PERKIN 2

Proton chemical shifts in NMR. Part 9.[1] Steric and electric field effects in chlorine substituent chemical shifts (SCS)

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A model for the prediction of the proton chemical shifts of chloroalkanes is given and applied to a variety of chloro compounds. These include chloro- and 1,1-dichloro-cyclohexane for which the proton spectra have been obtained and the individual proton chemical shifts assigned at −80 °C where the ring inversion is slowed sufficiently to give the spectra of the individual conformers. The proton spectra of 1-chloro- and 2-chloro-adamantane are also reported and completely assigned.

The chlorine 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. The long range (>three bonds) effects are shown to be due to the electric field of the C−Cl bond plus the steric effect of the chlorine atom.

This model (CHARGE4) predicts the proton chemical shifts of a variety of chloroalkanes over 70 data points spanning *ca.* 6.2 ppm with an rms error of 0.15 ppm. These compounds include chloroethanes, propanes, cyclohexanes, bornanes, norbornanes, adamantanes and steroids.

Analysis of the chlorine steric term shows that the quadratic term in the Buckingham equation is much too small to account for the observed steric effects which are considered to arise from van der Waal's interactions.

Introduction

Chlorine SCS in proton magnetic resonance have been investigated for many years, but the first comprehensive analysis of these effects was due to Zurcher.[2] He considered 12 methyl shifts in chlorosteroids, norbornyl chlorides and ethyl chloride and found that the data could be explained by the electric field effect of the C−Cl bond, but not by the C−Cl anisotropy or by the van der Waal's (*i.e.* steric) term. The one anomaly was the 10-CH_3 in 2-*endo*-chlorobornane which was ascribed to solvent effects.

Davis *et al.*[3] considered 23 methyl proton chemical shifts in chloro-androstanes and found that all but three could be fitted solely by the C−Cl electric field effect. The anomalies were the 1,3-*syn*-diaxial effects from 2β-, 4β- and 6β-chloroandrostanes on the 19-CH_3 protons where errors of *ca.* 0.3 ppm arose unless magnetic and electric field contributions were considered.

Gschwendtner and Schneider[4] presented data for ten shifts (seven methyl) in chlorocholestanes and esterenes and stated that 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. Later, Schneider *et al.*[5] studied 3α-chloroandrostane and 3α- and 3β-chloroandrostan-17-one, which provided more data than before but derived similar results. Schneider also noted that the chlorine SCS in 9-chloro-*trans*-decalin[6] were consistent with the steroid data, and thus predicted by electric field calculations alone.

Abraham *et al.*[7] obtained chlorine SCS in 2-chloro-bornane and -norbornane and noted that electric field plus either van der Waal's or anisotropy contributions were clearly evident as did Kaiser *et al.*[8] for 3-*endo*-chloro-, 3-*exo*-chloro- and 3,3-dichlorocamphor. The effects for the dichlorocamphor were also additive from the monochloro data for all except the nearest protons.

In a previous paper in this series[9] a model for the calculation of proton chemical shifts in complex molecules has been developed. This was based on the success of the partial atomic charges obtained by a semi-empirical treatment (CHARGE3) in predicting the proton chemical shifts of a variety of substituted methanes and ethanes in terms of 'through bond' α (1 bond), β (2 bond) and γ (3 bond) effects. The proton shifts in more complex molecules, *i.e.* over >three bonds, were interpreted in terms of a steric deshielding r^{-6} function plus a compensating 'push–pull' effect on the other methylene or methyl proton(s) not experiencing the direct steric effect to give a general account of proton chemical shifts.[9]

The central problem with all the above investigations is the multi-functional nature of the proton chemical shift and it was clear that a more rigorous analysis was required. More recently other mechanisms which could contribute to proton chemical shifts have been considered in detail. The effects of C−C anisotropy and of the methyl groups in complex hydrocarbons were evaluated to give an accurate calculation of proton chemical shifts in a variety of hydrocarbons.[10] Also, the linear electric field contribution of polar substituents was obtained by a detailed analysis of fluorine SCS in rigid molecules.[1] This treatment gave a value for the electric field coefficient (A_Z) in eqn. (1) 3.67×10^{-12} esu (63 ppm au), in excellent agreement

$$\delta_{\text{elec}} = \boldsymbol{A}_Z\boldsymbol{E}_Z + \boldsymbol{B}\boldsymbol{E}^2 \qquad (1)$$

with the most recent theoretical calculations[1] and thus allows the prediction of all electric field effects from the partial atomic charges on the substituents.

With these developments it is now possible to evaluate the more complex chlorine SCS which are examined here in detail and it will be shown that both electric field and van der Waal's (*i.e.* steric) contributions are necessary in order to fully explain these SCS.

Theory

In the CHARGE scheme[9] the effect of the substituent on atoms up to three bonds away was considered to be *via* through-bond effects. The *α* effect was dependent on the relative electronegativities of the atoms involved. The β effect is a function of both the electronegativity of the substituent and the polarisability of

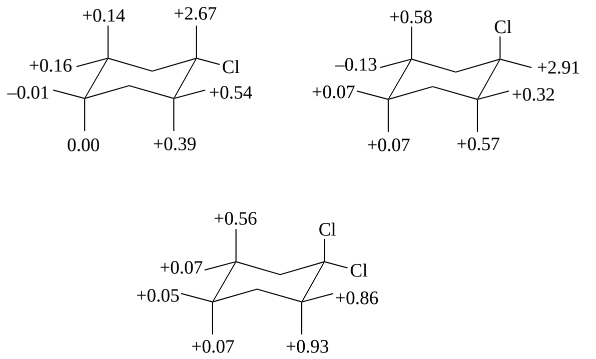


Fig. 1 Experimental (this work) chlorine SCS effects in chlorocyclohexanes

the atom affected. The γ effect was non-orientational and a function of the polarisability of the two atoms involved.

Mere inspection of the observed chlorine SCS data for cyclohexanes (Fig. 1), shows that while multiple substitution gives rise to aditive SCS, more than the simple linear electric field is involved. The chlorine SCS are larger than the corresponding fluorine SCS (*e.g.* H_{3a} in axial chlorocyclohexane 0.58 *vs.* 0.44 for fluorine[1]) even though the partial atomic charge on the chlorine atom is much less than that on the fluorine. Furthermore, the deshielding of H_{3a} and corresponding shielding of H_{3e} in axial-chlorocyclohexane is consistent with the push–pull effect and this suggests that steric interactions are involved.

To evaluate the steric effects of the chlorine substituent the simple r^{-6} term used earlier for chlorine was replaced by a similar function to that used previously for proton and carbon[9,10] [eqn. (2)] where r_{min} is the sum of the van der Waal's radii of the

$$\delta_{\text{steric}} = a_S(1/r^6 - 1/r_{\text{min}}{}^6) \qquad (2)$$
$$\delta_{\text{steric}} = 0 \text{ for } r \geqslant r_{\text{min}}$$

interacting atoms. The value of the van der Waal's radius for chlorine was taken from ref. 11 as 2.03 Å. Eqn. (2) has the computational advantage of a natural cut-off at $r = r_{\text{min}}$ thus preventing a large number of very small contributions being calculated.

Experimental

1-Chloroadamantane and chlorocyclohexane were obtained from Aldrich Ltd. and 2-chloroadamantane and 1,1-dichlorocyclohexane were obtained by literature preparations.[12,13] The solvents were obtained commercially, stored over molecular sieves and used without further purification.

^{1}H spectra were obtained on a Bruker AMX 400 spectrometer operating at 400.14 MHz for *ca.* 10 mg ml^{-1} solutions and with a probe temperature of *ca.* 25 °C, and referenced to $SiMe_4$. Typical conditions were: proton spectra 64 transients, spectral width 3100 Hz with 32 K data points, giving an acquisition time of 5 s and zero filled to 128 K to give a digital resolution of 0.025 Hz.

The geometries used in these calculations were obtained using *ab initio* theory with full geometry relaxation at the RHF/6-31G* level of theory.[14] For the C–Cl bonds the calculated bond lengths for chloroethane, axial- and equatorial-chlorocyclohexane of 1.799, 1.812 and 1.821 Å compare well with the observed bond lengths[15] of 1.802, 1.804 and 1.808 Å respectively. The C–Cl axial bond is slightly too long suggesting that the *ab initio* calculations may overestimate the through space steric interactions, but the relative energy difference between the axial and equatorial forms of 1.0 kcal mol^{-1} (1 cal = 4.184 J) compares favourably with the experimental values[16] of 0.34 to 0.65 kcal mol^{-1}.

Table 1 Proton and carbon chemical shifts (δ) of chlorocyclohexane in 50:50 $CDCl_3$–$CFCl_3$

Proton				Carbon		
	Room temp.	−85 °C			−85 °C	
Temp.	Average	Eq-Cl	Ax-Cl		Eq-Cl	Ax-Cl
1a	3.964	3.879	—	C_1	60.74	60.87
1e	—	—	4.585	C_2	37.37	33.70
2,6a	1.661	1.581	1.762	C_3	26.46	19.95
2,6e	2.058	2.218	1.997	C_4	24.68	25.61
3,5a	1.366	1.327	1.77[a]			
3,5e	1.812	1.838	1.55[a]			
4a	1.318	1.180	1.26[a]			
4e	1.544	1.678	1.750			

[a] Chemical shift *cf.* ^{1}H–^{13}C correlations.

Table 2 Observed *vs.* calculated proton chemical shifts (δ) for acyclic chloroalkanes

Molecule		Expt.[a]	CHARGE4
CH_3Cl	CH_3	3.05	3.12
CH_2Cl_2	CH_2	5.33	5.27
$CHCl_3$	CH	7.27	7.00
CH_3CH_2Cl	CH_2	3.57[b]	3.51
	CH_3	1.49	1.49
CH_3CHCl_2	CH	5.87[c]	5.72
	CH_3	2.23	2.12
CH_3CCl_3	CH_3	2.75	2.72
CH_3ClCH_2Cl	CH_2	3.69	3.85
$CH_2ClCHCl_2$	CH	5.74	5.85
	CH_2	3.97	4.18
$CHCl_2CHCl_2$	CH	5.94	5.99
CCl_3CHCl_2	CH	6.12[c]	6.12
$CH_3CH_2CH_2Cl$[d]	CH_2Cl	3.47[c]	3.58 (g), 3.44 (t)
	CVH_2	1.81	1.74 (g), 1.74 (t)
	CH_{23}	1.06	0.99 (g), 0.95 (t)
$(CH_3)_2CHCl$	CH	4.13	4.30
	CH_3	1.54	1.54
$C(CH_3)_3Cl$	CH_3	1.58	1.57

[a] Ref. 23 unless stated. [b] Ref. 24. [c] Ref. 25. [d] (*g*) *gauche*, (*t*) *trans* conformer.

Assignments

Chlorocyclohexane. The room temperature spectrum of chlorocyclohexane consists of the weighted average of the equatorial and axial chloro-conformer, with the equilibrium favouring the former. The spectrum consists of six multiplets with the 3-ax and 4-ax protons (defined by the position in the major equatorial chlorine conformer) overlapping.

In a 50:50 mixture of $CDCl_3$ and $CFCl_3$ at −80 °C the ring flipping was halted and no change was observed to −90 °C. The assignment of the equatorial isomer (80%) was initially based upon observation of the splitting pattern and confirmed by an COSY–DQF at −85 °C, and where there is overlap is in agreement with the assignments[17] of β and γ protons in [2,2,3,3,4,4,5,5-$^2H_8$]chlorocyclohexane.

The assignment of the minor axial conformer (20%) was complicated by the considerable overlap with the major form. The 1-eq, 2-eq and 2-ax multiplets were observable and defined by the COSY–DQF. Here, the 2-ax proton large triplet is partly obscured by an equatorial proton of the minor form. By integration this multiplet consisted of three protons in total identifying this as the 4-eq proton. Further, only one peak of the 4-ax proton is barely visible between the 3-ax and 4-ax multiplets of the major form. The positions of the shifts of the 3-ax, 3-eq and 4-ax protons were obtained from a HETCORR run at −85 °C. However, this leaves the assignment of the 3-ax and 3-eq protons which were based upon comparison with SCS data in *trans*-decalin and steroid analogues.[5,6,18]

Table 3 Observed[a] *vs.* calculated (CHARGE4, CH4) proton chemical shifts (δ) and SCS (ppm) for chlorocyclohexanes

	Chemical shift						SCS[b]					
	Equatorial		Axial		1,1-Dichloro		Equatorial		Axial		1,1-Dichloro	
Proton	Expt.	CH4	Expt.	CH4	Expt.	CH4	Expt.	CH4	Expt.	CH4	Expt.	CH4
1a (CH)	3.88	3.88	—	—	—	—	2.67	2.76	—	—	—	—
1e (CH)	—	—	4.59	4.49	—	—	—	—	2.91	2.80	—	—
2,6a	1.58	1.51	1.76	1.53	2.12	1.92	0.39	0.41	0.57	0.42	0.93	0.81
2,6e	2.22	2.12	2.00	2.12	2.54	2.52	0.54	0.43	0.32	0.43	0.86	0.83
3,5a	1.33	1.17	1.77	1.61	1.75	1.64	0.14	0.06	0.58	0.51	0.56	0.53
3,5e	1.84	1.81	1.55	1.65	1.75	1.68	0.16	0.12	−0.13	−0.04	0.07	−0.02
4a	1.18	1.20	1.26	1.13	1.24	1.17	0.00	0.09	0.07	0.02	0.05	0.07
4e	1.68	1.77	1.75	1.77	1.75	1.79	−0.01	0.08	0.07	0.07	0.07	0.10

[a] This work. [b] Calc. SCS *cf.* cyclohexane (ax = 1.11, eq = 1.69 ppm).

Table 4 Observed[a] *vs.* calculated proton chemical shifts (δ) and SCS (ppm) for 9-chloro-*trans*-decalin

	Chemical shift			SCS[b]		
		CHARGE4[c]			CHARGE4[c]	
Proton	Expt.[b]	6-31G*	*T*dec.	Expt.	6-31G*	*T*dec.
1,8a	1.46	1.29	1.43	0.53	0.28	0.42
1,8e	1.92	2.05	2.04	0.38	0.43	0.42
2,7a	1.87	1.77	1.85	0.62	0.61	0.68
2.7e	1.56	1.65	1.57	−0.11	−0.10	−0.18
3,6a	1.27	1.16	1.18	0.02	0.00	0.01
3,6e	1.73	1.81	1.81	0.06	0.06	0.06
4,5a	1.46	1.69	1.73	0.53	0.67	0.71
4,5e	1.30	1.51	1.43	−0.08	−0.12	−0.20
10 (CH)	1.26	0.93	1.07	0.38	0.06	0.20

[a] Shifts *cf.* ref. 18, SCS *cf. trans*-decalin ref. 10. [b] Calc. SCS *cf. trans*-decalin (1/4/5/8a = 1.02,. 1/4/5/8e = 1.63, 2/3/6/7a = 1.17, 2/3/6/7e = 1.75, 10 = 0.87 ppm). [c] 6-31G* = RHF/6-31G* full geometry optimisation. *T*dec. = *trans*-decalin base geometry + 9-Cl substituent.

Interestingly, the room temperature shifts based upon the ^{2}H 1D-TOCSY experiment[19] gave the assignment of 2-ax and 3-eq protons as the reverse of those in Table 1. However, observation of the proton coupling pattern clearly assigns the multiplet at 1.66 ppm as predominantly axial.

1-Chloroadamantane. The spectrum consists of two multiplets at δ 1.676 and 2.140 of integration 2:3 due to the overlap of the 4,6,10-axial/4,6,10-equatorial and 2,8,9/3,5,7 protons respectively. These were still unresolved at 400 MHz as a previous study[20] at 60 MHz had found.

2-Chloroadamantane. The spectrum is similar to that of bromoadamantane[21] except that the E (8,10-ax) protons no longer overlap with the G/H (5,7) proton multiplet. Assignments were based accordingly. They are in agreement with literature values[22] run at 60 MHz, except the E/F/G/H (5,7/8,10-ax) protons are now distinguishable.

1,1-Dichlorocyclohexane. The room temperature chemical shifts of 1,1-dichlorocyclohexane in 50:50 $CDCl_3$–$CFCl_3$ were at δ 2.302, 1.720 and 1.471 of integration 2:2:1 for the average of the 2, 3 and 4 protons respectively. At −80 °C the ring inversion is in slow exchange and the individual chemical shifts resolved with no further change observed to −90 °C. The assignment of axial or equatorial protons were made on the basis of the splitting patterns. The 3-ax and 3-eq protons showed no separation even after coalescence, and this pattern was further complicated by the coincidence with the 4-eq multiplet.

Results

The scheme was thus parametrised using the C−Cl linear electric field effect on distant protons (δ and beyond) with the A_Z coefficient of 63 ppm au as determined previously, along with the van der Waal's r^{-6} term and push–pull effect. It was noted that the CHARGE scheme slightly underestimated the deshielding effect of the chlorine substituent on methine protons and this term was increased by 8% for methine protons. Since the electric field effect is predetermined by the charge on the atoms as calculated within CHARGE4, the only adjustable term was the C−Cl steric effect [eqn. (2)]. The best value of a_s was determined by a lowest rms fit of the observed data. This gave a value of a_s of 150.0. It was further noted that the shielding push–pull effects from the chlorine steric interactions were cancelled out by the deshielding linear electric field contribution, resulting in essentially no long range effects on these methylene protons *e.g.* 3e-H in axial-chlorocyclohexane. The chlorine push–pull coefficient for methylene protons was thus enhanced from 50 to 75%, to give the observed shielding effects.

The observed and calculated proton chemical shifts and SCS for chloroalkanes are given in Tables 2–9. In Table 2 the values for both the *trans* and *gauche* conformers of 1-chloropropane are given, but in the case of 1,2-dichloro-, 1,1,2-dichloro- and 1,1,2,2-tetrachloro-ethane the shifts for both conformers are the same, due to the non-orientational nature of the through bond γ effect.

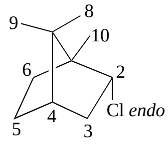
The initial calculated shifts for 9-chloro-*trans*-decalin (Table 4) were inconsistent with those for the axial-chloro-cyclohexane analogue (Table 3), in particular for the 1,8a (and 10) positions. Namely, the SCS effect for 2,6-ax proton in the chlorocyclohexane was calculated at +0.42 ppm, but the 1,8-ax proton in the *trans*-decalin with the same stereochemical position was calculated at only +0.28 ppm. Yet the observed SCS for these positions are almost identical (+0.53 ppm *vs.* +0.57 ppm). Clearly, the calculations for the 1,8a and 10 positions were unexpectedly shielded.

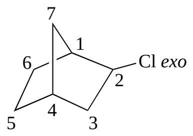
The same calculations were therefore performed using the RHF/6-31G* optimised unsubstituted *trans*-decalin geometry with a C−H bridge proton replaced by a C−Cl bond of the same length as calculated previously. This unstrained structure gave more realistic results for both 1,8a-H and 10-H. The results of CHARGE4 calculations for both of these geometries are given in Table 4.

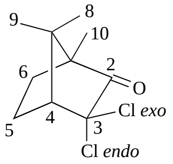
Since the unstrained (by the C−Cl bond) structure gives the closer agreement with the experimental shifts, which are also consistent with the cyclohexane value, it would appear this is the more valid geometry. The distortion of the *trans*-decalin ring caused by the 9-chloro substituent, presumably interacting with four parallel and close through space C−H bond protons, appears to be over-calculated by the RHF/6-31G* level. The consequential reduction in the H···H distances to 1a,8a-H and 10-H lead to the relative calculated increase in the shielding steric interactions, highlighting the sensitivity of the r^{-6} term to the chosen geometry.

The observed and calculated SCS in chlorobornanes and norbornanes ae given in Table 5. It should be noted that the

Table 5 Observed *vs.* calculated[a] SCS (ppm) for chlorobicyclo[2.2.1]heptanes







Proton	Bornane 2-*endo*-[b]		Norbornane 2-*exo*-[b]		Camphor 3*endo*-[c]		3-*exo*-[c]		3,3-Dichloro-[c]	
	Expt.	CH4	Expt.	CH4	Expt.	CH4	Expt.	CH4	Expt.	CH4
1 (CH)			0.20	0.21						
2*n*	—	—	2.71	2.65	—	—	—	—	—	—
2*x*	2.68	2.68	—	—	—	—	—	—	—	—
3*n*	0.22	0.46	0.75	0.44	—	—	2.03	2.52	—	—
3*x*	0.75	0.37	0.33	0.41	2.04	2.68	—	—	—	—
4 (CH)	0.08	0.10	0.12	0.11	0.22	0.22	0.16	0.22	0.58	0.43
5*n*	0.14	0.04	−0.09	0.09	0.73	0.90	−0.01	−0.15	0.93	0.88
5*x*	0.04	0.10	0.00	0.07	−0.16	−0.19	0.08	0.17	0.20	−0.12
6*n*	0.84	0.92	−0.02	0.01	−0.05	0.05	0.00	0.12	0.26	0.20
6*x*	−0.15	−0.21	0.14	0.11	0.06	0.10	−0.03	0.06	0.03	0.05
7a			0.06	−0.02						
7s			0.59	0.48						
8-Me	0.05	0.05			0.10	0.05	0.13	0.10	0.31	0.10
9-Me	0.05	0.04			0.11	0.04	0.01	0.03	0.15	0.03
10-Me	0.10	0.11			0.07	0.04	0.06	0.04	0.13	0.04

[a] Calc. SCS *cf.* bornane (2/6*n* = 0.97, 2/6*x* = 1.53, 3/5*n* = 1.09, 3/5*x* = 1.80, 4 = 1.75, 8/9-Me = 0.82, 10-Me = 0.99 ppm; *A* = *endo*, *x* = *exo*) or *cf.* norbornane (1/4 = 1.92, 7a/s = 1.30, *endo* = 1.30, *exo* = 1.50 ppm; a = *anti*, s = *syn*). [b] Ref. 7. [c] Expt. SCS *cf.* 3-*endo*-, 3-*exo*- and 3,3-dichlorocamphor. Ref. 8.

SCS for a single substituent derived from multi-functional compounds, as in the case of chlorocamphors, is dependent upon the non-interaction of the substituents.

Since the C=O group is adjacent to the C−Cl bond in 3-substituted camphors some interaction seems likely. The SCS effect of the β proton, *i.e.* the O=C−C*H*−Cl proton in 2-*endo*-bornane is +2.68 ppm, yet in 3-*endo*-camphor is only +2.04 ppm. The observed chlorocamphor SCS in Table 5 should be considered a less than definitive representation of the chlorobornane SCS effects.

The chlorine γ SCS in the bicycloheptanes in Table 5 appear anomalous around θ (∠HCCCl) *ca.* 120° (*cf.* 2*x*-H in 2-*endo*-chlorobornane, expt. +0.75 ppm *vs.* calc. +0.22 ppm). The experimental chlorine SCS for the 2-*endo*- and 2-*exo*-bicycloheptanes are +0.75 ppm (θ *ca.* 120°) which is much greater than the 0.2–0.3 ppm (θ *ca.* 0°). This chlorine effect is also observed[26] in acenaphthenes where the SCS = +0.46 ppm (θ *ca.* 120°) and +0.16 ppm (θ *ca.* 0°) and hexachlorobicyclo[2.2.1]heptanes, SCS = +0.59 ppm (θ *ca.* 120°) and +0.22 ppm (θ *ca.* 0°). Clearly, the non-orientational chlorine γ effect in the CHARGE4 scheme would not be expected to reproduce these effects.

In the case of the chloroandrostane data (Table 6) derived from 3-substituted-androstan-17-ones the interaction between the substituents would appear to be minimal. The validity of this presumption can be verified by comparison of the SCS data derived from 3α-chloroandrostane and 3α-chloro-androstan-17-one in Table 6.

The 1α and 1β protons were noted as overlapping signals, with reported SCS for 3α-chloro-androstane[5] as +0.23 ppm, yet the chemical shifts of 1α and 1β thus obtained are (0.89 + 0.23) 1.02 and (1.66 + 0.23) 1.89 ppm respectively, with a separation of 0.87 ppm between the protons. Clearly, this reported SCS is incorrect. The analogous SCS from 3α-chloro-androstan-17-one again reported[5] as overlapping signals gives chemical shifts for 1α at (0.89 + 0.60) 1.49 and for 1β also at (1.67–0.18) 1.49 ppm, confirming these that values are more reliable.

Apart from the above error the reported chlorine SCS from 3α-chloro-androstane and androstan-17-one are consistent. The distant protons agree within ±0.05 ppm, except for the 9-CH proton. The alkane SCS of +0.06 is less than half that from the ketone (+0.15), but is in agreement with the CHARGE4 calculations (+0.05 ppm).

The chlorine SCS on the *C* and *D* ring protons are similar to the analogous fluorine SCS data[1] in that they are more or less negligible at ±0.05 ppm.

The chlorine γ effects on 2-H, 9-H and 10-H in 1-chloro- and 1- and 3-H in 2-chloro-adamantane (Table 7) are remarkably good, and even the 3-H in the 2,4-dichloro-adamantanes (Table 8) with two γ effects appears additive and in agreement with the calculated values.

The long range effect in 2-chloro-adamantane (Table 7) of the deshielded sterically perturbed methylene proton (4,9-ax) and correspondingly shielded geminal proton (4,9-eq) shows the general applicability of the van der Waal's plus push–pull term to these systems. Similar effects are noted (see Table 8) in *trans*-2,4-dichloro-adamantane on the 10-*syn*/*anti*, 6-*syn*/*anti* and 9-ax/eq protons, and in the *cis*-2,4-conformer for the 6-*syn*/*anti* hydrogens.

Discussion

The generally good agreement between the observed and calculated chloride SCS is encouraging. Over the 70 parametrised chemical shifts spanning a range of δ of *ca.* 1.1 to 7.3 the CHARGE4 scheme fits the experimental data to an rms of 0.15 ppm, which is not much more than the combined errors in the observed data and in the calculations (*cf.* the 9-chloro-*trans*-decalin discussed earlier).

The value of the chlorine steric shielding coefficient (a_s) of 150.0 ppm $Å^{-6}$ is of some interest. This is slightly less than obtained previously (222.0 ppm $Å^{-6}$) using the simple r^{-6} term. This value allows us to examine the origins of the so called 'steric term', as this has been considered either as a distinct van der Waal's term or as the quadratic electric field effect. The latter given by Buckingham[29] on the δ scale is the BE^2 term in eqn. (1) which is also a function of the electric field squared (r^{-6}).

Table 6 Observed[a] *vs.* calculated[b] SCS (ppm) for chloro-androstanes

	3α-Chloro			3β-Chloro	
	Expt.[c]				
Proton	Alkane	Ketone	Calc. CHARGE4	Expt.[c] Ketone	Calc. CHARGE4
1α	0.23[d]	0.60[d]	0.49	0.13	0.07
1β	0.23[d]	−0.18[d]	−0.03	0.09	0.12
2α	0.36	0.42[d]	0.42	0.57[d]	0.43
2β	0.45	0.42[d]	0.43	0.31[c]	0.40
3α	—	—	—	2.63	2.75
3β	—	2.83	2.75	—	—
4α	0.37[d]	0.38	0.44	0.51	0.44
4β	0.51[d]	0.46	0.40	0.36	0.39
5 (CH)	0.64	0.67	0.61	0.10	0.03
6α	−0.02[d]	0.03[d]	0.00	0.06[d]	0.04
6β	−0.02[d]	0.03[d]	0.00	0.06[d]	0.05
7α	0.06	0.08	0.04	−0.01	0.01
7β	0.01	0.02	0.01	0.01	0.03
8 (CH)	0.00	0.01	−0.01	−0.01	0.02
9 (CH)	0.06	0.15	0.05	−0.03	0.00
11α	0.00	0.01	0.02	−0.05	0.01
11β	−0.01	0.01	0.00	0.03	0.02
12α	0.02	0.01	0.02	−0.01	0.00
12β	0.00	0.01	0.00	0.01	0.01
14 (CH)	0.02	0.02	0.02	−0.03	0.00
15α	0.00	0.02	0.01	−0.01	0.00
15β	0.00	0.01	−0.01	−0.01	0.01
16α	0.04[d]	0.02	0.01	0.00	0.00
16β	0.04[d]	−0.02	0.00	−0.02	0.01
17α	0.01	—	0.01	—	0.00
17β	0.01	—	0.00	—	0.01
18-Me	0.00	0.00	0.00	−0.01	0.00
19-Me	0.00	0.00	0.01	0.05	0.04

[a] Ref. 5. [b] Calc. SCS *cf.* 3α- and 3β-chloroandrostane *vs.* 5α-androstane, ref. 10. [c] Alkane = Expt. SCS *cf.* 3α-chloroandrostane. Ketone = Expt. SCS *cf.* 3α-chloro- and 3β-chloro-androstan-17-one. [d] Unresolved.

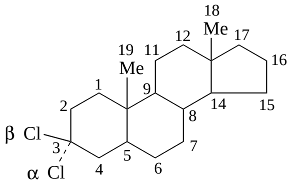
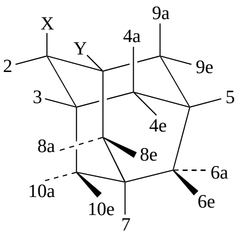


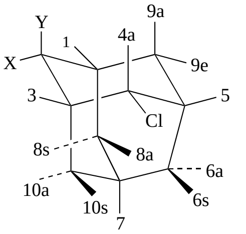
Table 7 Observed[a] *vs.* calculated[b] SCS for chloro-adamantanes



1-Chloro- (X = H, Y = Cl)			2-Chloro- (X = Cl, Y = H)		
Proton	Expt.[c]	CHARGE4	Proton	Expt.	CHARGE4
2,8,9	0.39	0.41	1,3 (CH)	0.20	0.21
3,5,7 (CH)	0.27	0.11	2 (CH)	2.65	2.50
4,6,10-ax	−0.08	0.07	4,9-ax	0.52	0.58
4,6,10-eq	−0.08	0.09	4,9-eq	−0.18	−0.09
			5 (CH)	−0.01	0.07
			6	0.01	0.05
			7 (CH)	−0.01	0.08
			8,10-ax	0.05	0.01
			8,10-eq	0.20	0.10

[a] Shifts this work, SCS *cf.* adamantane ref. 27. [b] Calc. SCS *cf.* adamantane (CH = 1.98, CH_2 = 1.35 ppm). [c] 2,8,9/3,5,7 and 4,6,10-ax/4,6,10-eq unresolved.

Table 8 Observed[a] *vs.* calculated[b] SCS for dichloro-adamantanes



2(ax),4(eq)-Dichloro- (X = H, Y = Cl)			2(eq),4(eq)-Dichloro- (X = Cl, Y = H)		
Proton	Expt.	CHARGE4	Proton	Expt.	CHARGE4
1 (CH)	0.18	0.28	1,5 (CH)	0.16	0.28
2-eq (CH)	2.76	2.57	2,4-ax (CH)	2.51	2.47
3 (CH)	0.45	0.41	3 (CH)	0.39	0.41
4-ax (CH)	3.07	3.19	6,8-*anti*	−0.18	−0.05
5 (CH)	0.18	0.28	6,8-*syn*	0.51	0.63
6-*anti*	−0.17	−0.05	7 (CH)	−0.02	0.14
6-*syn*	0.52	0.63	9-ax	0.01	0.01
7 (CH)	—	0.14	9-eq	0.36	0.20
8-*anti*	0.11[c]	0.15	10	0.33	0.51
8-*syn*	0.11[c]	0.05			
9-ax	0.60	0.58			
9-eq	0.05	0.01			
10-*anti*	−0.17	−0.11			
10-*syn*	0.71	0.71			

[a] Shifts ref. 28, SCS *cf.* adamantane ref. 27. [b] Calc. SCS *cf.* adamantane (CH = 1.98, CH_2 = 1.35 ppm). [c] Unresolved.

The observed SCS of the chloro substituent in axial-chlorocyclohexane on the 3-ax proton (0.58 ppm) is made up of 0.20 ppm due to the C–Cl linear electric field contribution and 0.15 ppm from the H···Cl steric term (total 0.51, Table 3) in the CHARGE4 scheme. Using the B value calculated by Grayson and Raynes[30] of 68 ppm au, the quadratic electric field effect using a chlorine charge of −0.155 electrons (*cf.* CHARGE4) and H···Cl distance of 2.974 Å (*cf.* HF/6-31G* geometry) is only 1.6×10^{-3} ppm. Similarly, the experimental chlorine SCS in 2-*endo*-chlorobornane on the 6-*endo* proton (0.84 ppm) is calculated in the scheme to consist of 0.23 ppm linear electric field and 0.34 ppm steric contributions (total 0.92, Table 5). In contrast the quadratic electric field term with a charge of −0.142 electrons at the closer distance of 2.677 Å would give only 2.1×10^{-3} ppm effect. The quadratic electric field effect would appear to be two orders of magnitude too small to account for the CHARGE4 steric term.

While consideration of other substituents may help to further illustrate the importance of the various terms, for protons it would appear that the quadratic electric field effect even from the polar C–Cl group is negligible and that the steric term is entirely due to van der Waal's interactions.

This conclusion is supported by the similar magnitude of the steric coefficient found here to the values obtained by Abraham and Holker[31] (163 ppm Å^{-6}) for the methyl···proton intramolecular van der Waal's interaction, confirming the general origin of this term.

In summary, the long range chlorine SCS can be represented by a combination of linear electric field and van der Waal's contributions, without the need for any anisotropy effects. This methodology should be extendible to other substituted hydrocarbons, such as bromoalkanes, ethers and alcohols. The additional inclusion of magnetic anisotropy effects would probably be needed for substituents with double and triple bonds, *e.g.* C=O, C=S, C=N–R and C≡N. These substituents are being investigated in our laboratories at present.

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