^{1}H chemical shifts in NMR: Part 20[1]

Anisotropic and steric effects in halogen substituent chemical shifts (SCS), a modelling and *ab-initio* investigation

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Abstract

The ^{1}H NMR spectra of the 1-halonapthalenes were recorded and assigned. This data together with the known ^{1}H chemical shifts of the halobenzenes and of H-5 in 4-halophenanthrenes was used to investigate different models of halogen SCS using the CHARGE programme. 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) as well as 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-halonapthalenes 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 *ab-initio* GIAO technique and by the ACD data base programme. The recommended basis set for the iodo compounds (Lan12DZ) gave very poor calculated shifts and this suggests that ^{1}H chemical shifts of 4th 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 programme 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 rms errors and the CHARGE programme is shown to be more accurate for the compounds considered here than the other two methods. The different philosophy's of these programmes are discussed together with the results obtained.

Introduction

Halogen ^{1}H SCS have been calculated and discussed for many years,[2-6] yet there is still no agreement as to the detailed mechanism of these shifts. Zurcher[2] in a pioneering study used the electric field of the C-X bond dipole to explain the chlorine SCS in chlorosteroids. Adding an anisotropy term improved his data only slightly. The C-Cl anisotropy was small $(0-5 \times 10^{-30}$ cm^3/molecule) and positive. Homer et. al.[3] 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[4] analysed chloro and bromo SCS in halosteroids 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. The best agreement was obtained when the magnetic dipole was placed at the halogen atom.

More recently Schneider et. al.[5] 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 but the correlation worsened going from chlorine to bromine and iodine. Later Abraham et al[7, 8] found that both the C-X electric field and a steric contribution were needed to calculate halogen SCS's for a range of Cl, Br and I alkanes. However fluorine SCS were explained using only the C-F electric field. They obtained good agreement with the observed shifts for a range of haloalkanes.

All the above models of halogen SCS considered only aliphatic systems. There is little data on the calculation of proton SCS's in haloaromatics. Urmani[9] in a study of 2-phenylthiazolidines, 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. Note that these parameters are derived from pH and rate

constants and therefore 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. Abraham et al[6] calculated ^{1}H shifts in halobenzenes 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. Similar effects were observed for the 3,5eq protons of 1eq-chlorocyclohexane[7, 8] and it was suggested that these shifts may be due to a through bond W effect. We shall show that this meta effect is due to the aromatic ring and can be incorporated into the CHARGE model. Also in an investigation of hydrogen bonding in phenols[10] it was noted that the halogen steric term given previously[7, 8] was always much too large for the OH proton of 2-halophenols. It is therefore necessary to determine the steric term for aromatic halogen compounds. Aromatic compounds with a proton in spatial proximity to the halogen substituent and more than three bonds removed are the 1-halonapthalenes and 4-halophenanthrenes. The chemical shifts of H-5 in 4-halophenanthrenes have been given[11]. Here we present the assignments of the ^{1}H spectra of all the 1-halonapthalenes and show that the calculation of these ^{1}H chemical shifts can be well reproduced by the CHARGE method.

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[12]. Pualy et. al.[12] 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 variation in the methodology such as the geometry, basis set etc. 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[13]

calculated the ^{1}H shifts of a range of aromatic aldehydes and phenols and Colombo et al[14] used these calculations to determine the configuration of the 3-hydroxy metabolites of a synthetic steroid tibolone. The major problem with these calculations is the basis set dependence. Colombo et al[14] 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 0.5-1.5ppm, depending on the particular proton considered. Thus this method cannot be used to calculate the ^{1}H shifts of an unknown compound as an uncertainty of 1.5ppm 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[15] programme.

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[16] as an example. There are few publications[17] on ^{1}H NMR predictions by ACD. Brühl et al[18] found that for ^{13}C predictions of pyridines ACD gave good answers. Masunov[19] 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 is not obtained in the same solvent or concentration less good predictions may be produced. Masunov also noted that better results are obtained if the user interacts with the data base 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[1,20] 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 a 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 polarisability of atom I. There is also a γ effect from atom L given by the product of the atomic polarisabilities of atoms I and L for I = H and L = F, Cl, Br, I. However for chain atoms (C, N, O, S etc.) the γ effect (i.e. C.C.C.H) is parameterised separately and is given by A+Bcosθ where θ is the C.C.C.H dihedral angle and A and B empirical parameters.

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

$$\delta = 160.84q - 6.68 \tag{1}$$

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[8] (eqn. 2) where a_S is the steric coefficient for any given atom.

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

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

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

The electric field for a single bonded atom (e.g. Cl) is calculated as 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 eqn (eqn 4) , where R is the distance of the

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

perturbing group to the nucleus of interest in Å, φ is the angle between the vector R and the symmetry axis and $\Delta\chi$ (χ_{parl} - χ_{perp}) the molar anisotropy of the C≡C bond. 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 eqn 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[21-23]. The equivalent dipole approximation (eqn. 5) was used to calculate the ring current shifts.   In eqn. 5, *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

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

and fc the π-electron current density for the ring, being 1.0 for substituted benzenes.

The π electron densities are calculated from Huckel theory theory[22, 23]. The standard coulomb and resonance integrals for the Huckel routine are given by eqn.6,

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

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

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 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.7 where Δq_α and Δq_β are the excess π electron density at the α and β carbon atoms.

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

The above contributions are added to eqn.1 to give the calculated shift of eqn.8.

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

Application to Haloaromatics

In the CHARGE scheme the halogen SCS 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 rationalised 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) from X (model B). The result is a shielding cone as described by figure 1. (model B). This model is consistent with the large *shielding* effect observed on the C^{13} shift of a carbon atom directly attached to a heavy halogen atom and also partially accounts for the negative SCS's of the para and meta protons[6] of halo benzenes.
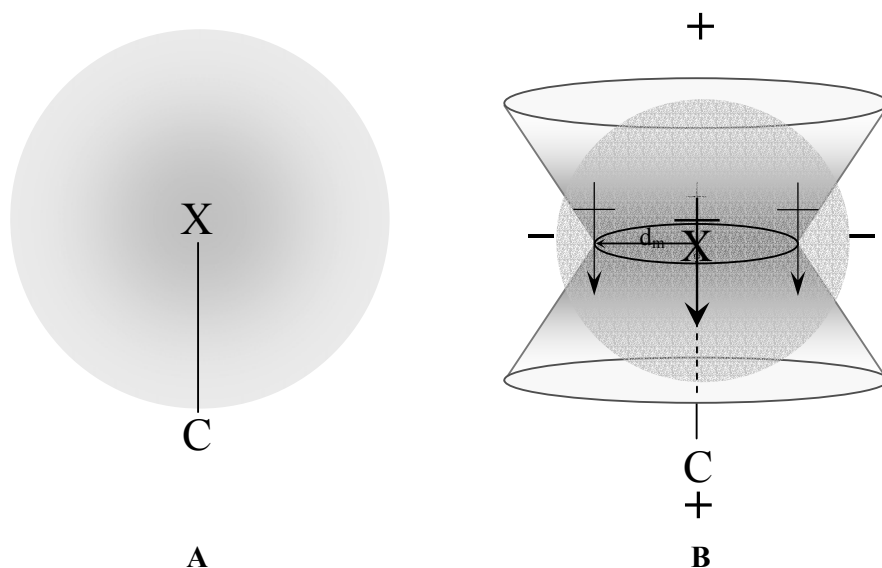

Figure. 1. Models of C-X shielding. A only steric term, B steric plus an anisotropy term.

Experimental

All the compounds and solvents were obtained commercially. The 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 400.13MHz for proton and 100.63MHz for carbon. COSY, HMQC and HMBC experiments were also performed. The ^{1}H and COSY spectra of all the naphthalenes were also obtained at 700MHz at GSK Stevenage. The spectra were recorded in 10mg cm^{-3} solutions (^{1}H) and ca.30mg cm^{-3} (^{13}C) in CDCl$_3$ with

a probe temperature of ca 300K and referenced to TMS unless indicated otherwise. Typical running conditions (^{1}H 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.

Computational

All the structures were minimized using the Gaussian 98W program[15] at the B3LYP level of theory with the 6-31G** basis set, except the substituted bromobenzenes which were minimised much quicker using the MMFF94 forcefield in PCModel[24]. For the Iodo compounds the 6-31G** could not be used the recommended basis set (Lanl2DZ)[25] produced bondlengths which were in poor agreement with experimental. The C-C bondlengths of the benzene ring are hardly affected by the halogen substituent (c.f. calculated, benzene 1.395 Å, chlorobenzene 1.395Å, bromobenzene 1.395Å) thus the basic geometry of the benzene ring was used and C-I bondlength for iodobenzene taken as the experimental value of 2.05Å[26]. For the iodo naphthalene and phenanthrene no experimental geometries are available. In the calculated structures of the chloro and bromo naphthalenes and phenanthrenes the C-X bond length is elongated slightly compared to the halobenzenes, probably due to steric interactions and the same effect would be expected for the iodo compounds. Therefore slightly longer C-I bondlengths were used for iodo-naphthalene (2.07Å) and phenanthrene (2.09Å). For the aliphatic systems the same procedure was adopted and the experimental C-I bondlength of 2.14Å used.

The GIAO calculations were performed using the same B3LYP theory and 6-31G** basis set. The chemical shifts were referenced to methane (minimised and calculated in the same manner) and converted to TMS using the methane experimental chemical shift (δ=0.23ppm). The SCS values were referenced to cyclohexane, benzene and naphthalene

which were treated 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[16] 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 halo naphthalenes were previously assigned by Cerfontain et. al.[11] but some of these assignments were found to be incorrect. For the fluorine compound C2 was assigned from the characteristic ^{2}J(C-F) coupling, and the HMQC plot gave the assignment of H2. 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 napthalenes the COSY plot was sufficient to assign the spectra as H8 and H3 were readily assigned.

The 1-halocyclohexanes were previously assigned from spectra at -85°C using a 50:50 mixture of CDCl$_3$ and CFCl$_3$[7, 8]. A re-examination of these spectra suggested that the assignments of the 4ax proton of 1ax- and 1eq-chlorocyclohexane should be reversed. The ^{1}H chemical shifts of the halobenzenes were taken from the previously reported data measured in CDCl$_3$[27]. The ^{1}H chemical shifts of 2-substituted bromobenzenes in CDCl$_3$ solution were taken from the Aldrich spectral library[28] and easily assigned and are given in table 4.

The H5 protons of 4-halophenanthrenes were assigned in CCl$_4$[11] thus the SCS's reported here are referenced to phenanthrene in CCl$_4$[6]. These chemical shifts are given in table 2, the halobenzenes in table 5 and those of the1-halonapthalenes in table 7.

Results

The (CHARGE) calculated chemical shift for the H-8 proton in 1-fluoronapthalene was in good agreement with the observed shift. This was as expected as the fluorine SCS has no steric contribution and is solely due to the electric field effect. For Cl, Br and I the calculated SCS were too large, due 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 (halo-benzene/naphthalene) were used and the results are given in table 1. In model A the halogen steric coefficients for the napthalenes 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.

Table 1. Comparison of ModelA and ModelB.

	Model A		Model B		
	a_s(alkanes)*	a_s(aromatic)*	a_s*	$\Delta\chi^{C-X**}$	d_m *
Chloro	2.305	2.205	2.117	12	0.5
Bromo	2.518	2.236	2.136	17	1
Iodo	2.720	2.265	2.221	22	1.2

* (Å)
** (x 10^{-30} cm^3/molecule)

Both models gave improved results compared to the original steric term. The rms error (observed – calculated shifts) was < 0.1ppm 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.

Table 2. Observed* 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
*Ref [11]			
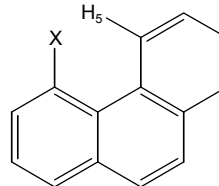
The "meta" effect

The failure of the classic steric, π-electron and electric field effects to explain the SCS on the meta protons in halobenzenes was noted by Abraham et. al.[6] who suggested that this may be due to a through bond W effect, since the 3,5eq proton chemical shifts of the 1-eq-halocyclohexanes were also not calculated very well by CHARGE. However the current model of CHARGE accurately predicts the 1-eq-halocyclohexanes chemical shifts. In the 1-halonaphthalenes (table 6.) the magnitude of the SCS on the meta protons is larger than in the corresponding halobenzenes and this 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 3,5 eq. protons in 1-eq halocyclohexanes and of the meta protons in halo benzenes and napthalenes 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

Table 3. Observed vs Calculated SCS's of 3,5 eq-H in 1-eq-halocyclohexanes and meta protons of halobenzenes and halonaphthalenes.

|	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

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 of the iodo compound is

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very overestimated (most likely since a different basis set had to be used) but it follows the general trend.

The C-3 carbon in the halobenzenes is calculated both in CHARGE (using the Huckel 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.

Table 4. Observed[28] vs CHARGE calculated ^{1}H chemical shifts for ortho substituted Bromobenzenes.

X		H3	H4	H5	H6
-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
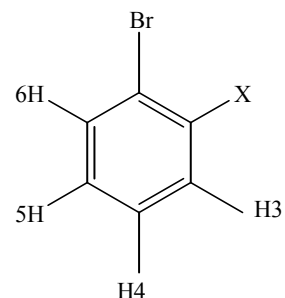
In order to obtain more detailed data on this effect, a set of ortho-substituted bromo benzenes were selected and the bromo SCS determined. Bromobenzenes were used since the SCS of the halogen on the meta proton is quite large and also the geometry of the bromobenzenes is more reliable than that of the iodo-compounds when modelled. The observed data (table 4) shows clearly a remarkable effect. The meta effect is present in all cases for H5 but not for H3. The effect practically disappears for H3 if there is any atom other than hydrogen on the ortho position. Using additive tables[29] the SCS of the H3 proton of o-methyl bromobenzene is –0.28 (obs -0.16) whilst the H5 proton is -0.30 (obs –0.33). The large discrepancy at the H3 proton disappears if the meta SCS of the halogen (-0.8) 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[30, 31]. The remarkable meta effect was reproduced in CHARGE by simply introducing a γ effect from C-1 to the meta proton provided that no alpha 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 and thus this contribution cannot be isolated and determined. Support for this treatment comes from the $^3J_{CH}$ coupling. A ^{13}C experiment with gated ^1H decoupling allowed this coupling to be determined. In bromobenzene the $^3J_{CH}$ coupling (C1-H3) was 10.6 Hz. whereas in 9-bromoanthracene the $^3J_{CH}$ (C9-H1) coupling was only 6.3 Hz. This large reduction is most likely due to the W orientation of C1 and H3 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. Thus the CHARGE model now accurately predicts the ^1H chemical shifts for any aromatic halogen compound.

Quantum chemical NMR calculations

An alternative method for ^1H NMR prediction is the quantum mechanical GIAO method. This method was used to calculate the chemical shift of the haloaromatics and haloalkanes investigated here and the results 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 ^1H NMR calculations.

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

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

*   Ref [27]
**   Geometry optimisation and GIAO calculation at B3LYP/6-31G(d,p)
*** Geometry optimisation and GIAO calculation at B3LYP/LanL2DZ

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

	1-ax	1eq	2,6-ax	2,6-eq	3,5-ax	3,5-eq	4-ax	4-eq
Eq-Cl*	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**	*4.142*		*1.799*	*2.227*	*1.576*	*1.911*	*1.482*	*1.723*
Ax-Cl*		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**		*4.658*	*1.827*	*2.113*	*2.232*	*1.567*	*1.497*	*1.867*
Eq-Br*	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**	*4.377*		*1.974*	*2.333*	*1.599*	*1.911*	*1.530*	*1.731*
Ax-Br*		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**		*4.981*	*1.926*	*2.167*	*2.415*	*1.575*	*1.501*	*1.880*
Eq-I*	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***	*3.269*		*1.334*	*1.123*	*0.755*	*0.802*	*0.787*	*0.597*
Ax-I*		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***		*3.873*	*1.135*	*1.056*	*1.456*	*0.650*	*0.674*	*0.942*

*   Ref [7, 8] (In 50:50 mix of CDCl$_3$ and CFCl3 at −85ºC)
**   Geometry optimisation and GIAO calculation at B3LYP/6-31G(d,p)
*** Geometry optimisation and GIAO calculation at B3LYP/LanL2DZ

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 are producing 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 precisions using this method. In conclusion it is quite 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 to other ^{1}H chemical shift predictors. The two main approaches to ^{1}H chemical shift predictions (apart from CHARGE) are the *ab-initio* GIAO calculations or the database approach.

ACD[16] 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/631G(d,p) level using Gaussian98.

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

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

| Halogen		H2	H3	H4	H5	H6	H7	H8
-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
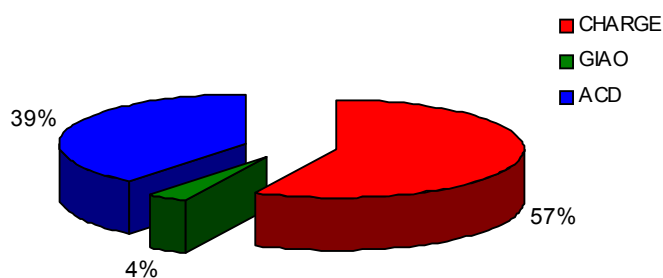
Fig 2.   Pie chart of best prediction from the different models.
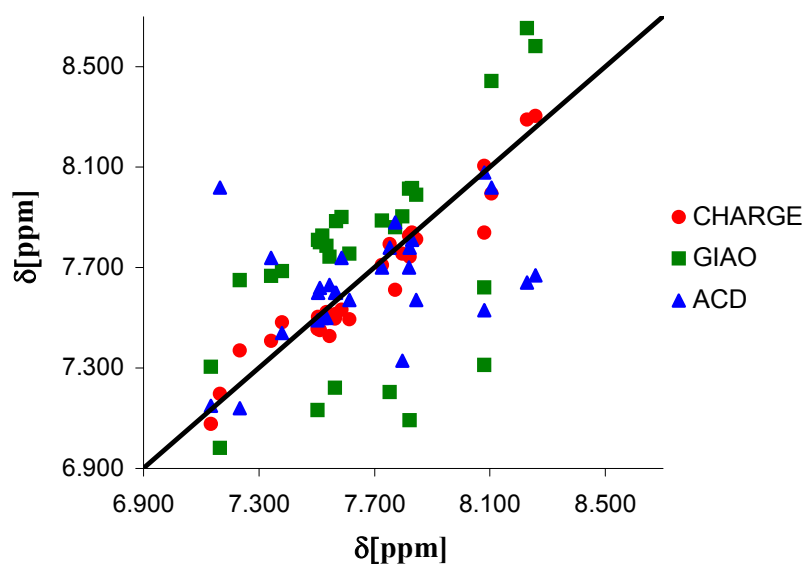

Fig 3.   Scatter plot of experimental vs predicted chemical shifts.

It is however of interest to see how good the correlation is to the experimental data 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 for GIAO and 0.42 for ACD. The rms 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 halocompounds 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.
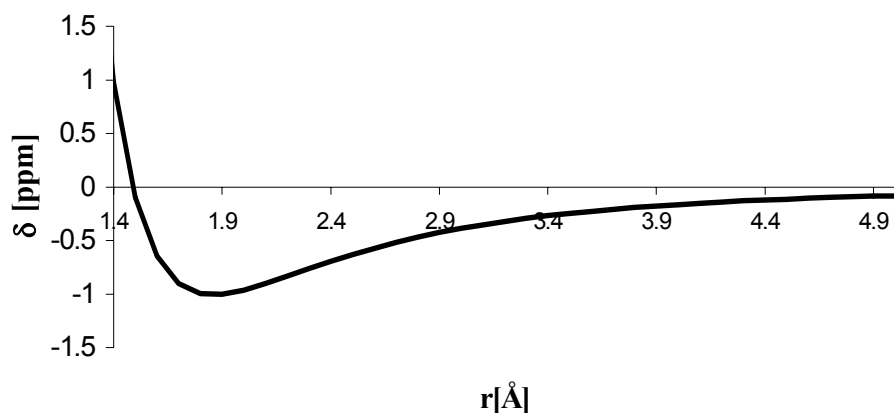
Figure 4. The combined steric and anisotropy effect of a Cl atom along the C-Cl bond.

It is of interest to consider this result in more detail and figure 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 1.5Å 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 fully explain 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 quite 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[13]. However the amount of time used (typically several hours for geometry minimisation and an nmr calculation) using the GIAO model is a severe constraint to it's 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 3,5/4 ax protons of the 1-ax-

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).

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 gamma 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 parameterisations have been obtained from data using dilute solutions in $CDCl_3$, so that environmental factors are included in the calculations.

Conclusion

The through space contribution 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 rms errors. The Lanl2DZ basis set, which is recommended[25] 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 prediction.

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