechanical GIAO method. This method was used to calculate the chemical shifts of the haloaromatics and haloalkanes investigated here and the results are compared with the observed and CHARGE-calculated chemical shifts in Tables 5–7.

The CHARGE-calculated chemical shifts compare very well with the observed shifts now that the *meta* effect is included. The GIAO calculations are less accurate and we note that the LanL2DZ method used for iodo compounds is too inaccurate to be of use in ^{1}H NMR calculations.

For the aliphatic compounds there is generally good agreement between both the CHARGE/GIAO-calculated and the experimental data. The protons of interest for the through-space model are the axial protons and for these protons the CHARGE calculations produce better answers. Again we note that the LanL2DZ basis set is clearly insufficient for ^{1}H NMR calculations. This suggests that any post-third-row atoms (post-Br) cannot be calculated to any meaningful precision using this method. In conclusion, it is clear that the calculations by CHARGE better reproduce the observed shifts than the GIAO calculations.

Proton prediction: a comparative study

It is of some interest to compare the CHARGE model with other ^{1}H chemical shift predictors. The two main approaches

Table 5. Observed vs calculated ^{1}H chemical shifts for halobenzenes

	Ortho	*Meta*	*Para*
Cl[a]	7.343	7.296	7.246
CHARGE	*7.312*	*7.378*	*7.242*
GIAO[b]	*7.491*	*7.545*	*7.451*
Br[a]	7.499	7.237	7.296
CHARGE	*7.489*	*7.374*	*7.276*
GIAO[b]	*7.588*	*7.534*	*7.466*
I[a]	7.670	7.070	7.300
CHARGE	*7.714*	*7.341*	*7.282*
GIAO[c]	*7.054*	*6.878*	*6.831*

[a] Ref. 32.

[b] Geometry optimization and GIAO calculation at B3LYP/6–31G(d,p).

[c] Geometry optimization and GIAO calculation at B3LYP/LanL2DZ.

Table 6. Observed vs calculated ^{1}H chemical shifts for halocyclohexanes

	1ax	1eq	2,6ax	2,6eq	3,5ax	3,5eq	4ax	4eq
Eq-Cl[a]	3.879		1.581	2.218	1.327	1.838	1.18	1.678
CHARGE	3.884		1.456	2.089	1.256	1.746	1.185	1.695
GIAO[b]	4.142		1.799	2.227	1.576	1.911	1.482	1.723
Ax-Cl[a]		4.585	1.762	1.997	1.77	1.55	1.26	1.75
CHARGE		4.323	1.622	2.080	1.711	1.613	1.283	1.708
GIAO[b]		4.658	1.827	2.113	2.232	1.567	1.497	1.867
Eq-Br[a]	4.086		1.75	2.334	1.348	1.8	1.215	1.72
CHARGE	4.049		1.558	2.189	1.210	1.708	1.242	1.664
GIAO[b]	4.377		1.974	2.333	1.599	1.911	1.530	1.731
Ax-Br[a]		4.805	1.81	2.076	1.79	1.596	1.24	1.78
CHARGE		4.474	1.729	2.182	1.723	1.620	1.162	1.701
GIAO[b]		4.981	1.926	2.167	2.415	1.575	1.501	1.880
Eq-I[a]	4.183		1.966	2.447	1.358	1.668	1.299	1.803
CHARGE	4.14		1.706	2.333	1.176	1.672	1.208	1.638
GIAO[c]	3.269		1.334	1.123	0.755	0.802	0.787	0.597
Ax-I[a]		4.96	1.525	2.063	1.72	1.62	1.261	1.73
CHARGE		4.563	1.874	2.325	1.633	1.599	1.141	1.678
GIAO[c]		3.873	1.135	1.056	1.456	0.650	0.674	0.942

[a] Refs 12 and 13 (in 50 : 50 $CDCl_3$–$CFCl_3$ at −85 °C).

[b] Geometry optimization and GIAO calculation at B3LYP/6–31G(d,p).

[c] Geometry optimization and GIAO calculation at B3LYP/LanL2DZ.

Table 7. Observed vs calculated ^{1}H chemical shifts in 1-halonaphthalenes

Halogen		H-2	H-3	H-4	H-5	H-6	H-7	H-8
F	$CDCl_3$	7.134	7.381	7.613	7.845	7.535	7.511	8.106
	CHARGE	7.078	7.482	7.495	7.812	7.523	7.451	7.995
	GIAO	7.305	7.687	7.756	7.990	7.787	7.800	8.444
	ACD	7.150	7.440	7.570	7.570	7.500	7.620	8.020
Cl	$CDCl_3$	7.545	7.343	7.725	7.820	7.505	7.567	8.257
	CHARGE	7.427	7.408	7.710	7.828	7.503	7.517	8.304
	GIAO	7.743	7.668	7.887	8.015	7.811	7.885	8.582
	ACD	7.630	7.740	7.700	7.700	7.600	7.600	7.670
Br	$CDCl_3$	7.772	7.234	7.797	7.831	7.519	7.586	8.229
	CHARGE	7.613	7.369	7.755	7.839	7.505	7.533	8.291
	GIAO	7.861	7.650	7.904	8.016	7.827	7.902	8.655
	ACD	7.880	7.140	7.330	7.810	7.500	7.740	7.640
I	$CDCl_3$	8.080	7.164	7.821	7.753	7.502	7.564	8.080
	CHARGE	7.871	7.225	7.787	7.834	7.496	7.536	8.167
	GIAO	7.312	6.980	7.091	7.205	7.133	7.222	7.621
	ACD	7.530	8.020	7.780	7.780	7.490	7.600	8.080

to ^{1}H chemical shift predictions (apart from CHARGE) are the *ab initio* GIAO calculations or the database approach.

ACD[21] uses a database approach to calculate chemical shifts and is widely used in industry. The version used here is the basic ACD/HNMR Predictor 5.0 without any add-ons or patch files.

The GIAO calculations were performed at the B3LYP/6–31G(d,p) level using Gaussian98.[20]

The dataset we use here for comparison are the halonaphthalenes, and the results are given in Table 7 and Figs 2 and 3. We first look at which model produces the greatest number of hits closest to the actual chemical shift. This is shown in Fig. 2. CHARGE produces the largest amount of best hits closely followed by ACD.

It is of interest, however, to see how good the correlation with the experimental data is since the reliability of a predictor is of importance. The scatter plot (Fig. 3) shows that although ACD makes many accurate predictions it also gives a number of poor results. This is because if the compound in question is not in the database it is bound to produce poorer results, hence the greater scatter of the data points. The actual correlation coefficient, *r*, is 0.96 for CHARGE 0.57

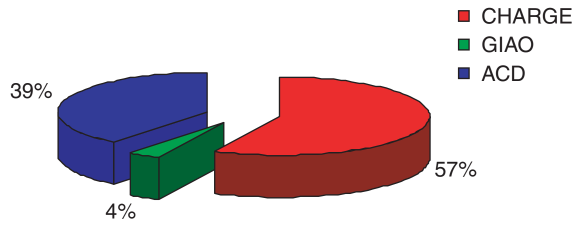


Figure 2. Pie chart of best prediction from the different models.

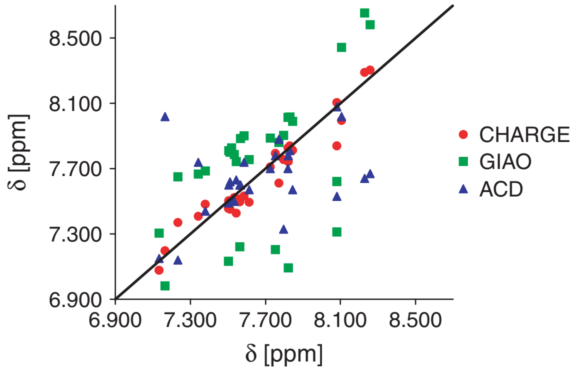


Figure 3. Scatter plot of experimental vs predicted chemical shifts.

for GIAO and 0.42 for ACD. The r.m.s. error values are 0.06 for CHARGE, 0.34 for GIAO and 0.18 for ACD.

DISCUSSION

Early investigations used either an electric field or an anisotropy term to explain the SCS of halo compounds. The importance of steric effects and/or the magnetic anisotropy of the C—X bond was not determined unequivocally. However, no investigation considered aromatic systems or protons near to the halogen such as H-8 in 1-halonaphthalenes or H-5 in 4-halophenanthrenes. By considering both aliphatic and aromatic halo compounds with close protons we have shown that the halogen SCS can be explained quantitatively by including the C—X anisotropy together with electric field and steric contributions. To take account of the large electron cloud of the halogens, the C—X anisotropy is given by the sum of four equal dipoles equally displaced from the centre of the halogen atom.

It is of interest to consider this result in more detail and Fig. 4 shows the shielding for a chlorine atom along the C—Cl bond on the basis of this model. Similar results were obtained for Br and I. We note that atoms closer than 1.5 Å parallel to the magnetic dipole are deshielded. Beyond this point, the sum of the anisotropy and steric effect is shielding, reaching its maximum at a distance of 1.9 Å. Since the proton cannot be nearer than 2 Å (the van der Waals radius of chlorine is 2.03 Å), this means that the net effect of the steric and anisotropy terms along the C—X bond will always be shielding. This also contributes to the shielding of the *meta* protons even though the effect is too small to explain fully the large negative SCS for these protons.

The comparative study on the halonaphthalenes consisted of only 28 protons but some useful observations can be made. The GIAO calculations followed the general trend fairly well although there were a number of exceptions and the whole dataset seemed to be superimposed above the observed values, which has been observed before.[18] However, the amount of time used (typically several hours for geometry minimization and an NMR calculation) using the GIAO model is a severe constraint to its use for proton prediction in a practical laboratory. It is of interest to note the relatively large discrepancy of the GIAO calculated shift compared with the experimental shift for the 3,5/4ax protons of the 1ax-halocyclohexanes. There is a large steric and anisotropy effect on these protons, which appears to be very overestimated by the GIAO method. This trend is also seen for the H-8 protons of the 1-halonaphthalenes, suggesting a general overestimation of the halogen long range effect in the GIAO calculations [using the B3LYP/6–31G(d,p) theory and basis set].

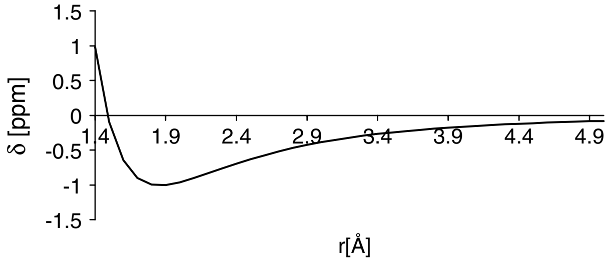


Figure 4. The combined steric and anisotropy effect of a Cl atom along the C — Cl bond.

The GIAO calculations were useful in elucidating the π-effects of the halogen substituents as the *ab initio* calculations in the GIAO method are more fundamental (and computationally much more extensive) than the Hückel theory used in CHARGE. From the GIAO calculations it was clear that the discrepancy at the *meta* proton of the haloaromatics was not due to any of the through-space contributions considered here. The large negative SCS on the *meta* protons in halogenated aromatics was reproduced as a γ-effect from the carbon attached to the halogen and this was supported by the observed three-bond C–H couplings. The non-additivity of the halogen SCS on the *meta* proton (the SCS disappears if there is an α-substituent) is of interest as additive tables are still one of the most commonly used aids for spectral assignment.

The ACD database gave more accurate predictions than GIAO, presumably because these compounds existed in their database. The ACD predictions were, however, more inconsistent than the GIAO calculations, as expected since they are not based on any calculations. We note also that the CHARGE parameterizations were obtained from data using dilute solutions in $CDCl_3$, so that environmental factors are included in the calculations.

CONCLUSION

The through-space contributions of halogens to ^{1}H chemical shifts have been revised in the CHARGE model to include aromatic compounds. The previous model was found to be inadequate to explain very close-range effects (< 2.5 Å). The

CHARGE scheme now uses an anisotropy term combined with steric and electric field terms to explain the long-range effects of the halogens in both aromatic and aliphatic systems. A remarkable *meta* SCS in halobenzenes was observed which is not additive when a 2-substituent is present. This was reproduced in CHARGE as a *meta* effect from C-1. The new model gives a better account of the observed data considered here than either the GIAO or ACD methods when assessed by pie charts, scatter plots or r.m.s. errors. The Lanl2DZ basis set, which is recommended[30] for Gaussian98 calculations of post-third-row atoms, gives unreliable geometries and poor NMR calculations.

CHARGE provides a rapid and practically useful model which now includes haloaromatics to give reliable ^{1}H chemical shift predictions.

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