

Proton Chemical Shifts in NMR. Part 10.[†]
Bromine and Iodine Substituent Chemical Shifts (SCS) and an Analysis of the
Contributions to the SCS in halocyclohexanes.

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A model for the prediction of the proton chemical shifts in substituted alkanes (CHARGE4) has been extended to include a variety of bromo- and iodo-alkanes. These include iodo- and bromo-cyclohexane and trans-1,2-dibromo-cyclohexane for which the proton chemical shifts in the distinct conformers have been obtained at low temperatures where the ring inversion is slow on the NMR time scale.

The bromine and iodine SCS are shown to be multifunctional. The short range effects (three bonds or less) are calculated from the partial atomic charges obtained from the CHARGE scheme. Bromine and iodine substituents beta to a methine proton produce an enhanced SCS, which increases with the number of attached carbons i.e. $RR'CHX > RCHXY$ ($R,R' =$ alkyl group). The long range ($>$ three bonds) effects are shown to be due to the electric field of the C-X ($X=Br$ or I) bond plus the steric effect of the halogen atom. This model predicts bromine SCS in a variety of cyclic bromoalkanes over 118 data points with an error of 0.07 ppm, and iodine SCS over 96 data points to 0.09 ppm. Systems considered include halo-ethanes, propanes, cyclohexanes, bornanes, norbornanes, adamantanes and steroids.

The accurate prediction of bromine and iodine SCS together with the previous analyses of the chloro and fluoro SCS allows the proton SCS in axial and equatorial halocyclohexanes to be analysed in terms of the calculated contributions in CHARGE4, i.e. charge, steric, linear electric field and magnetic anisotropy terms.

The β and γ halogen SCS are determined by charge effects. The β (CHX) proton chemical shifts are in the order $F > I > Br > Cl$ for both the axial and equatorial conformers. This order is accounted for by a general electronegativity function plus a heavy atom effect (where $I > Br > Cl$). In contrast the γ (vicinal) proton SCS are in the order $F < Cl < Br < I$ and also show no orientation dependence. These are given by a polarisability functional dependence in CHARGE4.

Protons in a 1,3-syn-diaxial orientation with the substituent i.e. H_{3,5ax} in the axial conformer are heavily influenced by the direct steric effect of the halogen substituent for Cl, Br and I, but the influence of the C-X linear electric field is also appreciable. The other proton of this methylene group (H_{3,5eq}) has a compensating 'push-pull' upfield shift. For fluorine no steric effects are observed. The C-X linear electric field term is the dominant interaction for the remaining protons. In particular all the proton SCS in the equatorial conformer (except the β and γ SCS) are given by this term. The general good agreement with the observed SCS supports this interpretation though the influence of other interactions is possible for certain protons. No C-X anisotropy term was needed in this scheme.

The characterisation of the chlorine, bromine and iodine steric terms shows that the steric term coefficients are proportional to the polarisability, but not to the ionisation energy of the

[†] For Part 9, see Ref. 1

substituent, supporting the interpretation that this term is due to van der Waal's interactions and not to the quadratic electric field.

Introduction

Although the effect of substituents on proton chemical shifts has been described in numerous investigations over many years there is still no generally accepted explanation of their substituent chemical shifts. Electric field, anisotropy and steric effects have all been proposed for bromine and iodine substituents but no quantitative explanation given^{2,3,4}. Bothner-By and Naar-Colin² in a pioneering investigation noted the anomalous inductive effects of the higher halogens but were not able to quantify their explanations apart from noting a correlation with the molecular electric dipole. A more rigorous analysis by Davis et al.³ considered bromine SCS on 11 methyl protons in bromo-androstanes, where all but three could be fitted solely by the C-Br electric field term. The anomalies were the same as for the chlorine SCS, being the 1,3-syn diaxial effects from 2 β , 4 β and 6 β -bromo-androstanes on the 19-CH₃ protons where errors of ca. 0.3 ppm arose unless the magnetic anisotropy term was included as well. Similar effects were noted for the bromine SCS in the ethylene ketal of 5-bromo-pentacyclodecan-6-one.

Schneider and coworkers^{4a} analysed data for 11 protons (7 methyl) in bromo- and iodo-cholestanes and esterenes, and later for 3 α and 3 β -bromo- and iodo-androstan-17-one^{4b} where the electric field term produced results of the correct sign and magnitude in contrast to the anisotropy calculations. Differences for close substituents were considered to derive from inductive through bond effects, with a possible minor role for steric effects. In a further investigation Schneider and Jung⁵ noted that the bromine and iodine SCS in 9-halo-trans-decalins were consistent with the steroid data and thus predictable by electric field calculations alone, except for the shielded methine γ protons.

Abraham et al.^{6,7} obtained bromine SCS in 2-exo- and 2-endo-bromonorbornane, 1-bromo- and 2-bromo-adamantane and 2-exo-iodonorbornane and noted that both electric field and either van der Waal's or anisotropy contributions were required to explain the chemical shifts. Kaiser et al.⁸ examined 3-endo- and 3-exo- bromo- and iodo-camphor and suggested that electric field and steric terms would explain the observed SCS, with inductive contributions on the beta protons.

In previous papers in this series^{1,9-11} a model (CHARGE4) for the calculation of proton

chemical shifts in halo-substituted alkanes has been developed based on a semi-classical calculation

of the partial atomic charges in these molecules together with quantitative evaluations of the polar, steric and anisotropic contributions of the substituents. The substituent effect of the fluoro substituent was shown to be due largely to the direct inductive effect of the fluorine for protons two-bonds (β) and three bonds (γ) from the fluorine atom but for more distant protons the influence of the electric field of the C-F bond was a major factor¹¹. Studies on the more complex case of the chlorine substituent showed that it was necessary to include the direct steric effects of the chlorine atom to obtain a quantitative explanation of chlorine SCS¹. For the more distant protons this steric term is deshielding and in the case of X..H steric effects on a CH₂ or CH₃ group the protons not directly experiencing the steric perturbation suffered a corresponding ‘push-pull’ *shielding* effect. In chloro-alkanes it was also shown that the steric term was distinct and greater than the minimal quadratic electric field effect. However, the interpretation of the steric term as a van der Waal’s interaction still awaits confirmation.

We shall show here that the CHARGE4 scheme can give an accurate prediction of bromo and iodo SCS in a variety of substituted alkanes, thus these calculations give the first quantitative account of the halogen SCS in these systems. This good agreement allows us to consider the partitioning of the SCS into the various contributions given by CHARGE4. Here we shall compare and contrast the halogen SCS in the light of these calculations and determine their significance to the individual proton chemical shifts in cyclohexanes.

Computational Model

In the CHARGE scheme⁹ the effect of a substituent on atoms up to three bonds away is considered to be through bond effects. The α effect (1 bond) is dependent on the relative electronegativities of two adjacent atoms. The β effect (2 bond) is a function of both the electronegativity of the substituent and the polarisability of the atom being considered. The γ effect (3 bond) is non-orientational and a function of the polarisability of the two atoms involved. These partial atomic charges (q) are linearly converted to chemical shifts by equation 1.

$$\delta_{\text{charge}} = 160.84 q - 6.68 \quad (1)$$

For hydrocarbons a C-C anisotropy term was introduced based upon McConnell's formulation¹⁰ with the magnetic vector pointing along the C-C bond and acting from the mid-point. This was applied to all bonds except those immediately adjacent to the protons being

considered (i.e. H-C_α-C_β).

The long range (> 3 bonds) effect of a substituent is due to any geometry distortion and linear electric field contributions based upon Buckingham's equation¹² (equation 2)

$$\delta_{\text{electric}} = A_Z E_Z \quad (2)$$

and a steric term given by equation 3.

$$\begin{aligned} \delta_{\text{steric}} &= a_S (1/r^6 - 1/r_{\text{min}}^6) \\ \delta_{\text{steric}} &= 0 \text{ for } r \geq r_{\text{min}} \end{aligned} \quad (3)$$

The linear electric field effect of the substituent has been characterised and defined in the fluorine and chlorine SCS^{1,11} yielding a value of A_Z of 63 ppm au (3.67 × 10⁻¹² esu). The steric term (equation 3) has a cut-off at r_{min} which was taken for chlorine as the van der Waal's radius. A similar procedure is adopted for bromine and iodine using van der Waal's radii of 2.18 and 2.32Å respectively.^{13,14}

Experimental

Bromo-, iodo- and trans-1,2-dibromocyclohexane were obtained from Aldrich Ltd. The solvents were obtained commercially, stored over molecular sieves and used without further purification.

¹H and ¹³C spectra were obtained on a Bruker AMX 400 spectrometer operating at 400.14 MHz for proton and 100.63 MHz for carbon. Spectral conditions were identical to those given in Ref. 1. In previous calculations^{1,9-11} the geometries for all molecules were taken from ab initio HF/6-31G* calculations¹⁵. However, since this basis set is only defined for atoms in the range H to Cl, the geometries of both bromo- and iodo-alkanes were obtained from the molecular mechanics program PCModel¹⁴. To avoid any inconsistency in the SCS the base alkane values were recalculated using PCModel geometries, yielding only small shift changes (< 0.1 ppm).

All the compounds were run in a 50:50 mixture of CDCl₃:CFCl₃ at -80°C, where the ring inversion was slow on the NMR time scale and no change was observed to -90°C, with the temperature measured using the thermocouple on the AMX400. Conformer populations were obtained at -80°C by integration of the 1 position protons. Proton chemical shifts from HET-CORR plots are considered accurate to ±0.02 ppm.

Spectral Assignments

Bromocyclohexane. The assignment of the major equatorial isomer (82%, $\Delta G = 0.58 \text{ kcal mol}^{-1}$) was complicated by the overlap of the 2,6-ax, 3,5-eq, and 4-eq protons at δ 1.70-1.85. The 1-ax, 2,6-eq, 3,5-ax and 4-ax positions were confirmed by the COSY-DQF correlations, and the remaining protons distinguished by a HET-CORR. The assignments agree with those for β and γ protons in 2,2,3,3,4,4,5,5-d₈-bromo-cyclohexane¹⁶.

The minor axial conformer (18%) showed considerable overlap with the major form. The 1-eq, 2,6-eq and 3,5-eq multiplets were clearly observable and defined by the COSY-DQF. The 2,6-ax, 3,5-ax and 4-eq protons were obscured under the multiplet at δ 1.70-1.85, and the 4-ax beneath that of the major conformer. The chemical shifts were determined by the HET-CORR correlations, with the assignment of H₄ based upon $\delta_{\text{eq}} > \delta_{\text{ax}}$, in agreement with bromine SCS effects in trans-decalins and steroids^{4,5}.

Iodocyclohexane. The assignment of the major equatorial conformer (80%, $\Delta G = 0.54 \text{ kcal mol}^{-1}$) was based upon integration and splitting patterns, and confirmed by the COSY-DQF. The 3-ax and 4-ax protons showed some overlap, and surprisingly $\delta_{4e} > \delta_{3e}$.

Table 1: Proton and carbon chemical shifts (δ) of bromo- and iodo-cyclohexane in 50:50 CDCl₃:CFCl₃ at -85°C.

	Proton					Carbon			
	Eq-Br	Ax-Br	Eq-I	Ax-I		Eq-Br	Ax-Br	Eq-I	Ax-I
1ax	4.086	-	4.183	-	C ₁	53.67	56.66	32.07	39.39
1eq	-	4.805	-	4.960	C ₂	38.28	34.42	40.39	35.92
2,6ax	1.75*	1.81*	1.966	1.525	C ₃	27.58	20.73	28.98	22.36
2,6eq	2.334	2.076	2.447	2.063	C ₄	24.64	25.58	24.69	25.70
3,5ax	1.348	1.79*	1.358	1.72*					
3,5eq	1.80*	1.596	1.668	1.62*					
4ax	1.215	1.24*	1.299	1.261					
4eq	1.72*	1.78*	1.803	1.73*					

* Chemical shift cf. ¹³C-¹H correlations.

In the minor axial conformer (20%) the 1-eq, 2-ax and 2-eq protons were clearly visible. These were confirmed by the COSY-DQF. One triplet of the 4-ax proton's quartet of triplets could be seen to high field of the 4-ax proton of the major form. The patterns of the 3-ax, 3-eq

and 4-eq protons were obscured by overlap with the equatorial conformer, and were defined by a HET-CORR. The assignment of $\delta_{3a} > \delta_{3e}$ was based upon the observation of the triplet $^3J_{ax-eq}$ (3.2 Hz) at 1.69 ppm, and lack thereof at 1.60 ppm. For the equatorial proton the $^3J_{ax-eq}$ coupling is obscured at the resolution obtained by the additional $^3J_{eq-eq}$ couplings leading to a broad peak. This assignment is in agreement with the axial-iodine SCS effects in trans-decalins and steroids^{4,5}.

Trans-1,2-Dibromocyclohexane. The assignment of the major diaxial form (76%, $\Delta G = 0.47$ kcal mol⁻¹) was based upon the splitting patterns and confirmed by the COSY-DQF. The 1,2-eq protons (δ 4.704) correlated to the 3,6-ax (δ 2.445) and 3,6-eq protons (δ 1.927). These in turn showed couplings to 4,5-ax (δ 1.822) and 4,5-eq (δ 1.638).

For the minor di-equatorial conformer (24%) the 1,2-ax (δ 4.084), 3,6-eq (δ 2.536) and 4,5-ax (δ 1.412) protons were visible with the assignment of 3,6-ax (δ 1.93) and 4,5-eq (δ 1.81) protons determined by the COSY-DQF.

FIGURE 1

Results

Comparison of the bromine and iodine SCS in cyclohexanes with the chlorine SCS given previously (Figure 1 and Table 9) shows similar contributions. We have therefore adopted the same procedure as for the calculation of chlorine SCS i.e. the long range effects are due to electric field plus steric effects. Since the charge on the bromine or iodine atom is smaller than on chlorine in the same molecule, but the observed effects are the same or slightly greater (cf. the SCS for H_{3ax} in the axial conformer of 0.60 (Br), 0.53 (I), vs. 0.58 (Cl) ppm, Table 9) the bromine and iodine steric contributions should be somewhat greater than for chlorine.

The linear electric field effect of the substituent has already been characterised and defined from the fluorine and chlorine SCS. Thus for the bromo and iodo alkanes the electric field contribution to the bromo and iodo SCS is completely determined. The only unknown parameters for long range SCS are the a_s coefficient in equation 3 and the push-pull coefficient.

The chemical shift of the protons beta to the substituent have hitherto been given quite accurately from the atomic charges calculated by the CHARGE scheme⁹. However, there is an enhanced deshielding effect of the bromine and iodine substituents on methine protons, in

particular where the proton is beta to two carbon atoms. Thus the bromine beta effect was increased by 19% for RCHXBr ($X \neq C$) and 47% for RR'CHBr (R, R' = alkyl) methine protons. Similarly for iodo-alkanes the beta effect on methine protons was increased by 47% for RCHXI and by 105% for RR'CHI protons. However, for the highly polarisable iodine atom, even the beta methylene protons were experimentally more deshielded than calculated in the presence of a beta carbon, and the iodine beta effect was increased by 28% to compensate.

The long range SCS were best fitted by a value of a_s in equation 1 of 255.0 with the push-

Table 2: Observed vs. calculated chemical shifts (δ) for acyclic bromo- and iodo-alkanes.

Molecule		X=Br		X=I	
		Obs. ^A	Calc.	Obs. ^A	Calc.
CH ₃ X	CH ₃	2.68	2.79	2.16	2.21
CH ₂ X ₂	CH ₂	4.94	4.74	3.90	3.79
CHX ₃	CH	6.82	6.34	4.91 ^B	5.12
CH ₃ CH ₂ X	CH ₂	3.36	3.19	3.15	3.08
	CH ₃	1.65	1.65	1.86	1.87
CH ₃ CHX ₂	CH	5.86 ^B	5.68	5.24 ^C	5.36
	CH ₃	2.47	2.42	2.96	2.83
CH ₂ XCH ₂ X	CH ₂	3.63	3.63	3.64 ^D	3.65
CH ₂ XCHX ₂	CH	5.61 ^E	5.85	-	-
	CH ₂	4.04	4.04	-	-
CHX ₂ CHX ₂	CH	6.03	6.01	-	-
CH ₃ CH ₂ CH ₂ X ^F	CH ₂ X	3.36	3.25(g), 3.13(t)	3.16	3.14(g), 3.02(t)
	CH ₂	1.89	1.84(g), 1.84(t)	1.86	1.99(g), 1.99(t)
	CH ₃	1.04	0.94(g), 0.98(t)	1.04	0.96(g), 0.93(t)
(CH ₃) ₂ CHX	CH	4.20	4.46	4.24	4.55
	CH ₃	1.71	1.69	1.88	1.91
C(CH ₃) ₃ X	CH ₃	1.76	1.71	1.95 ^G	1.93
(CH ₃) ₂ CHCH ₂ X ^F	CH ₂	3.31 ^H	3.16(g), 3.31(t)	3.15 ^H	3.05(g), 3.21(t)
	CH	1.98	2.03(g), 2.03(t)	1.73	2.10(g), 2.10(t)
	CH ₃	1.03	0.99(g), 1.01(t)	1.01	0.97(g), 0.99(t)
(CH ₃) ₃ CCHX ₂	CH	-	-	5.21 ^G	5.10
	CH ₃	-	-	1.19	0.99

^A Ref. 17 unless stated. ^B Ref. 18. ^C Pure liquid, Ref. 19. ^D Ref. 20. ^E Ref. 21. ^F (g) gauche, (t) trans conformer. ^G Ref. 22. ^H Ref. 9.

pull coefficient at 50% for bromine and corresponding values of 405.0 and 40% for iodine.

The observed and calculated proton chemical shifts for acyclic molecules and the SCS for cyclic bromo- and iodo-alkanes are given in Tables 2 to 9. In Table 2 the values for both the

trans and gauche conformers of 1-halo- and 2-methyl-1-halo- propanes are given but for the haloethanes the shifts for both conformers are the same, due to the non-orientational nature of the through bond γ effect.

The steric effect in the halocyclohexanes (Tables 3 and 9) eg. 3,5-ax in axial-bromocyclohexane (calc. 0.60 ppm vs. obs. 0.58 ppm) and in axial-iodocyclohexane (calc. 0.56 vs. obs. 0.53 ppm) well replicates the observed SCS. In 9-substituted-trans-decalins (Table 4) the calculated SCS show slightly greater deviation from the observed, although problems with the geometry have been noted for 9-chloro-trans-decalin¹.

Table 3: Observed^A vs. calculated^B SCS (ppm) for trans-1,2-dibromo-cyclohexane.

Proton	Conformer	Diequatorial-		Diaxial-	
		Obs.	Calc.	Obs.	Calc.
1,2ax (CH)		2.89	3.18	-	-
1,2eq (CH)		-	-	3.02	3.14
3,6ax		0.74	0.57	1.26	1.07
3,6eq		0.86	0.62	0.25	0.47
4,5ax		0.22	0.10	0.63	0.59
4,5eq		0.13	0.16	-0.04	0.00

^A This work. ^B Calc. SCS cf. cyclohexane (ax = 1.08, eq = 1.69 ppm).

Schneider⁵ reported the anomalous shielding effect in the 9-halo-trans-decalins (for bromine and iodine SCS) on the 10-position protons, and this is supported by the CHARGE4 calculations. In the case of iodine the shielding effect is even greater than the deshielding effect on the 1,8-ax proton, and this data point was thus excluded from the paramatrisation of the scheme. Clearly, there is some additional effect occurring through the C-C bridge than is calculated by the CHARGE4 non-orientational γ effect (see later).

The observed and calculated SCS in bromo and iodo-bornanes and norbornanes are given in Table 5. The steric shielding on the 6n proton in endo-bromobornane (calc. 0.84 vs. obs. 0.91 ppm) and the 7s proton in exo-halonorbornanes reflect the observed effects. The smaller size of the push-pull coefficient for iodine than bromine can be seen experimentally in the SCS effects on the 7-anti protons. In 2-exo-iodobornane the H-7a SCS is +0.17 ppm, greater than for the iodo-norbornane (+0.11 ppm), yet the 7-syn protons are similarly shielded (+0.74 and +0.68 ppm) and the linear electric field effect is less (cf. CHARGE4 partial atomic charge, I = -0.089

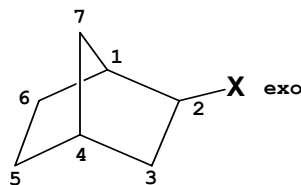
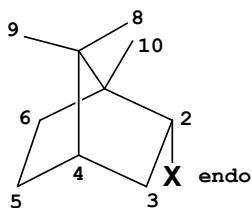
electrons and Br = -0.125 electrons). The relative deshielding of the 7-anti proton may thus be attributed to a smaller iodine push-pull shielding effect.

Table 4: Observed^A vs. calculated^B SCS (ppm) for 9-bromo- and 9-iodo-trans-decalin.

Proton	Bromo-		Iodo-	
	Obs.	Calc.	Obs.	Calc.
1,8-ax	0.54	0.40	0.46	0.51
1,8-eq	0.52	0.55	0.68	0.70
2,7-ax	0.70	0.69	0.82	0.72
2,7-eq	-0.08	-0.10	-0.01	-0.11
3,6-ax	0.05	-0.01	0.11	-0.02
3,6-eq	0.05	0.05	0.04	0.04
4,5-ax	0.48	0.75	0.44	0.77
4,5-eq	-0.23	-0.12	-0.25	-0.13
10 (CH)	-0.04	0.10	-1.20	0.14

^A Obs. shifts cf. Ref. 23, SCS cf. trans-decalin Ref. 10. ^B Calc. cf. trans-decalin (1/3/4/8-ax = 1.00, 1/3/4/8-eq = 1.63, 2/3/6/7-ax = 1.13, 2/3/6/7-eq = 1.74, 9/10 = 0.83 ppm).

Table 5: Observed vs. calculated^A SCS (ppm) for bromo- and iodo- bicyclo[2.2.1] heptanes.



Proton	X = Br				X = I	
	2-endo ^B		2-exo ^B		2-exo ^C	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
1 (CH)			0.32	0.26	0.41	0.33
2n	-	-	2.83	2.84	2.82	2.91
2x	2.83	2.78	-	-	-	-
3n	0.87	0.54	0.87	0.52	0.97	0.67
3x	0.82	0.48	0.60	0.53	0.76	0.65
4 (CH)	0.06	0.08	0.12	0.03	0.06	0.08
5n	0.14	0.02	-0.08	0.06	-0.06	0.05
5x	0.04	0.08	0.01	0.07	0.02	0.05
6n	0.84	0.91	0.02	0.02	0.07	-0.01
6x	-0.07	-0.14	0.17	0.09	0.10	0.06
7a			0.11	-0.04	0.17	-0.04
7s			0.68	0.54	0.74	0.48
8-Me	0.05	0.04				
9-Me	0.04	0.03				
10-Me	0.14	0.09				

^A Calc. SCS cf. bornane (2/6n = 0.99, 2/6x = 1.51, 3/5n = 1.10, 3/5x = 1.79, 4 = 1.74, 8/9-Me = 0.83, 10-Me = 0.97 ppm) or cf. norbornane (1/4 = 1.92, 7a/s = 1.30, endo = 1.30, exo = 1.50 ppm) ^B Ref. 7. ^C Obs. SCS cf. 3-endo- and 3-exo- bromo- and iodo-camphor. Ref. 8.

Considering the uncertainties in the experimental SCS due to signal overlap at the 1,2,4 and 6 positions in the 3-halo-androstanes (Table 6) the calculated SCS are encouraging. On the 5-position protons where the experimental data is more reliable in the 3 α -halo substituent the scheme predicts the SCS extremely well.

Table 6: Observed^A vs. calculated^B SCS (ppm) for bromo- and iodo-androstanes.

Proton	X = Br				X = I			
	3 α -		3 β -		3 α -		3 β -	
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.
1 α	0.65*	0.55	0.16	0.05	0.64*	0.52	0.16	0.03
1 β	-0.13*	-0.05	0.06	0.11	-0.14*	-0.05	-0.09	0.09
2 α	0.49*	0.51	0.69*	0.52	0.47*	0.66	0.68*	0.66
2 β	0.49*	0.55	0.51*	0.54	0.24*	0.70	0.79*	0.69
3 α	-	-	2.80	2.95	-	-	2.93	3.03
3 β	3.05	2.94	-	-	3.26	3.04	-	-
4 α	0.43*	0.51	0.58*	0.51	0.48*	0.65	0.72*	0.65
4 β	0.43*	0.52	0.58*	0.52	0.21*	0.67	0.72*	0.66
5 (CH)	0.72	0.69	0.12	0.04	0.68	0.67	0.11	0.02
6 α	0.03*	0.03	0.08*	0.03	0.06*	0.02	0.05*	0.02
6 β	0.03*	-0.01	0.08*	0.03	0.06*	0.00	0.05*	0.02
7 α	0.09	0.03	-0.01	0.01	0.12	0.02	-0.01	0.01
7 β	0.02	0.01	0.01	0.03	0.03	0.01	0.01	0.02
8 (CH)	0.02	0.00	0.00	0.02	0.03	0.00	-0.01	0.01
9 (CH)	0.18	0.04	-0.02	0.02	0.18	0.02	-0.03	0.02
11 α	0.02	0.01	-0.05	-0.01	0.03	0.01	-0.07	-0.01
11 β	0.02	-0.01	0.05	0.02	0.02	-0.01	0.03	0.02
12 α	0.04	0.02	0.00	0.00	0.04	0.01	-0.02	0.00
12 β	0.03	0.00	0.01	0.01	0.02	0.00	0.00	0.01
14 (CH)	0.04	0.02	-0.02	0.01	0.05	0.01	-0.02	0.01
15 α	0.03	0.01	0.00	0.00	0.04	0.01	-0.01	0.00
15 β	0.00	-0.01	0.00	0.00	0.01	0.00	-0.01	0.00
16 α	0.04	0.00	0.02	0.00	0.03	0.00	0.01	0.00
16 β	-0.02	0.00	-0.02	0.01	-0.01	0.00	-0.03	0.01
17 α	-	0.01	-	0.00	-	0.01	-	0.00
17 β	-	0.00	-	0.01	-	0.00	-	0.01
18-Me	0.00	0.00	0.00	0.00	0.00	0.00	-0.01	0.00
19-Me	0.01	0.01	0.07	0.03	0.02	0.01	0.07	0.02

* Unresolved. ^A Obs. SCS cf. 3 α - and 3 β - bromo- and iodo-androstan-17-one, Ref. 4. ^B Calc. SCS cf. 3 α - and 3 β - bromo- and iodo-androstan-17-one vs. 5 α -androstan-17-one (Ref. 10).

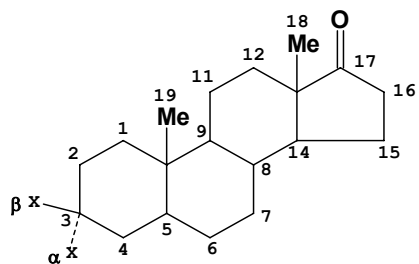
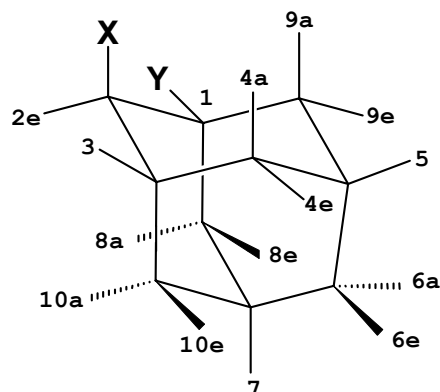


Table 7: Observed vs. calculated^A SCS for bromo- and iodo- adamantanes.

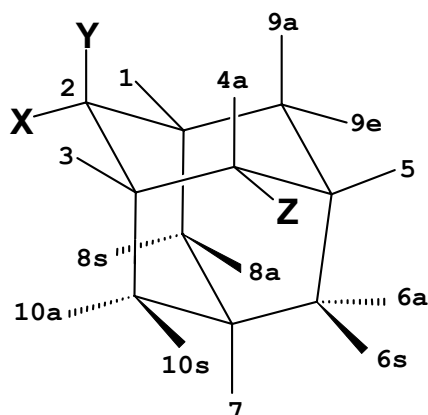


Proton	1-Halo-				2-Halo-				
	X=H, Y=Br		X=H, Y=I		X=Br, Y=H		X=I, Y=H		
	Obs. ^B	Calc.	Obs. ^C	Calc.	Obs. ^B	Calc.	Obs. ^D	Calc.	
2,8,9	0.62	0.51	0.88	0.65	1,3 (CH)	0.28	0.26	0.29	0.33
3,5,7 (CH)	0.23	0.09	0.10	0.07	2 (CH)	2.92	2.67	3.25	2.73
4,6,10-ax	-0.02	0.06	0.11*	0.04	4,9-ax	0.59	0.64	0.63	0.62
4,6,10-eq	-0.02	0.06	0.11*	0.05	4,9-eq	-0.13	-0.12	-0.04	-0.10
					5 (CH)	0.01	0.06	0.03*	0.05
					6	-0.01	0.03	0.04	0.03
					7 (CH)	0.01	0.06	0.03*	0.04
					8,10-ax	0.22	0.19	0.20*	-0.02
					8,10-eq	0.11	0.07	0.20*	0.04

* Unresolved. ^A Calc. SCS cf. adamantane (CH=1.98, CH₂=1.35 ppm). ^B Obs. SCS cf. Ref. 6. ^C Shifts cf. Ref. 24, SCS cf. adamantane Ref. 25. ^D Shifts cf. Ref. 26, SCS cf. adamantane Ref. 25.

In 2-bromoadamantane (Table 7) both the calculated γ SCS (calc. +0.26, obs. +0.28 ppm) and the steric effects on the 4,9-ax (calc. +0.64, obs. 0.59 ppm) and push-pull on the 4,9-eq (calc. -0.12, obs. -0.13 ppm) demonstrate the applicability of these terms to the caged structures. The calculated electric field effects on the 8,10 position protons are also in very good agreement with the observed SCS.

Table 8: Observed^A vs. calculated^B SCS for dibromo- and diiodo- adamantanes.



Proton	2(ax),4(eq)-dihalo-				2(eq),4(eq)-dihalo-				
	X=H, Y/Z=Br		X=H, Y/Z=I		X/Z=Br, Y=H		X/Z=I, Y=H		
	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	
1 (CH)	0.28	0.32	0.23	0.37	1,5 (CH)	0.28	0.32	0.31	0.37
2-eq (CH)	2.98	2.74	3.21	2.76	2,4-ax (CH)	2.75	2.67	3.14	2.67
3 (CH)	0.54	0.51	0.43	0.65	3 (CH)	0.51	0.51	0.49	0.65
4-ax (CH)	3.40	3.41	3.73	3.48	6,8-anti	-0.12	-0.08	-0.02	-0.08
5 (CH)	0.28	0.32	0.27	0.38	6,8-syn	0.60	0.69	0.65	0.66
6-anti	-0.13	-0.08	-0.07	-0.08	7 (CH)	-0.02	0.12	-0.02	0.09
6-syn	0.49	0.69	0.61	0.66	9-ax	0.16	0.03	0.40*	-0.04
7 (CH)	-	0.12	-	0.09	9-eq	0.45	0.14	0.40*	0.08
8-anti	0.18*	0.10	0.20*	0.06	10	0.50	0.57	0.61	0.55
8-syn	0.18*	0.05	0.20*	0.01					
9-ax	0.71	0.63	0.76	0.59					
9-eq	0.12	-0.02	0.10	-0.04					
10-anti	-0.02	-0.11	0.15	-0.14					
10-syn	0.69	0.75	0.80	0.70					

* Unresolved. ^A Shifts Ref. 27, SCS cf. adamantane Ref. 25. ^B Calc. SCS cf. adamantane (CH=1.98, CH₂=1.35 ppm).

The average and rms errors of the observed vs. calculated SCS for the cyclic bromo-alkanes studied are 0.07 and 0.10 ppm over the 118 parameterised data points. For the 96 parameterised data points in cyclic iodo-alkanes the average and rms errors are only slightly worse at 0.09 and 0.14 ppm.

Contributions to the Proton SCS in Halocyclohexanes

The above excellent agreement of the observed and calculated bromine and iodine SCS clearly demonstrates the general applicability of the scheme to the calculation of proton chemical shifts in halo-substituted alkanes. This agreement allows us to consider in more detail the proton chemical shifts in all the halocyclohexanes. The observed shifts are shown in Figure 1 and the observed and calculated SCS are given in Table 9. The CHARGE scheme predicts the halogen SCS to within a rms of 0.088 ppm over the 62 data points in Table 9 (excluding the H2ax/H2eq in axial iodo-cyclohexane). While a better fit may be possible for the above data points alone, the scheme represents an average over a range of molecular systems and as such the conclusions derived herein should be applicable to a wide range of haloalkanes.

Table 9: Experimental and calculated SCS in axial and equatorial halocyclohexanes.

Substituent	H		F		Cl		Br		I	
	Expt.	Calc. ^A	Expt.	Calc. ^B	Expt.	Calc. ^C	Expt.	Calc. ^D	Expt.	Calc. ^D
<u>Axial halogen</u>										
1-eq	1.68	1.69	3.26	3.41	2.91	2.80	3.13	3.96	3.28	3.05
2-ax	1.19	1.11	0.24	0.30	0.57	0.42	0.62	0.53	0.34	0.68
2-eq	1.68	1.69	0.35	0.29	0.32	0.43	0.40	0.52	0.38	0.67
3-ax	1.19	1.11	0.44	0.37	0.58	0.51	0.60	0.58	0.53	0.56
3-eq	1.68	1.69	0.06	0.06	-0.13	-0.04	-0.08	-0.05	-0.07	-0.05
4-ax	1.19	1.11	0.09	0.02	0.07	0.02	0.05	0.01	0.07	0.01
4-eq	1.68	1.69	-0.10	0.07	0.07	0.07	0.10	0.07	0.05	0.06
<u>Equatorial halogen</u>										
1-ax	1.19	1.11	3.30	3.42	2.67	2.78	2.90	2.95	2.99	3.03
2-ax	1.19	1.11	0.23	0.26	0.39	0.41	0.56	0.52	0.78	0.67
2-eq	1.68	1.69	0.47	0.29	0.54	0.43	0.65	0.53	0.77	0.67
3-ax	1.19	1.11	0.09	0.09	0.14	0.06	0.16	0.05	0.17	0.03
3-eq	1.68	1.69	0.18	0.14	0.16	0.12	0.12	0.10	-0.01	0.08
4-ax	1.19	1.11	-0.07	0.11	0.00	0.09	0.03	0.07	0.10	0.05
4-eq	1.68	1.69	-0.03	0.09	-0.01	0.08	0.04	0.07	0.12	0.06

^A Chemical shifts, cf. Ref. 10 ^B Ref. 11. ^C Ref. 1. ^D this work.

On the basis of this good agreement it is possible to examine the relative size of the various contributions to the proton chemical shift of halocyclohexanes. It is first necessary to

consider the contributions for cyclohexane itself and these are given in Table 10 taken from Ref. 10.

Table 10: Contributions to the calculated shifts of the protons in cyclohexane¹⁰.

Contribution	Proton axial	equatorial
Charge	1.550	1.550
H..H steric	-0.188	0.000
C-C anisotropy	-0.168	0.141
C-H linear electric field	-0.086	0.000
Total calculated	1.11	1.69
Experimental	1.19	1.68

Note that the calculated charge density is the same for the axial and equatorial protons. This is because the inductive term in CHARGE4 is non-orientational, thus the value for axial or equatorial protons with the same connectivity to either axial or equatorial substituents or the ring carbons is identical. The only other effect on the equatorial protons is the C-C anisotropy contribution which remains unchanged on substitution. In contrast the axial protons experience C-C anisotropy, H..H steric and C-H electric field contributions and the latter two will of course be removed with the introduction of an axial substituent. Thus the effect of ‘removing’ an equatorial hydrogen is zero, but the effect of removing an axial hydrogen is to decrease the shielding of the remaining axial protons.

Charge contributions. The calculated through bond contributions to the chemical shift of halocyclohexanes are given in Figure 2. For the β (CHX) protons i.e. 1ax and 1eq the chemical shifts are not in the order of the electronegativity of the halogen atom but for both the axial and equatorial substituents the order is $F > I > Br > Cl$ (Figure 1). This was noted earlier for the average chemical shifts of the β methine protons in halocyclohexanes at room temperature and attributed to an increase in the contribution of possible resonance forms². In the CHARGE4 scheme this ordering is catered for by two opposing through bond effects. The β charge term is given by a general electronegativity term^{9,28} with an explicit correction for the heavy halogen

atoms in the order $I > Br > Cl$.

FIGURE 2

In contrast the deshielding effect of the halogen at the γ protons i.e. H2ax and H2eq increases in the order $F < Cl < Br < I$ for the equatorial conformer, but in the axial form H2eq is essentially constant at 2.04δ and H2ax is anomalous in axial iodo-cyclohexane (Figure 1). There is also no obvious orientational dependence of the γ SCS supporting the CHARGE4 treatment. In CHARGE4 the γ effect is proportional to the polarisability of the substituent and this simple relationship gives generally good agreement with the observed SCS.

For β and γ protons this is the only factor in the halogen SCS. There are small indirect ring deformation contributions amounting to ca. -0.03 to 0.02 ppm due to the variation of the other factors. For the more distant protons there is no charge effect of the substituent in CHARGE4 and the charge term has the cyclohexane ring value of 1.55 ppm. The SCS on these protons are thus due to the other contributions.

Steric contributions. The steric function (equation 3) does not operate on the β and γ protons, thus the only protons in cyclohexanes perturbed by the halogen substituent are H3,5ax in axial halo-cyclohexanes. For all the other axial protons the steric term is the cyclohexane H..H shielding at ca. -0.2 ppm, (Table 10). For the equatorial protons the natural cut-off (r_{\min}) results in no steric contributions. Steric deshielding of H3ax and push-pull shielding on H3eq results in $\delta_{eq} < \delta_{ax}$ for H3ax and H3eq in axial chloro-, bromo- and iodo-cyclohexane in contrast to the usual situation, mirroring the experimental data (Figure 1).

FIGURE 3

The X..H steric contribution in the 1,3 syn di-axial orientation increases with halogen size (Figure 3) from 0.00 ppm for fluorine to $+0.26$ ppm for iodine, but the total steric term on H3ax also includes one H..H shielding effect as one of the 1,3-syn diaxial H..H interactions in cyclohexane is replaced by an X..H deshielding term. Thus the overall effect for fluorine is shielding, but deshielding for the other halogens.

H3eq experiences a 'push-pull' effect which is a function of the deshielding effect on H3ax. Consequently, for fluorine this is zero, but for Cl, Br and I the proportionality constants

vary to give an approximately constant contribution at ca. -0.1 ppm.

Electric field contributions. In equation 2 the component of the electric field along the bond (E_z) is dependent upon the relative orientation of the C-X and H-C bonds, as well as the halogen atom charge and X..H distance. The charge on the halogen decreases in the order $F > Cl > Br > I$, and this should be the determining effect for any particular proton. In the equatorial conformer the SCS on the H3 and H4 protons are entirely due to the electric field term, thus these provide a good test of this calculation. For H3eq both the observed and the calculated SCS are in the expected order ($F > Cl > Br > I$) though the observed decrease is rather larger than that calculated. However the observed trend for the H3ax protons ($F < Cl < Br < I$) is reversed from that calculated. The H4 protons also show a similar opposing trend though here the SCS are small and subject to larger errors due to the complexity of the spectra in this region. Clearly other mechanisms are influencing these SCS and one possible explanation is that the steric effects of the heavy halogens may extend further than the r_{min} cut-off would predict. The CHARGE4 scheme uses cut-offs at 3.63, 3.78 and 3.92 Å for H..Cl, H..Br and H..I respectively whereas the corresponding H3ax..X distances are somewhat greater at ca 4.5 to 4.8 Å.

FIGURE 4

In axial halocyclohexanes the SCS is multifunctional with both the steric and electric field terms present thus it is only possible to examine the calculated electric field contribution (Figure 4). The closest 'long range' proton is H3ax and a steady decrease in the electric field contribution with decreasing charge is observed from 0.24 ppm for fluorine ($q = -0.213$ electrons) to 0.14 ppm for iodine ($q = -0.098$ electrons) (Figure 4a). For H3ax and H4ax the SCS also includes one C-H electric field contribution from the missing proton. This contribution is shielding at ca. -0.04 ppm per 1,3-syn C-H bond. For the equatorial protons the cut-off eliminates all C-H linear electric field contributions.

For the more distant protons the C-X electric field contribution is much smaller. The contribution to H3eq is virtually identical to H4eq and about twice that of H4ax. The increase in the C-X bond length down the group and variations in ring deformation due to the 1,3-syn diaxial halogen interactions, particularly for Cl vs. F, compensate for the charge decrease. Hence, the contribution for H3eq is ca. 0.05 to 0.06 ppm, and for H4ax ca. 0.02 to 0.03 ppm

for all halogen substituents.

A detailed account of the contributions to the SCS of H3ax and H3eq in axial halocyclohexanes is given in Table 11.

Table 11: Contributions to the SCS of the 3-ax and 3-eq protons in axial halocyclohexanes.

Contribution	Halogen	F	Cl	Br	I
<u>3-axial</u>					
C-X electric		0.237	0.201	0.178	0.136
X..H steric		0.000	0.151	0.228	0.258
Δ (C-H electric)		0.043	0.043	0.045	0.045
Δ (H..H steric)		0.092	0.099	0.111	0.107
Δ (C-C anisotropy)		0.000	0.011	0.015	0.013
Total calculated		0.371	0.505	0.578	0.558
Experimental		0.44	0.58	0.60	0.53
<u>3-equatorial</u>					
C-X electric		0.054	0.067	0.062	0.053
X..H push-pull		0.000	-0.113	-0.114	-0.103
Δ (C-C anisotropy)		0.001	0.004	0.002	0.004
Total calculated		0.055	-0.043	-0.050	-0.047
Experimental		0.06	-0.13	-0.08	-0.07

It can be seen that the removal of the proton by the axial substituent contributes a significant proportion of the SCS at ca. 0.12 ppm, and this should not be neglected in any comprehensive analysis of SCS effects. There is also a slight change in the C-C anisotropy contribution due to ring deformation. The electric field term is larger than the steric term for fluorine and chlorine, but for bromine and iodine this is reversed.

For H3eq in Table 11 the C-X linear electric field is of the opposite sign to the observed SCS for all but fluorine. However, the larger shielding push-pull contribution for the heavier halogen atoms gives the overall observed shielding.

The chloro-, bromo- and iodo- steric terms are compared in Figure 5. As expected the steric contribution has I>Br>Cl for any given distance. Some illustrative points are marked on

each curve representing increasing distances in the order: the 5-endo proton in 3-endo-halo-bornanes, the 3-axial proton in axial halocyclohexanes and the 7-syn proton in exo-halo-norbornanes. The calculated steric effect on H3ax is similar to that on H7syn, and this matches with the observed SCS. The chloro SCS^{1,9} for H3ax is +0.54 ppm and for H7syn +0.59 ppm.

FIGURE 5

In contrast H5endo is much closer to the halogen substituent with a larger calculated steric contribution, and the observed SCS is greater at +0.84 ppm. The distances for similar systems such as halo-trans-decalins and androstanes lie within the range shown above.

For the syn 1,3-diaxial protons the major contribution to the halo (X= Cl, Br and I) SCS is thus the steric contribution, although the C-X electric field contribution is not negligible. From Table 11 it can amount over half the value of the steric term, and the contribution from the removal of the proton needs also to be accounted for. The effect on close through space protons in Figure 5 ($< 2.6\text{\AA}$) is calculated to increase rapidly, although this remains to be substantiated by experimental data.

The importance of the linear electric field is thus evident for the other 'long range' protons, as the steric function has an intrinsic cut-off. This agrees with the analyses of Schneider on trans-decalins and steroids. Whether the electric field term is subject to some shielding effect due to obstructing bonds would require a more extensive analysis. The 4 position protons in fluoro-cyclohexane (see Table 9) are in poor agreement with the calculated SCS and neglecting any electric field term would improve the fit. There may be solvent effects¹¹ in this case as reaction electric field effect would be greatest for the substituent with the largest halogen charge but in general solvent effects are expected to be minimal as all samples were run in low concentration in non-polar solvents (50:50 CDCl₃:CFC₃).

Discussion

Bothner-By and Naar-Colin² have noted unusual SCS on β protons in isopropyl and cyclohexyl halides (RR'CHX) which were inconsistent with the halogen electronegativity alone. They attributed this in part to the increase of the contribution of possible resonance forms. Further, the importance of these forms would increase "with increasing atomic number of the

halogen and with increasing branching on the α -carbon.” This effect is reproduced in this study, and accounted for by an enhancement of the bromine and iodine β effects on methine protons, and for iodine on methylene protons. Such effects are greater for iodine than for bromine, and the effect of two beta carbons (RR'CHX) greater than for one (RCHXY).

This argument may also be applied to the γ protons, although only the unusual 10 position proton SCS effects in 9-bromo- and 9-iodo-trans-decalin show obvious shielding. Here, the α and β -carbons across the bridge are surrounded by the maximum number of carbons i.e. X-C(R)(R')-C(R'')(R''')-H increasing steric compression² and possibly these contributions.

Determination of the bromine and iodine steric coefficients, along with the chlorine¹, and average hydrogen and carbon¹⁰ values allows comparison with previously derived van der Waal's terms. Abraham and Holker²⁹ calculated the intramolecular van der Waal's effect from a methyl group in 2-bromo-3-oxo-steroids using the intermolecular van der Waal's equation of Raynes et al.³⁰ (equation 4);

$$\sigma_{VDW} = -3B\alpha I / r^6 \quad (4)$$

where α and I are the polarisability and ionisation potential of the substituent. They derived a value of 163 ppm \AA^{-6} for the methyl group using a B value of 1.0×10^{-18} esu. Later determinations of the dispersion constant (B) by Tribble et al.³¹ empirically, and the shielding hyperpolarisability by Grayson and Raynes³² using finite-field SCS calculations, suggested values of 0.27 and 0.23×10^{-18} esu. These results suggest a more realistic value of $3B\alpha I$ of ca. 42 ppm \AA^{-6} .

For the polar substituents (Cl, Br and I) the a_s coefficients are 150.0, 255.0 and 405.0 ppm \AA^{-6} compared to ca. 100 ppm \AA^{-6} calculated by equation 4. These are of the same order of magnitude, in contrast to the quadratic electric field which produced results two orders of magnitude too small to account for the CHARGE4 steric term¹.

Further the ratios of the Cl, Br and I a_s coefficients of 1:1.7 :2.7 is similar to the ratios of the polarisabilities³¹ (1:1.54:2.55), but not the first ionisation energies³³ (1:0.91:0.82) again supporting the origin of this term as due to van-der-Waals interactions and not to the quadratic electric field.. This relationship could also be useful in determining the steric effect for other substituents where the polarisability of the atom is known.

In contrast to the results of equation 4 the shielding coefficient for carbon has an

average value of 260.0 ppm Å⁻⁶. One problem with this comparison is the interdependence of the carbon and hydrogen coefficients, since both terms are invariably involved in methyl group effects. In the CHARGE4 scheme the H..H steric interactions are *shielding* in contrast to a *deshielding* effect predicted from equation 4. Thus the carbon a_s value would be expected to be more deshielding than the sum of the coefficients, 3BαI from equation 4.

The decrease in the size of the push-pull coefficient for the halogen atoms (Cl = 75%, Br = 50% and I = 40%) may be a consequence of the increased polarisability of the atom. Alternatively, the angle between the halogen atom and the affected H-C-H bond may be important. For instance, in 2-exo-halo-norbornanes¹⁴ the X-H_{7s}-C₇ angle increases from 97.6° for the chloro substituent to 100.0° for bromine and 101.6° for iodine, partly as a consequence of the increased C-X (X= Cl, Br and I) bond length. However, more data would be needed to substantiate this hypothesis.

Conclusion

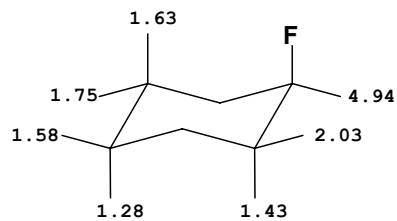
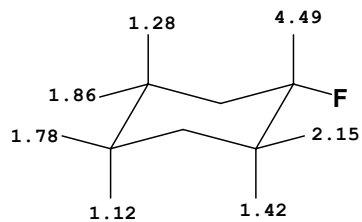
The CHARGE4 scheme has been successfully extended to calculate the proton chemical shifts of bromo- and iodo-alkanes. The charge contribution to the halogen SCS is dominant for β and γ protons. For more distant protons the largest contribution is the C-X steric term when the proton is in a syn-1,3-diaxial arrangement to the halogen. For other distant protons the C-X electric field term is dominant. However, a complete analysis requires a combination of all three terms.

Acknowledgements

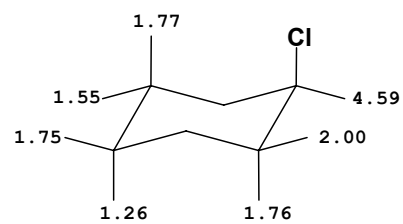
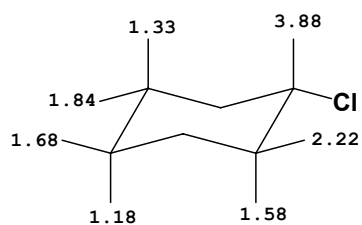
We thank ZENECA Pharmaceuticals Ltd for a fully funded research studentship (M.A.W.), and we pleased to acknowledge the assistance of Dr. P. D. Mallinson and the University of Liverpool central computing facility for the operation of GAUSSIAN92 and 94.

Figure 1: Experimental (Ref. 1, 11 and this work) proton chemical shifts in (a) fluoro- (b) chloro- (c) bromo- and (d) iodo-cyclohexanes.

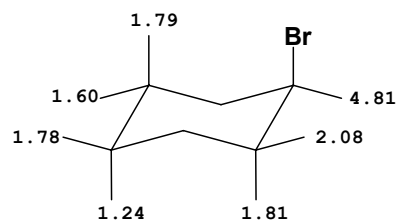
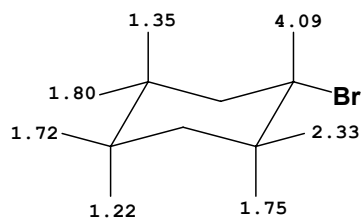
(a)



(b)



(c)



(d)

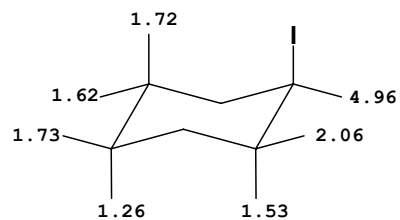
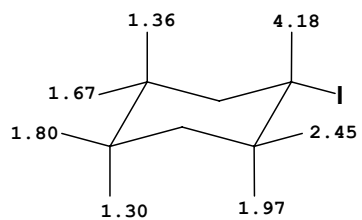
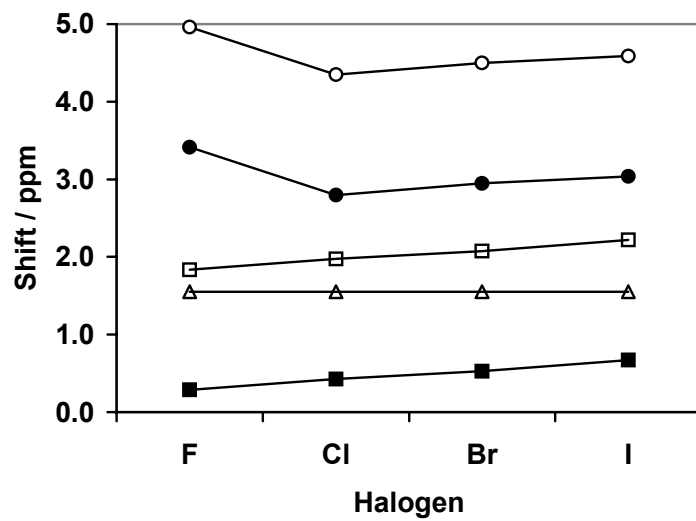
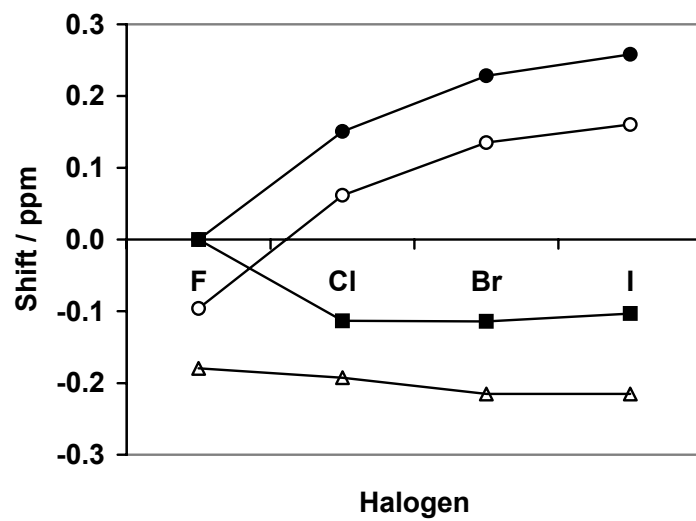


Figure 2: The charge contribution to the chemical shift of cyclohexanes.



Charge contributions: (o) δ total charge [1ax/1eq], (•) δ halogen charge [1ax/1eq], (□) δ total charge [2ax/2eq], (Δ) δ total charge [3ax/3eq/4ax/4eq], and (■) δ halogen charge [2ax/2eq].

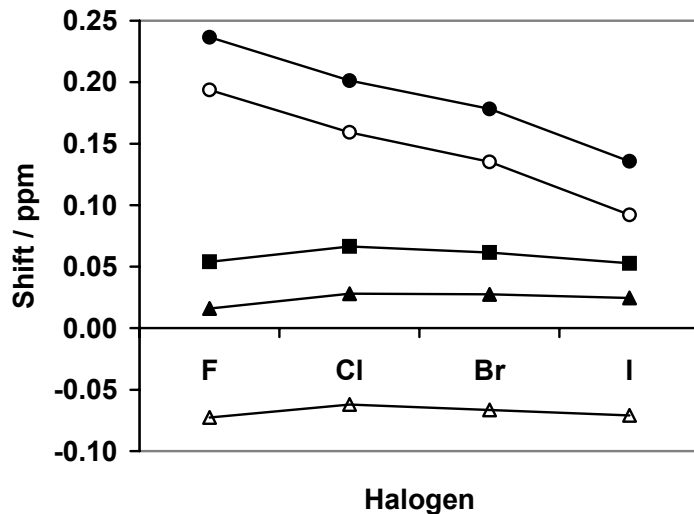
Figure 3: The steric and push-pull contributions to the chemical shift of halocyclohexanes.



Steric contributions: (●) δ X..H steric [3ax], (○) δ total steric [3ax], (■) δ X..H push-pull [3eq], and (△) δ total steric [4ax].

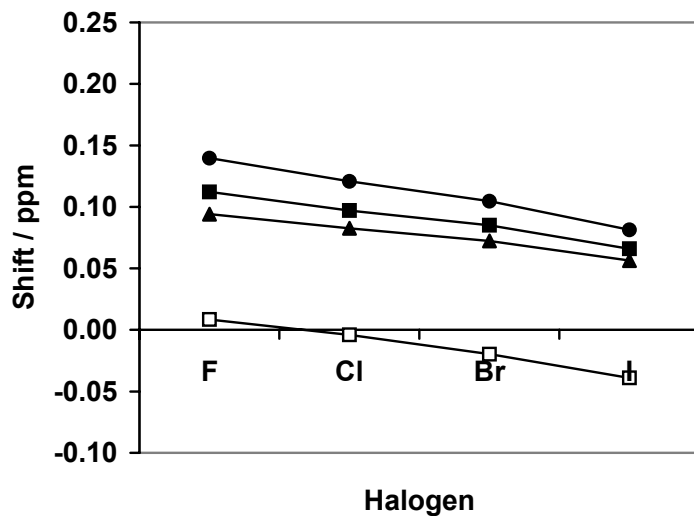
Figure 4: The linear electric field contributions to the chemical shift of (a) axial and (b) equatorial halocyclohexanes.

(a)



Electric field contributions: (●) δ C-X electric [3ax], (○) δ total electric [3ax], (■) δ C-X electric [3eq], (▲) δ C-X electric [4ax], and (△) δ total electric [4ax].

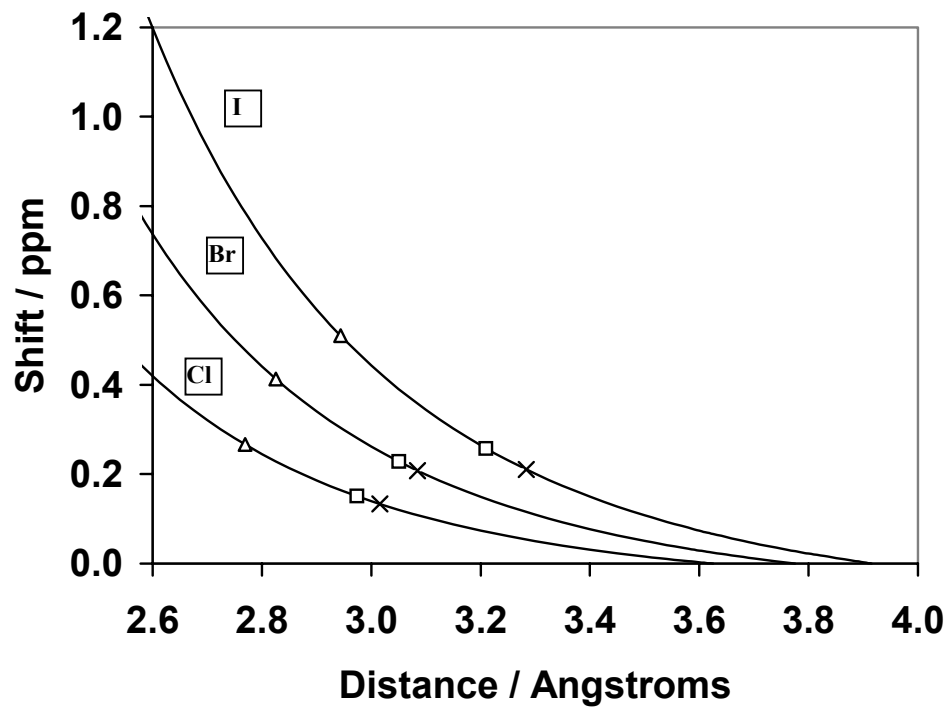
(b)



Electric field contributions: (●) δ C-X electric [3eq], (□) δ C-X electric [3ax], (▲) δ C-X electric [4eq], and (△) δ total electric [3ax].

Figure 5: The steric contribution to the chemical shift as a function of the X..H distance for

chlorine (bottom line), bromine (middle line) and iodine (top line).



Protons marked: (Δ) $H_{5\text{-endo}}$ in 3-endo-halo-bornanes, (\square) $H_{3\text{-axial}}$ in axial-halo-cyclohexanes, and (\times) $H_{7\text{-syn}}$ in exo-halo-norbornanes.

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